International Workshop on Quantitative Biology 2012

November 22nd, 2012 thursday,
University of Tokyo, Komaba II Campus

INTERNATIONAL WORKSHOP ON QUANTITATIVE BIOLOGY 2012

Nov. 22nd, 2012 thursday,
University of Tokyo, Komaba II Campus

Supported by
Royal Society, UK

Transdisciplinary Research Integration Center (TRIC) of Research Organization of Information and Systems (ROIS)

Research Group on Engineering in Medicine and Biology, Institute of Industrial Science, the University of Tokyo, Japan

Preface

Dear Colleagues,

International workshop on Quantitative Biology 2012 focuses on recent advances in measuring and modeling dynamic cellular processes, organized by motivated members of Japanese Society for Quantitative Biology (http://q-bio.jp/wiki/English).

Quantitative cell biology experts from Japan, Europe, US and Asia have been invited to participate in this workshop in order to make up world-wide networks between researchers within these areas.
The topics of the sessions of the conference are 'Theories and analyses for exploring mesocopic world', 'Power of Engineering in New Facets of Biology', 'Estimation of Model Parameters using Time-series Data' and 'Advances in probing cytoskeletal and chromosomal dynamics in dividing cells'.

The 'Data-driven Estimation of Model Parameters' session is sponsored by "data assimilation" project in Transdisciplinary Research Integration Center (TRIC) of Research Organization of Information and Systems (ROIS: http://www.rois.ac.jp/english) in Japan, to promote the application of "data assimilation method" to biological problems. The invited speakers in the 'Advances in probing cytoskeletal and chromosomal dynamics in dividing cells' session and the closing speaker of the workshop, Prof. Madan Rao, are supported by a UK-Japan Joint project grant from Royal Society, UK to promote the development of automated image processing tools for modelling cell division control mechanisms.

The talks during the one-day workshop will be in English to help the international audience that would be attending the workshop. Two poster sessions have been planned to encourage students and young researchers to participate at the workshop.

This special one-day international sessions will be held on the 22nd of November 2012, together with the 5th Annual meeting of the Japanese Society for Quantitative Biology in Tokyo (23rd - 25th November 2012).

We hope that all the participants will have fruitful time during this workshop.

Organizers,

Tetsuya Kobayashi (University of Tokyo)
Viji Mythily Draviam (University of Cambridge)
Akatsuki Kimura (National Institute of Genetics)
Noriko Hiroi (Keio University)
Akira Funahashi (Keio University)
Yoshitaka Suetsugu (National Institute of Agrobiological Sciences)
Rinshi Kasai (Kyoto University)
Yoshiyuki Arai (Osaka University)
Yuki Tsukada (Nagoya University)
Naoki Irie (RIKEN CDB)
Hiroshi Kimura (Tokai University)
Ziya Kalay (Kyoto University)
Peter Carlton (Kyoto University)
Jason Shoemaker (JST)

Acknowledgement

We greatly appreciate Prof. Oka, Biosciences and Informatics Department of Keio University (Japan), for the supportive advices to start the workshop. Special thanks are also due to Ms. Kazumi Arimoto, Kyoto University (Japan), Ms. N. Sujatha, Natinal Center for Biosciences (India), the general affairs section and the supplies section in the school of Science and Technology, Keio University (Japan), for their diligent work in organization of the workshop. In addition we thank group members from Draviam group, University of Cambridge (UK), Kobayashi Lab, the University of Tokyo (Japan), Funahashi Lab, Keio University (Japan), Mr. Pieter van Wyk and Mr. Muhammad Ahmad Ruiz, Keio University (Japan) for their valuable help for the organization of the workshop.

Map of Komaba II Campus of the University of Tokyo

Higashi-Kitazawa station (Odakyu line)

Yoyogi-Uehara station (Chiyoda line)

Ikenoue station (Keio Inogashira line)

Institute of Industrial Science

1. General Research Experiment Bldg. (Convention hall)
2. Research Bldg.
3. Library
4. Restaurant & Meeting Rooms
5. Central Workshop
6. Bild. S

○ Smorking Areas

The Workshop Venue

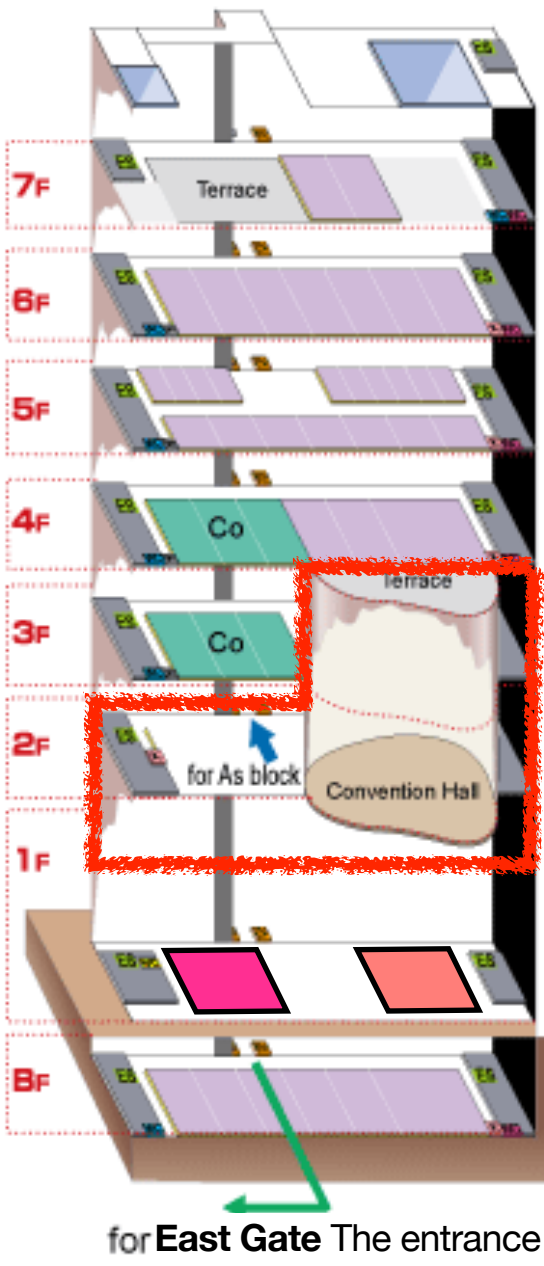
Komaba-Todaimae station (Keio Inogashira line)

Research Center for Advanced Science and Technology

Collaborative Research Bldg. (CCR Bldg.)

EV Elevator & Stairs
ES Emaergency Stairs
WC WC (Men)
WC WC (Women)
WC WC (Handicapped)
K Kettle Room
Sm Smoking Room
Co Conference Room

An block



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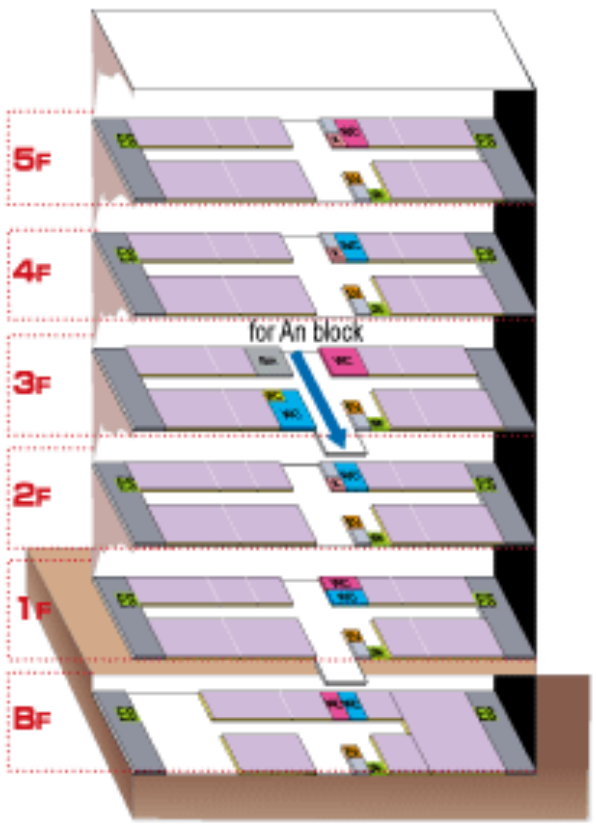

The Workshop Venue
Convention Hall (Talks)
Lounge (Posters)
Reception will be set up at the entrance of convention hall, 2F.

Cafeteria (1F)

Restaurant (1F)

for **East Gate** The entrance of Building An is at 1F.

Map of surrounding area of Komaba II Campus

Access to Komaba Campus

Odakyu Line, Higashi Kitazawa Station (connect to Shinjuku), 7 min walk.
Chiyoda Line, Yoyogi Uehara Station (connect to Tokyo/Otemachi), 12 min walk.
Keio Inogashira Line, Komaba Todai Mae or Ikenoue Station (connect to Shibuya), 10 min walk

Train / Flight connections

Train

Tokaido Shinkansen (from southern/western area in Japan)
connects to Shinagawa station.
Tohoku Shinkansen (from northern area in Japan)
connects to Tokyo/Otemachi station.

Flight

International Airport (Narita)
JR Narita Express connects to Tokyo/Otemachi station.
Domestic&International Airport (Haneda)
Keisei line connects to Shinagawa station.

Shinagawa - Shibuya: Yamanote line, 15 min
Otemachi - YoyogiUehara: Chiyoda line, 25 min

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chair: Yoshiyuki Arai & Rinshi Kasai

[1] Prof. Madan Rao (National Center for Biological Sciences, India)
Title: "Active clustering and patterning at the surface of living cells"

[2] Dr. Chun-Biu Li (Hokkaido University, Research Institute for Electronic Science, Japan)

Title: "Modeling Single Molecule Kinetics Objectively from Dwell-time time series"

[3] Dr. Ziya Kalay (Kyoto University, iCeMS, Japan)

Title: "Molecular encounters at the mesoscale: effects of low numbers and confinement"

Coffee Break (11:30 - 11:50)

Session II. Power of Engineering in New Facets of Biology

11:50 - 12:50

chair: Jason Shoemaker & Herve Guillou

[1] Dr. Doug Murray (Keio University, Institute for Advanced Biosciences, Japan)
Title: "Towards Grokking Yeast"

[2] Dr. Yannick Rondelez (University of Tokyo & LIMMS/CNRS-IIS, Japan & France)

Title: "In vitro models of gene regulatory networks"

Poster Session & Lunch Break (12:50 - 14:50)

Session III. Data-driven Estimation of Model Parameters ("data assimilation method" project)

14:50 - 16:10

chair: Akatsuki Kimura

[1] Dr. Hiromichi Nagao (Insitute of Statistical Mathematics, Japan)
Title: "Foundation of Data Assimilation and Its Application to Intracellular Fluid Dynamics"

[2] Dr. Antonio Celani (Institut Pasteur, France)
Title: "Noninvasive inference of the molecular chemotactic response using bacterial trajectories"

[3] Dr. Timothy J. Stasevich (Osaka University, Japan)
Title: "Mathematical modeling of the RNA polymerase II transcription cycle based on live-cell imaging of post-translational modifications"

Coffee Break (16:10 - 16:30)

Session IV. Advances in probing cytoskeletal and chromosomal dynamics in dividing cells

16:30 - 18:30

chair: Viji Mythily Draviam & Akira Funahashi

[1] Prof. Tomoyuki Tanaka (University of Dundee, Cell and Molecular Biology, UK)
Title: "Chromosome acrobatics on the mitotic spindle"

[2] Prof. Yoshinori Watanabe

(University of Tokyo, Laboratory of Chromosome Dynamics Institute of Molecular and Cellular Biosciences, Japan)
Title: "Tension across centromeres refines centromeric protection by shugoshin"

[3] Dr. Akatsuki Kimura (National Institute of Genetics, Cell Architecture Laboratory, Japan)

Title: "Size regulation of mitotic spindle in the C. elegans embryo"

[4] Dr. Viji M Draviam (the University of Cambridge, Department of Genetics, UK)

Title: "Role of microtubule ends in defining the plane of cell division and accuracy of chromosome segregation"

Closing Remarks (18:30 ~ 18:40) Prof. Madan Rao

Free Discussion at the Poster Session Room (18:40 - 20:00)

Opening Remarks

at Convention Hall
9:50 ~ 10:00

Prof. Yasuyuki Sakai

Organs and Biosystems Engineering Laboratory
Institute of Industrial Science,
the University of Tokyo
http://envchem.iis.u-tokyo.ac.jp/sakai/index.php?

Prof. Yasuyuki Sakai is the one of the remarkable leaders of the 3D organization of cultured organ/tissue-derived cells applicating microfluidics systems.
He is involved in the Research group on Engineering in Medicine and Biology of Institute of Industrial Science.
Prof.Sakai has been chosen as a Fellow of the American Institute for Medical and Biological Engineering.（Feb.20, 2012）

Session 1

Theories and analyses for exploring mesocopic world
10:00 - 11:30 at Convention Hall

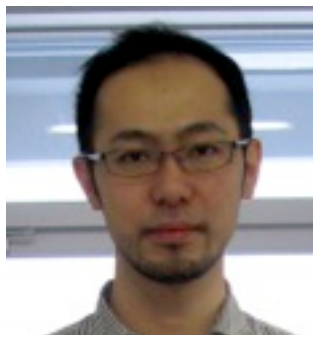
Co-chairs: Yoshiyuki Arai & Rinshi Kasai

Session 1: Theories and analyses for exploring mesocopic world

Co-Chairs

Dr. Yoshiyuki Arai

Laboratories for Biomolecular Science and Engineering,
The institute of scientific and industrial research, Osaka University



He is one of the organizers committee of this International Workshop on Quantitative Biology, who has contributed to organize Session 1 and editing abstract booklet. His introduction is p56.

Dr. Rinshi Kasai

Institute for Frontier Medical Sciences, Kyoto University

He is one of the organizers committee of this International Workshop on Quantitative Biology. He gave critical advise to arrange a part of Session 4 and contributed to organize Session 1.

Session 1-1 **10:00 - 10:30**

Active clustering and patterning at the surface of living cells

Madan Rao[1, 2]

1. Raman Research Institute, Bangalore, India
2. National Centre for Biological Sciences, Bangalore, India

Abstract

I will discuss a model of an active composite cell surface wherein certain class of cell surface molecules form dynamic nanoclusters as a consequence of being actively driven by cortical actomyosin. The active composite model makes several predictions which we verify using high resolution fluorescence methods. I will discuss some consequences to the cellular regulation of chemical reactions. Towards the end I will discuss some work on the spontaneous generation of actomyosin rings and cables in fission yeast.

Keywords : *active composite cell surface, cortical actomyosin, FRET, active hydrodynamics, GPI-anchored proteins*

Prof. Madan Rao

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Session 1-2 **10:30 - 11:00**

Modeling Single Molecule Kinetics Objectively from Dwell-time time series

Chun-Biu Li* and Tamiki Komatsuzaki

Research Institute for Electronic Science, Hokkaido University, Japan

Abstract

Complex dynamics of a wide range of biophysical systems, such as the opened/closed gating of ion channels, the On/Off fluorescent kinetics in single enzymatic turnovers, are often probed experimentally in the form of time series with finite discrete levels. Statistics of the dwell-time time series, the stationary state distributions (SSDs) associated with the chronological sequence of the lengths of time that the system dwells at each level, have been studied to infer the underlying dynamics and kinetics of the system. However, it is well known that the underlying kinetic scheme, a hidden Markov model (HMM) composed of states and state transitions, cannot be identified uniquely from the SSDs of dwell-times because some states and the associated transitions of the underlying HMM are hidden and cannot be resolved by finite-level measurements. Here, I present an information-theoretic framework to quantify the amount of excessive information contained in a given HMM that is not warranted by the measured dwell-time statistics. In this framework, the HMM with minimum excessive information can be uniquely identified and it is regarded as the most objective representation one can extract from the observed data. The minimum excessive information enables us to compare the degree of identifiability of the underlying HMM for measurements of the same system using different observables. The method is applied to a single molecule (SM) enzymatic turnover experiment, and the origin of dynamic disorder is discussed in terms of the network properties of the HMM.

Keywords : *single molecule, kinetic scheme, hidden Markov Model, time series, information theory*

Dr. Chun-Biu Li

cbli@es.hokudai.ac.jp

Reference:

[1] T.M. Cover, J.A. Thomas, “Elements of Information Theory”, John Wiley & Sons, Inc. (1991)
[2] C.B. Li, T. Komatsuzaki, “Extracting the Underlying Unique Reaction Scheme from a Single-Molecule Time Series”, Cell Signaling Reactions: Single-Molecular Kinetic Analysis, Springer, (2010)

Session 1-3 **11:00 - 11:30**

Molecular encounters at the mesoscale: effects of low numbers and confinement

Ziya Kalay

Institute for Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University, Japan

Abstract

In this talk, I will present our recent results on reaction kinetics in a system where reactant density is low and the medium contains confining domains. During the last two decades, single molecule observations indicated that plasma membrane proteins and lipids can become temporarily confined in compartments of a meshwork induced by the actin cytoskeleton, with a compartment size that varies between ~30-300 nm. Motivated by this, we investigated how confinement would affect the kinetics of reversible dimerization of membrane molecules, since dimer formation can activate proteins and influence cell signaling. Performing theoretical analysis and Monte Carlo simulations, we found that the average rate of molecular encounters is unchanged, while its variance significantly increases with confinement strength, at low reactant densities. Therefore, molecules encounter less frequently in the presence of confining domains, but following each encounter they sustain many collisions. Based on this, we argue that confinement has two important implications on reaction kinetics in the plasma membrane: 1) higher order reactions would be facilitated, as confinement leads to temporary increase in local concentrations, 2) confinement causes molecules to undergo bursts of interactions rather than continuously interacting at low rates. The second effect is particularly interesting as it suggests that confinement may regulate signaling by adjusting the spatio-temporal pattern of interactions between signaling molecules. Lastly, I will present an exact solution for a Brownian particle reversibly binding to a target in two-dimensions, and discuss how it can be used to extract reaction rates from experimental data.

Keywords : *reaction kinetics, confinement effects, single molecule observations*

Dr. Ziya Kalay

zkalay@icems.kyoto-u.ac.jp

References

[1] Z. Kalay, T. K. Fujiwara, and A. Kusumi. Confining domains lead to reaction bursts: reaction kinetics in the plasma membrane. PLoS ONE, 7(3):e32948, 2012.

[2]Z. Kalay. Exact Green's functions for a Brownian particle reversibly binding to a fixed target in a finite, two-dimensional, circular domain. J. Phys. A, 45:235001, 2012.

[3]Z. Kalay. Reaction kinetics in the plasma membrane. Biotechnology Journal, 7:745–752, 2012.

Session 2

Power of Engineering in New Facets of Biology

11:50 - 12:50 at Convention Hall

Co-chairs: Jason Shoemaker & Herve Guillou

Message from Co-Chairs:
This session focuses on distinct works that cleverly apply engineering tools to resolve complex biological questions. The first seminar presents how automated fermentation systems can be integrated with mathematical modeling to robustly control yeast metabolite production. The second seminar discusses the use of microfluidic devices to create artificial gene regulatory networks. These networks can be systematically manipulated in a highly controlled manner to reveal critical aspects of the signaling architecture thus elucidating Nature's gene regulation strategies.

Session 2: Power of Engineering in New Facets of Biology

Co-Chairs

Dr. Jason Shoemaker

Japanese Science and Technology Agency
ERATO Infection-induced Host Response Project

Dr. Herve Guillou

Institute of Industry and Engineering, University of Tokyo

Session 2-1 **11:50 - 12:20**

Towards Grokking Yeast

Dougie Murray

Institute for Advanced Biosciences, Keio University, Japan

Abstract

High Density cultures of yeast auto-synchronize their physiology, resulting in a demarcation of anabolic and catabolic processes. Here, I present our recent data on quantifying chromatin, membrane, metabolite and flux dynamics. How these data are integrated and our modeling approaches will be discussed.

Keywords :

Dr. Douglas Murray

dougie@ttck.keio.ac.jp

Session 2-2 **12:20 - 12:50**

In vitro models of gene regulatory networks

Yannick Rondelez

University of Tokyo & LIMMS/CNRS-IIS, Janap & France

Abstract

Molecular programming" provides tools for the building of in vitro circuits that reproduce some of the architectures and functions of biological regulatory network.Can we use these artificial assemblies to learn something about the organization of biological systems? I will illustrate this approach with a discussion about the possible role of molecular competition on cellular decision making.

Keywords : *In vitro models, reaction networks, dynamic systems, molecular programming*

Dr. Yannick Rondelez

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Poster Session

12:50 - 14:50 at Lounge

Abstracts are listed in page 27 ~ 54

Session 3

Data-driven Estimation of Model Parameters
14:50 - 16:10 at Convention Hall

chair: Akatsuki Kimura

Session 3: Data-driven Estimation of Model Parameters

Chair

Dr. Akatsuki Kimura

Cell Architecture Laboratory, National Institute of Genetics, Japan

He is one of the organizers committee of this International Workshop on Quantitative Biology, also the speaker of Session 4. He has contributed to organize this year's annual meeting of Japanese society for Quantitative Biology during 23rd ~ 25th November in the University of Tokyo, Komaba II campus, too.

Session 3-1 **14:50 - 15:10**

Foundation of Data Assimilation and Its Application to Intracellular Fluid Dynamics

Hiromichi Nagao*[1,2], Ritsuya Niwayama[2,3], Akatsuki Kimura[2,3], and Tomoyuki Higuchi[1,2]

1. The Institute of Statistical Mathematics, Research Organization of Information and Systems, Japan,
2. Transdisciplinary Research Integration Center, Japan,
3. National Institute of Genetics, Research Organization of Information and Systems, Japan

Abstract

Data assimilation (DA) is a fundamental technique that combines numerical simulation models and observational/experimental data through a Bayesian estimation of continuously changing status behind target systems. DA was originally developed in geophysical areas, especially in meteorology and oceanology, and is nowadays applied in other various fields of science such as space, life and industrial sciences. The eventual goal of DA is to provide next-generation simulation models that can predict future statuses.

In this study, DA is applied for the first time to the intracellular fluid dynamics focusing on the cytoplasmic streaming in Caenorhabditis elegans embryo, which is observed shortly after the fertilization. Niwayama et al. [Proc. Natl. Acad. Sci., 2011] proposed a hydrodynamic simulation model that qualitatively reproduces the velocity distribution in the cell measured by the particle image velocimetry. The purpose of the present work is to quantitatively obtain the spatial and temporal distributions of the force generated by the molecular motors, which is considered to drive the cytoplasmic streaming. A number of "particles", each of which is a realization of a set of model parameters, are sampled from an assumed prior distribution function associated with the apparent velocity structure along the cell wall starting from the anterior to the posterior. Then the hydrodynamic simulation calculates a likelihood function, which is a measure of how the simulation well explains the observation, for each particle. Finally, the targeting posterior distribution function is obtained on the basis of the Bayes' theorem. The estimated force distribution that is reconstituted from the maximum-a-posteriori solution, which attains the posterior distribution function maximum, is found no longer to be proportional to the velocity distribution. This fact may indicate strong forces are generated even at region where the streaming is slow.

In the presentation, we introduce the foundations of DA and discuss the new findings associated with the relation between the driving force and the velocity distributions associated with the cytoplasmic streaming in C. elegans embryo.

Keywords : *data assimilation, cytoplasmic streaming, Caenorhabditis elegans, particle filter, Bayesian statistics*

Dr. Hiromichi Nagao

hnagao@ism.ac.jp

Session 3-2 **15:10 - 15:40**

Noninvasive inference of the molecular chemotactic response using bacterial trajectories

Jean-Baptiste Masson[1], Guillaume Voisinne[2], Jerome Wong-Ng[3], Antonio Celani*[4], and Massimo Vergassola[5]

1. Physics of Biological Systems, Institut Pasteur, 75724 Paris Cedex 15, France
2. Unité de Recherche Associée 2171, Centre National de la Recherche Scientifique, F-75015 Paris, France

Abstract

The quality of sensing and response to external stimuli constitutes a basic element in the selective performance of living organisms. Here we consider the response of Escherichia coli to chemical stimuli. For moderate amplitudes, the bacterial response to generic profiles of sensed chemicals is reconstructed from its response function to an impulse, which then controls the efficiency of bacterial motility. We introduce a method for measuring the impulse response function based on coupling microfluidic experiments and inference methods: The response function is inferred using Bayesian methods from the observed trajectories of bacteria swimming in microfluidically controlled chemical fields. The notable advantages are that the method is based on the bacterial swimming response, it is noninvasive, without any genetic and/or mechanical preparation, and assays the behavior of the whole flagella bundle. We exploit the inference method to measure responses to aspartate and α-methylaspartate—measured previously by other methods—as well as glucose, leucine, and serine. The response to the attractant glucose is shown to be biphasic and perfectly adapted, as for aspartate. The response to the attractant serine is shown to be biphasic yet imperfectly adapted, that is, the response function has a nonzero (positive) integral. The adaptation of the response to the repellent leucine is also imperfect, with the sign of the two phases inverted with respect to serine. The diversity in the bacterial population of the response function and its dependency upon the background concentration are quantified.

Keywords : *Baxterial chemotaxis*

Dr. Antonio Celani

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Session 3-3 **15:40 - 16:10**

Mathematical modeling of the RNA polymerase II transcription cycle based on live-cell imaging of post-translational modifications

Timothy J. Stasevich*[1], Yoko Hayashi-Takanaka[1], Yuko Sato[1], James G. McNally[2], and Hiroshi Kimura[1]

1. Graduate School of Frontier Biosciences, Osaka University, Japan
2. Laboratory of Receptor Biology and Gene Expression, National Institutes of Health, USA

Abstract

Post-translational protein modifications play a fundamental role in gene regulation, but the dynamics of these modifications remain difficult to quantify in living cells. Part of the problem is that standard labeling techniques based on permanent fluorescent fusion tags such as GFP are unable to distinguish modified forms of the same protein. For example, although GFP has been used to visualize the live-cell dynamics of RNA polymerase II (pol II), it has been difficult to distinguish actively elongating forms of pol II (phosphorylated at serine 2) from freely diffusing (unphosphorylated) or initiated but stationary forms (phosphorylated at serine 5). This complicates the analysis of pol II transcription dynamics and leaves some doubt about deduced results. Here we overcome this difficulty using FabLEM (Fab-based Live Endogenous Modification labeling), a recently developed technique utilizing fluorescent antigen binding fragments (Fab) to reversibly label protein modifications in living cells with minimal disturbance [1]. Specifically, we are visualizing pol II phosphorylation in conjunction with histone acetylation at an activated gene array in single living cells. By timing the recruitment of these modifications to the gene array, this work is the first to distinguish in vivo transcription initiation kinetics from recruitment and elongation kinetics. This data place tight constraints on quantitative models for pol II transcription and enable unbiased and accurate estimates of model parameters. In contrast to previous live-cell analyses of pol II kinetics, our data now argue that the transition from initiation to elongation is highly efficient, approaching values over 80%. This efficient promoter escape appears to be driven by histone H3K27 acetylation, as elongating forms of pol II accumulate more quickly at arrays with more acetylation. Surprisingly, initiated forms of pol II accumulate at the same rate regardless of array acetylation level, indicating that enhanced array accessibility is not the main factor contributing to the high transcription efficiency. Our data therefore demonstrate that, in addition to facilitating chromatin decondensation, histone acetylation can also regulate distinct steps of the pol II transcription cycle.

Keywords : *transcription, rna polymerase II, histone modifications, gene expression*

Dr. Timothy J. Stasevich

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References

[1] Y. Hayashi-Takanaka, K. Yamagata, T. Wakayama, T.J. Stasevich, T. Kainuma, T. Tsurimoto, M. Tachibana, Y. Shinkai, H. Kurumizaka, N. Nozaki, and H. Kimura, "Tracking epigenetic histone modifications in single cells using Fab-based live endogenous modification labeling," Nucleic Acids Res., 39, 6475-6488 (2011).

Session 4

Advances in probing cytoskeletal and chromosomal dynamics in dividing cells

16:30 - 18:30 at Convention Hall

Co-chairs: Viji Draviam & Akira Funahashi

Message from Co-Chairs:

This session focuses on recent breakthroughs in our understanding of two main cytoskeletal events that drive cell division: chromosome segregation and spindle orientation. The first two seminars will present how microtubules capture chromosomes and pull sister chromatids apart during cell division. In here, lessons learnt from yeast models will be presented to explore how chromosome-microtubule attachment is established, monitored and corrected. The last two seminars will bring forth recent modelling efforts developed to understand how the movements of the mitotic spindle are powered in worms and human cells. Together, this session will bring a palette of cutting-edge probes, novel models and open questions that can further our knowledge on mechanisms that control mitosis.

Session 4: Advances in probing cytoskeletal and chromosomal dynamics in dividing cells

Co-Chairs

Dr. Viji Draviam

Department of Genetics, University of Cambrisge

She is one of the organizers committee of this International Workshop on Quantitative Biology, who has organized Session 4 with Dr. Noriko Hiroi, Dr. Rinshi Kasai, Dr. Akatsuki Kimura and Dr. Akira Funahashi. Her detailed introduction is in p55.

Dr. Akira Funahashi

Systems Biology Laboratory,
Biosciences and Informatics Department,
Keio University

He is one of the organizers committee of this International Workshop on Quantitative Biology, who has contributed the UK-Japan co-operative project with Dr. Viji Draviam. He has contributed to organize this year's annual meeting of Japanese society for Quantitative Biology during 23rd ~ 25th November in the University of Tokyo, Komaba II campus, too. He will give a tutorial about "Numerical Calculation and Quantitative Biology" on 23rd, 10:00 - 12:00 (admission free). His introduction is in p56.

Session 4-1 **16:30 - 17:00**

Chromosome acrobatics on the mitotic spindle

Tomoyuki Tanaka

Wellcome Trust Centre for Gene Regulation & Expression College of Life Sciences, University of Dundee

Abstract

Keywords :

Prof. Tomoyuki Tanaka

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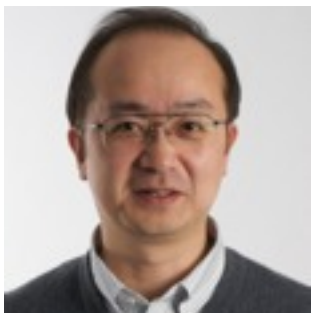

Session 4-2 **17:00 - 17:30**

Tension across centromeres refines centromeric protection by shugoshin

Yoshinori Watanabe

Institute of Molecular Cellular Biosciences, University of Tokyo, Japan

Abstract

Successful partitioning of chromosomes in mitosis relies on the bipolar attachment of sister chromatids (chromosome bi-orientation). At the center of paired kinetochores (the inner centromere), shugoshin Sgo1 protects centromeric cohesin from dissociation by a prophase pathway, and the CPC (chromosomal passenger complex) plays a crucial role in correcting erroneous microtubule-kinetochore attachment. Sgo1 and CPC form a complex at the inner centromeres depending on two histone phosphorylations, H2A-pT120 and H3-pT3, which are mediated by kinetochore-associated kinase Bub1 and cohesin-associated kinase Haspin, respectively. Because Sgo1 favors H2A-pT120-enriched sites, Sgo1 redistributes from the inner centromeres to kinetochores at the metaphase-anaphase transition. This redistribution of Sgo1 is essential for de-protecting cohesin and separating chromosomes at anaphase. Moreover, we reveal that the centromeric heterochromatin plays a crucial role in limiting Sgo1 redistribution during metaphase, a disorder of that might be the major reason for the chromosomal instability widely observed in cancer cells.

Keywords : *shugoshin, mitosis, kinetochore, centromere*

Prof. Yoshinori Watanabe

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Session 4-3 **17:30 - 18:00**

Size regulation of mitotic spindle in the *C. elegans* embryo

Yuki Hara, Akatsuki Kimura

Cell Architecture Laboratory, National Institute of Genetics, Japan

Abstract

The mitotic spindle is a supramolecular machinery critical for accurate chromosome segregation. During animal development, various sizes of the mitotic spindle appear [1]. The regulation of the spindle length, which is the distance between two spindle poles, has been well studied. However, little is known about the control of the spindle width, which is the width of the microtubules at the center of the spindle. Previous studies have suggested that the spindle is able to self-organize its shape and thereby maintain a constant aspect ratio between its length and width. In this study, we quantified the widths of metaphase spindles of various sizes that appear during embryogenesis in Caenorhabditis elegans. As expected, the spindle width correlated well with the spindle length; however, the aspect ratio between the length and the width of the spindle was not constant. From the results of our study, we formulated an equation for calculating the spindle width as a function of the spindle length. Furthermore, we proposed a possible force-balance model based on this equation for setting the spindle width.

Keywords : *mitotic spindle, size, C. elegans, microtubule, chromosome*

Dr. Akatsuki Kimura

akkimura@nig.ac.jp

References

[1] Hara Y., Kimura A. *Curr. Biol.* **19**, 1549-1554 (2009)

Session 4-4 **18:00 - 18:30**

Role of microtubule ends in defining the plane of cell division and accuracy of chromosome segregation

Naoka Tamura[1], Roshan Shrestha[1], Ihsan Zulkipli[1], Francesco Iorio[4], Adam Corrigan[2], Noriko Hiroi[3], Jessica Patel[1], Akira Funahashi[3], Athene Donald[2], Julio Saez Rodriguez[4] and Viji Draviam*[1]

1. Department of Genetics, University of Cambridge, UK
2. Department of Physics, Cavendish Laboratory, University of Cambridge, UK
3. Department of Biosciences and Informatics, Keio University, Japan
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Abstract

During cell division, the growth and shrinkage of microtubules increases dramatically by nearly ten-folds. This global change in microtubule dynamics must be accompanied by site-specific changes at distinct microtubule attachment sites to ensure the accurate segregation of chromosomes and proper orientation of the spindle. It is important to understand mechanisms that control mitotic microtubule dynamics because both chromsome missegregation and spindle misorientation can promote tumourigenesis. Using a combination of high-resolution live- cell microscopy, microtubule and chromosome tracking tools, siRNA mediated protein depletion, anti-microtubule drug treatment and transcriptomal network analysis, we have studied the consequence of perturbing microtubule dynamics in the processes of chromosome segregation and spindle orientation in human cells. Our findings show that mitotic microtubule destabilising motors, Kif2B and Kif2C are required for chromosome segregation but not spindle orientation. However, when microtubule dynamics is perturbed globally using a microtubule pausing agent, 2ME2, spindle orientation is severely perturbed, and chromosome movements are merely delayed. Interestingly, 2ME2 treatment does not block the active rotation of spindles towards the correct orientation but it interferes with the spindles remaining tethered at the correct orientation. This finding of a microtubule pausing agent perturbing spindle orientation but not chromosome segregation inspired us to look into novel and subtle microtubule stabilising drugs. For this purpose, we used an unbiased approach of first defining a global transcriptomal signature for microtubule stabilisation using Paclitaxel treated cells and then searching for a similar microtubule stabilization associated transcriptional signature in cells treated with 164 distinct small molecule perturbagens, including FDA approved drugs. This search has unraveled novel microtubule stabilisers that delay mitosis to varying extent. I will summarise how our basic findings on microtubule mediated mitotic events has helped us highlight clinically significant lesions in microtubule dynamics that affect mitotic outcome.

Keywords : *EB1, mitotic spindle, microtubules, chromosome segregation, human cells*

Dr. Viji Draviam

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Closing Remarks

at Convention Hall
18:30 - 18:40

Prof. Madan Rao

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He is the professor of Raman Research Institute and Theory Physics Group in National Center for Biological Sciences in India. He focuses the research about the dynamics of cytoskeleton and their regulatory proteins, and the dynamics of organelles and flux mass in nonequilibrium environment. He has many remarkable publications in his fields. The most recent publication is;

K. Gowrishankar, S. Ghosh, S. Saha, Ruma, C., S. Mayor, M. Rao, (2012), Active remodeling of cortical actin regulates spatiotemporal organization of cell surface molecules, Cell 149 : 1353-1367.

Poster Abstracts (1 ~ 28)

Poster Session 12:50 - 14:50

Free Discussion 18:40 - 20:00

at Lounge

Poster 01

Acceleration of Stochastic Biochemical Simulation by GPU

Kei Sumiyoshi, Noriko Hiroi, and Akira Funahashi

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Abstract

In the system biology, the deterministic approach is often used to understanding biochemical systems. The deterministic approach describes the system with molar concentration, and results in a same outcome for every realizations. However, when understanding a system with small number of molecules, such as biochemical networks in a single cell, a simulation must be run by the stochastic approach, instead of the deterministic approach. There is an algorithm called SSA (Stochastic Simulation Algorithm) which simulates the stochastic behavior of a spatially homogeneous system. SSA uses pseudo random uniform numbers to create stochastic behaviors in the system. Since the stochastic approach have different values in each result, multiple realization is required to obtain a statistical data on the stochastic model, therefore resulting a large computational cost to analyze a stochastic model. As simulating a stochastic model with SSA, we have implemented a simulator with parallel computation method, by using the characteristic of GPU (Graphics Processing Unit), which enables multiple realization on the same time sequence, therefore this parallel method gets multiple results at once in a shorter calculation time, comparing with performing all those simulations sequentially. During the simulation, every time course is recorded on each time steps for analyzing purpose. The simulator has adapt to SBML (System Biology Markup Language), to enable a simulation for any stochastic model. We have also improved a simulator by optimizing an access of GPU memory, and this implementation lead to a significant improvement of the computational performance. We tested a performance by running multiple realizations of SSA, using the model called decay-dimerization model. This model has four reactions and three species involving, which shows a stochastic behavior. Using the parallel computation by GPU, the simulation time have accelerated about sixty times faster, compared to the sequential method by CPU.

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Poster 02

Design and Implementation of GPU accelerated biochemical ODE simulator

Kazushige Nakamura, Kazuki Hirata, Noriko Hiroi, and Akira Funahashi

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Abstract

Describing the biochemical network by ODE (Ordinary Differential Equations) is a most commonly used method in mathematical modeling. To verify and analyze a mathematical model, it is necessary to perform parameter fitting with experimental and quantitative data. In addition, the computation for parameter estimation and fitting requires multiple simulations to solve such problems, moreover, the initial value might affect the dynamics of the model if it contains chaotic system, and thus we require multiple simulations for different initial values. Currently, the well known biochemical network simulators, such as COPASI and CellDesigner, have ODE solvers, which enables users to simulate their mathematical model, but these simulators are executed on CPU, which requires iteration of simulations for parameter estimation and analysis of the dynamical system.From above reasons, we have implemented an accelerated biochemical network simulator using GPU (Graphics Processing Unit) which can be used by researchers at the individual user level. With our implementation, calculations of ODEs are executed on the GPU by dynamically loading mathematical model represented in SBML (Systems Biology Markup Language). SBML is a de-facto standard model representing language for computational modeling of biological systems. Supporting SBML in our simulator will become a great advantage to support researchers who have already created their model in SBML, or familiar with software packages which supports SBML.We have implemented a simulator which can solve and simulate a simple SBML files by parallel computational method using GPU. An ODE simulations are accelerated about 50 times faster by using our GPU approach in single- precision, and about 20 times faster in double-precision, compared to sequential implementation on CPU.

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Poster 03

Implementation of spatial model simulator and its SBML support

Tatsuhiro Matsui, Noriko Hiroi, and Akira Funahashi

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Abstract

Our goal is to provide user friendly spatial model simulator for SBML spatial extension supporting models.

In this research, we have built a spatial model simulator, which can import an SBML model following the definition by spatial model extension (proposed in 2010.10.8), and simulate advection-diffusion-reaction equations. The method of spatial discretization is explicit finite difference method (diffusion: Forward-Time Central-Space method, advection: CIP method), and time integration is classical Runge-Kutta method.
This simulator defines the shape of geometries, such as cells and nuclei, with numerical formulae or gray scale images data. Users can export the simulation results by PNG files (image data) and text files (numerical data).
We are planning to implement diffusion and advection on a curved surface including a cell membrane, and an implicit method.

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Poster 04

Bio-Flow layout algorithm: an auto-layout algorithm of biochemical networks

Takaaki Chishiki, Noriko Hiroi, and Akira Funahashi

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Abstract

Motivation:
Constructing various large biological networks and updating existing biological networks are promoted nowadays. The context of biochemical pathways is represented as an important feature in those networks, because intuitive understanding of large networks are possibly easier by visualizing the context with up-to-down flow and left-to-right flow. However available auto-layout algorithms for visualizing biological networks do not consider the context of biochemical pathways. It makes difficult the intuitive understanding of outputs of current auto-layout algorithms. On the other hand, it is not practical to draw large diagrams manually with consideration about the context of biological pathways. Here we propose a new layout algorithm with considering the context of biochemical pathways. We named the new algorithm as Bio-Flow layout algorithm.

Results:
Bio-Flow layout algorithm first finds out the longest path of the biological networks. This pathway is called main-path, which consists of main-molecules. Next, molecules connecting with the main-molecules are extracted. If they are reactants, they are placed at upper-right position of connecting molecules. If they are products, they are placed at lower-right of connecting molecules. By repeating this process, all the remaining molecules of the network are placed according to the distance from the main path. We built a software which can extract the necessary information for visualization from Systems Biology Markup Language (SBML) files.

Conclusions:
Bio-Flow layout algorithm has potential to be developed as a suitable automatic-visualization method of biochemical networks to help intuitive understanding of large networks with providing the essence of the knowledge of biochemical context.

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Poster 05

Understanding the characteristics of intracellular reaction space from the point of view of bio-molecular organization

Takahiro Okuhara, Akito Tabira, Noriko Hiroi and Akira Funahashi

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Abstract

Many of the biochemical modeling methods has been established with the assumption that they stands *in vitro* environment. However, motion of the biochemical molecules *in vivo* is restricted by crowding factors, whereas the molecules *in vitro* can move freely. Because of such differences in molecular motility, it is possible that the nature of reaction *in vivo* is different from that *in vitro*.Therefore, considering the effect of crowding environment on biochemical reactions is important to estimate in vivo molecular behavior precisely.
In our previous studies, static intracellular environment has been estimated as a fractal structure. The fractal structure transform the protein diffusion in vivo into anomalous and confined diffusions. These diffusion styles were estimated the cause of *in vivo*-like characteristics of biochemical reactions that is quick-response and slow exhaustion; the mechanism to produce robustness of living systems which consists of sequential biochemical reactions. These results suggested that fractal structures which is represented by fractal dimension is important for the modeling of biochemical reactions *in vivo*.
In this study, we reconstructed three different crowding environments by computer simulations, and analysed reactants behaviors in those three models of reaction environment, which are organized with different hypothetical aggregation processes of environmental molecules. One is a simple randomly-arrangement model of environmental molecules. The second is random diffusion limited aggregation(DLA) model which is a modified DLA model. The third is Cluster Cluster Aggregation(CCA) model.
We found that the motility of reactants in random DLA and CCA environment changed when the environments were occupied at the level of percolation boundary (40.7%).
Based on the observation by TEM (transmission electron microscope), background molecular density of intracellular environment is about 41%. This value is close to and over the percolation threshold. This could mean that the molecular diffusion in vivo is confined because of the percolation of environmental molecules, however the relative occupation level is not sufficient and the organization process is important.
Both of the perimeter of environmental molecules and the intermediate region between environmental molecules indicated fractal dimensions which are smaller than Euclidian dimension (2), nevertheless the structure of randomized environmental molecules indicated closer dimension to Euclidian dimension.

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Poster 06

Fabrication of a microfluidic device for long term cell culturing with spatiotemporal fluid-control system

Takumi Hiraiwa, Noriko Hiroi, and Akira Funahashi

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Abstract

Some cellular functions appear by the appropriate arrangement of those cells. For example, the formation of required interaction between neuronal cells allows them to be functional as a ”brain” from a group of cells without any organized function. Such transformation of the cellar behavior is interesting and supposed to be significant as a control mechanism of biological phenomena. To elucidate the mechanisms which underlie behind those cellular behaviors is the target to be solved. However, to analyse these mechanisms by bulk experimental systems conquer the following difficulties. It has been suggested that cells arrangement and network formation are controlled by localization changes of intracellular molecules; and that is controlled by the distribution of extracellular factors in cell culturing environment. It is merely possible to control the diffusion pattern of extracellular stimuli by bulk systems. As the result, those systems often fail to reproduce an expected cell culturing environment.

In this study, we fabricated a microfluidic device that can control the spatial pattern of liquid stimuli and accurate concentration gradient by using Microcontact Printing (μCP). The following effects are expected by using this device.

1.Using a plug flow and laminar flow to the microchannel in this device, this device can give a precisely patterned stimulation to the cells.
2.Since researchers can design any pattern of cell arrangement by μCP, we can test and find effective condition of patterning. Moreover, by choosing the materials of μCP, we can try the other kind of cell lines apart from neural network analyses.

In this study, SK-N-SH, a human neuroblastoma cells were given squared pattern and stimulated by retinoic acid (RA) by laminar flow. We checked whether the cells survive and differentiate normally under flow.

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Poster 07

Development of microfluidics systems for Flexible and Automated Biological Experiments

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Abstract

Microfluidics devices are the tools which allow us to manipulate and analyse minute volumes of fluid. They poses number of potential advantages compared to conventional systems, including lower fabrication costs, reduced reagent consumption and dead-volume, and improved performance due to the possibility of performing multiple analyses on a single chip.

Microfluidics devices had been developed for biological assays by fitted existing methods to microvolume fluidic systems. On the other hand, the application of these devices for serious biological studies are still rare. The complex procedures for manipulation makes hard to handle those devices. The user unfriendliness is one of the cause of difficulty to enhance the number of the applications. Also the same reason make a distance far to develop particular type of experimental system. Thus we planned to develop general purpose experimental devices which can apply to any kind of biological assays.

We developed two types of devices for each purpose. One is a “substrate” device which has the ability to do continuous analysis by connecting devices which have various function. The other is a “functional” device which has the ability to perform various biological analyses.

The functional device consists of three layers to materialize its function as a filter circuit. Filter circuit means a system which extracts target from materials.

By pressurize the extract, it goes through to the filter and be sent to the next functional device. On this process, extract through the substrate device. Substrate device can connect between different devices continuously. We designed independent functional devises and connect them via substrate device.

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Poster 08

Establishment of Compression Algorithm aimed for efficient analysis on Biological sequences

Mitsunari Kobayashi, Noriko Hiroi and Akira Funahashi

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Abstract

With development of next-generation sequencers, acquirable amount of sequence data has been growing rapidly. An ordinary next-generation sequencer generates 6 billions of short read during 11 days. Assembly softwares reconstruct short reads into an original sequence. Mapping is one of the sequence assembly methods, which decides the position of short reads on the original sequences by using a reference sequence. The differences between the reference sequence and the short reads raise difficulties on computing the precise positions of short reads on the original sequences. Also the calculation time and amount of memory occupancy are substantial because of the enormous data sizes.

On the other hand, hardware resources on personal computers for such analyses have limitations. How to optimize the use of these resources on computer is one of the significant problems to save not only the space of hardware resources but also its analyzing time.

To overcome the problems, we focused on the redundancy of sequence data. Biological sequences contain redundancy which is derived from repetitive sequences. Removing this redundancy by data compression and optimizing the use of the hardware resources may potentially solve the problem.

Although many compression algorithms for text data exist, because those compression algorithms for biological sequences simply aim to store the data in smaller space, compressed data by those algorithms are required to be decompressed for further analyses. We aimed to compress the data as they would be applicable directly for further analyses, as the result the time for analyses will be also saved as same as the data space. First, we are planning to establish the new compression algorithm which can produce suitably formatted, compressed data for mapping without via decompression.

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Poster 09

Single particle simulations reveal effects of molecular crowding on biochemical signaling

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Abstract

Signal transduction pathway is a sophisticated information processing system consisting of biochemical reactions. Although a cell is significantly different from ideal conditions assumed in conventional biochemical-reaction theories, the effect of "cellular environment", such as clustering, compartmentalization and macromolecular crowding, on biochemical reaction networks is poorly understood. In this study, molecular crowding effects on dynamics of biochemical reactions and signal transduction pathways were quantitatively determined by particle-level simulations. We have previously shown that re-binding of kinases to substrates can remarkably increase the processivity of dual-phosphorylation reactions and change the response characteristics. To quantify the significance *in vivo*, we simulated diffusion-controlled reactions in crowded medium and measured re-binding probabilities at the single-particle level. As a result, re-binding was highly enhanced by molecular crowding and its time dependency was nonlinearly changed at microscopic level even though the kinetics at macroscopic level followed the conventional equations in dilute media. The rate law revised on the basis of these calculations enables the quantitative modeling and analysis of biochemical networks in intracellular environments with crowding. In particular, the results were applied to the MEK-ERK system and validated with experimental measurements.

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Poster 10

Effect of adaptation currents on columnar oscillations

David Colliaux[1], Pierre Yger[2], Kunihiko Kaneko[1]

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Abstract

Large-scale modelling and simulation of cortical neurodynamics should integrate the effects of neuron diversity and precise connection circuits. We consider insights from phenomenological models to avoid unreachable parameter search.

The numerical study at the single cell level shows that adaptation may affect both the threshold and the gain of th response curve. The dynamics is then switched from monostable to bistable by slow linear and/or non-linear adaptation currents at the mean field level. Oscillatory dynamics in adapting and non adapting regimes are qualitatively different. Our study aims at bridging scales from the neuron to the cortical map and should be useful for designing large scale models.

This sheds light on the diversity of oscillations in the different brain areas during sleep (from spindle waves to slow wave) which could be related to the cell types in their tissues. The neuromodulation is also known to regulate these currents (dopamine for example) and can then trigger changes at the population level.

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Poster 11

Dynamic monomer-dimer equilibrium of a prototypical GPCR, beta2 adrenergic receptor: a single molecule imaging study

Rinshi Kasai

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Abstract

Beta2 adrenergic receptor (BAR) is a well-studied prototypical GPCR. However, whether it exists as monomers or dimers is controversial. Generally, for class A GPCRs, which BAR belongs to, the existence and function of dimers remain unresolved. Here, we fully determined the dynamic equilibrium between BAR monomers and dimers at 37°C, using a single-molecule imaging method. This is the second molecule, for which dissociation-association equilibrium is fully characterized in the membrane. The determined constants for BAR (for comparison with another class A GPCR, the values for formyl peptide receptor, FPR, are given, which was the first molecule for such determination; Kasai et al. 2011 J. Cell Biol.) are the following: the two-dimensional dimer dissociation constant = 1.6 (3.6) copies/square microns; a dimer lifetime of 80 (90) ms [a dissociation rate constant of 12.6 (11.0) /s]; and a 2D association rate constant of 7.9 (3.1) /[copies/square microns]/s. Rough agreement of these values between BAR and FPR suggests that class A GPCRs tend to form transient dimers with their lifetimes of ~85 ms. These values were determined for non-engaged receptor, but were unchanged by liganding. Under a BAR (FPR) physiological expression level of ~260 (2.1) copies/square microns [740,000 (6,000) copies/cell] in dog heart cells (neutrophils), 95% (42%) of the molecules exist as dimers. Note that the dimer lifetimes are the same irrespective of the receptor density, whereas the monomer lifetimes become shorter with an increase of the receptor density.

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Poster 12

The temporal coordination of cellular metabolism

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Abstract

Cellular metabolism, the interconversion of small molecules by enzymatic reactions, is a tightly coordinated process that requires integration of diverse environmental and intracellular cues. The metabolic network's stoichiometry can be reconstructed from various databases, however the principles that shape the network's state remain largely elusive.
Here, we present an evolutionary in-silico approach which allows the prediction of optimal steady state flux distributions within a cell in dependency of constant external concentrations as well as the detection of optimal regulation structures in fluctuating environments. In our context, the respective objective function is the amount of biomass a cell can produce in a certain time intervall, i.e. growth rate. While the network's stoichiometry is fixed, the rate constants and the regulation terms are altered during the evolution process until the cells converge into a state which is then assumed to be the optimal one with respect to their environment. Where it is applicable, the results obtained by this approach are compared with the analytical solution which are in a very good agreement.
The examined system consists of only two elementary flux modes but still shows a considerable degree of complexity. In a constant environment, one observes a switch between these two flux modes; the position of the switch depends on the ratio of the external metabolite concentrations. In a flucuating environment, cells evolve a regulation structure which temporally seperates the production of biomass and the production of its precursors. Cells having such a regulation pattern show an increased biomass production compared to cells that are evolved in the same environment but are not allowed to regulate their metabolism. By applying this method to other, more realistic networks one might elucidate the role and function of feedback mechanisms that are well described but not completely understood.

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Poster 13

Cell-to-cell variability-oriented modeling of cells

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Abstract

Mathematical modeling of the dynamics of cells is a popular approach in systems biology. However, in general, it is not an easy task to determine the biochemical parameters from experiments. In particular, since many experimental measurements focus on relative changes in molecular concentrations, the estimation of absolute concentrations of each molecular species in a cell tends to be a bottleneck in parameter estimation. In the paper, Phys. Rev. E 84, 062903, we have proposed a general framework to model intra-cellular signal transduction and gene regulatory dynamics based on cell-to-cell variability. In this framework, each relevant molecular species is approximated by a node taking a binary value, and interactions among them are characterized by typical time scale parameters for the interactions. The dynamics of the system are then formalized as a set of linear differential equations for the probabilities of all possible states, whose marginal probabilities correspond to the observed quantities in bulk experiments. Thus, our framework allows us to construct mathematical models without requiring the knowledge of absolute concentrations of molecular species. Here, we further discuss the generalization of this framework for application to systems with cell-cell interaction, cell differentiation or apoptosis. These systems can be modeled in our framework by relaxing the constraints on the stochastic rate matrix which defines the differential equations.

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Poster 14

Cells can sense when they are home - Rigidity sensing of cardiac cells leads to cell-morphological and cell-physiological optimization

Marcel Hoerning[1], Satoru Kidoaki[2] and Kenichi Yoshikawa[3]

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Abstract

We show, though investigations in the spontaneous substrate-induced modulation of synchronized beating in cultured cardiomyocyte tissue, that when the rigidity of the cardiac cell culture environment matches that of the cardiac cells, the tissue functionality and entrainment dynamics enhances and lead to a closer approximation to native cell functionality [1]. Systematically studies on entrainment dynamics of spontaneous originated waves showed that the main entrainment-frequency increases with the increase in substrate rigidity, and the entrainment stability of spontaneous originated waves become maximized when the substrate rigidity and cell rigidity (~4 kiloPascals) matches. Further, independent studies on the calcium transient alternates (CTA) in high frequency-paced tissue showed an significant increase in the critical period. CTA is known to be responsible for life-threatening arrhythmia in a real beating heart.

[1] Hoerning et al., Biophysical Journal 102, 3, 379-387, 2012

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Poster 15

Segmentation and Classification method for Liver Cell Nuclei in HCC histology images

Chamidu Atupelage, Hiroshi Nagahashi, Masahiro Yamaguchi, Fumikazu Kimura, Tokiya Abe, Akinori Hashiguchi, Michiie Sakamoto

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Abstract

Hepatocellular carcinoma (HCC) histopathology images are graded based on the textural and morphological characteristics of the liver cell nuclei. In a whole slide image (WSI) of biopsy specimen tumor regions are erratically distributed and a selected region of interest (ROI) may contain different types of cells such as liver cells, fiber cells, endothelial cells, etc. Especially, in fiber regions, different kind of irregular nuclei structures are appeared. To imitate the pathological investigation on HCC, computational systems need to segment the nuclei and subsequently, extract the characteristics of them. Most of the nuclei segmentation methods accomplish the task by segmenting every possible nucleus in the images because nuclei are appeared as darker compared to pink background and concave shape. In this study, we propose a multifractal computation based textural feature descriptor to be used for nuclei segmentation, fiber region detection, and liver cell nuclei classification. We evaluated the proposed method by employing the classified liver cell nuclei for tumor detection of H&E stained liver biopsy samples.

The proposed method, at first extracts the textural feature of HCC histology image collection. The extracted pixel's features are used for three tasks: nuclei segmentation, fiber region detection, and liver cell nuclei classification. Each task is carried out in order to supervised learning scheme. In task 1, we segment every possible nucleus such as liver cell nuclei, fiber cell nuclei, endothelial cell nuclei, histiocytes, and lymphocyte. Task 2 detect the fiber regions and exclude the nuclei that they overlapped with fiber regions. Using the expert's annotations, task 3 classifies the liver cell nuclei as tow class classification. Finally, we extract the textural, morphological, and spatial distribution characteristics of the liver cell nuclei and the textural characteristics of surrounded texture of the nuclei (part of the cytoplasm) for tumor classification.

We utilized H&E stained HCC biopsy image dataset to analyze the effectiveness of the proposed method. We investigate the effectiveness of each task by carrying out two class classification: non-neoplastic tissues vs. tumors. In the experiment, task 1 utilizes every segmented nuclei, task 2 uses the nuclei excluding the fiber region, task 3 uses only liver cell nuclei. The experimental results obtained 93.21% for task1, 94.38% for task 2, and 97.85% for task 3. In particular, excluding nuclei in fiber region has contribute to increase the CCR about 1% and utilizing only liver cell nuclei again increases the CCR about 3%. The experimental results provide the significance of the proposed multifractal feature descriptor, approach of liver cell classification, and nuclei feature extraction routines.

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Poster 16

Reconsidering the mechanistic view of embryogenesis

Naoki Irie, Shigeru Kuratani, Intl. Joint turtles genome consortium

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Abstract

Recent advancement in developmental biology highlighted surprising conservation of molecular mechanisms in vertebrate embryogenesis. Especially, clarifications of cascade-like molecular mechanisms that are expected to connect from DNA to actual embryonic structures further strengthened our “mechanistic view of life”. For example, developmentally earlier structures (e.g. body axis) are more important in that they become basic ground for the later embryonic structures.

On the other hand, apparent discrepancy with this viewpoint has been suggested form recent findings in search for the relationship between evolution and development. Based on our comparative gene expression analysis, temporally upstream genetic programs, such as those in cleavage, gastrulation turned out to be rather divergent among vertebrate species. What is important, even after the evolutionarily diverged early stages, embryos passed through hourglass-like conserved stages at organogenesis period. These observations implicate unexpected flexibility of early-to-mid developmental programs, challenging the mechanistic view of embryogenesis. We further show that turtles also follow this hourglass-like rule, which has long been believed to have unorthodox body plan as a vertebrate.

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Poster 17

Understanding the Self-Organisation of Amino Acid Regulation in Yeast

Kalesh Sasidharan*[1], Douglas B. Murray[1], Rainer Machné[2,3] and Masaru Tomita[1,4]

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4. Systems Biology Program, Graduate School of Media and Governance, Keio University, Fujisawa, Japan

Abstract

When Saccharomyces cerevisiae are grown continuously, cellular processes auto-synchronise resulting in stable oscillatory dynamics. Respiration is the most readily measured oscillatory parameter, however, transcriptome-wide and metabolome-wide studies indicate that the oscillation functions to temporally separate catabolic and anabolic processes. Consistent with this, the production of amino acids has distinct phase relationships with the oscillation cycle. Intracellular amino acids show different oscillation patterns during the respiration cycle, for example, the concentrations of serine and glutamine peak prior to asparagine, glutamate, methionine and valine during an oscillation cycle. Furthermore the oscillation is highly sensitive to amino acid and Rapamycin perturbations. Taken together these data indicate a role for the major amino acid regulator Gcn4p in the regulation of oscillatory dynamics, where the Gcn4p is activated by non-aminoacylated tRNAs. Here we show that the ratio between aminoacylated and non-aminoacylated tRNAs oscillates in-phase with respiration cycle, indicating the observed Gcn4p dynamics result from translational activation by the cyclic amino acid synthesis and aminoacylation of tRNAs. Closer examination using CE-MS quantification of amino acids that were bound to the aminoacylated tRNAs and ATP availability were used to explore the role of tRNA aminoacylation in the oscillatory regulation and the concentration response of individual amino acids; thus, revealing the dynamic activation of amino acid biosynthesis via the Gcn4 gene network (the immediate neighbours) during the respiration cycle.

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Poster 18

High-speed, high-magnification tracking system for fluorescence imaging of freely moving *C. elegans*

Yuki TSUKADA[1], Chen MIN[2], Koichi HASHIMOTO[2], Ikue MORI[1]

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2. Intelligent Control Systems Laboratory, Department of System Information Sciences, Graduate School of Information Sciences, Tohoku University

Abstract

Genetically encoded calcium indicators enabled to monitor activity of neurons without invasive manipulation, thus calcium imaging techniques have been shedding light on our knowledge on neuronal functions. Combining these techniques with automated tracking system, we can monitor activity of neurons even in freely moving worms. However, tracking with high magnification needs quick responses to keep a target region in a microscopic field; focus change during the tracking is obstacle for acquiring enough quality of fluorescence images for monitoring calcium concentrations. This problem should inevitably occur when we focus on some of the interneurons, where the only small neurite region looks responding to a stimulus. To solve such problems, we have developed a high-speed tracking system that enables to track freely moving worms with high-magnification (50x) objective lens. Our system tracks an animal with continuous transparent light, and is based on pattern matching of specified region, thus we could select any regions of interest along the animal body. Real-time linux enables to control high-speed motorized stage in μs order response. In addition, auto-focus system is implemented with three cameras with different focal depths, meaning that the system enables to perform high-speed autofocus by comparing simultaneously acquired images from the different depths. Our tracking and autofocus system could avoid photo-bleaching of fluorescence probes because the transparent light uses different wave length and is independent from the light for calcium imaging. With these systems, we are currently targeting RIA and AIY interneurons because their activities were only monitored with neurite or process in the calcium imaging experiments with fixed-worms. We hope that the acquired images should expand a potential for calcium imaging with the neurites.

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Poster 19

A mathematical model for human gut microbial ecosystem

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Abstract

Since the discovery of Lactobacillus in 1907 in Bulgaria, the relationship between intestinal bacteria and the health of their host has been attracting attention of many researchers. Owing to the innovative development of sequencing technique recently, various studies have reported on the function and property of intestinal bacteria. The results imply that the influence of intestinal bacteria to their host's physiology is wider than expected, ad even relations to food allergy or obesity are discussed.
Although intestinal bacteria is now a key issue from the viewpoint of immunology and pathology, their responses to perturbations is still a very challenging research topic due to the high inter-individual variability that enables us to distinguish even genetically identical twin. Several recent studies also indicate that intestinal microbiota can be largely affected by various external factors such as meals or psychic stress. All these results suggest that the species population in microbiota is fluctuating in relatively short time depending on host's act in daily life.

We performed 16S rRNA gene sequencing of bacteria DNA in 21 dissected sections prepared from small to large intestines of 6 mice to analyze the bacteria composition in each section. By comparing the quantitatively measured population distribution of bacteria species in 21 intestinal sections obtained from the 16S sequence analysis, we investigated the common feature of intestinal flora ecosystem. We also developed a simple mathematical model to be able to explain the primary force shaping the ecosystem in the mouse intestine.

This study highlights the possibility of existence of a fundamental principle independent to of individual and inter-species variation. We will further present an application of our mathematical model to human gut microbiota.

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Poster 20

Molecular dynamics and concentration in raft and boundary domains in actin-depleted plasma membrane vesicles as revealed by single-molecule imaging

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Abstract

Compartmentalization of the cellular plasma membrane has been considered a critical mechanism for regulating molecular interactions occurring in the plane of the membrane, by varying local molecular concentration and dynamics within and across the compartments. Among various compartments, raft domains, enriched in sterols, sphingolipids, and proteins anchored by saturated aliphatic lipid tails, have been drawing extensive attention but remained elusive due to their nano-meso-scale sizes. Recently developed plasma membrane vesicles (PMVs), which are largely depleted of the actin filaments (actin-based membrane skeleton) but contain virtually the full complement of lipids and proteins of native membranes, provide a unique platform for investigating raft domains because, by lowering the temperature, micron-sized raft-like, liquid-ordered-phase (Lo)-like domains can be induced. Here, using these PMVs with coexisting domains and single-molecule imaging-tracking methods, we examined molecular dynamics and concentration of various molecules in raft and boundary domains. One of the most interesting findings is that GPI-APs, although they preferentially partition into the Lo-like raft domains, continually move back and forth between Lo-like domains and the bulk domain, showing very dynamic partitioning, without any particular concentration in the boundary domain. Their diffusion coefficient within the boundary region has been measured for the first time: it was in the middle of the values for the Lo-like domain and the bulk domain. Other observations using molecules with various levels of raft affinity will be reported and discussed in the context of signal transduction.

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Poster 21

Non-equilibrium thermodynamics of cytoskeleton-mediated signaling in cells

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Abstract

Recent findings suggest that chemical reactions between signaling molecules can be facilitated or inhibited by the cytoskeleton. The cytoskeleton is an actively remodeled cellular structure driven by molecular motors that can bind/unbind to filaments and microtubules. Due to the stochastic nature of these binding/unbinding events, dynamics of the cytoskeleton is influenced by an "active noise" in addition to the thermal noise. Therefore, the cytoskeleton and any biochemical reaction network that is coupled to it should be characterized by an "effective temperature", which in turn characterizes the modification in reaction rates due to cytoskeletal activity. We consider assemblies of cytoskeletal filaments that can act as quasi-enzymes in a broad set of biochemical reactions. In the linear response regime, we calculate effective temperature using Fluctuation-Response Theorem for such reaction networks. Using the same network far from equilibrium, we again calculate effective temperature invoking Large Deviation Theory to find the rate function from its steady state. Based on these calculations, experimental measurements could be analyzed to calculate effective temperature as a function of concentration of reactants, acto-myosin contractility and 'real' or canonical temperature.

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Poster 22

A multiplex and sensitive RNA quantification method for determining the absolute amounts of mRNAs without reverse transcription processes

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Abstract

Microarray-based technologies are one of the most widely used quantitative approaches for transcriptome analyses which play key roles in understanding of transcriptional regulation mechanisms and gene functions. However, there are some important challenges to be solved for the technologies. One of them is the standardization of gene expression data because microarray-based methods merely provide the relative quantities of target-gene transcripts of different samples measured on the same microarray. Without the standardization no extensive comparisons of expression data, especially such as inter-gene comparisons, are available. Another important challenge is the direct quantification of transcripts without reverse transcription processes, which involve a potential cause of multiple biases interfering with the proper quantification of transcripts. The most simple and accurate way for solving these problem is to determine the absolute amounts of transcripts (mRNA copies per cell) without the process of cDNA synthesis, while none of the conventional microarray-based methods satisfies both of these features.

Here, we describe a novel RNA quantification method using microarrays which enables to determine the absolute amounts of target mRNAs directly from total RNA without reverse transcription processes. The method is based on a technique in which target mRNAs are converted into well-designed DNA tags called DNA-Coded Numbers (DCNs) through the photo-chemical ligation of two chemically synthetic DNA oligonucleotides, both of which specifically bind to the target. The converted DCNs are then amplified by PCR and finally detected on microarrays. The conversion to DCNs also provides other advantages such as the use of common microarrays with the same set of probes and no need for sample labeling processes. The method was validated by using chemically synthetic RNA samples of known quantities and total RNA samples prepared from mouse liver. We demonstrated that the absolute amounts of mRNAs were quantified with a high sensitivity (15 zmol) in reproducible manner.

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Poster 23

Quantitative Analysis of DNA Microarray Hybridization Kinetics

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Abstract

DNA hybridization is one of the most fundamental processes in biology. Developing a better understanding of the kinetic and dynamic properties of DNA hybridization will thus help elucidation and biotechnological application of numerous biological processes involving DNA hybridization. Recent studies have shown that a qualitative influence of stable self-folded DNA structures on hybridization kinetics using several particular sequences. In order to quantitatively study the effect, kinetic data obtained by using many different sequences are essential. For this requirement, the measurement with DNA microarrays is promising because one can observe hybridization of hundreds of DNA sequences at a time. However, using DNA microarrays, the detailed measurement of the time course of hybridization is basically difficult due to a washing treatment needed for the quantification of hybridized targets at every time point.

In this work, we developed a method to measure hybridization kinetics of a hundred of DNA sequences using a microarray and determine their hybridization rates. One major feature of our method is the design of the microarray. Our microarray can obtain data at six different time points of the hybridization on a single microarray-plate because there are spatially separated six sets of a hundred kinds of DNA probe sequences on the plate and all of the sets can be subjected to a washing treatment at once. The other one is the model for curve fitting. We derived the fitting equation from the simple two-state model similar to a previous work. However, we found that the equation is difficult to accurately determine the hybridization rates because it has too many parameters. Thus we have developed an approximation capable of being confirmed experimentally as well as a method for determining an adjustable parameter value by a simple experiment.

By using the developed method we determined the hybridization rates of 100 DNA sequences with a uniform length (23 nt) and ΔG (the free energy change with duplex formation) as well as no stable self-folded structures. As a result, we found a relation between the hybridization rate and the stability of less-stable secondary structures.

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Poster 24

Thermo-dynamicity affects neuronal cellular function

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Abstract

Background:
Physiological homeostasis maintains the intracellular temperature within appropriate range. For a mammalian cell, the range should be between 32 - 41 ℃. When the intracellular temperature is kept within the range, the reaction rate constant which is promotional to absolute temperature could change 3.0% of the largest case at the most.These fact prevent to attract attention to the dynamicity of intracellular temperature. However, some of highly organized biological systems are started to be known that they may be sensitive to temperature. For example, circadian rhythm, which has temperature compensation mechanism for keeping its rhythm, was suggested the amplitude of key molecules is affected by the change of temperature [1].
On the other hand, the development of fluorescent polymeric thermometers let us map of intracellular temperature with high resolutions. Thus, we investigated if the other highly organized system, differentiation, could involves sensitive mechanisms to the changes of temperature and could vary cellular behaviors.

Results:
We performed the fluorescence lifetime imaging of plasma membrane of SK-N-SH cells which can differentiate into neuronal cells. The thermometer we used was CMFDA. Our observation suggested that distribution of temperature is not uniform on the surface of neuronally differentiated cells. The difference of temperature within a cell was about 2.5 ℃ between a cell body and dendrites or a growth cone.
We adopted the above results to our long term memory model by changing the rate constants of model equations dependent on the temperature of the compartment, which those reactions are connected. The simulation results showed that if the temperature is low at the whole cellular membrane, we could not reconstruct any long-term maintenance of synapses. Moreover, if the temperature is low at specific compartment of a cell, long-term maintenance of spines were enhanced.

Conclusions:
These results showed the probability that a little heterogeneity of intracellular temperature distribution affects the highlyer life function, even each reaction rate in the mechanisms is not affected strongly.

[1] Generic temperature compensation of biological clocks by autonomous regulation of catalyst concentration
Tetsuhiro S. Hatakeyama and Kunihiko Kaneko
PNAS, doi: 10.1073/pnas.1120711109

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Poster 25

Metabolite Exchanges and Respiratory Synchronization in E. coli

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and Systems Biology Program, Graduate School of Media and Governance, Keio University

Abstract

The bacterium Escherichia coli (E. coli) is an excellent and simple model to study fundamental cellular processes. While E. coli is considered as a unicellular organism, metabolic interactions between cells may form the basis of community-oriented activities in vivo. Respiratory oscillations that suggest population-wide synchronized activity have been previously observed in high-density continuous cultures of E. coli and yeast but the process remains poorly characterized. To explore this phenomenon, here we used capillary electrophoresis mass spectrometry (CE-MS) to analyze the dynamics of extracellular metabolites during spontaneously emerging respiratory oscillations in E. coli. The dynamics of multiple secreted metabolites and respiratory activity appear to reveal a temporal sorting of metabolic activities. A major shift in metabolic function seemed to correspond with large changes in the level of the amino acid valine as well as changes in some other metabolites, suggesting a shift between catabolic and anabolic activity. Our results also suggest functional links between the dynamics of secreted metabolic products, the respiratory oscillations during continuous culture, and possible emergence of collective behavior in this unicellular bacterial model organism.

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Poster 26

Tuning the transcriptome: Global energy-driven chromatin dynamics

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Abstract

Previous studies using continuously-grown yeast have shown metabolism and transcription are oscillatory, suggesting an unknown global regulatory mechanism(s).
Recently a Discrete Fourier Transform analysis method was used on two oscillatory transcriptome sets to define 7 consensus clusters of gene expression. When compared with a large compendium of high-throughput data, differential promoter structures and nucleosome occupancy patterns (and the energetic requirements for remodelling) were implicated in temporal cluster development.
Subsequent time-series experimental data on the metabolome and nucleosome positioning over several oscillation cycles supports the role of cellular energetic state shaping the transcriptional landscape via nucleosome remodelling, revealing global nucleosome repositioning events that correlate with high levels of ATP availability.
Taken together our data provides a simplified view of the global transcriptional regulation driven by the energetic state of the cells attenuating chromatin structure.

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Poster 27

in vivo oriented modeling with consideration of the effect of intracellular crowding

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Abstract

The intracellular environment is known to be a crowded and inhomogeneous space. Such an *in vivo* environment differs from a well-diluted, homogeneous environment for biochemical reactions. However, the effects of both crowdedness and the inhomogeneity of environment on the behavior of a mobile particle and biochemical reactions have not yet been investigated sufficiently.

We performed Fluorescence Correlation Spectroscopy (FCS) and Transmission Electron Microscope(TEM) image analyses and constructed ordinary differential equation (ODE) models and stochastic models of molecular behaviors based on those data. Also we built artificial reaction spaces by fractal models, which are assumed to be non-reactive solid obstacles in a reaction space with crevices that function as operating ranges for mobile particles threading the space, with the exact amount of solid structures estimated from TEM images. Our ordinary differential equation models showed that physiological environment induces quick response - slow exhaustion reactions, which were originated in the anomalous molecular behavior and confined intracellular structures.

We fitted the empiric functions to the results of our Monte Carlo simulation with various conditions in order to find parameter ranges which are consistent with the results from FCS measurements. The empiric functions showed that the Stokes–Einstein relation $D \propto 1/r$ is not valid for the cytoplasmic nonreactive obstacles. It may due to the varied radii of microscopic structures exhibit varied viscosity.

In order to reconstruct *in vivo* environment *in silico*, choosing a suitable condition of a surface-to-volume ratio of the operating range was significant. With such condition, the characteristics of sub-cellular compartments engender larger mean square displacement of a mobile particle than that of particles in smaller compartments. Subsequently, the particles start to show confined particle-like behavior. These results are compatible with our results of ODE models, which predicted that a physiological environment would produce quick response and slow exhaustion reactions.

Our result can be applied to any biochemical reaction *in vivo* and have a potential to bring different results from *in vitro* assuming calculations.

1. Noriko Hiroi, Takahiro Okuhara, Takeshi Kubojima, Keisuke Iba, Akito Tabira, Shuji Yamashita, Yasunori Okada, Tetsuya J. Kobayashi, and Akira Funahashi. **"Physiological inracellular crowdedness is defined by perimeter to area ratio of subcellular compartments"** *Frontiers in Fractal Physiology* July 2012 accepted
2. Noriko Hiroi, Michael Klann, Keisuke Iba, Pablo deHeras Ciechomski, Shuji Yamashita, Akito Tabira, Takahiro Okuhara, Takeshi Kubojima, Yasunori Okada, Kotaro Oka, Robin Mange, Michael Unger, Akira Funahashi, and Heinz Koeppl. **"From Microscopy Data to *in silico* Environments for *in vivo* Oriented Simulations"** *EURASIP Journal on Bioinformatics and Systems Biology* May. 2012. http://bsb.eurasipjournals.com/content/2012/1/7/abstract
3. Noriko Hiroi, James Lu, Keisuke Iba, Akito Tabira, Shuji Yamashita, Yasunori Okada, Flamm Christoph, Kotaro Oka, Gottfried Koehler, Akira Funahashi. **"Physiological environment induce quick response - slow exhaustion reactions"** *Frontiers in Systems Physiology* August. 2011. http://www.frontiersin.org/systems_physiology/10.3389/fphys.2011.00050/abstract

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Poster 28

Morphogen-dependent growth control mechanism in the Drosophila wing disc

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Abstract

In the Drosophila wing disc, BMP-homolog Dpp functions as a morphogen for Antero-Posterior patterning whereas it also functions as a mitogen. Because the tissue growth is uniform under the non-uniform Dpp gradient, cell cycle control by Dpp is not a simple concentration-dependent manner. Recently, Wartlick et al.(2011) found that each cell divides when perceived Dpp level has increased by 1.4-fold since last division. Here we propose biochemical network models for achieving such complex behavior which are the extended models of Fold-Change Detection.

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The main target of his group (laboratory for quantitative biology) is to solve the question why biological systems can behave robustly, stably and flexibly in ever-changing environment even though they are built with stochastically operating components such as intracellular reactions. To this end, the group has recently developed new theory for computation with stochastic components by employing information theory and statistical theory. In addition, to verify the robustness of biological systems to intrinsic stochasticity, the group is also working on image and data analysis of complex biological phenomena such as early embryogenesis, epigenetics, polarity formation, and immune systems as collaborations with experimentalists. For a recent review on his group's work, please see:

1. Theoretical Aspects of Cellular Decision-Making and Information-Processing, TJ Kobayashi, A Kamimura, Advances in Systems Biology, 275-291

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Her research group uses a combination of molecular, biochemical, cell biological and modelling techniques to learn about how microtubules are controlled to ensure proper cell division. Because cell division defects can drive aneuploidy and tissue disorganisation in cancers, her research findings are relevant to unsolved problems in both fundamental and clinical biology. Her current research interests include automated single-cell image analysis, microtubule behaviour and regulation, chromosome segregation and spindle positioning in human cells.

For a recent review on her group's work, please see:

1. Microtubule plus-ends within a mitotic cell are 'moving platforms' with anchoring, signalling and force-coupling roles. Open Biol., (accepted)

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She started to develop her career in Molecular Biology and Biochemistry, and currently works in Systems Biology and Quantitative Biology area. Her research interest includes *in vivo* crowding, molecular mechanisms of higher-functions of central nerve systems, microfluidics technology and image informatics. Most recent publications are;

1. **Takizawa H, Hiroi N and Funahashi A. Mathematical Modeling of Sustainable Synaptogenesis by Repetitive Stimuli Suggests Signaling Mechanisms. PLoS One (accepted)**
2. **Hiroi N, Okuhara T, Kubojima T, Iba K, Tabira A, Yamashita S, Okada Y, Kobayashi TJ and Funahashi A. Physiological inracellular crowdedness is defined by perimeter to area ratio of subcellular compartments. Frontiers in Fractal Physiology (accepted)**

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He received his BE, ME, and PhD degrees in Computer Science from Keio University, Japan, in 1995, 1997, and 2000 respectively. He was a Research Fellow of the Japan Society of the Promotion of Science (DC1) from 1997 to 2000, and a Research Associate in the Department of Information Technology, Mie University, Japan, from 2000 to 2002. He then joined Kitano Symbiotic Systems Project, JST and The Systems Biology Institute as a researcher before moving to Keio University in 2007. His research interests include the area of systems biology, computational biology, interconnection network and parallel processing.

1. **MP van Iersel, et al.(2012) Software support for SBGN maps: SBGN-ML and LibSBGN. Bioinformatics, 28, 2016-2021.**
2. **N Hiroi, et al (2012) From microscopy data to in silico environments for in vivo-oriented simulations. EURASIP J Bioinfo Sys Bio.1, 7**

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Recent articles;

1. **M Shimomura, et al.(2009) KAIKObase: an integrated silkworm genome database and data mining tool. BMC Genomics, 10, 486.**
2. **M Osanai-Futahashi, et al (2009) Genome-wide screening and characterisation of transposable elements and their distribution analysis in the silkworm, Bombyx mori. Insec Biochem Mol Biol. 38, 1046-1057.**

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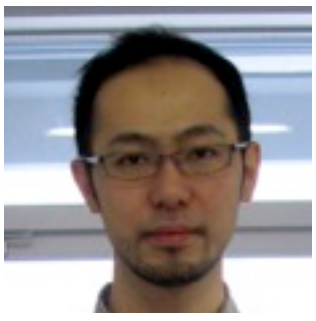

He started to develop his career in Single molecule Biophysics and Cellular dynamics, and currently works in Biophysics area. His research interest includes developing novel optical microscopy, microfluidic technology, single molecule imaging, image processing and spying minority of biological phenomena. Most recent publications are;

1. **Saito k, Chang Yu-Fen, Horikawa K, Hatsugai N, Higuchi Y, Hashida M, Yoshida Y, Matsuda T, Arai Y, and Nagai T. A luminescent protein for high-speed single-cell and whole-body imaging. Nature Communications, accepted.**
2. **Chang, Y.-F., Arai, Y., and Nagai, T. (2012). Optogenetic activation during detector "dead time" enables compatible real-time fluorescence imaging. Neuroscience Research 73, 341–347.**

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Recent articles:
1: N. Irie, S. Kuratani, Nature Communications, 2 : 248., 2011
2: N. Irie, Reproductive System & Sexual Disorders, 2011, S1:002

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1. M.M. Chowdhury, H. Kimura, T. Fujii, Y. Sakai, "Induction of alternative fate other than default neuronal fate of embryonic stem cells in a membrane-based two-chambered microbioreactor by cell-secreted BMP4", Biomicrofluidics, vol.6,014117, 2012
2. J. Kawada, H. Kimura, H. Akutsu, Y. Sakai, T. Fujii, "Spatiotemporally controlled delivery of soluble factors for stem cell differentiation", Lab on a Chip, vol.12, no.21, pp.4508-4515, 2012

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INTERNATIONAL WORKSHOP ON QUANTITATIVE BIOLOGY 2012

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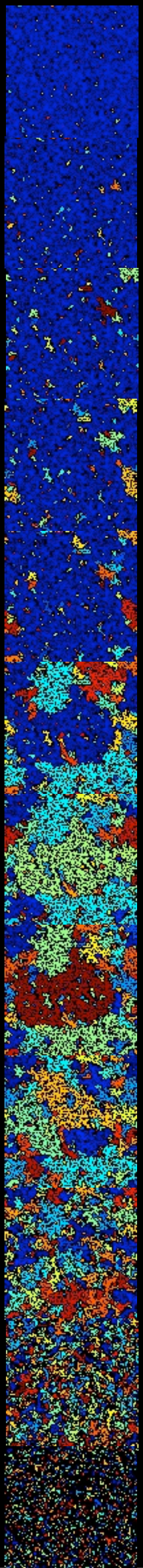

International Workshop on Quantitative Biology 2012

Nov. 22nd, 2012 thursday,
University of Tokyo, Komaba II Campus

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