北京大學 PEKING UNIVERSITY

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

2019 A3 Workshop on Mathematical Life Science

Peking University

May 10-12, 2019

北京大學 PEKING UNIVERSITY

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

2019 A3 Workshop on Interdisciplinary Research Connecting Mathematics and Biology

Venue: May 10 at Lecture Hall, JingChunYuan No. 82 JiaYiBing, BICMR, Peking University
May 11-12 at Room 77201, JingChunYuan No.78, BICMR, Peking University

Scientific committee:

Pingwen Zhang (Peking University)

Yasumasa Nishiura (Tohoku University)

Hyeonbae Kang (Inha University)

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Sungrim Seirin-Lee (Hiroshima University, Japan)

Masakazu Akiyama (Hokkaido University, Japan)

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Accommodation:

Zhongguanyuan Global Village Hotel, No. 1 Building (北京大学中关新园 1 号楼) No. 216 Zhongguancun North Road, Haidian District, Beijing 100871, China
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Shaoyuan Hotel (勺园酒店), near the west gate, in Peking University campus.
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Room 77201, BICMR
Lecture Hall, Jiayibing Building
西门 West Gate
西侧门 Side West Gate
东侧门 Side East Gate
东门 East Gate
东南门 Southeast Gate
南门 South Gate
西南门 Southwest Gate
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Zhongguancun North Street
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Qinghua South Road
Ke Xue Road
Jing Yuan Road
Wei Ming Lake
Shaoyuan Hotel
截图(Alt + A)
中关新园
Zhongguanyuan Global Village

Workshop Program

May 9, 2019 Registration

11:00-20:00： Zhongguanyuan Global Village Hotel, No. 1 Building

Day 1 (May 10, 2019)

Morning Session **Chair: Hao Ge**		
Time	**People**	**Titles /Activities**
8:50-9:00	**Opening remarks**	
9:00-9:45	Fuchou Tang (PKU)	Decoding the gene regulation network in human germline cells by single-cell functional genomics approaches
9:45-10:15	Honda Naoki (Kyoto U.)	Deciphering animal behavioral strategy by inverse reinforcement learning
10:15-11:00	**Coffee Break and group photo**	
Chair: Jae Kyoung Kim		
11:00-11:30	Lei Zhang (PKU)	Control of stem cells in both embryo and plant
11:30-12:00	Jinzhi Lei (Tsinghua U.)	Leukemic cell plasticity induces immune escape after CD19 chimeric antigen receptor T cell therapy of acute B lymphoblastic leukemia
12:00-14:00	**Lunch**	
Afternoon Session **Chair: Jinzhi Lei**		
14:00-14:30	Sungrim Seirin-Lee (Hiroshima U.)	Pattern Formation from Cell to Dermatology
14:30-15:00	Rui Liu (SCUT)	Detecting the early-warning signal of the critical transition for complex diseases
15:00-15:30	Masakazu Akiyama (Hokkaido U.)	A mathematical model of somite elongation
15:30-16:00	**Coffee Break**	
Chair: Rui Liu		
16:00-16:10	Hiroaki Imoto (Osaka U.)	Mathematical modelling of signal-dependent cyclin/cdk network driving mammalian cell cycle

16:10-16:20	Jaehyoung Hong (KAIST)	Analyzing the sleep patterns of shift workers using mathematical model
16:20-16:30	Xiaolu Guo (Peking U.)	The Nonequilibrium Mechanism of Noise Enhancer synergizing with Activator in HIV Latency Reactivation
16:30-16:40	Yoshifumi Asakura (Kyoto University)	System identification of mechano-chemical epithelial sheet dynamics
16:40-16:50	Daewook Kim (KAIST)	Systems pharmacology model reveals the sources of the inter- and intraspecies variability in drug efficacy
16:50-17:00	Kuan Tao (Peking U.)	Mathematical models on cell polarity and migration coupled with mechano-chemical factors
17:00-17:10	Yasushi Okuchi (Kyoto U.)	A Machine Learning Method to Reconstruct Spatial Gene Expression Profile in Tissues from Single-cell RNA-seq Data
17:10-17:20	EuiMin Jeong (KAIST)	Mathematical Modeling to Reveal Molecular Differences Causing Pacemaker-neuron-dependent Rhythm Alteration by Mutant
17:20-17:30	Xiaopei Jiao (Tsinghua U.)	A mathematical model of chronic myeloid leukemia driven by neoplastic microenvironment
18:00	**Dinner**	

Day 2 (May 11, 2019)

Morning Session
Chair: Lei Zhang

Time	People	Titles /Activities
9:00-9:45	Jaeyoung Sung (CAU)	Chemical Dynamics in Living Cells
9:45-10:15	Jae Kyoung Kim (KAIST)	Analyzing timeseries data of biological systems with hidden components
10:15-10:45	**Coffee Break and Group photo**	
Chair: Sungrim Seirin-Lee		
10:45-11:30	Satoshi Sawai (U. Tokyo)	Deciphering morphology landscape of fast migrating cells by dynamical systems modeling and machine learning
11:30-11:45	Seunggyu Lee (NIMS)	Mathematical model for formation of fingerprint

11:45-12:00	Ji-Hyun Kim (CAU)	Frequency spectrum of biological noise: a probe of reaction mechanism and dynamics
12:00-14:00	**Lunch**	
Afternoon Session **Chair: Jaeyoung Sung**		
14:00-14:30	Yangjin Kim (Konkuk U.)	Role of microenvironment in regulation of tumor growth
14:30-15:00	Ji Hyun Bak (KIAS)	Olfactory receptor code for effective odor discrimination
15:00-15:30	Huanfei Ma (Suzhou U.)	Analysis of high-dimensional short-term time series data
15:30-16:00	**Coffee Break**	
Chair: Huanfei Ma		
16:00-16:10	Gen Honda (U. Tokyo)	Analysis of plasticity in amoeboid morphology toward the comprehensive understanding of cell migration
16:10-16:20	Donggu Lee (Konkuk U.)	Dynamics of N1 and N2 neutrophils and lung cancer development in response to TGFbeta and IFN beta
16:20-16:30	Wei Zhao (Peking U.)	Network design principle for dual function of adaptation and noise attenuation
16:30-16:40	Tomohiro Nakahara (Hiroshima U.)	The geometrical effect for the size of cell polarity domain in asymmetric cell division
16:40-16:50	Hyukpyo Hong (KAIST)	Product-Form Stationary Distributions for Non-Complex Balanced Networks
16:50-17:00	Peijie Zhou (Peking U.)	Understanding Single-cell Transciptomics Analysis Methods: from Dynamical Systems Models
17:00-17:10	Kosuke Okuno (Hiroshima U.)	Diversity of cell fate by cell membrane-binding dynamics in the Notch-Delta signalling pathway
17:10-17:20	Junho Lee (Konkuk U.)	Synergistic Effects of Bortezomib-OV Therapy and Anti-Invasive Strategies in Glioblastoma: A mathematical model
17:20-17:30	Shun He (Peking U.)	The Application of D-trace Loss in High-dimensional Compositional Data Network Analysis
18:00	**Dinner**	

Day 3 (May 12, 2019)

Morning Session **Chair: Hyeonbae Kang**		
Time	**People**	**Titles /Activities**
9:00-9:45	Qing Nie (UC Irvine)	Multiscale modeling of cell fate dynamics
9:45-10:15	Sat byul Seo (Kyungnam U.)	Mathematical model for identifying relations among neurotransmission.
10:15-10:45	**Coffee Break**	
Chair: Nie Qing		
10:45-11:15	Ping Wei (Peking U.)	Synthetic NF-kB: a building approach to study complex signaling behaviors
11:15-11:45	Yasufumi Yamada (Hiroshima U.)	Acoustic navigation method based on echolocation strategies employed by bats
11:45-12:00	**Concluding remarks and farewell**	
12:00-14:00	**Lunch**	
Afternoon Session: Free Discussion		

Abstracts of Invited Talks

A mathematical model of somite elongation.

Masakazu Akiyama[1]
in collaboration with
Takamichi Suhida[1], Yue Tong[2], Kametani Harunobu[2], Shimada Atsuko[2], Takeda Hiroyuki[2]

1. Hokkaido University
2. University of Tokyo

Collective cell migration has been investigated as a self-organization phenomenon in life activities. Recently, rotational phenomena of collective cell migrations observed in morphogenesis are focused. For example, In zebrafish somite formation process, cells within the somite autonomously rotate. Very interesting at this time, the somite elongates in the direction of the rotation axis. It is not clear what mechanism this phenomenon is caused by. Our goal is to extract essential mechanisms of collective cell migrations in morphogenesis from mathematical modeling. So, we have already constructed a model for 2-dimensional cell migration [1]. This model can simulate the collective cell migration by considering the cells as particles. On the other hand, we could not apply this model to three-dimensional morphogenesis like the somite elongation process. In order to solve the problem, we couple Phase Filed (a mathematical model to describe crystal growth) model and our 2D cell migration model and constructed a new 3D cell migration model. With this new model, we were able to clarify the effect of cell rotation motion on the somite elongation. In the lecture, we would like to introduce the new 3D model and several numerical calculation results.

[1] M. Akiyama, T. Sushida, S. Ishida and H. Haga. (2017). Mathematical model of collective cell migrations based on cell polarity, Dev Growth Differ, Number of 2017, doi: 10.1111/dgd.12381.

Olfactory receptor code for effective odor discrimination

Ji Hyun Bak, KIAS

Olfaction, or the sense of smell, identifies and discriminates different odors that carry distinct behavioral signals. The onset of olfactory sensing is the selective responses of a family of receptors to the odor-carrying molecules, called the olfactory receptor code. I will present our ongoing effort to understand the human olfactory receptor code. We characterize the observed statistical properties from experimental data, and propose a relevant optimization problem that is consistent with the observations.

Frequency spectrum of biological noise: a probe of reaction mechanism and dynamics

Ji-Hyun Kim, CAU

Even in the steady-state, the number of biomolecules in living cells fluctuates dynamically, and the frequency spectrum of this chemical fluctuation carries valuable information about the dynamics of the reactions creating these biomolecules. Recent advances in single-cell techniques enable direct monitoring of the time-traces of the protein number in each cell; however, it is not yet clear how the stochastic dynamics of these time-traces is related to the reaction mechanism and dynamics. Here, we derive a rigorous relation between the frequency-spectrum of the product number fluctuation and the reaction mechanism and dynamics, starting from a generalized master equation. This relation enables us to analyze the time-traces of the protein number and extract information about dynamics of mRNA number and transcriptional regulation, which cannot be directly observed by current experimental techniques. We demonstrate our frequency spectrum analysis of protein number fluctuation, using the gene network model of luciferase expression under the control of the Bmal 1a promoter in mouse fibroblast cells. We also discuss how the dynamic heterogeneity of transcription and translation rates affects the frequency-spectra of the mRNA and protein number.

Analyzing time series data of biological systems with hidden components

Jae Kyoung Kim, Korea Advanced Institute of Science and Technology (KAIST)

Despite dramatic advances in experimental techniques, many facets of intracellular dynamics remain hidden, or can be measured only indirectly. In this talk, I will describe two strategies to analyze timeseries data of biochemical reaction networks with the hidden parts. Then, I will illustrate how these strategies are used to understand the processes of protein maturation and drug metabolism.

Role of microenvironment in regulation of tumor growth

Yangjin Kim, Konkuk University

In this talk, I will present some recent mathematical models of cancer growth and development which focus on designing anti-cancer strategies. We investigate the role of microenvironment in regulation of cellular dispersion and tumor growth. The results of the models will be compared with experimental data and some new

directions of how to develop the new, innovative strategies of anti-invasion of tumor cells will be discussed.

Mathematical model for formation of fingerprint

Seunggyu Lee, NIMS

We can find complex patterns at fingertipes of most of primates including human being, which is called fingerprint. Since the patterns are not identical even between enzygotic twins, it has been applied to distinguish each individuals. However, there is still no established theory about pattern formation. In this work, we propose a mathematical model for fingerprint formation related with distribution of sweat gland duct on curved manifod.

Leukemic cell plasticity induces immune escape after CD19 chimeric antigen receptor T cell therapy of acute B lymphoblastic leukemia

Jinzhi Lei, Tsinghua University

Many patients suffer relapse after chimeric antigen receptor (CAR) therapy, the underlying mechanism remains unclear. Here, we applied second-generation CD19 CAR-T cells to mice injected with NALM-6-GL cells; 60% of the mice relapsed within 3 months. The relapsed tumors retained CD19 expression but exhibited a profound increase in CD34 transcription, which led to a hypothesis that CAR-T treatment induced tumor cells to transition to hematopoietic stem-like cells (HSLCs) and myeloid-like cells and hence escape of CAR-T targeting. A computational model was developed based on this proposed hypothesis. Model simulation verified the experimental observations and predicted that CAR-T cell-induced cell plasticity can lead to tumor relapse. Our simulations and mouse experiments further indicated that CD19+ relapse could be prevented by the combined administration of CAR-19 and CD123-targeted CAR-modified (CAR-123) T cells administered at specific ratios. These findings highlight the mechanism of CAR-T stress-induced stem-like tumor cell transition in CD19+ relapse. This work is in collaboration with Dr. Xiaosong Zhong (Beijing Shijitan Hospital).

Detecting the early-warning signal of the critical transition for complex diseases

Rui Liu, SCUT

Complex disease progression, such as cancer, is generally a nonlinear process with three stages, i.e., normal state, pre-disease state, and disease state, where the pre-

disease state is the critical state just before disease appearance. Traditional biomarkers aim to identify the disease state by exploiting the information of differential expressions for the observed molecules between the normal and disease states, but may fail for the pre-disease state because there are generally no significant differences between the normal and pre-disease states. Thus, it is a challenging task to identify the pre-disease state, which actually implies the disease prediction.

In this talk, by exploiting the information of differential associations among the observed molecules between the normal and pre-disease states, we present a temporal differential network based computational method to accurately identify the pre-disease state or predict the occurrence of severe disease. The theoretical foundation of this work is the quantification of the critical state before the transition into a deteriorated stage during disease progression using dynamical network biomarkers. Specifically, considering that there is one stationary Markov process in each state, a probability index, inconsistency score (I-score), is proposed to quantitatively measure the change of the stationary processes from the normal state so as to detect the pre-disease state. In other words, a drastic increase of I-score implies the high inconsistency with the preceding stable state and thus signals the upcoming critical transition.

Analysis of high-dimensional short-term time series data

Huanfei Ma, Suzhou University

In the big data era, many time series data sets have a large amount of variables measured simultaneously while the samples in time are limited. In this talk I will introduce our recent works on the analysis of such high-dimensional short-term data, including the causality analysis and system dynamics reconstruction.

Deciphering animal behavioral strategy by inverse reinforcement learning

Honda Naoki[1]
in collaboration with
Shoichiro Yamaguchi[2], Muneki Ikeda[3], Yuki Tsukada[3], Shunji Nakano[3], Ikue Mori[3], Shin Ishii[2]

1. Research Center for Dynamic Living Systems, Graduate School of Biostudies, Kyoto University
2. Graduate School of Informatics, Kyoto University

3. Department of Biological Science, Graduate School of Science, Nagoya University

Understanding animal decision-making has been a fundamental problem in neuroscience. Many studies analyze actions that represent decision-making in behavioral tasks, in which rewards are artificially designed with specific objectives. However, it is impossible to extend this artificially designed experiment to a natural environment, because in a natural environment, the rewards for freely-behaving animals cannot be clearly defined. To this end, we must reverse the current paradigm so that rewards are identified from behavioral data. In this study, we developed a new reverse-engineering method (inverse reinforcement learning) that can estimate reward-based representation of the behavioral strategy from time-series behavioral data. As a particular target, we focused on thermotactic behavior in C. elegans. Using this method, we found that the thermotactic strategy comprised mixture of two strategies: directed migration (DM) and isothermal migration (IM). First, the DM is a strategy that the worms use both information of absolute and temporal derivative of temperature to efficiently reach to specific temperature, which can explain observation that the worms migrate toward the fed temperature. Second, the IM is a strategy that the worms track along a constant temperature, which reflects isothermal tracking well observed in previous studies. We further applied our method to the starved worms and then found that the worms avoid the starved temperature by using information only of absolute temperature but not of its temporal derivative. In this way, our method is able to clarify how the worms process thermosensory state in their thermotactic strategy. Thus, this study presents and validates a novel approach that should propel the development of new, more effective experiments to identify behavioral strategies and decision-making in animals.

Reference:

Yamaguchi S, Naoki H* et al., Identification of animal behavioral strategies by inverse reinforcement learning. *PLoS Computational Biology* 14(5): e1006122 (2018)

Multiscale modeling of cell fate dynamics

Qing Nie

Departments of Mathematics and Developmental & Cell Biology
NSF-Simons Center for Multiscale Cell Fate Research
University of California, Irvine

Cells make fate decisions in response to dynamic environmental and pathological stimuli as well as cell-to-cell communications. Recent technological breakthroughs have enabled to gather data in previously unthinkable quantities at single cell level, starting to suggest that cell fate decision is much more complex, dynamic, and

stochastic than previously recognized. Multiscale interactions, sometimes through cell-cell communications, play a critical role in cell decision-making. Dissecting cellular dynamics emerging from molecular and genomic scale in single-cell demands novel computational tools and multiscale models. In this talk, I will present our recent works on analyzing single-cell molecular data, and their connections with cellular and spatial tissue dynamics. Our mathematical approaches bring together optimization, statistical physics, ODEs/PDEs, and stochastic simulations along with machine learning techniques. By utilizing our newly developed computational tools along with their close integrations with new datasets collected from our experimental collaborators, we are able to investigate several complex systems during development and regeneration to uncover new mechanisms in cell fate determination.

Deciphering morphology landscape of fast migrating cells by dynamical systems modeling and machine learning

Satoshi Sawai[1]
in collaboration with
Daisuke Imoto[1], Nen Saito[2], Gen Honda[1], Motohiko Ishida[1], Taihei Fujimori[1], Chika Okimura[3], Yoshiaki Iwadate[3]

1. Graduate School of Arts and Sciences, University of Tokyo
2. Universal Biology Institute, Graduate School of Science, University of Tokyo
3. Faculty of Science, Yamaguchi University

Morphology of various cell-types are largely context-dependent and plastic. Studies over the years have described the shape dynamics of migrating cells mathematically; most successful being the dumpling-like shaped fish keratocytes. Due to the complexity and the dynamic nature, mathematical descriptions of amoeboid cells remain a challenge. The social amoeba *Dictyostelium* has served as a model system for cell migration, chemotaxis, phagocytosis and other cellular dynamics that accompanies large plasma membrane deformation [1-6]. In combination with the regulatory logics of biochemical networks [2-4], experimental and mathematical analyses are bringing to light the importance of cell shape itself in deciphering how the direction of cell migration is determined. In this talk, I will introduce a minimalistic model that describes the essential regulatory logics underlying complex morphology of amoeboid cells. The proposed model recapitulates the overall cell forms observed in freely migrating *Dictyostelium*, neutrophils and fish keratocyte. Similarities between the simulated data and real cell data were assessed by feature extraction techniques and machine learning by deep neural networks. Our numerical analyses suggest that the combination and a balance between the degree of transients / confinement of the protrusive dynamics versus stability of global polarity is central to determinant of cell morphology. We will demonstrate applicability of our approach

to analyzing the migratory response in chemotattractant field [2,3] and cell-cell adhesion [1].

1. T. Fujimori, A. Nakajima, N. Shimada, S. Sawai (2019) Tissue self-organization based on collective cell migration by contact activation of locomotion and chemotaxis. ***Proc. Natl. Acad. Sci. USA*** in press
2. K. Kamino, Y. Kondo, A. Nakajima, M. Honda-Kitahara, K. Kaneko, S. Sawai (2017) Fold-change detection and scale-invariance of cell-cell signaling in social amoeba. ***Proc. Natl. Acad. Sci. USA*** 114 (21): E4149-E4157.
3. A. Nakajima, S. Ishihara, D. Imoto and S. Sawai (2014) Rectified directional sensing in long-range cell migration. ***Nat. Commun.*** 5, 5367.
4. D. Taniguchi‡, S. Ishihara‡, T. Oonuki, M. Honda-Kitahara, K. Kaneko and S. Sawai (2013) Phase geometries of two-dimensional excitable waves govern self-organized morphodynamics of amoeboid cells. ***Proc. Natl. Acad. Sci. USA.*** 110 (13), 5016-5021. (‡ Equal contribution)
5. T. Gregor, K. Fujimoto, N. Masaki and S. Sawai (2010) The onset of collective behavior in social amoebae. ***Science*** 328 (5981), 1021-1025.
6. S. Sawai, P.T. Thomason and E.C. Cox (2005) An autoregulatory circuit for long-range self-organization in Dictyostelium cell populations. ***Nature*** 433 (7023) , 323-326.

Pattern Formation from Cell to Dermatology

Sungrim Seirin-Lee[1]
in collaboration with
T. Skegawa[3], T. Nakahara[1], H. Ishii[3], S-I. Ei[3] (Talk 1)
Y. Yanase[4], S. Takahagi[4], M. Hide[4] (Talk 2)

1. Department of Mathematics, Hiroshima University
2. JST PRESTO
3. Department of Mathematics, Hokkaido University
4. Department of Dermatology, Hiroshima University

Mathematical modelling is now very common interdisciplinary tool in life science, and the role of mathematical model is spreading to multiple fields in multiple forms. In this talk, I would like to introduce two approaches of mathematical modeling on (pure) mathematics and medical science. In the first talk, I will show a general mechanism of polarity location problem arisen in asymmetric cell division and show how such mechanism can be generalized to a mathematical (analytical) problem. In the second talk, I will show a new possibility of the role of mathematical modeling that may contribute to the clinical medicine of dermatology with the example of Urticaria.

Mathematical model for identifying relations among neurotransmission.

Sat byul Seo, Kyungnam University

We develop a mathematical model to emulate spontaneous and evoked neurotransmissions resulted from glutamate release within a single synapse. In order to identify the spatial relation among neurotransmissions, we consider quantitative factors, such as the size of synapses, inhomogeneity of diffusion coefficients, the geometry of synaptic cleft, and the release rate of neurotransmitter, that will affect postsynaptic currents. The computed results match well with existing experimental findings and provide a quantitative map of boundaries of physical constraints for having independent synaptic fusion events.

Chemical Dynamics in Living Cells

Jaeyoung Sung, CAU

We introduce a new type of kinetic network model and kinetic theory for biological networks, enabling an accurate quantitative description of chemical dynamics of complex biological networks. An advantage of this approach is its applicability to biological networks producing biomolecules with arbitrary lifetime distributions to which the conventional approaches, such as the classical chemical kinetics, chemical master equation, and chemical Langevin equation are not directly applicable. Another advantage of our approach is that it enables quantitative investigation into vibrant biological networks composed of complicated chemical processes, e.g., multi-step or multi-channel reactions whose rates have both intrinsic and extrinsic fluctuation. We demonstrate the advantages of our approach by providing an unprecedented quantitative explanation of non-classical chemical dynamics observed in various biological systems including single enzymes, in vivo motor-protein multiplexes, and cell systems with various synthetic gene networks. Time-permitting, we will also discuss how the frequency-spectrum of biological noise is related to the structure and dynamics of biological networks and the lifetime distribution of the biomolecules.

Decoding the gene regulation network in human germline cells by single-cell functional genomics approaches

Fuchou Tang, Peking University

Human germline cells are crucial for maintenance of the species. However, the developmental trajectories and heterogeneity of human germline cells remain largely unknown. We performed single-cell RNA-seq and DNA methylome sequencing analyses of human germline cells in female and male human embryos spanning several critical developmental stages. We found that female fetal germ cells (FGCs) undergo four distinct sequential phases characterized by mitosis, retinoic acid

signaling, meiotic prophase, and oogenesis. Male FGCs develop through stages of migration, mitosis, and cell-cycle arrest. Individual embryos of both sexes simultaneously contain several subpopulations, highlighting the asynchronous and heterogeneous nature of FGC development. Moreover, we observed reciprocal signaling interactions between FGCs and their gonadal niche cells, including activation of the bone morphogenic protein (BMP) and Notch signaling pathways. Our work provides key insights into the crucial features of human germline cells during their highly ordered mitotic, meiotic, and gametogenetic processes in vivo.

Synthetic NF-kB: a building approach to study complex signaling behaviors

Ping Wei, Peking University

The precise dynamic features in cell signaling play crucial roles in regulating various cellular functions. Due to the complexity and redundancy in natural cells, it remains challenging to completely understand how the complex temporal behaviors are programmed in parameters or structures of the signaling circuits. To overcome such problems, we took a synthetic approach to reconstitute the human nuclear factor κB (NF-κB) system in S. cerevisiae. This simple but highly tunable circuit allows us to systematically explore the design principles of oscillatory signaling dynamics.

Acoustic navigation method based on echolocation strategies employed by bats

Yasufumi Yamada[1]
in collaboration with
Yuma Watabe[1], Shizuko Hiryu[2], Ryo kobayashi[1]

1. Hiroshima University
2. Doshisha University

Bats are the one of the unique sensing animals who perceives the 3-dimensional space by an echolocation. Echolocation is the biological active SONAR system which is bats emit the ultrasonic pulses and analyse the returning echo from surroundings. From an engineering point of view, echolocation design seems to be quite simple owe to be consist of only one transmitter and two receivers. Despite of this, bats accomplish not only acrobatic 3-dimensional flight but also flight for capturing prey in a real time. So far, it has been unclear that how do bats localize the target coordination accurately even in such a moving condition. Our purpose is to understand the 3-dimensiona localization process employed by bats based on mathematical and practical investigation.

Here, we focused on CF-FM bats that reproduce the compound signal which consist short duration down-sweep FM component and constant frequency (CF) component with long duration. In our previous measurement with *Rhinolophus ferrumequinum nippon* (CF-FM bats) during flight, echolocation sounds has often induced the frequency beat which was caused by the interference of the pulse and the Doppler shifted echo. Especially, intense frequency beat has been observed in interferences of those CF components. Based on those observations, we assume that bats apply frequency beat information to localise the accurate object position.

In this study, we constructed a method for 2-Dimensional localization process with binaural frequency beat information. In addition, we also evaluated the proposed method by the practical experiments with automatic sensing systems equipped with one transmitter and two receivers. Finally, we will discuss about the 3-dimensional processing method combined with frequency beat information and sound intensity information obtained from right and left ears.

Control of Stem Cells in both Embryo and Plant

Zhang Lei
Beijing International Center for Mathematical Research & Center for Quantitative Biology, Peking University

Development and regeneration require plant and animal cells to make decisions based on their locations. In this talk, I will start with the dual role of Nanog during stem cell differentiation and reprogramming. A stochastic five-node network model shows the low-Nanog state can enhance cell differentiation through serving as an intermediate state to reduce the energy barrier of transition. Then I will present a mathematical model to study feedback of organs on shoot apical stem cells by auxin transport switch. We find that auxin transport from leaf primordia inhibits the establishment of polar auxin transport out of the meristem. In aberrant leaf development mutant and leaf removal plant, the inhibition from leaf primordia is interrupted and auxin transports out of the meristem, leading to enlarged stem cell and stem cell region. The joint work Qing Nie (UC Irvine), Chao Tang (PKU), Yuling Jiao (CAS).

Abstracts of Short Talks

System identification of mechano-chemical epithelial sheet dynamics

Yoshifumi Asakura[1]
in collaboration with
Yohei Kondo[2], Kazuhiro Aoki[2], Honda Naoki[1]

1. Research Center for Dynamic Living Systems, Graduate School of Biostudies, Kyoto University
2. Exploratory Research Center on Life and Living Systems (ExCELLS), National Institute of Natural Sciences

Collective migration of epithelial cells is a fundamental process of multi-cellular organisms. Our recent study using live imaging with FRET-based biosensor discovered that cell migration within an epithelial sheet is oriented by traveling waves of ERK activation [1]. However, how the cells make a decision on migration direction by integrating mechano-chemical signals has remained still elusive. Here, we performed system identification approach to extract a hidden control role in the epithelial sheet dynamics in a data-driven manner. We first mathematically formulated ERK-regulated intercellular mechanical interaction as a continuum mechanics model. In this continuum model, migration velocity change is determined by several mechano-chemical signals: cellular density, ERK activity, velocity field and their temporal and/or spatial derivatives. We thus quantified the migration velocity and the mechano-chemical signals of all cells by using cell tracking and image processing on time-lapse images. We analyzed their time-series data with help of machine learning and then obtained a reverse-engineered model, which describes how the cells intracellularly process these mechano-chemical signals. We also confirmed that this model has an ability to forecast cell migration, hence showing validity of the model. By interpreting the data-driven continuum model at the cellular level, we elucidated intercellular mechanical interaction is up-regulated by temporal derivative of ERK signal. Therefore, our system identification approach would be greatly powerful to understand mechano-chemical epithelial sheet dynamics.

Reference:

1. Aoki K, Kondo Y, Naoki H, Hiratsuka T, Itoh RE and Matsuda M: Propagating Wave of ERK Activation Orients Collective Cell Migration. *Developmental Cell* 43, 305–317 (2017)

The Nonequilibrium Mechanism of Noise Enhancer synergizing with Activator in HIV Latency Reactivation

Xiaolu Guo, Peking University

Reactivating HIV latency and then simultaneously eliminating it by antiretroviral therapy has become a leading strategy in curing HIV. Recently single-cell screening experiments have shown the drug synergy between two categories of biomolecules, activator (AC) and noise enhancer (NE): NE can amplify the reactivation of latent HIV induced by AC, although NE itself cannot reactivate HIV latency, i.e. 1+1>2. Based on the detailed analysis of a two-state effective model, we uncover out two necessary conditions for this type of drug synergy: 1. The decreasing of transition rate from the LTR-off state to the LTR-on state by NE is highly inhibited by AC when both are present; 2. The transition rate from the LTR-on state back to the LTR-off state without AC/NE binding as well as positive feedback should not be very low. Then we propose an eight-state mechanistic model with both AC/NE-DNA binding kinetics and positive feedback of Tat circuit, which can not only successfully reproduce all the known important experimental observations but also provide further mechanistic insights into the drug synergy for curing HIV infection. We show that in order to achieve their drug synergy, the regulation of HIV LTR expression through the binding of AC/NE with DNA molecule must operate out of equilibrium with energy dissipation. Specific mechanisms with energy input are found out by our model, which can successfully prevent the inhibition of NE upon the reactivation of LTR-on state (binding of RNAP) in the presence of AC binding. Also we illustrate that only when the timescale of LTR turning off (unbinding of RNAP) is comparable to the timescale of Tat production under self-positive-feedback, the synergy of AC and NE on the transcription rate at gene state level can pass to the protein expression level. Finally, the cell-fate Waddington landscape shows that AC makes the latent state valley on the shallower and wider, while NE dig out a new valley on the active state when AC is already bound. Therefore, our model reveals a general nonequilibrium mechanism underpinning the noise enhanced drug synergy. Such a proposed mechanism should be useful for identifying new drug synergy or regulating the existing drug synergy in HIV or a diverse class of virus infection therapies.
This is a joint work with Lei Zhang and Hao Ge.

The Application of D-trace Loss in High-dimensional Compositional Data Network Analysis

Shun He, Peking University

The development of high-throughput sequencing technologies for 16S rRNA gene profiling provides higher quality compositional data for microbe communities. Inferring the direct interaction network under a specific condition and

understanding how the network structure changes between two different environmental or genetic conditions are two important topics in biological studies. However, the compositional nature and high dimensionality of the data are challenging in the context of network and differential network recovery. To address this problem in the present paper, we proposed two new loss functions to incorporate the data transformations developed for compositional data analysis into D-trace loss for network and differential network estimation, respectively. The sparse matrix estimators are defined as the minimizer of the corresponding lasso penalized loss. Our method is characterized by its straightforward application based on the ADMM algorithm for numerical solution. Simulations show that the proposed method outperforms other state-of-the-art methods in network and differential network inference under different scenarios. Finally, as an illustration, our method is applied to a mouse skin microbiome data.

Analysis of plasticity in amoeboid morphology toward the comprehensive understanding of cell migration.

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Migrating morphologies of eukaryotic cells are different according to cell types. Crucial factors in determining cell shape are the size and persistence of the leading edge, which range from small and transient protrusions in *Dictyostelium* amoeba to broad and constant lamellipodia in fish keratocytes. It has been revealed, however, that cell shapes and their migrating ways have some plasticity and could undergo drastic changes depending on the surrounding environment, among which substrate conditions have been shown to be one of the critical parameters in mesenchymal cells [Liu *et al*., 2015] and keratocytes [Riaz & Versaevel *et al*., 2016][Barnhart *et al*., 2017]. How is it in fast-moving *Dictyostelium* amoeba? Here we show that, depending on the adhesive conditions, the polarized morphology of *Dictyostelium* cells is altered from the archetypal shape elongated in the front-back axis to a more laterally extended fan-like shape. Strongly-adhered cells form a thin and large protrusion enriched in dendritic F-actin, resembling lamellipodia in animal cells. Using the phase field model coupled with reaction-diffusion dynamics, we have succeeded in producing the various cell shapes ranging from longitudinally-elongated, *Dictyostelium*-like shape to laterally-elongated, keratocyte-like shape [Imoto *et al*., in preparation]. We are now going to introduce the physical parameters into the mathematical model for corresponding to the experimental results. In poster session, we would like to discuss the experimental results based on the imaging analyses and the expansion of our present model.

Product-Form Stationary Distributions for Non-Complex Balanced Networks

Hyukpyo Hong， KAIST

In many biochemical reaction networks, the number of molecules of each species in the network is low. Because it leads to large fluctuations in the system, a stochastic model is commonly used to understand such networks with a low number of molecules. The stochastic model describes the dynamics of the distribution of the number of molecules using the chemical master equation (CME). While solving CME analytically is nearly impossible in the presence of nonlinear reactions, recent studies have found that such calculation is possible for special types of networks such as feedforward loop and complex balanced network. In this talk, I will introduce a more general class of networks whose stationary distribution can be derived analytically. Furthermore, using this approach, I will illustrate how the exact stationary distributions of various systems such as SIS model, the dimerization models, and the duplication model can be easily derived.

Analyzing the sleep patterns of shift workers using mathematical model

Jaehyoung Hong， KAIST

While shift workers suffer from excessive daytime sleepiness and insomnia, the cause of daytime sleepiness and insomnia remains unclear. To identify such cause, we analyzed complicated sleep patterns of 23 nurses on a rotating shift schedule collected for 14 days from Samsung hospital. For this, we use an established neuronal population model of the sleep-wake cycle which includes mutual inhibition between wake-promoting and sleeppromoting neurons, as well as drive consisting of circadian rhythm and the homeostatic sleep pressure. This analysis leads to the development of a new index called Sufficient Sleep Percentage (SSP) which is the first index to predict daytime sleepiness and insomnia of shift workers from their sleep patterns. This shows how the mathematical model can be used to provide optimal sleep-wake schedules to improve sleep qualities of shift workers.

Mathematical modelling of signal-dependent cyclin/cdk network driving mammalian cell cycle

Hiroaki Imoto[1], Kyoichi Ebata[1], Shigeyuki Magi[1], Suxian Zhang[1], Mariko Okada[1]

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Irreversible cell-cycle transition is important for cellular development because it provides directionality for the process. Previous studies showed that a bistable Rb-E2F underlies the restriction point and plays critical roles for irreversible G1/S transition. However, it still remains unclear how the upstream signaling dynamics quantitatively affect the irreversibility and its timing in this process. To better understand how the complex signaling activities triggered by the ErbB receptor families regulate molecules involved in cell cycle entry, we developed a comprehensive mathematical model integrating the processes of ErbB signaling transduction network, early transcriptional regulation and cell cycle regulation. Our integrated model was calibrated against a wide range of experimental data and accounted for the prediction of the mechanism of ligand-specific cellular output. The result of theoretical analysis provides insights into what molecular mechanisms are necessary for irreversible transition.

Mathematical Modeling to Reveal Molecular Differences Causing Pacemaker-neuron-dependent Rhythm Alteration by Mutant

EuiMin Jeong, KAIST

Circadian (~24h) behavior of Drosophila is regulated by about 150 pacemaker neurons. In each pacemaker neurons, to generate and maintain 24h rhythm, circadian gene expression is driven by transcriptional-translational feedback loop (TTFL). Although all of TTFLs in each pacemaker neurons based on negative feedback between activator and repressor, molecular rhythms are altered differently when repressor binding to activator is disrupted by mutant; for oscillation of repressor protein, amplitude is largely reduced in one neuronal group, but not in another neuronal group. To investigate this unexpected phenomenon, we established the mathematical model based on mass action kinetics. By analyzing conditions which the model generates rhythm, we predicted the difference of molecular composites of two neuronal groups causing pacemaker-neuron-dependent rhythm alteration. This prediction is confirmed by the follow up experiment. Our work shows that clockworks at the molecular level have a critical role for rhythm generation of each pacemaker neurons.

A mathematical model of chronic myeloid leukemia driven by neoplastic microenvironment

Xiaopei Jiao, Tsinghua University

Chronic myeloid leukemia (CML) is an important blood system disease which can deeply disturb normal hematopoietic system. With the development of medical technology, though there are a lot of clinical data so far, the evolution and transition of all phases in CML progression are still unclear. In order to quantitate the dynamics of CML, we propose a mathematical macroscopic model. At cell population level we consider four major compartments containing seven types of cells including normal hematopoietic system, leukemia system, bone marrow microenvironment (BME) and immune system. By considering experimental evolutional data, we determine quantitative relations among four major compartments and fit the whole phases of progression well. And our model predicts important biological functions of BME during CML occurrence and progression. Next we also propose a therapeutic model based on our macroscopic model. Here we consider two situations of therapy such as remission and relapse. By comparing clinical individual data, our model can fit and predict individual patient data well in both remission and relapse cases. This shows the robustness of our model. In our therapeutic model, we simulate influences of different TKI doses, different time to stop treatment and different therapeutic strategies systematically. Finally, we make detailed mathematical analysis for the macroscopic model, obtain global behavior of this dynamical system. Our model provides a systematic framework to describe global progression in CML and give some novel strategies for clinical therapy.

Systems pharmacology model reveals the sources of the inter- and intraspecies variability in drug efficacy

Daewook Kim, KAIST

The majority of previous studies investigate the drug efficacy only in nocturnal species (e.g. mice) although humans are diurnal. Here, using diurnal monkeys, we examine the effect of a daily (circadian) clock-modulator drug, and find the high variability in its effect between diurnal monkeys and nocturnal mice. To identify the source of the interspecies variability, we used the systems pharmacology model, which accurately simulates the intracellular action of the drug and thus its effect in the circadian clock. This revealed that the interspecies variability in the drug effect is due to the different sensitivity of nocturnal and diurnal animals to environment light, the natural clock-modulator. Furthermore, via a combination of the model simulation and experiment, we found the molecular biomarker to predict the drug effect, which explains the high interindividual variability in the drug response. Based on these

findings, we developed a model-based precision medicine strategy to treat circadian disruption. Our works show how the mathematical model can be used to reveal an unrecognized biological variable in drug efficacy translation between nocturnal and diurnal animals and enable precision medicine.

Dynamics of N1 and N2 neutrophils and lung cancer development in response to TGFbeta and IFN beta

Donggu Lee, Konkuk University

Neutrophils provide rapid innate immune functions in various dis- eases. However, tumor-associated neutrophils (TANs) and neutrophils elastase (NE) can either promote or suppress tumor growth via tumor-microenvironment crosstalk. We developed and analyzed a mathematical model to address the critical question of how NE affects the phenotypic switches between N1 and N2 TANs and tumor growth patterns in a tumor microenvironment. We analyze dynamics of TANs and tumors in response to various biochemical stimuli including NE, TGF-β, and IFN-β. Several optimal anti-tumor strategies including DNase I were developed in an effort to slow down tumor growth. The model predictions were in good agreement with experimental data. A positive correlation between the N2-to-N1 ratio and tumor progression were observed. The mathematical model also predicts the various growth patterns of a tumor in several key parameter sets.

Synergistic Effects of Bortezomib-OV Therapy and Anti-Invasive Strategies in Glioblastoma

Junho Lee, Konkuk University

It is well-known that the tumor microenvironment (TME) plays an important role in the regulation of tumor growth and the efficacy of anti-tumor therapies. Recent studies have demonstrated the potential of combination therapies, using oncolytic viruses (OVs) in conjunction with proteosome inhibitors for the treatment of glioblastoma, but the role of the TME in such therapies has not been studied. In this paper, we develop a mathematical model for combination therapies based on the proteosome inhibitor bortezomib and the oncolytic herpes simplex virus (oHSV), with the goal of understanding their roles in bortezomib-induced endoplasmic reticulum (ER) stress, and how the balance between apoptosis and necroptosis is affected by the treatment protocol. We show that the TME plays a significant role in anti-tumor efficacy in OV combination therapy, and illustrate the effect of different spatial patterns of OV injection. The results illustrate a possible phenotypic switch

within tumor populations in a given microenvironment, and suggest new anti-invasion therapies.

The geometrical effect for the size of cell polarity domain in asymmetric cell division

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Asymmetric cell division is an elegant development process to create cell diversity. In this process, a mother cell creates polarity in both membrane and cytosol by distributing her substrates and components asymmetrically before cell division. In C. elegans embryo, the membrane polarity of PAR proteins and the cytosol polarity of MEX-5/6 have been considered to play an important role in asymmetric cell division. Theoretically it has been shown that the interplay between the two polarities is critical to induce the robust polarity formation [1]. On the other hand, the underlying mechanism of PAR polarity formation has been well-studied in both experiment and mathematical modeling, because PAR polarity is the most upstream and regulates the whole process of asymmetric division including the decision of position of cell cleavage surface. However, how the size of PAR polarity domain is determined is not well-studied, and it has been remained still elusive. In this study, we identified the factors that determine the size of PAR polarity domain, and explored how the factors are intertwined to decide the size of PAR and MEX-5/6 domain. To explore the geometrical effect of cell readily, we introduced a mathematical modeling using phase-field method. We found that both biophysical amount of MEX-5/6 and cell geometry can play an important role in determining the size of PAR polarity domain. Our study suggests that the size of PAR polarity domain in the membrane can be determined by not only biochemical reactions but also the collaboration of cell geometry and biophysical amount of cytoplasmic proteins MEX-5/6.

[1] T. Nakahara and S. Seirin-Lee, Role of cytoplasmic protein MEX-5/6 on cell polarity formation of asymmetric cell division, (2019) submitted.

A Machine Learning Method to Reconstruct Spatial Gene Expression Profile in Tissues from Single-cell RNA-seq Data

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Spatial patterns of gene expression are crucial for understanding the functions of cells and the cellular constitutions of multicellular organs. Recently, new approaches have been emerged to reconstruct spatial profiles of genome-wide gene expression across multicellular systems from single-cell RNA sequencing (scRNA-seq) data. The scRNA-seq inevitably requires tissue dissociation into individual cells, involving the lack of spatial information. Previous studies compensated for the lost spatial information of scRNA-seq data by referring available spatial gene expression observed by in situ hybridization method, which then reconstructed spatial gene expression profiles. However, there were many genes that cannot be well reconstructed, and such unsatisfactory reconstructions could be due to unnatural heuristics in previous studies. Here we developed a general machine learning method to reconstruct spatial gene expression profiles. We then demonstrated that our method was able to more accurately estimate spatial gene expression profiles in Drosophila early embryos, compared with the previous one. In addition, we confirmed the validity of our method by further applying to data of zebrafish early embryos and mammalian liver lobules. Therefore, our method should be a powerful and generally applicable tool to reconstruct spatial gene expression profile from scRNA-seq data in any multicellular systems.

Diversity of cell fate by cell membrane-binding dynamics in the Notch-Delta signalling pathway

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Our body is composed of 250 kinds of cells which have various functions. Notch-Delta signalling is one of well-known cell-to-cell signalling pathway and plays an important

role in determining the fate of the adjacent cell. Notch signalling is very conserved system evolutionarily and plays a critical role in several developmental processes of the multicellular organism. Notch is the membrane binding receptor which directly binds with Delta ligand in surrounding cells, and it is known that the dynamics of notch-delta binding in the membrane such as cis-inhibition influences the determination of cell fate. During the neurogenic phase of mouse brain development, only a part of neural precursor cells differentiates into neurons and such a determination of the cell fate is regulated by some specific combination of notch and delta concentrations. In this study, we consider two different types of notch-delta binding dynamics and finds how the binding dynamics can influence the combination of notch and delta concentrations in a cell. Our study suggests that notch-delta binding dynamics can critically affect the choice of cell fate and the specific numbers of specific cell fate can be regulated by the binding rate of notch-delta between adjacent cells.

Mathematical models on cell polarity and migration coupled with mechano-chemical factors

Kuan Tao, Peking University

A series of complex cell behaviors, such as cell polarization, deformation and migration, are regulated by complex biochemical networks within cells and mechanical factors of cell membranes, protrusive/retraction force and so on. Here, we firstly present a cell polarization model incorporating the interplay between Rac GTPase, filamentous actin (F-actin), and cell membrane tension. Based on both our model and the experimental results, cell polarization is more sensitive to stimuli under low membrane tension, and high membrane tension improves the robustness and stability of cell polarization such that polarization persists under random perturbations. Meanwhile, our simulations are the first to recapitulate the experimental results described by Houk et al., revealing that aspiration (elevation of tension) and release (reduction of tension) result in a decrease in and recovery of the activity of Rac-GTP, respectively, and that the relaxation of tension induces new polarity of the cell body when a cell with the pseudopod- neck-body morphology is severed. Furthermore, we establish mechano-chemical models and demonstrate that the regulation of cell tension exerts a non-monotonic effect on cell migration with involvement of random noise or internal fluctuations, which is newly revealed through biological experiments and confirmed theoretically in our work for the first time. In general, elevation from cell tension enhances the streamline position of cell body in the first place. Hence an optimal migration ability exists before tension totally inhibits the extension of lamellipodiums. Meanwhile, when cell movement is purely controlled by chemoattractants without any randomness, cell tension inhibits motility monotonically.
The joint work with Lei Zhang and Feng Liu.

Network Design Principle for Dual Function of Adaptation and Noise Attenuation

Wei Zhao, Peking University

Many signaling systems execute adaptation under noisy circumstances. While the adaptation or noise attenuation has been studied separately, how to achieve these two competing functions simultaneously remains elusive. To explore such dual function, we first explore three-node enzymatic regulation networks, and identify an intrinsic trade-off existing between good sensitivity and noise attenuation in the three-node networks. Although fine-tuning timescales in three-node adaptive networks can partially mediate such trade-off, it introduces prolonged adaptation time and unrealistic parameter constraints. This trade-off can be minimized in four-node networks, in which the adaptation module and the noise attenuation module can be effectively decoupled to achieve dual function. There exist constraints on assembling the two modules in order to allow high performance of dual function. Maintaining the system sensitivity is a bottleneck and the time scales of the two modules need to be well coordinated. By scrutinizing seven biological systems, we find that adaptive networks are often associated with a noise attenuation module. The obtained design principles are then studied using two examples: Dictyostelium discoideum chemotaxis and p53 signaling network. Our approach may be applicable to finding network design principles for other dual and multiple functions.
The joint work with Lingxia Qiao, Chao Tang, Qing Nie and Lei Zhang.

Understanding Single-cell Transciptomics Analysis Methods from Dynamical Systems Models

Peijie Zhou, Peking University

Rapid advances of single-cell RNA sequencing experiments and data analysis revolutionize our approach to explore cell-fate decision process. In the meantime, cell state transitions are effectively modeled by dynamical systems in computational systems biology.
In this talk, we will discuss the interplay between data-driven and model-based approaches to study cell development, focusing on the single-cell data analysis algorithms inspired by the dynamical systems models. We will first review the relationship between the diffusion map (DM), a widely applied dimension reduction tool to visualize single-cell development lineage, and the over-damped Langevin equation (OLE), a basic model for the stochastic dynamics of gene expression. By exploring the multi-scale structure of DM-based random walk, we rigorously connect the corresponding coarse-grained dynamics to the Kramers

transition rate theory for OLE. The connections naturally lead to the introduction of multi-resolution method for transient cells (MuTrans), a new algorithm to dissect transition cells and construct cell-fate landscape for single-cell transcriptomics data. In addition, links between non-equilibrium stochastic process and state-of-the-art analysis tools for large-scale single cell datasets, such as population balance analysis (PBA) and Waddington optimal transport (WOT), will also be discussed.