# 2006 Program on the Development, Assessment and Utilization of Complex Computer Models

## Biosystems Modeling Workshop

**March 5-7, 2007**

## SPEAKER ABSTRACTS

**Guillaume Bonnet**
University of California, Santa Barbara
Department of Statistics and Applied Probability
bonnet@pstat.ucsb.edu

"On Some Stochastic Oscillator Problems Related to Biological Rhythms"

Biological systems often present regular oscillatory characteristics. Circadian, neurological and cardiac rhythms are just three of the most familiar examples of such phenomenon. In order to understand the underlined system, deterministic mathematical models have been proposed and analyzed, following the seminal works of Winfree, Kuramoto and Strogatz in particular. However, empirical observations, in particular in molecular networks, show that stochastic models should be more appropriate. There exist a rapidly growing literature on such models, some of which have a long history in mechanical engineering and Physics. Central issues includes the sustainability and precision of the oscillations. For Biological systems, the synchronization behavior among coupled systems of oscillators is of crucial importance as well.

In this talk, I will first attend to give an overview of the type of models, known results, and empirical observations from various fields. In an attempt to give rigorous formulation to such problems, I will then show how probabilistic tools, in particular the theory of random dynamical systems (in the sense of Arnold), can give rigorous explanations to some of the experimental observations, can point to some overlooked issues, and more generally give the right framework for further theoretical investigations to biologically motivated problems. Moving towards more realistic models of stochastic oscillators for chemical networks, I will also present some ongoing related work on a stochastic Lotka-Volterra system.

**Kevin Brown**
Harvard University
Department of Molecular and Cellular Biology
kevin@mcb.harvard.edu

"Sophisticated Statistical Mechanics of Sloppy Models"

Models of intracellular protein signaling networks can have tens to hundreds of dynamical variables and as many, if not more, rate parameters drawn from chemical kinetics. Almost all of these parameters are unknown and data are often sparse, making the models only barely determined. There is a famous aphorism in physics: "Give me four parameters and I can fit an elephant. Give me five and I can make it wag its tail." When one considers that even simple models may have tens or hundreds of parameters and such models get more complex very quickly, an attempt to generate meaningful and useful models of biological regulation appears even more daunting. My collaborators and I use methods from statistical physics - ensemble theory, spectral decomposition, Monte Carlo simulation - to analyze and understand these large, poorly constrained models. Our insights into the "cost surface" geometry of signaling networks have revealed them to be only one representative of a new universality class of multiparameter models constrained by data; other examples include fitting sums of exponentials to radioactive decays, varying parameters of variational wave functions used in quantum Monte Carlo calculations, and fitting empirically derived atomic potentials.

**Adrian Dobra**
University of Washington
Department of Statistics
adobra@stat.washington.edu

"Efficient Stochastic Search Algorithms for "Large p" Regression with Dependent Covariates"

We describe and compare novel stochastic search methods for exploring high-dimensional model spaces. Key issues involve estimation, prediction and variable selection in the presence of dependencies among candidate predictors. We show how to transform stochastic algorithms for regression model search into corresponding methods for covariance estimation in gaussian models. We illustrate our approaches using simulated data as well as real datasets from breast cancer and heart genomics.

**Daniel Gillespie**
Gillespie Consulting
GillespieDT@mailaps.org

"Stochastic Chemical Kinetics"

**Thomas Kepler**
Duke University
Department of Immunology/Biostatistics & Bioinformatics
kepler@duke.edu

"Computational Systems Immunology"

**Samuel Kou**
Harvard University
Department of Statistics
kou@stat.harvard.edu

"Stochastic Challenges in Single-Molecule Biophysics"

Recent advances in nanotechnology allow scientists to follow a biological process on a single molecule basis. These advances also raise many challenging stochastic modeling and statistical inference problems. First, by zooming in on single molecules, recent nano-scale experiments reveal that some classical stochastic models derived from oversimplified assumptions are no longer valid. Second, the stochastic nature of the experimental data and the presence of latent processes much complicate the statistical inference. In this talk we will use (i) the modeling of enzymatic reaction pathways and (ii) the modeling of subdiffusion phenomenon in enzymatic conformational fluctuation to illustrate the stochastic challenges in single-molecule biophysics.

**Maya Mincheva**
University of Wisconsin – Madison
Department of Mathematics
mincheva@math.wisc.edu

"Dynamical Properties of Biochemical Reaction Networks"

An important problem in modern cellular biology is to understand the dynamics of interactions in complex networks of genes, proteins and enzymes. Mathematical models of biochemical reaction networks result in large systems of differential equations that are usually nonlinear and have many unknown parameters. Because of these unknown parameters (e.x. reaction rate constants) direct numerical simulation of the dynamics is practically impossible. On the other hand, important properties of the biochemical systems are determined only by the network structure, and do not depend on the unknown parameters. We describe how a bipartite graph associated with the biochemical reaction network can be used to predict its dynamical properties, such as multistability and oscillations. This analysis generalizes the positive/negative feedback cycle conditions for instability.

In more general models, instabilities can be caused by diffusion or delays. Similar network conditions relate the structure of the same bipartite graph to delay-induced oscillations or Turing instability.

**Lea Popovic**
Cornell University
Department of Mathematics
popovic@math.cornell.edu

"Model Reduction Techniques for Biochemical Networks"

In this talk I will emphasize theoretical tools for analysis of biochemical networks which use the multi-scale nature of such systems. I will describe possible ways of reducing the dimensionality of the system. I will also discuss an approach to analyzing the initial state of the system.

**Herschel Rabitz**
Princeton University
Department of Chemistry
hrabitz@princeton.edu

"Drawing Together Aspects of Systems Engineering and Systems Biology"

Systems engineering is a rich subject and similarly, systems biology is expected to be equally as rich given the broad scope of phenomena involved. Some specific aspects of systems biology will be discussed covering (a) control of bionetworks, (b) experimental design of genetic circuits, (c) optimal parameter identification, and (d) an algorithm for accelerating the discovery of efficacious molecular agents. These advances are a work in progress, and a summary of the activities will be presented.

**Greg Rempala**
University of Louisville
Department of Mathematics
g.rempala@louisville.edu

"Tutorial on Stochastic Models in Chemical Kinetics"

The talk shall give a brief overview of the stochastic models of chemical kinetics. It will outline in particular the classical Markov model of chemical reactions under the law of mass action as well as its various approximations obtained by e.g., applying the law of large numbers and functional central limit theorem. Some basic representations of the stochastic kinetic models helpful in developing simulation schemes shall be also discussed.

**Eberhard Voit**
Georgia Institute of Technology
Department of Biomedical Engineering
eberhard.voit@bme.gatech.edu

"Tutorial on Biochemical Network Modelling"

In this tutorial, I will present different approaches to modeling and understanding biochemical systems and discuss research topics that are presently not addressed in a satisfactory manner and await further investigation.