Research statement

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My general research interests lie in modeling, numerical computation and computer simulations in the area of mathematical biology. Some of my current research projects involve mathematical modeling of physical and biological problems as well as rigorous mathematical analysis of these problems. A brief description about some of my ongoing research projects is given in the following.

[A.] (With Eva Farre, plant biology, MSU) Circadian clocks have been shown to be necessary for optimal growth and survival in many organisms. Although circadian clocks in different species utilize distinct proteins, they appear to maintain the same overall pattern of regulation based on the combination of transcriptional regulatory loops with post-translational regulation. Therefore, the understanding of the molecular mechanisms regulating the clock in some plants will complement similar studies in other systems in order to understand the design principles governing circadian oscillators.

The focus of this project is to understand the dynamics of the plant circadian clock using mathematical models in the model plant Arabidopsis thaliana. Our first objective is to study the mechanisms and kinetics of light regulated transcription of clock components. Objective two is to develop mathematical and experimental tools to optimize the parameter estimation process of the clock regulatory network. Our third objective is to develop a mathematical model of the plant circadian clock that will result in quantitative predictions of the systems behavior. This model will incorporate new mechanistic data as well as the improved parameter values. This model will allow us to understand critical characteristics of circadian clocks such as the robustness of circadian oscillations, clock resetting by light and the sensing of photoperiod changes.

[B.] (With D. Arnosti at the Dept. of Biochemistry, MSU) Analysis of transcriptional regulatory networks in Drosophila involves integrating a large variety of information, including the quantitative levels of regulatory proteins, patterns and levels of gene transcription, measured by in situ hybridization and gene arrays, and patterns of putative regulatory motifs in cis regulatory regions. One way to process large amounts of genetic data is through dynamic network models. A variety of methods for the modeling and simulation of genetic regulatory networks have been proposed, such as approaches based on differential equation models and stochastic models. Most of the differential equation models are ODE systems. Such dynamic systems do not consider the spatial properties of

the gene regulation. However substantial amount of experimental data shows that gene expressions depend on distance, position, affinity and stoichiometry. We propose to explore more general partial differential equation systems for gene regulatory network with a general framework of reaction-diffusion-chemotaxis systems.

The general goal of this project is to establish research collaborations between mathematicians and experimental biologists at the Michigan State University and to train the graduate students in doing research in interdisciplinary fields. The initial areas of focus are mathematical modeling and computer simulations for gene expression and regulation. A key objective of contemporary gene regulatory studies is to understand the activity of the transcriptional apparatus at a quantitative level. The central goal of our project is to meld modeling approaches with quantitative determinations of transcriptional switch activity for a limited set of relatively well-characterized transcriptional regulators in the Drosophila blastoderm embryo.

Unlike other current high level network approaches that treat gene switches as black boxes, this project is to study in details the cis regulatory rules that affect the efficacy of transcriptional repressors in the context of blocks of activator sites within enhancer. The main feature of our model which differs from other existing models is that we originate our model at the DNA level to incorporate some of the fine details of regulatory elements, e.g., affinity and covering range. This new model of transcriptional regulation will aid mechanistic understanding of transcriptional regulatory mechanisms, provide new insights on the evolution of gene regulatory elements and networks, and will supply tools for predicting the quantitative output of cis regulatory elements.

[C.] Numerical analysis of reaction--diffusion systems and reaction--diffusion--chemotaxis systems. For over four decades, reaction-diffusion systems have been the main mathematical tool for studying pattern formation problems in chemistry and biology. However, research on numerical algorithms and large scale computation for reaction--diffusion systems only became possible and important in recent years because of advances in computer sciense. Another major development in the field is using reaction--diffusion--chemotaxis systems for pattern formation's research. Reaction--diffusion—chemotaxis systems are more general than reaction--diffusion systems in the sense that they also consider particles moving up to gradients. Such systems can be applied to problems where reaction-diffusion systems fail.

My interests in this field is to design and implement fast numerical algorithms for solving reaction-diffusion and reaction--diffusion—chemotaxis systems. I have obtained results in the following directions:

- ADI (Alternating Direction Implicit) schemes. One of my current research projects concerns with developing efficient numerical methods for solving pattern formation models (reaction-diffusion equations and reaction-diffusion-chemotaxis equations) in cell biology. I developed several ADI schemes which are specially efficient for these models. The basic idea of virtually all ADI type of schemes for 2-dimensional problems consists of two steps, one step being implicit in x direction and the next step being implicit in y direction. The special feature that is essential for applying ADI to reaction-diffusion system is to use one step implicit and the next step explicit alternating for the nonlinear reaction functions. I have published several papers on this subject.

- Multigrid techniques. Fully implicit schemes are the straightforward way to overcome the stability restriction for the explicit schemes. However the difficulty there is that a banded system of linear equations needs to be solved at each time step. The system is unlike the one resulting from ADI, which is tridiagonal and can be solved with a cost of the same order as that of the system. General algebraic systems are usually solved by iterative methods. For a banded matrix such as the one obtained by fully implicit scheme for reaction--diffusion equations, each iterative step costs O(N^2) where N^2 is the number of discrete points for a 2-dimensional problem. If the number of iterations for each time step is kept low, the fully implicit scheme would be an alternative for solving pattern formation problems. My idea is that multigrid techniques can make the fully implicit scheme efficient by reducing the number of iterations at every step. Significant progress has been made in this direction.

- Multi-stage strategy. Another approach to reaction--diffusion--chemotaxis problem is to change the PDE system to an ODE system. Then find efficient numerical methods to solve the ODE system. This concerns with finding efficient ways to accelerate the convergence of nonsymmetric approximations (such as spectral approximations) of parabolic equations to steady state. The methods can potentially be applied to solving general nonsymmetric system of linear equations for which there are lack of efficient numerical algorithms even after decades of extensive research. Optimal m-stage Runge-Kutta schemes have been developed to accelerate convergence

to steady state. We consider various shapes of geometric closures of the eigenvalues. On a semi-disc region which contains all eigenvalues, for m=1,2, explicit formulas are found for optimal parameters and for m > 2, a numerical procedure is designed to find optimal parameters. For many examples, our algorithms give faster convergence. Our goal is to apply the algorithm to practical problems.