I am particularly interested in mathematical and computational analysis of biological models closely related to different biological problems. I apply ODE, PDE and stochastic equation to describe models, and compare the simulation results with actual data in order to validate the model so that it can be useful for making new hypotheses in biology.

The main focus of my studies is robust cell polarization and pattern formation of biological systems and I am also interested in studying inflammatory diseases and cancer modeling. I have worked in collaboration with other faculties from different experimental laboratories and my results are supported by experimental data and closely related to different biological problems. The projects I worked on are listed as follows:

1. **Multi-stage Stem Cell Lineages and Tissue Stratification**
2. **Morphogen-mediated Patterning: Formation, Stochasticity and Tradeoffs**
3. **Mathematical Studies of Cell Polarization Patterns**
4. **Mathematical Model of Inflammatory Bowel Diseases and Colon Cancer**
5. **Robust and Efficient Numerical Methods for Pattern Formation**

In the following, I will briefly describe each of the projects, and in the last section, I will discuss my future research plans.

1 Multi-stage Stem Cell Lineages and Tissue Stratification

Studies [17] have shown that multi-stage cell lineages, which include stem cell and multiple progenitor cell stages, are under feedback regulation from different growth factors. The existence of regulation is critical for hemostasis of tissue growth during embryonic development and generation of a robust spatial stratification.

Stability of the system of multi-stage cell lineage through negative feedback control

Regulation is particularly important for rapid regeneration when death of a large number of cells is induced. In our paper [13], ODE models have been presented for the cell lineages and we have systematically studied the conditions of existence, uniqueness and stability of steady state of the system with an application to the olfactory epithelium. Our results suggest that two factors, auto regulation of the proliferation of transit amplifying progenitor cells and a low death rate of terminally differentiated cells, enhance the stability and robustness of the system. This project is in collaboration with some biologists including A. Lander, A. Calof and K. Gokoffski (Development and Cell Biology, UC Irvine).

Spatial dynamics of multi-stage cell lineages in tissue stratification: PDE model with moving boundary

To investigate the spatial dynamics of different types of cells in lineages, we extended the non-spatial ODE model by including growth of tissue using a PDE model with moving boundary. In a joint work with C.-S. Chou (Mathematics, Ohio State University) et al. [5], we found that inter-regulation among different growth factors are responsible for developing layers of different types of cells in the tissues. We also showed that the feedback on cell cycle from the growth factor is important for forming temporary "stem cell niche", the term that generally refers to the microenvironment where the stem cells reside and sustain their renewing functions, during the development of the tissue. Our findings are consistent with the experimental results our collaborators have observed.

2 Morphogen-mediated Patterning: Formation, Stochasticity and Tradeoffs

A central theme in the development of multicellular organisms is that fields of cells are patterned by gradients of signaling molecules, known as morphogens, in a concentration dependent manner. Most studies have focused on patterning induced by the morphogen gradients in an "ideal" environment [10]. We are interested in the robustness of morphogen gradient formation and their downstream responses in a noisy environment such as in an in-vivo biological system.

Free extracellular diffusion creates the Dpp morphogen gradient of the *Drosophila* wing disc

How morphogen gradients form has long been a subject of controversy. The strongest support for the view that morphogens do not simply spread by free diffusion has come from a variety of studies of the Decapentaplegic (Dpp) gradient of the *Drosophila* larval wing disc. In a joint work with S. Zhou (Development and Cell Biology, UC Irvine) et al. [26], our experimental data and mathematical simulations strongly support the view that the Dpp gradient of the *Drosophila* wing disc forms by free, extracellular diffusion, coupled with uptake by cell-surface receptors and subsequent degradation. These findings resolve a major, longstanding question about morphogen gradient formation and provide a solid framework for interpreting experimental observations of morphogen gradient dynamics.

Robust and precise morphogen-mediated pattering: Stochasticity, Tradeoffs and Mechanisms

In a joint work with A. Lander (Development and Cell Biology, UC Irvine), Q. Nie and F. Y. M. Wan (Mathematics, UC Irvine) [9], we have built a mathematical method to measure the fluctuations in morphogen production and the stochasticity of binding events. With this method, we showed that the strategies for achieving robust gradients must perform with different tradeoffs. Computation and analysis of various regulation strategies suggest that self-enhanced morphogen clearance is able to overcome specific kinds of noise. This study also gives an insight for systems with co-receptor feedback or relative slope of the morphogen gradient [20] to improve our understanding on how a morphogen gradient is translated into a long-range robust signal.

3 Mathematical Studies of Cell Polarization Patterns

Cell polarization, in which substances previously uniformly distributed become asymmetrically localized, is fundamental to various cellular processes such as differentiation, migration and development [24]. Failure in polarization may lead to lethality or dysfunctionality of the cells. How cell polarity is established and maintained has been a central question in cell biology.

Mathematical analysis of spontaneous emergence of cell polarity: Random budding pattern

The fundamental mechanisms for cell polarization remain controversial, but it is known that polarity development typically involves the localization of signaling molecules to a proper location of the cell membrane. While cell polarity is often induced by intracellular or extracellular spatial cues, spontaneous polarization (the so-called symmetry breaking) may also occur in the absence of spatial cues [21]. In a recent study it was proved that spontaneous polarization occurs when the lateral diffusion of inactive signaling molecules is much faster than that of active signaling molecules. This conclusion leaves an important question of how cell polarity emerges when these molecules diffuse at similar rates, as observed in many biological systems.

In our paper with H.-O. Park (Mathematics, Ohio State University) and C.-S. Chou (Mathematics, Ohio State University) [16], we formulated a generic non-local reaction-diffusion model with general forms of positive feedback. We applied Turing stability analysis [23] to identify parameter conditions for achieving cell polarization. Our results show that spontaneous polarization can be achieved even when active and inactive signaling molecules diffuse at similar rates. In addition, different forms of positive feedback are explored to show that a non-local molecule-mediated feedback is important for sharping the localization as well as giving rise to fast dynamics to achieve robust polarization.

Polarization patterns of diploid daughter cells in budding yeast

The Cdc42 GTPase is a key signaling molecules in cell polarization in budding yeast. Although previous studies in budding yeast suggested positive feedback loops whereby Cdc42 becomes polarized, these mechanisms do not include spatial cues, neglecting the normal patterns of budding. In this project, we presented a two-equation reaction-diffusion model of cell polarization, including spatial cues. In [14], we combined live cell imaging and mathematical modeling to understand how diploid daughter cells establish polarity preferentially at the pole distal to the previous division site despite the presence of two landmark cues at distal pole and proximal pole. We reported that both spatial landmarks and GTP hydrolysis of Cdc42 by Rga1 controls the robust Cdc42-GTP polarization in diploid daughter cells.

4 Mathematical Model of Inflammatory Bowel Diseases and Colon Cancer

Gut mucosal homeostasis depends on complex interactions among the microbiota, the intestinal epithelium, and the gut associated immune system. A breakdown in some of these interactions may precipitate inflammation. Inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis are chronic inflammatory disorders of the gastrointestinal tract [1]. Crohn's disease affects approximately 1.4 million Americans with a peak onset occurring at 15-30 years of age. Patients with ulcerative colitis or Crohn's disease are at risk of developing colorectal cancer as a result of chronic inflammation of their colon.

Roles of T cells in inflammatory bowel disease: Interplay among Th1, Th2 and Treg cells

The initial stages of IBD are marked by an abnormally high level of pro-inammatory helper T cells, Th1. In later stages, Th2 helper cells may dominate while the Th1 response may dampen. The interaction among the T cells includes the regulatory T cells (Treg). In our paper with R. Arsenescu (Internal Medicine, Ohio State University) and A. Friedman (Mathematics, Ohio State University) [11], we developed a mathematical model by a system of differential equations with terms nonlocal in the space spanned by the concentrations of cytokines that represents the interaction among T cells through a cytokine signaling network. The model demonstrates how the abnormal levels of T cells observed in inammatory bowel diseases can arise from abnormal regulation of Th1 and Th2 cells by Treg cells.

From inflammatory bowel disease to colon cancer

In a joint work with E. Martin (Surgery, Ohio State University), C. Hitchcock (Pathology, Ohio State University) and A. Friedman (Mathematics, Ohio State University) [15], we constructed a model of colon cancer associated with inflammatory bowel diseases. Our model involves APC and TP53 genes, under chronic inflammation, as well as NF-κB, β-catenin, MUC1 and MUC2. Different from normal colon mucosa, the inflamed colon mucosa undergoes genetic mutations, affecting, in particular, tumor suppressors TP53 and APC gene. Our model demonstrated that increased level of cells with TP53 mutations results in abnormal growth and proliferation of the epithelium; further increase in the epithelium proliferation

results from additional APC mutations. The model may serve as a conceptual framework for further data-based study of inflammatory disease and colon cancer.

5 Robust and Efficient Numerical Methods for Pattern Formation

How to efficiently compute the steady state solutions of a system of reaction-diffusion equations with many diffusible species? Solving the system using temporal schemes usually is slow due to constraints on the time steps. The constraints arise due to stiffness of the reactions and differential speed of the diffusions. To explore conditions for generating solutions consistent with the experimental observation, e.g. Turing patterns [23], one needs to explore a large set of parameters, e.g. 1 million parameters, especially, when analytical estimates are difficult, to search for patterns. For such systematic exploration, fast and robust steady state solvers are required.

In [12], we developed a method, called **adaptive implicit Euler with inexact solver (AIIE)**, that combines a temporal scheme and Newton's method to achieve a fast and robust method for searching Turing patterns. When the guess is close to the steady state, Newton's method converges to the steady state rapidly but it does not guarantee that it will converge to Turing patterns. Using the temporal scheme to obtain a better initial guess can increase the chance that Newton's method converges to Turing patterns. We suggested some ways for gradually switching temporal scheme to Newton's method: two-grid method [25], FAS [4] and Newton's method with modified Jacobian matrix. Each can be applied to combine the advantages of temporal scheme and Newton's method. By comparing with different methods, such as implicit Euler method and Newton's method, our method is showed to be a robust and efficient tool for searching Turing patterns. Figure 1 shows the form of a three-dimensional pattern computed by AIIE for Gray-Scott model [19]. With same numerical setting, Newton's method failed for convergence.

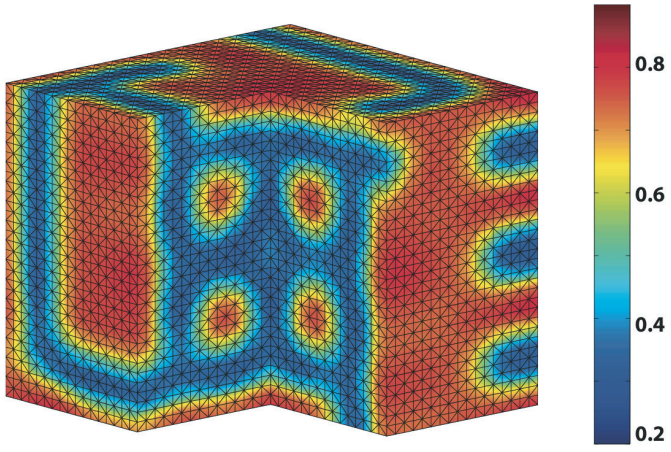

Figure 1: An example of three-dimensional pattern computed by AIIE for Gray-Scott model [19]. Newton's method does not converge for this case.

6 Ongoing and Future Projects

The aim of my studies is to understand how life is developing in all diversities. This includes biological pattern formation, as well as growth and death controls in cells and tissues. Recent experimental studies suggested that the mechanisms for biological patterning also play an important role in tissue growth as well as cancer proliferation. In my ongoing and future studies, we extend our research on robust pattern formation by including the study of growth control. In the following part, I will list some ongoing and future projects to demonstrate how I pursue my aim in future.

6.1 Balance between Morphogen Control and Mechanical Stress: Growth Model with Moving Boundary

Unlike patterning function of morphogen gradient, how morphogen affects the growth of tissue is much less studied. Recent experimental studies on development of *Drosophila* wing imaginal disc indicate that the morphogen gradient is not only responsible for patterning, but also plays an important role in wing disc growth [18]. In particular, it is observed that there is no growth without any morphogen and proliferation is uniform in the wing disc with a spatially graded morphogen [20]. Several studies showed that the cell growth is regulated by concentration level and slope of the morphogen gradient. Also, some studies suggested that stress and compression force acting on the cell affect the local growth rate.

We are building a new model for *Drosophila* wing disc system on a growing domain. The model explores the dynamic of tissue growth governed by morphogen distribution and how the morphogen gradient changes during the development. In our model, the preliminary simulations showed that mechanic force is critical for controlling the final size of tissue and achieving uniform proliferation. At the same time, we are interested in how the regulated growth process affects the pattern formation during development and it was less studied before. By including the dynamics of morphogen distribution, we are able to study how growth and pattern formation interact with each other. For example, if we include stochastic effect in the model, it may show that the regulation of growth plays an important role for reducing noise in pattern formation.

6.2 Robustness Study on Stochastic Model of Morphogen-Expander System

Pattern of developmental tissue is encoded by morphogen gradient through driving different processes of cell differentiation in corresponding concentration ranges. Several experimental and mathematical studies showed that morphogen overexpression has no essential effect on patterning but the mechanisms behind that remain controversial. The expansion-repression mechanism [2], which was studied only for achieving scaling of patterning with organ size, may play an important role for overcoming the effect of morphogen overexpression. In this project, we are studying the expansion-repression mechanism through introducing a spatial stochastic morphogen-expander system which includes morphogen, receptor, non-signaling receptor and expander. We believe that the expansion-repression mechanism can improve the robustness against the change of morphogen production rate and the stochasticity of binding events.

6.3 Oscillatory Behavior of Cdc42 Polarization Induced by Coupled Positive and Negative Feedback Loops

In budding yeast system, negative feedback mechanism was recently proposed to explain oscillatory behavior of the polarity factor clusters [7] but the exact mechanism remains unknown. From our preliminary studies, we believe that it is impossible to achieve oscillatory behavior through independent positive and negative feedback loops. A mathematical model with coupled negative and positive loops may be important for explaining the dynamics of oscillatory behavior. We extend our previous model [14] to be a two-dimensional model on the cell membrane and it includes a key factor Ste20 which is an important

link between negative and positive feedback loops. This study provides an insight on the role of negative feedback in robust budding yeast polarization.

6.4 Tumor Margin Detection Using Fluorodeoxyglucose (FDG)

One of the critical problems in the treatment of cancer is the recurrence of the disease sometime after surgery. Indeed, up to 30% of patients who undergo resection surgery require reoperation, mostly due to incomplete resection, and at present there are no validated methods for tumor margin detection [8]. Thus there is a need to develop such methods, applicable in real-time. In this project, we consider an approach based on FDG injection into the tumor, which provides a view of the cancer by PET imaging. We are developing a PDE model which includes, in addition to tumor cells and FDG, also VEGF and oxygen and glucose transported by blood vessels. Our model has a potential to make quantitative predictions with regard to the tumor margin.

6.5 Hybrid Spatial Stochastic Numerical Method: Stochastic PDE (SPDE) and Reaction-Diffusion Stochastic Simulations Algorithm (RDSSA)

In the system of Dpp morphogen in *Drosophila* wing disc, a signal gradient is decreasing along the anterior-posterior axis, from the center of production region to the edge of wing disc. The length of anterior-posterior axis is over 200 μm and decay length of a signal gradient is around 17 μm [3, 9] so the concentration of signal molecules has a large range that the maximum and the minimum have around fold difference. A single stochastic scheme is not able to compute such system that includes two different spatial regions with large difference of molecular concentrations so development of hybrid model is necessary for solving such kind of system. We are developing a hybrid method combining RDSSA [22] and SPDE [6] for solving morphogen-receptor system. A preliminary result shown in Figure 2 demonstrates a simulation for the morphogen-receptor system [9] by applying hybrid stochastic method of numerical SPDE and RDSSA. Comparing with deterministic methods, SPDEs approach is much suitable to capture stochastic behaviors in a biological system so a hybrid method with RDSSA and SPDE is one of the future main approaches for improvement of stochastic simulations of spatial systems.

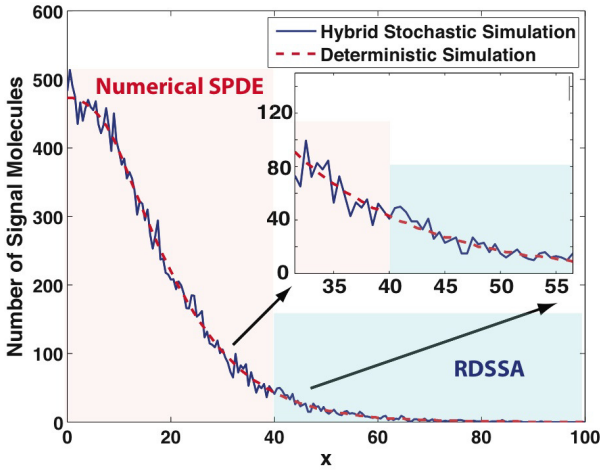

Figure 2: A simulation for the morphogen-receptor system [9] by applying hybrid stochastic method of numerical SPDE and RDSSA. Blue line is the result of hybrid stochastic simulation and red dashed line is the result of deterministic simulation.

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