# REPORT DOCUMENTATION PAGE

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| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | Scott Grafton |
| UU | UU | UU | UU | | 19b. TELEPHONE NUMBER 805-893-3045 |

# RPPR Final Report
as of 01-May-2020

Agency Code:

Proposal Number: 55012LSICB **Agreement Number: W911NF-09-D-0001**
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DUNS Number: 094878394 EIN: 956006145W
**Report Date:** 28-Feb-2019 Date Received: 30-Aug-2019
**Final Report** for Period Beginning 01-Dec-2008 and Ending 30-Nov-2018
**Title:** Institute for Collaborative Biotechnologies
**Begin Performance Period:** 01-Dec-2008 **End Performance Period:** 30-Nov-2018
**Report Term:** 0-Other

Submitted By: MD Scott Grafton Email: scott.grafton@psych.ucsb.edu
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**Distribution Statement:** 1-Approved for public release; distribution is unlimited.

**STEM Degrees:** **STEM Participants:**

**Major Goals:** The goal of the work that was accomplished by the Army's Institute for Collaborative Biotechnologies was to conduct research and development in partnership with the Army to understand and translate solutions from highly evolved biological systems into new high-performance technologies, materials and systems for the Army and its soldiers.

This final report for the 2013-2018 ICB UARC projects in four research focus areas: (1) Systems and Synthetic Biology, (2) Bio-Inspired Materials, (3) Biotechnology Tools, and (4) Cognitive Neuroscience.

These research focus areas were well aligned with recent science and technology priorities of the Army and the Department of Defense.

Faculty and researchers from the University of California at Santa Barbara, the California Institute of Technology and the Massachusetts Institute of Technology performed the work.

**Accomplishments:** The reader is encouraged to consult the comprehensive 171-page PDF final report for the "Most Significant Results and Impact over the Five-Year Period (12/1/2013 - 11/30/2018)" for each of the 25 ICB UARC 2013-2018 projects in the four ICB research focus areas: (1) Systems and Synthetic Biology, (2) Bio-Inspired Materials, (3) Biotechnology Tools, and (4) Cognitive Neuroscience.

**Training Opportunities:** Nothing to Report

**Results Dissemination:** The reader is encouraged to consult the comprehensive 171-page PDF final report for the "Comprehensive List of Publications over the Five-Year Period (12/1/2013 - 11/30/2018)" for each of the 25 ICB UARC 2013-2018 projects in the four ICB research focus areas: (1) Systems and Synthetic Biology, (2) Bio-Inspired Materials, (3) Biotechnology Tools, and (4) Cognitive Neuroscience.

**Honors and Awards:** Nothing to Report

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**Protocol Activity Status:**

**Technology Transfer:** The reader is encouraged to consult the comprehensive 171-page PDF final report for the "Transitions to the Army and Industry during the Final Reporting (3/1/2016 - 11/30/2018)" for each of the 25 ICB UARC 2013-2018 projects in the four ICB research focus areas: (1) Systems and Synthetic Biology, (2) Bio-Inspired Materials, (3) Biotechnology Tools, and (4) Cognitive Neuroscience.

**PARTICIPANTS:**

**Participant Type:** Other Professional
**Participant:** Brett Beisecker
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Other Professional
**Participant:** John Bushnell
**Person Months Worked:** 6.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Other Professional
**Participant:** Bailey Clincy
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Other Professional
**Participant:** Joel Evans
**Person Months Worked:** 7.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Other Professional
**Participant:** David Gay
**Person Months Worked:** 8.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Other Professional
**Participant:** Christine Griffin
**Person Months Worked:** 6.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Other Professional
**Participant:** Tiffany Higbee
**Person Months Worked:** 6.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Other Professional
**Participant:** Elliot Hong
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Other Professional
**Participant:** Shayna Ingram
**Person Months Worked:** 7.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Other Professional
**Participant:** Elizabeth Jensen
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Other Professional
**Participant:** Lucille Rojas
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

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as of 01-May-2020

**Participant Type:** Faculty
**Participant:** Linda Petzold
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: Y
Other Collaborators:

**Participant Type:** Other Professional
**Participant:** Stephanie Lupo
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Gregory Campbell
**Person Months Worked:** 4.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Evan Janzen
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Ranajay Saha
**Person Months Worked:** 6.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Zhuowei Cheng
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N

Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Brian Mitchell
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Michelle O'Malley
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Non-Student Research Assistant
**Participant:** Susanna Seppala
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Jakkarin Limwongyut
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Luana Llanes
**Person Months Worked:** 4.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Alex Moreland
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:

National Academy Member: N
Other Collaborators:

**Participant Type:** Staff Scientist (doctoral level)
**Participant:** Chenyao Nie
**Person Months Worked:** 4.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Staff Scientist (doctoral level)
**Participant:** Bri Spinner Queenan
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Matthew Begley
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Leanne Friedrich
**Person Months Worked:** 4.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Drew Melchert
**Person Months Worked:** 4.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Steven Wehmeyer
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:

International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Maxwell Berkow
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Undergraduate Student
**Participant:** Tristan Chan
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Nathan Prisco
**Person Months Worked:** 4.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Michael Schmithorst
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Staff Scientist (doctoral level)
**Participant:** Kris Delaney
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Neil Dolinski
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:

International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Douglas Grzetic
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Joshua Lequieu
**Person Months Worked:** 8.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Zachariah Page
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Sheng-Ping Liang
**Person Months Worked:** 4.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Daniel Morse
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Lesley Chan
**Person Months Worked:** 2.00 **Funding Support:**

Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Michael Gordon
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Ryan Ley
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Pavel Shapturenka
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Amanda Ruschel
**Person Months Worked:** 6.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Francis Zok
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Undergraduate Student
**Participant:** Julia Adams

**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Julian Gerson
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Tod Kippin
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Mari Purpura
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Undergraduate Student
**Participant:** Serina Williams
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Non-Student Research Assistant
**Participant:** Samuel Curtis
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty

**Participant:** Kevin Plaxco
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Kyle Ploense
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Alexander Eden
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Mike Garcia
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Hyunjin Kim
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Sean Mackenzie
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

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**Participant Type:** Undergraduate Student
**Participant:** Nathaniel Shankute
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Dipanjana Das
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Cristo Garduno Luna
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Jordan Garrett
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Barry Giesbrecht
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Mary Maclean
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

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as of 01-May-2020

**Participant Type:** Graduate Student (research assistant)
**Participant:** Anne Milner
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Jean Carlson
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Joshua Mueller
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Chantal Nguyen
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Viktoriya Babenko
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Michelle Marneweck
**Person Months Worked:** 4.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Allison Shapiro
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Evan Layher
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Michael Miller
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Non-Student Research Assistant
**Participant:** Omary Saleem
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Tyler Santander
**Person Months Worked:** 13.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Guillermo Bazan
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N

Other Collaborators:

**Participant Type:** Non-Student Research Assistant
**Participant:** Scott Mahan
**Person Months Worked:** 9.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Yude Su
**Person Months Worked:** 9.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Jennifer Brown
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Staff Scientist (doctoral level)
**Participant:** Susanna Seppala
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Emily Sun
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Thomas Bullock
**Person Months Worked:** 9.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:

National Academy Member: N
Other Collaborators:

**Participant Type:** Undergraduate Student
**Participant:** Liann Jimmons
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Non-Student Research Assistant
**Participant:** Jamie Raymer
**Person Months Worked:** 14.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Alexander Boone
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Scott Grafton
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Non-Student Research Assistant
**Participant:** Ronnie Garcia
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Jongbok Lee
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:

International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Amir Tahmasebipour
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Courtney Durdle
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Sara Leslie
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Evan Chiswick
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Technician
**Participant:** Hsinhwa Lee
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Madeline Dery
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:

International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Andrea Wallace
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Kristala Prather
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Cynthia Ni
**Person Months Worked:** 9.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Stephanie Doong
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Kevin Fox
**Person Months Worked:** 10.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Elizabeth Proctor
**Person Months Worked:** 1.00 **Funding Support:**

Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Undergraduate Student
**Participant:** Keira Ahern
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Undergraduate Student
**Participant:** Kristina Stoyanova
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Stephen Van Nostrad
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty
**Participant:** Jim Heath
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Matt Idso
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Non-Student Research Assistant
**Participant:** Rick Edmark

**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Postdoctoral (scholar, fellow or other postdoctoral position)
**Participant:** Sunga Hong
**Person Months Worked:** 6.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Yapeng Su
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Samuel Ho
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Bradley Silverman
**Person Months Worked:** 4.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Xinran Liu
**Person Months Worked:** 4.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Faculty

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**Participant:** Richard Murray
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Andrew Shur
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Joseph Meyerowitz
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Staff Scientist (doctoral level)
**Participant:** Sabine Brinkmann-Chen
**Person Months Worked:** 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Kai Chen
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Kevin Yang
**Person Months Worked:** 5.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

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**Participant Type:** Graduate Student (research assistant)
**Participant:** James Parkin
**Person Months Worked:** 3.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**Participant Type:** Graduate Student (research assistant)
**Participant:** Rory Williams
**Person Months Worked:** 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

**ARTICLES:**

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Organometallic Chemistry
Publication Identifier Type: Publication Identifier:
Volume: Issue: First Page #:
Date Submitted: Date Published:
Publication Location:
**Article Title:** Binding modes of a dimethyliminopentanone ligand on nickel pre-catalysts toward olefin polymerization
**Authors:**
**Keywords:**
**Abstract:** see attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review E
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevE.83.056307
Volume: 83 Issue: 5 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Hydronium-dominated ion transport in carbon-dioxide-saturated electrolytes at low salt concentrations in nanochannels
**Authors:**
**Keywords:** None.
**Abstract:** Nanochannel ion transport is known to be governed by surface charge at low ionic concentrations. In this paper, we show that this surface charge is typically dominated by hydronium ions arising from dissolution of ambient atmospheric carbon dioxide. Taking the hydronium ions into account, we model the nanochannel conductance at low salt concentrations and identify a conductance minimum before saturation at a value independent of salt concentration in the dilute limit. Via the Poisson–Boltzmann equation, our model self-consistently couples chemical-equilibrium dissociation models of the silica wall and of the electrolyte bulk, parametrized by the dissociation reaction constants. Experimental data with aqueous KCl solutions in 165-nm-high silica nanochannels are described well by our model, both with and without extra hydronium from added HCl.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Theoretical Ecology
Publication Identifier Type: DOI Publication Identifier: 10.1007/s12080-010-0075-z
Volume: 4 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Integrate-and-fire models of insolation-driven entrainment of broadcast spawning in corals
**Authors:**
**Keywords:** Bioenergetic integrate-and-fire model, Broadcast spawning, Entrainment, Insolation, Coral reproduction, Biological rhythms, Computational biology
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Ecology
Publication Identifier Type: Publication Identifier:
Volume: 92 Issue: 2 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Stochastic growth reduces population fluctuationsin Daphnia–algal systems
**Authors:**
**Keywords:** Daphnia; growth variability; multiple attractors; quasi-cycles; robustness; stability; stagestructuredmodels; stochastic population dynamics.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biological Bulletin
Publication Identifier Type: Publication Identifier:
Volume: 220 Issue: 3 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Effects of Light Dynamics on Coral Spawning Synchrony
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Protein Engineering Design and Selection
Publication Identifier Type: DOI Publication Identifier: 10.1093/protein/gzq063
Volume: 23 Issue: 11 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Efficient screening of fungal cellobiohydrolase class I enzymes for thermostabilizing sequence blocks by SCHEMA structure-guided recombination
**Authors:**
**Keywords:** biofuel/cellulase, directed evolution, proteinrecombination, protein thermostability, CBH I, Cel7A
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Computational Neuroscience
Publication Identifier Type: Publication Identifier:
Volume: 23 Issue: 6 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** A Computational Model of How Cholinergic InterneuronsProtect Striatal-dependent Learning
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Annals of the New York Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1111/j.1749-6632.2010.05874.x
Volume: 1224 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Human category learning 2.0
**Authors:**
**Keywords:** categorization; memory system interactions; automaticity; striatum
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1523/JNEUROSCI.2393-10.2010
Volume: 30 Issue: 42 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Evidence for Cortical Automaticity in Rule-Based Categorization
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Memory & Cognition
Publication Identifier Type: DOI Publication Identifier: 10.3758/s13421-010-0041-4
Volume: 39 Issue: 3 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Information–integration category learning and the human uncertainty response
**Authors:**
**Keywords:** Metacognition . Categorization . Proceduralmemory . Non-declarative memory . Uncertainty
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Psychonomic Bulletin & Review
Publication Identifier Type: DOI Publication Identifier: 10.3758/s13423-010-0047-8
Volume: 18 Issue: 2 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Pigeons' categorization may be exclusively nonanalytic
**Authors:**
**Keywords:** Category learning . Comparative cognition .Pigeons . Rules . Analytic/nonanalytic cognition . Implicit/explicit cognition
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Procceedings of the Nanotech 2011 Conference and Expo
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Capillary Electrophoresis in Nanouidic Channels
**Authors:**
**Keywords:** nanouidics, nanochannel, capillary elec-trophoresis, statistical mechanics, computational uiddynamics
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Theoretical Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jtbi.2010.11.023
Volume: 272 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Stochastic reduction method for biological chemical kinetics using time-scale separation
**Authors:**
**Keywords:** Stochastic modereduction, Linear noiseapproximation, Gene regulation, Concentration fluctuations, Singular perturbation
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.200903677
Volume: 22 Issue: 8 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Improved Performance of Polymer Bulk Heterojunction Solar Cells Through the Reduction of Phase Separation via Solvent Additives
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nano Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/nl101923m
Volume: 10 Issue: 10 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Effect of Processing Additive on the Nanomorphology of a Bulk Heterojunction Material
**Authors:**
**Keywords:** Polymer solar cell, bulk heterojunction, processing additive, transmission electron microscopy, bipolar field effecttransistor
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja1016156
Volume: 132 Issue: 29 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Modification of the Optoelectronic Properties of Membranes via Insertion of Amphiphilic Phenylenevinylene Oligoelectrolytes
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Materials Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1039/c0jm02544e
Volume: 21 Issue: 4 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Nanostructure design of amorphous FePO4 facilitated by a virus for 3 V lithium ion battery cathodes
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Automatic Control
Publication Identifier Type: DOI Publication Identifier: 10.1109/TAC.2010.2049278
Volume: 55 Issue: 11 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Dynamic Vehicle Routing for Translating Demands: Stability Analysis and Receding-Horizon Policies
**Authors:**
**Keywords:** Autonomous vehicles, dynamic vehicle routing,minimum Hamiltonian path, queueing theory.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review E
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevE.81.025204
Volume: 81 Issue: 2 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Robotic reactions: Delay-induced patterns in autonomous vehicle systems
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Procceedings of the 2011 American Control Conference
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** On Opinion Dynamics in Heterogeneous Networks
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** International Journal of Wildland Fire
Publication Identifier Type: Publication Identifier:
Volume: 20 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Modelling long-term fire regimes of southern Californiashrublands
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

# RPPR Final Report
as of 01-May-2020

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: Publication Identifier:
Volume: 7 Issue: 6 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Learning, Memory, and the Role of Neural NetworkArchitecture
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** NeuroImage
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2010.09.006
Volume: 54 Issue: 2 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Conserved and variable architecture of human white matter connectivity
**Authors:**
**Keywords:** Complex network analysis, Diffusion imaging, Reproducibility, Hierarchical modularity, Rentian scaling
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1018985108
Volume: 108 Issue: 18 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Dynamic reconfiguration of human brain networks during learning
**Authors:**
**Keywords:** complex network ! time-dependent network, fMRI, motor learning, community structure
**Abstract:** See atttached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1523/JNEUROSCI.0382-11.2011
Volume: 31 Issue: 17 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Emerging Evidence of Connectomic Abnormalities in Schizophrenia
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

# RPPR Final Report
as of 01-May-2020

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0018298
Volume: 6 Issue: 3 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Pupillometric Evidence for the Decoupling of Attention from Perceptual Input during Offline Thought
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja200054z
Volume: 133 Issue: 26 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Understanding and Controlling Organic–Inorganic Interfaces in Mesostructured Hybrid Photovoltaic Materials
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Mechanics and Physics of Solids
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jmps.2010.09.004
Volume: 59 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Multiscale mass-spring models of carbon nanotube foams
**Authors:**
**Keywords:** Carbon nanotubefoams, Bi-stable springs, Multiscale behavior, Strain localization, Hysteresis
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Chemical Biology
Publication Identifier Type: DOI Publication Identifier: 10.1021/cb200039s
Volume: 6 Issue: 8 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Protease-Resistant Peptide Ligands from a Knottin Scaffold Library
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

# RPPR Final Report
as of 01-May-2020

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Biological Rhythms
Publication Identifier Type: Publication Identifier:
Volume: 26 Issue: 4 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Wavelet Measurement Suggests Cause ofPeriod Instability in Mammalian CircadianNeurons
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IET Systems Biology
Publication Identifier Type: DOI Publication Identifier: 10.1049/iet-syb.2009.0064
Volume: 5 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Distribution-based sensitivity metric for highly variable biochemical systems
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Automatica
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.automatica.2011.01.074
Volume: 47 Issue: 6 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** On influences of global and local cues on the rate of synchronization of oscillator networks
**Authors:**
**Keywords:** Rate of synchronization, Global cue, Local cue, Oscillators, Circadian rhythm, Entrainment
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** BMC Systems Biology
Publication Identifier Type: DOI Publication Identifier: 10.1186/1752-0509-4-161
Volume: 4 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Confidence from uncertainty - A multi-target drug screening method from robust control theory
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 2010 American Control Conference, San Francisco, CA
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** The exponential synchronization of Kuramotooscillator networks in the presence of combinedglobal and local cues
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 2011 Amercian Control Conference, San Francisco, CA
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Computationally Implement-able Sufficient Conditions for theSynchronisation of Coupled Dynamical Systems with Time Delays inthe Coupling
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 49th IEEE Conference on Decision and Control, Atlanta, GA
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** The influences of global and local cues on thesynchronization rate of interconnected oscillatornetworks subject to time delays
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 48th Annual Allerton Conference on Communication, Control, and Computing, Allerton, IL.
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** The synchronization rate of oscillator networkssubject to delayed and directed interaction
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of The 9th IFAC Symposiumon Dynamics and Control of Process Systems (DYCOPS), Leuven, Belgium
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Modelling of Detailed Insulin ReceptorKinetics Affects Sensitivity and Noise inthe Downstream Signalling Pathway
**Authors:**
**Keywords:** Insulin, diabetes, signalling pathway, sensitivity analysis, drug target, stochasticmodelling
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 2011 Amercian Control Conference, San Francisco, CA
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Computationally Implement-able Sufficient Conditions for the Synchronisation of Coupled Dynamical Systems with Time Delays inthe Coupling
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Science
Publication Identifier Type: DOI Publication Identifier: 10.1126/science.1200705
Volume: 333 Issue: 6039 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Glycolytic Oscillations and Limits on Robust Efficiency
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Automatica
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.automatica.2011.02.040
Volume: 47 Issue: 6 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Analysis of autocatalytic networks in biology
**Authors:**
**Keywords:** Autocatalytic pathways, Glycolysis, Quantitative analysis, Compositional analysis, Nonlinear systems
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 49th IEEE Conference on Decision and Control, Atlanta, GA
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Performance Limitations in Autocatalytic Networks in Biology
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Optical Society of Americal
Publication Identifier Type: Publication Identifier:
Volume: 27 Issue: 12 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Ideal observer analysis for task normalization ofpattern classifier performance applied to EEG andfMRI data
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Physical Chemistry B
Publication Identifier Type: DOI Publication Identifier: 10.1021/jp101413a
Volume: 114 Issue: 31 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Phase Separation in Symmetric Mixtures of Oppositely Charged Rodlike Polyelectrolytes
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Computational Physics
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jcp.2010.12.008
Volume: 230 Issue: 5 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** A second-order discretization of the nonlinear Poisson–Boltzmann equation over irregular geometries using non-graded adaptive Cartesian grids
**Authors:**
**Keywords:** Nonlinear Poisson–Boltzmann equation, Non-graded adaptive grid, Octree data structure, Second-order discretization Arbitrary geometries Supercapacitors
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Computational Physics
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jcp.2011.02.010
Volume: 230 Issue: 10 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** A Poisson–Boltzmann solver on irregular domains with Neumann or Robin boundary conditions on non-graded adaptive grid
**Authors:**
**Keywords:** Finite Difference method, Adaptive grid, OctreeLevel setIrregular domain, Poisson–Boltzmann solver, Neumann boundary condition, Robin boundary condition
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Computational Physics
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jcp.2009.10.017
Volume: 229 Issue: 3 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Efficient symmetric discretization for the Poisson, heat and Stefan-type problems with Robin boundary conditions
**Authors:**
**Keywords:** Level set method, Robin boundary condition, Stefan, Poisson, Diffusion, Irregular domains
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 27th Army Science Conference, Oralando, FL
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Physics-Based Models of Brain Structure Connectivity Informed by Diffusion-Weighted Imaging
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Neuron
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuron.2010.11.002
Volume: 68 Issue: 4 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Human Posterior Parietal Cortex Flexibly Determines Reference Frames for Reaching Based on Sensory Context
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Functional Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adfm.201000305
Volume: 20 Issue: 14 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** In situ Mechanical Testing Reveals Periodic Buckle Nucleation and Propagation in Carbon Nanotube Bundles
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201001793
Volume: 22 Issue: 41 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Batch Fabrication of High-Performance Planar Patch-Clamp Devices in Quartz
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biomedical Microdevices
Publication Identifier Type: DOI Publication Identifier: 10.1007/s10544-010-9488-0
Volume: 13 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Flow optimization study of a batch microfluidics PET tracer synthesizing device
**Authors:**
**Keywords:** Flow optimization, Microfluidic, Positronemission tomography, Fluorescence imaging, Microreactor, Numerical modeling
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1005632107
Volume: 107 Issue: 24 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Colorimetric detection of DNA, small molecules, proteins, and ions using unmodified gold nanoparticles and conjugated polyelectrolytes
**Authors:**
**Keywords:** biosensor, aptamer, visual detection, thrombin detection, cocaine detection
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja104998m
Volume: 132 Issue: 41 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** An Electrochemical Supersandwich Assay for Sensitive and Selective DNA Detection in Complex Matrices
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences
Publication Identifier Type: Publication Identifier:
Volume: 368 Issue: 1930 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Stochastic hybrid systems for studyingbiochemical processes
**Authors:**
**Keywords:** stochastic hybrid systems; stochastic chemical kinetics; moment dynamics; momentclosure; gene regulatory networks; gene autoregulation; negative feedback
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Transactions of the Institute of Measurement and Control
Publication Identifier Type: DOI Publication Identifier: 10.1177/0142331208097841
Volume: 32 Issue: 5 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Stability of delay impulsive systems with application to networked control systems
**Authors:**
**Keywords:** delay hybrid systems; delay impulsive systems; networked control systems;stability
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 2010 American Control Conference
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Optimal Estimation on the Graph Cycle Space
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the International Conference and Exhibition of Unammaned Aerial Vehicles
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** GeoTrack: An Autonomous Closed-loop Target Tracking System for Small UAVNetworks
**Authors:**
**Keywords:** Small Unmanned Air Vehicles (SUAVs), ┌ Swarm control, ┌ Video tracking, ┌ Multi-sensor fusion andtracking, ┌ Geo-location, ┌ Embedded processing
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 2nd IFAC Workshop on Distributed Estimation and Control in Networked Systems (NecSys'10)
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Optimal Redundant Transmission for StateEstimation with Packet Drops
**Authors:**
**Keywords:** Packet drops, state estimation, limited communication
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 49th IEEE Conference on Decision and Control, Atlanta, GA
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Construction of Lyapunov Functions for Piecewise-DeterministicMarkov Processes
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1000985
Volume: 6 Issue: 11 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Analysis of Stochastic Strategies in Bacterial Competence: A Master Equation Approach
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 49th IEEE Conference on Decision and Control, Atlanta, GA
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Parameter Identification of Biological NetworksUsing Extended Kalman Filtering and X▼2 Criteria
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 49th IEEE Conference on Decision and Control, Atlanta, GA
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Model Reduction of Polynomial Dynamical Systems UsingDifferential Algebra
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1001099
Volume: 7 Issue: 3 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Training Signaling Pathway Maps to Biochemical Data with Constrained Fuzzy Logic: Quantitative Analysis of Liver Cell Responses to Inflammatory Stimuli
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 2011SPIE Biosystems Conference
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Cellular defense processes regulated bypathogen-elicited receptor signaling
**Authors:**
**Keywords:** Systems biology; cell signaling; computational modeling; pathogen/host interactions; microbial infection
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Lab on a Chip
Publication Identifier Type: DOI Publication Identifier: 10.1039/c0lc00447b
Volume: 11 Issue: 4 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Suspended microchannel resonators with piezoresistive sensors
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Review of Scientific Instruments
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.3534825
Volume: 82 Issue: 2 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** High precision particle mass sensing using microchannel resonators in the second vibration mode
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1104651108
Volume: 108 Issue: 27 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Measuring single-cell density
**Authors:**
**Keywords:** cell size, apoptosis, hematology, biosensor, suspended microchannel resonator
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review E
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevE.84.026304
Volume: 84 Issue: 2 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Energy dissipation in microfluidic beam resonators: Effect of Poisson's ratio
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of IMECE2010, ASME International Mechanical Engineering Congress and Exposition, Vancouver, British Columbia
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Analysis Tools for Thermally Driven Microfluidics
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** NeuroImage
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2010.11.066
Volume: 55 Issue: 2 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Parietal cortex tracks the amount of information retrieved even when it is not the basis of a memory decision
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Discrete and Continuous Dynamical Systems - Series A
Publication Identifier Type: DOI Publication Identifier: 10.3934/dcds.2010.28.1413
Volume: 28 Issue: 4 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Charge-balanced spike timing control for phase models of spiking neurons
**Authors:**
**Keywords:** Mathematical neuroscience, control, phase models
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Experimental Biology
Publication Identifier Type: DOI Publication Identifier: 10.1242/jeb.043406
Volume: 214 Issue: 5 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Twilight spectral dynamics and the coral reef invertebrate spawning response
**Authors:**
**Keywords:** color vision, irradiance, mass spawning, twilight.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nano Today
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.nantod.2010.02.004
Volume: 5 Issue: 2 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Sonication-accelerated catalytic synthesis of oxide nanoparticles
**Authors:**
**Keywords:** Sonication, Vapor diffusioncatalysis, Ceria, Barium titanate, Nanoparticles
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Crystal Growth & Design
Publication Identifier Type: DOI Publication Identifier: 10.1021/cg100708q
Volume: 10 Issue: 10 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Unusual Evolution of Ceria Nanocrystal Morphologies Promoted by a Low-Temperature Vapor Diffusion Based Process
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Physical Chemistry C
Publication Identifier Type: DOI Publication Identifier: 10.1021/jp108222z
Volume: 114 Issue: 45 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Vapor-Diffusion-Controlled Sol-Gel Synthesis of Flaky Lithium Vanadium Oxide and Its Electrochemical Behavior
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Dalton Transactions
Publication Identifier Type: DOI Publication Identifier: 10.1039/c0dt01558j
Volume: 40 Issue: 6 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Cd1-xZnxO [0.05 ?x? 0.26] synthesized by vapor-diffusion induced hydrolysis and co-nucleation from aqueous metal salt solutions
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Protocols
Publication Identifier Type: DOI Publication Identifier: 10.1038/nprot.2010.138
Volume: 6 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Large-scale engineered synthesis of BaTiO3 nanoparticles using low-temperature bioinspired principles
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Ceramics International
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.ceramint.2010.08.040
Volume: 37 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Engineering grain size and electrical properties of donor-doped barium titanate ceramics
**Authors:**
**Keywords:** C. Electrical properties; Ceramics; Chemical synthesis; Crystal growth
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the Materials Research Society Symposium
Publication Identifier Type: Publication Identifier:
Volume: 1199 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Low temperature growth and laser-induced phase transformation of perovskite oxide filmsfor uncooled IR detector applications
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201004203
Volume: 23 Issue: 20 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Gate-Tunable Surface Processes on a Single-Nanowire Field-Effect Transistor
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nano Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/nl1031309
Volume: 11 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Visualizing Chromatographic Separation of Metal Ions on a Surface-Enhanced Raman Active Medium
**Authors:**
**Keywords:** Surface-enhanced Raman spectroscopy, chromatography, separation, metal carboxylates
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nano Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/nl102495j
Volume: 10 Issue: 10 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Aptamer-Mediated Surface-Enhanced Raman Spectroscopy Intensity Amplification
**Authors:**
**Keywords:** Aptamers, surface enhanced Raman spectroscopy, AFM, nanoparticles, sensors
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the IEEE/RSJ International Conference on Intelligent Robots and Systems
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** An insect-inspired autocorrelation model for visual flight control in acorridor
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Ecological Modelling
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.ecolmodel.2011.01.004
Volume: 222 Issue: 7 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Impact of excess and harmful radiation on energy budgets in scleractinian corals
**Authors:**
**Keywords:** Dynamic energy budget (DEB) theory, Syntrophy, Symbiosis, Endosymbiont, Scleractinian coral, Mutualism, Photoinhibition, Photodamage, Coral bleaching
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Langmuir
Publication Identifier Type: DOI Publication Identifier: 10.1021/la200837z
Volume: 27 Issue: 14 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Distinct Conformations of DNA-Stabilized Fluorescent Silver Nanoclusters Revealed by Electrophoretic Mobility and Diffusivity Measurements
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.3522769
Volume: 134 Issue: 4 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Automated estimation of rare event probabilities in biochemical systems
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IET Systems Biology
Publication Identifier Type: DOI Publication Identifier: 10.1049/iet-syb.2009.0057
Volume: 5 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Legitimacy of the stochastic Michaelis–Menten approximation
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.3576123
Volume: 134 Issue: 13 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Michaelis–Menten speeds up tau-leaping under a wide range of conditions
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.3493460
Volume: 133 Issue: 17 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** State-dependent biasing method for importance sampling in the weighted stochastic simulation algorithm
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Applied Physics Letters
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.3467259
Volume: 97 Issue: 6 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Tunable acoustophoretic band-pass particle sorter
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1014753108
Volume: 108 Issue: 17 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Selection of phage-displayed peptides on live adherent cells in microfluidic channels
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja203981w
Volume: 133 Issue: 23 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Genetic Analysis of H1N1 Influenza Virus from Throat Swab Samples in a Microfluidic System for Point-of-Care Diagnostics
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review Letters
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevLett.105.144503
Volume: 105 Issue: 14 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Suppression of Electro-Osmotic Flow by Surface Roughness
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ChemBioChem
Publication Identifier Type: DOI Publication Identifier: 10.1002/cbic.201000419
Volume: 11 Issue: 15 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Live-Cell Imaging of Cellular Proteins by a Strain-Promoted Azide-Alkyne Cycloaddition
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja1083909
Volume: 132 Issue: 51 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Cleavable Biotin Probes for Labeling of Biomolecules via Azide-Alkyne Cycloaddition
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Current Opinion in Chemical Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cbpa.2010.09.013
Volume: 14 Issue: 6 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Residue-specific incorporation of non-canonical amino acids into proteins: recent developments and applications
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 2011 SIAM International Conference on Data Mining
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** On Flow Authority Discovery in Social Networks
**Authors:**
**Keywords:** Social networks, graph mining
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 2011International Conference on Managment of Data
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Assessing and Ranking Structural Correlations in Graphs
**Authors:**
**Keywords:** Graph, Structural Correlation, Hitting Time
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Functional Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adfm.201100493
Volume: 21 Issue: 16 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Gecko-Inspired Dry Adhesive for Robotic Applications
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 27th Army Science Conference, Orlando, FL.
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Gecko-Inspired Dry Adhesive For Applications Robotic
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the 49th IEEE Conference on Decision and Control, Atlanta, GA
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Proc. The influences of global and local cues on the synchronization rate of interconnected oscillator networks subject to time delays
**Authors:**
**Keywords:** None.
**Abstract:** See attached
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Sea Research
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.seares.2011.04.004
Volume: 66 Issue: 4 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Entrainment of cell division in phytoplankton with dynamic energy budgets
**Authors:**
**Keywords:** Dynamic Energy Budget Theory (DEB) Model, Entrainment, Algae, Cell-Cycle
**Abstract:** We explore the entrainment behavior of cell division in phytoplankton in the context of Dynamic Energy Budget (DEB) theory. In particular, we explore the range of DEB and environmental parameter values within which a cell divides at regular intervals in a periodic light environment with abundant nutrients and investigate the impact of parameter values on the phase of cell division. We consider three types of cells that differ in the evolution of surface area to volume ratio during the cell cycle: cells with a constant shape (isomorphs), cells with a constant surface area (V0-morphs) and cells with a constant surface area to volume ratio (V1-morphs), the latter being the default choice in studies on the population dynamics of unicellular organisms because of its desirable mathematical implications. Only in isomorphs and V0-morphs, however, cell division can be entrained to a periodic light. Regular cell division in V1 is purely coincidental, as it depends on exact choices for parameter
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Synthetic Biology
Publication Identifier Type: DOI Publication Identifier: 10.1021/sb300014t
Volume: 1 Issue: 0 First Page #: 221
Date Submitted: Date Published:
Publication Location:
**Article Title:** SCHEMA-Designed Variants of Human Arginase I and II Reveal Sequence Elements Important to Stability and Catalysis
**Authors:**
**Keywords:** enzyme engineering, arginase, homologous recombination, SCHEMA library design, active learning, protein stability
**Abstract:** Arginases catalyze the divalent cation-dependent hydrolysis of L-arginine to urea and L-ornithine. There is significant interest in using arginase as a therapeutic antineogenic agent against L-arginine auxotrophic tumors and in enzyme replacement therapy for treating hyperargininemia. Both therapeutic applications require enzymes with sufficient stability under physiological conditions. To explore sequence elements that contribute to arginase stability we used SCHEMA-guided recombination to design a library of chimeric enzymes composed of sequence fragments from the two human isozymes Arginase I and II. We then developed a novel active learning algorithm that selects sequences from this library that are both highly informative and functional. Using high-throughput gene synthesis and our two-step active learning algorithm, we were able to rapidly create a small but highly informative set of seven enzymatically active chimeras that had an average variant distance of 40 mutations from the
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** WIREs Cognitive Science
Publication Identifier Type: DOI Publication Identifier: 10.1002/wcs.1172
Volume: 3 Issue: 3 First Page #: 363
Date Submitted: Date Published:
Publication Location:
**Article Title:** Automaticity and multiple memory systems
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Mathematical Psychology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jmp.2011.04.003
Volume: 55 Issue: 4 First Page #: 273
Date Submitted: Date Published:
Publication Location:
**Article Title:** A tutorial on computational cognitive neuroscience: Modeling the neurodynamics of cognition
**Authors:**
**Keywords:** Computational cognitive neuroscience, neural network modelling, neuroscience
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Psychological Research
Publication Identifier Type: DOI Publication Identifier: 10.1007/s00426-011-0348-1
Volume: 76 Issue: 3 First Page #: 292
Date Submitted: Date Published:
Publication Location:
**Article Title:** Learning and transfer of category knowledge in an indirect categorization task
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Neural Networks
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neunet.2012.02.033
Volume: 32 Issue: 0 First Page #: 74
Date Submitted: Date Published:
Publication Location:
**Article Title:** Simulating the effects of dopamine imbalance on cognition: From positive affect to Parkinson’s disease
**Authors:**
**Keywords:** Dopamine, COVIS, Parkinson's disease, Positive affect, Computational modelling
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Comparative Psychology
Publication Identifier Type: DOI Publication Identifier: 10.1037/a0026031
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Implicit and explicit category learning by capuchin monkeys (Cebus apella).
**Authors:**
**Keywords:** Explicit categorization, Primate cognition, Comparative cognition, Category learning, Capuchin monkeys
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chemistry - A European Journal
Publication Identifier Type: DOI Publication Identifier: 10.1002/chem.201103237
Volume: 18 Issue: 3 First Page #: 756
Date Submitted: Date Published:
Publication Location:
**Article Title:** Supramolecular Electrostatic Nanoassemblies for Bacterial Forensics
**Authors:**
**Keywords:** Biosensors, Forensics, Fluorescent probes, FRET, Microbiology, Self-assembly
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Mechanics and Physics of Solids
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jmps.2012.03.002
Volume: 60 Issue: 8 First Page #: 1545
Date Submitted: Date Published:
Publication Location:
**Article Title:** Micromechanical models to guide the development of synthetic ‘brick and mortar’ composites
**Authors:**
**Keywords:** Composites, Micromechanics, Strength, Modulus, Nacre
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nanoscale
Publication Identifier Type: DOI Publication Identifier: 10.1039/c2nr30115f
Volume: 4 Issue: 11 First Page #: 3405
Date Submitted: Date Published:
Publication Location:
**Article Title:** Virus-templated iridium oxide–gold hybrid nanowires for electrochromic application
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Small
Publication Identifier Type: DOI Publication Identifier: 10.1002/smll.201102036
Volume: 8 Issue: 7 First Page #: 1006
Date Submitted: Date Published:
Publication Location:
**Article Title:** Graphene Sheets Stabilized on Genetically Engineered M13 Viral Templates as Conducting Frameworks for Hybrid Energy-Storage Materials
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ECS Transactions
Publication Identifier Type: DOI Publication Identifier: 10.1149/1.4717963
Volume: 41 Issue: 41 First Page #: 55
Date Submitted: Date Published:
Publication Location:
**Article Title:** Genetically Programming Interfaces between Active Materials, Conductive Pathway and Current Collector in Li-Ion Batteries
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Social Cognitive and Affective Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1093/scan/nsr057
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Attitudes trigger motor behavior through conditioned associations: neural and behavioral evidence
**Authors:**
**Keywords:** Attitudes, Embodiment, Social cognition, Social neuroscience, Motor behavior, Action
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Automatica
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.automatica.2011.06.010
Volume: 47 Issue: 9 First Page #: 2067
Date Submitted: Date Published:
Publication Location:
**Article Title:** On vehicle placement to intercept moving targets
**Authors:**
**Keywords:** Coverage control, Pursuit-evasion games, Optimization, Autnomous and multi-agent systems
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Automatic Control
Publication Identifier Type: DOI Publication Identifier: 10.1109/TAC.2011.2158130
Volume: 57 Issue: 1 First Page #: 90
Date Submitted: Date Published:
Publication Location:
**Article Title:** Consensus Computation in Unreliable Networks: A System Theoretic Approach
**Authors:**
**Keywords:** Autonomous agents, Consensus algorithms, Distributed control, Fault detection, Intrusion detection, Multi-agent systems, Network topology, Network theory (graphs), Sensor Networks
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Automatica
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.automatica.2012.02.025
Volume: 48 Issue: 5 First Page #: 747
Date Submitted: Date Published:
Publication Location:
**Article Title:** Distributed estimation via iterative projections with application to power network monitoring
**Authors:**
**Keywords:** Power systems, State estimation, Monitoring, Algebraic approaches, Distributed detection, System security
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** NeuroImage
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2011.10.002
Volume: 59 Issue: 3 First Page #: 2196
Date Submitted: Date Published:
Publication Location:
**Article Title:** Altered resting state complexity in schizophrenia
**Authors:**
**Keywords:** Schizophrenia, Functional connectivity, Network analysis, Graph theory, Resting state
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0033706
Volume: 7 Issue: 4 First Page #: 33706
Date Submitted: Date Published:
Publication Location:
**Article Title:** Insulation for Daydreams: A Role for Tonic Norepinephrine in the Facilitation of Internally Guided Thought
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Neuron
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuron.2012.03.038
Volume: 74 Issue: 5 First Page #: 936
Date Submitted: Date Published:
Publication Location:
**Article Title:** Differential Recruitment of the Sensorimotor Putamen and Frontoparietal Cortex during Motor Chunking in Humans
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja2038529
Volume: 133 Issue: 40 First Page #: 16023
Date Submitted: Date Published:
Publication Location:
**Article Title:** Molecular Optimization of Multiply-Functionalized Mesoporous Films with Ion Conduction Properties
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Tissue Engineering and Regnerative Medicine
Publication Identifier Type: DOI Publication Identifier: 10.1002/term.1458
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Differentiation of human pluripotent stem cells to retinal pigmented epithelium in defined conditions using purified extracellular matrix proteins
**Authors:**
**Keywords:** Retinal pigmented epithelium, Induced pluripotent stem cells, Human embryonic stem cells, Age-related macular degeneration, Pluripotent stem cells, Extracellular matrix, Intergrins, Laminin
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Applied Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.3699184
Volume: 111 Issue: 7 First Page #: 74314
Date Submitted: Date Published:
Publication Location:
**Article Title:** Nonlinear viscoelasticity of freestanding and polymer-anchored vertically aligned carbon nanotube foams
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nanotechnology
Publication Identifier Type: DOI Publication Identifier: 10.1088/0957-4484/22/42/425705
Volume: 22 Issue: 42 First Page #: 425705
Date Submitted: Date Published:
Publication Location:
**Article Title:** Effect of density variation and non-covalent functionalization on the compressive behavior of carbon nanotube arrays
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Nano
Publication Identifier Type: DOI Publication Identifier: 10.1021/nn202262j
Volume: 5 Issue: 10 First Page #: 7713
Date Submitted: Date Published:
Publication Location:
**Article Title:** Synthesis and Characterization of Carbon Nanotube–Polymer Multilayer Structures
**Authors:**
**Keywords:** Carbon nanotubes, Multilayer, Energy absorption, Bucky paper, Strain rate, Bulk density
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Composite Structures
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.compstruct.2011.04.034
Volume: 93 Issue: 11 First Page #: 3013
Date Submitted: Date Published:
Publication Location:
**Article Title:** Modeling and in situ identification of material parameters for layered structures based on carbon nanotube arrays
**Authors:**
**Keywords:** Carbon nanotubes, Multilayer foams, Buckling, Mechnical properties
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Carbon
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.carbon.2011.04.066
Volume: 49 Issue: 11 First Page #: 3631
Date Submitted: Date Published:
Publication Location:
**Article Title:** Tailoring the microstructure and mechanical properties of arrays of aligned multiwall carbon nanotubes by utilizing different hydrogen concentrations during synthesis
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Carbon
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.carbon.2012.05.021
Volume: 50 Issue: 12 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** In situ synthesis of metal oxides in carbon nanotube arrays and mechanical properties of the resulting structures
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1002379
Volume: 8 Issue: 2 First Page #: 1002379
Date Submitted: Date Published:
Publication Location:
**Article Title:** Modeling Cortisol Dynamics in the Neuro-endocrine Axis Distinguishes Normal, Depression, and Post-traumatic Stress Disorder (PTSD) in Humans
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1103557108
Volume: 108 Issue: 0 First Page #: 15624
Date Submitted: Date Published:
Publication Location:
**Article Title:** Architecture, constraints, and behavior
**Authors:**
**Keywords:** Complexity
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201200214
Volume: 24 Issue: 28 First Page #: 3838
Date Submitted: Date Published:
Publication Location:
**Article Title:** Nanoemulsion Composite Microgels for Orthogonal Encapsulation and Release
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Materials
Publication Identifier Type: DOI Publication Identifier: 10.1038/nmat3248
Volume: 11 Issue: 4 First Page #: 344
Date Submitted: Date Published:
Publication Location:
**Article Title:** Mesoporous organohydrogels from thermogelling photocrosslinkable nanoemulsions
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review E
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevE.85.016325
Volume: 85 Issue: 1 First Page #: 16325
Date Submitted: Date Published:
Publication Location:
**Article Title:** Scattering and nonlinear bound states of hydrodynamically coupled particles in a narrow channel
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** NeuroImage
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2011.07.009
Volume: 59 Issue: 1 First Page #: 94
Date Submitted: Date Published:
Publication Location:
**Article Title:** Neural decoding of collective wisdom with multi-brain computing
**Authors:**
**Keywords:** Multi-brain computing, Collective wisdom, Neural decoding, Perceptual decisions, Group decisions
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Vision
Publication Identifier Type: DOI Publication Identifier: 10.1167/11.5.14
Volume: 11 Issue: 5 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Visual search: A retrospective
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Research in Computational Molecular Biology
Publication Identifier Type: Publication Identifier:
Volume: 0 Issue: 0 First Page #: 287
Date Submitted: Date Published:
Publication Location:
**Article Title:** Simulatenous reconstruction of multiple signaling pathways via the prize-collecting Steiner forest problem
**Authors:**
**Keywords:** Prize-collecting Steiner forest, Signaling pathways, Multiple network reconstruction
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.3674305
Volume: 136 Issue: 2 First Page #: 24903
Date Submitted: Date Published:
Publication Location:
**Article Title:** Investigation of the interfacial tension of complex coacervates using field-theoretic simulations
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0024436
Volume: 6 Issue: 9 First Page #: 24436
Date Submitted: Date Published:
Publication Location:
**Article Title:** Electrophysiological Evidence for Spatiotemporal Flexibility in the Ventrolateral Attention Network
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Memory & Cognition
Publication Identifier Type: DOI Publication Identifier: 10.3758/s13421-012-0204-6
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Individual differences in shifting decision criterion: A recognition memory study
**Authors:**
**Keywords:** Memory, Decision making, Individual differences, Recognition
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** NeuroImage
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2011.05.064
Volume: 59 Issue: 1 First Page #: 14
Date Submitted: Date Published:
Publication Location:
**Article Title:** Decoding intention: A neuroergonomic perspective
**Authors:**
**Keywords:** Action understanding, Action semantics, N400, Mu-rhythm, Body motion
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Psychological Science
Publication Identifier Type: DOI Publication Identifier: 10.1177/0956797611429802
Volume: 23 Issue: 6 First Page #: 598
Date Submitted: Date Published:
Publication Location:
**Article Title:** Telling the Right Hand From the Left Hand: Multisensory Integration, Not Motor Imagery, Solves the Problem
**Authors:**
**Keywords:** Motor processes, Perception, Human body, Decision making
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nanoscale
Publication Identifier Type: DOI Publication Identifier: 10.1039/c2nr30474k
Volume: 4 Issue: 11 First Page #: 3373
Date Submitted: Date Published:
Publication Location:
**Article Title:** Effects of morphology on the micro-compression response of carbon nanotube forests
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Applied Physics Letters
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.3697686
Volume: 100 Issue: 12 First Page #: 121910
Date Submitted: Date Published:
Publication Location:
**Article Title:** A microstructurally motivated description of the deformation of vertically aligned carbon nanotube structures
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Nano
Publication Identifier Type: DOI Publication Identifier: 10.1021/nn300376j
Volume: 6 Issue: 3 First Page #: 2189
Date Submitted: Date Published:
Publication Location:
**Article Title:** Higher Recovery and Better Energy Dissipation at Faster Strain Rates in Carbon Nanotube Bundles: An
**Authors:**
**Keywords:** Vertically aligned carbon nanotubes, Compression, Mechanical properties, Energy storage, Recovery
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja2064389
Volume: 133 Issue: 45 First Page #: 18280
Date Submitted: Date Published:
Publication Location:
**Article Title:** Iterative in Situ Click Chemistry Assembles a Branched Capture Agent and Allosteric Inhibitor for Akt1
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Energy Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/aenm.201100667
Volume: 2 Issue: 3 First Page #: 304
Date Submitted: Date Published:
Publication Location:
**Article Title:** Nanomorphology of PCDTBT:PC70BM Bulk Heterojunction Solar Cells
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE TRANSACTIONS ON AEROSPACE AND ELECTRONIC SYSTEMS
Publication Identifier Type: Publication Identifier:
Volume: 47 Issue: 4 First Page #: 2637
Date Submitted: Date Published:
Publication Location:
**Article Title:** Cooperative search by UAV teams: A model predictive approach using dynamic graphs
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Signal Processing
Publication Identifier Type: Publication Identifier:
Volume: 59 Issue: 6 First Page #: 2834
Date Submitted: Date Published:
Publication Location:
**Article Title:** Optimal Estimation on the Graph Cycle Space
**Authors:**
**Keywords:** Distributed algorithms, Graph theory, Iterative algorithms, Network theory, State estimation
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Tribology Letters
Publication Identifier Type: DOI Publication Identifier: 10.1007/s11249-011-9746-1
Volume: 42 Issue: 1 First Page #: 117
Date Submitted: Date Published:
Publication Location:
**Article Title:** High-Speed Friction Measurements Using a Modified Surface Forces Apparatus
**Authors:**
**Keywords:** Friction test methods, Boundary lubrication test methods
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biochemical Society Transactions
Publication Identifier Type: DOI Publication Identifier: 10.1042/BST20110633
Volume: 40 Issue: 1 First Page #: 133
Date Submitted: Date Published:
Publication Location:
**Article Title:** Multi-pathway network analysis of mammalian epithelial cell responses in inflammatory environments
**Authors:**
**Keywords:** Cell signalling, Hepatocellular carcinoma, Inflammation, Liver, Logic, Mathematical model.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biotechnology Journal
Publication Identifier Type: DOI Publication Identifier: 10.1002/biot.201100222
Volume: 7 Issue: 3 First Page #: 374
Date Submitted: Date Published:
Publication Location:
**Article Title:** Querying quantitative logic models (Q2LM) to study intracellular signaling networks and cell-cytokine interactions
**Authors:**
**Keywords:** Constrained fuzzy logic model, G-CSF, Multi-scale model, Signaling network
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACM Transactions on Sensor Networks
Publication Identifier Type: DOI Publication Identifier: 10.1145/1993042.1993047
Volume: 8 Issue: 1 First Page #: 5
Date Submitted: Date Published:
Publication Location:
**Article Title:** Multiple-Target Tracking With Binary Proximity Sensors
**Authors:**
**Keywords:** Tracking, Sensor fusion, Counting problems, Probabilistic algorithims
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE/ACM Transactions on Networking
Publication Identifier Type: DOI Publication Identifier: 10.1109/TNET.2011.2122343
Volume: 19 Issue: 5 First Page #: 1513
Date Submitted: Date Published:
Publication Location:
**Article Title:** Interference Analysis for Highly Directional 60-GHz Mesh Networks: The Case for Rethinking Medium Access Control
**Authors:**
**Keywords:** 60-Ghz networks, Interference analysis, Medium access control (MAC), millimeter (mm) wave networks, Wireless mesh networks
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/ac300034r
Volume: 84 Issue: 3 First Page #: 1240
Date Submitted: Date Published:
Publication Location:
**Article Title:** Quantifying Particle Coatings Using High-Precision Mass Measurements
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Physics D: Applied Physics
Publication Identifier Type: DOI Publication Identifier: 10.1088/0022-3727/45/18/185301
Volume: 45 Issue: 18 First Page #: 185301
Date Submitted: Date Published:
Publication Location:
**Article Title:** A theoretical and experimental study of ac electrothermal flows
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** NeuroImage
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2011.05.060
Volume: 59 Issue: 1 First Page #: 83
Date Submitted: Date Published:
Publication Location:
**Article Title:** Individual differences in cognitive style and strategy predict similarities in the patterns of brain activity between individuals
**Authors:**
**Keywords:** fMRI, Inter-individual variability, Cognitive style, Encoding strategies, Memory retrieval
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Energy Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/aenm.201100481
Volume: 2 Issue: 3 First Page #: 309
Date Submitted: Date Published:
Publication Location:
**Article Title:** Hydrothermal Realization of High-Power Nanocomposite Cathodes for Lithium Ion Batteries
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Materials Research
Publication Identifier Type: DOI Publication Identifier: 10.1557/jmr.2011.397
Volume: 27 Issue: 2 First Page #: 410
Date Submitted: Date Published:
Publication Location:
**Article Title:** Transforming large-scale industrially produced carbon nanotubes to high-performance electrode materials for lithium-ion batteries
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201101847
Volume: 23 Issue: 36 First Page #: 4152
Date Submitted: Date Published:
Publication Location:
**Article Title:** Reversible Tuning of SERS Hot Spots with Aptamers
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nano Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/nl300351j
Volume: 12 Issue: 4 First Page #: 2088
Date Submitted: Date Published:
Publication Location:
**Article Title:** Plasmonic Properties of Gold Nanoparticles Separated from a Gold Mirror by an Ultrathin Oxide
**Authors:**
**Keywords:** Surface plasmons, Nanoparticles, Gold mirror, Dielectric layer, Near-field coupling, SERS
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1109490108
Volume: 108 Issue: 40 First Page #: 16559
Date Submitted: Date Published:
Publication Location:
**Article Title:** Quantitative ratiometric discrimination between noncancerous and cancerous prostate cells based on neuropilin-1 overexpression
**Authors:**
**Keywords:** Surface-enhanced Raman spectroscopy biomarker, Cancel cell identification, Multiplexing, Silver nanoparticles
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1100060108
Volume: 108 Issue: 40 First Page #: 784
Date Submitted: Date Published:
Publication Location:
**Article Title:** Timing molecular motion and production with a synthetic transcriptional clock
**Authors:**
**Keywords:** Cell-free circuits, Modularity, Genelets, DNA nanotechnology
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review E
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevE.85.031901
Volume: 85 Issue: 3 First Page #: 31901
Date Submitted: Date Published:
Publication Location:
**Article Title:** Bioinspired, mechanical, deterministic fractal model for hierarchical suture joints
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Microfluidics and Nanofluidics
Publication Identifier Type: DOI Publication Identifier: 10.1007/s10404-011-0884-4
Volume: 12 Issue: 0 First Page #: 411
Date Submitted: Date Published:
Publication Location:
**Article Title:** Electrokinetic characterization of individual nanoparticles in nanofluidic channels
**Authors:**
**Keywords:** Total internal reflection fluorescence, Nanofluidics, Nanoparticles
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** BMC Bioinformatics
Publication Identifier Type: DOI Publication Identifier: 10.1186/1471-2105-13-68
Volume: 13 Issue: 1 First Page #: 68
Date Submitted: Date Published:
Publication Location:
**Article Title:** Accelerated maximum likelihood parameter estimation for stochastic biochemical systems
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** BMC Research Notes
Publication Identifier Type: DOI Publication Identifier: 10.1186/1756-0500-5-163
Volume: 5 Issue: 1 First Page #: 163
Date Submitted: Date Published:
Publication Location:
**Article Title:** WAVOS: a MATLAB toolkit for wavelet analysis and visualization of oscillatory systems
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review E
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevE.85.042901
Volume: 85 Issue: 4 First Page #: 42901
Date Submitted: Date Published:
Publication Location:
**Article Title:** Reaction-diffusion master equation in the microscopic limit
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.3668100
Volume: 135 Issue: 23 First Page #: 234108
Date Submitted: Date Published:
Publication Location:
**Article Title:** State-dependent doubly weighted stochastic simulation algorithm for automatic characterization of stochastic biochemical rare events
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Bioinformatics
Publication Identifier Type: DOI Publication Identifier: 10.1093/bioinformatics/btr401
Volume: 27 Issue: 17 First Page #: 2457
Date Submitted: Date Published:
Publication Location:
**Article Title:** StochKit2: software for discrete stochastic simulation of biochemical systems with events
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja2115663
Volume: 134 Issue: 7 First Page #: 3346
Date Submitted: Date Published:
Publication Location:
**Article Title:** Quantification of Transcription Factor Binding in Cell Extracts Using an Electrochemical, Structure-Switching Biosensor
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201109115
Volume: 51 Issue: 20 First Page #: 4896
Date Submitted: Date Published:
Publication Location:
**Article Title:** Rapid, Sensitive, and Quantitative Detection of Pathogenic DNA at the Point of Care through Microfluidic Electrochemical Quantitative Loop-Mediated Isothermal Amplification
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie
Publication Identifier Type: DOI Publication Identifier: 10.1002/ange.201103482
Volume: 123 Issue: 47 First Page #: 11176
Date Submitted: Date Published:
Publication Location:
**Article Title:** Polarity-Switching Electrochemical Sensor for Specific Detection of Single-Nucleotide Mismatches
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ChemBioChem
Publication Identifier Type: DOI Publication Identifier: 10.1002/cbic.201100592
Volume: 12 Issue: 18 First Page #: 2745
Date Submitted: Date Published:
Publication Location:
**Article Title:** Two-Step, PCR-Free Telomerase Detection by Using Exonuclease III-Aided Target Recycling
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0026925
Volume: 6 Issue: 11 First Page #: 26925
Date Submitted: Date Published:
Publication Location:
**Article Title:** Screening of Peptide Libraries against Protective Antigen of Bacillus anthracis in a Disposable Microfluidic Cartridge
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/ac201269f
Volume: 83 Issue: 17 First Page #: 6883
Date Submitted: Date Published:
Publication Location:
**Article Title:** Improving Aptamer Selection Efficiency through Volume Dilution, Magnetic Concentration, and Continuous Washing in Microfluidic Channels
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201101149
Volume: 50 Issue: 36 First Page #: 8295
Date Submitted: Date Published:
Publication Location:
**Article Title:** Rapid mRNA-Display Selection of an IL-6 Inhibitor Using Continuous-Flow Magnetic Separation
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physics of Fluids
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.3605693
Volume: 23 Issue: 7 First Page #: 72003
Date Submitted: Date Published:
Publication Location:
**Article Title:** Concentration polarization and second-kind electrokinetic instability at an ion-selective surface admitting normal flow
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Lab on a Chip
Publication Identifier Type: DOI Publication Identifier: 10.1039/c2lc21020g
Volume: 12 Issue: 5 First Page #: 954
Date Submitted: Date Published:
Publication Location:
**Article Title:** Increasing the detection speed of an all-electronic real-time biosensor
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Materials Science
Publication Identifier Type: DOI Publication Identifier: 10.1007/s10853-012-6598-5
Volume: 47 Issue: 18 First Page #: 6621
Date Submitted: Date Published:
Publication Location:
**Article Title:** Effects of material heterogeneities on the compressive response of thiol-ene pyramidal lattices
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ChemBioChem
Publication Identifier Type: DOI Publication Identifier: 10.1002/cbic.201100277
Volume: 12 Issue: 14 First Page #: 2137
Date Submitted: Date Published:
Publication Location:
**Article Title:** A BODIPY-Cyclooctyne for Protein Imaging in Live Cells
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Accounts of Chemical Research
Publication Identifier Type: DOI Publication Identifier: 10.1021/ar200144y
Volume: 44 Issue: 9 First Page #: 677
Date Submitted: Date Published:
Publication Location:
**Article Title:** Noncanonical Amino Acids in the Interrogation of Cellular Protein Synthesis
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja3004667
Volume: 134 Issue: 20 First Page #: 8551
Date Submitted: Date Published:
Publication Location:
**Article Title:** Two-Strain, Cell-Selective Protein Labeling in Mixed Bacterial Cultures
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Langmuir
Publication Identifier Type: DOI Publication Identifier: 10.1021/la3004855
Volume: 28 Issue: 23 First Page #: 8746
Date Submitted: Date Published:
Publication Location:
**Article Title:** Vertical Anisotropic Microfibers for a Gecko-Inspired Adhesive
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Micromechanics and Microengineering
Publication Identifier Type: DOI Publication Identifier: 10.1088/0960-1317/22/3/035004
Volume: 22 Issue: 3 First Page #: 35004
Date Submitted: Date Published:
Publication Location:
**Article Title:** Parametric amplification in a resonant sensing array
**Authors:**
**Keywords:** None.
**Abstract:** See attached.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Protein Engineering Design and Selection
Publication Identifier Type: DOI Publication Identifier: 10.1093/protein/gzs058
Volume: 25 Issue: 12 First Page #: 827
Date Submitted: Date Published:
Publication Location:
**Article Title:** Highly thermostable fungal cellobiohydrolase I (Cel7A) engineered using predictive methods
**Authors:**
**Keywords:** CBH I; Cel7A; cellulase; protein engineering
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1002713
Volume: 8 Issue: 10 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Random Field Model Reveals Structure of the Protein Recombinational Landscape
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1215251110
Volume: 110 Issue: 3 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** PNAS Plus: Navigating the protein fitness landscape with Gaussian processes
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Psychonomic Bulletin & Review
Publication Identifier Type: DOI Publication Identifier: 10.3758/s13423-012-0312-0
Volume: 19 Issue: 6 First Page #: 1202
Date Submitted: Date Published:
Publication Location:
**Article Title:** Procedural learning of unstructured categories
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Neuroscience & Biobehavioral Reviews
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neubiorev.2012.09.003
Volume: 36 Issue: 10 First Page #: 2355
Date Submitted: Date Published:
Publication Location:
**Article Title:** Implicit and explicit categorization: A tale of four species
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Energy & Environmental Science
Publication Identifier Type: DOI Publication Identifier: 10.1039/c2ee22839d
Volume: 5 Issue: 11 First Page #: 9449
Date Submitted: Date Published:
Publication Location:
**Article Title:** Conjugated oligoelectrolytes increase current response and organic contaminant removal in wastewater microbial fuel cells
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201204271
Volume: 25 Issue: 11 First Page #: 1593
Date Submitted: Date Published:
Publication Location:
**Article Title:** Conjugated Oligoelectrolytes Increase Power Generation in E. Coli Microbial Fuel Cells
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Chemistry Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1039/c3cp50437a
Volume: 15 Issue: 16 First Page #: 5867
Date Submitted: Date Published:
Publication Location:
**Article Title:** Improving charge collection in Escherichia coli–carbon electrode devices with conjugated oligoelectrolytes
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Energy & Environmental Science
Publication Identifier Type: DOI Publication Identifier: 10.1039/c3ee00071k
Volume: 6 Issue: 6 First Page #: 1761
Date Submitted: Date Published:
Publication Location:
**Article Title:** A lipid membrane intercalating conjugated oligoelectrolyte enables electrode driven succinate production in Shewanella
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Mechanics and Physics of Solids
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jmps.2012.09.014
Volume: 61 Issue: 5 First Page #: 1265
Date Submitted: Date Published:
Publication Location:
**Article Title:** Peeling of a tape with large deformations and frictional sliding
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Bioconjugate Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/bc300130z
Volume: 23 Issue: 7 First Page #: 1478
Date Submitted: Date Published:
Publication Location:
**Article Title:** M13 Bacteriophage Display Framework That Allows Sortase-Mediated Modification of Surface-Accessible Phage Proteins
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Energy & Environmental Science
Publication Identifier Type: DOI Publication Identifier: 10.1039/c2ee21156d
Volume: 5 Issue: 8 First Page #: 8328
Date Submitted: Date Published:
Publication Location:
**Article Title:** Virus-templated Au and Au–Pt core–shell nanowires and their electrocatalytic activities for fuel cell applications
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** SIAM Journal on Control and Optimization
Publication Identifier Type: DOI Publication Identifier: 10.1137/11082751X
Volume: 50 Issue: 5 First Page #: 2763
Date Submitted: Date Published:
Publication Location:
**Article Title:** Opinion Dynamics in Heterogeneous Networks: Convergence Conjectures and Theorems
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review E
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevE.86.041306
Volume: 86 Issue: 4 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Influence of network topology on sound propagation in granular materials
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chaos: An Interdisciplinary Journal of Nonlinear Science
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4790830
Volume: 23 Issue: 1 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Robust detection of dynamic community structure in networks
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0050268
Volume: 7 Issue: 11 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** BICAR: A New Algorithm for Multiresolution Spatiotemporal Data Fusion
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1201890109
Volume: 109 Issue: 0 First Page #: 10612
Date Submitted: Date Published:
Publication Location:
**Article Title:** Functionalization of a protosynaptic gene expression network
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0056118
Volume: 8 Issue: 4 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Dynamics of Polymer Molecules with Sacrificial Bond and Hidden Length Systems: Towards a Physically-Based Mesoscopic Constitutive Law
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
as of 01-May-2020

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1216402109
Volume: 109 Issue: 46 First Page #: 18661
Date Submitted: Date Published:
Publication Location:
**Article Title:** Inaugural Article: Dynamic network structure of interhemispheric coordination
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1219562110
Volume: 110 Issue: 15 First Page #: 6169
Date Submitted: Date Published:
Publication Location:
**Article Title:** Structural foundations of resting-state and task-based functional connectivity in the human brain
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Complex Networks
Publication Identifier Type: DOI Publication Identifier: 10.1093/comnet/cnt001
Volume: 1 Issue: 1 First Page #: 83
Date Submitted: Date Published:
Publication Location:
**Article Title:** Dynamic network centrality summarizes learning in the human brain
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Biology
Publication Identifier Type: DOI Publication Identifier: 10.1088/1478-3975/10/2/025002
Volume: 10 Issue: 2 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Diversity of T-cell responses
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201202293
Volume: 24 Issue: 45 First Page #: 6071
Date Submitted: Date Published:
Publication Location:
**Article Title:** Use of X-Ray Diffraction, Molecular Simulations, and Spectroscopy to Determine the Molecular Packing in a Polymer-Fullerene Bimolecular Crystal
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** STEM CELLS Translational Medicine
Publication Identifier Type: DOI Publication Identifier: 10.5966/sctm.2012-0163
Volume: 2 Issue: 5 First Page #: 384
Date Submitted: Date Published:
Publication Location:
**Article Title:** Rapid and Efficient Directed Differentiation of Human Pluripotent Stem Cells Into Retinal Pigmented Epithelium
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Mechanics Research Communications
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.mechrescom.2012.07.006
Volume: 45 Issue: 0 First Page #: 58
Date Submitted: Date Published:
Publication Location:
**Article Title:** Continuum limits of bistable spring models of carbon nanotube arrays accounting for material damage
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Multiscale Modeling & Simulation
Publication Identifier Type: DOI Publication Identifier: 10.1137/12087311X
Volume: 11 Issue: 2 First Page #: 545
Date Submitted: Date Published:
Publication Location:
**Article Title:** Multiscale Mass-Spring Models of Carbon Nanotube Arrays Accounting for Mullins-like Behavior and Permanent Deformation
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Composite Structures
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.compstruct.2012.09.013
Volume: 96 Issue: 0 First Page #: 745
Date Submitted: Date Published:
Publication Location:
**Article Title:** Modeling microscale instabilities in compressed carbon nanotube bundles using multistable spring models
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nanotechnology
Publication Identifier Type: DOI Publication Identifier: 10.1088/0957-4484/24/25/255707
Volume: 24 Issue: 25 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Rate-independent dissipation and loading direction effects in compressed carbon nanotube arrays
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Carbon
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.carbon.2012.09.020
Volume: 52 Issue: 0 First Page #: 193
Date Submitted: Date Published:
Publication Location:
**Article Title:** Control of microstructural heterogeneities in carbon nanotube foams
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Science
Publication Identifier Type: DOI Publication Identifier: 10.1126/science.1223710
Volume: 337 Issue: 6098 First Page #: 1094
Date Submitted: Date Published:
Publication Location:
**Article Title:** Identification of Small Molecule Activators of Cryptochrome
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Automatic Control
Publication Identifier Type: DOI Publication Identifier: 10.1109/TAC.2012.2215772
Volume: 58 Issue: 4 First Page #: 989
Date Submitted: Date Published:
Publication Location:
**Article Title:** Exponential Synchronization Rate of Kuramoto Oscillators in the Presence of a Pacemaker
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Signal Processing
Publication Identifier Type: DOI Publication Identifier: 10.1109/TSP.2012.2208109
Volume: 60 Issue: 10 First Page #: 5583
Date Submitted: Date Published:
Publication Location:
**Article Title:** Optimal Phase Response Functions for Fast Pulse-Coupled Synchronization in Wireless Sensor Networks
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Signal Processing
Publication Identifier Type: DOI Publication Identifier: 10.1109/TSP.2012.2205685
Volume: 60 Issue: 10 First Page #: 5293
Date Submitted: Date Published:
Publication Location:
**Article Title:** Energy-Efficient Pulse-Coupled Synchronization Strategy Design for Wireless Sensor Networks Through Reduced Idle Listening
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Soft Matter
Publication Identifier Type: DOI Publication Identifier: 10.1039/c2sm25931a
Volume: 8 Issue: 41 First Page #: 10676
Date Submitted: Date Published:
Publication Location:
**Article Title:** Collective dynamics of small clusters of particles flowing in a quasi-two-dimensional microchannel
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1523/JNEUROSCI.5876-11.2012
Volume: 32 Issue: 28 First Page #: 9499
Date Submitted: Date Published:
Publication Location:
**Article Title:** Feature-Independent Neural Coding of Target Detection during Search of Natural Scenes
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1523/JNEUROSCI.5840-12.2013
Volume: 33 Issue: 18 First Page #: 7846
Date Submitted: Date Published:
Publication Location:
**Article Title:** Neural Representations of Contextual Guidance in Visual Search of Real-World Scenes
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Annual Review of Psychology
Publication Identifier Type: DOI Publication Identifier: 10.1146/annurev-psych-113011-143817
Volume: 64 Issue: 1 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Shifting Gears: Seeking New Approaches for Mind/Brain Mechanisms
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Vision Research
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.visres.2012.10.006
Volume: 85 Issue: 0 First Page #: 80
Date Submitted: Date Published:
Publication Location:
**Article Title:** Both memory and attention systems contribute to visual search for targets cued by implicitly learned context
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1002619
Volume: 8 Issue: 8 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Combining the Finite Element Method with Structural Connectome-based Analysis for Modeling Neurotrauma: Connectome Neurotrauma Mechanics
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** NeuroImage
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2012.12.012
Volume: 69 Issue: 0 First Page #: 120
Date Submitted: Date Published:
Publication Location:
**Article Title:** Escaping the here and now: Evidence for a role of the default mode network in perceptually decoupled thought
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Applied Mechanics
Publication Identifier Type: DOI Publication Identifier: 10.1115/1.4024179
Volume: 40 Issue: 4 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Uniaxial Tension of a Class of Compressible Solids With Plastic Non-Normality
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Acta Mechanica Sinica
Publication Identifier Type: DOI Publication Identifier: 10.1007/s10409-012-0117-4
Volume: 28 Issue: 4 First Page #: 1115
Date Submitted: Date Published:
Publication Location:
**Article Title:** Deformation of plastically compressible hardening-softening-hardening solids
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Applied Physics Letters
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4802080
Volume: 102 Issue: 22 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Buckling-driven delamination of carbon nanotube forests
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201206147
Volume: 52 Issue: 7 First Page #: 1953
Date Submitted: Date Published:
Publication Location:
**Article Title:** Transmembrane Protein Activation Refined by Site-Specific Hydration Dynamics
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biophysical Journal
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.bpj.2012.11.3831
Volume: 104 Issue: 2 First Page #: 472
Date Submitted: Date Published:
Publication Location:
**Article Title:** Structural Insight into Proteorhodopsin Oligomers
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biomacromolecules
Publication Identifier Type: DOI Publication Identifier: 10.1021/bm301384y
Volume: 13 Issue: 0 First Page #: 4089
Date Submitted: Date Published:
Publication Location:
**Article Title:** Enhanced Bioactivity of Internally Functionalized Cationic Dendrimers with PEG Cores
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja4019447
Volume: 135 Issue: 17 First Page #: 6649
Date Submitted: Date Published:
Publication Location:
**Article Title:** Striped, Ellipsoidal Particles by Controlled Assembly of Diblock Copolymers
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja309044z
Volume: 134 Issue: 49 First Page #: 20139
Date Submitted: Date Published:
Publication Location:
**Article Title:** Improved Performance of Protected Catecholic Polysiloxanes for Bioinspired Wet Adhesion to Surface Oxides
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Integrative Biology
Publication Identifier Type: DOI Publication Identifier: 10.1039/c2ib20110k
Volume: 5 Issue: 1 First Page #: 87
Date Submitted: Date Published:
Publication Location:
**Article Title:** In situ click chemistry: from small molecule discovery to synthetic antibodies
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201203786
Volume: 25 Issue: 12 First Page #: 1706
Date Submitted: Date Published:
Publication Location:
**Article Title:** Effects of Impurities on Operational Mechanism of Organic Bulk Heterojunction Solar Cells
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Algorithms
Publication Identifier Type: DOI Publication Identifier: 10.3390/a6010084
Volume: 6 Issue: 1 First Page #: 84
Date Submitted: Date Published:
Publication Location:
**Article Title:** Dubins Traveling Salesman Problem with Neighborhoods: A Graph-Based Approach
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACM Transactions on Sensor Networks
Publication Identifier Type: DOI Publication Identifier: 10.1145/2480730.2480733
Volume: 9 Issue: 3 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Localization with sparse acoustic sensor network using UAVs as information-seeking data mules
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Automatic Control
Publication Identifier Type: DOI Publication Identifier: 10.1109/TAC.2012.2192356
Volume: 57 Issue: 10 First Page #: 2588
Date Submitted: Date Published:
Publication Location:
**Article Title:** Jump Control of Probability Densities With Applications to Autonomous Vehicle Motion
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Automatica
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.automatica.2012.06.009
Volume: 48 Issue: 8 First Page #: 1612
Date Submitted: Date Published:
Publication Location:
**Article Title:** Redundant data transmission in control/estimation over lossy networks
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja400448f
Volume: 135 Issue: 8 First Page #: 2979
Date Submitted: Date Published:
Publication Location:
**Article Title:** A Genetically Encoded AND Gate for Cell-Targeted Metabolic Labeling of Proteins
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Langmuir
Publication Identifier Type: DOI Publication Identifier: 10.1021/la301783q
Volume: 28 Issue: 31 First Page #: 11527
Date Submitted: Date Published:
Publication Location:
**Article Title:** Friction and Adhesion of Gecko-Inspired PDMS Flaps on Rough Surfaces
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Friction
Publication Identifier Type: DOI Publication Identifier: 10.1007/s40544-013-0011-5
Volume: 1 Issue: 2 First Page #: 114
Date Submitted: Date Published:
Publication Location:
**Article Title:** Recent advances in gecko adhesion and friction mechanisms and development of gecko-inspired dry adhesive surfaces
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Molecular & Cellular Proteomics
Publication Identifier Type: DOI Publication Identifier: 10.1074/mcp.M112.018655
Volume: 12 Issue: 1 First Page #: 245
Date Submitted: Date Published:
Publication Location:
**Article Title:** Normalization and Statistical Analysis of Multiplexed Bead-based Immunoassay Data Using Mixed-effects Modeling
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biochemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/bi300846p
Volume: 51 Issue: 38 First Page #: 7433
Date Submitted: Date Published:
Publication Location:
**Article Title:** Measurement and Modeling of Signaling at the Single-Cell Level
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0050085
Volume: 7 Issue: 11 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Non Linear Programming (NLP) Formulation for Quantitative Modeling of Protein Signal Transduction Pathways
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** BMC Systems Biology
Publication Identifier Type: DOI Publication Identifier: 10.1186/1752-0509-6-133
Volume: 6 Issue: 1 First Page #: 133
Date Submitted: Date Published:
Publication Location:
**Article Title:** CellNOptR: a flexible toolkit to train protein signaling networks to data using multiple logic formalisms
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Wireless Communications
Publication Identifier Type: DOI Publication Identifier: 10.1109/TWC.2013.012513.121029
Volume: 12 Issue: 3 First Page #: 1418
Date Submitted: Date Published:
Publication Location:
**Article Title:** A Scalable Architecture for Distributed Transmit Beamforming with Commodity Radios: Design and Proof of Concept
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Nanophotonics
Publication Identifier Type: DOI Publication Identifier: 10.1117/1.JNP.7.073092
Volume: 7 Issue: 1 First Page #: 73092
Date Submitted: Date Published:
Publication Location:
**Article Title:** Combined surface-enhanced Raman spectroscopy biotags and microfluidic platform for quantitative ratiometric discrimination between noncancerous and cancerous cells in flow
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/ac302497y
Volume: 84 Issue: 22 First Page #: 9700
Date Submitted: Date Published:
Publication Location:
**Article Title:** Free-Surface Microfluidics/Surface-Enhanced Raman Spectroscopy for Real-Time Trace Vapor Detection of Explosives
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0058525
Volume: 8 Issue: 3 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** How the Spatial Position of Individuals Affects Their Influence on Swarms: A Numerical Comparison of Two Popular Swarm Dynamics Models
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Royal Society Interface
Publication Identifier Type: DOI Publication Identifier: 10.1098/rsif.2013.0386
Volume: 10 Issue: 85 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Optical parameters of the tunable Bragg reflectors in squid
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nano Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/nl3005447
Volume: 12 Issue: 6 First Page #: 2912
Date Submitted: Date Published:
Publication Location:
**Article Title:** Robust SERS Enhancement Factor Statistics Using Rotational Correlation Spectroscopy
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja3046662
Volume: 134 Issue: 28 First Page #: 11384
Date Submitted: Date Published:
Publication Location:
**Article Title:** Remote Sensing by Plasmonic Transport
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1211902109
Volume: 109 Issue: 48 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** PNAS Plus: Synergistic dual positive feedback loops established by molecular sequestration generate robust bimodal response
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Mechanical Behavior of Biomedical Materials
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jmbbm.2012.11.003
Volume: 19 Issue: 0 First Page #: 75
Date Submitted: Date Published:
Publication Location:
**Article Title:** Mechanics of composite elasmoid fish scale assemblies and their bioinspired analogues
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Virtual and Physical Prototyping
Publication Identifier Type: DOI Publication Identifier: 10.1080/17452759.2012.731369
Volume: 7 Issue: 4 First Page #: 261
Date Submitted: Date Published:
Publication Location:
**Article Title:** Digital anisotropy: A variable elasticity rapid prototyping platform
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Mechanics and Physics of Solids
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jmps.2012.10.004
Volume: 61 Issue: 4 First Page #: 1144
Date Submitted: Date Published:
Publication Location:
**Article Title:** A generalized mechanical model for suture interfaces of arbitrary geometry
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Mechanical Behavior of Biomedical Materials
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jmbbm.2012.07.006
Volume: 15 Issue: 0 First Page #: 70
Date Submitted: Date Published:
Publication Location:
**Article Title:** Bio-inspired interfacial strengthening strategy through geometrically interlocking designs
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/ac400081p
Volume: 85 Issue: 5 First Page #: 2991
Date Submitted: Date Published:
Publication Location:
**Article Title:** Separation of Ions in Nanofluidic Channels with Combined Pressure-Driven and Electro-Osmotic Flow
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
as of 01-May-2020

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** BMC Systems Biology
Publication Identifier Type: DOI Publication Identifier: 10.1186/1752-0509-6-76
Volume: 6 Issue: 1 First Page #: 76
Date Submitted: Date Published:
Publication Location:
**Article Title:** URDME: a modular framework for stochastic simulation of reaction-transport processes in complex geometries
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Computational Physics
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jcp.2012.10.036
Volume: 235 Issue: 0 First Page #: 446
Date Submitted: Date Published:
Publication Location:
**Article Title:** Time dependent solution for acceleration of tau-leaping
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4801941
Volume: 138 Issue: 17 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Perspective: Stochastic algorithms for chemical kinetics
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IET Systems Biology
Publication Identifier Type: DOI Publication Identifier: 10.1049/iet-syb.2011.0038
Volume: 6 Issue: 4 First Page #: 102
Date Submitted: Date Published:
Publication Location:
**Article Title:** Linear noise approximation is valid over limited times for any chemical system that is sufficiently large
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4733563
Volume: 137 Issue: 3 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Automatic identification of model reductions for discrete stochastic simulation
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biophysical Journal
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.bpj.2013.03.053
Volume: 104 Issue: 11 First Page #: 2485
Date Submitted: Date Published:
Publication Location:
**Article Title:** Sequence and Temperature Dependence of the End-to-End Collision Dynamics of Single-Stranded DNA
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Applied and Environmental Microbiology
Publication Identifier Type: DOI Publication Identifier: 10.1128/AEM.03882-12
Volume: 79 Issue: 7 First Page #: 2302
Date Submitted: Date Published:
Publication Location:
**Article Title:** Microfluidic Chip-Based Detection and Intraspecies Strain Discrimination of Salmonella Serovars Derived from Whole Blood of Septic Mice
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Micromechanics and Microengineering
Publication Identifier Type: DOI Publication Identifier: 10.1088/0960-1317/22/7/075017
Volume: 22 Issue: 7 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** High-throughput, temperature-controlled microchannel acoustophoresis device made with rapid prototyping
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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as of 01-May-2020

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nucleic Acids Research
Publication Identifier Type: DOI Publication Identifier: 10.1093/nar/gks899
Volume: 40 Issue: 22 First Page #: 11777
Date Submitted: Date Published:
Publication Location:
**Article Title:** Selection is more intelligent than design: improving the affinity of a bivalent ligand through directed evolution
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chemical Communications
Publication Identifier Type: DOI Publication Identifier: 10.1039/c2cc36878a
Volume: 49 Issue: 4 First Page #: 397
Date Submitted: Date Published:
Publication Location:
**Article Title:** Controlling the function of DNA nanostructures with specific trigger sequences
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0043940
Volume: 7 Issue: 8 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Influence of Target Concentration and Background Binding on In Vitro Selection of Affinity Reagents
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/ac3026674
Volume: 84 Issue: 24 First Page #: 10756
Date Submitted: Date Published:
Publication Location:
**Article Title:** Acoustophoretic Sorting of Viable Mammalian Cells in a Microfluidic Device
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Acta Materialia
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.actamat.2012.07.053
Volume: 60 Issue: 19 First Page #: 6476
Date Submitted: Date Published:
Publication Location:
**Article Title:** Deformation stabilization of lattice structures via foam addition
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Chemical Biology
Publication Identifier Type: DOI Publication Identifier: 10.1021/cb300238w
Volume: 7 Issue: 8 First Page #: 1326
Date Submitted: Date Published:
Publication Location:
**Article Title:** State-Selective Metabolic Labeling of Cellular Proteins
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1216375110
Volume: 110 Issue: 13 First Page #: 4992
Date Submitted: Date Published:
Publication Location:
**Article Title:** Mutant methionyl-tRNA synthetase from bacteria enables site-selective N-terminal labeling of proteins expressed in mammalian cells
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Smart Materials and Structures
Publication Identifier Type: DOI Publication Identifier: 10.1088/0964-1726/22/2/025013
Volume: 22 Issue: 2 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** A microfabricated gecko-inspired controllable and reusable dry adhesive
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Applied Mechanics
Publication Identifier Type: DOI Publication Identifier: 10.1115/1.4007865
Volume: 80 Issue: 4 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Pyramidal Lattice Structures for High Strength and Energy Absorption
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Materials Letters
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.matlet.2013.04.048
Volume: 105 Issue: 0 First Page #: 155
Date Submitted: Date Published:
Publication Location:
**Article Title:** Ameliorating property gradients in photocured polymer lattices via thermal curing
**Authors:**
**Keywords:** See attached.
**Abstract:** See attached.
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Lab on a Chip
Publication Identifier Type: DOI Publication Identifier: 10.1039/c3lc50610j
Volume: 13 Issue: 24 First Page #: 4765
Date Submitted: Date Published:
Publication Location:
**Article Title:** Synthesis of biomimetic oxygen-carrying compartmentalized microparticles using flow lithography
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1307088110
Volume: 110 Issue: 46 First Page #: 4355
Date Submitted: Date Published:
Publication Location:
**Article Title:** A neuropeptide speeds circadian entrainment by reducing intercellular synchrony
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Nano
Publication Identifier Type: DOI Publication Identifier: 10.1021/nn402563f
Volume: 7 Issue: 8 First Page #: 7157
Date Submitted: Date Published:
Publication Location:
**Article Title:** Rapid Detection of Drugs of Abuse in Saliva Using Surface Enhanced Raman Spectroscopy and Microfluidics
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Macromolecules
Publication Identifier Type: DOI Publication Identifier: 10.1021/ma401804j
Volume: 46 Issue: 20 First Page #: 8383
Date Submitted: Date Published:
Publication Location:
**Article Title:** Comparison of Pseudospectral Algorithms for Field-Theoretic Simulations of Polymers
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Molecular & Cellular Proteomics
Publication Identifier Type: DOI Publication Identifier: 10.1074/mcp.M113.031914
Volume: 13 Issue: 5 First Page #: 1352
Date Submitted: Date Published:
Publication Location:
**Article Title:** Quantitative, Time-Resolved Proteomic Analysis by Combining Bioorthogonal Noncanonical Amino Acid Tagging and Pulsed Stable Isotope Labeling by Amino Acids in Cell Culture
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Langmuir
Publication Identifier Type: DOI Publication Identifier: 10.1021/la400949x
Volume: 29 Issue: 44 First Page #: 13614
Date Submitted: Date Published:
Publication Location:
**Article Title:** Aggregation Kinetics of SERS-Active Nanoparticles in Thermally Stirred Sessile Droplets
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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as of 01-May-2020

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Physical Chemistry B
Publication Identifier Type: DOI Publication Identifier: 10.1021/jp408241f
Volume: 118 Issue: 9 First Page #: 2414
Date Submitted: Date Published:
Publication Location:
**Article Title:** Convective Flows in Evaporating Sessile Droplets
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chaos: An Interdisciplinary Journal of Nonlinear Science
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4858457
Volume: 24 Issue: 1 First Page #: 131121
Date Submitted: Date Published:
Publication Location:
**Article Title:** Cross-linked structure of network evolution
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1003171
Volume: 9 Issue: 9 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Task-Based Core-Periphery Organization of Human Brain Dynamics
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Applied Mechanics
Publication Identifier Type: DOI Publication Identifier: 10.1115/1.4024992
Volume: 81 Issue: 3 First Page #: 310141
Date Submitted: Date Published:
Publication Location:
**Article Title:** Optimal Material Properties for Mitigating Brain Injury During Head Impact
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
as of 01-May-2020

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Cognitive, Affective and Behavioral Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.3758/s13415-013-0195-1
Volume: 13 Issue: 4 First Page #: 690
Date Submitted: Date Published:
Publication Location:
**Article Title:** fMRI reliability: Influences of task and experimental design
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Science Translational Medicine
Publication Identifier Type: DOI Publication Identifier: 10.1126/scitranslmed.3007988
Volume: 6 Issue: 222 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Molecular Network Analysis of Endometriosis Reveals a Role for c-Jun-Regulated Macrophage Activation
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Social Network Analysis and Mining
Publication Identifier Type: DOI Publication Identifier: 10.1007/s13278-014-0204-6
Volume: 4 Issue: 1 First Page #: 203
Date Submitted: Date Published:
Publication Location:
**Article Title:** Modeling individual topic-specific behavior and influence backbone networks in social media
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Neuroscience Methods
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jneumeth.2013.07.012
Volume: 219 Issue: 2 First Page #: 205
Date Submitted: Date Published:
Publication Location:
**Article Title:** Reproducible paired sources from concurrent EEG-fMRI data using BICAR
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0087380
Volume: 9 Issue: 2 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Measuring and Modeling Behavioral Decision Dynamics in Collective Evacuation
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Neural Networks and Learning Systems
Publication Identifier Type: DOI Publication Identifier: 10.1109/TNNLS.2014.2302898
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Single-Trial Classification of Event-Related Potentials in Rapid Serial Visual Presentation Tasks Using Supervised Spatial Filtering
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201400828
Volume: 26 Issue: 30 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Assembly of Viral Hydrogels for Three-Dimensional Conducting Nanocomposites
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1315866110
Volume: 110 Issue: 46 First Page #: 18460
Date Submitted: Date Published:
Publication Location:
**Article Title:** Quantitative selection and parallel characterization of aptamers
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Brain Imaging and Behavior
Publication Identifier Type: DOI Publication Identifier: 10.1007/s11682-013-9254-z
Volume: 8 Issue: 2 First Page #: 292
Date Submitted: Date Published:
Publication Location:
**Article Title:** Local termination pattern analysis: a tool for comparing white matter morphology
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Experimental Psychology
Publication Identifier Type: DOI Publication Identifier: 10.1037/a0030059
Volume: 142 Issue: 3 First Page #: 710
Date Submitted: Date Published:
Publication Location:
**Article Title:** Erasing the engram: The unlearning of procedural skills.
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Langmuir
Publication Identifier Type: DOI Publication Identifier: 10.1021/la403420f
Volume: 29 Issue: 48 First Page #: 15006
Date Submitted: Date Published:
Publication Location:
**Article Title:** JKR Theory for the Stick–Slip Peeling and Adhesion Hysteresis of Gecko Mimetic Patterned Surfaces with a Smooth Glass Surface
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Experimental Biology
Publication Identifier Type: DOI Publication Identifier: 10.1242/jeb.090415
Volume: 216 Issue: 19 First Page #: 3733
Date Submitted: Date Published:
Publication Location:
**Article Title:** Dynamic biophotonics: female squid exhibit sexually dimorphic tunable leucophores and iridocytes
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
as of 01-May-2020

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Langmuir
Publication Identifier Type: DOI Publication Identifier: 10.1021/la500274h
Volume: 30 Issue: 15 First Page #: 4375
Date Submitted: Date Published:
Publication Location:
**Article Title:** Theoretical Investigation of Bacteria Polarizability under Direct Current Electric Fields
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chemical Communications
Publication Identifier Type: DOI Publication Identifier: 10.1039/c3cc45094e
Volume: 49 Issue: 83 First Page #: 9624
Date Submitted: Date Published:
Publication Location:
**Article Title:** Increased ion conductance across mammalian membranes modified with conjugated oligoelectrolytes
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chemistry of Materials
Publication Identifier Type: DOI Publication Identifier: 10.1021/cm401912j
Volume: 26 Issue: 1 First Page #: 686
Date Submitted: Date Published:
Publication Location:
**Article Title:** Modification of Abiotic–Biotic Interfaces with Small Molecules and Nanomaterials for Improved Bioelectronics
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Nano
Publication Identifier Type: DOI Publication Identifier: 10.1021/nn404296k
Volume: 7 Issue: 10 First Page #: 9452
Date Submitted: Date Published:
Publication Location:
**Article Title:** A Chemically Synthesized Capture Agent Enables the Selective, Sensitive, and Robust Electrochemical Detection of Anthrax Protective Antigen
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0067590
Volume: 8 Issue: 7 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Intracellular Water Exchange for Measuring the Dry Mass, Water Mass and Changes in Chemical Composition of Living Cells
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Science Translational Medicine
Publication Identifier Type: DOI Publication Identifier: 10.1126/scitranslmed.3007095
Volume: 5 Issue: 213 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Real-Time, Aptamer-Based Tracking of Circulating Therapeutic Agents in Living Animals
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Royal Society Interface
Publication Identifier Type: DOI Publication Identifier: 10.1098/rsif.2014.0106
Volume: 11 Issue: 95 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Experimental determination of refractive index of condensed reflectin in squid iridocytes
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Annals of the New York Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1111/nyas.12404
Volume: 1316 Issue: 1 First Page #: 71
Date Submitted: Date Published:
Publication Location:
**Article Title:** A new perspective on the perceptual selectivity of attention under load
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4863990
Volume: 140 Issue: 5 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Validity conditions for stochastic chemical kinetics in diffusion-limited systems
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Optics Express
Publication Identifier Type: DOI Publication Identifier: 10.1364/OE.22.012808
Volume: 22 Issue: 11 First Page #: 12808
Date Submitted: Date Published:
Publication Location:
**Article Title:** Bio-inspired, sub-wavelength surface structures for ultra-broadband, omni-directional anti-reflection in the mid and far IR
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Optics Letters
Publication Identifier Type: DOI Publication Identifier: 10.1364/OL.39.000013
Volume: 39 Issue: 1 First Page #: 13
Date Submitted: Date Published:
Publication Location:
**Article Title:** Importance of diffuse scattering phenomena in moth-eye arrays for broadband infrared applications
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biotechnology and Bioengineering
Publication Identifier Type: DOI Publication Identifier: 10.1002/bit.25264
Volume: 111 Issue: 8 First Page #: 1471
Date Submitted: Date Published:
Publication Location:
**Article Title:** Anaerobic gut fungi: Advances in isolation, culture, and cellulolytic enzyme discovery for biofuel production
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201304373
Volume: 26 Issue: 1 First Page #: 10
Date Submitted: Date Published:
Publication Location:
**Article Title:** 25th Anniversary Article: Bulk Heterojunction Solar Cells: Understanding the Mechanism of Operation
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Computational Physics
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jcp.2014.02.004
Volume: 266 Issue: 2014 First Page #: 89
Date Submitted: Date Published:
Publication Location:
**Article Title:** Local error estimates for adaptive simulation of the reaction–diffusion master equation via operator splitting
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja503016b
Volume: 136 Issue: 23 First Page #: 8169
Date Submitted: Date Published:
Publication Location:
**Article Title:** Photoswitching Using Visible Light: A New Class of Organic Photochromic Molecules
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1003591
Volume: 10 Issue: 5 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Structurally-Constrained Relationships between Cognitive States in the Human Brain
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Synthetic Biology
Publication Identifier Type: DOI Publication Identifier: 10.1021/sb500024b
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Design and Implementation of a Biomolecular Concentration Tracker
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Physical Chemistry B
Publication Identifier Type: DOI Publication Identifier: 10.1021/jp408144g
Volume: 117 Issue: 51 First Page #: 16369
Date Submitted: Date Published:
Publication Location:
**Article Title:** The Intersection of Interfacial Forces and Electrochemical Reactions
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Functional Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adfm.201301960
Volume: 24 Issue: 5 First Page #: 574
Date Submitted: Date Published:
Publication Location:
**Article Title:** Biomimetic Bidirectional Switchable Adhesive Inspired by the Gecko
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Cognitive Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1162/jocn_a_00480
Volume: 26 Issue: 3 First Page #: 476
Date Submitted: Date Published:
Publication Location:
**Article Title:** Isolating the Neural Mechanisms of Interference during Continuous Multisensory Dual-task Performance
**Authors:**
**Keywords:** see Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Macro Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/mz400309d
Volume: 2 Issue: 8 First Page #: 677
Date Submitted: Date Published:
Publication Location:
**Article Title:** Strongly Phase-Segregating Block Copolymers with Sub-20 nm Features
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Neuropsychologia
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuropsychologia.2013.11.006
Volume: 53 Issue: 2014 First Page #: 122
Date Submitted: Date Published:
Publication Location:
**Article Title:** Lateral posterior parietal activity during source memory judgments of perceived and imagined events
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1003491
Volume: 10 Issue: 3 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Resolving Structural Variability in Network Models and the Brain
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201400183
Volume: 53 Issue: 27 First Page #: 7018
Date Submitted: Date Published:
Publication Location:
**Article Title:** A Facile Synthesis of Dynamic, Shape-Changing Polymer Particles
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Vision
Publication Identifier Type: DOI Publication Identifier: 10.1167/14.3.14
Volume: 14 Issue: 3 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** What do saliency models predict?
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nano Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/nl401758g
Volume: 13 Issue: 8 First Page #: 3796
Date Submitted: Date Published:
Publication Location:
**Article Title:** Improved Light Harvesting and Improved Efficiency by Insertion of an Optical Spacer (ZnO) in Solution-Processed Small-Molecule Solar Cells
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Integrative Biology
Publication Identifier Type: DOI Publication Identifier: 10.1039/c3ib40062j
Volume: 5 Issue: 11 First Page #: 1355
Date Submitted: Date Published:
Publication Location:
**Article Title:** Network analysis of differential Ras isoform mutation effects on intestinal epithelial responses to TNF-?
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Protein Science
Publication Identifier Type: DOI Publication Identifier: 10.1002/pro.2390
Volume: 23 Issue: 1 First Page #: 56
Date Submitted: Date Published:
Publication Location:
**Article Title:** A comparison of the folding kinetics of a small, artificially selected DNA aptamer with those of equivalently simple naturally occurring proteins
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1003139
Volume: 9 Issue: 7 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Spatial Stochastic Dynamics Enable Robust Cell Polarization
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Materials
Publication Identifier Type: DOI Publication Identifier: 10.1038/nmat3938
Volume: 13 Issue: 5 First Page #: 524
Date Submitted: Date Published:
Publication Location:
**Article Title:** Universal process-inert encoding architecture for polymer microparticles
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review E
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevE.88.012703
Volume: 88 Issue: 1 First Page #: 127031
Date Submitted: Date Published:
Publication Location:
**Article Title:** Sacrificial bonds and hidden length in biomaterials: A kinetic constitutive description of strength and toughness in bone
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja412473p
Volume: 136 Issue: 9 First Page #: 3597
Date Submitted: Date Published:
Publication Location:
**Article Title:** Silaindacenodithiophene-Based Molecular Donor: Morphological Features and Use in the Fabrication of Compositionally Tolerant, High-Efficiency Bulk Heterojunction Solar Cells
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1301740111
Volume: 111 Issue: 1 First Page #: 433
Date Submitted: Date Published:
Publication Location:
**Article Title:** Identification of secreted bacterial proteins by noncanonical amino acid tagging
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Applied and Environmental Microbiology
Publication Identifier Type: DOI Publication Identifier: 10.1128/AEM.03303-13
Volume: 80 Issue: 3 First Page #: 1042
Date Submitted: Date Published:
Publication Location:
**Article Title:** Functional Screening and In Vitro Analysis Reveal Thioesterases with Enhanced Substrate Specificity Profiles That Improve Short-Chain Fatty Acid Production in Escherichia coli
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Materials Science
Publication Identifier Type: DOI Publication Identifier: 10.1007/s10853-013-7945-x
Volume: 49 Issue: 6 First Page #: 2496
Date Submitted: Date Published:
Publication Location:
**Article Title:** Mechanical characterization of hollow ceramic nanolattices
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** SIAM Journal on Applied Dynamical Systems
Publication Identifier Type: DOI Publication Identifier: 10.1137/130934040
Volume: 13 Issue: 1 First Page #: 425
Date Submitted: Date Published:
Publication Location:
**Article Title:** Eulerian Opinion Dynamics with Bounded Confidence and Exogenous Inputs
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nonlinear Theory and Its Applications, IEICE
Publication Identifier Type: Publication Identifier:
Volume: 4 Issue: 3 First Page #: 198
Date Submitted: Date Published:
Publication Location:
**Article Title:** A Review of Parametric Resonance in Microelectromechanical Systems
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201305882
Volume: 52 Issue: 52 First Page #: 13975
Date Submitted: Date Published:
Publication Location:
**Article Title:** A Chemical Epitope-Targeting Strategy for Protein Capture Agents: The Serine 474 Epitope of the Kinase Akt2
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Nano
Publication Identifier Type: DOI Publication Identifier: 10.1021/nn404079v
Volume: 7 Issue: 11 First Page #: 9675
Date Submitted: Date Published:
Publication Location:
**Article Title:** Selection of Shape-Changing DNA Nanostructures Capable of Binding-Induced Cargo Release
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Communications
Publication Identifier Type: DOI Publication Identifier: 10.1038/ncomms3756
Volume: 4 Issue: 2756 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Biologically enhanced cathode design for improved capacity and cycle life for lithium-oxygen batteries
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1318602111
Volume: 111 Issue: 4 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Weighing nanoparticles in solution at the attogram scale
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Functional Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adfm.201301916
Volume: 24 Issue: 9 First Page #: 1275
Date Submitted: Date Published:
Publication Location:
**Article Title:** High-Rate Continuous Synthesis of Nanocrystalline Perovskites and Metal Oxides in a Colliding Vapor Stream of Microdroplets
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Frontiers in Computational Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.3389/fncom.2013.00177
Volume: 7 Issue: 177 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** A neurocomputational theory of how explicit learning bootstraps early procedural learning
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review X
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevX.3.041010
Volume: 3 Issue: 4 First Page #: 410101
Date Submitted: Date Published:
Publication Location:
**Article Title:** Microfluidic Microdialysis: Spatiotemporal Control over Solution Microenvironments Using Integrated Hydrogel Membrane Microwindows
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0076224
Volume: 8 Issue: 10 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** A Cocktail of Thermally Stable, Chemically Synthesized Capture Agents for the Efficient Detection of Anti-Gp41 Antibodies from Human Sera
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Applied Physics Letters
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4883001
Volume: 104 Issue: 23 First Page #: 2333052
Date Submitted: Date Published:
Publication Location:
**Article Title:** Structural and optoelectronic properties of hybrid bulk-heterojunction materials based on conjugated small molecules and mesostructured TiO2
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/ac402628t
Volume: 86 Issue: 2 First Page #: 1061
Date Submitted: Date Published:
Publication Location:
**Article Title:** Discrete Free-Surface Millifluidics for Rapid Capture and Analysis of Airborne Molecules Using Surface-Enhanced Raman Spectroscopy
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Signal Processing
Publication Identifier Type: DOI Publication Identifier: 10.1109/TSP.2014.2306180
Volume: 62 Issue: 8 First Page #: 2012
Date Submitted: Date Published:
Publication Location:
**Article Title:** Compressive Parameter Estimation in AWGN
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ELECTROPHORESIS
Publication Identifier Type: DOI Publication Identifier: 10.1002/elps.201300177
Volume: 35 Issue: 2014 First Page #: 412
Date Submitted: Date Published:
Publication Location:
**Article Title:** Separation behavior of short single- and double-stranded DNA in 1 micron and 100 nm glass channels
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Communications
Publication Identifier Type: DOI Publication Identifier: 10.1038/ncomms4421
Volume: 5 Issue: 3421 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Microfluidic probe for single-cell analysis in adherent tissue culture
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Macromolecules
Publication Identifier Type: DOI Publication Identifier: 10.1021/ma402566g
Volume: 47 Issue: 6 First Page #: 2037
Date Submitted: Date Published:
Publication Location:
**Article Title:** Toward Strong Thermoplastic Elastomers with Asymmetric Miktoarm Block Copolymer Architectures
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0072351
Volume: 8 Issue: 8 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Intra- and Inter-Frequency Brain Network Structure in Health and Schizophrenia
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Synthetic Biology
Publication Identifier Type: DOI Publication Identifier: 10.1021/sb400010m
Volume: 2 Issue: 12 First Page #: 690
Date Submitted: Date Published:
Publication Location:
**Article Title:** Hypocrea jecorina Cellobiohydrolase I Stabilizing Mutations Identified Using Noncontiguous Recombination
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Attention, Perception, & Psychophysics
Publication Identifier Type: DOI Publication Identifier: 10.3758/s13414-014-0659-6
Volume: 76 Issue: 5 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Cross-modal information integration in category learning
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Psychological Science
Publication Identifier Type: DOI Publication Identifier: 10.1177/0956797613509112
Volume: 25 Issue: 2 First Page #: 447
Date Submitted: Date Published:
Publication Location:
**Article Title:** Deferred Feedback Sharply Dissociates Implicit and Explicit Category Learning
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Current Opinion in Biotechnology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.copbio.2014.01.007
Volume: 28 Issue: 2014 First Page #: 103
Date Submitted: Date Published:
Publication Location:
**Article Title:** Extracting data from the muck: deriving biological insight from complex microbial communities and non-model organisms with next generation sequencing
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** NeuroImage
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2013.01.008
Volume: 71 Issue: 2013 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Brain activity across the development of automatic categorization: A comparison of categorization tasks using multi-voxel pattern analysis
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Psychonomic Bulletin & Review
Publication Identifier Type: DOI Publication Identifier: 10.3758/s13423-014-0661-y
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** General recognition theory with individual differences: a new method for examining perceptual and decisional interactions with an application to face perception
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1323618111
Volume: 111 Issue: 5 First Page #: 2040
Date Submitted: Date Published:
Publication Location:
**Article Title:** Spatiotemporal separation of PER and CRY posttranslational regulation in the mammalian circadian clock
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** BMC Systems Biology
Publication Identifier Type: DOI Publication Identifier: 10.1186/1752-0509-7-71
Volume: 7 Issue: 1 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Estimating confidence intervals in predicted responses for oscillatory biological models
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Frontiers in Human Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.3389/fnhum.2014.00334
Volume: 8 Issue: 334 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Accurate expectancies diminish perceptual distraction during visual search
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Frontiers in Human Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.3389/fnhum.2013.00627
Volume: 7 Issue: 627 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Post-perceptual processing during the attentional blink is modulated by inter-trial task expectancies
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Langmuir
Publication Identifier Type: DOI Publication Identifier: 10.1021/la400835n
Volume: 29 Issue: 34 First Page #: 10881
Date Submitted: Date Published:
Publication Location:
**Article Title:** Importance of Loading and Unloading Procedures for Gecko-Inspired Controllable Adhesives
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Knowledge and Data Engineering
Publication Identifier Type: DOI Publication Identifier: 10.1109/TKDE.2013.116
Volume: 26 Issue: 5 First Page #: 1158
Date Submitted: Date Published:
Publication Location:
**Article Title:** Interpreting the Public Sentiment Variations on Twitter
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja412695w
Volume: 136 Issue: 10 First Page #: 3736
Date Submitted: Date Published:
Publication Location:
**Article Title:** Synthesis, Characterization, and Biological Affinity of a Near-Infrared-Emitting Conjugated Oligoelectrolyte
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Current Opinion in Chemical Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cbpa.2013.10.007
Volume: 17 Issue: 6 First Page #: 902
Date Submitted: Date Published:
Publication Location:
**Article Title:** Innovation by homologous recombination
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Cognitive, Affective, & Behavioral Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.3758/s13415-013-0178-2
Volume: 13 Issue: 3 First Page #: 615
Date Submitted: Date Published:
Publication Location:
**Article Title:** Number of events and reliability in fMRI
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Communications
Publication Identifier Type: DOI Publication Identifier: 10.1038/ncomms3666
Volume: 4 Issue: 2666 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Engineering particle trajectories in microfluidic flows using particle shape
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Soft Matter
Publication Identifier Type: DOI Publication Identifier: 10.1039/c4sm00664j
Volume: 10 Issue: 28 First Page #: 5177
Date Submitted: Date Published:
Publication Location:
**Article Title:** Self-organizing microfluidic crystals
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie
Publication Identifier Type: DOI Publication Identifier: 10.1002/ange.201309334
Volume: 126 Issue: 19 First Page #: 4896
Date Submitted: Date Published:
Publication Location:
**Article Title:** Particle Display: A Quantitative Screening Method for Generating High-Affinity Aptamers
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Electrochemistry Communications
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.elecom.2014.01.025
Volume: 41 Issue: 2014 First Page #: 55
Date Submitted: Date Published:
Publication Location:
**Article Title:** Comparison of flavins and a conjugated oligoelectrolyte in stimulating extracellular electron transport from Shewanella oneidensis MR-1
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Automatic Control
Publication Identifier Type: DOI Publication Identifier: 10.1109/TAC.2013.2270072
Volume: 59 Issue: 1 First Page #: 211
Date Submitted: Date Published:
Publication Location:
**Article Title:** Intercellular Delay Regulates the Collective Period of Repressively Coupled Gene Regulatory Oscillator Networks
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Automatica
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.automatica.2013.02.051
Volume: 49 Issue: 6 First Page #: 1838
Date Submitted: Date Published:
Publication Location:
**Article Title:** The influence of global cues and local coupling on the rate of synchronization in the presence of time delays
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Signal Processing
Publication Identifier Type: DOI Publication Identifier: 10.1109/TSP.2013.2275511
Volume: 61 Issue: 21 First Page #: 5193
Date Submitted: Date Published:
Publication Location:
**Article Title:** Statistical Analysis of the Pulse-Coupled Synchronization Strategy for Wireless Sensor Networks
**Authors:**
**Keywords:** See Atttached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201310059
Volume: 53 Issue: 12 First Page #: 3227
Date Submitted: Date Published:
Publication Location:
**Article Title:** Accurate Zygote-Specific Discrimination of Single-Nucleotide Polymorphisms Using Microfluidic Electrochemical DNA Melting Curves
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Annals of Biomedical Engineering
Publication Identifier Type: DOI Publication Identifier: 10.1007/s10439-013-0878-3
Volume: 42 Issue: 2 First Page #: 299
Date Submitted: Date Published:
Publication Location:
**Article Title:** Chemical Tools for Temporally and Spatially Resolved Mass Spectrometry-Based Proteomics
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
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# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Hepatology
Publication Identifier Type: DOI Publication Identifier: 10.1002/hep.26490
Volume: 58 Issue: 4 First Page #: 1315
Date Submitted: Date Published:
Publication Location:
**Article Title:** The small molecule, genistein, increases hepcidin expression in human hepatocytes
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Immunology
Publication Identifier Type: DOI Publication Identifier: 10.4049/jimmunol.1302291
Volume: 192 Issue: 1 First Page #: 123
Date Submitted: Date Published:
Publication Location:
**Article Title:** Qualitatively Different T Cell Phenotypic Responses to IL-2 versus IL-15 Are Unified by Identical Dependences on Receptor Signal Strength and Duration
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Psychonomic Bulletin & Review
Publication Identifier Type: DOI Publication Identifier: 10.3758/s13423-013-0578-x
Volume: 21 Issue: 4 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Is state-trace analysis an appropriate tool for assessing the number of cognitive systems?
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1523/JNEUROSCI.5173-13.2014
Volume: 34 Issue: 20 First Page #: 6860
Date Submitted: Date Published:
Publication Location:
**Article Title:** Feature Interactions Enable Decoding of Sensorimotor Transformations for Goal-Directed Movement
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Applied Mechanics
Publication Identifier Type: DOI Publication Identifier: 10.1115/1.4024408
Volume: 81 Issue: 1 First Page #: 110061
Date Submitted: Date Published:
Publication Location:
**Article Title:** Compressive Response of Pyramidal Lattices Embedded in Foams
**Authors:**
**Keywords:** See Attached
**Abstract:** See Attached
**Distribution Statement:** 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Materials
Publication Identifier Type: DOI Publication Identifier: 10.1038/nmat4037
Volume: 1.3E+001 Issue: 9.0E+000 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Surface-initiated self-healing of polymers in aqueous media
**Authors:**
**Keywords:** None.
**Abstract:** Polymeric materials that intrinsically heal at damage sites under wet or moist conditions are urgently needed for biomedical and environmental applications. Although hydrogels with self-mending properties have been engineered by means of mussel-inspired metal-chelating catechol-functionalized polymer networks, biological self-healing in wet conditions, as occurs in self-assembled holdfast proteins in mussels and other marine organisms, is generally thought to involve more than reversible metal chelates. Here we demonstrate self-mending in metal-free water of synthetic polyacrylate and polymethacrylate materials that are surface-functionalized with mussel-inspired catechols. Wet self-mending of scission in these polymers is initiated and accelerated by hydrogen bonding between interfacial catechol moieties, and consolidated by the recruitment of other non-covalent interactions contributed by subsurface moieties. The repaired and pristine samples show similar mechanical properties, sugge
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Neuropsychologia
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuropsychologia.2014.12.011
Volume: 6.7E+001 Issue: 0 First Page #: 132
Date Submitted: Date Published:
Publication Location:
**Article Title:** Maintaining a cautious state of mind during a recognition test: A large-scale fMRI study
**Authors:**
**Keywords:** Recognition memory; Decision criterion; Individual differences; Lateral parietal cortex; Lateral prefrontal cortex; fMRI
**Abstract:** Decision criterion is an important factor in recognition memory, determining the amount of evidence required to judge an item as previously encountered. For a typical recognition memory test involving the prior study of a set of items, a conservative criterion establishes a higher standard of evidence for recognition and designates fewer items as previously studied. In contrast, a liberal criterion establishes a lower standard of evidence and designates more items as previously studied. Therefore, the hit rate and the correct rejection rate on a recognition memory test can be affected by both the memory strength of the studied items and the criterion used to make that judgment. Yet most neuroimaging studies of the successful retrieval effect (a contrast between hits and correct rejections) fail to measure or consider decision criterion. The goal of the current fMRI study with ninety-five participants was to directly manipulate decision criteria on two tests of recognition memory by var
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Soft Matter
Publication Identifier Type: DOI Publication Identifier: 10.1039/C4SM01400F
Volume: 1.0E+001 Issue: 3.8E+001 First Page #: 7595
Date Submitted: Date Published:
Publication Location:
**Article Title:** Synthesis of colloidal microgels using oxygen-controlled flow lithography
**Authors:**
**Keywords:** None.
**Abstract:** We report a synthesis approach based on stop-flow lithography (SFL) for fabricating colloidal microparticles with any arbitrary 2D-extruded shape. By modulating the degree of oxygen inhibition during synthesis, we achieved previously unattainable particle sizes. Brownian diffusion of colloidal discs in bulk suggests the out-of-plane dimension can be as small as 0.8 ?m, which agrees with confocal microscopy measurements. We measured the hindered diffusion of microdiscs near a solid surface and compared our results to theoretical predictions. These colloidal particles can also flow through physiological microvascular networks formed by endothelial cells undergoing vasculogensis under minimal hydrostatic pressure (?5 mm H2O). This versatile platform creates future opportunities for on-chip parametric studies of particle geometry effects on particle passage properties, distribution and cellular interactions.
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Acknowledged Federal Support:

**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Mucosal Immunology
Publication Identifier Type: DOI Publication Identifier: 10.1038/mi.2015.51
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Increased levels of inflammatory cytokines in the female reproductive tract are associated with altered expression of proteases, mucosal barrier proteins, and an influx of HIV-susceptible target cells
**Authors:**
**Keywords:** None.
**Abstract:** Elevated inflammatory cytokines (EMCs) at mucosal surfaces have been associated with HIV susceptibility, but the underlying mechanisms remain unclear. We characterized the soluble mucosal proteome associated with elevated cytokine expression in the female reproductive tract. A scoring system was devised based on the elevation (upper quartile) of at least three of seven inflammatory cytokines in cervicovaginal lavage. Using this score, HIV-uninfected Kenyan women were classified as either having EMC (n=28) or not (n=68). Of 455 proteins quantified in proteomic analyses, 53 were associated with EMC (5% false discovery rate threshold). EMCs were associated with proteases, cell motility, and actin cytoskeletal pathways, whereas protease inhibitor, epidermal cell differentiation, and cornified envelope pathways were decreased. Multivariate analysis identified an optimal signature of 16 proteins that distinguished the EMC group with 88% accuracy. Three proteins in this signature were neutrop
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support:

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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Current Opinion in Chemical Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cbpa.2014.09.008
Volume: 2.2E+001 Issue: 0 First Page #: 35
Date Submitted: Date Published:
Publication Location:
**Article Title:** Experimental fitness landscapes to understand the molecular evolution of RNA-based life
**Authors:**
**Keywords:** None.
**Abstract:** In evolutionary biology, the relationship between genotype and Darwinian fitness is known as a fitness landscape. These landscapes underlie natural selection, so understanding them would greatly improve quantitative prediction of evolutionary outcomes, guiding the development of synthetic living systems. However, the structure of fitness landscapes is essentially unknown. Our ability to experimentally probe these landscapes is physically limited by the number of different sequences that can be identified. This number has increased dramatically in the last several years, leading to qualitatively new investigations. Several approaches to illuminate fitness landscapes are possible, ranging from tight focus on a single peak to random speckling or even comprehensive coverage of an entire landscape. We discuss recent experimental studies of fitness landscapes, with a special focus on functional RNA, an important system for both synthetic cells and the origin of life.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1038/nn.3993
Volume: 1.8E+001 Issue: 5.0E+000 First Page #: 744
Date Submitted: Date Published:
Publication Location:
**Article Title:** Learning-induced autonomy of sensorimotor systems
**Authors:**
**Keywords:** None.
**Abstract:** Distributed networks of brain areas interact with one another in a time-varying fashion to enable complex cognitive and sensorimotor functions. Here we used new network-analysis algorithms to test the recruitment and integration of large-scale functional neural circuitry during learning. Using functional magnetic resonance imaging data acquired from healthy human participants, we investigated changes in the architecture of functional connectivity patterns that promote learning from initial training through mastery of a simple motor skill. Our results show that learning induces an autonomy of sensorimotor systems and that the release of cognitive control hubs in frontal and cingulate cortices predicts individual differences in the rate of learning on other days of practice. Our general statistical approach is applicable across other cognitive domains and provides a key to understanding time-resolved interactions between distributed neural circuits that enable task performance.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Frontiers in Psychology
Publication Identifier Type: DOI Publication Identifier: 10.3389/fpsyg.2014.01290
Volume: 5.0E+000 Issue: 1.29E+003 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Acute exercise and aerobic fitness influence selective attention during visual search
**Authors:**
**Keywords:** attention, visual search, distraction, physical activity, exercise, fatigue, aerobic fitness, VO2max
**Abstract:** Successful goal directed behavior relies on a human attention system that is flexible and able to adapt to different conditions of physiological stress. However, the effects of physical activity on multiple aspects of selective attention and whether these effects are mediated by aerobic capacity, remains unclear. The aim of the present study was to investigate the effects of a prolonged bout of physical activity on visual search performance and perceptual distraction. Two groups of participants completed a hybrid visual search flanker/response competition task in an initial baseline session and then at 17-min intervals over a 2 h 16 min test period. Participants assigned to the exercise group engaged in steady-state aerobic exercise between completing blocks of the visual task, whereas participants assigned to the control group rested in between blocks. The key result was a correlation between individual differences in aerobic capacity and visual search performance, such that those ind
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Control Systems Technology
Publication Identifier Type: Publication Identifier:
Volume: 2.3E+001 Issue: 1.0E+000 First Page #: 13
Date Submitted: Date Published:
Publication Location:
**Article Title:** State estimation of multiagent systems under impulsive noise and disturbances
**Authors:**
**Keywords:** None.
**Abstract:** We address the problem of estimating the state of a multiagent system based on measurements corrupted by impulsive noise and whose dynamics are subjected to impulsive disturbances. The qualifier impulsive refers to the fact that noise and disturbances are relatively small most of the time, but occasionally take large values. Noise and disturbances are modeled as mixtures of Gaussian and Laplacian processes, leading to a maximum-likelihood estimator that can be computed by solving a convex sum-of-norms optimization that can be solved online very efficiently. The approach has been validated both in simulation using synthetic data and in real hardware using a team of unmanned air vehicles equipped with an onboard video camera, inertial sensors, and Global Positioning System to cooperatively geolocate and track a ground-moving target agent.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** RSC Advances
Publication Identifier Type: DOI Publication Identifier: 10.1039/C5RA02944A
Volume: 5.0E+000 Issue: 4.8E+001 First Page #: 37970
Date Submitted: Date Published:
Publication Location:
**Article Title:** Carbon nanotube–polyaniline core–shell nanostructured hydrogel for electrochemical energy storage
**Authors:**
**Keywords:** None.
**Abstract:** Conductive polymer hydrogels, which synergize the advantageous features of hydrogels and conductive materials, have been utilized in many electrochemical energy storage applications. Here, we introduce phytic acid as (1) a dispersing agent for pristine multi-walled carbon nanotubes (MWNTs) in aqueous solution containing aniline and as (2) a gelator to form polyaniline (PANI)-based hydrogels after polymerization. The PANI-based hydrogels exhibit nanowire-based mesoporous networks with high surface area and electrical conductivity. The nanostructured core (MWNT)–shell (PANI) hydrogels show an improvement on the electrical conductivity from 0.21 to 1.54 S cm?1 as the loading of MWNTs increases from 0 to 5.0 wt%. The conducting nanowire-based networks with MWNT loadings of 3.0 wt% in the hydrogel provide efficient electron transport pathways that exhibit a maximal specific capacity of 609 F g?1. The scalable and facile synthesis demonstrates excellent electrochemical performance, rendering
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/ac504076k
Volume: 8.7E+001 Issue: 1.0E+000 First Page #: 821
Date Submitted: Date Published:
Publication Location:
**Article Title:** Array-based Discovery of Aptamer Pairs
**Authors:**
**Keywords:** None.
**Abstract:** Affinity reagent pairs that recognize distinct epitopes on a target protein can greatly improve the sensitivity and specificity of molecular detection. Importantly, such pairs can be conjugated to generate reagents that achieve two-site “bidentate” target recognition, with affinities greatly exceeding either monovalent component. DNA aptamers are especially well-suited for such constructs, because they can be linked via standard synthesis techniques without requiring chemical conjugation. Unfortunately, aptamer pairs are difficult to generate, primarily because conventional selection methods preferentially yield aptamers that recognize a dominant “hot spot” epitope. Our array-based discovery platform for multivalent aptamers (AD-MAP) overcomes this problem to achieve efficient discovery of aptamer pairs. We use microfluidic selection and high-throughput sequencing to obtain an enriched pool of aptamer sequences. Next, we synthesize a custom array based on these sequences, and perform p
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Speech, Language, and Hearing Research
Publication Identifier Type: DOI Publication Identifier: 10.1044/2015_JSLHR-S-14-0193
Volume: 5.8E+001 Issue: 0 First Page #: 268
Date Submitted: Date Published:
Publication Location:
**Article Title:** Anomalous White Matter Morphology in Adults Who Stutter
**Authors:**
**Keywords:** None.
**Abstract:** AIMS: Developmental stuttering is now generally considered to arise from genetic determinants interacting with neurologic function. Changes within speech-motor white matter (WM) connections may also be implicated. These connections can now be studied in great detail by high-angular-resolution diffusion magnetic resonance imaging. Therefore, diffusion spectrum imaging was used to reconstruct streamlines to examine white matter connections in people who stutter (PWS) and in people who do not stutter (PWNS). METHOD: WM morphology of the entire brain was assayed in 8 right-handed male PWS and 8 similarly aged right-handed male PWNS. WM was exhaustively searched using a deterministic algorithm that identifies missing or largely misshapen tracts. To be abnormal, a tract (defined as all streamlines connecting a pair of gray matter regions) was required to be at least one 3rd missing, in 7 out of 8 subjects in one group and not in the other group. RESULTS: Large portions of bilateral arcuate
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Psychophysiology
Publication Identifier Type: DOI Publication Identifier: 10.1111/psyp.12385
Volume: 5.2E+001 Issue: 4.0E+000 First Page #: 481
Date Submitted: Date Published:
Publication Location:
**Article Title:** Simultaneous acquisition of functional magnetic resonance images and impedance cardiography
**Authors:**
**Keywords:** MRI; Impedance cardiography; Autonomic nervous system
**Abstract:** While simultaneous acquisition of electrocardiography (ECG) data during MRI is a widely used clinical technique, the effects of the MRI environment on impedance cardiography (ICG) data have not been characterized. We collected echo planar MRI scans while simultaneously recording ECG and thoracic impedance using carbon fiber electrodes and customized amplifiers. Here, we show that the key changes in impedance (dZ/dt) and features of the ECG waveforms are not obstructed during MRI. We present a method for ensemble averaging ICG/ECG signals collected during MRI and show that it performs comparably with signals collected outside the MRI environment. These results indicate that ICG can be used during MRI to measure stroke volume, cardiac output, preejection period, and left ventricular ejection time.
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**Journal:** Macromolecules
Publication Identifier Type: DOI Publication Identifier: 10.1021/ma501547h
Volume: 4.7E+001 Issue: 1.9E+001 First Page #: 6836
Date Submitted: Date Published:
Publication Location:
**Article Title:** Molecular Interactions and Ordering in Electrically Doped Polymers: Blends of PBTTT and F4TCNQ
**Authors:**
**Keywords:** None.
**Abstract:** Identifying how small molecular acceptors pack with polymer donors in thin and thick (bulk) films is critical to understanding the nature of electrical doping by charge transfer. In this study, the packing structure of the molecular acceptor tetrafluorotetracyanoquinodimethane (F4TCNQ) with the semiconducting polymer poly (2,5-bis(3-tetradecylthiophen-2-yl)thieno[3,2-b]thiophene) (PBTTT-C14) is examined. A combination of solid-state NMR, synchrotron X-ray scattering, and optical spectroscopy was used to determine the packing motif for blends of PBTTT-C14 and F4TCNQ in thin and bulk films. These results indicate that F4TCNQ and PBTTT-C14 order in a cofacial arrangement where charge transfer is near 100% efficient in the solid state. These results provide crucial insights into the structures and compositions of ordered domains in doped semiconducting polymers and suggest a model for the microstructure where the location of the molecular acceptors are correlated rather than randomly disper
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chem. Commun.
Publication Identifier Type: DOI Publication Identifier: 10.1039/C4CC09599E
Volume: 5.1E+001 Issue: 1.2E+001 First Page #: 2335
Date Submitted: Date Published:
Publication Location:
**Article Title:** Label free detection of nucleic acids by modulating nanochannel surfaces
**Authors:**
**Keywords:** None.
**Abstract:** We develop surface-modified 100 nm silica nanofluidic channels that change in measured conductivity upon exposure to single- or double-stranded DNA. Through careful monitoring of both electromigrative and advective current in the channel, we can detect nanomolar concentrations of DNA. These results can be exploited for inexpensive, all-electronic DNA sensors.
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**Journal:** Journal of Experimental Psychology: Learning, Memory, and Cognition
Publication Identifier Type: DOI Publication Identifier: 10.1037/a0038853
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Procedural Learning During Declarative Control
**Authors:**
**Keywords:** None.
**Abstract:** There is now abundant evidence that human learning and memory are governed by multiple systems. As a result, research is now turning to the next question of how these putative systems interact. For instance, how is overall control of behavior coordinated, and does learning occur independently within systems regardless of what system is in control? Behavioral, neuroimaging, and neuroscience data are somewhat mixed with respect to these questions. Human neuroimaging and animal lesion studies suggest independent learning and are mostly agnostic with respect to control. Human behavioral studies suggest active inhibition of behavioral output but have little to say regarding learning. The results of two perceptual category-learning experiments are described that strongly suggest that procedural learning does occur while the explicit system is in control of behavior and that this learning might be just as good as if the procedural system was controlling the response. These results are consist
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Brain and Cognition
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.bandc.2014.09.008
Volume: 9.2E+001 Issue: 0 First Page #: 1
Date Submitted: Date Published:
Publication Location:
**Article Title:** Context-dependent savings in procedural category learning
**Authors:**
**Keywords:** Basal ganglia; Procedural learning; Context
**Abstract:** Environmental context can have a profound influence on the efficacy of intervention protocols designed to eliminate undesirable behaviors. This is clearly seen in drug rehabilitation clinics where patients often relapse soon after leaving the context of the treatment facility. A similar pattern is commonly observed in controlled laboratory studies of context-dependent savings in instrumental conditioning, where simply placing an animal back into the original conditioning chamber can renew an extinguished instrumental response. Surprisingly, context-dependent savings in human procedural learning has not been carefully examined in the laboratory. Here, we provide the first known empirical demonstration of contextdependent savings in a perceptual categorization task known to recruit procedural learning. We also present a computational account of these savings using a biologically detailed model in which a key role is played by cholinergic interneurons in the striatum.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Stem Cells Translational Medicine
Publication Identifier Type: DOI Publication Identifier: 10.5966/sctm.2014-0079
Volume: 3.0E+000 Issue: 9.0E+000 First Page #: 1066
Date Submitted: Date Published:
Publication Location:
**Article Title:** ROCK Inhibition Extends Passage of Pluripotent Stem Cell-Derived Retinal Pigmented Epithelium
**Authors:**
**Keywords:** Embryonic stem cells; Retinal pigmented epithelium; Cellular therapy; Cell culture; Cell proliferation
**Abstract:** Human embryonic stem cells (hESCs) offer a potentially unlimited supply of cells for emerging cell-based therapies. Unfortunately, the process of deriving distinct cell types can be time consuming and expensive. In the developed world, age-related macular degeneration (AMD) is the leading cause of blindness in the elderly, with more than 7.2 million people afflicted in the U.S. alone. Both hESC-derived retinal pigmented epithelium (hESC-RPE) and induced pluripotent stem cell-derived RPE (iPSC-RPE) are being developed for AMD therapies by multiple groups, but their potential for expansion in culture is limited. To attempt to overcome this passage limitation, we examined the involvement of Rho-associated, coiled-coil protein kinase (ROCK) in hESC-RPE and iPSC-RPE culture. We report that inhibiting ROCK1/2 with Y-27632 allows extended passage of hESC-RPE and iPSC-RPE. Microarray analysis suggests that ROCK inhibition could be suppressing an epithelial-to-mesenchymal transition through var
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Royal Society Interface
Publication Identifier Type: DOI Publication Identifier: 10.1098/rsif.2014.1346
Volume: 1.2E+001 Issue: 1.04E+002 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Stick-slip friction of gecko-mimetic flaps on smooth and rough surfaces
**Authors:**
**Keywords:** None.
**Abstract:** The discovery and understanding of gecko ‘frictional-adhesion’ adhering and climbing mechanism has allowed researchers to mimic and create gecko-inspired adhesives. A few experimental and theoretical approaches have been taken to understand the effect of surface roughness on synthetic adhesive performance, and the implications of stick–slip friction during shearing. This work extends previous studies by using a modified surface forces apparatus to quantitatively measure and model frictional forces between arrays of polydimethylsiloxane gecko footpad-mimetic tilted microflaps against smooth and rough glass surfaces. Constant attachments and detachments occur between the surfaces during shearing, as described by an avalanche model. These detachments ultimately result in failure of the adhesion interface and have been characterized in this study. Stick–slip friction disappears with increasing velocity when the flaps are sheared against a smooth silica surface; however, stick–slip was alwa
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**Journal:** Biomacromolecules
Publication Identifier Type: DOI Publication Identifier: 10.1021/bm501893y
Volume: 1.6E+001 Issue: 3.0E+000 First Page #: 1002
Date Submitted: Date Published:
Publication Location:
**Article Title:** Tough Coating Proteins: Subtle Sequence Variation Modulates Cohesion
**Authors:**
**Keywords:** None.
**Abstract:** Mussel foot protein-1 (mfp-1) is an essential constituent of the protective cuticle covering all exposed portions of the byssus (plaque and the thread) that marine mussels use to attach to intertidal rocks. The reversible complexation of Fe3+ by the 3,4-dihydroxyphenylalanine (Dopa) side chains in mfp-1 in Mytilus californianus cuticle is responsible for its high extensibility (120%) as well as its stiffness (2 GPa) due to the formation of sacrificial bonds that help to dissipate energy and avoid accumulation of stresses in the material. We have investigated the interactions between Fe3+ and mfp-1 from two mussel species, M. californianus (Mc) and M. edulis (Me), using both surface sensitive and solution phase techniques. Our results show that although mfp-1 homologues from both species bind Fe3+, mfp-1 (Mc) contains Dopa with two distinct Fe3+-binding tendencies and prefers to form intramolecular complexes with Fe3+. In contrast, mfp-1 (Me) is better adapted to intermolecular Fe3+ bin
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1004029
Volume: 1.1E+001 Issue: 1.0E+000 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Brain Network Adaptability across Task States
**Authors:**
**Keywords:** None.
**Abstract:** Activity in the human brain moves between diverse functional states to meet the demands of our dynamic environment, but fundamental principles guiding these transitions remain poorly understood. Here, we capitalize on recent advances in network science to analyze patterns of functional interactions between brain regions. We use dynamic network representations to probe the landscape of brain reconfigurations that accompany task performance both within and between four cognitive states: a task-free resting state, an attention-demanding state, and two memory-demanding states. Using the formalism of hypergraphs, we identify the presence of groups of functional interactions that fluctuate coherently in strength over time both within (task-specific) and across (task-general) brain states. In contrast to prior emphases on the complexity of many dyadic (region-to-region) relationships, these results demonstrate that brain adaptability can be described by common processes that drive the dynamic
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**Journal:** The Analyst
Publication Identifier Type: DOI Publication Identifier: 10.1039/C4AN01735H
Volume: 1.4E+002 Issue: 5.0E+000 First Page #: 1609
Date Submitted: Date Published:
Publication Location:
**Article Title:** Fluorescent silver nanocluster DNA probes for multiplexed detection using microfluidic capillary electrophoresis
**Authors:**
**Keywords:** None.
**Abstract:** DNA-stabilized fluorescent silver nanoclusters (AgNC DNA) are a new class of fluorophore that are formed by sequence specific interactions between silver and single-stranded DNA. By incorporating both target-binding and fluorescent-reporting sequences into a single synthetic DNA oligomer, AgNC DNA probes eliminate the need to conjugate dye or quencher molecules. In this study, we modify a AgNC DNA probe to demonstrate single-color multiplexed detection of DNA targets. We show that appending different lengths of poly-dT to the probe sequences tunes the electrophoretic mobility of AgNC DNA probes without affecting their fluorescence spectra. We use this to introduce a set of AgNC DNA probes selective for Hepatitis A, B and C target sequences that can be processed together in a simple, single-step protocol and distinguished with a resolution of 3.47 and signal to noise ratio of 17.23 in under 10 seconds by microfluidic capillary electrophoresis.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1038/nchem.2223
Volume: 7.0E+000 Issue: 0 First Page #: 455
Date Submitted: Date Published:
Publication Location:
**Article Title:** A protein-targeting strategy used to develop a selective inhibitor of the E17K point mutation in the PH domain of Akt1
**Authors:**
**Keywords:** None.
**Abstract:** Ligands that can bind selectively to proteins with single amino-acid point mutations offer the potential to detect or treat an abnormal protein in the presence of the wild type (WT). However, it is difficult to develop a selective ligand if the point mutation is not associated with an addressable location, such as a binding pocket. Here we report an all-chemical synthetic epitope-targeting strategy that we used to discover a 5-mer peptide with selectivity for the E17K-transforming point mutation in the pleckstrin homology domain of the Akt1 oncoprotein. A fragment of Akt1 that contained the E17K mutation and an I19[propargylglycine] substitution was synthesized to form an addressable synthetic epitope. Azide-presenting peptides that clicked covalently onto this alkyne-presenting epitope were selected from a library using in situ screening. One peptide exhibits a 10:1 in vitro selectivity for the oncoprotein relative to the WT, with a similar selectivity in cells. This 5-mer peptide was
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**Journal:** Vision Research
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.visres.2015.05.016
Volume: 1.13E+002 Issue: 0 First Page #: 137
Date Submitted: Date Published:
Publication Location:
**Article Title:** Optimal and human eye movements to clustered low value cues to increase decision rewards during search
**Authors:**
**Keywords:** Visual search; Rewards; Eye movements; Ideal searcher; Bayesian; Optimal
**Abstract:** Rewards have important influences on the motor planning of primates and the firing of neurons coding visual information and action. When eye movements to a target are differentially rewarded across locations, primates execute saccades towards the possible target location with the highest expected value, a product of sensory evidence and potentially earned reward (saccade to maximum expected value model, sMEV). Yet, in the natural world eye movements are not directly rewarded. Their role is to gather information to support subsequent rewarded search decisions and actions. Less is known about the effects of decision rewards on saccades. We show that when varying the decision rewards across cued locations following visual search, humans can plan their eye movements to increase decision rewards. Critically, we report a scenario for which five of seven tested humans do not preferentially deploy saccades to the possible target location with the highest reward, a strategy which is optimal whe
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0126203
Volume: 1.0E+001 Issue: 4.0E+000 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Distractor Suppression When Attention Fails: Behavioral Evidence for a Flexible Selective Attention Mechanism
**Authors:**
**Keywords:** None.
**Abstract:** Despite consistent evidence showing that attention is a multifaceted mechanism that can operate at multiple levels of processing depending on the structure and demands of the task, investigations of the attentional blink phenomenon have consistently shown that the impairment in reporting the second of two targets typically occurs at a late, or post-perceptual, stage of processing. This suggests that the attentional blink phenomenon may represent the operation of a unique attentional mechanism that is not as flexible as other attentional mechanisms. To test whether the attentional blink is a fixed or flexible phenomenon, we manipulated first target task demands (i.e., difficulty) and measured the influence this had on processing a subsequently presented distractor and the second target. If the attentional blink represents a mechanism that is fixed and consistently fails at a single stage of processing, then manipulations of task difficulty should not affect distractor processing. Howeve
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**Journal:** Journal of Molecular Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jmb.2014.06.015
Volume: 4.27E+002 Issue: 1.0E+000 First Page #: 205
Date Submitted: Date Published:
Publication Location:
**Article Title:** Directed Evolution of Gloeobacter violaceus Rhodopsin Spectral Properties
**Authors:**
**Keywords:** optogenetics; retinal; fluorescent proteins; opsins; proton pumps
**Abstract:** Proton-pumping rhodopsins (PPRs) are photoactive retinal-binding proteins that transport ions across biological membranes in response to light. These proteins are interesting for light-harvesting applications in bioenergy production, in optogenetics applications in neuroscience, and as fluorescent sensors of membrane potential. Little is known, however, about how the protein sequence determines the considerable variation in spectral properties of PPRs from different biological niches or how to engineer these properties in a given PPR. Here we report a comprehensive study of amino acid substitutions in the retinal-binding pocket of Gloeobacter violaceus rhodopsin (GR) that tune its spectral properties. Directed evolution generated 70 GR variants with absorption maxima shifted by up to ± 80 nm, extending the protein's light absorption significantly beyond the range of known natural PPRs. While proton-pumping activity was disrupted in many of the spectrally shifted variants, we identified
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201502451
Volume: 5.4E+001 Issue: 2.4E+001 First Page #: 7114
Date Submitted: Date Published:
Publication Location:
**Article Title:** Epitope Targeting of Tertiary Protein Structure Enables Target-Guided Synthesis of a Potent In-Cell Inhibitor of Botulinum Neurotoxin
**Authors:**
**Keywords:** botulinum neurotoxin; combinatorial screening; epitope targeting; peptides; target-guided synthesis
**Abstract:** Botulinum neurotoxin (BoNT) serotype?A is the most lethal known toxin and has an occluded structure, which prevents direct inhibition of its active site before it enters the cytosol. Target-guided synthesis by in?situ click chemistry is combined with synthetic epitope targeting to exploit the tertiary structure of the BoNT protein as a landscape for assembling a competitive inhibitor. A substrate-mimicking peptide macrocycle is used as a direct inhibitor of BoNT. An epitope-targeting in?situ click screen is utilized to identify a second peptide macrocycle ligand that binds to an epitope that, in the folded BoNT structure, is active-site-adjacent. A second in?situ click screen identifies a molecular bridge between the two macrocycles. The resulting divalent inhibitor exhibits an in?vitro inhibition constant of 165?pm against the BoNT/A catalytic chain. The inhibitor is carried into cells by the intact holotoxin, and demonstrates protection and rescue of BoNT intoxication in a human neur
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**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201501503
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Eutectic Syntheses of Graphitic Carbon with High Pyrazinic Nitrogen Content
**Authors:**
**Keywords:** None.
**Abstract:** Mixtures of phenols/ketones and urea show eutectic behavior upon gentle heating. These mixtures possess liquid-crystalline-like phases that can be processed. The architecture of phenol/ketone acts as structure-donating motif, while urea serves as melting-point reduction agent. Condensation at elevated temperatures results in nitrogen-containing carbons with remarkably high nitrogen content of mainly pyrazinic nature.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Cell
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cell.2014.11.051
Volume: 1.6E+002 Issue: 0 First Page #: 228
Date Submitted: Date Published:
Publication Location:
**Article Title:** A Qrr Noncoding RNA Deploys Four Different Regulatory Mechanisms to Optimize Quorum-Sensing Dynamics
**Authors:**
**Keywords:** None.
**Abstract:** Quorum sensing is a cell-cell communication process that bacteria use to transition between individual and social lifestyles. In vibrios, homologous small RNAs called the Qrr sRNAs function at the center of quorum-sensing pathways. The Qrr sRNAs regulate multiple mRNA targets including those encoding the quorum-sensing regulatory components luxR, luxO, luxM, and aphA. We show that a representative Qrr, Qrr3, uses four distinct mechanisms to control its particular targets: the Qrr3 sRNA represesluxR through catalytic degradation, represses luxM through coupled degradation, represses luxO through sequestration, and activates aphA by revealing the ribosome binding site while the sRNA itself is degraded. Qrr3 forms different base-pairing interactions with each mRNA target, and the particular pairing strategy determines which regulatory mechanism occurs. Combined mathematical modeling and experiments show that the specific Qrr regulatory mechanism employed governs the potency, dynamics, an
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**Journal:** Polymer Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1039/C4PY01766H
Volume: 6.0E+000 Issue: 1.1E+001 First Page #: 2029
Date Submitted: Date Published:
Publication Location:
**Article Title:** A robust platform for functional microgels via thiol–ene chemistry with reactive polyether-based nanoparticles
**Authors:**
**Keywords:** None.
**Abstract:** We herein report the development of crosslinked polyether particles as a reactive platform for the preparation of functional microgels. Thiol–ene crosslinking of poly(allyl glycidyl ether) in miniemulsion droplets – stabilized by a surface active, bio-compatible polyethylene glycol block copolymer – resulted in colloidal gels with a PEG corona and an inner polymeric network containing reactive allyl units. The stability of the allyl groups allows the microgels to be purified and stored before a second, subsequent thiol–ene functionalization step allows a wide variety of pH- and chemically-responsive groups to be introduced into the nanoparticles. The facile nature of this synthetic platform enables the preparation of microgel libraries that are responsive to different triggers but are characterized by the same size distribution, surface functionality, and crosslinking density. In addition, the utilization of a crosslinker containing cleavable ester groups renders the resulting hydrogel
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Communications
Publication Identifier Type: DOI Publication Identifier: 10.1038/ncomms5894
Volume: 5.0E+000 Issue: 4.894E+00First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Archaerhodopsin variants with enhanced voltage-sensitive fluorescence in mammalian and Caenorhabditis elegans neurons
**Authors:**
**Keywords:** None.
**Abstract:** Probing the neural circuit dynamics underlying behaviour would benefit greatly from improved genetically encoded voltage indicators. The proton pump ?Archaerhodopsin-3 (?Arch), an optogenetic tool commonly used for neuronal inhibition, has been shown to emit voltage-sensitive fluorescence. Here we report two ?Arch variants with enhanced radiance (Archers) that in response to 655?nm light have 3–5 times increased fluorescence and 55–99 times reduced photocurrents compared with ?Arch WT. The most fluorescent variant, Archer1, has 25–40% fluorescence change in response to action potentials while using 9 times lower light intensity compared with other ?Arch-based voltage sensors. Archer1 is capable of wavelength-specific functionality as a voltage sensor under red light and as an inhibitory actuator under green light. As a proof-of-concept for the application of ?Arch-based sensors in vivo, we show fluorescence voltage sensing in behaving Caenorhabditis elegans. Archer1's characteristics c
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**Journal:** Disease Models & Mechanisms
Publication Identifier Type: DOI Publication Identifier: 10.1242/dmm.017236
Volume: 8.0E+000 Issue: 5.0E+000 First Page #: 421
Date Submitted: Date Published:
Publication Location:
**Article Title:** Cellular models and therapies for age-related macular degeneration
**Authors:**
**Keywords:** AMD; RPE; Cell-culture models; hESC; iPSC; Stem-cell therapy
**Abstract:** Age-related macular degeneration (AMD) is a complex neurodegenerative visual disorder that causes profound physical and psychosocial effects. Visual impairment in AMD is caused by the loss of retinal pigmented epithelium (RPE) cells and the light-sensitive photoreceptor cells that they support. There is currently no effective treatment for the most common form of this disease (dry AMD). A new approach to treating AMD involves the transplantation of RPE cells derived from either human embryonic or induced pluripotent stem cells. Multiple clinical trials are being initiated using a variety of cell therapies. Although many animal models are available for AMD research, most do not recapitulate all aspects of the disease, hampering progress. However, the use of cultured RPE cells in AMD research is well established and, indeed, some of the more recently described RPE-based models show promise for investigating the molecular mechanisms of AMD and for screening drug candidates. Here, we discu
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Computational Physics
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jcp.2014.06.025
Volume: 2.74E+002 Issue: 0 First Page #: 524
Date Submitted: Date Published:
Publication Location:
**Article Title:** The time dependent propensity function for acceleration of spatial stochastic simulation of reaction–diffusion systems
**Authors:**
**Keywords:** Spatial stochastic simulation; Reaction–diffusion; Time dependent propensity
**Abstract:** The inhomogeneous stochastic simulation algorithm (ISSA) is a fundamental method for spatial stochastic simulation. However, when diffusion events occur more frequently than reaction events, simulating the diffusion events by ISSA is quite costly. To reduce this cost, we propose to use the time dependent propensity function in each step. In this way we can avoid simulating individual diffusion events, and use the time interval between two adjacent reaction events as the simulation stepsize. We demonstrate that the new algorithm can achieve orders of magnitude efficiency gains over widely-used exact algorithms, scales well with increasing grid resolution, and maintains a high level of accuracy.
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**Journal:** International Journal of Solids and Structures
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.ijsolstr.2014.04.001
Volume: 5.1E+001 Issue: 1.8E+001 First Page #: 3003
Date Submitted: Date Published:
Publication Location:
**Article Title:** Peeling of an elastic membrane tape adhered to a substrate by a uniform cohesive traction
**Authors:**
**Keywords:** Adhesion; Peeling; Interface/cohesive energy; Dugdale cohesive zone
**Abstract:** An analytical model is provided for the peeling of a tape from a surface to which it adheres through cohesive tractions. The tape is considered to be a membrane without bending stiffness and is initially attached everywhere to a flat rigid surface. The tape is assumed to deform in plane strain, and finite deformations in the form of elastic strains are accounted for. The cohesive tractions are taken to be uniform when the tape is within a critical interaction distance from the substrate and then to fall immediately to zero once this critical interaction distance is exceeded. When the distance between the tape and the substrate is zero, repulsive and attractive tractions balance to zero; in this segment, sliding of the tape relative to the substrate is forbidden when we pull the tape up somewhere in the middle, though we permit such sliding when the tape is peeled from one end. In the cohesive zone and where the tape is detached, the interaction of the tape with the substrate is frictio
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Bioengineered
Publication Identifier Type: DOI Publication Identifier: 10.1080/21655979.2015.1060379
Volume: 6.0E+000 Issue: 4.0E+000 First Page #: 204
Date Submitted: Date Published:
Publication Location:
**Article Title:** Driving biomass breakdown through engineered cellulosomes
**Authors:**
**Keywords:** anaerobic fungi, biofuels, cellulase, cellulosome, lignocellulose, CBM, Carbohydrate Binding Module, ELISA, Enzyme-Linked Immunosorbent Assay, GH, Glycoside Hydrolase, GST, Glutathione S-Transferase, SLH, Surface Layer Homology
**Abstract:** Extraction of sugar is the rate-limiting step in converting unpretreated biomass into value-added products through microbial fermentation. Both anaerobic fungi and anaerobic bacteria have evolved to produce large multi-cellulase complexes referred to as cellulosomes, which are powerful machines for biomass deconstruction. Characterization of bacterial cellulosomes has inspired synthetic "designer" cellulosomes, consisting of parts discovered from the native system that have proven useful for cellulose depolymerization. By contrast, the multi-cellulase complexes produced by anaerobic fungi are much more poorly understood, and to date their composition, architecture, and enzyme tethering mechanism remain unknown and heavily debated. Here, we compare current knowledge pertaining to the cellulosomes produced by both bacteria and fungi, including their application to synthetic enzyme-tethered systems for tunneled biocatalysis. We highlight gaps in knowledge and opportunities for discovery,
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**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja502985g
Volume: 1.36E+002 Issue: 2.7E+001 First Page #: 9608
Date Submitted: Date Published:
Publication Location:
**Article Title:** Importance of the Donor:Fullerene Intermolecular Arrangement for High-Efficiency Organic Photovoltaics
**Authors:**
**Keywords:** None.
**Abstract:** The performance of organic photovoltaic (OPV) material systems are hypothesized to depend strongly on the intermolecular arrangements at the donor:fullerene interfaces. A review of some of the most efficient polymers utilized in polymer:fullerene PV devices, combined with an analysis of reported polymer donor materials wherein the same conjugated backbone was used with varying alkyl substituents, supports this hypothesis. Specifically, the literature shows that higher-performing donor–acceptor type polymers generally have acceptor moieties that are sterically accessible for interactions with the fullerene derivative, whereas the corresponding donor moieties tend to have branched alkyl substituents that sterically hinder interactions with the fullerene. To further explore the idea that the most beneficial polymer:fullerene arrangement involves the fullerene docking with the acceptor moiety, a family of benzo[1,2-b:4,5-b?]dithiophene–thieno[3,4-c]pyrrole-4,6-dione polymers (PBDTTPD deriv
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Cortex
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cortex.2014.10.011
Volume: 6.4E+001 Issue: 0 First Page #: 123
Date Submitted: Date Published:
Publication Location:
**Article Title:** Learning robust cortico-cortical associations with the basal ganglia: An integrative review
**Authors:**
**Keywords:** Basal ganglia; Prefrontal cortex; Premotor cortex; Supplementary motor area; Fronto-striatal connectivity
**Abstract:** This article focuses on the interaction between the basal ganglia (BG) and prefrontal cortex (PFC). The BG are a group of nuclei at the base of the forebrain that are highly connected with cortex. A century of research suggests that the role of the BG is not exclusively motor, and that the BG also play an important role in learning and memory. In this review article, we argue that one important role of the BG is to train connections between posterior cortical areas and frontal cortical regions that are responsible for automatic behavior after extensive training. According to this view, one effect of BG trial-and-error learning is to activate the correct frontal areas shortly after posterior associative cortex activation, thus allowing for Hebbian learning of robust, fast, and efficient cortico-cortical processing. This hypothesized process is general, and the content of the learned associations depends on the specific areas involved (e.g., associations involving premotor areas would be
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**Journal:** Physical Review E
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevE.91.023312
Volume: 9.1E+001 Issue: 0 First Page #: 23312
Date Submitted: Date Published:
Publication Location:
**Article Title:** Reaction rates for mesoscopic reaction-diffusion kinetics
**Authors:**
**Keywords:** None.
**Abstract:** The mesoscopic reaction-diffusion master equation (RDME) is a popular modeling framework frequently applied to stochastic reaction-diffusion kinetics in systems biology. The RDME is derived from assumptions about the underlying physical properties of the system, and it may produce unphysical results for models where those assumptions fail. In that case, other more comprehensive models are better suited, such as hard-sphere Brownian dynamics (BD). Although the RDME is a model in its own right, and not inferred from any specific microscale model, it proves useful to attempt to approximate a microscale model by a specific choice of mesoscopic reaction rates. In this paper we derive mesoscopic scale-dependent reaction rates by matching certain statistics of the RDME solution to statistics of the solution of a widely used microscopic BD model: the Smoluchowski model with a Robin boundary condition at the reaction radius of two molecules. We also establish fundamental limits on the range of
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**Journal:** Annual Reviews in Control
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.arcontrol.2014.09.001
Volume: 3.8E+001 Issue: 2.0E+000 First Page #: 155
Date Submitted: Date Published:
Publication Location:
**Article Title:** Modeling and analysis of networked control systems using stochastic hybrid systems
**Authors:**
**Keywords:** None.
**Abstract:** This paper aims at familiarizing the reader with Stochastic Hybrid Systems (SHSs) and enabling her to use these systems to model and analyze Networked Control Systems (NCSs). Towards this goal, we introduce two different models of SHSs and a set of theoretical tools for their analysis. In parallel with the presentation of the mathematical models and results, we provide a few simple examples that illustrate the use of SHSs to models NCSs.
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Volume: 8.1E+001 Issue: 6.0E+000 First Page #: 1949
Date Submitted: Date Published:
Publication Location:
**Article Title:** Oligopolyphenylenevinylene-Conjugated Oligoelectrolyte Membrane Insertion Molecules Selectively Disrupt Cell Envelopes of Gram-Positive Bacteria
**Authors:**
**Keywords:** None.
**Abstract:** The modification of microbial membranes to achieve biotechnological strain improvement with exogenous small molecules, such as oligopolyphenylenevinylene-conjugated oligoelectrolyte (OPV-COE) membrane insertion molecules (MIMs), is an emerging biotechnological field. Little is known about the interactions of OPV-COEs with their target, the bacterial envelope. We studied the toxicity of three previously reported OPV-COEs with a selection of Gram-negative and Gram-positive organisms and demonstrated that Gram-positive bacteria are more sensitive to OPV-COEs than Gram-negative bacteria. Transmission electron microscopy demonstrated that these MIMs disrupt microbial membranes and that this occurred to a much greater degree in Gram-positive organisms. We used a number of mutants to probe the nature of MIM interactions with the microbial envelope but were unable to align the membrane perturbation effects of these compounds to previously reported membrane disruption mechanisms of, for example
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**Journal:** International Journal of Hydrogen Energy
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Volume: 3.9E+001 Issue: 3.4E+001 First Page #: 19407
Date Submitted: Date Published:
Publication Location:
**Article Title:** Repression of hydrogen uptake using conjugated oligoelectrolytes in microbial electrolysis cells
**Authors:**
**Keywords:** Microbial electrolysis cell; Conjugated oligoelectrolytes; Hydrogen recycling; Hydrogen production; Methane inhibition
**Abstract:** DSBN+, a conjugated oligoelectrolyte (COE), was added to microbial electrolysis cells (MECs) to improve hydrogen recovery. The volume of hydrogen gas recovered in a fed-batch cycle of mixed culture MECs increased by 126× compared to controls (no COE addition), mainly by preventing the loss of hydrogen to methane production. Performance in pure culture MECs fed with Geobacter sulfurreducens increased by factors of 10.5 in terms of energy yield, 2.1 in COD removal, and 11.8 in hydrogen yield. Hydrogen gas recycling was reduced, and the volume of hydrogen gas recovered increased by 6.5× compared to controls. Minimal methane production and a lack of hydrogen gas uptake by G. sulfurreducens suggested that the COEs increased hydrogen recoveries by interfering with hydrogen uptake by hydrogenotrophic methanogens but also by exoelectrogenic bacteria. COEs may therefore be useful for inhibiting the activities of certain hydrogenases, although the mechanism of inhibition needs further investigat
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**Journal:** Accounts of Chemical Research
Publication Identifier Type: DOI Publication Identifier: 10.1021/ar500456w
Volume: 4.8E+001 Issue: 4.0E+000 First Page #: 911
Date Submitted: Date Published:
Publication Location:
**Article Title:** Integrated Electrochemical Microsystems for Genetic Detection of Pathogens at the Point of Care
**Authors:**
**Keywords:** None.
**Abstract:** The capacity to achieve rapid, sensitive, specific, quantitative, and multiplexed genetic detection of pathogens via a robust, portable, point-of-care platform could transform many diagnostic applications. And while contemporary technologies have yet to effectively achieve this goal, the advent of microfluidics provides a potentially viable approach to this end by enabling the integration of sophisticated multistep biochemical assays (e.g., sample preparation, genetic amplification, and quantitative detection) in a monolithic, portable device from relatively small biological samples. Integrated electrochemical sensors offer a particularly promising solution to genetic detection because they do not require optical instrumentation and are readily compatible with both integrated circuit and microfluidic technologies. Nevertheless, the development of generalizable microfluidic electrochemical platforms that integrate sample preparation and amplification as well as quantitative and multipl
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**Journal:** Stem Cells Translational Medicine
Publication Identifier Type: DOI Publication Identifier: 10.5966/sctm.2014-0038
Volume: 3.0E+000 Issue: 1.2E+001 First Page #: 1526
Date Submitted: Date Published:
Publication Location:
**Article Title:** Reprogramming Human Retinal Pigmented Epithelial Cells to Neurons Using Recombinant Proteins
**Authors:**
**Keywords:** Lineage reprogramming; Protein transduction; Retinal pigmented epithelium; Neuron; Cell penetrating peptide
**Abstract:** Somatic cells can be reprogrammed to an altered lineage by overexpressing specific transcription factors. To avoid introducing exogenous genetic material into the genome of host cells, cell-penetrating peptides can be used to deliver transcription factors into cells for reprogramming. Position-dependent C-end rule (CendR) cell- and tissue-penetrating peptides provide an alternative to the conventional cell-penetrating peptides, such as polyarginine. In this study, we used a prototypic, already active CendR peptide, RPARPAR, to deliver the transcription factor SOX2 to retinal pigmented epithelial (RPE) cells. We demonstrated that RPE cells can be directly reprogrammed to a neuronal fate by introduction of SOX2. Resulting neuronal cells expressed neuronal marker mRNAs and proteins and downregulated expression of RPE markers. Cells produced extensive neurites and developed synaptic machinery capable of dye uptake after depolarization with potassium. The RPARPAR-mediated delivery of SOX2 a
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**Journal:** Biomaterials
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.biomaterials.2015.06.006
Volume: 6.3E+001 Issue: 0 First Page #: 70
Date Submitted: Date Published:
Publication Location:
**Article Title:** Light-activated RNA interference in human embryonic stem cells
**Authors:**
**Keywords:** Human embryonic stem cells; Hollow gold nanoshell; RNA interference; TAT peptide; Near-infrared light; Differentiation
**Abstract:** We describe a near infrared (NIR) light-activated gene silencing method in undifferentiated human embryonic stem cell (hESC) using a plasmonic hollow gold nanoshell (HGN) as the siRNA carrier. Our modular biotin-streptavidin coupling strategy enables positively charged TAT-peptide to coat oligonucleotides-saturated nanoparticles as a stable colloid formation. TAT-peptide coated nanoparticles with dense siRNA loading show efficient penetration into a wide variety of hESC cell lines. The siRNA is freed from the nanoparticles and delivered to the cytosol by femtosecond pulses of NIR light with potentially exquisite spatial and temporal control. The effectiveness of this approach is shown by targeting GFP and Oct4 genes in undifferentiated hESC (H9). The accelerated expression of differentiation markers for all three germ layers resulting from Oct4 knockdown confirms that this method has no detectable adverse effects that limit the range of differentiation. This biocompatible and NIR laser
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**Journal:** Journal of Molecular Biology
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Volume: 4.27E+002 Issue: 6.0E+000 First Page #: 1278
Date Submitted: Date Published:
Publication Location:
**Article Title:** Functional Consequences of the Oligomeric Assembly of Proteorhodopsin
**Authors:**
**Keywords:** oligomers; seven-transmembrane proteins; electron paramagnetic resonance; protein–detergent complex
**Abstract:** The plasma membrane is the crucial interface between the cell and its exterior, packed with embedded proteins experiencing simultaneous protein–protein and protein–membrane interactions. A prominent example of cell membrane complexity is the assembly of transmembrane proteins into oligomeric structures, with potential functional consequences that are not well understood. From the study of proteorhodopsin (PR), a prototypical seven-transmembrane light-driven bacterial proton pump, we find evidence that the inter-protein interaction modulated by self-association yields functional changes observable from the protein interior. We also demonstrate that the oligomer is likely a physiologically relevant form of PR, as crosslinking of recombinantly expressed PR reveals an oligomeric population within the Escherichia coli membrane (putatively hexameric). Upon chromatographic isolation of oligomeric and monomeric PR in surfactant micelles, the oligomer exhibits distinctly different optical absor
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**Journal:** Chemical Communications
Publication Identifier Type: DOI Publication Identifier: 10.1039/C4CC03888F
Volume: 5.0E+001 Issue: 8.2E+001 First Page #: 12329
Date Submitted: Date Published:
Publication Location:
**Article Title:** Aptamer-based cell imaging reagents capable of fluorescence switching
**Authors:**
**Keywords:** None.
**Abstract:** We describe an aptamer-conjugated polydiacetylene imaging probe (ACP) that shows highly specific fluorescence switching upon binding to epithelial cancer cells that overexpress the tumor biomarker protein EpCAM (epithelial cell adhesion molecule) on their surface.
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**Journal:** Physical Review B
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevB.91.075436
Volume: 9.1E+001 Issue: 0 First Page #: 75436
Date Submitted: Date Published:
Publication Location:
**Article Title:** Charge transfer from delocalized excited states in a bulk heterojunction material
**Authors:**
**Keywords:** None.
**Abstract:** Charge generation in an organic photovoltaic blend was investigated using transient absorption spectroscopy. In films of pure electron donating material, subpicosecond spectral oscillations were observed and assigned to torsional modes associated with excited state relaxation and localization. These modes are systematically suppressed in the presence of fullerene, indicating that a significant fraction of charge transfer occurs prior to excited state localization.
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**Journal:** Annals of the New York Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1111/nyas.12640
Volume: 1.339E+003 Issue: 0 First Page #: 176
Date Submitted: Date Published:
Publication Location:
**Article Title:** Multimodal neuroimaging evidence linking memory and attention systems during visual search cued by context
**Authors:**
**Keywords:** contextual cueing; visual search; attention; memory; hippocampus; EEG; fMRI; multimodal imaging
**Abstract:** Visual search can be facilitated by the learning of spatial configurations that predict the location of a target among distractors. Neuropsychological and functional magnetic resonance imaging (fMRI) evidence implicates the medial temporal lobe (MTL) memory system in this contextual cueing effect, and electroencephalography (EEG) studies have identified the involvement of visual cortical regions related to attention. This work investigated two questions: (1) how memory and attention systems are related in contextual cueing; and (2) how these systems are involved in both short- and long-term contextual learning. In one session, EEG and fMRI data were acquired simultaneously in a contextual cueing task. In a second session conducted 1 week later, EEG data were recorded in isolation. The fMRI results revealed MTL contextual modulations that were correlated with short- and long-term behavioral context enhancements and attention-related effects measured with EEG. An fMRI-seeded EEG source a
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Volume: 6.0E+000 Issue: 9.0E+000 First Page #: 1431
Date Submitted: Date Published:
Publication Location:
**Article Title:** A synthetic strategy for the preparation of sub-100 nm functional polymer particles of uniform diameter
**Authors:**
**Keywords:** None.
**Abstract:** An amphiphilic block copolymer surfactant is used to impart peripheral surface functionality to polymer nanoparticles synthesized via emulsion polymerization. Particles ranged in size from ca.55 nm by SEM (ca. 82 nm by DLS) to just over 200 nm. Particles displaying latent functionality were readily functionalized directly after polymerization using a fluorescent dye.
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**Journal:** RSC Advances
Publication Identifier Type: DOI Publication Identifier: 10.1039/C4RA10339D
Volume: 5.0E+000 Issue: 2.1E+001 First Page #: 16549
Date Submitted: Date Published:
Publication Location:
**Article Title:** Robust transparent mesoporous silica membranes as matrices for colorimetric sensors
**Authors:**
**Keywords:** None.
**Abstract:** Transparent functionalized mesoporous silica membranes have been prepared with high surface areas ([similar]500 m2 g?1) that exhibit high sensitivities for colorimetric detection and sensing of dilute heavy-metal ions (e.g., Pb2+).
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**Journal:** Cognitive, Affective, & Behavioral Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.3758/s13415-015-0357-4
Volume: 1.5E+001 Issue: 3.0E+000 First Page #: 662
Date Submitted: Date Published:
Publication Location:
**Article Title:** Lateral posterior parietal activity during reality monitoring discriminations of memories of high and low perceptual vividness
**Authors:**
**Keywords:** Episodic memory . Inferior parietal . Parietalcortex . Recollection
**Abstract:** Regions of the lateral posterior parietal cortex (PPC) tend to be more active during recognition of previously studied items compared to correct rejection of unstudied items. Previously, we demonstrated that this effect is source-specific. While items that were encoded through visual perception elicited robust successful retrieval activity in the lateral PPC during a subsequent source memory test, items that were visually imagined did not elicit this effect. Memories of perceived events typically contain more perceptually-based contextual details than memories of imagined events. Therefore, source-based differences in lateral parietal activity might be due to a difference in the perceptual vividness of memories of perceived and imagined events. The goal of the present study was to test this hypothesis. Participants perceived and imagined items in both high and low perceptual vividness conditions. Experiment 1 demonstrated that memories for items encoded in the high vividness conditions
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Publication Identifier Type: DOI Publication Identifier: 10.1039/C4CP03197K
Volume: 1.6E+001 Issue: 3.8E+001 First Page #: 20436
Date Submitted: Date Published:
Publication Location:
**Article Title:** The conjugated oligoelectrolyte DSSN+ enables exceptional coulombic efficiency via direct electron transfer for anode-respiring Shewanella oneidensis MR-1—a mechanistic study
**Authors:**
**Keywords:** None.
**Abstract:** Shewanella oneidensis MR-1 was cultivated on lactate with poised graphite electrode acceptors (E = +0.2 V vs. Ag/AgCl) in order to explore the basis for sustained increases in anodic current output following the addition of the lipid-intercalating conjugated oligoelectrolyte (COE), 4,4?-bis(4?-(N,N-bis(6??-(N,N,N-trimethylammonium)hexyl)amino)-styryl)stilbene tetraiodide (DSSN+). Microbial cultures, which were spiked with DSSN+, exhibit a [similar]2.2-fold increase in charge collected, a [similar]3.1-fold increase in electrode colonization by S. oneidensis, and a [similar]1.7-fold increase in coulombic efficiency from 51 ± 10% to an exceptional 84 ± 7% without obvious toxicity effects. Direct microbial biofilm voltammetry reveals that DSSN+ rapidly and sustainably increases cytochrome-based direct electron transfer and subsequently increases flavin-based mediated electron transfer. Control experiments indicate that DSSN+ does not contribute to the current in the absence of bacteria.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Royal Society Interface
Publication Identifier Type: DOI Publication Identifier: 10.1098/rsif.2015.0054
Volume: 1.2E+001 Issue: 1.06E+002First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Accuracy of the Michaelis-Menten approximation when analysing effects of molecular noise
**Authors:**
**Keywords:** Michaelis –Menten, stochastic models, reaction – diffusion master equation
**Abstract:** Quantitative biology relies on the construction of accurate mathematical models, yet the effectiveness of these models is often predicated on making simplifying approximations that allow for direct comparisons with available experimental data. The Michaelis–Menten (MM) approximation is widely used in both deterministic and discrete stochastic models of intracellular reaction networks, owing to the ubiquity of enzymatic activity in cellular processes and the clear biochemical interpretation of its parameters. However, it is not well understood how the approximation applies to the discrete stochastic case or how it extends to spatially inhomogeneous systems. We study the behaviour of the discrete stochastic MM approximation as a function of system size and show that significant errors can occur for small volumes, in comparison with a corresponding mass-action system. We then explore some consequences of these results for quantitative modelling. One consequence is that fluctuation-induced
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Science
Publication Identifier Type: DOI Publication Identifier: 10.1002/advs.201500149
Volume: 0 Issue: 0 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** High-Throughput Contact Flow Lithography
**Authors:**
**Keywords:** contact flow lithography; encoded particles; high-throughput; hydrogel; microfluidics
**Abstract:** High-throughput fabrication of graphically encoded hydrogel microparticles is achieved by combining flow contact lithography in a multichannel microfluidic device and a high capacity 25 mm LED UV source. Production rates of chemically homogeneous particles are improved by two orders of magnitude. Additionally, the custom-built contact lithography instrument provides an affordable solution for patterning complex microstructures on surfaces.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Investigative Ophthalmology & Visual Science
Publication Identifier Type: DOI Publication Identifier: 10.1167/iovs.14-15835
Volume: 5.6E+001 Issue: 2.0E+000 First Page #: 1002
Date Submitted: Date Published:
Publication Location:
**Article Title:** Canonical/Beta-Catenin Wnt Pathway Activation Improves Retinal Pigmented Epithelium Derivation From Human Embryonic Stem Cells
**Authors:**
**Keywords:** retinal pigmented epithelium, human embryonic stem cells, age-related maculardegeneration, Wnt signaling, fluorescent reporters
**Abstract:** Purpose.: The purpose of this study was to better understand the role canonical/?-catenin Wnt signaling plays in the differentiation of human embryonic stem cells (hESCs) into retinal pigmented epithelium (RPE), with the goal of improving methods for derivation. Methods.: Fluorescent reporters were generated to monitor RPE differentiating from hESCs by using a previously described 14-day derivation protocol. Reporters were used to test the effects of the canonical/?-catenin Wnt pathway agonist CHIR99021 on differentiating RPE. Cells derived from differentiation studies were characterized by lineage-specific transcription factor expression, morphology, pigmentation, and function. The RPE derivation efficiency was determined from percentage positive PMEL17 expression. Results.: Fluorescent reporters mimicked expression of endogenous genes during 14-day differentiation to RPE. Analysis of Wnt pathway gene expression showed that the pathway components are expressed in differentiating RPE
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**Journal:** STEM CELLS
Publication Identifier Type: DOI Publication Identifier: 10.1002/stem.2010
Volume: 3.3E+001 Issue: 8.0E+000 First Page #: 2363
Date Submitted: Date Published:
Publication Location:
**Article Title:** Concise Review: Making Stem Cells Retinal: Methods for Deriving Retinal Pigment Epithelium and Implications for Patients With Ocular Disease
**Authors:**
**Keywords:** Retinal pigment epithelium;Embryonic stem cells; Induced pluripotent stem cells; Retinal diseases; Macular degeneration; Cell differentiation
**Abstract:** Stem cells provide a potentially unlimited source of cells for treating a plethora of human diseases. Regenerative therapies for retinal degenerative diseases are at the forefront of translation to the clinic, with stem cell-derived retinal pigment epithelium (RPE)-based treatments for age-related macular degeneration (AMD) already showing promise in human patients. Despite our expanding knowledge of stem cell biology, methods for deriving cells, including RPE have remained inefficient. Thus, there has been a push in recent years to develop more directed approaches to deriving cells for therapy. In this concise review, we summarize recent efforts that have been successful in improving RPE derivation efficiency by directing differentiation from human pluripotent stem cells using developmental cues important for normal RPE specification and maturation in vivo. In addition, potential obstacles for clinical translation are discussed. Finally, we review how derivation of RPE from human indu
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** NeuroImage
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2014.10.058
Volume: 1.05E+002 Issue: 0 First Page #: 145
Date Submitted: Date Published:
Publication Location:
**Article Title:** Out of control: Diminished prefrontal activity coincides with impaired motor performance due to choking under pressure
**Authors:**
**Keywords:** None.
**Abstract:** There are three non-exclusive theoretical explanations for the paradoxical collapse of performance due to large financial incentives. It has been proposed that “choking under pressure” is either due to distraction, interference via an increase in top-down control and performance monitoring, or excessive levels of arousal in the face of large losses. Given the known neural architecture involved in executive control and reward, we used fMRI of human participants during incentivized motor performance to provide evidence to support and/or reconcile these competing models in a visuomotor task. We show that the execution of a pre-trained motor task during neuroimaging is impaired by high rewards. BOLD activity occurring prior to movement onset is increased in dorsolateral prefrontal cortex and functional connectivity between this region and motor cortex is likewise increased just prior to choking. However, the extent of this increase in functional connectivity is inversely related to a parti
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**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1401883111
Volume: 1.11E+002 Issue: 3.3E+001 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Robust efficiency and actuator saturation explain healthy heart rate control and variability
**Authors:**
**Keywords:** system identification; optimal control; respiratory sinus arrhythmia
**Abstract:** The correlation of healthy states with heart rate variability (HRV) using time series analyses is well documented. Whereas these studies note the accepted proximal role of autonomic nervous system balance in HRV patterns, the responsible deeper physiological, clinically relevant mechanisms have not been fully explained. Using mathematical tools from control theory, we combine mechanistic models of basic physiology with experimental exercise data from healthy human subjects to explain causal relationships among states of stress vs. health, HR control, and HRV, and more importantly, the physiologic requirements and constraints underlying these relationships. Nonlinear dynamics play an important explanatory role—most fundamentally in the actuator saturations arising from unavoidable tradeoffs in robust homeostasis and metabolic efficiency. These results are grounded in domain-specific mechanisms, tradeoffs, and constraints, but they also illustrate important, universal properties of comp
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Communications
Publication Identifier Type: DOI Publication Identifier: 10.1038/ncomms5120
Volume: 5.0E+000 Issue: 4.12E+003 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Inertio-elastic focusing of bioparticles in microchannels at high throughput
**Authors:**
**Keywords:** None.
**Abstract:** Controlled manipulation of particles from very large volumes of fluid at high throughput is critical for many biomedical, environmental and industrial applications. One promising approach is to use microfluidic technologies that rely on fluid inertia or elasticity to drive lateral migration of particles to stable equilibrium positions in a microchannel. Here, we report on a hydrodynamic approach that enables deterministic focusing of beads, mammalian cells and anisotropic hydrogel particles in a microchannel at extremely high flow rates. We show that on addition of micromolar concentrations of hyaluronic acid, the resulting fluid viscoelasticity can be used to control the focal position of particles at Reynolds numbers up to Re?10,000 with corresponding flow rates and particle velocities up to 50?ml?min?1 and 130?m?s?1. This study explores a previously unattained regime of inertio-elastic fluid flow and demonstrates bioparticle focusing at flow rates that are the highest yet achieved.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physics of Fluids
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4901330
Volume: 2.6E+001 Issue: 0 First Page #: 112002
Date Submitted: Date Published:
Publication Location:
**Article Title:** Electrophoretic mobility of a spherical nanoparticle in a nanochannel
**Authors:**
**Keywords:** None.
**Abstract:** Numerical simulation is used to calculate accurately the electrophoretic mobility of a charged spherical nanoparticle confined in a nanochannel, under a weakly applied electric field. Classic models for electrophoretic mobility are valid only in the linear regime of small particle zeta potential, and for an unbounded fluid domain. However, these models fail to predict the electrophoretic mobility measured experimentally in bounded nanochannels. We adopt asymptotically expanded formulations and solve the fully coupled equations on a 3D finite element domain. Factors affecting particle mobility include electrolyte concentration, channel size, and zeta potentials on both the particle surface and channel walls. Specifically, spherical particles are examined with diameters 2a = 10 and 50 nm, in a 100 nm high channel. The non-dimensional electric double layers were varied between 0.1 < ?a < 100. The results indicate that the mobility of a particle located at the nanochannel centerline agrees
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1003712
Volume: 1.0E+001 Issue: 1.0E+001 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Resolving Anatomical and Functional Structure in Human Brain Organization: Identifying Mesoscale Organization in Weighted Network Representations
**Authors:**
**Keywords:** None.
**Abstract:** Human brain anatomy and function display a combination of modular and hierarchical organization, suggesting the importance of both cohesive structures and variable resolutions in the facilitation of healthy cognitive processes. However, tools to simultaneously probe these features of brain architecture require further development. We propose and apply a set of methods to extract cohesive structures in network representations of brain connectivity using multi-resolution techniques. We employ a combination of soft thresholding, windowed thresholding, and resolution in community detection, that enable us to identify and isolate structures associated with different weights. One such mesoscale structure is bipartivity, which quantifies the extent to which the brain is divided into two partitions with high connectivity between partitions and low connectivity within partitions. A second, complementary mesoscale structure is modularity, which quantifies the extent to which the brain is divided
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**Journal:** Journal of Vacuum Science and Technology B
Publication Identifier Type: DOI Publication Identifier: 10.1116/1.4895966
Volume: 3.2E+001 Issue: 5.0E+000 First Page #: 51213
Date Submitted: Date Published:
Publication Location:
**Article Title:** Simple colloidal lithography method to fabricate large-area moth-eye antireflective structures on Si, Ge, and GaAs for IR applications
**Authors:**
**Keywords:** None.
**Abstract:** A two-step colloidal lithography process (Langmuir–Blodgett dip coating + reactive ion etching) was developed to fabricate single and double-sided moth-eye structures in Si, Ge, and GaAs for antireflection applications in the IR. Large increases in transmittance were obtained in all three material platforms (up to 97% single-side and 91% absolute transmittance) over the ??=?4?20+??m region. Effective medium theory and the transfer matrix method were used to predict IR optical response of moth-eye substrates as well as investigate the effect of protuberance shape on antireflectance behavior. Overall, it is demonstrated that colloidal lithography and etching provide an easy and generic way to synthesize moth-eyes in different IR material platforms.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Optics Letters
Publication Identifier Type: DOI Publication Identifier: 10.1364/OL.40.001512
Volume: 4.0E+001 Issue: 7.0E+000 First Page #: 1512
Date Submitted: Date Published:
Publication Location:
**Article Title:** Enhancing near-infrared light absorption in PtSi thin films for Schottky barrier IR detectors using moth-eye surface structures
**Authors:**
**Keywords:** None.
**Abstract:** Si-based Schottky barrier infrared detectors typically use thin (1–10 nm) PtSi or Pd2Si layers grown on Si substrates as an absorption medium. Herein, we demonstrate the use of sub-wavelength moth-eye (ME) structures on the Si substrate of such detectors to enhance absorption of near infrared (NIR) light in the active PtSi layer to increase detector efficiency. Absorbance enhancement of 70%–200% in the ? 1–2.5 ?m range is demonstrated in crystalline PtSi films grown via electron beam evaporation of Pt and subsequent vacuum annealing. Low total reflectance (<10%) was measured for ME films, demonstrating the efficacy of the ME effect. Effective mediumapproximation calculations show that absorption enhancement at short wavelengths is partially due to forward scattering, which increases the effective optical path length in PtSi. Results also suggest that ME structuring of substrates is a general and low-cost method to enhance absorption in a variety of IR material platforms used for back-
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**Journal:** Brain Research
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.brainres.2015.02.016
Volume: 1.606E+003 Issue: 0 First Page #: 86
Date Submitted: Date Published:
Publication Location:
**Article Title:** Neural evidence reveals the rapid effects of reward history on selective attention
**Authors:**
**Keywords:** Attention; Reward; ERP
**Abstract:** Selective attention is often framed as being primarily driven by two factors: task-relevance and physical salience. However, factors like selection and reward history, which are neither currently task-relevant nor physically salient, can reliably and persistently influence visual selective attention. The current study investigated the nature of the persistent effects of irrelevant, physically non-salient, reward-associated features. These features affected one of the earliest reliable neural indicators of visual selective attention in humans, the P1 event-related potential, measured one week after the reward associations were learned. However, the effects of reward history were moderated by current task demands. The modulation of visually evoked activity supports the hypothesis that reward history influences the innate salience of reward associated features, such that even when no longer relevant, nor physically salient, these features have a rapid, persistent, and robust effect on ear
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Attention, Perception, & Psychophysics
Publication Identifier Type: DOI Publication Identifier: 10.3758/s13414-015-0851-3
Volume: 7.7E+001 Issue: 5.0E+000 First Page #: 1515
Date Submitted: Date Published:
Publication Location:
**Article Title:** Irrelevant reward and selection histories have different influences on task-relevant attentional selection
**Authors:**
**Keywords:** Selective attention; Attentional capture; Reward
**Abstract:** Task-relevant and physically salient features influence visual selective attention. In the present study, we investigated the influence of task-irrelevant and physically nonsalient reward-associated features on visual selective attention. Two hypotheses were tested: One predicts that the effects of target-defining task-relevant and task-irrelevant features interact to modulate visual selection; the other predicts that visual selection is determined by the independent combination of relevant and irrelevant feature effects. These alternatives were tested using a visual search task that contained multiple targets, placing a high demand on the need for selectivity, and that was data-limited and required unspeeded responses, emphasizing early perceptual selection processes. One week prior to the visual search task, participants completed a training task in which they learned to associate particular colors with a specific reward value. In the search task, the reward-associated colors were pr
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**Journal:** Frontiers in Human Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.3389/fnhum.2014.00839
Volume: 8.0E+000 Issue: 8.39E+002 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Divergent hemispheric reasoning strategies: reducing uncertainty versus resolving inconsistency
**Authors:**
**Keywords:** reasoning; split-brain; lateralization; delusions; inference making
**Abstract:** Converging lines of evidence from diverse research domains suggest that the left and right hemispheres play distinct, yet complementary, roles in inferential reasoning. Here, we review research on split-brain patients, brain-damaged patients, delusional patients, and healthy individuals that suggests that the left hemisphere tends to create explanations, make inferences, and bridge gaps in information, while the right hemisphere tends to detect conflict, update beliefs, support mental set-shifts, and monitor and inhibit behavior. Based on this evidence, we propose that the left hemisphere specializes in creating hypotheses and representing causality, while the right hemisphere specializes in evaluating hypotheses, and rejecting those that are implausible or inconsistent with other evidence. In sum, we suggest that, in the domain of inferential reasoning, the left hemisphere strives to reduce uncertainty while the right hemisphere strives to resolve inconsistency. The hemispheres' diver
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**Journal:** ACS Synthetic Biology
Publication Identifier Type: DOI Publication Identifier: 10.1021/sb500358y
Volume: 3.0E+000 Issue: 1.2E+001 First Page #: 875
Date Submitted: Date Published:
Publication Location:
**Article Title:** Synthetic Biology of Multicellular Systems: New Platforms and Applications for Animal Cells and Organisms
**Authors:**
**Keywords:** None.
**Abstract:** Like life itself, synthetic biology began with unicellular organisms. Early synthetic biologists built genetic circuits in model prokaryotes and yeast because of their relative biological simplicity and ease of genetic manipulation. With superior genetic tools, faster generation times, and better-understood endogenous gene expression machinery, prokaryotes and yeast were (and remain) appealing hosts for the engineering of synthetic systems. Now in its second decade, synthetic biology in unicellular organisms has produced myriad synthetic genetic circuits, a number of industrial applications, and fundamental new biological insights unlikely to have emerged from nonsynthetic approaches.
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**Journal:** Proceedings of the National Academy of Sciences
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Volume: 1.11E+002 Issue: 3.6E+001 First Page #: 13034
Date Submitted: Date Published:
Publication Location:
**Article Title:** Directed evolution of a far-red fluorescent rhodopsin
**Authors:**
**Keywords:** optogenetics; opsins; bioelectricity; voltage sensor; near-infrared
**Abstract:** Microbial rhodopsins are a diverse group of photoactive transmembrane proteins found in all three domains of life. A member of this protein family, Archaerhodopsin-3 (Arch) of halobacterium Halorubrum sodomense, was recently shown to function as a fluorescent indicator of membrane potential when expressed in mammalian neurons. Arch fluorescence, however, is very dim and is not optimal for applications in live-cell imaging. We used directed evolution to identify mutations that dramatically improve the absolute brightness of Arch, as confirmed biochemically and with live-cell imaging (in Escherichia coli and human embryonic kidney 293 cells). In some fluorescent Arch variants, the pKa of the protonated Schiff-base linkage to retinal is near neutral pH, a useful feature for voltage-sensing applications. These bright Arch variants enable labeling of biological membranes in the far-red/infrared and exhibit the furthest red-shifted fluorescence emission thus far reported for a fluorescent pr
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**Journal:** Integrative Biology
Publication Identifier Type: DOI Publication Identifier: 10.1039/C4IB00294F
Volume: 7.0E+000 Issue: 8.0E+000 First Page #: 904
Date Submitted: Date Published:
Publication Location:
**Article Title:** Identification of drug-specific pathways based on gene expression data: application to drug induced lung injury
**Authors:**
**Keywords:** None.
**Abstract:** Identification of signaling pathways that are functional in a specific biological context is a major challenge in systems biology, and could be instrumental to the study of complex diseases and various aspects of drug discovery. Recent approaches have attempted to combine gene expression data with prior knowledge of protein connectivity in the form of a PPI network, and employ computational methods to identify subsets of the protein–protein-interaction (PPI) network that are functional, based on the data at hand. However, the use of undirected networks limits the mechanistic insight that can be drawn, since it does not allow for following mechanistically signal transduction from one node to the next. To address this important issue, we used a directed, signaling network as a scaffold to represent protein connectivity, and implemented an Integer Linear Programming (ILP) formulation to model the rules of signal transduction from one node to the next in the network. We then optimized the
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**Journal:** Science
Publication Identifier Type: DOI Publication Identifier: 10.1126/science.1255908
Volume: 3.45E+002 Issue: 6.202E+00First Page #: 1322
Date Submitted: Date Published:
Publication Location:
**Article Title:** Strong, lightweight, and recoverable three-dimensional ceramic nanolattices
**Authors:**
**Keywords:** None.
**Abstract:** Ceramics have some of the highest strength- and stiffness-to-weight ratios of any material but are suboptimal for use as structural materials because of their brittleness and sensitivity to flaws.We demonstrate the creation of structural metamaterials composed of nanoscale ceramics that are simultaneously ultralight, strong, and energy-absorbing and can recover their original shape after compressions in excess of 50% strain. Hollow-tube alumina nanolattices were fabricated using two-photon lithography, atomic layer deposition, and oxygen plasma etching. Structures were made with wall thicknesses of 5 to 60 nanometers and densities of 6.3 to 258 kilograms per cubic meter. Compression experiments revealed that optimizing the wall thickness-to-radius ratio of the tubes can suppress brittle fracture in the constituent solid in favor of elastic shell buckling, resulting in ductile-like deformation and recoverability.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review Letters
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevLett.113.097701
Volume: 1.13E+002 Issue: 9.0E+000 First Page #: 97701
Date Submitted: Date Published:
Publication Location:
**Article Title:** Enhanced Charging Kinetics of Porous Electrodes: Surface Conduction as a Short-Circuit Mechanism
**Authors:**
**Keywords:** None.
**Abstract:** We use direct numerical simulations of the Poisson-Nernst-Planck equations to study the charging kinetics of porous electrodes and to evaluate the predictive capabilities of effective circuit models, both linear and nonlinear. The classic transmission line theory of de Levie holds for general electrode morphologies, but only at low applied potentials. Charging dynamics are slowed appreciably at high potentials, yet not as significantly as predicted by the nonlinear transmission line model of Biesheuvel and Bazant. We identify surface conduction as a mechanism which can effectively “short circuit” the high-resistance electrolyte in the bulk of the pores, thus accelerating the charging dynamics and boosting power densities. Notably, the boost in power density holds only for electrode morphologies with continuous conducting surfaces in the charging direction.
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Publication Identifier Type: DOI Publication Identifier: 10.1038/nbt.3044
Volume: 3.2E+001 Issue: 1.2E+001 First Page #: 1268
Date Submitted: Date Published:
Publication Location:
**Article Title:** A load driver device for engineering modularity in biological networks
**Authors:**
**Keywords:** None.
**Abstract:** The behavior of gene modules in complex synthetic circuits is often unpredictable. After joining modules to create a circuit, downstream elements (such as binding sites for a regulatory protein) apply a load to upstream modules that can negatively affect circuit function. Here we devised a genetic device named a load driver that mitigates the impact of load on circuit function, and we demonstrate its behavior in Saccharomyces cerevisiae. The load driver implements the design principle of timescale separation: inclusion of the load driver's fast phosphotransfer processes restores the capability of a slower transcriptional circuit to respond to time-varying input signals even in the presence of substantial load. Without the load driver, we observed circuit behavior that suffered from a 76% delay in response time and a 25% decrease in system bandwidth due to load. With the addition of a load driver, circuit performance was almost completely restored. Load drivers will serve as fundamental
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nano Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/nl504676v
Volume: 1.5E+001 Issue: 5.0E+000 First Page #: 2917
Date Submitted: Date Published:
Publication Location:
**Article Title:** Improving the Capacity of Sodium Ion Battery Using a Virus-Templated Nanostructured Composite Cathode
**Authors:**
**Keywords:** Sodium ion battery; amorphous FePO4; biotemplated active material; SWCNT; high-power rechargeable battery
**Abstract:** In this work we investigated an energy-efficient biotemplated route to synthesize nanostructured FePO4 for sodium-based batteries. Self-assembled M13 viruses and single wall carbon nanotubes (SWCNTs) have been used as a template to grow amorphous FePO4 nanoparticles at room temperature (the active composite is denoted as Bio-FePO4-CNT) to enhance the electronic conductivity of the active material. Preliminary tests demonstrate a discharge capacity as high as 166 mAh/g at C/10 rate, corresponding to composition Na0.9FePO4, which along with higher C-rate tests show this material to have the highest capacity and power performance reported for amorphous FePO4 electrodes to date.
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Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0108624
Volume: 9.0E+000 Issue: 9.0E+000 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Prioritisation and Network Analysis of Crohn's Disease Susceptibility Genes
**Authors:**
**Keywords:** None.
**Abstract:** Recent Genome-Wide Association Studies (GWAS) have revealed numerous Crohn's disease susceptibility genes and a key challenge now is in understanding how risk polymorphisms in associated genes might contribute to development of this disease. For a gene to contribute to disease phenotype, its risk variant will likely adversely communicate with a variety of other gene products to result in dysregulation of common signaling pathways. A vital challenge is to elucidate pathways of potentially greatest influence on pathological behaviour, in a manner recognizing how multiple relevant genes may yield integrative effect. In this work we apply mathematical analysis of networks involving the list of recently described Crohn's susceptibility genes, to prioritise pathways in relation to their potential development of this disease. Prioritisation was performed by applying a text mining and a diffusion based method (GRAIL, GPEC). Prospective biological significance of the resulting prioritised list
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** International Journal of Crashworthiness
Publication Identifier Type: DOI Publication Identifier: 10.1080/13588265.2015.1038866
Volume: 2.0E+001 Issue: 5.0E+000 First Page #: 483
Date Submitted: Date Published:
Publication Location:
**Article Title:** A concept for mitigating head injury under translational blunt impact
**Authors:**
**Keywords:** head injury, foams, impact
**Abstract:** This study assesses a bi-layer composite concept for mitigating the severity of injury due to translational blunt impact of an unprotected head at moderately high speeds. The concept comprises crushable foam and a stiff face-sheet on the impacting face. Approximate analytical models for acceleration–time histories of prototypical impact scenarios are used to guide the design. The key design variables probed experimentally are the crushing strength of the underlying foam and the tile size. The efficacy of the composite systems and the foams alone is ascertained through a series of drop impact tests with an instrumented head-form at a representative impact velocity (6.7 m/s, 15 mph), using three commercial viscoelastic foams, with and without face-sheets. The measurements are analysed in terms of five performance metrics: the peak acceleration, the Gadd severity index (GSI), the head injury criterion (HIC), the skull fracture correlate (SFC) and the head impact power (HIP). The experimen
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**Journal:** IEEE Transactions on Automatic Control
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Volume: 6.0E+001 Issue: 6.0E+000 First Page #: 1710
Date Submitted: Date Published:
Publication Location:
**Article Title:** Synchronization of Pulse-Coupled Oscillators on (Strongly) Connected Graphs
**Authors:**
**Keywords:** Multi-agent systems; networks; pulse-coupled oscillators; synchronization
**Abstract:** The synchronization of pulse-coupled oscillators (PCOs) interacting on general (strongly) connected graphs is addressed. It is shown that the network synchronizes if the phases are contained in an arc of length less than ?, for every (strongly) connected interaction topology. Moreover, global synchronization is feasible in the all-to-all, strongly rooted, and connected bidirectional cases. Examples, counter-examples, and numerical simulations are given to illustrate the analytical findings.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Automatica
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.automatica.2014.10.111
Volume: 5.2E+001 Issue: 0 First Page #: 202
Date Submitted: Date Published:
Publication Location:
**Article Title:** Global synchronization of pulse-coupled oscillators interacting on cycle graphs
**Authors:**
**Keywords:** Pulse-coupled oscillators; Synchronization; Hybrid systems; Phase response curve; Cycle graphs
**Abstract:** The importance of pulse-coupled oscillators (PCOs) in biology and engineering has motivated research to understand basic properties of PCO networks. Despite the large body of work addressing PCOs, a global synchronization result for networks that are more general than all-to-all connected is still unavailable. In this paper we address global synchronization of PCO networks described by cycle graphs. It is shown for the bidirectional cycle case that as the number of oscillators in the cycle grows, the coupling strength must be increased in order to guarantee synchronization for arbitrary initial conditions. For the unidirectional cycle case, the strongest coupling cannot ensure global synchronization yet a refractory period in the phase response curve is sufficient to enable global synchronization. Analytical findings are confirmed by numerical simulations.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nano Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/nl502078m
Volume: 1.4E+001 Issue: 8.0E+000 First Page #: 4837
Date Submitted: Date Published:
Publication Location:
**Article Title:** M13 Virus-Directed Synthesis of Nanostructured Metal Oxides for Lithium–Oxygen Batteries
**Authors:**
**Keywords:** Biotemplation; Li-oxygen battery; M13 virus; nanowire synthesis; cobalt manganese oxides; composite structure
**Abstract:** Transition metal oxides are promising electrocatalysts for both water oxidations and metal–air batteries. Here, we report the virus-mediated synthesis of cobalt manganese oxide nanowires (NWs) to fabricate high capacity Li–O2 battery electrodes. Furthermore, we hybridized Ni nanoparticles (NPs) on bio Co3O4 NWs to improve the round trip efficiency as well as the cycle life of Li–O2 batteries. This biomolecular directed synthesis method is expected to provide a selection platform for future energy storage electrocatalysts.
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**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/ja5079464
Volume: 1.36E+002 Issue: 4.2E+001 First Page #: 15010
Date Submitted: Date Published:
Publication Location:
**Article Title:** Synthetic Aptamer-Polymer Hybrid Constructs for Programmed Drug Delivery into Specific Target Cells
**Authors:**
**Keywords:** None.
**Abstract:** Viruses have evolved specialized mechanisms to efficiently transport nucleic acids and other biomolecules into specific host cells. They achieve this by performing a coordinated series of complex functions, resulting in delivery that is far more efficient than existing synthetic delivery mechanisms. Inspired by these natural systems, we describe a process for synthesizing chemically defined molecular constructs that likewise achieve targeted delivery through a series of coordinated functions. We employ an efficient “click chemistry” technique to synthesize aptamer-polymer hybrids (APHs), coupling cell-targeting aptamers to block copolymers that secure a therapeutic payload in an inactive state. Upon recognizing the targeted cell-surface marker, the APH enters the host cell via endocytosis, at which point the payload is triggered to be released into the cytoplasm. After visualizing this process with coumarin dye, we demonstrate targeted killing of tumor cells with doxorubicin. Important
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Communications
Publication Identifier Type: DOI Publication Identifier: 10.1038/ncomms8070
Volume: 6.0E+000 Issue: 7.07E+003First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** High-speed multiple-mode mass-sensing resolves dynamic nanoscale mass distributions
**Authors:**
**Keywords:** None.
**Abstract:** Simultaneously measuring multiple eigenmode frequencies of nanomechanical resonators can determine the position and mass of surface-adsorbed proteins, and could ultimately reveal the mass tomography of nanoscale analytes. However, existing measurement techniques are slow (<1?Hz bandwidth), limiting throughput and preventing use with resonators generating fast transient signals. Here we develop a general platform for independently and simultaneously oscillating multiple modes of mechanical resonators, enabling frequency measurements that can precisely track fast transient signals within a user-defined bandwidth that exceeds 500?Hz. We use this enhanced bandwidth to resolve signals from multiple nanoparticles flowing simultaneously through a suspended nanochannel resonator and show that four resonant modes are sufficient for determining their individual position and mass with an accuracy near 150?nm and 40 attograms throughout their 150-ms transit. We envision that our method can be read
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**Journal:** ACS Nano
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsnano.5b00750
Volume: 9.0E+000 Issue: 4.0E+000 First Page #: 4328
Date Submitted: Date Published:
Publication Location:
**Article Title:** Rapid Identification by Surface-Enhanced Raman Spectroscopy of Cancer Cells at Low Concentrations Flowing in a Microfluidic Channel
**Authors:**
**Keywords:** SERS; microfluidics; cancer diagnostics; multiplexed; chemometrics
**Abstract:** Reliable identification and collection of cells from bodily fluids is of growing interest for monitoring patient response to therapy and for early detection of disease or its recurrence. We describe a detection platform that combines microfluidics with surface-enhanced Raman spectroscopy (SERS) for the identification of individual mammalian cells continuously flowing in a microfluidics channel. A mixture of cancerous and noncancerous prostate cells was incubated with SERS biotags (SBTs) developed and synthesized by us, then injected into a flow-focused microfluidic channel, which forces the cells into a single file. The spectrally rich SBTs are based on a silver nanoparticle dimer core labeled with a Raman-active small reporter molecule paired with an affinity biomolecule, providing a unique barcode whose presence in a composite SERS spectrum can be deconvoluted. Individual cancer cells passing through the focused laser beam were correctly identified among a proportionally larger numbe
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Langmuir
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.langmuir.5b00300
Volume: 3.1E+001 Issue: 1.5E+001 First Page #: 4402
Date Submitted: Date Published:
Publication Location:
**Article Title:** Direct Measurements of Colloidal Solvophoresis under Imposed Solvent and Solute Gradients
**Authors:**
**Keywords:** None.
**Abstract:** We describe a microfluidic system that enables direct visualization and measurement of diffusiophoretic migration of colloids in response to imposed solution gradients. Such measurements have proven difficult or impossible in macroscopic systems due to difficulties in establishing solution gradients that are sufficiently strong yet hydrodynamically stable. We validate the system with measurements of the concentration-dependent diffusiophoretic mobility of polystyrene colloids in NaCl gradients, confirming that diffusiophoretic migration velocities are proportional to gradients in the logarithm of electrolyte concentration. We then perform the first direct measurement of the concentration-dependent “solvophoretic” mobility of colloids in ethanol–water gradients, whose dependence on concentration and gradient strength was not known either theoretically or experimentally, but which our measurements reveal to be proportional to the gradient in the logarithm of ethanol mole fraction. Finall
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Lab on a Chip
Publication Identifier Type: DOI Publication Identifier: 10.1039/C4LC00141A
Volume: 1.4E+001 Issue: 1.7E+001 First Page #: 3300
Date Submitted: Date Published:
Publication Location:
**Article Title:** Induced charge electroosmosis micropumps using arrays of Janus micropillars
**Authors:**
**Keywords:** None.
**Abstract:** We report on a microfluidic AC-driven electrokinetic pump that uses Induced Charge Electro-Osmosis (ICEO) to generate on-chip pressures. ICEO flows occur when a bulk electric field polarizes a metal object to induce double layer formation, then drives electroosmotic flow. A microfabricated array of metal–dielectric Janus micropillars breaks the symmetry of ICEO flow, so that an AC electric field applied across the array drives ICEO flow along the length of the pump. When pumping against an external load, a pressure gradient forms along the pump length. The design was analyzed theoretically with the reciprocal theorem. The analysis reveals a maximum pressure and flow rate that depend on the ICEO slip velocity and micropillar geometry. We then fabricate and test the pump, validating our design concept by demonstrating non-local pressure driven flow using local ICEO slip flows. We varied the voltage, frequency, and electrolyte composition, measuring pump pressures of 15–150 Pa. We use the
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Stem Cells Translational Medicine
Publication Identifier Type: DOI Publication Identifier: 10.5966/sctm.2014-0179
Volume: 4.0E+000 Issue: 2.0E+000 First Page #: 165
Date Submitted: Date Published:
Publication Location:
**Article Title:** Defined Culture of Human Embryonic Stem Cells and Xeno-Free Derivation of Retinal Pigmented Epithelial Cells on a Novel, Synthetic Substrate
**Authors:**
**Keywords:** Human embryonic stem cells; Retinal pigmented epithelium; Synthemax II-SC substrate; Age-related macular degeneration; Parylene-C
**Abstract:** Age-related macular degeneration (AMD), a leading cause of blindness, is characterized by the death of the retinal pigmented epithelium (RPE), which is a monolayer posterior to the retina that supports the photoreceptors. Human embryonic stem cells (hESCs) can generate an unlimited source of RPE for cellular therapies, and clinical trials have been initiated. However, protocols for RPE derivation using defined conditions free of nonhuman derivatives (xeno-free) are preferred for clinical translation. This avoids exposing AMD patients to animal-derived products, which could incite an immune response. In this study, we investigated the maintenance of hESCs and their differentiation into RPE using Synthemax II-SC, which is a novel, synthetic animal-derived component-free, RGD peptide-containing copolymer compliant with good manufacturing practices designed for xeno-free stem cell culture. Cells on Synthemax II-SC were compared with cultures grown with xenogeneic and xeno-free control subs
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**Journal:** Control Engineering Practice
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.conengprac.2014.07.007
Volume: 3.2E+001 Issue: 0 First Page #: 28
Date Submitted: Date Published:
Publication Location:
**Article Title:** Vision-based target tracking with a small UAV: Optimization-based control strategies
**Authors:**
**Keywords:** Unmanned aerial vehicle; Target tracking; Motion planning; Autonomous vehicle
**Abstract:** This paper considers the problem of a small, fixed-wing UAV equipped with a gimbaled camera autonomously tracking an unpredictable moving ground vehicle. Thus, the UAV must maintain close proximity to the ground target and simultaneously keep the target in its camera?s visibility region. To achieve this objective robustly, two novel optimization-based control strategies are developed. The first assumes an evasive target motion while the second assumes a stochastic target motion. The resulting optimal control policies have been successfully flight tested, thereby demonstrating the efficacy of both approaches in a real-world implementation and highlighting the advantages of one approach over the other.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Langmuir
Publication Identifier Type: DOI Publication Identifier: 10.1021/la504511j
Volume: 3.1E+001 Issue: 1.2E+001 First Page #: 3577
Date Submitted: Date Published:
Publication Location:
**Article Title:** Quantitative Characterization of the Colloidal Stability of Metallic Nanoparticles Using UV–vis Absorbance Spectroscopy
**Authors:**
**Keywords:** None.
**Abstract:** Plasmonic nanoparticles are used in a wide variety of applications over a broad array of fields including medicine, energy, and environmental chemistry. The continued successful development of this material class requires the accurate characterization of nanoparticle stability for a variety of solution-based conditions. Although many characterization methods exists, there is an absence of a unified, quantitative means for assessing the colloidal stability of plasmonic nanoparticles. We present the particle instability parameter (PIP) as a robust, quantitative, and generalizable characterization technique based on UV–vis absorbance spectroscopy to characterize colloidal instability. We validate PIP performance with both traditional and alternative characterization methods by measuring gold nanorod instability in response to different salt (NaCl) concentrations. We further measure gold nanorod stability as a function of solution pH, salt, and buffer (type and concentration), nanoparticle
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**Journal:** Journal of Polymer Science Part B: Polymer Physics
Publication Identifier Type: DOI Publication Identifier: 10.1002/polb.23458
Volume: 5.2E+001 Issue: 9.0E+000 First Page #: 611
Date Submitted: Date Published:
Publication Location:
**Article Title:** Progressive transition from resonant to diffuse reflection in anisotropic colloidal films
**Authors:**
**Keywords:** biomimetic; coatings; self-assembly; thin films
**Abstract:** The synthesis and characterization of highly ordered three-dimensional photonic crystals have been the subjects of intense study over the past two decades due to the unique ability of these structures to control light at the nanoscale. Building on that work in recent years, increasing interest is now focused on the unique optical properties of disordered and quasi-ordered photonic structures. We present a study of the effects of shape anisotropy and disorder on the specular reflection properties of polymer-based colloidal films comprised of rod-shaped subunits of varying aspect ratio. We characterize the specular reflectance properties of these films as a function of their increasing levels of disorder, demonstrating progressive transition from resonant reflection to diffuse reflection. The onset of the diffuse reflection is governed by particle size.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Automatica
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.automatica.2014.10.012
Volume: 5.0E+001 Issue: 1.1E+001 First Page #: 2822
Date Submitted: Date Published:
Publication Location:
**Article Title:** Quadratic control of stochastic hybrid systems with renewal transitions
**Authors:**
**Keywords:** Markov renewal processes; Semi-Markov processes; Optimal control; Stochastic hybrid systems; Renewal transitions
**Abstract:** We study the quadratic control of a class of stochastic hybrid systems with linear continuous dynamics for which the lengths of time that the system stays in each mode are independent random variables with given probability distribution functions. We derive a condition for finding the optimal feedback policy that minimizes a discounted infinite horizon cost. We show that the optimal cost is the solution to a set of differential equations with unknown boundary conditions. Furthermore, we provide a recursive algorithm for computing the optimal cost and the optimal feedback policy. The applicability of our result is illustrated through a numerical example, motivated by stochastic gene regulation in biology.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Origins of Life and Evolution of Biospheres
Publication Identifier Type: DOI Publication Identifier: 10.1007/s11084-014-9392-3
Volume: 4.4E+001 Issue: 4.0E+000 First Page #: 319
Date Submitted: Date Published:
Publication Location:
**Article Title:** Molecular Crowding and Early Evolution
**Authors:**
**Keywords:** Crowding; Excluded volume effect; Protocell; Vesicle; Evolution; Fitness landscape; RNA; Neutral network; Evolutionary optimization
**Abstract:** The environment of protocells might have been crowded with small molecules and functional and non-specific polymers. In addition to altering conformational equilibria, affecting reaction rates and changing the structure and activity of water, crowding might have enhanced the capabilities of protocells for evolutionary innovation through the creation of extended neutral networks in the fitness landscape.
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**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0102821
Volume: 9.0E+000 Issue: 7.0E+000 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Coevolutionary Immune System Dynamics Driving Pathogen Speciation
**Authors:**
**Keywords:** None.
**Abstract:** We introduce and analyze a within-host dynamical model of the coevolution between rapidly mutating pathogens and the adaptive immune response. Pathogen mutation and a homeostatic constraint on lymphocytes both play a role in allowing the development of chronic infection, rather than quick pathogen clearance. The dynamics of these chronic infections display emergent structure, including branching patterns corresponding to asexual pathogen speciation, which is fundamentally driven by the coevolutionary interaction. Over time, continued branching creates an increasingly fragile immune system, and leads to the eventual catastrophic loss of immune control.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Physical Chemistry C
Publication Identifier Type: DOI Publication Identifier: 10.1021/jp508819w
Volume: 1.18E+002 Issue: 4.4E+001 First Page #: 25374
Date Submitted: Date Published:
Publication Location:
**Article Title:** Understanding and Promoting Molecular Interactions and Charge Transfer in Dye-Mediated Hybrid Photovoltaic Materials
**Authors:**
**Keywords:** None.
**Abstract:** The performances of hybrid organic–inorganic photovoltaics composed of conjugated polymers and metal oxides are generally limited by poor electronic coupling at hybrid interfaces. In this study, physicochemical interactions and bonding at the organic–inorganic interfaces are promoted by incorporating organoruthenium dye molecules into self-assembled mesostructured conjugated polymer–titania composites. These materials are synthesized from solution in the presence of surfactant structure-directing agents (SDA) that solubilize and direct the nanoscale compositions and structures of the conjugated polymer, dye, and inorganic precursor species. Judicious selection of the SDA and dye species, in particular, exploits interactions that direct the dye species to the inorganic–organic interfaces, leading to significantly enhanced electronic coupling, as well as increased photoabsorption efficiency. This is demonstrated for the hydrophilic organoruthenium dye N3, used in conjunction with alkylen
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**Journal:** Nature Communications
Publication Identifier Type: DOI Publication Identifier: 10.1038/ncomms6031
Volume: 5.0E+000 Issue: 5.031E+00First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Retro-biosynthetic screening of a modular pathway design achieves selective route for microbial synthesis of 4-methyl-pentanol
**Authors:**
**Keywords:** None.
**Abstract:** Increasingly complex metabolic pathways have been engineered by modifying natural pathways and establishing de novo pathways with enzymes from a variety of organisms. Here we apply retro-biosynthetic screening to a modular pathway design to identify a redox neutral, theoretically high yielding route to a branched C6 alcohol. Enzymes capable of converting natural E. colimetabolites into ?4-methyl-pentanol (?4MP) via ? coenzyme A (?CoA)-dependent chemistry were taken from nine different organisms to form a ten-step de novo pathway. Selectivity for ?4MP is enhanced through the use of key enzymes acting on acyl-CoA intermediates, a ? carboxylic acid reductase from Nocardia iowensis and an alcohol dehydrogenase from Leifsonia sp. strain S749. One implementation of the full pathway from ?glucose demonstrates selective carbon chain extension and acid reduction with ?4MP constituting 81% (90±7?mg?l?1) of the observed alcohol products. The highest observed ? 4MP titre is 192±23?mg?l?1. These resul
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/jacs.5b02881
Volume: 1.37E+002 Issue: 1.9E+001 First Page #: 6160
Date Submitted: Date Published:
Publication Location:
**Article Title:** Creating Extremely Asymmetric Lamellar Structures via Fluctuation-Assisted Unbinding of Miktoarm Star Block Copolymer Alloys
**Authors:**
**Keywords:** None.
**Abstract:** We report the creation of highly asymmetric lamellar structures with a well-designed miktoarm star block copolymer of the S(IS?)3 type, where S and S? are polystyrenes of different lengths and I is poly(isoprene). The domain spacing can be tuned continuously from 37 nm to over 300 nm when the miktoarm star block copolymer is blended with suitable molecular weight polystyrene homopolymers. Beyond the unbinding transition of the lamellar phase, extremely asymmetric lamellar structures were obtained with up to 97 wt % polystyrene, remarkably leaving the poly(isoprene) layers intact at only 3 wt %!
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**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1410796111
Volume: 1.11E+002 Issue: 4.2E+001 First Page #: 15048
Date Submitted: Date Published:
Publication Location:
**Article Title:** Intrinsic disorder as a generalizable strategy for the rational design of highly responsive, allosterically cooperative receptors
**Authors:**
**Keywords:** ultrasensitivity, intrinsically disordered proteins, biosensors, synthetic biology, ribozymes
**Abstract:** Control over the sensitivity with which biomolecular receptors respond to small changes in the concentration of their target ligand is crucial to many cellular processes and likely could be of value in many biotechnologies. In nature, this control is often achieved using “Hill-type” allosteric cooperativity, an elegant mechanism that has, unfortunately, hitherto proven difficult to achieve via generalizable design strategies. In response, we demonstrate here a quantitative and apparently versatile means of rationally introducing this useful mechanism into a range of normally noncooperative receptors. We achieve in the best of our examples cooperativity, and thus sensitivity, experimentally indistinguishable from the theoretically expected maximum.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201403777
Volume: 5.3E+001 Issue: 3.6E+001 First Page #: 9471
Date Submitted: Date Published:
Publication Location:
**Article Title:** Using the Population-Shift Mechanism to Rationally Introduce “Hill-type” Cooperativity into a Normally Non-Cooperative Receptor
**Authors:**
**Keywords:** allosterism; cooperative effects; DNA; sensors; synthetic biology
**Abstract:** Allosteric cooperativity, which nature uses to improve the sensitivity with which biomolecular receptors respond to small changes in ligand concentration, could likewise be of use in improving the responsiveness of artificial biosystems. Thus motivated, we demonstrate here the rational design of cooperative molecular beacons, a widely employed DNA sensor, using a generalizable population-shift approach in which we engineer receptors that equilibrate between a low-affinity state and a high-affinity state exposing two binding sites. Doing so we achieve cooperativity within error of ideal behavior, greatly steepening the beacon’s binding curve relative to that of the parent receptor. The ability to rationally engineer cooperativity should prove useful in applications such as biosensors, synthetic biology and “smart” biomaterials, in which improved responsiveness is of value.
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Publication Identifier Type: DOI Publication Identifier: 10.1038/nbt.3063
Volume: 3.2E+001 Issue: 1.2E+001 First Page #: 1241
Date Submitted: Date Published:
Publication Location:
**Article Title:** Functional optimization of gene clusters by combinatorial design and assembly
**Authors:**
**Keywords:** None.
**Abstract:** Large microbial gene clusters encode useful functions, including energy utilization and natural product biosynthesis, but genetic manipulation of such systems is slow, difficult and complicated by complex regulation. We exploit the modularity of a refactored Klebsiella oxytoca nitrogen fixation (nif) gene cluster (16 genes, 103 parts) to build genetic permutations that could not be achieved by starting from the wild-type cluster. Constraint-based combinatorial design and DNA assembly are used to build libraries of radically different cluster architectures by varying part choice, gene order, gene orientation and operon occupancy. We construct 84 variants of thenifUSVWZM operon, 145 variants of the nifHDKY operon, 155 variants of the nifHDKYENJoperon and 122 variants of the complete 16-gene pathway. The performance and behavior of these variants are characterized by nitrogenase assay and strand-specific RNA sequencing (RNA-seq), and the results are incorporated into subsequent design cyc
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Cognition
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cognition.2015.02.006
Volume: 1.39E+002 Issue: 0 First Page #: 105
Date Submitted: Date Published:
Publication Location:
**Article Title:** Categorization training increases the perceptual separability of novel dimensions
**Authors:**
**Keywords:** Perceptual separability; Perceptual independence; Category learning; General recognition theory
**Abstract:** Perceptual separability is a foundational concept in cognitive psychology. A variety of research questions in perception – particularly those dealing with notions such as “independence,” “invariance,” “holism,” and “configurality” – can be characterized as special cases of the problem of perceptual separability. Furthermore, many cognitive mechanisms are applied differently to perceptually separable dimensions than to non-separable dimensions. Despite the importance of dimensional separability, surprisingly little is known about its origins. Previous research suggests that categorization training can lead to learning of novel dimensions, but it is not known whether the separability of such dimensions also increases with training. Here, we report evidence that training in a categorization task increases perceptual separability of the category-relevant dimension according to a variety of tests from general recognition theory (GRT). In Experiment 1, participants who received pre-training
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**Journal:** Biophysical Journal
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Volume: 1.07E+002 Issue: 1.1E+001 First Page #: 2712
Date Submitted: Date Published:
Publication Location:
**Article Title:** Amplitude Metrics for Cellular Circadian Bioluminescence Reporters
**Authors:**
**Keywords:** None.
**Abstract:** Bioluminescence rhythms from cellular reporters have become the most common method used to quantify oscillations in circadian gene expression. These experimental systems can reveal phase and amplitude change resulting from circadian disturbances, and can be used in conjunction with mathematical models to lend further insight into the mechanistic basis of clock amplitude regulation. However, bioluminescence experiments track the mean output from thousands of noisy, uncoupled oscillators, obscuring the direct effect of a given stimulus on the genetic regulatory network. In many cases, it is unclear whether changes in amplitude are due to individual changes in gene expression level or to a change in coherence of the population. Although such systems can be modeled using explicit stochastic simulations, these models are computationally cumbersome and limit analytical insight into the mechanisms of amplitude change. We therefore develop theoretical and computational tools to approximate the
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Publication Identifier Type: DOI Publication Identifier: 10.1021/nn502277d
Volume: 8.0E+000 Issue: 8.0E+000 First Page #: 8141
Date Submitted: Date Published:
Publication Location:
**Article Title:** Mapping Orientational Order in a Bulk Heterojunction Solar Cell with Polarization-Dependent Photoconductive Atomic Force Microscopy
**Authors:**
**Keywords:** bulk heterojunction; long-range order; liquid crystal; photoconductive atomic force microscopy; conjugated small molecule; organic photovoltaics
**Abstract:** New methods connecting molecular structure, self-organization, and optoelectronic performance are important for understanding the current generation of organic photovoltaic (OPV) materials. In high power conversion efficiency (PCE) OPVs, light-harvesting small-molecules or polymers are typically blended with fullerene derivatives and deposited in thin films, forming a bulk heterojunction (BHJ), a self-assembled three-dimensional nanostructure of electron donors and acceptors that separates and transports charges. Recent data suggest micrometer-scale orientational order of donor domains exists within this complex nanomorphology, but the link to the optoelectronic properties is yet unexplored. Here we introduce polarization-dependent, photoconductive atomic force microscopy (pd-pcAFM) as a combined probe of orientational order and nanoscale optoelectronic properties (?20 nm resolution). Using the donor 7,7?-(4,4-bis(2-ethylhexyl)-4H-silolo[3,2-b:4,5-b?] dithiophene-2,6-diyl)bis(6-fluoro-4
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Publication Identifier Type: DOI Publication Identifier: 10.1021/nn5058936
Volume: 9.0E+000 Issue: 1.0E+000 First Page #: 584
Date Submitted: Date Published:
Publication Location:
**Article Title:** Critical Role of Adsorption Equilibria on the Determination of Surface-Enhanced Raman Enhancement
**Authors:**
**Keywords:** SERS; equilibrium constant; binding energy; enhancement factor; Langmuir isotherm
**Abstract:** Surface-enhanced Raman spectroscopy (SERS) is a useful technique for probing analyte–noble metal interactions and determining thermodynamic properties such as their surface reaction equilibrium constants and binding energies. In this study, we measure the binding equilibrium constants and Gibbs free energy of binding for a series of nitrogen-containing aromatic molecules adsorbed on Klarite substrates. A dual Langmuir dependence of the SERS intensity on concentration was observed for the six species studied, indicating the presence of at least two different binding energies. We relate the measured binding energies to the previously described SERS enhancement value (SEV) and show that the SEV is proportional to the traditional SERS enhancement factor G, with a constant of proportionality that is critically dependent on the adsorption equilibrium constant determined from the dual Langmuir isotherm. We believe the approach described is generally applicable to many SERS substrates, both as
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biotechnology and Bioengineering
Publication Identifier Type: DOI Publication Identifier: 10.1002/bit.25308
Volume: 1.11E+002 Issue: 1.2E+001 First Page #: 2390
Date Submitted: Date Published:
Publication Location:
**Article Title:** Engineered thermostable fungal cellulases exhibit efficient synergistic cellulose hydrolysis at elevated temperatures
**Authors:**
**Keywords:** cellulase; endoglucanase; cellobiohydrolase; thermostability; synergy; biofuels
**Abstract:** A major obstacle to using widely available and low-cost lignocellulosic feedstocks to produce renewable fuels and chemicals is the high cost and low efficiency of the enzyme mixtures used to hydrolyze cellulose to fermentable sugars. One possible solution entails engineering current cellulases to function efficiently at elevated temperatures in order to boost reaction rates and exploit several other advantages of a higher temperature process. Here, we describe the creation of the most stable reported fungal endoglucanase, a derivative of Hypocrea jecorina (anamorph Trichoderma reesei) Cel5A, by combining stabilizing mutations identified using consensus design, chimera studies, and structure-based computational methods. The engineered endoglucanase has an optimal temperature that is 17°C higher than wild type H. jecorina Cel5A, and hydrolyzes 1.5 times as much cellulose over 60 h at its optimum temperature compared to the wild type enzyme at its optimal temperature. This enzyme compleme
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Brain Imaging and Behavior
Publication Identifier Type: DOI Publication Identifier: 10.1007/s11682-014-9351-7
Volume: 9.0E+000 Issue: 1.0E+000 First Page #: 115
Date Submitted: Date Published:
Publication Location:
**Article Title:** One dataset, many conclusions: BOLD variability's complicated relationships with age and motion artifacts
**Authors:**
**Keywords:** Individual differences; Correlation analysis; FMRI analysis methods; Confound correction
**Abstract:** In recent years, the variability of the blood-oxygen level dependent (BOLD) signal has received attention as an informative measure in its own right. At the same time, there has been growing concern regarding the impact of motion in fMRI, particularly in the domain of resting state studies. Here, we demonstrate that, not only does motion (among other confounds) exert an influence on the results of a BOLD variability analysis of task-related fMRI data—but, that the exact method used to deal with this influence has at least as large an effect as the motion itself. This sensitivity to relatively minor methodological changes is particularly concerning as studies begin to take on a more applied bent, and the risk of mischaracterizing the relationship between BOLD variability and various individual difference variables (for instance, disease progression) acquires real-world relevance.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/ac5022419
Volume: 8.6E+001 Issue: 1.8E+001 First Page #: 9236
Date Submitted: Date Published:
Publication Location:
**Article Title:** Transformation of Personal Computers and Mobile Phones into Genetic Diagnostic Systems
**Authors:**
**Keywords:** None.
**Abstract:** Molecular diagnostics based on the polymerase chain reaction (PCR) offer rapid and sensitive means for detecting infectious disease, but prohibitive costs have impeded their use in resource-limited settings where such diseases are endemic. In this work, we report an innovative method for transforming a desktop computer and a mobile camera phone—devices that have become readily accessible in developing countries—into a highly sensitive DNA detection system. This transformation was achieved by converting a desktop computer into a de facto thermal cycler with software that controls the temperature of the central processing unit (CPU), allowing for highly efficient PCR. Next, we reconfigured the mobile phone into a fluorescence imager by adding a low-cost filter, which enabled us to quantitatively measure the resulting PCR amplicons. Our system is highly sensitive, achieving quantitative detection of as little as 9.6 attograms of target DNA, and we show that its performance is comparable t
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**Journal:** IEEE Transactions on Automatic Control
Publication Identifier Type: DOI Publication Identifier: 10.1109/TAC.2014.2342072
Volume: 6.0E+001 Issue: 5.0E+000 First Page #: 1392
Date Submitted: Date Published:
Publication Location:
**Article Title:** Collective Oscillation Period of Inter-Coupled Biological Negative Cyclic Feedback Oscillators
**Authors:**
**Keywords:** None.
**Abstract:** A number of biological rhythms originate from networks comprised of multiple cellular oscillators. But analytical results are still lacking on the collective oscillation period of intercoupled gene regulatory oscillators, which, as has been reported, may be different from that of an autonomous oscillator. Based on cyclic feedback oscillators, we analyze the collective oscillation pattern of coupled cellular oscillators. First we give a condition under which the oscillator network exhibits oscillatory and synchronized behavior. Then we estimate the collective oscillation period based on a novel multivariable harmonic balance technique. Analytical results are derived in terms of biochemical parameters, thus giving insight into the basic mechanism of biological oscillation and providing guidance in synthetic biology design.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Mechanics and Physics of Solids
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jmps.2015.03.011
Volume: 8.0E+001 Issue: 0 First Page #: 68
Date Submitted: Date Published:
Publication Location:
**Article Title:** GPU-based simulations of fracture in idealized brick and mortar composites
**Authors:**
**Keywords:** None.
**Abstract:** Stiff ceramic platelets (or bricks) that are aligned and bonded to a second ductile phase with low volume fraction (mortar) are a promising pathway to produce stiff, high-toughness composites. For certain ranges of constituent properties, including those of some synthetic analogs to nacre, one can demonstrate that the deformation is dominated by relative brick motions. This paper describes simulations of fracture that explicitly track the motions of individual rigid bricks in an idealized microstructure; cohesive tractions acting between the bricks introduce elastic, plastic and rupture behaviors. Results are presented for the stresses and damage near macroscopic cracks with different brick orientations relative to the loading orientation. The anisotropic macroscopic initiation toughness is computed for small-scale yielding conditions and is shown to be independent of specimen geometry and loading configuration. The results are shown to be in agreement with previously published experim
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**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/ac504209m
Volume: 8.7E+001 Issue: 5.0E+000 First Page #: 2811
Date Submitted: Date Published:
Publication Location:
**Article Title:** Hybridization Thermodynamics of DNA Oligonucleotides during Microchip Capillary Electrophoresis
**Authors:**
**Keywords:** None.
**Abstract:** Capillary electrophoresis (CE) is a powerful analytical tool for performing separations and characterizing properties of charged species. For reacting species during a CE separation, local concentrations change leading to nonequilibrium conditions. Interpreting experimental data with such nonequilibrium reactive species is nontrivial due to the large number of variables involved in the system. In this work we develop a COMSOL multiphysics-based numerical model to simulate the electrokinetic mass transport of short interacting ssDNAs in microchip capillary electrophoresis. We probe the importance of the dissociation constant, KD , and the concentration of DNA on the resulting observed mobility of the dsDNA peak, ?w, by using a full sweep of parametric simulations. We find that the observed mobility is strongly dependent on the DNA concentration and KD , as well as ssDNA concentration, and develop a relation with which to understand this dependence. Furthermore, we present experimental m
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201500487
Volume: 2.7E+001 Issue: 1.9E+001 First Page #: 2958
Date Submitted: Date Published:
Publication Location:
**Article Title:** Membrane-Intercalating Conjugated Oligoelectrolytes: Impact on Bioelectrochemical Systems
**Authors:**
**Keywords:** None.
**Abstract:** Conjugated oligoelectrolytes (COEs), molecules that are defined by a ?-delocalized backbone and terminal ionic pendant groups, have been previously demonstrated to effectively reduce charge-injection/extraction barriers at metal/organic interfaces in thin-film organic-electronic devices. Recent studies demonstrate a spontaneous affinity of certain COEs to intercalate into, and align within, lipid bilayers in an ordered orientation, thereby allowing modification of membrane properties and the functions of microbes in bioelectrochemical and photosynthetic systems. Several reports have provided evidence of enhanced current generation and bioproduction. Mechanistic approaches suggest that COEs influence microbial extracellular electron transport to abiotic electrode surfaces via more than one proposed pathway, including direct electron transfer and meditated electron transfer. Molecular dynamics simulations as a function of molecular structure suggest that insertion of cationic COEs result
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**Journal:** Advanced Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adma.201404167
Volume: 2.7E+001 Issue: 1.1E+001 First Page #: 1908
Date Submitted: Date Published:
Publication Location:
**Article Title:** Inter-Aromatic Distances in Geobacter Sulfurreducens Pili Relevant to Biofilm Charge Transport
**Authors:**
**Keywords:** None.
**Abstract:** Geobacter sulfurreducens pili are implicated in facilitating electron transfer to electrode surfaces. Comparisons are made between the conductivity of pili and that of doped organic semiconductors, invoking mechanisms such as “electron hopping” or “metallic conduction”. Analysis of inter-aromatic distances in these pili models shows that charge-carrier transport involving only the ?-conjugated system of GS pili is negligible.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLoS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0115826
Volume: 1.0E+001 Issue: 2.0E+000 First Page #: 0
Date Submitted: Date Published:
Publication Location:
**Article Title:** Optimal Vaccination in a Stochastic Epidemic Model of Two Non-Interacting Populations
**Authors:**
**Keywords:** None.
**Abstract:** Developing robust, quantitative methods to optimize resource allocations in response to epidemics has the potential to save lives and minimize health care costs. In this paper, we develop and apply a computationally efficient algorithm that enables us to calculate the complete probability distribution for the final epidemic size in a stochastic Susceptible-Infected-Recovered (SIR) model. Based on these results, we determine the optimal allocations of a limited quantity of vaccine between two non-interacting populations. We compare the stochastic solution to results obtained for the traditional, deterministic SIR model. For intermediate quantities of vaccine, the deterministic model is a poor estimate of the optimal strategy for the more realistic, stochastic case.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Materials Interfaces
Publication Identifier Type: DOI Publication Identifier: 10.1002/admi.201400466
Volume: 2.0E+000 Issue: 5.0E+000 First Page #: 1400466
Date Submitted: Date Published:
Publication Location:
**Article Title:** Clumping Criteria of Vertical Nanofibers on Surfaces
**Authors:**
**Keywords:** adhesion; clumping; nanofiber arrays; nanowires; nanotubes
**Abstract:** The side–side, side–tip, and tip–tip clumping of nanofibers, including nanowires and nanotubes on surfaces, is a common problem that can diminish their optical, electrical, and mechanical performance. However, these different clumping configurations brought much complexity and confused researchers to predict or design the desired clumping or nonclumping. In this study, a universal model in the unified formula for the critical clumping criteria for three contact geometries of nanofiber arrays is derived in terms of two-dimensionless geometric and mechanical parameters, based on the length, radius, spacing, Young's modulus, and adhesion energy of the nanofibers. The model provides an easy way to predict the sequences of the three clumping configurations, which are successfully verified by analyzing various clumping structures reported in the literatures. This study provides new insights into, and methods for, designing nanofiber arrays on surfaces to achieve desired clumping or nonclumpi
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**Journal:** PLOS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0137540
Volume: 10 Issue: 9 First Page #: e0137540
Date Submitted: 7/27/16 12:00AM Date Published: 9/28/15 7:00AM
Publication Location:
**Article Title:** On the Inference of Functional Circadian Networks Using Granger Causality
**Authors:** Arya Pourzanjani, Erik D. Herzog, Linda R. Petzold, Daniele Marinazzo
**Keywords:** Circadian oscillators
**Abstract:** Being able to infer one way direct connections in an oscillatory network such as the suprachiastmatic nucleus (SCN) of the mammalian brain using time series data is difficult but crucial to understanding network dynamics. Although techniques have been developed for inferring networks from time series data, there have been no attempts to adapt these techniques to infer directional connections in oscillatory time series, while accurately distinguishing between direct and indirect connections. In this paper an adaptation of Granger Causality is proposed that allows for inference of circadian networks and oscillatory networks in general called Adaptive Frequency Granger Causality (AFGC). Additionally, an extension of this method is proposed to infer networks with large numbers of cells called LASSO AFGC. The method was validated using simulated data from several different networks.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4921638
Volume: 142 Issue: 20 First Page #: 204108
Date Submitted: 7/29/16 12:00AM Date Published: 5/27/15 7:00AM
Publication Location:
**Article Title:** Adaptive deployment of model reductions for tau-leaping simulation
**Authors:** Sheng Wu, Jin Fu, Linda R. Petzold
**Keywords:** Stochastic processes; Enzyme kinetics; Poisson's equation; Trajectory models; Collective models
**Abstract:** Multiple time scales in cellular chemical reactionsystems often render the tau-leaping algorithm inefficient. Various model reductions have been proposed to accelerate tau-leaping simulations. However, these are often identified and deployed manually, requiring expert knowledge. This is time-consuming and prone to error. In previous work, we proposed a methodology for automatic identification and validation of model reduction opportunities for tau-leaping simulation. Here, we show how the model reductions can be automatically and adaptively deployed during the time course of a simulation. For multiscale systems, this can result in substantial speedups.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review E
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevE.93.013307
Volume: 93 Issue: 1 First Page #: 013307
Date Submitted: 7/29/16 12:00AM Date Published: 1/19/16 4:00PM
Publication Location:
**Article Title:** Reaction rates for a generalized reaction-diffusion master equation
**Authors:** Stefan Hellander, Linda Petzold
**Keywords:** reaction-diffusion master equation
**Abstract:** It has been established that there is an inherent limit to the accuracy of the reaction-diffusion master equation. Specifically, there exists a fundamental lower bound on the mesh size, below which the accuracy deteriorates as the mesh is refined further. In this paper we extend the standard reaction-diffusion master equation to allow molecules occupying neighboring voxels to react, in contrast to the traditional approach, in which molecules react only when occupying the same voxel. We derive reaction rates, in two dimensions as well as three dimensions, to obtain an optimal match to the more fine-grained Smoluchowski model and show in two numerical examples that the extended algorithm is accurate for a wide range of mesh sizes, allowing us to simulate systems that are intractable with the standard reaction-diffusion master equation.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1521178113
Volume: 113 Issue: 16 First Page #: 4512
Date Submitted: 7/29/16 12:00AM Date Published: 4/19/16 7:00AM
Publication Location:
**Article Title:** Functional network inference of the suprachiasmatic nucleus
**Authors:** John H. Abel, Kirsten Meeker, Daniel Granados-Fuentes, Peter C. St. John, Thomas J. Wang, Benjamir
**Keywords:** systems biology; synchronization; circadian oscillator; biological clock; mathematical model
**Abstract:** In mammals, circadian rhythms are controlled by a network of neurons in the brain. The structure of this network dictates organism-wide behavior and adaptation to the environment. We used a neurotoxin to desynchronize this circadian network and then used tools from information theory to determine which cells communicate to establish synchronization. Our results show that this functional network consists of two densely-connected cores, surrounded by sparsely connected shell regions. These findings represent the first time, to our knowledge, that this network has been examined at single cell resolution and show that the importance of these core network regions is independent of light input.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Science
Publication Identifier Type: DOI Publication Identifier: 10.1126/science.aad1431
Volume: 351 Issue: 6278 First Page #: 1192
Date Submitted: 7/29/16 12:00AM Date Published: 2/18/16 8:00AM
Publication Location:
**Article Title:** Early-branching gut fungi possess a large, comprehensive array of biomass-degrading enzymes
**Authors:** K. V. Solomon, C. H. Haitjema, J. K. Henske, S. P. Gilmore, D. Borges-Rivera, A. Lipzen, H. M. Brewer,
**Keywords:** bioprocessing
**Abstract:** The fungal kingdom is the source of almost all industrial enzymes in use for lignocellulose bioprocessing. We developed a systems-level approach that integrates transcriptomic sequencing, proteomics, phenotype, and biochemical studies of relatively unexplored basal fungi. Anaerobic gut fungi isolated from herbivores produce a large array of biomass-degrading enzymes that synergistically degrade crude, untreated plant biomass and are competitive with optimized commercial preparations from Aspergillus and Trichoderma. Compared to these model platforms, gut fungal enzymes are unbiased in substrate preference due to a wealth of xylan-degrading enzymes. These enzymes are universally catabolite-repressed and are further regulated by a rich landscape of noncoding regulatory RNAs. Additionally, we identified several promising sequence-divergent enzyme candidates for lignocellulosic bioprocessing.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Current Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cub.2015.06.016
Volume: 25 Issue: 19 First Page #: R953
Date Submitted: 7/29/16 12:00AM Date Published: 10/5/15 2:00PM
Publication Location:
**Article Title:** The RNA World as a Model System to Study the Origin of Life
**Authors:** Abe Pressman, Celia Blanco, Irene A. Chen
**Keywords:** ribozymes
**Abstract:** Understanding how life arose is a fundamental problem of biology. Much progress has been made by adopting a synthetic and mechanistic perspective on originating life. We present a current view of the biochemistry of the origin of life, focusing on issues surrounding the emergence of an RNA World in which RNA dominated informational and functional roles. There is cause for optimism on this difficult problem: the prebiotic chemical inventory may not have been as nightmarishly complex as previously thought; the catalytic repertoire of ribozymes continues to expand, approaching the goal of self-replicating RNA; encapsulation in protocells provides evolutionary and biophysical advantages. Nevertheless, major issues remain unsolved, such as the origin of a genetic code. Attention to this field is particularly timely given the accelerating discovery and characterization of exoplanets.
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**Journal:** ACS Synthetic Biology
Publication Identifier Type: DOI Publication Identifier: 10.1021/acssynbio.5b00090
Volume: 5 Issue: 4 First Page #: 287
Date Submitted: 7/29/16 12:00AM Date Published: 8/11/15 7:00AM
Publication Location:
**Article Title:** Engineering Transcriptional Regulator Effector Specificity Using Computational Design and
**Authors:** Emmanuel L. C. de los Santos, Joseph T. Meyerowitz, Stephen L. Mayo, Richard M. Murray
**Keywords:** cell-free systems; computational protein design; in vitro biological circuit prototyping; protein engineering; synthetic biology; TX-TL
**Abstract:** The pursuit of circuits and metabolic pathways of increasing complexity and robustness in synthetic biology will require engineering new regulatory tools. Feedback control based on relevant molecules, including toxic intermediates and environmental signals, would enable genetic circuits to react appropriately to changing conditions. In this work, variants of qacR, a tetR family repressor, were generated by computational protein design and screened in a cell-free transcription–translation (TX-TL) system for responsiveness to a new targeted effector. The modified repressors target vanillin, a growth-inhibiting small molecule found in lignocellulosic hydrolysates and other industrial processes. Promising candidates from the in vitro screen were further characterized in vitro and in vivo in a gene circuit. The screen yielded two qacR mutants that respond to vanillin both in vitro and in vivo.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Molecular Systems Biology
Publication Identifier Type: DOI Publication Identifier: 10.15252/msb.20156663
Volume: 12 Issue: 5 First Page #: 869
Date Submitted: 7/29/16 12:00AM Date Published: 5/17/16 7:00AM
Publication Location:
**Article Title:** A population-based temporal logic gate for timing and recording chemical events
**Authors:** Victoria Hsiao, Yutaka Hori, Paul WK Rothemund, Richard M Murray
**Keywords:** DNA memory; event detectors; integrases; population analysis; stochastic biomolecular models
**Abstract:** Engineered bacterial sensors have potential applications in human health monitoring, environmental chemical detection, and materials biosynthesis. While such bacterial devices have long been engineered to differentiate between combinations of inputs, their potential to process signal timing and duration has been overlooked. In this work, we present a two?input temporal logic gate that can sense and record the order of the inputs, the timing between inputs, and the duration of input pulses. Our temporal logic gate design relies on unidirectional DNA recombination mediated by bacteriophage integrases to detect and encode sequences of input events. For an E. coli strain engineered to contain our temporal logic gate, we compare predictions of Markov model simulations with laboratory measurements of final population distributions for both step and pulse inputs.
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**Journal:** CPT: Pharmacometrics & Systems Pharmacology
Publication Identifier Type: DOI Publication Identifier: 10.1002/psp4.12042
Volume: 4 Issue: 10 First Page #: 559
Date Submitted: 7/29/16 12:00AM Date Published: 10/10/15 7:00AM
Publication Location:
**Article Title:** Physiome-on-a-Chip: The Challenge of “Scaling” in Design, Operation, and Translation of Microphysiological Systems
**Authors:** CL Stokes, M Cirit, DA Lauffenburger
**Keywords:** microphysiological system
**Abstract:** Scaling of a microphysiological system (MPS) or physiome-on-a-chip is arguably two interrelated, modeling-based activities: on-platform scaling and in vitro-in vivo translation. This dual approach reduces the need to perfectly rescale and mimic in vivo physiology, an aspiration that is both extremely challenging and not substantively meaningful because of uncertain relevance of any specific physiological condition. Accordingly, this perspective offers a tractable approach for designing interacting MPSs and relating in vitro results to analogous context in vivo.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Obesity
Publication Identifier Type: DOI Publication Identifier: 10.1002/oby.21243
Volume: 24 Issue: 1 First Page #: 102
Date Submitted: 7/29/16 12:00AM Date Published: 1/1/16 8:00AM
Publication Location:
**Article Title:** Th17 cytokines differentiate obesity from obesity-associated type 2 diabetes and promote TNF? production
**Authors:** Blanche Ip, Nicholas A. Cilfone, Anna C. Belkina, Jason DeFuria, Madhumita Jagannathan-Bogdan, Mir
**Keywords:** inflammation
**Abstract:** OBJECTIVE:T cell inflammation plays pivotal roles in obesity-associated type 2 diabetes (T2DM). The identification of dominant sources of T cell inflammation in humans remains a significant gap in understanding disease pathogenesis. It was hypothesized that cytokine profiles from circulating T cells identify T cell subsets and T cell cytokines that define T2DM-associated inflammation. METHODS:Multiplex analyses were used to quantify T cell-associated cytokines in ?CD3/?CD28-stimulated PBMCs, or B cell-depleted PBMCs, from subjects with T2DM or BMI-matched controls. Cytokine measurements were subjected to multivariate (principal component and partial least squares) analyses. Flow cytometry detected intracellular TNF? in multiple immune cell subsets in the presence/absence of antibodies that neutralize T cell cytokines. RESULTS:T cell cytokines were generally higher in T2DM samples, but Th17 cytokines are specifically important for classifying individuals correctly as T2DM.
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**Journal:** Scientific Reports
Publication Identifier Type: DOI Publication Identifier: 10.1038/srep16622
Volume: 5 Issue: First Page #: 16622
Date Submitted: 7/29/16 12:00AM Date Published: 11/13/15 8:00AM
Publication Location:
**Article Title:** Identification of neurotoxic cytokines by profiling Alzheimer's disease tissues and neuron culture viability screening
**Authors:** Levi B. Wood, Ashley R. Winslow, Elizabeth A. Proctor, Declan McGuone, Daniel A. Mordes, Matthew P
**Keywords:** Cell death in the nervous system; Regulatory networks
**Abstract:** Alzheimer's disease (AD) therapeutics based on the amyloid hypothesis have shown minimal efficacy in patients, suggesting that the activity of amyloid beta (A?) represents only one aspect of AD pathogenesis. Since neuroinflammation is thought to play an important role in AD, we hypothesized that cytokines may play a direct role in promoting neuronal death. Here, we profiled cytokine expression in a small cohort of human AD and control brain tissues. We identified AD-associated cytokines using partial least squares regression to correlate cytokine expression with quantified pathologic disease state and then used neuron cultures to test whether cytokines up-regulated in AD tissues could affect neuronal viability. This analysis identified cytokines that were associated with the pathological severity. Of the top correlates, only TNF-? reduced viability in neuron culture when applied alone.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Journal of Selected Topics in Signal Processing
Publication Identifier Type: DOI Publication Identifier: 10.1109/JSTSP.2016.2520899
Volume: 10 Issue: 3 First Page #: 514
Date Submitted: 8/4/16 12:00AM Date Published: 1/22/16 8:00AM
Publication Location:
**Article Title:** Compressive Channel Estimation and Tracking for Large Arrays in mm-Wave Picocells
**Authors:** Zhinus Marzi, Dinesh Ramasamy, Upamanyu Madhow
**Keywords:** 60 GHz, Compressive, RF beamforming, mm wave, picocells
**Abstract:** We propose and investigate a compressive architecture for estimation and tracking of sparse spatial channels in millimeter (mm) wave picocellular networks. The base stations are equipped with antenna arrays with a large number of elements (which can fit within compact form factors because of the small carrier wavelength) and employ radio frequency (RF) beamforming, so that standard least squares adaptation techniques (which require access to individual antenna elements) are not applicable. We focus on the downlink, and show that "compressive beacons," transmitted using pseudorandom phase settings at the base station array, and compressively processed using pseudorandom phase settings at the mobile array, provide information sufficient for accurate estimation of the two-dimensional (2D) spatial frequencies associated with the directions of departure of the dominant rays from the base station, and the associated complex gains.
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**Journal:** International Journal of Adaptive Control and Signal Processing
Publication Identifier Type: DOI Publication Identifier: 10.1002/acs.2631
Volume: Issue: First Page #:
Date Submitted: 8/4/16 12:00AM Date Published: 10/5/15 7:00AM
Publication Location:
**Article Title:** Approximate optimal adaptive control for weakly coupled nonlinear systems: A neuro-inspired approach
**Authors:** Luis Rodolfo García Carrillo, Kyriakos G. Vamvoudakis, João Pedro Hespanha
**Keywords:** optimal control
**Abstract:** This paper proposes a new approximate dynamic programming algorithm to solve the infinite-horizon optimal control problem for weakly coupled nonlinear systems. The algorithm is implemented as a three-critic/four-actor approximators structure, where the critic approximators are used to learn the optimal costs, while the actor approximators are used to learn the optimal control policies. Simultaneous continuous-time adaptation of both critic and actor approximators is implemented, a method commonly known as synchronous policy iteration. The adaptive control nature of the algorithm requires a persistence of excitation condition to be a priori guaranteed, but this can be relaxed by using previously stored data concurrently with current data in the update of the critic approximators. Appropriate robustifying terms are added to the controllers to eliminate the effects of the residual errors, leading to asymptotic stability of the equilibrium point of the closed-loop system.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Intelligent & Robotic Systems
Publication Identifier Type: DOI Publication Identifier: 10.1007/s10846-015-0270-7
Volume: 82 Issue: 1 First Page #: 135
Date Submitted: 8/4/16 12:00AM Date Published: 10/5/15 7:00AM
Publication Location:
**Article Title:** Stochastic Optimal Coordination of Small UAVs for Target Tracking using Regression-based Dynamic Programming
**Authors:** Steven A. P. Quintero, Michael Ludkovski, João P. Hespanha
**Keywords:** Target tracking, Unmanned aerial vehicle, Autonomous vehicle, Regression Monte Carlo, Motion planning, Probabilistic planning
**Abstract:** We study the problem of optimally coordinating multiple fixed-wing UAVs to perform vision-based target tracking, which entails that the UAVs are tasked with gathering the best joint vision-based measurements of an unpredictable ground target. We utilize an analytic expression for the error covariance associated with the fused measurements of the target's position, and we employ stochastic fourth-order models for all vehicles, thereby incorporating a high degree of realism into the problem formulation. While dynamic programming can generate an optimal control policy that minimizes the expected value of the fused geolocation error covariance over time, it is accompanied by significant computational challenges due to the curse of dimensionality. In order to circumvent this challenge, we present a novel policy generation technique that combines simulation-based policy iteration with a robust regression scheme.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Neural Networks and Learning Systems
Publication Identifier Type: DOI Publication Identifier: 10.1109/TNNLS.2015.2487972
Volume: Issue: First Page #: 1
Date Submitted: 8/22/16 12:00AM Date Published:
Publication Location:
**Article Title:** Asymptotically Stable Adaptive-Optimal Control Algorithm With Saturating Actuators and Relaxed Persistence of Excitation
**Authors:** Kyriakos G. Vamvoudakis, Marcio Fantini Miranda, Joao P. Hespanha
**Keywords:** Approximate dynamic programming (ADP), optimal control, reinforcement learning, saturating actuators
**Abstract:** This paper proposes a control algorithm based on adaptive dynamic programming to solve the infinite-horizon optimal control problem for known deterministic nonlinear systems with saturating actuators and nonquadratic cost functionals. The algorithm is based on an actor/critic framework, where a critic neural network (NN) is used to learn the optimal cost, and an actor NN is used to learn the optimal control policy. The adaptive control nature of the algorithm requires a persistence of excitation condition to be a priori validated, but this can be relaxed using previously stored data concurrently with current data in the update of the critic NN. A robustifying control term is added to the controller to eliminate the effect of residual errors, leading to the asymptotically stability of the closed-loop system. Simulation results show the effectiveness of the proposed approach for a controlled Van der Pol oscillator and also for a power system plant.
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Nano
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsnano.5b06066
Volume: 10 Issue: 1 First Page #: 930
Date Submitted: 8/4/16 12:00AM Date Published: 12/22/15 8:00AM
Publication Location:
**Article Title:** Mussel-Inspired Anchoring of Polymer Loops That Provide Superior Surface Lubrication and Antifouling Properties
**Authors:** Taegon Kang, Xavier Banquy, Jinhwa Heo, Chanoong Lim, Nathaniel A. Lynd, Pontus Lundberg, Dongy
**Keywords:** antifouling; catechol; lubrication; polymer loops; surface forces apparatus
**Abstract:** We describe robustly anchored triblock copolymers that adopt loop conformations on surfaces and endow them with unprecedented lubricating and antifouling properties. The triblocks have two end blocks with catechol-anchoring groups and a looping poly(ethylene oxide) (PEO) midblock. The loops mediate strong steric repulsion between two mica surfaces. When sheared at constant speeds of ?2.5 ?m/s, the surfaces exhibit an extremely low friction coefficient of ?0.002–0.004 without any signs of damage up to pressures of ?2–3 MPa that are close to most biological bearing systems. Moreover, the polymer loops enhance inhibition of cell adhesion and proliferation compared to polymers in the random coil or brush conformations. These results demonstrate that strongly anchored polymer loops are effective for high lubrication and low cell adhesion and represent a promising candidate for the development of specialized high-performance biomedical coatings.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Biomaterials Science & Engineering
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsbiomaterials.5b00252
Volume: 1 Issue: 11 First Page #: 1121
Date Submitted: 8/4/16 12:00AM Date Published: 10/8/15 7:00AM
Publication Location:
**Article Title:** Mussel Coating Protein-Derived Complex Coacervates Mitigate Frictional Surface Damage
**Authors:** Dusty Rose Miller, Saurabh Das, Kuo-Ying Huang, Songi Han, Jacob N. Israelachvili, J. Herbert Waite
**Keywords:** adhesion; biomimetic; HA; hyaluronic acid; interface; mcfp-1; Mytilus californianus foot protein 1; wear protection
**Abstract:** The role of friction in the functional performance of biomaterial interfaces is widely reckoned to be critical and complicated but poorly understood. To better understand friction forces, we investigated the natural adaptation of the holdfast or byssus of mussels that live in high-energy surf habitats. As the outermost covering of the byssus, the cuticle deserves particular attention for its adaptations to frictional wear under shear. In this study, we coacervated one of three variants of a key cuticular component, mussel foot protein 1, mfp-1 [(1) Mytilus californianus mcfp-1, (2) rmfp-1, and (3) rmfp-1-Dopa], with hyaluronic acid (HA) and investigated the wear protection capabilities of these coacervates to surfaces (mica) during shear. Native mcfp-1/HA coacervates had an intermediate coefficient of friction (? ?0.3) but conferred excellent wear protection to mica with no damage from applied loads, F?, as high as 300 mN (pressure, P, > 2 MPa).
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Optica
Publication Identifier Type: DOI Publication Identifier: 10.1364/OPTICA.3.000108
Volume: 3 Issue: 1 First Page #: 108
Date Submitted: 8/4/16 12:00AM Date Published: 1/19/16 8:00AM
Publication Location:
**Article Title:** Biological analogs of RGB pixelation yield white coloration in giant clams
**Authors:** Amitabh Ghoshal, Elizabeth Eck, Daniel E. Morse
**Keywords:** color mixing
**Abstract:** Giant clams utilize two mechanisms to produce white coloration analogous to that from RGB pixelated electro-optical displays. In the first, the mixed reflection from tight clusters of differently colored iridescent cells yields white. In the second, cells containing subcellular Bragg reflectors with heterogeneous lamellar spacings reflect multiple wavelengths to appear white at the macroscopic scale. Both mechanisms represent unique systems of structural color that produce white by color mixing.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chem. Sci.
Publication Identifier Type: DOI Publication Identifier: 10.1039/C5SC03046C
Volume: 7 Issue: 3 First Page #: 2023
Date Submitted: 8/4/16 12:00AM Date Published:
Publication Location:
**Article Title:** Tuning cell surface charge in E. coli with conjugated oligoelectrolytes
**Authors:** Chelsea Catania, Alexander W. Thomas, Guillermo C. Bazan
**Keywords:** Cationic conjugated oligoelectrolytes
**Abstract:** Cationic conjugated oligoelectrolytes (COEs) varying in length and structural features are compared with respect to their association with E. coli and their effect on cell surface charge as determined by zeta potential measurements. Regardless of structural features, at high staining concentrations COEs with longer molecular dimensions associate less, but neutralize the negative surface charge of E. coli to a greater degree than shorter COEs.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ChemSusChem
Publication Identifier Type: DOI Publication Identifier: 10.1002/cssc.201500194
Volume: 8 Issue: 21 First Page #: 3718
Date Submitted: 8/4/16 12:00AM Date Published: 11/9/15 8:00AM
Publication Location:
**Article Title:** Increased Microbial Butanol Tolerance by Exogenous Membrane Insertion Molecules
**Authors:** Jamie Hinks, Yaofeng Wang, Artur Matysik, Rachel Kraut, Staffan Kjelleberg, Yuguang Mu, Guillermo C
**Keywords:** conjugated oligoelectrolyte
**Abstract:** Butanol is an ideal biofuel, although poor titers lead to high recovery costs by distillation. Fluidization of microbial membranes by butanol is one of the major factors limiting titers in butanol-producing bioprocesses. Starting with the hypothesis that certain membrane insertion molecules would stabilize the lipid bilayer in the presence of butanol, we applied a combination of in?vivo and in?vitro techniques within an in?silico framework to describe a new approach to achieve solvent tolerance in bacteria. Single-molecule tracking of a model supported bilayer showed that COE1-5C, a five-ringed oligo-polyphenylenevinylene conjugated oligoelectrolyte (COE), reduced the diffusion rate of phospholipids in a microbially derived lipid bilayer to a greater extent than three-ringed and four-ringed COEs. Furthermore, COE1-5C treatment increased the specific growth rate of E.?coli K12 relative to a control at inhibitory butanol concentrations.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Bioelectrochemistry
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.bioelechem.2015.07.001
Volume: 106 Issue: First Page #: 379
Date Submitted: 8/4/16 12:00AM Date Published: 7/22/15 7:00AM
Publication Location:
**Article Title:** Conjugated oligoelectrolyte represses hydrogen oxidation by Geobacter sulfurreducens in microbial electrolysis cells
**Authors:** Jia Liu, Huijie Hou, Xiaofen Chen, Guillermo C. Bazan, Hiroyuki Kashima, Bruce E. Logan
**Keywords:** conjugated oligoelectrolyte
**Abstract:** A conjugated oligoelectrolyte (COE), which spontaneously aligns within cell membranes, was shown to completely inhibit H2 uptake by Geobacter sulfurreducens in microbial electrolysis cells. Coulombic efficiencies that were 490±95%, due to H2 recycling between the cathode and microorganisms on the anode, were reduced to 86±2% with COE addition. The use of the COE resulted in a 67-fold increase in H2 gas recovery, and a 4.4-fold increase in acetate removal. Current generation, H2 recovery and COD removals by Geobacter metallireducens, which cannot use H2, were unaffected by COE addition. These results show that this COE is an effective H2 uptake inhibitor, and that it can enable improved and sustained H2 gas recovery in this bioelectrochemical system.
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**Journal:** Chem. Commun.
Publication Identifier Type: DOI Publication Identifier: 10.1039/C5CC01724F
Volume: 51 Issue: 45 First Page #: 9294
Date Submitted: 8/4/16 12:00AM Date Published:
Publication Location:
**Article Title:** Pendant ionic groups of conjugated oligoelectrolytes govern their ability to intercalate into microbial membranes
**Authors:** A. W. Thomas, C. Catania, L. E. Garner, G. C. Bazan
**Keywords:** Conjugated oligoelectrolytes
**Abstract:** Conjugated oligoelectrolytes (COEs) bearing pyridinium and carboxylate groups are synthesized, characterized, and compared to the trimethylammonium analogue from which they are derived. All COEs are able to spontaneously intercalate into liposomes, whereas only positively charged COEs intercalate into E. coli membranes. Membrane intercalation is determined necessary for performance enhancement in microbial fuel cells.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Advanced Optical Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adom.201500297
Volume: 3 Issue: 10 First Page #: 1454
Date Submitted: 8/4/16 12:00AM Date Published: 8/6/15 7:00AM
Publication Location:
**Article Title:** Improved Amplified Spontaneous Emission of Dye-Doped Functionalized Mesostructured Silica Waveguide Films
**Authors:** Manuel G. Ramírez, Justin P. Jahnke, Matthias J. N. Junk, José M. Villalvilla, Pedro G. Boj, José A. Qui
**Keywords:** Amplified spontaneous emission
**Abstract:** Amplified spontaneous emission (ASE) in dye-doped mesostructured silica films, deposited directly over fused silica substrates, is demonstrated with low thresholds. Due to functionalization of the silica network with phenyl groups, the refractive index of the active layer is sufficiently increased to impart waveguiding properties that lead to highly efficient ASE. Such functionalization eliminates the need for a separate low-refractive-index layer between the active film and the substrate, as is often used to achieve waveguiding properties with silica mesostructured materials, though which is typically accompanied by significant optical losses that reduce overall ASE performance. By forming a high-quality waveguide without the need for a separate low-refractive-index layer, significantly improved properties are obtained, with ASE thresholds as low as 8 kW cm?2.
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**Journal:** ACS Nano
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Volume: 10 Issue: 1 First Page #: 930
Date Submitted: 8/4/16 12:00AM Date Published: 12/22/15 8:00AM
Publication Location:
**Article Title:** Mussel-Inspired Anchoring of Polymer Loops That Provide Superior Surface Lubrication and Antifouling Properties
**Authors:** Taegon Kang, Xavier Banquy, Jinhwa Heo, Chanoong Lim, Nathaniel A. Lynd, Pontus Lundberg, Dongy
**Keywords:** antifouling; catechol; lubrication; polymer loops; surface forces apparatus
**Abstract:** We describe robustly anchored triblock copolymers that adopt loop conformations on surfaces and endow them with unprecedented lubricating and antifouling properties. The triblocks have two end blocks with catechol-anchoring groups and a looping poly(ethylene oxide) (PEO) midblock. The loops mediate strong steric repulsion between two mica surfaces. When sheared at constant speeds of ?2.5 ?m/s, the surfaces exhibit an extremely low friction coefficient of ?0.002–0.004 without any signs of damage up to pressures of ?2–3 MPa that are close to most biological bearing systems. Moreover, the polymer loops enhance inhibition of cell adhesion and proliferation compared to polymers in the random coil or brush conformations. These results demonstrate that strongly anchored polymer loops are effective for high lubrication and low cell adhesion and represent a promising candidate for the development of specialized high-performance biomedical coatings.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Polymer Science Part A: Polymer Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1002/pola.27749
Volume: 53 Issue: 23 First Page #: 2685
Date Submitted: 8/4/16 12:00AM Date Published: 12/1/15 8:00AM
Publication Location:
**Article Title:** A facile synthesis of catechol-functionalized poly(ethylene oxide) block and random copolymers
**Authors:** Kaila M. Mattson, Allegra A. Latimer, Alaina J. McGrath, Nathaniel A. Lynd, Pontus Lundberg, Zachary M
**Keywords:** polyethylene oxide
**Abstract:** Herein we develop a facile synthetic strategy for the functionalization of well-defined polyether copolymers with control over the number and location of catechol groups. Previously, the functionalization of polyethylene oxide (PEO)-based polymers with catechols has been limited to functionalization of the chain ends only, hampering the synthesis of adhesive and antifouling materials based on this platform. To address this challenge, we describe an efficient and high-yielding route to catechol-functionalized polyethers, which could allow the effects of polymer architecture, molecular weight, and catechol incorporation on the adhesive properties of surface-anchored PEO to be studied.
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**Journal:** Macromolecules
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.macromol.5b01713
Volume: 48 Issue: 21 First Page #: 7774
Date Submitted: 8/4/16 12:00AM Date Published: 10/26/15 7:00AM
Publication Location:
**Article Title:** One-Pot “Click” Fabrication of Slide-Ring Gels
**Authors:** Takuya Murakami, Bernhard V. K. J. Schmidt, Hugh R. Brown, Craig J. Hawker
**Keywords:** Slide-ring (SR) gels
**Abstract:** Slide-ring (SR) gels have been fabricated through a convenient one-pot approach using thiol–ene click chemistry. Pseudo-polyrotaxanes of monothiolated ?-cyclodextrin threaded on poly(allyl glycidyl ether)-block-poly (ethylene glycol)-block-poly(allyl glycidyl ether) were prepared in water by sonication and subsequently photo-cross-linked by UV irradiation. The pseudo-polyrotaxanes were characterized through dynamic light scattering analysis and nuclear Overhauser enhancement spectroscopy with the chemical and physical properties of the resulting SR gels being compared to the corresponding covalent gels. In contrast to these covalent gels, the SR gels showed comparable elasticity but exhibited high stretchability and tunable degradability under acidic conditions. We believe this simple and efficient fabrication method will expand and facilitate future applications of SR gels.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Applied Materials & Interfaces
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsami.5b06910
Volume: 7 Issue: 44 First Page #: 24656
Date Submitted: 8/4/16 12:00AM Date Published: 10/22/15 7:00AM
Publication Location:
**Article Title:** Formation, Removal, and Reformation of Surface Coatings on Various Metal Oxide Surfaces Inspired by Mussel Adhesives
**Authors:** Taegon Kang, Dongyeop X. Oh, Jinhwa Heo, Han-Koo Lee, Seunghwan Choy, Craig J. Hawker, Dong S
**Keywords:** catechol; DOPA; reversible coating; self-assembled monolayer
**Abstract:** Mussels survive by strongly attaching to a variety of different surfaces, primarily subsurface rocks composed of metal oxides, through the formation of coordinative interactions driven by protein-based catechol repeating units contained within their adhesive secretions. From a chemistry perspective, catechols are known to form strong and reversible complexes with metal ions or metal oxides, with the binding affinity being dependent on the nature of the metal ion. As a result, catechol binding with metal oxides is reversible and can be broken in the presence of a free metal ion with a higher stability constant. It is proposed to exploit this competitive exchange in the design of a new strategy for the formation, removal, and reformation of surface coatings and self-assembled monolayers (SAM) based on catechols as the adhesive unit.
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**Journal:** ACS Macro Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsmacrolett.5b00350
Volume: 4 Issue: 7 First Page #: 731
Date Submitted: 8/4/16 12:00AM Date Published: 7/24/15 7:00AM
Publication Location:
**Article Title:** Metallopolymer-Based Shape Anisotropic Nanoparticles
**Authors:** Bernhard V. K. J. Schmidt, Johannes Elbert, Daniel Scheid, Craig J. Hawker, Daniel Klinger, Markus Ga
**Keywords:** anisotropic nanoparticles
**Abstract:** The formation of nanostructured shape anisotropic nanoparticles from poly(ferrocenylsilane)-b-poly(2-vinylpyridine) (PFS-b-P2VP) block copolymers is presented. Ellipsoidal particles with an axially stacked lamellar structure and nanosheets with a hexagonal structure of PFS cylinders are obtained under neutral wetting conditions through the use of a mixed surfactant system during self-assembly. In contrast to traditional systems, the resulting particle structure is strongly influenced by crystallization of the PFS domains under colloidal confinement with lamella-forming PFS-b-P2VP block copolymers leading to cylindrical morphologies. A blending approach was developed to control this morphological change and by the addition of PFS homopolymers, ellipsoidal particles with a lamellar structure could also be obtained. Ultimately, the spatial control over two orthogonal functionalities was exploited to demonstrate morphology transitions for nanosheets upon the exposure to methanol as solvent
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Soft Matter
Publication Identifier Type: DOI Publication Identifier: 10.1039/C5SM01374G
Volume: 11 Issue: 31 First Page #: 6173
Date Submitted: 8/4/16 12:00AM Date Published: 7/7/15 7:00AM
Publication Location:
**Article Title:** Catechol-based layer-by-layer assembly of composite coatings: a versatile platform to hierarchical nano-materials
**Authors:** C. X. Wang, A. Braendle, M. S. Menyo, C. W. Pester, E. E. Perl, I. Arias, C. J. Hawker, D. Klinger
**Keywords:** nano-materials
**Abstract:** Inspired by the marine mussel's ability to adhere to surfaces underwater, an aqueous catechol-based dip coating platform was developed. Using a catechol-functionalized polyacrylamide binder in combination with inorganic nanoparticles enables the facile fabrication of robust composite coatings via a layer-by-layer process. This modular assembly of well-defined building blocks provides a versatile alternative to electrostatic driven approaches with layer thickness and refractive indices being readily tunable. The platform nature of this approach enables the fabrication of hierarchically ordered nano-materials such as Bragg stacks.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Green Chem.
Publication Identifier Type: DOI Publication Identifier: 10.1039/C6GC00273K
Volume: 18 Issue: 9 First Page #: 2619
Date Submitted: 8/4/16 12:00AM Date Published:
Publication Location:
**Article Title:** A bio-facilitated synthetic route for nano-structured complex electrode materials
**Authors:** Maryam Moradi, Jae Chul Kim, Jifa Qi, Kang Xu, Xin Li, Gerbrand Ceder, Angela M. Belcher
**Keywords:** polyanions
**Abstract:** We investigate an energy-efficient synthesis that merges the bio-templated technique and solid-state reactions to produce nano-structured lithiated polyanions. With the aid of bio-templates based on an M13 virus, the thermal budget of an annealing process can be reduced, and the nano-structured characteristics of the precursors are preserved in the product. This method enables us to successfully prepare monoclinic LiMnBO3 with an average particle size of 20 nm in a 1 h annealing process, showing improved electrochemical properties compared with the conventionally synthesized one. Thus, we consider that this bio-facilitated method can open up an environmentally-friendly pathway to produce nano-structured electrode materials with an enhanced performance.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Extreme Mechanics Letters
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.eml.2015.09.003
Volume: 5 Issue: First Page #: 37
Date Submitted: 8/4/16 12:00AM Date Published: 9/15/15 7:00AM
Publication Location:
**Article Title:** Acoustic field controlled patterning and assembly of anisotropic particles
**Authors:** Rachel R. Collino, Tyler R. Ray, Rachel C. Fleming, Camille H. Sasaki, Hossein Haj-Hariri, Matthew R. E
**Keywords:** Highly-organized particle assembly
**Abstract:** Highly-organized particle assembly at the microscale offers the potential to transform fields ranging from medical diagnostics to materials-by-design. Here, we demonstrate tunable ordering and alignment of microscale particles, including ~10×50 ?m glass rods and SU-8 brick and bowtie particles, via acoustic excitation, which produces columns with controlled spacing or highly-regular 'brick-and-mortar' packing. The method does not require surface functionalization and is broadly agnostic to colloidal chemistry or particle properties. We show that particle anisotropy promotes alignment and ordering even in the presence of flow, and can be used to increase the efficiency of particle delivery and sorting. Acoustically-assembled microstructures are preserved via photopolymerization of hydrogel matrices or binding with DNA 'mortar;' the latter provides sufficient stability and flexibility to fold ribbon-like structures in solution by tuning the direction of the acoustic waves.
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**Journal:** Extreme Mechanics Letters
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Volume: 5 Issue: First Page #: 1
Date Submitted: 8/4/16 12:00AM Date Published: 9/5/15 7:00AM
Publication Location:
**Article Title:** The impact of stochastic microstructures on the macroscopic fracture properties of brick and mortar composites
**Authors:** J. William Pro, Rone Kwei Lim, Linda R. Petzold, Marcel Utz, Matthew R. Begley
**Keywords:** non-uniform microstructures; brick and mortar
**Abstract:** This paper examines the effect of non-uniform microstructures on the macroscopic fracture properties of idealized brick and mortar composites, which consist of rigid bricks bonded with elastic–plastic mortar that ruptures at finite strain. A simulation tool that harnesses the parallel processing power of graphics processing units (GPUs) was used to simulate fracture in virtual specimens, whose microstructures were generated by sampling a probability distribution of brick sizes. In the simulations, crack advance is a natural outcome of local ruptures in the cohesive zones bonding the bricks: the macroscopic initiation toughness for small-scale yielding is inferred by correlating the critical load needed to advance a pre-defined crack with an associated far-field energy release rate. Quantitative connections between the statistical parameters defining heterogeneous brick distributions and the statistics of initiation toughness are presented.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Nano
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsnano.5b06215
Volume: 10 Issue: 2 First Page #: 2054
Date Submitted: 8/4/16 12:00AM Date Published: 1/13/16 8:00AM
Publication Location:
**Article Title:** Mechanics of an Asymmetric Hard–Soft Lamellar Nanomaterial
**Authors:** Weichao Shi, Glenn H. Fredrickson, Edward J. Kramer, Christos Ntaras, Apostolos Avgeropoulos, Quen
**Keywords:** asymmetric lamellae; crazes; glassy/rubbery nanolayers; miktoarm block copolymers; self-assembly; voids
**Abstract:** Nanolayered lamellae are common structures in nanoscience and nanotechnology, but most are nearly symmetric in layer thickness. Here, we report on the structure and mechanics of highly asymmetric and thermodynamically stable soft–hard lamellar structures self-assembled from optimally designed PS1-(PI-b-PS2)3 miktoarm star block copolymers. The remarkable mechanical properties of these strong and ductile PS (polystyrene)-based nanomaterials can be tuned over a broad range by varying the hard layer thickness while maintaining the soft layer thickness constant at 13 nm. Upon deformation, thin PS lamellae (<100 nm) exhibited kinks and predamaged/damaged grains, as well as cavitation in the soft layers. In contrast, deformation of thick lamellae (>100 nm) manifests cavitation in both soft and hard nanolayers.
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**Journal:** Journal of Polymer Science Part B: Polymer Physics
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Volume: 54 Issue: 2 First Page #: 169
Date Submitted: 8/4/16 12:00AM Date Published: 8/29/16 7:00AM
Publication Location:
**Article Title:** Morphology re-entry in asymmetric PS-PI-PS' triblock copolymer and PS homopolymer blends
**Authors:** Weichao Shi, Wei Li, Kris T. Delaney, Glenn H. Fredrickson, Edward J. Kramer, Christos Ntaras, Apostc
**Keywords:** morphology variation
**Abstract:** Here, we report the morphology variation in a series of PS-b-PI-b-PS' asymmetric triblock copolymer and PS homopolymer (hPS) blends, where PS' and PS are polystyrene blocks with a molecular weight ratio of approximately 0.11 and PI is poly(isoprene). We find that adding a small amount of hPS results in significant order–order transition (OOT) boundary deflection toward higher PS volume fractions fPS, which is accompanied by morphology re-entry. For example, the neat triblock copolymer with a PS?+?PS' volume fraction of fPS?=?0.38 exhibits a lamellar microphase; adding a small amount of hPS reverts the morphology into a hexagonal phase with PS cylinders, while further increasing the hPS fraction leads to normal OOTs from PS cylinders to lamellae, to PI cylinders and finally to spheres. The morphology variation reported here is significantly different from that reported in binary blends of diblock or symmetric triblock copolymer with homopolymer.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1509120112
Volume: 112 Issue: 37 First Page #: 11502
Date Submitted: 8/4/16 12:00AM Date Published: 9/15/15 7:00AM
Publication Location:
**Article Title:** Resilient 3D hierarchical architected metamaterials
**Authors:** Lucas R. Meza, Alex J. Zelhofer, Nigel Clarke, Arturo J. Mateos, Dennis M. Kochmann, Julia R. Greer
**Keywords:** hierarchical nanolattices; structural metamaterial; recoverable damage; tolerance
**Abstract:** Hierarchically designed structures with architectural features that span across multiple length scales are found in numerous hard biomaterials, like bone, wood, and glass sponge skeletons, as well as manmade structures, like the Eiffel Tower. It has been hypothesized that their mechanical robustness and damage tolerance stem from sophisticated ordering within the constituents, but the specific role of hierarchy remains to be fully described and understood. We apply the principles of hierarchical design to create structural metamaterials from three material systems: (i) polymer, (ii) hollow ceramic, and (iii) ceramic–polymer composites that are patterned into self-similar unit cells in a fractal-like geometry. In situ nanomechanical experiments revealed (i) a nearly theoretical scaling of structural strength and stiffness with relative density, which outperforms existing nonhierarchical nanolattices; (ii) recoverability, with hollow alumina samples recovering up to 98%...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Colloid and Interface Science
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jcis.2015.08.039
Volume: 461 Issue: First Page #: 32
Date Submitted: 8/4/16 12:00AM Date Published: 8/21/15 7:00AM
Publication Location:
**Article Title:** Electrophoretic mobility of spherical particles in bounded domain
**Authors:** Yu-Wei Liu, Sumita Pennathur, Carl D. Meinhart
**Keywords:** Double layer overlapping; Double layer polarization; Electrophoresis; Mobility
**Abstract:** In this study, we improve on our 3D steady-state model of electrophoretic motion of spherical particles in bounded fluidic channels (Liu et al., 2014) to include the effect of nonsymmetric electrolytes, and further validate this improved model with detailed comparisons to experimental data. Specifically, we use the experimentally-measured particle mobilities from the work of Semenov et al. (2013), Napoli et al. (2011), and Wynne et al. (2012) to determine the corresponding particle zeta potentials using our model, and compare these results with classical theory. Incorporating the effects of nonsymmetric electrolytes, EDL polarization, and confinement, we show that our improved model is applicable to a wide range of practical experimental conditions, for example, particles that have high zeta potentials in a bounded channel filled with nonsymmetric electrolyte solutions, where classical theory is not applicable.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Langmuir
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.langmuir.5b03934
Volume: 32 Issue: 2 First Page #: 569
Date Submitted: 8/4/16 12:00AM Date Published: 12/21/15 8:00AM
Publication Location:
**Article Title:** Changes in Spectra and Conformation of Hairpin DNA-Stabilized Silver Nanoclusters Induced by Stem Sequence Perturbations
**Authors:** Jackson Travis Del Bonis-O'Donnell, Sumita Pennathur, Deborah K. Fygenson
**Keywords:** electrophoresis
**Abstract:** It is well-known that even small perturbations of the DNA sequence can drastically and unpredictably disrupt or alter the fluorescence of DNA-stabilized silver nanoclusters (DNA-AgNCs). Understanding how the structure of DNA affects the nanocluster that it stabilizes is the key to rationalizing such effects. We approach this challenge by strategically modifying the stem sequence of a hairpin DNA that hosts a spectrally pure, red-emitting nanocluster. Most of our modifications (base composition, sequence orientation, and loop location) reduce AgNC fluorescence in purity and shift it in wavelength, but one modification (appending poly(thymidine) to the 3? end of the stem) is inert with respect to fluorescence. Microfluidic capillary electrophoresis reveals that all of the modifications induce conformational changes of the DNA and that the original, spectrally pure nanocluster exists in two structurally distinct conformations.
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**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1514412113
Volume: 113 Issue: 5 First Page #: E597
Date Submitted: 8/4/16 12:00AM Date Published: 1/19/16 8:00AM
Publication Location:
**Article Title:** SutA is a bacterial transcription factor expressed during slow growth in
**Authors:** Brett M. Babin, Megan Bergkessel, Michael J. Sweredoski, Annie Moradian, Sonja Hess, Dianne K. Nev
**Keywords:** Pseudomonas aeruginosa; slow growth; transcription; proteomics; BONCAT
**Abstract:** Microbial quiescence and slow growth are ubiquitous physiological states, but their study is complicated by low levels of metabolic activity. To address this issue, we used a time-selective proteome-labeling method [bioorthogonal noncanonical amino acid tagging (BONCAT)] to identify proteins synthesized preferentially, but at extremely low rates, under anaerobic survival conditions by the opportunistic pathogen Pseudomonas aeruginosa. One of these proteins is a transcriptional regulator that has no homology to any characterized protein domains and is posttranscriptionally up-regulated during survival and slow growth. This small, acidic protein associates with RNA polymerase, and chromatin immunoprecipitation (ChIP) followed by high-throughput sequencing suggests that the protein associates with genomic DNA through this interaction.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chem. Sci.
Publication Identifier Type: DOI Publication Identifier: 10.1039/C5SC03340C
Volume: 7 Issue: 3 First Page #: 1797
Date Submitted: 8/4/16 12:00AM Date Published:
Publication Location:
**Article Title:** Time-resolved proteomic analysis of quorum sensing in Vibrio harveyi
**Authors:** John D. Bagert, Julia C. van Kessel, Michael J. Sweredoski, Lihui Feng, Sonja Hess, Bonnie L. Bassler,
**Keywords:** quorum sensing
**Abstract:** Bacteria use a process of chemical communication called quorum sensing to assess their population density and to change their behavior in response to fluctuations in the cell number and species composition of the community. In this work, we identified the quorum-sensing-regulated proteome in the model organism Vibrio harveyi by bio-orthogonal non-canonical amino acid tagging (BONCAT). BONCAT enables measurement of proteome dynamics with temporal resolution on the order of minutes. We deployed BONCAT to characterize the time-dependent transition of V. harveyi from individual- to group-behaviors. We identified 176 quorum-sensing-regulated proteins at early, intermediate, and late stages of the transition, and we mapped the temporal changes in quorum-sensing proteins controlled by both transcriptional and post-transcriptional mechanisms.
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**Journal:** Chemistry & Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.chembiol.2015.06.020
Volume: 22 Issue: 8 First Page #: 1108
Date Submitted: 8/4/16 12:00AM Date Published: 8/20/15 7:00AM
Publication Location:
**Article Title:** Genetically Encoded Spy Peptide Fusion System to Detect Plasma Membrane-Localized Proteins In Vivo
**Authors:** Claire N. Bedbrook, Mihoko Kato, Sripriya Ravindra Kumar, Anupama Lakshmanan, Ravi D. Nath, Fei S
**Keywords:** cellular state
**Abstract:** Membrane proteins are the main gatekeepers of cellular state, especially in neurons, serving either to maintain homeostasis or instruct response to synaptic input or other external signals. Visualization of membrane protein localization and trafficking in live cells facilitates understanding the molecular basis of cellular dynamics. We describe here a method for specifically labeling the plasma membrane-localized fraction of heterologous membrane protein expression using channelrhodopsins as a case study. We show that the genetically encoded, covalent binding SpyTag and SpyCatcher pair from the Streptococcus pyogenes fibronectin-binding protein FbaB can selectively label membrane-localized proteins in living cells in culture and in vivo in Caenorhabditis elegans.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Peptide Science
Publication Identifier Type: DOI Publication Identifier: 10.1002/psc.2858
Volume: 22 Issue: 4 First Page #: 196
Date Submitted: 8/4/16 12:00AM Date Published: 2/16/16 8:00AM
Publication Location:
**Article Title:** Degradation of Akt using protein-catalyzed capture agents
**Authors:** Ryan K. Henning, Joseph O. Varghese, Samir Das, Arundhati Nag, Grace Tang, Kevin Tang, Alexander
**Keywords:** protein-catalyzed capture
**Abstract:** Abnormal signaling of the protein kinase Akt has been shown to contribute to human diseases such as diabetes and cancer, but Akt has proven to be a challenging target for drugging. Using iterative in situ click chemistry, we recently developed multiple protein-catalyzed capture (PCC) agents that allosterically modulate Akt enzymatic activity in a protein-based assay. Here, we utilize similar PCCs to exploit endogenous protein degradation pathways. We use the modularity of the anti-Akt PCCs to prepare proteolysis targeting chimeric molecules that are shown to promote the rapid degradation of Akt in live cancer cells. These novel proteolysis targeting chimeric molecules demonstrate that the epitope targeting selectivity of PCCs can be coupled with non-traditional drugging moieties to inhibit challenging targets.
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**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201505243
Volume: 54 Issue: 45 First Page #: 13219
Date Submitted: 8/4/16 12:00AM Date Published: 9/17/15 7:00AM
Publication Location:
**Article Title:** A General Synthetic Approach for Designing Epitope Targeted Macrocyclic Peptide Ligands
**Authors:** Samir Das, Arundhati Nag, JingXin Liang, David N. Bunck, Aiko Umeda, Blake Farrow, Matthew B. Cop
**Keywords:** peptide binders
**Abstract:** We describe a general synthetic strategy for developing high-affinity peptide binders against specific epitopes of challenging protein biomarkers. The epitope of interest is synthesized as a polypeptide, with a detection biotin tag and a strategically placed azide (or alkyne) presenting amino acid. This synthetic epitope (SynEp) is incubated with a library of complementary alkyne or azide presenting peptides. Library elements that bind the SynEp in the correct orientation undergo the Huisgen cycloaddition, and are covalently linked to the SynEp. Hit peptides are tested against the full-length protein to identify the best binder. We describe development of epitope-targeted linear or macrocycle peptide ligands against 12 different diagnostic or therapeutic analytes. The general epitope targeting capability for these low molecular weight synthetic ligands enables a range of therapeutic and diagnostic applications, similar to those of monoclonal antibodies.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Bacteriology
Publication Identifier Type: DOI Publication Identifier: 10.1128/JB.00435-15
Volume: 198 Issue: 1 First Page #: 168
Date Submitted: 8/4/16 12:00AM Date Published: 10/19/15 7:00AM
Publication Location:
**Article Title:** Water and Small-Molecule Permeation of Dormant Bacillus subtilis Spores
**Authors:** Scott M. Knudsen, Nathan Cermak, Francisco Feijó Delgado, Barbara Setlow, Peter Setlow, Scott R. Ma
**Keywords:** microchannel resonator
**Abstract:** We use a suspended microchannel resonator to characterize the water and small-molecule permeability of Bacillus subtilis spores based on spores' buoyant mass in different solutions. Consistent with previous results, we found that the spore coat is not a significant barrier to small molecules, and the extent to which small molecules may enter the spore is size dependent. We have developed a method to directly observe the exchange kinetics of intraspore water with deuterium oxide, and we applied this method to wild-type spores and a panel of congenic mutants with deficiencies in the assembly or structure of the coat. Compared to wild-type spores, which exchange in approximately 1 s, several coat mutant spores were found to have relatively high water permeability with exchange times below the ?200-ms temporal resolution of our assay.
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**Journal:** Frontiers in Psychology
Publication Identifier Type: DOI Publication Identifier: 10.3389/fpsyg.2015.01320
Volume: 6 Issue: 1320 First Page #:
Date Submitted: 8/4/16 12:00AM Date Published: 9/8/15 7:00AM
Publication Location:
**Article Title:** Dubious decision evidence and criterion flexibility in recognition memory
**Authors:** Justin Kantner, Jean M. Vettel, Michael B. Miller
**Keywords:** memory
**Abstract:** When old–new recognition judgments must be based on ambiguous memory evidence, a proper criterion for responding “old” can substantially improve accuracy, but participants are typically suboptimal in their placement of decision criteria. Various accounts of suboptimal criterion placement have been proposed. The most parsimonious, however, is that subjects simply over-rely on memory evidence – however faulty – as a basis for decisions. We tested this account with a novel recognition paradigm in which old–new discrimination was minimal and critical errors were avoided by adopting highly liberal or conservative biases. In Experiment 1, criterion shifts were necessary to adapt to changing target probabilities or, in a “security patrol” scenario, to avoid either letting dangerous people go free (misses) or harming innocent people (false alarms). Experiment 2 added a condition in which financial incentives drove criterion shifts.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroscience.2015.08.046
Volume: 307 Issue: First Page #: 138
Date Submitted: 8/4/16 12:00AM Date Published: 10/29/15 7:00AM
Publication Location:
**Article Title:** Multiple stages of information processing are modulated during acute bouts of exercise
**Authors:** T. Bullock, H. Cecotti, B. Giesbrecht
**Keywords:** EEG; ERP; aerobic exercise; attention; cognition; physical activity
**Abstract:** Acute bouts of aerobic physical exercise can modulate subsequent cognitive task performance and oscillatory brain activity measured with electroencephalography (EEG). Here, we investigated the sequencing of these modulations of perceptual and cognitive processes using scalp recorded EEG acquired during exercise. Twelve participants viewed pseudo-random sequences of frequent non-target stimuli (cars), infrequent distractors (obliquely oriented faces) and infrequent targets that required a simple detection response (obliquely oriented faces, where the angle was different than the infrequent distractors). The sequences were presented while seated on a stationary bike under three conditions during which scalp recorded EEG was also acquired: rest, low-intensity exercise, and high-intensity exercise. Behavioral target detection was faster during high-intensity exercise compared to both rest and low-intensity exercise.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Science
Publication Identifier Type: DOI Publication Identifier: 10.1126/science.aad1431
Volume: 351 Issue: 6278 First Page #: 1192
Date Submitted: 8/4/16 12:00AM Date Published: 2/18/16 8:00AM
Publication Location:
**Article Title:** Early-branching gut fungi possess a large, comprehensive array of biomass-degrading enzymes
**Authors:** K. V. Solomon, C. H. Haitjema, J. K. Henske, S. P. Gilmore, D. Borges-Rivera, A. Lipzen, H. M. Brewer,
**Keywords:** lignocellulose bioprocessing
**Abstract:** The fungal kingdom is the source of almost all industrial enzymes in use for lignocellulose bioprocessing. We developed a systems-level approach that integrates transcriptomic sequencing, proteomics, phenotype, and biochemical studies of relatively unexplored basal fungi. Anaerobic gut fungi isolated from herbivores produce a large array of biomass-degrading enzymes that synergistically degrade crude, untreated plant biomass and are competitive with optimized commercial preparations from Aspergillus and Trichoderma. Compared to these model platforms, gut fungal enzymes are unbiased in substrate preference due to a wealth of xylan-degrading enzymes. These enzymes are universally catabolite-repressed and are further regulated by a rich landscape of noncoding regulatory RNAs. Additionally, we identified several promising sequence-divergent enzyme candidates for lignocellulosic bioprocessing.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Metabolic Engineering
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.ymben.2015.10.010
Volume: 33 Issue: First Page #: 28
Date Submitted: 8/4/16 12:00AM Date Published: 11/10/15 8:00AM
Publication Location:
**Article Title:** Modular and selective biosynthesis of gasoline-range alkanes
**Authors:** Micah J. Sheppard, Aditya M. Kunjapur, Kristala L.J. Prather
**Keywords:** Alkanes; Biofuel; E. coli; Gasoline; Metabolic engineering; Synthetic biology
**Abstract:** Typical renewable liquid fuel alternatives to gasoline are not entirely compatible with current infrastructure. We have engineered Escherichia coli to selectively produce alkanes found in gasoline (propane, butane, pentane, heptane, and nonane) from renewable substrates such as glucose or glycerol. Our modular pathway framework achieves carbon-chain extension by two different mechanisms. A fatty acid synthesis route is used to generate longer chains heptane and nonane, while a more energy efficient alternative, reverse-?-oxidation, is used for synthesis of propane, butane, and pentane. We demonstrate that both upstream (thiolase) and intermediate (thioesterase) reactions can act as control points for chain-length specificity. Specific free fatty acids are subsequently converted to alkanes using a broad-specificity carboxylic acid reductase and a cyanobacterial aldehyde decarbonylase (AD).
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**Journal:** Journal of Analytical & Bioanalytical Techniques
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Volume: Issue: S13 First Page #:
Date Submitted: 8/4/16 12:00AM Date Published:
Publication Location:
**Article Title:** Interplay between Peptide Length, Ionic Strength and pH in Electrophoretic Separations of Polyglutamate
**Authors:** Neeraja Venkateswaran, Joshua M Kogot, Sumita Pennathur
**Keywords:** Capillary electrophoresis; Microfluidics; Peptides; Ionic strength; Persistence length; Electrostatics; Polyglutamate; Species selectivity
**Abstract:** A fundamental study of peptide transport behavior provides information about length dependent transport and sequence structure relationships. In these highly accurate investigations of peptide electrokinetic properties and peptide conformations using a Micro-Electro-Mechanical Systems (MEMS)-fabricated capillary zone electrophoresis (CZE) platform, we demonstrate accurate and repeatable separations of polyglutamate peptides of two different lengths (10 and 20 amino acids). We investigate this separation phenomenon as a function of electrolyte concentration and ionic composition, counter-ion radius, ionic strength and pH. We report a length-dependent counter-ion species selectivity and enhanced separation at pH much higher than the pKa of the peptides that can aid in understanding the relationship between the function of biological peptides and their microenvironments.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Annals of the New York Academy of Sciences
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Volume: 1359 Issue: 1 First Page #: 47
Date Submitted: 8/4/16 12:00AM Date Published: 10/1/15 7:00AM
Publication Location:
**Article Title:** Hemispheric lateralization in reasoning
**Authors:** Benjamin O. Turner, Nicole Marinsek, Emily Ryhal, Michael B. Miller
**Keywords:** neural loci
**Abstract:** A growing body of evidence suggests that reasoning in humans relies on a number of related processes whose neural loci are largely lateralized to one hemisphere or the other. A recent review of this evidence concluded that the patterns of lateralization observed are organized according to two complementary tendencies. The left hemisphere attempts to reduce uncertainty by drawing inferences or creating explanations, even at the cost of ignoring conflicting evidence or generating implausible explanations. Conversely, the right hemisphere aims to reduce conflict by rejecting or refining explanations that are no longer tenable in the face of new evidence. In healthy adults, the hemispheres work together to achieve a balance between certainty and consistency, and a wealth of neuropsychological research supports the notion that upsetting this balance results in various failures in reasoning, including delusions. However, support for this model from the neuroimaging literature is mixed.
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**Journal:** IEEE Transactions on Wireless Communications
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Volume: 15 Issue: 3 First Page #: 2039
Date Submitted: 8/9/16 12:00AM Date Published: 3/2/16 12:00AM
Publication Location:
**Article Title:** A Scalable Architecture for Distributed Receive Beamforming: Analysis and Experimental Demonstration
**Authors:** Franois Quitin, Andrew. T. Irish, Upamanyu Madhow
**Keywords:** Distributed MIMO; beamforming; cooperative reception; synchronization
**Abstract:** We propose, analyze, and demonstrate an architecture for scalable cooperative reception. In a cluster of N + 1 receive nodes, one node is designated as the final receiver, and the N other nodes act as amplify-and-forward relays, which adapt their phases such that the relayed signals add up constructively at the designated receiver. This yields received SNR scaling linearly with N, while avoiding the linear increase in overhead incurred by a direct approach in which received signals are separately quantized and transmitted for centralized processing. By transforming the task of long-distance distributed receive beamforming into one of local distributed transmit beamforming, we can leverage a scalable one-bit feedback algorithm for phase synchronization. We show that time division between the long-distance and local links eliminates the need for explicit frequency synchronization.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLOS One
Publication Identifier Type: DOI Publication Identifier: 10.1371/ journal.pone.0152950
Volume: 11 Issue: 4 First Page #: e0152950
Date Submitted: 8/9/16 12:00AM Date Published: 4/4/16 5:26PM
Publication Location:
**Article Title:** Optimizing real-time vaccine allocation in a stochastic SIR model
**Authors:** C. Nguyen and J. M. Carlson
**Keywords:** Vaccines; Vaccination and immunization; Infectious disease epidemiology; Spatial epidemiology; Probability distribution; Transportation; Disease dynamics; Pertussis
**Abstract:** Real-time vaccination following an outbreak can effectively mitigate the damage caused by an infectious disease. However, in many cases, available resources are insufficient to vaccinate the entire at-risk population, logistics result in delayed vaccine deployment, and the interaction between members of different cities facilitates a wide spatial spread of infection. Limited vaccine, time delays, and interaction (or coupling) of cities lead to tradeoffs that impact the overall magnitude of the epidemic. These tradeoffs mandate investigation of optimal strategies that minimize the severity of the epidemic by prioritizing allocation of vaccine to specific subpopulations. We use an SIR model to describe the disease dynamics of an epidemic which breaks out in one city and spreads to another. We solve a master equation to determine the resulting probability distribution of the final epidemic size.
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**Journal:** Nature
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Volume: 6 Issue: First Page #: 8414
Date Submitted: 8/9/16 12:00AM Date Published: 10/1/15 5:51PM
Publication Location:
**Article Title:** Controllability of structural brain networks
**Authors:** Shi Gu, Fabio Pasqualetti, Matthew Cieslak, Qawi K. Telesford, Alfred B. Yu, Ari E. Kahn, John D. Meda
**Keywords:** Biological sciences; Neuroscience; Systems biology; Applied physics
**Abstract:** Cognitive function is driven by dynamic interactions between large-scale neural circuits or networks, enabling behaviour. However, fundamental principles constraining these dynamic network processes have remained elusive. Here we use tools from control and network theories to offer a mechanistic explanation for how the brain moves between cognitive states drawn from the network organization of white matter microstructure. Our results suggest that densely connected areas, particularly in the default mode system, facilitate the movement of the brain to many easily reachable states. Weakly connected areas, particularly in cognitive control systems, facilitate the movement of the brain to difficult-to-reach states. Areas located on the boundary between network communities, particularly in attentional control systems, facilitate the integration or segregation of diverse cognitive systems.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Methods
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.ymeth.2016.05.012
Volume: 106 Issue: First Page #: 86
Date Submitted: 8/22/16 12:00AM Date Published: 5/19/16 7:00AM
Publication Location:
**Article Title:** Computational analysis of fitness landscapes and evolutionary networks from in vitro evolution experiments
**Authors:** Ramon Xulvi-Brunet, Gregory W. Campbell, Sudha Rajamani, José I. Jiménez, Irene A. Chen
**Keywords:** In vitro evolution; RNA selection; Fitness landscape
**Abstract:** In vitro selection experiments in biochemistry allow for the discovery of novel molecules capable of specific desired biochemical functions. However, this is not the only benefit we can obtain from such selection experiments. Since selection from a random library yields an unprecedented, and sometimes comprehensive, view of how a particular biochemical function is distributed across sequence space, selection experiments also provide data for creating and analyzing molecular fitness landscapes, which directly map function (phenotypes) to sequence information (genotypes). Given the importance of understanding the relationship between sequence and functional activity, reliable methods to build and analyze fitness landscapes are needed. Here, we present some statistical methods to extract this information from pools of RNA molecules. We also provide new computational tools to construct and study molecular fitness landscapes.
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**Journal:** ACS Nano
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Volume: 10 Issue: 5 First Page #: 5243
Date Submitted: 8/22/16 12:00AM Date Published: 5/3/16 7:00AM
Publication Location:
**Article Title:** Particles with Tunable Porosity and Morphology by Controlling Interfacial Instability in Block Copolymer Emulsions
**Authors:** Kang Hee Ku, Jae Man Shin, Daniel Klinger, Se Gyu Jang, Ryan C. Hayward, Craig J. Hawker, Bumjoo
**Keywords:** porous particle; block copolymer; interfacial instability; emulsion droplet; drug-delivery
**Abstract:** A series of porous block copolymer (BCP)?particles with controllable morphology and pore sizes was? fabricated by tuning the interfacial behavior of BCP droplets?in oil-in-water emulsions. A synergistic adsorption of? polystyrene-b-poly(4-vinylpyridine) (PS-b-P4VP) BCPs?and sodium dodecyl sulfate (SDS) to the surface of the? emulsion droplet induced a dramatic decrease in the?interfacial tension and generated interfacial instability at?the particle surface. In particular, the SDS concentration?and the P4VP volume fraction of PS-b-P4VP were key? parameters in determining the degree of interfacial?instability, leading to different types of particles including micelles, capsules, closed-porosity particles, and open-porosity particles with tunable pore sizes ranging from 10 to 500 nm. The particles with open-porosity could be used as pH- responsive, high capacity delivery systems where the uptake and release of multiple dyes could be achieved.
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**Journal:** Journal of Ocular Pharmacology and Therapeutics
Publication Identifier Type: DOI Publication Identifier: 10.1089/jop.2016.0022
Volume: 32 Issue: 5 First Page #: 317
Date Submitted: 8/22/16 12:00AM Date Published: 6/9/16 7:00AM
Publication Location:
**Article Title:** Induced Pluripotent Stem Cell-Derived Retinal Pigmented Epithelium: A Comparative Study Between Cell Lines and Differentiation Methods
**Authors:** Lyndsay L. Leach, Roxanne H. Croze, Qirui Hu, Vignesh P. Nadar, Tracy N. Clevenger, Britney O. Penr
**Keywords:** induced pluripotent stem cell-derived retinal pigmented epithelium
**Abstract:** Purpose: The application of induced pluripotent stem cell-derived retinal pigmented epithelium (iPSC-RPE) in patients with retinal degenerative disease is making headway toward the clinic, with clinical trials already underway. Multiple groups have developed methods for RPE differentiation from pluripotent cells, but previous studies have shown variability in iPSC propensity to differentiate into RPE. Methods: This study provides a comparison between 2 different methods for RPE differentiation: (1) a com- monly used spontaneous continuously adherent culture (SCAC) protocol and (2) a more rapid, directed dif- ferentiation using growth factors. Integration-free iPSC lines were differentiated to RPE, which were characterized with respect to global gene expression, expression of RPE markers, and cellular function. Results: We found that all 5 iPSC lines (iPSC-1, iPSC-2, iPSC-3, iPSC-4, and iPSC-12) generated RPE using the directed differentiation protocol.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Graefe's Archive for Clinical and Experimental Ophthalmology
Publication Identifier Type: DOI Publication Identifier: 10.1007/s00417-016-3386-y
Volume: 254 Issue: 8 First Page #: 1553
Date Submitted: 8/22/16 12:00AM Date Published: 6/22/16 7:00AM
Publication Location:
**Article Title:** Subretinal implantation of a monolayer of human embryonic stem cell-derived retinal pigment epithelium: a feasibility and safety study in Yucatán minipigs
**Authors:** Michael J. Koss, Paulo Falabella, Francisco R. Stefanini, Marcel Pfister, Biju B. Thomas, Amir H. Kasha
**Keywords:** Animal model; Human embryonic stem cells; Macular degeneration; Preclinical trial; Retinal pigment epithelium
**Abstract:** PURPOSE: A subretinal implant termed CPCB-RPE1 is currently being developed to surgically replace dystrophic RPE in patients with dry age-related macular degeneration (AMD) and severe vision loss. CPCB-RPE1 is composed of a terminally differentiated, polarized human embryonic stem cell-derived RPE (hESC-RPE) monolayer pre-grown on a biocompatible, mesh-supported submicron parylene C membrane. The objective of the present delivery study was to assess the feasibility and 1-month safety of CPCB-RPE1 implantation in Yucatán minipigs, whose eyes are similar to human eyes in size and gross retinal anatomy. METHODS: This was a prospective, partially blinded, randomized study in 14 normal-sighted female Yucatán minipigs (aged 2 months, weighing 24-35 kg). Surgeons were blinded to the randomization codes and postoperative and post-mortem assessments were performed in a blinded manner.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nanoscale
Publication Identifier Type: DOI Publication Identifier: 10.1039/C6NR03827A
Volume: 8 Issue: 30 First Page #: 14489
Date Submitted: 8/22/16 12:00AM Date Published:
Publication Location:
**Article Title:** A universal design for a DNA probe providing ratiometric fluorescence detection by generation of silver nanoclusters
**Authors:** Jackson Travis Del Bonis-O'Donnell, Daniel Vong, Sumita Pennathur, Deborah Kuchnir Fygenson
**Keywords:** DNA-stabilized silver nanoclusters
**Abstract:** DNA-stabilized silver nanoclusters (AgNCs), the fluorescence emission of which can rival that of typical organic fluorophores, have made possible a new class of label-free molecular beacons for the detection of single-stranded DNA. Like fluorophore-quencher molecular beacons (FQ-MBs) AgNC-based molecular beacons (AgNC-MBs) are based on a single-stranded DNA that undergoes a conformational change upon binding a target sequence. The new conformation exposes a stretch of single-stranded DNA capable of hosting a fluorescent AgNC upon reduction in the presence of Ag+ ions. The utility of AgNC-MBs has been limited, however, because changing the target binding sequence unpredictably alters cluster fluorescence. Here we show that the original AgNC-MB design depends on bases in the target-binding (loop) domain to stabilize its AgNC. We then rationally alter the design to overcome this limitation.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Anaerobe
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.anaerobe.2015.11.008
Volume: 38 Issue: First Page #: 39
Date Submitted: 8/24/16 12:00AM Date Published: 11/24/15 8:00AM
Publication Location:
**Article Title:** Robust and effective methodologies for cryopreservation and DNA extraction from anaerobic gut fungi
**Authors:** Kevin V. Solomon, John K. Henske, Michael K. Theodorou, Michelle A. O'Malley
**Keywords:** Anaerobic fungi; Cryopreservation; Genome isolation; Gut fungi; Next generation sequencing; Microbiome; Genome sequencing; Non-model microbes
**Abstract:** Cell storage and DNA isolation are essential to developing an expanded suite of microorganisms for biotechnology. However, many features of non-model microbes, such as an anaerobic lifestyle and rigid cell wall, present formidable challenges to creating strain repositories and extracting high quality genomic DNA. Here, we establish accessible, high efficiency, and robust techniques to store lignocellu- lolytic anaerobic gut fungi long term without specialized equipment. Using glycerol as a cryoprotectant, gut fungal isolates were preserved for a minimum of 23 months at ┌80 ¶C. Unlike previously reported approaches, this improved protocol is non-toxic and rapid, with samples surviving twice as long with negligible growth impact. Genomic DNA extraction for these isolates was optimized to yield samples compatible with next generation sequencing platforms (e.g. Illumina, PacBio).
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Mechanics and Physics of Solids
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jmps.2016.04.008
Volume: Issue: First Page #:
Date Submitted: 8/24/16 12:00AM Date Published: 4/6/16 7:00AM
Publication Location:
**Article Title:** Load sharing in Bioinspired fibrillar adhesives with backing layer interactions and interfacial misalignment
**Authors:** Mattia Bacca, Jamie A. Booth, Kimberly L. Turner, Robert M. McMeeking
**Keywords:** Fibrillar adhesion; gecko adhesion; biomimetics; load sharing; contact mechanics
**Abstract:** Bio-inspired fibrillar adhesives rely on the utilization of short-range intermolecular forces harnessed by intimate contact at fibril tips. The combined adhesive strength of multiple fibrils can only be utilized if equal load sharing (ELS) is obtained at detachment. Previous investigations have highlighted that mechanical coupling of fibrils through a compliant backing layer gives rise to load concentration and the nucleation and propagation of interfacial flaws. However, misalignment of the adhesive and contacting surface has not been considered in theoretical treatments of load sharing with backing layer interactions. Alignment imperfections are difficult to avoid for a flat-on-flat interfacial configuration. In this work we demonstrate that interfacial misalignment can significantly alter load sharing and the kinematics of detachment in a model adhesive system.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of The Royal Society Interface
Publication Identifier Type: DOI Publication Identifier: 10.1098/rsif.2016.0285
Volume: 13 Issue: 120 First Page #: 20160285
Date Submitted: 8/24/16 12:00AM Date Published: 7/6/16 7:00AM
Publication Location:
**Article Title:** Wavelength-specific forward scattering of light by Bragg-reflective iridocytes in giant clams
**Authors:** Amitabh Ghoshal, Elizabeth Eck, Michael Gordon, Daniel E. Morse
**Keywords:** Tridacna; Symbiodinium; solar; photonic; refractive index; Mie
**Abstract:** A surprising recent discovery revealed that the brightly reflective cells (‘irido- cytes’) in the epithelia of giant clams actually send the majority of incident photons ‘forward’ into the tissue. While the intracellular Bragg reflectors in these cells are responsible for their colourful back reflection, Mie scattering produces the forward scattering, thus illuminating a dense population of endosymbiotic, photosynthetic microalgae. We now present a detailed micro-spectrophotometric characterization of the Bragg stacks in the iridocytes in live tissue to obtain the refractive index of the high-index layers (1.39 to 1.58, average 1.44+0.04), the thicknesses of the high- and low-index layers (50–150 nm), and the numbers of pairs of layers (2–11) that participate in the observed spectral reflection. Based on these measurements, we performed electromagnetic simulations to better understand the optical behaviour of the iridocytes.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Extreme Mechanics Letters
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.eml.2016.04.003
Volume: 8 Issue: First Page #: 96
Date Submitted: 8/28/17 12:00AM Date Published: 4/23/16 2:00PM
Publication Location:
**Article Title:** Deposition of ordered two-phase materials using microfluidic print nozzles with acoustic focusing
**Authors:** Rachel R. Collino, Tyler R. Ray, Rachel C. Fleming, James D. Cornell, Brett G. Compton, Matthew R. B
**Keywords:** Additive manufacturing; 3D printing; Microfluidics; Acoustic waves
**Abstract:** The deposition of multiphase materials with microstructural control would enable new fabrication modalities, such as spatial variation in composition and the integration of microstructure and structural features. In this work, acoustically-excited microfluidic print nozzles were used to tailor the microstructure of printed composite filaments consisting of SiC fibers, solid $BaTiO_3$ spheres, or hollow $SiO_2$ spheres in an epoxy matrix. The results demonstrate that acoustic focusing is a promising technique to control microparticles and deposit two-phase ordered structures using a single nozzle. In addition to tuning the microstructure within a single print line, the overall concentration of particles can be increased by focusing the particle stream in a branched geometry, enabling the deposition of material with higher particle volume fractions than the initial ink composition.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Materials
Publication Identifier Type: DOI Publication Identifier: 10.1038/nmat4719
Volume: Issue: First Page #:
Date Submitted: 8/24/16 12:00AM Date Published: 8/8/16 7:00AM
Publication Location:
**Article Title:** The nanocomposite nature of bone drives its strength and damage resistance
**Authors:** Ottman A. Tertuliano, Julia R. Greer
**Keywords:** Biomineralization; Mechanical properties; Scaling laws
**Abstract:** In human bone, an amorphous mineral serves as a precursor to the formation of a highly substituted nanocrystalline apatite. However, the precise role of this amorphous mineral remains unknown. Here, we show by using transmission electron microscopy that 100–300 nm amorphous calcium phosphate regions are present in the disordered phase of trabecular bone. Nanomechanical experiments on cylindrical samples, with diameters between 250 nm and 3,000 nm, of the bone's ordered and disordered phases revealed a transition from plastic deformation to brittle failure and at least a factor-of-2 higher strength in the smaller samples. We postulate that this transition in failure mechanism is caused by the suppression of extrafibrillar shearing in the smaller samples, and that the emergent smaller-is-stronger size effect is related to the sample-size scaling of the distribution of flaws.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Analytical & Bioanalytical Techniques
Publication Identifier Type: DOI Publication Identifier: 10.4172/2155-9872.1000318
Volume: 7 Issue: 3 First Page #:
Date Submitted: 8/24/16 12:00AM Date Published:
Publication Location:
**Article Title:** Assessing Stability, Durability, and Protein Adsorption Behavior of Hydrophilic Silane Coatings in Glass Microchannels
**Authors:** Sean Williams, Neeraja Venkateswaran, Travis Del Bonis O'Donnell, Pete Crisalli, Sameh Helmy, Maria
**Keywords:** Non-specific adsorption; Microfluidic separations; Protein-surface interactions; Surface coatings; Silane coatings
**Abstract:** Microfluidics-based separation of biomolecules has numerous applications, including fundamental characterization of biomolecules, sequencing of genomes for biological functions, biometric fingerprinting, and identification of pathogens and genetic diseases. One of the main drawbacks, however, for making microfluidic based separations more commercially viable is the non-specific adsorption of biomolecules at the channel walls during separations. Herein, we compare five commonly employed surface coatings, and evaluate their performance in terms of successful silanization of channel surface walls, long term stability, and antifouling performance, using BSA or IgG as model proteins. We compare adsorption of fluorescently-tagged proteins on glass slides with those confined within channels, showing similar behavior with static measurements, but differences when incorporating electrokinetic flow.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 0-Other
**Journal:** Please Delete
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2016.05.078
Volume: Issue: First Page #:
Date Submitted: 8/30/19 12:00AM Date Published: 6/1/16 11:00AM
Publication Location:
**Article Title:** Please Delete
**Authors:** Please Delete
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**Abstract:** Please Delete
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Consciousness and Cognition
Publication Identifier Type: Publication Identifier: 10.1016/j.concog.2015.12.003
Volume: 40 Issue: First Page #: 79
Date Submitted: 8/24/16 12:00AM Date Published: 1/5/16 8:19PM
Publication Location:
**Article Title:** Consciousness isn't all-or-none: evidence for partial awareness during the attentional blink
**Authors:** James C. Elliott, Benjamin Baird, Barry Giesbrecht
**Keywords:** Attention; Partial awareness; Attentional blink
**Abstract:** Alternative views of the nature of consciousness posit that awareness of an object is either an all-or-none phenomenon or that awareness can be partial, occurring independently for different levels of representation. The all-or-none hypothesis predicts that when one fea- ture of an object is identified, all other features should be consciously accessible. The par- tial awareness hypothesis predicts that one feature may reach consciousness while others do not. These competing predictions were tested in two experiments that presented two targets within a central stream of letters. We used the attentional blink evoked by the first target to assess consciousness for two different features of the second target. The results provide evidence that there can be a severe impairment in conscious access to one feature even when another feature is accurately reported.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 5-Submitted
**Journal:** Journal of Experimental Psychology: Human Perception and Performance
Publication Identifier Type: DOI Publication Identifier: 10.1037/xhp0000101
Volume: 41 Issue: 6 First Page #: 1588
Date Submitted: 8/24/16 12:00AM Date Published:
Publication Location:
**Article Title:** Flexible human collective wisdom
**Authors:** Mordechai Z. Juni, Miguel P. Eckstein
**Keywords:** group decision making; signal detection theory; ideal observer analysis; Bayesian optimal; wisdom of crowds
**Abstract:** Group decisions typically outperform individual decisions. But how do groups combine their individual decisions to reach their collective decisions? Previous studies conceptualize collective decision-making using static combination rules, be it a majority-voting rule or a weighted averaging rule. Unknown is whether groups adapt their combination rules to changing information environments. We implemented a novel paradigm for which information obeyed a mixture of distributions, such that the optimal Bayesian rule is non-linear and often follows minority opinions, while the majority rule leads to suboptimal but above chance performance. Using perceptual (Exp1) and cognitive (Exp2) signal detection tasks, we switched the information environment halfway through the experiments to a mixture of distributions without informing participants. Groups gradually abandoned the majority rule to follow any minority opinion advocating signal presence with high confidence.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Cell Chemical Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.chembiol.2017.02.008
Volume: 24 Issue: 3 First Page #: 415
Date Submitted: 8/28/17 12:00AM Date Published: 3/2/17 8:00AM
Publication Location:
**Article Title:** Directed Evolution of a Bright Near-Infrared Fluorescent Rhodopsin Using a Synthetic Chromophore
**Authors:** Lukas Herwig, Austin J. Rice, Claire N. Bedbrook, Ruijie K. Zhang, Antti Lignell, Jackson K.B. Cahn, Ha
**Keywords:** synthetic chromophore substitution, directed evolution, protein engineering, near-infrared fluorescence, Archaerhodopsin, live-cell imaging
**Abstract:** By engineering a microbial rhodopsin, Archaerhodopsin-3 (Arch), to bind a synthetic chromophore, merocyanine retinal, in place of the natural chromophore all-trans-retinal (ATR), we generated a protein with exceptionally bright and unprecedentedly red-shifted near-infrared (NIR) fluorescence. We show that chromophore substitution generates a fluorescent Arch complex with a 200-nm bathochromic excitation shift relative to ATR-bound wild-type Arch and an emission maximum at 772 nm. Directed evolution of this complex produced variants with pH-sensitive NIR fluorescence and molecular brightness 8.5-fold greater than the brightest ATR-bound Arch variant. The resulting proteins are well suited to bacterial imaging; expression and stability have not been optimized for mammalian cell imaging. By targeting both the protein and its chromophore, we overcome inherent challenges associated with engineering bright NIR fluorescence into Archaerhodopsin. This work demonstrates an efficient strategy fo
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1700269114
Volume: 114 Issue: 13 First Page #: E2624
Date Submitted: 8/28/17 12:00AM Date Published: 3/11/17 12:00AM
Publication Location:
**Article Title:** Structure-guided SCHEMA recombination generates diverse chimeric channelrhodopsins
**Authors:** Claire N. Bedbrook, Austin J. Rice, Kevin K. Yang, Xiaozhe Ding, Siyuan Chen, Emily M. LeProust, Vivi
**Keywords:** membrane proteins; channelrhodopsin; structure-guided recombination; chimeragenesis
**Abstract:** Integral membrane proteins (MPs) are key engineering targets due to their critical roles in regulating cell function. In engineering MPs, it can be extremely challenging to retain membrane localization capability while changing other desired properties. We have used structure-guided SCHEMA recombination to create a large set of functionally diverse chimeras from three sequence-diverse channelrhodopsins (ChRs). We chose 218 ChR chimeras from two SCHEMA libraries and assayed them for expression and plasma membrane localization in human embryonic kidney cells. The majority of the chimeras express, with 89% of the tested chimeras outperforming the lowest-expressing parent; 12% of the tested chimeras express at even higher levels than any of the parents. A significant fraction (23%) also localize to the membrane better than the lowest-performing parent ChR. Most (93%) of these well-localizing chimeras are also functional light-gated channels.
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**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201701964
Volume: 56 Issue: 23 First Page #: 6519
Date Submitted: 8/28/17 12:00AM Date Published: 4/26/17 2:00PM
Publication Location:
**Article Title:** Anaerobic Respiration on Self-Doped Conjugated Polyelectrolytes: Impact of Chemical Structure
**Authors:** Nathan D. Kirchhofer, Samantha R. McCuskey, Cheng-Kang Mai, Guillermo C. Bazan
**Keywords:** conjugated polyelectrolytes; electron transport; microbial electrochemical cells; self-doped polymers; structure–activity relationships
**Abstract:** We probe anaerobic respiration of bacteria in the presence of conjugated polyelectrolytes (CPEs). Three different CPEs were used to probe how structural variations impact biocurrent generation from Shewanella oneidensis MR-1. For the self-doped anionic CPE only, absorption spectroscopy shows that the addition of S. oneidensis MR-1 leads to the disappearance of the polaron (radical cation) band at >900?nm and an increase in the band at 735?nm due to the neutral species, consistent with electron transfer from microbe to polymer. Microbial three-electrode electrochemical cells (M3Cs) show an increase in the current generated by S. oneidensis MR-1 with addition of the self-doped CPE relative to other CPEs and controls. These experiments combined with in situ cyclic voltammetry suggest that the doped CPE facilitates electron transport to electrodes and reveal structure–function relationships relevant to developing materials for biotic/abiotic interfaces.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Phys. Chem. Chem. Phys.
Publication Identifier Type: DOI Publication Identifier: 10.1039/C6CP03583C
Volume: 18 Issue: 27 First Page #: 17815
Date Submitted: 8/28/17 12:00AM Date Published: 6/8/16 2:00PM
Publication Location:
**Article Title:** Biofilm as a redox conductor: a systematic study of the moisture and temperature dependence of its electrical properties
**Authors:** Hung Phan, Matthew D. Yates, Nathan D. Kirchhofer, Guillermo C. Bazan, Leonard M. Tender, Thuc-Qu
**Keywords:** Microbial Biofilms, Redox, Electrical Conductivity
**Abstract:** Some microbial biofilms are electrically conductive. However, the mechanism of electron transport remains unclear. Here, we show that lm-scale long-distance electron transport through electrodegrown Geobacter sulfurreducens biofilms occurs via redox conduction, as determined by electrical measurements performed under varied hydration states and temperatures.
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**Journal:** Small
Publication Identifier Type: DOI Publication Identifier: 10.1002/smll.201600697
Volume: 12 Issue: 35 First Page #: 4873
Date Submitted: 8/28/17 12:00AM Date Published: 7/21/16 7:00AM
Publication Location:
**Article Title:** Encapsulated Conjugated Oligomer Nanoparticles for Real-Time Photoacoustic Sentinel Lymph Node Imaging and Targeted Photothermal Therapy
**Authors:** Xiaolei Cai, Xiaofeng Liu, Lun-De Liao, Aishwarya Bandla, Ji Min Ling, Yu-Hang Liu, Nitish Thakor, Guill
**Keywords:** Encapsulated Conjugated Oligomer Nanoparticles Real-Time Photoacoustic Sentinel Lymph Node Imaging Targeted Photothermal Therapy
**Abstract:** Noninvasive and nonionizing imaging of sentinel lymph nodes (SLN) is highly desirable for the detection of breast cancer metastasis through sentinel lymph node biopsy. Photoacoustic (PA) imaging is an emerging imaging technique that can serve as a suitable approach for SLN imaging. Herein, novel conjugated oligomer based nanoparticles (NPs) with strong NIR absorption, good biocompatibility, excellent PA contrast, and good photothermal conversion effi ciency are reported. Real-time PA imaging of SLN reveals high resolution of the NPs via injection from the left forepaw pad. In addition, the surface functionalized NPs can target breast cancer cells and kill them effi ciently and specifi cally through photothermal therapy upon 808 nm laser irradiation. This work shows great potential of the nanoparticle PA contrast agent to serve as a multifunctional probe for photothermal therapy at SLNs to achieve the inhibition of cancer cell metastasis in the near future.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chem. Sci.
Publication Identifier Type: DOI Publication Identifier: 10.1039/C6SC00630B
Volume: 7 Issue: 9 First Page #: 5714
Date Submitted: 8/28/17 12:00AM Date Published: 6/1/16 7:00AM
Publication Location:
**Article Title:** Influence of molecular structure on the antimicrobial function of phenylenevinylene conjugated oligoelectrolytes
**Authors:** Hengjing Yan, Zachary D. Rengert, Alexander W. Thomas, Carolin Rehermann, Jamie Hinks, Guillermo
**Keywords:** molecular structure antimicrobial function conjugated oligoelectrolytes
**Abstract:** Conjugated oligoelectrolytes (COEs) with phenylenevinylene (PV) repeat units are known to spontaneously intercalate into cell membranes. Twelve COEs, including seven structures reported here for the first time, were investigated for the relationship between their membrane disrupting properties and structural modifications, including the length of the PV backbone and the presence of either a tetraalkylammonium or a pyridinium ionic pendant group. Optical characteristics and interactions with cell membranes were determined using UV-Vis absorption and photoluminescence spectroscopies, and confocal microscopy. Toxicity tests on representative Gram-positive (Enterococcus faecalis) and Gram-negative (Escherichia coli) bacteria reveal generally greater toxicity to E. faecalis than to E. coli and indicate that shorter molecules have superior antimicrobial activity. Increased antimicrobial potency was observed in threering COEs appended with pyridinium ionic groups but not with COEs with four o
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** RSC Adv.
Publication Identifier Type: DOI Publication Identifier: 10.1039/C6RA23083K
Volume: 6 Issue: 102 First Page #: 100300
Date Submitted: 8/28/17 12:00AM Date Published: 10/14/16 7:00AM
Publication Location:
**Article Title:** Membrane permeabilization by conjugated oligoelectrolytes accelerates whole-cell catalysis
**Authors:** Chelsea Catania, Caroline M. Ajo-Franklin, Guillermo C. Bazan
**Keywords:** Membrane permeabilization; conjugated oligoelectrolytes; catalysis
**Abstract:** Conjugated oligoelectrolytes (COEs) boost the electrical performance of a wide range of bioelectrochemical systems, yet their mechanismof action remains incompletely understood. One possiblemode of action is that COEs permeabilize the cell envelope. We thus examined the effect of tetracationic COE, DSSN+, on the permeability of the inner and outer membrane of Escherichia coli by detecting extracellular activity of normally periplasmic and cytoplasmic enzymes. DSSN+ increases the release of the periplasmic enzyme alkaline phosphatase (ALP) up to 20-fold, but does not significantly change the release of the cytoplasmic enzyme b-galactosidase. Additionally, DSSN+ caused a 2-fold increase in the turnover of a cytoplasmic substrate. These studies present a more complete understanding of the mechanism of action in bioelectrochemical systems and pivot future applications of COEs towards a method for improving wholecell catalysis.
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**Journal:** J. Mater. Chem. A
Publication Identifier Type: DOI Publication Identifier: 10.1039/C6TA07148A
Volume: 4 Issue: 40 First Page #: 15457
Date Submitted: 8/28/17 12:00AM Date Published: 9/16/16 7:00AM
Publication Location:
**Article Title:** Biomimetic wiring and stabilization of photosynthetic membrane proteins with block copolymer interfaces
**Authors:** Patrick O. Saboe, Emelia Conte, Stanley Chan, Hasin Feroz, Bryan Ferlez, Megan Farell, Matthew F. P
**Keywords:** biomimetic wiring; photosynthetic membrane proteins; block copolymer
**Abstract:** Integrating photosynthetic membrane proteins with non-biological materials such as polymers and electrodes is attractive, as it could allow new ways of harvesting solar energy for direct electrical power, sensing, or chemical production. However, such integration is challenging, as these proteins have to be “wired” to electrodes and oriented to maximize light capture and electron transfer all while maintaining long-term activity. In this work we present a durable and unique solution to the challenges of stabilization and wiring of photosynthetic membrane proteins on electrodes. A block copolymer, poly(butadiene)12-poly(ethylene oxide)8 (PB12-PEO8), that mimics the bilayer assembly of lipids was used to stabilize photosystem I (PSI) in a near-native hydrophobic environment. At high protein concentrations, large, highly packed planar membranes (4 nm thick) were formed, which allowed high surface loading of protein at the electrode interface. To “wire” these membranes with metal electrode
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**Journal:** Carbon
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Volume: 100 Issue: First Page #: 90
Date Submitted: 8/28/17 12:00AM Date Published: 4/1/16 7:00AM
Publication Location:
**Article Title:** New insights into the thermal reduction of graphene oxide: Impact of oxygen clustering
**Authors:** Priyank V. Kumar, Neelkanth M. Bardhan, Guan-Yu Chen, Zeyang Li, Angela M. Belcher, Jeffrey C. Grc
**Keywords:** graphene
**Abstract:** Graphene has attracted interest for a number of applications ranging from electronics, optoelectronics to membrane-based technologies. The thermal reduction of chemically exfoliated graphene oxide (GO) sheets represents an important step for large-scale, solution-based graphene synthesis. Therefore, understanding the reduction process and being able to provide new handles to control the resulting sheet properties is highly desirable. Using atomistic calculations combined with experiments, we study and demonstrate the impact of one such new handle – oxygen clustering on the graphene basal plane – on the structural and electrical properties of reduced GO (rGO) structures. Our calculations reveal that the number of oxygen and carbon atoms removed from the graphene plane during reduction can be tuned depending on the degree of oxygen clustering, without altering the reduction temperature.
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**Journal:** Advanced Functional Materials
Publication Identifier Type: DOI Publication Identifier: 10.1002/adfm.201603203
Volume: 27 Issue: 4 First Page #: 1603203
Date Submitted: 8/28/17 12:00AM Date Published: 1/26/17 8:00AM
Publication Location:
**Article Title:** M13 Virus Aerogels as a Scaffold for Functional Inorganic Materials
**Authors:** Sung Mi Jung, Jifa Qi, Dahyun Oh, Angela Belcher, Jing Kong
**Keywords:** inorganic materials; aerogels
**Abstract:** The filamentous M13 viruses are widely used as a bio-template to assemble many different functional structures. In this work, based on its shape anisotropy, reasonable aspect ratio (length to diameter of ?130), and low density, freestanding, bulk 3D aerogels are assembled from M13 for the first time. These ultralight porous structures demonstrate excellent mechanical properties with elastic behavior up to 90% compression. Furthermore, as the genome of M13 virus can be rationally engineered so that proteins on its capsid or ends can specifically bind to various inorganic materials, aerogels made from inorganic-complexed M13 structures with versatile functionalities are also developed. As examples for mono- and multi-component structures, M13-Ru and M13-CoFe2O4 are explored in this work. This method enables the production of a wide variety of freestanding inorganic material aerogels with extensive opportunities for bio-scaffolds, energy storage, thermoelectrics, catalysis, etc.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Nano
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsnano.6b06979
Volume: 11 Issue: 2 First Page #: 1548
Date Submitted: 8/28/17 12:00AM Date Published: 1/13/17 8:00AM
Publication Location:
**Article Title:** Enhanced Cell Capture on Functionalized Graphene Oxide Nanosheets through Oxygen Clustering
**Authors:** Neelkanth M. Bardhan, Priyank V. Kumar, Zeyang Li, Hidde L. Ploegh, Jeffrey C. Grossman, Angela M.
**Keywords:** enhanced cell capture efficiency; graphene oxide; improved functionalization; microfluidic-free; oxygen clustering; phase transformation; thermal annealing
**Abstract:** With the global rise in incidence of cancer and infectious diseases, there is a need for the development of techniques to diagnose, treat, and monitor these conditions. The ability to efficiently capture and isolate cells and other biomolecules from peripheral whole blood for downstream analyses is a necessary requirement. Graphene oxide (GO) is an attractive template nanomaterial for such biosensing applications. Favorable properties include its two-dimensional architecture and wide range of functionalization chemistries, offering significant potential to tailor affinity toward aromatic functional groups expressed in biomolecules of interest. However, a limitation of current techniques is that as-synthesized GO nanosheets are used directly in sensing applications, and the benefits of their structural modification on the device performance have remained unexplored.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLOS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1005178
Volume: 12 Issue: 11 First Page #:
Date Submitted: 8/28/17 12:00AM Date Published: 11/23/16 8:00AM
Publication Location:
**Article Title:** Individual Differences in Dynamic Functional Brain Connectivity across the Human Lifespan
**Authors:** Elizabeth N. Davison, Benjamin O. Turner, Kimberly J. Schlesinger, Michael B. Miller, Scott T. Grafton, I
**Keywords:** fMRI; hypergraph analysis; dynamic network theory
**Abstract:** Individual differences in brain functional networks may be related to complex personal identifiers, including health, age, and ability. Dynamic network theory has been used to identify properties of dynamic brain function from fMRI data, but the majority of analyses and findings remain at the level of the group. Here, we apply hypergraph analysis, a method from dynamic network theory, to quantify individual differences in brain functional dynamics. Using a summary metric derived from the hypergraph formalism—hypergraph cardinality—we investigate individual variations in two separate, complementary data sets. The first data set ("multi-task") consists of 77 individuals engaging in four consecutive cognitive tasks. We observe that hypergraph cardinality exhibits variation across individuals while remaining consistent within individuals between tasks; moreover, the analysis of one of the memory tasks revealed a marginally significant correspondence between hypergraph cardinality and age.
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**Journal:** NeuroImage
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Volume: 146 Issue: First Page #: 741
Date Submitted: 8/28/17 12:00AM Date Published: 2/1/17 8:00AM
Publication Location:
**Article Title:** Age-dependent changes in task-based modular organization of the human brain
**Authors:** Kimberly J. Schlesinger, Benjamin O. Turner, Brian A. Lopez, Michael B. Miller, Jean M. Carlson
**Keywords:** Aging; Dynamic networks; Modularity; fMRI
**Abstract:** As humans age, cognition and behavior change significantly, along with associated brain function and organization. Aging has been shown to decrease variability in functional magnetic resonance imaging (fMRI) signals, and to affect the modular organization of human brain function. In this work, we use complex network analysis to investigate the dynamic community structure of large-scale brain function, asking how evolving communities interact with known brain systems, and how the dynamics of communities and brain systems are affected by age. We analyze dynamic networks derived from fMRI scans of 104 human subjects performing a word memory task, and determine the time-evolving modular structure of these networks by maximizing the multislice modularity, thereby identifying distinct communities, or sets of brain regions with strong intra-set functional coherence.
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**Journal:** Nucleic Acids Research
Publication Identifier Type: DOI Publication Identifier: 10.1093/nar/gkx540
Volume: 45 Issue: 14 First Page #: 8167
Date Submitted: 8/28/17 12:00AM Date Published: 6/21/17 7:00AM
Publication Location:
**Article Title:** Analysis of in vitro evolution reveals the underlying distribution of catalytic activity among random sequences
**Authors:** Abe Pressman, Janina E. Moretti, Gregory W. Campbell, Ulrich F. Müller, Irene A. Chen
**Keywords:** catalytic activity
**Abstract:** The emergence of catalytic RNA is believed to have been a key event during the origin of life. Understanding how catalytic activity is distributed across random sequences is fundamental to estimating the probability that catalytic sequences would emerge. Here, we analyze the in vitro evolution of triphosphorylating ribozymes and translate their fitnesses into absolute estimates of catalytic activity for hundreds of ribozyme families. The analysis efficiently identified highly active ribozymes and estimated catalytic activity with good accuracy. The evolutionary dynamics follow Fisher's Fundamental Theorem of Natural Selection and a corollary, permitting retrospective inference of the distribution of fitness and activity in the random sequence pool for the first time. The frequency distribution of rate constants appears to be log-normal, with a surprisingly steep dropoff at higher activity.
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**Journal:** The Journal of Physical Chemistry Letters
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Volume: 8 Issue: First Page #: 4155
Date Submitted: 8/28/17 12:00AM Date Published: 8/15/17 7:00AM
Publication Location:
**Article Title:** Macroscopic Structural Compositions of ?-Conjugated Polymers: Combined Insights from Solid-State NMR and Molecular Dynamics Simulations
**Authors:** Anton Melnyk, Matthias J. N. Junk, Michael D. McGehee, Bradley F. Chmelka, Michael Ryan Hansen, D
**Keywords:** molecular dynamics simulations
**Abstract:** Molecular dynamics simulations are combined with solid-state NMR measurements to gain insight into the macroscopic structural composition of the ?-conjugated polymer poly(2,5-bis(3-tetradecyl-thiophen-2-yl)thieno [3,2-b]thiophene) (PBTTT). The structural and dynamical properties, as established by the NMR analyses, were used to test the local structure of three constitutient mesophases with (i) crystalline backbones and side chains, (ii) lamellar backbones and disordered side chains, or (iii) amorphous backbones and side chains. The relative compositions of these mesophases were then determined from the deconvolution of the 1H and 13C solid-state NMR spectra and dynamic order parameters. Surprisingly, on the basis of molecular dynamics simulations, the powder composition consisted of only 28% of the completely crystalline mesophase, while 23% was lamellar with disordered side chains and 49% amorphous.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/jacs.7b05269
Volume: Issue: First Page #:
Date Submitted: 8/28/17 12:00AM Date Published: 7/20/17 7:00AM
Publication Location:
**Article Title:** Proton-Based Structural Analysis of a Heptahelical Transmembrane Protein in Lipid Bilayers
**Authors:** Daniela Lalli, Matthew N. Idso, Loren B. Andreas, Sunyia Hussain, Naomi Baxter, Songi Han, Bradley F.
**Keywords:** membrane proteins
**Abstract:** The structures and properties of membrane proteins in lipid bilayers are expected to closely resemble those in native cell-membrane environments, although they have been difficult to elucidate. By performing solid-state NMR measurements at very fast (100 kHz) magic-angle spinning rates and at high (23.5 T) magnetic field, severe sensitivity and resolution challenges are overcome, enabling the atomic-level characterization of membrane proteins in lipid environments. This is demonstrated by extensive 1H-based resonance assignments of the fully protonated heptahelical membrane protein proteorhodopsin, and the efficient identification of numerous 1H–1H dipolar interactions, which provide distance constraints, inter-residue proximities, relative orientations of secondary structural elements, and protein–cofactor interactions in the hydrophobic transmembrane regions.
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**Journal:** Current Opinion in Systems Biology
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Volume: 1 Issue: First Page #: 16
Date Submitted: 8/29/17 12:00AM Date Published: 2/24/17 4:00PM
Publication Location:
**Article Title:** An operational view of intercellular signaling pathways
**Authors:** Yaron E. Antebi, Nagarajan Nandagopal, Michael B. Elowitz
**Keywords:** intercellular signaling pathways
**Abstract:** Animal cells use a conserved repertoire of intercellular signaling pathways to communicate with one another. These pathways are well-studied from a molecular point of view. However, we often lack an “operational” understanding that would allow us to use these pathways to rationally control cellular behaviors. This requires knowing what dynamic input features each pathway perceives and how it processes those inputs to control downstream processes. To address these questions, researchers have begun to reconstitute signaling pathways in living cells, analyzing their dynamic responses to stimuli, and developing new functional representations of their behavior. Here we review important insights obtained through these new approaches, and discuss challenges and opportunities in understanding signaling pathways from an operational point of view.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The Journal of Physical Chemistry B
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.jpcb.6b05704
Volume: 120 Issue: 31 First Page #: 7615
Date Submitted: 8/29/17 12:00AM Date Published: 7/14/16 7:00AM
Publication Location:
**Article Title:** Recent Developments in Fully Fluctuating Field-Theoretic Simulations of Polymer Melts and Solutions
**Authors:** Kris T. Delaney, Glenn H. Fredrickson
**Keywords:** Langevin sampling
**Abstract:** We review the latest developments in computational methods for direct simulation of fully fluctuating field theories of polymeric assemblies. In this context, we describe a newly developed theoretical and computational framework for accurately computing fluctuation-corrected phase diagrams of mesostructured polymer systems and report the first such complete phase diagram for a diblock copolymer melt. The method is based on complex Langevin sampling of a UV regularized field-theoretic model, with Helmholtz free energies computed using thermodynamic integration. UV regularization ensures that the free energies do not have an arbitrary reference; they can be compared between incommensurate phases, permitting for the first time the computation of order–order transitions with fluctuation corrections. We further demonstrate that computed free energies are accurate in the disordered phase by comparison to perturbation theory on the one-loop level.
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**Journal:** The Journal of Chemical Physics
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Volume: 145 Issue: First Page #: 154104
Date Submitted: 8/29/17 12:00AM Date Published: 10/17/16 2:00PM
Publication Location:
**Article Title:** Statistical field theory description of inhomogeneous polarizable soft matter
**Authors:** Jonathan M. Martin, Wei Li, Kris T. Delaney, Glenn H. Fredrickson
**Keywords:** statistical field theory
**Abstract:** We present a new molecularly informed statistical field theory model of inhomogeneous polarizable soft matter. The model is based on fluid elements, referred to as beads, that can carry a net monopole of charge at their center of mass and a fixed or induced dipole through a Drude-type distributed charge approach. The beads are thus polarizable and naturally manifest attractive van der Waals interactions. Beyond electrostatic interactions, beads can be given soft repulsions to sustain fluid phases at arbitrary densities. Beads of different types can be mixed or linked into polymers with arbitrary chain models and sequences of charged and uncharged beads. By such an approach, it is possible to construct models suitable for describing a vast range of soft-matter systems including electrolyte and polyelectrolyte solutions, ionic liquids, polymerized ionic liquids, polymer blends, ionomers, and block copolymers, among others.
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**Journal:** Attention, Perception, & Psychophysics
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Volume: 78 Issue: 7 First Page #: 2241
Date Submitted: 8/29/17 12:00AM Date Published: 4/15/16 7:00AM
Publication Location:
**Article Title:** Irrelevant learned reward associations disrupt voluntary spatial attention
**Authors:** Mary H. MacLean, Gisella K. Diaz, Barry Giesbrecht
**Keywords:** Attention: Selective; Attentional capture; Cognitive and attentional control
**Abstract:** Attention can be guided involuntarily by physical salience and by non-salient, previously learned reward associations that are currently task-irrelevant. Attention can be guided voluntarily by current goals and expectations. The current study examined, in two experiments, whether irrelevant reward associations could disrupt current, goal-driven, voluntary attention. In a letter-search task, attention was directed voluntarily (i.e., cued) on half the trials by a cue stimulus indicating the hemifield in which the target letter would appear with 100 % accuracy. On the other half of the trials, a cue stimulus was presented, but it did not provide information about the target hemifield (i.e., uncued). On both cued and uncued trials, attention could be involuntarily captured by the presence of a task-irrelevant, and physically non-salient, color, either within the cued or the uncued hemifield.
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**Journal:** Journal of Cognitive Neuroscience
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Volume: 29 Issue: 4 First Page #: 605
Date Submitted: 8/29/17 12:00AM Date Published: 4/1/17 7:00AM
Publication Location:
**Article Title:** Acute Exercise Modulates Feature-selective Responses in Human Cortex
**Authors:** Tom Bullock, James C. Elliott, John T. Serences, Barry Giesbrecht
**Keywords:** feature-selective neural response
**Abstract:** An organism's current behavioral state influences ongoing brain activity. Nonhuman mammalian and invertebrate brains exhibit large increases in the gain of feature-selective neural responses in sensory cortex during locomotion, suggesting that the visual system becomes more sensitive when actively exploring the environment. This raises the possibility that human vision is also more sensitive during active movement. To investigate this possibility, we used an inverted encoding model technique to estimate feature-selective neural response profiles from EEG data acquired from participants performing an orientation discrimination task. Participants (n = 18) fixated at the center of a flickering (15 Hz) circular grating presented at one of nine different orientations and monitored for a brief shift in orientation that occurred on every trial. Participants completed the task while seated on a stationary exercise bike at rest and during low- and high-intensity cycling.
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**Journal:** Optics Express
Publication Identifier Type: DOI Publication Identifier: 10.1364/OE.25.015778
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Date Submitted: 8/29/17 12:00AM Date Published: 6/27/17 2:00PM
Publication Location:
**Article Title:** Enhanced light extraction from free-standing InGaN/GaN light emitters using bio-inspired backside surface structuring
**Authors:** Christopher D. Pynn, Lesley Chan, Federico Lora Gonzalez, Alex Berry, David Hwang, Haoyang Wu, Ta
**Keywords:** Photoluminescence; Scattering, rough surfaces;Semiconductor materials
**Abstract:** Light extraction from InGaN/GaN-based multiple-quantum-well (MQW) light emitters is enhanced using a simple, scalable, and reproducible method to create hexagonally close-packed conical nano- and micro-scale features on the backside outcoupling surface. Colloidal lithography via Langmuir-Blodgett dip-coating using silica masks (d = 170-2530 nm) and Cl2/N2-based plasma etching produced features with aspect ratios of 3:1 on devices grown on semipolar GaN substrates. InGaN/GaN MQW structures were optically pumped at 266 nm and light extraction enhancement was quantified using angle-resolved photoluminescence. A 4.8-fold overall enhancement in light extraction (9-fold at normal incidence) relative to a flat outcoupling surface was achieved using a feature pitch of 2530 nm. This performance is on par with current photoelectrochemical (PEC) nitrogen-face roughening methods, which positions the technique as a strong alternative for backside structuring of c-plane devices.
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Volume: 35 Issue: 1 First Page #: 011201
Date Submitted: 8/29/17 12:00AM Date Published: 1/1/17 8:00AM
Publication Location:
**Article Title:** Fabrication and optical behavior of graded-index, moth-eye antireflective structures in CdTe
**Authors:** Lesley Chan, Amitabh Ghoshal, Eric A. DeCuir, Yuan Ping Chen, Daniel E. Morse, Michael J. Gordon
**Keywords:** antireflective structures
**Abstract:** A simple and scalable method, based on dip-coat colloidal lithography, mask reduction, and plasma-based pattern transfer, is presented to create graded-index, moth eye-inspired antireflective features on II–VI semiconductors. Hexagonal arrays of isolated conical frusta with tunable geometry (top diameter?=?200–1300?nm, pitch?=?310–2530?nm, and height?=?790–7100?nm) were realized by isotropic etching of various size silica colloid masks before pattern transfer into the underlying substrate. Substantial increases in single-side direct and total infrared (IR) transmission across the 4–20??m range (9%–15% for CdTe thin films and 18% for bulk CdTe) were achieved, in excellent agreement with transfer matrix calculations and finite difference time domain optical simulations. The fabrication method presented can be used to enhance efficiency in multiple IR application areas including photovoltaics, optical system components, detectors, and focal plane array imagers.
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**Journal:** Human Brain Mapping
Publication Identifier Type: DOI Publication Identifier: 10.1002/hbm.23699
Volume: 38 Issue: 9 First Page #: 4744
Date Submitted: 8/29/17 12:00AM Date Published: 9/1/17 7:00AM
Publication Location:
**Article Title:** Cohesive network reconfiguration accompanies extended training
**Authors:** Qawi K. Telesford, Arian Ashourvan, Nicholas F. Wymbs, Scott T. Grafton, Jean M. Vettel, Danielle S. B
**Keywords:** connectomics; dynamic networks; functional magnetic resonance imaging; graph theory; motor learning
**Abstract:** Human behavior is supported by flexible neurophysiological processes that enable the fine-scale manipulation of information across distributed neural circuits. Yet, approaches for understanding the dynamics of these circuit interactions have been limited. One promising avenue for quantifying and describing these dynamics lies in multilayer network models. Here, networks are composed of nodes (which represent brain regions) and time-dependent edges (which represent statistical similarities in activity time series). We use this approach to examine functional connectivity measured by non-invasive neuroimaging techniques. These multilayer network models facilitate the examination of changes in the pattern of statistical interactions between large-scale brain regions that might facilitate behavior.
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Volume: 11 Issue: 7 First Page #: e0158465
Date Submitted: 8/29/17 12:00AM Date Published: 7/8/16 2:00PM
Publication Location:
**Article Title:** Coupling between Theta Oscillations and Cognitive Control Network during Cross-Modal Visual and Auditory Attention: Supramodal vs Modality-Specific Mechanisms
**Authors:** Wuyi Wang, Shivakumar Viswanathan, Taraz Lee, Scott T. Grafton
**Keywords:** fMRI; theta oscillations
**Abstract:** Cortical theta band oscillations (4–8 Hz) in EEG signals have been shown to be important for a variety of different cognitive control operations in visual attention paradigms. However the synchronization source of these signals as defined by fMRI BOLD activity and the extent to which theta oscillations play a role in multimodal attention remains unknown. Here we investigated the extent to which cross-modal visual and auditory attention impacts theta oscillations. Using a simultaneous EEG-fMRI paradigm, healthy human participants performed an attentional vigilance task with six cross-modal conditions using naturalistic stimuli. To assess supramodal mechanisms, modulation of theta oscillation amplitude for attention to either visual or auditory stimuli was correlated with BOLD activity by conjunction analysis. Negative correlation was localized to cortical regions associated with the default mode network and positively with ventral premotor areas.
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**Journal:** IEEE Journal of Selected Topics in Signal Processing
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Volume: 10 Issue: 7 First Page #: 1189
Date Submitted: 8/29/17 12:00AM Date Published: 10/1/16 7:00AM
Publication Location:
**Article Title:** Graph Frequency Analysis of Brain Signals
**Authors:** Weiyu Huang, Leah Goldsberry, Nicholas F. Wymbs, Scott T. Grafton, Danielle S. Bassett, Alejandro Ri
**Keywords:** functional brain network, fMRI, filtering, graph signal processing, motor learning, network theory
**Abstract:** This paper presents methods to analyze functional brain networks and signals from graph spectral perspectives. The notion of frequency and filters traditionally defined for signals supported on regular domains such as discrete time and image grids has been recently generalized to irregular graph domains and defines brain graph frequencies associated with different levels of spatial smoothness across the brain regions. Brain network frequency also enables the decomposition of brain signals into pieces corresponding to smooth or rapid variations. We relate graph frequency with principal component analysis when the networks of interest denote functional connectivity. The methods are utilized to analyze brain networks and signals as subjects master a simple motor skill. We observe that brain signals corresponding to different graph frequencies exhibit different levels of adaptability throughout learning.
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Volume: 11 Issue: First Page #:
Date Submitted: 8/29/17 12:00AM Date Published: 5/1/17 7:00AM
Publication Location:
**Article Title:** Differential Recruitment of Parietal Cortex during Spatial and Non-spatial Reach Planning
**Authors:** Pierre-Michel Bernier, Kevin Whittingstall, Scott T. Grafton
**Keywords:** arm reaching movements, parieto-frontal network, movement planning, EEG, fMRI
**Abstract:** The planning of goal-directed arm reaching movements is associated with activity in the dorsal parieto-frontal cortex, within which multiple regions subserve the integration of arm- and target-related sensory signals to encode a motor goal. Surprisingly, many of these regions show sustained activity during reach preparation even when target location is not specified, i.e., when a motor goal cannot be unambiguously formed. The functional role of these non-spatial preparatory signals remains unresolved. Here this process was investigated in humans by comparing reach preparatory activity in the presence or absence of information regarding upcoming target location. In order to isolate the processes specific to reaching and to control for visuospatial attentional factors, the reaching task was contrasted to a finger movement task. Functional MRI and electroencephalography (EEG) were used to characterize the spatio-temporal pattern of reach-related activity in the parieto-frontal cortex.
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**Journal:** ACS Macro Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsmacrolett.6b00830
Volume: 5 Issue: 12 First Page #: 1391
Date Submitted: 8/29/17 12:00AM Date Published: 12/2/16 8:00AM
Publication Location:
**Article Title:** pH-Tunable Thermoresponsive PEO-Based Functional Polymers with Pendant Amine Groups
**Authors:** Joonhee Lee, Alaina J. McGrath, Craig J. Hawker, Byeong-Su Kim
**Keywords:** thermoresponsive polymers
**Abstract:** Thermoresponsive polymers exhibiting lower critical solution temperatures (LCSTs) in aqueous solution have garnered considerable attention for the development of smart materials. Herein, we report the synthesis and properties of pH-tunable thermoresponsive poly(ethylene oxide) (PEO)-based functional polymers bearing pendant amine groups with varying cloud points. Well-defined poly(ethylene oxide-co-allyl glycidyl ether) (P(EO-co-AGE)) copolymers were prepared via controlled anionic ring-opening copolymerization of ethylene oxide (EO) with 10 mol % of a functional allyl glycidyl ether (AGE) comonomer. Facile, modular thiol–ene click chemistry was then employed to introduce a library of different aminothiols as side chains to the initial P(EO-co-AGE) copolymer.
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Date Submitted: 8/29/17 12:00AM Date Published: 9/9/16 7:00AM
Publication Location:
**Article Title:** Stimulation-Based Control of Dynamic Brain Networks
**Authors:** Sarah Feldt Muldoon, Fabio Pasqualetti, Shi Gu, Matthew Cieslak, Scott T. Grafton, Jean M. Vettel, Dar
**Keywords:** nonlinear brain dynamics
**Abstract:** The ability to modulate brain states using targeted stimulation is increasingly being employed to treat neurological disorders and to enhance human performance. Despite the growing interest in brain stimulation as a form of neuromodulation, much remains unknown about the network-level impact of these focal perturbations. To study the system wide impact of regional stimulation, we employ a data-driven computational model of nonlinear brain dynamics to systematically explore the effects of targeted stimulation. Validating predictions from network control theory, we uncover the relationship between regional controllability and the focal versus global impact of stimulation, and we relate these findings to differences in the underlying network architecture. Finally, by mapping brain regions to cognitive systems, we observe that the default mode system imparts large global change despite being highly constrained by structural connectivity.
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**Journal:** Chem. Commun.
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Volume: 52 Issue: First Page #: 10525
Date Submitted: 8/29/17 12:00AM Date Published: 8/1/16 7:00AM
Publication Location:
**Article Title:** Controlled drug release to cancer cells from modular one-photon visible light-responsive micellar system
**Authors:** Saemi O. Poelma, Seung Soo Oh, Sameh Helmy, Abigail S. Knight, G. Leslie Burnett, H. Tom Soh, Crai
**Keywords:** small molecules
**Abstract:** We present a one-photon visible light-responsive micellar system for efficient, on-demand delivery of small molecules. Release is mediated by a novel class of photochromic material – donor–acceptor Stenhouse adducts (DASAs). We demonstrate controlled delivery of small molecules such as the chemotherapeutic agent (paclitaxel) to human breast cancer cells triggered by micellar switching with low intensity, visible light.
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**Journal:** Advanced Materials
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Publication Location:
**Article Title:** Engineering Surfaces through Sequential Stop-Flow Photopatterning
**Authors:** Christian W. Pester, Benjaporn Narupai, Kaila M. Mattson, David P. Bothman, Daniel Klinger, Kenneth V
**Keywords:** flow chemistry; lithography; patterning; photochemistry; polymer surfaces
**Abstract:** Solution-exchange lithography is a new modular approach to engineer surfaces via sequential photopatterning. An array of lenses reduces features on an inkjet-printed photomask and reproduces arbitrarily complex patterns onto surfaces. In situ exchange of solutions allows successive photochemical reactions without moving the substrate and affords access to hierarchically patterned substrates.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Polymer Science Part A: Polymer Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1002/pola.28490
Volume: 55 Issue: 7 First Page #: 1156
Date Submitted: 8/29/17 12:00AM Date Published: 4/1/17 7:00AM
Publication Location:
**Article Title:** Structural Versatility in Slide-Ring Gels: Influence of Co-Threaded Cyclodextrin Spacers
**Authors:** Takuya Murakami, Bernhard V. K. J. Schmidt, Hugh R. Brown, Craig J. Hawker
**Keywords:** slide-ring gel; polyrotaxane; supramolecular chemistry; hydrogel; click chemistry
**Abstract:** We describe a one-pot strategy for the fabrication of novel slide-ring (SR) gels based on supramolecular polyrotaxane structures with cyclodextrin-derived cross-links and additional free cyclodextrin ring spacers co-threaded onto the polymer backbones. Photoinitiated thiol-yne click coupling leads to facile hydrogel fabrication from pseudo-polyrotaxanes prepared in situ from ?-cyclodextrin derivatives and bifunctional polyethylene glycol (PEG). The obtained SR gels were characterized by NMR spectroscopy using a polyrotaxane model compound with the ratio of cyclodextrin sliding spacers to PEG backbone controlled by adjusting the feed ratio of the starting materials. This structural tuning leads to dramatic changes in the rheological properties, mechanical properties, and swelling behavior of the SR gels. In addition, the coupling of simple synthetic procedures with enhanced properties offers a versatile approach to novel elastomeric materials.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1038/nchem.2713
Volume: 9 Issue: First Page #: 537
Date Submitted: 8/30/17 12:00AM Date Published: 1/30/17 8:00AM
Publication Location:
**Article Title:** Engineering live cell surfaces with functional polymers via cytocompatible controlled radical polymerization
**Authors:** Jia Niu, David J. Lunn, Anusha Pusuluri, Justin I. Yoo, Michelle A. O'Malley, Samir Mitragotri, H. Tom Sc
**Keywords:** Bioconjugate chemistry; Chemical modification; Polymer synthesis; Synthetic biology
**Abstract:** The capability to graft synthetic polymers onto the surfaces of live cells offers the potential to manipulate and control their phenotype and underlying cellular processes. Conventional grafting-to strategies for conjugating preformed polymers to cell surfaces are limited by low polymer grafting efficiency. Here we report an alternative grafting-from strategy for directly engineering the surfaces of live yeast and mammalian cells through cell surface-initiated controlled radical polymerization. By developing cytocompatible PET-RAFT (photoinduced electron transfer-reversible addition-fragmentation chain-transfer polymerization), synthetic polymers with narrow polydispersity (Mw/Mn?<?1.3) could be obtained at room temperature in 5?minutes. This polymerization strategy enables chain growth to be initiated directly from chain-transfer agents anchored on the surface of live cells using either covalent attachment or non-covalent insertion, while maintaining high cell viability.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Peptide Science
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Volume: 108 Issue: 2 First Page #: e22934
Date Submitted: 8/30/17 12:00AM Date Published: 3/1/17 8:00AM
Publication Location:
**Article Title:** Protein catalyzed capture agents with tailored performance for in vitro and in vivo applications
**Authors:** Matthew B. Coppock, Candice R. Warner, Brandi Dorsey, Joshua A. Orlicki, Deborah A. Sarkes, Bert T.
**Keywords:** biological stability, protective antigen, protein catalyzed capture agent, synthetic anti-body, thermal stability, peptide, vascular endothelial growth factor
**Abstract:** We report on peptide-based ligands matured through the protein catalyzed capture (PCC) agent method to tailor molecular binders for in vitro sensing/diagnostics and in vivo pharmacokinetics parameters. A vascular endothelial growth factor (VEGF) binding peptide and a peptide against the protective antigen (PA) protein of Bacillus anthracis discovered through phage and bacterial display panning technologies, respectively, were modified with click handles and subjected to iterative in situ click chemistry screens using synthetic peptide libraries. Each azide-alkyne cycloaddition iteration, promoted by the respective target proteins, yielded improvements in metrics for the application of interest. The anti-VEGF PCC was explored as a stable in vivo imaging probe. It exhibited excellent stability against proteases and a mean elimination in vivo half-life (T1/2) of 36 min.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Scientific Reports
Publication Identifier Type: DOI Publication Identifier: 10.1038/srep34942
Volume: 6 Issue: First Page #:
Date Submitted: 8/30/17 12:00AM Date Published: 10/10/16 7:00AM
Publication Location:
**Article Title:** Synergistic Communication between CD4+ T Cells and Monocytes Impacts the Cytokine Environment
**Authors:** Sarah B. Schrier, Abby S. Hill, Deborah Plana, Douglas A. Lauffenburger
**Keywords:** CD4+ T Cells
**Abstract:** Physiological cytokine environments arise from factors produced by diverse cell types in coordinated concert. Understanding the contributions of each cell type in the context of cell-cell communication is important for effectively designing disease modifying interventions. Here, we present multi-plexed measurement of 48 cytokines from a coculture system of primary human CD4+ T cells and monocytes across a spectrum of stimuli and for a range of relative T cell/monocyte compositions, coupled with corresponding measurements from PBMCs and plasma from the same donors. Computational analysis of the resulting data-sets elucidated communication-independent and communication-dependent contributions, including both positive and negative synergies. We find that cytokines in cell supernatants were uncorrelated to those found in plasma.
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**Journal:** CPT: Pharmacometrics & Systems Pharmacology
Publication Identifier Type: DOI Publication Identifier: 10.1002/psp4.12104
Volume: 5 Issue: 10 First Page #: 544
Date Submitted: 8/30/17 12:00AM Date Published: 10/1/16 7:00AM
Publication Location:
**Article Title:** Systematic Analysis of Quantitative Logic Model Ensembles Predicts Drug Combination Effects on Cell Signaling Networks
**Authors:** MK Morris, DC Clarke, LC Osimiri, DA Lauffenburger
**Keywords:** cell signaling
**Abstract:** A major challenge in developing anticancer therapies is determining the efficacies of drugs and their combinations in physiologically relevant microenvironments. We describe here our application of "constrained fuzzy logic" (CFL) ensemble modeling of the intracellular signaling network for predicting inhibitor treatments that reduce the phospho-levels of key transcription factors downstream of growth factors and inflammatory cytokines representative of hepatocellular carcinoma (HCC) microenvironments. We observed that the CFL models successfully predicted the effects of several kinase inhibitor combinations. Furthermore, the ensemble predictions revealed ambiguous predictions that could be traced to a specific structural feature of these models, which we resolved with dedicated experiments, finding that IL-1? activates downstream signals through TAK1 and not MEKK1 in HepG2 cells.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLOS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0170975
Volume: 12 Issue: 2 First Page #: e0170975
Date Submitted: 8/30/17 12:00AM Date Published: 2/8/17 8:00AM
Publication Location:
**Article Title:** Advances in the quantification of mitochondrial function in primary human immune cells through extracellular flux analysis
**Authors:** Dequina Nicholas, Elizabeth A. Proctor, Forum M. Raval, Blanche C. Ip, Chloe Habib, Eleni Ritou, Tom
**Keywords:** immune response
**Abstract:** Numerous studies show that mitochondrial energy generation determines the effectiveness of immune responses. Furthermore, changes in mitochondrial function may regulate lymphocyte function in inflammatory diseases like type 2 diabetes. Analysis of lymphocyte mitochondrial function has been facilitated by introduction of 96-well format extracellular flux (XF96) analyzers, but the technology remains imperfect for analysis of human lymphocytes. Limitations in XF technology include the lack of practical protocols for analysis of archived human cells, and inadequate data analysis tools that require manual quality checks. Current analysis tools for XF outcomes are also unable to automatically assess data quality and delete untenable data from the relatively high number of biological replicates needed to power complex human cell studies.
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**Journal:** Biomaterials
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.biomaterials.2017.03.030
Volume: 130 Issue: First Page #: 90
Date Submitted: 8/30/17 12:00AM Date Published: 3/23/17 7:00AM
Publication Location:
**Article Title:** On-demand dissolution of modular, synthetic extracellular matrix reveals local epithelial-stromal communication networks
**Authors:** Jorge Valdez, Christi D. Cook, Caroline Chopko Ahrens, Alex J. Wang, Alexander Brown, Manu Kumar,
**Keywords:** Biomaterials; Matrix; Signaling; Sortase; Systems biology
**Abstract:** Methods to parse paracrine epithelial-stromal communication networks are a vital need in drug development, as disruption of these networks underlies diseases ranging from cancer to endometriosis. Here, we describe a modular, synthetic, and dissolvable extracellular matrix (MSD-ECM) hydrogel that fosters functional 3D epithelial-stromal co-culture, and that can be dissolved on-demand to recover cells and paracrine signaling proteins intact for subsequent analysis. Specifically, synthetic polymer hydrogels, modified with cell-interacting adhesion motifs and crosslinked with peptides that include a substrate for cell-mediated proteolytic remodeling, can be rapidly dissolved by an engineered version of the microbial transpeptidase Sortase A (SrtA) if the crosslinking peptide includes a SrtA substrate motif and a soluble second substrate.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** The ISME Journal
Publication Identifier Type: DOI Publication Identifier: 10.1038/ismej.2016.161
Volume: 11 Issue: First Page #: 825
Date Submitted: 8/30/17 12:00AM Date Published: 12/6/16 8:00AM
Publication Location:
**Article Title:** Direct single-cell biomass estimates for marine bacteria via Archimedes' principle
**Authors:** Nathan Cermak, Jamie W Becker, Scott M Knudsen, Sallie W Chisholm, Scott R Manalis, Martin F Polz
**Keywords:** Archimedes' principle
**Abstract:** Microbes are an essential component of marine food webs and biogeochemical cycles, and therefore precise estimates of their biomass are of significant value. Here, we measured single-cell biomass distributions of isolates from several numerically abundant marine bacterial groups, including Pelagibacter (SAR11), Prochlorococcus and Vibrio using a microfluidic mass sensor known as a suspended microchannel resonator (SMR). We show that the SMR can provide biomass (dry mass) measurements for cells spanning more than two orders of magnitude and that these estimates are consistent with other independent measures. We find that Pelagibacterales strain HTCC1062 has a median biomass of 11.9±0.7?fg per cell, which is five- to twelve-fold smaller than the median Prochlorococcus cell's biomass (depending upon strain) and nearly 100-fold lower than that of rapidly growing V. splendidus strain 13B01.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Biotechnology
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Volume: 34 Issue: 10 First Page #: 1052
Date Submitted: 8/30/17 12:00AM Date Published: 9/5/16 7:00AM
Publication Location:
**Article Title:** High-throughput measurement of single-cell growth rates using serial microfluidic mass sensor arrays
**Authors:** Nathan Cermak, Selim Olcum, Francisco Feijó Delgado, Steven C Wasserman, Kristofor R Payer, Mark
**Keywords:** Biomedical engineering; Biophysics; Cell biology
**Abstract:** Methods to rapidly assess cell growth would be useful for many applications, including drug susceptibility testing, but current technologies have limited sensitivity or throughput. Here we present an approach to precisely and rapidly measure growth rates of many individual cells simultaneously. We flow cells in suspension through a microfluidic channel with 10–12 resonant mass sensors distributed along its length, weighing each cell repeatedly over the 4–20 min it spends in the channel. Because multiple cells traverse the channel at the same time, we obtain growth rates for >60 cells/h with a resolution of 0.2 pg/h for mammalian cells and 0.02 pg/h for bacteria. We measure the growth of single lymphocytic cells, mouse and human T cells, primary human leukemia cells, yeast, Escherichia coli and Enterococcus faecalis.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Cortex
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cortex.2017.04.002
Volume: 91 Issue: First Page #: 126
Date Submitted: 8/30/17 12:00AM Date Published: 4/15/17 7:00AM
Publication Location:
**Article Title:** Influence of response bias and internal/external source on lateral posterior parietal successful retrieval activity
**Authors:** Danielle R. King, Michael B. Miller
**Keywords:** Parietal; Reality monitoring; Response bias; Source memory; Successful retrieval
**Abstract:** In studies of recognition memory, regions of the lateral posterior parietal cortex exhibit greater activity (as indexed by the fMRI BOLD signal) during correct recognition of "old" (studied) items than correct rejection of "new" (unstudied) items. This effect appears to be source-sensitive, with greater activity associated with recognition of perceived than imagined events. Parietal successful retrieval activity also varies with response bias, or the tendency to be conservative about making "old" judgments. Here, we examined whether differences in response bias associated with recognition judgments of perceived and imagined events could account for source-based differences in LPPC activity. Participants perceived and imagined items in response to cue words and then at test, made recognition judgments in blocks that knowingly contained either a high or low proportion of old to new trials.
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**Journal:** Journal of Polymer Science Part B: Polymer Physics
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Volume: 54 Issue: 18 First Page #: 1889
Date Submitted: 8/30/17 12:00AM Date Published: 9/15/16 7:00AM
Publication Location:
**Article Title:** Angle-dependent light scattering by highly uniform colloidal rod-shaped microparticles: Experiment and simulation
**Authors:** Roy Rotstein, Aym Berges, Samir Mitragotri, Daniel E. Morse, Martin Moskovits
**Keywords:** colloids; light scattering; optical properties
**Abstract:** While extensive theoretical work has been devoted to analyzing scattering behavior for nonspherical particles, few experimental studies of the light-scattering properties of such particles are available, largely because of the difficulty of synthesizing such particles with uniform geometries. Here we report the synthesis of highly uniform, volume-equivalent rod-shaped colloidal particles prepared from their commercial spherical counterparts, on which we performed light scattering experiments as a function of scattering angle for micro rods with varying aspect ratio and volume. These results were compared to values calculated using the T-Matrix method. Good agreement with theoretical predictions was found for the experimentally measured scattering cross sections and the angular dependence of the scattering intensity.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Current Opinion in Chemical Engineering
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.coche.2016.09.003
Volume: 14 Issue: First Page #: 103
Date Submitted: 8/30/17 12:00AM Date Published: 11/1/16 7:00AM
Publication Location:
**Article Title:** Microbial communities for bioprocessing: lessons learned from nature
**Authors:** Xuefeng “Nick” Peng, Sean P Gilmore, Michelle A O’Malley
**Keywords:** bioprocessing
**Abstract:** Microbial bioprocessing has evolved from the use of undefined natural consortia to the construction of synthetic communities tailored to specific processes and bioproducts. This evolution is enabled by recent advances in biotechnology, including cultivation of non-model microbes, metabolic engineering, bioinformatics, and numerical modeling. Equipped with these powerful tools, engineers have designed co-cultures and consortia with an expanded set of capabilities, mainly via ‘bottom-up’ approaches that tether isolates together in culture. Here, we present a brief review of the opportunities, challenges, and recent developments in consortia-based bioprocessing with a focus on lignocellulosic biomass conversion. With improved understanding of microbial community composition and function, we further present a vision to harness defined consortia down-selected from nature via ‘top down’ approaches.
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**Journal:** Microbial Cell Factories
Publication Identifier Type: DOI Publication Identifier: 10.1186/s12934-016-0611-7
Volume: 15 Issue: 212 First Page #:
Date Submitted: 8/30/17 12:00AM Date Published: 8/24/16 7:00AM
Publication Location:
**Article Title:** Mapping the membrane proteome of anaerobic gut fungi identifies a wealth of carbohydrate binding proteins and transporters
**Authors:** Susanna Seppälä, Kevin V. Solomon, Sean P. Gilmore, John K. Henske, Michelle A. O'Malley
**Keywords:** Microbial engineering; Membrane proteins; Anaerobic fungi; Carbohydrate binding proteins; Lignocellulose
**Abstract:** We report the first comprehensive characterization of the membrane protein machinery of biotechnologically relevant anaerobic gut fungi. Apart from identifying conserved machinery for protein sorting and secretion, we identify a large number of putative solute transporters that are of interest for biotechnological applications. Notably, our data suggests that the fungi display a plethora of carbohydrate binding domains at their surface, perhaps as a means to sense and sequester some of the sugars that their biomass degrading, extracellular enzymes produce.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Genetics
Publication Identifier Type: DOI Publication Identifier: 10.1038/ng.3859
Volume: 49 Issue: 6 First Page #: 964
Date Submitted: 8/30/17 12:00AM Date Published: 5/8/17 7:00AM
Publication Location:
**Article Title:** Widespread adenine N6-methylation of active genes in fungi
**Authors:** Stephen J Mondo, Richard O Dannebaum, Rita C Kuo, Katherine B Louie, Adam J Bewick, Kurt LaButti,
**Keywords:** Epigenetics; Epigenomics; Gene regulation
**Abstract:** N6-methyldeoxyadenine (6mA) is a noncanonical DNA base modification present at low levels in plant and animal genomes but its prevalence and association with genome function in other eukaryotic lineages remains poorly understood. Here we report that abundant 6mA is associated with transcriptionally active genes in early-diverging fungal lineages5. Using single-molecule long-read sequencing of 16 diverse fungal genomes, we observed that up to 2.8% of all adenines were methylated in early-diverging fungi, far exceeding levels observed in other eukaryotes and more derived fungi. 6mA occurred symmetrically at ApT dinucleotides and was concentrated in dense methylated adenine clusters surrounding the transcriptional start sites of expressed genes; its distribution was inversely correlated with that of 5-methylcytosine.
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**Journal:** Nature Microbiology
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Volume: 2 Issue: First Page #: 17087
Date Submitted: 8/30/17 12:00AM Date Published: 5/30/17 7:00AM
Publication Location:
**Article Title:** A parts list for fungal cellulosomes revealed by comparative genomics
**Authors:** Charles H. Haitjema, Sean P. Gilmore, John K. Henske, Kevin V. Solomon, Randall de Groot, Alan Kuo,
**Keywords:** Fungal genetics; Microbiome; Multienzyme complexes; Proteomics
**Abstract:** Cellulosomes are large, multiprotein complexes that tether plant biomass-degrading enzymes together for improved hydrolysis. These complexes were first described in anaerobic bacteria, where species-specific dockerin domains mediate the assembly of enzymes onto cohesin motifs interspersed within protein scaffolds. The versatile protein assembly mechanism conferred by the bacterial cohesin–dockerin interaction is now a standard design principle for synthetic biology. For decades, analogous structures have been reported in anaerobic fungi, which are known to assemble by sequence-divergent non-catalytic dockerin domains (NCDDs). However, the components, modular assembly mechanism and functional role of fungal cellulosomes remain unknown5,6. Here, we describe a comprehensive set of proteins critical to fungal cellulosome assembly, including conserved scaffolding proteins unique to the Neocallimastigomycota.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Applied Physics Letters
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4982968
Volume: 110 Issue: First Page #: 181605
Date Submitted: 8/30/17 12:00AM Date Published: 5/4/17 7:00AM
Publication Location:
**Article Title:** A process to fabricate fused silica nanofluidic devices with embedded electrodes using an optimized room temperature bonding technique
**Authors:** Seth Boden, P. Karam, A. Schmidt, S. Pennathur
**Keywords:** nanofluidic systems
**Abstract:** Fused silica is an ideal material for nanofluidic systems due to its extreme purity, chemical inertness, optical transparency, and native hydrophilicity. However, devices requiring embedded electrodes (e.g., for bioanalytical applications) are difficult to realize given the typical high temperature fusion bonding requirements (? 1000?°C). In this work, we optimize a two-step plasma activation process which involves an oxygen plasma treatment followed by a nitrogen plasma treatment to increase the fusion bonding strength of fused silica at room temperature. We conduct a parametric study of this treatment to investigate its effect on bonding strength, surface roughness, and microstructure morphology. We find that by including a nitrogen plasma treatment to the standard oxygen plasma activation process, the room temperature bonding strength increases by 70% (0.342?J?m2 to 0.578?J?m2).
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**Journal:** Physical Review Fluids
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Volume: 2 Issue: First Page #: 042201(R)
Date Submitted: 8/30/17 12:00AM Date Published: 4/26/17 7:00AM
Publication Location:
**Article Title:** Inertial particle dynamics in the presence of a secondary flow
**Authors:** Mike Garcia, Sumita Pennathur
**Keywords:** microfluidic channel
**Abstract:** The manipulation of particles using inertial lift forces has broad implications in the separation, concentration and sorting of particles. In this work, we show that in the presence of a secondary flow, equilibrium locations of particles subject to inertial lift can be spatially varying. Using a well-defined microfabricated straight microfluidic channel with perpendicular permeate channels, we perform experiments over a range of particle sizes and inlet and outlet flow rates to highlight different focusing regimes. We show that a permeate flow can control the equilibrium location of particles and can be used to interrogate the balance between inertial and permeate forces.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ELECTROPHORESIS
Publication Identifier Type: DOI Publication Identifier: 10.1002/elps.201700029
Volume: 38 Issue: First Page #: 1245
Date Submitted: 8/30/17 12:00AM Date Published: 5/11/17 7:00AM
Publication Location:
**Article Title:** Optimal MEMS device for mobility and zeta potential measurements using DC electrophoresis
**Authors:** Pascal R. Karam, Andrei Dukhin, Sumita Pennathur
**Keywords:** DC Electrophoresis; Electrophoretic mobility; Microfluidics; Zeta potential measurement
**Abstract:** We have developed a novel microchannel geometry that allows us to perform simple DC electrophoresis to measure the electrophoretic mobility and zeta potential of analytes and particles. In standard capillary geometries, mobility measurements using DC fields are difficult to perform. Specifically, measurements in open capillaries require knowledge of the hard to measure and often dynamic wall surface potential. Although measurements in closed capillaries eliminate this requirement, the measurements must be performed at infinitesimally small regions of zero flow where the pressure driven-flow completely cancels the electroosmotic flow (Komagata Planes). Furthermore, applied DC fields lead to electrode polarization, further questioning the reliability and accuracy of the measurement. In contrast, our geometry expands and moves the Komagata planes to where velocity gradients are at a minimum, and thus knowledge of the precise location of a Komagata plane is not necessary.
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**Journal:** Microfluidics and Nanofluidics
Publication Identifier Type: DOI Publication Identifier: 10.1007/s10404-016-1815-1
Volume: 20 Issue: 150 First Page #:
Date Submitted: 8/30/17 12:00AM Date Published: 10/16/16 7:00AM
Publication Location:
**Article Title:** Numerical investigation of micro- and nanochannel deformation due to discontinuous electroosmotic flow
**Authors:** Joseph M. de Rutte, Kjeld G. H. Janssen, Niels R. Tas, Jan C. T. Eijkel, Sumita Pennathur
**Keywords:** Electrokinetic; Microfluidics; Nanofluidics; Deformation
**Abstract:** Large pressures can induce detrimental deformation in micro- and nanofluidic channels. Although this has been extensively studied for systems driven by pressure and/or capillary forces, deflection in electrokinetic systems due to internal pressure gradients caused by non-uniform electric fields has not been widely explored. For example, applying an axial electric field in a channel with a step change in conductivity and/or surface charge can lead to internally generated pressures large enough to cause cavitation, debonding, and/or channel collapse. Finite electric double layers within nanofluidic channels can further complicate the physics involved in the deformation process. In order to design devices and experimental procedures that avoid issues resulting from such deformation, it is imperative to be able to predict deformation for given system parameters.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Langmuir
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.langmuir.7b00731
Volume: 33 Issue: 23 First Page #: 5642
Date Submitted: 8/30/17 12:00AM Date Published: 5/19/17 7:00AM
Publication Location:
**Article Title:** Two-Dimensional Electric Double Layer Structure with Heterogeneous Surface Charge
**Authors:** Christopher McCallum, Sumita Pennathur, Dirk Gillespie
**Keywords:** density functional theory
**Abstract:** In this work we present a systematic study of the lateral (parallel to the wall) and normal (perpendicular to the wall) nanostructure of the electric double layer at a heterogeneous interface between two regions of different surface charges, often found in nanoscale electrochemical devices. Specifically, classical density functional theory (DFT) is used to probe a cation concentration range of 10 mM to 1 M, for valences of +1, + 2, and +3, and a diameter range of 0.15–0.9 nm over widely varying surface charges (between ?0.15 and +0.15 C/m2). The DFT results predict significant lateral and normal nanostructure in the form of ion concentration oscillations. These results are directly compared with those from Poisson–Boltzmann theory, showing significant deviation between the two theories, not only in the concentration profiles, but also in the sign of the electrostatic potential.
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**Journal:** The Journal of Chemical Physics
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Volume: 145 Issue: First Page #: 184113
Date Submitted: 8/30/17 12:00AM Date Published: 11/14/16 8:00AM
Publication Location:
**Article Title:** A framework for discrete stochastic simulation on 3D moving boundary domains
**Authors:** Brian Drawert, Stefan Hellander, Michael Trogdon, Tau-Mu Yi, Linda Petzold
**Keywords:** systems biology
**Abstract:** We have developed a method for modeling spatial stochastic biochemical reactions in complex, three-dimensional, and time-dependent domains using the reaction-diffusion master equation formalism. In particular, we look to address the fully coupled problems that arise in systems biology where the shape and mechanical properties of a cell are determined by the state of the biochemistry and vice versa. To validate our method and characterize the error involved, we compare our results for a carefully constructed test problem to those of a microscale implementation. We demonstrate the effectiveness of our method by simulating a model of polarization and shmoo formation during the mating of yeast. The method is generally applicable to problems in systems biology where biochemistry and mechanics are coupled, and spatial stochastic effects are critical.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLOS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1005220
Volume: 12 Issue: 12 First Page #: e1005220
Date Submitted: 8/30/17 12:00AM Date Published: 12/8/16 8:00AM
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**Article Title:** Stochastic Simulation Service: Bridging the Gap between the Computational Expert and the Biologist
**Authors:** Brian Drawert, Andreas Hellander, Ben Bales, Debjani Banerjee, Giovanni Bellesia, Bernie J. Daigle, Ge
**Keywords:** Stochastic Simulation
**Abstract:** We present StochSS: Stochastic Simulation as a Service, an integrated development environment for modeling and simulation of both deterministic and discrete stochastic biochemical systems in up to three dimensions. An easy to use graphical user interface enables researchers to quickly develop and simulate a biological model on a desktop or laptop, which can then be expanded to incorporate increasing levels of complexity. StochSS features state-of-the-art simulation engines. As the demand for computational power increases, StochSS can seamlessly scale computing resources in the cloud. In addition, StochSS can be deployed as a multi-user software environment where collaborators share computational resources and exchange models via a public model repository. We demonstrate the capabilities and ease of use of StochSS with an example of model development and simulation at increasing levels of complexity.
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**Journal:** SIAM Journal on Scientific Computing
Publication Identifier Type: DOI Publication Identifier: 10.1137/15M1014784
Volume: 38 Issue: 3 First Page #: C179
Date Submitted: 8/31/17 12:00AM Date Published: 6/1/16 7:00AM
Publication Location:
**Article Title:** MOLNs: A Cloud Platform for Interactive, Reproducible, and Scalable Spatial Stochastic Computational Experiments in Systems Biology Using PyURDME
**Authors:** Brian Drawert, Michael Trogdon, Salman Toor, Linda Petzold, Andreas Hellander
**Keywords:** simulation software, spatial stochastic simulation, systems biology, computational experiments, cloud computing
**Abstract:** Computational experiments using spatial stochastic simulations have led to important new biological insights, but they require specialized tools and a complex software stack, as well as large and scalable compute and data analysis resources due to the large computational cost associated with Monte Carlo computational workflows. The complexity of setting up and managing a large-scale distributed computation environment to support productive and reproducible modeling can be prohibitive for practitioners in systems biology. This results in a barrier to the adoption of spatial stochastic simulation tools, effectively limiting the type of biological questions addressed by quantitative modeling. In this paper, we present PyURDME, a new, user-friendly spatial modeling and simulation package, and MOLNs, a cloud computing appliance for distributed simulation of stochastic reaction-diffusion models. MOLNs is based on IPython and provides an interactive programming platform for development of sha
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Accounts of Chemical Research
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.accounts.6b00276
Volume: 49 Issue: 9 First Page #: 1884
Date Submitted: 8/31/17 12:00AM Date Published: 8/26/16 7:00AM
Publication Location:
**Article Title:** Using Nature’s “Tricks” To Rationally Tune the Binding Properties of Biomolecular Receptors
**Authors:** Francesco Ricci, Alexis Vallée-Bélisle, Anna J. Simon, Alessandro Porchetta, Kevin W. Plaxco
**Keywords:** Biomolecular receptors
**Abstract:** The biosensor community has long focused on achieving the lowest possible detection limits, with specificity (the ability to differentiate between closely similar target molecules) and sensitivity (the ability to differentiate between closely similar target concentrations) largely being relegated to secondary considerations and solved by the inclusion of cumbersome washing and dilution steps or via careful control experimental conditions. Nature, in contrast, cannot afford the luxury of washing and dilution steps, nor can she arbitrarily change the conditions (temperature, pH, ionic strength) under which binding occurs in the homeostatically maintained environment within the cell. This forces evolution to focus at least as much effort on achieving optimal sensitivity and specificity as on achieving low detection limits, leading to the “invention” of a number of mechanisms, such as allostery and cooperativity.
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Volume: 88 Issue: 21 First Page #: 10452
Date Submitted: 8/31/17 12:00AM Date Published: 9/23/16 7:00AM
Publication Location:
**Article Title:** Survey of Redox-Active Moieties for Application in Multiplexed Electrochemical Biosensors
**Authors:** Di Kang, Francesco Ricci, Ryan J. White, Kevin W. Plaxco
**Keywords:** Multiplexed electrochemical biosensors
**Abstract:** Recent years have seen the development of a large number of electrochemical sandwich assays and reagentless biosensor architectures employing biomolecules modified via the attachment of a redox-active "reporter." Here we survey a large set of potential redox reporters in order to determine which exhibits the best long-duration stability in thiol-on-gold monolayer-based sensors and to identify reporter "sets" signaling at distinct, nonoverlapping redox potentials in support of multiplexing and error correcting ratiometric or differential measurement approaches. Specifically, we have characterized the performance of more than a dozen potential reporters that are, first, redox active within the potential window over which thiol-on-gold monolayers are reasonably stable and, second, are available commercially in forms that are readily conjugated to biomolecules or can be converted into such forms in one or two simple synthetic steps.
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**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.analchem.6b03227
Volume: 88 Issue: 23 First Page #: 11654
Date Submitted: 8/31/17 12:00AM Date Published: 12/2/16 8:00AM
Publication Location:
**Article Title:** Maximizing the Signal Gain of Electrochemical-DNA Sensors
**Authors:** Philippe Dauphin-Ducharme, Kevin W. Plaxco
**Keywords:** biosensors
**Abstract:** Electrochemical DNA (E-DNA) sensors have emerged as a promising class of biosensors capable of detecting a wide range of molecular analytes (nucleic acids, proteins, small molecules, inorganic ions) without the need for exogenous reagents or wash steps. In these sensors, a binding-induced conformational change in an electrode-bound "probe" (a target-binding nucleic acid or nucleic-acid-peptide chimera) alters the location of an attached redox reporter, leading to a change in electron transfer that is typically monitored using square-wave voltammetry. Because signaling in this class of sensors relies on binding-induced changes in electron transfer rate, the signal gain of such sensors (change in signal upon the addition of saturating target) is dependent on the frequency of the square-wave potential pulse used to interrogate them, with the optimal square-wave frequency depending on the structure of the probe, the nature of the redox reporter, and other features of the sensor.
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**Journal:** Journal of the American Chemical Society
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Volume: 138 Issue: 49 First Page #: 15809
Date Submitted: 8/31/17 12:00AM Date Published: 11/6/16 7:00AM
Publication Location:
**Article Title:** Dual-Reporter Drift Correction To Enhance the Performance of Electrochemical Aptamer-Based Sensors in Whole Blood
**Authors:** Hui Li, Netzahualcóyotl Arroyo-Currás, Di Kang, Francesco Ricci, Kevin W. Plaxco
**Keywords:** Electrochemical aptamer-based sensors
**Abstract:** The continuous, real-time monitoring of specific molecular targets in unprocessed clinical samples would enable many transformative medical applications. Electrochemical aptamer-based (E-AB) sensors appear to be a promising approach to this end because of their selectivity (performance in complex samples, such as serum) and reversible, single-step operation. E-AB sensors suffer, however, from often-severe baseline drift when challenged in undiluted whole blood. In response we report here a dual-reporter approach to performing E-AB baseline drift correction. The approach incorporates two redox reporters on the aptamer, one of which serves as the target-responsive sensor and the other, which reports at a distinct, nonoverlapping redox potential, serving as a drift-correcting reference.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1613458114
Volume: 114 Issue: 4 First Page #: 645
Date Submitted: 8/31/17 12:00AM Date Published: 1/24/17 8:00AM
Publication Location:
**Article Title:** Real-time measurement of small molecules directly in awake, ambulatory animals
**Authors:** Netzahualcóyotl Arroyo-Currás, Jacob Somerson, Philip A. Vieira, Kyle L. Ploense, Tod E. Kippin, Kevin
**Keywords:** aptamer; square-wave voltammetry; in vivo; E-DNA; precision medicine
**Abstract:** The development of a technology capable of tracking the levels of drugs, metabolites, and biomarkers in the body continuously and in real time would advance our understanding of health and our ability to detect and treat disease. It would, for example, enable therapies guided by high-resolution, patient-specific pharmacokinetics (including feedback-controlled drug delivery), opening new dimensions in personalized medicine. In response, we demonstrate here the ability of electrochemical aptamer-based (E-AB) sensors to support continuous, real-time, multihour measurements when emplaced directly in the circulatory systems of living animals. Specifically, we have used E-AB sensors to perform the multihour, real-time measurement of four drugs in the bloodstream of even awake, ambulatory rats, achieving precise molecular measurements at clinically relevant detection limits and high (3 s) temporal resolution.
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Volume: 11 Issue: 1 First Page #: 461
Date Submitted: 8/31/17 12:00AM Date Published: 12/22/16 8:00AM
Publication Location:
**Article Title:** Simultaneous Measurement of the Dissolution Kinetics of Responsive DNA Hydrogels at Multiple Length Scales
**Authors:** Anna J. Simon, Luke T. Walls-Smith, Matthew J. Freddi, Faye Yi Fong, Vladimir Gubala, Kevin W. Plaxc
**Keywords:** aptamers; gels; macromolecular assemblies; rheology; smart materials; soft matter
**Abstract:** Recent years have seen increasing study of stimulus-responsive hydrogels constructed from aptamer-connected DNA building blocks. Presumably due to a lack of simple, quantitative tools with which to measure gel responsiveness, however, the literature describing these materials is largely qualitative. In response, we demonstrate here simple, time-resolved, multiscale methods for measuring the response kinetics of these materials. Specifically, by employing trace amounts of fluorophore-quencher labeled cross-linkers and the rheology of entrapped fluorescent particles, we simultaneously measure dissolution at molecular, hundred-nanometer, and hundred-micron length-scales. For our test-bed system, an adenine-responsive hydrogel, we find biphasic response kinetics dependent on both effector concentration and depth within the gel and a dissolution pattern uniform at scales longer than a few times the monomer–monomer distance.
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**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201700748
Volume: 56 Issue: 26 First Page #: 7492
Date Submitted: 8/31/17 12:00AM Date Published: 6/19/17 7:00AM
Publication Location:
**Article Title:** A Biomimetic Phosphatidylcholine-Terminated Monolayer Greatly Improves the In Vivo Performance of Electrochemical Aptamer-Based Sensors
**Authors:** Hui Li, Philippe Dauphin-Ducharme, Netzahualcóyotl Arroyo-Currás, Claire H. Tran, Philip A. Vieira, Sha
**Keywords:** E-AB sensors
**Abstract:** The real-time monitoring of specific analytes in?situ in the living body would greatly advance our understanding of physiology and the development of personalized medicine. Because they are continuous (wash-free and reagentless) and are able to work in complex media (e.g., undiluted serum), electrochemical aptamer-based (E-AB) sensors are promising candidates to fill this role. E-AB sensors suffer, however, from often-severe baseline drift when deployed in undiluted whole blood either in?vitro or in?vivo. We demonstrate that cell-membrane-mimicking phosphatidylcholine (PC)-terminated monolayers improve the performance of E-AB sensors, reducing the baseline drift from around 70?% to just a few percent after several hours in flowing whole blood in?vitro. With this improvement comes the ability to deploy E-AB sensors directly in?situ in the veins of live animals, achieving micromolar precision over many hours without the use of physical barriers or active drift-correction algorithms.
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**Journal:** Journal of the American Chemical Society
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Volume: 139 Issue: 32 First Page #: 11207
Date Submitted: 8/31/17 12:00AM Date Published: 7/16/17 7:00AM
Publication Location:
**Article Title:** Calibration-Free Electrochemical Biosensors Supporting Accurate Molecular Measurements Directly in Undiluted Whole Blood
**Authors:** Hui Li, Philippe Dauphin-Ducharme, Gabriel Ortega, Kevin W. Plaxco
**Keywords:** Electrochemical biosensors
**Abstract:** The need to calibrate to correct for sensor-to-sensor fabrication variation and sensor drift has proven a significant hurdle in the widespread use of biosensors. To maintain clinically relevant (±20% for this application) accuracy, for example, commercial continuous glucose monitors require recalibration several times a day, decreasing convenience and increasing the chance of user errors. Here, however, we demonstrate a “dual-frequency” approach for achieving the calibration-free operation of electrochemical biosensors that generate an output by using square-wave voltammetry to monitor binding-induced changes in electron transfer kinetics. Specifically, we use the square-wave frequency dependence of their response to produce a ratiometric signal, the ratio of peak currents collected at responsive and non- (or low) responsive square-wave frequencies, which is largely insensitive to drift and sensor-to-sensor fabrication variations.
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**Journal:** Journal of the American Chemical Society
Publication Identifier Type: DOI Publication Identifier: 10.1021/jacs.5b08980
Volume: 138 Issue: 13 First Page #: 4278
Date Submitted: 8/31/17 12:00AM Date Published: 3/18/16 7:00AM
Publication Location:
**Article Title:** Engineered Aminoacyl-tRNA Synthetase for Cell-Selective Analysis of Mammalian Protein Synthesis
**Authors:** Alborz Mahdavi, Graham D. Hamblin, Granton A. Jindal, John D. Bagert, Cathy Dong, Michael J. Swere
**Keywords:** proteome dynamics
**Abstract:** Methods for cell-selective analysis of proteome dynamics will facilitate studies of biological processes in multicellular organisms. Here we describe a mutant murine methionyl-tRNA synthetase (designated L274GMmMetRS) that charges the noncanonical amino acid azidonorleucine (Anl) to elongator tRNAMet in hamster (CHO), monkey (COS7), and human (HeLa) cell lines. Proteins made in cells that express the synthetase can be labeled with Anl, tagged with dyes or affinity reagents, and enriched on affinity resin to facilitate identification by mass spectrometry. The method does not require expression of orthogonal tRNAs or depletion of canonical amino acids. Successful labeling of proteins with Anl in several mammalian cell lines demonstrates the utility of L274GMmMetRS as a tool for cell-selective analysis of mammalian protein synthesis.
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**Journal:** Journal of the American Chemical Society
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Volume: 138 Issue: 46 First Page #: 15098
Date Submitted: 8/31/17 12:00AM Date Published: 11/10/16 8:00AM
Publication Location:
**Article Title:** Chemoenzymatic Labeling of Proteins for Imaging in Bacterial Cells
**Authors:** Samuel H. Ho, David A. Tirrell
**Keywords:** protein imaging
**Abstract:** Reliable methods to determine the subcellular localization of bacterial proteins are needed for the study of prokaryotic cell biology. We describe here a simple and general technique for imaging of bacterial proteins in situ by fluorescence microscopy. The method uses the eukaryotic enzyme N-myristoyltransferase to modify the N-terminus of the protein of interest with an azido fatty acid. Subsequent strain-promoted azide–alkyne cycloaddition allows conjugation of dyes and imaging of tagged proteins by confocal fluorescence microscopy. We demonstrate the method by labeling the chemotaxis proteins Tar and CheA and the cell division proteins FtsZ and FtsA in Escherichia coli. We observe distinct spatial patterns for each of these proteins in both fixed and live cells. The method should prove broadly useful for protein imaging in bacteria.
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**Journal:** Current Opinion in Chemical Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cbpa.2016.12.026
Volume: 36 Issue: First Page #: 50
Date Submitted: 8/31/17 12:00AM Date Published: 1/12/17 8:00AM
Publication Location:
**Article Title:** Cell-selective proteomics for biological discovery
**Authors:** Shannon E Stone, Weslee S Glenn, Graham D Hamblin, David A Tirrell
**Keywords:** proteome
**Abstract:** Cells alter the proteome to respond to environmental and developmental cues. Global analysis of proteomic responses is of limited value in heterogeneous environments, where there is no 'average' cell. Advances in sequencing, protein labeling, mass spectrometry, and data analysis have fueled recent progress in the investigation of specific subpopulations of cells in complex systems. Here we highlight recently developed chemical tools that enable cell-selective proteomic analysis of complex biological systems, from bacterial pathogens to whole animals.
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**Journal:** Journal of the Mechanics and Physics of Solids
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Volume: 96 Issue: First Page #: 184
Date Submitted: 8/31/17 12:00AM Date Published: 7/7/16 7:00AM
Publication Location:
**Article Title:** Periodic truss structures
**Authors:** Frank W. Zok, Ryan M. Latture, Matthew R. Begley
**Keywords:** Cellular materials; Structures
**Abstract:** Despite the recognition of the enormous potential of periodic trusses for use in a broad range of technologies, there are no widely-accepted descriptors of their structure. The terminology has been based loosely either on geometry of polyhedra or of point lattices: neither of which, on its own, has an appropriate structure to fully define periodic trusses. The present article lays out a system for classification of truss structure types. The system employs concepts from crystallography and geometry to describe nodal locations and connectivity of struts. Through a series of illustrative examples of progressively increasing complexity, a rational taxonomy of truss structure is developed. Its conceptual evolution begins with elementary cubic trusses, increasing in complexity with non-cubic and compound trusses as well as supertrusses, and, finally, with complex trusses.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Sensors and Actuators A: Physical
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.sna.2017.06.016
Volume: Issue: First Page #:
Date Submitted: 8/31/17 12:00AM Date Published: 6/24/17 7:00AM
Publication Location:
**Article Title:** Acoustic control of microstructures during direct ink writing of two-phase materials
**Authors:** Leanne Friedrich, Rachel Collino, Tyler Ray, Matthew Begley
**Keywords:** Microfluidics, 3D Printing, Acoustic waves, Rheology, Polymer matrix composites
**Abstract:** New methods to 3D print multiphase materials with tailored microstructures could expand additive manufacturing capabilities to include structures with unprecedented complexity. One promising technique to control microstructure is acoustic focusing, a method by which particles in a fluid are manipulated by acoustic waves. By combining acoustic focusing with direct ink writing (where fluid inks are solidified after extrusion), the distribution of particles in fluid matrices can be modified throughout print lines. Here, we describe the design space for acoustic focusing with direct ink writing and explore the associated trade-offs, for inks composed of epoxy resin, silica, acetone, and glass microspheres. Increasing silica content increases the viscosity, widening the spatial distribution of particles, but it improves the preservation of printed shapes.
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Volume: 13 Issue: 10 First Page #: e1005786
Date Submitted: 8/22/18 12:00AM Date Published: 10/3/17 5:00AM
Publication Location:
**Article Title:** Machine learning to design integral membrane channelrhodopsins for efficient eukaryotic expression and plasma membrane localization
**Authors:** Claire N. Bedbrook, Kevin K. Yang, Austin J. Rice, Viviana Gradinaru, Frances H. Arnold, Costas D. Ma
**Keywords:** membrane proteins
**Abstract:** There is growing interest in studying and engineering integral membrane proteins (MPs) that play key roles in sensing and regulating cellular response to diverse external signals. A MP must be expressed, correctly inserted and folded in a lipid bilayer, and trafficked to the proper cellular location in order to function. The sequence and structural determinants of these processes are complex and highly constrained. Here we describe a predictive, machine-learning approach that captures this complexity to facilitate successful MP engineering and design. Machine learning on carefully-chosen training sequences made by structure-guided SCHEMA recombination has enabled us to accurately predict the rare sequences in a diverse library of channelrhodopsins (ChRs) that express and localize to the plasma membrane of mammalian cells. These light-gated channel proteins of microbial origin are of interest for neuroscience applications, where expression and localization to the plasma membrane..
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**Journal:** Bioinformatics
Publication Identifier Type: DOI Publication Identifier: 10.1093/bioinformatics/bty178
Volume: 34 Issue: 15 First Page #: 2642
Date Submitted: 8/22/18 12:00AM Date Published: 8/1/18 5:00AM
Publication Location:
**Article Title:** Learned protein embeddings for machine learning
**Authors:** Kevin K Yang, Zachary Wu, Claire N Bedbrook, Frances H Arnold
**Keywords:** Machine-learning
**Abstract:** Motivation: Machine-learning models trained on protein sequences and their measured functions can infer biological properties of unseen sequences without requiring an understanding of the underlying physical or biological mechanisms. Such models enable the prediction and discovery of sequences with optimal properties. Machine-learning models generally require that their inputs be vectors, and the conversion from a protein sequence to a vector representation affects the mod- el's ability to learn. We propose to learn embedded representations of protein sequences that take advantage of the vast quantity of unmeasured protein sequence data available. These embeddings are low-dimensional and can greatly simplify downstream modeling. Results: The predictive power of Gaussian process models trained using embeddings is comparable to those trained on existing representations, which suggests that embeddings enable accurate predictions despite having orders of magnitude fewer dimensions...
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**Journal:** Angewandte Chemie
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Volume: 130 Issue: 27 First Page #: 8201
Date Submitted: 8/22/18 12:00AM Date Published: 7/1/18 12:00AM
Publication Location:
**Article Title:** Informed Molecular Design of Conjugated Oligoelectrolytes To Increase Cell Affinity and Antimicrobial Activity
**Authors:** Cheng Zhou, Geraldine W. N. Chia, James C. S. Ho, Thomas Seviour, Talgat Sailov, Bo Liedberg, Staff
**Keywords:** antimicrobial activity, cell affinity, conjugated oligoelectrolytes, membrane disruption
**Abstract:** Membrane-intercalating conjugated oligoelectrolytes (COEs) are emerging as potential alternatives to conventional, yet increasingly ineffective, antibiotics. Three readily accessible COEs, belonging to an unreported series containing a stilbene core, namely D4, D6, and D8, were designed and synthesized so that the hydrophobicity increases with increasing side-chain length. Decreased aqueous solubility correlates with increased uptake by E. coli. The minimum inhibitory concentration (MIC) of D8 is 4 mg mL 1 against both E. coli and E. faecalis, with an effective uptake of 72 %. In contrast, the MIC value of the shortest COE, D4, is 128 mg mL 1 owing to the low cellular uptake of 3%. These findings demonstrate the application of rational design to generate efficacious antimicrobial COEs that have potential as low-cost antimicrobial agents.
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Volume: 9 Issue: 2294 First Page #:
Date Submitted: 8/22/18 12:00AM Date Published: 6/1/18 12:00AM
Publication Location:
**Article Title:** Achieving high permeability and enhanced selectivity for Angstrom-scale separations using artificial water channel membranes
**Authors:** Yue-xiao Shen, Woochul Song, D. Ryan Barden, Tingwei Ren, Chao Lang, Hasin Feroz, Codey B. Henc
**Keywords:** Synthetic polymer membranes
**Abstract:** Synthetic polymer membranes, critical to diverse energy-efficient separations, are subject to permeability-selectivity trade-offs that decrease their overall efficacy. These trade-offs are due to structural variations (e.g., broad pore size distributions) in both nonporous membranes used for Angstrom-scale separations and porous membranes used for nano to micron-scale separations. Biological membranes utilize well-defined Angstrom-scale pores to provide exceptional transport properties and can be used as inspiration to overcome this trade-off. Here, we present a comprehensive demonstration of such a bioinspired approach based on pillar[5] arene artificial water channels, resulting in artificial water channel-based block copolymer membranes. These membranes have a sharp selectivity profile with a molecular weight cutoff of ~500Da, a size range challenging to achieve with current membranes, while achieving a large improvement in permeability...
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Volume: 8 Issue: 19 First Page #: 10284
Date Submitted: 8/22/18 12:00AM Date Published:
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**Article Title:** Membrane adaptation limitations in Enterococcus faecalis underlie sensitivity and the inability to develop significant resistance to conjugated oligoelectrolytes
**Authors:** Gayatri Shankar Chilambi, Iris H. Gao, Bo Kyeong Yoon, Soohyun Park, Lisa M. Kawakami, Vikashini R
**Keywords:** antibiotic resistant bacteria
**Abstract:** The growing problem of antibiotic resistant bacteria, along with a dearth of new antibiotics, has redirected attention to the search for alternative antimicrobial agents. Conjugated oligoelectrolytes (COEs) are an emerging class of antimicrobial agents which insert into bacterial cell membranes and are inhibitory against a range of Gram-positive and Gram-negative bacteria. In this study, the extent of COE resistance that Enterococcus faecalis could achieve was studied. Enterococci are able to grow in hostile environments and develop resistance to membrane targeting antibiotics such as daptomycin in clinical settings. Herein we expand our knowledge of the antimicrobial mechanism of action of COEs by developing COE-resistant strains of E. faecalis OG1RF. Evolution studies yielded strains with a moderate 4–16 fold increase in antimicrobial resistance relative to the wild type. The resistant isolates accumulated agent-specific mutations associated with the liaFSR operon...
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**Journal:** Angewandte Chemie International Edition
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Volume: 56 Issue: First Page #: 16063
Date Submitted: 8/26/18 12:00AM Date Published: 3/7/17 5:41PM
Publication Location:
**Article Title:** Antibacterial Narrow-Band-Gap Conjugated Oligoelectrolytes with High Photothermal Conversion Efficiency
**Authors:** Bing Wang, Guangxue Feng, Martin Seifrid, Ming Wang, Bin Liu, Guillermo C. Bazan
**Keywords:** antimicrobial activity, conjugated oligoelectrolytes, near-infrared radiation, photothermal therapy
**Abstract:** Two conjugated oligoelectrolytes (COEs), WMG1 and WMG2, were designed with the goal of achieving near infrared absorption and high photothermal conversion efficiency. Specifically, electron-rich thiophene and electron-poor benzo[1,2-c :4,5-c']bis[1,2,5]thiadiazole subunits were introduced into the conjugated core to modulate the optical gap and to reduce the fluorescence emission efficiency. WMG1 and WMG2 show absorption maxima at around 800 nm, which favors tissue penetration. Although relatively small in size, WMG1 and WMG2 exhibit photothermal conversion efficiencies of circa 60 % and 54 %, respectively. WMG1 shows dark toxicity to the Gram positive bacterium B. subtilis and good photothermal killing efficiency toward both B. subtilis and Gram negative E. coli, features that demonstrate the promising potential of the COE molecular design for photothermal applications.
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Publication Identifier Type: DOI Publication Identifier: 10.1016/j.chempr.2017.05.002
Volume: 2 Issue: 6 First Page #: 760
Date Submitted: 8/23/18 12:00AM Date Published: 6/1/17 5:00AM
Publication Location:
**Article Title:** Conjugated-Polymer-Amplified Sensing, Imaging, and Therapy
**Authors:** Wenbo Wu, Guillermo C. Bazan, Bin Liu
**Keywords:** conjugated polymers
**Abstract:** Signal amplification is one of the simplest and most effective strategies for effi- ciently improving the performance of emerging sensing, imaging, and therapy technologies. For the amplification of detection signals and enhancement of therapeutic effects, the light-harvesting and energy-transfer properties of conjugated polymers (CPs) have made this class of materials a key platform for amplifying detection signatures that betray the presence of biomarkers and enhancing therapeutic action. In this review, we first summarize CP-ampli- fied fluorescence sensing in homogeneous solution and on solid supports. We then discuss how CPs can be integrated into amplified in vitro and in vivo imag- ing with the use of both fluorescence and self-luminesce phenomena. We further illustrate and examine the importance of CPs as amplifiers through examples of enhanced photodynamic therapy. To conclude, we discuss the challenges, opportunities, and perspectives for the future development of this field.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201701146
Volume: 56 Issue: 18 First Page #: 5031
Date Submitted: 8/23/18 12:00AM Date Published: 4/1/17 12:00AM
Publication Location:
**Article Title:** A Membrane-Intercalating Conjugated Oligoelectrolyte with High-Efficiency Photodynamic Antimicrobial Activity
**Authors:** Bing Wang, Ming Wang, Alexander Mikhailovsky, Shu Wang, Guillermo C. Bazan
**Keywords:** conjugated oligoelectrolyte
**Abstract:** A membrane-intercalating conjugated oligoelectrolyte (COE), PTTP, was designed and synthesized with the goal of providing red-shifted absorption spectra relative to previously synthesized COE analogs. Specifically, electron-rich and electron-poor subunits were introduced in the conjugated backbone to modulate the band gap. PTTP exhibits maxima of absorption at 507 nm and of emission at 725 nm. PTTP can also efficiently function to generate singlet oxygen in situ (FD 20%) and has appropriate topology and dimensions to interact with lipid membranes. The resulting rapid membrane insertion and sensitizing ability provide PTTP with a highly efficient antibacterial capability under a low light dose (0.6 J cm 2) toward Gram-negative bacteria E. coli, making it a remarkably efficient optically mediated antimicrobial agent.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Colloid and Interface Science
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jcis.2018.05.110
Volume: 529 Issue: First Page #: 599
Date Submitted: 8/23/18 12:00AM Date Published: 11/1/18 5:00AM
Publication Location:
**Article Title:** In situ characterization of low-viscosity direct ink writing: Stability, wetting, and rotational flows
**Authors:** Leanne Friedrich, Matthew Begley
**Keywords:** 3D printing, direct ink writing, lubrication theory, contact angle, contact line
**Abstract:** Hypothesis: Direct ink writing (DIW) of composites can be coupled with magnetic, electric, or acoustic fields to control spatial variations of microstructure that enhance performance. The use of such external fields often requires inks with lower viscosities than conventional DIW, which presents new challenges with regards to maintaining the stability of printed lines and targeted microstructures. In-situ monitoring of the print bead, combined with slot-die models, can be used to predict printing modality and guide printing protocols for low viscosity inks.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Materials Research Letters
Publication Identifier Type: DOI Publication Identifier: 10.1080/21663831.2018.1431317
Volume: 6 Issue: 3 First Page #: 191
Date Submitted: 8/23/18 12:00AM Date Published: 2/1/18 6:00AM
Publication Location:
**Article Title:** Scaling relationships for acoustic control of two-phase microstructures during direct-write printing
**Authors:** Rachel R. Collino, Tyler R. Ray, Leanne M. Friedrich, James D. Cornell, Carl D. Meinhart, Matthew R. B
**Keywords:** Additive manufacturing, composites, direct-write, acoustic waves
**Abstract:** Acoustic forces can align and consolidate particles in fluids, enabling microstructural control of two-phase materials at time-scales compatible with direct-write printing of composites. This paper presents key scaling relationships for acoustically-assisted direct-write printing that describe char- acteristic time-scales for assembly and alignment of particles during printing. Critical combinations of system parameters (including particle and nozzle dimensions, acoustic excitation amplitude, vis- cosity, and flow rate) are defined that govern particle focusing and assembly in the print stream. The results can be used to identify combinations of printing protocols and nozzle configurations that control particle packing parallel and transverse to the print direction.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Nano
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsnano.8b02720
Volume: Issue: First Page #:
Date Submitted: 8/23/18 12:00AM Date Published: 7/1/18 12:00AM
Publication Location:
**Article Title:** DNA Origami and G-Quadruplex Hybrid Complexes Induce Size Control of Single-Walled Carbon Nanotubes
**Authors:** Hiroshi Atsumi, Angela M. Belcher
**Keywords:** DNA origami, single-walled carbon nanotubes (SWNTs), DNA-wrapped SWNTs, G-quadruplex, SWNT lengths, hemin, luminol
**Abstract:** DNA self-assembly has enabled the programmable fabrication of nanoarchitectures, and these nano-architectures combined with nanomaterials have provided several applications. Here, we develop an approach for cutting single-walled carbon nanotubes (SWNTs) of predetermined lengths, using DNA origami and G-quadruplex hybrid complexes. This approach is based on features of DNA: (1) wrapping SWNTs with DNA to improve the dispersibility of SWNTs in water; (2) using G-quadruplex DNA to confine hemin in close proximity to SWNTs and enhance the biological activation of hydrogen peroxide by hemin; and (3) forming DNA origami platforms to allow for the precise placement of G-quadruplexes, enabling size control. These integrated features of DNA allow for temporally efficient cutting of SWNTs into desired lengths, thus expanding the availability of SWNTs for applications in the fields of nanoelectronics, nanomedicine, nanomaterials, and quantum physics, as well as in fundamental studies.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chemistry of Materials
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.chemmater.7b02571
Volume: 29 Issue: 16 First Page #: 6993
Date Submitted: 8/23/18 12:00AM Date Published: 7/1/17 12:00AM
Publication Location:
**Article Title:** Mediated Growth of Zinc Chalcogen Shells on Gold Nanoparticles by Free-Base Amino Acids
**Authors:** Matthew T. Klug, Noémie-Manuelle Dorval Courchesne, Yoonkyung E. Lee, Dong Soo Yun, Jifa Qi, Nim
**Keywords:** amino acids
**Abstract:** Herein, we report a method that uses free-base amino acids to mediate the controlled hydrothermal growth of amorphous zinc oxide (a-ZnO) or nanocrystalline zinc sulfide (c-ZnS) shells on gold nanoparticles. By screening through a set of 13 candidate amino acids, we have identified four as being capable of mediating inorganic shell growth using an aqueous, low-temperature, one-pot process. In particular, unaggregated and monodisperse sols of exceptional quality are produced using L-histidine, which preserves colloidal stability and mediates the growth of continuous and remarkably uniform a-ZnO shells with a tunable thickness between 2 and 25 nm while avoiding the nucleation of free particles. By coupling spectral extinction measurements with generalized Mie theory calculations, we estimated the complex refractive index of the a-ZnO shell to be 1.47 + i0. 09. It is expected not only that our Au@a-ZnO core?shell particles are suitable for both energy and biological applications but also...
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**Journal:** IEEE Transactions on Network Science and Engineering
Publication Identifier Type: DOI Publication Identifier: 10.1109/TNSE.2017.2651070
Volume: 4 Issue: 2 First Page #: 83
Date Submitted: 8/23/18 12:00AM Date Published: 4/1/17 5:00AM
Publication Location:
**Article Title:** Competitive Propagation: Models, Asymptotic Behavior and Quality-Seeding Games
**Authors:** Wenjun Mei, Francesco Bullo
**Keywords:** Competitive propagation, independence approximation, network structure, stability analysis, non-cooperative game, seeding, product quality
**Abstract:** In this paper we propose a class of propagation models for multiple competing products over a social network. We consider two propagation mechanisms: social conversion and self conversion, corresponding, respectively, to endogenous and exogenous factors. A novel concept, the product-conversion graph, is proposed to characterize the interplay among competing products. According to the chronological order of social and self conversions, we develop two Markov-chain models and, based on the independence approximation, we approximate them with two corresponding difference equations systems. Our theoretical analysis on these two approximated models reveals the dependency of their asymptotic behavior on the structures of both the product-conversion graph and the social network, as well as the initial condition. In addition to the theoretical work, we investigate via numerical analysis the accuracy of the independence approximation and the asymptotic behavior of the Markov-chain model...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Dynamic Systems, Measurement, and Control
Publication Identifier Type: DOI Publication Identifier: 10.1115/1.4035874
Volume: 139 Issue: 8 First Page #: 081011
Date Submitted: 8/23/18 12:00AM Date Published: 5/1/17 12:00AM
Publication Location:
**Article Title:** Cloud-Supported Coverage Control for Persistent Surveillance Missions
**Authors:** Jeffrey R. Peters, Sean J. Wang, Amit Surana, Francesco Bullo
**Keywords:** Surveillance
**Abstract:** A cloud-supported coverage control scheme is proposed for multi-agent, persistent surveillance missions. This approach decouples assignment from motion planning operations in a modular framework. Coverage assignments and surveillance parameters are managed on the cloud and transmitted to mobile agents via unplanned and asynchronous exchanges. These updates promote load-balancing, while also allowing effective pairing with typical path planners. Namely, when paired with a planner satisfying mild assumptions, the scheme ensures that (i) coverage regions remain connected and collectively cover the environment, (ii) regions may go uncovered only over bounded intervals, (iii) collisions (sensing overlaps) are avoided, and (iv) for time-invariant event likelihoods, a Pareto optimal configuration is produced in finite time. The scheme is illustrated in simulated missions.
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**Journal:** Network Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1162/NETN_a_00025
Volume: 1 Issue: 4 First Page #: 446
Date Submitted: 8/23/18 12:00AM Date Published: 12/1/17 6:00AM
Publication Location:
**Article Title:** Sensitivity analysis of human brain structural network construction
**Authors:** Kuang Wei, Matthew Cieslak, Clint Greene, Scott T. Grafton, Jean M. Carlson
**Keywords:** Tractography, Brain networks, Human Connectome Project, Connectomics, White matter connectivity
**Abstract:** "Network neuroscience leverages diffusion-weighted magnetic resonance imaging and tractography to quantify structural connectivity of the human brain. However, scientists and practitioners lack a clear understanding of the effects of varying tractography parameters on the constructed structural networks. With diffusion images from the Human Connectome Project (HCP), we characterize how structural networks are impacted by the spatial resolution of brain atlases, total number of tractography streamlines, and grey matter dilation with various graph metrics. We demonstrate how injudicious combinations of highly refined brain parcellations and low numbers of streamlines may inadvertently lead to disconnected network models with isolated nodes. Furthermore, we provide solutions to significantly reduce the likelihood of generating disconnected networks. In addition, for different tractography parameters, we investigate the distributions of values taken by various graph metrics across..
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLOS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0187715
Volume: 12 Issue: 12 First Page #:
Date Submitted: 8/23/18 12:00AM Date Published: 12/1/17 6:00AM
Publication Location:
**Article Title:** Improving resolution of dynamic communities in human brain networks through targeted node removal
**Authors:** Kimberly J. Schlesinger, Benjamin O. Turner, Scott T. Grafton, Michael B. Miller, Jean M. Carlson, Dani
**Keywords:** human brain networks
**Abstract:** Current approaches to dynamic community detection in complex networks can fail to identify multi-scale community structure, or to resolve key features of community dynamics. We propose a targeted node removal technique to improve the resolution of community detection. Using synthetic oscillator networks with well-defined “ground truth” communities, we quantify the community detection performance of a common modularity maximization algorithm. We show that the performance of the algorithm on communities of a given size deteriorates when these communities are embedded in multi-scale networks with communities of different sizes, compared to the performance in a single-scale network. We demonstrate that targeted node removal during community detection improves performance on multi-scale networks, particularly when removing the most functionally cohesive nodes. Applying this approach to network neuroscience, we compare dynamic functional brain networks derived from fMRI data taken during...
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**Journal:** PLOS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1006001
Volume: 14 Issue: 2 First Page #:
Date Submitted: 8/23/18 12:00AM Date Published: 2/1/18 6:00AM
Publication Location:
**Article Title:** In silico analysis of antibiotic-induced Clostridium difficile infection: Remediation techniques and biological adaptations
**Authors:** Eric W. Jones, Jean M. Carlson
**Keywords:** SIR modeling
**Abstract:** In this paper we study antibiotic-induced C. difficile infection (CDI), caused by the toxin-producing C. difficile (CD), and implement clinically-inspired simulated treatments in a computational framework that synthesizes a generalized Lotka-Volterra (gLV) model with SIR modeling techniques. The gLV model uses parameters derived from an experimental mouse model, in which the mice are administered antibiotics and subsequently dosed with CD. We numerically identify which of the experimentally measured initial conditions are vulnerable to CD colonization, then formalize the notion of CD susceptibility analytically. We simulate fecal transplantation, a clinically successful treatment for CDI, and discover that both the transplant timing and transplant donor are relevant to the the efficacy of the treatment, a result which has clinical implications. We incorporate two nongeneric yet dangerous attributes of CD into the gLV model, sporulation and antibiotic-resistant mutation, and for each...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Current Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cub.2018.01.014
Volume: 28 Issue: 4 First Page #: 526
Date Submitted: 8/23/18 12:00AM Date Published: 2/1/18 12:00AM
Publication Location:
**Article Title:** Analysis of Evolutionarily Independent Protein-RNA Complexes Yields a Criterion to Evaluate the Relevance of Prebiotic Scenarios
**Authors:** Celia Blanco, Marco Bayas, Fu Yan, Irene A. Chen
**Keywords:** RNA World, origin of life, genetic code, arginine, prebiotic chemistry
**Abstract:** A central difficulty facing study of the origin of life on Earth is evaluating the relevance of different proposed prebiotic scenarios. Perhaps the most established feature of the origin of life was the progression through an RNA World, a prebiotic stage dominated by functional RNA. We use the appearance of proteins in the RNA World to understand the prebiotic milieu and develop a criterion to evaluate proposed synthetic scenarios. Current consensus suggests that the earliest amino acids of the genetic code were anionic or small hydrophobic or polar amino acids. However, the ability to interact with the RNA World would have been a crucial feature of early proteins. To determine which amino acids would be important for the RNA World, we analyze non-biological protein-aptamer complexes in which the RNA or DNA is the result of in vitro evolution. This approach avoids confounding effects of biological context and evolutionary history. We use bioinformatic analysis and molecular dynamics..
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Communications
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Volume: 9 Issue: 2313 First Page #:
Date Submitted: 8/23/18 12:00AM Date Published: 6/1/18 5:00AM
Publication Location:
**Article Title:** Lipid vesicles chaperone an encapsulated RNA aptamer
**Authors:** Ranajay Saha, Samuel Verbanic, Irene A. Chen
**Keywords:** RNA aptamer
**Abstract:** The organization of molecules into cells is believed to have been critical for the emergence of living systems. Early protocells likely consisted of RNA functioning inside vesicles made of simple lipids. However, little is known about how encapsulation would affect the activity and folding of RNA. Here we find that confinement of the malachite green RNA aptamer inside fatty acid vesicles increases binding affinity and locally stabilizes the bound conformation of the RNA. The vesicle effectively ‘chaperones’ the aptamer, consistent with an excluded volume mechanism due to confinement. Protocellular organization thereby leads to a direct benefit for the RNA. Coupled with previously described mechanisms by which encapsulated RNA aids membrane growth, this effect illustrates how the membrane and RNA might cooperate for mutual benefit. Encapsulation could thus increase RNA fitness and the like- lihood that functional sequences would emerge during the origin of life.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Applied Materials & Interfaces
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsami.8b06009
Volume: 10 Issue: 30 First Page #: 25337
Date Submitted: 8/23/18 12:00AM Date Published: 7/1/18 5:00AM
Publication Location:
**Article Title:** Highly Graphitic Mesoporous Fe,N-Doped Carbon Materials for Oxygen Reduction Electrochemical Catalysts
**Authors:** Donghun Kim, Niels P. Zussblatt, Hoon T. Chung, Shona M. Becwar, Piotr Zelenay, Bradley F. Chmelka
**Keywords:** electrocatalyst; graphitic carbon; iron, nitrogen-doped carbon; mesoporous carbon; nonprecious metal catalyst
**Abstract:** The synthesis, characterization, and electrocatalytic properties of mesoporous carbon materials doped with nitrogen atoms and iron are reported and compared for the catalyzed reduction of oxygen gas at fuel cell cathodes. Mixtures of common and inexpensive organic precursors, melamine, and formaldehyde were pyrolyzed in the presence of transition-metal salts (e.g., nitrates) within a mesoporous silica template to yield mesoporous carbon materials with greater extents of graphitization than those of others prepared from small-molecule precursors. In particular, Fe,N-doped carbon materials possessed high surface areas (?800 m2/g) and high electrical conductivities (?19 S/cm), which make them attractive for electrocatalyst applications. The surface compositions of the mesoporous Fe,N-doped carbon materials were postsynthetically modified by acid washing and followed by high-temperature thermal treatments, which were shown by X-ray photoelectron spectroscopy to favor the formation of...
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**Journal:** Journal of the American Chemical Society
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Volume: 140 Issue: 11 First Page #: 3892
Date Submitted: 8/23/18 12:00AM Date Published: 3/1/18 6:00AM
Publication Location:
**Article Title:** Functionally Active Membrane Proteins Incorporated in Mesostructured Silica Films
**Authors:** Justin P. Jahnke, Matthew N. Idso, Sunyia Hussain, Matthias J. N. Junk, Julia M. Fisher, David D. Phan
**Keywords:** mesostructured silica
**Abstract:** A versatile synthetic protocol is reported that allows high concentrations of functionally active membrane proteins to be incorporated in mesostructured silica materials. Judicious selections of solvent, surfactant, silica precursor species, and synthesis conditions enable membrane proteins to be stabilized in solution and during subsequent coassembly into silica–surfactant composites with nano- and mesoscale order. This was demonstrated by using a combination of nonionic (n-dodecyl-?-d-maltoside or Pluronic P123), lipid-like (1,2-diheptanoyl-sn-glycero-3-phosphocholine), and perfluoro-octanoate surfactants under mild acidic conditions to coassemble the light-responsive transmembrane protein proteorhodopsin at concentrations up to 15 wt% into the hydrophobic regions of worm-like mesostructured silica materials in films. Small-angle X-ray scattering, electron paramagnetic resonance spectroscopy, and transient UV–visible spectroscopy analyses established that proteorhodopsin molecules...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Arthroscopy: The Journal of Arthroscopic & Related Surgery
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.arthro.2017.08.250
Volume: 34 Issue: 2 First Page #: 581
Date Submitted: 8/23/18 12:00AM Date Published: 2/1/18 6:00AM
Publication Location:
**Article Title:** Adipose Stem Cells Incorporated in Fibrin Clot Modulate Expression of Growth Factors
**Authors:** Kelsy R. Siegel, Tracy N. Clevenger, Dennis O. Clegg, Duncan A. Proctor, Christopher S. Proctor
**Keywords:** Whole blood
**Abstract:** Purpose: To evaluate the platelet capture rate of whole blood fibrin clots and the expression, secretion, and retention of the growth factors vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF) from fibrin clots and to determine how these levels may be modulated by allogeneic adipose-derived stem cells (ASCs). Methods: Whole blood from 10 human volunteers was transferred to a clotting device and the platelet capture rate determined. Two experimental conditions and 1 control were evaluated over 2 weeks in vitro. Clots made from human whole blood without ASCs, clot(?)ASC, were compared with clots with ASCs incorporated, clot(+)ASC, and a control group of synthetic polyethylene glycol gels with ASCs incorporated, control(+)ASCs. All conditions were examined for secretion and retention of VEGF, PDGF, and bFGF via enzyme-linked immunosorbent assay and immunohistochemistry. The analysis of platelet retention for clots...
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**Journal:** Nature Biotechnology
Publication Identifier Type: DOI Publication Identifier: 10.1038/nbt.3860
Volume: 35 Issue: 8 First Page #: 765
Date Submitted: 8/23/18 12:00AM Date Published: 5/1/17 5:00AM
Publication Location:
**Article Title:** HLA-E-expressing pluripotent stem cells escape allogeneic responses and lysis by NK cells
**Authors:** Germán G Gornalusse, Roli K Hirata, Sarah E Funk, Laura Riolobos, Vanda S Lopes, Gabriel Manske, I
**Keywords:** stem cells
**Abstract:** Polymorphisms in the human leukocyte antigen (HLA) class I genes can cause the rejection of pluripotent stem cell (PSC)-derived products in allogeneic recipients. Disruption of the Beta-2 Microglobulin (B2M) gene eliminates surface expression of all class I molecules, but leaves the cells vulnerable to lysis by natural killer (NK) cells. Here we show that this 'missing-self' response can be prevented by forced expression of minimally polymorphic HLA-E molecules. We use adeno-associated virus (AAV)-mediated gene editing to knock in HLA-E genes at the B2M locus in human PSCs in a manner that confers inducible, regulated, surface expression of HLA-E single-chain dimers (fused to B2M) or trimers (fused to B2M and a peptide antigen), without surface expression of HLA-A, B or C. These HLA-engineered PSCs and their differentiated derivatives are not recognized as allogeneic by CD8+ T cells, do not bind anti-HLA antibodies and are resistant to NK-mediated lysis. Our approach provides...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLOS Computational Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pcbi.1005743
Volume: 13 Issue: 10 First Page #:
Date Submitted: 8/23/18 12:00AM Date Published: 10/1/17 5:00AM
Publication Location:
**Article Title:** Object detection through search with a foveated visual system
**Authors:** Emre Akbas, Miguel P. Eckstein, Wolfgang Einhäuser
**Keywords:** foveated vision
**Abstract:** Humans and many other species sense visual information with varying spatial resolution across the visual field (foveated vision) and deploy eye movements to actively sample regions of interests in scenes. The advantage of such varying resolution architecture is a reduced computational, hence metabolic cost. But what are the performance costs of such processing strategy relative to a scheme that processes the visual field at high spatial reso- lution? Here we first focus on visual search and combine object detectors from computer vision with a recent model of peripheral pooling regions found at the V1 layer of the human visual system. We develop a foveated object detector that processes the entire scene with varying resolution, uses retino-specific object detection classifiers to guide eye movements, aligns its fovea with regions of interest in the input image and integrates observations across multiple fixations. We compared the foveated object detector against a non-foveated version..
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**Journal:** Current Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cub.2017.07.068
Volume: 27 Issue: 18 First Page #: 2827
Date Submitted: 8/23/18 12:00AM Date Published: 9/1/17 5:00AM
Publication Location:
**Article Title:** Humans, but Not Deep Neural Networks, Often Miss Giant Targets in Scenes
**Authors:** Miguel P. Eckstein, Kathryn Koehler, Lauren E. Welbourne, Emre Akbas
**Keywords:** neural networks
**Abstract:** Even with great advances in machine vision, animals are still unmatched in their ability to visually search complex scenes. Animals from bees [1, 2] to birds [3] to humans [4–12] learn about the statistical relations in visual environments to guide and aid their search for targets. Here, we investigate a novel manner in which humans utilize rapidly acquired information about scenes by guiding search toward likely target sizes. We show that humans often miss targets when their size is inconsistent with the rest of the scene, even when the targets were made larger and more salient and observers fixated the target. In contrast, we show that state-of-the-art deep neural networks do not exhibit such deficits in finding mis- scaled targets but, unlike humans, can be fooled by target-shaped distractors that are inconsistent with the expected target's size within the scene. Thus, it is not a human deficiency to miss targets when they are inconsistent in size with the scene; instead, it...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1610732114
Volume: 114 Issue: 21 First Page #:
Date Submitted: 8/23/18 12:00AM Date Published: 5/1/17 12:00AM
Publication Location:
**Article Title:** The wisdom of crowds for visual search
**Authors:** Mordechai Z. Juni, Miguel P. Eckstein
**Keywords:** group decision rules, signal detection theory, ideal observer analyses, wisdom of crowds
**Abstract:** Decision-making accuracy typically increases through collective integration of people's judgments into group decisions, a phenomenon known as the wisdom of crowds. For simple perceptual laboratory tasks, classic signal detection theory specifies the upper limit for collective integration benefits obtained by weighted aver- aging of people's confidences, and simple majority voting can often approximate that limit. Life-critical perceptual decisions often involve searching large image data (e.g., medical, security, and aerial imagery), but the expected benefits and merits of using different pooling algorithms are unknown for such tasks. Here, we show that expected pooling benefits are significantly greater for visual search than for single-location perceptual tasks and the prediction given by classic signal detection theory. In addition, we show that simple majority voting obtains inferior accuracy benefits for visual search relative to averaging and weighted averaging of observers'...
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**Journal:** Journal of Vision
Publication Identifier Type: DOI Publication Identifier: 10.1167/17.2.16
Volume: 17 Issue: 2 First Page #:
Date Submitted: 8/23/18 12:00AM Date Published: 3/1/17 6:00AM
Publication Location:
**Article Title:** Temporal and peripheral extraction of contextual cues from scenes during visual search
**Authors:** Kathryn Koehler, Miguel P. Eckstein
**Keywords:** scene context, visual search, scene perception, peripheral processing, contextual guidance
**Abstract:** Scene context is known to facilitate object recognition and guide visual search, but little work has focused on isolating image-based cues and evaluating their contributions to eye movement guidance and search performance. Here, we explore three types of contextual cues (a co-occurring object, the configuration of other objects, and the superordinate category of background elements) and assess their joint contributions to search performance in the framework of cue-combination and the temporal unfolding of their extraction. We also assess whether observers' ability to extract each contextual cue in the visual periphery is a bottleneck that determines the utilization and contribution of each cue to search guidance and decision accuracy. We find that during the first four fixations of a visual search task observers first utilize the configuration of objects for coarse eye movement guidance and later use co- occurring object information for finer guidance. In the absence of contextual...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Cell
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cell.2017.08.015
Volume: 170 Issue: 6 First Page #: 1184
Date Submitted: 8/24/18 12:00AM Date Published: 9/1/17 5:00AM
Publication Location:
**Article Title:** Combinatorial Signal Perception in the BMP Pathway
**Authors:** Yaron E. Antebi, James M. Linton, Heidi Klumpe, Bogdan Bintu, Mengsha Gong, Christina Su, Reed Mc
**Keywords:** bone morphogenetic protein
**Abstract:** The bone morphogenetic protein (BMP) signaling pathway comprises multiple ligands and receptors that interact promiscuously with one another and typically appear in combinations. This feature is often explained in terms of redundancy and regulatory flexibility, but it has remained unclear what signal-processing capabilities it provides. Here, we show that the BMP pathway processes multi-ligand inputs using a specific repertoire of computations, including ratiometric sensing, balance detection, and imbalance detection. These computations operate on the relative levels of different ligands and can arise directly from competitive receptor-ligand interactions. Furthermore, cells can select different computations to perform on the same ligand combination through expression of alternative sets of receptor variants. These results provide a direct signal-processing role for promiscuous receptor-ligand interactions and establish operational principles for quantitatively controlling cells...
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**Journal:** Science
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Volume: 360 Issue: First Page #:
Date Submitted: 8/24/18 12:00AM Date Published: 5/1/18 5:00AM
Publication Location:
**Article Title:** Morphogen gradient reconstitution reveals Hedgehog pathway design principles
**Authors:** Pulin Li, Joseph S. Markson, Sheng Wang, Siheng Chen, Vipul Vachharajani, Michael B. Elowitz
**Keywords:** Sonic Hedgehog pathway
**Abstract:** In developing tissues, cells estimate their spatial position by sensing graded concentrations of diffusible signaling proteins called morphogens. Morphogen-sensing pathways exhibit diverse molecular architectures, whose roles in controlling patterning dynamics and precision remain unclear. Here, combining cell-based in vitro gradient reconstitution, genetic re-wiring, and mathematical modeling, we systematically analyzed the unique architectural features of the Sonic Hedgehog pathway. The combination of double-negative regulatory logic and negative feedback through the PTCH receptor accelerates gradient formation and improves robustness to variation in the morphogen production rate compared to alternative designs. The ability to isolate morphogen patterning from concurrent developmental processes, and to compare the patterning behaviors of alternative, re-wired, pathway architectures offers a powerful way to understand and engineer multicellular patterning.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Cell Systems
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.cels.2018.01.011
Volume: 6 Issue: 2 First Page #: 216
Date Submitted: 8/24/18 12:00AM Date Published: 2/1/18 6:00AM
Publication Location:
**Article Title:** Molecular Time Sharing through Dynamic Pulsing in Single Cells
**Authors:** Jin Park, Marta Dies, Yihan Lin, Sahand Hormoz, Stephanie E. Smith-Unna, Sofia Quinodoz, María Jesı
**Keywords:** stochastic time-sharing dynamics
**Abstract:** In cells, specific regulators often compete for limited amounts of a core enzymatic resource. It is typically assumed that competition leads to partitioning of core enzyme molecules among regulators at constant levels. Alternatively, however, different regulatory species could time share, or take turns utilizing, the core resource. Using quantitative time-lapse microscopy, we analyzed sigma factor activity dynamics, and their competition for RNA polymerase, in individual Bacillus subtilis cells under energy stress. Multiple alternative sigma factors were activated in ~1-hr pulses in stochastic and repetitive fashion. Pairwise analysis revealed that two sigma factors rarely pulse simultaneously and that some pairs are anti-correlated, indicating that RNAP utilization alternates among different sigma factors. Mathematical modeling revealed how stochastic time-sharing dynamics can emerge from pulse-generating sigma factor regulatory circuits actively competing for RNAP. Time sharing...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Macromolecules
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.macromol.7b01106
Volume: 50 Issue: 16 First Page #: 6263
Date Submitted: 8/24/18 12:00AM Date Published: 8/1/17 5:00AM
Publication Location:
**Article Title:** Field-Theoretic Simulations of Fluctuation-Stabilized Aperiodic “Bricks-and-Mortar” Mesophase in Miktoarm Star Block Copolymer/Homopolymer Blends
**Authors:** Yi-Xin Liu, Kris T. Delaney, Glenn H. Fredrickson
**Keywords:** Bricks-and-Mortar
**Abstract:** A new class of thermoplastic elastomers possessing unusual mechanical properties has recently been discovered in binary blends of A-b-(B-b- A?)n miktoarm star block copolymers and A homopolymers that spontaneously form an unusual, thermodynamically stable, aperiodic “bricks-and-mortar” (B&M) mesophase morphology. The B&M mesophase is believed to be stabilized by thermal fluctuations as in the well-known case of the bicontinuous microemulsion phase. Here, two-dimensional field-theoretic simulations are used to study the equilibrium self-assembly of such miktoarm polymer binary blends. As expected, the B&M mesophase is not present in the mean-field phase diagram obtained with self-consistent field theory, but complex Langevin (CL) simulations, which fully incorporate thermal fluctuation effects, reveal dramatic changes to the phase diagram. A region of strong fluctuations results in the emergent stabilization of the B&M mesophase in a broad composition channel positioned between...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Macromolecules
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.macromol.8b00394
Volume: 51 Issue: 9 First Page #: 3369
Date Submitted: 8/24/18 12:00AM Date Published: 4/1/18 5:00AM
Publication Location:
**Article Title:** SCFT Study of Diblock Copolymer Melts in Electric Fields: Selective Stabilization of Orthorhombic
**Authors:** Jonathan M. Martin, Wei Li, Kris T. Delaney, Glenn H. Fredrickson
**Keywords:** self-consistent field theory
**Abstract:** Using self-consistent field theory (SCFT), we explore the phase behavior of a diblock copolymer (BCP) melt in an applied electric field, with different dielectric constants assigned to each monomer type. The electric field penalizes the interfaces between species domains that are not parallel to the field. Under the present mean-field approximation, lamellar and cylindrical structures reorient to align their interfaces with the electric field, such that these mesophases will have the same electrostatic free energy contribution as the mixed (disordered) state, and their relative stability will remain unchanged. In contrast, sphere and network phases do not have an axis of dielectric uniformity; consequently, the preferred orientation and morphological response of these phases must be determined numerically. We compute the phase diagram for a BCP melt in the presence of an applied electric field by comparing the free energy of each phase at its thermodynamically preferred orientation...
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**Journal:** The Journal of Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.5025720
Volume: 148 Issue: 204903 First Page #:
Date Submitted: 8/24/18 12:00AM Date Published: 5/1/18 5:00AM
Publication Location:
**Article Title:** The effective chi parameter in polarizable polymeric systems: One-loop perturbation theory and field-theoretic simulations
**Authors:** Douglas J. Grzetic, Kris T. Delaney, Glenn H. Fredrickson
**Keywords:** field-theoretic simulation
**Abstract:** We derive the effective Flory-Huggins parameter in polarizable polymeric systems, within a recently introduced polarizable field theory framework. The incorporation of bead polarizabilities in the model self-consistently embeds dielectric response, as well as van der Waals interactions. The latter generate a ? parameter (denoted ? ?) between any two species with polarizability contrast. Using one-loop perturbation theory, we compute corrections to the structure factor S(k) and the dielectric function ?ˆ(k) for a polarizable binary homopolymer blend in the one-phase region of the phase diagram. The electrostatic corrections to S(k) can be entirely accounted for by a renormalization of the excluded volume parameter B into three van der Waals-corrected parameters BAA, BAB, and BBB, which then determine ? ?. The one-loop theory not only enables the quantitative prediction of ? ? but also provides useful insight into the dependence of ? ? on the electrostatic environment...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Bioinspiration & Biomimetics
Publication Identifier Type: DOI Publication Identifier: 10.1088/1748-3190/aab738
Volume: 13 Issue: 041001 First Page #:
Date Submitted: 8/24/18 12:00AM Date Published: 5/1/18 5:00AM
Publication Location:
**Article Title:** Moth eye-inspired anti-reflective surfaces for improved IR optical systems & visible LEDs fabricated with colloidal lithography and etching
**Authors:** Lesley W Chan, Daniel E Morse, Michael J Gordon
**Keywords:** anti-reflective surfaces
**Abstract:** Near- and sub-wavelength photonic structures are used by numerous organisms (e.g. insects, cephalopods, fish, birds) to create vivid and often dynamically-tunable colors, as well as create, manipulate, or capture light for vision, communication, crypsis, photosynthesis, and defense. This review introduces the physics of moth eye (ME)-like, biomimetic nanostructures and discusses their application to reduce optical losses and improve efficiency of various optoelectronic devices, including photodetectors, photovoltaics, imagers, and light emitting diodes. Light–matter interactions at structured and heterogeneous surfaces over different length scales are discussed, as are the various methods used to create ME-inspired surfaces. Special interest is placed on a simple, scalable, and tunable method, namely colloidal lithography with plasma dry etching, to fabricate ME-inspired nanostructures in a vast suite of materials. Anti-reflective surfaces and coatings for IR devices and enhancing...
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**Journal:** Journal of Optics
Publication Identifier Type: DOI Publication Identifier: 10.1088/2040-8986/aa8fbb
Volume: 19 Issue: 114007 First Page #:
Date Submitted: 8/24/18 12:00AM Date Published: 10/1/17 5:00AM
Publication Location:
**Article Title:** Biomimetic nanostructures in ZnS and ZnSe provide broadband anti-reflectivity
**Authors:** Lesley Chan, E A DeCuir Jr, R Fu, Daniel E. Morse, Michael J. Gordon
**Keywords:** biomimetic photonics, anti-reflection coating, ZnS, ZnSe, finite difference time domain simulations
**Abstract:** Graded-index, moth eye-inspired anti-reflective features were fabricated in ZnS and ZnSe via nanosphere lithography using a Langmuir–Blodgett dip-coating method with plasma-based mask reduction and pattern transfer. Arrays of hexagonally close-packed conical frusta (top diameter = 300 nm, pitch = 690 nm, height = 2800 nm) were realized by isotropic etching (size-reduction) of the colloidal mask with CF4/Ar, followed by pattern transfer into the substrate using CH4/H2 plasma etching. Substantial increases in broadband transmission were achieved across the 2–20 ?m range, yielding 23% and 26% single-side transmission improvement, and 92% and 88% absolute double-side transmission for ZnS and ZnSe, respectively, in excellent agreement with finite difference time domain (FDTD) optical simulations. Experimental differences in direct versus total transmission, and the general fall off of transmission at short wavelengths, were attributed to diffuse forward scattering and diffractive effects...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Network Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1162/netn_a_00035
Volume: 2 Issue: 3 First Page #: 362
Date Submitted: 8/24/18 12:00AM Date Published: 8/1/18 5:00AM
Publication Location:
**Article Title:** Effect of different spatial normalization approaches on tractography and structural brain networks
**Authors:** Clint Greene, Matt Cieslak, Scott T. Grafton
**Keywords:** Diffusion MRI, Tractography, Spatial normalization, Brain networks, Connectomes
**Abstract:** To facilitate the comparison of white matter morphologic connectivity across target populations, it is invaluable to map the data to a standardized neuroanatomical space. Here, we evaluated direct streamline normalization (DSN), where the warping was applied directly to the streamlines, with two publically available approaches that spatially normalize the diffusion data and then reconstruct the streamlines. Prior work has shown that streamlines generated after normalization from reoriented diffusion data do not reliably match the streamlines generated in native space. To test the impact of these different normalization methods on quantitative tractography measures, we compared the reproducibility of the resulting normalized connectivity matrices and network metrics with those originally obtained in native space. The two methods that reconstruct streamlines after normalization led to significant differences in network metrics with large to huge standardized effect sizes, reflecting...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1706693114
Volume: 114 Issue: 30 First Page #: 7963
Date Submitted: 8/24/18 12:00AM Date Published: 7/1/17 5:00AM
Publication Location:
**Article Title:** Harm to self outweighs benefit to others in moral decision making
**Authors:** Lukas J. Volz, B. Locke Welborn, Matthias S. Gobel, Michael S. Gazzaniga, Scott T. Grafton
**Keywords:** decision making
**Abstract:** How we make decisions that have direct consequences for ourselves and others forms the moral foundation of our society. Whereas economic theory contends that humans aim at maximizing their own gains, recent seminal psychological work suggests that our behavior is instead hyperaltruistic: We are more willing to sacrifice gains to spare others from harm than to spare ourselves from harm. To investigate how such egoistic and hyperaltruistic tendencies influence moral decision making, we investigated trade-off decisions combining monetary rewards and painful electric shocks, administered to the participants themselves or an anonymous other. Whereas we replicated the notion of hyperaltruism (i.e., the willingness to forego reward to spare others from harm), we observed strongly egoistic tendencies in participants' unwillingness to harm themselves for others' benefit. The moral principle guiding intersubject trade-off decision making observed in our study is best described as...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLOS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0184344
Volume: 12 Issue: 10 First Page #:
Date Submitted: 8/24/18 12:00AM Date Published: 10/1/17 5:00AM
Publication Location:
**Article Title:** Learning about learning: Mining human brain sub-network biomarkers from fMRI data
**Authors:** Petko Bogdanov, Nazli Dereli, Xuan-Hong Dang, Danielle S. Bassett, Nicholas F. Wymbs, Scott T. Grafl
**Keywords:** fMRI, biomarker
**Abstract:** Modeling the brain as a functional network can reveal the relationship between distributed neurophysiological processes and functional interactions between brain structures. Existing literature on functional brain networks focuses mainly on a battery of network properties in "resting state" employing, for example, modularity, clustering, or path length among regions. In contrast, we seek to uncover functionally connected subnetworks that predict or correlate with cohort differences and are conserved within the subjects within a cohort. We focus on differences in both the rate of learning as well as overall performance in a sensorimotor task across subjects and develop a principled approach for the discovery of discriminative sub- graphs of functional connectivity based on imaging acquired during practice. We discover two statistically significant subgraph regions: one involving multiple regions in the visual cortex and another involving the parietal operculum and planum temporale.
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**Journal:** Brain Structure and Function
Publication Identifier Type: DOI Publication Identifier: 10.1007/s00429-017-1508-x
Volume: 223 Issue: 2 First Page #: 635
Date Submitted: 8/24/18 12:00AM Date Published: 9/1/17 5:00AM
Publication Location:
**Article Title:** A probabilistic atlas of fiber crossings for variability reduction of anisotropy measures
**Authors:** Lukas J. Volz, Matt Cieslak, Scott T. Grafton
**Keywords:** Diffusion MRI, Human Connectome Project, Voxel-wise comparison, White matter, Human anatomy
**Abstract:** Diffusion imaging enables assessment of human brain white matter (WM) in vivo. WM microstructural integrity is routinely quantified via fractional anisotropy (FA). However, FA is also influenced by the number of differentially oriented fiber populations per voxel. To date, the precise statistical relationship between FA and fiber populations has not been characterized, complicating microstructural integrity assessment. Here, we used 630 state-of-the-art diffusion datasets from the Human Connectome Project, which allowed us to infer the number of fiber populations per voxel in a model-free fashion. Beyond the known impact on mean FA, variance of anisotropy distributions was drastically impacted, not only for FA, but also the more recent anisotropy indices generalized FA and multidimensional anisotropy. To ameliorate this bias, we introduce a probabilistic WM atlas delineating the number of distinctly oriented fiber populations per voxel. Our atlas shows that the majority of WM voxels...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Psychophysiology
Publication Identifier Type: DOI Publication Identifier: 10.1111/psyp.13018
Volume: 55 Issue: 4 First Page #:
Date Submitted: 8/24/18 12:00AM Date Published: 4/1/18 5:00AM
Publication Location:
**Article Title:** Quantifying rapid changes in cardiovascular state with a moving ensemble average
**Authors:** Matthew Cieslak, William S. Ryan, Viktoriya Babenko, Hannah Erro, Zoe M. Rathbun, Wendy Meiring, R
**Keywords:** analysis/statistical methods, autonomic, cardiovascular, fMRI, heart rate, impedance cardiography
**Abstract:** MEAP, the moving ensemble analysis pipeline, is a new open-source tool designed to perform multisubject preprocessing and analysis of cardiovascular data, including electrocardiogram (ECG), impedance cardiogram (ICG), and continuous blood pressure (BP). In addition to traditional ensemble averaging, MEAP implements a moving ensemble averaging method that allows for the continuous estimation of indices related to cardiovascular state, including cardiac output, preejection period, heart rate variability, and total peripheral resistance, among others. Here, we define the moving ensemble technique mathematically, highlighting its differences from fixed-window ensemble averaging. We describe MEAP's interface and features for signal processing, artifact correction, and cardiovascular-based fMRI analysis. We demonstrate the accuracy of MEAP's novel B point detection algorithm on a large collection of hand-labeled ICG waveforms. As a proof of concept, two subjects completed a series...
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**Journal:** NeuroImage
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2017.12.039
Volume: 169 Issue: First Page #: 473
Date Submitted: 8/25/18 12:00AM Date Published: 4/1/18 5:00AM
Publication Location:
**Article Title:** Analytic tractography: A closed-form solution for estimating local white matter connectivity with diffusion MRI
**Authors:** Matthew Cieslak, Tegan Brennan, Wendy Meiring, Lukas J. Volz, Clint Greene, Alexander Asturias, Sub
**Keywords:** diffusion MRI, white matter connectivity, analytic tractography
**Abstract:** White matter structures composed of myelinated axons in the living human brain are primarily studied by diffusion-weighted MRI (dMRI). These long-range projections are typically characterized in a two-step process: dMRI signal is used to estimate the orientation of axon segments within each voxel, then these local orientations are linked together to estimate the spatial extent of putative white matter bundles. Tractography, the process of tracing bundles across voxels, either requires computationally expensive (probabilistic) simulations to model uncertainty in fiber orientation or ignores it completely (deterministic). Furthermore, simulation necessarily generates a finite number of trajectories, introducing “simulation error” to trajectory estimates. Here we introduce a method to analytically (via a closed-form solution) take an orientation distribution function (ODF) from each voxel and calculate the probabilities that a trajectory projects from a voxel into each directly...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** NeuroImage
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.neuroimage.2018.01.050
Volume: 172 Issue: First Page #: 390
Date Submitted: 8/25/18 12:00AM Date Published: 5/1/18 5:00AM
Publication Location:
**Article Title:** Spatial coherence of oriented white matter microstructure: Applications to white matter regions associated with genetic similarity
**Authors:** Haraldur T. Hallgrímsson, Matthew Cieslak, Luca Foschini, Scott T. Grafton, Ambuj K. Singh
**Keywords:** diffusion imaging, population similarity, heritable influence, white matter, region discovery
**Abstract:** We present a method to discover differences between populations with respect to the spatial coherence of their oriented white matter microstructure in arbitrarily shaped white matter regions. This method is applied to diffusion MRI scans of a subset of the Human Connectome Project dataset: 57 pairs of monozygotic and 52 pairs of dizygotic twins. After controlling for morphological similarity between twins, we identify 3.7% of all white matter as being associated with genetic similarity (35.1 k voxels, p < 10 4 , false discovery rate 1.5%), 75% of which spatially clusters into twenty-two contiguous white matter regions. Furthermore, we show that the orientation similarity within these regions generalizes to a subset of 47 pairs of non-twin siblings, and show that these siblings are on average as similar as dizygotic twins. The regions are located in deep white matter including the superior longitudinal fasciculus, the optic radiations, the middle cerebellar peduncle...
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Volume: Issue: First Page #:
Date Submitted: 8/25/18 12:00AM Date Published: 5/1/18 5:00AM
Publication Location:
**Article Title:** Limiting motor skill knowledge via incidental training protects against choking under pressure
**Authors:** Taraz G. Lee, Daniel E. Acuña, Konrad P. Kording, Scott T. Grafton
**Keywords:** cognitive control and automaticity, implicit vs. explicit memory, attention and executive control, skill acquisition
**Abstract:** The paradoxical harmful effects of motivation and incentives on skilled performance (Bchoking under pressure^) are observed in a wide variety of motor tasks. Two theories of this phenomenon suggest that choking under pressure occurs due to maladaptive attention and top-down control, either through distraction away from the task or interference via an overreliance on controlled processing of a skilled task. A third theory, overmotivation (or overarousal), suggests that under pressure, Binstinctive^ or Pavlovian approach/withdrawal responses compete with the desired response. Only the two former theories predict that choking under pressure would be less likely to occur if an individual is unaware of the skill over which to assert top-down control. Here we show that only participants who train and perform with premovement cues that allowed for preparatory movement planning choke under pressure due to large monetary incentives, and that this effect is independent of the level of skill...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Polymer Science Part A: Polymer Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1002/pola.29007
Volume: 56 Issue: 12 First Page #: 1259
Date Submitted: 8/25/18 12:00AM Date Published: 6/1/18 5:00AM
Publication Location:
**Article Title:** PET-RAFT as a facile strategy for preparing functional lipid-polymer conjugates
**Authors:** Akira Watanabe, Jia Niu, David J. Lunn, Jimmy Lawrence, Abigail S. Knight, Mengwen Zhang, Craig J. H
**Keywords:** gold nanoparticles, lipid–polymer conjugates, PET?RAFT, self?assembly
**Abstract:** From readily available starting materials, we report a facile synthesis of lipid–polymer conjugates (LPCs). Easy access to multigram quantities of a dialkyl lipid chain transfer agent allows a range of LPCs to be prepared bearing well?defined hydrophilic polymer head?groups, controlled molecular weights and low dispersity by photoelectron transfer RAFT polymerization (PET?RAFT). As dictated by the lipid packing parameters, the resulting LPCs were suitable for solution?phase self?assembly, both independently and in combination with naturally occurring phospholipids, affording micelles, smaller vesicle?like structures, or stabilized large unilamellar vesicles. Notably, co?assembly of LPCs and phospholipids bearing mutually orthogonal fluorophores showed negligible phase separation/aggregation. To demonstrate the versatility of these LPCs, the RAFT chain?end was removed, affording thiol?terminated LPCs that could be used for the manipulation and stabilization of gold nanoparticle...
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**Journal:** Journal of the American Chemical Society
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Volume: 140 Issue: 5 First Page #: 1945
Date Submitted: 8/25/18 12:00AM Date Published: 1/1/18 6:00AM
Publication Location:
**Article Title:** Controlled Formation and Binding Selectivity of Discrete Oligo(methyl methacrylate) Stereocomplexes
**Authors:** Jing M. Ren, Jimmy Lawrence, Abigail S. Knight, Allison Abdilla, Raghida Bou Zerdan, Adam E. Levi, Be
**Keywords:** stereocomplex
**Abstract:** The triple-helix stereocomplex of poly(methyl methacrylate) (PMMA) is a unique example of a multistranded synthetic helix that has significant utility and promise in materials science and nanotechnology. To gain a fundamental understanding of the underlying assembly process, discrete stereoregular oligomer libraries were prepared by combining stereospecific polymerization techniques with automated flash chromatography purification. Stereocomplex assembly of these discrete building blocks enabled the identification of (1) the minimum degree of polymerization required for the stereocomplex formation and (2) the dependence of the helix crystallization mode on the length of assembling precursors. More significantly, our experiments resolved binding selectivity between helical strands with similar molecular weights. This presents new opportunities for the development of next-generation polymeric materials based on a triple-helix motif.
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**Journal:** ACS Macro Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsmacrolett.7b00587
Volume: 6 Issue: 10 First Page #: 1109
Date Submitted: 8/25/18 12:00AM Date Published: 9/1/17 5:00AM
Publication Location:
**Article Title:** Rapid Visible Light-Mediated Controlled Aqueous Polymerization with In Situ Monitoring
**Authors:** Jia Niu, Zachariah A. Page, Neil D. Dolinski, Athina Anastasaki, Andy T. Hsueh, H. Tom Soh, Craig J. H
**Keywords:** PET–RAFT
**Abstract:** We report a simple procedure for rapid, visible light-mediated, controlled radical polymerization in aqueous solutions. Based on the photoelectron transfer reversible addition–fragmentation chain transfer (PET–RAFT) polymerization, fast chain propagation at room temperature in water was achieved in the presence of reductant and without prior deoxygenation. A systematic study correlating irradiation intensity and polymerization kinetics, enabled by in situ nuclear magnetic resonance spectroscopy, provided optimized reaction conditions. The versatility of this procedure was demonstrated through a rapid triblock copolymer synthesis, and incorporation of water-labile activated esters for direct conjugation of hydrophilic small molecules and proteins. In addition, this technique boasts excellent temporal control and provides a wide range of macromolecular materials with controlled molecular weights and narrow molecular weight distributions.
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Volume: 139 Issue: 39 First Page #: 13735
Date Submitted: 8/25/18 12:00AM Date Published: 9/1/17 5:00AM
Publication Location:
**Article Title:** A Versatile and Efficient Strategy to Discrete Conjugated Oligomers
**Authors:** Jimmy Lawrence, Eisuke Goto, Jing M. Ren, Brenden McDearmon, Dong Sub Kim, Yuto Ochiai, Paul G
**Keywords:** discrete conjugated oligomers
**Abstract:** An efficient and scalable strategy to prepare libraries of discrete conjugated oligomers (? = 1.0) using the combination of controlled polymerization and automated flash chromatography is reported. From this two-step process, a series of discrete conjugated materials from dimers to tetradecamers could be isolated in high yield with excellent structural control. Facile and scalable access to monodisperse libraries of different conjugated oligomers opens pathways to designer mixtures with precise composition and monomer sequence, allowing exquisite control over their physical, optical, and electronic properties.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Polymer Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1039/C7PY00713B
Volume: 8 Issue: First Page #: 4637
Date Submitted: 8/25/18 12:00AM Date Published:
Publication Location:
**Article Title:** RAFT-mediated, visible light-initiated single unit monomer insertion and its application in the synthesis of sequence-defined polymers
**Authors:** Changkui Fu, Zixuan Huang, Craig J. Hawker, Graeme Moad, Jiangtao Xu, Cyrille Boyer
**Keywords:** RAFT, SUMI
**Abstract:** In this communication, we report a catalyst-free methodology for single unit monomer insertion (SUMI) into reversible addition–fragmentation chain transfer (RAFT) agents initiated by low intensity visible light. This method is applicable to broad range of monomer families (monosubstituted vinyl monomers) and allows for the preparation of the corresponding single monomer insertion product in high yields (typically >90%; isolated yields after chromatography 60–80%). The fidelity of the end-functional SUMI products is demonstrated with use of the SUMI products in RAFT polymerization and by using the tools of conventional chemistry (thiol–ene and esterification reactions). A uniform oligomer comprising five discrete vinyl monomer repeat units was synthesized by an iterative strategy comprising three consecutive SUMI reactions and two intermediate esterification and thiol–ene steps. We thus demonstrate a new protocol for incorporating the rich functionality of available vinyl monomers...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Polymer Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1039/C7PY00773F
Volume: 8 Issue: First Page #: 4528
Date Submitted: 8/25/18 12:00AM Date Published:
Publication Location:
**Article Title:** Highly stable Au nanoparticles with double hydrophilic block copolymer templates: correlation between structure and stability
**Authors:** Eunyong Seo, Sang-Ho Lee, Sangho Lee, Soo-Hyung Choi, Craig J. Hawker, Byeong-Su Kim
**Keywords:** gold nanoparticles
**Abstract:** We herein report a facile synthetic method for preparing gold nanoparticles (Au NPs) with superior colloidal stability using a series of double hydrophilic block copolymers (DHBC), poly(ethylene oxide)-block-poly (acrylic acid) (PEO-b-PAA), as a template (Au@DHBC NPs). Due to the presence of a well-defined polymeric shell around the Au NPs, this DHBC-based synthetic method provides superior stability when compared to conventional citrate-based synthesis. We have investigated NP performance by systematically varying the molecular weight of the interacting PAA block from 5000 g mol?1 to 27[thin space (1/6-em)]000 g mol?1. Interestingly, the size of the Au NPs did not significantly depend on the molecular weight of the PAA block and the density of DHBC present around a single NP decreased upon an increase in the molecular weight of the PAA block. Cyanide etching of Au@DHBC NPs further confirmed the presence of DHBC with different densities around the NPs, resulting in tunable stability.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie International Edition
Publication Identifier Type: DOI Publication Identifier: 10.1002/anie.201610223
Volume: 56 Issue: 29 First Page #: 8376
Date Submitted: 8/25/18 12:00AM Date Published: 7/1/17 5:00AM
Publication Location:
**Article Title:** Synthesis of Discrete Oligomers by Sequential PET-RAFT Single-Unit Monomer Insertion
**Authors:** Jiangtao Xu, Changkui Fu, Sivaprakash Shanmugam, Craig J. Hawker, Graeme Moad, Cyrille Boyer
**Keywords:** photopolymerization, RAFT polymerization, sequence control, single unit monomer insertion
**Abstract:** Uniform synthetic polymers with precisely defined molar mass and monomer sequence (primary structure) have many potential high?value applications. However, a robust and versatile synthetic strategy for these materials remains one of the great challenges in polymer synthesis. Herein we describe proof?of?principle experiments for a modular strategy to produce discrete oligomers by a visible?light?mediated radical chain process. We utilize the high selectivity provided by photo?induced electron/energy transfer (PET) activation to develop efficient single unit monomer insertion (SUMI) into reversible addition–fragmentation chain?transfer (RAFT) agents. A variety of discrete oligomers (single unit species, dimers, and, for the first time, trimers) have been synthesized by sequential SUMI in very high yield under mild reaction conditions. The trimers were used as building blocks for the construction of uniform hexamers and graft copolymers with precisely defined branches.
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**Journal:** ChemPhotoChem
Publication Identifier Type: DOI Publication Identifier: 10.1002/cptc.201600045
Volume: 1 Issue: 4 First Page #: 125
Date Submitted: 8/25/18 12:00AM Date Published: 2/1/17 6:00AM
Publication Location:
**Article Title:** A Versatile Approach for In Situ Monitoring of Photoswitches and Photopolymerizations
**Authors:** Neil D. Dolinski, Zachariah A. Page, Fabian Eisenreich, Jia Niu, Stefan Hecht, Javier Read?de?Alaniz, C
**Keywords:** front propagation, kinetics, molecular switches, NMR spectroscopy, photopolymerization
**Abstract:** A simple, inexpensive, and modular method to directly illuminate NMR samples for in?situ analysis of photochemical transformations is reported. The versatility of this technique is demonstrated by analyzing the light?induced propagating front for small?molecule photoswitches and the kinetics of photocontrolled living radical polymerizations. In?situ measurements allow oxygen?sensitive and rapid photoevents to be studied in detail, leading to reliable determination of photoswitching quantum yields and polymerization rates. By systematically tuning light intensity, a direct relationship between propagation rate and intensity is revealed. Of particular note is the facile translation of the conditions identified through this NMR analysis to analogous benchtop experiments with insight into the nature of the photoreactive species.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Macromolecules
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.macromol.7b00165
Volume: 50 Issue: 6 First Page #: 2375
Date Submitted: 8/25/18 12:00AM Date Published: 3/1/17 6:00AM
Publication Location:
**Article Title:** Dual-Gated Supramolecular Star Polymers in Aqueous Solution
**Authors:** Bernhard V. K. J. Schmidt, Dennis Kugele, Jonas von Irmer, Jan Steinkoenig, Hatice Mutlu, Christian Rü
**Keywords:** dynamic light scattering
**Abstract:** We introduce the formation of a dual responsive supramolecular star polymer system, displaying gated self-assembly behavior. The redox- and thermoresponsive star polymers are based on a 6-fold ?-CD functionalized core molecule and RAFT-derived ferrocene end functionalized poly(N,N-dimethylacrylamide) (PDMA) and poly(N,N-diethylacrylamide) (PDEA) linear polymers. Complex formation is analyzed via various methods including dynamic light scattering (DLS). Chemical redox triggers, namely NaOCl and ascorbic acid, as well as electrochemical triggers can be utilized to shift the star polymers to the unbound state via CD/ferrocene complex dissociation. Moreover, heating above the lower critical solution temperature (approximately 34 °C) allows for a change from the coil to the globular state of the star polymers in the case of PDEA arms. For PDMA arms, heating to 70 °C allows shifting of the system to the unbound state. The response of the supramolecular star polymers is carefully studied...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.analchem.8b00706
Volume: 90 Issue: 15 First Page #: 8824
Date Submitted: 8/25/18 12:00AM Date Published: 7/1/18 5:00AM
Publication Location:
**Article Title:** Allosteric Inhibitor of KRas Identified Using a Barcoded Assay Microchip Platform
**Authors:** Amy M. McCarthy, Jungwoo Kim, A. Katrine Museth, Ryan K. Henning, John E. Heath, Emma Winson, .
**Keywords:** Protein catalyzed capture agents
**Abstract:** Protein catalyzed capture agents (PCCs) are synthetic antibody surrogates that can target a wide variety of biologically relevant proteins. As a step toward developing a high-throughput PCC pipeline, we report on the preparation of a barcoded rapid assay platform for the analysis of hits from PCC library screens. The platform is constructed by first surface patterning a micrometer scale barcode composed of orthogonal ssDNA strands onto a glass slide. The slide is then partitioned into microwells, each of which contains multiple copies of the full barcode. Biotinylated candidate PCCs from a click screen are assembled onto the barcode stripes using a complementary ssDNA-encoded cysteine-modified streptavidin library. This platform was employed to evaluate candidate PCC ligands identified from an epitope targeted in situ click screen against the two conserved allosteric switch regions of the Kirsten rat sarcoma (KRas) protein. A single microchip was utilized for the simultaneous...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Angewandte Chemie
Publication Identifier Type: DOI Publication Identifier: 10.1002/ange.201802269
Volume: 130 Issue: First Page #: 6320
Date Submitted: 8/25/18 12:00AM Date Published: 5/1/18 12:00AM
Publication Location:
**Article Title:** Modulating the Folding Landscape of Superoxide Dismutase 1 with Targeted Molecular Binders
**Authors:** David N. Bunck, Beatriz Atsavapranee, Anna K. Museth, David VanderVelde, James R. Heath
**Keywords:** Hochdurchsatz-Screening, Neurodegenerative Erkrankungen, Peptide, Proteinfaltung, Superoxid-Dismutase
**Abstract:** Amyotrophic lateral sclerosis, or Lou Gehrig's disease, is characterized by motor neuron death, with average survival times of two to five years. One cause of this disease is the misfolding of superoxide dismutase?1 (SOD1), a phenomenon influenced by point mutations spanning the protein. Herein, we used an epitope?specific high?throughput screen to identify a peptide ligand that stabilizes the SOD1 native conformation and accelerates its folding by a factor of 2.5. This strategy may be useful for fundamental studies of protein energy landscapes as well as designing new classes of therapeutics.
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**Journal:** Chemistry - A European Journal
Publication Identifier Type: DOI Publication Identifier: 10.1002/chem.201704752
Volume: 24 Issue: 15 First Page #: 3760
Date Submitted: 8/25/18 12:00AM Date Published: 3/1/18 6:00AM
Publication Location:
**Article Title:** Epitope-Targeted Macrocyclic Peptide Ligand with Picomolar Cooperative Binding to Interleukin-17F
**Authors:** Bert T. Lai, Jeré A. Wilson, Jacquie Malette?Loredo, Suresh M. Pitram, Nicole A. LaBerge, James R. He
**Keywords:** click chemistry; combinatorial chemistry; cooperative effects; macrocyclic ligands; peptides
**Abstract:** The IL?17 cytokine family is associated with multiple immune and autoimmune diseases and comprises important diagnostic and therapeutic targets. This work reports the development of epitope?targeted ligands designed for differential detection of human IL?17F and its closest homologue IL?17A. Non?overlapping and unique epitopes on IL?17F and IL?17A were identified by comparative sequence analysis of the two proteins. Synthetic variants of these epitopes were utilized as targets for in situ click screens against a comprehensive library of synthetic peptide macrocycles with 5?mer variable regions. Single generation screens yielded selective binders for IL?17F and IL?17A with low cross?reactivity. Macrocyclic peptide binders against two distinct IL?17F epitopes were coupled using variable length chemical linkers to explore the physical chemistry of cooperative binding. The optimized linker length yielded a picomolar affinity binder, while retaining high selectivity. The presented method...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** IEEE Transactions on Automatic Control
Publication Identifier Type: DOI Publication Identifier: 10.1109/TAC.2016.2604921
Volume: 62 Issue: 5 First Page #: 2286
Date Submitted: 8/25/18 12:00AM Date Published: 5/1/17 5:00AM
Publication Location:
**Article Title:** Control With Minimal Cost-Per-Symbol Encoding and Quasi-Optimality of Event-Based Encoders
**Authors:** Justin Pearson, Joao P. Hespanha, Daniel Liberzon
**Keywords:** Event-Based Encoders
**Abstract:** We consider the problem of stabilizing a continuous-time linear time-invariant system subject to communication constraints. A noiseless finite-capacity communication channel connects the process sensors to the controller/actuator. The sensor’s state measurements are encoded into symbols from a finite alphabet, transmitted through the channel, and decoded at the controller/actuator. We suppose that the transmission of each symbol costs one unit of communication resources, except for one special symbol in the alphabet that is “free” and effectively signals the absence of transmission. We explore the relationship between the encoder’s average bit-rate, its average consumption of communication resources, and the ability of the controller and encoder/decoder pair to stabilize the process. We present a necessary and sufficient condition for the existence of a stabilizing controller and encoder/decoder pair, which depends on the encoder’s average bit-rate, its average resource consumption...
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**Journal:** International Journal of Robust and Nonlinear Control
Publication Identifier Type: DOI Publication Identifier: 10.1002/rnc.3814
Volume: 27 Issue: 18 First Page #: 4381
Date Submitted: 8/27/18 12:00AM Date Published: 5/1/17 12:00PM
Publication Location:
**Article Title:** Set-based fault detection and isolation for detectable linear parameter-varying systems
**Authors:** Daniel Silvestre, Paulo Rosa, João P. Hespanha, Carlos Silvestre
**Keywords:** fault detection and isolation, unobservable LPV, coprime factorization, distributed
**Abstract:** In the context of fault detection and isolation of linear parameter?varying systems, a challenging task appears when the dynamics and the available measurements render the model unobservable, which invalidates the use of standard set?valued observers. Two results are obtained in this paper, namely, using a left?coprime factorization, one can achieve set?valued estimates with ultimately bounded hyper?volume and convergence dependent on the slowest unobservable mode; and by rewriting the set?valued observer equations and taking advantage of a coprime factorization, it is possible to have a low?complexity fault detection and isolation method. Performance is assessed through simulation, illustrating, in particular, the detection time for various types of faults.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Information Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.ins.2017.10.029
Volume: 426 Issue: First Page #: 61
Date Submitted: 8/25/18 12:00AM Date Published: 2/1/18 12:00AM
Publication Location:
**Article Title:** Self-Triggered and Event-Triggered Set-Valued Observers
**Authors:** Daniel Silvestre, Paulo Rosa, João P. Hespanha, Carlos Silvestre
**Keywords:** State estimation, Fault detection, Self-triggered, Networked control systems
**Abstract:** This paper addresses the problem of reducing the required network load and computational power for the implementation of Set-Valued Observers (SVOs) in Networked Control System (NCS). Event- and self-triggered strategies for NCS, modeled as discrete-time Linear Parameter-Varying (LPV) systems, are studied by showing how the triggering condition can be selected. The methodology provided can be applied to determine when it is required to perform a full (“classical”) computation of the SVOs, while providing low-complexity state overbounds for the remaining time, at the expenses of temporarily reducing the estimation accuracy. As part of the procedure, an algorithm is provided to compute a suitable centrally symmetric polytope that allows to find hyper-parallelepiped and ellipsoidal overbounds to the exact set-valued state estimates calculated by the SVOs. By construction, the proposed triggering techniques do not influence the convergence of the SVOs, as at some subsequent time...
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**Journal:** IEEE Transactions on Industrial Electronics
Publication Identifier Type: DOI Publication Identifier: 10.1109/TIE.2016.2630658
Volume: 64 Issue: 5 First Page #: 4296
Date Submitted: 8/25/18 12:00AM Date Published: 5/1/17 5:00AM
Publication Location:
**Article Title:** Online Optimal Operation of Parallel Voltage-Source Inverters Using Partial Information
**Authors:** Kyriakos G. Vamvoudakis, Joao P. Hespanha
**Keywords:** Game theory, learning, parallel voltage- source inverters (VSIs)
**Abstract:** In this paper, a novel optimal learning algo- rithm for partially unknown voltage-source inverters (VSIs) operating in parallel is presented. The algorithm designs game-theory-based distributed controllers to provide the appropriate working voltage magnitude and frequency at the load by converting dc voltage to ac voltage at the par- allel VSIs. It takes advantage of information from the neigh- boring low pass L–C filters to improve harmonic distortion and guarantee equal sharing of the load current across the VSIs while avoiding current circulation during transient and ensuring stability and robustness. It builds upon the ideas of approximate dynamic programming (ADP) and uses only partial information of the system and the exosystem, which is connected only to some of the VSIs. The proposed frame- work was tested in simulations to show its effectiveness.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** PLOS Biology
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pbio.2002417
Volume: 16 Issue: 3 First Page #:
Date Submitted: 8/25/18 12:00AM Date Published: 3/1/18 6:00AM
Publication Location:
**Article Title:** The colonic epithelium plays an active role in promoting colitis by shaping the tissue cytokine profile
**Authors:** Jesse Lyons, Phaedra C. Ghazi, Alina Starchenko, Alessio Tovaglieri, Katherine R. Baldwin, Emily J. Pc
**Keywords:** epithelial cells
**Abstract:** Inflammatory bowel disease (IBD) is a chronic condition driven by loss of homeostasis between the mucosal immune system, the commensal gut microbiota, and the intestinal epithelium. Our goal is to understand how these components of the intestinal ecosystem cooperate to control homeostasis. By combining quantitative measures of epithelial hyperplasia and immune infiltration with multivariate analysis of inter- and intracellular signaling, we identified epithelial mammalian target of rapamycin (mTOR) signaling as a potential driver of inflammation in a mouse model of colitis. A kinetic analysis of mTOR inhibition revealed that the pathway regulates epithelial differentiation, which in turn controls the cytokine milieu of the colon. Consistent with our in vivo analysis, we found that cytokine expression of organoids grown ex vivo, in the absence of bacteria and immune cells, was dependent on differentiation state. Our study suggests that proper differentiation of epithelial cells is ...
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**Journal:** Current Opinion in Biotechnology
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Volume: 52 Issue: First Page #: 9
Date Submitted: 8/25/18 12:00AM Date Published: 8/1/18 5:00AM
Publication Location:
**Article Title:** In vivo systems biology approaches to chronic immune/inflammatory pathophysiology
**Authors:** Alina Starchenko, Douglas A Lauffenburger
**Keywords:** immune system dysregulation
**Abstract:** Systems biology offers an emphasis on integrative computational analysis of complex multi-component processes to enhance capability for predictive insights concerning operation of those processes. The immune system represents a prominent arena in which such processes are manifested for vital roles in physiology and pathology, encompassing dozens of cell types and hundreds of reciprocal interactions. Chronic, debilitating pathologies involving immune system dysregulation have become recognized as increasing in incidence over recent decades. While clinical consequences of immune dysregulation in such pathologies are well characterized, treatment options remain limited and focus on ameliorating symptoms. Because it is difficult to recapitulate more than a severely limited facet of the immune system in vitro, application of systems biology approaches to autoimmune and inflammatory pathophysiology in vivo has opened a new door toward discerning disease sub-groups and developing...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Integrative Biology
Publication Identifier Type: DOI Publication Identifier: 10.1039/C6IB00245E
Volume: 9 Issue: 4 First Page #: 265
Date Submitted: 8/25/18 12:00AM Date Published:
Publication Location:
**Article Title:** Local remodeling of synthetic extracellular matrix microenvironments by co-cultured endometrial epithelial and stromal cells enables long-term dynamic physiological function
**Authors:** Christi D. Cook, Abby S. Hill, Margaret Guo, Linda Stockdale, Julia P. Papps, Keith B. Isaacson, Dougla
**Keywords:** extracellular matrix
**Abstract:** Mucosal barrier tissues, comprising a layer of tightly-bonded epithelial cells in intimate molecular communication with an underlying matrix-rich stroma containing fibroblasts and immune cells, are prominent targets for drugs against infection, chronic inflammation, and other disease processes. Although human in vitro models of such barriers are needed for mechanistic studies and drug development, differences in extracellular matrix (ECM) needs of epithelial and stromal cells hinder efforts to create such models. Here, using the endometrium as an example mucosal barrier, we describe a synthetic, modular ECM hydrogel suitable for 3D functional co-culture, featuring components that can be remodeled by cells and that respond dynamically to sequester local cell-secreted ECM characteristic of each cell type. The synthetic hydrogel combines peptides with off-the-shelf reagents and is thus accessible to cell biology labs. Specifically, we first identified a single peptide as suitable...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
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Volume: Issue: First Page #:
Date Submitted: 8/25/18 12:00AM Date Published: 7/1/18 5:00AM
Publication Location:
**Article Title:** Systems Modeling Identifies Divergent Receptor Tyrosine Kinase Reprogramming to MAPK Pathway Inhibition
**Authors:** Allison M. Claas, Lyla Atta, Simon Gordonov, Aaron S. Meyer, Douglas A. Lauffenburger
**Keywords:** "Triple negative breast cancer; EGFR; Her2; Met; Axl; Mek inhibition; Erk inhibition; BET inhibition "
**Abstract:** Targeted cancer therapeutics have demonstrated more limited clinical efficacy than anticipated, due to both intrinsic and acquired drug resistance. Underlying mechanisms have been largely attributed to genetic changes, but a substantial proportion of resistance observations remain unexplained by genomic properties. Emerging evidence shows that receptor tyrosine kinase (RTK) reprogramming is a major alternative process causing targeted drug resistance, separate from genetic alterations. Hence, the contributions of mechanisms leading to this process need to be more rigorously assessed.
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**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.analchem.8b00510
Volume: 90 Issue: 13 First Page #: 7930
Date Submitted: 8/25/18 12:00AM Date Published: 6/1/18 5:00AM
Publication Location:
**Article Title:** Dielectrophoretic Nanoparticle Aggregation for On-Demand Surface Enhanced Raman Spectroscopy Analysis
**Authors:** Reza Salemmilani, Brian D. Piorek, Rustin Y. Mirsafavi, Augustus W. Fountain, Martin Moskovits, Carl D
**Keywords:** SERS, Principal component analysis
**Abstract:** Rapid chemical identification of drugs of abuse in biological fluids such as saliva is of growing interest in healthcare and law enforcement. Accordingly, a label-free detection platform that accepts biological fluid samples is of great practical value. We report a microfluidics-based dielectrophoresis-induced surface enhanced Raman spectroscopy (SERS) device, which is capable of detecting physiologically relevant concentrations of methamphetamine in saliva in under 2 min. In this device, iodide-modified silver nanoparticles are trapped and released on-demand using electrodes integrated in a microfluidic channel. Principal component analysis (PCA) is used to reliably distinguish methamphetamine-positive samples from the negative control samples. Passivation of the electrodes and flow channels minimizes microchannel fouling by nanoparticles, which allows the device to be cleared and reused multiple times.
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**Journal:** Communications Biology
Publication Identifier Type: DOI Publication Identifier: 10.1038/s42003-018-0073-z
Volume: 1 Issue: 62 First Page #:
Date Submitted: 8/25/18 12:00AM Date Published: 6/1/18 5:00AM
Publication Location:
**Article Title:** Small sample sizes reduce the replicability of task-based fMRI studies
**Authors:** Benjamin O. Turner, Erick J. Paul, Michael B. Miller, Aron K. Barbey
**Keywords:** functional magnetic resonance imaging
**Abstract:** Despite a growing body of research suggesting that task-based functional magnetic resonance imaging (fMRI) studies often suffer from a lack of statistical power due to too-small samples, the proliferation of such underpowered studies continues unabated. Using large independent samples across eleven tasks, we demonstrate the impact of sample size on replicability, assessed at different levels of analysis relevant to fMRI researchers. We find that the degree of replicability for typical sample sizes is modest and that sample sizes much larger than typical (e.g., N?=?100) produce results that fall well short of perfectly replicable. Thus, our results join the existing line of work advocating for larger sample sizes. Moreover, because we test sample sizes over a fairly large range and use intuitive metrics of replicability, our hope is that our results are more understandable and convincing to researchers who may have found previous results advocating for larger samples inaccessible.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Memory
Publication Identifier Type: DOI Publication Identifier: 10.1080/09658211.2017.1393090
Volume: 26 Issue: 5 First Page #: 653
Date Submitted: 8/25/18 12:00AM Date Published: 11/1/17 5:00AM
Publication Location:
**Article Title:** Cross-task and cross-manipulation stability in shifting the decision criterion
**Authors:** Amy Frithsen, Justin Kantner, Brian A. Lopez, Michael B. Miller
**Keywords:** Response bias, criterion, recognition memory
**Abstract:** In recognition memory experiments participants must discriminate between old and new items, a judgment influenced by response bias. Research has shown substantial individual differences in the extent to which people will strategically adjust their response bias to diagnostic cues such as the prior probability of an old item. Despite this significant between subject variability, shifts in bias have been found to be relatively predictive within individuals across memory tests. Experiment 1 sought to determine whether this predictability extends beyond memory. Results revealed that the amount a subject shifted response bias in a recognition memory task was significantly predictive of shifting in a visual perception task, suggesting that shifting can generalise outside of a specific testing domain. Experiment 2 sought to determine how predictive shifting would be across two manipulations well known to induce shifts in bias: a probability manipulation and a response payoff manipulation.
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**Journal:** APL Materials
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4985758
Volume: 5 Issue: 10 First Page #: 104801
Date Submitted: 8/26/18 12:00AM Date Published: 8/1/17 5:00AM
Publication Location:
**Article Title:** Molecular mechanism of reflectin's tunable biophotonic control: Opportunities and limitations for new optoelectronics
**Authors:** Robert Levenson, Daniel G. DeMartini, Daniel E. Morse
**Keywords:** optoelectronics
**Abstract:** Discovery that reflectin proteins fill the dynamically tunable Bragg lamellae in the reflective skin cells of certain squids has prompted efforts to design new reflectin-inspired systems for dynamic photonics. But new insights into the actual role and mechanism of action of the reflectins constrain and better define the opportunities and limitations for rationally designing optical systems with reflectin-based components. We and our colleagues have discovered that the reflectins function as a signal-controlled molecular machine, regulating an osmotic motor that tunes the thickness, spacing, and refractive index of the tunable, membrane-bound Bragg lamellae in the iridocytes of the loliginid squids. The tunable reflectin proteins, characterized by a variable number of highly conserved peptide domains interspersed with positively charged linker segments, are restricted in intra- and inter-chain contacts by Coulombic repulsion. Physiologically, this inhibition is progressively...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1700317114
Volume: 114 Issue: 34 First Page #: 9056
Date Submitted: 8/26/18 12:00AM Date Published: 8/1/17 5:00AM
Publication Location:
**Article Title:** Dual-reporter SERS-based biomolecular assay with reduced false-positive signals
**Authors:** Tracy T Chuong, Alessia Pallaoro, Chelsea A. Chaves, Zhe Li, Joun Lee, Michael Eisenstein, Galen D. S
**Keywords:** surface-enhanced Raman spectroscopy, SERS, protein detection, nanoparticle, ELISA
**Abstract:** We present a sensitive and quantitative protein detection assay that can efficiently distinguish between specific and nonspecific target binding. Our technique combines dual affinity reagents with surface-enhanced Raman spectroscopy (SERS) and chemometric analysis. We link one Raman reporter-tagged affinity reagent to gold nanoparticles and another to a gold film, such that protein-binding events create a "hot spot" with strong SERS spectra from both Raman reporter molecules. Any signal generated in this context is indicative of recognition by both affinity labels, whereas signals generated by nonspecific binding lack one or the other label, enabling us to efficiently distinguish true from false positives. We show that the number of hot spots per unit area of our substrate offers a quantitative measure of analyte concentration and demonstrate that this dual-label, SERS-linked aptasensor assay can sensitively and selectively detect human ?-thrombin in 1% human serum with a limit of...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.analchem.6b03797
Volume: 89 Issue: 3 First Page #: 1684
Date Submitted: 8/26/18 12:00AM Date Published: 1/1/17 6:00AM
Publication Location:
**Article Title:** Detection of Papaverine for the Possible Identification of Illicit Opium Cultivation
**Authors:** Rustin Y. Mirsafavi, Kristine Lai, Neal D. Kline, Augustus W. Fountain, Carl D. Meinhart, Martin Moskovit
**Keywords:** surface-enhanced Raman spectroscopy
**Abstract:** Papaverine is a non-narcotic alkaloid found endemically and uniquely in the latex of the opium poppy. It is normally refined out of the opioids that the latex is typically collected for, hence its presence in a sample is strong prima facie evidence that the carrier from whom the sample was collected is implicated in the mass cultivation of poppies or the collection and handling of their latex. We describe an analysis technique combining surface-enhanced Raman spectroscopy (SERS) with microfluidics for detecting papaverine at low concentrations and show that its SERS spectrum has unique spectroscopic features that allows its detection at low concentrations among typical opioids. The analysis requires approximately 2.5 min from sample loading to results, which is compatible with field use. The weak acid properties of papaverine hydrochloride were investigated, and Raman bands belonging to the protonated and unprotonated forms of the isoquinoline ring of papaverine were identified.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Processes
Publication Identifier Type: DOI Publication Identifier: 10.3390/pr6010007
Volume: 6 Issue: 7 First Page #:
Date Submitted: 8/26/18 12:00AM Date Published: 1/1/18 6:00AM
Publication Location:
**Article Title:** In Silico Identification of Microbial Partners to Form Consortia with Anaerobic Fungi
**Authors:** St. Wilken, Mohan Saxena, Linda Petzold, Michelle O'Malley
**Keywords:** anaerobic fungi; in silico modeling; microbial consortia; dynamic flux balance analysis; non-model organism; lignocellulose
**Abstract:** Lignocellulose is an abundant and renewable resource that holds great promise for sustainable bioprocessing. However, unpretreated lignocellulose is recalcitrant to direct utilization by most microbes. Current methods to overcome this barrier include expensive pretreatment steps to liberate cellulose and hemicellulose from lignin. Anaerobic gut fungi possess complex cellulolytic machinery specifically evolved to decompose crude lignocellulose, but they are not yet genetically tractable and have not been employed in industrial bioprocesses. Here, we aim to exploit the biomass-degrading abilities of anaerobic fungi by pairing them with another organism that can convert the fermentable sugars generated from hydrolysis into bioproducts. By combining experiments measuring the amount of excess fermentable sugars released by the fungal enzymes acting on crude lignocellulose, and a novel dynamic flux balance analysis algorithm, we screened potential consortia partners by qualitative...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biotechnology and Bioengineering
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Volume: 115 Issue: First Page #: 874
Date Submitted: 8/26/18 12:00AM Date Published: 4/1/18 5:00AM
Publication Location:
**Article Title:** Metabolic characterization of anaerobic fungi provides a path forward for bioprocessing of crude lignocellulose
**Authors:** John K. Henske, St. Elmo Wilken, Kevin V. Solomon, Chuck R. Smallwood, Vaithiyalingam Shutthananc
**Keywords:** anaerobic fungi, biomass hydrolysis, bioprocessing, cellulase, sugar metabolism
**Abstract:** The conversion of lignocellulose?rich biomass to bio?based chemicals and higher order fuels remains a grand challenge, as single?microbe approaches often cannot drive both deconstruction and chemical production steps. In contrast, consortia based bioprocessing leverages the strengths of different microbes to distribute metabolic loads and achieve process synergy, product diversity, and bolster yields. Here, we describe a biphasic fermentation scheme that combines the lignocellulolytic action of anaerobic fungi isolated from large herbivores with domesticated microbes for bioproduction. When grown in batch culture, anaerobic fungi release excess sugars from both cellulose and crude biomass due to a wealth of highly expressed carbohydrate active enzymes (CAZymes), converting as much as 49% of cellulose to free glucose. This sugar?rich hydrolysate readily supports growth of Saccharomyces cerevisiae, which can be engineered to produce a range of value?added chemicals.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biotechnology for Biofuels
Publication Identifier Type: DOI Publication Identifier: 10.1186/s13068-017-0997-4
Volume: 10 Issue: 305 First Page #:
Date Submitted: 8/26/18 12:00AM Date Published: 12/1/17 6:00AM
Publication Location:
**Article Title:** Transcriptomic characterization of Caecomyces churrovis: a novel, non-rhizoid-forming lignocellulolytic anaerobic fungus
**Authors:** John K. Henske, Sean P. Gilmore, Doriv Knop, Francis J. Cunningham, Jessica A. Sexton, Chuck R. Sn
**Keywords:** Anaerobic fungi, Neocallimastigomycota, Cellulase, Enzyme, Cellulosome
**Abstract:** Anaerobic gut fungi are the primary colonizers of plant material in the rumen microbiome, but are poorly studied due to a lack of characterized isolates. While most genera of gut fungi form extensive rhizoidal networks, which likely participate in mechanical disruption of plant cell walls, fungi within the Caecomyces genus do not possess these rhizoids. Here, we describe a novel fungal isolate, Caecomyces churrovis, which forms spherical sporangia with a limited rhizoidal network yet secretes a diverse set of carbohydrate active enzymes (CAZymes) for plant cell wall hydrolysis. Despite lacking an extensive rhizoidal system, C. churrovis is capable of growth on fibrous substrates like switchgrass, reed canary grass, and corn stover, although faster growth is observed on soluble sugars. Gut fungi have been shown to use enzyme complexes (fungal cellulosomes) in which CAZymes bind to non-catalytic scaffoldins to improve biomass degradation efficiency. However, transcriptomic analysis...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Biochemical Engineering Journal
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Volume: 130 Issue: First Page #: 83
Date Submitted: 8/26/18 12:00AM Date Published: 2/1/18 12:00AM
Publication Location:
**Article Title:** Substrate-based differential expression analysis reveals control of biomass degrading enzymes in Pycnoporus cinnabarinus
**Authors:** John K. Henske, Stephen D. Springer, Michelle A. O'Malley, Alison Butler
**Keywords:** Pynoporus, White rot fungi, Lignocellulose. Peroxidase, Cellulase, Next generation sequencing
**Abstract:** uWhite rot fungi possess a powerful ability to degrade recalcitrant lignin within plant biomass. Pycnoporus cinnabarinus PB 94 accomplishes lignin degradation through the combined activity of laccases, peroxidases, and their supporting enzymes. Assembly of the de novo transcriptome for PB 94 resulted in identification of 45,286 transcripts, including isoforms, and a predicted 27,990 genes. Differential expression analysis revealed how the expression of these ligninolytic enzymes was dictated by the nature of the substrate. Growth on lignin containing poplar and switchgrass resulted in as much as a 285-fold increase in expression of peroxidases (auxiliary activity family AA2) and a 36-fold increase in expression of alcohol oxidases (auxiliary activity family AA3) compared to growth on soluble sugars. These findings suggest that expression of these enzyme classes was controlled by the presence of lignin, or triggered by an aromatic break out product of lignin degradation. Laccases...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Metabolic Engineering
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.ymben.2017.09.008
Volume: 44 Issue: First Page #: 45
Date Submitted: 8/26/18 12:00AM Date Published: 9/1/17 5:00AM
Publication Location:
**Article Title:** The importance of sourcing enzymes from non-conventional fungi for metabolic engineering and biomass breakdown
**Authors:** Susanna Seppälä, St. Elmo Wilken, Doriv Knop, Kevin V. Solomon, Michelle A. O'Malley
**Keywords:** Fungi, Lignocellulose, Enzyme, Cellulase, Cellulosome, Anaerobic fungi
**Abstract:** A wealth of fungal enzymes has been identified from nature, which continue to drive strain engineering and bioprocessing for a range of industries. However, while a number of clades have been investigated, the vast majority of the fungal kingdom remains unexplored for industrial applications. Here, we discuss selected classes of fungal enzymes that are currently in biotechnological use, and explore more basal, non-conventional fungi and their underexploited biomass-degrading mechanisms as promising agents in the transition towards a bio-based society. Of special interest are anaerobic fungi like the Neocallimastigomycota, which were recently found to harbor the largest diversity of biomass-degrading enzymes among the fungal kingdom. Enzymes sourced from these basal fungi have been used to metabolically engineer substrate utilization in yeast, and may offer new paths to lignin breakdown and tunneled biocatalysis. We also contrast classic enzymology approaches with emerging...
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**Journal:** Frontiers in Microbiology
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Volume: 8 Issue: 1657 First Page #:
Date Submitted: 8/26/18 12:00AM Date Published: 9/1/17 5:00AM
Publication Location:
**Article Title:** PCR and Omics Based Techniques to Study the Diversity, Ecology and Biology of Anaerobic Fungi: Insights, Challenges and Opportunities
**Authors:** Joan E. Edwards, Robert J. Forster, Tony M. Callaghan, Veronika Dollhofer, Sumit S. Dagar, Yanfen Ch
**Keywords:** anaerobic fungi, Neocallimastigomycota, rumen, phylogeny, genomics, (meta) transcriptomics, proteomics, metabolomics
**Abstract:** Anaerobic fungi (phylum Neocallimastigomycota) are common inhabitants of the digestive tract of mammalian herbivores, and in the rumen, can account for up to 20% of the microbial biomass. Anaerobic fungi play a primary role in the degradation of lignocellulosic plant material. They also have a syntrophic interaction with methanogenic archaea, which increases their fiber degradation activity. To date, nine anaerobic fungal genera have been described, with further novel taxonomic groupings known to exist based on culture-independent molecular surveys. However, the true extent of their diversity may be even more extensively underestimated as anaerobic fungi continue being discovered in yet unexplored gut and non-gut environments. Additionally many studies are now known to have used primers that provide incomplete coverage of the Neocallimastigomycota. For ecological studies the internal transcribed spacer 1 region (ITS1) has been the taxonomic marker of choice, but due to various...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** BMC Genomics
Publication Identifier Type: DOI Publication Identifier: 10.1186/s12864-017-4036-4
Volume: 18 Issue: 639 First Page #:
Date Submitted: 8/26/18 12:00AM Date Published: 8/1/17 5:00AM
Publication Location:
**Article Title:** Genomic analysis of methanogenic archaea reveals a shift towards energy conservation
**Authors:** Sean P. Gilmore, John K. Henske, Jessica A. Sexton, Kevin V. Solomon, Susanna Seppälä, Justin I Yoo
**Keywords:** Methanogenesis, Archaea, Metabolism, Anaerobes, Energy
**Abstract:** Background: The metabolism of archaeal methanogens drives methane release into the environment and is critical to understanding global carbon cycling. Methanogenesis operates at a very low reducing potential compared to other forms of respiration and is therefore critical to many anaerobic environments. Harnessing or altering methanogen metabolism has the potential to mitigate global warming and even be utilized for energy applications. Results: Here, we report draft genome sequences for the isolated methanogens Methanobacterium bryantii, Methanosarcina spelaei, Methanosphaera cuniculi, and Methanocorpusculum parvum. These anaerobic, methane-producing archaea represent a diverse set of isolates, capable of methylotrophic, acetoclastic, and hydrogenotrophic methanogenesis. Assembly and analysis of the genomes allowed for simple and rapid reconstruction of metabolism in the four methanogens. Comparison of the distribution of Clusters of Orthologous Groups (COG) proteins to a sample of...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nano Letters
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.nanolett.7b04736
Volume: 18 Issue: 2 First Page #: 1191
Date Submitted: 8/26/18 12:00AM Date Published: 1/1/18 6:00AM
Publication Location:
**Article Title:** An Experimental Approach to Systematically Probe Charge Inversion in Nanofluidic Channels
**Authors:** Kuang-Hua Chou, Christopher McCallum, Dirk Gillespie, Sumita Pennathur
**Keywords:** charge inversion; current monitoring; electric double layer; ?-potential
**Abstract:** "Charge inversion of the surfaces of nanofluidic channels occurs in systems with high-surface charge and/or highly charged ions and is of particular interest because of applications in biological and energy conversion systems. However, the details of such charge inversion have not been clearly elucidated. Specifically, although we can experimentally and theoretically show charge inversion, understanding at what conditions charge inversion occurs, as well how much the charge-inverting ions change the surface, are not known. Here, we show a novel experimental approach for uniquely finding both the ?-potential and adsorption time of charge inverting ions in aqueous nanofluidic systems. "
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Chemical Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.1021/acschemneuro.7b00444
Volume: 9 Issue: 4 First Page #: 849
Date Submitted: 8/26/18 12:00AM Date Published: 12/1/17 6:00AM
Publication Location:
**Article Title:** DNA-Stabilized Silver Nanoclusters as Specific, Ratiometric Fluorescent Dopamine Sensors
**Authors:** Jackson T. Del Bonis-O'Donnell, Ami Thakrar, Jeremy Wain Hirschberg, Daniel Vong, Bridget N. Queen
**Keywords:** biosensor; DNA-stabilized silver nanoclusters; dopamine; Neurotransmitter
**Abstract:** Neurotransmitters are small molecules that orchestrate complex patterns of brain activity. Unfortunately, there exist few sensors capable of directly detecting individual neurotransmitters. Those sensors that do exist are either unspecific or fail to capture the temporal or spatial dynamics of neurotransmitter release. DNA-stabilized silver nanoclusters (DNA-AgNCs) are a new class of biocompatible, fluorescent nanostructures that have recently been shown to offer promise as biosensors. In this work, we identify two different DNA sequences that form dopamine-sensitive nanoclusters. We demonstrate that each sequence supports two distinct DNA-AgNCs capable of providing specific, ratiometric fluorescent sensing of dopamine concentration in vitro. DNA-Ag nanoclusters therefore offer a novel, low-cost approach to quantification of dopamine, creating the potential for real-time monitoring in vivo.
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**Journal:** The Journal of Chemical Physics
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4975167
Volume: 146 Issue: 064101 First Page #:
Date Submitted: 8/26/18 12:00AM Date Published: 2/1/17 12:00AM
Publication Location:
**Article Title:** Reaction rates for reaction-diffusion kinetics on unstructured meshes
**Authors:** Stefan Hellander, Linda Petzold
**Keywords:** stochastic model
**Abstract:** The reaction-diffusion master equation is a stochastic model often utilized in the study of biochemical reaction networks in living cells. It is applied when the spatial distribution of molecules is important to the dynamics of the system. A viable approach to resolve the complex geometry of cells accurately is to discretize space with an unstructured mesh. Diffusion is modeled as discrete jumps between nodes on the mesh, and the diffusion jump rates can be obtained through a discretization of the diffusion equation on the mesh. Reactions can occur when molecules occupy the same voxel. In this paper, we develop a method for computing accurate reaction rates between molecules occupying the same voxel in an unstructured mesh. For large voxels, these rates are known to be well approximated by the reaction rates derived by Collins and Kimball, but as the mesh is refined, no analytical expression for the rates exists. We reduce the problem of computing accurate reaction rates to a pure...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of The Royal Society Interface
Publication Identifier Type: DOI Publication Identifier: 10.1098/rsif.2017.0480
Volume: 14 Issue: 133 First Page #: 20170480
Date Submitted: 8/26/18 12:00AM Date Published: 8/1/17 10:00AM
Publication Location:
**Article Title:** Using stochastic epidemiological models to evaluate conservation strategies for endangered amphibians
**Authors:** Brian Drawert, Marc Griesemer, Linda R. Petzold, Cheryl J. Briggs
**Keywords:** chytridiomycosis, Batrachochytrium dendrobatidis, epidemiological models, stochastic models
**Abstract:** Recent outbreaks of chytridiomycosis, the disease of amphibians caused by the fungal pathogen Batrachochytrium dendrobatidis (Bd), have contributed to population declines of numerous amphibian species worldwide. The devastating impacts of this disease have led researchers to attempt drastic conservation measures to prevent further extinctions and loss of biodiversity. The conservation measures can be labour-intensive or expensive, and in many cases have been unsuccessful. We developed a mathematical model of Bd outbreaks that includes the effects of demographic stochasticity and within-host fungal load dynamics. We investigated the impacts of one-time treatment conservation strategies during the disease outbreak that occurs following the initial arrival of Bd into a previously uninfected frog population. We found that for all versions of the model, for a large fraction of parameter space, none of the one-time treatment strategies are effective at preventing disease-induced...
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Volume: 8 Issue: 10721 First Page #:
Date Submitted: 8/26/18 12:00AM Date Published: 7/1/18 12:00AM
Publication Location:
**Article Title:** Control of neural systems at multiple scales using model-free, deep reinforcement learning
**Authors:** Brian A. Mitchell, Linda R. Petzold
**Keywords:** Deep Deterministic Policy Gradients
**Abstract:** Recent improvements in hardware and data collection have lowered the barrier to practical neural control. Most of the current contributions to the field have focus on model-based control, however, models of neural systems are quite complex and difficult to design. To circumvent these issues, we adapt a model-free method from the reinforcement learning literature, Deep Deterministic Policy Gradients (DDPG). Model-free reinforcement learning presents an attractive framework because of the flexibility it offers, allowing the user to avoid modeling system dynamics. We make use of this feature by applying DDPG to models of low-level and high-level neural dynamics. We show that while model-free, DDPG is able to solve more difficult problems than can be solved by current methods. These problems include the induction of global synchrony by entrainment of weakly coupled oscillators and the control of trajectories through a latent phase space of an underactuated network of neurons. While this...
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**Journal:** Journal of Biological Rhythms
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Volume: Issue: First Page #:
Date Submitted: 8/28/18 12:00AM Date Published: 8/7/18 10:00AM
Publication Location:
**Article Title:** Model-based Inference of a Directed Network of Circadian Neurons
**Authors:** David McBride, Linda Petzold
**Keywords:** Circadian; Suprachiasmatic Nucleu; Network; Inference; Computational
**Abstract:** The suprachiasmatic nucleus (SCN) is the master clock of the brain. It is a network of neurons that behave like biological oscillators, capable of synchronizing and maintaining daily rhythms. The detailed structure of this network is still unknown, and the role that the connectivity pattern plays in the networks ability to generate robust oscillations has yet to be fully elucidated. In recent work, we used an information theory-based technique to infer the structure of the functional network for synchronization, from bioluminescence reporter data. Here, we propose a computational method to determine the directionality of the connections between the neurons. We find that most SCN neurons have a similar number of incoming connections, but the number of outgoing connections per neuron varies widely, with the most highly connected neurons residing preferentially in the core.
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Volume: 89 Issue: 22 First Page #: 2185
Date Submitted: 8/26/18 12:00AM Date Published: 10/1/17 5:00AM
Publication Location:
**Article Title:** High Surface Area Electrodes Generated via Electrochemical Roughening Improve the Signaling of Electrochemical Aptamer-Based Biosensors
**Authors:** Netzahualcóyotl Arroyo-Currás, Karen Scida, Kyle L. Ploense, Tod E. Kippin, Kevin W. Plaxco
**Keywords:** electrochemical, aptamer-based
**Abstract:** The electrochemical, aptamer-based (E-AB) sensor platform provides a modular approach to the continuous, real-time measurement of specific molecular targets (irrespective of their chemical reactivity) in situ in the living body. To achieve this, however, requires the fabrication of sensors small enough to insert into a vein, which, for the rat animal model we employ, entails devices less than 200 ?m in diameter. The limited surface area of these small devices leads, in turn, to low faradaic currents and poor signal-to-noise ratios when deployed in the complex, fluctuating environments found in vivo. In response we have developed an electrochemical roughening approach that enhances the signaling of small electrochemical sensors by increasing the microscopic surface area of gold electrodes, allowing in this case more redox-reporter-modified aptamers to be packed onto the surface, thus producing significantly improved signal-to-noise ratios. Unlike previous approaches to achieving...
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**Journal:** The Analyst
Publication Identifier Type: DOI Publication Identifier: 10.1039/C8AN00337H
Volume: 143 Issue: First Page #: 2531
Date Submitted: 8/26/18 12:00AM Date Published: 4/24/18 5:00AM
Publication Location:
**Article Title:** Exploiting the conformational-selection mechanism to control the response kinetics of a “smart” DNA hydrogel
**Authors:** Anna J. Simon, Luke T. Walls-Smith, Kevin W. Plaxco
**Keywords:** crosslink geometry
**Abstract:** The sequence-specific hybridization and molecular recognition properties of DNA support the construction of stimulus-responsive hydrogels with precisely controlled crosslink geometry. Here we show that, as predicted by the conformational selection mechanism, the response kinetics of such a hydrogel can be tuned over orders of magnitude by modulating the thermodynamic stability of its crosslinks.
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**Journal:** Soft Matter
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Volume: 13 Issue: First Page #: 5421
Date Submitted: 8/26/18 12:00AM Date Published: 6/27/17 5:00AM
Publication Location:
**Article Title:** Tuning phase and aging of DNA hydrogels through molecular design
**Authors:** Dan T. Nguyen, Omar A. Saleh
**Keywords:** DNA hydrogels, polymer networks
**Abstract:** The programmable, sequence-dependent hybridization of DNA has spurred the development of DNA hydrogels, polymer networks that swell in water and are comprised either entirely or partially of DNA. Specific applications require hydrogels of particular structure for optimal functionality. Here, we use self-assembling, multi-valent DNA nanostars to examine how hydrogel structure is influenced by the non-equilibrium dynamics of its interacting components. We show that hydrogel aging kinetics – from an arrested, solid-like percolated network to an equilibrium, phase-separated liquid analogous to coacervates – are modulated by DNA hybridization strength and ion-specific nanostar internal flexibility. Together, our results demonstrate strategies to control hydrogel kinetic phenomena, and thus the hydrogel structure, through the rational design of gel-forming elements and solvent conditions.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Acta Materialia
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.actamat.2017.12.060
Volume: 149 Issue: First Page #: 78
Date Submitted: 8/26/18 12:00AM Date Published: 5/1/18 5:00AM
Publication Location:
**Article Title:** Effects of nodal fillets and external boundaries on compressive response of an octet truss
**Authors:** Ryan M. Latture, Ricardo X. Rodriguez, Larry R. Holmes, Frank W. Zok
**Keywords:** Cellular solids; Computer simulations; Digital image correlation; Mechanical property
**Abstract:** Additive manufacturing has enabled fabrication of weight-efficient periodic trusses over a wide range of length scales. The principal objective of the present study is to address two coupled aspects of truss design and performance: (i) the extent to which circular nodal fillets enhance node stiffness and alleviate stress concentrations, and (ii) the extent to which external boundaries affect local strut strains. To this end, octet trusses with and without filleted nodes were fabricated out of a hard thermoplastic and tested in compression, with digital image correlation used to monitor axial and bending strut strains and nodal rotations. Complementary finite element simulations were also performed. Macroscopic compressive failure occurs through bending and buckling of certain inclined struts followed by tensile rupture of struts oriented perpendicular to the loading direction. The struts experiencing the highest tensile strain and most prone to rupture are those located along the...
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**Journal:** Journal of Materials Research
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Date Submitted: 8/26/18 12:00AM Date Published: 2/1/18 6:00AM
Publication Location:
**Article Title:** Design and mechanical properties of elastically isotropic trusses
**Authors:** Ryan M. Latture, Matthew R. Begley, Frank W. Zok
**Keywords:** cellular (material type); elastic properties; strength
**Abstract:** The present article addresses design of stiff, elastically isotropic trusses and their mechanical properties. Isotropic trusses are created by combining two or more elementary cubic trusses in appropriate proportions and with their respective nodes lying on a common space lattice. Two isotropic binary compound trusses and many isotropic ternary trusses are identified, all with Young's moduli equal to the maximal possible value for isotropic strut-based structures. In finite-sized trusses, strain elevations are obtained in struts near the external free boundaries: a consequence of reduced nodal connectivity and thus reduced constraint on strut deformation and rotation. Although the boundary effects persist over distances of only about two unit cell lengths and have minimal effect on elastic properties, their manifestations in failure are more nuanced, especially when failure occurs by modes other than buckling (yielding or fracture). Exhaustive analyses are performed to glean insights..
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
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Volume: 115 Issue: 12 First Page #: 2964
Date Submitted: 8/26/18 12:00AM Date Published: 3/1/18 12:00PM
Publication Location:
**Article Title:** Layered dynamic regulation for improving metabolic pathway productivity in Escherichia coli
**Authors:** Stephanie J. Doong, Apoorv Gupta, Kristala L. J. Prather
**Keywords:** metabolic engineering; synthetic biology; dynamic regulation
**Abstract:** Microbial production of value-added chemicals from biomass is a sustainable alternative to chemical synthesis. To improve product titer, yield, and selectivity, the pathways engineered into microbes must be optimized. One strategy for optimization is dynamic pathway regulation, which modulates expression of pathway-relevant enzymes over the course of fermentation. Metabolic engineers have used dynamic regulation to redirect endogenous flux toward product formation, balance the production and consumption rates of key intermediates, and suppress production of toxic intermediates until later in the fermentation. Most cases, however, have utilized a single strategy for dynamically regulating pathway fluxes. Here we layer two orthogonal, autonomous, and tunable dynamic regulation strategies to independently modulate expression of two different enzymes to improve production of D-glucaric acid from a heterologous pathway. The first strategy uses a previously described pathway-independent...
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# RPPR Final Report
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Physical Review Applied
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevApplied.9.044008
Volume: 9 Issue: 044008 First Page #:
Date Submitted: 8/27/18 12:00AM Date Published: 4/1/18 7:00PM
Publication Location:
**Article Title:** Energy Harvesting with a Liquid-Metal Microfluidic Influence Machine
**Authors:** Christopher Conner, Tim de Visser, Joshua Loessberg, Sam Sherman, Andrew Smith, Shuo Ma, Maria
**Keywords:** microfluidics
**Abstract:** We describe and demonstrate an alternative energy-harvesting technology based on a microfluidic realization of a Wimshurst influence machine. The prototype device converts the mechanical energy of a pressure-driven flow into electrical energy, using a multiphase system composed of droplets of liquid mercury surrounded by insulating oil. Electrostatic induction between adjacent metal droplets drives charge through external electrode paths, resulting in continuous charge amplification and collection. We demonstrate a power output of 4 nW from the initial prototype and present calculations suggesting that straightforward device optimization could increase the power output by more than 3 orders of magnitude. At that level, the power efficiency of this energy-harvesting mechanism, limited by viscous dissipation, could exceed 90%. The microfluidic context enables straightforward scaling and parallelization, as well as hydraulic matching to a variety of ambient mechanical energy sources...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Sensors
Publication Identifier Type: DOI Publication Identifier: 10.1021/acssensors.7b00787
Volume: 3 Issue: 2 First Page #: 360
Date Submitted: 8/26/18 12:00AM Date Published: 11/1/17 5:00AM
Publication Location:
**Article Title:** Subsecond-Resolved Molecular Measurements in the Living Body Using Chronoamperometrically Interrogated Aptamer-Based Sensors
**Authors:** Netzahualcóyotl Arroyo-Currás, Philippe Dauphin-Ducharme, Gabriel Ortega, Kyle L. Ploense, Tod E. K
**Keywords:** aptamer; chronoamperometry; E-AB; electrochemical sensors; in vivo; precision medicine
**Abstract:** Electrochemical, aptamer-based (E-AB) sensors support the continuous, real-time measurement of specific small molecules directly in situ in the living body over the course of many hours. They achieve this by employing binding-induced conformational changes to alter electron transfer from a redox-reporter-modified, electrode-attached aptamer. Previously we have used voltammetry (cyclic, alternating current, and square wave) to monitor this binding-induced change in transfer kinetics indirectly. Here, however, we demonstrate the potential advantages of employing chronoamperometry to measure the change in kinetics directly. In this approach target concentration is reported via changes in the lifetime of the exponential current decay seen when the sensor is subjected to a potential step. Because the lifetime of this decay is independent of its amplitude (e.g., insensitive to variations in the number of aptamer probes on the electrode), chronoamperometrically interrogated E-AB sensors...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Review of Scientific Instruments
Publication Identifier Type: DOI Publication Identifier: 10.1063/1.4939197
Volume: 87 Issue: 014301 First Page #:
Date Submitted: 8/26/18 12:00AM Date Published: 1/1/16 6:00AM
Publication Location:
**Article Title:** A thin permeable-membrane device for single-molecule manipulation
**Authors:** Chang-Young Park, David R. Jacobson, Dan T. Nguyen, Sam Willardson, Omar A. Saleh
**Keywords:** permeable-membrane device
**Abstract:** Single-molecule manipulation instruments have unparalleled abilities to interrogate the structure and elasticity of single biomolecules. Key insights are derived by measuring the system response in varying solution conditions; yet, typical solution control strategies require imposing a direct fluid flow on the measured biomolecule that perturbs the high-sensitivity measurement and/or removes interacting molecules by advection. An alternate approach is to fabricate devices that permit solution changes by diffusion of the introduced species through permeable membranes, rather than by direct solution flow through the sensing region. Prior implementations of permeable-membrane devices are relatively thick, disallowing their use in apparatus that require the simultaneous close approach of external instrumentation from two sides, as occurs in single-molecule manipulation devices like the magnetic tweezer. Here, we describe the construction and use of a thin microfluidic device appropriate...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Soft Matter
Publication Identifier Type: DOI Publication Identifier: 10.1039/C6SM00222F
Volume: 12 Issue: 23 First Page #: 5089
Date Submitted: 8/26/18 12:00AM Date Published:
Publication Location:
**Article Title:** Electrostatics and depletion determine competition between 2D nematic and 3D bundled phases of rod-like DNA nanotubes
**Authors:** Chang-Young Park, Deborah K. Fygenson, Omar A. Saleh
**Keywords:** Electrostatics
**Abstract:** Rod-like particles form solutions of technological and biological importance. In particular, biofilaments such as actin and microtubules are known to form a variety of phases, both in vivo and in vitro, whose appearance can be controlled by depletion, confinement, and electrostatic interactions. Here, we utilize DNA nanotubes to undertake a comprehensive study of the effects of those interactions on two particular rod-like phases: a 2D nematic phase consisting of aligned rods pressed against a glass surface, and a 3D bundled network phase. We experimentally measure the stability of these two phases over a range of depletant concentrations and ionic strengths, finding that the 2D phase is slightly more stable than the 3D phase. We formulate a quantitative model of phase stability based on consideration of pairwise rod–rod and rod–surface interactions; notably, we include a careful accounting of solution electrostatics interactions using an effective-charge strategy. The model is...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Fungal Genetics and Biology
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.fgb.2018.09.004
Volume: 121 Issue: First Page #: 1
Date Submitted: 2/16/19 12:00AM Date Published: 12/1/18 6:00AM
Publication Location:
**Article Title:** Catabolic repression in early-diverging anaerobic fungi is partially mediated by natural antisense transcripts
**Authors:** Kevin V. Solomon, John K. Henske, Sean P. Gilmore, Anna Lipzen, Igor V. Grigoriev, Dawn Thompson,
**Keywords:** Antisense, RNA, Anaerobic fungi, Catabolic regulation
**Abstract:** Early-diverging anaerobic fungi (order: Neocallimastigomycota), lignocelluolytic chytrid-like fungi central to fiber degradation in the digestive tracts of large herbivores, are attractive sources of cellulases and hemi- cellulases for biotechnology. Enzyme expression is tightly regulated and coordinated through mechanisms that remain unelucidated to optimize hydrolytic efficiency. Our analysis of anaerobic fungal transcriptomes reveals hundreds of cis-natural antisense transcripts (cis-NATs), which we hypothesize play an integral role in this regulation. Through integrated genomic and transcriptomic sequencing on a range of catabolic substrates, we validate these NATs in three species (Anaeromyces robustus, Neocallimasix californiae, and Piromyces finnis), and analyze their expression patterns and prevalence to gain insight into their function. NAT function was diverse and conserved across the three fungal genomes studied, with 10% of all metabolic process NATs associated with...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** AIChE Journal
Publication Identifier Type: DOI Publication Identifier: 10.1002/aic.16395
Volume: 64 Issue: 12 First Page #: 4263
Date Submitted: 2/16/19 12:00AM Date Published: 12/1/18 12:00AM
Publication Location:
**Article Title:** Biomass-degrading enzymes are catabolite repressed in anaerobic gut fungi
**Authors:** John K. Henske, Sean P. Gilmore, Charles H. Haitjema, Kevin V. Solomon, Michelle A. O'Malley
**Keywords:** anaerobic fungi, cellulases, biofuel, regulation, Neocallimastigales
**Abstract:** Anaerobic fungi are among the most active plant-degrading microbes in nature. Increased insight into the mechanisms and environmental cues that regulate fungal hydrolysis would better inform bioprocessing strategies to depolymerize lignocellulose. Here, we compare the response of three strains of anaerobic fungi (Piromyces finnis, Anaeromyces robustus, and Neocallimastix californiae) to catabolite regulation by simple carbohydrates. Anaerobic fungi exhibited high enzymatic activity against crystalline cellulose, which was repressed upon incubation with free sugars. Cellulolytic degradation was also inhibited when fungi were exposed to sugars they did not metabolize, suggesting a general mode of catabolite repression. RNA-Seq experiments in the presence of excess glucose confirmed repression of carbohydrate active enzymes during sugar uptake, and offer a path towards unmasking the function of co-regulated genes that could be involved in biomass degradation.
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Publication Identifier Type: DOI Publication Identifier: 10.1146/annurev-biophys-052118-115333
Volume: 48 Issue: 1 First Page #:
Date Submitted: 2/16/19 12:00AM Date Published: 1/2/19 6:00AM
Publication Location:
**Article Title:** Molecular Fitness Landscapes from High-Coverage Sequence Profiling
**Authors:** Celia Blanco, Evan Janzen, Abe Pressman, Ranjay Saha, Irene A. Chen
**Keywords:** tness landscape, high-throughput sequencing, ribozyme, deep mutational scanning
**Abstract:** The function of fitness (or molecular activity) in the space of all possible sequences is known as the fitness landscape. Evolution is a random walk on the fitness landscape, with a bias toward climbing hills. Mapping the topography of real fitness landscapes is fundamental to understanding evolution, but previous efforts were hampered by the difficulty of obtaining large, quantitative data sets. The accessibility of high-throughput sequencing (HTS) has transformed this study, enabling large-scale enumeration of fitness for many mutants and even complete sequence spaces in some cases. We review the progress of high-throughput studies in mapping molecular fitness landscapes, both in vitro and in vivo, as well as opportunities for future research. Such studies are rapidly growing in number. HTS is expected to have a profound effect on the understanding of real molecular fitness landscapes.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 3-Accepted
**Journal:** RSC Advances
Publication Identifier Type: DOI Publication Identifier: 10.1039/C8RA08069K
Volume: 8 Issue: 70 First Page #: 39849
Date Submitted: 2/16/19 12:00AM Date Published: 11/14/18 12:00PM
Publication Location:
**Article Title:** Interactions of a paracyclophane-based conjugated oligoelectrolyte with biological membranes
**Authors:** Jakkarin Limwongyut, Yang Liu, Gayatri Shankar Chilambi, Thomas Seviour, Jamie Hinks, Yuguang Mu
**Keywords:** conjugated oligoelectrolyte
**Abstract:** A three-dimensional conjugated oligoelectrolyte (COE) bearing a [2.2]paracyclophane unit (COE2-3-pCp) was synthesized. Its biological activity was determined both in vivo and in silico within the context of membrane perturbation and biocompatibility. Molecular dynamics simulations indicate that, compared to its linear analog (COE2-3C), COE2-3-pCp introduces more lipid disorder with higher extent of membrane thinning. COE2-3-pCp also exhibits a higher MIC towards E. coli K12 and yeast, while maintaining similar levels of membrane permeabilization. These findings suggest a new design of COEs as biocompatible cell permeabilizers.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chemistry of Materials
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.chemmater.8b02848
Volume: 30 Issue: 17 First Page #: 5836
Date Submitted: 2/16/19 12:00AM Date Published: 8/22/18 5:00AM
Publication Location:
**Article Title:** Conjugated Oligoelectrolytes: Materials for Acceleration of Whole Cell Biocatalysis
**Authors:** Bing Wang, Stephanie L. Fronk, Zachary D. Rengert, Jakkarin Limwongyut, Guillermo C. Bazan
**Keywords:** Biocatalysis
**Abstract:** Biocatalysis refers to the application of enzymes or whole cells in chemical synthesis.[1] Such bioconversion processes provide advantages that include mild reaction conditions, the capability for multistep reactions, high stereo-, regio-, and chemoselectivity, and relatively inexpensive purification protocols.[2?4] Whole cell biocatalysis specifically is advantageous since the natural environment for enzymes and the ability of cells to regenerate cofactors are maintained.[5-7]
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**Journal:** Advanced Biosystems
Publication Identifier Type: DOI Publication Identifier: 10.1002/adbi.201700053
Volume: 1 Issue: First Page #: 1700053
Date Submitted: 2/16/19 12:00AM Date Published: 6/16/17 5:00AM
Publication Location:
**Article Title:** Membrane Protein Insertion into and Compatibility with Biomimetic Membranes
**Authors:** Tingwei Ren, Mustafa Erbakan, Yuexiao Shen, Eduardo Barbieri, Patrick Saboe, Hasin Feroz, Hengjing
**Keywords:** amphiphilic block copolymers, biomimetic membranes, fluorescence correlation spectroscopy (FCS), hydrophobicity mismatch, membrane proteins
**Abstract:** Membrane protein and membrane protein–mimic functionalized materials are rapidly gaining interest across a wide range of applications, including drug screening, DNA sequencing, drug delivery, sensors, water desalination, and bioelectronics. In these applications, material performance is highly dependent on activity-per-protein and protein packing density in bilayer and bilayer-like structures collectively known as biomimetic membranes. However, a clear understanding of, and accurate tools to study these properties of biomimetic membranes does not exist. This paper presents methods to evaluate membrane protein compatibility with biomimetic membrane materials. The methods utilized provide average single protein activity, and for the first time, provide experimentally quantifiable measures of the chemical and physical compatibility between proteins (and their mimics) and membrane materials. Water transport proteins, rhodopsins, and artificial water channels are reconstituted into the...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chem
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.chempr.2017.01.001
Volume: 2 Issue: 2 First Page #: 240
Date Submitted: 2/16/19 12:00AM Date Published: 2/9/17 6:00AM
Publication Location:
**Article Title:** A Ferrocene-Based Conjugated Oligoelectrolyte Catalyzes Bacterial Electrode Respiration
**Authors:** Nathan D. Kirchhofer, Zachary D. Rengert, Frederick W. Dahlquist, Thuc-Quyen Nguyen, Guillermo C. E
**Keywords:** electron transport
**Abstract:** For emerging bioelectronic technologies, charge-transfer processes remain rate limited by energy-level mismatching and poor contacts at biotic-abiotic interfaces. Direct chemical modification of these interfaces represents an underdeveloped approach for amplifying biocatalyzed current production. We present the synthesis and application of DSFO+, a redox-active molecule that is designed for membrane affinity and that catalytically couples to biological respiratory transmembrane electron transport, similarly to a heme-containing protein. DSFO+ was employed with three strains of Shewanella oneidensis MR-1 (an electrogenic wild-type and two non-electrogenic knockout mutants) and amplified anodic biocurrent in all strains without toxicity at a physiologically relevant redox potential. Of particular interest, DSFO+ increased metabolic efficiency and biological electron production, thus stimulating respiratory biocurrent production in non-electrogenic bacterial phenotypes. The overall...
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**Journal:** Carbohydrate Polymers
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Volume: 151 Issue: First Page #: 480
Date Submitted: 2/17/19 12:00AM Date Published: 10/20/16 5:00AM
Publication Location:
**Article Title:** 13 C NMR assignments of regenerated cellulose from solid-state 2D NMR spectroscopy
**Authors:** Alexander Idström, Staffan Schantz, Johan Sundberg, Bradley F. Chmelka, Paul Gatenholm, Lars Nords
**Keywords:** 13C CP/MAS NMR, 2D correlation NMR, Regenerated cellulose, Mercerized cellulose, Assignment, Deconvolution
**Abstract:** From the assignment of the solid-state 13C NMR signals in the C4 region, distinct types of crystalline cellulose, cellulose at crystalline surfaces, and disordered cellulose can be identified and quantified. For regenerated cellulose, complete 13C assignments of the other carbon regions have not previously been attainable, due to signal overlap. In this study, two-dimensional (2D) NMR correlation methods were used to resolve and assign 13C signals for all carbon atoms in regenerated cellulose. 13C-enriched bacterial nanocellulose was biosynthesized, dissolved, and coagulated as highly crystalline cellulose II. Specifically, four distinct 13 C signals were observed corresponding to conformationally different anhydroglucose units: two signals assigned to crystalline moieties and two signals assigned to non-crystalline species. The C1, C4 and C6 regions for cellulose II were fully examined by global spectral deconvolution, which yielded qualitative trends of the relative populations...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Soft Matter
Publication Identifier Type: DOI Publication Identifier: 10.1039/C4SM00642A
Volume: 10 Issue: First Page #: 5618
Date Submitted: 2/17/19 12:00AM Date Published: 6/10/14 5:00AM
Publication Location:
**Article Title:** Surface effects on the structure and mobility of the ionic liquid C6C1ImTFSI in silica gels
**Authors:** Moheb Nayeri, Matthew T. Aronson, Diana Bernin, Bradley F. Chmelka, Anna Martinelli
**Keywords:** silica gels
**Abstract:** We report on how the dynamical and structural properties of the ionic liquid 1-hexyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (C6C1ImTFSI) change upon different degrees of confinement in silica gels. The apparent diffusion coefficients of the individual ions are measured by 1H and 19F pulsed field gradient nuclear magnetic resonance (PFG-NMR) spectroscopy, while the intermolecular interactions in the ionogels are elucidated by Raman spectroscopy. In addition, the local structure of the ionic liquid at the silica interface is probed by solid-state NMR spectroscopy. Importantly, we extend this study to a wider range of ionic liquid-to-silica molar ratios (x) than has been investigated previously, from very low (high degree of confinement) to very high (liquid-like gels) ionic liquid contents. Diffusion NMR measurements indicate that a solvation shell, with a significantly lower mobility than the bulk ionic liquid, forms at the silica interface.
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**Journal:** The Journal of Physical Chemistry C
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.jpcc.6b06238
Volume: 120 Issue: 30 First Page #: 16887
Date Submitted: 2/17/19 12:00AM Date Published: 6/29/16 5:00AM
Publication Location:
**Article Title:** Correlating Surface-Functionalization of Mesoporous Silica with Adsorption and Release of Pharmaceutical Guest Species
**Authors:** Victoria Morales, Matthew N. Idso, Moisés Balabasquer, Bradley Chmelka, Rafael A. García-Muñoz
**Keywords:** Mesoporous Silica
**Abstract:** We present here a detailed molecular-level understanding of the interactions among surface-functionalized mesoporous SBA-15 silica and pharmaceutical guests that influence macroscopic adsorption and release behaviors. A model drug species, methylprednisolone sodium succinate, was adsorbed on the surfaces of functionalized mesoporous SBA-15 silica materials with different aminoalkyl species and without or with C60 fullerene moieties. Zeta potential measurements show that the electrostatic interactions among methylprednisolone species and modified silica surfaces are important for the adsorption and release of the methylprednisolone molecules. Complementary one and two-dimensional (2D) solid-state 13C{1H} NMR measurements provide evidence for specific intermolecular interactions between adsorbed methylprednisolone species and different types of functionalized silica surfaces. In particular, correlated 13C and 1H signal intensities from the methylprednisolone alkyl moieties and the...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Chemistry of Materials
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.chemmater.8b03926
Volume: 30 Issue: 22 First Page #: 8352
Date Submitted: 2/17/19 12:00AM Date Published: 11/8/18 6:00AM
Publication Location:
**Article Title:** Solvent-Free Synthesis of High-Performance Polyhexahydrotriazine (PHT) Thermosets
**Authors:** Revital Kaminker, E. Benjamin Callaway, Neil D. Dolinski, Stephanie M. Barbon, Masashi Shibata, Heng
**Keywords:** Polyhexahydrotriazines
**Abstract:** Polyhexahydrotriazines (PHT) are promising high-performance thermosets exhibiting enhanced thermal and mechanical properties. Here, we demonstrate a new solvent-free approach for the fabrication of PHT based on low-melting-point diamines enabling the production of adhesives with comparable properties to well-established epoxy adhesives. Structure–property relationships were supported by small molecule model reactions that mimic the cross-linking hexahydrotriazine (HT) cores and allowed the unique reactivity of benzylamine building blocks to be demonstrated. Through a variety of spectroscopic and physical techniques, this increased molecular level understanding of monomer design led to the ability to tune acidic degradation and thermal properties.
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**Journal:** Advanced Materials
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Volume: 30 Issue: 31 First Page #: 1800364
Date Submitted: 2/17/19 12:00AM Date Published: 8/2/18 5:00AM
Publication Location:
**Article Title:** Solution Mask Liquid Lithography (SMaLL) for One-Step, Multimaterial 3D Printing
**Authors:** Neil D. Dolinski, Zachariah A. Page, E. Benjamin Callaway, Fabian Eisenreich, Ronnie V. Garcia, Rober
**Keywords:** 3D printing, photochemistry, photochromism
**Abstract:** A novel methodology for printing 3D objects with spatially resolved mechanical and chemical properties is reported. Photochromic molecules are used to control polymerization through coherent bleaching fronts, providing large depths of cure and rapid build rates without the need for moving parts. The coupling of these photoswitches with resin mixtures containing orthogonal photo?crosslinking systems allows simultaneous and selective curing of multiple networks, providing access to 3D objects with chemically and mechanically distinct domains. The power of this approach is showcased through the one?step fabrication of bioinspired soft joints and mechanically reinforced “brick?and?mortar” structures.
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**Journal:** Nanoscale
Publication Identifier Type: DOI Publication Identifier: 10.1039/C8NR04864A
Volume: 11 Issue: 3 First Page #: 1091
Date Submitted: 2/17/19 12:00AM Date Published: 1/21/19 6:00AM
Publication Location:
**Article Title:** Highly adjustable 3D nano-architectures and chemistries
**Authors:** Jacqueline F. Ohmura, F. John Burpo, Chamille J. Lescott, Alan Ransil, Youngmin Yoon, William C. Rec
**Keywords:** 3D nano-architectures
**Abstract:** Porous metal nanofoams have made significant contributions to a diverse set of technologies from separation and filtration to aerospace. Nonetheless, finer control over nano and microscale features must be gained to reach the full potential of these materials in energy storage, catalytic, and sensing applications. As biologics naturally occur and assemble into nano and micro architectures, templating on assembled biological materials enables nanoscale architectural control without the limited chemical scope or specialized equipment inherent to alternative synthetic techniques. Here, we rationally assemble 1D biological templates into scalable, 3D structures to fabricate metal nanofoams with a variety of genetically programmable architectures and material chemistries. We demonstrate that nanofoam architecture can be modulated by manipulating viral assembly, specifically by editing the viral surface coat protein, as well as altering templating density. These architectures were...
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**Journal:** The International Journal of High Performance Computing Applications
Publication Identifier Type: DOI Publication Identifier: 10.1177/1094342015593395
Volume: 30 Issue: 2 First Page #: 186
Date Submitted: 2/17/19 12:00AM Date Published: 7/13/15 5:00AM
Publication Location:
**Article Title:** High-performance simulation of fracture in idealized 'brick and mortar' composites using adaptive Monte Carlo minimization on the GPU
**Authors:** Rone Kwei Lim, J William Pro, Matthew R Begley, Marcel Utz, Linda R Petzold
**Keywords:** Graphics processing unit, fracture simulation, nacre, brick and mortar structures, Monte-Carlo, Compute Unified Device Architecture
**Abstract:** Simulation of the nonlinear mechanical response of materials with explicit representation of microstructural features is extremely challenging. These models typically involve a very large number of degrees of freedom, and are prone to convergence difficulties when searching for roots to nonlinear equilibrium equations. We focus on an idealized material model that is motivated by the microstructure of synthetic nacre: individual 'bricks' (representing ceramic platelets) interact through nonlinear cohesive springs (representing a small volume fraction of polymer that bonds the platelets). The model simulates composite fracture through rupture of the cohesive springs. The problem is cast in terms of energy minimization and is essentially described by 'nearest neighbor' interactions. The principal focus of this paper is to illustrate the computational gains achievable by the strategic marriage of robust, global Monte Carlo minimization algorithms to the graphics processing unit...
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**Journal:** Physical Review Fluids
Publication Identifier Type: DOI Publication Identifier: 10.1103/PhysRevFluids.2.124203
Volume: 2 Issue: 124203 First Page #:
Date Submitted: 2/17/19 12:00AM Date Published: 12/21/17 6:00AM
Publication Location:
**Article Title:** Analyte preconcentration in nanofluidic channels with nonuniform zeta potential
**Authors:** A. Eden, C. McCallum, B. D. Storey, S. Pennathur, C. D. Meinhart
**Keywords:** Electric double layers, Electrokinetic flows, EngineeringInduced-charge flows, Nanoscale flow devices
**Abstract:** It is well known that charged analytes in the presence of nonuniform electric fields concentrate at locations where the relevant driving forces balance, and a wide range of ionic stacking and focusing methods are commonly employed to leverage these physical mechanisms in order to improve signal levels in biosensing applications. In particular, nanofluidic channels with spatially varying conductivity distributions have been shown to provide increased preconcentration of charged analytes due to the existence of a finite electric double layer (EDL), in which electrostatic attraction and repulsion from charged surfaces produce nonuniform transverse ion distributions. In this work, we use numerical simulations to show that one can achieve greater levels of sample accumulation by using field-effect control via wall-embedded electrodes to tailor the surface potential heterogeneity in a nanochannel with overlapped EDLs. In addition to previously demonstrated stacking and focusing...
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**Journal:** ELECTROPHORESIS
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Volume: Issue: First Page #:
Date Submitted: 2/17/19 12:00AM Date Published: 12/31/18 6:00AM
Publication Location:
**Article Title:** Confinement effects on DNA hybridization in electrokinetic micro- and nanofluidic systems
**Authors:** Alex M. Downs, Christopher McCallum, Sumita Pennathur
**Keywords:** DNA Hybridization, Kinetic capillary, Microfluidic separations, Nanofluidics
**Abstract:** Spatial confinement, within cells or micro? and nanofabricated devices, impacts the conformation and binding kinetics of biomolecules. Understanding the role of spatial confinement on molecular behavior is important for comprehending diverse biological phenomena, as well as for designing biosensors. Specifically, the behavior of molecular binding under an applied electric field is of importance in the development of electrokinetic biosensors. Here, we investigate whether confinement of DNA oligomers in capillary electrophoresis impacts the binding kinetics of the DNA. To infer the role of confinement on hybridization dynamics, we perform capillary electrophoresis measurements on DNA oligomers within micro? and nanochannels, then apply first?order reaction dynamics theory to extract kinetic parameters from electropherogram data. We find that the apparent dissociation constants at the nanoscale (i.e., within a 100 nm channel) are lower than at the microscale...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Micromechanics and Microengineering
Publication Identifier Type: DOI Publication Identifier: 10.1088/1361-6439/aaa6a8
Volume: 28 Issue: 035007 First Page #:
Date Submitted: 2/17/19 12:00AM Date Published: 1/31/18 6:00AM
Publication Location:
**Article Title:** A repeatable and scalable fabrication method for sharp, hollow silicon microneedles
**Authors:** H Kim, L S Theogarajan, S Pennathur
**Keywords:** microneedles, fabrication, HF-HNO3, silicon
**Abstract:** Scalability and manufacturability are impeding the mass commercialization of microneedles in the medical field. Specifically, microneedle geometries need to be sharp, beveled, and completely controllable, difficult to achieve with microelectromechanical fabrication techniques. In this work, we performed a parametric study using silicon etch chemistries to optimize the fabrication of scalable and manufacturable beveled silicon hollow microneedles. We theoretically verified our parametric results with diffusion reaction equations and created a design guideline for a various set of miconeedles (80–160 μm needle base width, 100–1000 μm pitch, 40–50 μm inner bore diameter, and 150–350 μm height) to show the repeatability, scalability, and manufacturability of our process. As a result, hollow silicon microneedles with any dimensions can be fabricated with less than 2% non-uniformity across a wafer and 5% deviation between different processes. The key to achieving such high uniformity and...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** ACS Pharmacology & Translational Science
Publication Identifier Type: DOI Publication Identifier: 10.1021/acsptsci.8b00033
Volume: 1 Issue: 2 First Page #: 110
Date Submitted: 2/17/19 12:00AM Date Published: 10/5/18 5:00AM
Publication Location:
**Article Title:** High-Precision Control of Plasma Drug Levels Using Feedback-Controlled Dosing
**Authors:** Netzahualcóyotl Arroyo-Currás, Gabriel Ortega, David A. Copp, Kyle L. Ploense, Zoe A. Plaxco, Tod E.
**Keywords:** aminoglycosides, antibiotics, therapeutic drug monitoring, controlled drug delivery, biosensing
**Abstract:** By, in effect, rendering pharmacokinetics an experimentally adjustable parameter, the ability to perform feedback-controlled dosing informed by high-frequency in vivo drug measurements would prove a powerful tool for both pharmacological research and clinical practice. Efforts to this end, however, have historically been thwarted by an inability to measure in vivo drug levels in real time and with sufficient convenience and temporal resolution. In response, we describe a closed-loop, feedback-controlled delivery system that uses drug level measurements provided by an in vivo electrochemical aptamer-based (E-AB) sensor to adjust dosing rates every 7 s. The resulting system supports the maintenance of either constant or predefined time-varying plasma drug concentration profiles in live rats over many hours. For researchers, the resultant high-precision control over drug plasma concentrations provides an unprecedented opportunity to (1) map the relationships between pharmacokinetics...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Molecules
Publication Identifier Type: DOI Publication Identifier: 10.3390/molecules23040912
Volume: 23 Issue: 4 First Page #: 912
Date Submitted: 2/17/19 12:00AM Date Published: 4/15/18 5:00AM
Publication Location:
**Article Title:** Electrochemical Aptamer-Based Sensors for Rapid Point-of-Use Monitoring of the Mycotoxin Ochratoxin A Directly in a Food Stream
**Authors:** Jacob Somerson, Kevin Plaxco
**Keywords:** food taint, E-AB sensor, biosensor, mycotoxin, point-of-care, electrochemical sensor, aptamer
**Abstract:** The ability to measure the concentration of specific small molecules continuously and in real-time in complex sample streams would impact many areas of agriculture, food safety, and food production. Monitoring for mycotoxin taint in real time during food processing, for example, could improve public health. Towards this end, we describe here an inexpensive electrochemical DNA-based sensor that supports real-time monitor of the mycotoxin ochratoxin A in a flowing stream of foodstuffs.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** mBio
Publication Identifier Type: DOI Publication Identifier: 10.1128/mBio.01593-17
Volume: 8 Issue: 5 First Page #:
Date Submitted: 2/17/19 12:00AM Date Published: 10/24/17 5:00AM
Publication Location:
**Article Title:** Selective Proteomic Analysis of Antibiotic-Tolerant Cellular Subpopulations in Pseudomonas aeruginosa Biofilms
**Authors:** Brett M. Babin, Lydia Atangcho, Mark B. van Eldijk, Michael J. Sweredoski, Annie Moradian, Sonja Hess
**Keywords:** BONCAT, Pseudomonas aeruginosa, antibiotic resistance, biofilms, proteomics
**Abstract:** Biofilm infections exhibit high tolerance against antibiotic treatment. The study of biofilms is complicated by phenotypic heterogeneity; biofilm subpopu- lations differ in their metabolic activities and their responses to antibiotics. Here, we describe the use of the bio-orthogonal noncanonical amino acid tagging (BONCAT) method to enable selective proteomic analysis of a Pseudomonas aeruginosa biofilm subpopulation. Through controlled expression of a mutant methionyl-tRNA synthe- tase, we targeted BONCAT labeling to cells in the regions of biofilm microcolonies that showed increased tolerance to antibiotics. We enriched and identified proteins synthesized by cells in these regions. Compared to the entire biofilm proteome, the labeled subpopulation was characterized by a lower abundance of ribosomal pro- teins and was enriched in proteins of unknown function. We performed a pulse- labeling experiment to determine the dynamic proteomic response of the tolerant subpopulation...
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Frontiers in Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.3389/fnins.2018.00705
Volume: 12 Issue: First Page #:
Date Submitted: 2/17/19 12:00AM Date Published: 10/11/18 5:00AM
Publication Location:
**Article Title:** Failure to Affect Decision Criteria During Recognition Memory With Continuous Theta Burst Stimulation
**Authors:** Evan Layher, Tyler Santander, Lukas J. Volz, Michael B. Miller
**Keywords:** continuous theta burst stimulation (cTBS), recognition memory, criterion shifting, functional magnetic brain imaging (fMRI), prefrontal cortex
**Abstract:** A decision criterion establishes the minimum amount of memory evidence required for recognition. When a liberal criterion is set, items are recognized based on weak evidence whereas a conservative criterion requires greater memory strength for recognition. The decision criterion is a fundamental aspect of recognition memory but little is known about the underlying neural mechanisms of maintaining a criterion. We used continuous theta burst stimulation (cTBS) with the goal of inhibiting prefrontal cortex excitability while participants performed recognition tests. We hypothesized that inhibiting the right inferior frontal gyrus (rIFG), right middle frontal gyrus (rMFG), and right dorsolateral prefrontal cortex (rDLPFC) would cause participants to establish less conservative decision criteria without affecting recognition memory performance. Participants initially performed recognition memory tests while maintaining conservative decision criteria during fMRI scanning. Peak activity...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Frontiers in Human Neuroscience
Publication Identifier Type: DOI Publication Identifier: 10.3389/fnhum.2018.00410
Volume: 12 Issue: First Page #:
Date Submitted: 2/17/19 12:00AM Date Published: 10/25/18 5:00AM
Publication Location:
**Article Title:** The Neural Basis of Individual Differences in Directional Sense
**Authors:** Heather Burte, Benjamin O. Turner, Michael B. Miller, Mary Hegarty
**Keywords:** spatial cognition, navigation, allocentric headings, sense-of-direction, individual differences
**Abstract:** Individuals differ greatly in their ability to learn and navigate through environments. One potential source of this variation is “directional sense” or the ability to identify, maintain, and compare allocentric headings. Allocentric headings are facing directions that are fixed to the external environment, such as cardinal directions. Measures of the ability to identify and compare allocentric headings, using photographs of familiar environments, have shown significant individual and strategy differences; however, the neural basis of these differences is unclear. Forty-five college students, who were highly familiar with a campus environment and ranged in self-reported sense-of-direction, underwent fMRI scans while they completed the Relative Heading task, in which they had to indicate the direction of a series of photographs of recognizable campus buildings (i.e., “target headings”) with respect to initial “orienting headings.” Large individual differences were found in accuracy...
**Distribution Statement:** 3-Distribution authorized to U.S. Government Agencies and their contractors
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Proceedings of the National Academy of Sciences
Publication Identifier Type: DOI Publication Identifier: 10.1073/pnas.1809349115
Volume: 115 Issue: 51 First Page #: E11951
Date Submitted: 2/17/19 12:00AM Date Published: 12/1/18 6:00AM
Publication Location:
**Article Title:** Microbiome interactions shape host fitness
**Authors:** Alison L. Gould, Vivian Zhang, Lisa Lamberti, Eric W. Jones, Benjamin Obadia, Nikolaos Korasidis, Alex
**Keywords:** microbiome, higher-order interactions, fitness landscape, Drosophila, life history tradeoffs
**Abstract:** Gut bacteria can affect key aspects of host fitness, such as development, fecundity, and lifespan, while the host, in turn, shapes the gut microbiome. However, it is unclear to what extent individual species versus community interactions within the microbiome are linked to host fitness. Here, we combinatorially dissect the natural microbiome of Drosophila melanogaster and reveal that interactions between bacteria shape host fitness through life history tradeoffs. Empirically, we made germ-free flies colonized with each possible combination of the five core species of fly gut bacteria. We measured the resulting bacterial community abundances and fly fitness traits, including development, reproduction, and lifespan. The fly gut promoted bacterial diversity, which, in turn, accelerated development, reproduction, and aging: Flies that reproduced more died sooner. From these measurements, we calculated the impact of bacterial interactions on fly fitness by adapting the mathematics...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Royal Society Open Science
Publication Identifier Type: DOI Publication Identifier: 10.1098/rsos.180563
Volume: 5 Issue: 8 First Page #: 180563
Date Submitted: 2/17/19 12:00AM Date Published: 8/29/18 5:00AM
Publication Location:
**Article Title:** Novel magnetic resonance technique for characterizing mesoscale structure of trabecular bone
**Authors:** Chantal Nguyen, Kimberly J. Schlesinger, Timothy W. James, Kristin M. James, Robert L. Sah, Koichi M
**Keywords:** magnetic resonance, osteoporosis, histomorphometry, trabecular bone
**Abstract:** Osteoporosis, characterized by increased fracture risk and bone fragility, impacts millions of adults worldwide, but effective, non-invasive and easily accessible diagnostic tests of the disease remain elusive. We present a magnetic resonance (MR) technique that overcomes the motion limitations of traditional MR imaging to acquire high-resolution frequency-domain data to characterize the texture of biological tissues. This technique does not involve obtaining full two-dimensional or three-dimensional images, but can probe scales down to the order of 40 ?m and in particular uncover structural information in trabecular bone. Using micro-computed tomography data of vertebral trabecular bone, we computationally validate this MR technique by simulating MR measurements of a 'ratio metric' determined from a few k-space values corresponding to trabecular thickness and spacing. We train a support vector machine classifier on ratio metric values determined from healthy and simulated...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Fire Technology
Publication Identifier Type: DOI Publication Identifier: 10.1007/s10694-018-0770-7
Volume: Issue: First Page #:
Date Submitted: 2/17/19 12:00AM Date Published: 9/21/18 5:00AM
Publication Location:
**Article Title:** Modeling Individual and Group Evacuation Decisions During Wildfires
**Authors:** Chantal Nguyen, Kimberly J. Schlesinger, Fangqiu Han, Izzeddin Gür, Jean M. Carlson
**Keywords:** Decision making, Group evacuation, Stochastic models, Machine learning
**Abstract:** Quantifying factors that affect evacuation decision making remains a challenging task. Progress is crucial for developing predictive models of collective behavior and for designing effective policies to guide the action of populations during wildfires. We conduct a controlled behavioral experiment to probe factors influencing evacuation decision making in the face of an impending virtual wildfire. We consider competing factors that influence small groups and the community as a whole. Based on our data, we develop two distinct but complementary empirically-driven approaches to characterize individual and group evacuation decision making. Our first approach is a stochastic model that predicts evacuation of a population of individuals guided by the same decision-making strategy, which we define to be a continuous function of key experimental variables such as the likelihood of the disaster and the availability of resources. We extend this model to investigate strategy shifts leading to...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Frontiers in Physiology
Publication Identifier Type: DOI Publication Identifier: 10.3389/fphys.2018.01131
Volume: 9 Issue: First Page #:
Date Submitted: 2/17/19 12:00AM Date Published: 8/21/18 5:00AM
Publication Location:
**Article Title:** Effects on Cognitive Functioning of Acute, Subacute and Repeated Exposures to High Altitude
**Authors:** Matiram Pun, Veronica Guadagni, Kaitlyn M. Bettauer, Lauren L. Drogos, Julie Aitken, Sara E. Hartman
**Keywords:** altitude, cognition, hypoxia, brain, CANTAB, AMS/LLS, SpO2, ALMA
**Abstract:** Objective: Neurocognitive functions are affected by high altitude, however the altitude effects of acclimatization and repeated exposures are unclear. We investigated the effects of acute, subacute and repeated exposure to 5,050 m on cognition among altitude-naïve participants compared to control subjects tested at low altitude. Methods: Twenty-one altitude-naïve individuals (25.3 ± 3.8 years, 13 females) were exposed to 5,050 m for 1 week (Cycle 1) and re-exposed after a week of rest at sea-level (Cycle 2). Baseline (BL, 520 m), acute (Day 1, HA1) and acclimatization (Day 6, HA6, 5,050 m) measurements were taken in both cycles. Seventeen control subjects (24.9 ± 2.6 years, 12 females) were tested over a similar period in Calgary, Canada (1,103 m). The Reaction Time (RTI), Attention Switching Task (AST), Rapid Visual Processing (RVP) and One Touch Stockings of Cambridge (OTS) tasks were administered and outcomes were expressed in milliseconds/frequencies. Lake Louise Score (LLS)...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of the Mechanics and Physics of Solids
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.jmps.2018.10.019
Volume: 124 Issue: First Page #: 489
Date Submitted: 2/21/19 12:00AM Date Published: 3/1/19 6:00AM
Publication Location:
**Article Title:** Defect Sensitivity of Truss Strength
**Authors:** Ryan M. Latture, Matthew R. Begley, Frank W. Zok
**Keywords:** Cellular solids, (A) fracture, (A) stress concentrations, (C) finite elements
**Abstract:** Periodic trusses with missing or defective struts may exhibit reduced strength relative to those of otherwise pristine trusses. The principal goal of the present study is to determine the extent to which individual strut defects and free surfaces, both separately and together, elevate strains in neighboring struts and, in turn, the effects of strain elevations on truss strength, especially in trusses made from elastic-brittle materials. The goals are pursued through finite element analyses of three stretch-dominated truss structures with low relative density under uniaxial compressive loading. In all cases considered, strain elevations due to bulk defects (distant from free surfaces) are comparable to or lower than those associated with the surfaces themselves. Although defects located at truss corners and truss edges cause the highest elevations in strut strains, their effects on truss strength are small (5–25%). Guidelines are presented for the minimal tensile fracture strain of...
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**Journal:** Science Signaling
Publication Identifier Type: DOI Publication Identifier: 10.1126/scisignal.aan3580
Volume: 11 Issue: First Page #:
Date Submitted: 2/21/19 12:00AM Date Published: 2/27/18 6:00AM
Publication Location:
**Article Title:** Integrated in vivo multiomics analysis identifies p21-activated kinase signaling as a driver of colitis
**Authors:** Jesse Lyons, Douglas K. Brubaker, Phaedra C. Ghazi, Katherine R. Baldwin, Amanda Edwards, Myriam
**Keywords:** ulcerative colitis
**Abstract:** Crohn's disease and ulcerative colitis are forms of inflammatory bowel disease (IBD), which have limited therapeutic options. Thus, a better understanding of the molecular mechanisms underlying IBD is needed to develop new treatment strategies. Lyons et al. combined RNA microarray, total protein mass spectrometry, and phosphoprotein mass spectrometry analyses of tissues isolated from a mouse model of colitis. Integration of these data sets enabled tracking from gene expression to protein phosphorylation in individual animals over time. Computational analysis of the data identified discrepancies between transcriptomic and proteomic measurements and predicted that the kinase Pak1 mediated colonic inflammation. Treatment of mice with a pharmacological inhibitor of Pak1 ameliorated disease, highlighting the importance of proteomic measurement to the understanding of disease pathogenesis.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Nature Methods
Publication Identifier Type: DOI Publication Identifier: 10.1038/s41592-019-0326-x
Volume: Issue: First Page #:
Date Submitted: 2/24/19 12:00AM Date Published: 2/1/19 6:00AM
Publication Location:
**Article Title:** Noninvasive monitoring of single-cell mechanics by acoustic scattering
**Authors:** Joon Ho Kang, Teemu P. Miettinen, Lynna Chen, Selim Olcum, Georgios Katsikis, Patrick S. Doyle, Scc
**Keywords:** Biophysical methods, Cell growth
**Abstract:** The monitoring of mechanics in a single cell throughout the cell cycle has been hampered by the invasiveness of mechanical measurements. Here we quantify mechanical properties via acoustic scattering of waves from a cell inside a fluid-filled vibrating cantilever with a temporal resolution of?<?1?min. Through simulations, experiments with hydrogels and the use of chemically perturbed cells, we show that our readout, the size-normalized acoustic scattering (SNACS), measures stiffness. To demonstrate the noninvasiveness of SNACS over successive cell cycles, we used measurements that resulted in deformations of?<?15?nm. The cells maintained constant SNACS throughout interphase but showed dynamic changes during mitosis. Our work provides a basis for understanding how growing cells maintain mechanical integrity, and demonstrates that acoustic scattering can be used to noninvasively probe subtle and transient dynamics.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Macromolecules
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.macromol.6b01514
Volume: 49 Issue: 18 First Page #: 6910
Date Submitted: 5/4/19 12:00AM Date Published: 9/1/16 12:00AM
Publication Location:
**Article Title:** Correlated Diffusivities, Solubilities, and Hydrophobic Interactions in Ternary Polydimethylsiloxane–Water–Tetrahydrofuran Mixtures
**Authors:** Stephen H. Donaldson, Justin P. Jahnke, Robert J. Messinger, Åsa Östlund, David Uhrig, Jacob N. Isra
**Keywords:** Hydrophobic Interactions
**Abstract:** Bulk thermodynamic and kinetic properties of mixtures are generally composition dependent, often in complicated ways, especially for partially miscible and multicomponent systems. Combined 1H chemical shift, 1H diffusion NMR, and surface forces analyses establish the compositional dependences of water solubility and self-diffusion in ternary polymeric polydimethylsiloxane–water–tetrahydrofuran (THF) mixtures. The addition of THF significantly increases the solubility of water, while decreasing its diffusivity, in hydrophobic polydimethylsiloxane. Minimum values for the self-diffusivities of both water and THF coincide with a minimum in the hydrophobic adhesion energy between silicone polymer thin films near the same binary composition of 0.20 mole fraction THF. Such interrelated diffusivities, solubilities, and hydrophobic interactions are analyzed with respect to hydrogen bonding among the constituent species to account for the bulk physical properties of technologically important...
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Science Signaling
Publication Identifier Type: DOI Publication Identifier: 10.1126/scisignal.aal1601
Volume: 11 Issue: 520 First Page #:
Date Submitted: 5/4/19 12:00AM Date Published: 3/1/18 6:00AM
Publication Location:
**Article Title:** Inflammatory but not mitogenic contexts prime synovial fibroblasts for compensatory signaling responses to p38 inhibition
**Authors:** Douglas S. Jones, Anne P. Jenney, Brian A. Joughin, Peter K. Sorger, Douglas A. Lauffenburger
**Keywords:** signaling responses
**Abstract:** In rheumatoid arthritis (RA), inflammation is driven by the increased activity of the kinase p38 MAPK. However, p38 MAPK inhibitors are ineffective in patients. Using synovial fibroblasts and synovial fluid from RA patients, Jones et al. found that unlike cells in proliferative conditions, such as those in which cancer cells are grown (from which many network models have been built), p38 MAPK was a critical inducer of negative cross-talk to the MAPK-related, JNK pathway in cells grown in the inflammatory context associated with RA. Thus, inhibiting p38 facilitated JNK activity and the perpetuation of inflammatory cytokine production. Culturing the same cells under proliferative conditions switched the dominant point of negative cross-talk between the MAPK pathways to the kinase MEK. Inhibitors of the upstream kinase TAK1 curbed the activity of both the p38 and JNK pathways in the cells and, hence, might be effective in RA patients.
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**Publication Type:** Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
**Journal:** Journal of Dynamic Systems, Measurement, and Control
Publication Identifier Type: DOI Publication Identifier: 10.1115/1.4042669
Volume: 141 Issue: 6 First Page #: 064501
Date Submitted: 5/4/19 12:00AM Date Published: 2/21/19 6:00AM
Publication Location:
**Article Title:** Unmanned Aerial Vehicle Surveillance Under Visibility and Dwell-Time Constraints
**Authors:** Jeffrey R. Peters, Amit Surana, Grant S. Taylor, Terry S. Turpin, Francesco Bullo
**Keywords:** Unmanned aerial vehicles, Surveillance, Approximation, Construction, Algorithms, Imaging
**Abstract:** A framework is introduced for planning unmanned aerial vehicle (UAV) flight paths for visual surveillance of ground targets, each having particular viewing requirements. Specifically, the framework is designed for instances in which each target is associated with a set of imaging parameters, including a desired: (i) tilt angle, (ii) azimuth, with the option of a 360?deg view, and (iii) dwell-time. Tours are sought to image the targets, while minimizing both the total mission time and the time required to reach the initial target. An ?-constraint scalarization is used to pose the multi-objective problem as a constrained optimization, which, through careful discretization, can be approximated as a discrete graph-search. It is shown that, in many cases, this approximation is equivalent to a generalized traveling salesperson problem (GTSP). A heuristic procedure for solving the discrete approximation and recovering solutions to the full routing problem is presented and illustrated...
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**CONFERENCE PAPERS:**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 1-Published
**Conference Name:** 2015 54th IEEE Conference on Decision and Control (CDC)
Date Received: 29-Jul-2016 Conference Date: 15-Dec-2015 Date Published:
Conference Location: Osaka
**Paper Title:** Quasi-optimality of event-based encoders
**Authors:** Justin Pearson, Joao P. Hespanha, Daniel Liberzon
Acknowledged Federal Support: **Y**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 1-Published
**Conference Name:** ICC 2015 - 2015 IEEE International Conference on Communications
Date Received: 04-Aug-2016 Conference Date: 08-Jun-2015 Date Published:
Conference Location: London, United Kingdom
**Paper Title:** Scaling wideband distributed transmit beamforming via aggregate feedback
**Authors:** M. F. Gencel, M. E. Rasekh, U. Madhow
Acknowledged Federal Support: **Y**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 1-Published
**Conference Name:** 2015 IEEE International Symposium on Information Theory (ISIT)
Date Received: 04-Aug-2016 Conference Date: 14-Jun-2015 Date Published:
Conference Location: Hong Kong, Hong Kong
**Paper Title:** Distributed transmit beamforming with one bit feedback revisited: How noise limits scaling
**Authors:** Muhammed Faruk Gencel, Maryam Eslami Rasekh, Upamanyu Madhow
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**Publication Type:** Conference Paper or Presentation **Publication Status:** 1-Published
**Conference Name:** 37th Annual Meeting of the Cognitive Science Society
Date Received: 09-Aug-2016 Conference Date: 22-Jul-2015 Date Published: 25-Jul-2015
Conference Location: Austin, TX
**Paper Title:** Scene inversion slows the rejection of false positives through saccade exploration during search
**Authors:** Kathryn Koehler, Miguel P. Eckstein
Acknowledged Federal Support: **Y**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 1-Published
**Conference Name:** International Conference on Advances in Geographic Information Systems
Date Received: 09-Aug-2016 Conference Date: 03-Nov-2015 Date Published: 06-Nov-2015
Conference Location: Seattle, WA
**Paper Title:** Tracking 3-Dimensional Fiber Bundles: A Reeb Graph Approach to Tractography
**Authors:** J. Sun, M. Cieslak, S. Grafton, S. Suri
Acknowledged Federal Support: **Y**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 1-Published
**Conference Name:** FOSBE 2015 Conference Proceedings
Date Received: 24-Aug-2016 Conference Date: 09-Aug-2015 Date Published: 09-Aug-2015
Conference Location: Boston, MA
**Paper Title:** GillesPy: A python package for stochastic model building and simulation
**Authors:** John H Abel, Brian Drawert, Andreas Hellander, Linda R Petzold
Acknowledged Federal Support: **Y**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 5-Submitted
**Conference Name:** SEED 2016
Date Received: 31-Aug-2017 Conference Date: 18-Jul-2016 Date Published: 21-Jul-2016
Conference Location: Chicago, IL
**Paper Title:** The role of single occupancy effects on integrase dynamics in a cell-free system
**Authors:** Georgios Artavanis, Victoria Hsiao, Clarmyra A. Hayes, Richard M. Murray
Acknowledged Federal Support: **Y**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 5-Submitted
**Conference Name:** SEED 2016
Date Received: 31-Aug-2017 Conference Date: 19-Jul-2016 Date Published: 21-Jul-2016
Conference Location: Chicago, IL
**Paper Title:** Design and application of stationary phase combinatorial promoters
**Authors:** Victoria Hsiao, Aileen Cheng, Richard M. Murray
Acknowledged Federal Support: **Y**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 5-Submitted
**Conference Name:** SEED 2016
Date Received: 31-Aug-2017 Conference Date: 18-Jul-2016 Date Published: 21-Jul-2016
Conference Location: Chicago, IL
**Paper Title:** Engineering pulsatile communication in bacterial consortia
**Authors:** James M. Parkin, Victoria Hsiao, Richard M. Murray
Acknowledged Federal Support: **Y**

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**Publication Type:** Conference Paper or Presentation **Publication Status:** 5-Submitted
**Conference Name:** SEED 2016
Date Received: 31-Aug-2017 Conference Date: 18-Jul-2016 Date Published: 21-Jul-2016
Conference Location: Chicago, IL
**Paper Title:** Repressing Integrase attachment site operation with CRISPR- Cas9 in E. coli
**Authors:** Andrey Shur, Richard M. Murray
Acknowledged Federal Support: **Y**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 3-Accepted
**Conference Name:** Proceedings of the Summer Computer Simulation Conference
Date Received: 31-Aug-2017 Conference Date: 24-Jul-2016 Date Published: 26-Jul-2016
Conference Location: Montreal, Quebec, Canada
**Paper Title:** Collective Decision Dynamics in Group Evacuation: Behavioral Experiment and Machine Learning Models
**Authors:** Chantal Nguyen, Fangqiu Han, Kimberly J. Schlesinger, Izzeddin Gür, Jean M. Carlson
Acknowledged Federal Support: **Y**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 1-Published
**Conference Name:** 2017 American Control Conference (ACC)
Date Received: 23-Aug-2018 Conference Date: 24-May-2017 Date Published:
Conference Location: Seattle, WA, USA
**Paper Title:** Coverage control with anytime updates for persistent surveillance missions
**Authors:** Jeffrey R. Peters, Sean J. Wang and Francesco Bullo
Acknowledged Federal Support: **Y**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 1-Published
**Conference Name:** the 2017 CHI Conference
Date Received: 23-Aug-2018 Conference Date: 06-May-2017 Date Published:
Conference Location: Denver, Colorado, USA
**Paper Title:** Attention Allocation Aid for Visual Search
**Authors:** Arturo Deza, Jeffrey R. Peters, Grant S. Taylor, Amit Suran, Miguel P. Eckstein
Acknowledged Federal Support: **Y**

**Publication Type:** Conference Paper or Presentation **Publication Status:** 1-Published
**Conference Name:** 2017 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)
Date Received: 24-Aug-2018 Conference Date: 05-Mar-2017 Date Published:
Conference Location: New Orleans, LA
**Paper Title:** Brain signal analytics from graph signal processing perspective
**Authors:** Leah Goldsberry, Weiyu Huang, Nicholas F. Wymbs, Scott T. Grafton, Danielle S. Bassett, Alejandro Ril
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**Authors:** Brian Drawert, Nimish Thakore, Brian Mitchell, Erik Pioro, John Ravits, Linda R. Petzold
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**Authors:** Chantal Nguyen, Kimberly J. Schlesinger, and Jean M. Carlson
Acknowledged Federal Support: **Y**

# Army's Institute for Collaborative Biotechnologies

## Final Report for ICB UARC 2014 – 2018

### ARO Contract W911NF-09-D-0001

### December 1, 2013 – November 30, 2018

**Systems and Synthetic Biology** ..... SSB-1

**Bio-inspired Materials** ..... BIM-1

**Biotechnology Tools** ..... BTT-1

**Cognitive Neuroscience** ..... CNS-1

# Army's Institute for Collaborative Biotechnologies

## Final Report for ICB UARC Task Order 31

### ARO Contract W911NF-09-D-0001

### December 1, 2013 – November 30, 2018

**Stochastic Biological Oscillators, Circadian Rhythms, and Cognition**
*Linda R. Petzold (UCSB)* ..... SSB-2

**Engineering Synthetic Cellulose-degrading Complexes from Gut Fungi in *Saccharomyces cerevisiae***
*Michelle A. O'Malley (UCSB)* ..... SSB-8

**Macromolecular Design from Sequence-Activity Analysis**
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**Single- and Multi-Cellular Biomolecular Detection of Environmental Events**
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**Synthetic Development – Engineering of Self-Patterning**
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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Stochastic Biological Oscillators, Circadian Rhythms, and Cognition**

**Project Leader:** **Linda R. Petzold (UCSB)**

**Collaborators:** **Scott Grafton (UCSB); Frank Doyle (Harvard); Erik Herzog (Wash. U.); Jean Vettel, Javi Garcia and Nina Lauharatanahirun (ARL-HRED)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

*Fundamental Algorithms and Public Domain Software for Simulation of Discrete Stochastic Systems*. For many years, mathematical modeling of physically-based systems has made extensive use of algorithms and software for the solution of ordinary differential equations (ODEs) and partial differential equations (PDEs). We have developed an extensive toolbase for the solution of these systems. As research and technology has moved into smaller and smaller scales, the actions of individual molecules can determine the fate of the system. This has been shown to be the case, for example, in cell biology. Discrete stochastic simulation (Markov processes) can capture these effects. When we began this work, a few, simple, algorithms had been proposed and were in use in a relatively small number of labs in cell biology. All were directed at well-mixed (non-spatially-dependent) systems, and there was no public-domain software to speak of. We developed extensive theory and algorithms for both well-mixed and spatially-dependent systems, and released the public-domain software package StochSS, for both well-mixed and spatially-dependent systems in up to 3 dimensions with support for cloud computing.

*Uncovering Design Principles of Circadian Oscillators.* Using the experimental results from Erik Herzog's (Wash. U.) lab, we inferred the functional network for synchronization of slices of mouse Suprachiasmatic Nucleus (SCN). We found that, in general, neurons in the core of the SCN had considerably more connections than those in the shell, and that the cores of the two lobes of the SCN were very densely connected. In subsequent work and using a completely different methodology, we inferred the directionality of the connections. We found that virtually all neurons had a small number of incoming connections. On the other hand, the topology of outgoing connections was was not nearly so homogeneous. In general, neurons in the core had substantially greater numbers of outgoing connections than neurons in the shell. In recent (not yet published) work, we show that this type of directional network has advantages for synchronization and entrainment. Finally, we studied how the SCN network grows and develops in utero, and for the first few days after birth. We found through analysis of experimental results that development of the SCN occurs in stages. First, cell-autonomous oscillation begins on embryonic days E14-E15, followed by synchronization on E17 and finally, development of the core and shell by postnatal day P2.

*Principles of Motor Learning.* In recent work with Scott Grafton, Jean Vettel, Javi Garcia and Nina Lauharatanahirun, we have studied the neural dynamics underlying the exploration-exploitation tradeoff in motor learning, and found that the probability densities of whole-brain, task-active regional activity (as measured by fMRI BOLD) and behavioral performance evolve according to a Fokker-Planck equation during the acquisition of a motor skill. Our results reveal that the evolution of neural dynamics during motor learning achieves the unique, optimal state-action density to balance the exploration-exploitation tradeoff.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

We have had three major objectives during this project period:

1. Develop methodologies for neural control
2. Characterize the changes in the brain in the process of learning.
3. Extend our public domain stochastic simulation software package StochSS to provide greater capabilities.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

For objective 1, the development of methodologies for neural control, we note that most of the current contributions to the field have focused on model-based control. However, models of neural systems are quite complex and difficult to design. To circumvent these issues, our strategy has been to focus on model-free (data-driven) approaches.

For objective 2, characterization of changes in the brain as a response to learning, our strategy has been to develop fundamental principles for the evolution of activity in the brain as a response to learning, guided by data from experiments in the Grafton and Vettel groups.

For objective 3, extending our public domain stochastic simulation software, our strategy has been to address the needs of the research community, as we perceive them both from conferences and professional interactions, as well as from our own multidisciplinary research.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1. Methodologies for Neural Control*

Recent improvements in hardware and data collection have lowered the barrier to practical neural control. Most of the current contributions to the field have focused on model-based control, via dynamical systems [1-8] or statistical models [9-13]. However, models of neural systems are quite complex and difficult to design. To circumvent these issues, we adapted a model-free method from the reinforcement learning literature, Deep Deterministic Policy Gradients (DDPG) [14], as shown in **Figure 1**. Model-free reinforcement learning presents an attractive framework because of the flexibility it offers, allowing the user to avoid modeling system dynamics. We made use of this feature by applying DDPG to models of low-level and high-level neural dynamics. We showed that while model-free, DDPG is able to solve more difficult problems than can be solved by current methods. These problems include the induction of global synchrony by entrainment of weakly coupled oscillators and the control of trajectories through a latent phase space of an underactuated network of neurons. Results from the control of weakly coupled oscillators are shown in **Figure 2**. While this work has been performed on simulated systems, it suggests that advances in modern reinforcement learning may enable the solution of fundamental problems in neural control and movement towards more complex objectives in real systems. This work appeared in *Scientific Reports* in 2018.

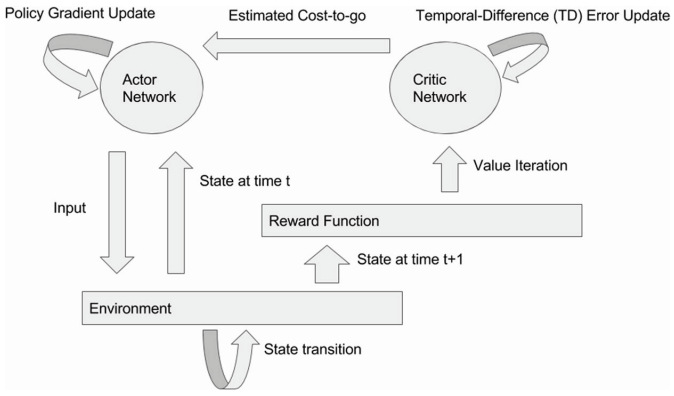



**Figure 1.** Diagram of the DDPG algorithm. The core components of this algorithm are the actor network (i.e., the policy), the critic network (i.e., the value function), and the environment (in this work, either the SLIF or Kuramoto model). The environment accepts inputs from the actor network and produces a state transition. The new state and action used to generate it are passed to the reward function. The reward function passes an update to the critic network, which estimates the value of the state-action pair at the current timestep. The parameters of the actor network are updated using the new policy gradient and the parameters of the critic network are updated using the new TD-error.

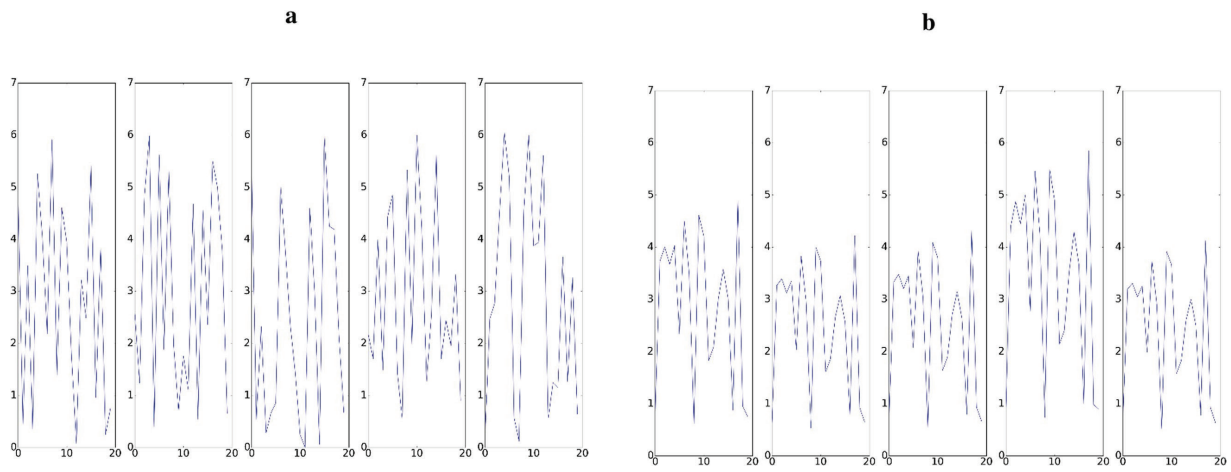



**Figure 2.** Examples demonstrating induction of synchronization by controller for weakly coupled oscillators. For all plots, the vertical axis is the phase and the horizontal axis is timestep. For both sections a and b, five plots are included generated from five randomly selected oscillators from the network of 20 oscillators. (**a**) Phases for oscillators before global synchronization has been induced by the controller. (**b**) Phases for oscillators after global synchronization has been induced by the controller. This level of synchronization can be observed after a few hundred training episodes have been observed.

### *4.2 Characterization of Changes in the Brain in the Process of Learning*

The exploration-exploitation tradeoff is posed in motor control as a balance between exploratory actions and high-performance actions. While an essential part of learning, the neural dynamics underlying this tradeoff are not well understood. In this 6-week longitudinal learning study, participants practiced a set of motor sequences each day, and neuroimaging data was collected on day 1, 14, 28, and 42 to capture the neural correlates of the learning process. In our analysis, we first modeled the underlying neural and behavioral dynamics during learning.

Our results, as shown in **Figure 3**, demonstrate that the densities of whole-brain activity, task-active regional activity (where neural activity is measured by FMRI BOLD) and behavioral performance evolve according to a Fokker-Planck equation during the acquisition of a motor skill. This is the population-level version of the Drift-Diffusion equation often used to model decision making [15,16].

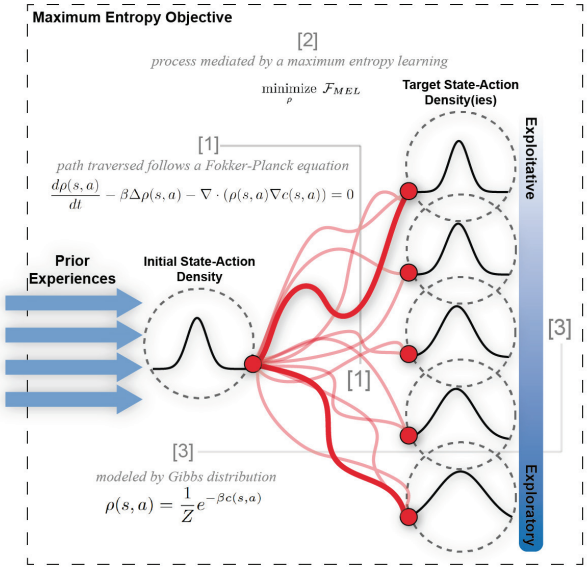



**Figure 3.** Overview of the findings of this work. Previous experience is embodied in the initial state-action density before any learning. Based on the form of the dynamics of this density (red lines, [**1**]), this density is modeled as a Gibb's distribution [**3**]. The eventual target of these dynamics is largely influenced by the temperature parameter. This coefficient tunes the entropy of the state-action density, as shown by the Maximum Entropy Objective [**2**]. The entropy of the state-action density is a model for how exploratory a subject is with respect to a given task.

This finding suggests that the maximum entropy framework is appropriate to characterize motor learning, where the brain concurrently and explicitly optimizes the entropy of the state-action density (i.e., the joint density over neural activity and behavior, respectively) and the expected cost under this density. The former tunes the exploratory character of the state-action density and the latter provides improved performance of the policy. We then developed a novel variant of inverse reinforcement learning to retrieve the cost function optimized by the brain during the learning process and used this method can also be used to retrieve the parameter used to balance exploration and exploitation.

Collectively, our insights reveal that the evolution of neural dynamics during motor learning achieves the unique, optimal state-action density to balance the exploration-exploitation tradeoff.

### *4.3 Software for Discrete Stochastic Simulation*

Our algorithm for dealing with moving boundaries in spatial stochastic simulation was implemented in our public domain software PyURDME, which is the computational engine for spatial stochastic simulation in StochSS. It will be made available soon in StochSS.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

The work on characterization of changes in the brain in the process of learning was performed in collaboration with Jean Vettel, Javi Garcia and Nina Lauharatanahirun of the U.S. Army Research Laboratory Human Research and Engineering Directorate (ARL-HRED). StochSS is in the public domain and available for download at stochss.org.

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)


D. McBride and L. Petzold. Model-based inference of a directed network of circadian neurons. Journal of Biological Rhythms, August 2018. 10.1177/0748730418790402.

B. A. Mitchell and L. R. Petzold. Control of neural systems at multiple scales using model-free, deep reinforcement learning. Scientific Reports, July 2018. 10.1038/s41598-018-29134-x.

B. Drawert, M. Griesemer, L. R. Petzold and C. J. Briggs. Using stochastic epidemiological models to evaluate conservation strategies for endangered amphibians. Journal of the Royal Society Interface, August 2017. 10.1098/rsif.2017.0480.

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F. Nunez, Y. Wang and F. J. Doyle III. Global synchronization of pulse-coupled oscillators interacting on cycle graphs. Automatica, February 2015. 10.1016/j.automatica.2014.10.111.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Engineering Synthetic Cellulose-degrading Complexes from Gut Fungi in *Saccharomyces cerevisiae***

**Project Leader:** **Michelle A. O'Malley (UCSB)**

**Collaborators:** **M. Scott Shell (UCSB); Chris Sund and Matt Perisin (ARL-SEDD); and Andrezj Joachimiak (Argonne National Laboratory)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

Anaerobic fungi are resident within the digestive tract of large herbivores, where they have evolved to express intricate, MegaDalton multi-enzyme complexes called fungal cellulosomes that depolymerize crude plant biomass into fermentable sugars (**Figure 1**). This project enabled the engineering of synthetic lignocellulose-degrading enzyme complexes inspired by anaerobic gut fungi, which are capable of converting lignocellulosic materials to sugars and value-added products. Cellulosomes are superior for biomass hydrolysis, because they deliver all of the necessary cellulase enzymes in a concentrated, targeted manner directly to the substrate. In contrast with cellulosomes from bacteria, fungal cellulosomes have evolved unique abilities to hydrolyze recalcitrant, fibrous lignocellulose, and they display a wider range of enzymatic diversity, particularly for enzymes that degrade xylan and pectin, as well as those that modify lignin. Despite these desirable attributes, the protein composition, multi-enzyme assembly mechanism, and superstructure of fungal cellulosomes remained elusive for the past 30 years prior to the initiation of this project.

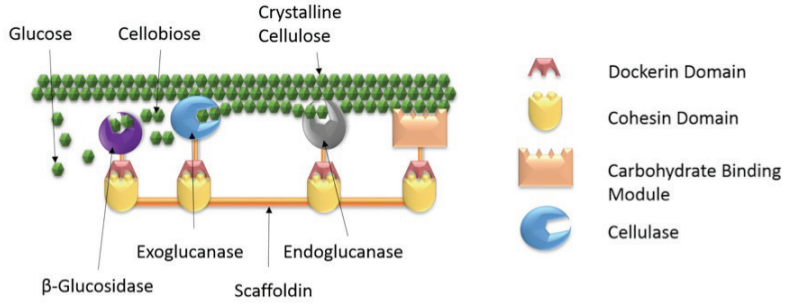



**Figure 1.** *Anaerobic gut fungi produce cellulosomes for synergistic hydrolysis of lignocellulose.* Complex assembly is mediated by dockerin-fused catalytic enzymes, which can bind to a non-catalytic scaffold that is anchored to the cell membrane.

We have leveraged our unique expertise to isolate, cultivate, and characterize gut fungi to illuminate the "parts" (enzymes, scaffold, and accessory proteins) that comprise fungal cellulosomes for the first time. A panel of novel anaerobic fungi were extracted from the environment, and were characterized with genomic, transcriptomic, and proteomic tools to decipher the design rules that govern cellulosome complex formation across fungal genera. Together, this dataset serves as a foundation for genetic engineering of anaerobic fungi and early-branching eukaryotes, and a new tool for transient transformation was developed to test gene function. To build robust, synthetic, cellulosome-inspired complexes that break down plant biomass into in the model industrial yeast *Saccharomyces cerevisiae*, enzymes were produced in yeast and found to associate with native cellulosomes and as well as synthetic enzyme complexes. We also developed a set of design rules to "graft" fungal dockerin domains to exogenous enzymes to recruit new enzymes into cellulosomes and broaden thermal stability of the complex. This effort also enabled a crystal structure to be generated in collaboration with Argonne National Laboratory for a glycosyl hydrolase (GH) family 5 enzyme. Following identification of the interacting protein domains of fungal cellulosomes, we further piloted a molecular dynamics simulation approach to illuminate the mechanism of complex formation and methods to tune binding the affinity of multi-enzyme complexes made in yeast.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

Initial phases of this project identified the modular "parts" that comprise fungal cellulosomes, which are now primed for transfer into microbial systems that are more easily controlled. The final phase of this project focused on the design synthetic fungal cellulosomes *de novo*, as well as to develop the tools to manipulate native cellulosomes – both approaches will open new routes to tunneled biocatalysis that could be extended to any multi-step enzymatic process. Specific Aims for the 2016-2018 phase of the project were to (1) develop a genetic engineering toolkit for anaerobic fungi, (2) determine the molecular structure of the native cohesin-dockerin duplex from anaerobic fungi, and (3) graft "minimal" dockerin and cohesion domains onto exogenous thermostable enzymes to implement a synthetic, thermostable enzyme complex.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

Nature has evolved a powerful machine to break down lignocellulose by producing cellulosomes from anaerobic gut fungi. We deciphered the natural design of these structures to guide in the synthesis of cellulosome-inspired complexes for simultaneous lignocellulose depolymerization and bioproducting in the yeast *S. cerevisiae*. In order to accomplish this goal, it is necessary to carefully evaluate how native cellulosomes are produced in anaerobic fungi so that production and secretion strategies in a non-native heterologous host (e.g., yeast) can be sufficiently emulated. With this knowledge in hand, we can also "unravel" native fungal cellulosomes and insert exogenous dockerin-fused enzymes within native complexes—this will create hybrid complexes that can incorporate entirely new enzymatic activities. In this manner, we will synthesize hybrid and fully synthetic enzyme complexes with tailored properties for direct use in consolidated bioprocessing.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *Aim 1: Genetic Engineering of Anaerobic Fungi and Fungal Cellulosomes*

Due to the lack of genetic tools to manipulate anaerobic fungi, most of our understanding of gut fungal cellulosomes comes from transferring their enzymes and modular assembly components to genetically tractable, heterologous hosts such as *E. coli* or yeast. Because gut fungi are distantly related to these organisms, expression of gut fungal proteins often leads to little or no gene expression, or lack of enzymatic function due to the absence of post-translational modifications required for their activity, such as glycosylation and disulfide bond formation. As a result, we are limited in fully understanding how cellulosomes function and even assemble in their native systems. To overcome these challenges, genetic modification of gut fungi will allow us to overexpress and purify enzymes directly in their native host. Additionally, this approach guarantees proper protein biogenesis (and post-translational modification) machinery that may be required for fungal cellulosome expression and activity.

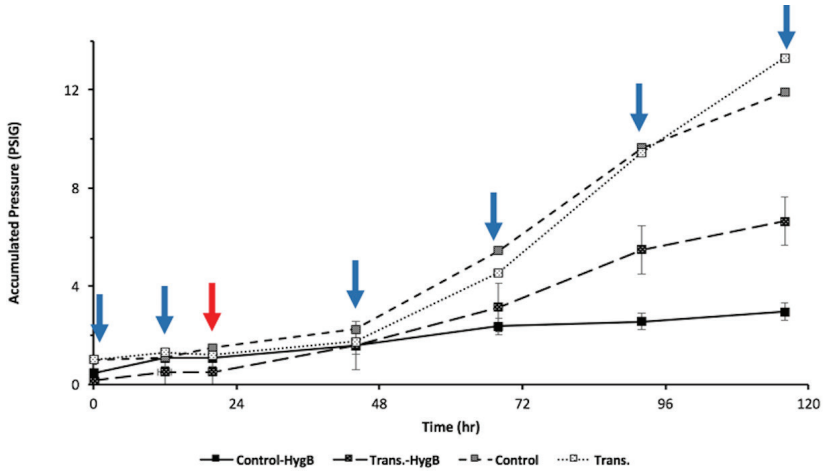



**Figure 2.** *Anaerobic gut fungi are transiently transformed and selected with a hygromycin marker.* Transformed zoospores demonstrated higher growth as measured through pressure accumulation in serum bottles relative to untransformed controls. Blue arrows indicated where measurements were taken, while the red arrow denotes addition of 100ug/mL of HygB.

Recently, we developed a method to stably genetically transform anaerobic gut fungi, which has never been successfully reported in the literature. We know that gut fungal zoospores (cells in the early stage of their life cycle) are amenable to transformation by electroporation (DNA uptake during electroshock). During electroporation, zoospores are capable of taking in foreign extracellular plasmid DNA, and then are able to express the genetic reporter encoded on the plasmid as they mature. In this case, the genetic reporter is the GusA enzyme, which hydrolyzes the reagent X-gluc, creating an easily observable blue colony formation. With these promising results, we seek to harness this method to gain a deeper understanding of fungal biomass degradation by genetic modification of cellulosome components directly in their native host.

In the past year, we incorporated a drug resistance marker into our delivery construct and tested genomic stability. These markers are advantageous to those based on autotrophies (e.g., *ura3*, *leu2*) since they do not require *a priori* knowledge of the genomic sequence, and the genes that encode drug resistance lack homology to the fungal genome. Among several candidates, we found that the drug marker for Hygromycin B (HygB) enabled selection of transformants (**Figure 2**), both through electroporation and also through natural competency. With a reliable genetic marker now available, we will leverage the new high-resolution draft genome sequences we obtained for *Neocallimastix*, *Anaeromyces*, and *Piromyces* strains to evaluate the strength of putative promoters in the anaerobic fungi, and also to delete (and overexpress) components of fungal cellulosomes. Another exciting avenue enabled by this finding is the introduction of fluorescent labels into anaerobic fungi, which will permit us to track the secretion of enzymes and cellulosome motifs in the native anaerobic fungal system.

***Aim 2: Determine the Molecular Structure of the Dockerin-Cohesin Duplex in Anaerobic Fungi***

To gain an understanding of the interaction between the fungal cellulosome building blocks – namely cohesin and dockerin – structural information is required to identify key residues involved in cellulosome assembly. The structure of a single fungal dockerin domain has previously been solved using NMR spectroscopy, and a double dockerin has been characterized through homology modeling. However, no structural information of the cohesin exists, or of fungal dockerins fused directly to enzymes, as these was only recently discovered in year 2015 of this project.

While we are still pursuing the high-resolution structure determination of a fungal dockerin-cohesin interaction, X-ray crystallography has been used with Dr. Andrzej Joachimiak (Argonne National Laboratory) to solve the structure of a glycosyl hydrolase family 5 from *Piromyces finnis*. Recently, Argonne has successfully purified stable dockerin-cohesin duplex and we expect to generate the first crystal structures of this duplex within the coming years – if successful, this would capture the high-resolution structure of the fungal dockerin-cohesin interaction for the first time. Overall, both crystallization and complementary approaches like molecular dynamic simulation and modeling will provide complementary insight into this novel fungal dockerin-cohesin interaction found in nature, and guide in fine-tuning this interaction for synthetic systems.

***Aim 3: Graft Dockerin Domains onto Exogenous Enzymes to Implement into Synthetic Cellulosomes***

While designer cellulosomes have been synthesized from the cohesin, dockerin, and scaffoldin domains found across anaerobic bacteria, analogous domains from anaerobic fungi have not yet been explored as synthetic biology tools. Like cellulosome-producing bacteria, anaerobic fungi are typically found in the rumen and hindgut of large herbivores, where approximately 30% of their CAZymes are cellulosome-associated. Recently, comparative genomics coupled with proteomic validation revealed a family of repeat-rich, non-catalytic scaffoldins in the genomes of five anaerobic fungi that form a specific interaction with dockerin-fused enzymes from fungi. However, as yet there are no design rules to implement the newly discovered fungal cellulosome domains from the anaerobic fungi of the *Neocallmastigomycota*. Since fungal dockerins exist at either the N- or C- terminal of proteins and in tandem repeats, elucidating the type and placement of fungal dockerins is necessary for optimal design of synthetic enzymes and synthetic fungal cellulosomes. A number of potential advantages are likely to be served by these fungal cellulosomes, since they include a much wider repertoire of cellulases with dockerin domains compared to bacterial cellulosomes, including GH3, GH6, and GH45. Therefore, utilizing the native fungal cellulosomes as templates for engineering chimeric enzymes will likely enable the inclusion of new classes of enzymes, including those that expand the activity and stability of these enzyme complexes.

Towards the goal of engineering a thermostable enzyme complexes for biomass utilization, we combined the cellulosome parts from fungal cellulosomes and the cellulases from the thermophile *T. maritima* to engineer thermo-

stable chimeric enzymes capable of inclusion in synthetic fungal cellulosomes (**Figure 3**). Thermostable enzymes are catalytically active at high temperatures (70-90°C), yet are also stable at moderate temperatures (50-70°C), resulting in decreased required enzyme titers. For example, *Thermotoga maritima* is a hyper-thermophilic bacterium capable of growing at temperatures up to 90°C in deep sea vents, and whose enzymes are likely amenable to high temperature bio-processing. While it utilizes a number of cellulases and hemicellulases, they are freely diffusive and not contained in cellulosome complexes. Finding ways to link thermostable enzymes into enzyme complexes could improve the properties of the enzymes even further through synergistic targeting of the enzymes and alignment of the active sites. From the fungal cellulosome "parts list", we deciphered design rules for placement of dockerin domains on multi-modular CAZymes for inclusion in synthetic fungal cellulosomes. These design rules extend to a wider array of catalytic domains than those found in bacterial cellulosomes and can effectively work to engineer multi-domain CAZymes with favorable properties such as thermostability.

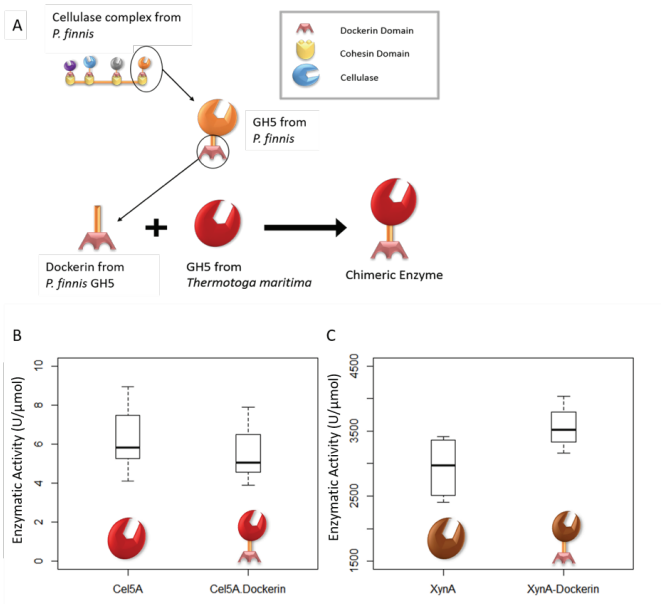



**Figure 3.** *Design of chimeric CAZymes for synthetic fungal cellulosomes in yeast.* **A)** For optimal dockerin placement, the dockerin and linker sequence was taken from the closest-related sequence in P. finnis and grafted in the same location on the on chimeric T. maritima CAZymes. The CMCase or Xylanase activity at 80°C was comparable for both the native enzyme and the enzyme with the grafted dockerin domain for both a GH5 (Cel5A, panel **B**) and a GH10 (XynA, panel **C**).

As a first step to systematically design chimeric proteins, the dockerin-containing proteins from recently sequenced genomes of the anaerobic fungi *P. finnis, N. californiae, and A. robustus* were analyzed. *Neocallimastix californiae* contains 422 Dockerin domain proteins (DDPs), nearly double the 223 DDPs found in anaerobic bacterium *Ruminococcus flavifaciens* FD-1, which is widely regarded as the most diverse repertoire in bacterial cellulosomes. The other two members of the *Neocallimastigomycota* that currently have high quality genomes published*, P. finnis* and *A. robustus,* also contain more DDPs than *R. flavifaciens*, with 227 and 276 DDPs, respectively.

One major difference between fungal DDPs and bacterial DDPs is the type and placement of dockerin domains on the catalytic enzymes. In fungal DDPs, dockerin domains are frequently found on either the N- or C- terminus of catalytic domains and in multiple copies (tandem repeats), whereas bacterial dockerins are almost exclusively found at the C- terminus with only a single domain present. Given this, we hypothesized that the dockerin type and placement was specific to each glycoside hydrolase (GH) enzyme type and therefore sought to characterize the GH type and dockerin location in fungal DDPs. In total from fungal cellulosomes, about 60% of dockerin domains are found more proximal to the CAZyme C- terminus compared to the catalytic domain. Some domains, including the GH2, GH8, GH11, GH26, GH38, and GH48, contain dockerin domains on the C- terminus exclusively. In these cases, it is likely that the N- terminus is inaccessible or buried within the catalytic domain such that N- terminal dockerins would adversely affect the catalytic activity. Many of the CAZymes believed to originate from bacteria contain dockerin domains at the C- terminus, which mirrors the placement of dockerins on similar CAZymes in bacterial cellulosomes. The GH6 and GH45 are both domains found in fungal cellulosomes, but not typically found in bacterial cellulosomes. Interestingly, these are also the two catalytic domains where dockerin domains are more likely to be found on the N- terminus than the C- terminus. Finally, the most common dockerin repeat motif was a double dockerin found in ~60% of dockerin domain proteins (DDPs), followed by triple dockerins and then single dockerins. While the purpose of tandem repeats remains unknown, this data suggests that double dockerins are the best modular unit to employ when designing chimeric multi-domain proteins.

A GH5 from *T. maritima* was chosen for chimeric design because GH5s have relatively conserved dockerin placement, with the majority existing on the C- terminus in fungi. In particular, the GH5 chosen had the highest protein sequence similarity to several genes in *P. finnis,* all of which had two dockerin domains at the C- terminus of native anaerobic fungi. As a result of this analysis, the catalytic domain was cloned from *T. maritima* and the double dockerin from a GH5_4 was cloned from *P. finnis.* A schematic for the design of the chimeric enzyme is shown in **Figure 3**. These proteins were termed Cel5A and Cel5A-Dockerin for the protein with and without the fungal dockerin domain, respectively. The *T. maritima* GH5 was previously characterized as an endoglucanase active at 80°C and pH ~5, and therefore Carboxy-Methyl Cellulose (CMC) was used as the substrate to characterize activity at that temperature and pH. As seen in **Figure 3.B**, there was no significant difference between the activities of the two proteins, suggesting that the technique was successful in creating an active chimeric protein. The technique for chimeric design was extended to an endoxylanase (XynA) from *T. maritima*, which was identified as similar to dockerin-tagged proteins in *P. finnis.* As shown in **Figure 3.C**, there was no significant difference between the activities on xylan of XynA and XynA-Dockerin proteins.

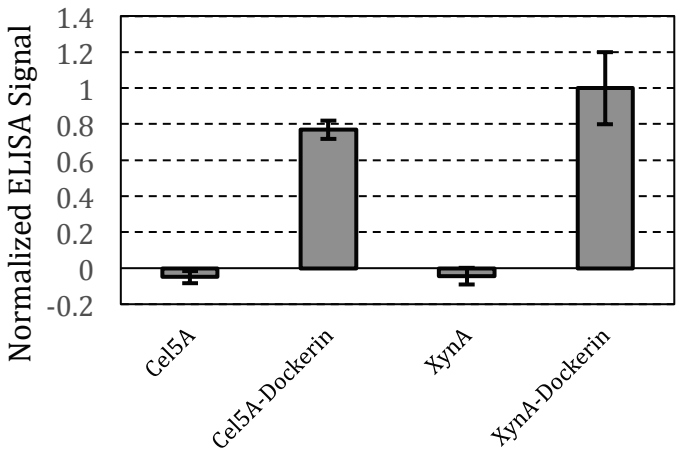



**Figure 4.** *Chimeric enzymes bind to native fungal cellulosomes.* Cel5A, Cel5A-Dockerin, XynA, and XynA-Dockerin were tested for interaction with cellulosome isolated from *P. finnis*. Only proteins with fungal dockerin domains (Cel5A-Dockerin and XynA-Dockerin) showed appreciable binding over background. Concentrations used were 3 μM for each protein, or 3 times the measured $K_D$ previously reported, indicative of maximal binding signal for cellulosome-binding proteins. Values displayed are the average of 3 replicates ± standard deviation as shown in error bars.

Confirming the activity of the catalytic domain is critical to demonstrate effectiveness of the chimeric enzyme, however to be utilized in synthetic cellulosomes we must confirm activity of the grafted dockerin domain. We utilized an ELISA assay against purified fungal cellulosomes to test whether the grafted dockerin domain could interact with native fungal cellulosome. As shown in **Figure 4**, the Cel5A-Dockerin and XynA-Dockerin both showed interaction with native cellulosome from *P. finnis,* whereas Cel5A and XynA showed negligible at concentrations 3 times higher than the previously determined $K_D$. These results confirm that the grafted dockerin domains retain binding activity, and are properly constructed for inclusion in synthetic fungal cellulosomes.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

Matt Perisin (ARL-SEDD) and Chris Sund (ARL-SEDD) visited UCSB in 2016 and 2017 for research collaboration and planning purposes.

PhD student Jennifer Brown visited Matt Perisin (ARL-SEDD) at ARL in 2018 for 2 weeks of research collaboration to develop tools for RNA-Sequencing of anaerobes and Matt Perisin visited Prof. O'Malley's laboratory for 2 weeks in 2016 to learn how to cultivate anaerobic fungi.

Matt Perisin (ARL-SEDD) attended an ARO-funded Microbial Consortia and Biofilm Engineering workshop held at UCSB in March 2017 led by Prof. O'Malley.

Prof. O'Malley has discussed collaborative research with several companies interested in biomass-degrading enzymes, including BP, DuPont, DSM, and BASF.

## 6. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

K. V. Solomon, J. K. Henske, S. P. Gilmore, A. Lipzen, I. Grigoriev, D. A. Thompson and M. A. O'Malley, Catabolic repression in early-diverging anaerobic fungi is partially mediated by natural antisense transcripts, *Fungal Genetics & Biology*, December 2018. 10.1016/j.fgb.2018.09.004.

J. K. Henske, S. P. Gilmore, C. H. Haitjema, K. V. Solomon and M. A. O'Malley, Biomass-degrading enzymes are catabolite repressed in anaerobic gut fungi, *AIChE Journal*, August 2018. 10.1002/aic.16395.

J. K. Henske, S. D. Springer, M. A. O'Malley and A. Butler. Substrate-based differential expression analysis reveals control of biomass degrading enzymes in *Pycnoporus cinnabarinus*. *Biochemical Engineering Journal*, December 2017. 10.1016/j.bej.2017.11.015.

J. K. Henske, S. P. Gilmore, D. Knop, F. J. Cunningham, J. A. Sexton, C. R. Smallwood, V. Shutthanandan, J. E. Evans, M. K. Theodorou and M. A. O'Malley. Transcriptomic characterization of *Caecomyces churrovis*: a novel, non-rhizoid-forming lignocellulolytic anaerobic fungus. *Biotechnology for Biofuels*, December 2017. 10.1186/s13068-017-0997-4.

J. K. Henske, S. E. Wilken, K. V. Solomon, C. R. Smallwood, V. Shutthanandan, J. E. Evans, M. K. Theodorou and M. A. O'Malley. Metabolic characterization of anaerobic fungi provides a path forward for bioprocessing of crude lignocellulose. *Biotechnology and Bioengineering*, December 2017. 10.1002/bit.26515.

J. E. Edwards, R. J. Forster, T. M. Callaghan, V. Dollhofer, S. S. Dagar, Y. Cheng, J. Chang, S. Kittelmann, K. Fliegerova, A. K. Puniya, J. K. Henske, S. P. Gilmore, M. A. O'Malley, G. W. Griffith and H. Smidt. PCR and Omics Based Techniques to Study the Diversity, Ecology and Biology of Anaerobic Fungi: Insights, Challenges and Opportunities. *Frontiers in Microbiology,* September 2017. 10.3389/fmicb.2017.01657.

S. Seppäläa, S. E. Wilken, D. Knopa, K. V. Solomo and M. A. O'Malley. The importance of sourcing enzymes from non-conventional fungi for metabolic engineering and biomass breakdown. *Metabolic Engineering*, September 2017. Genomic analysis of methanogenic archaea reveals a shift towards energy conservation.

S. P. Gilmore, J. K. Henske, J. A. Sexton, K. V. Solomon, S. Seppälä, J. I. Yoo, L. M. Huyett, A. Pressman, J. Z. Cogan, V. Kivenson, X. Peng, Y. Tan, D. L. Valentine and M. A. O'Malley. Genomic analysis of methanogenic archaea reveals a shift towards energy conservation. *BMC Genomics*, August 2017. 10.1186/s12864-017-4036-4.

C. H. Haitjema, S. P. Gilmore, J. K. Henske, K. V. Solomon, R. deGroot, A. Kuo, S J. Mondo, A. A. Salamov, K. LaButti, Z. Zhao, J. Chiniquy, K. Barry, H.M. Brewer, S. O. Purvine, A. T. Wright, M. Hainaut, B. Boxma, T. van Alen, J. H. P. Hackstein, B. Henrissat, S. E. Baker, I. V. Grigoriev and M. A. O'Malley. A parts list for fungal cellulosomes revealed by comparative genomics. *Nature Microbiology*, May 2017. 10.1038/nmicrobiol.2017.87.

S. J. Mondo, R. O. Dannebaum, R. Kuo, K. LaButti, S. Haridas, A. Kuo, A. Salamov, S. R. Ahrendt, A. Lipzen, W. Sullivan, W. Andreopolous, A. Clum, E. Lindquist, C. Daum, G. Ramamoorthy, A. Gryganskyi, D. Dulley, J. Magnuson, T. Y. James, M. A. O'Malley, J. E. Stajich, J. W. Spatafora, A. Visel and I. V. Grigoriev. Widespread adenine N6-methylation of active genes in fungi. *Nature Genetics*, May 2017. 10.1038/ng.3859.

S. Seppala, K. V. Solomon, S. P. Gilmore, J. K. Henske and M. A. O'Malley. Mapping the membrane proteome of anaerobic fungi identifies a wealth of carbohydrate binding proteins and transporters. *Microbial Cell Factories*, December 2016. 10.1186/s12934-016-0611-7.

X. Peng, S. P. Gilmore and M. A. O'Malley. Microbial communities for bioprocessing: lessons learned from nature. *Current Opinion in Chemical Engineering*, November 2016. 10.1016/j.coche.2016.09.003.

G.J. Li, et al. (+134 additional authors including Solomon, Henske, J.K., Haitjema, C.H., Gilmore, S.P., Theodorou, M.K. and O'Malley, M.A). Fungal diversity notes 253-366: taxonomic and phylogenetic contributions to fungal taxa. *Fungal Diversity*, May 2016. 10.1007/s13225-016-0366-9.

K.V. Solomon, C. H. Haitjema, J. K. Henske, S. P. Gilmore, D. Borges-Rivera, A. Lipzen, H. M. Brewer, S. O. Purvien, A. T. Wright, M. K. Theodorou, I. V. Grigoriev, A. Regev, D. A. Thompson and M. A. O'Malley. Early-branching gut fungi possess a large comprehensive array of biomass-degrading enzymes. *Science*, March 2016. 10.1126/science.aad1431.

S. P. Gilmore, J. K. Henske and M. A. O'Malley. Driving biomass breakdown through engineered cellulosomes. *Bioengineered*, June 2015. 10.1080/21655979.2015.1060379.

C. H. Haitjema, K. V. Solomon, J. K. Henske, M. K. Theodorou, and M. A. O'Malley. Anaerobic gut fungi: Advances in isolation, culture, and cellulolytic enzyme discovery for biofuel production. *Biotechnol. Bioeng.,* May 2014. 10.1002/bit.25264.

K. V. Solomon, C. H. Haitjema, D. Thompson and M. A. O'Malley. Extracting data from the muck: deriving biological insight from complex microbial communities and non-model organisms with next generation sequencing. *Curr. Opin. Biotechnol*., February 2014. 10.1016/j.copbio.2014.01.007.

**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Macromolecular Design from Sequence-Activity Analysis**

**Project Leader:** **Irene A. Chen (UCSB)**

**Collaborators:** **Ulrich Muller (UCSD); Jed Eberly (ERDC); and Margaret Hurley (ARL-SEDD)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

The primary objective of this project was to improve and systematize the design and discovery of functional RNAs, and to study their integration into simple synthetic cells. Our main results were:

*Development of methods to optimize identification and characterization of highly active RNA sequences from high-throughput sequencing analysis of* in vitro *evolution experiments*. Functional RNA, such as aptamers and ribozymes, could be a basis for a minimal synthetic cell. To aid discovery of functional RNA, we first developed computational methods for identifying all possible functional families from *in vitro* evolution of a library of RNA covering sequence space [1], thus mapping the complete 'fitness landscape', including evolutionary distances among functional sequences. A new feature of this analysis compared to traditional analysis is that it shows whether global optimization of function is possible through *in vitro* selection. Second, we developed a method to analyze a diverse pool of ribozymes to estimate their rate constants from fitness data. In this method, the performance of a sequence during two branches of selection (high and low stringency) is compared and related to a model for first-order kinetics. This method led to identification of >10-fold improved ribozymes with minimal experimental screening compared to standard methods [2] (collaboration with Ulrich Muller at UCSD), with good correlation between predicted and measured ribozyme activity. We further developed a massively parallel assay for directly measuring ribozyme rate constants by high-throughput sequencing (kinetic sequencing, or *k*-Seq; Pressman et al., submitted). In this assay, a diverse pool is to subject to the reaction, samples samples in a concentration and/or time series are collected, and products are separated and sequenced to obtain a quantitative curve of product formation over the reaction series. We obtained approximately $10^4$-$10^5$ measurements and validated these measurements by comparison of a number of isolated sequences to a standard biochemical assay. Third, we characterized protein subsequences known to bind aptamers, with advice from Dr. Margaret Hurley (ARL-SEDD), to aid prediction of aptamer-binding sites on proteins [3]. We also reviewed these methods and the potential contributions of high-throughput sequencing to RNA evolution [4].

*Characterization of the biophysical effect on RNA from encapsulation inside vesicles*. Understanding how encapsulation inside a simple membrane affects RNA folding and activity is essential to building a minimal synthetic cell based on RNA. We studied the encapsulation of an RNA aptamer for the fluorescent small molecule malachite green, inside large unilamellar vesicles (~60 nm diameter) with a variety of vesicle membrane types [5]. We found that aptamer activity was enhanced when encapsulated, which corresponded with an increase in the thermal stability of the binding site. We suggest that the mostly likely mechanism for this observation is a confinement effect, as the confined region disfavors extended states and thus gives a relative stabilization to the compact, folded state. Comparison to a theoretical model of polymer confinement gave a good quantitative match.

*Exploration of evolvability of riboswitches*. Control of gene expression is an important aspect of synthetic biology. Riboswitches are functional RNA sequences upstream of genes that control gene expression, through the conformational change of an RNA aptamer when bound to a target metabolite. Riboswitches may turn expression on or off depending on the detailed mechanism. We sought to determine the extent to which the strength of the riboswitch could be tuned, and whether its polarity could be altered (i.e., evolve an 'off' switch into an 'on' switch). Such versatility would be useful for controlling a genetic program involving multiple transcripts. Our preliminary data indicates that variants of the preQ1 riboswitch can be selected with reversed polarity (G. Campbell, unpublished data), indicating that the switching properties of riboswitches may be evolved within a useful regime.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

The overall goal of this synthetic biology project was to improve and systematize the design and discovery of functional RNAs, and to study the integration of functional RNAs into synthetic cells. RNAs are highly interesting components for synthetic biology, as they possess a broad and expanding palette of known functions. One may envision a synthetic cell in which all metabolism is carried out by a minimal number of RNA components [1]. Functional RNAs, including aptamers (sequences that bind specific targets) and ribozymes (sequences that catalyze chemical reactions), are usually discovered through *in vitro* evolution. In this process, random RNA sequences are subjected to iterative rounds of selection and amplification, such that functional sequences come to dominate the initially diverse population.

In our first objective, we were developing computational and experimental methods to optimize the identification of highly active RNA sequences from *in vitro* evolution experiments and to extract biochemical and biophysical information about these sequences from the sequencing data. High-throughput sequencing has the potential to yield many more measurements than traditional techniques. In a collaborative study of triphosphorylation ribozymes (Ulrich Muller, UCSD), our results showed that we were indeed able to identify substantially improved ribozymes and to predict their rate constants [2]. This chemical activity is of special interest for synthetic cells based on RNA, since chemical activation (e.g., by triphosphate) is necessary for RNA replication, but the computational methods are potentially applicable to a variety of RNA selections. In this past year, we further developed an experimental approach to directly measure the kinetic activity of ribozymes in a diverse pool obtained through *in vitro* evolution (kinetic sequencing, or *k*-Seq). We also sought to understand the biophysical characteristics of proteins that bind aptamers, through a meta-analysis of the known structures of RNA aptamers with protein targets (with advice from Dr. Margaret Hurley, ARL) [3]. Since aptamers typically bind relatively small regions on target proteins, we characterized those regions, with the goal of predicting likely sites of interaction between proteins and RNA aptamers (i.e., prior to *in vitro* evolution). The projects in the first objective sought to thus improve the discovery and characterization of functional RNAs.

Our second objective was to integrate functional RNAs into both artificial cells and *E. coli*. While modern cells rely on transcription and translation to transform genetic information into phenotypes, artificial cells based on functional RNA have the potential to dispense with these complicated machineries. However, the biophysical environment inside an artificial cell is likely to be quite different from the environment of most experiments (bulk solution). For example, macromolecular crowding, confinement from encapsulation, and interactions with the encapsulating surface may alter the activity of functional RNAs (**Figure 1.a**). Therefore, we studied how encapsulation inside vesicles affects binding of RNA aptamers to small molecules, as well as folding and conformational changes, focusing on the biophysical effect of confinement.

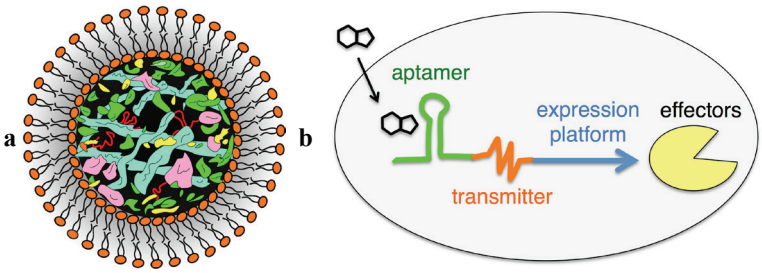



**Figure 1.** Functional RNAs and cells. (**a**) Encapsulated RNAs experience a crowded and confined environment compared to bulk solution. (**b**) In microbes, riboswitches turn gene expression on or off in response to a cell-permeable small molecule. Binding of the aptamer triggers a conformational switch that affects exposure of a terminator/ antiterminator stem-loop or a ribosome-binding site.

While artificial cells hold much promise as self-contained, stripped-down biological systems, introduction of synthetic biological elements into *E. coli* (or other microbes) is also of high interest, given the wealth of biological machinery that can be of potential use. RNAs have excellent potential for designability, as their secondary structures are relatively predictable and they use a smaller basis set of residues compared to proteins (4 vs. 20). Along these lines, we are carrying out an *in vitro* selection for riboswitches, non-coding RNA sequences found upstream of mRNAs, which control gene expression in response to small molecules. Binding between a riboswitch aptamer and its target alters gene expression through conformational changes to an intervening *transmitter* domain (**Figure 1.b**). Our approach is to apply *in vitro* selection to the transmitter of the small preQ$_1$ riboswitch to map its sequence-activity relationship, with the goal of learning to design riboswitch transmitters with altered or optimized properties.

Together, these two objectives will improve our ability to discover, characterize, and design functional RNA for synthetic biology.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

In our prior year of ICB support, we developed a method to infer chemical activities of ribozymes from evolutionary fitness data from *in vitro* evolution experiments. However, such inference is indirect, as fitness can be influenced by factors unrelated to chemical activity. This year, we developed a new experimental strategy to directly measure chemical activities in a massively parallel kinetic assay, termed kinetic sequencing (*k*-Seq; **Figure 2**). In this test case, we studied ribozymes selected to self-aminoacylate using an activated amino acid (biotinylated tyrosine oxazolone, or BYO). In a traditional gel-based assay to measure the rate constant of reaction, a single RNA sequence would be mixed with BYO and product formation monitored by gel shift of the RNA in the presence of streptavidin. Instead, in *k*-Seq, we reacted a heterogeneous pool obtained from *in vitro* selection, which contained many different RNA sequences, with BYO and isolated the aminoacylated RNAs using streptavidin beads. These RNAs were analyzed by high-throughput sequencing (HTS), yielding the relative abundance of each sequence in the products, which were converted to absolute concentrations by comparison to a standard of known concentration in the product pool. Rate constants and maximum amplitude of reaction were obtained from the dependence of product formation on the concentration of BYO. In principle, an analogous approach could be used to analyze multiple time points of reaction or for a full suite of reactions to determine Michaelis-Menten kinetics. The validity of the *k*-Seq approach was determined by comparison of kinetic parameters determined by *k*-Seq with those determined by a traditional assay for a subset of sequences.

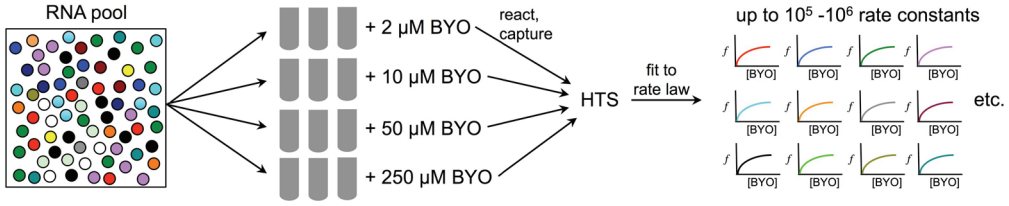



**Figure 2**. In *k*-Seq, an RNA pool enriched for active ribozymes is reacted at multiple substrate (BYO) concentrations, in triplicate. Reacted RNA is captured through affinity tagging and then reverse-transcribed and sequenced. Activity curves are constructed for sequences detected in the enriched pool.

In the analysis of aptamer-binding proteins, our previous work had pointed toward the importance of positively charged amino acids. To better characterize the significance and nature of these interactions, we developed a new metric for propensity of a given amino acid to occur at the protein-aptamer interface. This propensity metric compares the interfacial probability with the expected surface frequency, which improves upon prior metrics because it is insensitive to biases inherent to structure determination. In addition, we analyzed the nature of the aptamer-protein interactions by classifying the chemical interactions (hydrophobic, hydrogen bonding, pi-pi interactions, etc.) using the ENTANGLE software [6]. Finally, advised by Dr. Margaret Hurley (ARL-SEDD), we carried out molecular dynamics simulations to understand the importance of electrostatic and van der Waals contributions to the energy of the complex.

To understand how the environment of a simple artificial cell would affect the activity of functional RNA, we encapsulated the RNA inside large unilamellar vesicles and measured its activity and folding. An aptamer was used for the initial studies; binding of this aptamer to the small molecule malachite green can be monitored by an increase in fluorescence upon binding. In addition, the local and global structure can be probed by fluorescence and circular dichroism melting studies, as well as by chemical probing methods. An interesting advantage of studying the excluded volume effect in vesicles compared to crowding agents is that chemical effects (e.g., from surfactant micelles) can be controlled for by using a control of exposure to vesicles without encapsulation. Studies with different vesicle types and different crowding agents were used to investigate the mechanism of the effects observed.

To probe riboswitch evolvability, we studied the minimal $preQ_1$ riboswitch, which turns off transcription through formation of a terminator signal when the aptamer is bound to the small molecule metabolite $preQ_1$. Riboswitches can be used to tune gene expression in response to the metabolite signal. We randomized the switching region of the $preQ_1$ riboswitch and selected for sequences that have altered switching, focusing on either enhancement of the fold-

change of transcription, or reverse polarity (turning transcription on in response to preQ$_1$). Selection was performed by transcription in the presence and absence of preQ$_1$ and separation of the full-length and truncated transcripts by gel electrophoresis. Individual bands corresponding to full-length vs. truncated transcripts were excised and sequenced, and the relative abundance of each sequence was scored for the effect on gene expression. Selected variants were then tested in isolation to validate the effect of the mutations on riboswitch function.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

*Kinetic sequencing*. Using the developed method *k*-Seq, described above, we analyzed the ribozymes resulting from a selection for aminoacylation activity. Using *k*-Seq, ~$10^5$ unique sequences, out of ~$4^{21}$ (4 x $10^{12}$) possibilities, were found to have activity >10-fold above the non-catalytic background rate. To determine how well *k*-Seq results corresponded to results of the standard assay, we chose ten sequences that are close to the consensus sequences of the high- or medium-activity families (with all five motifs and submotifs represented) and measured aminoacylation activity by the gel-shift assay [7]. Rate constants determined from *k*-Seq matched well with gel-shift measurements (**Figure 3**). For most sequences with sequencing data count > 10, and nearly all sequences with count > 100, the noise of *k*-Seq measurements appeared to be within a factor of 2. These results demonstrated the viability of *k*-Seq methodology for massively parallel kinetic measurements.

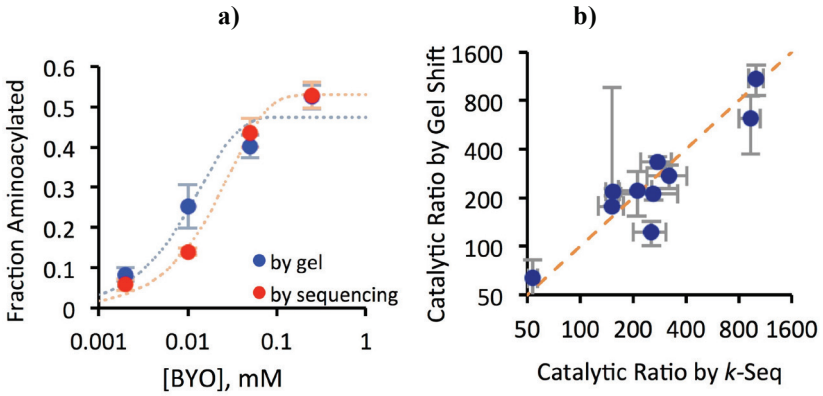



**Figure 3**. Validation of *k*-Seq method. **(a)** Aminoacylation at various substrate (BYO) concentrations for a ribozyme, observed by both gel shift and *k*-Seq. Error bars correspond to standard deviation among triplicates. **(b)** Correlation between catalytic ratio of ten ribozymes, measured by gel shift assay and *k*-Seq. Error bars correspond to standard deviation among triplicates ($R^2$ = 0.87). Dotted orange line: line of unity.

*Aptamer-protein interactions*. The analysis of chemical interactions in aptamer-protein complexes revealed that arginine was by far the most dominant amino acid. While arginine and lysine exhibited similar propensity for the aptamer-protein interface in the electrostatic mode of interaction, arginine was the highest contributor in all other modes (**Figure 4**). These results, and others, indicate that arginine contributes strongly to the tendency of a peptide to interact with an RNA aptamer [3].

*Encapsulation of functional RNA*. We previously reported that the affinity of the malachite green aptamer is significantly increased when encapsulated compared to free solution containing vesicles. This year, we performed several experiments to understand the mechanism of this effect. We ruled out changes in substrate or $Mg^{2+}$ concentration and chemical interactions with the membrane. In addition, data on crowding agents as well as a theoretical model support confinement analogous to an excluded volume effect. These results suggest that RNA activity and folding are enhanced upon encapsulation though a generalizable effect [5].

*Riboswitch evolvability*. Our selection on the preQ1 riboswitch for sequences with different activity scored tens of thousands of variants. Several variants were chosen for assay in isolation and displayed either increased 'off' activity or even 'on' activity (**Figure 5**). These results show that riboswitches can be fined tuned for desired gene expression characteristics.

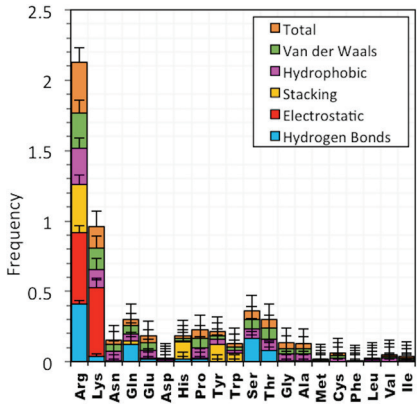



**Figure 4**. Relative frequency of each amino acid in each kind of interaction (hydrogen bonds, electrostatic, stacking, hydrophobic, or Van der Waals and for all together) averaged over protein-aptamer complexes.

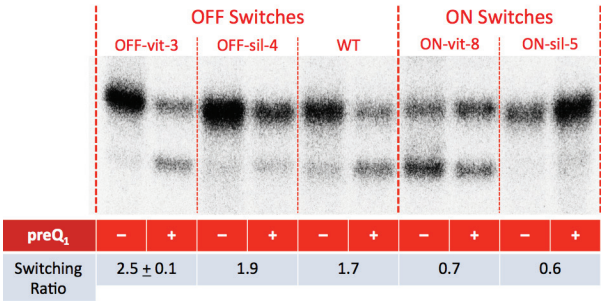



**Figure 5**. Transcription of riboswitch variants obtained from *in vitro* selection in the presence or absence of ligand preQ1. The switching ratio (ratio between amount of full-length transcript in the absence and presence of ligand) is shown. Two 'off' switches with altered tuning are shown in addition to wild-type, and two 'on' switches are shown.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

We were advised by Dr. Margaret Hurley (ARL-SEDD), who is expert in molecular dynamics (MD) simulations and analysis of large data sets. This collaboration began during the ICB-Army Systems and Synthetic Biology Research Collaboration Planning Meeting held at Caltech in April 2015. Dr. Hurley's advice early on helped Dr. Celia Blanco in my group learn basic MD techniques to estimate energetic contributions in protein-aptamer structures.

The computational tools we developed can be used for analysis of sequence data from *in vitro* evolution experiments from Dr. Jed Eberly (ERDC).

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[8] To conserve space, please use a numerical citation-sequence system. In sections, place citations within text on the line using numbers enclosed in square brackets [12], [3, 4], [4–9].
[9] *Do not use footnotes, endnotes or symbolic reference linking,* as they will not survive compilation.

## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

C. Blanco, E. Janzen, A. Pressman, R. Saha and I. A. Chen. Molecular fitness landscapes from high-coverage sequence profiling. *Annual Reviews of Biophysics*, January 2019. 10.1146/annurev-biophys-052118-115333.

R. Saha, S. Verbanic and I. A. Chen. Lipid vesicles chaperone an encapsulated RNA aptamer. *Nature Communications*, June 2018. 10.1038/s41467-018-04783-8.

A. Pressman, J. E. Moretti, G. W. Campbell, U. F. Muller and I.A. Chen. Analysis of in vitro evolution dynamics estimates ribozyme rates and the underlying distribution of activity among random sequences. *Nucleic Acids Research*, August 2017. 10.1093/nar/gkx540.

R. Xulvi-Brunet, G.W. Campbell, S. Rajamani, J. I. Jimenez and I. A. Chen. Computational analysis of fitness landscapes and evolutionary networks from in vitro evolution experiments. *Methods*, May 2016. 10.1016/j.ymeth.2016.05.012.

A. Pressman, C. Blanco and I. A. Chen. The RNA world as a model system to study the origin of life. *Current Biology*, October 2015. 10.1016/j.cub.2015.06.016.

R. Saha, A. Pohorille and I. A. Chen. Molecular crowding and early evolution. *Origins of Life and Evolution of Biospheres*, January 2015. 10.1007/s11084-014-9392-3.

S. S. Athavale, B. Spicer and I. A Chen. Experimental fitness landscapes to understand the molecular evolution of RNA-based life. *Current Opinion in Chemical Biology*, September 2014. 10.1016/j.cbpa.2014.09.008.

**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Single- and Multi-Cellular Biomolecular Detection of Environmental Events**

**Project Leader:** **Richard M. Murray (Caltech)**

**Collaborators:** **John Deuber (UC Berkeley); Stephen L. Mayo (Caltech); Paul Rothemund (Caltech) and Chris Warner (ERDC)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

We designed a two-input temporal logic gate that can sense and record the order of the inputs, the timing between inputs, and the duration of input pulses [1]. Our temporal logic gate design relies on unidirectional DNA recombination mediated by bacteriophage integrases to detect and encode sequences of input events. For an *E. coli* strain engineered to contain our temporal logic gate, we compared predictions of Markov model simulations with laboratory measurements of final population distributions for both step and pulse inputs. Although single cells were engineered to have digital outputs, stochastic noise created heterogeneous single-cell responses that translated into analog population responses. Furthermore, when single-cell genetic states were aggregated into population-level distributions, these distributions contained unique information not encoded in individual cells. Thus, final differentiated sub-populations could be used to deduce order, timing, and duration of transient chemical events.

We also constructed a proof of concept synthetic circuit that can be used to create a similar chronological record of events in the DNA of a living *E. coli* [2]. In our system, phage-based serine integrases were employed to sequentially integrate pieces of DNA corresponding to which stimulus is being detected. We showed that placing attB and attP sites close together on a piece of DNA prevents intramolecular reactions and enables repeated integration events to expand a genetic locus proportionally to integrase induction and abundance of plasmid DNA. We also showed that dCas9 binding can prevent integrase from reacting with an attachment site, and in so doing we can control which piece of DNA is integrated by the induction of different guide RNAs. These results represent significant steps towards an event logger that is capable of recording the ordering and magnitude of any number of molecular events. Such a system may be useful in studying complex biological phenomena such as biofilm formation, quorum sensing, or signaling in the gut.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

The overall goal of this project was to develop a set of biomolecular circuits capable of monitoring the local environment around a cell, detecting the presence of specific signals present in that environment, and then logging the temporal patterns of those signals. Our objective for the final reporting was to demonstrate a working "event logger" circuit that makes use of integrase-based insertion of sequences of DNA to keep track of environmental events over a long period of time. We have carried out preliminary demonstrations showing the ability of this circuit to create DNA "logs" based on the temporal pattern of signals present in the environment and read those logs using DNA sequencing.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

We explored two methods for doing this: insertion of DNA sequencing from “ink plasmids” into the genomic DNA of an organism, which served as a recording tape, and transfer of DNA from one organism to another through conjugation. In both cases, the source DNA for different events was provided by plasmids whose integrase attachment sites can be blocked by dCas9 combined with guide RNAs that are expressed as a function of the particular strain or presence of different environmental signals. This technique allows different sequences of DNA to be inserted in the chromosome of the host microbe in a manner that creates a "tape" of events that have been detected.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1. Continuous Event Recording in Living Cells*

Biological records of events can be found in tree rings, sedimentary layers, arctic ice cores, and many other places in nature. In these records, past events are encoded into a biological context and later decoded by the researcher. Climate information, for example, can be extrapolated from tree ring isotope content and growth conditions can be inferred from ring thickness. A tree ring is fairly durable and has good temporal resolution, but since we cannot control what information is recorded or the physical scale at which recording takes place, tree rings are not considered as useful sentinels for specific environmental or clinically relevant events.

In this work we are developing a genetic memory system which can be used to record the history of chemical events in the genome of living bacteria. The system is designed such that transcription from a specific promoter results in a continuous insertion of a known set of DNA sequences, in chronological order. The prevalence of synthetic promoters that can detect all kinds of stimuli [1] allows the system to be re-programmed to detect different events; tuning of other circuit components can affect the time resolution of recording and other parameters.

The system consists of three components (**Figure 1**): the recording circuit, the memory locus, and the ink plasmids. Ink plasmids (**A**) provide raw material for recording. Red triangles are Bxb1 attB sites, blue triangles are Bxb1 attP sites. Orange and Green plasmids represent different "barcodes" that are used to record different "events". The recording circuit (**B**) controls ink plasmid integration. Bxb1 integrase is induced by salicylate and catalyzes ink plasmid integration into the memory locus (**C**). To distinguish between green and orange plasmids, dcas9 can repress integrase activity through the use of g1 and g2, which are driven by promoters that are triggered by events of interest. Dcas9 can bind next to and occlude attP sites on the green or orange plasmid, depending on which guide RNA (g1 or g2) is present. In this case, pBAD, activated by arabinose, and pCin, activated by 3-oxo-C6-HL. pTet activated by anhydrotetracycline (ATC) regulates the production of dcas9, which modulates the strength of repression (**C**) The memory locus consists of an integrase attachment site on the genome, flanked by unique primers that are used to amplify the record for sequencing (not shown). Since both ink plasmids contain the same attP site sequence, either plasmid can be integrated into the attB site on the genome. After integration, the old attB site is converted into attL and attR, and a new attB site is brought in with the plasmid. Boxed numbers are counting the number of integrations, starting with zero, to one, continuing onwards until the pool of ink plasmids is depleted and N integrations have occurred. Since an entire ink plasmid is integrated, it creates a similar record on either side of the attB site on the genome, and only one side needs to be sequenced to read the record.

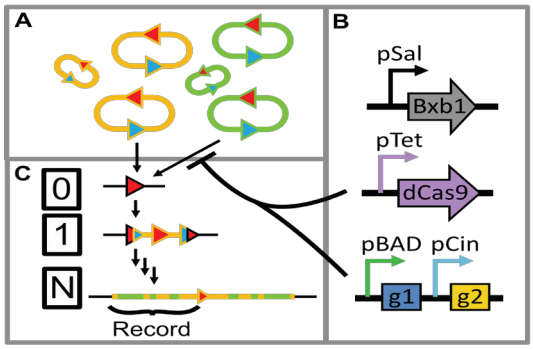



**Figure 1.** Schematic of event recording system. The recording circuit consists of a transcriptional network that controls the production of integrase, dCas9, and guide RNAs. The memory locus is the location in the genome of *E coli* where recordings are stored. Finally, the ink plasmids provide DNA raw material for insertion into the memory locus by the recording circuit.

In the past year, significant progress has been made in developing a recording circuit with minimal leaky expression, ink plasmids that provide effective DNA raw material, and a memory locus that facilitates readout of the recorded events. We have also made good progress on assembling these three components to produce a very preliminary prototype of the full recording system, capable of detecting two orthogonal chemical inducers. To select which of two unique ink plasmids to integrate, we have chosen to employ catalytically dead Cas9 (dcas9) [2], [3], and to this end it was useful to quantify the most effective guide RNA sequence to employ the most integrase repression while also providing the most changeable nucleotides (**Figure 2**). A guide RNA that is offset 12 nucleotides from the integrase attachment site, therefore overlapping the site by 8 nucleotides, was found to effectively repress integrase activity as well as a fully overlapping guide, while also having 12 changeable bases. This finding paves the way for producing a recorder system with many orthogonal ink plasmids that can all be effectively utilized.

### *4.2. Engineering an Addressable Packet-Based Intercellular Communication System using Plasmid Conjugation*

As the field of synthetic biology moves from engineering individual cells to engineering populations of cells which work together, it becomes increasingly more important to develop frameworks for intercellular communication which can accommodate the transfer of information-dense messages. This issue is particularly relevant to work in molecular event detection and recording—many of the promising applications for event recording require not only that humans should be able to read out a series of recorded events, but that cells themselves should be able to interpret and respond to these recordings. If cells are recording events via details such as duration, time, amplitude, and type, the amount and the dimensionality of the information quickly scales beyond the capacities of existing intercellular communication systems. As such, it is necessary to develop frameworks that allow high-bandwidth information transfer between cells in order to capitalize on the potential of molecular event-recording technology.

In this regard we are currently developing an intercellular communication system based on conjugation, a type of horizontal gene transfer in which one cell sends a copy of a plasmid into a neighboring recipient cell. Unlike conventional quorum sensing-based communication systems, in which the transferred message is encoded in the identity and concentration of an AHL molecule, here the message is encoded within the DNA sequence of a plasmid. The encoding scheme is flexible and user-defined—for example, different messages could correspond to plasmids with different transcription factors which activate different responses in recipient cells. Moreover, because the information is encoded within DNA, integrases and other in vivo DNA-editing techniques can be used by the cells to dynamically modify the content and interpretation of the message.

To expand the capabilities enabled by plasmid-based signaling, we are developing a modular framework for addressable packet-based intercellular communication, in which an 'address' region contained on the plasmid determines which strains within a population are able to receive the message. In this system, each strain in a population expresses Cas9 and a unique identifying gRNA. The address region on the message plasmid consists of gRNA binding sites which prevent strains expressing the corresponding gRNAs from receiving the plasmid—upon receipt, the message plasmid will be cleaved by Cas9 and degraded. The gRNA binding sites in the address region are flanked by integrase attachment sites which allow cells to dynamically insert, delete, and swap binding sites from the plasmid. In this way the cells can alter the flow of information transfer between the strains in the population.

As a proof-of-concept demonstration of our addressable communication system, we are constructing a linear signal transduction path within a three-strain coculture (**Figure 2.a**). In this system, three strains exist within a bulk culture, but message plasmids can only be transferred from initial sender to final receiver via an intermediate strain. The message plasmid begins in Strain A and can be transferred to Strain B, but cannot be transferred to Strain C because it contains the binding site associated with Strain C's gRNA. Once the message plasmid enters a cell in Strain B, the cell uses integrase-mediated cassette exchange to swap the binding site on the message plasmid with the site associated with the gRNA for Strain A. This allows the message plasmid to be sent to Strain C, while simultaneously preventing it from 'backtracking' to Strain A. A gRNA in strain B is not required because Strain C lacks the conjugation machinery (FMob) required to send plasmids.

The linear-path architecture is easily scalable to populations with larger numbers of strains, requiring n-2 orthogonal integrases and n orthogonal gRNAs for an n-node linear path. We have designed a 4- strain path with two integrases (TP901, Bxb1) and four gRNAs (**Figure 2.b**). For conciseness, intermediate plasmid states and degradation are not shown. All n-strain linear paths with $n \geq 4$ take this same architecture, in which the address region on the message plasmid consists of n-2 binding sites that are swapped by each sequential intermediate strain in the path.

Our system has the advantage of being built upon well-established properties of existing genetic constructs, such as the orthogonality of gRNA binding and the efficiency of integrase-mediated cassette exchange. However, there are still some additional properties that must be demonstrated individually. In particular: (1) Is the rate of conjugation fast enough for multiple rounds of transfer to occur within a population in a reasonable span of time? (2) Does Cas9-mediated cleavage of a plasmid cause plasmid degradation in vivo? (3) Is Cas9-mediated plasmid cleavage efficient enough to prevent receipt of transferred plasmids?

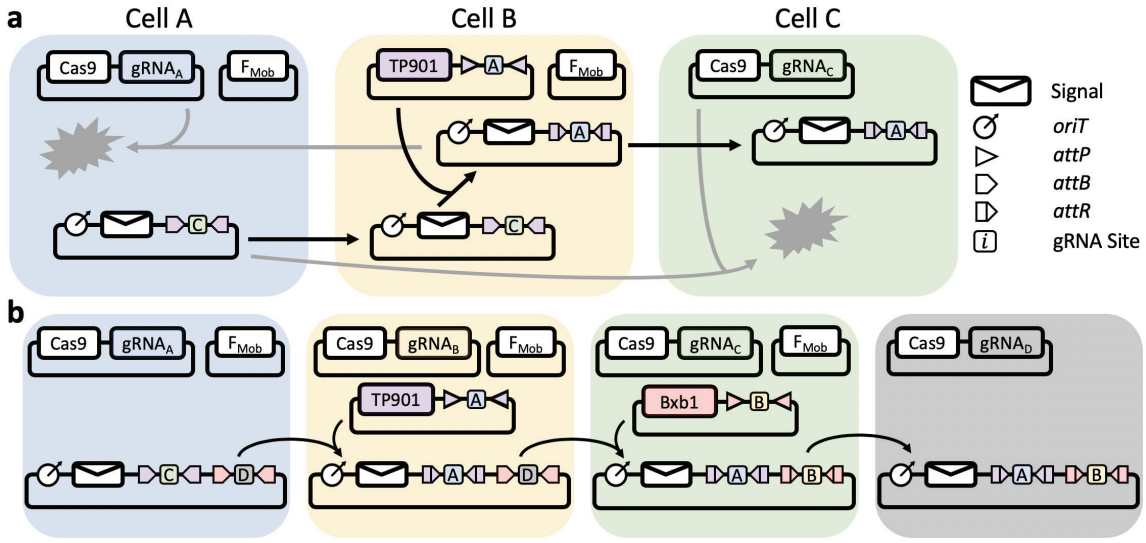



**Figure 2.** A linear-path package routing system. (**a**) 3 strain pathway. (**b**) 4 strain pathway.

We have experimentally validated the first two of these properties (**Figure 3**). It only remains to demonstrate Cas9-mediated blocking of plasmid receipt, and to combine the individual components together into the full circuit and test its functionality.

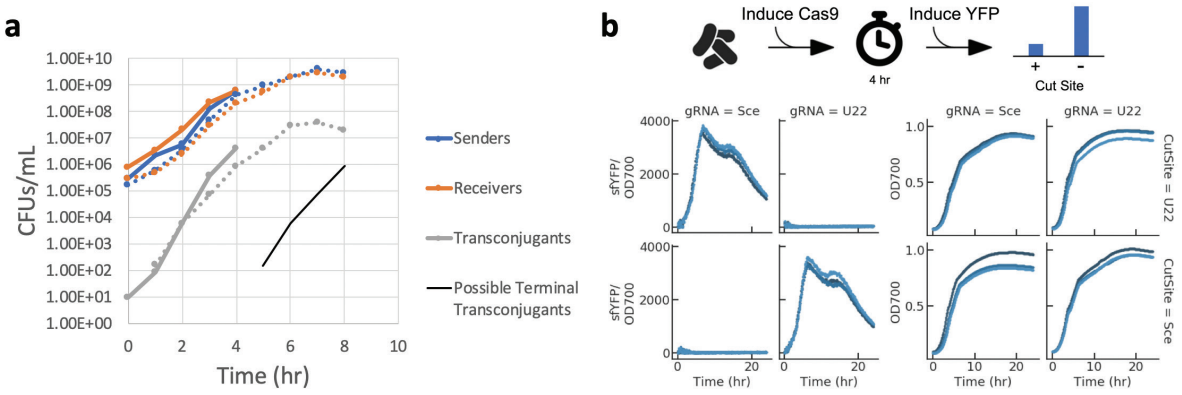



**Figure 3.** Experimental demonstrations of required properties for the conjugation circuit. (**a**) A timecourse of cell density, measured in colony forming units (CFUs), for senders, receivers, and transconjugants (receivers that have received the message plasmid). Strains are distinguished when counting CFUs by unique antibiotic resistance profiles. By 4 hours, the transconjugant population reaches the initial density of the senders and receivers at the beginning of the experiment, implying that a potential terminal transconjugant population (a third strain which can only receive the message plasmid from the transconjugants— Cell C in **Figure 1.a**) would have 3-4 hours to grow before the full population reaches stationary phase around 7-8 hours into the experiment. The black line is a representation depicting what the timecourse of this terminal transconjugant population might look like. Solid and dashed colored lines represent two replicates conducted on different days. (**b**) A demonstration of Cas9-mediated plasmid degradation. Cells expressing Cas9 and one of two gRNAs ('Sce' or 'U22') and containing a plasmid with an inducible YFP construct and one of the two gRNA binding sites are grown for 4 hours without selection for the YFP plasmid. The cells are then induced to activate the YFP—when the gRNA matches the binding site on the YFP plasmid, no YFP is induced because the plasmid has been degraded within the 4 hours. Otherwise, the Cas9 does not cleave the plasmid so YFP induces normally.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

We have had substantial interaction with researchers at the Army Research Laboratory (Jim Sumner, Chris Warner), Edgewood Chemical and Biological Center (Peter Emanuel, John McManus), and the Environmental Laboratory at the Army Engineer Research and Development Center (ERDC). In August 2018 we visited each of these sites for 1 day each and presented the results or our work as well as discussing future collaborations. Our work over the years has led to multiple additional projects, including a 2017-2019 project with ARL-SEDD and three projects starting in 2019 with ARL-SEDD, ECBC, and ERDC.

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

V. Hsiao, Y. Hori, P. W. K. Rothemund and R. M. Murray. A population-based temporal logic gate for timing and recording chemical events. *Molecular Systems Biology*, May 2016. 10.15252/msb.20156663.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Synthetic Development – Engineering of Self-Patterning**

**Project Leader:** **Michael B. Elowitz (Caltech)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

During embryonic development and in response to injury, tissues must establish precise spatial arrangements of specific cell types. A major challenge is to understand the genetic circuits underlying such patterning and to repurpose them to enable controlled tissue regeneration. The new field of synthetic biology provides a new way to tackle these challenges by systematically constructing and analyzing minimal genetic circuits within interacting cells. This project takes a critical step towards engineering self-patterning multicellular systems by bringing a bottom-up, synthetic, and single-cell approach to the central problem of long-range pattern formation.

Long-range tissue patterning is orchestrated by diffusible signaling molecules called morphogens. In order to use morphogens for rational design of tissues, we need to quantitatively understand how morphogens, regulatory proteins, and the design of the circuit architecture control morphogen gradients in space and time. In the past five years, we have made major progresses towards addressing these questions using two ubiquitous families of morphogens: bone morphogenetic proteins (BMPs) and Sonic hedgehog (SHH). Major results include the following:

*Reconstituted dynamic morphogen gradients in mammalian cell culture.* We genetically engineered 'sender' cell lines that secrete BMPs or SHH, and 'receiver' cell lines that read out morphogen concentrations. Co-culture of senders and receivers enables direct visualization and quantitative analysis of gradient formation in space and time [1]. We also constructed mathematical models of gradient formation to make testable predictions.

*Quantitatively characterized the effects of modulators on BMP/SHH gradient in open-loop designs.* Secreted or membrane-bound interactors of BMP and SHH are critical in gradient formation, but how they function remained unclear [2–6]. Using our synthetic system, we quantitatively analyzed their operational capabilities. For example, we demonstrated that a few modulators of BMP are sufficient for enabling shuttling behavior of BMP gradient.

*Constructed self-regulating gradients with minimal synthetic closed-loop circuits that confer robustness.* Relatively simple circuit designs have been proposed to confer patterning robustness. We modeled, designed, and constructed synthetic feedback circuits of various architecture, and discovered that a coupled bifunctional negative feedback design makes the SHH signaling gradient more robust to variations in the ligand production rate [1].

*Discovered novel communication capability enabled by promiscuous morphogen ligand-receptor interaction.* Most morphogen pathways employ multiple ligands and receptors that interact promiscuously with each other. Combining computational modeling and quantitative experimental measurements, we revealed that the promiscuous ligand-receptor interaction creates specificity of cell-cell communication in the BMP pathway [7].

The work expands synthetic biology, which is currently focused primarily on microbial organisms, to multicellular mammalian systems. It provides a basis for a new approach to regenerative therapy based on the engineering of tissues that could self-pattern *in vitro* or, eventually, *in vivo*. This is a critical step for developing an Army capability in regenerative biomedicine to deal with traumatic injury as well as disease on a vast scale, on and off the battlefield. It also has the potential to enable additional Army applications in disease detection, and protein and biomaterials synthesis.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

*Objective 1. Further Characterize the Molecular and Biochemical Mechanisms of the Gradient Modulators.* We have shown that Chordin can lengthen BMP gradients in a manner consistent with shuttling, but we have not yet observed two key patterns predicted by the shuttling model—sharpening (or spatial focusing of ligands) and action-at-a-distance (responses that peak away from the source). By varying the stoichiometry of Chordin and BMP and the configuration of senders and receivers, we will determine whether we can experimentally realize such patterns. We also will compare the effects of Chordin to those of the fly homolog Sog, which has different biochemical properties [8] that may permit different patterns to be realized. Finally, we will study several other BMP modulators in our open-loop system, such as Sizzled, an inhibitor of the protease that cleaves Chordin [6], and Pentagone, proposed to compete with BMP for interaction with proteoglycans on the cell surface [9].

*Objective 2. Design and Construction of Feedback Circuits to Implement Gradient Scaling and travelling waves.* Once the properties of the pathway modulators are characterized in an open-loop manner, we can engineer closed-loop circuits and understand how non-intuitive behaviors arise from these circuits. We will focus on two important patterning mechanisms: gradient scaling and travelling waves.

*Gradient scaling:* We will use our synthetic system to test two circuits that have been proposed to mediate scaling, one in *Xenopus* dorsoventral patterning [4] and the other in the *Drosophila* wing disc [10]. Both circuits are examples of the expansion-repression scaling motif proposed by Barkai and colleagues [9]. In the *Xenopus*-inspired case, the "morphogen" is actually the BMP inhibitor Chordin, whose cleavage by the protease Tolloid is inhibited by Sizzled, a diffusible molecule whose expression is induced by BMP (and hence inhibited by Chordin) [4]. In the *Drosophila*-inspired case, the morphogen is BMP and the expander is the secreted, proteoglycan-binding Pentagone [10]. We will construct and test these different designs in our synthetic patterning system.

*Travelling Waves of SHH:* In fly eye development, Hedgehog (Hh) signals progress in a posterior-to-anterior orientation, which induces the wave-like differentiation of ommatidia in the eye imaginal disc [11]. This process is proposed to be mediated by indirect upregulation of Hh itself. This mechanism has shown to be conserved in vertebrate retinal development. Intuitively, a positive feedback loop, in which HH signaling induces the production of HH itself, together with the spatial diffusion property of HH could potentially produce travelling waves. We will test this hypothesis experimentally by reconstituting a traveling HH wave.

*Objective 3. Analyze a Broader Set of BMP Ligand Interactions.* In our work on BMP pathway multiplicity, we studied three pairs of BMP ligands that exhibit distinct computational integration behaviors [7]. One pair combines additively, another pair combines in a ratiometric fashion, and, for the third pair, either ligand alone activates, while both together do not. This work raises two questions that we will pursue in this funding period. First, how does the BMP pathway integrate other ligand pairs? Second, what computations arise for more than two ligands?

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

*The Use of Synthetic Biology to Understand Morphogen-Based Patterning.* We reconstituted morphogen gradient formation piece by piece, using the tools of synthetic biology to express morphogenetic signaling pathways and regulatory components in naïve mammalian cells [1]. This bottom-up approach has allowed us to study the function of each component in a controlled and simplified setting at the level of single cells. This is necessary because conventional approaches based on top-down genetic dissection of complex developmental processes *in vivo* are limited in their ability to address certain types of questions more important for understanding and designing tissues. For example, what genetic circuit architectures are sufficient for correct patterning behaviors in real tissues? What are the design principles underlying the choice of particular regulatory circuits for specific patterns? What are the minimal requirements for self-patterning of tissues? These issues are uniquely amenable to a synthetic approach. Even more specific questions about the functions of particular molecules, such as extracellular regulators of morphogen mobility, can be uniquely addressed in this system.

*Single-Cell Resolution Quantitative Time-Lapse Analysis.* The bottom-up *in vitro* system enables us to observe pattern formation with unprecedented spatio-temporal resolution and quantitative accuracy down to the level of individual cells. To achieve this, we have developed new capabilities in quantitative single-cell time-lapse analysis

of the synthetic circuits described here [1]. Morphogenetic patterning dynamics have been difficult to examine with this level of detail in embryonic systems.

*Computational modeling.* Our projects integrate computational models with experimental designs and measurements. In the BMP specificity project, we constructed mathematical models that can describe and predict signaling activity based on the ligand-receptor binding affinity and the signaling efficiency of the ligand-receptor complex [7]. In the morphogen gradient project, we constructed PDE models to simulate the spatio-temporal dynamics of gradient formation based on biochemically and physically reasonable parameters [1].

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1 Further Characterize the Molecular and Biochemical Mechanisms of the Gradient Modulators*

All morphogens, including BMP and SHH, are extensively regulated by extracellular proteins that modulate their diffusion, degradation, and signaling capabilities. Our synthetic morphogen system provides a platform for the systematic and rigorous study of these modulator's modes of action, which has been difficult to pinpoint precisely in the complex milieu of an embryo. Using this synthetic platform, we quantitatively analyzed several BMP modulators, including Noggin, Chordin, Twisted Gastrulation (Twsg) and BMP-1.

*Cell line construction:* We first constructed two dual sender cell lines that express BMP4 together with either Noggin (Sender-N) or Chordin (Sender-C) under the control of 4-Hydroxytamoxifen (4-OHT) or doxycycline (Dox), respectively (**Figure 1.A**). To examine the effects of BMP-1 protease, we engineered an abscisic acid (ABA)-inducible system into the previously constructed BMP4 receiver cells to control the level of BMP-1. The receiver cells turn on a fluorescence protein (H2B-Citrine) in response to BMP4 signaling.

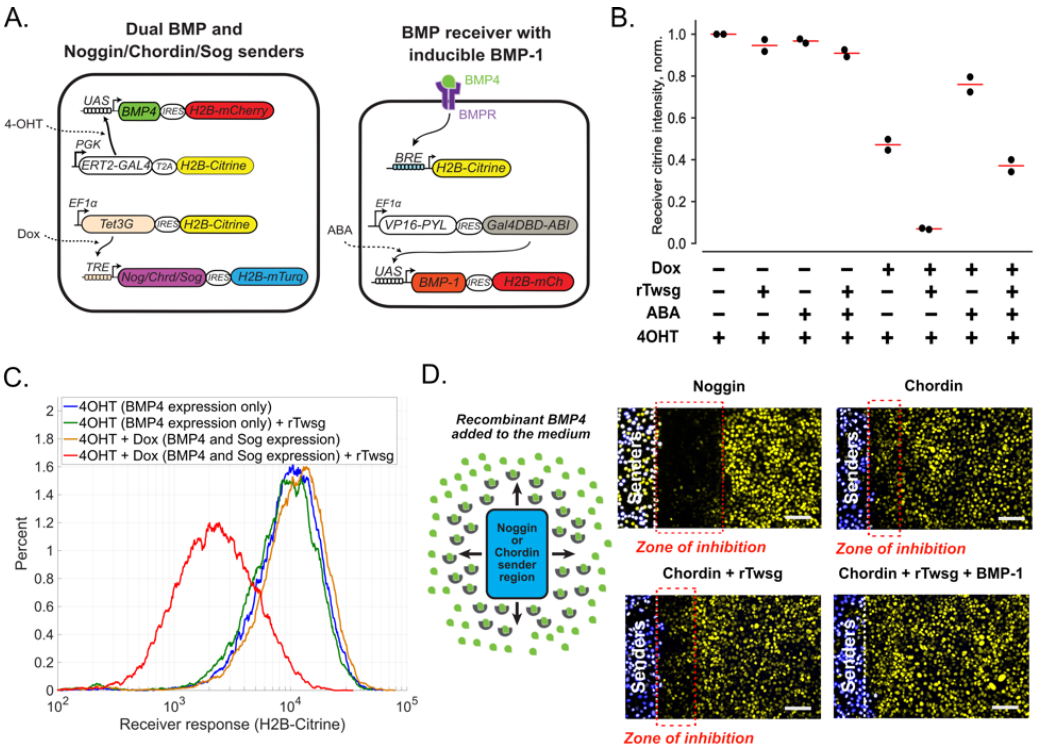



**Figure 1.** *Reconstitution of BMP-modulator interactions in synthetic morphogen system.* (**A**) Design of dual BMP and Noggin, Chordin or Sog senders, and a BMP receiver with inducible BMP-1. (**B**) Interactions among BMP and Chordin, Twsg, BMP-1 can be reconstituted in synthetic morphogen system. Dox concentration: 40ng/ml; rTwsg concentration: 10nM; ABA concentration: 100μM; 4OHT concentration: 50nM. (**C**) Fly homolog Sog inhibited mouse BMP4 signaling in a Twsg-dependent manner. (**D**) Noggin and Chordin formed spatial gradients. Chordin gradient can be further modulated by the addition of recombinant Twsg (rTwsg) and the expression of BMP-1. Scale bar: 100μm.

We co-cultured Sender-C and receivers, and induced BMP4 expression in Sender-C. After 24h, we analyzed activation of receiver cells using flow cytometry (**Figure 1.B**). Sender-C cells efficiently activated receiver cells, and this activation was reduced by co-induction of Chordin expression (**Figure 1.B**, lane 1 and 5, panel 1 and 3). Addition of recombinant Twsg (rTwsg), which facilitates Chordin-BMP interactions [12], strengthened inhibition by Chordin (**Figure 1.B**, lane 5 and 6, panel 3 and 4). By contrast, expression of BMP-1 protease, which cleaves Chordin to release BMP ligands [13], partially relieved BMP suppression by Chordin (**Figure 1.B**, lane 5-8). Co-culturing experiment using Sender-N cells and receivers showed strong inhibition of BMP signaling by Noggin, and Twsg and BMP-1 had no effects on BMP4-Noggin interactions (not shown). Using a similar strategy, we also investigated the effects of Sog, a Chordin fly homolog [14]. We constructed a dual BMP and Sog senders (Sender-S, **Figure 1.A**), and performed the co-culture experiment with receivers. Surprisingly, fly homolog Sog inhibits mouse BMP4 signaling in a Twsg-dependent manner (**Figure 1.C**). Therefore, Chordin can partially inhibit BMP4 in the absence of Twsg, and Twsg strengthens Chordin's inhibition, while Sog strictly requires Twsg for BMP4 inhibition. This key difference may enable us to engineer more diverse patterns using different homologs of Chordin.

*Gradient formation:* We next tested whether these modulators could themselves form spatial gradients similar to BMP gradients shown in previous report. We co-cultured a region of sender cells adjacent to receiver cells, induced Chordin or Noggin expression, then added recombinant BMP4 to the medium 24h later. After 12h of BMP4 exposure, we analyzed the resulting signaling gradients using fluorescence microscopy (**Figure 1.D**). For both Chordin and Noggin, we observed striking zones of inhibition adjacent to the sender cells. Notably, Chordin gradient could be modulated by addition of rTwsg and induction of BMP-1 protease expression (**Figure 1.D**), while Noggin gradient was not affected by either Twsg or BMP-1 (not shown). The spatial gradient results were thus consistent with results in **Figure 1.B**. Based on these results, we are working on reconstituting BMP shuttling by tuning Chordin, Twsg and BMP-1 in our synthetic morphogen system.

### *4.2. Design and Construction of Feedback Circuits to Implement Gradient Scaling and Travelling Waves*

*Self-scaling BMP gradient:* To create a self-scaling gradient, we chose an expansion-repression circuit based on Chordin and Sizzled [4]. The circuit is based on a triple negative regulation among Sizzled, BMP-1, Chordin and BMP4, as well as transcriptional activation of Sizzled by BMP4 (**Figure 2.A**). In Xenopus, Sizzled expands Chordin distribution by stabilizing Chordin, presumably by antagonizing Xolloid activity (Xenopus homolog of BMP-1) [4]. To examine whether Xenopus Sizzled could stabilize mouse Chordin in our synthetic morphogen system, we constructed a constitutive Sizzled-expressing cell line. To test the effects of Sizzled, we collected conditioned medium of Sizzled-expressing cell line (Szl CM) and added it into the co-culture of Sender-C and receivers. Addition of Szl CM strengthened Chordin's inhibition by BMP4 signaling, possibly through antagonized the effect of BMP-1 protease (**Figure 2.B**, lane 14 and 16). Based on this, we will construct cell line containing the full circuit, and tuning various BMP modulators to reconstitute self-scaling gradient.

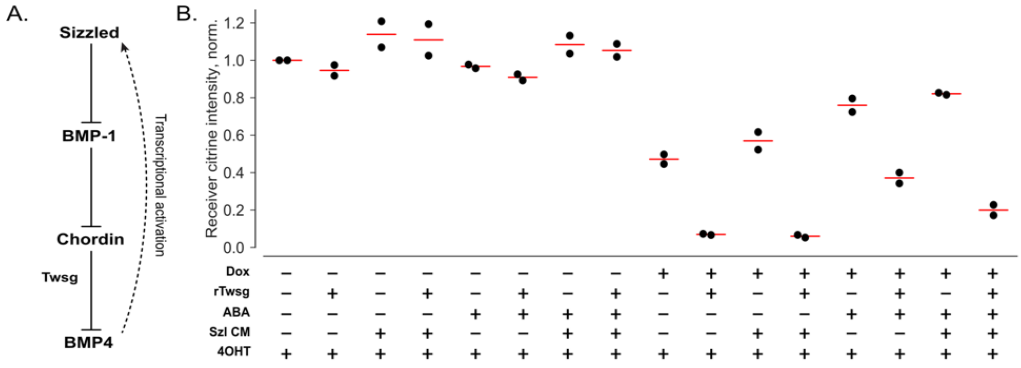



**Figure 2.** *Sizzled strengthened Chordin inhibitory activity.* (**A**) Sizzled strengthened Chordin inhibitory activity through double negative regulation among Sizzled, BMP-1 and Chordin. Inhibition of Chordin activity by BMP-1 has been shown in **Figure 1.B** Co-culture experiment of Sender-C and receivers confirmed that all three negative regulations in **Figure 2.A** could be reconstituted in synthetic morphogen system. This includes Chordin inhibition of BMP4 signaling with or without Twsg (lane 1,2,9,10), BMP-1 inhibition of Chordin activity (lane 9,10,13,14) and Sizzled inhibition of BMP-1 (lane 13-16).

*Travelling Waves of SHH:* We designed and characterized a minimal circuit to reconstitute the travelling SHH signaling wave *in vitro*. The synthetic circuit is composed of a positive feedback loop and a negative feedback loop. The positive feedback loop ensures the propagation of the SHH signal across space, and the negative feedback loop controls the directionality of the wave propagation and potentially generates travelling pulsatile signals, instead of a spatial gradient. We characterized the design of the feedback circuits and selected clonal cell populations with either single feedback loop or both loops. We hvave not yet observed travelling waves, possibly due to basal leaky expression of SHH, low dynamic range of tunable feedback gene expression, and/or the slow dynamics of signaling response to SHH. We are continuing to analyze these issues.

### *4.3. Expand the BMP Multiplicity Study*

*Experiments:* To identify the computations performed on every possible combination of BMP ligands (thousands of combinations), we developed a high-throughput, robotic-based screen system (**Figure 3.A**). Of the 91 possible pairs based on 14 commercially-available BMP ligands, the majority of responses are additive, and nearly as many are ratiometric in NMuMG cells (**Figure 3.B**). Only two have an imbalance response. Moreover, every ligand is a "contextual" ligand, whose ability to activate the pathway depends on the other ligand present. However, many ligands have the same context-dependence (e.g., BMP2, 4, 5, 6, 7, 9 are all additive with each other, but ratiometric with GDFs), indicating that the fourteen possible ligands fall into three groups of equivalent signals.

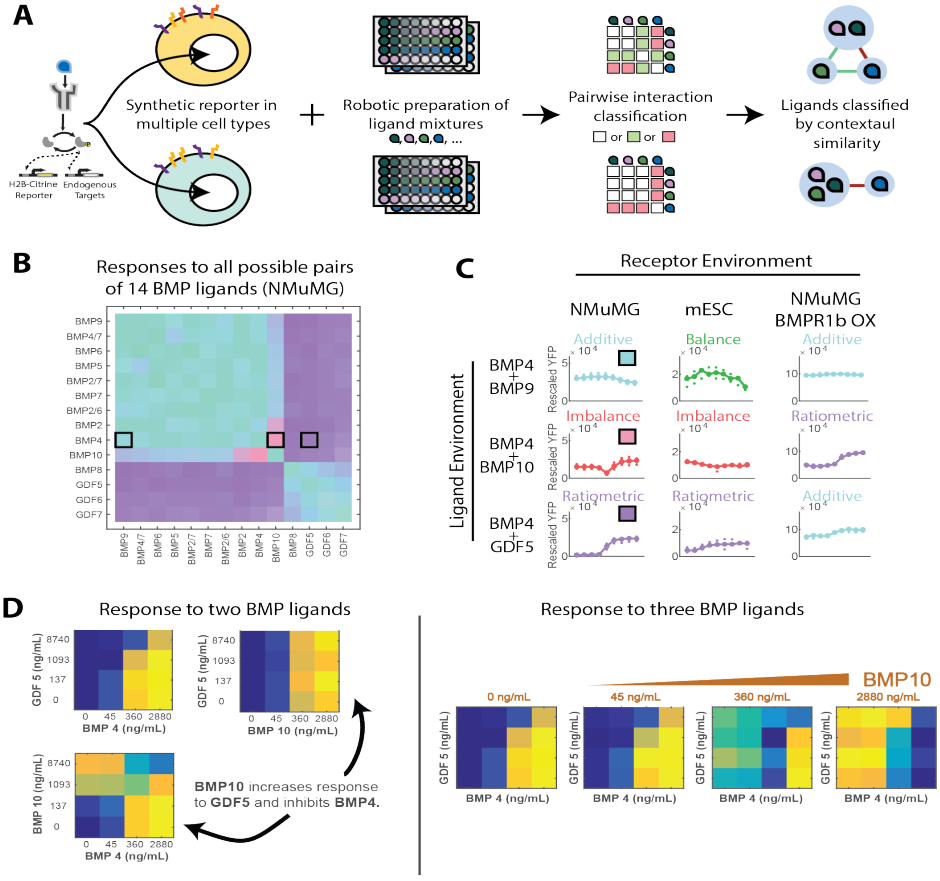



**Figure 3.** *Classifying archetypal responses to BMP pairs shows contextual ligand responses, reprogrammed responses in new cell types, and predictable responses to combinations of more than two ligands.* (**A**) A robot prepares over a thousand ligand combinations and adds them to cell lines engineered to fluorescently report BMP pathway activity, which allows global analysis of all pairwise responses and the similarity of each ligand's response profile. (**B**) Responses to all possible pairs of BMP ligands are classified by color. Most behaviors are additive (light blue) or ratiometric (purple), and only two are imbalance (red). (**C**) In different cell types (NMuMG, mESC, and NMuMG engineered to express missing receptor BMPR1b), any of the three behaviors types can be changed. (**D**) Responses to a combination of three ligands follow qualitative expectations based on pairwise responses. Colors indicate low YFP (blue) and high YFP (yellow).

We also found that these ligand properties are not robust to changes in receptor expression, and that receptor context is as important as ligand context when predicting pathway response (**Figure 3.C**). For one example of each archetypal response observed in NMuMG (additive, ratiometric, imbalance), the response type was different in a new cell line. The additive response to BMP4 with BMP9 in NMuMG becomes balance in mESC, though the imbalance and ratiometric behaviors are preserved. Conversely, overexpressing BMPR1b in NMuMG changes the imbalance to ratiometric and the ratiometric to additive, while preserving the additive response to BMP4 with BMP9. While it is unclear which receptor differences between mESC and NMuMG cells drive the balance behavior, GDF5's preferred interaction with BMPR1b [15] may explain the change to an additive response, as GDF5 is now able to form signal-producing complexes (additive response), rather than merely competing for receptors without activating the pathway (ratiometric response).

In most developmental contexts, BMPs are expressed in combinations of more than two ligands, so an understanding of pairwise responses alone does not capture the full capability of the BMP pathway [16]. Therefore, we measured responses to a combination of three ligands (**Figure 3.D**). Unlike pairwise responses, where the response to the combination of ligands could not be predicted from the single ligand responses alone, responses to three ligands followed the qualitative behavior expected from the pairwise response. The pairwise responses indicate that BMP10 and BMP4 inhibit each other, GDF5 inhibits BMP4, and GDF5 has no effect on the response to BMP10. Thus, the addition of BMP10 inverts the ratiometric response to BMP4 and GDF5 (i.e., regions of high activation have low responses, and vice versa).

*Model simulation:* Having characterized the integration of select ligand triplets experimentally, we sought to more systematically investigate the possible interactions of three ligands by expanding the mathematical model. In the model, we generated many random sets of biochemical parameters, describing the affinities with which signaling complexes form and the efficiencies with which they phosphorylate Smad proteins. We then simulated the resulting responses for these random parameter sets, yielding a diverse array of possible input-output functions (**Figure 4**). As in our experimental results, these responses largely appeared to be generalizations of the archetypal pairwise responses seen with two ligands, including ratiometric, imbalance, and balance functions; however, even this relatively small set of archetypes could be combined in many ways. These examples illustrate the astonishing repertoire of signaling behaviors possible in the BMP pathway with as few as three ligands. Taken together, the experimental and theoretical insights we have achieved regarding multiplicity and promiscuity in signaling pathways will help us better understand the functional capabilities of ligand combinations *in vivo* and predict ligand combinations to achieve desired behaviors.

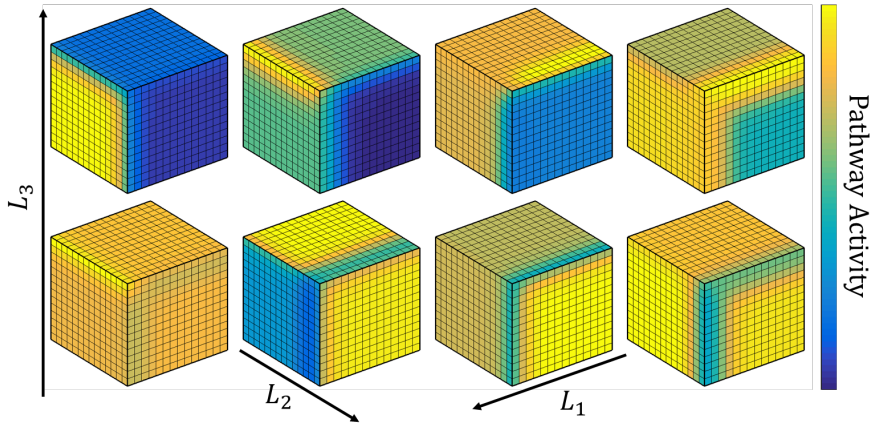



**Figure 4.** *Mathematical model of BMP signaling generates diverse array of responses to three ligands***.** Select examples from simulations of many random parameter sets are shown. Complete analysis of titrations of three ligands generates a cube; for visualization, the outer surface, corresponding to the maximal ligand concentration considered, is shown as a hexagon. The axes for increasing levels of each ligand are shown; the center of each hexagon represents maximal concentration of all three ligands. Color indicates relative pathway activity. These examples suggest that many three-ligand behaviors can be viewed as generalization of pairwise response archetypes (for each of the three possible pairs), such as ratiometric (first row, first column), balance (first row, second column), or imbalance (second row, second column).

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

The Army deals with traumatic injury as well as disease on a vast scale, on and off the battlefield, and has a direct interest in advancing regenerative medicine. One fundamental challenge is the replacement or repair of tissues in as "natural" a way as possible. Cells in regenerated or engineered tissue must have the right cues in order for them to develop into functional entities with correct gene expression patterns. Much effort is being devoted to identifying cell types, such as stem cells, that have the potential to develop into a variety of tissues. However, the question of how to spatially organize cell differentiation within the tissue remains both challenging and essential for real tissue engineering in regenerative medicine. To achieve this will require understanding fundamental principles of tissue patterning during natural embryonic development and developing new synthetic approaches that will enable the engineering of self-patterning tissues in a biomedical context.

The research pursued here was early stage in that its goal was to provide a foundation for applications that will be relevant for Army needs. We have now demonstrated a synthetic morphogen gradient platform in which spatial patterning can be systematically studied and engineered to enable regenerative therapies based on engineering tissues that self-pattern *in vitro* or, eventually, *in vivo*, of more direct Army relevance. We are now in a position to pursue two objectives: (a) develop a quantitative, predictive understanding of what circuit and signaling characteristics are sufficient for robust patterning, and (b) use this understanding to design and construct synthetic cellular systems that implement such circuit architectures. Both of these will expand synthetic biology to long-range spatial patterning in mammalian systems and are critical for developing Army applications in tissue engineering.

In the past funding period, we interacted with Army researchers on multiple occasions. These did not result in productive collaborations yet, predominantly because of the early stage of the work at that time. However, as synthetic mammalian biology is now rapidly growing, including through the approaches described above, applications are now being developed, and future collaborations with the Army should be feasible.

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### 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

R. Zhu, J. S. Markson, N. Nandagopal and M.B Elowitz. Reconstitution of Shuttling for Synthetic Spatial Patterning. In preparation.

P. Li, J. S. Markson, S. Wang, S. Chen, V. Vachharajani and M. B. Elowitz. Morphogen gradient reconstitution reveals Hedgehog pathway design principles. *Science*, April 2018. 10.1126/science.aao0645.

Y. E. Antebi, J. M. Linton, H. Klumpe, B. Bintu, M. Gong, C. Su, R. McCardell and M. B. Elowitz. Combinatorial Signal Perception in the BMP Pathway. *Cell*, September 2017. 10.1016/j.cell.2017.08.015.

Y. E. Antebi, N. Nandagopal and M. B. Elowitz. An operational view of intercellular signaling pathways. *Current Opinion in Systems Biology*, February 2017. 10.1016/j.coisb.2016.12.003.

J. S. Markson and M. B. Elowitz. Synthetic Biology of Multicellular Systems: New Platforms and Applications for Animal Cells and Organisms. *ACS Synth Biol.,* December 2014. 10.1021/sb500358y.

**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Multi-Scale Systems Analysis of Cell-Cell Communication Networks in Inflammation**

**Project Leader:** **Douglas A. Lauffenburger (MIT)**

**Collaborators:** **Lisa Leon (USARIEM); Kevin Haigis (Beth Israel Deaconess Medical Center); Linda Griffith (MIT); John Hambor and Erick Young (Boehringer-Ingelheim)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

A. Multi-scaling analysis of immune system-based inflammation in the gastrointestinal tract [1], [2] and [3]. Intestinal tissue samples from mice comparing inflamed conditions (genetic as well as biochemical) were interrogated with Luminex bead-based immunoassays, mass spectrometry, and RNA-sequencing platforms for transcriptomic, proteomic, and phosphoproteomic characterization. A battery of computational ontology enrichment, regulatory network, multi-variate classification, and statistical inference techniques elucidated key intracellular nodes and pathways pathologically dysregulated, with validation by dedicated experimental intervention studies.

B. Multi-scale analysis of immune system-based inflammation in endometrial pain and debilitation [4]. Peritoneal fluid samples from human subjects were interrogated with Luminex bead-based immunoassays and multi-plexed metalloprotease assays for proteomic and enzymatic activity characterization. Non-negative matrix factorization analysis identified a macrophage-associated cytokine signature as most strongly corresponding to pain, pathway expression analysis identified the JNK signaling pathway in macrophages as predominantly dysregulated leading to this signature, and protease activities involved in tissue lesion-forming cell invasion were found to be activated by the cytokine signature.

C. Multi-scale analysis of immune system-based inflammation in neurodegeneration [5]. Human subject cadaver brain tissue samples were interrogated with Luminex bead-based immunoassays and RNA microarrays for proteomic and transcriptomic characterization. Partial least-squares classification modeling and partial correlation network analysis of proteomic intra-cellular signaling and inter-cellular communication measurements generated a surprising prediction that VEGF, normally a neuroprotective factor, becomes neurotoxic in presence of amyloid aggregates. We also found a shift in neuronal multi-pathway kinase network activities caused by amyloid on VEGF signaling, and successfully tested the prediction of BDNF-mediated neuronal rescue via rebalancing of the kinase network activities.

D. Multi-scale analysis of immune system-based inflammation in diabetes [6] and [7]. Blood samples from human subjects, with diabetes or body mass index-matched controls, were interrogated by Luminex, flow cytometry, and Seahorse platforms for proteomic and metabolomic characterization. Th17 cell cytokines were found to be particularly important, and partial least-squares classification analyses indicated that B cells support Th17 inflammation in diabetes but not control subjects, while monocytes supported Th17 inflammation regardless of diabetes status. Addition of metformin suppressed the Th17 activity, diminishing the inflammatory state, in all subjects, via alteration of T cell fatty acid metabolism.

E. Construction of *in vitro* complex mixed-cell co-culture experimental systems for testing hypotheses concerning immune system-based inflammatory effects on tissue biology [8], [9] and [10]. Primary innate immune cells (macrophages, dendritic cells) and primary endometrial tissue cells, from human subjects, were co-cultured in 2D transwell and 3D synthetic matrix contexts and interrogated with Luminex bead-based immunoassays for proteomic characterization under inflammation-eliciting stimuli. Self-organizing maps, partial least-squares, and partial correlation network modeling found key aspects of immune/tissue cell communication involved in dysregulation of tissue cell phenotypic behavior.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

We continued advancing both methodology and utility in integrative network understanding of how multiple diverse cell types communicate via molecular processes to govern higher-level tissue, organ, and organism pathophysiology, especially in response to inflammatory injury and insult. This understanding clearly requires a multi-scale systems analysis approach, which we have been developing over the past half-decade largely via Army ICB support. Our primary objective for this recent period has been to test the hypothesis that communication between immune cells and from immune cells to tissue cells, via inflammatory cytokines and chemokines, influences tissue cell phenotypic behavior in ways that can be captured by computational network models. Validation of this hypothesis in particular applications will offer a potential capability for intervening in these networks for protection against pathologic debilitation of military personnel.

We have been pursuing this work with ultimate goal of understanding *in vivo* physiological communication networks, so we have given heavy attention to studies in human subjects and animal models. In order to test network model inferences in deepest mechanistic fashion, we have also been concurrently developing *in vitro* complex multi-cell type culture systems comprising immune cells and tissue cells. Finally, we have begun to explore computational frameworks for translating findings from animal model studies to human contexts, in order to enhance application relevance to the greatest extent possible. We have advanced our computational methodologies for new types of experimental data-sets (especially integration of heterogeneous types of omic measurements) in intestinal inflammatory disorder and concomitantly have increased our emphasis on military-related inflammatory pathologies including heat injury/stroke (HI/S) and post-traumatic stress disorder (PTSD) as they similarly involve debilitation due to inflammatory processes causing organ dysfunctions. These various project areas have been conducted in close partnerships with Kevin Haigis at Beth Israel Deaconess Medical Center in Boston, Lisa Leon at USARIEM in Natick, and with Brad Hyman at Massachusetts General Hospital in Boston.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

### *3.A. Inflammation-Related Cell-Cell Communication Networks in Neurodegeneration—with B Hyman, MGH*

The major portion of our effort this reporting period has been to develop novel computational analysis for inference of inflammatory contributions in neurodegeneration, based on examination of *in vivo* omics data. Our starting point has been a publicly available transcriptomic dataset [11], generated using transgenic PS2APP mice and age-matched non-transgenic controls. Cortical cap samples were isolated and FACS sorted for neuron, astrocyte, and microglia-specific samples. This RNA-seq dataset is unique because neuron, astrocyte, and microglia samples are specific and identifiable to individual animals.

While Gene Set Enrichment Analysis (GSEA) is a widely used method for identifying differences between control and disease samples at the transcriptomic level, it generally does not lead readily to actionable inferences because of the expansive and fairly arbitrary nature of defined gene sets. Instead, we are focusing on a new inference method, Pathway Responsive Genes (PROGENy), which matches transcriptional data with signaling pathway activity-induced transcriptional response [12]. We have partnered with the original developers of PROGENy to modify the method for diverse cell types. The algorithm scores signaling pathway activity based on expression of a core, pathway-specific gene set transcribed downstream of pathway activation; associated weights are determined via linear regression of gene expression against pathway inhibition and activation. Pathway score is the dot product of a mean-centered, variance-normalized gene expression vector and a pathway-specific vector of PROGENy weights.

Next, to ascertain what extracellular communication factors (*e.g.*, cytokines, growth factors, hormones, matrix) are responsible for the signaling pathway activities, we employ another technique recently published by our laboratory [13] (**Figure 1**). This methodology uses product-based scoring to assess the strength of ligand-receptor interactions, and the authors underscore the importance of a paired metric by demonstrating that high-scoring interactions are not exclusively driven by strong ligand or strong receptor gene expression alone. This methodological framework provides a unique opportunity to leverage the cell-type specificity of the Srinivasan transcriptomic dataset to interrogate neuron-glia communication. A null score distribution is generated using randomly matched ligand and receptor gene expression values and used to determine significance of high-scoring interactions. The database used for evaluating cell-cell communication includes 1800 ligand-receptor interaction pairs [14]. The number of interactions necessitates feature selection and supervised learning methods to down sample disease-relevant paracrine and autocrine signaling hypotheses. For feature selection we use LASSO and to evaluate the predictive

capacity of the selected features we use PLSDA. However, given its bias toward model shrinkage LASSO will randomly select one feature from a group of covarying, effective predictors. We address this limitation in two ways [15]: first, we modify a two-layered cross validation framework previously developed in the lab and map frequency of selected features across cross validation folds; second, we build correlation networks, selecting genes that with Spearman correlation coefficient (r) magnitude greater than 0.7 ($|r| > 0.7$) and false discovery rate less than 0.05 (BH FDR < 0.05). Following down-sampling of ligand and receptor genes, we use correlation coefficient calculations to expand networks using the selected model features as starting nodes. Feature selection is critical to help interpret the large number of ligand-receptor interactions scores and building correlation networks is necessary for imparting mechanistic insights in model-based hypothesis generation.

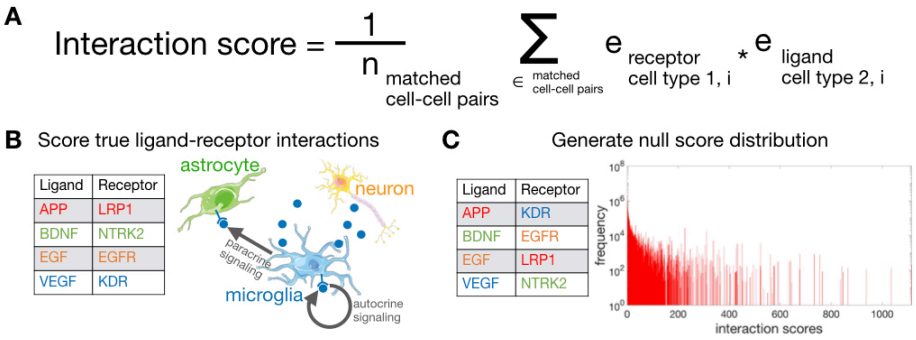



**Figure 1.** (**A**) Ligand-receptor interactions are evaluated using product-based scoring. The interaction score between two cells is the product of ligand expression on cell type 1 and receptor expression on cell type 2. When evaluating a ligand-receptor interaction between, for example, microglia and astrocytes, interaction scores will only be calculated using microglia and astrocytes isolated from the same animal. This decreases the number of interaction scores generated for a given ligand-receptor pair but preserves animal-specific information and animal-to-animal heterogeneity. (**B**) The first step is to score all true receptor-ligand interactions compiled from the database; example interactions are shown on the left. Interaction scores are specific to a cell-cell pair. Given the three cell types assessed and the bidirectional nature of communication, a total of nine cell-cell pairs are scored. (**C**) The second step is to generate cell-cell pair specific null score distributions, by scrambling ligand gene expression and receptor gene expression matrices and calculating scores for scrambled pairs. This preserves the data structure associated with ligand and receptor gene expression and also conserves animal-specific information. The null distribution permits estimation of a p-value for each interaction.

### *3.B. Inflammation-Related Network Dysregulation in Heat Stroke—with Leon, USARIEM*

Heat stroke is the most severe form of heat illness and is a serious medical issue for both civilians and the military, resulting in central nervous system dysfunction, organ failure, cardiovascular damage, and death. While a core body temperature over 40 °C has been used to diagnose heat stroke in those suffering symptoms, no definitive test exists to measure severity or predict outcome and recovery time. Heat stroke induces similar inflammatory response to infection, and prior viral or bacterial infection is known to exacerbate heat stroke pathology, including coagulopathy. Immune involvement in heat stroke pathology provides an opening for quantification of severity and prognostic time course. Shifts in profiles of blood cell populations as measured by complete blood count (CBC), as well as changes in levels of plasma coagulation markers, may serve as an indicator of heat stroke severity.

Our collaborators at USARIEM performed the following experimental procedure. Male C57BL/6J mice were implanted with radiotelemetry devices and intraperitoneally injected with poly I:C (simulates viral infection, 100 µg/kg), LPS (simulates bacterial infection, 50 µg/kg), or saline vehicle (~300 µL). After 48 or 72 hours recovery at 25 °C, mice were exposed to heat (T=39.5 °C) without food or water until reaching a maximum core body temperature $T_{c,max}$=42.4 °C. Unheated controls remained at 25 °C. Radiotelemetry recording of activity and $T_c$ were performed until mice were sacrificed at one of three time points: $T_{c,max}$, 1 day, or 7 days, for a total of 36 groups and N=13 mice per group. Mice were anesthetized with isoflurane and exsanguinated following thoracotomy and intracardiac puncture. A complete blood count (CBC) was performed, including white blood cell count, lymphocyte count, % lymphocytes, monocyte count, % monocytes, neutrophil count, % neutrophils, red blood cell count, hematocrit, mean corpuscular volume, width of red blood cell size distribution, hemoglobin, mean corpuscular hemoglobin concentration, platelet count, % platelets, mean platelet volume, and width of platelet size distribution.

Concentrations of the plasma coagulation factors D-dimer, thrombomodulin, thrombin/anti-thrombin complex, anti-thrombin, and tissue factor, along with that of granzyme B, a marker of liver damage, were assessed by ELISA. PLSR and PLSDA with variable importance of projection (VIP) scores identified a signature of blood factors that correlate with heat stroke pathology as measured by core body temperature and granzyme B concentration.

RNA was purified from 48 20 mg tissue samples of kidney using the RNeasy Mini Prep kit with DNase (Qiagen) according to manufacturer protocol. The 48 mice were selected from the larger cohort as 6 mice randomly chosen from each of the 8 sub-groups undergoing 48-hour post-injection incubation: saline- or poly I:C-treated, heated or unheated, sacrificed at $T_{c,max}$ or 1-day time point. RNAseq was performed by the MIT BioMicroCenter using Kapa mRNA hyperprep for library preparation and sequencing on a HiSeq2000 with read length of 40SE. Gene expression was mapped using the STAR/RSEM pipeline, using *Mus musculus* GRCm38.93 as a reference (available for download in GTF format from Ensembl). We estimated variance-mean dependence in count data and tested for differential expression based on a model using the negative binomial distribution with the DESeq package in R from the BioConductor repository. From the 48 original samples, 6 outliers were identified by principal component analysis (PCA), and later confirmed by quality control to be contaminated or feature low read counts. The remaining 42 samples were ranked using the log2-fold change and by PCA loadings and submitted for pre-ranked GSEA.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.A. Inflammation-Related Cell-Cell Communication Networks in Neurodegeneration (with Bradley Hyman, Massachusetts General Hospital)*

Our signaling pathway activity inference for neuron, astrocyte, and microglia from the mouse neurodegeneration dataset was conducted using PROGENy as described above. An overview of the resulting PROGENy scores is shown in **Figure 2**. Pathway scores were calculated for 7-month (**left**) and 13-month (**right**) samples. The majority of significant changes in signaling occur in neurons, with more pronounced changes in the 13-month neuron comparison. The shifts in neuronal signaling suggest a potential mechanism through which neuron-glia communication modulate Aβ-induced neurotoxicity. The dearth of astrocyte and microglia signaling between control and PS2APP mouse samples was surprising. However, it is possible that glia could mediate changes through other mechanisms; for example, glial proliferation would alter the neuron-glia ratio and could drive differences in neuronal signaling without affecting glial signaling inference.

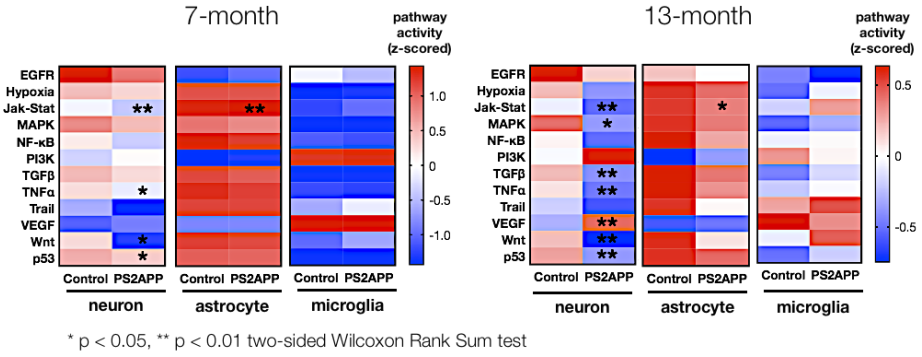



**Figure 2.** Pathway activity scores were calculated for neurons, astrocytes, and microglia at 7-month and 13-month time points using cell-type specific RNA-seq and PROGENy. Significance is based on the control vs disease (PS2APP) comparison within a given cell-type, at a specific time point; p-values were calculated using a two-sided Wilcoxon Rank Sum test.

In addition to high-level trends, we sought to interrogate PROGENy predictions against known disease biology and other commonly-used pathway activity inference methods. First, we checked that PROGENy could recapitulate known disease pathology. APP is a known binder of the Frizzled receptor while APOE proteins associated with AD disease risk are known binders of the Frizzled co-receptor LRP5/6. In Alzheimer's Disease, this results in decreased binding of the Wnt ligand to its receptor, decreased β-catenin localization to the nucleus, and subsequent loss of Wnt signaling pathway function. PROGENy successfully predicts this known disease biology, with decreased pathway activity scores for 7 and 13-month PS2APP mouse neurons relative to control. Astrocyte and microglia pathway activity are not statistically different across control and disease conditions. Results from PROGENy found all

predictions obtained by GSEA and identified predictions not captured through GSEA; important examples are increased Jak-Stat pathway activity in 7-month neurons and decreased TNF-a activity in 13-month neurons.

### *4.B. Inflammation-Related Network Dysregulation in Heat Stroke (with Lisa Leon, USARIEM)*

We found that CBC results can predict the differential in average Tc from night to day, an indication of heat stroke severity. Our PLSR model predicts changes in circadian thermoregulation from blood cell populations, and also separates subjects based on heat stroke time-course. Our findings indicate that heat stroke decimates immune cell populations, and that levels increase again with time after removal from heat. In addition, low platelet levels were also correlated with heat stroke severity, and their large size and broad size distribution indicate new, more active platelets are being released. As an independent verification of potential coagulopathy, we built a model correlating markers of coagulation with liver damage; increased levels of soluble thrombomodulin indicate upregulated activation of coagulation pathways, while elevated D-dimer levels demonstrate the presence of thrombosis and thrombolysis. Additionally, three animals with extreme pathology and liver damage presented with evidence of disseminated intravascular coagulation and fibrinolytic resistance, as exhibited by extreme high levels of soluble thrombomodulin but extreme low levels of D-dimer.

From the transcriptomic data we identified multiple up-regulated gene sets (inflammatory response, hypoxia, wound healing, coagulation) in the poly I:C-treated heat challenged animals compared to control animals (FDR q-value < 0.25) (**Figure 3.a-b**). To identify the most important genes transcripts in the response to heat stroke we performed principal component analysis using all non-zero transcripts (**Figure 3.c-d**). The two principal components separating the treatment groups revealed key players in heat stroke response related to the gene sets identified by GSEA: *hba* and *hbb*, components of hemoglobin; *lcn2*, involved in innate immunity and an early biomarker for acute kidney injury; *krt20*, a filament protein contributing to structural integrity of epithelial cells; *hspa1a* and *hspb1*, heat shock proteins that serve as protein folding chaperones in response to environmental stress; and *fgg* and *fga*, components of fibrinogen, the most abundant protein in blood clots. These results indicate pre-symptomatic, co-occurring inflammation-associated vascular damage and coagulopathy.

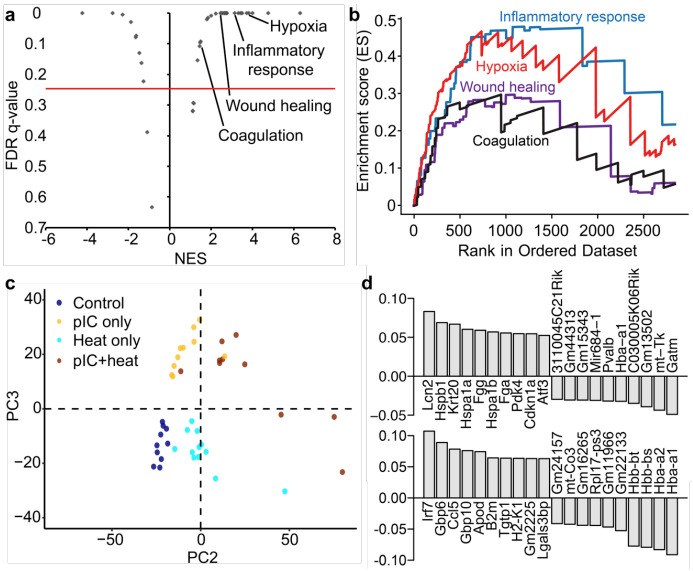



**Figure 3.** Transcription changes in genes related to vascular injury response in heat stroke. (**a**) volcano plot showing highly enriched gene sets (NES, normalized enrichment score) in kidneys of poly I:C-treated, heat-challenged mice, and their statistical significance as FDR q-value. Gene sets of special interest are highlighted. (**b**) For each gene set of interest, the enrichment score of each gene in the set plotted against that gene's rank in log2 expression for the entire gene expression dataset. (**c**) Principal component analysis of log2 gene transcripts separates groups by heat application (PC2, 9% of variation in gene transcripts) or poly I:C injection (PC3, 5% of variation in gene transcripts). (**d**) Top ten positive and top ten negative contributing gene transcripts to heat response (PC2, top) and poly I:C response (PC3, bottom).

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

We have continued our collaborative work with Lisa Leon and colleagues at USARIEM on the heat stroke application and are close to submission of a major manuscript in the coming few months. We have also gained the enthusiastic interest of Ed Perkins at ERDC, and are pursuing new applications with his group in neurotoxiciy starting in 2019.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Synthetic Biology - Refactoring the Genetics of Metal Nanocluster Synthesis**

**Project Leader:** **Christopher A. Voigt (MIT)**

**Collaborators:** **Rajesh Naik (AFRL) and Jeffrey Rimer (University of Houston)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

The physical properties of metal atoms arranged in nanoscale clusters differ from that observed in bulk materials. They have broad applications to the Army, but chemical routes for producing metal nanoclusters have several challenges. Over the five-year period of the funding, we focused on several biological systems that can produce intricate metal nanostructures and genetically engineered them to further understand and produce novel materials.

*Refactoring of Iron-Molybdenum cofactor (Fe-Mo-co) nanocluster synthesis.* 20-gene (25 kb) nitrogen fixation gene cluster in *Klebsiella* is mostly encoded for the synthesis of Fe-Mo-co, which requires 16-gene pathway. In the first three years of the funding, we completed refactoring the gene cluster encoding *Klebsiella oxytoca*. The complete refactored system consists of 37.5 kb of DNA and 80 genetic parts. The refactored gene cluster was improved 8-fold compared to the initial refactored cluster (**Figure 1.a**). The results were published in the journal *Nature Biotechnology*.

*Engineering size, shape and silica-coating of biological magnetic nanoparticles.* Magnetotactic bacteria produces magnetosomes composed of magnetite nanocrystals with precise sizes, shapes and physical properties. In the five-year period, we constructed a platform for engineering the magnetic nanoparticle in *M. magneticum*, and used it to produce novel materials. We established a stable and robust culture condition and magnetosome purification system and developed engineering tools for precise expression control in magnetospirillum (**Figure 1.b**). We also controlled the gene expression of *mamC* and *mms6* genes to produce size/shape controlled novel magnetic nanoparticles (**Figure 1.c-d**). In addition to size and shapes, synthesizing shell coatings of controlled thickness is important to balance the properties between the magnetic core and the insulating shell. In the past two years, we have developed a method to add silica shells of tunable thicknesses to magnetosomes using a peptide from diatoms (**Figure 1.e**).

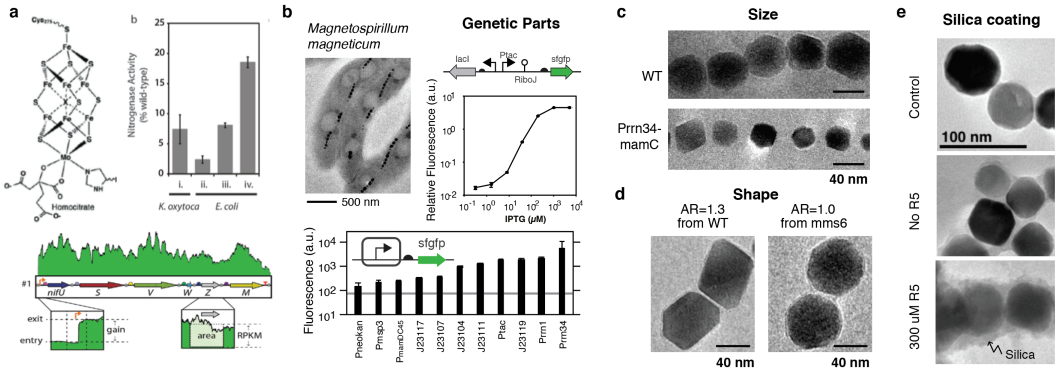



**Figure 1.** *Most significant results over five-year period.* (**a**) Refactoring Fe-Mo-co nanocluster synthesis from *K. oxytoca*. Fe-Mo-co nanoclusters (top left) biosynthesis requires 16-gene pathway. The refactored gene cluster was improved 8-fold (top right). The cluster was optimized by using the part-behavior analysis using RNA-seq (bottom). (**b**) Genetic parts including inducible (top right) and constitutive (bottom) promoters for *M. magneticum*. (**c**) MamC expression using the strongest promoter Prrn34 enabled smaller magnetosome (diameter median: 37 nm vs 50 nm in wt vs mms6, respectively). (**d**) Controlled Mms6 expression resulted in magnetosomes with round shape (AR; Aspect Ratio). See **Figure 2** for details. (**e**) R5 peptide from diatom was used to produce silica-coated magnetosomes with controlled thickness.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

The physical properties of metal atoms arranged in nanoscale clusters differ from that observed in bulk materials. For example, they can exhibit superparamagnetism, absorb electromagnetic radiation, and perform catalytic functions. As such, they have broad applications to the Army, including electronics, microelectromechanical systems (MEMS), ferrofluids, photonics, stealth technologies, catalysts, in the production and storage of energy, sensors, medical devices, and drug delivery [1]. Chemical routes for producing metal nanoclusters have several challenges, including: (i) control of size and shape, (ii) precision of atom placement and imperfections, (iii) low yields and high-cost separations, and (iv) toxic byproducts. In contrast, many relevant nanoclusters are produced in nature and these enzymatic pathways are highly precise. They would enable the access to new crystal growth patterns not possible with bulk chemistry and avoid crystal imperfections, which can cause scattering detrimental to photonic applications. Further, they provide a green manufacturing process whereby the nanoclusters are produced under ambient conditions in an aqueous environment. In the final reporting period, we focused on our effort on three topics: magnetic nanoparticles, silica nanoparticles, cellulosic 'living materials' and crystallin-based optical materials.

### *2.1. Synthesis of Genetically Engineered Magnetosomes with Different Sizes and Shapes*

*Magnetosomes* are composed of magnetite (iron oxide) nanocrystals with precise sizes, shapes, and physical properties that have been shown to be useful for photonic and medical applications that are directly relevant to Army applications. The formation of the magnetosome occurs in several steps, including the formation of inner membrane associated lipid organelles in which the nanoclusters are assembled. Our goal is to develop a genetic toolkit for *Magnetospirillum* and use it as a platform to engineer magnetosome genecluster to alter the physical properties of the magnetite crystals. Over the years, we have developped a stable culture system and genetic parts to genetically engineer *Magnetospirillum*. In the final reporting period, we used this platform to engineer the size/shape of magnetic nanoparticles.

### *2.2. Synthesis of Silica-Coated Magnetosomes as Core/Shell Nanoparticles with Tunable Shell Thickness and Silica-Coated DNA Origami Structures*

*Core-shell nanoparticles* are commonly synthesized to enhance a core nanoparticle's functionality by introducing a shell layer of a different material with additive properties. In the case of magnetosomes (magnetite), adding a silica shell can reduce particle aggregation, increase bio-compatibility, and insulate the magnetic properties. Controlling the shell thickness is an important factor for obtaining the balance of properties between the magnetic core and the insulating shell that enable these particles to be used in applications such as microwave absorption and imaging (e.g., MRI contrast agents).

The field of *DNA origami* has shown an amazing ability to create complex 2D and 3D structures at the nanoscale. Our objectives were two-fold. First, we aimed to leverage DNA origami to synthesize complex silica nanostructures by using the DNA as a template, whereupon after the silica coating was applied the organic material could be removed. Second, by coating the DNA with silica we aimed to make the DNA structures more bio-compatible so that they could be applied for applications such as bio-sensing, drug delivery, or bio-imaging.

### *2.3. Embedded ARL Projects on Cellulosic 'Living Materials' and Crystallin-Based Optical Materials*

During portions of the final reporting period, the Voigt lab hosted scientists from ARL who pursued two projects centered on genetically controlled materials production that may lead to new materials for magnetosome incorporation. One project aimed to understand and control the production of bacterial cellulose to create a hybrid 'living material' made of cells and cellulose. Controlled cellulose production would enable the production of biologically produced and patterned materials that could be used to template other materials of interest using engineered proteins. The second project aimed to explore the possibility of re-engineering proteins found in vertebrate eyes to make optically clear biomaterials. The overarching goal of this project is to express and assemble 'crystallin' proteins found in eye lenses to enable new lens architectures.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

### *3.1. Synthesis of Genetically Engineered Magnetosomes with Different Sizes and Shapes*

Genes responsible for magnetosomes formation is identified in many different magnetotactic bacteria icluding *mam*, *mad*, *man* genes [2]. *Magnetospirillums* are the most studied species with approximately 30 *mam* genes encoded by four major operons, *mamAB*, *mamGFDC*, *mms6F* and *mamXY*. Previous studies has demonstrated that the magnetosome morphology changes by knocking out these genes from the genome [3-5]. However, most of the knock-outs resulted in completely abolishing magnetosome formation or damaged the elaborate and uniform structure of the natural magnetosomes.

Until the previous years of funding, we have established a stable culture condition, plasmid, and strong promoters for gene expression in *M. magneticum*. In this final year, we used the strong promoters to express the magnetosome genes in *M. magneticum*. We cloned each gene from the magnetosome gene cluster and placed under the Ptac promoter. The expression was induced using IPTG, and the cells with the magnetosome affected was selected. We then recloned these genes under constitutive promoters, and the expression was enhanced as much as possible. We purified the magnetosomes to characterize the properties.

### *3.2. Synthesis of Silica-Coated Magnetosomes as Core/Shell Nanoparticles with Tunable Shell Thickness and Silica-Coated DNA Origami Structures*

Current methods for synthesizing core-shell nanoparticles often require long processing times with many steps, have difficulty producing thin shells of less than 20 nm thickness, or produce non-functional core-less particles [6]. Our approach was to use the R5 peptide from diatoms to catalyze the precipitation of a silica shell around magnetosomes. Our original strategy was to genetically engineer *Magnetospirillum* to produce the R5 conjugated to mamC, a magnetosome coat protein, resulting in R5 being displayed on the surface of the nanoparticles. However, after initial experiments, we found that R5 doped into a reaction with wild-type magnetosomes was also capable of producing silica shells. Building from these preliminary results, we changed our approach to solely focus on refining our method for synthesizing silica shells on wild-type magnetosomes using R5 doped into the reaction, which enabled us to evaluate how shell thickness is affected by changing the concentration of R5.

For the DNA origami structures, our initial approach was to test whether the same method for synthesizing silica core/shell nanoparticles could be applied to coat DNA nanostructures with silica. We started with a simple 6-helix DNA bundle structure, which is often used as the basis for creating more complex DNA structures. After preliminary results looked promising, we moved to a more complex 2D wheel structure and compared the R5 method to a recently published method [7]. We are currently refining the R5 method for DNA and are testing different silica sources, buffers, and acid concentrations to increase the percentage of DNA structures that are successfully coated and to control the thickness of the silica.

### *3.3. Embedded ARL Projects on Cellulosic 'Living Materials' and Crystallin-Based Optical Materials*

*Cellulosic 'living materials'. Gluconacetobacter sp.* extrude highly crystalline, high aspect-ratio glycan nanofibers, which are woven into a hydrogel-like matrix to form a bulk cellulose material. This work explored the implementation of synthetic biology in *Gluconacetobacter* to enable bacteria-guided construction of programmable materials through multiple routes: accessing cellulose synthase machinery for genetic control of cellulose nanofiber properties, design of fusion proteins that promote assembly onto cellulose scaffolds, and incorporation of additional strains as a consortia of multiple synthetic biology chassis. By simultaneously accessing the biosynthesis, functionalization, and embedded resident cells of cellulose, this work pursued bacterial cellulose as a hierarchically-tunable living material platform.

*Crystallin-based optical materials.* Crystallin proteins are expressed in lens cells of the vertebrate eye and are the source of its optical clarity and high refractive index [8]. While some crystallins have been previously expressed and purified, they have yet to be assembled into a functional material outside of the context of the eye lens. We built and tested expression systems for the efficient production of crystallins and crystallin fusion proteins in *Escherichia. coli*. These systems were used to produce a range of natural crystallins as well as crystallins fused to protein assembly domains. The initial work has focused on using SpyTag/Catcher [9] and intein [10] domains a that could enable the construction of large, covalently-linked crystallin complexes.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1. Synthesis of Genetically Engineered Magnetosomes with Different Sizes and Shapes*

Six magnetosome genes were placed under ptas promoter and fully induced to observe the effect they provide for the size and shape of magnetosomes. Among the gene tested, we discovered that expressing *mamC* will result in smaller diameter of magnetosomes. The strain with *mamC* placed under constitutive promoters with different strengths. The strain expressing *mamC* under strongest Prrn34 (a promoter derived from *Magnetpsirillum* genome) produced magnetosomes with small distributions (median 37 nm) compared to wild type magnetosomes (median 50 nm) (**Figure 2.a**). Meanwhile, mms6 gene expression increased the number of magnetosomes with rounded shape (**Figure 2.b**). Controlling the expression of the two genes, *mms6* and *mamC*, will enable the tuning of size and shape of magnetosome nanoparticles.

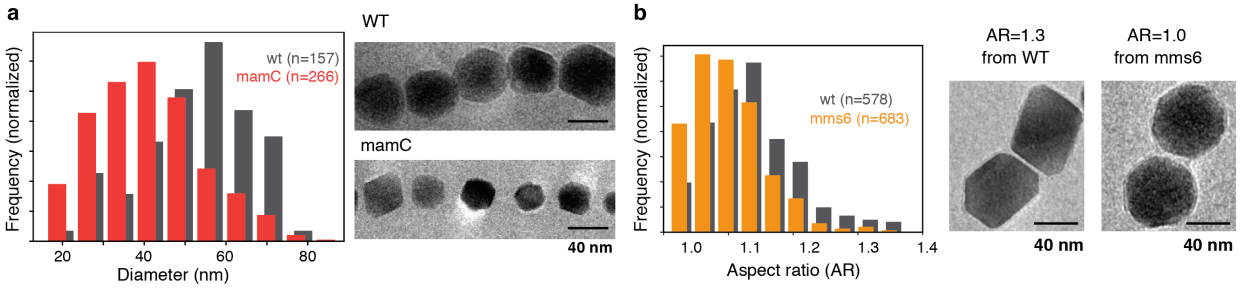



**Figure 2.** *Size and shape regulation of magnetosome nanoparticles by MamC and Mms6.* (**a**) MamC expression using a strong Prrn34 promoter resulted in smaller distribution of magnetosomes diameter. (**b**) The expression of mms6 gene (placed under Ptac promoter) was induced by 2 mM IPTG. The mms6-expressed cells produced larger ratio round-shaped magnetosomes.

### *4.2. Synthesis of Silica-Coated Magnetosomes as Core/Shell Nanoparticles with Tunable Shell Thickness and Silica-Coated DNA Origami Structures*

We have developed a new method for synthesizing silica shells using the R5 peptide from diatoms. We have shown that we are able to control the shell thickness, from 3.2 nm to 35 nm by titrating the concentration of R5 in the reaction (**Figure 3**). This method is straightforward and is performed in aqueous conditions at room temperature with one-hour to incubate R5 with the magnetosomes and a 30-minute reaction once the silica source is added. Although R5 is not covalently attached to the magnetosomes in any way, we are able to obtain highly specific silica synthesis only on the nanoparticles. We have also shown that this method is generalizable to a range of other metal oxide nanoparticle cores, including tantalum oxide, hafnium oxide, zinc oxide, and titanium oxide.

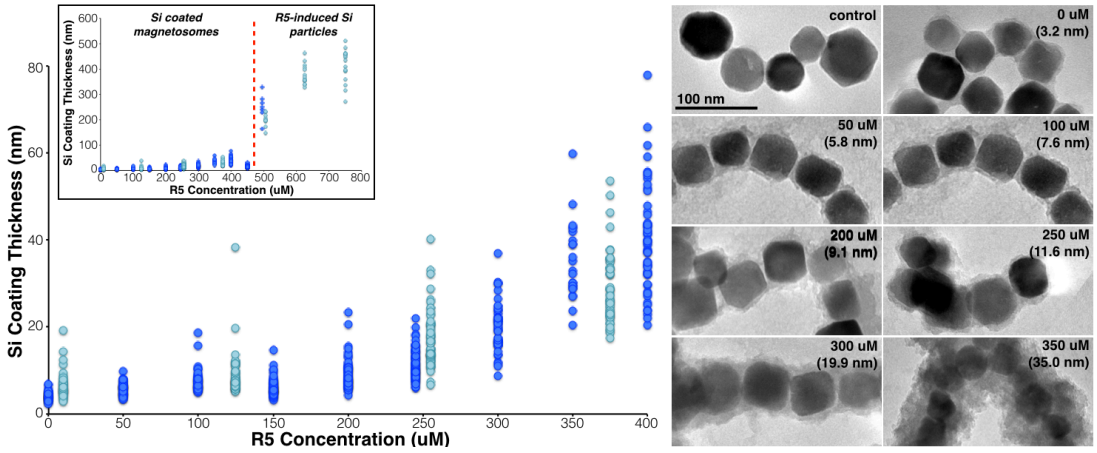



**Figure 3.** *Silica shell thickness on magnetosomes controlled by R5 concentration.* (**a**) Silica shell thickness measurements plotted for different concentrations of R5, two replicates shown in light and dark blue. Over 500 uM R5, we begin synthesizing larger silica-only particles. (**b**) Silica-coated magnetosomes synthesized with different concentrations of R5. The average shell thickness is given in parentheses.

Preliminary results show that the R5 peptide can be used to synthesize a silica coating on DNA nanostructures, where both a 6-helix bundle and a 2D wheel structure were tested (**Figure 4**). In comparison to a recently published method [7], our approach reduces the reaction time by 80x (from 5 days to 1.5 hours) and produces a thicker silica coating. Over the next year, we will continue developing this method to obtain more uniform silica coatings and to control the thickness of the silica.

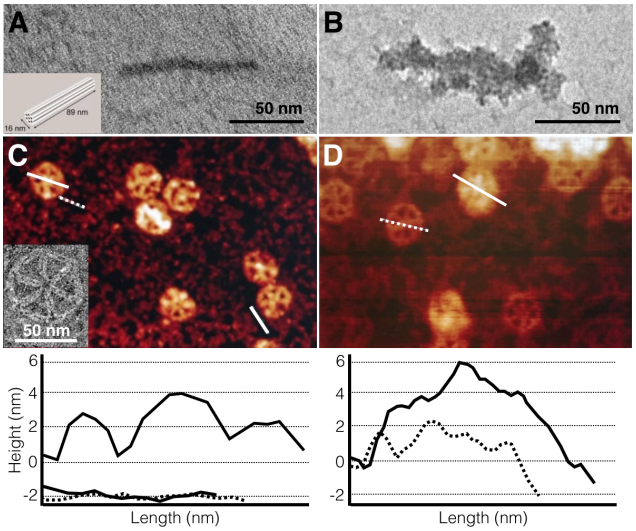



**Figure 4.** *Silica-coated DNA nanostructures.* (**a**) 6-helix bundle DNA structure. (**b**) 6-helix bundle coated with silica. (**c**) Silica-coated 2D wheel structures synthesized by the Liu method and height topography graph. (**d**) Silica-coated 2D wheel structure produced using R5 and height topography (the wheel with the dashed line has no silica coating).

### *4.3 Embedded ARL Projects on Cellulosic 'Living Materials' and Crystallin-Based Optical Materials*

*Cellulosic 'living materials'.* The use of cellulose as a robust platform for living material systems was established using in-house expertise from the host lab. A synthetic biology toolset and cloning protocols were verified in multiple cellulose-producing species, allowing strategies to genetically manipulate the cellulose synthase operon to be initiated. Cellulose-assembling proteins were demonstrated for facile and uniform functionalization, visualized at the nanofiber scale. Engineered *E. coli* and *Bacillus* strains were able to be cocultured with *Gluconacetobacter* by adjusting growth media. Finally, opportunities were identified for further intersection with host lab's capabilities, including the functionalization of biosynthesized nanoparticles onto cellulose scaffolds, high-resolution patterning of cell and protein features onto biomaterial substrates, and incorporation of advanced genetic circuits into living materials for sensing and response.

*Crystallin-based optical materials.* We expressed and purified high-refractive index crystallins from human, mouse, and octopus from *E.coli*. Of these, the human gamma-D crystallin expressed at a level suitable for materials assembly (>200mg/L). This protein was fused to between one and three SpyCatcher or SpyTag domains, expressed, and purified. Efficient assembly of up to three crystallin fusion proteins was observed, suggesting that this assembly strategy can be used to make large protein complexes. Unfortunately, crystallins with higher numbers of assembly domains (3+) were unable to be sufficiently expressed. Moving forward, we are re-building and optimizing expression systems to allow production of a wider variety of crystallins, as well as crystallins fused to increased numbers of assembly domains.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

- Dr. Padraig Molony (Lockheed Martin) had visited the lab on 12/6/2016 to discuss the application of magnetosomes, and the sample of purified wildtype bacterial magnetic nanoparticles were provided for preliminary experiments to spin-coat on a Kapton surface. The results were received on January 2017.
- The engineered magnetosome samples were sent on 2/3/2017. Dr. Molony has visited Voigt lab to discussed the results with Dr. Furubayashi on 5/1/2017.
- OSD Future Directions for Synthetic Biology in Energy and Materials meeting was hosted by Dr. Chris Voigt in March and hosted ARL researchers there.
- Dr. Chris Voigt is on the Advisory Board of ARAP, and has traveled to ARL for two meetings.
- Dr. Chris Voigt has visited ECBC in Aberdeen, Maryland in June, 2018.
- Dr. Chris Voigt has reviewed the Army Synthetic Biology Strategy in August, 2018.
- The MIT-Broad Foundry has provided phloroglucinol sensing system to ECBC (cell-free, via Dr. Michael Jewett, Northwestern University).
- The MIT-Broad Foundry has provided a phloroglucinol sensor vector and (separate) production vector to Dr. Catherine Germane (ARL).

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

***Publications***

M. Furubayashi and C. A. Voigt. Engineering magnetic nanoparticles in magnetotactic bacteria. In preparation.

J. A. N. Brophy, A. J. Triassi, B. L. Adams, R. L. Renberg, D. N. Stratis-Cullum, A. D. Grossman and C. A. Voigt. Engineered integrative and conjugative elements for efficient and inducible DNA transfer to undomesticated bacteria. *Nature Microbiology*, September 2018. 10.1038/s41564-018-0216-5.

M. J. Smanski, S. Bhatia, D. Zhao, Y. Park, L. B. A. Woodruff, G. Giannoukos, D. Ciulla, M. Busby, J. Calderon, R. Nicol, D. B. Gordon, D. Densmore and C. A. Voigt. Functional optimization of gene clusters by combinatorial design and assembly. *Nature Biotechnology*, December 2014. 10.1038/nbt.3063.

***Patents***

Inventors: A. K. Wallace, M. Furubayashi and C. A. Voigt. Energy Manipulating Biomaterials by R5 Silicates, Melanins, and Magnetosomes, US. Patent Application No.: 62/459251

Inventors: R. Nicol, C. A. Voigt, D. Benjamin Gordon and Y. Park. Proteomic Analysis with Nucleic Acid Identifiers, Application ID: 62131805, EFS ID: 21741229

Inventors: R. Nicol, L. Woodruff, T. Mikkelsen and C. A. Voigt. High-Throughput Assembly of Genetic Elements, Publication No: WO2015184016, International Application No: PCTUS2015032760

# Army's Institute for Collaborative Biotechnologies

## Final Report for ICB UARC Task Order 33

### ARO Contract W911NF-09-D-0001

### December 1, 2013 – November 30, 2018

**Reflectin-Inspired, Lightweight, Tunably Reconfigurable Photonic Materials**
*Daniel E. Morse (UCSB)* ..... BIM-2

**Understanding the Mechanism of Transmembrane Electron Transfer and its Influence on Intercellular Communication and Biofilm Diversification**
*Guillermo C. Bazan (UCSB)* ..... BIM-9

**Anisotropic Nanostructured Materials for Electrochemical and Photovoltaic Energy Conversion and Storage**
*Bradley F. Chmelka and Songi Han (UCSB)* ..... BIM-18

**Bio-inspired Photonic Surfaces for Broadband IR Detectors, LEDs, and Lightweight, Flexible Solar Platforms**
*Michael J. Gordon and Daniel E. Morse (UCSB)* ..... BIM-25

**Combining Bio-Inspired Self-Assembly with Chemical Functionalization in the Design of Discrete Oligomeric Building Blocks and High Performance Hydrogels**
*Craig J. Hawker (UCSB)* ..... BIM-32

**Self-assembled Conformable 3D Networks for Hybrid Electronic Materials**
*Angela M. Belcher (MIT)* ..... BIM-38

**Topology and Shape Optimization of Energy-Dispersive Cellular Structures**
*Frank W. Zok (UCSB)* ..... BIM-45

**Field-Assisted 3-Dimensional Printing of Bio-inspired Hierarchical Materials**
*Matthew R. Begley (UCSB)* ..... BIM-51

**Theoretical and Experimental Investigations of Energy-Dispersive Cellular Nanostructured Polymeric Materials**
*Glenn H. Fredrickson (UCSB)* ..... BIM-58

**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Reflectin-Inspired, Lightweight, Tunably Reconfigurable Photonic Materials**
**(Formerly: Bio-inspired, Lightweight, Polymer-based, Flexible Optoelectronics)**

**Project Leader:** **Daniel E. Morse (UCSB)**

**Collaborators:** **James Sumner, Cynthia Lundgren, Richard Fu and Kimberly Sablon, (ARL-SEDD); Charlene Mello (NSRDEC); Andreas Hampp (Raytheon Vision Systems Inc); Philip Wyatt (Wyatt Technology Corp)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

Our most significant result has been the elucidation of the molecular mechanism by which the reflectin proteins act as a molecular spring-loaded Coulombic sensor, controlling an osmotic motor that changes the refractive index contrast and lattice dimensions of a subcellular Bragg reflector to precisely and continually tune the color and intensity of light reflected from specialized cells in squid skin for camouflage and communication [1-10].

Analyzing and genetically engineering the cloned recombinant reflectin DNAs and the proteins they encode, we recently discovered a previously unsuspected, quantitatively predictive and highly precise relationship between the extent of charge neutralization and the resulting size and number of the neutralization-triggered reflectin assemblies, with very low polydispersity. Computational modeling of the energetics of reflectin folding and assembly, in concert with our biophysical analyses leveraged by genetic engineering, explain this finding, revealing that the block-copolymeric reflectin is analogous to a chain of alternating mechanical springs acting in opposition, with Coulombic repulsion of the cationic linkers opposing the entropic drive to condensation and phase-segregation encoded in the alternating repeated domains. Neutralization of that repulsion releases the restraining tension on the repeated, conserved peptide domains, enabling their rapid, entropically driven condensation and folding, with the emergence of previously cryptic phase segregation of hydrophobic surfaces that promote hierarchical assembly. Proceeding via liquid-liquid phase-segregation ("coacervation"), assembly of the multimers is rapidly arrested by formation of a tight network of internal cation-$\pi$ crosslinks. As a result of this rapid dynamic arrest, the size and corresponding number of multimers are precisely and predictively controlled, exactly proportional to the extent of charge neutralization. This in turn precisely and proportionally tunes the bulk material, its resulting physical properties, and the photonic behavior in the living cells.

Early in this project we found that accordion-like pleats or invaginations of the iridocyte cell membrane form multiple lamellae of a tunable Bragg reflector [4] that is the source of the iridescence [5] (**Figures 1, 2**). These lamellae contain 4 different reflectins [1, 8, 9] – members of a family of proteins thus far unique to various reflective tissues in molluscs. Contrary to a popular misconception, we find that the reflectins are not the source of the reflected color, but instead, the drivers of dynamic changes in the refractive index, thickness and spacing of the Bragg lamellae, and thus tunably control the brightness and color reflected from those subcellular, membrane-bound structures [1, 2, 4-9].

We confirmed that squid iridocytes are activated by cholinergic neurons that regulate iridescence via muscarinic acetylcholine receptors, and showed that these receptors activate a G protein-phospholipase-calcium/calmodulin-mediated signal transduction circuit that culminates in activation of a protein kinase to phosphorylate each of the reflectins in a site-specific manner, and that this phosphorylation is essential for the activation of reflectance and the progressive tuning of iridocyte color [1, 2, 4] (**Figure 2.**). *In vitro* analyses with the purified, recombinant reflectins (that we cloned and sequenced [8, 9] then revealed their mechanism of action – a puzzle that had remained since the discovery of these unique proteins a decade ago.

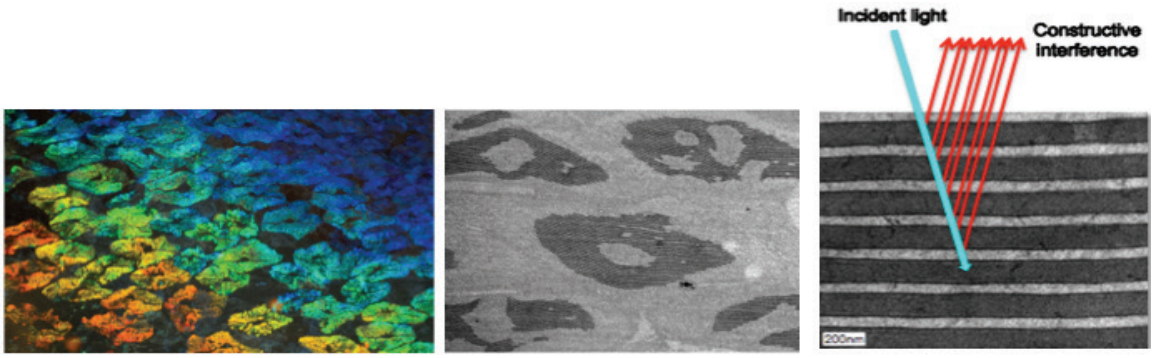



**Figure 1.** *Tunable Bragg lamellae in squid skin iridocytes provide tunable color of reflectance.* (**Left)** Darkfield image of *Doryteuthis pealeii* squid skin (40X magnification) under white light. Iridocyte cells appear flat in the plane of the tissue; avg. size ca. 20-40 μm wide x 2-5 μm thick. Application of the neurotransmitter ACh at upper right induced activation of a wave of colored reflectance. The dark area in the center of each cell corresponds to the position of the cell nucleus. (**Center**) TEM image of ultrathin cross-section of green iridocyte cells fixed with uranyl acetate showing Bragg lamellae; (**Right**) Higher magnification TEM of cell from center image, showing membrane-bound Bragg lamellae filled with densely staining reflectin proteins. Scale bar = 200 nm. From [2].

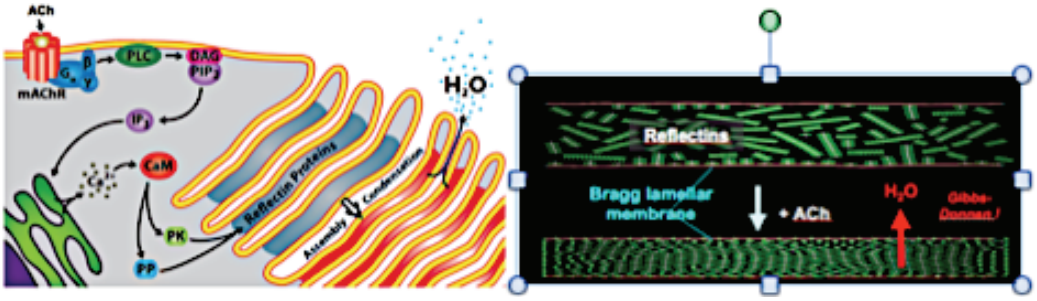



**Figure 2.** *Neurotransmitter-activated, reflectin-mediated, dynamic tuning of color and brightness.* (**Left**) Molecular details of the neurotransmitter (ACh)-triggered signal transduction circuit culminating in activation of the enzymatically catalyzed phosphorylation of reflectins, driving their condensation, with the resulting re-equilibration of electrostatic potential and osmotic pressure driving dehydration of the Bragg lamellae [4]. (**Right**) Diagram illustrating the Gibbs-Donnan-mediated reversible efflux of water, tuning the thickness and spacing of the Bragg lamellae (thus tuning the reflected color), following condensation of the reflectin proteins that also increased the refractive index contrast, thereby activating reflectance. Drawn from results in [4].

The tunable reflectins are transparent, carry no chromophores, and exhibit a unique structure with up to 6 canonical "repeat" motifs separated by histidine-rich linker peptides that are highly positively charged, giving the proteins pIs ranging from 8.6 to 8.9 [1, 8, 9]. As a result of their positive charge when in the "off" state, the reflectins are in Coulombic repulsion in the Bragg lamellae [1, 2, 4, 8, 9] (**Figure 2**.**right**). ACh-activated phosphorylation adds negative charges that neutralize the reflectins [1, 2, 4, 8, 9], overcoming their Coulombic repulsion and driving their condensation (increasing the intra-lamellar refractive index and thus activating reflectance) and subsequent assembly [2, 9]. These processes mask the reflectins' surface charges, driving a net diffusion of small counterions ($Cl^-$, $SO_4^{=2}$) across the lamellar membrane, with the resulting osmotic imbalance "pulling" water from the lamellae by Gibbs-Donnan-mediated reversible dehydration (demonstrated with $D_2O$) [4, 5, 9]. This dehydration reversibly shrinks the lamellae and their spacing, thus progressively changing the reflected color [4, 5] (**Figure 2**.**right**).

*In vitro* analyses with the purified, recombinant reflectins provided further understanding of the molecular processes driving this mechanism [2, 8, 9] (**Figure 3**.) Using titration of the positive charges of the reflectins by increasing pH to neutralize the positive charges of the histidine side chains in the metastable reflectins, as a surrogate for the neutralization resulting from ACh-triggered phosphorylation *in vivo*, we discovered that neutralization triggers condensation and the emergence of secondary and tertiary structure (that we analyzed by X-ray scattering, fluorescence resonance energy transfer (FRET) and surface plasmon resonance (SPR)), driving emergence of bifacially phase-segregated amphiphilic structures (alpha helices and beta-sheets) that act like 'molecular Velcro™' to drive the further, hierarchical assembly of the condensed oligomers [2, 9]. This tunably reversible control of

reflectin condensation and assembly exerts 3 effect that activate the efflux of water (that we monitored directly with $D_2O$ tracer [4]) that shrinks the Bragg lamellae to produce the tunable change in reflected wavelength: (1) reducing the particle number-concentration of reflectins, they activate the colligative change osmotic pressure d2iving dehydration; (2) they exclude the coordinating small ions to drive an ionic efflux across the Bragg lamellar membranes to activates aGibbs-Donnan-mediated dehydration; and (3) they directly exclude water from the condensing and assembling proteins, thus furthering the dehydration [10].

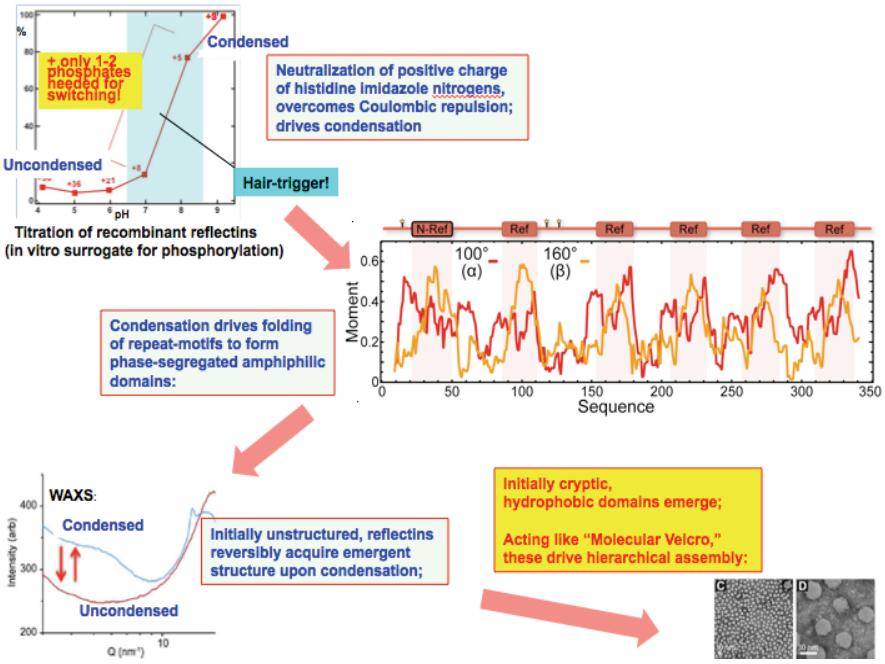



**Figure 3.** Recent findings completing our elucidation of the molecular mechanism by which reflectins control tunability of biophotonic behavior in squid skin cells [9]. Condensation of reflectin is triggered with hair-trigger sensitivity; phase-segregated hydrophobic domains then emerge by folding of each of the canonical repeat domains (heavy bars in protein map above central plot); wide-angle X-ray scattering confirms emergence of beta-sheet structure; TEM confirms subsequent hierarchical assembly.

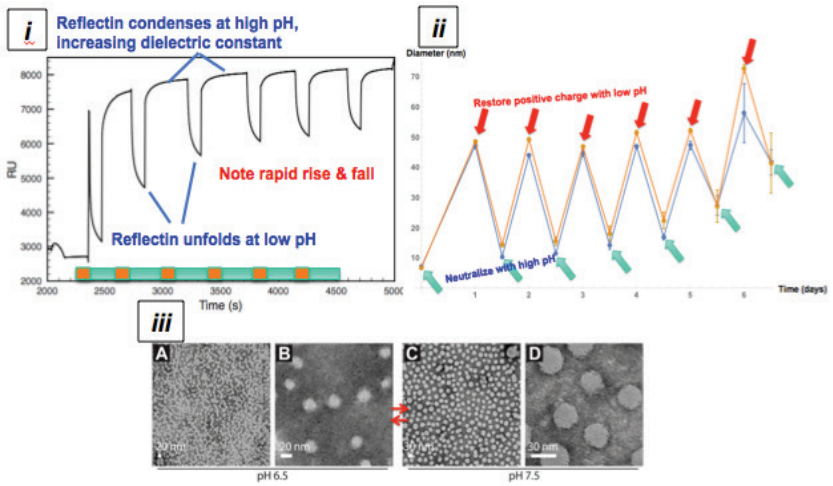



**Figure 4.** Physical evidence confirming the mechanism described above [9]. *(i)* Surface plasmon resonance of gold film cyclically tuned by condensation off reflectin attached at low concentration to prevent assembly. Time-scale in seconds; green = pH 4.5, orange = pH 7.5. *(ii)* DLS shows cyclical changes in hierarchical assembly of reflectin driven by same changes in charge as in *(i);* diameter cycles from ca. 5 nm to ca. 50 nm. And is stable for days. *(iii)* TEM confirms results of DLS; A and B = low and high magnification of 23 nm complexes at pH 6.5; C and D = low and high magnification of 48 nm complexes at pH 7.5

We further analyzed the charge-neutralization-driven reversible condensation and hierarchical assembly of the purified recombinant reflectins and demonstrated their repeated cyclability (**Figure 4.**), by surface plasmon resonance (SPR) tuned by condensation of reflectin tethered to gold, and by dynamic light scattering (DLS) and TEM. The SPR and DLS data clearly confirm that the sequential processes are readily reversible and repeatedly cyclable, as they are *in vivo,* with the dimensions of the reflectin assemblies in the "off" and activated states measured *in vitro* by dynamic light scattering and TEM agreeing closely with one another and with measurements *in vivo* [9].

In research pursued in this project, we also discovered that an overlayer of brightly reflective, wavelength-tunable Mie-scattering cells in giant clams (genus *Tridacna*) significantly enhances solar photon capture, and the resulting photosynthesis, by endosymbiotic algae organized in columnar pillars below the reflectors (11-14). As discussed at length with our Army and Industry partners, this discovery suggests a path for significant enhancement of efficiency of lightweight, flexible arrays and 3D converters for solar energy.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

Our objectives during the final reporting period of this project have been two-fold: (1) to use the powers of genetic engineering and computational modeling to leverage analyses by high-resolution X-ray diffraction, cryo-electron microscopy, electron paramagnetic resonance (EPR), dynamic light scattering DLS, circular dichroism and isotope transport studies, to arrive at a definitive elucidation of the underlying molecular mechanisms by which the reflectin proteins dynamically tune biophotonic behavior; and (2) to then translate our discoveries to develop a reflectin-inspired, lightweight, tunable photonic device that can serve as a prototype for higher efficiency, lightweight photonic systems for Army applications. The enabling principles and devices we aimed to deliver should provide generic platforms for lightweight, tunable systems for optical communications, switching and energy technology insertions into multiple additional Army systems.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

To realize our first objective, we genetically modified our cloned and fully sequenced DNAs coding for the reflectin molecules, using standard procedures as described in our latest publication [10]. These modifications included site-specific substitutions, permitting us to add additional negative- or positive-charge amino acids at sites in the reflectins corresponding exactly to those we had previously identified as the sites of phosphorylation that activate the photonic changes in the living cells [8]. Other genetic modifications produced deletions of specific domains of the proteins, corresponding to selected conserved domains and cationic linkers. Both the normal (wild-type) and genetically engineered proteins were encoded on recombinant DNA plasmids, expressed in bacteria, and purified for analysis, all as previously described [8-10]. High-resolution small-angle X-ray scattering (SAXS) was performed at the Stanford Synchrotron Research Laboratory using a unique flow-cell of our design to exclude effects of small variations in capillary wall diameters [10], and high-resolution cryo-TEM analyses were performed at the Molecular Foundry at the Berkeley National Laboratory, and EPR analyses were performed with spin-labeled reflectin after genetic engineering to remove one or the other of the two naturally occurring cysteine residues, thus permitting unambiguous analyses of the two singly-labeled proteins.

To realize our second objective, plasmonic opto-electric platforms consisting of nano-arrays of silicon pillars on thin gold substrates were fabricated by conventional lithographic techniques, characterized spectrophotometrically, optimized computationally for color-sensitivity to changes in refractive index, and prepared for optical tuning by low-voltage electrochemical control of reflectin assembly.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

As summarized above, we had learned how a neuronal signal activated phosphorylation of the reflectins to progressively drive charge-neutralization of the proteins, triggering their nucleation, condensation, folding and hierarchical assembly to consequently drive an osmotic motor that continuously adjusts the dimensions and refractive index of intracellular photonic nanostructures – either the lamellae of color-tunable Bragg reflectors or broadband Mie-scattering vesicles. In the final year of our project, by combining the power of genetic engineering of the cloned recombinant proteins with high-resolution physical analyses (by SAXS, EPR, DLS, CD, TEM and cryo-TEM) and computational modeling, we discovered how this behavior is encoded in reflectin's block copolymeric structure, consisting of repeated, highly conserved peptide domains separated by cationic linkers [10]. While the

conserved domains exhibit a strong thermodynamic drive to condense and fold, yielding newly emergent phase-segregated secondary structures with hydrophobic surfaces that potentially facilitate hierarchical assembly, this drive is antagonized by the Coulombic repulsion of the cationic linkers, imposing a dynamic tension on the conserved domains that can be progressively released by charge-neutralization of the cationic linkers. This release is physiologically triggered by a neurotransmitter activated signal transduction cascade that culminates in site-specific phosphorylation of the reflectins, thus triggering activation of what amounts to a spring-loaded, ultra-sensitive, precise and energy efficient molecular biosensor.

Our latest analyses have now revealed a previously unsuspected, quantitatively predictive and highly precise relationship between *the extent of charge neutralization* and the resulting *size (and number)* of the reflectin assemblies, with very narrow polydispersity (**Figure 5**). Our computational modeling of the energetics of reflectin folding and assembly, in concert with our analyses by SAXS, cryo-TEM and EPR explain this finding, revealing that the block-copolymeric protein is analogous to that of a chain of alternating mechanical springs acting in opposition, with Coulombic repulsion of the cationic linkers opposing the entropic drive to condensation and phase-segregation encoded in the repeated domains. Neutralization of that repulsion releases the restraining tension on the repeated domains, enabling their rapid, entropically driven condensation and folding, with the emergence of previously cryptic phase segregation of hydrophobic surfaces that promote hierarchical assembly. Proceeding via liquid-liquid phase-segregation ("coacervation"), as observed by microscopy and EPR analyses, assembly of the multimers is rapidly arrested by formation of a tight network of internal cation-π crosslinks. As a result of this rapid dynamic arrest, the size and corresponding number of multimers are precisely and predictively controlled, exactly proportional to the extent of charge neutralization (**Figure 5**). This in turn precisely and proportionally tunes the bulk materials property.

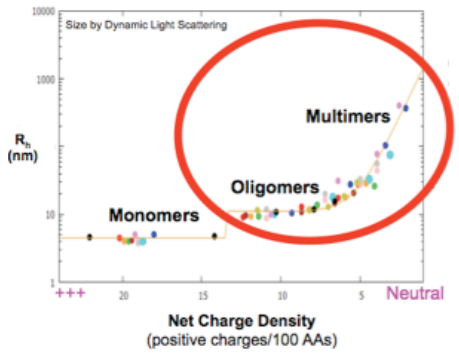



**Figure 5.** Neutralization of Coulombic repulsion precisely fine-tunes assembly of reflectin A1 and its genetically altered variants. Hydrodynamic radius ($R_H$) experimentally measured by dynamic light scattering is plotted as a function of the calculated net charge density for all or parts of reflectin A1 wild-type and its mutationally altered variants at varying pH values (all at 10 micromolar concentration). Linear net charge density was reduced either by pH-titration, genetic insertion of negatively charged residues, or removal of positively charged residues. [10]

The process is highly sensitive, remarkably precise, reversible, repeatedly cyclable and energy efficient. The integrated mechanism could thus be described as "Fire, Lock and Reload," as illustrated in **Figure 6**.

Our efforts to translate the above findings to a reflectin-tuned optical device are still ongoing. Responding to guidance from our Army partners (cf. §5, below), we changed direction from our initial aim of producing a reflectin-inspired, tunable polymer to directly harnessing the reflectin protein itself to tune photonic behavior. Accordingly, we have fabricated a test-bed platform consisting of a nano-array of silicon posts on a thin gold substrate, to provide structural color from the post array, tunable by interaction with the plasmonic surface wave of electrons generated by illumination of the gold surface, with uniquely high sensitivity to tuning by modulation of the local refractive index. Our plan is to modulate that local refractive index, and thus, tune the color reflected from the device, by electrochemical control of reflectin assembly, as illustrated in **Figure 7**.

In collaboration with UCSB's Professor Mike Gordon, arrays of nanoscale posts on gold substrates were fabricated by interference lithography, their reflectance spectra characterized spectrophotometrically, and sensitivity to refractive index optimized by finite difference time domain (FDTD) computational analyses. Low-voltage (ca. 0.8 V) electrochemical control of reflectin charge-neutralization and resulting condensation and assembly was found feasible by cyclable neutralization of histidine (the predominant cationic residue in reflectin) at -/+ 0.8 V, preparing these efforts for final integration, testing, and publication of results.

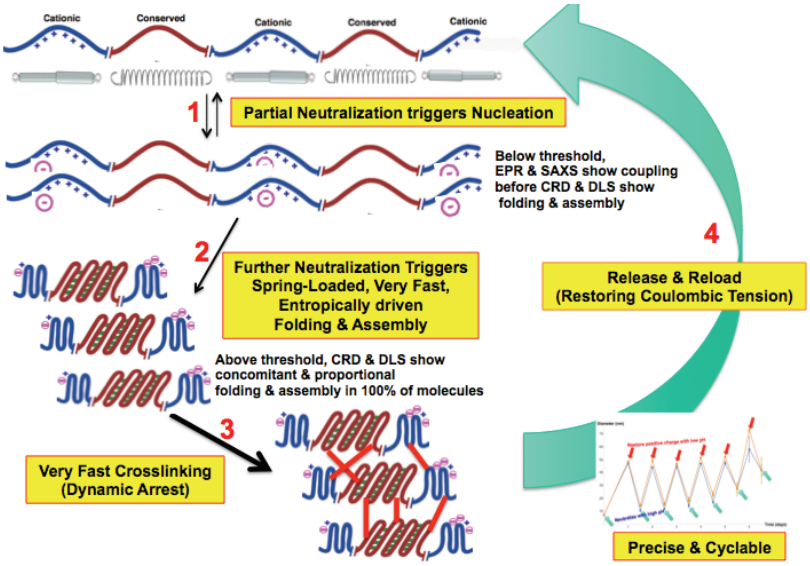



**Figure 6.** "Fire, Lock and Reload" – the integrated mechanism of reflectin-mediated sensing, response and re-setting, as described above [10]

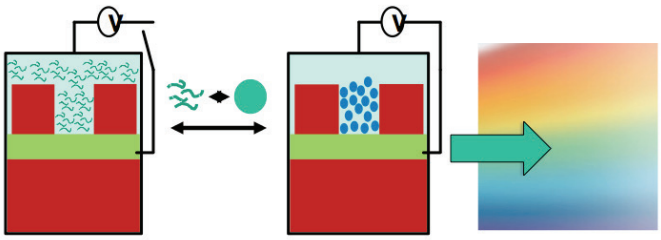



**Figure 7**. Schematic of reflectin-tuned nanophotonic device under development. Array of nanoscale silicon posts on thin layer of gold, infiltrated with solution of reflectin. Low voltage potential is applied to neutralize Coulombic repulsion of reflectins (cf. **Figure 5**, above), thereby increasing local refractive index to modulate the plasmonic tuning of structural color from the post-array.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

Our interactions with Army and Industry scientists and technology leaders during this final reporting period have included the following:

Dr. James Sumner, Biotechnology Leader, ARL-SEDD: Provided guidance on changes in Army vision for transition pathway and proposed prototype development.

Dr. Richard Fu, Flexible Electronics, ARL-SEDD: Provided guidance on fabrication design for lightweight, flexible electro-optical materials and devices, and guidance on Army requirements and opportunities. Co-author on related project publication.

Dr. Charlene Mello, Chief Scientist, NSRDEC: Provided guidance on transition path and Army requirements and opportunities for Soldier systems.

Dr. Andreas Hampp, Division Leader, Raytheon Vision Systems Inc. (Goleta, CA): Provided guidance on transition to lightweight electro-optical materials and devices. Co-author on related project publication.

Dr. Philip Wyatt, Founder and CEO, Wyatt Technology Corp. (Goleta, CA): Guidance on electro-optical characterization methods and advanced instrumentation.

Guidance from our Army partners during this period led us to change direction from our initial aim of producing a reflectin-inspired, tunable polymer to directly harnessing the reflectin protein itself to tune photonic behavior, as described in §4 and **Figure 7**, above.

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

R. Levenson, C. Bracken, C. Sharma, P. Kohl, Y. Li, J. Santos, C. Arata and Daniel E. Morse. Neutralization of a distributed Coulombic switch precisely tunes reflectin assembly. *Nature Communications*, in press. 10.1101/456442.

R. Levenson, D. G. DeMartini and D. E. Morse. Molecular mechanism of reflectin's tunable biophotonic control: Opportunities and limitations for new optoelectronics. *APL Materials*, August 2017. 10.1063/1.4985758.

A. Ghoshal, E. Eck, M. Gordon and D. E. Morse. Wavelength-specific forward scattering of light by Bragg-reflective iridocytes in giant clams. *J. Royal Society Interface*, July 2016. 10.1098/rsif.2016.0285.

A. Ghoshal, E. Eck and D. E. Morse. Biological analogs of RGB pixilation yield white coloration in giant clams. *Optica*, January 2016. 10.1364/OPTICA.3.000108.

A. Ghoshal, D. G. DeMartini, E. Eck and D. E. Morse. Experimental determination of refractive index of condensed reflectins in squid iridocytes. *J. R. Soc. Interface*, June 2014. 10.1098/rsif.2014.0106.

R. Rotstein, S. Mitragotri, M. Moskovitz and D. E. Morse. Progressive transition from resonant to diffuse reflection in anisotropic colloidal films. *Polymer Physics,* February 2014. 10.1002/polb.23458.

**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Understanding the Mechanism of Transmembrane Electron Transfer and its Influence on Intercellular Communication and Biofilm Diversification**

**Project Leader:** **Guillermo C. Bazan (UCSB)**

**Collaborators:** **James J. Sumner and Christian J. Sund (ARL-SEDD);**
**Steven P. Harvey (ECBC); Derek R. Lovley (UMass Amherst);**
**Arum Han (Texas A&M); Bruce Logan and Manish Kumar (Penn State);**
**Joachim S.C. Loo and Jamie Hinks (Nanyang Technological University);**
**Mike Mahan and Rick Dahlquist (UCSB) and Shelly Minteer (University of Utah)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

Work supported through the ICB in this period cycle has focused predominantly on the understanding and application of conjugated oligoelectrolytes (COEs) that spontaneously insert into microbial membranes (**Figure 1**). These studies have led to the following major significant results:

i) The demonstration that conjugated oligoelectrolytes (COEs) increase the power generation of microbial fuel cells (MFCs) and the photocurrent generation and electrical contacts in thylakoid-based photobioelectro-chemical devices.

ii) The demonstration that COEs are useful agents for tailoring the product distribution generated from catalytically active biological films. Specifically, we demonstrated that product selectivity in microbial electrolysis cells derived from wastewater biofilms can be biased toward desirable hydrogen production by inhibiting the activities of certain hydrogenases.

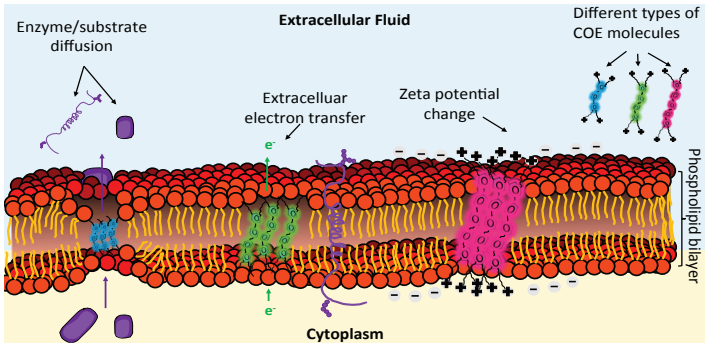



**Figure 1**. The insertion of COEs into cell membranes leads to a continuum of microbe modifying effects that are relevant within the context of basic science and technological applications.

iii) A comprehensive mechanistic picture of how COEs accelerate extracellular electron transfer (EET) in *Shewanella oneidensis*.

iv) The delineation of how COE molecular structure can be tailored so that upon intercalation the resulting microbial membranes (a) become more rigid and thus endow the microbes with increased resistance to environmental stress, (b) are more permeable, while keeping microbial vitality, and thereby increase the rates of biocatalytic processes, and (c) are severely perturbed thereby giving rise to broad spectrum antibiotic activity.

v) The design of redox-active COEs that mimic the function of multiheme proteins responsible for electron transport in anaerobic bacteria. Moreover, the molecular properties can be designed through density functional theory so that the resulting potential at which charges are removed from bacteria are prespecified.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

The general objectives for this funding cycle concern studies on how COEs and related materials can be used to tailor biotic/abiotic interfaces comprised of electrodes and living microorganisms, and the extent to which such materials may be used to improve whole cell catalysis through controlled permeabilization of membranes. Specifically, we use electrochemical and chemical analysis techniques to obtain mechanistic insight into the extent to which ferrocene-containing COEs increase charge extraction by either direct electron transfer or diffusion-mediated mechanisms. Through chemical diversity, we sought to understand to what extent the potential at which electrons can be extracted from *Shewanella oneidensis* correlates to the oxidation potential of the COEs. Towards a different objective and in collaboration with the research group of Dr. James Sumner (ARL-SEDD), efforts were also dedicated to the completion of a program where COEs are bound to gold electrode surfaces with the goal of establishing whether the resulting interfaces can more intimately couple to metabolic intermediates inside the cells. A new type of COE chemical structure was also designed and synthesized. Previously, with the exception of ferrocene containing COEs, all structural variations contain a conjugated framework that is planar and appear to lead to substantial aggregation within lipid bilayer membranes. We thus targeted a COE with a [2.2] paracyclophane structure that endows the overall conjugated framework with a three-dimensional aspect ratio and the possibility of actuating electron transport via through-space interactions. The molecular topology of the molecule was also envisioned to discourage close contacts. Finally, we planned to establish a collaborative program with the research group of Prof. Mike Mahan (UCSB) to examine how different COE structures modify the intrinsic fitness of different microorganisms.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

Our scientific strategies and approaches are built on our expertise to design molecular and polymeric systems that have appropriate optical, electronic and self-assembly properties for specifically effecting a target response in microbes. The impact upon association with microbes is studied through bioelectrochemical techniques, examination of catalytic reactions, a range of structural and optical characterization techniques, and the use of microbiology tools and techniques.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1. Bioelectronics*

Bioelectrochemical systems (BES) rely on exoelectrogenic microbes that exchange electrons with an electrode through the process of extracellular electron transfer (EET) [1]. These emerging bioelectrochemical technologies include microbial fuel cells for wastewater remediation and bioelectrosynthesis platforms that use microbes to carry out desired chemical reactions [2-5]. The functional activity of bacteria in these devices is determined by the efficiency of interfacial charge transfer between the cells and the electrode [6,7]. Materials that promote charge transport across these abiotic/biotic interfaces is therefore an area of interest. Membrane-intercalating molecules and conductive polymers represent two means to improve the electronic coupling of microbes to external electrodes.

Finding general methods by which EET can be improved will increase the breadth of potential bioelectronics applications. Insertion of artificial constructs into microbial membranes has been shown to increase their ability to electronically communicate with abiotic components [8, 9]. One class of relevant molecular systems designed and synthesized by our group are known as COEs, and they contain an electronically delocalized backbone bearing ionic charged groups [10-15]. Redox-active COEs were recently designed to mimic the mechanism of charge transport in naturally occurring membrane-bound proteins that move electrons through a sequence of iron-containing cytochromes [16, 17].

The redox-active COE containing a single ferrocene unit, abbreviated as DSFO+ (**Figure 2.a**), was found to increase biologically-derived current by 45 ± 14% over controls in microbial three-electrode electrochemical cells (M3Cs) employing *Shewanella oneidensis* MR-1 [16]. When operating M3Cs at the oxidation potential of DSFO+ (270 mV vs Ag/AgCl), current amplification arose from an increase in the coulombic efficiency and current collected per cell. Examination by cyclic voltammetry revealed that the increase in current was not due to direct/mediated electron transfer (DET/MET) mechanisms through membrane proteins or flavins, respectively, but rather through a process that relies on the redox properties of DSFO+. In this way, DSFO+ was also able to partially rescue the electrogenic character in non-electrogenic mutant strains of *S. oneidensis* MR-1.

A second generation of redox-active COEs was recently designed [17]. The new molecules, namely DVFBO and F4-DVFBO in **Figure 2.a**, extend the dimensionality of DSFO+, while reducing the number of charged groups per molecule to increase the driving force for membrane association. The two COEs have similar membrane affinity and toxicity, but fluorination of the core results in a higher oxidation potential (422 ± 5 mV compared to 365 ± 4 mV vs Ag/AgCl for the neutral precursors chloroform). When the working electrode is poised below the oxidation potential of the COEs ($E_{CA}$ = 200 mV) in M3Cs containing *Shewanella oneidensis* MR-1, addition of DVFBO and $F_4$-DVFBO produces negligible biocurrent enhancement compared to controls, see **Figure 2.b**. At $E_{CA}$ = 365 mV, DVFBO increases steady-state biocurrent by 67 ± 12% relative to controls, while the increase with $F_4$-DVFBO is just 30 ± 5%. Cyclic voltammetry supports that DVFBO increases catalytic biocurrent and that $F_4$-DVFBO has less impact, consistent with their oxidation potentials. As MET, DET, and electrode colonization were not increased by COE addition, *the overall result is the ability to increase and regulate electron transfer from microbial species exclusively via tailoring of the COE redox properties*.

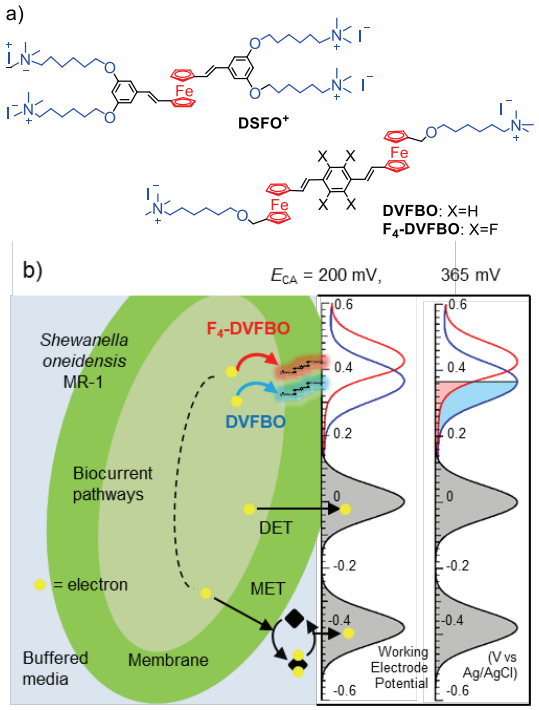



**Figure 2.** (**a**) Structural evolution of redox-active COEs and (**b**) schematic representation of biocurrent pathways available to *Shewanella oneidensis* MR-1.

Conjugated polyelectrolytes (CPEs), which have been used as interlayers for mediating charge recombination and extraction in organic optoelectronic devices [18-28], represent an under-explored class of pH-neutral polymeric materials for further improving biotic/abiotic contacts. A set of three CPEs with varying backbone structures and pendant ionic functionalities (**Figure 3.a**) were used to evaluate the impact of these molecular features on biocurrent outputs [29]. CPEs were added to M3Cs poised at 0.3 V containing *S. oneidensis* MR-1. **Figure 3.b** shows that CPE-CDT-$SO_3$, a self-doped p-type anionic CPE, amplifies steady-state biocurrent output by 2.7 ± 0.7-fold relative to positive controls. The anionic polymer CPE-F-$SO_3$ does not statistically alter steady-state current density, while the cationic CPE-CDT-$NMe_3$ reduces steady-state current density compared to positive controls. Electrochemical characterization indicates that the dominant mechanism of biocurrent amplification by CPE-CDT-$SO_3$ is increased direct electron transfer. By absorbance spectroscopy, *S. oneidensis* MR-1 donates metabolic electrons to CPE-CDT-K, thereby de-doping the polymer. These experiments combined with in situ cyclic voltammetry indicate that the doped CPE facilitates electron transport to electrodes and reveal structure–function relationships relevant to developing materials for biotic/abiotic interfaces.

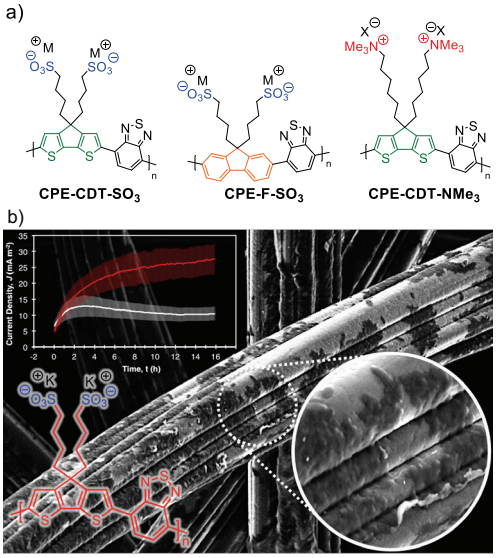



**Figure 3.** (**a**) Chemical structure of CPEs and (**b**) scanning electron microscopy image of carbon fiber working electrode with bacterial colonization after CPE-CDT-$SO_3$ addition. Inset is current density over time (white trace is control and red trace is with 10 µM CPE-CDT-$SO_3$).

As a means to expand the utility of COEs for bioelectrochemical systems, we developed a novel structure containing a thiol functionality for the purpose of directly functionalizing gold electrodes. Electrode-tethered redox mediators have previously been utilized in microbial fuel cells to overcome the practical shortcomings of soluble additives (especially in the context of flow-based operations) [30]. In these systems, the redox mediators are permanently localized where they can be most effective – the biotic-abiotic interface. In addition to increased electrical communication at the biotic-abiotic interface, our system has the further

benefit of enhanced physical interactions between microbes and the electrode surface. As depicted in **Figure 4**, the core of the surface-bound COE may intercalate into microbial membranes and anchor microbes to the electrode.

In collaboration with Dr. James Sumner and his colleagues at ARL-SEDD, the novel surface-binding COE was tested in MFCs using non-electrogenic *E. coli* K-12. A graduate student in our group, Alex Moreland, worked at ARL-SEDD on this effort. The results demonstrate enhanced MFC performance following anode functionalization (**Figure 5**). The peak power of devices containing functionalized anodes was twice that of devices using bare gold anodes. In addition, the time to reach peak power was reduced from 4 hours to 2 hours. This reduction in turn-on time and increase in peak power could have significant implications for additional Army-relevant technologies, such as cell-based biosensing. Relative to our previously reported solution-based COE systems, this monolayer-based system requires three orders of magnitude less COE to achieve comparable increases in MFC performance. Additionally, by tethering the COE to the anode the potential for the COE to enter the waste stream is reduced and there is a possibility for recycling the COE by re-using the electrode. The results of this collaborative project have been prepared in a co-authored manuscript to be submitted in mid 2019.

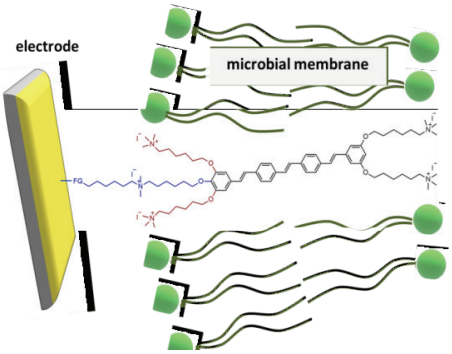



**Figure 4.** Idealized depiction of microbial membrane interaction with traditional membrane-intercalating COE (red) and novel surface-bound COE (blue).

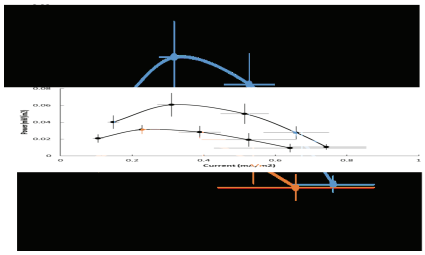


**Figure 5.** Power generation characterization of the MFCs with unfunctionalized gold anodes (orange) and COE-functionalized gold anodes (blue). Error bars show 1 standard deviation away from the mean.

In a continuing collaboration with Dr. James Sumner, we developed new analogues of the surface-binding COE described above (**Figure 6**). In place of the gold-binding thiol moiety, these new analogues contain various functional handles which are pertinent to bioconjugation [31]. Of particular interest is the use of these novel "membrane anchors" for manipulating cell-cell interactions and forming biocomposites. Alex Moreland, visited ARL-SEDD in August of 2018 to develop this technology. Highlights include facilitating cell adhesion to a glass substrate (**Figure 7.a**), directing cell-cell interactions between yeast and bacteria (**Figure 7.b**), and decorating bacterial membranes with proteins (data not shown because of space limitations). Following the positive results in these proof-of-concept experiments, work is ongoing in both labs to apply this technology to practical applications.

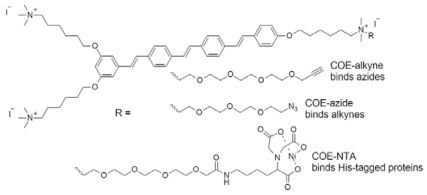



**Figure 6.** Structures of novel COEs designed for bioconjugation in cell-cell interaction and biocomposite applications.

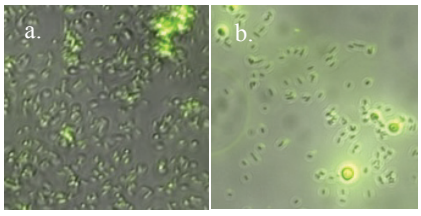



**Figure 7.** (a) *E. coli* cells attached to azide-functionalized glass through COE-alkyne (b) Physical interaction of yeast and *E. coli* cells facilitated by COE-alkyne and COE-azide.

### *4.2. Biocatalysis*

Depending on the molecular structure details, certain COEs can increase membrane permeability. This ability opens up an opportunity to apply these materials in whole cell biocatalysis applications. Such processes are described by chemical conversions using cellular enzymes —— with advantages over conventional chemical syntheses as they require mild reaction conditions, are highly stereoselective, and require

relatively inexpensive purifications [32-34]. In our study, the conversion of fumaric acid to L-malic acid by yeast cells (*S. cerevisiae*), which has a rate-limiting step at the transportation of chemicals across the membrane, was chosen as a model system to demonstrate membrane permeabilization (**Figure 8**) [35-37]. Four different COEs were studied and compared with the commonly used membrane-permeabilizing agent, hexadecyltrimethylammonium bromide (CTAB). The results show that cells treated with DSSN+, DSBN+, COE1-4py increased reaction yield compared to untreated cells.

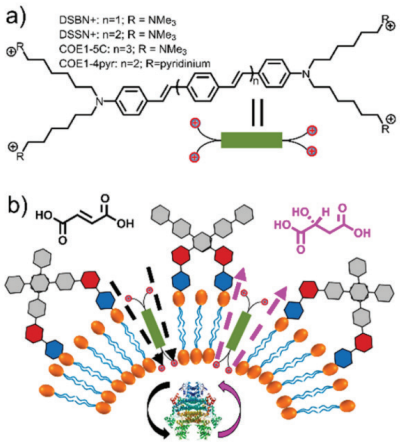



**Figure 8.** Illustration of COE structures and mechanism for accelerating biocatalysis. (a) COEs used in the study; (b) cartoon illustration of COE (green rectangle with pendant groups) intercalation into yeast lipid bilayer to accelerate the transformation of fumaric acid to L-malic acid. The diagram is not to scale.

Unlike CTAB, COEs are capable of achieving larger reaction rates without compromising cell viability even in reused cells [38]. [Difference in molecular structures of COEs yields different reaction rates. We found that change in ionic pendant groups had little effect on rate enhancement whereas modulating length of the molecules led to significantly different degree of reaction rate enhancement. The reaction rates were enhanced 14-, 9-fold for DSBN+ and DSSN+, respectively. No enhancement was found with COE1-5C. These findings suggest a correlation between molecular structure, especially the length of the molecules, and degree of cell permeabilization.

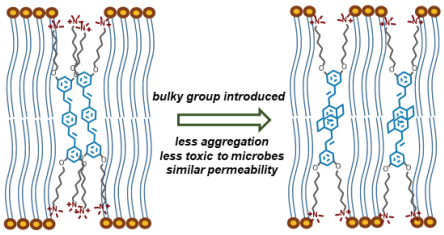



**Figure 9.** Cartoon illustration of the structural evolution from COE2-3C to COE2-3-pCp. Although COE2-3-pCp induced higher lipid disorder, it has less tendency to aggregate in membranes and lower toxicity to *E. coli* and yeast while maintaining a similar level of cell permeabilization as COE2-3C.

From our previous study whole cell biocatalysis applications, all of the COEs studied so far contains only planar, two-dimensional conjugated fragments. Another possible structural variation that has not been considered in the past concerns introducing more dimensionality to the conjugated core of the molecule. Thus, to investigate the effect of increased dimensionality, a COE containing a [2.2]paracyclophane (pCp) unit, which is a non-planar rigid conjugated moiety, was synthesized, namely COE2-3-pCp (**Figure 9**). COE2-3-pCp was studied and compared with COE2-3C, its linear analog with similar molecular length by both experiments and molecular dynamic simulations. COE2-3-pCp has very similar association profile to COE2-3C [39]. Interestingly, while COE2-3-pCp has higher minimum inhibitory concentration (MIC) values than COE2-3C on both *E. coli* (4-fold) and yeast (2-fold), simulations on Gram-negative bacteria membrane model suggests that COE2-3-pCp increases membrane disorder and thinning effect to the higher extent than COE2-3C. Furthermore, the models suggest that there was a 36% reduction in the time that COE2-3-pCp exists as an aggregate in the membrane relative to COE2-3C, which is likely a factor that offset its antimicrobial activity. Their ability to permeabilize membranes and improve whole cell biocatalysis was tested both in lipid vesicles and living cells. In *E. coli* system, calcein leakage assay and ONPG turnover assay were utilized while extracellular ATP assay and fumaric acid conversion experiment were utilized in yeast system. We found that COE2-3-pCp and COE2-3C permeabilize lipid bilayers to a similar extent, albeit the lower antimicrobial efficacy of COE2-3-pCp. Our findings suggest the strategic designs of COEs to attenuate growth inhibition, while inducing membrane permeabilization.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

As described in §4.1, the collective effort on COE mediated EET enhancement benefits from a strong interaction with the research group of Dr. James Sumner at ARL-SEDD. As an interesting aside, it is worth noting that the originally-funded ICB work on conjugated polyelectrolytes at UCSB and Sirigen now forms the basis of Becton Dickinson's very successful BD Horizon Brilliant™ Violet Reagents, which allows researchers to identify cell populations with lower receptor density than previously possible and is widely used in flow dell cytometry.

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Anisotropic Nanostructured Materials for Electrochemical and Photovoltaic Energy Conversion and Storage**

**Project Leaders:** **Bradley F. Chmelka and Songi Han (UCSB)**

**Collaborators:** **Michelle O'Malley (UCSB); Frances H. Arnold (Caltech); Guido Pintacuda (CNRS-Lyon, France); Lyndon Emsley (EPFL, Switzerland)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

A versatile synthetic protocol was developed with ICB support that allows high concentrations of functionally active membrane proteins to be incorporated in robust synthetic host materials. This was specifically demonstrated for nanostructured silica-surfactant materials with high loadings (up to 19 wt%) of the transmembrane protein proteorhodopsin, a light-activated $H^+$-pump, that is promising for solar-to-electrochemical energy conversion. Proteorhodopsin (PR) is found in the cell membranes of marine plankton and, as shown schematically in **Figure 1.a**, absorbs green light to transfer $H^+$ cations actively from the cell's interior cytoplasm to its exterior environment [1]. During the 5-year contract period, we have developed the protocols to express PR recombinantly in *E. coli*, to separate chromatographically PR into micellar surfactant solutions containing monomers or oligomers, and to co-assemble PR in these solutions with soluble network-forming silica precursors into mechanically robust silica-surfactant-PR films (**Figure 1.b**). The high expression capacity of PR in *E. coli* is expected to be scalable to tens of grams of PR per batch in. industrial-sized 1000-liter bioreactors. Compositional, structural and dynamical analyses demonstrated that PR monomers or oligomers exhibited distinct photocycle kinetics and properties in micelles, in native-like lipids [2-4], or upon incorporation into synthetic nanostructured silica host membranes. Notably, PR molecules in nanostructured silica membranes were shown to be functionally active, even at high PR loadings (>15 wt%) [5]. In addition, the synthetic protocol was shown to be general, as demonstrated by the incorporation of functionally-active cytochrome c, a peripheral membrane protein enzyme involved in electron transport, into nanostructured silica-cationic surfactant films [5]. The resulting insights enable synthetic abiotic host materials to be adjusted and optimized with respect to their compositions and structures, local environments, and corresponding synthesis and processing protocols to harness and optimize the selective functions of membrane proteins, such as PR and other ion-conducting or charge-conducting guest species in novel materials and devices that convert solar energy into electrochemical energy or other responses.

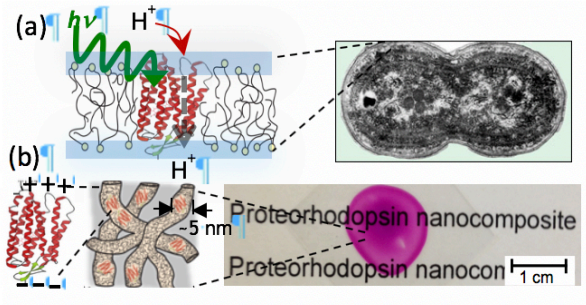



**Figure 1.** (**a**) Schematic diagram of a proteorhodopsin (PR) trans-membrane protein molecule in a lipid bilayer of marine plankton (photo, right: John Waterbury, Woods Hole); PR actively pumps $H^+$ cations under illumination by green light. (**b**) Photo of a synthetic nanostructured silica-surfactant membrane with 5 wt% proteorhodopsin, showing a macroscopically uniform distribution of PR [5].

In addition, early progress during this contract period resulted in the successful development of bio-inspired materials for solar-to-electrical or chemical-to-electrical energy conversion that were transitioned to other funding sources. Specifically, new molecular-level insights obtained from powerful two-dimensional (2D) solid-state NMR spectroscopy analyses enabled the design, syntheses, and testing of novel conjugated polymers for processable organic solar cells [6-8] and of novel non-precious-metal mesoporous carbon electrocatalysts for uses in batteries and hydrogen- or natural gas-powered fuel cells [9-12]. Our organic-optoelectronics research efforts are now being supported by the U.S. Office of Naval Research and an industrial partner, while our carbon electrocatalyst pursuits are being supported by a large ERC grant from the U.S. Department of Energy.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

Our scientific and engineering objectives were to measure, understand, and exploit the molecular-level interactions and local environments of novel surface functionalities and/or functionally active membrane protein molecules to develop new biologically-inspired materials with novel photo-responsive, ion-conducting, or charge-transfer properties and demonstrate their performances. During this reporting period, we focused predominantly on testing our overarching hypotheses that (1) synthetic nanostructured silica-surfactant materials could represent a versatile platform for integrating functionally active membrane proteins, such as proteorhodopsin, in high concentrations into a robust synthetic host matrix, (2) that illumination of PR-containing nanostructured silica membranes would induce local conformational dynamics of the PR guest molecules that would result in $H^+$ pumping; and (3) that 2D solid-state NMR analyses of non-precious-metal nitrogen-containing nanostructured carbon materials could provide new atomic-scale insights for improving their properties for electrocatalyst, supercapacitor, or water treatment applications. Completing manuscripts for publication in the areas above was also a high priority.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

Judicious selections of solvent, surfactant, silica precursors, and synthesis conditions enabled high loadings of membrane proteins to be stabilized in solution and during subsequent co-assembly into silica-surfactant composites with nano- and mesoscale order. Access to a variety of state-of-the-art analytical techniques provided detailed insights on resulting material compositions and structures (e.g., at surfaces, orientational ordering, and species distributions), protein function (e.g., dynamics, activity, and stability), and macroscopic properties (e.g., light absorbance, ion conduction, and mechanical robustness) over multiple length and time scales. In particular, solid-state $^{1}H$,$^{13}C$,$^{15}N$ nuclear magnetic resonance (NMR) and electron paramagnetic resonance (EPR) spectroscopy measurements were used to analyze the molecular compositions, structures, and dynamics of proteorhodopsin (PR) membrane protein molecules in synthetic nanostructured silica host materials, as functions of different stabilizing surfactants, nanochannel surface compositions, extents of hydration, pH, and synthesis conditions. Transient UV-visible optical absorbance spectra provided quantitative information on the apparent rate coefficients associated with the formation of PR photo-cycle intermediates in micelles, native-like lipids, and in nanostructured silica host materials, which were correlated back to the NMR and EPR results to improve our materials synthesis protocols. Similarly, solid-state $^{1}H$,$^{13}C$,$^{15}N$ NMR analyses were used to measure at an atomic-level the types and distributions of nitrogen and Fe species in novel Pt-free nanoporous carbon electrocatalysts. The results were correlated with synthesis conditions and the macroscopic properties of the Fe,N-carbon materials to provide crucial feedback for improving their electrocatalytic properties.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

Nanostructured silica-surfactant materials with high concentrations of the transmembrane protein proteorhodopsin, a light-activated $H^+$-pump, are promising for solar-to-electrochemical energy conversion. We obtained detailed atomic-level insights on the structure, dynamics, and functional activity of proteorhodopsin molecules incorporated into synthetic silica membranes. Transient optical spectroscopy analyses shown in **Figure 2** yield apparent rate coefficients associated with interconversion of proteorhodopsin conformers during the light-activated photocycle [13]. After excitation by a 10 ns laser pulse at 532 nm, transient absorbances were measured at different wavelengths that correspond to different photocycle intermediates of PR [14]: *L*/*M* (410 nm, purple), ground state (500 nm, blue), *K* (570 nm, green), and *N*/*O* (590, nm red). As clearly seen in the left and right panels of **Figure 2**, the optical absorbances of proteorhodopsin at different wavelengths are sensitive to the hydration and pH of the nanochannel environments. These time-resolved UV-visible results of PR in the synthetic silica materials are in close agreement with those reported for PR in near-native lipid environments under acidic or alkaline conditions [14], suggesting that the protein retains its native-like functional integrity. Slightly different kinetics of the photo-

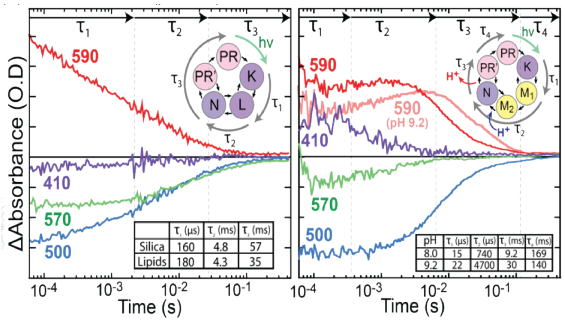



**Figure 2.** Time-resolved UV-visible absorption spectra of proteorhodopsin in nanostructured silica (left) hydrated at 100% relative humidity for >1 month and (right) after exposure to buffered solutions at pH 8.0 or 9.2 [13]. Insets: schematic diagrams of the photochemical reaction cycles of PR in lipid membranes, as reported by Lakatos, et al. [14].

intermediates reflect variations in the structural and dynamical properties of PR caused by differences in local chemical environments or by confinement, which can be tuned to adjust the $H^+$ pumping kinetics of the PR guest molecules in the synthetic silica membranes.

Detailed atomic-level insights on PR structure and interactions within the synthetic nanostructured silica matrices were obtained from solid-state three-dimensional (3D) NMR analyses, which were conducted in collaboration with Dr. Guido Pintacuda at the Center for Very-High-Field NMR in Lyon, France and with Dr. Lyndon Emsley, now at the EPFL in Lausanne, Switzerland. The combined use of proton dilution (by partial deuteration), high MAS rates (60-110 kHz), and high magnetic fields (19-24 Tesla, 800-1000 MHz for $^1$H) provided sensitive and resolved NMR spectra of PR in native-like lipids [15] and in synthetic nanostructured silica membranes [13]. As shown in **Figure 3.a**, narrow $^1$H, $^{13}$C, and $^{15}$N signals reflect the exceptional homogeneity of the local protein environments from which assignments of most backbone resonances of proteorhodopsin are established, as indicated in **Figure 3.b**. Such highly resolved spectra furthermore permit comparisons of the local molecular structures and dynamics of proteorhodopsin in different host environments, specifically in native-like lipids and in nanostructured silica membranes, which are shown to be very similar [13]. Interestingly, subtle differences are also distinguished (**Figure 4.a,b**) that arise from interactions between hydrophobic protein regions and the stabilizing surfactant species and confinement of PR molecules in the silica nanochannels. Together, the results establish the atomic-level structures and dynamics of proteorhodopsin molecules within the synthetic nanostructured silica-surfactant host membrane and demonstrate the efficacy of these materials for incorporating functional membrane protein properties in robust abiological environments.

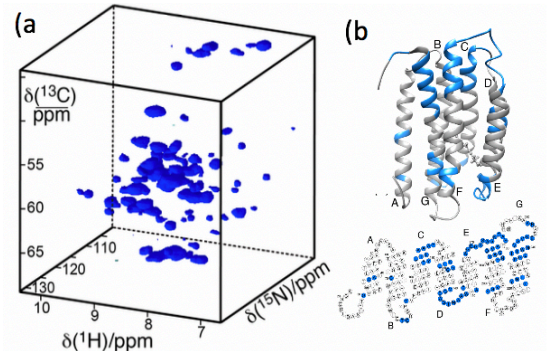



**Figure 3.** (a) Solid-state 3D $^1$H, $^{13}$C, $^{15}$N NMR spectrum (acquired at 60 kHz MAS, 19 T) of 13 wt% $^2$H, $^{13}$C, $^{15}$N-labeled proteorhodopsin in hydrated nanostructured silica at 300 K; (b) ribbon representation of proteorhodopsin structure with key assigned residues shown in cyan [13].

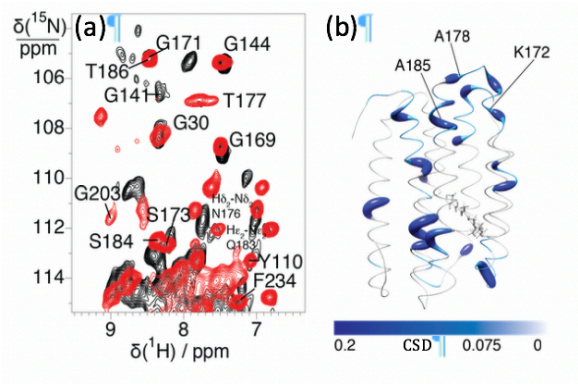



**Figure 4.** (**a**) Comparison between solid-state $^1$H{$^{15}$N} correlation NMR spectra of proteorhodopsin in hydrated nanostructured silica (black) versus native-like lipids (red). (**b**) Ribbon representation of PR structure, showing residues with significant chemical shift differences (CSD) for PR in nanostructured silica versus lipid hosts [13].

We have demonstrated that nanostructured silica materials can be processed into large self-supporting membranes that permit facile integration and robust operation with bench-scale electrochemical devices for solar-to-electrochemical energy conversion. Key progress was enabled by our establishment of the importance and capacities to control humidity (~75% relative humidity), pH (3.5–4.5), and substrate type and dimensions during synthesis and processing of the PR-containing membranes [5]. In particular, the humidity and pH conditions ensured relatively slow cross-linking of the silica network during solvent evaporation and surfactant-PR self-assembly, which resulted in optically transparent nanostructured membranes with controllable thicknesses (100 nm to >1 mm), increased 2D area dimensions (10 cm$^2$), and favorable flexural and compressive strengths that facilitate integration of the membranes into electrochemical devices. For example, such nanostructured PR-silica membranes could be combined with nanostructured carbon supercapacitor materials that enable energy storage of potentials up to 1 V in aqueous electrolytes [16]. High-surface-area nanoporous supercapacitor materials have high cation-exchange capacities, which can be used to store the $H^+$ ions that are transported across illuminated nanostructured PR-silica membranes. Electrochemical potentials of 0.5 V have been reported across lipid membranes containing bacteriorhodopsin, a close PR homologue, under constant illumination conditions [17]. Recent progress in the Chmelka group, which was supported by a separate expired 6.2 ICB project, led to the development of new

nanoporous carbon materials for applications as non-precious-metal electrocatalysts to promote oxygen-reduction reactions at fuel cell cathodes [9,10]. We have adapted the synthesis protocol to prepare similar nanoporous carbons with uniform pore dimensions of ca. 1.5 nm, high surface areas (>1000 $m_2$ /g), high electrical conductivities, and with anionic nitrogenous surface sites, that interact with $H^+$ cations [11,12]. The resulting nanoporous carbon materials exhibit the properties of double-layer super-capacitors, with approximately double the capacity of $H^+$ ions, compared to commercially-available carbon nanotube supercapacitors. These results represent key progress towards developing devices that efficiently convert solar-to-electrochemical energy, operate robustly under mechanical stresses and strains, and can be charged and discharged many times while retaining performance.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

Prof. Chmelka has direct interactions with a number of Army researchers concerning the development, understanding, and use of functionalized nanostructured materials for Army applications, especially those that address the energy-related needs of the U.S. Army, such as portable and lightweight energy sources. Such interactions have arisen as a result of Prof. Chmelka's visits to U.S. Army facilities and include interactions with Dr. Justin Jahnke, Dr. David Baker and Dr. David Mackie (ARL-Sensors and Electron Devices Directorate, Adelphi, Maryland) in the areas of ion-conducting membranes and energy-harvesting from food waste, with Dr. Ed Perkins, Dr. Charles Weiss, and Dr. Robert Moser (U.S. Army Corps of Engineers, Engineer Research and Development Center, Vicksburg, MS) for characterization of structural materials, with Dr. Ray Brennan, Dr. Victoria Blair, and Dr. Josh Orlicki (RDECOM, Weapons and Materials Research Directorate, Aberdeen Proving Ground, MD) in the areas of rare-earth-doped ceramics, armor materials, and their atomic-scale characterization by NMR, and Dr. Augustus (Way) Fountain and Dr. Greg Peterson (Edgewood Chemical Biological Center, Aberdeen Proving Ground, MD) regarding materials for breathing protection. Our materials synthesis and NMR characterization capabilities are currently not available within Army (or other DoD) research facilities, presenting a broad complementary interface of skills, instrumentation, and applications that we are in discussions with Army partners (listed above) to obtain funding to exploit. During this reporting period Dr. Justin Jahnke, who previously conducted his PhD studies with Prof. Chmelka at UCSB with ICB support and was subsequently a post-doctoral researcher at USARL, became a permanent member of the technical staff at USARL-SEDD.

Opportunities for collaboration and transition of our ICB-supported work have been augmented by our success in leveraging funding from external sources. This included Prof. Chmelka's strong partnership with Dr. Piotr Zelenay in the Electrochemical Devices Group at the Los Alamos National Laboratory (LANL), where many of our ICB team's materials were integrated into membrane-electrode assemblies and tested. In addition, both Prof. Chmelka and Prof. Han were co-PIs on separate funding that was obtained from the U.S. Army Forward Element Command—Atlantic (RFEC–A) in London (program director Dr. Robb Wilcox), in conjunction with the U.S. Army International Technology Center—Atlantic and USARL (ARO program director Dr. Stephanie McElhinny), to support collaborative measurements of PR structure with Prof. Guido Pintacuda and Prof. Lyndon Emsley at the Center for Very-High-Field NMR Spectroscopy in Lyon, France. This project was initiated by our UCSB groups; however all funds were allocated directly and exclusively to the Lyon team to conduct high-field solid-state NMR measurements of membrane proteins using their internationally unique facilities. Prof. Chmelka's separate 6.2 ICB project, led by Teledyne Scientific and Imaging, with Dr. James Sumner from the USARL provided access to Teledyne's device-integration and manufacturing capabilities to scale syntheses, processing, and assembly of microbial fuel cell devices for Army clients, as well as commercial markets. (Our final report for this 6.2 project was submitted and presented at the USARL in Adelphi in May 2016.) These partners provided expertise that assisted us with integrating our materials into electrochemical devices, testing full-scale devices, and providing performance benchmarks and feedback for materials optimization. Over the past three years, we submitted three ICB proposals for new 6.2 projects with industrial partners (Teledyne and Hutchison) and diverse Army groups, though they were not approved for funding. There is substantial interest in our novel proton-exchange membrane materials, functionalized mesoporous carbons, and new synthetic host materials for membrane proteins from industry and within the Army, and we will continue to discuss with and seek Army partners for their integration into new devices and applications.

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

Z. J. Berkson, S. Becwar, N. P. Zussblatt, N. A. Prisco, N. Fechler, C. Hunt, G. Ménard and B. F. Chmelka. Atomic-scale origins of oxygen reduction activity in non-precious-metal mesoporous Fe,N-carbon electrocatalysts with high nitrogen contents. *Nature Chemistry*, to be submitted.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Bio-inspired Photonic Surfaces for Broadband IR Detectors, LEDs, and Lightweight, Flexible Solar Platforms**

**Project Leaders:** **Michael J. Gordon and Daniel E. Morse (UCSB)**

**Collaborators:** **Eric DeCuir Jr. and Richard Fu, Y.P. Chen (ARL-SEDD); Jonathan Ward and Alya Elhawary (Lockheed Martin); Nibir Dhar (CERDEC-NVESD); Steve DenBaars, Shuji Nakamura and Tal Margalith (UCSB)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

In this ICB-funded project, we have (1) developed a facile, scalable, and substrate-agnostic method [1, 2] to realize bio-inspired, moth eye anti-reflective surfaces (ME-ARSs, **Figure 1**) in a variety of material platforms (group IV, II-VI and III-nitride semiconductors; metal oxides; and polymers); (2) quantitatively demonstrated that ME-ARS surfaces exhibit broadband and omni-directional anti-reflectivity in the mid- and far-IR that exceeds the performance of commercial interference-based AR coatings [3]; (3) collaborated with ARL-SEDD scientists to translate ME patterning to II-VI materials for EO/IR systems of high priority for Army applications [4-6]; and (4) developed both far- and near-field optical modeling that quantitatively predicts photonic behavior of ME-structured interfaces with geometric features from 10 nm to 100+ μm [7]. We have also extended the ME-ARS processing methodology to III-nitrides ($In_xGa_{1-x}N$) and optical meta-materials, resulting in six provisional patent applications [8-13] in collaboration with UCSB's Solid State Lighting and Energy Electronics Center (SSLEEC), to: (5) enhance light extraction from InGaN LEDs by 5-fold [14], (6) relieve strain in multi-quantum well LED structures to enhance internal quantum efficiency and allow greater In incorporation, allowing more efficient green and red light emitters; (7) realize substrate-releasable InGaN nano-LEDs for ultra-high density, near-eye, and flexible display applications; (8) create patternable micro- and nano-LEDs by combining ME-ARS with substrate templating; and (9) create high contrast grating (HCG) meta-materials in $TiO_2$ and GaN that function as tunable color reflectors for photonic devices such as resonant cavity LEDs. The ME-ARS process involves a novel combination of colloidal lithography, surfactant-assisted dip coating, and reactive ion etching (RIE), allowing independent control of ME feature geometry, creation of ME features in any material, and easy integration into standard cleanroom processing protocols.

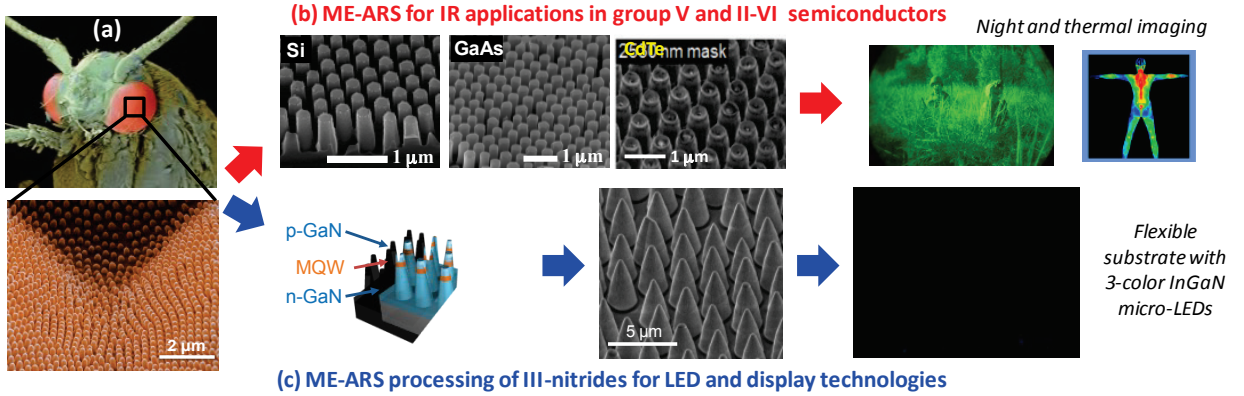



**Figure 1.** (**a**) Anti-reflective structures on a moth's eye. Results of ME-ARS processing of various materials for (**b**) IR imaging applications (Si, Ge, CdTe) and (**c**) III-nitrides ($In_xGa_{1-x}N$) for LEDs and display applications.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

### *2.1. IR Materials and Devices*

Adapt moth-eye anti-reflective surface (ME-ARS) protocols to Army-priority optoelectronic materials for EO/IR detection and imaging (e.g., ZnSe, ZnS, Ge, and CdTe/HgCdTe) and incorporate ME-ARS into EO/IR subcomponents (e.g., lenses, windows, substrates, filters, etc.).

Understand how key descriptors of sub-λ surface structure affect reflection and transmission in the IR using theory and experiment to design, fabricate, characterize and optimize high-performance anti-reflective surfaces (ARSs) for Army applications in EO/IR detection, imaging, and lightweight, flexible solar platforms.

### *2.2. III-Nitride Photonics*

Demonstrate and apply ME-ARS to critical optical interfaces to increase the light extraction and power conversion efficiency of III-nitride-based optoelectronic materials for LEDs, sensing, and other solid-state lighting applications critically important to the Army.

Create micron and sub-micron scale light emitters (i.e., nano-LEDs) and micro/nano-LED patterns in III-nitride materials by combining ME-ARS protocols with topographic templates. Develop protocols to release and solubilize micro/nano-LED sub-units, through sacrificial etching and chemical modification of their surfaces.

Investigate how size affects the strain state and internal quantum efficiency of micro/nano-LEDs through detailed x-ray, photo-, electro-, and cathodoluminescence measurements. Carry out detailed optical and electrical characterization, and iterative optimization of nano-LEDs and patterns.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

### *3.1. ME-ARS Processing*

The ME-ARS process we have developed is based on a unique combination of colloidal lithography, Langmuir-Blodgett (LB) dip coating, and reactive ion etching (RIE) [1]. By adjusting the colloid material, size, surface functionalization, LB deposition pressure, plasma-based mask 'trimming', and mask transfer steps, a wide variety of ME surfaces with well-defined and tunable geometries (e.g., feature size, pitch, height, and profile) can be realized in any material (**Figure 2**). We have also recently adapted the ME-ARS protocol to the III-nitrides, and combined it with templated assembly, 'flip-chip' processing [13], and photoelectrochemical (PEC) etching, to fabricate micro/nano-LEDs, nanowire LED patterns, and substrate releasable InGaN nano-LEDs (**Figure 3**), respectively.

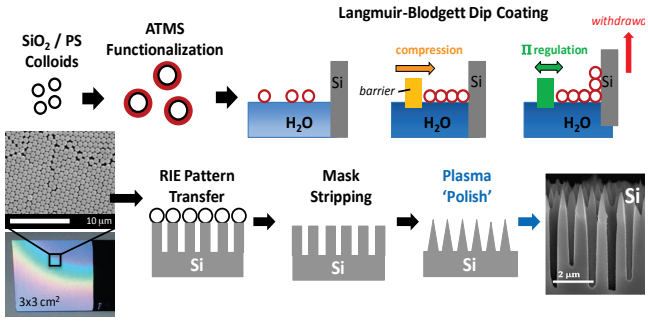



**Figure 2.** ME-ARS processing protocol involving dip-coating of colloids and plasma-based pattern transfer.

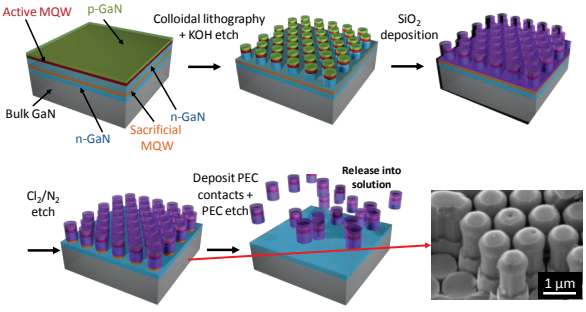



**Figure 3.** Processing scheme incorporating ME-ARS method (cf. **Figure 2)** to create and release InGaN nano-LEDs from a substrate for subsequent solution-based processing.

### *3.2. Optical Benchmarking and Simulations*

Throughout this project, we have developed (**Figure 4**) a suite of experimental measurement systems and protocols to fully characterize the photon balance and performance of ME-ARS in different material systems, as well as

developed effective medium theory and finite difference time domain (FDTD) optical simulations to calculate, design, and optimize the optical response of ME-ARS.

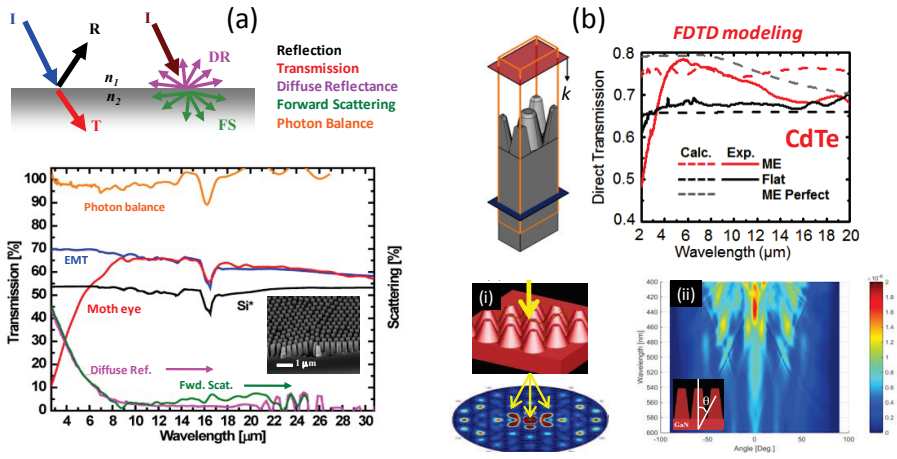



**Figure 4.** (**a**) Example of optical benchmarking of ME-ARS in Si. All components of the 'photon balance' at the ME-ARS interface are measured, including direct transmission, reflection, diffuse reflectance and forward scattering [7]. (**b**) Example of FDTD modeling of ME-ARS for CdTe focal plane array substrates [5] from ARL (**top**) and GaN (**bottom**) for enhanced light extraction. (**i**) and (**ii**) are far-field scattering pattern and angular divergence vs. wavelength, respectively, for GaN ME-ARS.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1. Challenging IR Materials*

Based on our initial success of creating ME-ARS in common short wave-IR (SWIR) semiconductors, and in consultation with scientists at ARL-SEDD and CERDEC-NVSED, we successfully extended the ME-ARS process to high-priority mid- (MWIR) and long-wave (FWIR) IR materials such as ZnS and ZnSe [4], as well as CdTe and MBE-grown CdTe materials from ARL used for focal plane array substrates [5]. For example, **Figure 5** demonstrates how double-sided ME-ARS can increase the transmission of ZnS and ZnSe optics over an entire decade of wavelengths spanning the MWIR to LWIR spectral range, providing potential performance advantages for optical systems proposed for next-generation, two-color IR imaging.

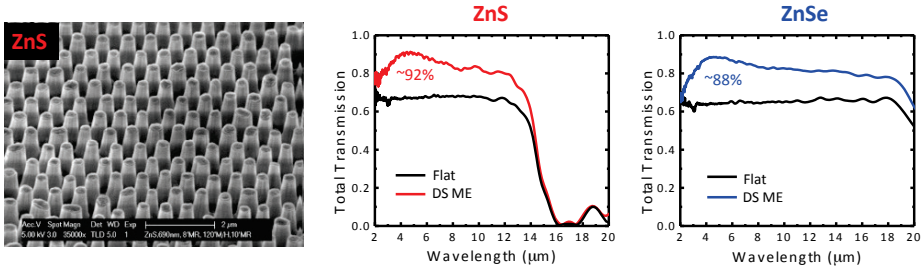



**Figure 5.** SEM of ME-ARS in a ZnS optical window and IR transmission measurements of double-sided ME-ARS on ZnS and ZnSe windows compared to their flat-surface counterparts [4].

### *4.2. Enhancing Light Extraction from III-nitride LEDs*

The transmission enhancement afforded by ME-ARS in IR materials suggests that a similar approach could be used to enhance light extraction from the substrate-air interface in LEDs. To this end, we successfully extended and adapted our ME-ARS processing methodology to GaN materials (**Figure 6**). Photoluminescence (PL) measurements with InGaN/GaN multi-quantum well (MQW) emitter structures demonstrate that ME-ARS can increase light extraction by a factor of ~4–8 compared to an unstructured surface [14], thus delivering a direct increase in overall power efficiency of nitride LEDs. In addition, angle-resolved PL measurements in panel (c) show that ME-ARS do not affect the angular distribution of light emission, and that ME-ARS are competitive with the industry-standard photoelectrochemical (PEC) roughening method, the latter of which *will not work* on higher efficiency semi- and non-polar GaN materials.

### *4.3. Patterned Arrays of InGaN micro/nano-LEDs*

The successful patterning of micro- and nanoscale features into InGaN materials shown in §4.2 was further developed, by combining the ME-ARS process with topographic templates, to create arbitrary patterns and arrays of

InGaN nanowire light emitters in 'entrenched' and 'free-standing' configurations (**Figure 7**) as a prelude to ultimately creating InGaN-based pixilated displays. Photoresist templates created using standard, low-resolution photolithography were used to direct colloidal mask organization, and following liftoff of the resist, resulted in isolated mask patterns that were subsequently transferred into the InGaN device stack.

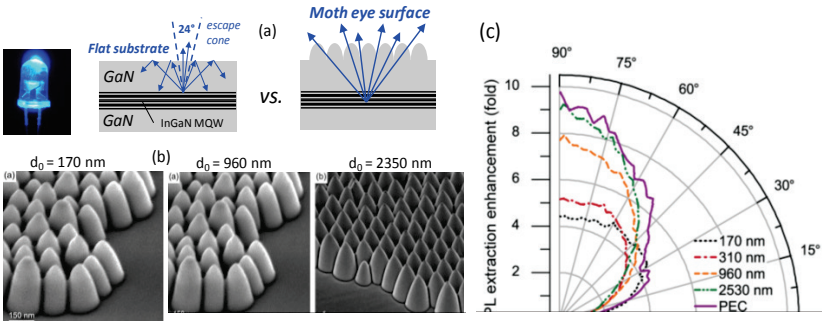



**Figure 6.** (**a**) InGaN MQW emitter structure for blue and white light LEDs, showing the first-pass light extraction problem of multiple internal reflections (escape cone 24°) and alleviation by moth eye patterning. (**b**) Moth eye patterning of semi-polar GaN-based device structures. (**c**) Angle-dependent enhancement in light extraction (PL) from ME-structured vs. flat surface MQW devices in *semi-polar GaN* [14].

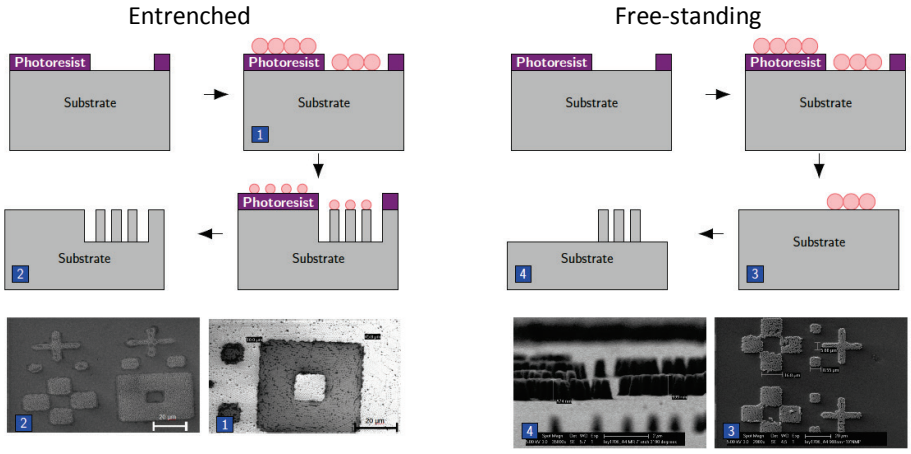



**Figure 7.** Example of processing scheme and SEM results of using topo-graphic templates to direct the ME-ARS colloidal masking process. Both entrenched and free-standing InGaN nanorod LEDs can be created in any pattern by combining traditional low-resolution optical lithography and ME-ARS patterning methods.

### *4.4. InGaN nano-LEDs and Strain Relaxation via Nanopatterning*

High density, flexible, and portable-power display technologies of the future are not likely to be based on LCDs and/or OLEDs due to their low power conversion efficiencies (< 10%), short lifetimes, and burn-in. Instead, we showed that these challenges could be addressed using III-nitride materials using our technology to fabricate and assemble uniquely high efficiency (>50%), sub-micron-scale RGB light emitters. Toward this end, we have developed a new materials manufacturing paradigm, based on ME-ARS-enabled pattering and sacrificial PEC etching, to create, release and solubilize micro/nanoscale LED sub-units (**Figure 8**).

In addition, we have shown that our nanopatterning technology can relieve biaxial strain and increase the internal quantum efficiency of multi-quantum well light emitters when lattice mismatched $In_xGa_{1-x}N$ is grown on GaN and sapphire (**Figure 9**). In this case, ME-ARS patterning of InGaN at lateral dimensions < 500 nm, i.e., fabricating nano-LEDs, can relax strain by up to 20-30% (as measured by x-ray diffraction reciprocal space maps - RSMs) and consequently increase photoluminescence efficiency. We are working to combine this fabrication protocol with electrostatic and/or chemically-assisted printing to ultimately realize multi-color (RGB), flexible displays

(**cf. Figure 1**) with lower power consumption and greater brightness, durability and longevity than OLED-based displays for a variety of DoD display applications.

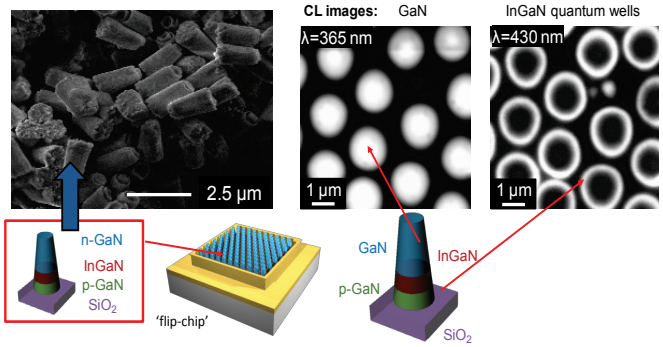



**Figure 8.** Demonstration of fabrication and substrate release of InGaN nano-LEDs, along with cathodoluminescence (CL) images of light emission from the GaN cap and InGaN quantum well light emitting 'active' regions.

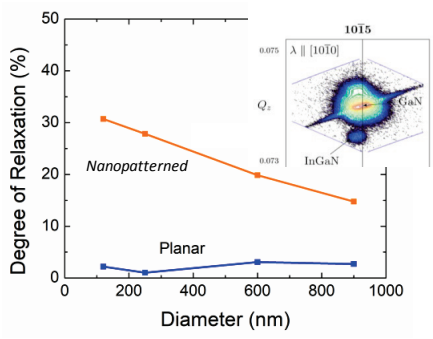



**Figure 9.** Example of strain relaxation achieved in InGaN nano-LEDs vs. planar films as measured via x-ray diffraction reciprocal space mapping (inset). RSM shows offset of InGaN peak in $Q_x$ direction, indicative of relaxation. Units of RSM are [1/Å].

### *4.5. High Contrast (meta-material) Gratings (HCGs)*

Eliminating pixel crosstalk, i.e., color mixing and blur due to isotropic light emission, is a new challenge to be solved for next generation ultra-high density displays. One approach is to surround the active LED or light emitting region with a low profile (sub-λ thick), high contrast grating (HCG, **Figure 10.a**) or meta-material surface that fosters interference in the plane of the grating, rather than perpendicular to it, as in the case of more bulky and harder-to-deposit distributed Bragg reflectors (DBR). We have designed, simulated (**Figure 10.b**), and developed a fabrication protocol to realize such HCGs in various materials [11] by combining the ME-ARS method with a metal mask, low resolution photolithography, and $XeF_2$ etching of sacrificial spacers. Prototype HCGs have been created (**Figure 10.c**) and initial optical testing has generated very promising results. These photonic structures will eventually be incorporated into InGaN devices to realize resonant cavity LEDs with directional emission.

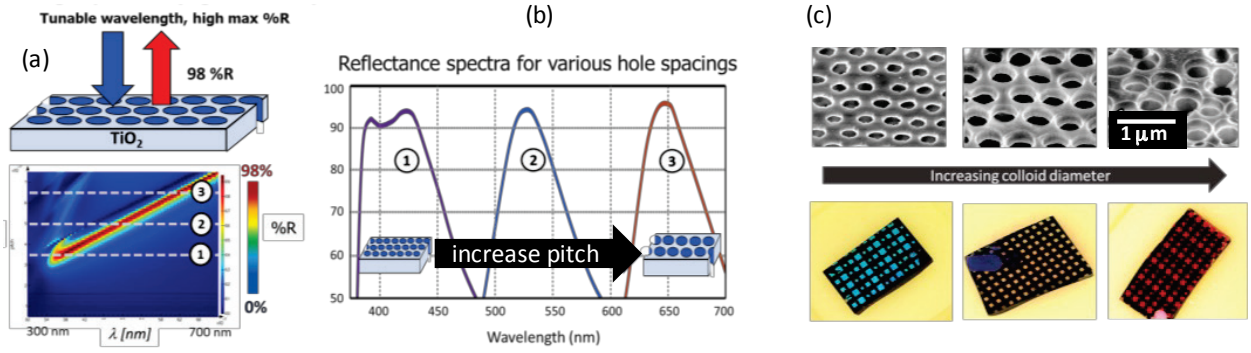



**Figure 10.** (**a**) Schematic design and FDTD simulation of $TiO_2$-air high contrast grating (HCG) reflectivity for different geometries. (**b**) Simulated reflectance spectra of various $TiO_2$ HCGs, demonstrating wavelength tunability. (**c**) SEMs and optical photos of prototype HGCs, nominally designed and fabricated for reflection in the blue, yellow, and red spectral ranges.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

During the final review period, we were actively collaborating with ARL-SEDD scientists Drs. Eric DeCuir Jr., Richard Fu, and Jonathan Schuster, scientists at the Army's Night Vision lab (CERDEC-NVESD), including Dr. Nibir Dhar (NVESD Chief Scientist) and his team, as well as Lockheed-Martin (LM) PI/PM Dr. Jonathan Ward and materials engineer Alya Elhawary. Our collaborative work entailed exchanges of II-VI samples grown at ARL for mask deposition, patterning and characterization at UCSB, and identification and processing of Army priority EO/IR

materials (e.g., ZnS, ZnSe, Ge) for IR imaging applications. These collaborations resulted in submission of an ICB 6.2 project proposal, entitled "Increasing performance and power efficiency of visible and infrared light technologies using bio-inspired, anti-reflective surfaces", from our ICB-UCSB/ARL-SEDD/CERDEC-NVESD/LM team, focusing on transitioning our ME-ARS methodology to Army and LM priority applications, including 3rd generation iFLIR (Program of Record), improved night/day observation devices (INOD), LM's Stalker XE UAV, and GaAs flexible solar cells (via the Army's ManTech program). Unfortunately, the 6.2 project was not selected for funding. We have also explored potential collaborations and submitted white papers with Anand Sampath (ARL-SEDD), Richard Fu (ARL-SEDD), Ken Jones (ARL) & TARDEC as related to our III-nitride work.

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)


L. W. Chan, D. E. Morse and M. J. Gordon. Moth eye-inspired anti-reflective surfaces for improved IR optical systems & visible LEDs fabricated with colloidal lithography and etching. (Invited Review.) *Bioinspiration & Biomimetics*, May 2018. 10.1088/1748-3190/aab738.

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F. L. Gonzalez, D. E. Morse and M. J. Gordon. Importance of diffuse scattering phenomena in moth-eye arrays for broadband infrared applications. *Optics Letters*, January 2014. 10.1364/OL.39.000013.

**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Combining Bio-Inspired Self-Assembly with Chemical Functionalization in the Design of Discrete Oligomeric Building Blocks and High Performance Hydrogels**

**Project Leader:** **Craig J. Hawker (UCSB)**

**Collaborators:** **Kato L. Killops (ECBC); Don Cropek and Kyoo Jo (ERDC); Tanya Chantawansri, Andy Hsieh and David Mackie (ARL); Dan Morse, Tom Soh, Herb Waite, Javier Read de Alaniz, Ed Kramer and Glenn Fredrickson (UCSB); Hugh Brown (Wooloongong, Australia) and Bumjoon Kim (KAIST) and Nate Lynd (Texas).**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

The central theme and most significant impact during this program has been the development of versatile synthetic approaches to a wide range of new material systems with improved and/or novel properties. This increased performance will ultimately allow greater protection for the warfighter. Selected new research areas which have been highly cited and influential in the soft materials arena include

*1.1) Development of a mixed surfactant approach to ellipsoidal microparticles exhibiting unique internal morphologies*. The robust nature of this method allows for multiple morphologies to be reproducibly and exclusively obtained [1-2]. For example, axially stacked, ellipsoidal particles were able to undergo dramatic and reversible shape changes triggered by pH that were not observed for either the non-crosslinked systems or the corresponding spherical particles (**Figure 1**). The simplicity and generality of this synthetic strategy allows access to novel, shape anisotropic and responsive polymer particles with applications from photonics to biomedical delivery devices.

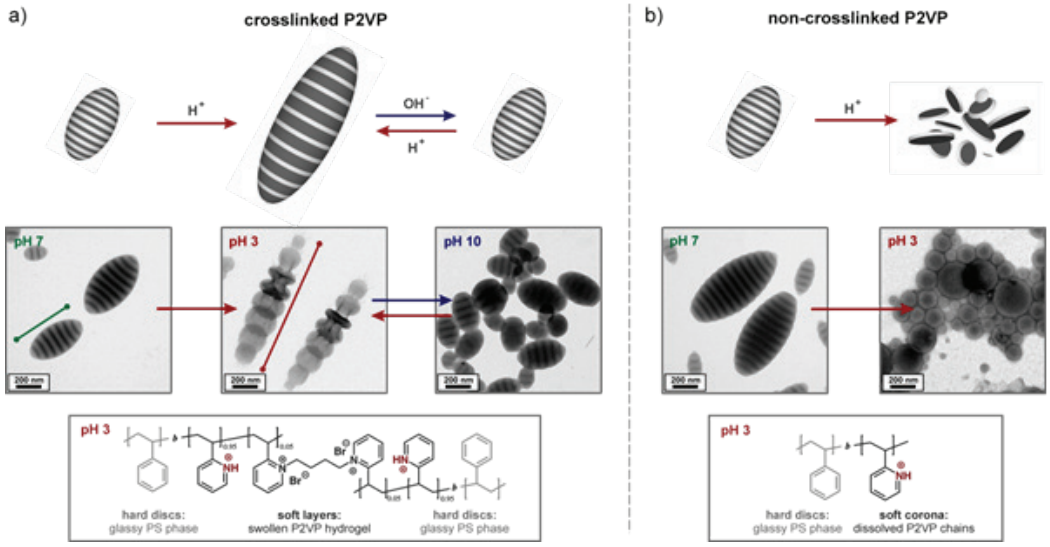



**Figure 1.** Investigations on the pH-responsive behavior of PS-b-P2VP ellipsoidal particles with axially stacked lamellae: **a**) pH-triggered dynamic shape change for particles with crosslinked (5 mol-% 1,4-dibromobutane) P2VP domains due to swelling/deswelling of the P2VP-based hydrogel discs. The demonstrated variation of the aspect ratio was fully reversible for at least three cycles; **b**) discrete nanodiscs were obtained for non-crosslinked systems due to solubilization of P2VP chains.

*1.2) Discovery of synthetic strategies for incorporation of biomimetic chemical motifs—inspired by marine organisms—into functional materials.* Eugenol (clove oil) was identified as a low-cost, bio-renewable starting material and using novel boron-catalyzed Lewis acid chemistry, a variety of catechol-based building blocks were prepared and incorporated into functional materials. To illustrate the versatile nature of this approach, fabrication of hierarchically ordered nano-materials such as Bragg stacks with tunable layer thickness and refractive indices was demonstrated [3]. This sequential coating method could also be applied to a wide variety of surfaces from the inner walls of plastic tubing, to the formation of optical coatings on glass slides (**Figure 2**). Significantly, these films were shown to be solvent resistant and could withstand conditions of high salt and extreme pH values. The robust nature of these nanocomposites is attributed to the strong catechol binding in tandem with the multi-valent effect derived from the polyfunctional polymer backbone. This strategy, applicable to assembly of stimuli responsive catechol copolymers and nanoprobes, holds promise for progress toward the fabrication of robust thin-film sensors for sensing analytes in flow or gas.

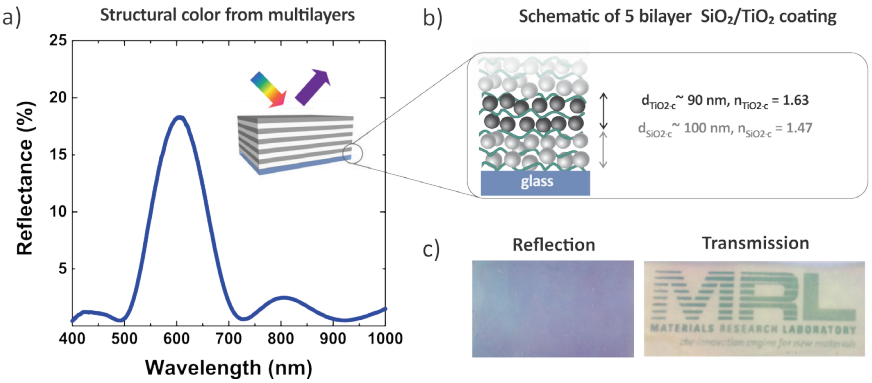



**Figure 2.** Bragg stacks coatings on glass substrates: Structural colour from multilayer composites. Ten alternating layers of low refractive index $SiO_2$ composite and high refractive index $TiO_2$ composite (5 bilayers) were deposited onto a glass substrate. **a)** Experimental reflectance spectrum exhibits a Bragg peak at 600 nm. **b)** Schematic representation of $SiO_2$-composite films and $TiO_2$-composite films, indicating the thickness *d* and refractive index *n* of individual layers. **c)** Structural colour is observed in reflection. In transmission, films are transparent.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

*2.1) Discover synthetic routes to a library of discrete functional oligomers.* Inspired by monodisperse natural systems (i.e., peptides, nucleic acids, etc.), these libraries will allow the influence of monodisperse and discrete structures on the morphology and properties of synthetic polymeric materials to be investigated for the first time.

*2.2) Develop a continuous 3D printing method—SMaLL—for the generation of monolithic, polymeric structures with distinct regions of differing biological, mechanical and chemical properties (e.g., localized domains of biological molecules and systems; gradient hard/soft materials with 3-D structural control).*

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

A novel methodology for printing 3D objects with spatially resolved mechanical and chemical properties, termed SMaLL, was developed. In this novel system, photo-chromic molecules are used to control lateral resolution through coherent bleaching fronts, providing large depths of cure and rapid build rates without the need for moving parts.

An efficient and scalable strategy to prepare libraries of discrete conjugated oligomers (Đ = 1.0) using the combination of controlled polymerization and automated flash chromatography was reported. From this 2-step process, a series of discrete conjugated materials from dimers to tetradecamers could be isolated in high yield with excellent structural control.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

In the SMaLL process, the coupling of these photoswitches with resin mixtures containing orthogonal photocrosslinking systems allows for simultaneous and selective curing of multiple networks, providing access to 3D-objects with chemically and mechanically distinct domains [4]. By using tunable, visible wavelength

photoswitches, in combination with orthogonal crosslinking reactions, a single resin formulation can be employed for the facile, one-step printing of complex, bio-inspired structures. Performance and build rates were significantly enhanced compared to traditional techniques such as stereolithography (SLA). The fabrication of soft joints and brick-and-mortar architectures showcases the utility of SMaLL for printing novel all-polymer composites with well-defined regions of different mechanical and chemical properties (**Figure 3**). Ongoing research includes the integration of multi-material resins into dynamic printing processes to access more advanced hierarchical 3D structures.

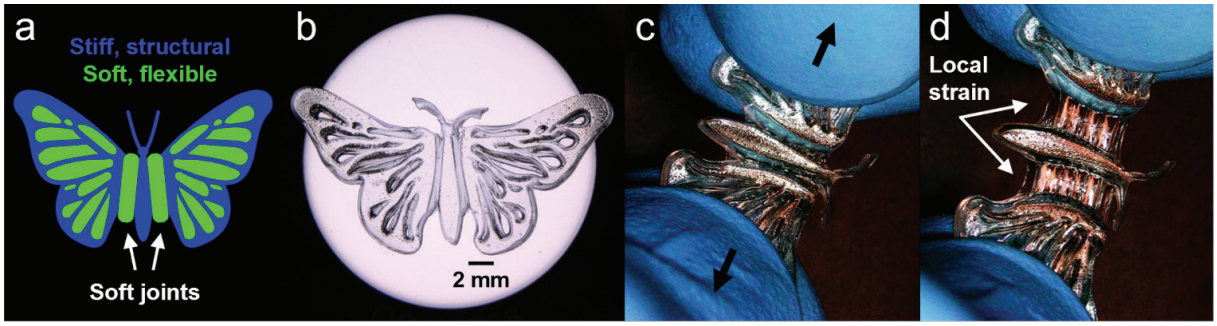



**Figure 3.** Demonstration of soft joints with SMaLL multi-material printing. **a**) Digital butterfly design with blue areas correlating to stiff sections and green areas to soft joints. **b**) Optical micrograph of the dried butterfly sample. **c**) Butterfly specimen stretched outward from the body, **d**) showing selective straining in the soft joints.

The combination of controlled polymerization and automated chromatographic separation was demonstrated to be a highly efficient and powerful approach to the preparation of discrete conjugated oligomer libraries [5]. This significantly increases the availability of a wide range of oligomers with high structural purity and in synthetically useful quantities. This methodology also offers unprecedented opportunities for tuning electronic and photonic properties. By simple mixing of discrete oligomers (e.g., all thiophene mixture) or by controlling the placement of functional units, dramatic changes in photoluminescence is achieved, illustrating the significant potential of these discrete conjugated building blocks for designer materials and nanoscale assemblies (**Figure 4**). Facile and scalable access to monodisperse libraries of different oligomers, from conjugated to random coil systems, opens facile pathways to designer mixtures with precise composition and materials with sequence-specific structure, allowing exquisite control over their physical and optoelectronic properties.

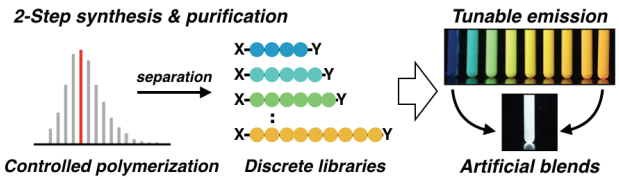



**Figure 4.** Combination of controlled polymerization with automated chromatographic separation leads to scalable quantities of precise oligomers with tunable physical and optical properties.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

The development of next generation, bio-enabled materials for the demanding needs of the Army requires access to new lightweight polymeric structures and processing strategies. One aim of this program was to develop a new 3D printing platform—SMaLL—that addresses the challenge of agile, adaptive and versatile processing for preparing bio-enabled structures that have new and/or improved properties when compared to both traditional synthetic systems as well as natural materials. These fundamental investigations will result in the development of flexible and new capabilities for the Army in this manufacturing science, while also finding widespread use in the development of unique materials for Army related applications in the areas of sensors, chem bio-catalysis, photonic crystals and functional coatings. To leverage the advances described above, collaborations have been established with a number of Army scientists and ICB researchers. Through a series of teleconferences, in-person meetings and white paper/proposal exchanges, this project has been refined in terms of bio-enabled targets and design criteria with input from Don Cropek (ERDC), Jason Dorvee (ERDC), Kyoo Jo (ERDC) and Eun Jung Kim (ERDC). Initial interactions have also been established with Reena Patel (ERDC) and Guillermo Riversos (ERDC) through individual discussions at an Army-ICB workshop to establish a framework for future modelling studies. In addition, complimentary expertise in a wide range of 3D printing techniques through the Agile Manufacturing Research

initiative at ARL (Larry Holmes) will provide immense benefit to the short-term and long-term scientific goals of the project. Additional discussions with Robert Lambeth (ARL-WMRD) on the design of new of chemistries for 3D printable ionic materials have been incorporated into the future targets for SMaLL. Project design and future collaborations with Chris Voigt (MIT) on the design and incorporation of novel biological building blocks into SMaLL and Katharina Ribbeck (MIT) on the development of bio-functionalized 3D printed materials is allowing the full impact and potential of this project to be demonstrated.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Self-assembled Conformable 3D Networks for Hybrid Electronic Materials**

**Project Leader:** **Angela M. Belcher (MIT)**

**Collaborators:** **Kang Xu (ARL-SEDD); F. John Burpo (West Point) and Jeffery Stuart (Lockheed Martin ATL)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

Lightweight high energy batteries and integration of batteries into textiles will lead to a reduction in total soldier load as well as the incessant need for battery resupply. The ability to fabricate lightweight and micro-scale batteries will enable to powering of devices ranging from micro-sensors to macro-scale devices requiring conformable power supplies. Biological systems, which assemble ornate, inorganic structures under environmentally friendly conditions, can be used to template inorganic structures that push the boundaries of energy storage technologies. Applying this paradigm, we have used M13 bacteriophage as a template for the synthesis of energy storage materials and the assembly of composite materials with improved performance. We have demonstrated that biological systems provide routes to access high-performance energy storage structures that are difficult or impossible to synthesize via other means. In our approach to develop environmentally friendly materials and ambient condition syntheses for lightweight batteries, M13 virus scaffold has been used to produce 3D inorganic material for next generation high energy storage technologies like Li-air, Li-ion, Li-S and sodium ion battery electrodes with excellent electrochemical performance that can hardly be achieved via other methods.

In order to improve the reversibility of high capacity lithium oxygen batteries, we have demonstrated a class of earth abundant transition metal oxides as air battery catalysts. Morphological control for air flowing 3D conductive networks formed of gold, nickel, cobalt, and nickel/gold alloys was characterized via alteration of several synthesis variables in the M13 nano-network templating method that has been developed by the Belcher lab. In order to improve the power density of batteries we have continued to synthesize bio-templated metal nanofoams as current collectors, demonstrating the production of bio-templated nickel foam monoliths and large-format batteries. Additionally, several current collectors and support structures for cathode synthesis of these nano-networks were explored. Results indicate that stainless-steel meshes will yield robust cathode supports for implementing phage-derived networks into lithium-air cells.

With respect to lithium-ion batteries, we used the M13 virus to template both carbon nanotube/manganese borate composites for lithium-ion batteries and carbon nanofibers for Li-S batteries. For battery fabrication, biotemplated metal networks were integrated into nickel nanofoam substrates and were shown to be suitable three-dimensional current collectors for high-rate lithium manganese oxide electrodes. In order to take advantage of the excellent charge transport afforded by this percolating network of thin metal nanowires, control over active material thickness was demonstrated using eletrodeposition. It was shown that active materials with thicknesses ranging from 10 nm to 50 nm could be easily deposited by varying the number of deposition pulses. Using this methodology very high rate batteries were achieved, retaining 20% of their discharge capacity at 40C. Lastly, we have demonstrated novel bio-template zinc sulfide nanofibers as the anodes and transition metal oxides as the cathodes for sodium-ion batteries. Bio-templating plays an important role in enhancing sodium ion mobility and kinetics in the electrodes, thus improve the electrochemical cycling stability and capacity of these batteries. Due to the abundance of sodium, this alternative-working ion may play an important role as increasing demand for lithium results in high global prices. Our work opens the ability to develop next generation high energy electronic materials and engineer batteries designed to a specific Army use precisely.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

The objective of this program is to employ M13 bacteriophage for the growth and assembly of novel materials and architectures in energy storage and catalysis applications. In addition to the bio-templated synthesis of new catalyst materials for application to next-generation batteries, lithium-oxygen and lithium-sulfur battery systems, we continued to explore novel bio-templated nanomaterials for sodium ion batteries. We produced metal sulfides and sodium transition metal oxides, using M13 bacteriophage as a template to prepare nanostructures that are electrochemically active to be used as both anodes and cathodes for sodium ion batteries. We have modified M13 as a biological template for the low temperature aqueous synthesis of several materials that have properties of interest for next generation high energy and inexpensive rechargeable batteries.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

Developing appropriate electrode materials for sodium ion batteries with good electrochemical performance remains unsolved in energy storage technology. Biological systems, which assemble ornate, inorganic structures under environmentally friendly conditions, can be used to template inorganic structures that push the boundaries of energy storage technologies. Applying this paradigm, we have used M13 bacteriophage as a template for the synthesis of energy storage materials and the assembly of composite materials with improved performance. This work has demonstrated that biological systems provide routes to access high-performance sodium ion battery electrodes that are difficult or impossible to synthesize via other means.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1. Biotemplated Zinc Sulfide Nanofibers as Anode Materials for Sodium-ion Batteries*

Sodium-ion batteries (SIBs) hold great promise for the next generation of energy storage devices because the natural abundance of sodium makes this element less of a future strategic concern than lithium, its high redox potential ($E_0$Na+/Na=-2.71V vs. S.H.E., only 0.3V above that of Li) and similar chemistry to lithium [1]. However, one of the key technological impediments to sodium-ion batteries is the availability of a low cost, high capacity anode material. Graphite, which is commonly used as the anode of lithium-ion batteries, does not intercalate a substantial quantity of sodium, showing low capacity and irreversibility as a sodium battery negative electrode [2]. In this work, we have demonstrated that biotemplated zinc sulfide nanofibers, prepared by using the M13 bacteriophage template have good potential to be used for this purpose. We investigated the effect of both annealing and molecular templated carbon-coating on the electrochemical performance of these materials. We found that biotemplated zinc sulfide nanofibers coated with a <2 nm carbon layer could deliver a reversible capacity of 603 mAh/g at 100 mA/g discharge rate, even with a high overall zinc sulfide loading of 70%. We were able to achieve an initial Coulombic efficiency as high as 71%, and stable cycling performance for at least 100 cycles.

To produce zinc sulfide nanofibers, we carry out the solution phase reaction of zinc acetate as the zinc precursor and thioacetamide as the *in situ* sulfur source in the presence of the M13 bacteriophage, acted as a physical template onto which zinc sulfide nanoparticles could nucleate. However, because of this strong protein-ion interaction and the fact that zinc is a divalent ion with substantial charge screening, bundling of the virus was observed as soon as the zinc precursor was added into a virus solution. To minimize this, we successfully employed three strategies: (1) minimizing precursor concentrations, (2) hot injecting reactants and (3) eliminating mechanical agitation. To improve electrochemical performance, the as-prepared zinc sulfide nanofibers were either modified with post annealing at 600 °C, or modified with a thin carbon coating (1~2 nm). The latter was done by coating the material was a layer of phenolic resin, followed by carbonization. A maximum

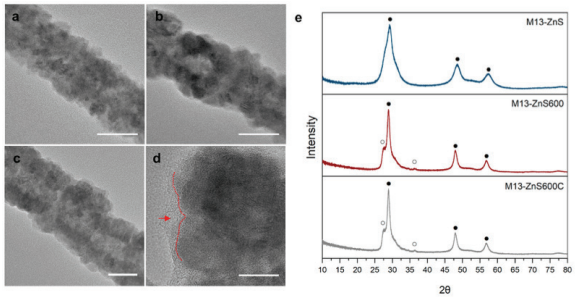



**Figure 1.** Morphological and structural comparisons between as-prepared zinc sulfide nanofibers, after annealing and after carbon-coating. Image (**a**) shows the as-prepared nanofiber with small primary particle size. Image (**b**) shows the nanofiber after annealing at 600 °C for 1 hour showing a slight increase in primary particle size. Image (**c**) and (**d**) are images of the nanofiber after carbon-coating. Scale bars: (**a-c**) 30 nm and (**d**) 15 nm. Image (**e**) shows the XRD diffractograms of Image (**f**) shows the XRD diffractograms. Peaks corresponding to β-ZnS are labelled with ♦.

carbonization temperature of 600 °C was used to avoid thermal decomposition of zinc sulfide at higher temperatures. We characterized the morphology of the ZnS nanofibers by using TEM (**Figure 1.a-d**). Each nanofiber was 500~1000 nm in length, around the same length as a single M13 bacteriophage, which suggested that each nanofiber contained only a single virus template. The phase purity and crystal structure of the ZnS nanofibers were confirmed using XRD shown in **Figure 1.e**. The primary particle size for the as-prepared nanofibers was 4.4 nm, while after annealing/carbon-coating, the particle size increased to 9.6/9.5 nm.

To test the electrochemical performance of the synthesized material, coin cells were assembled with Na metal as the counter electrode and ZnS as the anode. In this study, the electrolyte was 1 M $NaClO_4$ (sodium perchlorate) in a mixture of EC (ethylene carbonate) and PC (propylene carbonate) with a solvent volume ratio of 1:1. We ran initial galvanostatic cycles at 50 mA/g between 0 and 3 V to compare the effect of annealing and carbon-coating on accessible capacity (**Figure 2.a**). Annealing increased the reversible capacity from 252 mAh/g (280 mAh/g based on ZnS mass) to 498 mAh/g (498 mAh/g based on ZnS mass). This increase could in part be attributed to the increase in particle size, as the amount of particle interfaces/grain boundaries is reduced that increase the conductivity of the materials and decreases the solid-electrolyte interface area. Further increase in reversible capacity was achieved by carbon coating, with up to 531 mAh/g. This increase can be attributed to the decrease in interfacial resistance with annealing and a carbon coating as shown in **Figure 2.c**. The average discharge potential decreased to 0.37 V, but 1st cycle CE remained relatively unchanged at 71%. Galvanostatic cycling was continued for 100 cycles to investigate the effects of post-processing on capacity retention (**Figure 2.b**). The as-prepared nanofibers had a rapid initial drop in capacity, losing almost all capacity by the 10th cycle and retaining only 3% by the 100th cycle. Annealing significantly improved capacity retention. 50% of the 2nd cycle capacity could be retained until the 24th cycle, and after 100 cycles, the material still had 100 mAh/g of capacity. Carbon-coating improved capacity retention even further, retaining 178 mAh/g of capacity after 100 cycles.

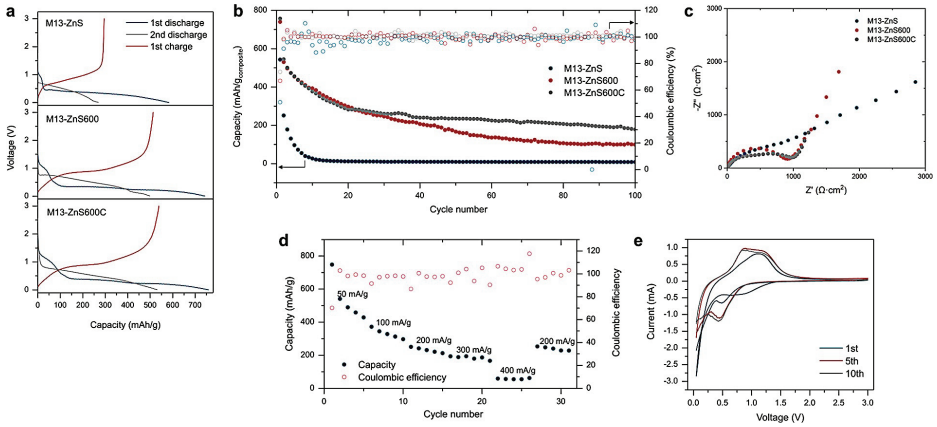



**Figure 2.** Electrochemical performance of biotemplated zinc sulfide nanofibers in SIBs against a sodium metal counter electrode. (**a**) Voltage profiles for the first- and second-cycle discharge, as well as the first-cycle charge at 50 mA/g. (**b**) Cycling stability of the different types of nanofibers at 50 mA/g charge and discharge rates between 0 and 3 V. The capacity is normalized against the total composite mass. (**c**) EIS spectra of the different samples. (**d**) Galvanostatic cycling performance of the carbon-coated nanofiber (M13-ZnS600C) at 50, 100, 200, 300, and 400 mA/g charge and discharge rates. (**e**) Cyclic voltammograms of sample M13-ZnS600C at a sweep rate of 0.1 mV/s for the 1st, 5th, and 10th cycles.

Both annealing and carbon-coating significantly improved the electrochemical performance of zinc sulfide nanofibers. We further investigated the stability of the carbon-coated nanofibers using galvanostatic cycling under different charge/discharge rates (**Figure 2.d**). The materials show a good rate capability and capacity retention at a relatively higher current density of 400 mA/g, with a reversible capacity of 252 mAh/g being recovered when the applied current density is switched to 200 mA/g. The CV measurement (**Figure 2.e**) of the carbon coated nanofiber at a scan rate of 1 mV/s also indicates that 1st irreversible reduction accounts for the initial sodium ion intercalation to the materials and the formation of SEI on the surface of the nanofiber. The following reduction (~0.5 V) and oxidation (~0.9 V) peaks at the 5th cycle match well with these peaks at the 10th cycle, suggesting a good reversibility of the carbon-coated ZnS nanofibers used as sodium ion battery anodes.

### *4.2. Developing High Energy Density Bio-templated Transition Metal Oxide Cathode Materials for SIBs*

In addition to developing biotemplated anode materials, cathode materials largely determine the energy density, lifespan and the tolerance of SIBs. Due to the larger ionic size of Na, it is challenge to design appropriate host cathode materials that are able to intercalate and deintercalated with sodium ion, therefore, increasing the electrochemical performance of advanced SIBs requires smart design of cathode material structures [3]. Among the cathode candidates, $NaTMO_2$ layered oxides (TM = transition metal) have attracted intensive attention due to their high energy density and feasible synthesis. Their Na+/vacancy-ordered superstructure depends on the Na concentration when explored in a limited electrochemical window, that largely determines the electrochemical properties like $Na^+$ kinetics, voltage plateau and cycling stability of the materials as the cathode for SIBs. In this work, we demonstrated a novel solution phase synthesis of a family of P2-type (prismatic) $NaNiMnXO_2$ (X= Ti, Sn, Si, Fe…) and their application for high energy sodium ion battery cathodes. By adding different doping atom X, we were able to control Na mobility and Na diffusion barrier in the transition metal oxide compounds, therefore, improving the cycling stability and rate capability of the cathode materials for rechargeable SIBs especially by doping with Ti. Additionally, with the aid of bio-templating, we were able to reduce the size of $NaNiMnTiO_2$ from micro scale to nano scale, further enhancing the $Na^+$ diffusivity in the compound [4-5]. As a result, it increases the capacity at even higher cycling rate. When applying the synthesized materials as sodium ion battery cathodes, the batteries display long cycle life with good capacity retention after 100 cycles at various current densities. These cathodes also bear a high average voltage of ~ 3.6 V, opening up a new route to design high energy and high rate cathode materials for SIB.

To produce nano-structured $NaNiMnTiO_2$, we used to genetically-engineer multifunctional M13 virus as the template to grow the material at room temperature. The developed material has an amorphous structure with an average particle size of ~20 nm, synthesized in a solution-based environment with the aid of the M13 virus. To improve the electrochemical performance, nano-structured $NaNiMnTiO_2$ has been annealed at 800°C for 1 hour to crystalize the material. To study the morphology and structure of the synthesized Bio-$NaNiMnTiO_2$, we characterized the material with transmission electron microscopy (TEM) and powder X-ray diffraction (XRD) techniques (**Figure 3**). XRD results show the transformation of the material from amorphous to crystalline structure and TEM confirms the morphology (nanowire) and nano- structured (~ 20 nm) characteristics of the bio-$NaNiMnTiO_2$ after annealing.

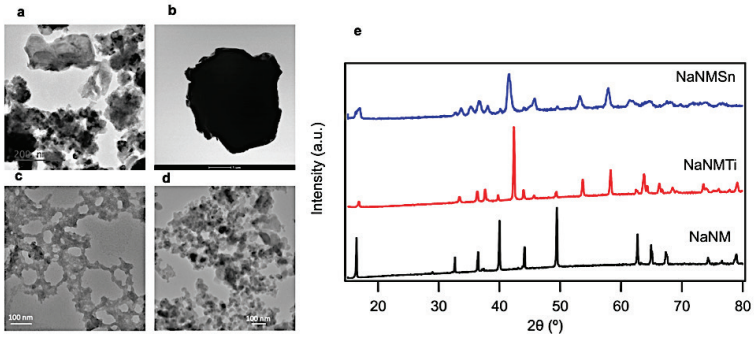



**Figure 3.** Morphological and structural comparisons between pristine and bio-NaNiMnTiO2. Image (**a**)-(**d**) are TEM micrographs showing pristine NaNiMnTiO2 structural changes due to annealing. Image (**c**)-(**d**) are TEM micrographs showing bio-NaNiMnTiO2 structural changes due to annealing. Image (**a**) shows the precursor of NaNiMnTiO2. Image (**b**) shows metal oxide compound annealing at 800 °C for 1 hour showing a huge increase in primary particle size. Image (**c**) shows the precursor of bio-NaNiMnTiO2. Image (**d**) shows the morphology of bio-NaNiMnTiO2 after annealing. Scale bars: (**a**) 200 nm, (**b**) 1 µm, (**c**) 100 nm and (**d**) 100 nm. Image (**e**) shows the XRD diffractograms of pristine NaNiMnXO2 after annealing with different doping atoms.

To test the electrochemical performance of the synthesized material, coin cells were assembled with Na metal as the cathode and $NaNiMnXO_2$ as the anode. The cells were cycled in galvanostatic mode with a voltage range of 2.5V to 4.15 V on Solartron Analytical 1470E potentiostat at room temperature. The voltage profiles of the battery with different doping atom in the $NaNiMnXO_2$ are shown in **Figure 4.a-d**. The electrode material without doping displays a two plateau in the voltage, indicating a slow sodium ion kinetic in the electrode compound. With the addition of heteroatom, the voltage plateau becomes sloppy and consistent and the capacity increase with the

addition of Ti. This indicates that heteroatom helps increase interatomic space and enhance sodium ion mobility in the compound. With the help of biotemplating, we were able to further increase the capacity and rate capability of the battery. As shown in **Figure 4.e** and **Figure 4.f**, the cell exhibits capacity of ~120 mAh/g at a rate of C/5 with biotemplating. Bio- $NaNiMnTiO_2$ cathode can be cycled at a current density up to 10C and recover its capacity when lowing the rate. These results confirm the reversibility and rate capability of the bio-templated $NaNiMnTiO_2$ as the cathode of sodium-ion battery for the first time.

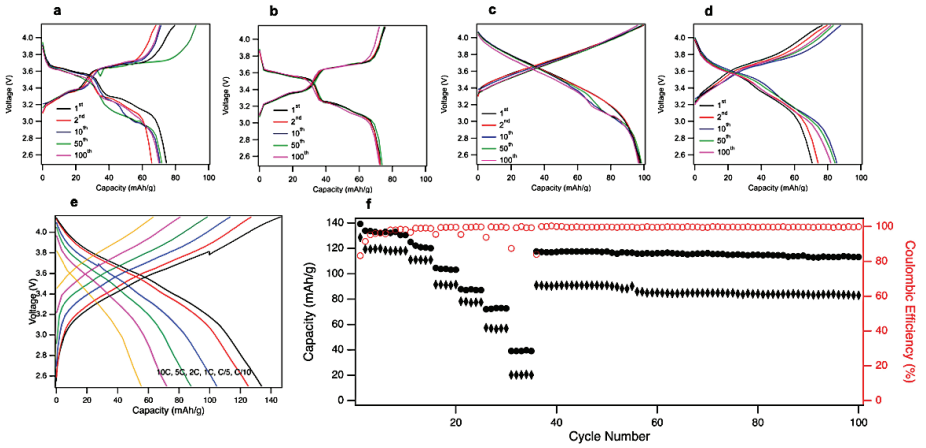



**Figure 4.** Electrochemical performance of the transition metal oxides in SIBs against a sodium metal counter electrode. (**a**) to (**d**) Voltage profiles of pristine $NaNiMnXO_2$ with different doping atoms for different cycles at 1C. (X= (**a**) no doping, (**b**) Si, (**c**) Ti, (**d**) Sn). (**e**) Voltage profiles of bio-$NaNiMnTiO_2$ at different rates. (**f**) Cycling stability of pristine and bio-$NaNiMnTiO_2$ at different current densities (C/10, C/5, 1C, 2C, 5C,10C and C/5).

### *4.3. Structural Ceramic Batteries (SCBs)*

As an alternative strategy to improving the properties of active materials themselves, structural batteries increase the portion of a vehicle mass composed of battery material by producing batteries able to serve as structural vehicle components. This strategy could dramatically improve the range of vehicles such as electric cars and UAVs. As typical battery chemistries are unable to result in rigid electrodes, we introduced a new patent-pending strategy for formulating electrodes using a ceramic binder that overcomes these challenges. The ceramic binds together particles in both electrodes and the separator, producing monolithic structures known as structural ceramic batteries (SCBs) that are able to transfer load both within and between electrode planes.

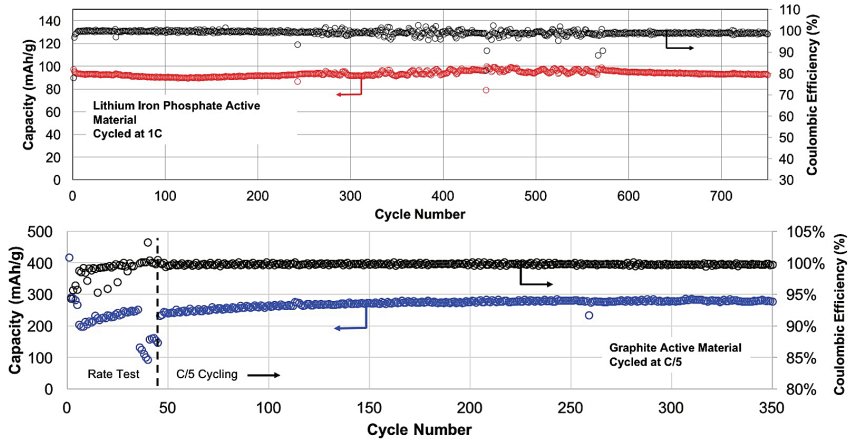



**Figure 5.** Electrochemical performance of structural battery cathodes (top) and anodes (bottom). In developing SCBs, it was necessary to find a rigid adhesive able to bind together battery components without impeding electrochemical function. Sodium trisilicate was identified as an adhesive ceramic able to achieve this. These tests demonstrate that the binder is compatible with well-known active materials, enabling structural batteries to increase vehicle range.

During the course of the project, we investigated multiple potential binder materials able to perform the functions of an adhesive across all three battery layers without disrupting electrochemical function. It was determined that sodium trisilicate, a well-known adhesive in other industries such as refractory materials and mineral paints, was a durable adhesive able to be used as a binder in a range of battery chemistries. We demonstrated compatibility through the construction of cells combining known active materials with silicate and conductive binder, showing that these cells are able to cycle for hundreds of cycles (**Figure 5**).

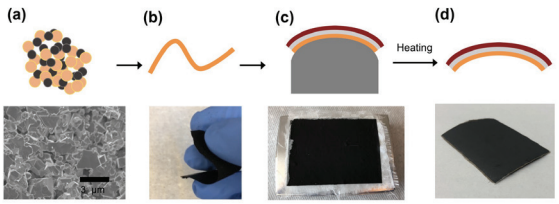



**Figure 6.** Manufacturing process for SCBs. Active materials (**a**) are processed into electrode sheets (**b**) containing active material, conductive additive, ceramic binder, and a polymer imparting flexibility. Sheets can be made for both electrodes and separator, and the three can be combined on a mold in order to conform to the shape of a vehicle component (**c**). With heating the flexible polymer is removed, leaving the rigid ceramic binder. The resulting part (**d**) is a rigid, load-bearing ceramic battery.

Furthermore, we demonstrated a manufacturing process by which full cells using SCBs are able to be produced as shown in **Figure 6**. Using this process, a flexible sheet employing both a rigid binder and a flexible binder is produced. These sheets are able to conform to a mold, and the flexible binder is subsequently burned out during heat treatment. The result is a rigid SCB able to conform to the shape of a part. The result is a manufacturable battery production process able to adapt to a wide variety of battery shapes.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

In battery projects, Kang Xu at ARL-SEDD has designed and provided electrolytes. Projects in developing sodium ion battery electrodes have been carried out in collaboration with Shell. Technology transition routes are currently being explored. Structural battery use in UAVs was the subject of an MIT Technology Fellowship Program commercialization project, with market research performed including discussing use case with Aerovironment and COL John Burpo at West Point.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Topology and Shape Optimization of Energy-Dispersive Cellular Structures**

**Project Leader:** **Frank W. Zok (UCSB)**

**Collaborators:** **Ricardo Rodriguez and L.J. Holmes (ARL-WMRD); Matt Begley (UCSB)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

A new *taxonomy of truss structures* has been devised. The taxonomic system is depicted in the form of a phylogenetic tree in **Figure 1**. It combines concepts from crystallography and geometry to describe nodal locations and strut connectivity. Its conceptual evolution begins with elementary cubic trusses, increasing in complexity with non-cubic and compound trusses as well as super-trusses, and, finally, with complex trusses. In addition to providing a rational framework for describing and understanding truss topology, the taxonomy has proven effective in conceptually constructing periodic trusses of progressively increasing complexity *in a systematic manner*. In turn, it has led to discovery of new topologies that exhibit unique combinations of stiffness and strength.

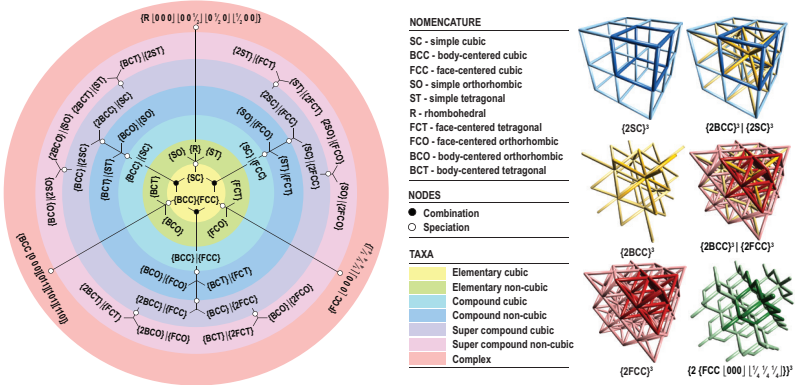



**Figure 1**: A phylogenetic tree depicting the (notional) evolution of truss structures (**left**). It begins at the center, with three elementary cubic trusses that are subsequently combined to form various compound trusses. Speciation of elementary and compound trusses can occur through changes in truss shape and size. Representative truss topologies are shown on the **right**.

Based on exhaustive computational studies and experiments on prototypical trusses, a number of key *design rules* have been established. For instance, to attain the full compressive (buckling) strength in $\{FCC\}$ trusses, the combination of tensile failure strain $\varepsilon_f$ of the constituent material and truss relative density $\rho$ must satisfy the criterion $\varepsilon_f / \rho \geq 0.25$; otherwise fracture of tensile struts precedes buckling. Results of this type have been used to rank the efficacy of combinations of topology, geometry and material properties in attaining high strength. When the buckling criterion is satisfied, $\{FCC\}$ trusses are superior to other truss types. In contrast, when $\varepsilon_f / \rho \leq 0.1$ (as it might be for ceramic trusses), the $\{BCC\}|\{SC\}$ binary truss is superior, with strengths exceeding those of $\{FCC\}$ trusses by a factor >2. Corresponding design rules for trusses that *absorb energy reversibly* through dynamic snap-through instabilities, couched in terms of strut orientation, truss relative density and material failure strain, have also been identified.

New insights have been gleaned regarding the sensitivity of truss strength to important structural features, notably *free surfaces, missing struts, and node geometry*. For example, in $\{FCC\}$ trusses, strength is influenced more by free surfaces (because of reduced nodal connectivity) than missing bulk struts. Even when missing struts are located in the most critical location at a free surface and the strain elevations are conflated with those due to the surface itself, their effects on truss strength are remarkably small (<5%). Results of this type have important implications in moving conceptual truss designs into the engineering domain.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

The long-term objective of the program was to establish a framework for enabling discovery of new topologies and geometries of cellular structures with unique mechanical and functional characteristics, including not only high strength, stiffness and robustness but also high energy absorption capacity. Building on accomplishments in earlier stages of this project [1, 2], the objectives of the work in the current reporting period were twofold: (i) ascertaining the role of key truss features—notably nodal fillets, free surfaces, and strut defects—on the mechanical performance of periodic trusses, and (ii) establishing a mechanistic framework for design of trusses with high reversible straining and energy absorption capacity through reversible snap-through instabilities.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

The research approach entails: (i) development and use of customized, highly-efficient, computer codes and material models that enable large-scale, parametric studies of non-linear truss response and failure; (ii) design, fabrication and mechanical testing of truss structures made by additive manufacturing routes (the latter being a major focus at ARL); and (iii) state-of-the-art experimental methods for high-fidelity, information-rich tests.

### *3.1 Defect Sensitivity of Strength*

Building on preceding developments in the taxonomy of truss topology [1] and design of strong, elastically-isotropic trusses [2] (from work completed in the preceding period and published during the current period), current studies focused on computational models of large deformation and failure of trusses, incorporating effects of free surfaces and of defects in the form of missing struts [3]. Although explicit integration of the equations of motion in finite element (FE) methods offer improved memory scaling with increasing model size, the times required to complete a single non-linear simulation preclude the possibility of large-scale, parametric studies. For context, using the explicit time integration capabilities of Abaqus/Explicit and running on a high-performance computer cluster, a simulation of crushing of an 11x11x11 cubic truss containing over 30,000 struts to a global compressive strain of 1% requires several days of computation time. Development of computational tools to perform parametric simulations on the scale required to fully characterize the design space of truss structures was therefore a high priority. To this end, a novel explicit integrator that improves upon the integration scheme of commercially available software was developed, thereby facilitating studies of previously uncharted scale. These FE tools were used to determine the extent to which individual strut defects and free surfaces, both separately and together, elevate strains in neighboring struts and, in turn, the effects of strain elevations on truss strength. Three prototypical stretch-dominated truss types, illustrated in **Figure 2**, were studied.

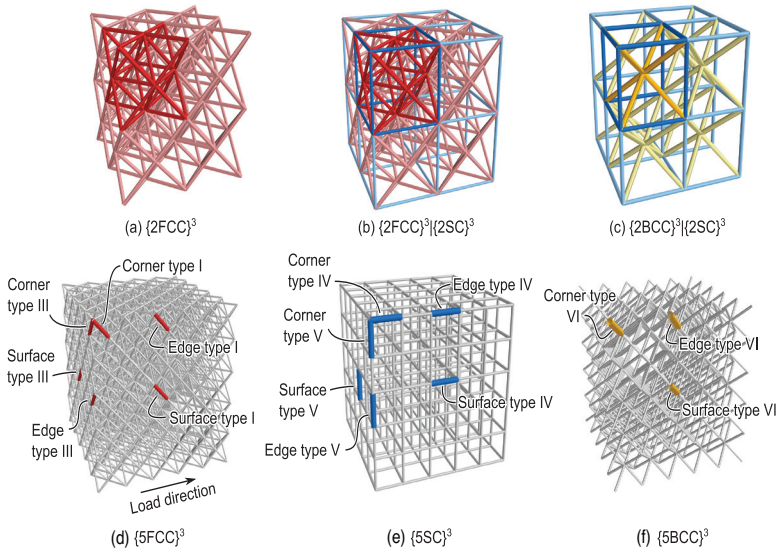



**Figure 2.** (**a-c**) Cubic trusses used for defect-sensitivty study. Unit cells indicated by darker colors. (**d-f**) Locations of surface, edge, and corner defects in each of the three constituent trusses [3].

### *3.2 Effects of Nodal Fillets on Truss Performance*

Through collaboration with ARL personnel (Ricardo Rodriguez, Larry Holmes), a series of stretch-dominated trusses was designed to probe effects of nodal fillets on truss strength and to critically assess the predictive capabilities of the FE models. Two sets of trusses – with and without nodal fillets – were printed using a production-level, through-vat stereolithography machine (**Figure 3**). Uniaxial compression tests were performed with 3D displacement fields obtained by digital image correlation (DIC). Three local deformation metrics were computed for all (>50) externally-visible struts: axial strut strain, bending strut strain, and nodal rotation. The individual struts were subsequently sorted in two ways: by orientation with respect to loading direction and by proximity to faces, edges, and corners. Complementary FE simulations were also performed [4].

### *3.3 Post-Buckling and Dynamic Response of Angled Struts in Elastic Trusses*

An exhaustive set of numerical solutions was obtained for the non-linear response of inclined, slender, elastic struts with initial imperfections over a complete range of slenderness ratios and angles (**Figure 4**). The results were used (i) to construct regime maps indicating the type of response (e.g., monotonic, reversible snap-through and irreversible snap-through), (ii) to compute the global stresses and strains associated with snap-through as well as the maximum material strains (to avoid failure), and (iii) to determine responses to multi-axial loading states [5]. Insights from the general solutions were used to derive a single degree-of-freedom, non-linear dynamic model; this model was used to elucidate the role of material damping and estimate cyclic dissipation [5].

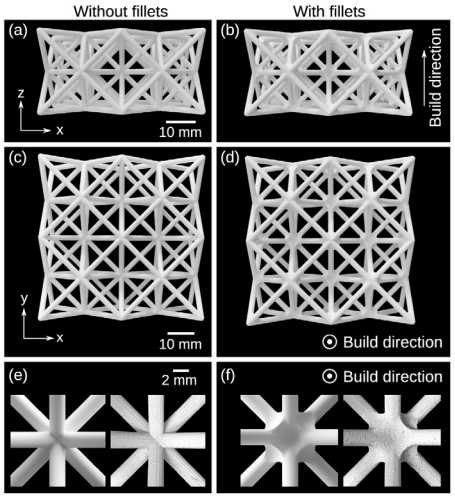



**Figure 3.** (**a–d**) Printed trusses with and without filleted nodes viewed in two orientations. (**e, f**) Higher magnification views of nodal regions in computer models (**left** image in each pair) and in the printed parts (**right** image) [4].

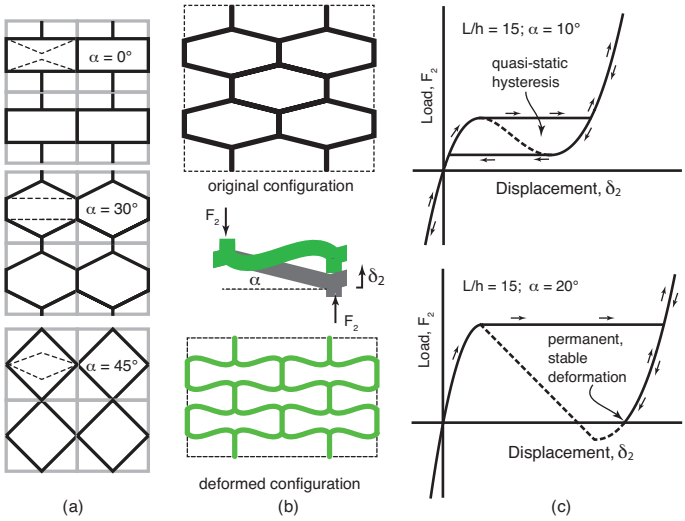



**Figure 4.** (**a**) Lattices with angled struts. (**b**) Original and deformed shapes when a hexagonal lattice is constrained against expansion and the angled struts experience snap-through. (**c**) Load-deflection curves for two strut angles, showing both reversible (**top**) and irreversible (**bottom**) snap-through [5].

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1 Defect Sensitivity of Truss Strength*

Coupled effects of defect type, defect location and tensile failure strain on the compressive stress-strain response of the three trusses are illustrated in **Figure 5** [3]. The key observations and conclusions follow. (i) Among the three trusses studied here, {*FCC*} is the most defect-tolerant. This is because the strain elevations around bulk strut defects (distant from free surfaces) are smaller than those *at* free surfaces. Even when defects are located at a free surface and the strain elevations from the defects are conflated with those due to the surface itself, their effects on local strut strains and compressive truss strength are remarkably small (≤5%). (ii) Somewhat greater strength reductions are obtained in the binary trusses when defects are situated at the corners (by about 20-25%), a result of the higher strain elevations around these defects. (iii) The full-strength potential of the {*FCC*} truss, dictated by

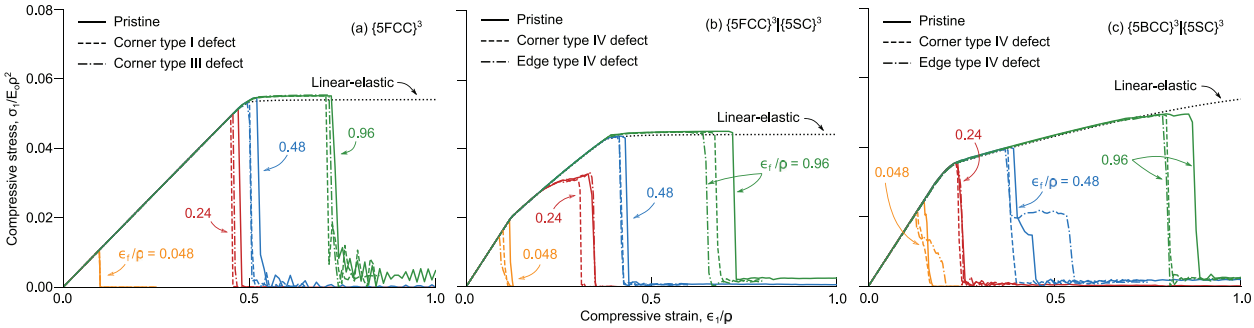



**Figure 5**. Stress-strain responses of the three trusses exhibit varying degrees of non-linearity, dependent on truss topology and material failure strain; the presence of strut defects and their locations within the truss play secondary roles. (**a**) The {FCC} truss undergoes a single buckling event at essentially a single stress, thereby producing effectively elastic-perfectly plastic response. (**b**, **c**) The two binary trusses undergo two buckling events, each associated with one of the two compressive strut populations. (The second buckling event in the {BCC} |{SC } truss occurs slightly beyond the maximum strain shown, at about $\varepsilon_f/\rho \approx 1.5$.) [3]

large-scale strut buckling, is only attained when the material failure strain exceeds a critical value of $\varepsilon_f/\rho \approx 0.25$ ($\rho$ being relative density). This condition is conceivably attainable with hard thermoplastics; a failure strain of $\varepsilon_f = 0.05$ would satisfy this condition for relative densities up to $\rho = 0.2$. In contrast, if the truss were made of a high-strength ceramic, where the failure strain (optimistically) may be $\varepsilon_f = 0.01$, the condition would only be satisfied for relative densities up to $\rho = 0.04$. (iv) When the condition for large-scale buckling is satisfied and the maximum possible strength is attained, the $\{FCC\}$ truss is preferred over the two binary trusses, since it attains its peak strength at the lowest level of material failure strain. Although in principle the binary $\{BCC\}|\{SC\}$ truss can achieve a slightly higher strength, this requires materials with much higher failure strains (by almost an order of magnitude). Because of the additional constraints on material properties and the greater geometrical complexity of this truss topology, the marginal strength gains would not likely warrant selection of this truss topology, unless the design necessarily required elastic isotropy in combination with high strength. (v) In cases in which the material failure strain falls well below that required to attain large-scale strut buckling, say $\varepsilon_f/\rho < 0.1$, as it might in low relative density ceramic trusses, the $\{BCC\}|\{SC\}$ truss would be preferred, since it exhibits the highest strength, more than twice that of the $\{FCC\}$ truss. This is a consequence of the higher truss stiffness and the lower tensile strains generated in the $\{BCC\}|\{SC\}$ truss.

### *4.2 Effects of Nodal Fillets on Truss Performance*

Measured and computed compressive stress-strain curves are summarized in **Figure 6** while the corresponding evolutions of strut strains are illustrated in **Figure 7**. The main role of fillets in the current truss system is to enhance the nodal stiffness and, in turn, reduce the degree of softening due to bending of compressive (type I and II) struts. In both truss types, the peak compressive stress is approached smoothly, consistent with the progressive nature of strut buckling. However, large-scale buckling is preceded by fracture of tensile (type III) struts intersecting the truss edges. Interestingly, the peak axial strains in the latter struts at the onset of strut fracture appear to be insensitive to the presence of fillets. Evidently either the fillets employed here play only a minor role in alleviating the stress concentrations at the nodes at which tensile fracture occurs or the failure strain is insensitive to these stress concentrations.

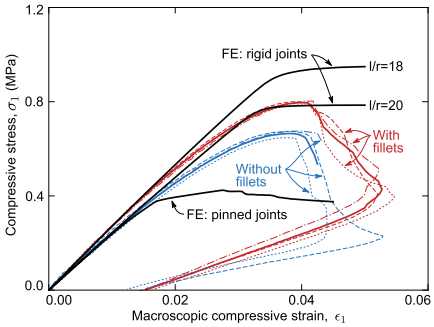



**Figure 6**. Compressive responses of trusses with and without filleted nodes and from FE. Dotted and dashed lines represent measured responses of individual test specimens whereas the solid colored lines represent averages. Here l/r is strut aspect ratio [4].

Strut strains at external boundaries invariably differ from those in the bulk. Type I corner struts, with nodal connectivities of only 3 and 8, experience the greatest amount of bending and are most prone to buckling. Type III edge struts, which have nodal connectivities of 5 and 8, experience the greatest axial (tensile) strains. Prior to buckling, the tensile strains are 50-100% greater than the nominal bulk value (for an infinite truss) and are usually the first to break. The results have

important implications in the performance of finite trusses. They also suggest strategies to mediate the detrimental effects of free surfaces through local (near-surface) modification of truss topology and geometry.

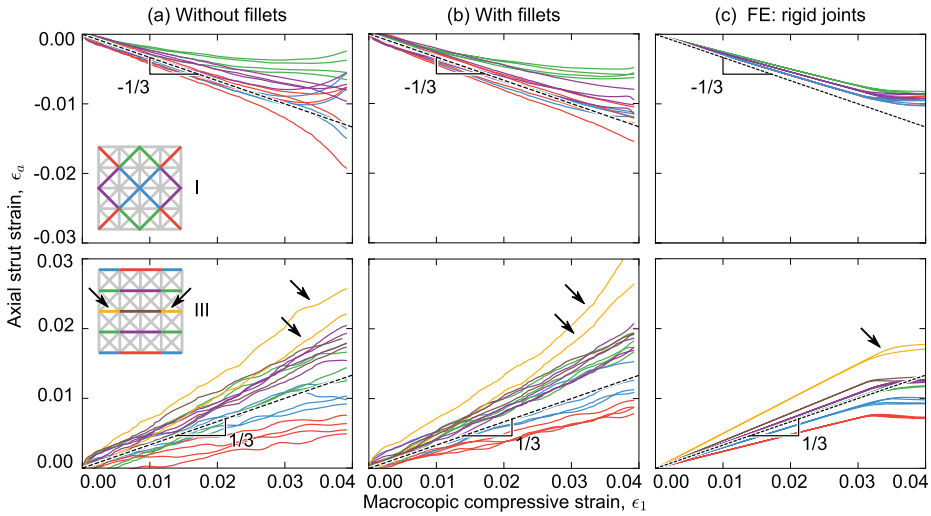



**Figure 7.** Evolution of measured axial strut strains in the two strut types (I and III) in trusses with and without filleted nodes as well as results from FE calculations (assuming rigid nodes). Results are further sorted on the basis of strut locations relative to free boundaries. Line colors correspond to strut colors in insets in (**a**). Dotted lines (with slopes of 1/3 and -1/3) represent analytic predictions for periodic boundary conditions and infinitesimal nodes. Arrows in bottom row indicate type III edge struts that experience the greatest axial strain and are the ones that rupture first.

### *4.3 Post-Buckling and Dynamic Response of Angled Struts in Elastic Trusses*

Regime maps depicting the nonlinear response of cellular materials that utilize angled struts are shown in **Figure 8**. The solutions enable a comprehensive view of the design space in that they provide: (i) all combinations of slenderness ratio and strut angle that produce snap-through behaviors and/or permit a second stable configuration; (ii) estimates of the macroscopic strains associated with the onset of buckling, and (iii) estimates of the material strains that result from instabilities. The results can be expected to be highly accurate for hexagonal lattices with relative densities in the range of $0.04<\rho<0.25$ and macroscopic strains less than 50%.

Behavioral types correlate strongly with relative density. As general rules, monotonic behavior is obtained for $\rho>0.4$, reversible snap-through for $0.25<\rho<0.4$, and irreversible snap-through for $\rho<0.25$. The resulting combinations of global stress and strain to achieve a prescribed response are immediately obtained from the maps in **Figure 8.b**,**c**. Also critical are the variations in peak material strain for each design; these generally range from 0.01 (at low densities) to 0.5 (at high densities). The latter suggests future work on designs with flexible nodes to reduce

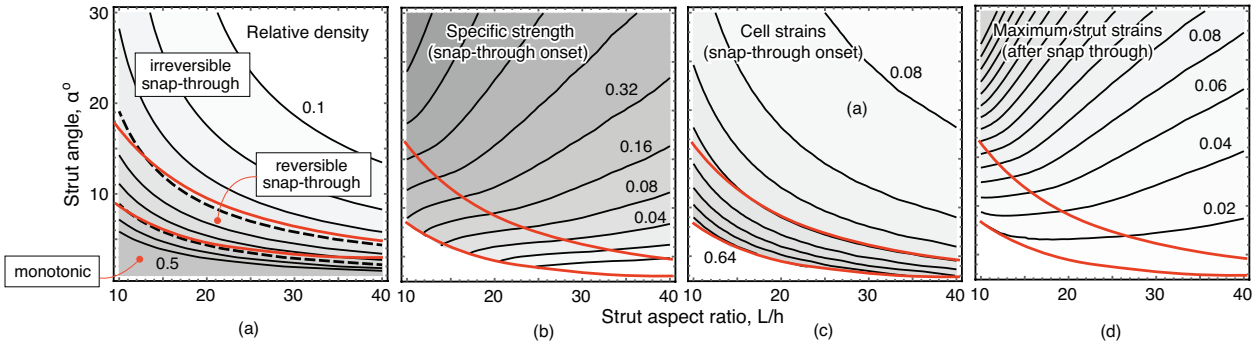



**Figure 8**. Response of diamond lattices subject to plane strain loading, showing contours of (**a**) relative density (in increments of 0.05), (**b**) specific strength (in increments of a factor of 2), (**c**) macroscopic strain at snap-through onset (in increments of 0.08), and (**d**) peak strut strain at the conclusion of snap-through (in increments of 0.02). The results can also be combined to construct maps showing hysteretic energy in the snap-through domain [5].

material strains and hence improve upon the robustness of the structure. The results also provide a framework for guiding critical experiments to evaluate the efficacy of candidate structures in achieving a prescribed response.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

Various conceptual and actual designs of truss structures (including hierarchical trusses described in previous reports) have been shared with ARL personnel, for their work in identifying processing limits for additive manufacturing of very lightweight structures. Here a major challenge involves producing unsupported struts of very high aspect ratio, especially in structures containing struts of vastly differing sizes, as found in hierarchical structures. In combination with complementary characterization and simulation work performed at UCSB in the current review period on trusses fabricated by ARL, the collaboration culminated in a jointly-authored publication [4].

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[3] R.M. Latture, M.R. Begley, F.W. Zok. Defect Sensitivity of Truss Strength. *Journal of the Mechanics and Physics of Solids*, 2019. 10.1016/j.jmps.2018.10.019

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[5] S. Wehmeyer, F.W. Zok, C. Eberl, P. Gumbsch, N. Cohen, R.M. McMeeking, M.R. Begley. Post-buckling and dynamic response of angled struts in elastic lattices. *Journal of Mechanics and Physics of Solids*, submitted 2018.

## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

S. Wehmeyer, F.W. Zok, C. Eberl, P. Gumbsch, N. Cohen, R.M. McMeeking and M.R. Begley. Post-buckling and dynamic response of angled struts in elastic lattices. *Journal of Mechanics and Physics of Solids*, submitted.

R.M. Latture, M.R. Begley and F.W. Zok. Defect Sensitivity of Truss Strength. *Journal of the Mechanics and Physics of Solids*, March 2019. 10.1016/j.jmps.2018.10.019.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Field-Assisted 3-Dimensional Printing of Bio-inspired Hierarchical Materials**

**Project Leader:** **Matthew R. Begley (UCSB)**

**Collaborators:** **Linda Petzold and Carl Meinhart (UCSB); Brett Compton (UTenn)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

This program addressed two critical needs in the development of bio-inspired hierarchical materials: (*i*) quantitative microstructure-property relationships that can be used to identify processing targets for enhanced performance [1-3], and (*ii*) effective strategies for on-the-fly microstructural control during 3D printing [4-8].

To address the first need, highly efficient GPU-based codes were developed to simulate fracture in bio-inspired materials (with a focus on nacre-like composites) [1,2]. These codes enable explicit quantitative connections between microstructure features and macroscopic performance; the speed of the simulations enables high through-put 'virtual testing' that allows the study of a wide variety of microstructures, including those with statistical variations inherent in real materials [3]. The codes combine predictor-corrector algorithm with Monte Carlo simulations to solve energy minimization problems, for large, non-linear systems involving millions of degrees of freedom; adaptive load-stepping provides a speed-up of more than 80X for large scale systems (as compared to direct energy minimization for a given load case.) This speed as achieved through the development of novel data structures that minimize the time required to perform MC minimization by separating the variables in a way that allows high degree of parallel processing efficiency on the GPU. Simulations of fracture in idealized nacre mimic were completed that make explicit connections between brick size, mortar properties, etc. and provide the scientific basis to develop tough bio-mimetic materials [2-3]. These simulations included stochastic microstructural features, by generating 'virtual specimens' whose architecture is construct from statistical descriptions of feature size and strength [3]. Virtual testing of a large number of specimens quantified the statistical variation in fracture resistance that arise from statistical variations in microstructural features; this represents the first-ever explicit connections between variability at the brick level and macroscopic performance [3]. The results demonstrated that small standard deviations in brick size (in the range 2-4%) lower the macroscopic toughness by 2-3X, which sets stringent processing targets for uniformity.

To address the second need, a comprehensive study of field-assisted printing was conducted to quantify relationships between field parameters, ink composition, printed microstructural features, and printing process parameters such as flow rates, nozzle dimensions, stand-off distance and scan speed [4-8]. At the start, the program demonstrated acoustic assembly of microparticles in static solutions and established theoretical framework to predict pattern formation and stability using closed-form solutions [4]. This work was extended to direct-write deposition to demonstrate on-the-fly assembly of two-phase composites that mimic nacre [5]. The program stablished quantitative links between ink composition, focusing outcomes and form-holding that serve as the foundation for future efforts to apply on-the-fly microstructural control across a number of applications (ranging from bio-mimetic materials to batteries) [6,7]. Critical printing guidelines were developed that identify various direct deposition printing regimes, such as droplet deposition, balanced line writing, and overflow [6,7]; the work produced methods to monitor printing using optical imaging and identify the onset of instabilities and presence of rotational flows, providing a foundation to expand the range of fluids that can be printed in this modality. Further, the program established complete scaling relationships that identify combinations of printing parameters and hardware that allow for printing of ordered, two-phase composite. These relationships provide clear guidelines for flow speeds, raster speeds and focusing parameters that achieve axial and transverse packing of particles in the print nozzle while avoiding jamming [8].

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

The objectives to this final reporting period were focused on identifying 3D printing approaches that enable on-the-fly microstructural control during direct write deposition. The following key questions were addressed: (*i*) what are the quantitative relationships between ink composition, rheology, and the degree to which particles can be aligned in printed lines? [6]; (*ii*) What are the quantitative relationships between ink composition, volumetric flow rates, and scanning parameters that ensure stable filament deposition? [7]; and (*iii*) What are the scaling relationships that relate ink properties, hardware features (e.g., nozzle size and length), printing parameters, and the efficacy of acoustic control of two-phase inks? [8].

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

The overarching strategy of this review period was to develop both *in-situ* and *post-priori* imaging techniques and image processing algorithms to quantify field-assisted printing behaviors [6, 7]. These were then used to make explicit, quantitative connections between ink composition, particle motions inside print nozzles (due to external fields), and final microstructures in deposited lines. **Figure 1** illustrates the experimental set-up used in the study.

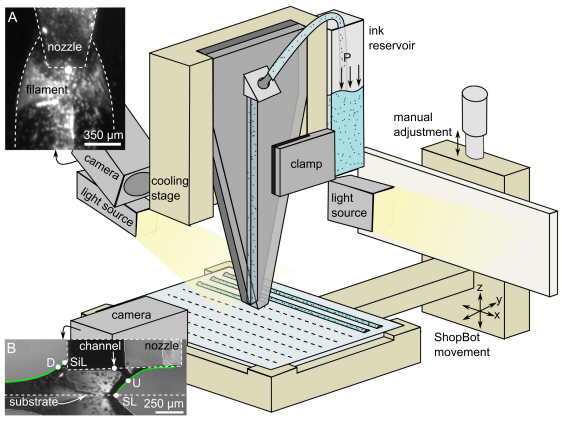



**Figure 1.** Overview of the printing set up used to study field-assisted printing of two-phase microstructures: optical imaging of the fluid inside the nozzle, the liquid bridge between nozzle and substrate, and deposited lines were used to quantify impact of process parameters.

A wide variety of epoxy ink compositions with suspended glass spheres were used in the study; acetone and silica flakes included to adjust rheology. **Figure 2** illustrates the broad range of shear-thinning behaviors that are obtainable with this system; the strategy is to exploit shear-thinning to facilitate focusing inside the nozzle (where low viscosity is needed to increase the impact of external fields) and form-holding outside the nozzle (where high viscosity is needed to limit the impact of wetting on the substrate) [6].

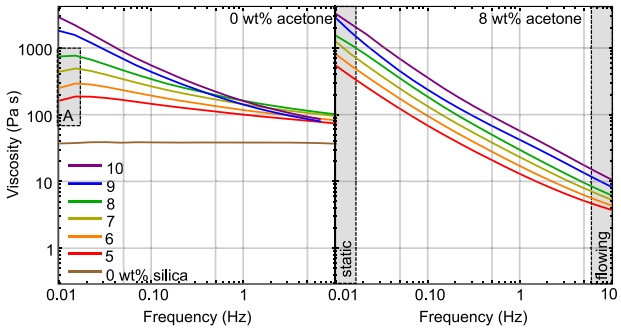



**Figure 2.** Rheology of epoxy inks used in the study, with added silicone and acetone used to control the base viscosity and degree-of shear thinning critical to effective 3D printing with direct-write deposition.

Inks were deposited using acoustic print nozzles developed in the ICB program [5-8]; in-situ optical video imaging of the particles *inside the nozzle* provide information regarding the effect of externally applied fields, while videos of the liquid bridge *outside the nozzle* provide information regarding printed line formation and droplet formation. Optical images of solidified, printed single-pass lines were used to quantify the distribution of particles in the final printed material.

The overarching strategy in this review period was to develop image processing algorithms that automatically process digital images to extract geometric parameters that quantify the impact of externally-applied fields. These algorithms involved automated routines to quantify particle locations (both inside the nozzle and in solidified printed material) and the edges of the liquid bridge between the nozzle and the substrate. These measurements then provide explicit, quantitative connections between process inputs (e.g., ink composition, particle size, acoustic field strength and frequency, volumetric flow rates in the nozzle, scan speed and stand-off distance) and process outcomes (e.g., the width of focused regions, particle densities, and wetting instabilities). [7]

These experiments were complemented with theoretical models of particle motions, which established key scaling relationships between processing parameters and the microstructure of printed two-phase microstructures [8]. Experiments were conducted to validate these models. In addition, models were developed identify the onset of droplet formation during deposition of a printed line; these models, in conjunction with in-situ observations of liquid bridge phenomena, provide a novel approach to in-situ monitoring of printing that can be exploited in process control algorithms to ensure efficacy of printing.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

**Figure 3** provides an illustration of the results generated from the study of ink composition [6]. Processing algorithms (applied to solidified, printed lines) were developed quantify the relationship between the width of focused particles and ink composition. These algorithms compute intensity profiles across the width of the channel that can be used to quantify the degree of focusing (**Figures 1.a-c**). The results demonstrate that focusing width decreases with silica content, as a result of the increase in ink viscosity (**Figure 1.d**). The impact of ink viscosity is highest for high focusing fields, which are capable of highly focused lines (**Figure 1.e**) that exhibit limited spreading at the lowest viscosity (i.e., lowest silica content, **Figure 1.f**). These results provide a clear indication of ideal ink compositions that provide the greatest degree of microstructural control [6,7].

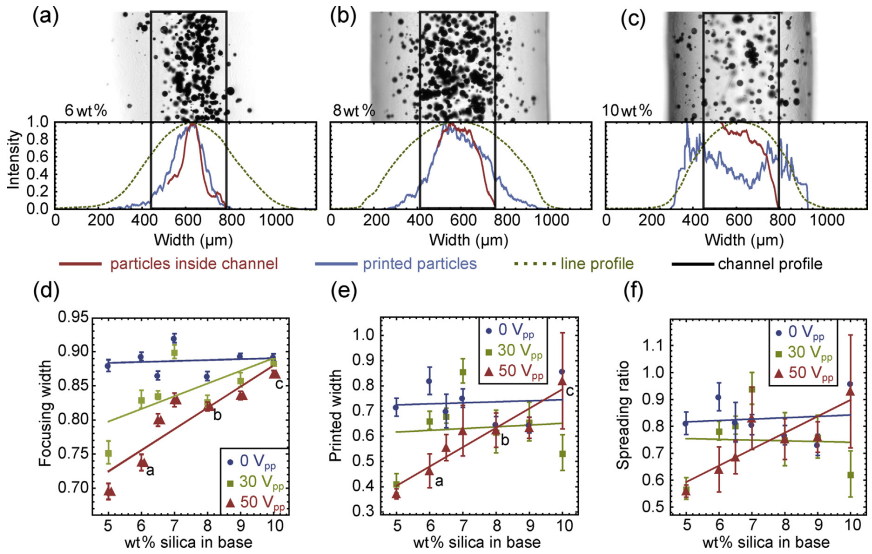



**Figure 3.** Illustrations of optical images of printed lines of two-phase microstructures, and the results of image processing to determine relationships between particle arrangements and ink composition [6].

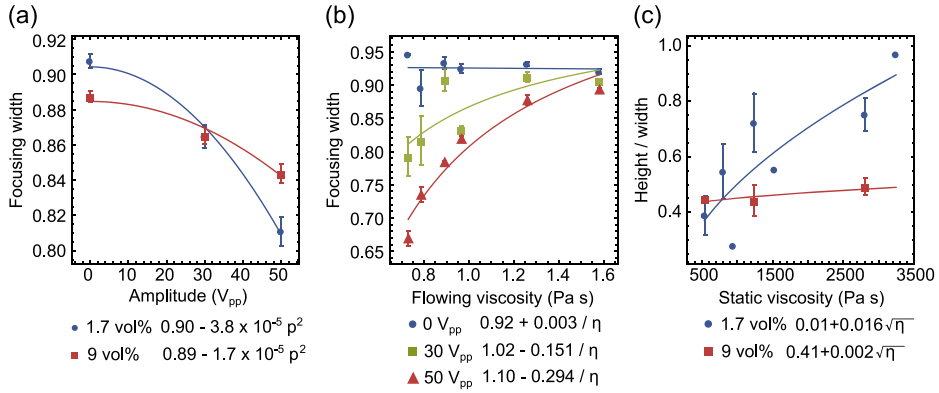



**Figure 4.** Illustrations of the relationship between focusing width and printed line form and printing process parameters, used to validate the scaling relationships identifying through theoretical modeling conducted in this program [6].

These experiments also provided validation of the theoretical models described at the end of this section, as illustrated in **Figure 4**. The models predict the dependence on focused line widths as a function of acoustic field pressures, fluid viscosity, nozzle length, etc.; quantitative measurements based on image processing of solidified, printed lines illustrate that the models provide accurate estimates of the degree of focusing as a function of acoustic field (**Figure 4.a**) and ink viscosity (**Figure 4.b**). The models were less effective in predicting the form factor (printed line height-to-width ratio), due to the complex nature of line spreading when particles are focused at the center (**Figure 4.c**).

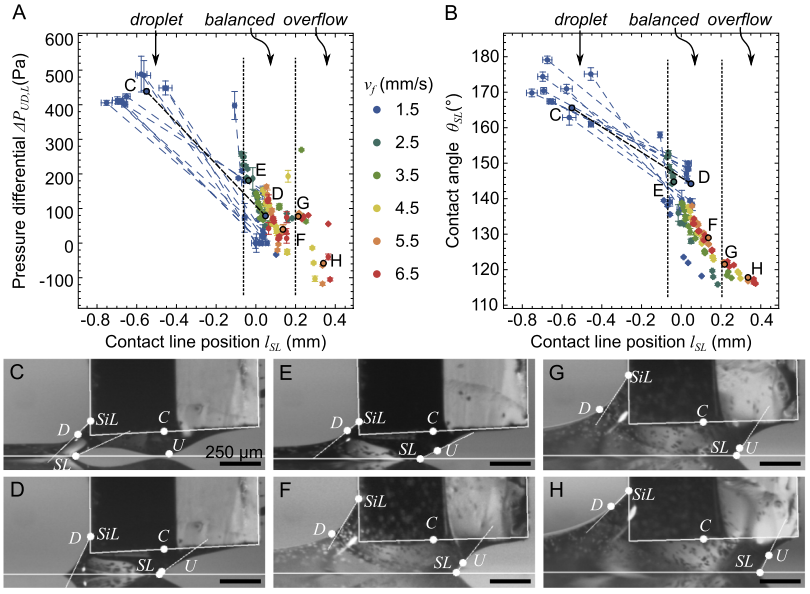



**Figure 5.** Optical images of the liquid bridge were used to identify key geometric features such as curvatures and contact angles, which are correlated with the onset of droplet formation during deposition of printed lines [7].

**Figure 5** provides an illustration of the use of optical imaging to characterize the behavior in liquid bridges formed between the printing nozzle and substrate [7]. Key geometric parameters of the bridge, such as curvatures used to compute pressure differentials (**Figure 5.a**), contact angles (**Figure 5.b**) and positions of the leading edge (**Figures 5.a-b**) were extracted using automated algorithms that post-process images of the bridge (**Figure 5.c**). These experiments were conducted across a broad range of ink compositions and printing parameters such as scan speed, stand-off-distance and volumetric flow rates. The results in **Figure 5.a-b** clearly illustrate that break-up of the printed line (to form droplets) can be directly correlated with geometric features of liquid bridge [7]; various printing regimes can be clearly identified, including droplet formation, balanced printing where the liquid bridge does not propagate head of the print nozzle, and overflow regimes where the fluid pushes ahead of the print nozzle. The balanced regime is the most desirable, as the experiments demonstrate this provides the least disruption of focused microstructure formed in the nozzle. The post-processing algorithms developed in this period provide a powerful opportunity to develop in-situ monitoring for direct write printing that avoids droplet formation to produce consistent printed features.

**Figure 6** provides complete regime maps indicating combinations of printing process parameters that avoid droplet formation [7]. In order for field-assisted printing to be effective, low viscosity inks are required to ensure particle motions inside the nozzle; this implies that effective microstructural control is achieved as close to the onset of droplet formation as possible. Closed-form analytical expressions based on slot-die analysis that indicate instabilities are superimposed on the maps shown in **Figure 6**; these expressions provide the basis to identify critical boundaries associated with droplet formation [7]. These models, in conjunction with in-situ monitoring based on optical image processing algorithms, provide a means to set initial printing parameters close to the onset of droplet formation (to preserve ordering from acoustic fields) and subsequently adjust process parameters (such as stand-off distance and scan speed) on-the-fly based on in-situ observations of the liquid bridge.

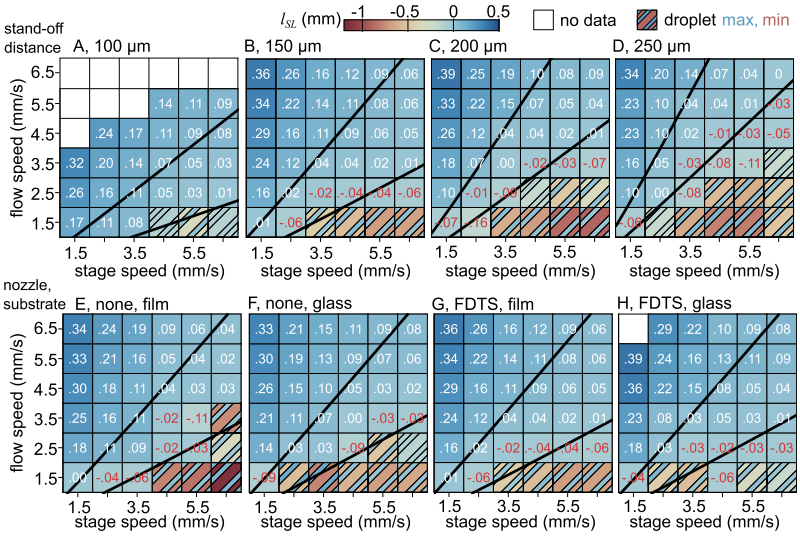



**Figure 6.** Printing regime maps indicating stable and unstable printing regimes as function of printing process parameters; such maps can be used to identify effective process parameters that avoid droplet formation.

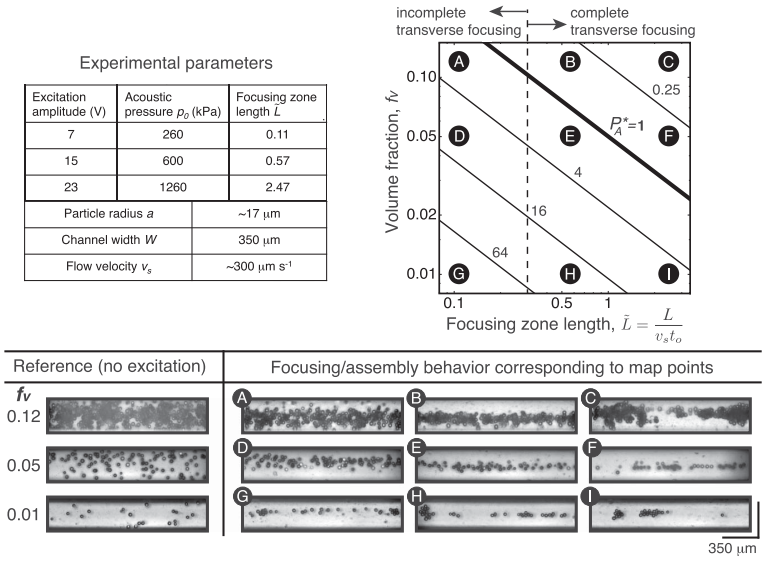



**Figure 7.** An illustration of a comprehensive map for field-assisted printing, which relates particle volume fraction and dimensionless nozzle length to the degree of transverse focusing and aggregation. Ideal combinations of ink composition and process parameters are indicated by the bold line in the figure; regions far from this line lead to either clumping (point C) that produces nozzle jamming, or disconnected regions of focused particles (points G-I) that would lead to a loss of functionality.

In addition to detailed studies of the printing process, a comprehensive theoretical framework was developed to predict the combination of field parameters, ink composition, and printing parameters that leads to effective field-assisted printing [8]. The principle challenge in this printing modality is to balance the time scales associated with (*i*) particle motions to the center of the channel, i.e., focusing, (*ii*) particle motions in the direction of the flow, i.e., aggregation, and (*iii*) the transport time of fluid through the nozzle. When the transverse focusing time is much faster than that associated with aggregation, one achieves discontinuous microstructures in the direction of the printed line (points G-I) in **Figure 7** [8]. If the axial aggregation time is much faster than the time spend in the nozzle, clumps of focused particles lead to jamming inside the nozzle (point C). When these times are balanced, one produces focused microstructures that are continuous along the print line (points B and E). A single printing parameter has been developed to identify combinations of fluid viscosity, volumetric flow rate, nozzle length, and

field strength associated with the balance of time scales [8]; this allows the results from this program to be translated to other ink-particle compositions, such that effective printing strategies can be identified *a priori*.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

The final reporting period has developed quantitative metrics that identify effective printing regimes for enhancing two-phase microstructures via field-assisted printing, including integrated in-situ process monitoring schemes that improve printing quality. While specific translations to the Army were unfortunately not developed in this period, the detailed, comprehensive publications achieved during this period set the stage for facile translations in the future.

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

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Collino, R., Ray, T., Friedrich, L., Cornell, J., Meinhart, C. and Begley, M. Scaling relationships for acoustic control of two-phase microstructures during direct-write printing. *Materials Research Letters*, February 2018. 10.1080/21663831.2018.1431317.

Friedrich, L., Collino, R., Ray, T. and Begley, M. Acoustic control of microstructures during direct ink writing of two-phase materials. *Sensors and Actuators A*, June 2017. 10.1016/j.sna.2017.06.016.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Theoretical and Experimental Investigations of Energy-Dispersive Cellular Nanostructured Polymeric Materials**

**Project Leader:** **Glenn H. Fredrickson (UCSB)**

**Collaborators:** **Edward J. Kramer and Kris T. Delaney (UCSB); Jan Andzelm and Tanya Chantawansri (ARL-WMRD) and Apostolos Avgeropoulos (U. Ioannina, Greece)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

This project led to the development of a remarkable new class of thermoplastic elastomers, which are uniquely hard, strong, and elastic, unlike any materials commercially available in the marketplace. The bio-inspiration for this work came from the cuticle coating on marine mussel fibrils, which is a protein material with a unique cellular morphology and a remarkable combination of high modulus (> 100 MPa) and greater than 90% elastic recovery to strains in excess of 100%.

Our synthetic analog of cuticle not only reproduces these physical properties, but unlike the natural material, can be easily melt processed and can be manufactured at large scale from inexpensive precursor monomers. The design was based on a "mikto-arm star" block copolymer architecture $PS_1$-(PI-$PS_2$)$_3$, in which three diblock copolymer PI-$PS_2$ arms are connected by their PI (polyisoprene) terminus at a central point, along with one high molecular weight polystyrene arm, $PS_1$. Crucially, in the design, the molecular weight ratio of the long $PS_1$ blocks to the short $PS_2$ blocks is approximately 8:1, which was arrived at by a computational approach utilizing self-consistent field theory (SCFT) [1].

Such mikto-arm block polymers alone are uniquely strong, hard, and elastic relative to conventional styrenic PS-PI-PS triblock elastomers manufactured by companies worldwide, but in pure form do not have the high modulus of cuticle [1]. We discovered [2] that by blending these polymers with high modulus polystyrene homopolymer, hPS, with a molecular weight intermediate between that of the $PS_1$ and $PS_2$ blocks, a remarkable cellular morphology was obtained, not unlike that of cuticle, but apparently produced by equilibrium self-assembly and fully stable under thermal and mechanical processing. This "bricks-and-mortar" phase, shown in a TEM micrograph in **Figure 1** has no precedent in the polymer science literature and represents a new paradigm in thermoplastic elastomer design. [2]

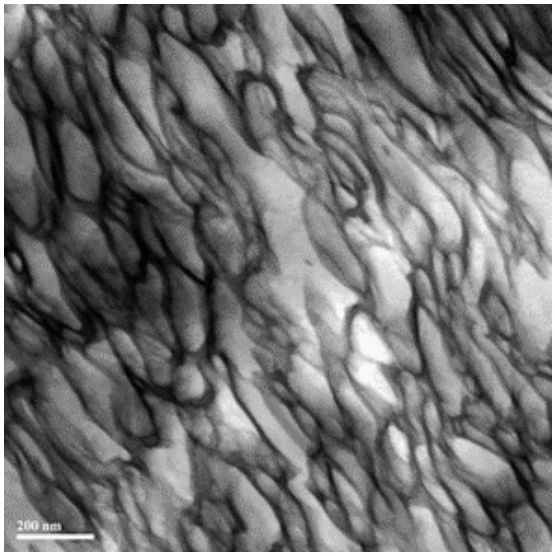



**Figure 1.** Transmission electron micrograph of the bricks-and-mortar phase achieved in a blend of $PS_1$-(PI-$PS_2$)$_3$ with hPS. The dark stained regions are continuous PI elastomer domains ("mortar") and the light regions are hard and discrete glassy PS domains ("bricks"). The scale bar is 200 nm. From [2].

We are continuing to collaborate with Kraton Polymers LLC, the leading manufacturer of styrenic block copolymers, to bring these unique polymer materials to the marketplace and available for Army applications in ballistic protection, and protective coatings for gear and equipment.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

In the first three years of the project, our experimental program made significant progress in understanding the self-assembly characteristics and mechanical properties of $A(BA')_3$ miktopolymer + A homopolymer blends, where A is chosen to be a hard, glassy polymer (e.g., polystyrene, PS) and B is a rubbery polymer (e.g., polyisoprene, PI). The outcome of this work included the exciting discovery of the "bricks-and-mortar" (B&M) phase [2], which emerges unexpectedly in a region of composition space adjacent to well-ordered hexagonally-packed cylinders or lamellae. This phase has many of the characteristics that are sought for developing a nano-cellular material with a unique combination of hardness, strength, toughness and elasticity, specifically the presence of apparently *discrete* hard domains occupying an unprecedented large (>70%) volume fraction of the material, intercalated by a low volume fraction of continuous rubbery domains. Importantly, of the compositions and phases studied, the B&M phase achieves the highest loading of discretely arranged hard material to date, resulting in a material with a very unusual and attractive balance of mechanical properties. The B&M morphology was therefore a target for further study and optimization. In the final reporting period, we shifted from a largely experimental focus to developing a deep theoretical understanding of how the B&M phase emerges, its structure and thermodynamics, and how it can be replicated across multiple families of synthetic materials.

From transmission electron microscopy (TEM, **Figure 1**) it is evident that the B&M phase possesses no long-range translational order; however, quasi-long-range orientational order is clearly present. These observations suggest that the B&M phase is a fundamentally new type of structured disordered phase, which, as described below, cannot be accessed by mean-field theory. Following our experimental characterization by SAXS and sectional cryo-TEM, we exhausted what can be experimentally inferred about the detailed three-dimensional morphology of this phase. In addition, the precise mechanism for the formation of the B&M phase remains a mystery. Understanding the origin and nature of this phase is vital for developing process-structure-property relations, realizing the phase in broader classes of alloys, and more generally explaining the emergence of self-assembled mesophases that do not possess long-range order. The project objectives in the final reporting period were therefore of a theoretical and computational nature:

1) *Improve and test computational tools for rigorously mapping mesophase diagrams of block copolymer alloys with fluctuation corrections included.*

2) *Develop a thorough theoretical understanding of the origin, equilibrium nature and detailed 3D morphology of the bricks-and-mortar phase.*

3) *Determine the consequences of polydispersity in molecular architecture.*

4) *Develop simulation-guided strategies for further property enhancement and cost reduction.*

5) *Develop a theoretical and computational methodology for incorporating charged species into the B&M phase, with an eye towards improving strength and enabling applications in portable power devices (e.g., solid electrolytes).*

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

Our primary approach to understanding the origin and morphological nature of the bricks-and-mortar phase involved the application of field-theoretic simulations. Two hypotheses were posited to interpret the B&M phase as a new type of equilibrium fluctuation-stabilized phase with no mean-field analog. In the first hypothesis, the phase is a continuation of the conventional disordered phase into a strongly segregated regime, similar to the bicontinuous microemulsion found in ternary polymer blends. The second hypothesis posits that the phase is distinct from all others, with the phase transition from disorder arising from a spontaneous breaking of rotational symmetry. As such, the B&M would be a type of *nematic phase*, similar to those observed in liquid crystals. Were the second hypothesis found to be correct, it would be the first example of a fluctuation-stabilized phase that is distinct from the isotropic disordered phase in block copolymer systems. Schematics of these two hypotheses are shown in **Figure 2**.

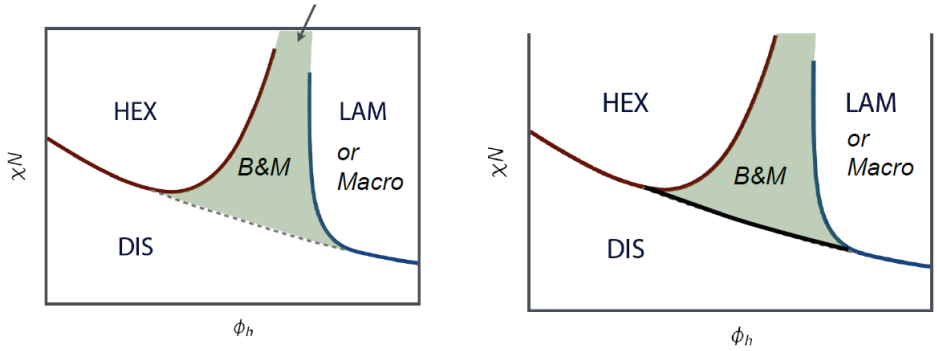



**Figure 2.** Schematic representations of possible fluctuation-corrected phase diagrams for miktoarm block copolymer and homopolymer blends. The cylinder (HEX) and lamellar (LAM) phases are common to both mean-field and fluctuation-corrected diagrams. The bricks-and-mortar phase (B&M) appears either as an invasion of disorder into the ordered phase envelope (**left**) or a distinct fluctuation-induced *nematic* phase (**right**). $\chi N$ is the Flory-Huggins segregation strength, and $\phi_h$ is the blend volume fraction of homopolymer.

The conclusion that the B&M phase is in equilibrium derives from its stability to very long (multi-day) anneal times, and the observation that distinct ordered phases nearby in composition space, e.g., lamellae or hexagonally packed cylinders, exhibit an exceptional degree of long-range translational and orientational order when prepared with equivalent protocols. While the B&M phase is clearly structured on the mesoscale, it is certainly not ordered in the strict sense, pointing to the importance of thermal fluctuations. Our hypotheses can be tested by computing the phase diagram of the blend *with all thermal fluctuation effects included* and comparing to mean-field theory without fluctuations. Under the first scenario, in which B&M is not thermodynamically distinct from the disordered phase, the fluctuation-stabilized, structured disordered phase should be indirectly detectable as a deflection of the order-disorder transition (ODT) envelope upon accounting for fluctuation corrections, showing an invasion of the disordered phase into the structured phase region (**Figure 2, left**). Thus a method for accurately computing the fluctuation-corrected ODT is required. Under the second scenario, an approach for quantifying the degree of translational and orientational order present in each phase is required, augmented by accurate rare-event sampling methods for avoiding metastability. For testing both of these hypotheses we will employ field-theoretic simulations using complex Langevin sampling (FTS-CL), which is the only simulation technique capable of resolving the 1nm to 1μm scales present in the B&M structure.

Self-consistent field theory (SCFT) has been widely used to study the equilibrium mesoscale self-assembly of block copolymer melts and alloys. For dense melts far from critical phase transitions, SCFT is significantly more efficient than particle-based simulations, which face the challenge of tracking and equilibrating a large number of strongly constrained microscopic degrees of freedom. However, SCFT is a *mean-field theory* that neglects composition fluctuations, and consequently the only phases that it can describe are well-ordered or unstructured (homogeneous) disordered phases. Our SCFT calculations have shown that the B&M phase is entirely absent from mean-field phase diagrams. While SCFT produces approximate and incomplete phase diagrams, it remains a useful tool providing the foundation for an analysis of fluctuation effects. Therefore, SCFT was applied in tandem with full field-theoretic simulations in the results described below.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

In pursuit of research objective 1), our team developed a unique computational capability [3] that allows for the first time the approximation-free construction of block copolymer phase diagrams with fluctuation effects fully included. The method is based on the fusion of four computational methods that were previously developed and refined in the Fredrickson group: i) complex Langevin (CL) sampling for circumventing the sign problem, yielding approximation-free, field-theoretic simulations of polymeric assemblies; ii) field-theoretic thermodynamic integration applied to polymer field theory for comparing relative stability of phases; iii) UV regularization to ensure a finite continuum limit to all operators in the theory; and iv) advanced highly stable and accurate time-integration algorithms permitting simulations of melts in the strong fluctuation limit, corresponding to experimentally relevant molecular weights. Prior calculations were limited to weaker fluctuations corresponding to molecular weights ~100x larger than the experimentally relevant regime. Taken together, these FTS-CL method developments allow

computation of the Helmholtz free energy of candidate phases with all fluctuation effects included, and without arbitrary resolution-dependent reference contributions that in prior work destroyed the ability to compare phases that are not mutually commensurate. Using the AB diblock copolymer melt as a test case, our new capability was used to compute the first approximation-free block copolymer phase diagram, shown in **Figure 3** [3]. The fluctuation-corrected AB diblock copolymer phase diagram shows three important characteristics: i) All structured phases except the double gyroid network have direct order-disorder transitions (ODTs). In contrast, mean-field (SCFT) theory predicts that intermediate sphere phases exist near the ODT. ii) The elusive Fddd network phase, predicted to be stable in SCFT, was not found to be stable to fluctuations. iii) The effects of fluctuations weaken rapidly away from the ODT. These characteristics, which agree qualitatively with experimentally determined phase diagrams, demonstrate the ability of our approach to provide fluctuation corrections to mean-field phase diagrams.

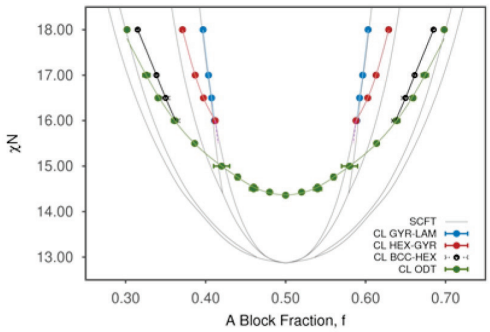



**Figure 3.** Complex Langevin (CL) phase diagram of a weakly compressible AB diblock copolymer melt with invariant degree of polymerization $\bar{N}\sim 10{,}000$. Fluctuation effects are evident by comparing to the mean-field SCFT reference phase diagram (light gray). From [3].

With the necessary theoretical and simulation tools in place, we next focused on project objective 2), seeking to understand the origins, structure, and properties of the B&M phase in mikto-polymer/homopolymer blends. In this pursuit, we were successful, demonstrating [4]:

1) *The B&M emerges continuously from the structureless disordered phase upon cooling with apparently no intervening phase transition.*
2) *The B&M phase at weak segregation or high temperature is isotropic (not nematic), with no evidence of quasi-long-range orientational order.*
3) *The morphologies accessed by FTS-CL simulations in sweeping homopolymer volume fraction were found to be qualitatively consistent with those observed experimentally using TEM.*

Findings 1) and 2), shown in **Figure 4**, essentially amount to a demonstration that the first hypothesis for the emergence of the B&M phase (left image in **Figure 2**) is the correct one. These findings are presented in detail in publication [4], including a proposed phase diagram shown in **Figure 5**, that hypothesizes a phase transition between an isotropic B&M phase observed in simulations near the ODT boundary and a nematic B&M phase at higher segregation strength/lower temperature.

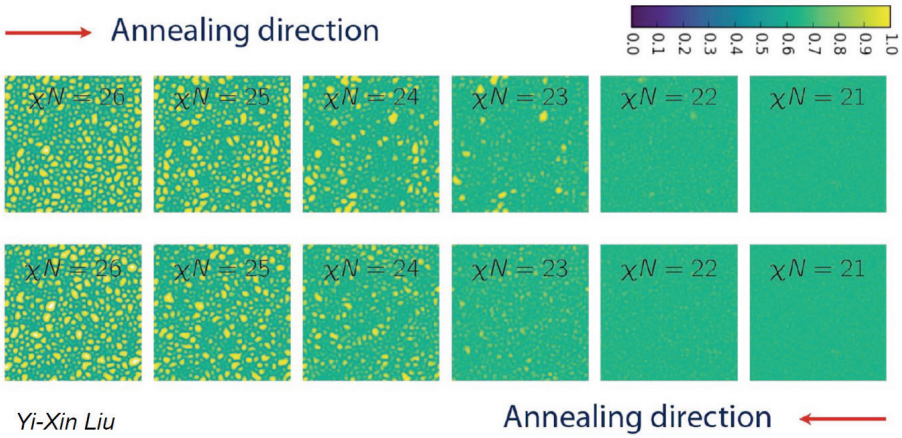



**Figure 4.** Snapshots of FTS-CL simulations of a mikto-polymer/homopolymer blend at a homopolymer volume fraction of 0.4 and with molecular weights chosen to match an experimental system exhibiting the B&M phase. χ is the Flory interaction parameter between A and B species polymer segments and N is the mikto-polymer degree of polymerization. Sweeping χN up/down corresponds to cooling/heating of the sample. We see that an isotropic cellular B&M phase appears continuously on cooling and disappears continuously on heating from the isotropic disordered melt.

We also progressed on the third and fourth objectives in §2 relating to the role of architectural polydispersity on A domain discreteness and B domain continuity by blending $A(BA')_n$ miktoarm polymers with various arm numbers, $n$. This is important because it quantifies the sensitivity to purity and tolerance for synthesis via low cost coupling strategies consistent with high volume manufacturing. Using FTS-CL, we demonstrated that the B&M phase is tolerant to significant polydispersity in arm number, by as much as 30% off the homogeneous target.

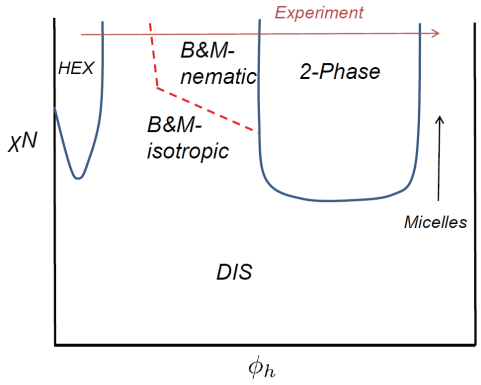



**Figure 5.** Proposed phase diagram for the mikto-polymer/homopolymer blend from [4]. HEX is the hexagonally packed cylinder mesophase and DIS is the isotropic disordered phase, which transitions continuously to the isotropic B&M phase. We hypothesize that a first order phase transition to a nematic B&M phase occurs at higher segregation strength, χN,

On the final objective of identifying methods to address ion-containing inhomogeneous polymers, we developed an exciting new theoretical framework for ion-containing polarizable soft matter [5]. In this approach, each polymer segment, solvent molecule, or ion can carry (optionally) a charge monopole, a fixed dipole, and/or an induced dipole via a Drude oscillator. Coulomb interactions are treated exactly and segments can further interact via non-electrostatic bonded or non-bonded potentials. The coarse-grained particle models containing these ingredients are then converted to "polarizable" statistical field theories using Hubbard-Stratonovich transforms. An exciting feature of this polarizable field theory framework is that it self-consistently embeds van der Waals interactions and produces consistent dielectric contrast when phase separation occurs. Most existing approaches, either atomistic or coarse grained, fail to properly account for changes in the local dielectric environment when ions cluster or partition into multiphasic domains. In our theory, the local dielectric properties follow automatically and consistently as a consequence of the fluctuating and coupled electrostatic and structural field variables [5].

Beyond developing this exciting new theoretical framework [5], we have made progress on exploiting it. In [6], we report on how models of this type can be adapted to study the effect of external electric fields on the development of morphology in block copolymers. Specifically, we show that the orthorhombic Fddd network phase, rarely observed in diblock copolymers, is stabilized by an external electric field. Reference [7] describes a detailed analytical and numerical study of the new theory in which correlations between dielectric screening and fluid structure are investigated in detail. This work is the first to demonstrate full FTS-CL simulations of a polarizable field theory model and to analytically extract and analyze van der Waals contributions to the Flory χ parameter of a polymer blend and diblock copolymer.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

We continued to interact with Jan Andzelm and Tanya Chantawansri at the ARL during the final reporting period. Our field-theoretic simulation code base, *PolyFTS*, was made available to ARL researchers via a royalty-free license from UCSB via the Complex Fluids Design Consortium (Fredrickson is Director).

We extended and deepened our interaction with Kraton Polymers LLC during the final reporting period. They have manufactured pilot scale (~100 kg) quantities of mikto-polymer elastomers and we have assisted them in understanding structure-property relations both as neat materials and in alloys. This relationship is continuing beyond the end of the ICB project.

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### 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

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J. M. Martin, W. Li, K. T. Delaney and G. H. Fredrickson. SCFT Study of Diblock Copolymer Melts in Electric Fields: Selective Stabilization of Orthorhombic Fddd Network Phase. *Macromolecules*, April 2018. 10.1021/acs.macromol.8b00394.

Y-X. Liu, K. T. Delaney and G. H. Fredrickson. Field-Theoretic Simulations of Fluctuation-Stabilized Aperiodic "Bricks-and-Mortar" Mesophase in Miktoarm Star Block Copolymer/ Homopolymer Blends. *Macromolecules*, August 2017. 10.1021/acs.macromol.7b01106.

J. M. Martin, W. Li, K. T. Delaney and G. H. Fredrickson. Statistical field theory description of inhomogeneous polarizable soft matter. *The Journal of Chemical Physics*, October 2016. 10.1063/1.4964680.

K. T. Delaney and G. H. Fredrickson. Recent developments in fully fluctuating field-theoretic simulations of polymer melts and solutions. *The Journal of Physical Chemistry B*, July 2016. 10.1021/acs.jpcb.6b05704.

W. Shi, G. H. Fredrickson, E. J. Kramer, C. Ntaras, A. Avgeropoulos, Q. Demassieux and C. Creton. Mechanics of an asymmetric hard−soft lamellar nanomaterial. *ACS Nano*, January 2016. 10.1021/acsnano.5b06215.

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W. Shi, N. A. Lynd, D. Montarnal, Y. Luo, G. H. Fredrickson, E. J. Kramer, C. Ntaras, A. Avgeropoulos and A. Hexemer. Toward strong thermoplastic elastomers with asymmetric miktoarm block copolymer architectures. *Macromolecules*, March 2014. 10.1021/ma402566g.

# Army's Institute for Collaborative Biotechnologies

## Final Report for ICB UARC Task Order 35

### ARO Contract W911NF-09-D-0001

### December 1, 2013 – November 30, 2018

**Fundamental Development of Novel Nanomaterials for Biomarker Detection**
*Sumita Pennathur, Carl D. Meinhart, and Luke S. Theogarajan (UCSB)* ..... BTT-2

**Exploring Key Design Parameters Exploited by Naturally Occurring Chemoperception Systems**
*Kevin W. Plaxco and Tod E. Kippin (UCSB)* ..... BTT-9

**Genetically Encoded AND Gates for Targeted Proteomic Analysis of Cellular Subpopulations in Heterogeneous Bacterial Communities**
*David A. Tirrell (Caltech)* ..... BTT-14

**Engineered Microbial Opsins using SCHEMA Recombination and Directed Evolution**
*Frances H. Arnold (Caltech)* ..... BTT-20

**Suspended Microchannel Resonators for Pathogen Analysis**
*Scott R. Manalis (MIT)* ..... BTT-27

**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Fundamental Development of Novel Nanomaterials for Biomarker Detection**
**(Formerly: Biomolecular Analysis and Characterization in Nanofluidic Channels)**

**Project Leaders:** **Sumita Pennathur, Carl D. Meinhart, and Luke S. Theogarajan (UCSB)**

**Collaborators:** **Jennifer Sekowski, Jennifer Gibbons and Vipin Rastogi (ECBC);**
**Ron Chairello (Alveo Technologies) and Josh Kogot (NRL, formerly at ARL)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

Our major results over the past five years are summarized below:

***Result 1: Fundamental Nanochannel Electrokinetics Studies with Embedded Electrodes***

Electrokinetic nanofluidics allows for the coupling of unique physics at the scale of biomolecules, which in turn leads to unique applications for separation, concentration, detection and analysis of molecules. However, to truly exploit these applications there is a need for a true fundamental understanding of all the coupling physics involves at such a scale. Towards that end, we have been able to make large strides in the understanding of such systems, including 1) developing a successful fabrication process that allows for electrodes to be placed within nanometer channels using low-temperature bonded methods [1]. In addition, since biological conditions represent a barrier to the use of glass-derived implantations as a result of the slow dissolution of glass into biological fluids and adhesion of proteins and small molecules to the glass surface, we assessed the structural stability, durability, and protein interactions of hydrophilic silane coatings in glass microchannels during electrokinetic flow. Variations amongst coating behaviors were shown to be indicative of coating density and uniformity, silanization procedures, and electrostatic interactions [2]. We also have discovered a novel concentration mechanism based on the manipulation of the electric double layers due to non-uniform surface charge [3]. Additionally, we performed fundamental computational simulations to understand spherical and rod-like transport in electrokinetic nanochannels [4], which we used to aid in our experimental studies of DNA transport and separation in nanochannels [5]. With our DNA separation data, we were able to determine the effect of confinement on the kinetics of DNA binding, specifically we have experimentally validated our previously developed theoretical COMSOL-based model to analyze the kinetics of reacting species in a microfluidic and nanofluidic capillary using DNA oligonucleotides with different sequences. This confirmation allows us to gain critical information on kinetic parameters in a faster and more accurate way than through currently existing methods [6-7]. Finally, we were able to develop significant insight into the details of bipolar electrode focusing and transient behavior in a nanochannels [8-9].

***Result 2: Developed a Successful Nanofluidic-based Biosensing Platform for Viral DNA/RNA.***

Over the past 5 years we made huge strides in our all-electronic DNA sensor. Specifically, we have been able to reproducibly and reliably electronically measure the amplification of Hepatitis C DNA using nanofluidic systems. This was performed in nanofluidic channels with isothermal DNA amplification (LAMP), and all-electronic sensing. We were able to show amplification in shorter times than traditional qPCR-based measurements. This work has spun out into a startup company, Alveo technologies. [10-11]

***Result 3: AgDNA for Universal Ratiometric Probes.***

Last fiscal cycle, we developed a capillary electrophoresis based multiplexed detection method using fluorescent silver DNA probes for HepA, HepB and HepC. However, the probe design initially used for these studies suffered from several shortcomings, mainly the tendency for the probe to not generate a fluorescent AgNC for some binding domain sequences. To overcome this, as well as provide added functionality, we engineered a new DNA-AgNC-

based sensor that provides ratiometric fluorescence emission for the sensitive, specific and low-cost detection of DNA. The DNA probe generates a green emitting AgNC in its hairpin state, and a red emitting AgNC after binding target. The ratiometric fluorescence provides a stable signal and rapid quantification of DNA concentration regardless of the choice of target, a dramatic improvement over similar turn-on fluorescent probes. We showed these probes to be also useful for neurotransmitter detection. [12-14]

***Results 4: Microneedles for ISF Extraction***

Here, we performed a parametric study using silicon etch chemistries to optimize the fabrication of scalable and manufacturable beveled silicon hollow microneedles. We theoretically verified our parametric results with diffusion reaction equations and created a design guideline for a various set of miconeedles (80–160 μm needle base width, 100–1000 μm pitch, 40–50 μm inner bore diameter, and 150–350 μm height) to show the repeatability, scalability, and manufacturability of our process. As a result, hollow silicon microneedles with any dimensions can be fabricated with less than 2% non-uniformity across a wafer and 5% deviation between different processes. Our proposed method is non-labor intensive, well defined by theory, and straightforward for wafer scale mass production, opening doors to a plethora of potential medical and biosensing applications. [15]

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

The main goals of most recent reporting period were to 1) develop a novel method to detect nucleic acids and other biomarkers using AgDNA that can act as a quick, simple and inexpensive ratiometric probe, (2) understand fundamentally with both numerical simulations and experiments the physics behind an electrode-laden nanochannel that can exploit the physics of the electric double layer in order to provide a new concentration mechanism for nucleic acids and biomarkers, and (3) develop a novel method to extract fluid using microneedles. These three fundamental objectives will be accomplished in an effort to build better biosensors for real-time monitoring that address Army needs.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

Since nanofluidic channels are on the same length scale as both the electric double layer that forms at a solid-liquid interface, and the biomolecules of interest, we can harness the physics coupling complex biological fluids and nanofluidic channels towards the realization of a unique, efficient technology that will potentially allow for a truly new regime of biomolecular analysis. For example, our ability to control the surface properties, flow velocity, and channel geometries enables the design of novel experiments that afford the unique possibility of experimentally probing the effects of biomolecular confinement and interaction behavior. Together with our theoretical models and characterization methods for nanochannel surfaces, we hope to gain unique insight into biomolecular behavior that may not be realized in more traditional systems. Additionally, since nanofluidic devices are fabricated using traditional MEMS (Micro-Electro-Mechanical Systems) technology, we have the ability to integrate electronics into the device, allowing for both optic- and electronic-based studies. Among other applications, this allows us to quantify the effects of fluorescent-based modifications on protein behavior. Most relevant, these sorts of systems may be able to mimic accurately the confined environment of biomolecules, giving much more accurate information about the behavior of the analytes.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1. Ratiometric Ag-DNA Probes [12-14]*

DNA-stabilized silver nanoclusters (AgNCs), the fluorescence emission of which can rival, and often exceed, that of typical organic fluorophores, have enabled a new class of label-free molecular beacons for the detection of single-stranded DNA. Like fluorophore-quencher molecular beacons (FQ-MBs), AgNC-based molecular beacons (AgNCMBs) are based on single-stranded DNA that undergoes a conformational change upon binding a target sequence. The new conformation exposes a stretch of single-stranded DNA capable of generating a fluorescent AgNC upon reduction in the presence of Ag+ ions. However, the utility of AgNC-MBs has been limited because changing the target binding sequence unpredictably alters cluster fluorescence. We demonstrated that the previous AgNC-MB design depends on bases in the target-binding (loop) region to stabilize its AgNC. We then rationally altered the design to overcome this limitation. By separating and lengthening the AgNC-stabilizing domain, we created a AgNC-hairpin probe with consistent performance for arbitrary target sequences. Our design supports

ratiometric fluorescence measurements of DNA target concentration, thereby providing a more sensitive and stable signal compared to turn-on AgNC probes. We demonstrated AgNC-MBs with nM sensitivity and single-nucleotide specificity, expanding the breadth of applicability of these cost-effective probes for biomolecular detection. Finally, we identified two different DNA sequences that form dopamine-sensitive nanoclusters. We demonstrate that each sequence supports two distinct DNA-AgNCs capable of providing specific, ratiometric fluorescent sensing of dopamine concentration *in vitro*. DNA-Ag nanoclusters therefore offer a novel, low-cost approach to quantification of dopamine, creating the potential for real-time monitoring *in vivo* (**Figure 1**).

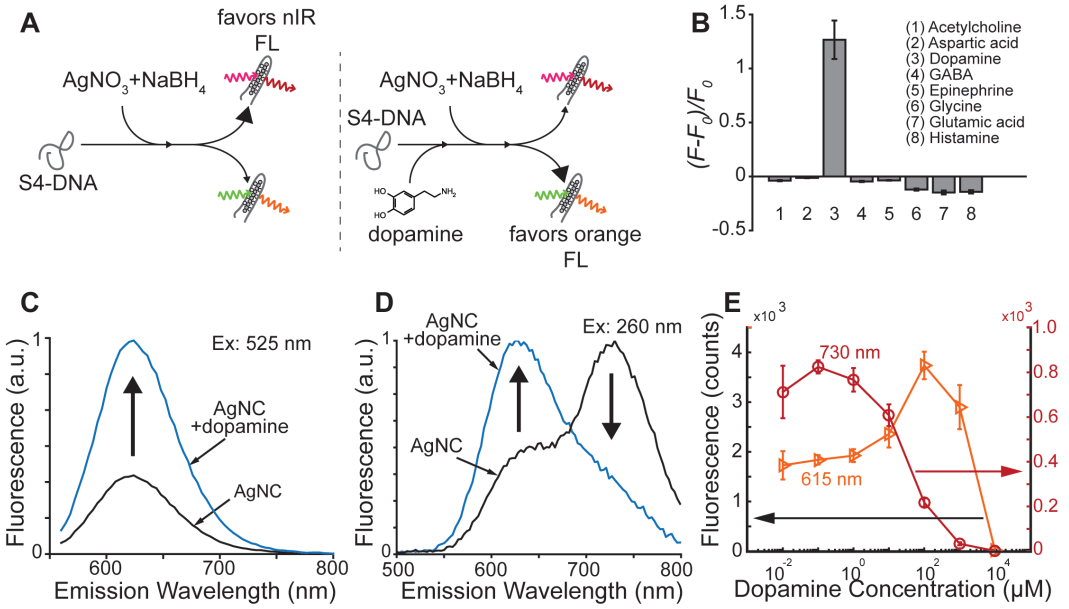



**Figure 1.** *DNA silver nanoclusters acts as ratiometric, "turn-on" dopamine sensors.* (**a**) Schematic summary of experimental results. DNA sequence S4 produces two spectrally distinct AgNC populations. Formation of the long-wavelength (nIR) population (640 nm excitation, 730 nm emission, top) is favored in the absence of dopamine, while formation of the short-wavelength (visible) population (535 nm excitation, 615 nm emission, bottom) is favored in the presence of dopamine. (**b**) Change in fluorescence emission intensity ($\Delta f$ = [F-$F_0$]/$F_0$) of AgNCs synthesized using DNA S4 in the presence of eight different NTs ([DNA] = 12.5 μM, [NT] = 50 μM). Fluorescence emission was collected at 610 nm using 525 nm excitation (peak excitation for the S4-AgNCs). Error bars indicate the standard deviation of n=3 replicate experiments. (**c-d**) Fluorescence emission spectra of S4-AgNCs assembled in the absence (gray) and presence (blue) of dopamine under 525 nm (**c**) and 260 nm (**d**) excitation. In the presence of dopamine, intensity at the lower wavelength emission peak (615 nm) more than doubles while intensity at the higher wavelength peak (730 nm emission) drops a comparable amount**.** (**e**) Fluorescence emission response of the two spectrally distinct AgNCs generated by S4 when different concentrations of dopamine are added prior to cluster synthesis. Orange triangles: 535 nm excitation, 615 nm emission nanoclusters; red circles: 640 nm excitation, 730 nm emission nanoclusters. One of the two AgNCs species (730 nm emission, red) was significantly quenched by moderate amounts of dopamine, while the other species (615 nm emission, orange) was enhanced by moderate amounts of dopamine.

### *4.2. Microneedle Fabrication [15]*

We performed a complete parametric study investigating the effects of variables such as chemical bath composition, die size, and pillar and filler area on the etch rates of silicon. Specifically, we etched silicon anisotropically by manipulating the dimensions of predefined silicon structures (filler and pillars) and found etch rate changes with respect to the variations in the characteristics length. **Figure 2.a** shows etch rates of pillar width in either a diffusion or reaction-controlled regime based on the spacing between pillars. We further explored these etch behaviors by equating the steady state diffusive flux to the first order reaction equation at the etch front:

$$\delta(t) = -\frac{D}{k} + \sqrt{\frac{D^2}{k^2} + 2DC_bAt} \qquad (1)$$

where δ is the etched distance, D is the diffusivity, k is the reaction constant, t is the etch time, $C_b$ is the bulk concentration, and A is the proportionality constant accounting for the density and molecular weight of the etch front. Taking the best fit for the reaction constant and diffusivity that matches the resulting etch profile of pillar tip with respect to time, we can theoretically fit our data to equation (1), as shown in **Figure 2**.**b**. The etch behavior of filler height is similar to that of the pillar width, where the etch rate is constant for the pillar pitch to height ratio that is larger than 2. However in this case, to best fit the experimental data, we assumed a second order reaction equation [ref] wothj an diffusivity of 3.34 x $10^{-9}$ $m^2$/s and reaction constants of $k_1$=1.00x$10^{-8}$ m/mol/s and $k_2$= 3.51 x$10^{-8}$ $m^4$/mol/s for the linear and quadratic term respectively.

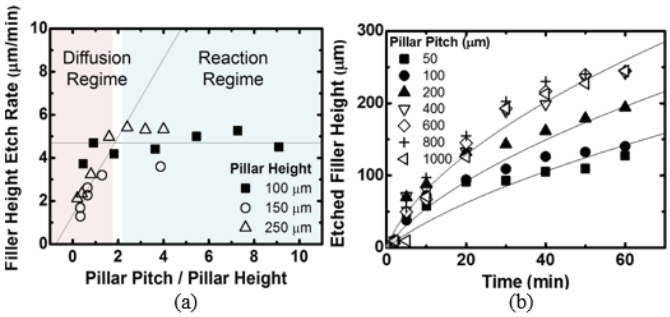



**Figure 2.** (**a**). Etch rate of the pillar tip vs. the ratio of pillar pitch to pillar height. At ratios under 2, the etching is diffusion limited, and etch rates are not constant with varying gap to height ratio. As the ratio increases, the etching is reaction limited due to the large spacing between pillars, and the etch rate is effectively constant. (**b**): The etched pillar width with respect to time for MN arrays of 250 μm in height. The lines represent the theoretical curve by equating diffusive flux and first order reaction equation, resulting in diffusivity of 3.34 x $10^{-9}$ $m^2$/s and reaction constant of 5.45 x $10^{-6}$ m/s. For the parametric study, we used 800 mL of HF (49%):HNO3 (69%) volume ratio of 1:19 for every 0.35 g of silicon

A wet HF-$HNO_3$ etch process and proper manipulation of predefined structures allows us to fabricate uniform and repeatable hollow sharp MN in a wafer with 1-μm sharp beveled tips, base width ranging from 80-200 μm, array pitches between 50-1000 μm, and heights between 150-350 μm. Due to the silicon nitride mask and filler materials of well-defined geometries, we can easily predict the etch behavior as we forced only the pillar tip width to sharpen and other dimensions to remain undisturbed. We further performed a parametric study and theoretically verified the data using a simple reaction-diffusion model. This allows for a robust parameter space with which to repeatedly and reliably fabricate hollow microneedles for the multitude of potential wearable applications.

### *4.4 Nanochannels with Embedded Electrodes [8-9]*

Charge inversion of the surfaces of nanofluidic channels occurs in systems with high-surface charge and/or highly charged ions and is of particular interest because of applications in biological and energy conversion systems. However, the details of such charge inversion have not been clearly elucidated. Specifically, although we can experimentally and theoretically show charge inversion, understanding at what conditions charge inversion occurs, as well how much the charge-inverting ions change the surface, are not known. Here, we show a novel experimental approach for uniquely finding both the ζ-potential and adsorption time of charge inverting ions in aqueous nanofluidic systems.

Bipolar electrodes (BPE) have far ranging analytical and industrial applications. However, eeelectrokinetic and electrochemical phenomena induced by applied electric fields is restricted to conditions of steady state, wherein the magnitude of the electric field is constant. Very limited information is available regarding the transition of BPE systems between perturbed and equilibrium states (i.e., once the applied electric field is removed). Without a complete mechanistic understanding of these transitions, in particular the dynamic interplay between electrons and ions as the system relaxes towards equilibrium, the ability to harness these phenomena productively—for analytical applications, clinical practice, or environmental remediation—is limited.

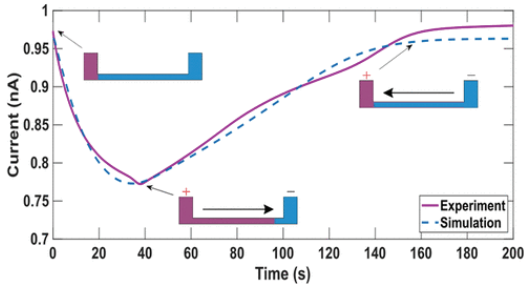



**Figure 3.** The experimental (solid line) and simulation (dashed line) results for different concentrations of Tris-buffered Ru(bpy)3Cl2 solution, as well as the CM results for 10 mM Tris displacing 24.7 mM Tris (dotted blue line). The 24.70 mM Tris (ζ1 = -43 mV and the conductivity = 3.063 mS/cm) filled the channel before the well was replaced with Ru(bpy)3Cl2. To match the experimental results, we found the adjustable parameters for (c) 5.0 mM Ru(bpy)3Cl2 + 10 mM Tris of ζ2 =7.5 mV and tads = 13.96 s (RMSD 2.67%)

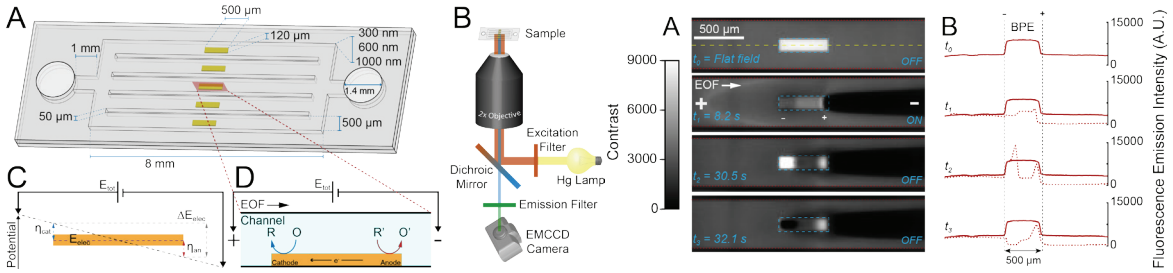



**Figure 4.** *Experimental approach and principles of bipolar electrochemistry, and real-time optical monitoring of nanoconfined bipolar electrochemistry.* **Top** (**A**) We fabricated glass-on-glass devices containing 5 nanochannels each with embedded bipolar electrodes (yellow) and used (**B**) an epifluorescence setup to monitor transient electrochemical and electrokinetic effects near nanoconfined BPE. (**C-D**) When a conductive substrate (e.g., BPE) is immersed within an ionic solution and exposed to an electric field, it polarizes. If the polarization is large enough to induce (**C**) sufficient overpotentials at each pole ($\eta_{cation}$ and $\eta_{anion}$), then (**D**) simultaneous oxidation and reduction reactions occur at opposing poles. We systematically revealed the unique electrokinetic, electrochemical, and fluorescent phenomena that occur upon removal of the electric field by varying electrolyte concentrations, pH, fluorophore charge, $E_{tot}$, and oxide growth on the BPE surface. **Bottom** (**A**) We tracked the fluorescence emission intensity of 100 µM fluorescein before ($t_0$), during ($t_1$) and after ($t_2$ and $t_3$) the application of $E_{tot}$ = 250 V in a 600 nm tall channel. (**B**) Fluorescent emission intensity profiles where quantified as a function of position along the length of the channel (indicated with yellow-dashed line in **A**). For reference, we added the flat field fluorescent intensity on all profiles. Note: Flat field fluorescence intensity at the BPE is double that elsewhere in the channel due to reflection from the metal surface. Application of the electric field induces polarization along the electrode and drives water electrolysis ($t_1$). Immediately after $E_{tot}$ is removed (at $t$ = 30 s), we observe enhancement of the fluorescence emission intensity at the left BPE pole and recovery of flat field fluorescence levels at the right pole ($t_2$), followed closely by rapid quenching at the left pole ($t_3$).

In the last year, we provide unprecedented insight into the rich, coupled electrochemical and electrokinetic effects that unfold near bipolar electrodes immediately upon removal of an electric field, as shown in **Figures 3-4**. We confine BPEs in well-defined nanochannels and optically monitor in real-time their field-induced fluid dynamics. We demonstrate, both experimentally and through numerical modeling, that the removal of an electric field produces solution-phase charge imbalances in the vicinity of the BPE poles. These imbalances induce intense and short-lived nonequilibrium electric fields that drive the rapid transport of ions towards specific BPE locations. We determined the origin of these electrokinetic effects by systematically varying the nature of the fluorophore, the concentration of electrolyte concentration, the strength of the applied field, and the growth of oxide on the BPE surface. Our dissection of ion transport events that occur in the aftermath of field-induced polarization provides new insights which improve our understanding of current analytical platforms and can drive the development of new micro- and nanoelectrochemical systems.

## 5.Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

We are currently working with Jennifer Sekowski at ECBC to try and incorporate our microneedles with her ISF detection research. Furthermore, we plan to explore nanofluidic electrode-based concentration mechanisms for Jennfier Gibbon and Jennifer Sekowski at ECBC. They have discovered miRNA signatures for neurotoxins that can potentially be detected in the interstitial fluid (IF) of soldiers. However, concentration of the miRNA in the IF will allow us to only require small sample amount that can be painlessly extracted from the soldier. Given our previous success with concentrating DNA using nanofluidic-based FASS focusing (data not shown), we believe we can further develop this nanofluidic electrode-based technology to transition directly to miRNA applications within the ECBC.

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

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C. Conner, T. de Visser, J. Loessberg, S. Sherman, A. Smith, S. Ma, M. T. Napoli, S. Pennathur and D. Weld. Energy Harvesting with a Liquid-Metal Microfluidic Influence Machine. *Physical Review Applied*, April 2018. 10.1103/PhysRevApplied.9.044008.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Exploring Key Design Parameters Exploited by Naturally Occurring Chemoperception Systems**

**Project Leaders:** **Kevin W. Plaxco and Tod E. Kippin (UCSB)**

**Collaborators:** **Brian Jamieson (Diagnostic Biochips); Gavi Begtrup (Eccrine Systems); Scott Ferguson (Aptitude Biomedical)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

The overarching goal of this research program has been to develop a *general* molecular sensing platform (i.e., that is independent of the specific chemical or enzymatic reactivity of its target analytes) that supports real-time, high frequency, high-precision measurements in complex sample streams and, in turn, high-precision feedback control over molecular concentrations. Specifically, we have built upon the biomimetic electrochemical aptamer-based sensor platform by (1) demonstrating the ability to re-engineer arbitrary aptamers to support homotropic cooperativity, the mechanism evolution uses to improve the steepness of binding curves thus improving measurement precision, (2) developing a number of drift correction and drift elimination methods so as to support long-duration measurements in complex, fluctuating environments, and (3) applying the system to achieve seconds-resolved feedback control over specific molecular analytes (e.g., chemostating) in highly complex and fluctuating environments, a mechanism that mimics the function of autoreceptor control over endogenous communication systems.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

The ability to precisely regulate the concentration of a molecular feedstock in real time in a fermenter or reactor or to precisely regulate plasma or tissue drug levels could significantly impact fields as diverse as autonomous manufacturing and clinical practice. The lack of real-time methods for measuring molecules in complex environments, however, had previously thwarted the development of such a technology. In response, have adapted Electrochemical Aptamer-Based (E-AB) sensors, a modular platform supporting the continuous measurement of, in theory, effectively any small molecule, to the problem of performing high-frequency molecular measurements in complex, highly variable environments and, in turn, using this information to perform closed-loop feedback control. Specifically, we have demonstrated the real-time measurement of multiple drugs in the blood live rats using E-AB sensors inserted through a 22-gauge catheter. The resultant seconds-resolved measurements achieve clinically relevant precision and specificity over the course of many hours. Over the final two years of this project Plaxco-Kippin collaboration focused on adapting E-AB sensors to the problem of feedback control over small molecule concentrations in complex environments, using the control over plasma drug levels in a living animal model (rats) as our test bed platform. That is, using seconds-resolved information provided by E-AB sensors to continuously optimize dosing, such that a drug's concentration is maintained at a fixed, optimal level or actively tracks a pre-defined, time-varying profile. Feedback control variables to be optimized include the relevant PID controller variables (plus exploration of more advanced feedback control algorithms) and also the measurement and delivery frequencies. For example, with the frequency of E-AB measurements being far more rapid than necessary, this provides an opportunity to perform signal averaging (or more sophisticated model-based techniques, such as Kalman filtering) to reduce noise associated with physiological events such as breathing and the pulse. Follow-on work aimed at creating non-linear profiles; specifically, the generation of human-like profiles in rats, which showcased our ability to mimic human pharmacokinetics. To ascertain precision and accuracy we compared our *in vivo* measurements with fixed-time-point measurements using standard laboratory methods. Briefly, blood collected from the tail (2-6 samples) was converted to plasma and analyzed via HPLC.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

During this period, we focused on the development of new drift avoidance and drift correction schemes and the implementation of E-AB sensors in a feedback control system able to rapidly achieve and stably maintain the

concentration of an arbitrary molecule in a flowing, complex, rapidly changing sample stream.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

The focus of this research program was the adaptation of electrochemical aptamer-based (E-AB) sensors to the problem of performing real-time feedback control over molecular concentrations in complex sample matrices, with feedback control over plasma drug levels *in vivo* in live animals being our test bed (**Figure 1**). To achieve this requires first that we can perform the high-frequency measurement of specific molecules irrespective of their chemical reactivity and in complex sample streams, an accomplishment we achieved early in this funding period [1].

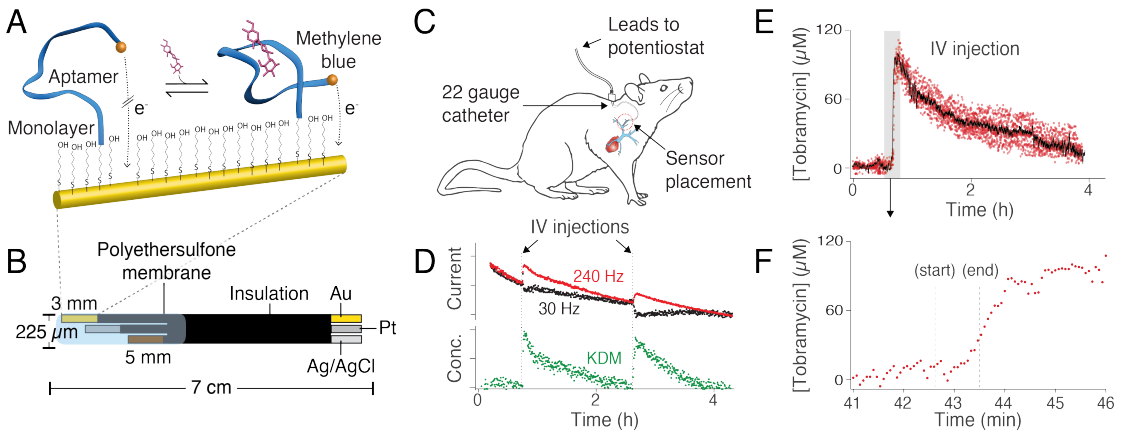



**Figure 1.** *A platform approach to high frequency, real-time molecular measurements in complex environments* [1]. Innovations enabling this include: (**A**) Reagentless, reversible, E-AB sensors, in which an aptamer re-engineered to undergo binding-induced folding is modified with a redox reporter and attached (via a self-assembled monolayer) to an electrode. The binding-induced conformational change causes a corresponding change in electron transfer rate that is easily measured using square wave voltammetry. (**B**) Bundled with its counter and reference electrodes, the resultant sensor is small enough and flexible enough to (**C**) be emplaced via a 22-gauge guide catheter. (**D**) We employ Kinetic Differential Measurements, which uses the difference between the signals generated at two different square wave frequencies (one at which the sensor signal increases upon target binding and a second at which the sensor signal decreases upon target binding) to correct for any drift seen *in vivo*. Critically, this approach employs a single aptamer on a single electrode, avoiding the problem of differential drift between a physically separated sensor/reference pair. (**E**) Using drift-corrected E-AB sensors we achieve excellent precision in the measurement of *in vivo* drug levels over the course of many hours. Shown in red, for example, are 3 s resolved tobramycin measurements made in the jugular of a live rat (black line: a 30 s rolling average computed in real-time). (**F**) Expansion of the injection period further highlights the approach's unprecedented, 3-second time resolution.

To achieve this required the development of ultra-high-surface area electrodes [2], an exhaustive search through the relevant square-wave voltammetric parameter space to optimize sensor performance [3], and a large-scale search for optimal redox reporters [4]. It also required the development of novel methods of avoiding or correcting for the drift invariably seen in complex sample streams. These include the use of biomimeic phosphatidyl-choline surface passivation [5] and the use of time-domain methods (chronoamperometry) [6] to eliminate drift and the use of dual-reporter drift correction [7]. Using these we have demonstrated the high-frequency (seconds resolved) measurements of multiple specific molecules in flowing blood within the living body (**Figure 2**) and in flowing foodstuffs [8]. More recently, we have employed chronoamperometry (rather than square wave voltammetry) [9] to push the time resolution of these measurements down to sub-second (**Figure 3**).

Our ultimate goal is to achieve feedback control over molecular concentration in complex, rapidly evolving sample matrices. We have achieved this to date for two drugs in the bloodstreams of live animals (**Figure 4**). To do so this we implemented a control algorithm taking input from an E-AB sensor placed intravenously in a rat and controlling drug infusion via a femoral vein catheter. Control was maintained using a proportional-integral-derivative (PID) controller, which continuously calculates the difference between the set point (the desired concentration) and the observed value (the actual concentration). To reduce this error, the controller applies a correction to the input (the drug delivery rate) that is based on proportional, integral, and derivative terms; the first, accounting for the present value of the discrepancy (is the current value is above or below the set point), the second, for accumulated past

errors (has movement been towards or away from the set point), and the third, for future errors (given the recent rate of change is the system likely to over/undershoot).

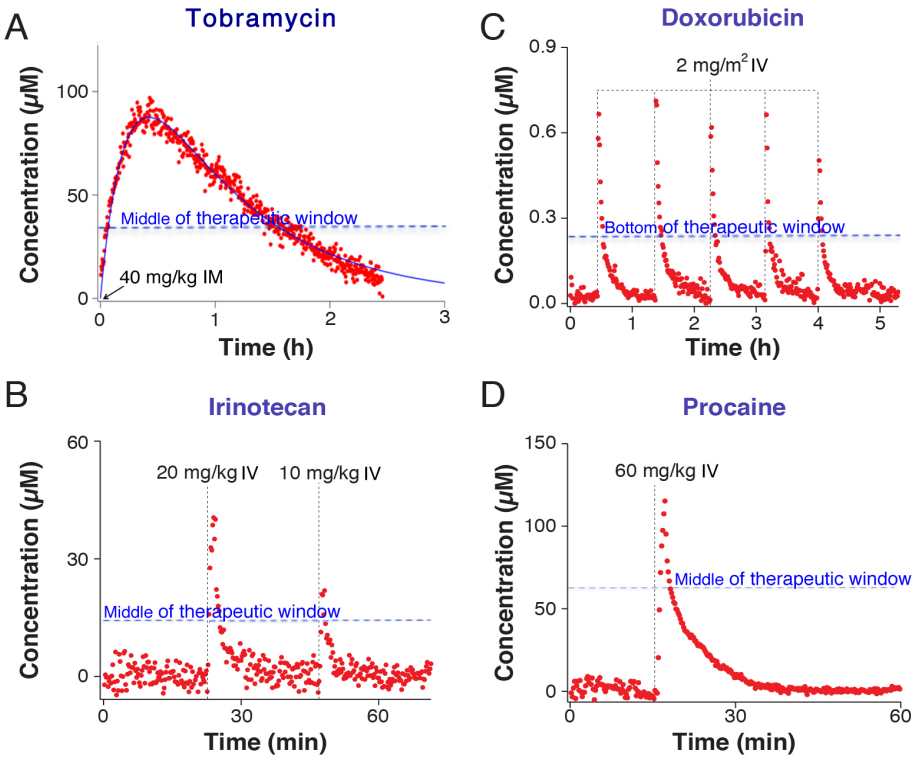



**Figure 2.** *A versatile platform supporting high-frequency molecular measurements in complex sample matrices.* E-AB sensors do not rely on the chemical reactivity of their target molecules, and thus the platform is, at least in theory, highly generalizable. To date we, and others, have demonstrated more than a dozen E-AB sensors, a half dozen of which we have deployed in situ in the living body. Shown, for example, are real-time measurements of (**A**) the antibiotic tobramycin, (**B**) the cancer chemotherapeutics irinotecan and (**C**) doxorubicin, and (**D**) the anesthetic procaine following the indicated doses delivered by IV injection.

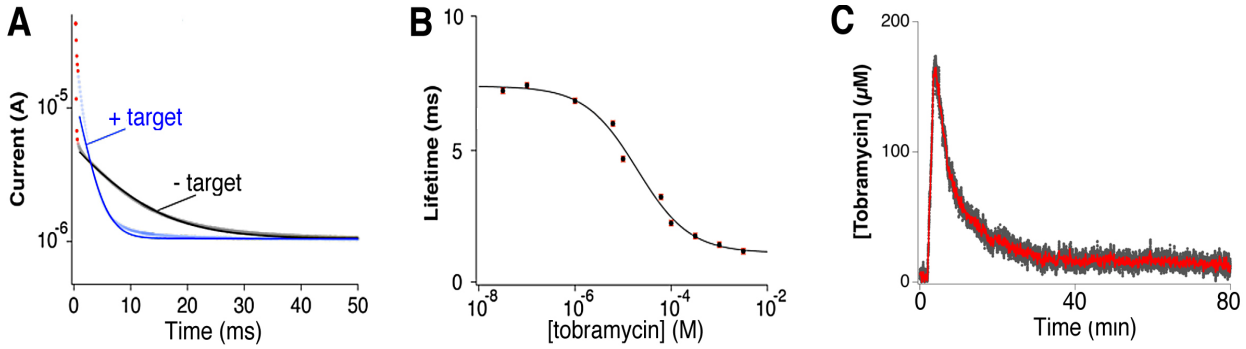



**Figure 3.** *Chronoaperometry: a drift-free approach to sub-second resolved* in vivo *drug measurements.* When an E-AB sensor is interrogated using chronoamperometry the lifetime of the resultant exponential current decay depends (**A**) strongly and (**B**) quantitatively on the fraction of its aptamers that are target-bound [Arroyo-Curras et al., 2018]. (**C**) And because an exponent's lifetime is independent of its amplitude, chronoamperometric E-AB sensors are inherently drift-free. Shown, for example, are *in vivo* (jugular) tobramycin measurements made using this approach with a sensor lacking a protective membrane. They also achieve exceptional time resolution; as shown here, measurements can be collected every 300 ms. The red line, a 30-point, real-time rolling average, illustrates the superb signal-to-noise this approach can achieve while still achieving few-second (here 9 s) time resolution. [6]

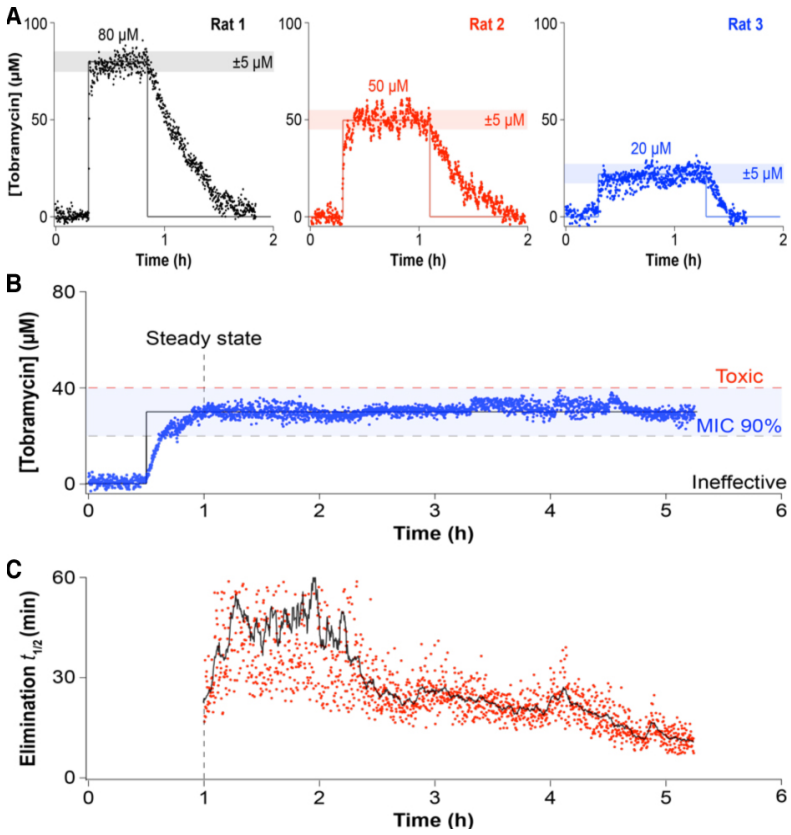



**Figure 4.** *Feedback control over plasma drug levels.* We have recently demonstrated closed-loop feedback control over plasma tobramycin levels in live rats [8]. (**A**) Here, for example, we present feedback-controlled pharmacokinetic profiles in which plasma concentrations were held at set points of 80, 50, or 20 µM for 40, 50, and 60 min, respectively, in three different rats. The precision afforded by actively optimizing the dosing rate every 7 s using real-time concentration measurements is reflected in variance of only ~ 5 µM around each set point. (**B**) Over longer runs feedback control can ensure that the drug's concentration remains in the middle of its therapeutic window. (**C**) Once steady state is achieved the instantaneous dosing rate informs on the instantaneous rate of drug elimination (given the not unreasonable assumption that the animal's volume distribution is fixed). These unprecedented, high resolution measurements (black curve: 3 min rolling average) of the drug's elimination half-life show that the drug's metabolism varies by more than a factor of three within this subject over the course of a few hours, thus highlighting the need for improved methods of drug delivery. Note: experimental duration is limited by animal welfare concerns (which precludes anesthesia of > 6 h) and not by sensor performance.

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### 6. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

N. Arroyo-Currás, G. Ortega, D. A. Copp, K. L. Ploense, Z. A. Plaxco, T. E. Kippin, J. P. Hespanha and K. W. Plaxco. High-precision control of plasma drug levels using feedback-controlled dosing. *ACS Pharm. Trans. Sci.,* October 2018. 10.1021/acsptsci.8b00033.

J. Somerson and K. W. Plaxco. Electrochemical aptamer-based sensors for rapid point-of-use monitoring of the mycotoxin Ochratoxin A directly in a food stream. *Molecules,* April 2018. 10.3390/molecules23040912.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Genetically Encoded AND Gates for Targeted Proteomic Analysis of Cellular Subpopulations in Heterogeneous Bacterial Communities**

**Project Leader:** **David A. Tirrell (Caltech)**

**Collaborators:** **Katherine Germane and Christian Sund (ARL-SEDD)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

*Objective.* The objective of our ICB-supported work over the period 12/1/2013 – 11/30/2018 has been to combine time-resolved and cell-selective protein labeling with quantitative proteomics to elucidate the dynamics of protein synthesis in biofilms and other phenotypically heterogeneous bacterial communities. We have developed new methods of proteomic analysis that provide unprecedented temporal and spatial selectivity, and we have used these methods to explore bacterial survival under oxygen- and nutrient-limited conditions, the temporal character of the quorum sensing response, and the behavior of antibiotic-resistant and iron-depleted subpopulations of cells in bacterial biofilms.

*Relevance to Army Needs.* Bacteria growing in biofilm communities exhibit important phenotypic differences as compared to those growing planktonically, including production and secretion of extracellular polymeric substances, reduced growth rates, and decreased susceptibility to antimicrobial agents. These differences contribute to the persistence of biofilms in chronic diseases; biofilms are present in infections of implanted medical devices and chronic wounds, including those suffered by U.S. service members. Gradients in oxygen, iron and other metabolites and nutrients lead to patterned physiological variations in biofilms, including variations in metabolism, protein expression, and genetic content. Because these factors can contribute to antibiotic resistance, phenotypic heterogeneity is a critically important characteristic of biofilms in chronic infections. Heterogeneity also complicates the development of effective strategies for elimination of biofilms from industrial and military facilities.

*Significant Results.* Among the most significant results of this work have been: i) discovery of a novel transcriptional regulator (SutA) important for biofilm formation, virulence factor production, and survival under anaerobic conditions by the bacterial pathogen *Pseudomonas aeruginosa*; ii) elucidation of the structural basis of transcriptional regulation by SutA; iii) identification of three new targets of the small regulatory RNA CyaR in *Escherichia coli*; iv) completion of the first time-resolved proteomic analysis of the quorum-sensing response in *Vibrio harveyi*; v) completion of the first proteomic analysis of the temporal response of an antibiotic-tolerant biofilm subpopulation to treatment with ciprofloxacin; and vi) identification of an iron-sensitive promoter ($P_{pvdF}$) that enables selective analysis of iron-depleted subpopulations of cells in *Pseudomonas* biofilms.

*Scientific and Technological Impact.* The methods and results developed in this program provide new insight into the mechanisms of bacterial survival under nutrient- and oxygen-limited conditions, tolerance to antibiotic treatment, and pathogenesis; facilitate identification of new targets for antibiotic action; and contribute to the development of effective strategies for the mitigation of biofilm growth, biofouling and corrosion in industrial and military installations.

*Commercial Impact.* The technology underlying the methods described here has been licensed to Life Technologies, Inc. Life Technologies offers for sale many of the key reagents needed for time-resolved and cell-selective proteomic analysis, including azidohomoalanine (Catalog # C10102), homopropargylglycine (Catalog # C10186), and a variety of dyes and kits for metabolic protein labeling. Bacterial strains developed in this work have been distributed to hundreds of laboratories around the world, either directly or through Addgene.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

Our primary objective during the period 3/1/2016 – 11/30/2018 was to develop genetically encoded AND gates that can be used to acquire time-resolved proteomic information from targeted subpopulations of cells of the pathogen *Pseudomonas aeruginosa.*

Gradients in oxygen, sulfur, iron and other metabolites and nutrients cause substantial phenotypic heterogeneity in clinical and environmental microbial communities, including variations in metabolism, protein expression, and genetic content. Because these factors can contribute to antibiotic resistance, phenotypic heterogeneity is a critically important characteristic of chronic infections. Conventional proteomic analyses of heterogeneous bacterial populations have been of limited value, because they provide only average protein compositions that obscure differences among cells that are in various physiological states. Furthermore, such analyses provide little temporal information, and afford limited insight into the mechanisms by which microbial communities transition between states. The methods developed in this project address both of these limitations of conventional proteomic analyses.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

The bio-orthogonal non-canonical amino acid tagging (BONCAT) method of proteomic analysis, developed in our laboratory with ICB support, enables enrichment and identification of selected subsets of cellular proteins. The initial demonstration of the BONCAT method used the methionine (Met) surrogate azidohomoalanine (Aha) as a metabolic label; addition of Aha to cells at selected time points provides temporal control of proteomic labeling. In contrast to Aha, which is incorporated into proteins in all cells through the action of the wild-type methionyl-tRNA synthetase (MetRS), the bulkier Met surrogate azidonorleucine (Anl) can be used to restrict labeling to cells that express a mutant form of the MetRS (designated NLL-MetRS). We have used BONCAT to selectively isolate and identify bacterial proteins from mixed cultures with mammalian cells [1, 2] and achieved cell-state selective proteomic analysis by driving NLL-MetRS expression with state-selective promoters [3].

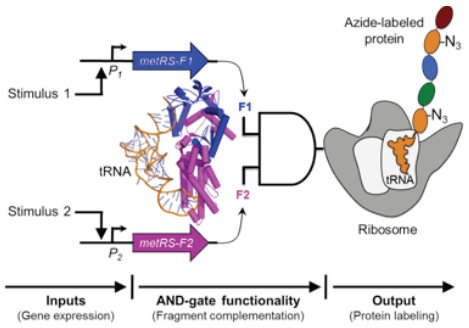



**Figure 1.** A genetic AND gate for proteomic labeling of cellular subpopulations. Two promoters (P1 and P2) are used as inputs to drive expression of MetRS fragments F1 and F2. tRNAMet is charged with Anl only when the MetRS fragments are both expressed, and associate to form a functional enzyme. Anl-labeled proteins can be separated from the rest of the protein pool and can be cleanly identified by high-throughput mass spectrometry.

In 2013, we described a significant advance in BONCAT technology, by using multiple promoters (P1 and P2) to regulate Anl incorporation into the *E. coli* proteome [4]. The approach relies on construction of a split MetRS that generates a translational output only in cells in which the P1 and P2 inputs are simultaneously on. The split MetRS functions as an AND gate to control protein labeling (**Figure 1**), and as such, provides unprecedented control in the targeting of cellular subpopulations for proteomic analysis.

In our initial demonstration of the AND gate method, we used an *E. coli* model system in which the fragments of the split synthetase were expressed under control of well-characterized *lac* and *ara*$_{BAD}$ promoters. During the 3/1/2016 – 11/30/2018 reporting period, we sought to develop methods that would allow us to target more physiologically relevant cellular subpopulations in *Pseudomonas* biofilms.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

Our first task was to identify promoters that could be used to target expression of the split NLL-MetRS to physiologically interesting cellular subpopulations. We first considered *uspK* (to probe cells exposed to low oxygen concentrations), *pvdS* (iron depletion) and *tonB* (depletion of sulfur). In earlier ICB-supported work, we had found good success in expressing NLL-MetRS under control of the stress promoter *rpoS* (characteristic of slow growth) [5]. Our initial experiments during this reporting period suggested that the *pvdS* system was promising, and further exploration led us to the related *pvdF* (pyoverdine synthetase F) promoter.

Iron is essential to bacterial life, and has been shown to serve as a signal for biofilm formation in *P. aeruginosa* [6, 7]. Iron limitation stimulates the twitching motility of cells on surfaces, compromising their ability to form biofilms [6]. Iron deprivation, which can occur through sequestration of iron by chelators or by blocking of the major iron acquisition systems, yields thin, flat biofilms rather than the mushroom-like structures that are more typical of *P. aeruginosa* [8]. *P. aeruginosa* has developed multiple iron uptake systems to support growth and infection. The high-affinity iron acquisition system utilizes the siderophore pyoverdine to bind iron and transport it into the cell. At low iron concentrations, the ferric uptake regulator (*Fur*), a major repressor of iron-responsive genes in *P. aeruginosa*, is released from the promoter region of the iron starvation sigma factor *pvdS*, which in turn induces the synthesis of pyoverdine [8-11]. Expression of pyoverdine influences the pathogenesis of *P. aeruginosa* through increased expression of the virulence genes ADP-ribosylating exotoxin A (*exoA*) and extracellular protease IV (*prpL*), ensuring a critical role for iron in promoting virulence [12, 13].

Our initial expectation was that expression of NLL-MetRS under control of *pvdS* would enable selective Anl-labeling of proteins made in iron-depleted cells. While we did, in fact, observe preferential labeling under low-iron conditions, the selectivity of the system was modest. We therefore examined the related *pvdF* promoter, which is activated by *pvdS*.

To test the utility of *pvdF* in controlling expression of NLL-MetRS in a state-selective manner, we first investigated its activity in planktonic cells. We fused the 1.5 kb region upstream of the endogenous *pvdF* gene just upstream of a copy of *NLL-MetRS* outfitted with a *C*-terminal hexahistidine tag to allow for Western blotting. This cassette was transposed into the *P. aeruginosa* PA14 genome to generate the transgenic PA14 strain $P_{pvdF}$*:NLL-MetRS*. The strain was grown in 1% TSB medium plus 1 mM $MgCl_2$ with or without 50 μM $FeCl_3$ to mid-exponential phase and treated with 1 mM Anl for 1 h. To assess the extent of Anl labeling, we treated cell lysates with alkyne-tetramethylrhodamine (alkyne-TAMRA), separated cellular proteins by SDS-PAGE, and imaged gel fluorescence (**Figure 2, top**). Coomassie staining was used to confirm consistent protein loading (**Figure 2**, **center**), and Western blotting to verify expression of NLL-MetRS (**Figure 2**, **bottom**). Anl labeling was essentially at background levels for cells grown in iron-supplemented medium. In contrast, strong protein labeling was observed for cells subject to iron starvation. As expected, wild-type PA14 cell lysates exhibited background fluorescence irrespective of iron concentration. To provide a positive control, *NLL-MetRS* was placed under control of the strong constitutive *trc* promoter. Anl labeling of $P_{trc}$*:NLL-MetRS* cells was strong and independent of iron concentration.

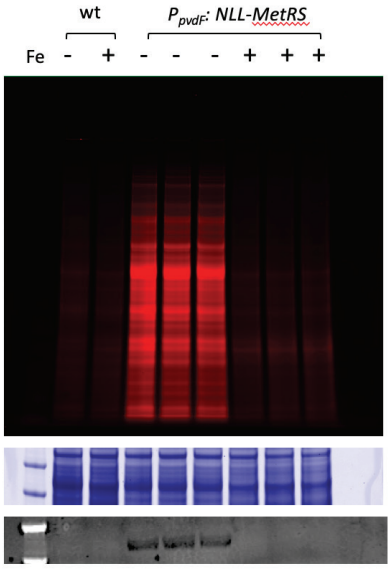



**Figure 2.** Iron-dependent labeling of $P_{pvdF}$*:NLL-MetRS* cells. **Top**: Gel stained with alkyne-TAMRA shows that $P_{pvdF}$*:NLL-MetRS* cells are stained only under conditions of iron-depletion (lanes 3-5 vs 6-8). Wild-type cells are not labeled (lanes 1 and 2). **Middle**: Coomassie staining confirms consistent loading among lanes. **Bottom**: Western blotting confirms selective expression of MetRS under conditions of iron depletion.

To test our ability to identify labeled proteins through BONCAT enrichment, we treated Anl-labeled lysates from wild-type and $P_{pvdF}$*:NLL-MetRS* cells with azadibenzocyclooctyne-conjugated agarose beads (DBCO-agarose beads). Enriched proteins were analyzed by LC-MS/MS, and total LC-MS/MS intensities were compared. The results confirmed that the pvdF promoter affords highly selective labeling of iron-depleted cells. Samples of $P_{pvdF}$*:NLL-MetRS* grown in iron-depleted media were labeled approximately 20-fold more strongly than those grown in 50 μM iron. $P_{pvdF}$*:NLL-MetRS* samples exhibited background slightly above that of wild-type samples, suggesting a low level of leaky expression.

To test labeling of iron-starved cellular subpopulations in biofilms, we grew films on glass cover slips under constant flow of TSB medium supplemented with 100 μM $FeCl_3$. After 4 days, biofilms were treated with Anl for 1.5 h. To visualize Anl incorporation, biofilms were fixed and treated with alkyne-TAMRA. SYTO 9 was used to counterstain all cells, irrespective of Anl labeling. As expected, Anl labeling was restricted to the interior regions of

*$P_{pvdF}$:NLL-MetRS* biofilms, where iron depletion is most severe (**Figure 3**). In contrast, *$P_{trc}$:NLL-MetRS* biofilms were labeled throughout. Anl labeling could not be detected in wild-type biofilms (**Figure 3**).

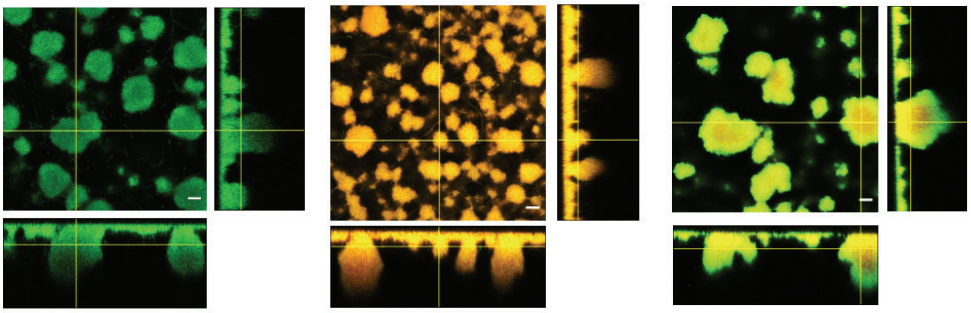


**Figure 3.** Fluorescence confocal microscopy of *P. aeruginosa* biofilms stained with SYTO 9 (green) and TAMRA-alkyne (red). From left: wild-type cells, *$P_{trc}$:NLL-MetRS* cells, and *$P_{pvdF}$:NLL-MetRS* cells. Scale bar; 10 microns.

To effect selective proteomic analysis of iron-starved cellular subpopulations in *Pseudomonas* biofilms, we grew films of both *$P_{pvdF}$:NLL-MetRS* and *$P_{trc}$:NLL-MetRS* strains (each in triplicate) for 4 days in silicone rubber tubing. After treatment with Anl for 3 h, cells were collected and lysed. Anl incorporation was verified by treating cell lysates with alkyne-TAMRA and imaging gel fluorescence after SDS-PAGE. *$P_{pvdF}$:NLL-MetRS* samples exhibited reduced fluorescence, consistent with selective labeling of the iron-depleted cellular subpopulation. Anl-labeled proteins were isolated via BONCAT enrichment and analyzed by LC-MS/MS. Intensity Based Absolute Quantification (iBAQ) was performed to obtain relative abundances of proteins identified in each sample. Label-free quantification (LFQ) was used to calculate relative abundances of proteins among all samples. Nearly 2300 proteins were identified among the six LC-MS/MS runs. Spearman's rank correlation coefficients for protein iBAQ values were calculated for each run, and revealed good correlation of protein abundances among triplicate samples of each strain. We further performed principal component analysis (PCA) using the protein LFQ values to visualize the variance of proteomic profiles among triplicates and the two different strains. Biological replicates from each strain were clustered together while samples from different strains were well separated, indicating consistency of proteomic profiles among triplicates and clear distinction between strains. We obtained the relative abundances (fold-changes) of proteins shared in the two strains using the LFQ values and their corresponding false-discovery-rate (FDR) adjusted *p*-values (**Figure 4**).

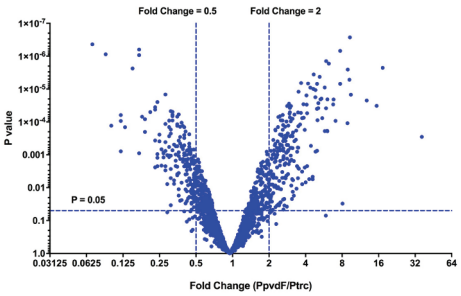



**Figure 4.** Differential expression of proteins in iron-depleted and control populations of cells in *P. aeruginosa* biofilms. Proteins shifted to the right were found in higher relative abundance in iron-depleted (*$P_{pvdF}$:NLL-MetRS*) cells; those shifted to the left were found in lower abundance in iron-depleted cells relative to *$P_{trc}$:NLL-MetRS* controls.

To characterize the proteomic responses of biofilm subpopulations subject to iron starvation, we first examined proteins that were significantly up-regulated in *$P_{pvdF}$:NLL-MetRS* samples (fold change > 2 and *p*-value < 0.05), or identified in *$P_{pvdF}$: NLL-MetRS* samples (in at least two of the three replicates) but not in any of the *$P_{trc}$:NLL-MetRS* samples. We used Gene Ontology (GO) enrichment analysis to categorize genes according to their molecular functions. Many of the genes we found to be up-regulated are involved in oxidative phosphorylation and ribosomal protein assembly, suggesting active metabolism, even in the iron-depleted biofilm interior. We then subjected all of the proteins identified in both strains to KEGG pathway analysis, in which relative abundances of proteins in each pathway were compared for *$P_{pvdF}$:NLL-MetRS* and *$P_{trc}$:NLL-MetRS* samples. Several pathways were found to be differentially expressed in the two strains, including oxidative phosphorylation, ribosomal protein assembly, and porin biosynthesis, consistent with our analysis of up-regulated genes. Nitrogen metabolism was also significantly up-regulated compared to the control, while flagellar assembly and bacterioferritin biosynthesis were down-regulated. The implications of these observations are under further consideration.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

The Principal Investigator participated in the Workshop on Microbial Consortia and Biofilms at UCSB in March 2017.

The Principal Investigator and Shannon Stone at Caltech assisted Katherine Germane of ARL with BONCAT experiments and analyses through October 2016.

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

B. M. Babin, L. Atangcho, M. B. van Eldijk, M. J. Sweredoski, A. Moradian, S. Hess, T. Tolker-Nielsen, D. K. Newman and D. A. Tirrell. Selective proteomic analysis of antibiotic-tolerant cellular subpopulations in *Pseudomonas aeruginosa* biofilms. *mBio*, October 2017. 10.1128/mBio.01593-17.

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A. Mahdavi, G. D. Hamblin, G. A. Jindal, J. D. Bagert, C. Dong, M. J. Sweredoski, S. Hess, E. M. Schuman and D. A. Tirrell. Engineered aminoacyl-tRNA synthetase for cell-selective analysis of mammalian protein synthesis. *Journal of the American Chemical Society*, March 2016. 10.1021/jacs.5b08980.

B. M. Babin, M. Bergkessel, M. J. Sweredoski, A. Moradian, S. Hess, D. K. Newman and D. A. Tirrell. SutA is a bacterial transcription factor expressed during slow growth in *Pseudomonas aeruginosa*. *Proc. Natl. Acad. Sci. U.S.A.*, February 2016. 10.1073/pnas.1514412113.

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J. D. Bagert, Y. J. Xie, M. J. Sweredoski, Y. Qi, S. Hess, E. M. Schuman, and D. A. Tirrell. Quantitative, time-resolved proteomic analysis by combining bioorthogonal noncanonical amino acid tagging and pulsed stable isotope labeling by amino acids in cell culture. *Mol. Cell. Proteomics*, May 2014. 10.1074/mcp.M113.031914.

K. P. Yuet and D. A. Tirrell. Chemical tools for temporally and spatially resolved mass spectrometry-based proteomics. *Ann. Biomed. Eng.,* February 2014. 10.1007/s10439-013-0878-3.

A. Mahdavi, J. Szychowski, J. T. Ngo, M. J. Sweredoski, R. L. J. Graham, S. Hess, O. Schneewind, S. K. Mazmanian, and D. A. Tirrell. Identification of secreted bacterial proteins by noncanonical amino acid tagging. *Proc. Natl. Acad. Sci. U.S.A.,* January 2014. 10.1073/pnas.1301740111.

**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Engineered Microbial Opsins using SCHEMA Recombination and Directed Evolution**

**Project Leader:** **Frances H. Arnold (Caltech)**

**Collaborators:** **Viviana Gradinaru and William Clemons (Caltech)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

During this project we pioneered the use of machine learning in protein engineering, as demonstrated with engineering integral membrane proteins (MPs), which are key engineering targets due to their critical roles in regulating cell function. In engineering MPs, it can be extremely challenging to retain membrane localization capability while changing other desired properties. We started by using structure-guided SCHEMA recombination to create a large set of functionally diverse chimeras from three sequence-diverse channelrhodopsins (ChRs). We chose 218 ChR chimeras from two SCHEMA libraries, constructed synthetic genes, and assayed them for expression and plasma membrane localization in human embryonic kidney cells. The majority of the chimeras expressed, with 89% of the tested chimeras outperforming the lowest-expressing parent; 12% of the tested chimeras express at even higher levels than any of the parents. A significant fraction (23%) also localize to the membrane better than the lowest-performing parent ChR. Most (93%) of these well-localizing chimeras are also functional light-gated channels. Many chimeras have stronger light-activated inward currents than the three parents, and some have unique off-kinetics and spectral properties relative to the parents.

A MP must be expressed, correctly inserted and folded in a lipid bilayer, and trafficked to the proper cellular location in order to function. The sequence and structural determinants of these processes are complex and highly constrained. Machine learning on carefully-chosen training sequences made by structure-guided SCHEMA recombination enabled us to accurately predict the rare sequences in this diverse library of channelrhodopsins (ChRs) that express and localize to the plasma membrane of mammalian cells. These light-gated channel proteins of microbial origin are of interest for neuroscience applications, where expression and localization to the plasma membrane is a prerequisite for function. We trained Gaussian process (GP) classification and regression models with expression and localization data from the 218 ChR chimeras chosen from our 118,098-variant library designed by SCHEMA recombination. We used these GP models to identify ChRs that express and localize well and showed that our models can elucidate sequence and structure elements important for these processes. We also used the predictive models to convert a naturally occurring ChR incapable of mammalian localization into one that localizes well.

Finally, we used this method to engineer ChRs whose current strength and light sensitivity enable, for the first time, minimally-invasive neuronal circuit interrogation. Current ChR tools applied to the mammalian brain require intracranial surgery for transgene delivery and implantation of invasive fiber-optic cables to produce light-dependent activation of a small volume of brain tissue [~1 $mm^3$]. To enable optogenetics for large brain volumes and without the need for invasive implants, our approach leveraged data and the significant literature of ChR variants to train statistical models for the design of new, high-conductance ChRs. With Gaussian Process models trained on a limited experimental set of 102 functionally characterized ChR variants, we designed high-conductance ChRs with unprecedented light sensitivity; these enable optogenetic activation of the nervous system via minimally-invasive systemic transgene delivery with viral vestor rAAV-PHP.eB. Our engineered ChRs enable light-induced neuronal excitation without invasive intracranial surgery for virus delivery or fiber optic implantation, i.e. they enable *minimally-invasive optogenetics*.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

Our goal has been to engineer ChRs to overcome limits in conductance and light sensitivity and extend the reach of optogenetic experiments. Engineering ChRs requires overcoming three major challenges. First, rhodopsins are trans-membrane proteins and inherently difficult to engineer because the sequence and structural determinants of membrane protein expression and plasma-membrane localization are highly constrained and poorly understood. Second, because properties of interest for neuroscience applications are assayed using low-throughput techniques such as patch-clamp electrophysiology, engineering by directed evolution is not feasible. And third, *in vivo* applications require either retention or optimization of multiple properties in a single protein tool; for example, we must optimize expression and localization in mammalian cells while simultaneously tuning kinetics, photocurrents, and spectral properties. We have developed a new, generally applicable protein engineering methodology in order to solve this problem.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

In work completed earlier in this project, we explored structure-guided recombination of three highly-functional ChR parents [CsChrimsonR (CsChrimR), C1C2, and CheRiff] by designing two 10-block recombination libraries with a theoretical size of ~120,000 (i.e. $2x3^{10}$) ChR variants [1]. Measuring expression, localization, and photocurrent properties of a subset of these chimeric ChRs showed that these recombination libraries are a rich source of functionally diverse sequences. That work produced 76 ChR variants with measured photocurrent properties, the largest single source of published ChR functional data [1]. In subsequent work, we generated an additional 26 ChR variants selected from the same recombination libraries [2], which we characterized for functional properties during this reporting period. Together, these 102 ChR variants from the recombination libraries provide the primary dataset used for model training in this work. We supplemented this dataset with data from other published sources including 19 ChR variants from nature, 14 single-mutant ChR variants, and 28 recombination variants from other libraries. As the data produced by other labs were not collected under the same experimental conditions as ours, they cannot be used for comparison for absolute ChR properties (i.e. photocurrent strength); however, these data do provide useful binary information on whether a sequence variant is functional or not. Thus, we used published data from other sources when training binary classification models for ChR function.

Our primary interest was modeling and optimization of three ChR properties: photocurrent strength, wavelength sensitivity, and off-kinetics. Enhancing ChR photocurrent strength would enable reliable neuronal activation even under low-light conditions. As a metric for the ChR activation spectrum, we used the normalized current strength induced by exposure to green light (560 nm). Different off-rates can be useful for specific applications: fast off-kinetics enable high-frequency optical stimulation, slow off-kinetics is correlated with increased light sensitivity, and very slow off-kinetics can be used for constant depolarization (step-function opsins). We used two parameters to characterize the off-kinetics: the time to reach 50% of the light-activated current and the photocurrent decay rate, $\tau_{off}$. In addition to opsin functional properties, it is also necessary to optimize or maintain plasma-membrane localization, a prerequisite for ChR function.

We trained a binary classification model to predict if a ChR sequence will be functional using all 102 training sequences from the recombination library as well as data from 61 sequence variants published by others. A ChR sequence was considered to be functional if its photocurrents were >0.1 nA upon light exposure, a threshold we set as an approximate lower bound for conductance necessary for neuronal activation. We used this trained classification model to predict whether uncharacterized ChR sequence variants were functional. To verify that the classification model is capable of accurate predictions, we performed 20-fold cross validation on the training data set and measured an area under the receiver operator curve (AUC) of 0.78, indicating good predictive power.

Next, we trained three regression models, one for each of the ChR photocurrent properties of interest. For these, we exclusively used data collected from our ChR recombination libraries. Once trained, these models were used to predict photocurrent strength, wavelength sensitivity of photocurrents, and off-kinetics of new, untested ChRs sequence variants. Again, to test whether these models make accurate predictions, we performed 20-fold cross validation on the training dataset and observed high correlation between predicted and measured properties as indicated by Pearson correlations between 0.65 – 0.9 for all models.

A ‘designer’ ChR is a ChR predicted by our models to have a useful combination of properties. We used a tiered approach to select designer ChRs. The first step was to eliminate all ChR sequences predicted to not localize to the

plasma membrane or predicted to be non-functional. To do this, we used the ChR function classification model along with our ChR localization classification model [2] to predict the probability of localization and function for each ChR sequence in the 120,000-variant recombination library. Not surprisingly, most ChR variants were predicted to not localize and not function. To focus on ChR variants predicted to localize and function, we set a threshold for the product of the predicted probabilities of localization and function; any ChR sequence above that threshold would be considered for the next tier of the process. We selected a conservative threshold of 0.4. Only 1,161 sequence variants passed the 0.4 threshold.

For the second tier of the selection process, we used the three regression models trained on all functional variants collected up to this point to predict the photocurrent strength, wavelength sensitivity of photocurrents, and off-kinetics for each of the remaining 1,161 ChR sequence variants above the predicted localization and function thresholds. From these, we selected ChR sequence variants predicted to have the highest photocurrent strength, most red-shifted or blue-shifted activation wavelengths, and variants with a range of off-kinetics from very fast to very slow. We selected 28 designer ChRs with different combinations of properties that were all predicted to be highly-functional (photocurrents > 0.2 nA) and capable of good membrane localization.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

We assessed photocurrent amplitude, wavelength sensitivity, and off-kinetics of the designer ChRs and the three parental ChRs [CsChrimR, CheRiff, and C1C2] (**Figure 1**). In addition to the 28 regression-model-predicted ChRs, we also assessed the top-performing ChRs from the classification models' predictions [ChR_9_4 (predicted from the classification localization model) and ChR_25_9 (classification function model)], for a total of 30 highly-functional model-predicted ChRs as well as the two negative control ChRs (ChR_29_10, ChR_30_10). Of the 30 model-predicted ChRs, we found 13 variants with significantly higher blue-light activated photocurrents than the top-performing parent (CheRiff) (**Figure 1.b**). Six variants exhibit significantly higher green-light activated photocurrents than CsChrimR (**Figure 1.b**). Eight variants have larger red-light activated photocurrents when compared with the blue-light activated parents (CheRiff and C1C2), though none significantly out-perform CsChrimR (**Figure 3.b**). Both ChR variants predicted to be non-functional by the models produce <0.03 nA currents.

Characterization of the 30 designer ChRs revealed that their off-kinetics span four orders of magnitude ($\tau_{off}$ = 10 ms – 1 min) (**Figure 3.c**). This range is quite remarkable given that all designer ChRs are built from sequence blocks of three parents that have very similar off-kinetics ($\tau_{off}$ = 30 – 50 ms). We found that 5 designer ChRs have significantly faster off-kinetics than the fastest parent, while 16 are significantly slower (**Figure 1.c**). Four ChRs have particularly slow off-kinetics with $\tau_{off}$ > 1 s. Short 1 ms-exposures to blue light elicits distinct profiles from selected ChRs: ChR_21_10 turns off rapidly, ChR_25_9 and ChR_11_10 turn off more slowly, and ChR_15_10 exhibits little decrease in photocurrent 0.5 s after the light was turned off (**Figure 1.c**).

Three designer ChRs exhibit interesting spectral properties. ChR_28_10's red-shifted spectrum matches that of CsChrimR, demonstrating that incorporating sequence elements from blue-shifted ChRs into CsChrimR can still generate a red-shifted activation spectrum (**Figure 1.e**). Two of the designer ChRs exhibit novel spectral properties: ChR_11_10 has a broad activation spectrum relative to the parental spectra, with similar steady-state current strength from 400 – 560 nm light and even maintain strong currents (0.7 ± 0.1 nA) when activated with 586 nm light (**Figure 1.e**). ChR_25_9, on the other hand, exhibits a narrow activation spectrum relative to the parental spectra, with a peak at 485 nm light (**Figure 1.e**).

We assessed the light sensitivity of the designer ChRs with enhanced photocurrents by measuring photocurrent strength at various irradiances (**Figure 1.d**). We refer to these high-photocurrent ChRs as 'high-conductance' ChRs. All high-conductance ChRs have significantly larger currents at all intensities of light tested. The high-conductance ChRs also demonstrate minimal decrease in photocurrent over the range of intensities tested ($10^{-1}$ – $10^{1}$ mW mm$^{-2}$), suggesting that photocurrents were saturated at these intensities and would only attenuate at much lower light intensities (**Figure 1.d**). The high-conductance ChRs are expressed at levels similar to the CsChrimR parent (the highest expressing parent).

We investigated whether these light-sensitive, high-conductance ChRs could provide optogenetic activation coupled with minimally-invasive gene delivery. Recently, we described the novel AAV capsid rAAV-PHP.eB [3] that produces broad transduction throughout the central nervous system with a single minimally-invasive intravenous

injection in the adult mouse. Systemic delivery of rAAV-PHP.eB vectors results in brain-wide transgene delivery with expression throughout large brain volumes without the need for invasive intracranial injections [3,4]. The use of rAAV-PHP.eB for optogenetic applications has been limited, however, by the lower multiplicity of infection with systemically delivered viral vectors than with direct injection. This results in insufficient opsin expression and light-evoked currents to evoke neuronal firing with lower-conductance channels (e.g., ChR2).

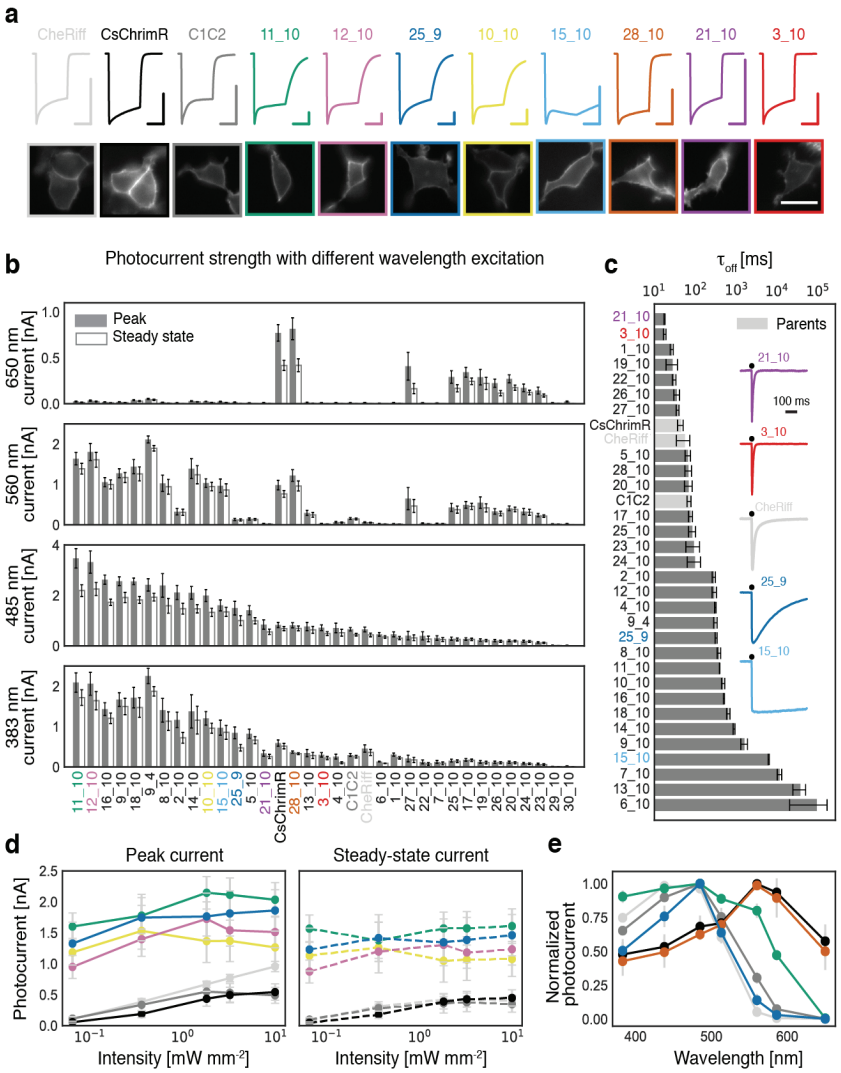



**Figure 1**. The model-predicted ChRs exhibit a large range of functional properties often far exceeding the parents. (**a**) Current trace after 0.5 s light exposure for select designer ChR variants with corresponding expression and localization in HEK cells. Vertical colored scale bar for each ChR current trace represents 0.5 nA, and horizontal scale bar represents 250 ms. Different color traces are labeled with each variant's name. The variant color presented in (**a**) is kept constant for all other panels. (**b**) Designer ChR measured peak and steady-state photocurrent with different wavelengths of light. 383 nm light at 1.5 mW mm$^{-2}$, 485 nm light at 2.3 mW mm$^{-2}$, 560 nm light at 2.8 mW mm$^{-2}$, and 650 nm light at 2.2 mW mm$^{-2}$. (**c**) Designer ChR off-kinetics decay rate ($\tau_{off}$) following a 1 ms exposure to 485 nm light (2.3 mW mm$^{-2}$). Parent ChRs are highlighted in light gray. Inset shows current traces with 1 ms light exposure for select ChRs compared with CheRiff. (**d**) Selected ChR variants' peak and steady-state photocurrent strength with varying light irradiances compared with parental ChRs. (**e**) Wavelength sensitivity of activation for select ChRs compared with parental ChRs.

We hypothesized that the high-conductance ChRs could overcome this limitation and allow large-volume optogenetic excitation following systemic transgene delivery. We systemically delivered rAAV-PHP.eB packaging either hi-ChR1-TS-eYFP, hi-ChR2-TS-eYFP, or ChR2(H134R)-TS-eYFP under the hSyn promoter and observed broad expression throughout the brain with expression strongest in the cortex (**Figure 2.e**). We then measured the

fraction of opsin-expressing cells with sufficient opsin-mediated currents for light-induced firing (**Figure 2.f**). Only 1/36 neurons expressing ChR2(H134R) produced light-induced firing, while 8/9 neurons expressing hi-ChR1 produced light-induced activity and 9/9 neurons expressing hi-ChR2 produced light-induced activity. We also observed high spike fidelity with low light levels in hi-ChR1 and hi-ChR2, consistent with observations in neuronal cultures (**Figure 2.f**). These results demonstrate the need for high-conductance opsins for applications where systemic delivery is desired.

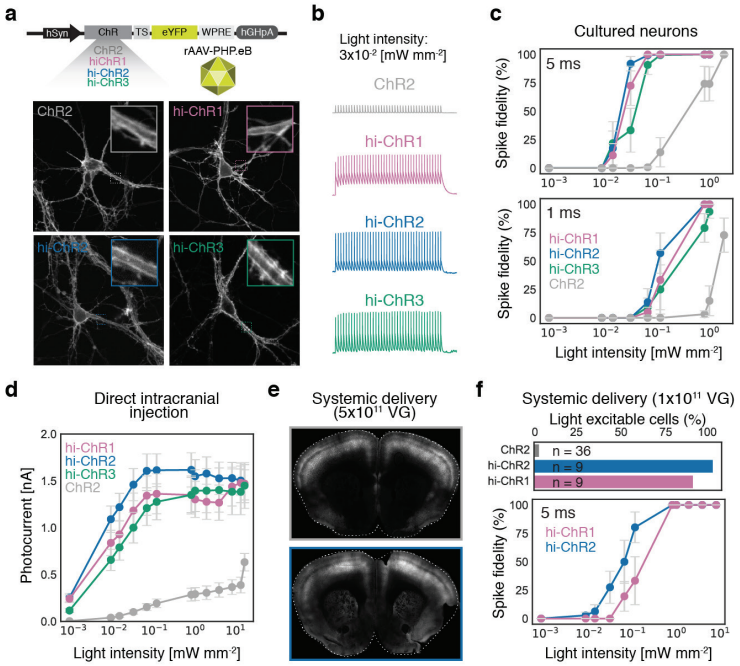



**Figure 2.** High-conductance ChR variants in cultured neurons (**a**-**c**) and in acute brain slices (**d**-**f**) outperform the commonly used ChR2(H134R). (**a**) High-conductance ChRs and the ChR2(H134R) control were cloned into an AAV vector with a trafficking signal (TS), eYFP, and WPRE and then packaged into rAAV-PHP.eB for expression in culture and *in vivo*. Cultured neurons expressing hi-ChR1, hi-ChR2, hi-ChR3, and ChR2(H134R). (**b**) Voltage traces of hi-ChR1, hi-ChR2, hi-ChR3, and ChR2(H134R) at 2 Hz with 5 ms pulsed low-intensity blue light stimulation ($3x10^{-2}$ mW $mm^{-2}$) shows robust neuronal firing for the high-conductance ChRs while ChR2(H134R) exhibits only sub-threshold light-induced depolarization. (**c**) Spike fidelity with varying intensity light of high-conductance ChRs and ChR2(H134R) for 5 ms and 1 ms light pulses with 2 Hz stimulation. (**d**) High-conductance ChR and ChR2(H134R) photocurrent strength with varying light irradiances in acute brain slice after direct injection of rAAV-PHP.eB packaged ChR constructs into the PFC. (**e**) Systemic delivery of rAAV-PHP.eB packaged hi-ChR2 or ChR2(H134R) ($5x10^{11}$ vg/animal) results in broad expression throughout the cortex. (**f**) The fraction of light excitable neurons in the PFC after systemic delivery of rAAV-PHP.eB packaged hi-ChR2 or ChR2(H134R) ($1x10^{11}$ vg/animal) measured by cell-attached recording in acute slice targeting only neurons expressing the eYFP marker. Spike fidelity with varying intensity light of high-conductance ChRs after systemic delivery ($1x10^{11}$ vg/animal). vg, viral genomes.

We next evaluated the optogenetic efficiency of the high-conductance opsins after systemic delivery using a well-established behavioral paradigm: optogenetic intracranial self-stimulation (oICSS) of dopaminergic neurons of the ventral tegmental area (VTA). We used systemic delivery of rAAV-PHP.eB packaging a double-floxed inverted open reading frame (DIO) containing either hi-ChR2-TS-eYFP or ChR2(H134R)-TS-eYFP into *Dat*-Cre mice. Three weeks after systemic viral delivery and stereotaxic implantation of fiber-optic cannulas above the VTA, mice were placed in an operant box and were conditioned to trigger a burst of 447 nm laser stimulation via nose poke. Animals expressing hi-ChR2 displayed robust optogenetic self-stimulation in a frequency-dependent and laser power-dependent manner. Higher frequencies (up to 20 Hz) and higher light power (up to 10 mW) promoting greater maximum operant response rate. Conversely, laser stimulation failed to reinforce operant responding in ChR2(H134R)-expressing animals; these results were consistent with results in acute slice where the light-induced currents of ChR2(H134R) are too weak at the low copy number produced by systemic delivery for robust neuronal activation.

In order to determine if hi-ChR2 would enable both minimally-invasive transgene delivery and minimally-invasive optical excitation, we assayed directional control of locomotion in freely moving animals by optogenetic stimulation of the right secondary motor cortex (M2), a well-established behavioral paradigm previously used to validate optogenetic tools[27]. In this assay, unilateral stimulation of M2 disrupts motor function in the contralateral lower extremities, causing mice to turn away from the stimulation side. We systemically administered rAAV-PHP.eB packaging either hi-ChR2-TS-eYFP or ChR2(H134R)-TS-eYFP under a CaMKIIa promoter for transgene expression in excitatory pyramidal neurons in the cortex. We secured a fiber-optic cannula guide to the surface of the thinned skull above M2 without puncturing the dura and therefore leaving the brain intact. Despite the presence of the highly optically scattering calavarial bone, stimulation with 20 mW 447 nm light induced left-turning behavior in animals expressing hi-ChR2 but not in animals expressing ChR2(H134R). Left-turning behavior terminated upon conclusion of optical stimulation. Behavioral effects were seen at powers as low as 10 mW, but the most consistent turning phenotypes were seen with 20 mW laser power. In order to ensure that turning behavior was not due to unexpected visual stimuli or heating caused by the stimulation laser, we repeated treadmill experiments using 671 nm light, which is outside the excitation spectrum of both opsins. 20 mW 671 nm light failed to induce turning in both hiChR2 and ChR2(H124R). Overall, these experiments demonstrate that hi-ChR2 is compatible with minimally-invasive systemic gene delivery and can enable minimally-invasive optogenetic excitation. This work will be published soon in Nature Methods [5].

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## 6. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)


Bedbrook, C.N., Yang, K.K., Robinson, J.E., Gradinaru, V., Arnold, F.H. Machine learning-guided channelrhodopsin engineering enables minimally-invasive optogenetics. *Nature Methods*, submitted.

Yang, K.K., Wu, Z., Bedbrook, C.N. and Arnold, F.H. Learned protein embeddings for machine learning. *Bioinformatics*, March 2018. 10.1093/bioinformatics/bty178.

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McIsaac, R.S., Bedrook, C.N. and Arnold, F.H. Recent advances in engineering microbial rhodopsins for optogenetics. *Current Opinion in Structural Biology*, August 2015. 10.1016/j.sbi.2015.05.001.

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McIsaac, R.S., Engqvist, M.K.M., Wannier, T., Rosenthal, A.Z., Herwig, L., Flytzanis, N.C., Imasheva, E.S., Lanyi, J.K., Balashov, S.P., Gradinaru, V. and Arnold, F.H. Directed evolution of a far-red fluorescent rhodopsin. *PNAS*, September 2014. 10.1073/pnas.1413987111.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Suspended Microchannel Resonators for Pathogen Analysis**

**Project Leader:** **Scott R. Manalis (MIT)**

**Collaborators:** **Peter Setlow (UCHC); Patrick Doyle (MIT Chemical Engineering) and Angelika Amon (MIT Biology)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

*1) Established a paradigm for non-invasively measuring stiffness of micro- and ultimately nanoscale objects with acoustics (Kang et al. Nature Methods, 2019).* Measuring stiffness by Atomic Force Microscopy (AFM) provides local measurements but is limited by low throughput and is invasive, lowering potential yield. We quantified mechanical properties via acoustic scattering of waves from a particle inside a fluid-filled vibrating cantilever resulting in < 15 nm deformations. Through simulations, experiments with hydrogels of varying elastic modulus and chemically perturbed cells, we show that our readout, the size-normalized acoustic scattering (SNACS), measures stiffness. We have performed SNACS measurements on bacteria spores and envision the approach could be used to assess the infectivity of individual viruses.

*2) Developed a high-throughput single-cell growth monitoring platform and observed rapid response of bacteria antibiotic and antimicrobial peptide treatments (Cermak et al. Nature Biotechnology 2016).* Resonant micromechanical mass sensors can precisely measure growth, but are limited to measuring one cell at a time. We developed an approach to precisely and rapidly measure growth rates of many cells simultaneously using and array of suspended microchannel resonator sensors, achieving a throughput of ~100 cells/h and a precision that is nearly 100-fold better than what can be achieved by quantitative phase microscopy. Our system reveals subpopulations of cells with divergent growth kinetics and enables assessing cellular growth responses to antibiotics or antimicrobial peptides within minutes.

*3) Discovered determinants of low water permeability of B. subtilis spores (Knudsen et al. Journal of Bacteriology 2016).* We developed a biophysical approach for directly measuring water-permeability of a panel of spore mutants which contained a range of defects in the outer coat layer of the spore. We then investigated the extent to which small molecules can access the interior of the spore by i) measuring the ability of small molecules to induce or inhibit germination in the various mutants, and ii) directly assessing the uptake of small molecules for wild-type and a severely damaged coat mutant (*cotE gerE*). Our results reveal that the inner membrane (IM) is not the barrier to water entering the spore core, and show that water exchange is not affected by the level of crosslinking in the cortex.

*4) Dynamically resolved nanoscale spatial mass distributions (Olcum et al. Nature Comm. 2015).* We developed a general platform for independently and simultaneously oscillating multiple modes of mechanical resonators, enabling frequency measurements that can precisely track fast transient signals within a user-defined bandwidth that exceeds 500 Hz. As a proof of concept, we use the suspended nanochannel resonator to show that the position and mass of individual nanoparticles could be resolved with an accuracy near 150 nm.

*5) Weighing nanoparticles in solution at the attogram scale (Olcum et al. PNAS 2014).* Physical characterization of nanoparticles is required for a wide range of applications. We developed a suspended nanochannel resonator that achieved a 1,000-fold improvement in mass resolution over the suspended microchannel resonator. We demonstrated the potential of this capability by comparing the mass distributions of exosomes produced by different cell types and by characterizing the yield of self-assembled DNA nanoparticle structures.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

1) Expand the capabilities of nano- and microchannel resonators for measuring physical properties of engineered and naturally occurring particles in the aqueous environment.

2) Apply nano- and microchannel resonators to problems related to pathogen analysis and detection.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

1) We utilized the vibration of a suspended microchannel resonator (SMR, **Figure 1.a, top**) as an acoustic energy source and investigated if the scattered acoustic fields from the cell could provide a signal to monitor its mechanical properties (**Figure 1.b**). The SMR is a cantilever-based microfluidic mass sensor that has previously been used to measure cell buoyant mass. Vibrating the SMR at its second mode (resonant frequency $f$) causes the vibration amplitude to vary along the length of the cantilever, with one local maximum (antinode) near the center and a zero-minimum (node) near the tip (**Figure 1.a, middle**). When a cell is at the antinode, the net change in mass (i.e. the buoyant mass of the cell) corresponds to a change in the kinetic energy of the system, and thus causes a shift in the resonant frequency of the SMR ($\Delta f/f|_{antinode}$) (**Figure 1.a**, **bottom** and Supplementary Note 1). When the cell is at the node, the net change in mass is not expected to shift the resonant frequency ($\Delta f/f|_{node} = 0$) because the vibration amplitude is zero and there is no change in kinetic energy. Surprisingly, we observed a consistent resonant frequency shift at the node ($\Delta f/f|_{node} \neq 0$) when we flowed a single cell or polystyrene bead in the SMR (**Figure 1.a, bottom**). Interestingly, this resonant frequency shift, which we termed "node deviation" ($\Delta f/f|_{node}$), was different for cells and beads of similar buoyant mass. We therefore hypothesized that i) node deviation corresponds to an energy change due to acoustic scattering from the cell's surface, ii) node deviation depends on cellular mechanical properties.

2) Our measurements of the water permeability of Bacillus subtilis spores were based on a set of paired measurements in which the buoyant mass of each spore was determined first in water (H2O) and then in deuterium oxide (D2O). These experiments demonstrated that water exchange was taking place on a second time-scale, but they lacked the precision for kinetic analysis. In order to achieve this precision, we have used a method in which spores are trapped at the end of the cantilever by inertial forces, and the fluid within the cantilever is quickly exchanged between the two fluids. Initially, the signal resulting from switching the fluid within the resonator dominates, however after ~100 ms this exchange reaches equilibrium and the signal from exchange of water within the spores can be observed on a millisecond time scale. This represents an improvement of ~2 orders of magnitude over similar measurements made by Raman spectroscopy.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

1) First, to determine if node deviation corresponds to acoustic scattering, we utilized Finite Element Method (FEM) simulations for fluid-structure acoustic interactions. This revealed that the acoustic pressures and velocities vary along the SMR similarly to the vibration amplitude (**Figure 1.c**). Positioning a particle at the node changes the acoustic velocities (**Figure 1.c**, inset). When we calculated the resonant frequency shift by integrating the acoustic energy terms obtained from the simulation, we obtained excellent agreement ($R^2$=0.984) with our measurements (**Figure 1.d**). We confirmed that the particle-fluid density difference has negligible effect on node deviation. To validate that acoustic effects can be measured independently of buoyant mass, we measured a bead in a density-matched fluid ($\rho_{fluid} = \rho_{bead}$). This resulted in zero resonant frequency shift at the antinode ($\Delta f/f|_{antinode} = 0$), but a noticeable resonant frequency shift at the node in both the experiment and simulation, which showed excellent agreement with each other ($R^2$=0.994, **Figure 1.e**). Additional measurements revealed that node deviation is independent of fluid velocity or vibration amplitude. Therefore, by measuring the resonant frequency shift at the node and antinode as cells flow through the SMR, it is possible to simultaneously and independently quantify the acoustic scattering and buoyant mass of the cell (**Figure 1.a, bottom).**

Next, we compared polystyrene particles with different volumes and observed that node deviation changes with particle volume (**Figure 1.f**). The volume dependence can be accounted for by utilizing the buoyant mass measurement. To establish the correlation between node deviation and stiffness, we fabricated hydrogels with varying elastic modulus by changing their chemical composition. Then, we characterized the elastic modulus of the hydrogels using AFM. We observed that the node deviation of the hydrogels increases monotonically with their

elastic modulus over the range 0.1-100kPa (**Figure 1.g**). We also observed that node deviation is not sensitive to particle shape for hydrogels of same elastic modulus and aspect ratios in the range of 1-2.5.

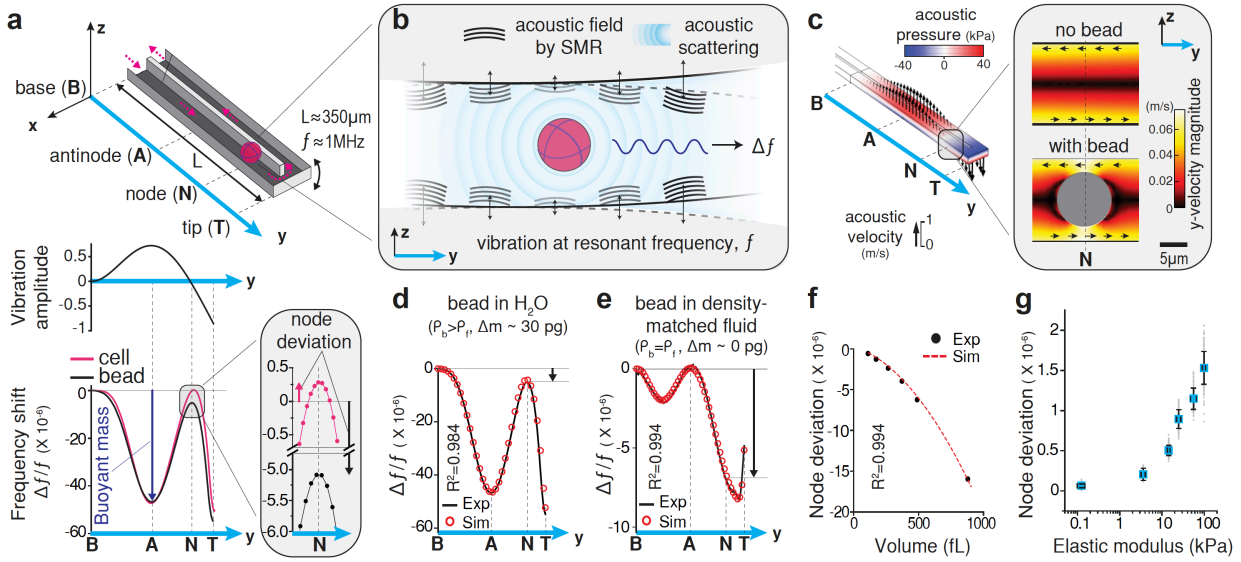



**Figure 1.** *Acoustic scattering causes a resonant frequency shift at the node of a suspended microchannel resonator (SMR)*. (**a**) **Top**, schematic of SMR with a particle flowing through the embedded fluidic channel. Pink arrows mark the particle trajectory. **Middle**, normalized vibration amplitude at the 2nd mode. **Bottom**, resonant frequency shift ($\Delta f/f$) from experiments with a single cell (pink) and a polystyrene bead (black). Vertical dotted lines mark the particle positions along the cantilever, as in top panel. Buoyant mass (size) is measured at the antinode ($\Delta f/f|_{antinode}$, blue arrow). Inset, $\Delta f/f$ at the node where node deviation is measured ($\Delta f/f|_{node,}$black and pink arrows). (**b**) Conceptual illustration of frequency shift due to acoustic scattering. A particle interacts with acoustic fields (black waves) generated by the SMR vibration (black arrows) at resonant frequency $f$. The particle-fluid interaction causes acoustic scattering (blue waves), which shifts the resonant frequency ($\Delta f$). The wavelength ($\lambda$) of the acoustic fields is depicted qualitatively ($\lambda$ ~ 1 mm, which is ~ 100 times the channel height). (**c**) Acoustic pressure (colors) and acoustic velocities (arrows) within SMR from Finite Element Method simulations. Inset, magnitudes of y-acoustic velocities with and without a polystyrene bead at the node. Black arrows show directions of y-acoustic velocities. (**d-e**) $\Delta f/f$ from simulations (red circles) and experiments (black lines) with polystyrene beads flowing through SMR filled with $H_2O$ (**d**) or density-matched fluid ($\rho_{bead} = \rho_{fluid}$) (**e**). Black arrows show node deviation. (**f**) Node deviation vs particle volume from simulations (red dashed line) and experiments (black dots) with polystyrene beads. (**g**) Node deviation vs mean elastic modulus, as measured using AFM indentation (Methods), for synthetic hydrogels of same volume (n=92, 115, 243, 146, 134 and 186 hydrogels for node deviation measurements, n=4 hydrogels for each AFM measurements). Data depicts mean (blue squares) ± s.d. (error bars).

Finally, we asked if mechanical properties of live cells could be probed by measuring node deviation. We implemented the well-established 'Cortical Shell – Liquid Core' model[1] in our FEM simulation (**Figure 2.a**), which highlights the role of actomyosin cortex in cell mechanics[2, 3]. We calculated that the acoustic interactions caused relatively small deformations (<15 nm) on the cell surface, suggesting that node deviation may be primarily governed by actomyosin cortex[4]. We then compared our FEM simulations with the node deviation of mouse lymphoblast (L1210) cells (**Figure 2.b**). FEM simulations yielded similar range signals to the experiments when we used elastic modulus of 4-8 MPa for the cortex (**Figure 2.b**), which is 1-2 orders of magnitude higher than previously reported value using AFM[3, 4]. This is likely due to the high frequency of our mechanical measurement (~1 MHz) compared to conventional frequency range of AFM operation (1-100 Hz) and a power-law relationship between apparent elastic modulus (E) and the frequency ($f$): $E \propto f^{0.2\text{-}0.3}$ [5]. Consistent with our results, a similar value was reported with other high-frequency stiffness measurements of red blood cells[6]. Next, to correct for cell size dependence of the node deviation measurement (**Figure 1.f**), we derived a size-independent acoustic scattering parameter from the iso-elasticity lines obtained from the FEM simulations (**Figure 2.b**). We called this the size-normalized acoustic scattering, SNACS (**Figure 2.b**). The iso-elasticity lines fit well with the measurements from hundreds of live cells. The FEM simulations indicated that SNACS increases with elastic modulus of the cortex ($E_{mod}$, **Figure 2.b**, inset) as well as with cortical thickness ($t_s$), but is insensitive to both intracellular pressure and cortical tension. We also tested three other mechanical models but none of them matched well with our observations.

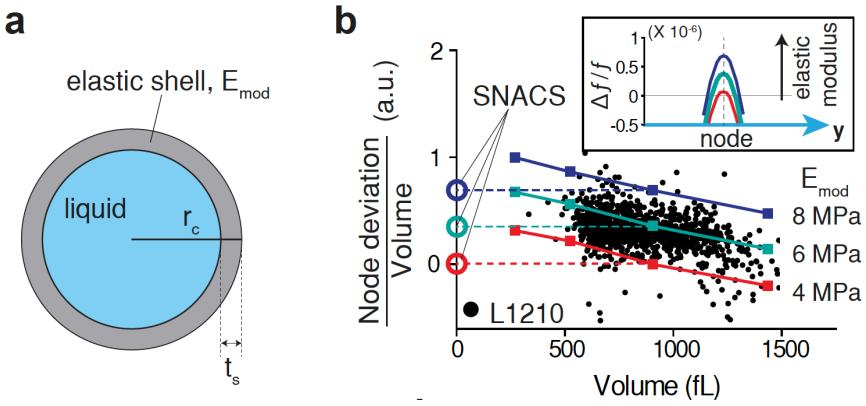



**Figure 2.** *Size-normalized acoustic scattering (SNACS) measures changes in mechanical properties of cells.* (**a**) Schematic of 'Cortical Shell – Liquid Core' model, where $E_{mod}$ is the elastic modulus of a shell. Cortical thickness ($t_s$) was set to 2% of the cell radius ($r_c$)[45]. (**b**) Node deviation (volume-normalized) vs volume V from experiments with L1210 cells (black dots) and simulations using the model for three values of cortical elastic modulus ($E_{mod}$, 4, 6 and 8 MPa, color lines). Vertical offsets of iso-elasticity lines define SNACS (Methods). Inset, $\Delta f/f$ from simulations with different cortical elastic modulus (4, 6 and 8 MPa, V = 900 fL).

2) We have used buoyant mass measurements in suspended microchannel resonators to investigate the extent to which molecules of different sizes can permeate within a spore. Briefly, some of the solvent space within the spore is not accessible to small molecules in solution, and the extent of this space varies with the size of the molecule. This 'molecular sieving' has been observed for spores previously before, however, our recent results suggest that this property may be tied to the low water-permeability of spores – a key factor in their resistance to being killed by heat and small-molecule disinfectants. We have found that the 'steepness' of the small-molecule exclusion profile is correlated with the rate at which water exchanges into the spores for a panel of mutations that make successive losses in the structure of the spores' outer coat. These results suggest that (as opposed to the inner membrane that surrounds the spore core) the outer layers of the spore may be responsible for spores' slow water-exchange.

Finally, we have begun to investigate the process of germination (the process by which an inactive spore transitions to a growing bacterium) based on changes in a spore's buoyant mass. We find that upon initiating germination, a population of spores will decrease in buoyant mass. The extent and kinetics of this change is consistent with the loss of Calcium dipicolinate from the core of the spore. It should be noted that, unlike the molecules studied above, these diffuse from within the inner membrane, as this loss of mass is observed for both wild-type spores, and a coat-deficient mutant (PS4150) that does not possess the molecular sieving observed for intact spores.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

I have had extensive discussions with Dr. Donald Cropek (ERDC-CERL) on using suspended micro- and nanochannel devices to characterize the biophysical and functional properties of multilamellar vesicle nanoreactors (MVNs) that his laboratory is producing. This led to a joint 6.1 proposal that we submitted and was recently selected for funding. The project focuses on the design and behavior of MVNs for controlled release of reactants, and if successful, will increase our understanding of controlling the segregation, initiation, kinetics, and yield of reactions within a confined volume, increasing the potential applications of these reactors. My lab received the first batch of MVNs in mid-January and we will soon acquire acoustic scattering measurements from these particles with the approach described in **Figure 1**.

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

Kang, J.H., Miettinen, T.P., Chen, L., Olcum, S., Katsikis, G., Doyle, P.S., and Manalis, S.R. Noninvasive monitoring of single-cell mechanics by acoustic scattering. *Nature Methods*, February 2019. 10.1038/s41592-019-0326-x.

Cermak, N., Becker, J.W., Knudsen, S.M., Chisholm, S.W., Manalis, S.M. and Polz, M.F. Direct single-cell biomass estimates for marine bacteria via Archimedes' principle. *International Society for Microbial Ecology Journal,* December 2016. 10.1038/ismej.2016.161.

Cermak, N., Olcum, S., Delgado, F.F., Wasserman, S.C., Payer, K.R., Murakami, M., Knudsen, S.M., Kimmerling, R.J., Stevens, M.M., Kikuchi, Y., Sandikci, A., Ogawa, M., Agache, V., Baléras, F., Weinstock, DM. and Manalis, S.R. v. High-throughput single-cell growth measurements using serial microfluidic mass sensor arrays. *Nature Biotechnology*, September 2016. 10.1038/nbt.3666.

Knudsen, S.M., Cermak, N., Feijó, F. D., Setlow, B., Setlow, P. and Manalis, S. R. Water and small-molecule permeation of dormant Bacillus subtilis spores. *Journal of Bacteriology*, October 2015. 10.1128/JB.00435-15.

Olcum, S., Cermak, N., Wasserman S. C., and Manalis, S. R. High-speed multiple-mode mass-sensing resolves dynamic nanoscale mass distributions. *Nature Communications*, May 2015. 10.1038/ncomms8070.

Olcum, S., Cermak, N., Wasserman, S. C., Christine, K. S., Atsumi, H., Payer, K. R., Shen, W., Lee, J. Belcher, A. M., Bhatia, S. N. and Manalis, S. R. Weighing nanoparticles in solution at the attogram scale. *Proc. Natl. Acad. Sci. U.S.A.*, January 2014. 10.1073/pnas.1318602111.

# Army's Institute for Collaborative Biotechnologies

## Final Report for ICB UARC Task Order 36

### ARO Contract W911NF-09-D-0001

### December 1, 2013 – November 30, 2018

**Action Selection Under Time-Pressure**
*Scott T. Grafton (UCSB)* ..... CNS-2

**Neural Indicators of Optimal and Adaptable Decision-Makers**
*Michael B. Miller (UCSB)* ..... CNS-11

**Cognitive Neuroscience Embedded in Large-Scale Models of Systems Dynamics**
*Jean M. Carlson (UCSB)* ..... CNS-18

**Identifying the Neural Biomarkers of Adaptive Cognition Under Fatigue and Stress**
*Barry Giesbrecht (UCSB)* ..... CNS-23

**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Action Selection Under Time-Pressure**

**Project Leader:** **Scott T. Grafton (UCSB)**

**Collaborators:** **Jean Carlson and Subash Suri (UCSB); Jean Vettel and Steve Thurman (ARL-HRED); Pete Khooshabeh (ICT/ARL-West); Dani Bassett (U Penn); Alan Macy (Biopac Corp.) and Matt Jaswa (DCS Corp.)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

### *1.1 Decision Making and Time Pressure*

During the reporting period we characterized brain networks that are associated with "choking" — the well-known performance failure that occurs under high payoff conditions. Our results suggest that prefrontal/executive control systems are recruited in the face of high payoff to overcome or compensate for potential performance failures. Individual differences suggest the recruitment of prefrontal/executive control systems is in response to potential failures and is not the cause of these failures. This argues against one major explanation for why people choke: Too much top down control. Choking is a critical issue in high stakes high tempo operations. Understanding the basis for this effect is key for developing mitigation strategies.

Using multivoxel pattern analysis of fMRI data we demonstrated that the brain state of choking has distinct neural antecedents relative to 'normal' performance. This suggests that choking under pressure is due to a maladaptive state that is qualitatively distinct from usual performance situations and may require fundamentally novel training strategies to ameliorate.

We also tested if self-knowledge about ability could make performance more susceptible to failures when there are high incentives. Using a sequence-learning task, it was discovered that explicit knowledge of a skill increased vulnerability to choking, whereas implicit retrieval did not. This identifies an important training strategy to mitigate performance failure.

### *1.2 Network Science and Cognition*

We applied mathematical tools from control and dynamical systems engineering to assess if the brain is theoretically "controllable", based on the macroscopic pattern of white matter connections (wiring). There is evidence for three types of controllability structural networks, each tied to a known functional network. These results provide a model for predicting the effects of brain stimulation, injury and training on different types of controlled behavior.

### *1.3 Peripheral Measures of Autonomic Reactivity*

We developed an MRI-compatible, carbon fiber electrode measurement protocol for acquiring impedance cardiography. We developed software for automated estimation of ejection fraction and cardiac output. From this vascular resistance is estimated. This is now a product from Biopac Corp.

We demonstrated that trial-by-trial changes in cardiovascular state (manipulated by pre-trial instructions) are correlated with subsequent abilities to apply peak muscular force and to control a pattern of forces. There are remarkable individual differences. This supports our model that state estimation based on sympathetic activity is a predictor for short-term performance capabilities.

For the first time, we demonstrated it is possible to discriminate a challenge response (vasodilation) from a threat response (vasoconstriction) on a trial-by-trial basis, and in an MRI environment.

### *1.4 Structural and Functional Connectomics*

In collaboration with investigators at ARL-HRED we created a platform-independent, stable of tools for visualizing brain connectivity data. It is linked to a large brain connectivity database and provides a new and important method for determining similarities and differences of brain connectivity across individuals.

We created a 375-million streamline database in standard atlas space to evaluate individual differences of white matter connectivity. This resource is available to ARL-HRED collaborators.

We developed a method for calculating Reeb graphs for simplifying structural connectivity data to compare individual differences in brain structure.

A probabilistic atlas of fiber crossings was developed to improve the estimation of "white matter integrity" in individual subjects based on diffusion scans.

We introduced streamline spatial normalization tools that are superior to all other available methods.

An analytic method for estimating the probability of brain connectivity was derived and show to be superior to current available probabilistic tools.

A variety of structural and functional methods were developed with collaborators and used to predict individual differences of learning and performance.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

*Objective 1. Central and Peripheral Physiologic Contributions to Robust Performance and Decision Making. This* work focuses on acquisition and analysis of physiologic measurements of the brain and peripheral autonomic nervous system in combination with tasks requiring accurate physical performance or precise decision making under challenging conditions. There are four focus points to be addressed:

- Identification of cortical areas that influence peripheral autonomic responses.
- Determine if inhibition of cortical areas with sympathetic projections influences the risk of performance failure (choking) in high precision motor tasks.
- Determine if inhibition of cortical areas with sympathetic projections influences decision making in conditions with conflicting risk and reward payoffs.
- Demonstrate feasibility of pattern classification of EEG and or fMRI data for detecting levels of uncertainty in simple laboratory paradigms requiring action decisions and control
- Develop improved technologies that characterize stress response based on peripheral physiologic measurements

*Objective 2. The Development and Application of Methods to Characterize Individual Differences of Brain Structure and Function that Predict Learning and Performance.* There are three parts to this objective:

- Develop quantitative methods that distinguish differences of brain structure and function.
- Employ methods of network analysis to predict individual differences of learning and performance
- Employ methods of network analysis to study controllability of the brain

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

*Objective 1. Central and Peripheral Physiologic Contributions to Robust Performance and Decision Making.* We have been able to identify some of the behavioral features that lead to performance failures under high pressure or incentives. In particular, awareness and self-appraisal of ability are strong manipulations of subsequent behavior. To do this, we tested human performance in tasks involving motor control, guided attention and simple motor planning tasks. In parallel, we have been able to show that there are remarkable individual differences in the autonomic response and this variability in the autonomic response may operate independently of incentives or appraisal. The continuing work sought to understand this interaction between self-appraisal, incentives/high stakes and peripheral

physiology in greater detail. In parallel, we continued to develop methods that measure and model state variables such as sleep and stress that can influence performance.

*Objective 2. The Development and Application of Methods to Characterize Individual Differences of Brain Structure and Function that Predict Learning and Performance.*

To develop quantitative methods that distinguish differences of brain structure and function we used several strategies. First, we improved on methods to spatially normalize diffusion information. Second, we looked at alternative metrics for quantifying local diffusion that could be used to describe how similar or different people are. We tested alternative methods for describing the strength of a structural connection based on diffusion scans. Critically, we tested the sensitivity of various approaches for describing connectivity matrices for the whole brain. For functional imaging, we developed methods for describing relationships between Finally, we tested a variety of methods that describe the relationship between brain structure and functional connectivity.

To employ methods of network analysis to predict individual differences of learning and performance we capitalized on a unique data set collected by the PI. It consisted of serial fMRI and structural brain scans collected in a cohort of 24 subjects who learned to perform difficult finger movement sequences on a keyboard over 6 weeks of training. The challenge problem for our network science collaborators was to develop robust methods that could predict individual differences in the rate at which people learn these motor skills.

To study brain controllability, we provided large datasets of brain structural and functional data to colleagues with expertise in control systems and engineering. From these data, a variety of methods integrating network and control theory were developed.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1 Neural Correlates of Decision Making and Performance*

Based on earlier work that used fMRI to map brain regions associated with choking under pressure, we developed a hypothesis that choking is a phenomenon that interacts with self-appraisal. Simply put, a person who is unaware of their performance capacity is unlikely to choke. We tested this using a well validated motor skill task in which subjects learn to execute sequences of movements. By manipulating learning conditions, the learning was either implicit or explicit. Using incentives to increase the chances of failure, we found that only those who were aware of the sequences they had learned choked. Implicit learning led to more stable, resilient learning and lower risk of choking [1]. In related work, we continued to study the neural substrates of motor planning to further identify the interactions between choking related brain networks and performance networks using EEG [2]. We also completed a series of studies that examined state variables that can influence performance. In one, we mapped neural systems associated with cognitive control of attention to different sensory modalities. Remarkably, we could readily distinguish sensory mode of attention from this fMRI and simultaneous EEG data [3]. In another, we collaborated with PIs at ARL-HRED to examine the reliability of measures of sleep quality as a prelude to mapping the relationship between sleep and performance in real world settings [4]. An additional aspect of this work was the characterization of autonomic drive as an additional metric of performer "state". As part of our effort to improve on methods to quantify changes of autonomic sympathetic drive on a moment to moment basis, we developed a novel analysis method to expedite processing of data from impedance cardiography using a moving ensemble averaging method [5]. This software is now being used at NSRDEC, ARL-West and also distributed to ARL-HRED.

### *4.2. Charactering Individual Differences of Brain Structure and Function*

During this final review period, we worked extensively both in-house and with collaborators at a number of institutions including ARL-HRED to improve on existing methods for modeling brain structural and functional data. For structural data, we evaluated classic diffusion measures such as "fractional anisotropy" and demonstrated that in the white matter there is local high variability between subjects that is determined by the number of crossing fibers at a given location [6]. We provided to Army collaborators and distributed on-line a probabilistic dataset that characterizes the likelihood of crossings for future data analysis efforts. This greatly improves the precision of analyses involving "white matter integrity" based on metrics such as fractional anisotropy and should enhance efforts to correlate individual differences of performance with white matter connectivity. We also completed a

comprehensive evaluation of the impact of different parameters that are typically used to generate structural connectomes on widely adopted network science metrics such as associativity and density [7].

This work provides clear guidelines on how to generate robust estimates of network metrics from streamline-based measures of connectivity. In parallel, we published a paper that provides a method and software for spatially normalizing streamlines, the most popular method for representing brain connectivity and demonstrated superiority over all other disseminated methodologies [8]. As an alternative to streamlines, which have significant problems for quantitative analysis, we developed a breakthrough analytic method for estimating the probability of connections between brain areas. This method is 16,000 faster and more accurate than probabilistic simulations and provides a practical means for mapping brain connections [9]. Software is freely available for implementing this method. We are now using it to develop disconnection graphs in patients with brain lesions. The method also allowed us to introduce new methods for assessing diffusion metrics at the voxel level [10].

In related work, we developed a method that compares local diffusion directions between subjects to generate a similarity index. As shown in **Figure 1**, the principle orientation directions at each voxel are calculated and differences between these directions in each pair of subjects are calculated. With this, we could identify where in the white matter the patterns of connectivity (**Figure 2**) are more or less similar for identical and dizygotic twins, siblings and unrelated subjects (**Figure 3**) [11]. This is a powerful new tool that could be used to correlate individual differences of performance with local white matter directional properties. In addition to advancing methods for assessing structural connections, we developed a series of related techniques for examining the network properties of functional brain networks using spectral analyses of time series on networks [12], from graph signal processing techniques [13, 14] and the clustering of brain network time series on Riemannian manifolds [15]. With these and simpler methods, we are now investigating the communities of brain networks using both brain structure and functional time series [16] and evaluating how state variables including gender and age shape these networks [17].

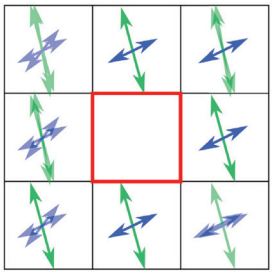


**Figure 1.** Voxel-wise measures of diffusion direction. The principle orientation for two subjects are overlain for each voxel adjacent to the center (red voxel). Differences of direction are tabulated and stored in the center voxel.

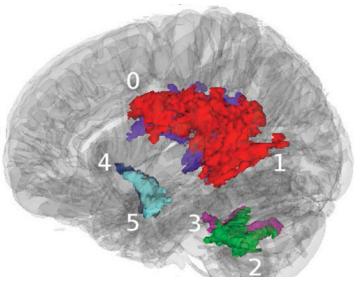



**Figure 2.** Voxels with directional structure that is more similar as a function of genetic relatedness.

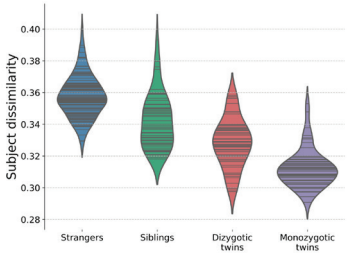



**Figure 3.** Composite index of similarity across all voxels, demonstrating overall differences of white matter directional structure as a function of genetic relatedness.

With an increasingly sophisticated set of tools employing the methods of network science that were developed by collaborators at ARL-HRED and elsewhere, we have been able to hone in on structural and functional network properties of the brain that predict how quickly different people learn a physical skill. For structural connectomes, we have not been able to demonstrate any change over time in the strength of brain connections as subjects train, contrary to previous studies using less reliable imaging techniques. Instead, what we discovered was a very simple pattern of differences in connectivity between subjects that predicted how fast they learn. Some were "wired" to learn faster than others. The areas that were most predictive link visual and motor planning areas. This is compatible with what is learned: a motor skill that is first instructed by vision and then because autonomous. This is the first study to predict individual differences of learning prior to training [18]. We also been able to use resting state functional data, acquired before subjects had ever been exposed to the learning task to predict differences in the rates of learning across subjects [19]. In addition, patterns of brain activity while they train can also be used to predict subject's rate of learning [20]. The dynamics of how these networks change over the course of training has also been an area of major interest. We see that flexibility in network reconfiguration plays an important role in how quickly people learn [21-24].

A fundamental challenge in engineering and dynamical systems modeling is to be able to determine if a particular system is controllable based on its structural organization or functional dynamics. During this review period, we used methods of control theory and applied them to brain structural and functional data to study controllability of the brain. Specifically, we asked if white matter structure constrains how the brain transitions from one cognitive state to another by drawing on recent advances in network control theory [25]. We found that attention and executive control systems are poised to affect a broad array of state transitions that cannot easily be classified by traditional engineering-based notions of control. This theoretical versatility comes with a vulnerability to injury. In patients with mild traumatic brain injury, we observed a loss of specificity in putative control processes, suggesting greater susceptibility to neurophysiological noise. What is particularly intriguing about this work is that it is possible to characterize the ability of the brain to make state transitions based solely on the underlying structural connectivity. We also examined other approaches for characterizing network controllability. For example, we tested a maximum entropy model of brain dynamics informed by white matter tractography (**Figure 4**). We demonstrated that the most probable brain states display common activation profiles across brain areas: local spatially-contiguous sets of brain regions reminiscent of cognitive systems are co-activated frequently [26]. The predicted activation rate of these systems was highly correlated with the observed activation rate measured in a separate resting state fMRI data set, validating the utility of the maximum entropy model in describing neurophysiological dynamics. We also used these approaches to study the system wide impact of regional stimulation by employing a data-driven computational model of nonlinear brain dynamics [27]. Validating predictions from network control theory, we identified relationships between regional controllability and the focal versus global impact of brain stimulation and linked these findings to differences in the underlying network architecture. This work forms an important step towards the development of personalized stimulation protocols for medical treatment or performance enhancement.

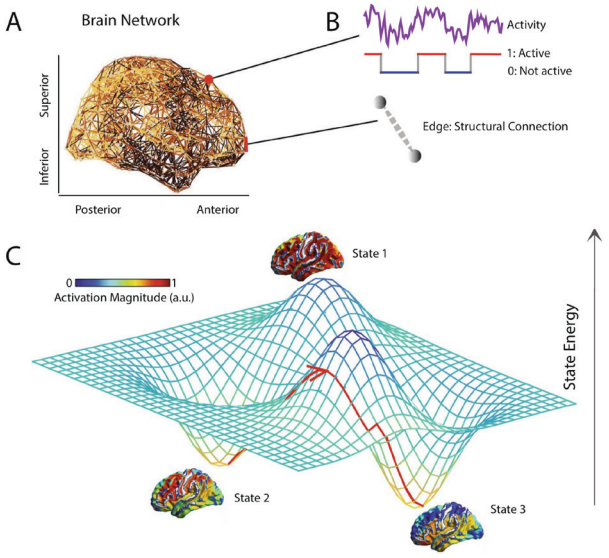



**Figure 4.** (**A**) A weighted structural brain network represents the number of white matter streamlines connecting brain regions. (**B**) We study a simplified model in which each brain region has a binary response; active or inactive. (**C**) A schematic of the energy landscape for the general case of continuously-valued brain states. We simplify this by using a maximum entropy model to infer the landscape of predicted (binary) activity patterns.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

Throughout this review period, we collaborated closely with investigators at ARL-HRED. The primary point of contact was Jean M. Vettel, who shares co-authorship with us on multiple peer-reviewed papers.

We continue to work closely with Ashley Oiknine and Peter Khooshabeh at ARL-WEST. They routinely use the "MEAP" physiological analysis software that we developed and they continue to perform experiments at UCSB.

We distributed three software tools during this review period to Army collaborators:

- D2I streamline/connectivity visualization software
- MITTENS, a software tool for analytic tractography
- MEAP, a software tool for impedance cardiography

We created, collated and distributed four datasets during this review period to Army collaborators:

- Probabilistic atlas of crossing fibers
- Full streamline connectivity atlas using 479 subject HCP dataset
- Longitudinal learning study with fMRI and structural MRI scans
- CRASH dataset

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* Coauthors failed to list ARO contract despite PI's request.

**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Neural Indicators of Optimal and Adaptable Decision-Makers**

**Project Leader:** **Michael B. Miller (UCSB)**

**Collaborators:** **Scott T. Grafton, Barry Giesbrecht and Miguel Eckstein (UCSB); Justin Kantner (Cal. State Northridge) and Jean M. Vettel (ARL-HRED)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

The 2009 report of the National Research Council Committee on Opportunities in Neuroscience for Future Army Applications explicitly states that "current and emerging insights from neuroscience, together with neural monitoring tools such as neuroimaging, can help the Army to optimize the decision making of its soldiers and officers in both these senses: first, by identifying and providing countermeasures to suboptimal decision making and, second, by identifying and making optimal use of individual variability in decision-making traits." Decisions to act on the battlefield, whether it's taking a particular route or identifying a potential enemy combatant, have to be made based on available evidence. When the strength of the evidence is uncertain or ambiguous, optimal decisions require setting a criterion for taking action that can adapt to a complex and changing environment, e.g., being careful not to harm civilians when battling enemy targets. Our lab leads the field in understanding the nature of individual differences in criterion shifting (the ability to make strategic adjustments to the threshold of evidence needed to act in order to optimize the possible outcomes, i.e., to be lenient or strict with the evidence) and the neural networks that support it. The most significant and impactful results from the last five years include the following.

*Criterion shifting is a stable and uniquely individualized cognitive trait and may be used to identify and assess good decision-makers*. We are the first lab to discover and report that while some individuals shift quite well, other individuals do not shift at all [1]. For instance, an individual who is too reliant on minimal evidence may fail to strategically adjust that criterion under stricter settings where false positives can be much more damaging than a miss. In the last five years, we discovered that this individualistic tendency is remarkably stable over time [2], and it generalizes across stimuli, tasks, situations, and decision domains [1,3-5]. This includes work done in collaboration with Dr. Jean Vettel at ARL-HRED.

*A network of brain regions in the prefrontal and parietal cortex is actively engaged when individuals act to carefully avoid false positives, which could provide a basis for neural intervention and monitoring*. We were the first to report this neural effect using fMRI [6], and we have recently replicated it [7], including a study in collaboration with Dr. Miguel Eckstein's lab showing that this pattern of neural activity generalizes across decision domains [8]. During this time period, we have also collaborated with Dr. Jean Vettel at ARL to find an analogous EEG signal that could possibly be used to monitor effective criterion placement in a real-world environment. Additionally, the functional and anatomical data collected from these fMRI studies have been used in collaboration with Dr. Scott Grafton and Dr. Jean Carlson's labs at UCSB, and Dr. Danielle Bassett's lab at the University of Pennsylvania to explore network connectivity, including a highly impactful report on the wiring pattern of white matter tracts within the brain that provides critical insight into the controllability of structural brain networks [9].

*Modeling current flow through individualized brain volumes can enhance the effectiveness of neurostimulation, a promising new technique to enhance good decision making*. Using our neuroimaging findings from the past five years, we have attempted to identify neural targets that may enhance decision making under transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). While this has been particularly challenging [10], we have recently developed a technique that combines precise neuroanatomical mapping using fMRI, simulating current flows from all possible electrode placements on the scalp, and individualizing that current flow to unique individual brains to effectively influence reasoning [11].

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

The broad objective of this research program is to understand sources of individual variability in brain activity as measured by fMRI and EEG to better assess the unique characteristics of individual minds that cannot be obtained using standard behavioral measures or self-report alone. The specific aspects of the mind that we are interested in are the psychological components of optimal and adaptable decision-making: namely, the placement and shifting of a decision criterion. During this time period, our research focused on these four questions.

1. Do individual tendencies in criterion shifting represent stable cognitive traits?
2. Does the neural activity associated with actions taken while avoiding false positives generalize across decision domains, e.g., memory and perceptual decision domains?
3. Are there analogous EEG oscillations to BOLD activity that can track with decision criteria in real time?
4. Can targeted and individualized neurostimulation be used to optimize individual criterion placement?

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

Establishing an appropriate criterion, or standard, for making a judgment or decision occurs many times throughout a day, from mundane judgments (e.g., "Have I read that report before?") to life-changing decisions (e.g., "Is that an enemy combatant that I am aiming at?"). And, the more uncertain the decision evidence is, the more critical the criterion placement. Yet, despite its ubiquitous and significant nature, little is known about the psychological and neural mechanisms that underlie the strategic placement and adjustment of a decision criterion. Our lab leads the field in studies about the nature of decision criteria at the individual level. For example, take the scenario described below:

*Army Scenario*: A soldier is tasked with screening all people that leave a village filled with known enemy combatants. He has memorized detailed photographs of the enemy combatants and his orders are to detain any person fitting those characteristics for further questioning. Unfortunately, discriminating true enemy combatants from innocent individuals is difficult at best. The soldier is instructed to use a liberal approach to his decisions, i.e., to pull aside any person that may seem familiar to the photographs he studied, even if it means inconveniencing and angering several non-combatants. The imperative is to avoid *missing* any enemy combatants at all costs. Fortunately, being liberal in his decisions comes naturally for this soldier. However, new intelligence arrives indicating that the enemy combatants have been spotted within the center of the village. The soldier is now ordered to enter the center of the village and hunt down and kill any of these enemy combatants. His ability to discriminate enemy combatants from innocent civilians has not changed, but now the soldier is instructed to be very conservative in his decisions, i.e., to only fire his weapon if he is absolutely *sure* the target is an enemy combatant. The imperative in this case is to avoid falsely identifying a civilian as an enemy combatant. Unfortunately, this soldier does not adapt his decision criteria to conservative situations very well and he is at risk of making a tragic error.

The scenario above requires the decider to adjust a criterion in order to optimize decisions (to maximize hits and correct rejections), even though the strength of the evidence itself (i.e., the ability to discriminate targets from nontargets) has not changed from one situation to the next. Under these circumstances, an appropriate criterion can greatly improve performance and ultimately save lives. However, we have discovered in our studies that, while some individuals can adapt their criterion effectively depending on the situation, others appear unable to adapt at all [1-5]. Further, based on our recent neuroimaging studies [6-8], we have discovered a large network of brain regions throughout the prefrontal and dorsal parietal cortex that become quite active when individuals are being cautious (using a conservative criterion) to respond "old" (previously studied) to a familiar target, but quite inactive when individuals are being lax (using a liberal criterion) to respond "old" to that same familiar target. It is as if the brain puts a foot on the brakes when trying to be cautious about a decision and takes the foot off the brakes when trying to be lax about a decision. Critically, however, the engagement/disengagement of these brain regions only occurs for those individuals who can effectively adapt their decision criterion from one situation to the next.

During this reporting period, we seek to understand the stability of these individual tendencies to shift or not shift over time, which may be used to assess individuals prior to putting them in situations that may lead to critical errors; to understand if the robust patterns of neural activity that track with criteria generalizes across decision domains, and if there are analogous EEG oscillations to the BOLD activity which could be used to monitor appropriate decision criteria in real time; and to determine if individualized and targeted neurostimulation may enable a direct neural intervention in order to optimize criteria placement and reduce critical errors.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1. Criterion Shifting: A Stable and Uniquely Individualized Cognitive Trait*

*Rationale.* Our research consistently shows tremendous *between*-subject variability in the degree to which people will shift a decision criterion when it is advantageous to do so [1]. However, investigating the *within*-subject variability of criterion shifting is important for understanding criterion shift strategies at an individual level. Our studies reveal that criterion shifting generalizes across stimuli [1], tasks [4], situations [3], and decision domains [5]. More recently we conducted test-retest reliability studies of criterion shifting during recognition memory tests to determine the degree to which an individual's criterion shift strategies represent a stable cognitive trait. These studies are the first to systematically assess and characterize the stability of criterion shifting over time. If criterion shifting is a stable cognitive trait, then it should be possible to predict whether certain individuals will adaptively shift decision criteria in real world situations, such as during combat. Thus, the Army could potentially avoid consequential decision errors by assigning personnel roles that are best suited for a particular individual's criterion shift tendencies.

*Methods.* In two separate studies, adult participants ($N$ = 39 for both) recruited at UCSB successfully completed 10 recognition memory task sessions on separate days across six weeks. During each session, participants completed three cycles of studying 100 face images followed by a 200-image recognition test block. Each test block contained two test conditions (conservative and liberal), where instructions explicitly informed participants of an advantage for establishing either a conservative or liberal criterion, respectively. In Study 1, participants earned money for correct responses, but lost money for false alarms (conservative) or misses (liberal). In Study 2, studied images appeared 25% (conservative) or 75% (liberal) of the time during the test blocks. At the end of each session participants received feedback based on the total amount of money earned (Study 1) or percentage of correct trials obtained (Study 2) over the entire session.

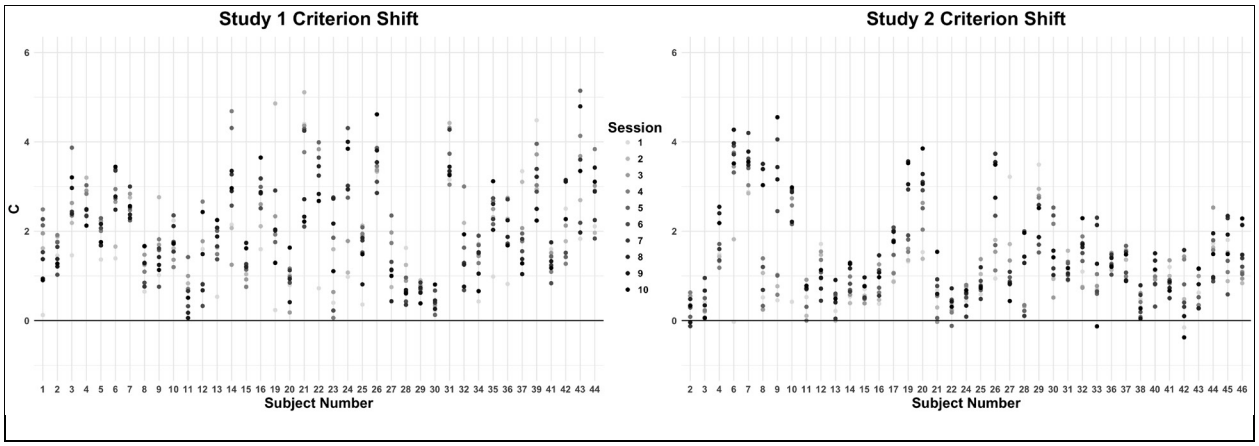



**Figure 1**. Criterion shift ($C$) values for each subject across the 10 sessions in Study 1 (**left**) and Study 2 (**right**).

*Results.* The mean session-to-session correlation coefficients of criterion shifting in Study 1, $M(r_{[37]}) = .76$, $p < .001$, and Study 2, $M(r_{[37]}) = .83$, $p < .001$, are remarkably high and comparable to other cognitive abilities believed to represent stable cognitive traits, such as visual working memory capacity ($M_{(r)} = .76$, $SD = .05$) [12]. The highly consistent stability in criterion shift tendencies relative to the vast individual differences across participants suggests that criterion shifting is a stable and uniquely individualistic cognitive trait. Some individuals consistently failed to adequately shift decision criteria despite conducting the task 10 times, whereas others consistently shifted criteria quite well (**Figure 1**). These results suggest that a person's tendency to shift decision criteria can be characterized and provides promise for developing an assessment tool for real world situations.

### *4.2. Neural Activity Associated with Avoiding False Positives Across Memory and Perceptual Decision Domains*

*Rationale.* A growing body of behavioral evidence suggests that criterion placement and shifting is a stable individual characteristic [1-5; §4.1]. We have further shown that brain activity associated with successful memory decisions is almost entirely driven by the conservativeness of one's decision criterion—that is, how careful he or she is about avoiding false positive memory decisions [6,7]. However, in order to further elucidate whether these

decisional processes are indeed inherent cognitive traits, it is critical to determine whether a common neural substrate persists across different decisional domains. We therefore conducted a study in collaboration with Dr. Eckstein to directly assess this hypothesis, testing both the generalizability of decisional behaviors and their neural representations.

*Methods.* Twenty-nine healthy young adults completed both memorial and perceptual decision tasks while undergoing fMRI scanning. In the memory task, participants studied a series of visual scenes and were later asked to make standard 'old' (previously-studied) or 'new' (unstudied) recognition judgments; in the perception task, participants viewed similar visual scenes and were asked to determine whether a person was 'present' or 'absent'. We additionally manipulated the decision evidence associated with each stimulus as 'low' or 'moderate'. For memory stimuli, a stimulus was presented either once or several times during encoding; perception stimuli were previously classified by a team of raters based on the difficulty of detecting a target. Finally, we manipulated criterion placement using a similar monetary reward/punishment scheme as described in §4.1 (Study 1). Functional MRI data were analyzed using both standard GLM-based techniques and a multivariate machine learning technique: sparse Bayesian multi-task multi-kernel learning (SBMTMKL). The latter allowed us to directly test whether we could make cross-task predictions of decisional processes based on shared neural representations.

*Results*. Consistent with our predictions, there was considerable cross-task stability in criterion placement and shifting behavior: individuals maintained a similar degree of decisional flexibility (or lack thereof) regardless of whether decision evidence was low ($r(28) = 0.86$, $p < .001$) or moderate ($r(28) = 0.83$, $p < .001$). Importantly, this was independent of actual discrimination performance: decision accuracy was only maintained across tasks when evidence was moderate and participants attempted to avoid false positives ($r(28) = 0.55$, $p = .002$). Mass-univariate analyses of successful decision-related activity further replicated our previous results in [6,7]: we observed robust patterns of frontoparietal activity *only* when participants engaged a conservative decision criterion (although cross-task similarity was strongest when decision evidence was moderate). Finally, we used SBMTMKL to determine whether successful decision-related activity allowed us to discriminate between evidence strength and criterion placement across tasks. As hypothesized, we could not discriminate between the strength of decision evidence (consistent with our behavioral results). However, we made significant cross-task predictions of liberal and conservative criterion placement, with models trained on perception data slightly outperforming models trained on memory data (balanced accuracy, $BAC = 77.59\%$, $p = .018$ vs. $BAC = 67.24\%$, $p = .033$). Together, these findings provide strong evidence that criterion placement and flexibility are stable cognitive traits with generalizable neural representations, independent of decisional accuracy.

### *4.3. Search for Analogous EEG Oscillations to BOLD Activity that Tracks with Decision Criterion by Simultaneous fMRI/EEG Recordings*

*Rationale.* Our previous fMRI research [6-8] revealed widespread frontoparietal BOLD activity that tracks with the degree to which an individual establishes a conservative decision criterion during recognition memory. Identifying an equivalent EEG biomarker may potentially lead to real-time monitoring of decision criteria via a mobile EEG tracking device to ensure a person has established an appropriately conservative criterion for a given situation. We originally collected data for a simultaneous fMRI/EEG study, but due to technical difficulties associated with collecting data, we (along with our collaborator Dr. Vettel) decided to conduct a separate EEG study without simultaneous fMRI. This EEG study follows a similar security patrol paradigm [3] as the original study and will still allow us to identify EEG signatures associated with the conservativeness of a decision criterion.

*Methods.* Participants complete two cycles of a study phase followed by a test phase during EEG recordings. The study session of each cycle involves viewing 140 face images once (low discriminability) or six times (moderate discriminability). Prior to the test blocks, individuals are told they are conducting a security patrol task for suspicious individuals. In the conservative condition, participants must avoid false positive identifications of innocent individuals as suspicious because identified individuals will be "hunted down and potentially injured." In the liberal condition, participants must not miss identifying suspicious individuals because they are "very dangerous" and identified individuals will simply undergo "further questioning."

*Results.* We have collected data for 25 out of an anticipated 60 individuals. Once the full dataset is collected we plan to thoroughly assess both Event Related Potentials (ERPs) and neural oscillations that are associated with maintaining a conservative vs. liberal criterion at low vs. moderate levels of familiarity. We anticipate completing data collection by the end of summer 2019.

### *4.4. Utilize Neurostimulation to Optimize Adaptable Decision Making*

*Rationale*. While neuroimaging methods have proved invaluable at uncovering the neurobiological substrates of cognitive processes, a critical caveat is that they are *correlational* in nature. In other words, they cannot provide conclusive evidence that brain activity in a given region *causes* a behavior, nor can they show that activity in a region is necessary/sufficient for a cognitive function. Neurostimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) offer the promise of identifying causal links between specific brain areas and behavior by directly manipulating neuronal excitability. Our lab has recently utilized these methods in an effort to modulate decision-making behaviors through focal targeting of several regions in the prefrontal cortex [10,11].

*Methods.* We describe two series of studies using neurostimulation. Study 1 (TMS) employed our standard recognition memory paradigm where criterion placement was manipulated across blocks of low or high target probability. Participants completed several sessions in which continuous theta burst stimulation (cTBS) was used to decrease neuronal excitability in the right inferior frontal gyrus (rIFG), right middle frontal gyrus (rMFG), or right dorsolateral prefrontal cortex (rDLPFC) prior to recognition testing—the spatial targets for stimulation within each region were derived on a subject-specific basis using previously-collected fMRI data [10]. Study 2 (tDCS) employed a novel probabilistic decision-making paradigm. Participants were asked to decide which of two US states were more likely based on a continuous presentation of demographic evidence. This allowed us to assess how evidence accumulation affected decision uncertainty. We induced left and right hemisphere bias by decreasing excitability in the contralateral IFG, hypothesizing that LH-bias would result in more certain decisions with a lower evidence threshold. A novel high-definition targeting technique provided subject-specific stimulation sites and estimates of actual current flow based on skull and brain morphology [11].

*Results*. In Study 1, cTBS proved ineffective at modulating criterion placement. However, we observed an unanticipated improvement in memory accuracy following cTBS to the rDLPFC. This finding warrants further exploration as we have not previously observed associations between successful decision-related activity in the rDLPFC and discrimination performance in fMRI studies. In Study 2, contrary to expectation, both LH- and RH-bias via tDCS resulted in more evidence accumulation (relative to a sham 'control' stimulation)—importantly, however, this was modulated by the actual current density at the stimulation site, such that 'stronger' stimulation predicted more evidence accumulation. Despite both bias conditions inducing more evidence accumulation overall, we also found a lower decisional threshold during RH-bias (consistent with our predictions). This, too, was further modulated by regional current density. A number of recent studies have identified factors that may drive the efficacy of neurostimulation techniques: to our knowledge, this is the first report demonstrating that current density—based on subject-specific brain morphology—predicts the extent of behavioral modification [11].

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

We have a strong track record of active and productive collaborations with Dr. Jean Vettel and her colleagues at ARL-HRED. Dr. Vettel has been critical to the projects involving combat scenarios [3], as well as the analysis of the data produced by the officer study [6]. Dr. Vettel is a co-author on many of our publications, and she continues to be indispensable in the design and analysis of our studies. We will particularly rely on her collaboration with the proposed EEG studies in project 4.3. We have also been in active discussions with ARL-West researchers, including Dr. Antony Passaro and Dr. Pete Khooshabeh, on a collaborative effort to develop our combat scenario paradigm into a virtual reality setting that may mimic real-world battlefield scenarios. In addition, we have communicated with Dr. Tad Brunye and Dr. Marianna Eddy of the Army NSRDEC at Natick to collaborate on neurostimulation projects. Dr. Brunye and Dr. Eddy are working on several tDCS projects that align nicely with our proposed tDCS studies. For example, they are investigating the impact of tDCS on target detection and memory inputs from posterior regions of the brain, including the medial temporal and parietal lobe. This research informs our neural model and complements our proposed effort to manipulate criterion placement by stimulating the prefrontal cortex. Dr. Brunye and Eddy are collaborators with Drs. Grafton, Giesbrecht, and myself on an ICB Congressional add-on, entitled RADARS, that includes a neurostimulation project investigating neural mechanisms of stress recovery.

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**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Cognitive Neuroscience Embedded in Large-Scale Models of Systems Dynamics**

**Project Leader:** **Jean M. Carlson (UCSB)**

**Collaborators:** **Scott Grafton, Michael Miller, Gregory Ashby, Benjamin Turner, Kenneth Kosik, Paul Hansma, Michael Goard, Julie Simpson, Linda Petzold, Wendy Meiring, Fabian Soto, Barry Giesbrecht, Jonathan Smallwood (UCSB); Ann Hermundstad (Janelia); Danielle Bassett (UPenn); Kevin Brown (UConn); Elizabeth Davison (Princeton); John Doyle (Caltech); Jesse A. Brown (UCSF); Sean Stromberg (Intellisis); Vibhas Deshpande (Siemens); Jean Vettel and Kaleb McDowell (ARL); Rueben Kraft (Penn State); C. Cajochen (Basel); Nicholas Wymbs (JHU); Mason A. Porter (UCLA); Ryan Kasper and Mary-Ellen Lynall (Cambridge); David Alderson, Emily Craparo and Thomas Otani (NPS); Kelvin Lim (UMinn) and Peter Mucha (UNC)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

This project advances the theoretical and computation foundations of network neuroscience in the context of Army-relevant applications. Focus areas include quantifying structure-function relationships that enable and constrain cognition, identifying tradeoffs between robustness and fragility in architecture and processing, and multiscale modeling and analysis linking neurons, brains, behavior, and groups. In collaboration with experts in psychology, neuroimaging, and molecular, cellular, and developmental biology, our team develops and applies quantitative methods derived from physics, complex systems, network theory, statistics, machine learning, control, and dynamical systems to obtain rigorous and robust characterization of networked systems across disparate scales.

In this five-year period, we expanded and refined methods to robustly identify brain network organization, quantified the implications at both individual and group levels, determined how these properties support behavior and performance under various cognitive demands, and explored the contribution of variation in individual brain networks and behavior to group-level collective decision making in situations involving risk and threat. We investigated the relationship between brain anatomy, functional correlations, and behavior. We developed robust statistical methods that use community detection and other techniques at varying resolutions to identify cohesive mesoscale structure in human brain organization. We provided a rigorous statistical comparison between empirically measured anatomical brain networks and various synthetic network models, allowing us to systematically probe the importance of physical embedding and temporal growth in brain networks, and to develop novel mathematical null models to identify group differences in network architecture.

We applied hypergraph analysis, a recent advance in dynamic network science developed by our group, to examine co-variation in functional brain dynamics during a variety of cognitive tasks and extends the analysis to quantify individual differences in patterns of dynamic organization. We used a range of dynamic network tools to investigate the variation in human functional brain dynamics as a function of age, discovering important age-related changes in both hypergraph and community structure and quantifying the differential contributions of distinct functional systems and circuits to these changes. We developed new methods for understanding and resolving community structure across spatial and temporal scales in weighted functional brain networks. We identified changes in functional community structure that accompany automatic and rule-based category learning in humans. We applied and extended modeling techniques from machine learning and dynamical systems theory to predict the effects of individual characteristics and strategies on group decision-making dynamics, incorporating data on realistic group behavior from a controlled experiment on decision making in a simulated threat scenario.

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

During this reporting period the project advanced the development and application of quantitative methods for robust characterization of cognitive and communication networks across disparate scales, including neuronal populations, individual brain networks and human groups subjected to stress, perturbations, and cognitive demand. We integrated *in silico* simulations of complex and dynamical systems with principled methods of system identification from data and optimal experimental design (**Figure 1**).

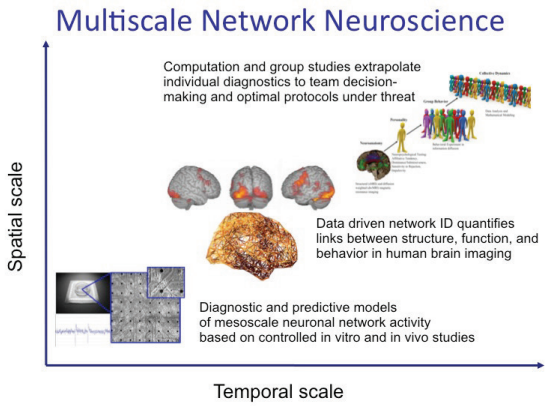



**Figure 1.** The project develops quantitative and predictive network-based methods and bridges scales through case studies involving neural circuits, brain imaging, and collective behavior.

At the smallest scales, we investigate behavior and communication within neuronal populations *in vivo* and *in vitro*. Theory and computational methods developed in the context of model systems inform our analysis of structural and functional brain networks in humans, where data is relatively sparse and/or low-resolution (human neuroimaging), but where parallel questions arise involving network identification, efficiency, robustness, manipulation, and control. Specific projects analyzed neural circuits in animal models to extend statistical tools for quantifying and validating patterns in the brain to other networked neuronal systems (*in vitro* neuron populations) and investigated implications of brain architecture for control and behavioral robustness and fragility. We quantified robust individual differences in large-scale brain networks and their relationship to behavior and aging. We explored consequences of neuroimaging diagnostics and information distribution patterns for individual performance in group decision making and population outcomes under threat.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

### *3.1. Brain Architecture and Functional Networks*

We develop network representations from structural MRI (DTI, DSI) and fMRI resting-state and cognitive task-based measurements. For statistical accuracy and robustness, we focus on data sets with a large number of subjects. These include the ICB Officer Study data, the Age-Memory data, and the Human Connectome Project. Our analysis includes identification of structure-function relationships, task switching between rest, attention, and memory, and correlations with demographic measures. We develop and apply dynamic network methods, including community detection and hypergraphs. This project validates results with rigorous statistics, null models, and ground truth simulations (**Figure 2**).

### *3.2. Decision Making in Threat Scenarios*

We conducted and analyzed a behavioral experiment involving individual and group decision-making in an evacuation scenario with a time-evolving disaster, and limited shelter capacity. Participants decide whether and when to evacuate in a series of 200 consecutive trials. We follow a model-experiment-model paradigm to analyze the data, extract predictive models, and correlate results with social media and other personality and risk profile diagnostics.

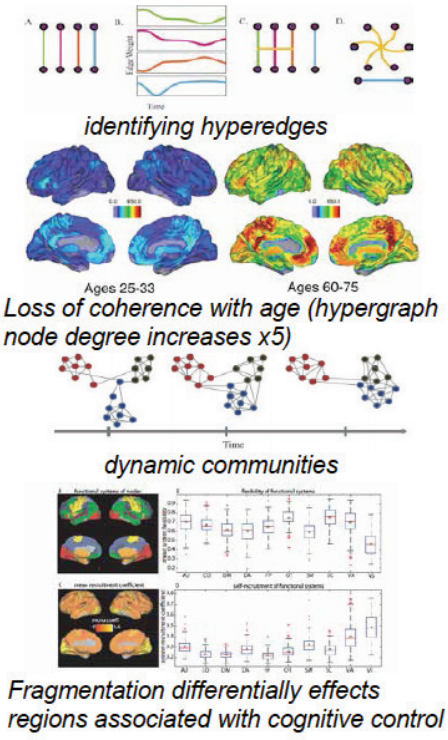



**Figure 2.** Brain Architecture and functional networks.

### *3.3. Mesoscale Dynamics in Neural Circuits*

In this reporting period we focused primarily on developing data driven models of drosophila grooming behavior, as a model system of neural circuits. Mathematical modeling of behavioral sequences yields insight into the rules and mechanisms underlying sequence generation. Grooming in *Drosophila melanogaster* is characterized by repeated execution of distinct, stereotyped actions in variable order. Experiments demonstrate that, following stimulation by an irritant, grooming progresses from an early phase dominated by anterior cleaning to a later phase with increased walking and posterior cleaning. We work with high resolution data from grooming experiments analyzed with machine learning to extract behavioral ethograms. We develop a series of data-driven Markov models that isolate and identify the factors governing grooming action selection and temporal dynamics.

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1. Brain Architecture and Functional Networks*

This project identified structure/function network relationships in neuroimaging data and used flexibility to quantify and predict age related differences among healthy subjects. Parallel studies of dynamic networks in ICB officer and age-memory data utilized dynamic community detection (a node-based diagnostic) and hypergraphs (an edge-based diagnostic) to quantify functional network organization and processing. We observed loss of coherence across the brain in older individuals (hyperedge node degree 5X larger for older subjects). We found that functional coherence of anatomical brain regions associated with cognitive control and bottom-up attention declines with age, as measured by higher flexibility, and more fragmented communities.

### *4.2. Decision Making in Threat Scenarios*

Empirical data from the evacuation behavioral experiments led to the development of a rate-based decision model that we investigated in the context of stochastic simulation. The model predicts collective behavior. We find that the model developed from individual experiments fails to predict behavior of individuals in a group context. Trial-to-trial fluctuations exceed Bayesian prediction. Instead, individual consistently over or under react based on recent experience. We used deep neural networks to predict precise evacuation times and used individual social media profiles to predict individual differences in the behavioral experiment (**Figure 3**).

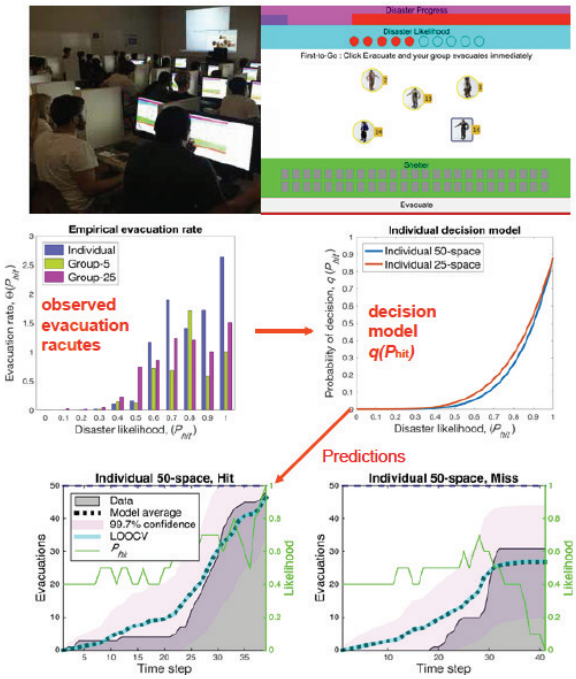



**Figure 3.** Decision making in threat scenarios. ICB behavioral experiment on evacuation decision making (**top**), generates data on risk and social influence on evacuation decision making used to generate models for individual and group behavior (**middle**), that are used to generate predictive models for timing of evacuation decisions.

### *4.3. Mesoscale Dynamics in Neural Circuits*

Analysis of temporally rich behavioral sequences provides a quantitative description of the rules underlying their generation. *Drosophila melanogaster* grooming behavior consists of many complex sequences involving repetitions of well-characterized actions. We leverage advances in machine vision to automatically annotate over 40 hours of video data of flies covered in dust and develop Markov models that reveal the existence of syntax in *D. melanogaster* grooming. We find that sequence organization depends on both grooming action identity and duration. Our results demonstrate that, although sensory input informs grooming decisions, internal dynamics may also guide individual transitions between grooming actions. By incorporating action durations into our models, we uncover multi-scale temporal dynamics that suggest the existence of neural circuits dedicated to sensory-independent decision-making. Our approach highlights the importance of incorporating

temporal information into behavioral models, as doing so illustrates the relative contributions of sensory input and internal dynamic to grooming sequence generation. This discovery suggests the existence of neural circuitry and activity that guides action selection through internally-generated dynamics. Additionally, the discovery of these principles governing grooming in *D. melanogaster* demonstrates the utility of incorporating temporal information when characterizing the syntax of complex behavioral sequences (**Figure 4**).

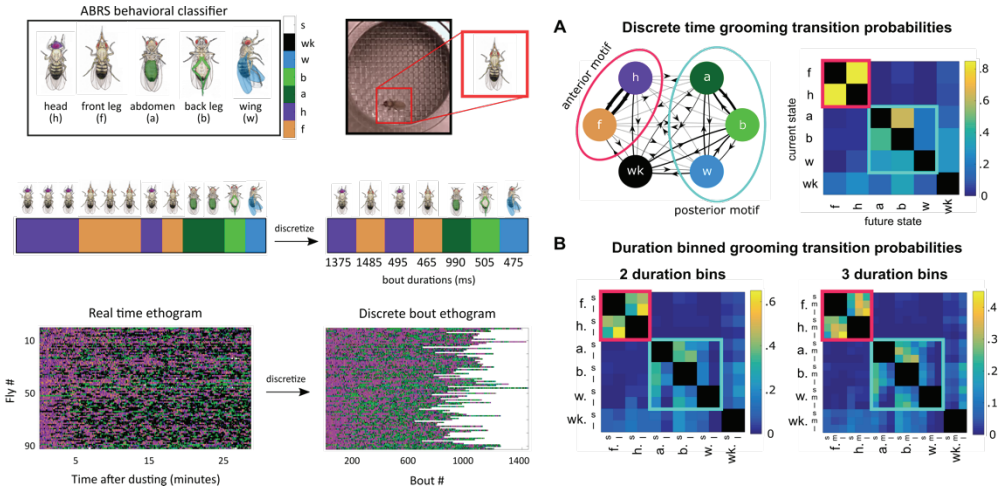



**Figure 4**. Mesoscale dynamics in neural circuits: (I) Large Scale ethogram data sets for *drosophila melanogaster* grooming behaviors, (II) Markov model extracts order and duration dependence in behavioral sequence generations.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

1. BioProtonics industry collaboration, aimed at designing and implementing real-time protocols for high resolution, localized MRI sampling, applicable to diagnostics of a wide variety of conditions, including bone loss, tumors, and neurodegenerative disorders (Kristin James and Timothy James).
2. Work on decision making in threat scenarios combining broadcast and social network information in collaboration with David Alderson, Thomas Otani, Emily Craparo and others at Naval Postgraduate School. Plans are in place to extend the experimental platform to study collective decision making in a cohort of military officers at NPS.
3. "Measuring and modeling collective decision making in group evacuations," ICB/ERDC Workshop on Sensory Feedbacks and Distributed Communication in Natural and Artificial Systems, April 28-29, 2016 (review article w/Dr. Bertrand Lemasson, US Army Environmental Laboratory at ERDC, and others to follow).
4. "Real time classification and and experimental design for *in vitro* neuronal networks", Collaboration with DARPA Exploratory Instrumentation Project: Neural Circuit Probe (Ken Kosik, Linda Petzold, Paul Hansma).
5. Dr. Theresa Straut, Human Protection Administrator, ARL Human Research and Engineering Directorate. April 12, 2016.
6. Dr. Bob Kokoska, former ICB Program Manager, and Dr. Fred Gregory, ARO Program Manager for Neurophysiology of Cognition. May 11, 2016.
7. BG (ret) Palmer and LTC Southern: ICB UARC Officer Study: Report on Results of Study I and Brainstorm Ideas for Study II. June 28, 2016.

## 6. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

A. L. Gould, V. Zhang, L. Lamberti, E. W. Jones, B. Obadia, N. Korasidis, A. Gavryushkin, J. M. Carlson, N. Beerenwinkel and W. B. Ludington. Microbiome interactions shape host fitness. *Proceedings of the National Academy of Sciences*, December 2018. 10.1073/pnas.1809349115.

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K. J. Schlesinger, B. O. Turner, S. T. Grafton, M. B. Miller and J. M. Carlson. Improving resolution of dynamic communities in human brain networks through targeted node removal. *PLOS One*, February 2018. 10.1371/journal.pcbi.1006001.

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C. Nguyen, K. J. Schlesinger and J. M. Carlson. Data-Driven Models for Individual and Group Decision Making. *2017 IEEE/ACM International Conference on Advances in Social Networks Analysis and Mining*, December 2017. 10.1145/3110025.3116204.

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A. M. Hermundstad, K. S. Brown, D. S. Bassett, E. M. Aminoff, A. Frithsen, A. Johnson, C. M. Tipper, M. B. Miller, S. T. Grafton and J. M. Carlson. Structurally-constrained relationships between cognitive states in the human brain. *PLOS Computational Biology*, May 2014. 10.1371/journal.pcbi.1003591.

J. M. Carlson, D. L. Alderson, S. P. Stromberg, D. S. Bassett, E. M. Craparo, F. Guiterrez-Villarreal and T. Otani. Measuring and modeling behavioral decision dynamics in collective evacuation. *PLoS One*, January 2014. 10.1371/journal.pone.0087380.

**ICB PROJECT FINAL REPORT**
**UARC CONTRACT W911NF-09-D-0001**
**December 1, 2013 – November 30, 2018**

**Project Title:** **Identifying the Neural Biomarkers of Adaptive Cognition Under Fatigue and Stress**

**Project Leader:** **Barry Giesbrecht (UCSB)**

## 1. Most Significant Results and Impact over Five-Year Period (12/1/2013 – 11/30/2018)

The overall goal of this research program was to identify neural biomarkers associated with the effects of changing task demands, stress, and mental and physical fatigue on adaptive cognition. *The primary biological inspiration for the proposed work is the Army Soldier, the dynamic tasks they perform, and the conditions under which they are performed*. Soldiers are required to make rapid and complex decisions, often under extreme uncertainty and risk. Compounding the complexity of this problem is that Soldiers must perform these tasks while being exposed to a variety of physical and psychological stressors. The dynamics of the interaction between adaptive cognitive capacity and external stressors are complex and not well understood. We bridged this gap in understanding by using neuroimaging methods to directly identify the neural biomarkers underlying adaptive cognition tasks performed under changing task demands, induced psychological stress, and physical fatigue. We had six significant outcomes:

1. *Development of robust protocols for measuring brain activity during physical exertion.* Our primary measure of brain activity is scalp recorded electroencephalography (EEG), which is easily contaminated by movement and sweating. We developed protocols for measuring brain activity and performance during exercise and related these changes to behavior, neuroendocrine markers of stress, aerobic capacity and brain activity (Bullock et al., 2014; 2015; 2017).
2. *Physical exertion affects multiple stages of human cognition.* Many studies have demonstrated consistent effects on higher order cognitive functioning post-exercise. We discovered that these cognitive functions are also modulated during exercise and we observed enhanced sensory responses, suggesting that exercise influences cortical excitability at the earliest stages of information processing (Bullock et al., 2015).
3. *Physical exertion alters neural coding.* Nonhuman mammalian and invertebrate brains exhibit large increases in the gain of feature-selective neural responses in sensory cortex during locomotion, suggesting that the visual system becomes more sensitive when actively exploring the environment. We applied a novel computational method to human EEG data acquired during a feature selective attention task while participants were engaged in exercise. The peak of the reconstructed feature-selective tuning profiles was highest during low-intensity exercise compared to rest and high-intensity exercise. Our results reveal the nature of exercise-induced gain on feature-selective coding in human sensory cortex and provide valuable evidence linking the neural mechanisms of behavior state across species (Bullock et al., 2017).
4. *Adaptive cognition is altered by reward.* One's previous experience with reward can enhance subsequent performance in future tasks when previously rewarded information is task relevant, even though there is no prospect for reward. Importantly, performance is impaired when the previously rewarded information is task irrelevant. We discovered corresponding rapid changes in brain activity, suggesting that the activity of neurons in visual cortex are altered by previous experience with reward, even when no reward is present (MacLean & Giesbrecht, 2015ab; MacLean et al., 2016).
5. *Working memory is mediated by multiple processes coded in the alpha frequency band of the human electroencephalogram.* Mental representations of behaviorally relevant visual features and locations are based on information sampled from the environment and can persist in visual short-term memory (VSTM) even in the absence of maintained external sensory input. We discovered that these representations are maintained by at least two distinct, both mediated by EEG oscillations in the alpha frequency band (MacLean et al., 2018).

## 2. Project Objectives during Final Reporting Period (3/1/2016 – 11/30/2018)

The dynamics of the interaction between adaptive cognitive capacity, mental fatigue, physical fatigue, and external stressors are complex. The overall purpose of this project is to use advanced human neuroimaging methods to identify the neural biomarkers underlying adaptive cognition tasks performed under changing task demands, induced psychological stress and physical fatigue. During the final reporting period we continued to focus on using multivariate computational techniques applied to scalp-recorded electroencephalography (EEG) data that allow us to estimate feature (e.g., orientation, color, motion) and location selective population-level neural codes. We had three main objectives. 1) To investigate the neural coding of information during bouts of intense physical activity. The *online* effects of physical activity on brain activity and adaptive cognitive capacities is not well understood and this work fills an important, Army-relevant, knowledge gap. 2) To investigate the neural coding of information maintained in working memory. Working memory is an essential cognitive function that allows humans to encode, maintain, and manipulate information that is essential for executing and obtaining current task goals. Measuring the content of working memory using EEG will allow us to investigate the adaptive mechanisms of cognitive control at rest, under physical stress, and mental fatigue. 3) To investigate the effects of multitasking on the location and feature specific neural coding of information. Many daily tasks involve managing priority between one or more subtasks, which places significant demands on attention and executive control mechanisms.

## 3. Scientific Strategies and Approaches during Final Reporting Period (3/1/2016 – 11/30/2018)

There were three key aspects to our empirical strategy during the final reporting period. First, we applied a novel multivariate computational technique that allows us to track the content and quality of the information carried by stimulus evoked and endogenous brain oscillations in various frequency bands. Specifically, this method can be used to estimate feature/location-selective neural response profiles reconstructed from spatially specific patterns of neural activity recorded via non-invasive human neuroimaging techniques. This computational technique, referred to as an *inverted encoding model* (IEM) has been applied to the BOLD signal measured with fMRI to estimate feature and spatially selective neural response profiles in retinotopically organized visual cortex [1-5]. More recently, this method has been used with scalp-recorded EEG to uncover the temporal dynamics of feature selective processing in the human brain [7] and the contents of spatial working memory [6]. An overview of this analytical approach is shown in **Figure 1**.

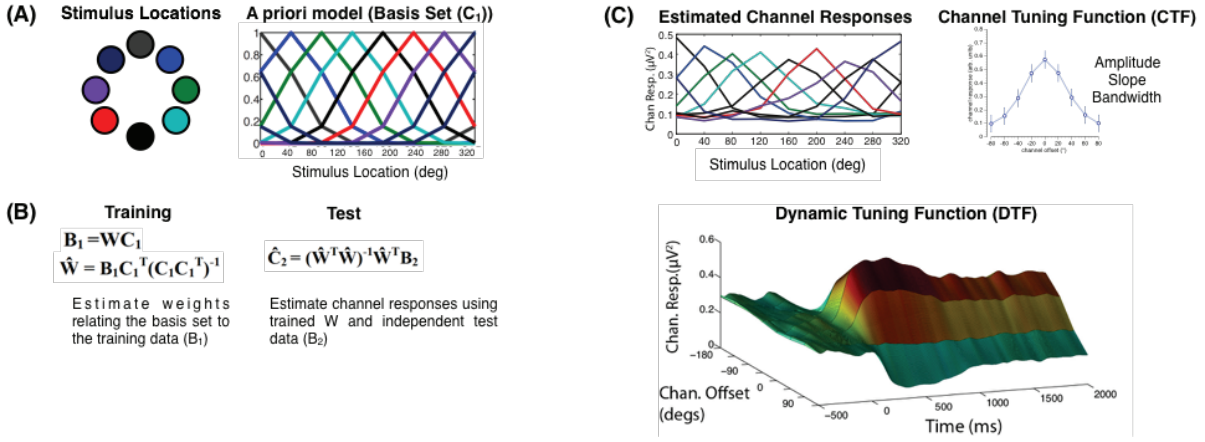



**Figure 1.** Overview of analytical approach. (**A**) The response at each possible stimulus location is modeled with an a priori (basis) function that assumes the peak response at a given location and a monotonically decreasing response as the distance away from a given location increases. The a priori model is approximated based on known physiology of the primate visual system. (**B**) An implementation of the general linear model is uses to estimate the least squares mapping (weights) between a set of training data and the a priori model. The weight matrix is then inverted and multiplied by the independent test data to obtain the channel response for each location. (**C**) The estimated channel response (i.e., from the Test phase in (**B**)) for each stimulus location. Because the stimulus space is circular, the channel responses can be shifted to a common reference point (centered), resulting in a Channel Tuning Function (CTF) that is plotted as a function of channel offset (degrees). CTFs can be characterized in terms of their amplitude (gain), slope and bandwidth (selectivity). CTFs can also be constructed through time using either a Hilbert transform or using wavelets, resulting in a Dynamic Tuning Function (bottom).

Second, we continued to develop protocols for reliably inducing state of arousal and mental fatigue using physical exercise and demanding continuous performance tasks. For example, we have developed protocols in the lab for testing how acute bouts of exercise modulate brain activity and behavior both during and after exercise [8-10]. Participants attend a pre-testing session where their ability to engage in physical activity is assessed (PAR-Q) and they then complete a VO2max test to measure their aerobic capacity. Participants then return and either perform an attention task after a bout/bouts of acute exercise [8] or during bouts of varying intensity exercise [9,10] (**Figure 2**).

## 4. Research Results and Accomplishments during Final Reporting Period (3/1/2016 – 11/30/2018)

### *4.1 Neural Coding of Feature Selective Information during Physical Activity (Bullock et al., 2017, J Cog Neuro)*

An organism's current behavioral state influences ongoing brain activity. Nonhuman mammalian and invertebrate brains exhibit large increases in the gain of feature-selective neural responses in sensory cortex during locomotion, suggesting that the visual system becomes more sensitive when actively exploring the environment. This raises the possibility that human vision is also more sensitive during active movement. To investigate this possibility, we used an inverted encoding model (IEM, **Figure 1**) technique to estimate feature-selective neural response profiles from electro-encephalography (EEG) data acquired from participants performing an orientation discrimination task. Participants ($n$ = 18) fixated at the center of a flickering (15 Hz) circular grating presented at one of nine different orientations and monitored for a brief shift in orientation that occurred on every trial. Participants completed the task while seated on a stationary exercise bike at rest and during low- and high-intensity cycling (**Figure 2**). Using a more traditional machine learning approach, we were able to decode (discriminate) the attended orientation using patterns of brain activity measured at the scalp (**Figure 3.a**). Using the IEM approach, which allows us to assess whether the underlying patterns covary with a set of a priori feature selective response profiles, we found that the peak of the reconstructed feature-selective tuning profiles was highest during low-intensity exercise compared to those estimated during rest and high-intensity exercise. When modeled, these effects were driven by changes in the gain of the tuning curve and in the profile bandwidth during low-intensity exercise relative to rest. Thus, despite profound differences in visual pathways across species, these data show that sensitivity in human visual cortex is also enhanced during locomotive behavior. Our results reveal the nature of exercise-induced gain on feature-selective coding in human sensory cortex and provide valuable evidence linking the neural mechanisms of behavior state across species.

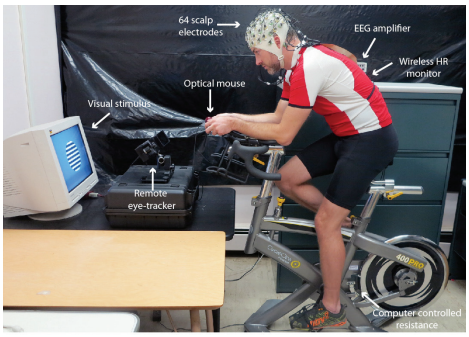



**Figure 2.** Equipment for inducing physical stress. Participants complete cognitive tasks while seated on a stationary exercise at rest and during bouts of cycling. EEG, eye-gaze, EKG and Actigraphy are monitored throughout the task.

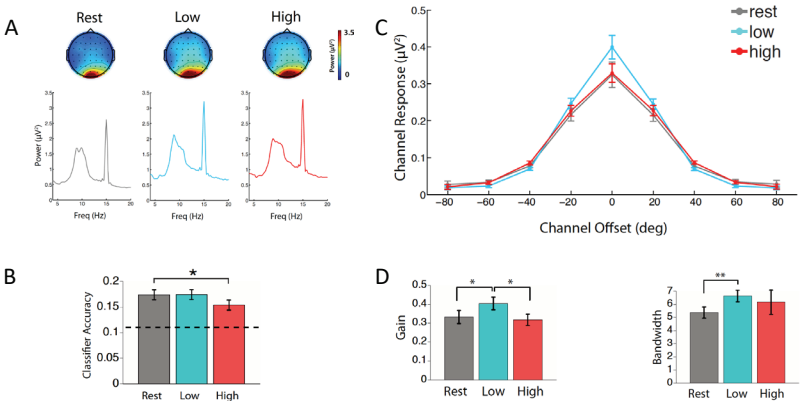



**Figure 3.** Feature selective neural coding during exercise. (**A**) EEG scalp topography of power at the frequency of the stimulus flicker in three different exercise intensity conditions (rest, low, and high). (**B**) Pattern classification analysis showing that stimulus orientation could be decoded from the patterns of EEG activity above chance (1/9) in rest and low intensity exercise conditions. (**C**) Channel tuning functions (CTF) from the IEM approach for rest, low and high intensity exercise conditions. (**D**) Least squares estimates of the gain (peak) and bandwidth (selectivity).

### *4.2 Reconstructing Spatial Visual Memories (MacLean, Bullock, & Giesbrecht, 2018, bioRxiv)*

Mental representations of behaviorally relevant visual features and locations are based on information sampled from the environment and can persist in visual short-term memory (VSTM) even in the absence of maintained external sensory input [6]. Both the selection (i.e., sampling) and retention of mental representations of locations, regardless of the source of information (i.e., external or internal), appear to be supported by processes associated with alpha band oscillations [6, 11-14]. In contrast to this common view, we recently provided evidence that at least two distinct processes associated with alpha-band oscillations support spatially selective representations: (1) a fast and continuous location selection process that is disrupted by a masking stimulus and that degrades without continued external visual input, and (2) a delayed process that emerges when external visual input is no longer available. Participants (n=18) performed a delayed spatial estimation task [e.g., 6], in which a single stimulus was briefly presented in the periphery, in one of eight possible locations on the circumference of an imaginary circle. Participants were instructed to attend covertly to the stimulus location, remember its location, and report the location after a short delay. The presence or absence of a masking checkerboard after the stimulus, and the state of the eyes during retention (open or closed) yielded four within-subject conditions: eyes open, eyes open + mask, eyes closed, eyes closed + mask. Using the IEM approach applied to EEG power in the alpha frequency band, we were able to reconstruct the location held in working memory in all conditions, whether the stimulus was disrupted with eye closure or a mask (**Figure 4**). In order to observe the dynamics of the process, or processes, supporting spatially selective representations in alpha under these different conditions we examined the inter-temporal and inter-conditional generalization of the IEM, in which the models are trained in one condition (and/or time point) and tested in other conditions (and/or time points). This analysis (not shown here due to space constraints) revealed that the patterns of generalization were quite specific. Indeed, there was evidence suggesting that alpha is not a unitary phenomenon, and that there are at least two distinct processes that support the selection and retention of behaviorally relevant locations that operate within the alpha frequency band: one that is fast and continuous, supporting selection of information from the sensory environment and that is disrupted by masking and no sustained visual input; and a second that is delayed relative to the first, emerging upon the cessation of sustained visual input.

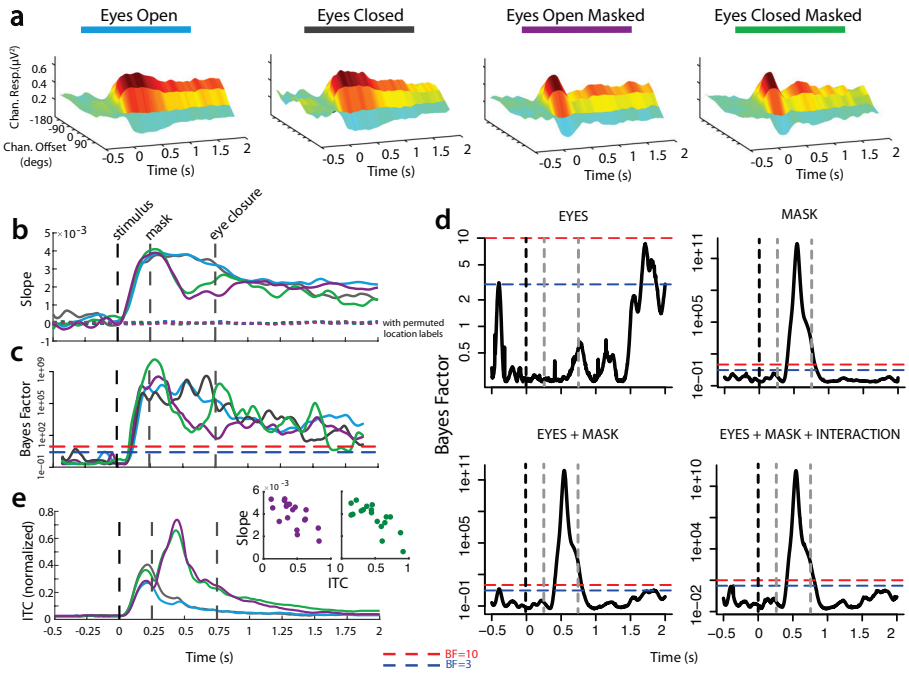



**Figure 4.** Results of the alpha-based inverted encoding model estimation of the stimulus location. **(a)** Estimated neural population response, or "channel" (offset of channel's preferred location from stimulus location: ±0,45,90,135, or 180˚), response (alpha-band power) starting 500 ms before onset of stimulus until end of retention period. **(b)** Linear regression weights of estimated channel response folded around 0˚ offset ("slope"), indicating the degree of spatial selectivity. **(c)** Bayes Factor (BF) of t-test comparing slope at each time point to slope of response estimated using permuted location labels. **(d)** BF of ANOVA for effects of eye closure and mask on slope. **(e)** Inter-trial coherence (ITC) indicating stimulus- and mask-evoked potentials and scatterplots of correlation between ITC and slope during the period of the mask-evoked potentials for masked conditions.

### *4.3 Reconstructing Spatial and Feature Selective Codes During Conditions of Mental Fatigue (Bullock et al., in progress)*

Adaptive, goal-directed behavior requires a cognitive system that supports sustained attention during prolonged tasks. Failures of sustained attention in these tasks can occur and can have very serious consequences in the real world. These failures are likely accompanied by fluctuations in patterns of underlying neural activity, but at present we lack a comprehensive understanding of these effects. Building on our previous work on continuous performance tasks [15], during the final performance period we investigated the neural mechanisms underpinning these cognitive failures during mental fatigue we recorded electroencephalography (EEG) while participants (n=18) engaged in variants of a demanding continuous target detection task, that, when executed for a long period of time, induces a state of mental fatigue. Using the IEM approach to estimate both feature and location selective processes during this task. While still ongoing, the current results indicate that feature selective responses were degraded significantly during periods when performance as lowest and mental fatigue was highest. Interestingly, location selective responses remained robust throughout the task, suggesting that even though human performance may be degraded, EEG may be used to extract information about behaviorally relevant information in the environment.

### *4.4 Additional Research Activities of Interest (Pun et al., 2018, Frontiers in Physiology)*

During the final reporting period, we were provided the opportunity to work with a set of deidentified behavioral data from workers at the Atacama High Altitude Observatory (Chile, 5050 m). As a part of their normal work schedule, these workers are exposed to repeated, acute conditions of high altitude, yet have to maintain high levels of cognitive function. Given that Army Soldiers are often deployed in similar extreme environments and maintain high levels of performance, working with this data set was an exceptional opportunity. The behavioral data we worked with was from a study of altitude naïve individuals (n=21), the purpose of which was to investigate the effects of acute, subacute and repeated exposure to 5,050 m on cognition among altitude-naïve participants compared to control subjects tested at low altitude. The central finding was that selective and sustained attention were impaired at altitude, but improved acclimatization. The gains in cognition with acclimatization during a first exposure were not carried over to repeated exposures.

## 5. Transitions to the Army and Industry during Final Reporting Period (3/1/2016 – 11/30/2018)

We have continued to engage with Army collaborators during the final reporting period. The majority of these efforts have included researchers at NSRDEC and the Tufts Center for Applied Brain and Cognitive Sciences (Marianna Eddy, Tad Brunyé, Erika Hussey). In the last reporting period the ICB team has made multiple visits to NSRDEC and Tufts for collaboration meetings. The main target of these collaborations is to develop a standardized set of exercise protocols that will allow us to reliably induce specific physiological states (e.g., fatigue) and investigate the effects of those states on a common set of cognitive tasks. This will be a large-scale project that we are titling: Brain, Exercise, and Standardized Testing or BEAST. BEAST is a synergistic project, capitalizing on the 6.1 work of our ICB team and the leveraging the expertise of our NSRDEC collaborators in fatigue science and large-scale field work (i.e., the MASTRE project conducted at Ft. Bragg). Additional transitional efforts include collaboration meetings with collaborators at ARL-HRED, including Jean Vettel, Stephen Thurman, Jon Touryan, and Anthony Ries.

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## 7. Comprehensive List of Publications over Five-Year Period (12/1/2013 – 11/30/2018)

M. Pun, V. Guadagni, K. M. Bettauer, L. L. Drogos, J. Aitken, S. E. Hartmann, M. Furian, L. Muralt, M. Lichtblau, P. R. Bader, J. M. Rawling, A. B. Protzner, S. Ulrich, K. E. Block, B. Giesbrecht and M. Poulin. Effects on cognitive functioning of acute, subacute, and repeated exposures to high altitude. *Frontiers in Physiology,* August 2018. 10.3389/fphys.2018.01131.

M. H. MacLean, T. Bullock and B. Giesbrecht. Dual process coding of recalled location in human oscillatory brain activity. *bioRxiv*, July 2018. 10.1101/361774.

T. Bullock, J. C. Elliott, J. T. Serences and B. Giesbrecht. Acute exercise modulates feature-selective responses in human cortex. *Journal of Cognitive Neuroscience*, April 2017. 10.1162/jocn_a_01082.

M. H. MacLean, G. K. Diaz and B. Giesbrecht. Irrelevant learned reward associations disrupt voluntary spatial attention. *Attention, Perception and Psychophysics*, October 2016. 10.3758/s13414-016-1103-x.

J. C. Elliott, B. Baird and B. Giesbrecht. Consciousness isn't all-or-none: Evidence for partial awareness during the attentional blink. *Consciousness and Cognition*, February 2016. 10.1016/j.concog.2015.12.00.

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M. H. MacLean and B. Giesbrecht. Neural evidence reveals the rapid effects of reward history on selective attention. *Brain Research*, May 2015. 10.1016/j.brainres.2015.02.016.

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