My research effort has been focused on ***Multi-scale and Stochastic Modeling, Analysis and Computation***, with applications to nano-optics and intra-cellular biochemical reacting networks. By putting theory into context of real applications, the research programs advance the frontiers of Applied Mathematics with novel solutions for cutting edge scientific problems. They have also promoted interdisciplinary activities across the campus of MSU through collaborations with research groups of C. Chan (Chemical Engineering and Molecular Biology) [2] and M. M. Koochesfahani (Mechanical Engineering) [3], and provided great training opportunities for the involved postdocs and graduate students. As a reward for their diligence, 3 of my former postdocs have successfully landed tenure track positions in research Universities in US and China such as Iowa State University and Xianmen University.

I. Multi-scale Modeling and Computation of Nano-Optical Responses

Recent advances in nano-optical technology have been made in a variety of fields such as molecular imaging, optical-mechanical systems, negative-index metamaterials, etc. The study of efficient and accurate numerical methods for multiphysical models of nano scale optical devices has become more important than ever. When size of the matter reaches nano scale, the energy level for the electron excitation becomes comparable to the wave length of the incident light. As a consequence, resonance between light and matter excitation generates new features in the observed signals. From the modeling point of view, it is imperative to consider the microscopic fields that are created by atomic electric charges in motion. In order to overcome the high computational cost of Quantum Electrodynamics Theory (QED), a semi-classical model has been recently developed in the form of a non-local response theory, in which the evolution of electromagnetic field (light) is described using the classical Maxwell's equation, and the motion of charged particles (matter) is treated quantum-mechanically by the Schrödinger equation.

To avoid solving the high-dimensional many-body Schrödinger equation, we have developed a multi-scale numerical method for the semi-classical theory of nano-optical responses. The current and charge densities are evaluated using the Time Dependent Current Density Functional Theory (TD-CDFT) and serve as concurrent solutions of the electromagnetic (EM) field obtained with Finite Element Methods, Discontinuous Galerkin Methods, etc. In the regime of linear response, joint with G. Bao and our former postdocs S. Luo and G. Hu, I have formulated a system of equations that couples the EM field and the current and charge densities. Application to complex systems such as metal enhanced organic photon driven nano structures shows that it is able to capture resonance frequencies of the nano-optical structure as well as microscopic features of the EM field. Efficient numerical schemes for nonlinear optical responses under strong external fields are also proposed and have shown successes. Multi-scale modeling, simulation and analysis for surface plasmonic nano particles are being investigated with my current postdoc R. Delgadillo. Most of the reference can be found in the review paper recently submitted to SIAM Review [1].

Modeling and computation of light driven nano devices. Optically manipulated nano devices have attracted a lot of recent interest with applications in solar energy harvesting, molecular engineering, molecular sensing and non-invasive regulation of intracellular reactions. One such example is a photoresponsive DNA nanomotor enhanced by silver nanowires. Illuminated by ultraviolet (UV) and visible lights, the nanomotor can switch back and forth between open and loop states, thereby converting photonic energy to mechanical energy. The mechanism is facilitated by incorporating azobenzene moieties that can change conformational structure through the cis-trans isomerisation. The efficiency of the conversion can be significantly enhanced by a plasmonic near-field coupling with silver nanoparticles, due to the spectral overlap between the azobenzene absorption band and plasmonic resonances of silver nanowires. Recent applications include photon manipulated drug release from nanocontainers, building nanostructures using photonic energy, a photocontrolled molecular beacon for mRNA detection in living cells, etc.

To fully understand the mechanism, we need to describe interactions between the EM field, electronic excitations and nuclear motions. To avoid the complexity of quantum mechanical treatment of nuclei, we describe them as classical points of charge by adopting the Ehrenfest dynamics, where the excitation of the electrons and the motion of the nuclei are separated under the single-determinant approximation and molecular dynamics is obtained by the mean-field approximation. Combined with semi-classical models for nano-optics based on TD-CDFT, this approach leads to a coupled Maxwell-Ehrenfest-Kohn-Sham system that provides a computationally practical model for the optically manipulated nanostructures. We also proposed a multiscale scheme to deal with the three level system with well-separated electromagnetic, molecular and electronic scales. Numerical results in the linear response regime show that the approach can resolve the resonant frequency initiating the nuclear motion. Further investigation will involve modeling and computation of metal enhancement and nonlinear processes such as fluorescence. Regularity and long time behaviors of solutions for the coupled Maxwell-Kohn-Sham system, which are vital for developing efficient and stable numerical methods, will also be studied.

Numerical methods for highly nonlinear nano-optical responses. Recent development in laser technology has led to reliable production of attosecond ($10^{-18}s$) pulses, which enables ultrafast and highly nonlinear photon excitations and allows real time molecular orbital imaging. In high order harmonic generations (HHG), the spectrum of the response light can extend over many orders of magnitudes at multiples of the driving frequency. What is of great practical interest is the optimal control of the efficiency and spectral characteristics of the harmonic radiation by modifying the incident pulse. It is well known that dynamical phenomena under strong laser pulses such as multiple ionization of atoms and molecules or higher order harmonic generations (HHG) are beyond the linear response regime. Time Dependent Density Functional Theory (TD-DFT) has been adopted as a major tool for investigating physics with intense laser pulses. Since we will focus on the situation of strong laser pulses, the magnetic field is so small that it

can be ignored. Therefore the vector potential, as the conjugate variable of the magnetic field, will also be removed from the Hamiltonian, which reduces TD-CDFT to TD-DFT since the current density is no longer a fundamental variable.

To accurately simulate long time propagations of these strong field processes involving higher order interactions, a large amount of time steps and grid points is very often needed if TD-DFT is adopted. In order to reduce the computational load, we developed a set of adaptive finite element methods (FEM) for time dependent Kohn-Sham equations. A heuristic error indicator is introduced for the adaptive mesh generation. The flexibility and adaptivity of FEM make it easier to design efficient methods for large systems in which the locality effect is significant. The effectiveness of the method is illustrated through examples such as the dynamical response of a lithium atom to an external electric field, where peharmonic orders appear at the odd numbers, which agrees with theoretical results. The current project is to conduct a detailed study of HHG and coupling with molecular dynamics.

Multiscale analysis of metal nano structures models. Metal nano structures have attracted a great deal of interest for being able to significantly enhance the local field due to light induced surface plasmons, and further affect optical scattering of molecular structures, which has led to successful applications in photovoltaics, sensing, spectroscopy and metamaterials. Theoretical efforts on understanding nano plasmonic systems have been focused on the quantum effects as a result of the reduced size, that can not be captured by macroscopic electrodynamics. DFT/TD-DFT based approaches for modeling optical properties of metal nano structures have the advantage of numerically and (relatively) theoretically tractable, especially in the regime of linear responses. The difficulty lies in the nonlinear effects, which will require not only time domain simulations for interactions between a large number of ions and electrons, but also model simplification and validation for nano scale systems. Currently, I am working with postdoc Ricardo Delgadillo on effective modeling for TD-DFT to deal with light localization and enhancement by metal nano particles. The theoretical issue bridge different models at atomistic and continuum scales will also be addressed, which will further shed light on efficient numerical methods.

II. Stochastic Simulation for Multi-scale Bio-chemical Reacting Networks

My research program is to design and analyze efficient numerical methods for simulating bio-chemical reacting networks involving gene regulation. A Gene Regulatory Network (GRN), describing all the reacting channels and species involved with gene expression, consists of a set of genes, proteins, small molecules and their mutual regulatory interactions. From the point of view of modeling, GRNs, unlike signaling and metabolism networks, involve fewer species and lower concentrations of molecules in a small volume within a cell; therefore stochastic effects have a significant impact on reaction pathways. Despite their accuracy, the standard stochastic simulation algorithms are necessarily inefficient for most of realistic problems with the multi-scale nature. Three

kinds of multi-scale properties of cellular reacting networks limit the applicability of the routine algorithms: 1.) multiple time scales induced by widely disparate reactions rates, 2.) multiple well separated concentration scales of reacting species, and 3.) rare events arising from the metastability of the system.

Nested Stochastic Simulation Algorithms for reacting networks with multiple time scales. It is well known that the reactions in intra-cellular networks occur on different time scales, e.g. the fast binding of RNA Polymerase to the DNA chain versus the relatively slower transcription process. For such a system, direct simulation will entail very small time steps to capture fast modes, which is not feasible with existing computational resources. Together with W. E and E. Vanden-Eijnden, I proposed the Nested Stochastic Simulation Algorithms (NSSA). The idea is to solve the effective reactions on the slow time scale by estimating the averaged coefficients on-the-fly with short time simulations of the fast reactions. We provided a rigorous and thorough analysis for the convergence and efficiency of the scheme, which enables us to find the optimal designing for the method. Recent simulation of large scale complex network such as the Yeast Cell Cycle model shows that NSSA has a tremendous advantage in practice over similar methods in terms of efficiency and applicability. Strong convergence analysis of the method, as well as speed-up with equilibrium of the fast processes simulated using τ-leaping method, have also been established, jointly with my former postdoc C. Huang.

Integrative modeling and simulation of Insulin response networks. I have been working with Prof. Christina Chan at Biochemistry and Molecular Biology of MSU to build an integrative model to understand the dynamic behavior of Protein Kinase R (PKR) and Insulin Receptor Substrate (IRS) signaling and regulation. The hepatic insulin signaling mediated by insulin receptor substrates IRS1 and IRS2 plays a central role in maintaining glucose homeostasis under different physiological conditions. Although functions of individual components in the signaling network have been extensively studied, our knowledge is still limited with regard to how the signals are integrated and coordinated in the complex network to render their functional roles. It has been identified by Chan's lab that as a downstream target of Insulin signaling pathway, PKR regulates the upstream transmitters, IRS1 and IRS2, through different mechanisms. Working with former postdoc C. Huang and graduate student J. Du and M. Wu, we have built a kinetic model that encompass all reactions from signaling transduction to gene regulation. A sensitivity analysis is applied to identify essential regulators for the signaling process. The model is also used to test NSSA and the result shows that the algorithm can significantly speed up the simulation.

Transition states for metastable chemical kinetic systems. With simple but intuitive information on chemical kinetics, Transition States (TS) remain essential in understanding complex reacting systems when the system is metastable. My student J. Du and I have been using the Transition Path Theory (TPT) to study the subject. By

generalizing the definition of probability current from adjacent states to reacting paths, we are able to rigorously define transition states as vertices with maximum probability flux. Results on the Toggle Switch model and Enzyme Kinetics model showed that it provides more insights than previous works. Right now, we are working on numerical techniques that can deal with larger and more realistic systems, especially challenges from high dimensional systems.

Numerical methods for chemical kinetic systems with delay. Delay is an important aspect of many biochemical processes, and plays a central role in the dynamics of genetic regulatory networks as it stems from the sequential assembly of first mRNA and then protein. Together with my postdoc Chuchu Chen, I am examining numerical methods for stochastic chemical kinetics with delay, on both finite and infinite time horizons. For fixed time intervals, we proved both the strong and weak convergence of the Euler method. It is shown that the mean square strong convergence is of order 1/2 and the weak convergence is of order 1 for the scheme. In order to establish the convergence orders, we prove an infinite dimensional Ito formula for tame functions acting on the segment process of the solution of stochastic delay differential equations (SDDEs) driven by Poisson random measures. It is interesting to note that the presence of the memory in the SDDEs requires the use of the Malliavin calculus and the anticipating stochastic analysis. Current effort is on higher order methods and efficient schemes for invariant measures. Large Deviation and Transition Path Theories for stochastic chemical kinetics with delay will also be studied, and applications will be focused on metastable systems with delay.

III. Sampling Time Effect on Estimation of Brownian Fluctuation

To put my expertise in stochastic modeling and analysis in use, I also worked with M. M. Koochesfahani and former graduate student S. Pouya to study the effect of finite detector integration/exposure time, in relation to interrogation time interval, on analysis of Brownian motion of small particles using numerical simulation of the Langevin equation for both free diffusion and hindered diffusion near a solid wall. Our calculation and experiments recover the known scaling law the estimated diffusion coefficient, and find a new nonlinear scaling behavior, for which we also provide an exact analytical solution.

[1] G. Bao, G. Hu, D. Liu and S. Luo, Modeling and computation of Nano-optics, submitted.

[2] C. Huang, M. Wu, J. Du, D. Liu and C. Chan, Systematic modeling for insulin signaling network mediated by IRS1 and IRS2, Journal of Theoretical Biology, 355, 40-52, 2014.

[3] S. Pouya, D. Liu, and M. Koochesfahani, Effect of finite sampling time on estimation of Brownian fluctuation, Journal of Fluid Mechanics, 767, 65-84, 2015.