# 2009-2010 Program on Stochastic Dynamics Final Report

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## 1. Introduction

This year-long SAMSI program was centered around the broad topic of Stochastic Dynamics with particular focus on analysis, computational methods, and applications of systems governed by stochastic differential equations. The term "Stochastic Dynamics" is one which resonates within many fields in statistics and applied mathematics. The numerical analyst designing algorithms for stochastic differential equations, the math biologist studying transport on the cellular level, the analyst trying to understand the effect of stochastic forcing and data in dynamical systems, the statistician trying to characterize the statistics of dynamic networks, and the mathematical modeler trying to bridge the gap between atomistic and continuum physics are all examples of research in stochastic dynamics. Unfortunately it is too often the case that research being done in one of the above scenarios is not being widely disseminated across the spectrum of statistics and applied math. This SAMSI program served to bring together experts in different but highly inter-related research specializations under the broader umbrella of stochastic dynamics in the hopes of creating collaborations which could potentially lead to exciting advances in particular research areas.

Particular successes of the program include:

- The establishment of a new collaboration, including two major grant proposals submitted to date, involving a probabilist (Scott McKinley), an applied mathematician (Peter Kramer), and a statistician (John Fricks) to develop a systematic stochastic modeling framework for intracellular transport connecting three important physical length scales.

- A sustained research effort across SAMSI programs, with applied mathematicians from the working group on *Numerical Methods for Stochastic Systems* (Peter Kramer and Sorin Mitran) joining with statisticians from the program on *Space-Time Analysis for Environmental Mapping, Epidemiology, and Climate Change program* (Jim Berger, Susie Bayarri, Murali Haran, Emily Kang, Hans Künsch) to explore how statistical aspects of multiscale computing methods could be enhanced.

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- Two research programs toward new modeling approaches in microswimming (Peter Kramer) and swarming (Amarjit Budhiraja, Oliver Diaz and Xin Liu) that were nucleated by presentations at the workshop on *Self-Organization and Multi-Scale Mathematical Modeling of Active Biological Systems* in October, 2009.

- Several ongoing collaborations between SAMSI postdocs on topics in stochastic neuronal dynamics and epidemic spread on networks.

- A project initiated and driven by two graduate students (Katherine Newhall and Amanda Traud) participating in the working group on *Network Dynamics*, now being prepared for submission for publication.

- Two workshops in the spring which were designed to resonate with the specific interests of the working groups, stimulating new ideas and helping to lead to several submitted publications.

Below, we first review the content of the workshops, and then summarize the activities of the working groups.

## 2. Workshops

Five workshops were organized as part of the program.

### 2.1. Opening Workshop & Tutorials, August 30 - September 2, 2009

Following the usual style of an opening workshop tutorials were given on Sunday, while from from Monday to Wednesday, invited speakers gave presentations. Following the talks, the research working groups formed and had their initial meetings at SAMSI.

**Speakers:** Mark Alber (University of Notre Dame), Anna Amirdjanova (University of Michigan), David Anderson (University of Wisconsin), Peter Baxendale (University of Southern California), Gerard Ben Arous (New York University), David Cai (New York University), Sandra Cerrai (University of Maryland), Lee DeVille (University of Illinois), Tim Elston (University of North Carolina), Alejandro Garcia (San Jose State University), Cindy Greenwood (Arizona State University), Martin Hairer (New York University), Peter Imkeller (Humboldt University Berlin), Markos Katsoulakis (University of Massachusetts at Amherst), Peter Kotelenez (Case Western University), Rachel Kuske (University of British Columbia), Kevin Lin (University of Arizona), Gabriel Lord (Heriot Watt University), Grant Lythe (University of Leeds), Katie Newhall (Rensselaer Polytechnic Institute), Houman Owhadi (California Institute of Technology), Grigorios Pavliotis (Imperial College, London), Lea Popovic (Concordia University), Mike Reed (Duke University), Gareth Roberts (University of Warwick), Christof Schuette (Free University, Berlin), Andrew Stuart (University of Warwick), Anja Sturm (University of Delaware), Eric Vanden Eijnden

(New York University), Mike West (Duke University), Darren Wilkinson (Newcastle University).

## 2.2. Workshop on Self-Organization and Multi-Scale Mathematical Modeling of Active Biological Systems, October 26-28, 2009

**Organizers:** Igor Aronson (Argonne National Laboratory), Leonid Berlyand (Penn State University)

**Topics:** How do seemingly random mixtures of molecular components and swimming microorganisms organize themselves into large-scale cellular structures and synchronize to execute collective motions? What is common to these processes? Can we model them mathematically and simulate them computationally? What can we learn about the biofluids flows and self-organization of biological systems by developing and analyzing mathematical models? The workshop brought together mathematicians, statisticians, biophysicists and engineers to discuss these questions and focus on the following mathematical and statistical issues:

- Homogenization and upscaling in active systems (suspensions of swimmers, cytoskeletal networks, biological tissue),

- Analysis of mathematical model of self-organization in biological systems,

- Novel computational algorithms for simulations of biological processes.

Complementary research thrusts include the statistical properties of self-organized collective states and macroscopic effects of intrinsic stochasticity in active systems, such as velocity and density fluctuations, phase transitions, critical behavior, rheology and constitutive relations.

**Speakers:** Anna Balazs (University of Pittsburgh), Andrea Bertozzi (UCLA), John Brady (Caltech), Suncica Canic (University of Houston), Thierry Collin (University of Bourdeaux), Margaret Gardel (University of Chicago), Jerry Golub (Haverford College), Yulia Gorb (Texas A&M), Michael Graham (University of Wisconsin-Madison), Danielle Hilhorst (Universite Paris-Sud), James Keener (University of Utah), Simona Mancini (Universite d'Orleans), Tim Pedley (University of Cambridge), Benoit Perthame (Universite Pierre et Marie Curie), Jacques Prost (ESPCI), and Michael Shelley (Courant Institute).

## 2.3. Workshop on Theory and Qualitative Behavior of Stochastic Dynamics, February 8-10, 2010

**Organizers:** Michael Cranston (University of California-Irvine), Yuri Bakhtin (Georgia Tech), Luc Rey-Bellet (University of Massachusetts), Jonathan Mattingly (Duke University)

**Topics:** Stochastic modeling is becoming ubiquitous in science and engineering. This conference brought together speakers addressing a number of advances in describing the qualitative dynamics of stochastic systems such as stochastic bifurcation, structure of invariant measures, metastability, averaging, and sub and super diffusive behavior. Although the presentations emphasized theoretical aspects of the subject, there was a bias toward results which shed light on relevant models of physical, biological or technological interest.

**Speakers:** Yuri Bakhtin (Georgia Tech), Peter Baxendale (USC), Dima Dolgapyat (University of Maryland), Paul Dupuis (Brown University), Barbara Gentz (University of Bielefeld), Stanislav Molchanov (UNC-Charlotte), Alexei Novikov (Penn State University), David Nualart (University of Kansas), Grigorios Pavliotis (Imperial College London), Luc Ray-Bellet (University of Massachusetts), Michael Scheutzow (Berlin University), Richard Sowers (University of Illinois)

### 2.4. Workshop on Molecular Motors, Neuron Models, and Epidemics on Networks, April 15-17, 2010

**Organizers:** Priscilla Greenwood (ASU), John Fricks (Penn State), Lea Popovic (Concordia), Scott Schmidler (Duke)

**Topics:** The workshop concentrated on primary topics of research in three of the SAMSI working groups. In addition to lectures by the speakers listed below, there were reports from the following working groups.

- *Molecular motors.* These are biological molecular machines that convert energy into motion, producing movement in living organisms, operating at a scale where thermal noise is significant. Because motor events are stochastic, they may be modeled in terms of random walks or Markov processes. An active topic is the stochastic dynamics of such models.

- *Neuron models.* Several well-known models are being studied with the aim of comparing the stochastic dynamics of the models. A fundamental question is, in what cases the transition from firing to quiescence and back is governed by boundary crossing times of a stochastic process, as opposed to large deviation times. The larger question for stochastic dynamics is the nature of transition times between domains of attraction of locally stable configurations.

- *Epidemics.* They have been defined on networks in various ways. One approach is to fix a network and define a version of a classical mean field epidemic model on that network by specializing the interaction equations to specific local interactions. The challenge is to devise models where solutions, or at least some of their properties, are accessible.

**Speakers:** Andrea Barriero (U. of Washington), Meredith Betterton (U. of Colorado), Susan Ditlevesen (Copenhagen), David Hunter (Penn State), David Kinderleher (Carnegie Mellon), Martina Morris (U. of Washington), Duane Nykamp (U. of Minnesota), Laura Sacerdote (Toronto), E. Volz (U. of Michigan), Hongyun Wang (UC Sanata Cruz)

**2.5. Transitions Workshop, November 17-19, 2010**

**Organizers:** Peter Kramer (Rensselaer Polytechnic Institute), Jonathan Mattingly (Duke University) and Sorin Mitran (UNC-Chapel Hill)

**Topics:** The Stochastic Dynamics transition workshop was an opportunity for the participants in the program to reconnect with each other and present the progress of sustained research efforts that have proceeded beyond the end of the program at SAMSI. Presentations were given from each of the working groups: Network Dynamics, Data Assimilation, Numerical Methods for Stochastic Systems, Qualitative Behavior of Stochastic Dynamical Systems, and Biological Stochastic Dynamics.

**Speakers:** Meredith Betterton (Colorado), John Fricks (PennState), Giles Hooker (Cornell), Peter Kramer (Rensselaer Polytechnic Institute), John Harlim (NCState), Peter Kotelenez (Case Western), Jonathan Mattingly (Duke University), Scott McKinley (Florida), Sorin Mitran (UNC Chapel Hill), Bruce Rogers (Duke), Ravi Srinivasan (Texas), Amanda Traub (NCState), Xueying Wang (Texas A&M), Jennifer Young (Rice)

## 3. Working Groups

Five research working groups were organized as part of the program.

**3.1. Working Group on Qualitative Behavior of Stochastic Dynamics**

**Group Leader: Jonathan Mattingly (Duke)**

**Participants:** Avanti Athreya (SAMSI), Hakima Bessaih (Univ. of Wyoming), Esteban Chavez (Duke), Cindy Greenwood (ASU), Oliver Diaz (Duke), Barbara Gentz (Universität Bielefeld), Boumedienne Hamzi (Duke), Badal Joshi (Duke), Tiffany Kolba (Duke), Jonathan Mattingly (Duke), Scott McKinley (Duke), Peter Mucha (UNC), Scott Schmidler (Duke), Ravi Srinivasan (Duke), Andrea Watkins (Duke)

**Topics:** The group studied a number of topics in the qualitative description of stochastic dynamics, such as stochastic resonance, Lyapunov exponents, quasi-invariant measures, h-transforms to condition stochastic systems, large deviation theory to understand nucleation in stochastic partial differential equations, structure of random attractors, and multiscale analysis in probability. Some

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of the work by members of this group is described under the heading of single neuron dynamics. A description of some of the other concrete results follows.

- *Planar dynamical systems:*

  Avanti Athreya, Tiffany Kolba, and Jonathan Mattingly are currently examining two specific systems with small additive noise where (a) without noise, the unperturbed ODE has regions of instability and/or finite-time blowup; and (b) with noise, the system seems to stabilize, either in the sense that near-periodic orbits emerge or in the sense that there exists a unique invariant probability measure (Scheutzow gave a nice example of such a system in a 1991 paper). For one of the dynamical systems under consideration, we know by asymptotic analysis how the invariant measure decays far from the origin, and we're still addressing the question of its existence. For the other, we are trying to see if we can reduce the problem of escape from a region of deterministic instability to a problem of escape from a double-well potential.

- *Variance reduction for stochastic differential equations:*

  In many applications of stochastic modeling, the dynamics are governed by an SDE depending on certain parameters and key quantities of interest are expressed as the expected value of an observable with respect to the invariant probability measure of the SDE, and computed by time-averaging over long trajectories. In some situations, for example when one wishes to optimize the expected value with respect to the parameters, it is desirable to compute the change, or sensitivity of the expected value with respect to variations in the parameter. A challenge is that sensitivities are typically relatively small quantities, so very long trajectories may be required to estimate them accurately.

  In an on-going effort to develop fast methods for computing sensitivities, Kevin Lin and Jonathan Mattingly are working on a class of methods based on couplings. The basic idea is to construct two correlated realizations of the SDE for nearby parameters in a way that ensures the two solutions remain near each other most of the time. One then obtains a direct, low-variance estimate of the sensitivity via integrating differences along the path. The current focus of the project is the numerical analysis of these methods. Specifically, an investigation of different coupling strategies and their effectiveness for some prototypical problems is being carried out, with the goal of understanding how details of the coupling construction and features of the stochastic dynamics together determine the scaling of numerical errors with respect to the parameter perturbation.

- *Sustained oscillations for density dependent Markov processes:*

  A paper has been written by Peter H. Baxendale and Priscilla E. Greenwood and submitted to the *Journal of Mathematical Biology*. Simulations of models of epidemics, biochemical systems, and other bio-systems

show that when deterministic models yield damped oscillations, stochastic counterparts show sustained oscillations at an amplitude well above the expected noise level. A characterization of damped oscillations in terms of the local linear structure of the associated dynamics is well known, but in general there remains the problem of identifying the stochastic process which is observed in stochastic simulations.

Here we show that in a general limiting sense the stochastic path describes a circular motion modulated by a slowly varying Ornstein-Uhlenbeck process. Numerical examples are shown for the Volterra predator-prey model, Sel'kov's model for glycolysis, and a damped linear oscillator.

### 3.2. Working Group on Numerical Methods for Stochastic Systems

### Group Leaders: Alina Chertock (NCSU), Sorin Mitran (UNC)

**Participants:** Anna Amirdjanova (Univ. of Michigan), Dave Anderson (Univ. of Wisconsin), Hakima Bessaih (Univ. of Wyoming), Alina Chertock (NCSU), Sean Cohen (UNCC), Dan Fovargue (UNC), John Fricks (Penn State), Peter Kramer (Rensselaer), Kevin Lin (Univ. of Arizona), Jonathan Mattingly (Duke), Michael Minion (UNC), Sorin Mitran (UNC), Carlos Mora (Universidad de Concepci???n), Anuj Mubayi (Univ. of Texas at Arlington), Hon Keung Tony Ng (SMU), Ravi Srinivasan (Duke), Ilya Timofeyev (Univ. of Houston)

**Topics:** The classical continuum equations arising in fluid flow, elasticity, or electromagnetic propagation in materials require constitutive laws to derive a closed-form system. The constitutive laws appropriate for a given set of equations can be derived in two ways: i) from phenomenological considerations such as the linear behavior underlying elastic deformation or Newtonian fluid flow, or ii) from averaging of kinetic theory results describing basic molecular dynamics. This has been possible for situations in which the microscopic behavior is close to thermodynamic equilibrium. In such cases, Gaussian statistics are well verified at the microscopic level and the moments of Gaussian distributions can be computed analytically.

However, many physical processes exhibit significant localized departure from Gaussian statistics. When a solid breaks, the motion of the atoms in the crystalline lattice along the crack propagation path is no longer governed by a Maxwell-Boltzmann distribution. When a material undergoes a phase change, large scale correlations among atoms are formed (or destroyed) which modify the typically Gaussian statistics of the equilibrium phases. Protein folding can be seen as a large-scale modulation imposed by polymer links of the Gaussian statistics of the component atoms. A common characteristic of these situations is that macroscopic features impose the departure from local thermodynamic equilibrium and macroscopic quantities of are practical interest. Crack propagation is initiated by a force acting on a solid and we wish to know how far the solid deforms before it breaks. In solidification, a heat flux evacuates energy

from the melt at some rate and we wish to characterize the type of order arising in the material.

In all such cases, a basic problem is how to extract the statistical distributions of physical quantities when the system is away from thermodynamic equilibrium. Knowledge of the distribution would allow local constitutive laws to be formulated. Direct numerical simulation is prohibitively expensive. Continuum level simulation is incomplete due to lack of constitutive laws. Furthermore, while it is clear that higher-order moments characterizing the microscopic statistical distribution are required, it is not known how many of these moments are needed and what their persistence time might be. The microscopic dynamics are stochastic but subject to multiple macroscopic constraints. One major statistical challenge is how to characterize the microscopic motion in a manner that can be used to derive a constitutive law. A basic computational question is how to advance the system in time efficiently at both the microscopic and macroscopic level. An analysis challenge is how to combine this knowledge and form (e.g. through asymptotic expansions) particular constitutive laws.

The numerics group has been discussing a number of multi-scale numerical methods that mix stochastic models at small scales with deterministic models at larger scales. Particular issues on which we focused included the incorporation of adaptive time stepping and the initialization of microscale simulations consistent with the macroscale constraints. In spring, Sorin Mitran rolled out his novel time-parallel continuum-kinetic-molecular (tpCKM) simulation scheme, which is designed to handle multiscale systems where the microscale statistics do not relax quickly relative to the macroscopic time scale. A third, mesoscopic, level of description was added and updated by an adaptive predictor-corrector approach through communication with both the macroscale and microscale simulations. Mitran and his graduate student Jennifer Young had separately been studying polymeric and cellular blebbing with this method, while the working group examined a one-dimensional string model where bonds could form and break on the microscale with rates dependent on the local stress. Implementations of both the classical Heterogeneous Multiscale Method and tpCKM method were explored.

One of the working groups in the contemporaneous Space-Time Analysis for Environmental Mapping, Epidemiology, and Climate Change, concerned with the "Interaction of Deterministic and Stochastic Models", developed a focused interest in multiscale computing and in particular the efforts of this Numerical Methods Working Group. This has led to a sustained collaboration across these two working groups, now dedicated to improving a statistical aspect of the communication between the mesoscale and microscale dynamics in the tpCKM method. Statistical issues in multiscale computing appear not to have been much pursued until now, but the close interaction of applied mathematicians and statisticians at SAMSI has identified new areas of research along this direction.

### 3.3. Working Group on Data Assimilation

**Group Leaders:**  Cindy Greenwood (ASU), John Harlim (NCSU), Peter Kramer (RPI)

**Participants:**  Cindy Greenwood (ASU), Boumendiene Hamzi (Duke), John Harlim (NCSU), Giles Hooker (Cornell), Peter Kramer (RPI), Huitian Lu (San Diego State University), Jonathan Mattingly (Duke), Anuj Mubayi (Univ. Texas at Arlington), Bruce Rogers (SAMSI)

**Topics:**  This group has been striving to explore questions of interest to both applied mathematicians and statisticians. To this end, we have focused on the problem of optimizing the design of experiments based on incoming data in a stochastic system, and which can be formulated as a stochastic control problem.

When collecting data from experimental systems, the experimenter may be able to control the quantities measured, the measurement times, estimation methods used for inference, and inputs into the system. We have focused on the control-type question of what process-informed input to a system will yield maximal information about parameters governing system dynamics. Two real-world applications have motivated this study:

- Single neuron experiments involve stimulating a neuron with an electrical current and measuring the electrical potential across the neuron membrane. Voltage measurements are typically available with very high frequency and accuracy; however complex models involving the interaction of several ion channels can underpin neural dynamics. In this context, experiments typically use step-inputs. Since these inputs can be readily coupled to output systems, an automated control process can be readily designed to maximize information about parameters of interest.

- An experimental ecology typically consists of a few species of microorganism kept in a chemostat (approx 500ml). In such systems ecological dynamics are of interest; predator-prey interactions, trait evolution or phenotype plasticity. These ecologies can be"tuned" by setting their ambient temperature, the amount of nutrient provided to the ecology, and the rate at which the ecology is diluted. These parameters are typically held at constant values, chosen based on intuition, and changed, again based on intuition, after observing the ecological dynamics. For such systems, measurements are less frequent and much noisier than for neural experiments, creating a more challenging, but possibly more important problem in providing principled programs for varying system settings depending on the observation history.

These two examples can be represented by a sequence of increasingly complex models for real-world experimental problems. In adapting stochastic control theory to the problem of experimental design, we have attempted to maximize the Fisher information about the parameters of interest.

The paradigm of input-control that attempts to maximize an objective can be represented within the framework of Control Theory. However, this is complicated by a number of factors:

- The optimal control is typically infinite, requiring either a restriction to a feasible range or some form of penalization. The use of these controls can also destroy the stationarity of the system being observed, making inferential methods more problematic.

- The evaluation of Fisher Information in noisily-observed nonlinear stochastic systems can be difficult and typically requires computationally expensive numerical approximation. Further, the Fisher Information is not representable as an integral over times, meaning the optimal control can depend on the entire sequence of past observations rather than, as is usually the case, the filtered estimate of the current state.

In order to derive algorithms to calculate the optimal control we have focused on two approximations. First, we represent the system in terms of discrete-valued states and input. This allows restrictions on the range of values that the input can take to be naturally enforced. Second, the Fisher Information is replaced with the Information that would be obtained were the states of the system to be observed exactly at all times. This framework reduces the problem to one of optimal control for noisily observed systems where it has been shown that the control may be chosen based on a filtered estimate of the current state.

It is, of course, important to understand the properties of these approximations. To that end we have investigated the case of a discrete-time linear system where algorithms to calculate the Fisher Information have been already developed. We have derived the optimal control for this problem and shown that the dependence of the optimal input on past observations decays exponentially as time moves forward. These calculations can be further used to suggest corrections to the approximate methods derived above.

Further areas of investigation include solving the complete control problem for discrete-valued systems, the approximation of control variables by basis expansions for higher-dimensional systems and the use of particle filter methods to evaluate Fisher Information, and the choice of measurement times and quantities.

These investigations have lead to a number of papers that are currently in preparation. One, based on the approximations above requires specialized particle-filter code to be developed for nonlinear systems, but is already underway. A second, based on the linear model and the accuracy of the approximations above is being prepared. A graduate student at Cornell University is currently working on deriving the optimal control in a discrete-state hidden Markov model with applications to Polymerase chain reaction systems and a paper resulting from this work is expected in the new year.

### 3.4. Working Group on Network Dynamics

**Group Leaders:**  Pierre Gremaud (NCSU), Peter Kramer (RPI), Peter Mucha (UNC)

**Participants:**  Avanti Athreya (SAMSI), Cindy Greenwood (ASU), Badal Joshi (Duke), Peter Kramer (RPI), Kevin Lin (Univ. of Arizona), Jonathan Mattingly (Duke), Scott McKinley (Duke), John McSweeney (SAMSI), Anuj Mubayi (Univ. of Texas at Arlington), Peter Mucha (UNC), Katie Newhall (Rensselaer), James Nolen (Duke), Bruce Rogers (ASU), Scott Schmidler (Duke), Ravi Srinivasan (Duke), Yi Sun (SAMSI), Rachel Thomas (Duke), Ilya Timofeyev (Univ. of Houston), Mandi Traud (UNC), Xueying Wang (SAMSI)

**Topics:**  This group organized under the common expectation that the network of connections coupling different stochastic processes are affected by the underlying structure of such couplings, but with little a priori expectation about which structural characterizations might matter. Our working group discussions revolved around three topic areas: (i) biological diseases and social contagions, as examples of dynamics spreading on a network; (ii) neuronal network dynamics, as an example of dynamical systems coupled by selected network topologies; and (iii) NSF research institute participation data (this example of a social network is familiar to participants and might help develop ideas about the utility of network analysis for the interests of this group).

- *Contagion Dynamics on Social Networks:*

  The first common broad system of interest within the working group was the study of diseases and social contagions on networks.

  John McSweeney and Bruce Rogers have considered the contact process (SIS epidemic) on a strongly clustered graph, described as a stochastic block model. In the simplest case there are two communities with the probability of an edge connecting two individuals within the same community p1 and the probability of an edge connecting two individuals between communities p2 much smaller than p1. In a range of parameters, a plot of the number of infected sites versus time shows a stair step: the epidemic reaches equilibrium in one community before spreading to the other. Work on this problem is continuing in the Dynamics ON Networks working group of the Complex Networks in collaboration with new postdoc David Sivakoff and Rick Durrett. A proof has been sketched and work is proceeding on a paper.

  Cindy Greenwood and Xueying Wang have been analyzing the pairwise closure approximation (PAC) theory for the stochastic SIRS model (where recovery from an infective state leads to a temporary immune state) [Ganna Rozhnova and Ana Nunues, 2009] and comparing it with the stochastic SIS model (where recovery from infection leads directly to a susceptible state) [Eames and Keeling] on regular graphs. In one limiting case of the

PAC theory for the SIRS model, the two dimensional principal component of the stochastic paths exhibits sustained stochastic oscillations, in the form of a Ornstein-Uhlenbeck process composed with a time dependent rotation. This work has led to a paper and was the subject of one of the presentations at the Transitions Workshop.

- *Neuronal Network Dynamics:*

  One subgroup has explored a key question in neuronal networks: how to derive quantitative descriptions and models for the collective behavior of a network of neurons starting from neuronal-level dynamical equations for the membrane voltage and a description of the topology of the network. Stochasticity enters the description typically to describe irregularity of signaling inputs, which are then propagated by the network dynamics. Particularly interesting collective behaviors include synchronous oscillations and the formation of mobile spatial patterns where neurons are firing intensely.

  A starting point for the subgroup's investigation is the kinetic theory approach developed by one of the opening workshop speakers, David Cai, and his co-workers to describe the overall network firing properties by coarse-graining the neuronal dynamics in a manner parallel to describing the evolution of a gas density by coarse-graining the dynamics of individual gas molecules.

  The subgroup also found particular interest in recent work by Liu and Nykamp on a "second-order" kinetic theory that has some promise for describing large-scale synchrony. These neuronal kinetic theories have so far not accounted for the spatial distribution (apart from the topological description) of the neurons, and the subgroup spent some time and effort thinking about how to incorporate a spatial component into the kinetic theories or some other mathematical framework that might make it possible to develop a sort of spatio-temporal continuum equations for the neuronal firing patterns that upscale in a quantitative way the neuronal-level description of the dynamics.

  In a related investigation, Katie Newhall, Mandi Traud, Peter Kramer and Peter Mucha have worked on a project which explores different discretizations of simple integrate-and-fire dynamics and the relation between statistical properties of the cascades in these models and the underlying network of interconnectivity. This project was actually initiated by the graduate students Newhall and Traud at the intersection of their research interests, with their advisors Kramer and Mucha providing subsequent guidance and focus with regard to approaching the question they posed. This work has been presented by Traud in a minisymposium at the SIAM Conference on the Life Sciences in July, 2010, by Newhall in a poster presentation at the opening workshop of the Complex Networks program at SAMSI in August 2010, and is in the process of being written up for submission to the journal *Chaos*.

- *Institute-Participation Data in Mathematics:*

  In order to develop network analysis experience and expertise more broadly within the working group, we endeavored to supplement our stochastic dynamics interest with social network analysis of a specific data set. There was particular interest leading to direct discussions with the NSF to try to efficiently gather public co-occurrence data about participants in programs and workshops at SAMSI and the other NSF-funded mathematical institutes. Working group discussions briefly explored standard software tools available for social network analysis which might be used on these data, along with more specialized tools of community detection and analysis of co-occurrence hypergraphs within the working group and other specialists local to the triangle area. However, no easy access to the data was immediately available from which to undertake this analysis within the group.

## 3.5. Working Group on Biological Stochastic Dynamics

**Group Leaders:**   Amarjit Budhiraja (UNC), Cindy Greenwood (ASU), Peter Kramer (Rensselaer)

**Participants:**   Mark Alber (Notre Dame), Avanti Athreya (SAMSI), Amarjit Budhiraja (UNC), Esteban Chavez (Duke), Amogh Deshpande (NCSU), Nuwan deSilva (Rensselaer), Oliver Diaz (Duke), John Fricks (Penn State), Cindy Greenwood (ASU), Kazi Ito (NCSU), Badal Joshi (Duke), Min Kang (NCSU), Peter Kramer (Rensselaer), Mimi Lin (Duke), Kevin Lin (Arizona), Huitian Liu (San Diego State), Scott McKinley (Duke), John McSweeney (SAMSI), Anuj Mubayi (Univ. of Texas at Arlington), Katie Newhall (Rensselaer), Lea Popovic (Concordia), Bruce Rogers (ASU), Ravi Srinivasan (Duke), Rachel Thomas (Duke), Xueying Wang (Ohio State University), Richard Yamada (University of Michigan)

**Topics:**   The explosion of interest in mathematical and statistical modeling and computation in the biological and medical sciences, where stochasticity is present at nearly every scale, has been one of the most exciting trends in the biosciences in the last ten years. A sizable group has organized at SAMSI to study applications of stochastic models and methods to questions in biology, ranging from the population to the cellular and down to the molecular level.

To begin the year, members presented pedagogical overviews of stochastic methods in biology as well as illustrations of research problems they had worked on and were interested to explore further. Stimulated by these discussions and the presentations at the opening workshop, six project areas were identified as having substantial interest by midyear. These were each discussed on a rotating basis during the weekly group meetings.

The molecular motor topic crystallized into a sustained coherent research collaboration between four participants, with the ongoing work presented at

two SIAM conferences thus far, a first publication being prepared, and two major grant proposals submitted.

The single neuron dynamics project has also continued beyond the end of the Stochastic Dynamics program, with at least one publication likely to be forthcoming.

While the microswimming project generated a sustained collaborative research focus on a recent experimental paper through the early spring, it was later abandoned as being less promising than originally thought. On the other hand, one of the visiting faculty has launched a new research project in this area with local collaborators through the stimulus provided by his time at SAMSI.

While the three other projects remained only in an exploratory phase, they helped broaden the exposure of the group, particularly the graduate students and postdocs to a wider range of topics of stochastic modeling in biology.

- *Molecular motors:*

  An active collaboration emerged from the working group concerning the modeling and analysis of systems of molecular motors bound to a single cargo. The central question concerns how the details of the stochastic model characterizing individual molecular motors, including their response to applied forces and proclivity to bind or unbind from the microtubule track, is reflected in the effective dynamics of the complex of the cargo bound to multiple molecular motors. The group's effort has primarily focused thus far on constructing a serious, physically consistent spatial model, and applying stochastic averaging techniques to derive effective equations for the motor-cargo complex from physically and biologically based stochastic dynamical equations for the individual components.

  Avanti Athreya, John Fricks, Peter Kramer, and Scott McKinley are currently writing up their work for publication under the title "Cooperative dynamics of kinesin and dynein type molecular motors". We plan to sustain this collaboration beyond this paper, and to this end, Fricks, Kramer, and McKinley, together with bioengineer William Hancock have submitted two major grants to the National Science Foundation's Focused Research Group (FRG) program and the Joint DMS/NIGMS Initiative to Support Research in the Area of Mathematical Biology. The work proposed in these grants would use the mesoscopic modeling developed by the group at SAMSI as a scaffold from which to build a mathematically integrated stochastic model for cellular transport, from the nanoscale to the microscale of the whole cell.

- *Stochastic Single Neuron Models:*

  Several collaborative subgroups worked between the biological stochastic dynamics group and the qualitative behavior working group in applying stochastic analysis techniques to single-neuron models.

  Cindy Greenwood together with short-term visitor Laura Sacerdote and collaborator Maria Teresa Giraudo have submitted a paper "How sample

paths of Leaky Integrate and Fire models are influenced by the presence of a firing threshold" to *Neural Computation*. This paper treats the statistics and simulation of sample voltage paths taken by a neuron conditioned on it not having fired (reached threshold) by a certain time.

Avanti Athreya, Badal Joshi, and Xueying Wang considered coherence and self-induced stochastic resonance in Morris-Lecar models for neurons. This project would advance the characterization of these phenomena by Vanden-Eijnden, Muratov, and DeVille in FitzHugh-Nagumo models to the more complex Morris-Lecar model. For a range of parameter values, the single neuron deterministic Morris-Lecar model has a stable fixed point, an unstable limit cycle and a stable limit cycle. Here the stable fixed point corresponds biologically to quiescence of the neuron while the stable limit cycle corresponds to firing an action potential or spiking. It has been shown by Rowat [*Neural Computation* 19, 1215???1250 (2007)] that noise plays a role in spontaneously switching between the two modes of quiescence and firing.

The group extended this work of Rowat into regimes where the deterministic model has only a stable fixed point but no stable limit cycles. Even in this parameter regime, having noise in the model can result in two modes of firing - quiescence and active, and the noise can cause spontaneous switching between the modes. Thus noise not only plays a role in switching, but introduces a completely new dynamic mode which does not exist in the deterministic model. This has important consequences for predicting the behavior of a neuron when an external current is applied. Along these lines, Avanti Athreya, Scott McKinley, and Ravi Srinivasan examined how to model escape from the stable equilibrium in Morris-Lecar models for a neuron, thinking of it as a "breathing potential" near the fixed point. It seems valid to take a small-noise limit in the Morris-Lecar model because the noise can come from ion channels or from input current, but large deviation approaches don't seem quite appropriate. Besides internal or channel noise in single neurons, another important source of noise arises in the synapse or the connection between neurons.

In an ongoing project, the subgroup is studying and classifying the range of behaviors of small networks of two or three neurons, connected in a feedforward or a feedback manner. In such small networks, the interaction of synaptic noise and channel noise can give rise to a range of novel and interesting behaviors. The idea is to develop a framework that would help qualitatively understand such small networks, and then possibly extend the insights to larger, more biologically realistic network sizes.

Particular questions being addressed by this subgroup, first by simulation, then to be followed up by analytic work are: How are the firing patterns generated by the Morris-Lecar and Fitzhugh-Nagumo models related when sinusoidal forcing, ion channel noise, and synaptic noise are included in these models? Is there a large deviation cycling effect in the Morris-Lecar

model as has been found in the Fitzhugh-Nagumo model, and how is this related to neuron firing?

A related question being pursued by some of the neuron subgroup members is inference from the spike activity of two neurons. Suppose we have data in the form of the time points when spikes occur as is usually depicted in raster plots. A cross-correlogram is a commonly used measure for quantifying the dependence structure, but it has its difficulties in interpretation, for example, in inferring the network architecture from the spiking activity of two neurons. For instance, if the spike times of two neurons are highly correlated, it can be because they are connected directly or indirectly to each other or it can happen because they receive common input. This question of how to distinguish these two cases is being approached from a modeling point of view. Suppose we start with two integrate and fire neurons which receive a common Poisson input. Can we predict the dependence structure in the spiking activity of the two neurons?

- *Microswimming:*

  A workshop at SAMSI in Fall 2009 on *Self-Organization and Multi- Scale Mathematical Modeling of Active Biological Systems* has provided many stimulating ideas to the group, with two subgroups pursuing specific projects.

  One subgroup studied in particular the paper "Dynamics of Enhanced Tracer Diffusion in Suspensions of Swimming Eukaryotic Microorganisms" by Leptos, Guasto, Gollub, et al. The results of this paper were presented by Gollub at the workshop. Experimental results for the dynamics of tracer particles in a flow generated by a suspension of swimming microorganisms showed a striking self-similar probability distribution for the displacement of a tracer with respect to time increment, which however did not correspond to any known stable law.

  The subgroup sought to develop simplified stochastic models for the dynamics of these tracer particles that could explain this observation. This project was eventually abandoned when questions began to arise about how exactly the data were being collected and processed, and the group concluded it was too far removed from the experiment to understand these issues in adequate detail in order to proceed with confidence in modeling.

  Another talk by Michael Shelley on kinetic theories for suspensions of microswimmers elicited a remark by Peter Mucha that, from his experience with non-living suspensions, a stochastic treatment of diffusion could lead to important differences from the deterministic treatment of diffusion often employed in kinetic theories. The issues of incorporating stochasticity more faithfully in the kinetic theory of Shelley was discussed in the working group, and has since been taken up by Peter Kramer at his home institution together with a collaborator Patrick Underhill and a graduate student.

- *Modeling Biological Swarmsusing Nonlinear Diffusions:*

Another subgroup was motivated by a different set of talks in the workshop on *Self-Organization and Multi-Scale Mathematical Modeling of Active Biological Systems*, particularly the one by Andrea Bertozzi on modeling the collective motion of biological organisms, e.g., locust swarms, fish schools, ant track formation, etc. Her approach employs, for example in work with Topaz, a two-dimensional continuum kinetic model with a nonlocal social interaction.

Amarjit Budhiraja, Oliver Diaz and Xin Liu are exploring the use of techniques from the theory of nonlinear diffusions to see if they can capture the key aspects of dynamical feature formation from the phenomenological continuum theories using a more fundamental stochastic particle system with a mean field type interaction. This nonlinear diffusion approach is expected to not only yield flexible and tractable simulation schemes but also give a greater insight to the underlying biological mechanism. The interacting particle models are expected to be related to the continuum models through a Propagation of Chaos limit. Rigorously establishing such hydrodynamic limit theorems and the associated fluctuation theorems is the long term goal of this working group. This work is currently in progress.

- *Reaction networks:*

John Fricks, Badal Joshi, John McSweeney, and Richard Yamada explored a specific genetic regulatory network in the suprachiasmatic nucleus, which is responsible for maintaining circadian rhythms. A detailed stochastic simulation of this network (which takes into account the finite number of molecules involved and the effectively random times at which they interact with each other) exhibits oscillations of concentration levels, a qualitative feature completely missed by a coarse-grained deterministic model for this network (based on mass-action principles). The group is seeking to explain the oscillations observed in the simulation through a coarse-grained theory that incorporates stochastic fluctuations, such as a van-Kampen (near-Gaussian) expansion.