北京大学
PEKING UNIVERSITY

北京国际数学研究中心
BEIJING INTERNATIONAL CENTER FOR MATHEMATICAL RESEARCH

2016 International Workshop on Interdisciplinary Research between Mathematics and Biology

Peking University

July 15-17, 2016

北京大学 PEKING UNIVERSITY

北京国际数学研究中心 BEIJING INTERNATIONAL CENTER FOR MATHEMATICAL RESEARCH

2016 International Workshop on Interdisciplinary Research between Mathematics and Biology

Dates: July 15: Registration; July 16 – 17: Workshop

Venue: Lecture Hall, JingChunYuan No. 82 JiaYiBing, BICMR, Peking University

Organizing committee:
Hao Ge (Peking University)
Tiejun Li (Peking University)
Qing Nie (University of California, Irvine)
Chao Tang (Peking University)
Lei Zhang (Peking University)

Sponsors:
NSFC Tianyuan Foundation,
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Beijing International Center for Mathematical Research (BICMR),
Center for Quantitative Biology (CQB),
Interdisciplinary Research Laboratory of Mathematics and Biology (Bio-Math Lab)

Workshop webpage:
http://www.bicmr.org/content/show/17-1721.html

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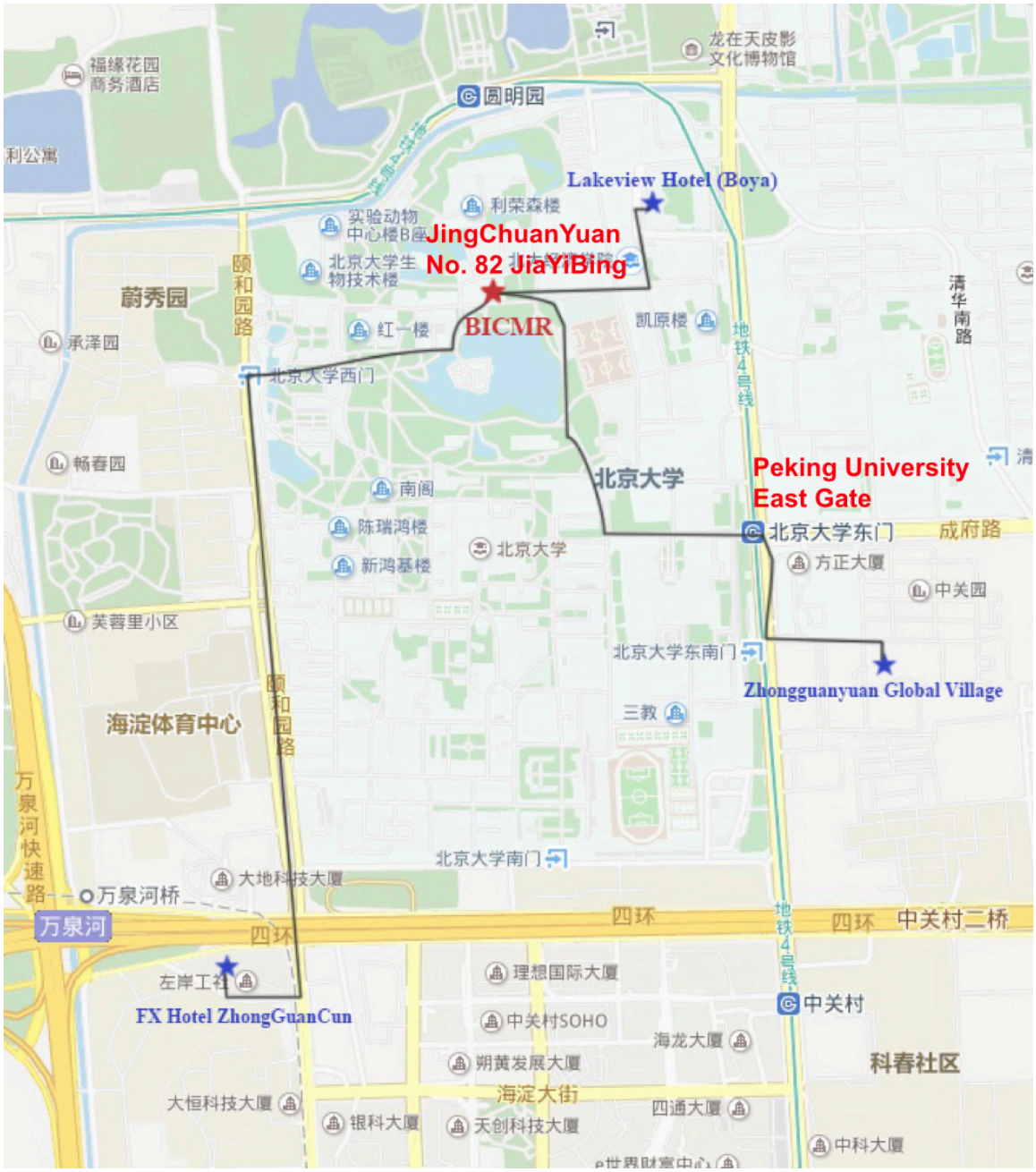

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Workshop Program

Day 1 (July 16, 2016)

Morning Session Chair: Qing Nie		
Time	**People**	**Titles /Activities**
8:45-9:00	**Opening remarks**	
9:00-9:40	John Reinitz U. of Chicago	Finding the rules of *cis*-regulatory logic from Drosophilidae to Sepsidae and back again
9:45-10:25	Lingchong You Duke University	Programming bacteria in time and space
10:30-10:50	**Coffee Break**	
Chair: John Reinitz		
10:50-11:30	Sheng Zhong UCSD	Mapping RNA-RNA interactome and RNA structure in vivo
11:35-12:15	Zhaohui Qin Emory University	RefEditor: Building Personalized Diploid Reference Genome to Improve Read Mapping and Genotype Calling in Next Generation Sequencing Studies
12:20-14:00	**Lunch**	
Afternoon Session **Chair: Sheng Zhong**		
14:00-14:40	Ed Monuki UC Irvine	Properties and objectives for BMP-FGF interactions in the developing forebrain
14:45-15:25	Yuling Jiao IGDB, CAS	Feedback from leaves controls cell fate in the shoot apical meristem by modulating auxin transport
15:30-15:50	**Coffee Break**	
Chair: Hao Ge		
15:50-16:30	Qi Wang CSRC & U. of South Carolina	Multiphase cell models for cytokinesis and cell migration on patterned substrate
16:35-17:15	Douglas Zhou SJTU	Spatiotemporal integration of synaptic inputs in neurons: computational modeling, analysis and experiments
18:00	**Dinner**	

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Day 2 (July 17, 2016)

Morning Session Chair: Tiejun Li		
Time	**People**	**Titles /Activities**
9:00-9:40	Sui Huang ISB, Seattle	High-dimensional critical state transitions in mammalian cells revealed by single-cell resolution gene expression profiling - new implications for cancer
9:45-10:25	David Umulis Purdue University	Quantification and modeling of BMP signaling during zebrafish embryo development
10:30-10:50	**Coffee Break**	
Chair: Sui Huang		
10:50-11:30	Yuhai Tu IBM	Multiscale modeling of E. coli chemotaxis: From molecules to behaviors
11:35-12:15	Maksim Plikus UC Irvine	A multi-scale model for the hair follicle reveals mechanism for rapid evolution of hair growth patterns
12:20-14:00	**Lunch**	
Afternoon Session **Chair: Maksim Pikus**		
14:00-14:40	Qing Nie UC Irvine	Stem Cells: Interplay Between Complex Data and Computational Models
14:45-15:25	Jianhua Xing U. of Pittsburgh	TGF-β signal transduction and cell fate decision
15:30-15:50	**Coffee Break**	
Chair: Jianhua Xing		
15:50-16:30	Chengcheng Huang U. of Pittsburgh	The space and time of neuronal variability in a spiking neuron network
16:35-17:15	Lei Zhang Peking University	Computation of Transition States and its Applications in Biology
18:00	**Dinner**	

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Abstract

1. **Finding the rules of *cis*-regulatory logic from Drosophilidae to Sepsidae and back again**
   John Reinitz, University of Chicago
   Abstract: A developing organism executes an exquisitely precise program of transcriptional control. This accuracy is enforced by natural selection, since failure to generate correct cell types in the right locations is fatal to the organism. This precision is encoded in *cis*-regulatory DNA, but the rules by which gene expression is read out from sequence have remained largely obscure. We are engaged in a long-term effort to understand these rules using a quantitative model of transcriptional control based on thermodynamics and phenomenological laws. Our model has both explanatory and predictive power for understanding the control of transcription at cellular resolution. In this talk I will discuss recent results in this area. These will include an explanation, supported by confirmed predictions, of how enhancer elements conserve function while not conserving sequence. I will also discuss a theory of the intact *Drosophila even-skipped* locus that correctly predicts the location and function of its constituent enhancers.

2. **Programming bacteria in time and space**
   Lingchong You, Duke University
   Abstract: Microbes are by far the most dominant forms of life on earth. In every imaginable habitat, they form complex communities that carry out diverse functions. Microbial communities drive the geochemical cycling of diverse chemicals and through these activities shape the earth's climate and environment. They are also intimately tied to human physiology and health. Members of each microbial community may compete for resources, collaborate to process the resources, or to cope with stress. They communicate with each other by producing and responding to signaling molecules. And they innovate by exchanging genetic materials. These interactions raise fundamental questions regarding the evolutionary and ecological forces that shape microbial consortia. Our lab has adopted a combination of quantitative biology and synthetic biology to explore these questions. We engineer gene circuits to program dynamics of one or more Escherichia coli bacterial populations, and use them to examine questions in cellular signal processing, evolution, ecology, and development. Analysis of these systems have provided insights into bacterial tolerance to antibiotics, developmental pattern formation and scaling, as well as strategies to use bacteria to fabricate functional materials.

3. **Mapping RNA-RNA interactome and RNA structure in vivo**
   Sheng Zhong, UCSD
   Abstract: The pervasive transcription of our genome presents a possibility of revealing new genomic functions by investigating RNA interactions. Current methods for mapping RNA-RNA interactions have to rely on an "anchor" protein or RNA, and often require molecular perturbations. Here we present the MARIO (Mapping RNA interactome in vivo) technology to massively reveal RNA-RNA interactions from unperturbed cells. We mapped tens of thousands of endogenous RNA-RNA interactions from mouse embryonic stem cells and brain. These data offered an opportunity to test a fundamental physical property. The experimentally derived RNA interactome is a scale-free network, which is not expected from currently perceived promiscuity in RNA-RNA interactions. Base pairing is observed at the interacting regions between long RNAs, including transposon transcripts, suggesting a class of regulatory sequences acting in trans. In addition, MARIO data reveal thousands of intra-molecule interactions, providing in vivo data on high-order RNA structures.

4. **RefEditor: Building Personalized Diploid Reference Genome to Improve Read Mapping and Genotype Calling in Next Generation Sequencing Studies**
   Zhaohui Qin, Emory University
   Abstract: A fundamental step in analyzing WGS and WES data is mapping short sequencing reads to the reference genome. Although many read mapping algorithms have been developed, the majority uses the universal reference genome and do not take sequence variants into consideration. In this work, we developed a novel strategy that utilizes genotypes obtained *a priori* to customize the universal haploid reference genome into a personalized diploid reference genome. The new strategy is implemented in a program named RefEditor. When applying RefEditor to real data, we achieved significant improvements in read mapping, variant discovery and genotype calling. Compared to standard approaches, RefEditor can significantly increase genotype calling consistency (from 43% to 61% at 4X coverage; from 82% to 92% at 20X coverage) and reduce Mendelian inconsistency across various sequencing depths. we believe the proposed strategy will be of high value in practice, which can also be applied to the scenario where multiple NGS experiments are conducted on the same cohort.
   The RefEditor sources are available at https://github.com/superyuan/refeditor.

5. **Properties and objectives for BMP-FGF interactions in the developing forebrain**
   Ed Monuki, University of California, Irvine
   Abstract: Like other complex tissues, induction and patterning of the forebrain is driven by interactions among multiple morphogens. In the dorsal forebrain, BMPs interact with FGFs emanating from multiple sources, but systems-level

understanding of the properties and objectives of these interactions is rudimentary. In this presentation, we first describe how the developing forebrain represents a classic BMP gradient system, then introduce an ultrasensitive, stem cell-intrinsic response to BMP signaling that impacts cell fate decisions and border formation. Using modeling and experimental approaches, we define how this ultrasensitivity arises from mutual BMP-FGF inhibition ("toggle switch") and how the kinetics of BMP signaling help to buffer and maintain the on-state. We then use new tools and methods to study and model FGF signaling kinetics, which reveal integration, off-state buffering, and the emergence of developmental delay with catchup in border formation and position. Collectively, these studies begin to illuminate the properties of BMP-FGF interactions that advantage the developing forebrain.

6. **Feedback from leaves controls cell fate in the shoot apical meristem by modulating auxin transport**
   Yuling Jiao, IGDB, CAS
   Abstract: Stem cells must balance self-renewal and differentiation; thus, stem cell activities are precisely controlled. In plants, the control circuits that underlie division and differentiation within meristems have been well studied but those that underlie feedback on meristems from lateral organs, such as leaves, remain largely unknown. Here we show that long-distance auxin transport mediates this feedback in a non-cell-autonomous manner. A low-auxin zone is associated with the shoot apical meristem (SAM) organization center, and is required for regulation of SAM size. Using computational model simulations, we show that auxin transport from leaves can inhibit auxin transport from the SAM through an auxin transport switch, and thus maintain SAM auxin homeostasis and SAM size. Genetic and microsurgical analyses confirmed the model's predictions. In addition, the model explains the surprising observation that *yabby* mutants exhibit oscillations of SAM size. Our study shows that plants use a distinct feedback control mechanism for long-distance regulation of stem cell activities.

7. **Multiphase cell models for cytokinesis and cell migration on patterned substrate**
   Qi Wang, CSRC & University of South Carolina.
   Abstract: We discuss a general multiphase cell model for cell motility and dynamics. In this model, various complex fluid models are employed to describe various components of a cell.
   For instance, the cell cortical layer is modeled as an active matter system, described by an active liquid constitutive model. Cell membrane is modeled as a diffuse interface using a phase filed model. The multiphase model can be cast in the generalized hydrodynamics following the generalized Onsager principle so that it is dissipative at the absence of the ATP activity. 2 and 3D numerical

simulations for cytokinesis and cell migration on patterned substrate will be presented.

8. **Spatiotemporal integration of synaptic inputs in neurons: computational modeling, analysis and experiments**
Douglas Zhou, Shanghai Jiao Tong University
Abstract: A neuron receives thousands of synaptic inputs from other neurons and integrates them to process information. Many experimental results demonstrate this integration could be highly nonlinear, yet few theoretical analyses have been performed to obtain a precise quantitative characterization. Based on asymptotic analysis of an idealized cable model, we derive a bilinear spatiotemporal integration rule for a pair of time-dependent synaptic inputs. Note that the above rule is obtained from idealized models. However, we have confirmed this rule both in simulations of a realistic pyramidal neuron model and in electrophysiological experiments of rat hippocampal CA1 neurons. Our results demonstrate that the integration of multiple synaptic inputs can be decomposed into the sum of all possible pairwise integration with each paired integration obeying a bilinear rule.

9. **High-dimensional critical state transitions in mammalian cells revealed by single-cell resolution gene expression profiling - new implications for cancer**
Sui Huang, Institute for Systems Biology, Seattle
Abstract : During mammalian development cells differentiate from a less mature state (stem and progenitor cells) to a more mature state. Similarly, in tumors cancer cells switch between multiple developmental states of distinct malignancy. These quasi-discrete phenotype transitions manifest gene network dynamics in that cells transition from one high-dimensional attractor state x in gene expression state space to another, a process that involves the alteration of expression level values x_i of M=1000s of genes. Because such attractor states are normally very stable differentiation (encoding the gene expression patterns x that define the molecular identity of cell types) an attractor transition during differentiation requires a controlled destabilization of the M-dimensional attractor state through some kind of bifurcation. Thus we expect that at a critical point, the “old” attractor disappears, allowing the cells to exit and “flow” into a nearby (“lower”) attractor state that is now accessible and represents the differentiated state. While critical transitions are well described for low-dimensional systems, and typically modelled as a fold-bifurcation exhibiting “early warning signals”, we now study the case for a high-dimensional system: the commitment of an immature cell to a particular differentiated lineage. Here critical slowing down and increase of autocorrelation in the fluctuation of state variable x as the hallmarks for an approach to the critical “tipping point” due to attractor “flattening”, can technically not be observed since gene expression

profiling requires destruction of a cell. Instead, we exploit the fact that we have an entire cell population of N=100s of cells which approximate a statistical ensemble of N systems that quasi-ergodically "map out" the state space structure. Then, with just a few snapshot single-cell resolution measurements of gene expression profiles of a cell population of N cells undergoing a phenotype change, we obtain the temporal change of the (NxM)-data matrix X(t), which reflects the cell population distribution in the M-dimensional state space. The change of the internal structure of X(t) over the several time points can reveal an imminent tipping point even without knowledge of the system equations dx/dt=F(x, mu), let alone, of any bifurcation parameter mu. For this purpose we introduce an empirical quantity, I_C computed for each time point t from the data matrices X(t). We show that it can predict an impending critical transition, that is, a fate commitment in multipotent blood precursor cells. If there is time, implications for cancer of this class of cell state transitions will be discussed.

10. Quantification and modeling of BMP signaling during zebrafish embryo development

Joseph Zinski1, Wei Dou2, Yan Huang2, Mary Mullins1, David Umulis2,2
1Department of Cell and Developmental Biology, University of Pennsylvania.
2Department of Agricultural & Biological Engineering, Purdue University.
3Department of Biomedical Engineering, Purdue University.

Abstract : Bone Morphogenetic Proteins (BMPs) act in developmental pattern formation as a paradigm of extracellular information that is passed from an extracellular morphogen to cells that process the information and differentiate into distinct cell types based on the morphogen level. Numerous extracellular modulators and feedback regulators establish and control the BMP signaling distribution along the dorsal-ventral (DV) embryonic axis in vertebrates to induce space and time-dependent patterns of gene expression. To identify how the dynamic pattern is regulated during development, we have developed a seamless data-to-model integration and optimization strategy. First, the nuclear intensities of fluorescent stained Phosphorylated-Smad5 (P-Smad) are acquired for each nuclei in each embryo from staged populations to provide a quantitative time-course for the BMP signaling gradient. Next, the nuclei are segmented to yield quantitative point-clouds of P-Smad level at each nuclei. The individual point clouds are registered to similarly staged embryos using a process called Coherent Point Drift (CPD) and the registered populations provide rigorous quantification and comparison of phenotype. To delineate the mechanism of BMP signal inhibition by the secreted binding proteins Chordin (Chd), and Noggin (Nog) a mathematical model was developed and optimized against the population data for wild type and combinations of the Chd mutants. We found a model that reproduced the experimentally observed patterning in WT embryos as well as a number of tested mutants. Models consistent with experimental behavior require that Chordin has a greater range than Noggin, that Noggin is not as freely diffusible, and that the BMP ligands are freely diffusible.

11. **Multiscale modeling of E. coli chemotaxis: From molecules to behaviors**

Yuhai Tu, IBM T. J. Watson Research Center, Yorktown Heights, NY 10598 & Center for Quantitative Biology, Peking University

Abstract: Over 40 years ago, Berg and Brown discovered that E. coli cells perform a run-and-tumble style random walk biased towards higher concentrations of attractants. Around the same time, a phenomenological model of chemotaxis was proposed by Keller and Segel based on a drift-diffusion equation. Since then, much progress has been made in uncovering the molecular mechanism of this cellular navigation system. In this talk, I will summarize some of our recent work in developing an ab initio approach to understand bacterial chemotaxis behaviors from interactions of the key signaling molecules inside the cell.

Based on a molecularly accurate description of the intracellular chemotaxis pathway [1], we have developed a mutliscale model [2, 3] to explain and predict bacterial chemotaxis behaviors in any given spatio-temporal varying chemical environments [4] as well as in other non-chemical environments (temperature, pH) [5]. Our study shows that the bacterial chemotaxis behavior is controlled by the E. coli's working memory. In slow varying environments, the Keller-Segel (KS) equation is recovered, with the macroscopic motility parameters now given by microscopic parameters of the signaling pathway. In fast varying environments, the KS equation breaks down due to finite relaxation time of the memory. A new chemotaxis equation that couples the cell density field with a course-grained memory field is developed and used to explain chemotaxis behaviors in fast varying environments successfully.

[1] "Quantitative modeling of bacterial chemotaxis: signal amplification and accurate adaptation", Yuhai Tu, Annu. Rev. Biophys., 42: 337-59, 2013.

[2] "Quantitative modeling of E. coli chemotaxis motion in environments varying in space and time", L. Jiang, Q. Ouyang, Yuhai Tu, Plos Comp. Bio., 6(4), e100735, 2010.

[3] "A pathway-based mean-field model for Escherichia coli chemotaxis", G. Si, T. Wu, Q. Ouyang, Yuhai Tu, Phys. Rev. Lett., 109, 048101-048105, 2012.

[4] "Frequency-dependent Escherichia coli chemotaxis behavior", X. Zhu, G. Si, N. Deng, Q. Ouyang, T. Wu, Z. He, L. Jiang, C. Lou, and Yuhai Tu, Phys. Rev. Lett., 108, 128101, 2012.

[5] "Behaviors and strategies of bacterial navigation in chemical and nonchemical gradients", Bo Hu, Yuhai Tu, Plos Comp. Bio., 10 (6), e1003672, 2014.

12. **A multi-scale model for the hair follicle reveals mechanism for rapid evolution of hair growth patterns**
Maksim Pikus, UC Irvine
Abstract: Recognized for periodicity and excitability, the hair follicle (HF) is a popular system for studying regeneration. We present a multi-scale mathematical model that accounts for the realistic HF morphology, and where hair-to-hair growth coordination emerges based on shared signaling. This model naturally produces stable periodicity and excitability of HF regeneration, and predicts BMP and WNT as core inhibitor and activator signals respectively. We scrutinized this prediction by examining BMP and WNT effects on HF growth phase timing. We show that increasing BMP or decreasing WNT signaling in mutant mice leads to a shorter growth phase and shorter hairs, while decreasing BMP signaling produces opposite effects. We also applied modeling to reveal that skin behaves as a heterogeneous excitable medium, composed of anatomic domains with distinct cycling dynamics and novel hair growth behaviors. Interactions between fast-cycling ventral and slow-cycling dorsal HF populations produce deterministic ventral-to-dorsal hair growth waves and bilaterally symmetric patterns in young mice. Ear skin behaves as a hyper-refractory domain with HFs that physiologically equilibrate in an extended telogen, do not propagate hair growth waves, and respond poorly to growth-inducing stimuli. Such hyper-refractivity relates to high levels of BMP ligands, in part secreted by auricular cartilage and muscle, tissues specific to the ear pinna. Additionally, homogenous hair waves can break at the boundaries with hyper-refractory ears and anatomically discontinuous eyelids, generating diffraction-like hair growth patterns. We posit that similar mechanisms for coupled regeneration with oscillator, hyper-refractory, and wave-breaker regions can operate in other actively renewing tissues and organs.

13. **Stem Cells: Interplay Between Complex Data and Computational Models**
Qing Nie,
Department of Mathematics
Department of Biomedical Engineering
Department of Developmental and Cell Biology
University of California, Irvine
Abstract: Stem cells are a critical building block of life. *Embryonic stem cells* can differentiate into cells forming ectoderm, endoderm and mesoderm during development, and *adult stem cells* can maintain the normal turnover of regenerative tissues (e.g. blood, skin, intestinal crypts). Recently, there has been an explosion of data on stem cells at various biological scales (e.g. gene expression and epigenetic measurements, lineage tracing, and molecules for intercellular communications). While data collected through different cell lines and animal models provide tremendous details on individual elements under various conditions, many gaps of knowledge and understanding remain on how

stem cells carry out their remarkable functions and complex tasks. Mathematical models connecting interacting elements at different scales enable integration of massive, heterogeneous datasets collected with varying methods. In this talk, I will present several computational modeling frameworks with different complexity on multistage cell lineages driven by stem cells, which account for diffusive signaling molecules, regulatory networks, individual cells, mechanics, and evolution. Questions of our interest include role of feedbacks, stem cell niche for spatial organization, crosstalk between epigenetic and gene regulations, and cellular plasticity. In particular, I will discuss our recent effort on connecting modeling and complex experimental data to elucidate principles for stem cell dynamics in development, regeneration, and diseases.

14. TGF-β signal transduction and cell fate decision

Jianhua Xing, University of Pittsburgh
Email: xing1@pitt.edu

Abstract Epithelial to mesenchymal transition (EMT), a process of transforming polygon-shaped epithelial cells with tight cell-to-cell attachment to spindle-like mesenchymal cells with loose or rare cell-to-cell attachment, has been suggested to play a key role in embryo development and many pathological processes such as fibrosis and cancer metastasis. Previous studies showed that exogenesis signals such as TGF-β can induce EMT in many mammalian epithelial cell lines. According to a well- established mechanism, transmembrane TGF-β receptors (TGFBR) receive the extracellular signal, pass downstream via the Smad transcription factor family, and activate multiple genes such as Snail1, a key regulator of EMT. However, our measurements and computational analysis reveal that Smad2/3 can not function as major transcriptional factors to directly induce Snail1 expression. After careful examination of the TGF-β Smad dependent and independent pathways, we hypothesize sustained Snail1 activation is achieved through a nested relay mechanism that involves Smads, Gli1/2 (a main component of the SHH pathway), and GSK3β (main components of the WNT pathway). Our combined mathematical modeling and quantitative measurements confirmed this hypothesis.

Currently for live cell imaging, we are using the CRISPR-Cas9 technique to fuse fluorescence proteins to selected players in the network. Compared to the wide application of CRISPR-based gene knockout, gene knockin is more challenging and less developed. A technical obstacle lies in generating the knockin constructs, for which the Gibson assembly approach often fails. Out of a $\sim 10^{45}$possible sequence space, we developed a computer-aided procedure to design three DNA segment linkers to optimize the assembly fidelity. Experimental tests on multiple genes confirmed that presence of the linkers leads to high yield of DNA constructs that we failed to make otherwise.

15. **The space and time of neuronal variability in a spiking neuron network**
Chengcheng Huang,
University of Pittsburgh
Abstract: Neural variability has important consequences on neural coding. The mechanism underlying neural variability is still poorly understood. The balanced network of excitation and inhibition successfully reproduces the Poissonian spiking statistics of individual neuron, however, it cannot explain the shared variability among neurons (noise correlation), which is commonly observed for cortical neurons. Recent experiments have shown that attention reduces correlation among neurons within visual cortex area and increases the correlation between cortical areas simultaneously (Ruff & Cohen, submitted). These effects can presumably improve the population code of visual stimuli. The observed opposite trends of change of correlations between-areas and within-area imposes further constraint on circuit mechanisms for attention. We found that a linear model, such as a balanced network, cannot explain the opposite trend of change in correlations. We developed a spiking neuron network with spatiotemporal dynamics, which can generate correlated variability internally. We are able to reproduce the attentional effects on noise correlation by depolarizing both excitatory and inhibitory populations.

16. **Computation of Transition States and its Applications in Biology**
Lei Zhang,
Peking University
Abstract: The dynamics of complex biological systems is often driven by multiscale, rare but important events. In this talk, I will first introduce the numerical methods for computing transition states, in particular, the Optimization-based Shrinking Dimer (OSD) method we recently proposed. Then I will give two applications of rare events and transition states in biology, including boundary sharpening in zebrafish hindbrain and neuroblast delamination in *Drosophila*. The joint work with Qiang Du (Columbia), Qing Nie (UC Irvine), Yan Yan (HKUST).