昆山杜克大学
DUKE KUNSHAN UNIVERSITY

Mathematics in Action (MiA2021): Modeling and analysis in molecular biology and electrophysiology

分子生物学及电生理学的数学建模及模拟

June 10 - June 13, 2021
@Duke Kunshan University
Venue: IB2028
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Sponsors :

- National Natural Science Foundation of China
- Mathematical Center for Interdiscipline Research, Soochow University
- Soochow University School of Mathematical Sciences, Soochow University
- Zu Chongzhi Center for Mathematics and Computational Sciences, Duke Kunshan University

Thursday 10th June (China Time)

Wednesday 9th -Thursday 10th June (EST US）

Theme: Biology-Math 12 Talks

Time	Chair	Speaker
8:30-9:00 *20:30-21:00*	Shixin Xu	DKU VCAA Scott MacEachern Jian-Guo Liu (Duke University) Chun Liu (Illinois Institute of Technology)
9:00-9:30 *21:00-21:30*	Chun Liu	Francisco Bezanilla (University of Chicago)
9:30-10:00 *21:30-22:00*		Brian M. Salzberg (University of Pennsylvania)
10:00-10:30 *22:00-22:30*	Break	Break
10:30-11:00 *22:30-23:00*	Francisco Bezanilla	Bob Eisenberg (Rush University Medical Center)
11:00-11:30 *23:00-23:30*		Huaxiong Huang (Beijing Normal University(Zhuhai)& UIC)
11:30-12:00 *23:30-24:00*		Bo Li (University of California, San Diego)
12:00-13:30 *00:00-1:30*	Break &Lunch	Break &Lunch
13:30-14:00 *1:30-2:00*	Xingye Yue	Tzyy-Leng Horng (Feng Chia University)
14:00-14:30 *2:00-2:30*		Benzhuo Lu (Chinese Academy of Sciences)
14:30-15:00 *2:30-3:00*	Break	Break
15:00-15:30 *3:00-3:30*	Benzhuo Lu	Zhennan Zhou (Peking University)
15:30-16:00 *3:30-4:00*		Hao Ge (Peking University)
16:00-20:00 *4:00-8:00*	Break& Dinner	Break& Dinner
20:00-20:30 *8:00-8:30*	Tzyy-Leng Horng	Qi Wang (University of South Carolina)
20:30-21:00 *8:30-9:00*		Zhiliang Xu (University of Notre Dame)
21:00-21:30 *9:00-9:30*		Yuan-Nan Young (New Jersey Institute of Technology)

Friday 11th June (China Time)

Thursday 10th -Friday 11th June (EST US）

Theme: Physics-Math 11 Talks

Time	Chair	Speaker
8:30-9:00 *20:30-21:00*	Bo Li	Ping Sheng (The Hong Kong University of Science and Technology)
9:00-9:30 *21:00-21:30*		Yinglong Miao (University of Kansas)
9:30-10:00 *21:30-22:00*	Break	Break
10:00-10:30 *22:00-22:30*	Ping Sheng	Weihua Geng (Southern Methodist University)
10:30-11:00 *22:30-23:00*		Cheng Wang (University of Massachusetts, Dartmouth)
11:00-11:30 *23:00-23:30*		Tiezheng Qian (The Hong Kong University of Science and Technology)
11:30-13:30 *23:30-1:30*	Break &Lunch	Break &Lunch
13:30-14:00 *1:30-2:00*	Shenggao Zhou	Wenjun Ying (Shanghai Jiaotong University)
14:00-14:30 *2:00-2:30*		Nir Gavish (Technion – Israel Institute of Technology)
14:30-15:00 *2:30-3:00*		Lei Zhang (Peking University)
15:00-20:00 *3:00-8:00*	Break& Dinner	Break& Dinner
20:00-20:30 *8:00-8:30*	Tiezheng Qiang	Ping Lin (University of Dundee)
20:30-21:00 *8:30-9:00*		Weiqing Ren (National University of Singapore)
21:00-21:30 *9:00-9:30*		Lizuo Liu (Southern Methodist University)

Saturday 12th June (China Time)

Friday 11th -Saturday 12th June (EST US）

Theme: Chemistry-Math11 Talks

Time	Chair	Speaker
8:30-9:00 *20:30-21:00*	Guowei Wei	Rudolf Podgornik (Chinese Academy of Sciences)
9:00-9:30 *21:00-21:30*		Zhenli Xu (Shanghai Jiaotong University)
9:30-10:00 *21:30-22:00*	Break	Break
10:00-10:30 *22:00-22:30*	Rudolf Podgornik	Guowei Wei (Michigan State University)
10:30-11:00 *22:30-23:00*		Jie Liang (University of Illinois at Chicago)
11:00-11:30 *23:00-23:30*		Hong Qian (University of Washington)
11:30-13:30 *23:30-1:30*	Break &Lunch	Break &Lunch
13:30-14:00 *1:30-2:00*	Wenjun Ying	Zhonghan Hu (Shandong University)
14:00-14:30 *2:00-2:30*		Dan Hu (Shanghai Jiaotong University)
14:30-15:00 *2:30-3:00*		Shuangliang Zhao (East China University of Science and Technology)
15:00-20:00 *3:00-8:00*	Break& Dinner	Break& Dinner
20:00-20:30 *8:00-8:30*	Zhenli Xu	Tony Maggs (Centre National de la Recherche Scientifique)
20:30-21:00 *8:30-9:00*		Huan-Xiang Zhou (University of Illinois at Chicago)
21:00-21:30 *9:00-9:30*		Fredric Cohen (Rush University)

Sunday 13th June (China Time)

Saturday 12th -Sunday 13th June (EST US）

Theme: Dynamics-Math 8 Talks

Time	Chair	Speaker
8:30-9:00 *20:30-21:00*	Qi Wang	Jian-Guo Liu (Duke University)
9:00-9:30 *21:00-21:30*		Weishi Liu (University of Kansas)
9:30-10:00 *21:30-22:00*	Break	Break
10:00-10:30 *22:00-22:30*	Jian-Guo Liu	Dexuan Xie (University of Wisconsin-Milwaukee)
10:30-11:00 *22:30-23:00*		Yuan Gao (Duke University)
11:00-11:30 *23:00-23:30*	Break &Lunch	Break &Lunch
11:30-13:30 *23:30-1:30*	Konstantinos Efstathiou	Zhigang Zheng (National Huaqiao University)
13:30-14:00 *1:30-2:00*		Huafei Ma (Soochow University)
14:00-14:30 *2:00-2:30*	Break	Break
15:00-15:30 *3:00-3:30*	Shixin Xu	Konstantinos Efstathiou (Duke Kunshan University)
15:30-16:00 *3:30-4:00*		Mauricio del Razo (University of Amsterdam)

VOLTAGE SENSORS AND ION CHANNEL OPENING

PROF. FRANCISCO BEZANILLA (UNIVERSITY OF CHICAGO)

ABSTRACT

The generation of the nerve impulse (action potential) depends on voltage-dependent sodium channels that must open before voltage-dependent potassium channels. We will briefly explain the voltage sensors that give voltage dependence of the ion channels. The voltage sensors have intrinsic charges in the channel protein which move in the cell membrane electric field and generate gating currents. Experiments with voltage clamp and site-directed fluorescence describe molecular details of the voltage sensor operation indicating the paths followed by the charged arginine residues within the protein core. A detailed study of the residues in the core show that the nature of the side chains determine that Na channels are faster than K channels. The canonical coupling of the voltage sensor to the conduction pore is via the linker between transmembrane segments S3 and S4. We will describe that the proximity of the S4 segment of the voltage sensor and the S5 segment of the pore region makes another noncanonical coupling pathway. The molecular basis of this pathway will be described.

RAPID CHANGES IN THE OPTICAL PROPERTIES OF MAMMALIAN NERVE TERMINALS

PROF. BRIAN M. SALZBERG (UNIVERSITY OF PENNSYLVANIA)

ABSTRACT

Intrinsic optical changes, accompany the action potential, and the consequent secretion of neuropeptides, in mammalian nerve terminals. These include light scattering changes, related to the action potential, action currents, and exocytosis, and, also intrinsic fluorescence changes related to mitochondrial oxidative phosphorylation. The light scattering changes are related to the small volume changes in the terminals, a “mechanical spike”, that we show can be detected using high bandwidth atomic force microscopy, and the intrinsic fluorescence changes are related to action potential production in the plasma membrane, through multiple intermediates. These will be discussed, including their likely origins.

IONS IN SOLUTIONS AND CHANNELS: ACCEPTED WISDOM, REVISITED

PROF. BOB EISENBERG (RUSH UNIVERSITY MEDICAL CENTER)

ABSTRACT

Ionic solutions determine many properties of living systems, nanosystems, and electrochemistry, including batteries. Ionic solutions are customarily analyzed in the tradition of thermodynamics extended by statistical mechanics. The statistical mechanics used is based on the theory of a perfect gas, in which point particles, without internal structure, let alone internal motions or dissipation, interact only with elastic collisions, isotropic at that, in the thermodynamic limit, in which boundary conditions do not appear, let alone confine. None of these assumptions apply to ionic solutions, even approximately, because molecules and water have internal structure, dissipate energy in inelastic anisotropic collisions. Indeed, ionic solutions are usually confined by boundary conditions that form devices of the greatest practical importance, like nerve fibers, cardiac muscle, and batteries. Devices do not function without flow and only exist in finite domains.

Ions and water in ionic solutions interact by electrodynamics, including time dependent terms important on the scale

of atoms. Ions interact strongly on all scales, and their interactions are not confined. Potentials on boundaries very far away create flows that allow living systems and batteries to function, often as devices. Electrodynamic interactions extend to infinity thanks to $\varepsilon_0 \partial E/\partial t$, as a glance at the sun or stars demonstrates. Indeed, in a mathematical sense, the thermodynamic limit does not exist (as a well defined uniquely determined quantity or function) in an unbounded system of charges. The sums of Coulomb's laws do not converge to a well defined, let alone uniform limit, in an infinite domain.

Electrodynamics at first glance may seem a weak foundation for theories and simulation, as weak as statistical mechanics. Electrodynamics classically includes a dielectric constant that is ill defined by reality, since no ionic solution has dielectric properties that can be reasonably approximated by a single positive constant. Once the dielectric constant is removed—or should I say exorcized?—mechanical models are needed to describe the response of charge to force. These models are of course specific, the opposite of universal and exact.

Electrodynamics without a dielectric constant is quite different from statistical mechanics. It provides a firm foundation for theory and simulation. To my considerable surprise, easily measured properties of charge movement are described by a universal and exact law, for ***any*** motions of matter or charge. Conservation of total current—that includes $\varepsilon_0 \partial E/\partial t$—is as universal and exact as the Maxwell equations themselves.

Written in one dimension, conservation of total current can become equality of current, so current in components of electronic circuits or ion channels can be described by ordinary differential equations in time, without a spatial variable at all, even for the nearly Brownian currents of thermal motion! In branched systems, conservation of current becomes Kirchhoff's law for total current that allows the design of integrated circuits, digital and analog.

Scientists are trained to be skeptical of universals. Scientists are trained to expect the particular and its parameters. To their discomfort, scientists see that the Maxwell equations without a dielectric constant are both exact and universal, without material parameters. It is reassuring that parameters are found in abundance in the models of charge movement needed to describe real ionic solutions.

It might be wise to build models of ionic solutions on the firm foundation of exact electrodynamics, ***abandoning the quicksand of statistical mechanics, and a dielectric constant, using instead explicit models*** of motions of charge and mass coupled to the Maxwell equations that describe electrodynamics everywhere, from inside atoms to between stars.

Actional Potentials, Spreading Depression and Potassium Clearance

PROF. HUAXIONG HUANG (Beijing Normal University(Zhuhai)&UIC)

ABSTRACT

In this talk, we give a brief historic view of Spreading Depression (SD), a pathological condition in the cortex discovered more than 80 years ago. The mechanism for SD has been a subject for debate over many years. One of the leading theories proposed in the 1950s is the accumulation of potassium in the extracellular space, which has been widely accepted today. Since potassium accumulates naturally in the extracellular space as a consequence of neuronal firings, the questions are, therefore, what happens if the potassium is not cleared, and how potassium is cleared from the extracellular space in a healthy brain. We attempt to answer these questions by carrying out mathematical analysis and computer simulations using mathematical models. We show that increased neuronal activities could lead to SD, and glial cells play a significant role in the clearance of potassium.

This is joint work with R.M. Miura, W. Yao, Y. Zhu, S. Xu, and R.S. Eisenberg.

COUPLING MONTE CARLO, VARIATIONAL IMPLICIT SOLVATION, AND BINARY LEVEL-SET FOR SIMULATIONS OF BIOMOLECULAR BINDING

PROF. BO LI (UNIVERSITY OF CALIFORNIA, SAN DIEGO)

ABSTRACT

We develop a hybrid approach that combines the Monte Carlo (MC) method, a variational implicit-solvent model (VISM), and a binary level-set method for the simulation of biomolecular binding in an aqueous solvent. The solvation free energy for the biomolecular complex is estimated by minimizing the VISM free-energy functional of all possible solute-solvent interfaces that are used as dielectric boundaries. This functional consists of the solute volumetric, solute-solvent interfacial, solute-solvent van der Waals interaction, and electrostatic free energy. Minimizing such a functional in each MC move is made possible by our new and fast binary level-set method. This method is based on the approximation of surface area by the convolution of an indicator function with a compactly supported kernel, and is implemented by simple flips of numerical grid cells locally around the solute-solvent interface. We apply our approach to the p53-MDM2 system for which the two molecules are approximated by rigid bodies. Our efficient approach captures some of the poses before the final bound state. All-atom molecular dynamics simulations with most of such poses quickly reach to the final bound state. Our work is a new step toward realistic simulations of biomolecular interactions. With further improvement of coarse graining and MC sampling, and combined with other models, our hybrid approach can be used to study the free-energy landscape and kinetic pathways of ligand binding to proteins. This is joint work with Zirui Zhang, Clarisse Ricci, Li-Tien Cheng, and J. Andy McCammon.

IV CURVE PREDICTION OF KCSA POTASSIUM CHANNEL

PROF. TZYY-LENG HORNG (FENG CHIA UNIVERSITY)

ABSTRACT

Ion channels are pore-forming trans-membrane proteins that allow ions to enter/leave cell. There are many important cell functions involving ion channels, e.g., establishing and regulating action potential in neurons and myocytes. The X-ray crystallographic structures of K channels reveal a common architecture of the pore. Four subunits are symmetrically arranged around the channel axis, with each subunit having at least two transmembrane helixes separated by a re-entrant P-loop and selectivity filter (SF). K channels are the most extensively studied family of ion channels, both experimentally and computationally, and KcsA structure has been the most popular one among K channels since it is the first K channel to be crystalized. SF of K channels is the essential element to their permeation and selectivity mechanisms. Each subunit contributes to SF with a conserved signature peptide, namely TVGYG in most of the channels. Four K-ion-binding sites exists inside SF, designated S1-S4 starting at the extracellular side. In addition, K ion can bind at the intracellular/extracellular vestibules of SF designated as S5 and S0 sites. SF is generally too narrow to accommodate a K ion with its hydration shell, and thus K ions must be dehydrated to enter SF, when attracted by the strong negative charges of carbonyl oxygens in SF. IV curve simulated from classic PNP equations has a serious mismatch with its experimental counterpart. This is due to ignorance of strong steric effect and dehydration that K ion encounters inside narrow SF. Here we modified classical PB/PNP model to Bikerman-Born-PB/PNP model by considering steric effect and solvation energy to cure this problem. Through Bikerman-Born-PB model, we found in SF K only occupies S0, S2, S3 and S5 leaving S1 and S4 to be void, which agrees well with hard knock-on MD simulations. The voidness of K at S1 and S4 sites makes these two sites being ion-depletion zones. These ion-depletion zones robustly persist even when voltage is applied across the membrane, and makes our Bikermna-Born-PNP model fail to produce any current when voltage is applied. Ion-depletion at S1 and S4 makes K ion to jump over these two sites during single-file permeation through SF. This site-jump-over behavior can not be modeled by PNP-type equations based on continuum, and is better modeled by chemical reaction. We have then constructed a reaction rate model and further estimated all the model rate constants by using macroscopic diffusion theories and MD simulations. With estimated rate constants, we predicted the IV curve by our rate model and compared with the experimental one (LeMasurier et al., 2001). Notably, all the major features of the experimental IV curve, namely the amount of current carried, the asymmetry, and the saturation at highly positive and negative voltages, appear quite well reproduced.

ON NUMERICAL ASPECTS OF POISSON-NERNST-PLANCK SYSTEM

PROF. BENZHUO LU (CHINESE ACADEMY OF SCIENCES)

ABSTRACT

The PNP is an electric-coupled covection-diffusion system. Some typical properties/performance for this PNP system need to be considered in numerical solution, such as accuracy, robustness, and some special structures of preserving positivity, energy dissipation, and flux conservation. In convection-dominated cases, the flux conservation seems a key factor influencing the overall performace of the numerical method. This talk reports our recent advances in FEM solution of the PNP-like systems. A PNP benchmark for numerical test, a stabilized FEM, an average FEM, and perfromance comparision are to be presented. The stability, accuracy, robustness (involving in cases of poor mesh quality), flux-conservation property are extensively tested in 3D simulations of geometrically complicated ion channels, nanopores, and semiconductor devices.

FOKKER-PLANCK EQUATIONS OF NEURON NETWORKS: JUSTIFICATION AND NUMERICAL SIMULATION

PROF. ZHENNAN ZHOU (PEKING UNIVERSITY)

ABSTRACT

In this talk, we are concerned with the Fokker-Planck equations associated with the Nonlinear Noisy Leaky Integrate-and-Fire model for neuron networks. Due to the jump mechanism at the microscopic level, such Fokker-Planck equations are endowed with an unconventional structure: transporting the boundary flux to a specific interior point. In the first part of the talk, we present an alternative way to derive such Fokker-Planck equations from the microscopic model based on a novel iterative expansion. With this formulation, we prove that the probability density function of the "leaky integrate-and-fire" type stochastic process is a classical solution to the Fokker-Planck equation. Secondly, we propose a conservative and positivity preserving scheme for these Fokker-Planck equations, and we show that in the linear case, the semi-discrete scheme satisfies the discrete relative entropy estimate, which essentially matches the only known long time asymptotic solution property. We also provide extensive numerical tests to verify the scheme properties, and carry out several sets of numerical experiments, including finite-time blowup, convergence to equilibrium and capturing time-period solutions of the variant models.

THE NONEQUILIBRIUM MECHANISM OF NOISE-ENHANCED DRUG SYNERGY IN HIV LATENCY REACTIVATION

PROF. HAO GE (PEKING UNIVERSITY)

ABSTRACT

The "shock and kill" strategy has become a promising way to cure HIV by eliminating latent HIV reservoirs, the main barrier to a clinical cure. Recently, single-cell screening experiments have shown the Noise-enhanced drug synergy on reactivating latent HIV. However, the underlying biomolecular mechanism is still a mystery. We propose here a generic model for HIV regulation and Tat transcription/translation. Using this model, we find out that the drug synergy is mainly determined by the magnitude and direction of energy input into the genetic regulatory kinetics of HIV promotor. We further show that the Noise-enhanced drug synergy requires the timescale of HIV promoter entering into a transcriptionally non-permissive state without drugs presented to be slower than the timescale of Tat transactivation. Our model reveals a generic nonequilibrium mechanism underpinning the Noise-enhanced drug synergy, which is useful for improving the drug effect and identifying other drug synergies on lentivirus latency reactivation.

A PHASE FIELD EMBEDDING METHOD FOR FLOW-ACTIVE PARTICLE INTERACTIONS

PROF. QI WANG (UNIVERSITY OF SOUTH CAROLINA)

ABSTRACT

We present a novel computational framework to numerically investigate fluid structure interaction using the phase field embedding. Each solid structure or soft matter structure immersed in the fluid, grossly referred to as the particle in this paper, is represented by a volume preserving phase field. The motion of the active particle is driven by the surrounding fluid velocity and its self-propelling velocity. A repulsive force exists between each pair of particles and between a particle and the boundary. The particle also exerts a drag force to the fluid. When the particle is solid, its state is described by a zero velocity gradient tensor and a phase field that defines its profile. A thermodynamically consistent hydrodynamic model is then derived for the fluid-particle ensemble by the generalized Onsager principle. Structure-preserving numerical algorithms are developed for the thermodynamically consistent model. Numerical tests are carried out to verify the rate of convergence and some numerical examples are given to demonstrate the usefulness of the computational framework for simulating fluid-structure interactions for self-propelling active particles.

MATHEMATICAL AND COMPUTATIONAL MODELING BLOOD CLOT FORMATION

PROF. ZHILIANG XU (UNIVERSITY OF NOTRE DAME)

ABSTRACT

Blood clotting is a multiscale process involving blood cells, fibrinogen polymerization, coagulation reactions, ligand-receptor interactions and blood plasma flow. In this talk, We will discuss models to cover a few aspects of blood clotting. In particular, a continuum model for studying the structural stability of clots utilized the phase field and energetic variational approaches and a discrete model studying fibrin network mechanics will be discussed.

THE MANY BEHAVIORS OF DEFORMABLE ACTIVE DROPLETS

PROF. YUAN-NAN YOUNG (NEW JERSEY INSTITUTE OF TECHNOLOGY)

ABSTRACT

Active fluids consume fuel at the microscopic scale, converting this energy into forces that can drive macroscopic motions over scales far larger than their microscopic constituents. In some cases, the mechanisms that give rise to this phenomenon have been well characterized, and can explain experimentally observed behaviors in both bulk fluids and those confined in simple stationary geometries. More recently, active fluids have been encapsulated in viscous drops or elastic shells so as to interact with an outer environment or a deformable boundary. Such systems are not as well understood. In this work, we examine the behavior of droplets of an active nematic fluid. We study their linear stability about the isotropic equilibrium over a wide range of parameters, identifying regions in which different modes of instability dominate. Simulations of their full dynamics are used to identify their nonlinear behavior within each region. When a single mode dominates, the droplets behave simply: as rotors, swimmers, or extensors. When parameters are tuned so that multiple modes have nearly the same growth rate, a pantheon of modes appears, including zigzaggers, washing machines, wanderers, and pulsators.

NOVEL PERSPECTIVES FROM THE HYDRODYNAMIC MODES: FLUCTUATION-DISSIPATION THEOREM, HYDRODYNAMIC BOUNDARY CONDITION, AND NONLOCAL CORRELATIONS IN THERMAL FLUCTUATIONS

PROF. PING SHENG (THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY)

ABSTRACT

In this talk I present newly acquired perspectives on some classical topics in hydrodynamic boundary condition, thermal fluctuations, and the fluctuation-dissipation theorem; all derived from the hydrodynamic modes (HMs)—the eigenfunctions of the Navier-Stokes equation under the Navier slip boundary condition.

We have obtained the analytic solution of the HMs for a 2D channel. By using the orthogonality and completeness properties of the solution, a simple expression of the fluctuation-dissipation theorem was obtained, involving only the eigenvalues of the HMs. In addition, we (over-) determine the position of the hydrodynamic boundary by (1) projecting the analytic solution form onto the molecular dynamic (MD) equilibrium configurations so as to obtain the decay rates from their time-correlation, (2) using Onsager's minimum dissipation theorem to determine the HM's eigenvalues and eigenfuctions from the decay rates, and (3) using HMs' orthogonality property to determine the precise position of the hydrodynamic boundary and the slip length. The latter is obtained from the dispersion relation of the analytic solution, once the other parameters are known. Invariably, the hydrodynamic position falls inside the fluid domain, 1 molecular size away from the liquid-solid interface.

In another development, we took note of the fact that the HMs represent collective fluid movements, each representing an independent degree of freedom and hence in thermal equilibrium is actuated by kBT/2 of thermal energy (from the equipartition theorem in statistical mechanics). This is quite different from the molecular dynamics or the kinetic theory point of view, where the accounting unit is the individual molecule and hence the time and spatial correlations of thermal fluctuations are always regarded as delta-function like, i.e., extremely short-ranged, governed by the elastic collision time and mean free path. While the thermal fluctuations time series can be reproduced statistically by using the HMs where their relative phases are random, it always remain an intriguing question on whether the collective motion aspect of the HMs can be manifest under certain circumstances. If so, it would introduce a new element into the statistical ensemble averaging in thermal equilibrium. We show that this can indeed be the case in mesoscopic samples where the boundary condition is periodically modulated so that the HMs with different periodicities are suppressed, whereas those with commensurate periodicities are phase-locked by the modulated boundary condition. Molecular dynamics verification of the extended spatial correlations represents the first time such a phenomenon has been observed.

*Work done in collaboration with Xiaohui Deng, Xiaoping Wang, Xiaoyu Wei, and Tiezheng Qian.

COMPUTING BIOMOLECULAR BINDING THERMODYNAMICS AND KINETICS FROM ACCELERATED MOLECULAR SIMULATIONS

PROF. YINGLONG MIAO (UNIVERSITY OF KANSAS)

ABSTRACT

Biomolecular recognition such as binding of small molecules and flexible peptides to target proteins plays key roles in cellular function. It is critical to characterize thermodynamics and kinetics of biomolecular recognition for drug design. However, such tasks have proven challenging in computational chemistry and biophysics. Building on a robust Gaussian accelerated molecular dynamics (GaMD) technique, we have developed selective Ligand GaMD (LiGaMD)[1] and Peptide GaMD (Pep-GaMD)[2] algorithms, which allow for highly efficient simulations of biomolecular binding. In LiGaMD, we selectively boost the nonbonded interaction energy of the small-molecule ligand to speed up its

dissociation. In Pep-GaMD, since peptides often fold with dramatic conformational changes during binding, a boost potential is applied to the total potential energy of the peptide (both non-bonded and bonded) in order to model the peptide high flexibility. In both algorithms, another boost potential can be applied to the remaining potential energy of the system to facilitate ligand and peptide rebinding. LiGaMD and Pep-GaMD have enabled, for the first time, microsecond all-atom simulations to capture repetitive dissociation and binding of small-molecule ligands and highly flexible peptides. Biomolecular binding free energies are calculated through reweighting of these simulations by cumulant expansion to the 2nd order ("Gaussian approximation"). Furthermore, biomolecular binding kinetics could be properly recovered using Kramers' rate theory, which accounts for barriers and curvatures of the free energy surfaces as well as biomolecular diffusion coefficients. As demonstrated on model systems, the calculated ligand/peptide binding free energies and kinetic rate constants are in excellent agreements with the available converged conventional molecular dynamics simulations and/or experimental data.

COMPUTATION OF PROTEIN PKA VALUES USING NUMERICAL AND MACHINE LEARNING ALGORITHMS

PROF. WEIHUA GENG (SOUTHERN METHODIST UNIVERSITY)

ABSTRACT

Protein pKa values are important quantities characterizing the ability of protein active sites to give up protons under different pH environment. These values can be measured using NMR by tracing chemical-shifts of some special atoms, which is however expensive and time-consuming. Alternatively, protein pKa values can be calculated by free energy changes subject to the protonation and deprotonation of active sites. To this end, the Poisson-Boltzmann model, which governs the electrostatics, needs to be solved efficiently and accurately for a great many times under the various charge distributions subject to titrating states. In this talk, we provide a framework and pipeline for the computation of protein pKa values using developed numerical PB solvers coupled with machine learning algorithms such as deep neural network (DNN). Simulation results are compared with experimental results for validation

A POSITIVITY PRESERVING, ENERGY STABLE AND CONVERGENT NUMERICAL SCHEME FOR THE POISSON-NERNST-PLANCK SYSTEM

PROF. CHENG WANG (UNIVERSITY OF MASSACHUSETTS, DARTMOUTH)

ABSTRACT

A finite difference numerical scheme is proposed and analyzed for the Poisson-Nernst-Planck equation (PNP) system. To understand the energy structure of the PNP model, we make use of the Energetic Variational Approach (EnVarA), so that the PNP system could be reformulated as a non-constant mobility, conserved gradient flow, with singular logarithmic energy potentials involved. To ensure the unique solvability and energy stability, the mobility function is explicitly treated, while both the logarithmic and the electric potential diffusion terms are treated implicitly, due to the convex nature of these two energy functional parts. The positivity-preserving property for both concentrations is established at a theoretical level. This is based on the subtle fact that the singular nature of the logarithmic term around the value of 0 prevents the numerical solution reaching the singular value, so that the numerical scheme is always well-defined. In addition, an optimal rate convergence analysis is provided in this work, in which many highly non-standard estimates have to be involved, due to the nonlinear parabolic coefficients. The higher order asymptotic expansion (up to third order temporal accuracy and fourth order spatial accuracy), the rough error estimate (to establish the discrete maximum norm bound), and the refined error estimate have to be carried out to accomplish such a convergence result. In our knowledge, this work will be the first to combine the following three theoretical properties for a numerical scheme for the PNP system: (i) unique solvability and positivity, (ii) energy stability, and (iii) optimal rate convergence. A few numerical results are also presented in this talk, which demonstrates the robustness of the proposed numerical scheme.

ONSAGER'S VARIATIONAL PRINCIPLE IN ACTIVE SOFT MATTER

PROF. TIEZHENG QIAN (THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY)

ABSTRACT

Onsager's variational principle (OVP) was originally proposed by Lars Onsager [L. Onsager, Phys. Rev., 1931, 37, 405–426]. This fundamental principle provides a powerful tool for formulating thermodynamically consistent models. It can also be employed to find approximate solutions, especially in the study of soft matter dynamics. In this work, OVP is extended and applied to the dynamic modelling of active soft matter. By incorporating the activity of biological systems into OVP, we develop a general approach to construct thermodynamically consistent models for better understanding the emergent behaviours of individual cells, cell aggregates, and tissues. This is a joint work with Dr. Xinpeng Xu.

Solution of the bidomain equations in computational cardiac electrophysiology with a composite backward differentiation formula

PROF. WENJUN YING (SHANGHAI JIAOTONG UNIVERSITY)

ABSTRACT

For numerically solving the bidomain equations in computational cardiac electrophysiology, a semi-implicit or an operator splitting method is usually preferred than a fully implicit time integration method even though it is known that both semi-implicit and operator splitting methods are not L-stable methods for stiff problems, including the bidomain equations. As many (if not most) researchers in the community have an impression that a fully implicit method is too complicated for someone to implement and too expensive for the computer to run. In this talk, we will present a fully implicit time integration method for the bidomain equations in multiple space dimensions. We will show by numerical simulation results that the bidomain equations may be solved very efficiently with the implicit method. The method is a composite backward differentiation formula (CBDF), L-stable for stiff problem. It was first proposed for implicitly modeling cardiac dynamics (the monodomain equation) along a cable in [Wenjun Ying, Donald Rose and Craig Henriquez, Efficient fully implicit time integration method for modeling cardiac dynamics, IEEE Trans. Biomed. Engrg, Vol 55 (12), pp. 2701-11, 2009]. The nonlinear equations resulting from the fully implicit discretization of the bidomain equations are solved with the Newton method. In multiple space dimensions, the linearized discrete equations are no longer tridiagonal and can not be solved with the Thomas algorithm. In our work, by a special arrangement of the equations, the discrete system has a very nice formulation. It is symmetric and non-negative definite and can be solved with a multilevel and multigrid iterative method. Some other techniques that we use to accelerate the Newton and multilevel/multigrid iterations will be reported in the talk.

FINITE DOMAIN EFFECTS IN STEADY-STATE SOLUTIONS OF POISSON-NERNST-PLANCK EQUATIONS

PROF. NIR GAVISH (TECHNION - ISRAEL INSTITUTE OF TECHNOLOGY)

ABSTRACT

Steady-state solutions of the Poisson-Nernst-Planck model are studied in the asymptotic limit of large, but finite domains. By using asymptotic matching for integrals, we derive an approximate solution for the steady-state equation

with exponentially small error with respect to the domain size. The approximation is used to quantify the extent of finite domain effects over the full parameter space. Surprisingly, already for small applied voltages (several thermal voltages), we found that finite domain effects are significant even for large domains (on the scale of hundreds of Debye lengths). Namely, the solution near the boundary, i.e., the boundary layer (electric double layer) structure, is sensitive to the domain size even when the domain size is many times larger than the characteristic width of the boundary layer. We focus on this intermediate regime between confined domains and 'essentially infinite' domains, and study how the domain size effects the solution properties. We conclude by providing an outlook to higher dimensions with applications to ion channels and porous electrodes.

Joint work with Doron Elad.

CONSTRUCTION OF SOLUTION LANDSCAPE ON THE ENERGY LANDSCAPE

PROF. LEI ZHANG (PEKING UNIVERSITY)

ABSTRACT

Energy landscape has been widely applied to many physical and biological systems. A long standing problem in computational math and physics is how to search for the entire family tree of possible stationary states, without unwanted random guesses, starting from a parent state on the energy landscape all the way down to energy minima? Here we introduce a novel concept "Solution Landscape", which is a pathway map consisting of all stationary points and their connections. Then we developed a general and efficient numerical method to construct the solution landscape, which not only identifies all possible minima, but also advances our understanding of how a complex system moves on the energy landscape. As an example, we solve the Landau-de Gennes energy to model a liquid crystal confined in square box; we illustrate the basic concepts by examining the multiple stationary solutions and the connected pathway maps of the model.

A PHASE FIELD MODELLING METHOD AND A DIFFUSE DOMAIN METHOD FOR VARIABLE DENSITY TWO-PHASE FLOWS WITH MOVING CONTACT LINES.

PROF. PING LIN (UNIVERSITY OF DUNDEE)

ABSTRACT

We will first show how to develop a thermodynamically consistent phase field model for the binary incompressible (quasi-incompressible) fluid with thermocapillary effects, which allows for the different properties (densities, viscosities and heat conductivities) of each fluid component. A sharp-interface limit analysis is carried out to show that the interfacial conditions of the classical sharp-interface conditions can be recovered or developed. We then apply the modelling method to derive a model for variable density moving contact line problems. Energy law preserving computational methods are developed for variable density models. We also present a diffuse domain method to deal with fixed or moving complex geometry. A number of illustrative computational examples will be presented.

INTERFACE PROFILES FOR CONTACT LINES ON ELASTIC MEMBRANE

PROF. WEIQING REN (NATIONAL UNIVERSITY OF SINGAPORE)

ABSTRACT

We consider a fluid interface in contact with an elastic membrane and study the static profiles of the interface and the membrane. Equilibrium conditions are derived by minimizing the total energy of the system with volume constraints. Asymptotic solutions are obtained in the limits as the bending modulus tends to infinity (stiff limit) and zero (soft limit), respectively. In the stiff limit, the leading-order solution is given by that of a droplet sitting on a rigid substrate with the contact angle satisfying the Young-Dupré equation; in the soft limit, a transition layer appears near the contact line and the interfaces exhibit constant curvatures in the outer region with apparent contact angles obeying Neumann's law. These solutions are validated by numerical experiments.

A LINEARIZED LEARNING WITH MULTISCALE DEEP NEURAL NETWORK FOR STATIONARY NAVIER-STOKES EQUATIONS WITH OSCILLATORY SOLUTIONS

PROF. LIZUO LIU (SOUTHERN METHODIST UNIVERSITY)

ABSTRACT

We present several linearized schemes that accelerate the convergences of training for those PDE problems containing nonlinear terms. The stationary nonlinear Navier-Stokes equation is what we study in this paper. To solve the stationary nonlinear Navier-Stokes equation, we introduce the idea of linearization of Navier-Stokes equation and iterative methods to treat the nonlinear convection term. Three forms of linearizations are considered. After a benchmark problem, we solve the highly oscillating stationary flows utilizing the proposed multi-scaled neural network and the linearized ideas in complex domains. The results show that multiscale deep neural network combining with the linearized schemes can be trained fast and accurately.

CHARGE SYMMETRY BROKEN COMPLEX COACERVATION

PROF. RUDOLF PODGORNIK (CHINESE ACADEMY OF SCIENCES)

ABSTRACT

Liquid-liquid phase separation has emerged as one of the important paradigms in the chemical physics as well as biophysics of charged macromolecular systems. We elucidate an equilibrium phase separation mechanism based on charge regulation, i.e., protonation-deprotonation equilibria controlled by pH, in an idealized macroion system which can serve as a proxy for simple coacervation. First, a low-density density functional calculation reveals the dominance of two-particle configurations coupled by ion adsorption on neighboring macroions. Then a binary cell model, solved on the Debye-Hückel as well as the full nonlinear Poisson-Boltzmann level, unveils the charge symmetry breaking as inducing the phase separation between low- and high-density phases as a function of pH. These results can be identified as a charge symmetry broken complex coacervation between chemically identical macroions.

RANDOM-BATCH EWALD METHOD FOR LONG-RANGE PARTICLE SYSTEMS

PROF. ZHENLI XU (SHANGHAI JIAOTONG UNIVERSITY)

ABSTRACT

The development of efficient methods for long-range systems plays important role in all-atom simulations of biomolecules and drug design. We present a random-batch Ewald (RBE) method for molecular dynamics simulations of particle systems with long-range Coulomb interactions. The RBE takes advantage of the random minibatch strategy for the force calculation between particles, leading to an order N algorithm. It is based on the Ewald splitting of the Coulomb kernel and the random importance sampling is employed in the Fourier part such that the force variance can be reduced. This new simulation method avoids the use of the FFT and greatly improves the scalability of the molecular simulations. We present numerical results to show the nice features of the algorithm.

MATH AND AI FOR COVID-19 VACCINES AND ANTIBODY DRUGS

PROF. GUOWEI WEI (MICHIGAN STATE UNIVERSITY)

ABSTRACT

We have introduced evolutionary de Rham-Hodge, multiscale cohomology, and persistent spectral graph to obtain high-level abstractions of protein-protein interactions. Our new mathematical tools significantly enhance AI's ability to handle excessively large datasets of complex biomolecules. Aided with our genotyping of near 300,000 SARS-CoV-2 genomes (https://users.math.msu.edu/users/weig/SARS-CoV-2_Mutation_Tracker.html), our math-AI approach gives rise to the cutting edge design and discovery of mutation-proof vaccines and antibody drugs.

PRINCIPLES OF CHROMATIN FOLDING AND MANY-BODY INTERACTIONS BY MINIMALIST 3D CHROMATIN POLYMER MODELS: STRUCTURE AND FUNCTION OF 3D GENOME

PROF. JIE LIANG (UNIVERSITY OF ILLINOIS AT CHICAGO)

ABSTRACT

3D organization of chromosomes in cell nucleus play important roles in genome functions. Essential information on chromatin structure has been gathered, largely from chromosome conformation capture (Hi-C), the experimental technique that measures pairwise interactions between genomic regions. Here we demonstrate how a minimalist 3D polymer model of chromatin can shed light on principles of genome organization. Our minimalist models are based on basic properties that 3D chromatin conformations: 1) must be self-avoiding, and satisfy and 2) the constraint of cell nuclei volume. To obtain correctly packed 3D chromatin polymer conformations in confined nucleus volume, we have overcome technical challenges and developed deep sampling methods. These methods allow us to generate properly-sampled large ensembles of 3D chromatin conformations. Our minimalist models can explain: a) the physical basis of scaling relationship such as contact probability of two regions and their genomic separation, b) the origin of the structures of topologically-associating domains. Without invoking any adjustable parameter, our model can also c) fold chromatin chains into 3D conformations using the small set of biological interaction, achieving high accuracy (R=0.96- 0.97). The single-cell 3D chromatin conformations in our model ensemble d) are in excellent agreement with single-cell experimental measurements, and e) can quantitatively characterize chromatin heterogeneity. We further discuss novel biological findings relating genome structures and genome function. These include orchestrated changes in chromatin heterogeneity during Drosophila embryogenesis, prominence of functional hubs of higher-order many-body interactions, their global landscape in active genomic regions, as well as the 1D signature of epigenetic modifications of many-body interactions as identified by machine learning. (See https://rdcu.be/cdgFv for a recent publication).

IN SEARCH OF THE MISSING INFORMATION: HEAT

PROF. HONG QIAN (UNIVERSITY OF WASHINGTON)

ABSTRACT

I shall discuss our recent understanding of the thermodynamic structure and large deviations theory.

A SYMMETRY-PRESERVING MEAN-FIELD APPROACH FOR ELECTROSTATICS

PROF. ZHONGHAN HU (SHANDONG UNIVERSITY)

ABSTRACT

An accurate handling of electrostatics in complex bulk or interfacial liquids is necessary to describe various physico-chemical processes in molecular simulation. To reduce the computational cost and to understand analytically the complex effect of long-ranged electrostatics, the so-called symmetry-preserving mean-field approach suggests that certain slowly varying component of the intermolecular potential, u_1, can be replaced by its average over the degrees of freedom in the directions with preserved symmetry of interest, <u_1>_sp. The same average applied for the overall intermolecular potential or the Columbic interaction, defined as the symmetry-preserving mean-field condition, therefore serves as a guiding constrain in building any accurate methods.

The SPMF approach has been benchmarked by an extreme case of a one-dimensional system, for which other mean-field approaches fail inevitably. In practice, we have exploited this approach for examples of three-dimensional realistic systems with various u_1 subject to planar or spherical symmetry. Moreover, analytically solvable mean-field equations have been made available to correct the failure of the current approach that violates the SPMF condition.

In this talk, I will demonstrate the usefulness of the idea in treating the long-range electrostatic screening effect which can not be captured by any existing effective truncation potential or other mean-field approach that might work well to describe structural, thermodynamic or even dielectric properties in bulk.

FINITE-TEMPERATURE DIMER METHOD FOR FREE ENERGY CALCULATIONS

PROF. DAN HU (SHANGHAI JIAOTONG UNIVERSITY)

ABSTRACT

The dimer method and its variants have been shown to be efficient in finding saddle points on potential surfaces. In the dimer method, the most unstable direction is approximately obtained by minimizing the total potential energy of the dimer. Then, the force in this direction is reversed to move the dimer toward saddle points. When the finite-temperature effect is important for a high-dimensional system, one usually needs to describe the dynamics in a low-dimensional space of reaction coordinates. In this case, transition states are collected as saddle points on the free energy surface. The traditional dimer method cannot be directly employed to find saddle points on a free energy surface since the surface is not known a priori. Here, we develop a finite-temperature dimer method for searching saddle points on the free energy surface. In this method, a constrained rotation dynamics of the dimer system is used to sample dimer directions and an efficient average method is used to obtain a good approximation of the most unstable direction. This approximated direction is then used in reversing the force component and evolving the dimer toward saddle points. Our numerical results suggest that the new method is efficient in finding saddle points on free energy surfaces.

FLOW EFFECT ON ION ADSORPTION IN SLIT PORES

PROF. SHUANGLIANG ZHAO (EAST CHINA UNIVERSITY OF SCIENCE AND TECHNOLOGY)

ABSTRACT

To describe the commonly existing coupling between adsorption dynamics and fluid flow, a non-equilibrium molecular model is developed, upon which we systematically investigate the dynamical adsorption of ionic components from confined flows onto the charged surfaces of nanoscale pores, and find that a competition relation exists between the adsorption and flow. Promoting flow speed suppresses the adsorption amount, while enhancing adsorption strength reduces the flow speed. With the increase of flow speed, the contact density of co-ion is enhanced while that of counter-ion is suppressed, and this leads to overall enhanced accumulation charge densities at pore surfaces. Besides, the accumulation charge density increases monotonically with the applied voltage in large pores, while displays a non-trivial relation with the applied voltage in small pores of several ion sizes. This work not only extends the theoretical framework of non-equilibrium molecular theories, but also provides novel insights into the regulation of interfacial dynamic processes.

DUAL ENERGIES IN ELECTROSTATICS

PROF. TONY MAGGS (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE)

ABSTRACT

The free energy of a system of charges can be formulated in many equivalent forms. Historically, much analytic and numerical work uses a formulation in terms of the electrostatic potential. Here, we show that dual formulations using the Maxwell displacement field lead to mathematically equivalent forms which are easier to interpret and work with. In particular such formulations lead to variational formulations which have a minimzing principle and can be sampled in Monte Caro simulation.

SHEAR RELAXATION GOVERNS DYNAMIC PROCESSES OF BIOMOLECULAR CONDENSATES

PROF. HUAN-XIANG ZHOU (UNIVERSITY OF ILLINOIS AT CHICAGO)

ABSTRACT

Phase-separated biomolecular condensates must respond agilely to biochemical and environmental cues in performing their wide-ranging cellular functions, but our understanding of condensate dynamics is lagging. Ample evidence now indicates biomolecular condensates as viscoelastic fluids, where shear stress relaxes at a finite rate, not instantaneously as in viscous liquids. Yet the fusion dynamics of condensate droplets has only been modeled based on viscous liquids, with fusion time given by the viscocapillary ratio (viscosity over interfacial tension). Here we used optically trapped polystyrene beads to measure the viscous and elastic moduli and the interfacial tensions of four types of droplets. Our results challenge the viscocapillary model, and reveal that the relaxation of shear stress governs fusion and other dynamic processes of condensates.

CELLS EXHIBIT TWO MODES FOR REGULATION OF CHOLESTEROL

PROF. FREDRIC COHEN (RUSH UNIVERSITY)

ABSTRACT

The overwhelming majority of cholesterol in a living body resides within cells. Two-thirds of this cholesterol is contained within plasma membranes where one-third of the molecules are cholesterol. Cholesterol binds to other lipids and many proteins through cholesterol recognition motifs and thus the consequences of cholesterol binding are central features of its actions and cellular control of cholesterol levels. The energy of cholesterol interactions, including binding, is quantified by the chemical potential of cholesterol within plasma membranes, μPM. We have developed a method to determine μPM and found that cells maintain either cholesterol content or μPM constant. Which of the two is maintained depends on the degree that the cells are externally stimulated. Cells minimally stimulated maintain μPM constant for varied extracellular cholesterol levels. But when strongly stimulated, for example, by growth factors, cells allow μPM to vary, and instead maintain their cholesterol content constant despite changes in the amount of external cholesterol. We suggest that when cells are quiescent, collective phenomena give rise to quasiparticles so that despite the multitude of lipids, the membrane effectively behaves as a two component system: in a two-component system, the chemical potential remains constant despite changes in one component—here cholesterol. Tracking intracellular signaling leads us to further suggest that augmented intracellular signaling resulting from extracellular stimulation regulates μPM to maintain cholesterol content.

STOCHASTIC AND PDE MODELS FOR NEURON NETWORKS: JUSTIFICATION AND NUMERICAL SIMULATION

PROF. JIAN-GUO LIU (DUKE UNIVERSITY)

ABSTRACT

In the mean field integrate-and-fire model, the dynamics of a typical neuron within a large network is modeled as a diffusion-jump stochastic process whose jump takes place once the voltage reaches a threshold. Due to the jump mechanism at the microscopic level, such Fokker-Planck equations are endowed with an unconventional structure: transporting the boundary flux to a specific interior point. In the first part of the talk, we present an alternative way to derive such Fokker-Planck equations from the microscopic model based on a novel iterative expansion. With this formulation, we prove that the probability density function of the "leaky integrate-and-fire" type stochastic process is a classical solution to the Fokker-Planck equation. Secondly, we will discuss computations for this system and propose a conservative and positivity preserving scheme for these Fokker-Planck equations. I will also discuss some related analysis for this type of stochastic process and PDE analysis.

PERMANENT CHARGE EFFECTS ON IONIC FLOW

PROF. WEISHI LIU (UNIVERSITY OF KANSAS)

ABSTRACT

Permanent charge is the most important structure of an ion channel. In this talk, we will report our studies toward an understanding of permanent charges on ionic flow via a quasi-one-dimensional Poisson-Nernst-Planck (PNP) model.

The permanent charges are limited to a special case of piecewise constant with one non-zero portion. For ionic mixtures with one cation species and one anion species, a fairly rich behavior of permanent charge effects is revealed from

rigorous analyses based on a geometric framework for PNP and from numerical simulations guided by the analytical results. For ionic mixtures with two cation species and one anion species, richer behavior is expected and our preliminary analytical results identify, in concrete manner, a number of these, including some not-so-intuitive behaviors.

RECENT ADVANCES IN POISSON–NERNST–PLANCK ION CHANNEL MODELING AND SIMULATION

PROF. DEXUAN XIE (UNIVERSITY OF WISCONSIN-MILWAUKEE)

ABSTRACT

Transport of ions through an ion channel pore is a fundamental process in cell biology but very challenging to simulate. A system of Poisson-Nernst-Planck (PNP) equations is one widely used tool for us to address this simulation challenge. In this talk, I will report the recent progresses that we made in the development of Poisson–Nernst–Planck ion channel (PNPIC) models and simulation tools. In particular, I will describe how we mimic an infinitely large ion channel membrane and deal with membrane charges via boundary value conditions and interface conditions. I will then show how we construct different chemical experiment environments numerically through treating bulk concentrations and diffusion coefficients as piecewise functions. Furthermore, I will describe important mathematical and numerical techniques that we developed to overcome the simulation difficulties caused by atomic charge singularity, exponential nonlinearity, and multiple physical domains. Finally, as applications, I will introduce our numerical tool for computing electric currents and our visualization tool for displaying the distributions of electrostatics and ionic concentrations across a membrane via an ion channel pore. This work was partially supported by the Simons Foundation, USA, through research award 711776.

CONFORMATIONAL TRANSITIONS IN BIOCHEMICAL REACTIONS: REVERSIBILITY AND OPTIMAL CONTROL

PROF. YUAN GAO (DUKE UNIVERSITY)

ABSTRACT

Conformational transitions are very important in biochemical reactions. Those slow transitions can be represented by a reversible/irreversible Langevin dynamics on an intrinsic manifold. We first reinterpret the transition paths theory from the stochastic optimal control viewpoint, which realizes the transitions almost surely. Based on collected high dimensional point clouds and nonlinear dimension reduction, we construct an approximated Voronoi tessellation for the reduced manifold. We then propose a finite volume method for the corresponding Fokker-Planck equations on manifold. This leads to an optimally controlled random walk on point clouds and enables efficient Monte Carlo simulations for mean transition path.

SUSTAINED OSCILLATIONS IN BIOLOGICAL NETWORKS

PROF. ZHIGANG ZHENG (NATIONAL HUAQIAO UNIVERSITY)

ABSTRACT

Sustained oscillations of networks of coupled non-oscillatory biological units imply a self organization through an appropriate feedback. In this talk, I will discuss some of our recent progresses.

RESERVOIR COMPUTING IN DATA DRIVEN SYSTEMS RECONSTRUCTION

PROF. HUAFEI MA (SOOCHOW UNIVERSITY)

ABSTRACT

Machine learning shows great potential in data driven research. In this talk, I would like to introduce several works on one specific machine learning method, Reservoir Computing, and discuss the applications of Reservoir Computing in nonlinear systems reconstruction based on time series data.

NON-STATIONARY STATES OF COUPLED SECOND-ORDER OSCILLATORS

PROF. KONSTANTINOS EFSTATHIOU (DUKE KUNSHAN UNIVERSITY)

ABSTRACT

Second-order oscillator networks generalize the famous Kuramoto model to take into account the effect of oscillator inertias and they present a much wider variety of dynamical behaviors. In particular, such systems may attain states that are not stationary. In these non-stationary states the order parameter, characterizing the degree of synchrony among oscillators, changes in time in an almost periodic manner. In this talk we demonstrate non-stationary states through numerical simulations and we associate their appearance to the formation of secondary synchronized clusters besides the main synchronized cluster. Then we discuss the role of inertia and of the frequency distribution of individual oscillators in the formation of secondary synchronized clusters using a combination of dynamical systems theory and simplified dynamical models.

MULTISCALE MOLECULAR KINETICS BY COUPLING MARKOV STATE MODELS AND REACTION-DIFFUSION DYNAMICS

PROF. MAURICIO DEL RAZO (UNIVERSITY OF AMSTERDAM)

ABSTRACT

A novel approach to simulate simple protein-ligand systems at large time- and length-scales is to couple Markov state models (MSMs) of molecular kinetics with particle-based reaction-diffusion (PBRD) simulations; this approach is named MSM/RD. Current formulations of MSM/RD lack an underlying mathematical framework to derive coupling schemes; they are limited to protein-ligand systems, where the ligand orientation and conformation switching are not taken into account; and they lack multi-particle extensions. In this work, we develop a general MSM/RD framework by coarse-graining molecular dynamics into hybrid switching diffusion processes, a class of stochastic processes that integrate continuous dynamics and discrete events into the same process. With this MSM/RD framework, it is possible to derive MSM/RD coupling schemes as discretizations of the underlying equations. It also allows conformation switching and the inclusion of all the rotational degrees of freedom. Given enough data to parametrize the model, it is capable of modeling protein-protein interactions over large time- and length-scales, and it can be extended to handle multiple molecules. We derive the MSM/RD framework, and we implement and verify it for two protein-protein benchmark systems and one multiparticle implementation to model the formation of pentameric ring molecules.