REPORT DOCUMENTATION PAGE

Form Approved OMB NO. 0704-0188

1. REPORT DATE (DD-MM-YYYY)	2. REPORT TYPE	3. DATES COVERED (From - To)
20-07-2018	Final Report	1-Aug-2014 - 31-Jul-2017

4. TITLE AND SUBTITLE	
Final Report: Multiscale Modeling/Inverse Problems: Forward and Inverse Methods for Stochastic Models of Diffusing Particles in Complex Biofluids	5a. CONTRACT NUMBER W911NF-14-1-0475
	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER 611102
6. AUTHORS	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAMES AND ADDRESSES	8. PERFORMING ORGANIZATION REPORT NUMBER
Pennsylvania State University Office of Sponsored Programs 110 Technology Center Building University Park, PA 16802 -7000	

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS (ES)	10. SPONSOR/MONITOR'S ACRONYM(S) ARO
U.S. Army Research Office P.O. Box 12211 Research Triangle Park, NC 27709-2211	11. SPONSOR/MONITOR'S REPORT NUMBER(S) 65335-MA.9

12. DISTRIBUTION AVAILIBILITY STATEMENT

Approved for public release; distribution is 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

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			John Fricks
UU	UU	UU	UU		19b. TELEPHONE NUMBER 480-965-3951

Standard Form 298 (Rev 8/98)
Prescribed by ANSI Std. Z39.18

RPPR Final Report
as of 01-Aug-2018

Agency Code:

Proposal Number: 65335MA **Agreement Number: W911NF-14-1-0475**

INVESTIGATOR(S):

Name: John Fricks
Email: jfricks@asu.edu
Phone Number: 4809653951
Principal: Y

Organization: **Pennsylvania State University**
Address: Office of Sponsored Programs, University Park, PA 168027000
Country: USA

DUNS Number: 003403953 EIN: 246000376
Report Date: 31-Mar-2016 Date Received: 20-Jul-2018
Final Report for Period Beginning 01-Aug-2014 and Ending 31-Jul-2017
Title: Multiscale Modeling/Inverse Problems: Forward and Inverse Methods for Stochastic Models of Diffusing Particles in Complex Biofluids
Begin Performance Period: 01-Aug-2014 **End Performance Period:** 31-Jul-2017
Report Term: 0-Other
Submitted By: John Fricks Email: jfricks@asu.edu
Phone: (480) 965-3951
Distribution Statement: 1-Approved for public release; distribution is unlimited.

STEM Degrees: 3 **STEM Participants:** 5

Major Goals: The objective of this grant has been to improve the scientific community's understanding of of experiments tracking individual particles in biofluids. The experiments consist of tracking and recording tracer particles propelled by the thermal motion of molecules in complex biofluids such as cytoplasm or lung mucus. The investigation is inherently nanometric in scale and thus rather delicate, and the recorded data displays manifold evidence of anomalous (non-Brownian) particle dynamics. Nevertheless, most analyses to date have relied on variations of the traditional method of moments (based on the sample mean, sample variance, etc.), and have often lacked any support from sound statistical methodology such as asymptotic theory. The work funded by this grant has built more robust methodology through maximum likelihood and spectral (wavelet) estimation, and has contributed to a new perception of the relation between stochastic and mechanistic models. By linking the data to particular models, the investigators have been developing statistical tests for which biological mechanisms are linked to particular aspects of the stochastic dynamics of tracer particles.

Our approach to the challenge of modeling anomalous diffusion has been both multifaceted and grounded in modern statistical techniques. On one side, Fricks and his student have focused on particle filters and maximum likelihood to put forward new statistical methodology that is both computationally fast and stable, a key issue when handling large bead path data sets provided by the David B. Hill Lab (UNC-Chapel Hill). On the more theoretical side, the other senior researcher, Didier, his students and collaborators in the USA and France have tackled both probabilistic and inferential aspects of the analysis of uni- and multidimensional scaling laws encountered in anomalous diffusion. This includes parametric identifiability issues in fractional models, asymptotic theory for standard statistical techniques in the biophysical literature, and new multivariate wavelet-based inferential methodology and its associated asymptotics. To summarize, our approach builds upon probabilistic modeling and robust inferential methodology in a field dominated by researchers from physics, engineering, and applied mathematics. This brings in not only new tools but also an entirely novel perspective on the problems under scrutiny.

There are a number of scientific barriers to modeling single-particle trajectories. In general, characterizing anomalous diffusion time series is difficult because of the wealth of potential models such as the continuous time random walk or fractional Brownian motion. Nevertheless, the underpinning of these models in the physics of fluids is unclear. In addition, there are a variety of practical issues that arise in the analysis of the experimental outputs. When tracking a particle at an accuracy of tens of nanometers, there are vibrations and shifts in the microscope that come through in the observations and induce somewhat unpredictable effects on the stochastic models, especially the estimated variance/covariance of the process. Fiducial markers and averaging over many particles have been used to reduce the effects of these influences, but the results have been mixed. One avenue of our research has been to create automated detection of anomalies most likely induced by these microscope movements, but this is an ongoing challenge that has not received sufficient attention in the literature.

Inferring the stochastic dynamics of small tracer particles in complex fluids allows us to explore a variety of biological systems and answer a number of fundamental biophysical questions. This includes the issue of how quickly viruses disperse through lung mucus, one factor in the time to infection. This is of key importance in the presence of lung disorders such as cystic fibrosis, which alters the viscoelastic properties of lung mucus. In a different direction, a better characterization of the stochastic dynamics of particles in cytoplasm will contribute to a more complete understanding of motor-driven transport, where the cargo is quite large and the stochastic dynamics could play a profound role. In addition to biological significance, this research is pressing ahead new stochastic models and statistical inference techniques that will certainly be applicable to other domain disciplines involving fractal systems, such as neurology and Internet traffic analysis.

Accomplishments: We have made significant progress on this project, with one accepted and four submitted journal articles, as well as several more nearing submission. Fricks and his student J. Bernstein have developed statistical estimators using particle filters and maximum likelihood methodology to infer whether a particle is bound to a surface and associated parameters (diffusion parameters, binding/unbinding rates, etc.). The method is computationally both fast and stable; these are key issues when fitting data from multiple bead paths, each with several thousands of observations. The paper on transient binding was published in the Journal of Theoretical Biology, one of the leading journals in mathematical biology.

With his student K. Zhang, Didier solved an open problem in the biophysical literature. The standard technique for characterizing the anomalous diffusion scaling law consists of performing a linear regression on a vector of sample mean squared displacement (MSD) terms, each of the latter corresponding to a lag value. Notwithstanding the fact that this estimator is found in almost every paper on anomalous diffusion, the literature lacked a basic result from the standpoint of statistical methodology, namely, the asymptotic distribution of the estimator. Didier and Zhang showed that when the diffusion exponent lies between 0 and 3/2, as the sample size goes to infinity the weak limit of the estimator is Gaussian; alternatively, when it lies between 3/2 and 2, the weak limit is non-Gaussian. Moreover, the convergence rates also depend on the value of the diffusion exponent. This paper was published in the Journal of Time Series Analysis.

Didier has also looked at anomalous diffusion from a multidimensional fractional perspective, which is by itself novel. A very general framework for the analysis of multivariate anomalous diffusion is the parametric family of operator fractional Brownian motion (OFBM). The latter generalizes the standard fractional Brownian motion (FBM) and allows for correlated particle coordinates. Like FBM, OFBM satisfies a scaling law. However, the latter is driven by a matrix Hurst exponent with distinct eigenvalues. This poses a very difficult statistical problem because matrix scaling involves mixtures of univariate power laws, with unknown coordinates. Didier and his collaborator P. Abry proposed the new wavelet eigenstructure approach. Instead of analyzing the entry-wise behavior of the wavelet spectrum as a function of the (wavelet) scales, the authors consider the evolution along scales of the eigenstructure of the wavelet spectrum. It is a remarkable fact that the power law driven by the smallest eigenvalue of the wavelet transform ends up revealing the smallest Hurst eigenvalue. This work appeared in the prestigious journal Bernoulli with follow-up work appearing in the Journal of Multivariate Analysis and IEEE Transactions on Signal Processing. Additional theoretical work by Didier appeared in Stochastic Processes and their Applications and Journal of Mathematical Analysis and Applications.

There is also significant work towards manuscripts that have yet to be submitted or are under review. One important manuscript is by Didier in collaboration with the Hill lab to establish more sound statistical methods in evaluating heterogeneity in particle tracking experiments; this work has been submitted to Journal of Physics A. Didier, Abry and Li (a student of Didier) also have a manuscript submitted to Statistical Inference for Stochastic Processes; in this paper, Didier et al use Wavelet regression to estimate dynamics of mixed fractional processes which is important in understanding multiple sources of sub-diffusivity for instance. A follow-up to this work on wavelet regression to tempered fractional Brownian motion, which could be thought of as a kind of short-range sub-diffusivity. Fricks and a student Shane Lubold are finalizing a manuscript on switching in stochastic diffusion paths, establishing important theoretical work connecting fine scale structure with longer scale diffusion patterns. Fricks and his student Jason Bernstein have another manuscript nearing submission which tackles inference for switching processes where a non-linear potential is present when the particle is bound.

In summary, this grant has enabled the support of three doctoral dissertations, eight published papers, two papers under review, and three more manuscripts close to completion. We have had some success in collaboration with domain scientists and in moving theoretical tools from probability and statistics towards a practical setting. The papers published are across a wide variety of disciplines including statistics, probability, mathematical biology, and physics journals—hopefully helping to connect a broad range of researchers to the challenges of stochastic diffusion in biofluids.

Training Opportunities: The training aspect of this grant was primarily through the mentoring of graduate students. Three students completed their doctoral programs with partial support from this grant, and a fourth is expected to finish next year. At least one publication (often more) emerged from the three completed dissertations.

Results Dissemination: Nothing to Report

Honors and Awards: Nothing to Report

Protocol Activity Status:

Technology Transfer: Nothing to Report

PARTICIPANTS:

Participant Type: PD/PI
Participant: John Fricks
Person Months Worked: 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Co-Investigator
Participant: Gustavo Didier
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: Jason Bernstein
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: Kui Zhang
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: Hui Li
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: Cooper Boniece
Person Months Worked: 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

DISSERTATIONS:

Publication Type: Thesis or Dissertation
Institution: Pennsylvania State University
Date Received: 30-Aug-2016 Completion Date: 8/1/16 10:06PM
Title: INFERENCE OF BIOPHYSICAL DIFFUSION WITH TRANSIENT BINDING USING PARTICLE FILTERS AND STOCHASTIC EM
Authors: Jason Bernstein
Acknowledged Federal Support: **Y**

Publication Type: Thesis or Dissertation
Institution: Tulane University
Date Received: 17-Jul-2018 Completion Date: 8/5/17 3:05PM
Title: Wavelet-based estimation for Gaussian and non-Gaussian mixed fractional processes
Authors: Hui Li
Acknowledged Federal Support: **N**

Publication Type: Thesis or Dissertation
Institution: Tulane University
Date Received: 17-Jul-2018 Completion Date: 4/4/17 7:00AM
Title: Asymptotic theory for the statistical analysis of anomalous diffusion in single particle tracking experiments
Authors: Kui Zhang
Acknowledged Federal Support: **N**

RPPR Final Report
as of 01-Aug-2018

Nothing to report in the uploaded pdf (see accomplishments)