Workshop on Mathematical Modeling and Scientific Computing in Biology and Life Sciences

Abstracts of Lectures

Day 1, Dec. 27th, Friday, 2013

Title: Stochastic dynamics and rare events in computational biology
Speaker: Tiejun Li, Peking University
Abstract:
I will introduce the recent results done by our group for the computational study of the stochastic dynamics in systems biology. The focus will be the analysis and design of tau-leaping methods and the rare event study for gene regulations.

Title: Community Identification in Networks
Speaker: Shuqin Zhang, Fudan University
Abstract:
As a fundamental problem in network study, community (module) identification has attracted much attention from different fields. Several classes of algorithms have been proposed for community structure detection and identification, including clustering techniques, modularity optimization, and other methods. In this talk, I will first introduce a normalized modularity optimization method with degree adjustment, which may solve the problems of the original modularity optimization method. Numerical experiments for both artificial networks and real networks demonstrate that our proposed method has better performance than existing ones, and average degree plays an important role in network community identification. I then introduce an effective method for common community identification from multiple networks under different conditions. The problem is formulated as an optimization model, which combines the community identification in each network and alignment of the communities from different networks together. Theoretical analysis of the model shows its rationality. The method is applied to two groups of gene co-expression networks for humans, which include one for three different cancers, and one for three tissues from the morbidly obese patients. The main functions of most communities for the corresponding disease have been addressed by other researchers, which may provide the theoretical basis for further studying the communities experimentally.

Title: Computation of Transition State and its Applications in System Biology
Speaker: Lei Zhang, Peking University
Abstract:
The dynamics of complex biological systems is often driven by multiscale, rare but important events. In this talk, I will introduce the numerical methods for computing transition states, and then give two examples in distinct biological systems: one is a multiscale stochastic model to investigate a novel noise attenuation mechanism that
relies on more noises in different cellular processes to coordinate cellular decisions during embryonic development; the other is a phase field model to study the neuroblast delamination in Drosophila.

**Title:** Subcritical bifurcation for spatially extended non-gradient systems  
**Speaker:** Xiang Zhou, City University of Hong Kong  
**Abstract:**  
A theory for noise-driven subcritical instabilities in spatially extended systems is put forward. The theory allows one to calculate the critical bifurcation parameter for a first-order phase transition in such non-equilibrium systems in the thermodynamic limit and analyse the mechanism of phase transition. Two examples with distinctive features are studied in detail to demonstrate the usefulness of the theory and the different scenarios that can occur in the thermodynamic limit of non-equilibrium systems. I expect to seek collaboration in application of this theory for real nonlinear problems arising from biology or neuroscience.

**Title:** Improving clinical diagnosis by high-throughput biotechnologies  
**Speaker:** Xianwen Ren, Chinese Academy of Medical Sciences  
**Abstract:**  
High-throughput biotechnologies, e.g., next-generation sequencing, microarrays and mass spectrometry, have revolutionized biomedical research. However, how to extract effective information from the flood of biomedical data becomes a big computational issue, which prevents the translation of these biotechnological advances to clinical bedside. For example, clinicians generally make diagnosis based on a few biomedical indexes but high-throughput technologies always produce data of thousands of genes. To fill this gap between biotechnological advances and clinical requirements, we propose two novel methods from the feature selection and feature extraction perspectives, which greatly improve the accuracy of diagnosis based on high-throughput gene expression data. And an open mathematical question is raised from practice.

**Title:** Optimization, Adaptation, and Initiation of Biological Transport Network  
**Speaker:** Dan Hu, Shanghai Jiao Tong University  
**Abstract:**  
Blood vessel systems and leaf venations are typical biological transport networks. The energy consumption for such a system to perform its biological functions is determined by the network structure. In the first part, I will talk about the optimized structure of the network, and show how the blood vessel system adapts itself to an optimized structure. Mathematical models are used to predict pruning vessels in the experiments of zebra fish. In the second part, I will discuss our recent discovery on modeling the initiation of transport networks. Simulation results are used to illustrate how a tree-like structure is obtained from a continuum adaptation equation set, and how loops can exist in our model. Possible further application of this model will also be discussed.
Title: Fluctuation and fidelity control of a non-proofreading polymerase
Speaker: Jin Yu, Beijing Computational Science Research Center
Abstract:
Polymerases catalyze gene replication and transcription. They modulate activation barriers of nucleotide incorporation and amplify intermediate free energy differentiation between the right and wrong nucleotides. It is essential for the polymerases to achieve sufficiently high fidelity at sufficiently high speed. We had found a small free energy bias in the translocation of an RNA polymerase (RNAP) that aids nucleotide selection [1]. We investigated further how polymerases select against wrong nucleotides efficiently with given kinetics for the right, and with controlled differentiation capacities [2]. We noticed that early selections on the reaction path outperform the late ones in error reduction. In particular, initial screening seems indispensable for lowering error rates without lowering much the speed. To see how exactly the nucleotide selection proceeds, we studied T7 RNAP in atomistic simulations [3]. We found that substantial nucleotide selection happens early, prior to full insertion of the nucleotide for complete Watson-Crick base pairing. A highly conserved residue brings up the small translocation energy bias by marginally stacking with the RNA-DNA hybrid. The residue blocks the active site prior to nucleotide binding, senses the nucleotide species upon pre-insertion, and selectively ‘gates’ the nucleotide during insertion. Our studies thus provide a kinetic survey of the non-proofreading selection system along with underlying molecular mechanisms.

References:

Title: Cell motility driven by motor proteins
Speaker: Yunxin Zhang, Fudan University
Abstract:
In this talk, motor protein related cell motility will be discussed. In brief, the following topics will be addressed: (1) mechanism of motor proteins, (2) cargo transportation by multiple motor proteins, (3) motor traffic along microtubule, and (4) dynamic of microtubule driven by motor proteins.

Day 2, Dec. 28th, Saturday, 2013
Title: Oscillations suppression, synchronization, and modulation
Speaker: Wei Lin, Fudan University
Abstract:
Oscillations are omnipresent in real world, from mechanics to engineering, from optics to astro and geophysics, and from economics to social science. In the human body, oscillators are particularly abundant and appear at many different levels. Different oscillations play different roles in different systems. The mechanisms for producing or preventing oscillations are under active investigations. This talk shows how to suppress, synchronize, and modulate oscillations in isolated system as well as in a network with a large number of coupled oscillators. In particular, the natural frequency of an oscillator is reported to be essentially important to realization of oscillations suppression and synchronization when time delays are taken into account. Also the feedback controls, which are normally used to suppress oscillations, are designed to modulate either the amplitude or the frequency of oscillations. All the analytical findings are potentially useful for uncovering the mechanisms of oscillation phenomena experimentally observed in a wide range of real systems.

Title: Mechanics and Statistics of Bacterial Locomotion  
Speaker: Hepeng Zhang, Shanghai Jiao Tong University  
Abstract:  
The first part of the talk focuses on the mechanical principle that a single bacterium uses to propel itself. We show that though widely-accepted resistive-force theory qualitatively describes the underlying principle of zero Reynolds number propulsion, it fails quantitatively in the biologically relevant regime due to the negligence of hydrodynamic interactions. In the second part, I will discuss a range of emerging phenomena observed in experimental systems consisting of many bacteria. These phenomena originate from interactions between self-propelled organisms; they include anomalous density fluctuation, scale-invariant correlation, turbulence-like flow pattern, and Jamming at high densities.

Title: Stochastic Resonance in Neural Processing and Perception: Several Mathematical Respects  
Speaker: Yanmei Kang, Xi’an Jiao Tong University  
Abstract:  
The talk is concentrating on stochastic resonance (SR) in neural systems, and it is organized into four parts. At first, after a simple introduction to stochastic resonance, basic mathematical theory on SR for general periodically modulated noisy systems will be introduced. Then, I will give a review on the importance and current tendency of SR in neural systems, and also look back the existing theoretic investigation based on first passage time distribution and firing rate developed for the simplest integrate-and-fire (IF) neuron model. Next I will introduce the technique of linear approximation and the most recent proceeding on correlation transmission in IF neural networks etc. Finally, I will talk to the role of negative correlation in neural systems, by referring to our work on supratreshold stochastic resonance in neural processing tuned by correlation (2012 Physical Review E 011923) and two newly-published papers related to signal-noise correlation on cell and neuron etc.
Title: Causal and Structural Connectivity of Neuronal Networks  
Speaker: Douglas Zhou, Shanghai Jiao Tong University  
Abstract:  
Current experimental techniques usually cannot probe the global interconnection pattern of a network. Thus, reconstructing or reverse-engineering the network topology of coupled nodes based upon observed data has become a very active research area. Most existing reconstruction methods are based on networks of oscillators with generally smooth dynamics. However, for nonlinear and non-smooth stochastic dynamical systems, e.g., neuronal networks, the reconstruction of the full topology remains a challenge. Here, we present a noninterventional reconstruction method, which is based on Granger causality theory, for the widely used conductance-based, integrate-and-fire type neuronal networks. For this system, we have established a direct connection between Granger causal connectivity and structural connectivity.

Title: Adult stem cells regeneration- the crosstalk between genetic and epigenetic regulation  
Speaker: Jinzhi Lei, Tsinghua University  
Abstract:  
Adult stem cells, which exist throughout the body, multiply by cell division to replenish dying cells or to promote regeneration to repair damaged tissues. To perform these functions during the lifetime of organs or tissues, stem cells need to maintain their populations in a faithful distribution of their epigenetic states, which are susceptible to stochastic fluctuations during each cell division, unexpected injury, and potential genetic mutations that occur during many cell divisions. However, it remains unclear how the three processes of differentiation, proliferation and apoptosis in regulating stem cells collectively manage these challenging tasks. Here, without considering any molecular details, we propose a genetic optimal control model for adult stem-cell regeneration that includes the three fundamental processes, along with cell division and adaptation based on differential fitnesses of phenotypes. Through analytical estimates and direct numerical simulations, we show that heterogeneous proliferation that depends on the epigenetic states of stem cells can improve the maintenance of stem-cell distribution to create balanced populations. A control strategy during each cell division is derived from the model, leading to a feedback mechanism involving heterogeneous proliferation that can accelerate regeneration with less fluctuation in the stem cell population. When mutation is allowed, apoptosis evolves to maximize the performance during homeostasis after multiple cell divisions. The overall modeling results highlight the importance of crosstalk between genetic and epigenetic regulation and the performance objectives during homeostasis in shaping a desirable heterogeneous distribution of stem cells in terms of epigenetic states. (Collaborations with Simon A. Levin and Qing Nie)
Title: Biological Network Comparison  
Speaker: Lingyun Wu, Chinese Academy of Sciences  
Abstract:  
The biological networks play important role in the systems biology. Due to the rapid development of high-throughput techniques, plenty of biological networks are built from the large scale experimental data as well as literature. But the huge network data have not been fully utilized due to the limited biological network analysis tools. Biological network comparison is one of the fundamental tasks in the field of biological network analysis, and has many applications. Although many models and algorithms were published, biological network comparison methods lag way behind the accumulation of network data. In this talk, I will briefly introduce the mathematical models and algorithms of biological network comparison, and report our recent progress.

Title: Finite element simulation of ion permeation in ion channel systems  
Speaker: Benzhuo Lu, Chinese Academy of Sciences  
Abstract:  
As it is hard to apply all-atomic model to simulate the whole process of ion permeation in ion channel, we use continuum electrodiffusion description for ion flow in the channel system. Electrodiffusion process exists in many apparently different physical objects such as electrolyte cell, nanofluidic device, charged porous media, and ion channel in biology. Real 3D ion channel is particularly difficult to simulate due to the multiscale nature of the transport process, the complex geometry/boundary of the channel protein system, and the singular charge distribution inside the channel protein(s). For this reason, there are so far only a very few softwares publicly available in this important area of biology. We will show our recent relevant works and plan to build up such a platform. In the first part, we’ll talk about the continuum models and numerical works. They include the Poisson-Boltzmann equation, the Poisson-Nernst-Planck equations and their improved forms, and some efficient algorithms we developed for the solution of these equations. In the second part, we will describe the molecular meshing problem which is essential for finite/boundary element modelings. We recently developed a novel and robust mesh generation tool TMSmesh that can handle complex and arbitrarily large biomolecular system. In the third part, I will give a brief introduction to an undergoing project of designing a visualization system, VCMM, to facilitate researches in this area. Finally, we will show applications using our parallel finite element solver to compute properties such as current-voltage characteristics (curves) and conductance to a few channel systems. The results agree well with those obtained with Brownian Dynamics simulations and experiments.

Title: Modeling Regulation in Complex Biological Systems  
Speaker: Yucheng Hu, Tsinghua University  
Abstract:  

The proper functioning of a complex biological system requires robust and precise regulation. Understanding the underlying control mechanisms is the key to understand life. In this talk I will present several models describing biological regulations at different scales: (i) a dynamical gene transcription model at sub-cellular level; (ii) a cell growth model at single cell level and (iii) a feedback control mechanism at population level. Jump processes and stochastic simulation are our main tools to study these models.

Day 3, Dec. 29th, Sunday, 2013

Title: On a Theory of Precise Neural Control in a Noisy System
Speaker: Wenlian Lu, Fudan University
Abstract: In this talk, I will introduce a novel computational paradigm based on modern control and optimization theory and biological observations. We investigate the ‘minimum-variance principle’ of a controlled dynamical system with noise, assuming that the noise inherent to the control signal is sub-Poisson. In this case, we find that the optimal solution of the stochastic controller is not an explicit function but is composed of a parameterized measure. Moreover, in contrast to the supra-Poisson or Poisson noise, this sort of parameterized measure can achieve precise control performance even in the presence of noise.

Title: Probing allostery through DNA: interplay between theory and experiments
Speaker: Hao Ge, Peking University
Abstract: Allostery is well documented for proteins but less recognized for DNA-protein interactions. Experimentalists reported that specific binding of a protein on DNA is substantially stabilized or destabilized by another protein bound nearby. The ternary complex’s free energy oscillates as a function of the separation between the two proteins with a periodicity of ~10 base pairs, the helical pitch of B-form DNA, and a decay length of ~15 base pairs. The binding affinity of a protein near a DNA hairpin is similarly dependent on their separation, which together with molecular dynamics simulations suggests that deformation of the double-helical structure is the origin of DNA allostery. We report a study of DNA deformations using a coarse grained mechanical model and quantitatively interpret the allosteric effects in protein-DNA binding affinity. We provide a simple but effective analytical model where DNA deformations upon protein binding are analyzed and spatial correlations of local deformations along the DNA are examined. The deformation of the DNA base orientations, which directly affect the major groove width, is found in both an analytical derivation and coarse-grained Monte Carlo simulations. This deformation oscillates with a period of 10 base pairs with an amplitude decaying exponentially.
from the binding site with a decay length $\approx 10$ base pairs as a result of the balance between two competing terms in DNA base-stacking energy.

References:
1. Kim, Sangjin; Broströmer, Erik; Xing, Dong; Jin, Jianshi; Chong, Shasha; Ge, Hao; Wang, Siyuan; Gu, Chan; Yang, Lijiang; Gao, Yi Qin; Su, Xiao-dong; Sun, Yujie; Xie, X. Sunney. "Probing Allostery Through DNA," Science 339, 816-819 (2013).
2. Xu, Xinliang; Ge, Hao; Gu, Chan; Gao, Yi Qin; Wang, Siyuan S.; Thio, Beng Joo Reginald; Hynes, James T.; Xie, X. Sunney; Cao, Jianshu. "Modeling Spatial Correlation of DNA Deformation: DNA Allostery in Protein Binding," J. Phys. Chem. B Online (2013)

Title: The role of pressure, cell multiplication and active motion in tumor growth PDE models
Speaker: Min Tang, Shanghai Jiao Tong University
Abstract:
Some recent work about the modeling and analysis of tumor growth PDE models are discussed. On the one hand, we build numerically connections of the individual based model coupling with some stochastic effect with the cell density based PDE models (advection reaction diffusion equation). On the other hand, the relations of the cell density based model and Hele-Shaw type free boundary problem are investigated analytically. The role of pressure, cell multiplication and active motion can be understood from these three different type of models at different levels.