# REPORT DOCUMENTATION PAGE

Form Approved OMB NO. 0704-0188

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| 1. REPORT DATE (DD-MM-YYYY) | 2. REPORT TYPE | 3. DATES COVERED (From - To) |
|---|---|---|
| 08-08-2016 | Final Report | 16-Sep-2013 - 15-Sep-2015 |

4. TITLE AND SUBTITLE
Final Report: Multiscale physics and the dynamics of muscle

5a. CONTRACT NUMBER
W911NF-13-1-0435

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER
611102

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

6. AUTHORS
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS (ES)
U.S. Army Research Office
P.O. Box 12211
Research Triangle Park, NC 27709-2211

10. SPONSOR/MONITOR'S ACRONYM(S)
ARO

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
64593-EG.4

12. DISTRIBUTION AVAILIBILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
The views, opinions and/or findings contained in this report are those of the author(s) and should not contrued as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT
Force generation by muscle is brought about by the complex interaction among millions of motor proteins (myosin cross-bridges), interacting in a highly structured compliant lattice of protein filaments (think and thin filaments). In every sense, muscle contractility is a problem of multi-scale physics: it spans scales from the dynamics that occur at few nanometers to those that characterize entire muscles and moving creatures. In addition, fluid dynamic, chemical, elastic and inertial processes all potentially contribute to the emergent dynamics of the interaction of myriad molecular motors that generate force and consume energy as humans and other animals manipulate objects

15. SUBJECT TERMS
muscle contraction, multiscale physics, x-ray diffraction

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 15. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | Thomas Daniel |
| UU | UU | UU | UU | | 19b. TELEPHONE NUMBER |
| | | | | | 206-543-1659 |

## Report Title

Final Report: Multiscale physics and the dynamics of muscle

## ABSTRACT

Force generation by muscle is brought about by the complex interaction among millions of motor proteins (myosin cross-bridges), interacting in a highly structured compliant lattice of protein filaments (think and thin filaments). In every sense, muscle contractility is a problem of multi-scale physics: it spans scales from the dynamics that occur at few nanometers to those that characterize entire muscles and moving creatures. In addition, fluid dynamic, chemical, elastic and inertial processes all potentially contribute to the emergent dynamics of the interaction of myriad molecular motors that generate force and consume energy as humans and other animals manipulate objects and move in their environment. We propose to experimentally test whether there are conditions under which key assumptions underlying models of force generation are violated. Using quick-release experiments on isolated muscle fibers in conjunction with high-speed laser and X-ray diffraction we will ask whether strain non-uniformities exist and whether elastic and viscous processes influence the basic mechanochemistry of force generation by molecular motor in muscle. We are focusing on a preliminary experiment that leverages recent advances in high-speed detectors and a unique muscle preparation.

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## Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

### (a) Papers published in peer-reviewed journals (N/A for none)

| Received | | Paper |
|---|---|---|
| 08/08/2016 | 2.00 | Simon Sponberg, Thomas L. Daniel, Adrienne L. Fairhall, Olaf Sporns. Dual Dimensionality Reduction Reveals Independent Encoding of Motor Features in a Muscle Synergy for Insect Flight Control, PLoS Computational Biology, (4 2015): . doi: 10.1371/journal.pcbi.1004168 |

**TOTAL:** 1

**Number of Papers published in peer-reviewed journals:**

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### (b) Papers published in non-peer-reviewed journals (N/A for none)

| Received | Paper |
|---|---|

**TOTAL:**

**Number of Papers published in non peer-reviewed journals:**

## (c) Presentations

>Molecular determinants of force generation in muscle: new directions for motor molecules. Keynote Speaker for the Graduate Symposium. Molecular Biology and Biochemistry Department, Simon Fraser University. 2015
>Molecular determinants of force generation in muscle: new directions for motor molecules. Department of Mechanical Engineering, Johns Hopkins University. 2015
>Multiscale dynamics and the mathematics of muscle. The Institute of Advanced Studies, Hong Kong University of Science and Technology. September 2015
>Molecular determinants of force generation in muscle. The Szent-Györgi Lecture at the Marine Biological Labs, Woods Hole July 2015

**Number of Presentations:** 4.00

## Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

| Received | | Paper |
|---|---|---|
| 08/08/2016 | 3.00 | . Automated analysis of muscle X-ray imaging with Monte-Carlo Markov-Chains., The First International Workshop on Data Management and Analytics for Medicine and Health Care, DMAH 2015. 04-SEP-15, Kohala Coast, Hawaii. : , |

**TOTAL:** **1**

**Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):**

## Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

**TOTAL:**

**Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):**

## (d) Manuscripts

Received Paper

**TOTAL:**

**Number of Manuscripts:**

## Books

| Received | Book |
|---|---|

**TOTAL:**

| Received | Book Chapter |
|---|---|

**TOTAL:**

## Patents Submitted

## Patents Awarded

## Awards

2014 Guggenheim Fellow (T Daniel)
2015 WRF Innovation Postdoctoral Fellow in Data Science (D. Williams Postdoc)
2016 NSF Career Award, Simon Sponberg (now Asst. Prof. Georgia Tech).

## Graduate Students

| NAME | PERCENT_SUPPORTED |
|---|---|
| **FTE Equivalent:** | |
| **Total Number:** | |

## Names of Post Doctorates

| NAME | PERCENT_SUPPORTED |
|---|---|
| Simon Sponberg | 0.50 |
| **FTE Equivalent:** | **0.50** |
| **Total Number:** | **1** |

## Names of Faculty Supported

| NAME | PERCENT_SUPPORTED | National Academy Member |
|---|---|---|
| Tom Daniel | 0.00 | |
| **FTE Equivalent:** | **0.00** | |
| **Total Number:** | **1** | |

## Names of Under Graduate students supported

| NAME | PERCENT_SUPPORTED |
|---|---|
| **FTE Equivalent:** | |
| **Total Number:** | |

## Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period: ...... 0.00

The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:...... 0.00

The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:...... 0.00

Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):...... 0.00

Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:...... 0.00

The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense ...... 0.00

The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:...... 0.00

## Names of Personnel receiving masters degrees

| NAME |
|---|
| **Total Number:** |

## Names of personnel receiving PHDs

| NAME |
|---|
| **Total Number:** |

## Names of other research staff

| NAME | PERCENT_SUPPORTED |
|---|---|
| **FTE Equivalent:** | |
| **Total Number:** | |

## Sub Contractors (DD882)

## Inventions (DD882)

## Scientific Progress

Preamble:

Force generation by muscle is brought about by the complex interaction among millions of motor proteins (myosin cross-bridges), interacting in a highly structured compliant lattice of protein filaments (think and thin filaments). In every sense, muscle contractility is a problem of multi-scale physics: it spans scales from the dynamics that occur at few nanometers to those that characterize entire muscles and moving creatures. In addition, fluid dynamic, chemical, elastic and inertial processes all potentially contribute to the emergent dynamics of the interaction of myriad molecular motors that generate force and consume energy as humans and other animals manipulate objects and move in their environment.

Unlike few other biological systems, muscle is formed as a highly structured system, with a nearly crystalline organization. Single cells (myofibers) are portioned into subcellular elements (myofibrils) that are formed of interdigitating systems of axial filaments – the thick and thin filaments. Thin filaments contain a double helical strand of actin monomers along with troponin/tropomyosin complexes that are involved in the regulation of contraction (see Figure 1 below). The molecular motor myosin constitutes the bulk of the thick filaments and has a portion (the cross-bridge) that extends radially in the form of a three-start helix.

The current paradigm for muscle contraction follows from the sliding filament hypothesis laid out in the 1950s by Huxley and co-workers (e.g. Huxley and Niedergerke, 1954; Huxley and Hanson, 1954). Following these key papers is more than fifty years of research that has culminated in a generally accepted view of muscle contraction (for a reviews see: Gordon et al., 2000; Spudich, 2001). Briefly, the notion held by the field today is that cross-bridges use chemical energy derived from ATP hydrolysis to drive an axial sliding motion between the thick filaments and thin filaments. Activation is controlled by intracellular Calcium concentrations that, at low levels prohibit interaction between cross-bridges and thin filaments. However, upon stimulation, Calcium released from intracellular storage sites (the sarcoplasmic reticulum) binds to troponin molecules situated along the thin filament. Troponin bound to Calcium and complexed with tropomyosin undergoes a conformational change that exposes binding sites to cross-bridges. On binding cross-bridges release mechanical strain energy derived from ATP hydrolysis and generate force.

Progress:

The project initiated a much larger missions in which we developed experimental and theoretical approaches to approaches to understanding the dynamics of muscle contraction. Muscle is active, regulated soft matter with material properties that arise from collective behaviors of motor molecules. Many historical assumptions (filaments only slide and do not move in radial directions, no elastic coupling, no viscous interactions and no inertial effects) had limited what we can conclude about this novel material. While we could not examine the consequences of all of those assumptions above, recent technological advances uniquely positioned us to address a significant number of these in an experimental paradigm that is only now coming on line.

Our 12month exploratory project to addressed a simple question: what are temporal and spatial dynamics of muscle contraction at the scale of nanometers and micrometers? An answer to this question will poise us to probe the collective behavior of millions of coupled motor molecules and to reveal emergent dynamics from this complex system. We had two specific short term objectives that are focused on developing the pilot experiments that will allow us to see when, if at all, the assumptions outlined above fail.

Objective 1: Establish a quick release paradigm. We will modify existing equipment in the Daniel lab to perform rapid release experiments on intact muscle fibers. The apparatus will be built to permit the goals of Objective 2 below and follows from our recent work

Objective 2: Measure spatial and temporal patterns of intracellular dynamics using real time fiber length control with simultaneous X-ray diffraction, laser diffraction and force measurements.

These two objectives will allowed us to determine that (a) rapid length perturbations are manifest as dynamic changes in radial and axial strains (e.g. Moeendarbary et al., 2013) and (b) the isovolumetric constraint associated with intact cell preparations, the lattice of protein filaments undergo significant radial changes as cells shorten (or lengthen). These objectives addressed key issues raised in the assumptions listed above. We developed preparations that permits precise timing control of activation with simultaneous measurements at many spatial scales using X-ray diffractometry (nm scale), laser diffractrometry (μm scale) and force and length measurements (cm scale). We combined all three technologies using insect muscle preparations at the Advanced Photon Source at the Argonne National Laboratories using recently developed methods.

As you will note, this seed grant, by partially supporting postdocs, gave rise to a paper and a conference proceeding. More importantly, it gave rise to a number of new efforts that are now underway with a mini-MURI sponsored by the ARO.

## Technology Transfer

As a result of the research initiated by this grant, we have had significant interaction with a national lab (The Argonne National Lab) as well as with idea exchange with Geoff Sipher at at the Army Research Labs in Aberdeen Proving Grounds

Preamble:

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