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University of Wisconsin - Madison 1.00
The Board of Regents of the University of Wisconsin S
Suite 6401
Madison, WI 53715 -1218

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a. REPORT	b. ABSTRACT	c. THIS PAGE			David Anderson
UU	UU	UU	UU		19b. TELEPHONE NUMBER 608-263-4943

RPPR Final Report
as of 21-Jun-2018

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INVESTIGATOR(S):

Name: David F Anderson
Email: anderson@math.wisc.edu
Phone Number: 6082634943
Principal: Y

Organization: **University of Wisconsin - Madison**
Address: The Board of Regents of the University of Wisconsin Sys, Madison, WI 537151218
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Begin Performance Period: 01-Aug-2014 **End Performance Period:** 31-Jul-2017
Report Term: 0-Other
Submitted By: David Anderson Email: anderson@math.wisc.edu
Phone: (608) 263-4943

STEM Degrees: 2 **STEM Participants:** 0

Major Goals: High level objective of the project.

The interactions between the molecular constituents of a cell are often depicted graphically as a reaction network. Reaction networks can be extraordinarily complex; for example, there are over 20,000 genes in the human genome and the proteins they encode may be modified in a variety of ways. Further, cellular systems often have different sub-systems that operate on multiple temporal and other scales, with the species operating at one scale greatly influencing those at a different scale. The reaction networks currently studied in the literature are typically so complex that numerical simulation is often the only way to analyze them. However, hidden within the complexity there are often underlying structures that, if properly quantified, give great insight into the dynamical or stationary behavior of the system. The objective of this project is to discover what the important structures hidden in the complexity of biochemical networks are, and how to infer system behavior, on short, medium, and long time frames, from them.

While we formally consider models from biochemistry, the mathematical models studied are quite universal. For example, many models at the level of populations (such as models of disease spread) satisfy equations with the same mathematical structure. One of the goals of systems and evolutionary biology is to combine models from the cellular level with those at the population level. Such twenty-first century models are already being developed, for example to understand the spread of malaria. These systems will be directly impacted by the project.

Specific objectives of the project.

The project had 9 stated objectives. These objectives focus on either stochastically or deterministically modeled biological interaction networks. Of note is that the objectives focus on developing fundamental mathematical theory that can be applied to a variety of models, ranging from intracellular systems to population dynamics.

Some brief background is necessary to describe the specific objectives of the project. If the abundances of the constituent molecules of a biochemical reaction system are sufficiently high then their concentrations are typically modeled by a coupled set of ordinary differential equations. If, however, the abundances are low then the standard deterministic models do not provide a good representation of the behavior of the system and stochastic models are used.
Mathematically, the stochastic models can be represented as solutions to a system of stochastic differential equations driven by unit-rate Poisson processes.

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Project 1 focuses on stochastically modeled systems that are multi-scale in nature and asks how to systematically reduce the size of the system. The reduced network should be easier to analyze, either analytically or computationally, yet still capture the main behavior of the original model. The developed reduction method should be amenable to algorithmic implementation so that it may find wide application.

Projects 2 - 5 focus on determining how the structure of the interaction network under consideration determine the qualitative behavior of the mathematical model. Both stochastic and deterministic models are investigated. In particular, questions related to the possible long time behavior, including extinctions, fixed points, and stationary distributions, are investigated. Of note is that the typical type of theorem being developed here is of the form "If a network satisfies conditions X, Y, and Z, then the behavior of the mathematical model is W." In particular, we are not studying specific systems, but whole classes of systems. In this sense, the work is "fundamental" in nature.

Projects 6 - 8 consider interaction networks on medium time scales. In particular, classes of models are considered in which a dramatic change in the behavior of the system, such as an extinction event, is guaranteed to occur at some point.

Before a system undergoes its extinction, it may settle to an apparent steady state, such as a quasi-stationary distribution, long before the event takes place. Characterizing these medium time scale distributions gives the behavior of the model on realistic time frames. Questions pertaining to medium time behavior of models is typically quite difficult to answer, though their answers are often of great use.

Project 9 investigates the possibility of a biochemical universality class by cataloging which models have distributions that either equal a Poisson distribution, or limit to a Poisson distribution.

Accomplishments: During the course of the proposal, we

* published 17 papers
* published 2 textbooks
* completed 2 PhD theses.

In these writings, the major goals of the proposal were both addressed and (largely) completed.

Training Opportunities: During the grant, two PhD students have completed their degrees. One postdoc and three other graduate students have also been partially supported. Support and training consisted of travel to relevant workshops and conferences.

Results Dissemination: During the course of the proposal, we

* published 17 papers
* published 2 textbooks
* completed 2 PhD theses.

We also presented at myriad workshops and conferences.

Honors and Awards: The PI was awarded the inaugural IMA Prize in Mathematics from the IMA (Institute for Mathematical Analysis).

The PI was named a Vilas Associate Award winner in 2016 by the University of Wisconsin-Madison.

Protocol Activity Status:

Technology Transfer: Nothing to Report

PARTICIPANTS:

Participant Type: PD/PI
Participant: David F Anderson
Person Months Worked: 10.00 **Funding Support:**

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Nothing to report in the uploaded pdf (see accomplishments)