THE 3rd WORKSHOP ON COMPUTATIONAL SYSTEMS BIOLOGY

第三届计算系统生物学研讨会

May 14- May 16, 2015

(Room 2001, East Guanghua Building, Fudan University)

Final Program

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II. CONFERENCE INFORMATION

REGISTRATION

Could all participants please register at the earliest opportunity.

The registration desk will be open at the Lobby of *Lantian Hotel* (蓝天宾馆), on Thusday May 14th from 13:30 – 17:30. There will also be an opportunity to register at the Room 2001, East Guanghua Building, Fudan University, on Friday May 15th from 08:00-08:30. If you have completed advanced registration process, your conference materials await collection at the Conference Registration Desk.

ACCOMMODATION

For invited speakers, your accommodation will be arranged at *Lantian Hotel* (蓝天宾馆). It is located at 2200 Huangxing Road (黄兴路 2200 号), which is near Orient Shopping Centre (东方商厦).

For students, your accommodation will be arranged at *Fudan Yanyuan Hotel* (复旦燕园宾馆). It is located at 270 Zhengtong Road (政通路 270 号), which is near the main campus of Fudan University.

VENUE

From May 15th to May 16th, our conference will take place at the Room 2001, East Guanghua Building, which is located in the Handan Campus of Fudan University, 220 Handan Road, Shanghai, P.R. China.

SHUTTLE BUS

From May 15th to May 16th, since Lantian Hotel has some distant from Fudan University, we will arrange a shuttle bus for you. The shuttle bus will wait for you at the gate of Lantian Hotel to take you to the conference venue and take you back to the Hotel after evening meals. Please note that the gathering time is *8:10 am* on May 15th, and *7:40 am* on May 16th.

MEALS

The Reception Banquet, at the evening of May 14th, will be held at the third floor of *Lantian Hotel* from 18:00 to 22:00. *Lunches* from May 15th to May 16th will be served at the third floor of Danyuan Restaurant from 12:15 to 14:00. *Banquet* on May 15th will be served at the Alumni hall (校友厅) on the second floor of Building No.2 of the Yanyuan Hotel. *Evening Meal* on May 16th will be served at the third floor Danyuan Restaurant.

MAP

III. ABSTRACT

Stem Cell Regeneration: From model to simulation

Jinzhi Lei
Zhou Pei-Yuan Center for Applied Mathematics, Tsinghua University

This talk presents the modelling of stem cell regeneration through the multi-scale model with cross talk between genetic and epigenetic regulation. Numerical scheme to study the model with GPU is also introduced. The GPU simulation is used to study the long-term regeneration of a group of stem cells with modifications of histone modification in each cell cycle.

数据驱动的脑功能网络时变特性及机制研究

张捷
复旦大学计算系统生物学中心

大数据时代的到来成为复杂网络领域一个机遇。由实测高维时间序列构造功能网络来研究复杂系统的情形很常见。如基因功能网络、脑功能网 络、生态网络、电网、传感器网络、股票价格网络等等。但如何利用海量 动态数据(比如高维时间序列)分析功能网络时变性的动力学特征,尤其 是挖掘功能网络的拓扑结构变化与时间序列动力学变化的关联,也成为复杂网络领域的一个挑战,对于阐明复杂网络系统的运作机制至关重要。为 了突破上述的研究瓶颈,我们将以脑功能网络为例,基于核磁共振-脑电大数据,提取脑功能网络拓扑结构与节点动力学的时变特征,建立脑功能网络时变性分析的一般非线性/统计方法。在此基础上,挖掘时变功能网络的拓扑结构变化与节点状态变化之间的关联。探索脑功能网络时变性产生和调控机制,寻找其在常见脑疾病中的改变规律。本项目将为复杂时 变网络研究提供新的思路,提出的方法和手段将适用于众多实际领域。

基因表达动力学

周天寿
中山大学数学与计算科学学院

基因表示是系统生物学的研究核心。单分子/单细胞测量技术的出现和发展使得基因表达动力学的研究进入一个新阶段。我结合自己课题组的研究情况,简要介绍基因表达动力学的研究现状、发展趋势等。

Fluctuating-rate model and stochastic phenotype transition of a single cell

Hao Ge
Biodynamic Optical Imaging Centre, Peking University

Multiple phenotypic states often arise in a single cell with different gene-expression states that undergotranscription regulation with positive feedback. Recent experiments show that, at least in E. coli, the genestate switching can be neither extremely slow nor exceedingly rapid as many previous theoreticaltreatments assumed. Rather, it is in the intermediate region which is difficult to handle mathematically.Under this condition, from a full chemical-master-equation description we derive a Fluctuating-rate model in which theprotein copy number, for a given gene state, follows a deterministic mean-field description while theprotein-synthesis rates fluctuate due to stochastic gene state switching. The simplified kinetics yields anonequilibrium landscape function, which, similar to the energy function for equilibrium fluctuation,provides the leading orders of fluctuations around each phenotypic state, as well as the transition ratesbetween the two phenotypic states. This rate formula is analogous to Kramers' theory for chemicalreactions.

Then we apply the fluctuating-rate model at single-cell level for Lac operon. We show that the stochastic gene-state switching can significantly broaden the environmental parameter ranges for the existence of bistability induced by positive feedback, which can be beneficial dealing with unpredictable environmental changes. We also demonstrate that the transition rates between different phenotypic states achieve the maximal value at the intermediate region of gene-state switching, and the barrier term in the Kramers'-like rate formula can also help to distinguish two categories of bistability. Our study highlights the constructive role of molecular fluctuations for the functioning of cells as individual biological entities.

神经元对突触输入信号整合的研究

周栋焯
上海交通大学自然科学研究院

神经元是大脑处理信息的最基本的单元，它是由树突、胞体和轴突这三部分构成，其中树突是接收上游神经元传递过来的电信号并对这些信号进行整合，从而激起胞体处的膜电位的改变，目前很多实验表明神经元的树突对于信号的整合过程是一个非线性过程，但是实验和理论上一直缺乏对于整合过程的精确定量的描述，我们从理想的模型出发，考虑一对突触输入的情况，利用渐进分析的方法得到了关于树突整合过程的解析定量的刻画，一对输入激起的胞体处的电压 VS 反应等于单个输入激起的胞体处的电压反应(V1 和 V2)的和，再加上某个分流系数 k 与 V1 和 V2 乘积的双线性项。正是由于该双线性项的存在，我们将该法则定义为双线性求和法则，令人惊讶的是，尽管这个双线性法则是基

于理想模型得到的，但是我们进一步的神经元的数值仿真模拟以及电生理实验，都验证了该双线性法则的适用性，我们的结果表明：神经元对于多个突触输入的整合效应可以分解为所有可能的每两对突触的输入的效应的和，其中任意两对突触的输入效应服从相应的双线性法则。

Control of Cellular Behaviors during Development of Spatial Pattern

Lei Zhang
Beijing International Center for Mathematical Research, Peking University

Development and regeneration require plant and animal cells to make decisions based on their locations. In this talk, I will first introduce a hybrid model for cell polarity by coupling a reaction diffusion system with membrane tension. Simulations demonstrate that membrane tension affects the spatial profile of Rac-GTP's distribution, the polarization time and the sensitivity to attractant. Our model can first explain results of aspiration-release experiment and the pseudopod-neck-cell body morphology severing experiment. Second, 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.

Mathematical modeling, optimization and Control for networks of complex diseases

Xiufen Zou
School of Mathematics and Statistics, Wuhan University

In this talk, I first introduce my group's work in identifying dynamical network biomarks of complex diseases. Then, I present the analysis of pathogenic mechanisms of influenza A virus (IAV) by combining mathematical model-based optimization and dynamical analysis. Finally, the control problems of complex diseases are discussed.

Identification of conformational B-cell epitopes from antigen sequences

Jianzhao Gao
School of Mathematical Sciences Nankai University

Epitopes are immunogenic regions in antigen protein. Identification of conformational B-cell epitopes is critical for immunological applications. Several machine learning methods have been proposed to identify conformational B-cell epitopes. However, the quality of these methods is not ideal. In this talk, we propose an ensemble method, which combined 12 support vector machine-based predictors, to predict the conformational B-cell epitopes, using an unbound dataset. Resampling methods are used to deal with an imbalanced labeled dataset. The proposed method achieves AUC of 0.642–0.672 on training dataset with 5-fold cross validation and AUC of 0.579–0.604 on test dataset.

Rare events for the Gillespie dynamics

Tiejun Li
School of Mathematical Sciences, Peking University

Rare events has been widely discussed in the material science and chemistry. However, it is also natural to understand some biological pheonomenon such as the bistability driven by jump type noise. I will lecture about this topic and introduce some recent progress in this field done by my group.

生物钟振子模型：联结动力学理论与生物学应用

杨凌
苏州大学数学科学学院

生物钟表现为以 24 小时为周期的动物活动/睡眠切换，以及植物叶片开/合等现象，而在细胞内的本质则是蛋白质浓度振荡。我们与生物学家密切合作，通过生物问题-建模-数值模拟-理论分析-实验验证 的流程，研究了一系列生物钟相关问题。这里介绍一些我们进行中的工作，抛砖引玉。

1). 相位多稳态现象：老鼠与人类共享同样的生物钟机制（相位类似），但老鼠晚间活动，人类则白天活动。更有意思的是，某种老鼠可以切换白天或黑夜活动，提示至少有两个稳定的相位可供选择。

2).振子的记忆能力：植物一般白天叶片张开，晚间垂下。如果在晚上给予光照，垂下的叶片会随之张开。有趣的是，在第二、第三天相同时间（没有光照），叶片也会张开。这种记忆是负反馈调控相关。

3).光牵引的拟标准映射：不同频率的光照/黑暗切换，可以导致生物钟周期的不同反应。我们从 ODE 模型出发，初步简化成与标准映射类似的映射，可以保留生物学现象的动力学本质。

4). 生物钟系统的失同步现象：在合适的相位给予合适强度的刺激（光照、温度），可使细胞群表现出无振幅现象，背后是失去相位同步问题。

P53 乙酰化调控的动力学研究

张小鹏
南京大学生物物理研究所

乙酰化在 p53 活性调控中扮演了关键的角色。通过建模研究，我们探讨了 DNA 损伤响应过程中 p53 乙酰化调控的动力学机制。一方面，p53 可通过 p53-miR-34a-SIRT1 这一反馈回路促进自身激活。依赖于 DNA 损伤强度，乙酰化 p53 的不同水平可导致细胞走向周期阻断或凋亡。另一方面，p53 蛋白 K120 位点可被 Tip60 乙酰化,这一修饰作用可特异性促发细胞凋亡。同时，Tip60b 本身的活性依赖其磷酸化状态，而 p53 可通过靶基因产物 PTEN 间接调控 Tip60 磷酸化。通过考虑不同反馈结构和 DNA 损伤强度的影响，我们发现在细胞命运抉择过程中 p53 呈现出丰富的动力学行为，如振荡和双稳，不同的 p53 动力学行为可指向不同的细胞命运。总之，p53 乙酰化调控的动力学研究对于理解其激活调控的分子机制具有重要意义。

磷酸根转移以及磷酸化反应在细胞信号转导中的作用研究

易鸣
华中农业大学理学院

1、我们的实验合作者发展了一种新颖的灵敏并且长程的顺磁弛豫增强的方法，最终成功获得了 KD≈25 mM 的蛋白质相互作用复合物结构。上述的极弱相互作用的复合体中的两个蛋白是大肠杆菌磷酸转移酶系统中的 EI 和 EIIAGlc 蛋白，它们之间能够进行磷酸基团的传递。我们理论分析发现当蛋白浓度超过 1 mM 时，则与之匹配的 KD 必须大于 1 mM，否则会造成信号传递“拥堵”，使信号蛋白浓度增加带来的“红利”消失。2、我们建立了一个关于芽殖酵母菌分子相互作用网络的全模型，细胞周期子系统与 MAPK 信号转导通路子系统通过 Ste5 和一个包含有 Far1、Fus3、Ste12 的模块发生相互作用。当 MAPK 通路下游蛋白 Fus3 被磷酸化后(Fus3PP)，Fus3PP 开始激活 Far1 和 Far1 转录因子 Ste12。理论证明发现由 Fus3、Far1 和 Ste12 形成的三结点前馈调节模块确保了细胞快速 arrest 及细胞状态的快速可逆。

Simplified models for describing molecular processes of multi-step reactions

Tianhai Tian
School of Mathematical Sciences, Monash University &
School of Statistics and Mathematics, Zhongnan University of Economics and Law

This talk will discuss two methods for simplifying stochastic models of multi-step reactions. The first method proposes a two-variable model using the concept of length to indicate the location of molecules in the multi-step reactions. The second method uses state-dependent time－delay reaction. The process of mRNA degradation is used to validate the proposed two methods. Comparing with the existing methods, simulations suggest that the proposed methods can provide accurate approximation of the multi-step reactions. In particular, our results suggest that the concept of half-life for measuring the decay of molecules may need reconsideration.

Spatiotemporal dynamics of affinity maturation in the germinal center

Yueheng Lan
Department of Physics, Tsinghua University

We develop a stochastic model of spatiotemporal dynamics of affinity maturation in the germinal center to investigate the role of T cells in the immune response.

With the postive feedback provided by the T cells, the maturation process is accelerated considerably. New competition mechanisms of B cells are introduced for limited resources of antigens and T cells. The results from the computation is in accordance with the experimental observation.

生物系统的重构方法

马欢飞
苏州大学数学科学学院，苏州大学系统生物学研究中心
林伟
复旦大学数学科学学院，复旦大学计算系统生物学中心

在复杂的生物系统中，一些结构与特殊动力学行为对于系统的深入理解扮演着重要的角色，从动力学上来说，系统的稳态和周期震荡是理解各种生物机制的切入点，从结构上来说，系统网络的有向调控结构是复杂调控机制的基础。因此，如何从模型或者仅仅从数据出发，重构出系统的各种动力学和结构上的特征，是一项具有挑战性和有意义的工作。我们将介绍近期我们在这方面研究工作的一些进展。

A biophysical model of CREB-modulated synaptic plasticity

Xuejuan Zhang[1],Guanghui Zhang[1], Albert Goldbeter[2], Jianfeng Feng[3,4]
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[4]*Centre for Scientific Computing, Warwick University, Coventry CV4 7AL, UK*

Long-term potentiation (LTP) and Long-term depression (LTD) are two major forms of synaptic plasticity which are thought to underlie learning and memory. The transcription factor CREB is crucial for synaptic plasticity. However, it is not clear how communication between synapse and nucleus are mediated, and whether CREB phosphorylation carries information about the sign in synaptic strength. To investigate the biochemical mechanisms of synaptic plasticity, we presented a detailed model that combines both the membrane electric behaviors of individual neurons and the interactions that lead to the control of CREB activity in the nucleus through calcium-triggered changes in the cAMP-PKA signaling pathway. The model qualitatively reproduces NMDAR-dependent LTP and LTD induced by different protocols such as varying the rate of presynaptic stimulation or the time of pre- and post-synaptic action potentials. The relationship between LTP (LTD) and neuronal excitability is examined and, in agreement with experimental results, we confirm that afterhyperpolarization (AHP) current is essential for the neuron to exhibit significant firing rate differences before and after learning. Our model, the first one in the literature to attempt to link nucleus dynamics to neuronal excitability, predicts that the competition of active and negative CREBs may be responsible for the bidirectional synaptic plasticity.

组合扰动以及在生物学中的应用

王瑞琦
上海大学理学院数学系

该报告主要介绍了如何基于动力系统的多参数扰动来研究生物中的多个调控之间或者多药物之间的协同性。该方法将应用到一个具体的疾病模型中。