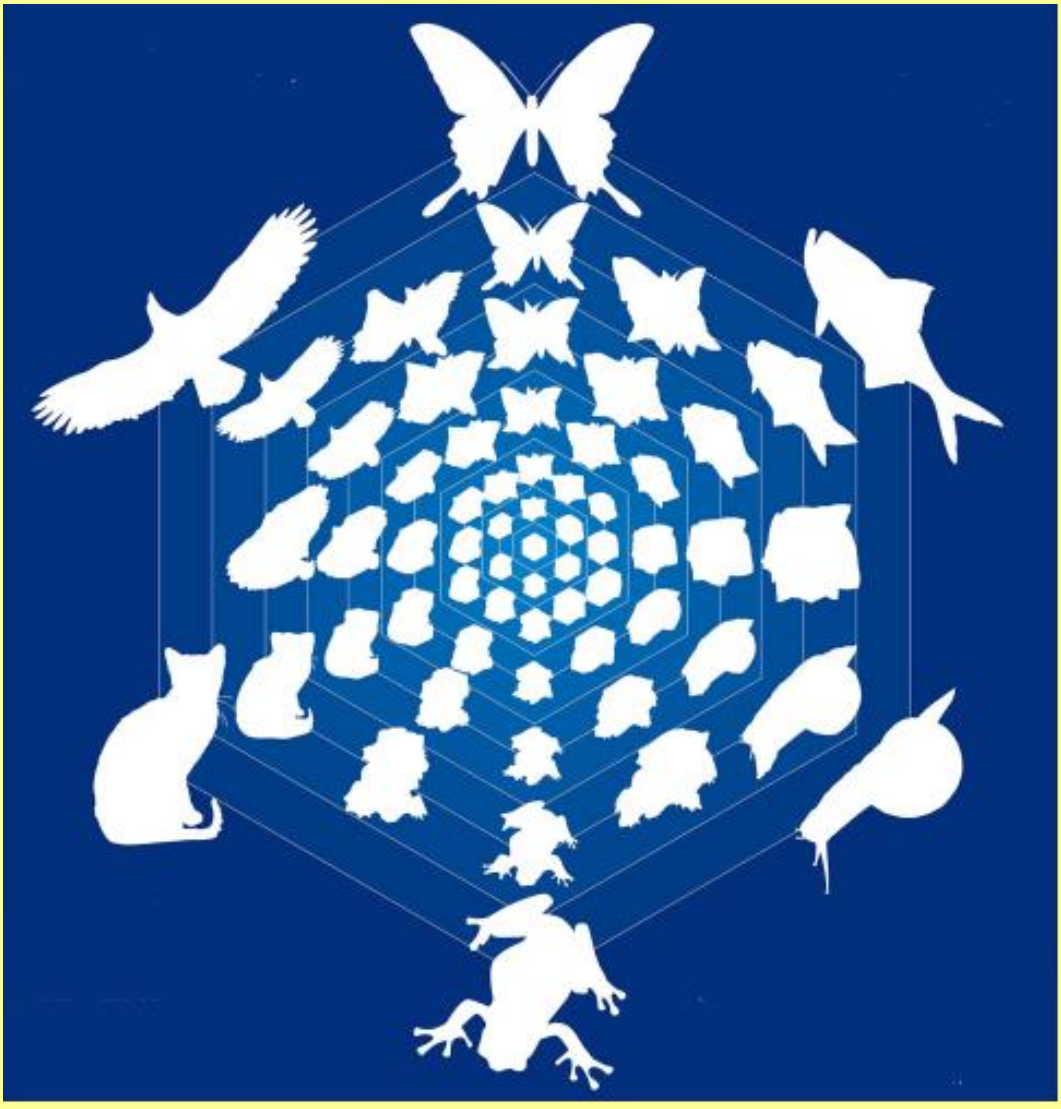
Report on UBI, 2016-2019
For the External Review in February, 2020



理学系研究科 生物普遍性研究機構

Universal Biology Institute

Graduate School of Science

The University of Tokyo

生物普遍性連携研究機構

Collaborative Research Organization for Universal Biology

The University of Tokyo

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Contents

1. UBI OVERVIEW

1.1 History

UBI, Universal Biology Institute (生物普遍性研究機構), was established in October 2016, in the Graduate School of Science at the University of Tokyo. UBI contracted with Quantitative Biology Center in Riken for cooperation agreement (October 2016). **Collaborative UBI** (Collaborative Research Organization for Universal Biology, 生物普遍性連携研究機構) has been established in December 2016 to advance collaboration and integrative studies between the Universal Biology Institute and the Research Center for Complex Systems Biology at the University of Tokyo.

2016 年 10 月　生物普遍性研究機構　(理学系研究科)　設立
2016 年 10 月　生物普遍性研究機構と理化学研究所生命システム研究センター（QBiC）
との間で連携協力協定を締結
2016 年 12 月　生物普遍性研究機構（理学系研究科）と複雑系生命システム研究センター
（総合文化研究科）との間で生物普遍性連携研究機構の設立

1.2　Directors (機構長)

Director of Collaborative UBI (生物普遍性連携研究機構) was Kunihiko Kaneko (金子邦彦 Dec 2016 ～ present).

Directors of Universal Biology (生物普遍性研究機構　理学系研究科) were Masaki Sano (佐野雅己 Oct 2016 ～Mar 2018) and Hideo Higuchi (樋口秀男 April 2018 ～present).

1.3 Research Objective

UBI performs theoretical and experimental researches to answer the fundamental question, " What is life ? ". UBI consists of five research groups to answer the question. (i) **Theoretical Group** uncovers universal characteristic in living systems taking advantage of dynamical systems theory and statistical physics. (ii) The goal of **Synthesis Group** is the construction of replicating cells in vitro. (iii) **Dynamics Reserch Group** aims to elucidate universal mechanisms in development and evolution in biological systems. (iv) **Measurement Group** develops a measurement system for single-molecule to single-cell level as well as imaging technique. (v) **Information Integration Group** develops information theory for thermodynamics and replicating system and also explores collective behavior of units with information processing.

(i) 理論部門

「生命とは何か」という根源的な問いに立ち向かうためには、「生きている状態」と「生きていない状態」の違いを解ることが必要になる。では、膨大な数の分子から構成される生物システムの何処を見れば、その生きているという状態を切り出せるであろうか？ゆらぎや環境変動に対する安定

性（ホメオスタシス）と、様々な状態間をダイナミックに辿ることができる可塑性の両立は、生物システムが持つ普遍的な性質であるが、それはどのようなメカニズムによって出現するのであろうか？実験技術の進展は、生物システムの様々な量を定量的に測ることを可能とし、またその機能を部分的に創りだしている。本部門では、そうした実験データを統合しつつ、生きている状態とその安定性・可塑性を記述する状態量を明らかにし、それに基づいた動的状態論の構築を目指している。

(ii) 構成部門

“What I cannot create, I do not understand” というファインマンの言葉があるが、「創る」ことは我々の理解を試す最も効果的な手段である。のみならず、生物のような複雑系の解析では、第一原理からの演繹的解析は多くの場合困難で、合成的解析(analysis-by-synthesis)すなわち「創って解析する」アプローチが有効である。また、地球上の生物という特殊例の解析から得られた結果の普遍性を検証するためには、「創る」ことが唯一の可能な手段であろう。この観点に立ち、本部門では、応用のためではなく、理解を深め・検証する方法論として、計測・理論など他部門と密接な連携の下に細胞機能・生命現象、さらには細胞それ自体の再構成を目指していく。

(iii) 動態部門

生物は多様な環境にさらされながら、代謝や集団化によって周りの環境を積極的に変えたり、別の環境へ移動したりと、時間と空間を自在に「辿り」ながら、複雑な生命システムとしての営みを発展させてきています。単細胞に見られる確率性と規則性が入り混じったような動き、変形、極性、分裂から、集団的な振る舞いへの自己組織的な遷移、発生に見られる３次元的な形態形成に至るまで、生物が示す階層を超えた時空間的な秩序形成には、分子や生物種を超えた共通のロジックが働いています。生物普遍性機構では、物理面と機能面の双方がいかなる形で相まって、細胞や多細胞組織のように複雑なシステムが形づくられてきたか、その背後にある共通の法則性を理解することを目指しています。理論、計測、構成、情報統計の４部門が普遍性機構の縦糸であるとすると、進化発生部門は他部門で培われた手法を総動員して発展させ、有機的に結び付ける横糸です。

(iv) 計測部門

近代生物学は、「測る」ことから始まったと言っても過言ではない。DNA やタンパク質の X 線回折像を元に構造を決定する際にも「距離や強度を測る」ことが基本となる。また、酵素の反応速度を測ることで、酵素機能を定量的に理解できた。近年進歩の著しい分子や細胞のイメージングの分野においても、光強度、色、距離を測ることからさまざまな分子機能・細胞機能が明らかとなる。現代においては、測ることがますます重要となっている。この観点に立ち、生物普遍性機構では、分子・細胞・個体を用いた高解像度測定や観察、大量のデータ解析、多種の量の測定、新しい測定法の開発の研究を行い、生命全体・細胞全体の構造や機能を定量的に理解することを目指している。

(v) 情報部門

物質、エネルギー、力、時間、空間は、物理学を構成する基本概念であるが、生命現象を理解する

ためには、これに情報の概念を加えることが不可欠である。生命はその起源において、情報を物質に蓄え、それを複製し、書き換える能力を獲得した。また、マクロレベルでも生物は自ら情報を選び取り、情報を生み出し、環境に働きかける。このように生命と情報のかかわりは、複数の階層に及んでいる。Maxwell の悪魔のパラドクスに代表される情報とエネルギーの関係、シグナル受容器の情報限界、走性メカニズムと適応、学習と予測、情報のシンボル化、脳と高次情報処理、生命の自発性・自主性など、生命現象のあらゆる階層において情報の意味と役割を明らかにすることは重要である。単なる物質の集まりからできた生命がどのようにして情報を獲得、生成し、ついには自分自身を考えることができるようになったのか、情報と物質やエネルギーの関係、情報と生命の協奏的な時空間発展、進化ダイナミクスとの関係、自発性獲得のメカニズム、それらに基づく新しい情報制御や学習アルゴリズムなどを研究することが本部門の目的である。

1.4 Organization

The structure of UBI was shown in Fig. 1.

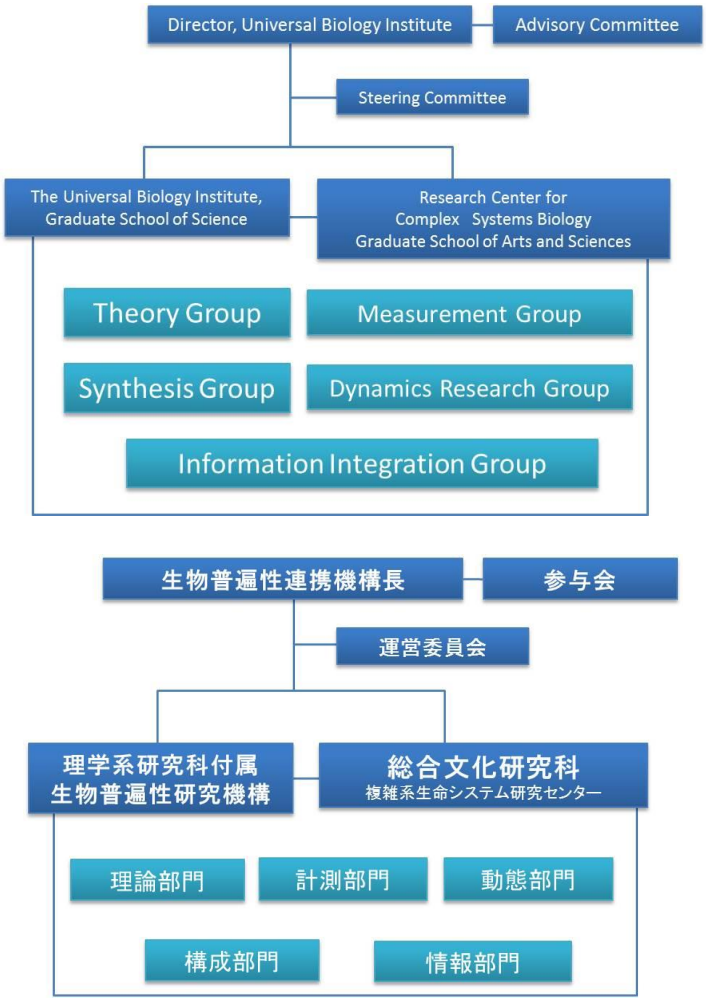


Fig.1. UBI organization structure (UBI 組織図)

1.5 UBI members

UBI members are constituted of the full-time (専任), concurrent (兼任) and associate (協力) members in the University of Tokyo (Table 1). The full-time members were Professor Chikara Furusawa (古澤 力 May 2016 ～ present), Associate Professor Shuji Ishihara (石原秀至、April 2017～April 2018), Lecturer Sousuke Ito (伊藤創祐 December 2018 ～ present), Assistant Professor Nen Saito (July 2016 ～present), and Assistant Professors, Saburo Tsuru (都留三良 April 2017～present), Tateno Michio (舘野道雄 September 2019～present) and Miki Umetani (梅谷実樹 July 2019～present). Research works of core members (full-time and concurrent members) were described in the next section, "Research Highlights".

UBI had visiting researchers from abroad and in Japan. They were Naoko Mitarai (Associate Professor, Niels Bohr Institute, Danish), Tsvi Tlusty (Professor, Institute for Basic Science, UNIST Korea), Nobuto Takeuchi (Associate Professor, University of Auck land, New Zealand) and Kyogo Kawaguchi (RIKEN Hakubi Fellow, Kobe, Japan). The visiting researchers stayed at UBI for typical lengths of 2 weeks through 2 months

Table 1. UBI members

部門 Groupes	名前 Name	所属 Affiliation Graduate School of	メンバー形態 Types of members
理論部門 Theory	古澤 力 Chikara Furusawa	理学系研究科 Science	専任 full-time
	伊藤創祐 Sosuke Ito	理学系研究科 Science	専任 full-time
	金子 邦彦 Kunihiko Kaneko	総合文化研究科 Art and Science	兼任 concurrent
	合原 一幸 Kazuyuki Aihara	生産技術研究所 Institue of Industrial Scinece	連携 associate
	池田 昌司 Atsushii Ikeda	総合文化研究科 Art and Science	兼任 concurrent
	石原 秀至 Shuji Ishihara	総合文化研究科 Art and Science	専任 concurrent
計測部門 Measurement	岡田 康志 Yasushi Okada	理学系研究科 Science	兼任 concurrent
	樋口 秀男 Hideo Higuchi	理学系研究科 Science	兼任 concurrent
	上田 泰己 Hiroki Ueda	医学系研究科 Medicine	連携 associate
	佐藤 守俊 Moritoshi Sato	総合文化研究科 Art and Science	兼任 concurrent
	若本 祐一 Yuich Wakamoto	総合文化研究科 Art and Science	兼任 concurrent
	船津 高志 Takashi Funatsu	薬学系研究科 Pharmaceutical Scineces	連携 associate

	矢島　潤一郎 Junichiro Yajima	総合文化研究科 Art and Science	兼任 concurrent
動態部門 Dynamic	武田　洋幸 Hiroyuki Takeda	理学系研究科 Science	兼任 concurrent
	入江　直樹 Naoki Irie	理学系研究科 Science	兼任 concurrent
	太田　邦史 Kunihiro Ohta	総合文化研究科 Art and Science	兼任 concurrent
	道上　達男 Tatsuo Michiue	総合文化研究科 Art and Science	兼任 concurrent
	澤井　哲 Satoshi Sawai	総合文化研究科 Art and Science	兼任 concurrent
構成部門 Synthesis	菅　裕明 Hiroaki Suga	理学系研究科 Science	兼任 concurrent
	野地　博行 Hiroyuki Noji	工学系研究科 Enginering	連携 associate
	北森武彦 Takehiko Kitamori	工学系研究科 Enginering	連携 associate
	豊田　太郎 Taro Toyota	総合文化研究科 Art and Science	兼任 concurrent
	竹内　昌治 Shouji Takeuchi	生産技術研究所　Institue of Industrial Scinece	連携 associate
	市橋　伯一 Norikazu Ichihashi	総合文化研究科 Art and Science	兼任 concurrent
	柳澤　実穂 Miho Yanagisawa	総合文化研究科 Art and Science	兼任 concurrent
情報部門 Inforation	黒田　真也 Shinya Kuroda	理学系研究科 Science	兼任 concurrent
	能瀬　聡直 Akinao Nose	新領域研究科 Frontier Sciences	連携 associate
	池上　高志 takashi Ikegami	総合文化研究科 Art and Science	兼任 concurrent
	福島　孝治 Koji Fukushima	総合文化研究科 Art and Science	兼任 concurrent
	小林　徹也 Tetsuya Kobayashi	生産技術研究所　Institue of Industrial Scinece	連携 associate

1.6 Steering Committee (運営委員会)

The decision of UBI is performed by steering committees of UBI and collabolative UBI. The committee approves the use of UBI budget, and personal affairs including appointments and disappointments of UBI members. Steering committees give advices about administration and directions of UBI. The current committee members are given in Table 2 and 3.

Table 2. Steering committees of collabolative UBI (生物普遍性連携機構)

名前 Name	所属 /職 affiliation/titile/position	任期 Term Fiscal year
武田 洋幸 Hiroyuki Takeda	理学系研究科長・教授 Dean, Graduate School of Science	2018-2019
太田 邦史 Kunihiro Ohta	総合文化研究科長・教授 Dean, Graduate School of Art and Science	2018-2019
金子 邦彦 Kunihiko Kaneko	生物普遍性連携研究機構長 総合文化研究科・教授 Director, Collaborative Research Organization for Universal Biology	2018-2019
樋口 秀男 Hideo Higuchi	生物普遍性研究機構長 理学系研究科 教授 Director, Universal Biology Institute	2018-2019
岡田 康志 Yasushi Okada	理学系研究科 教授 Professor, Graduate School of Science	2019-2020
澤井 哲 Satoshi Sawai	総合文化研究科・教授 Professor, Graduate School of Art and Science	2019-2020
合原 一幸 Kazuyuki Aihara	生産技術研究所・教授 Professor, Institue of Industrial Scinece	2018-2019

Table 3. Steering committees of UBI (生物普遍性機構)

名前 Name	所属 /職 affiliation/titile/position	任期 Term Fiscal year
金子 邦彦 Kunihiko Kaneko	生物普遍性連携研究機構長 総合文化研究科・教授 Director, Collaborative Research Organization for Universal Biology	2018-2019
樋口 秀男 Hideo Higuchi	生物普遍性研究機構長 理学系研究科・教授 Director, Universal Biology Institute	2018-2019
野地 博行 Hiroyuki Noji	工学系研究科 教授 Professor, Graduate School of Enginering	2018-2019
古澤 力 Chikara Furusawa	生物普遍性研究機構 教授 Professor, Universal Biology Institute	2019-2020
岡田 康志 Yasushi Okada	理学系研究科 教授 Professor, Graduate School of Science	2018-2019
黒田 真也 Shinya Kuroda	理学系研究科 教授 Professor, Graduate School of Science	2018-2019

2. Research Highlights

*Note: Detail reports of UBI members (Okada, Furusawa, Higuchi, Nose and Ito) in Department of Physics were attached at the end of this report and in the report of Department of physcis.

＊注：生物普遍性の物理専攻メンバー（岡田、古澤、樋口、能瀬、伊藤）に関しては、個別の報告書が本報告書の最後の章および物理学専攻の全体報告書にありますので詳細はそちらをご覧ください。

I: Theory Group

To answer the fundamental question, “What is life?”, we have uncovered universal characteristic in living systems.

I-A: Universal Laws and Macroscopic Theory [Kaneko and Furusawa]

A-i Universal Adaptation Law:

A macroscopic theory for cellular states with steady-growth is presented, based on consistency between cellular growth and molecular replication, as well as robustness of phenotypes against perturbations. First, global protein expression changes in {¥it Escherichia coli} after various environmental perturbations were shown to be proportional across components, across different types of environmental conditions. In general, adaptive changes in high-dimensional phenotypes are shown to be restricted so that global relationship across the changes in all components in a cell is uncovered both through adaptation and evolution.

・Kaneko, K., & Furusawa, C. Macroscopic theory for evolving biological systems akin to thermodynamics. Annual review of biophysics, 47, 273-290 (2018).

I-A-ii Evolutionary Dimension Reduction

We have proposed that dimension reduction from high-dimensional phenotypic states to a few degrees of freedom is achieved through evolution, which is essential to understand the universal proportionality law mentioned above. To examine if such dimension reduction is a result of evolution, we analyzed a cell model---with a huge number of components, that reproduces itself via a catalytic reaction network---and confirmed that common proportionality in the concentrations of all components is shaped through evolutionary processes. We found that the changes in concentration across all components in response to environmental and evolutionary changes are constrained to the changes along a one-dimensional major axis, within a huge-dimensional state space. On the basis of these observations, we propose a theory in which such constraint in phenotypic changes are achieved both by evolutionary robustness and plasticity and formulate this proposition in terms of dynamical systems. Accordingly, broad

experimental and numerical results on phenotypic changes caused by evolution and adaptation are coherently explained."

・Furusawa C & Kaneko K. Formation of Dominant Mode by Evolution in Biological Systems,Phys. Rev. E. 97(4), 042410 (2018)

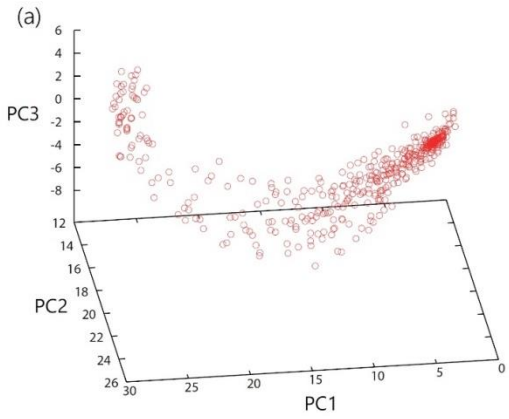


Fig.2 The change of chemical concentrations with environmental changes in principal-component space. Component concentrations at randomly chosen various environments are presented using an evolved reaction network. We found that the changes in concentration across all components in response to environmental and evolutionary changes are constrained to the changes along a one-dimensional major axis, within a huge-dimensional state space.

I-A-iii Transition from exponential-growth to stationary phases

Microorganisms generally go into the 'sleep phase' under starved condition. Theory for such transition is proposed as the breakdown of steady-growth. A general law between the starvation time and lag-time to recover the cellular growth is derived, as is consistent with experimental reports..

・Himeoka, Y., & Kaneko, K.. Theory for transitions between exponential and stationary phases: universal laws for lag time. Physical Review X, 7(2), 021049 (2017).

I-B: Origin of central dogma as a result of symmetry breaking:[Kaneko&Takeuchi]

Through simulations and theory of multi-level evolution, we demonstrated that the central dogma of molecular biology, i.e., separation of information and function is derived as a general consequence of symmetry breaking.

・Kaneko,K & Takeuchi, N. "The origin of the central dogma through conflicting multilevel selection" Proc. Roy. Soc. B, 286: 20191359. (2019)

I-C: Theory for Multicellular Development [Ishihara]

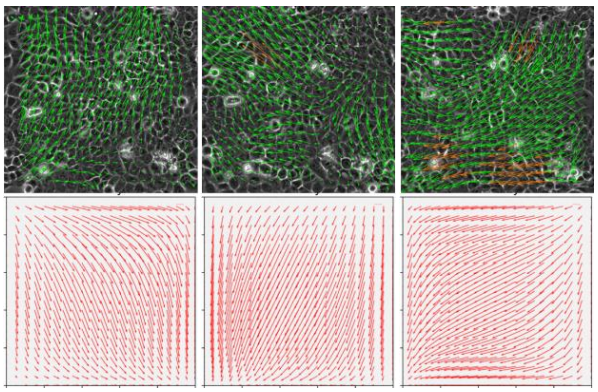
A continuum model of tissue mechanics was formulated using cellular-level mechanical ingredients and cell morphogenetic processes, including cellular shape changes and cellular rearrangements. This model incorporates stress and deformation tensors, which can be compared with experimental data. Focusing on the interplay between cell shape changes and cell rearrangements, we elucidated dynamical behavior underlying passive relaxation, active

contraction-elongation, and tissue shear flow, including a mechanism for contraction-elongation, whereby tissue flows perpendicularly to the axis of cell elongation. This study provides an integrated scheme for the understanding of the orchestration of morphogenetic processes in individual cells to achieve epithelial tissue morphogenesis.

・S.Ishihara, P. Marcq, K. Sugimura. From cells to tissue: A continuum model of epithelial mechanics. Phys. Rev. E 96, 022418 (2017).

・V. Nier, et al. Kalman inversion stress microscopy. Biophys. J. 115, 1808-1816 (2018).

Fig.3 Cultured HaCaT cells show oscillation in their collective migration. We developed a method to quantify internal stress in the cells, by which we performed correlation analysis among the velocity, stress, cell shape, and traction force. Mathematical model was derived based on the analysis to explain the onset of the oscillatory motion. (Top) Velocity field of the cell movement. (Bottom) Oscillating bahavior was reproduces by the mathematical model.



*Other studies include prediction of dynamical systems by randomly distributed embedding method [Aihara group]. Also, Kaneko published 'Universal Biology', the first book on this field (in Japanese).

II Synthesis Group

The ultimate goal is the construction of replicating cells in vitro. Toward the goal, the following research has developed by closely collaborating with the Measurement and Theory groups.

II-A: Coevolution of Cooperation in Synthesized Evolving System [Ichihashi]

Important characteristics in life is the evolvability. We have already established in-vitro evolving system containing several molecule species. To allow for further development of complexity during the early evolution of life, cooperation among independently replicating molecules is essential. Generally, this process is vulnerable to parasitic or selfish entities, which can easily appear and destroy such cooperation. How this fragile cooperation process appeared and was sustained during the evolution is one of the largest mysteries. Theoretical studies indicated that spatial structures, such as compartments, allow sustainable replication and the evolution of cooperative replication, although this has yet to be confirmed experimentally. In this study, we constructed a molecular cooperative replication system, in which two types of RNAs, encoding replication or metabolic enzymes, cooperate for their replication in compartments, and performed long-term replication experiments to examine the

sustainability and evolution of the RNAs. We demonstrated that the cooperative relationship of the two RNAs could be sustained at a certain range of RNA concentrations, even experiencing the appearance of parasites. Our results represent the first experimental evidence supporting the sustainability and robustness of molecular cooperation at the evolutionary timescale.

・Mizuuchi, R. and Ichihashi, N. Sustainable replication and coevolution of cooperative RNAs in an artificial cell-like system. Nat Ecol Evol. 2 (10), 1654-1660 (2018).

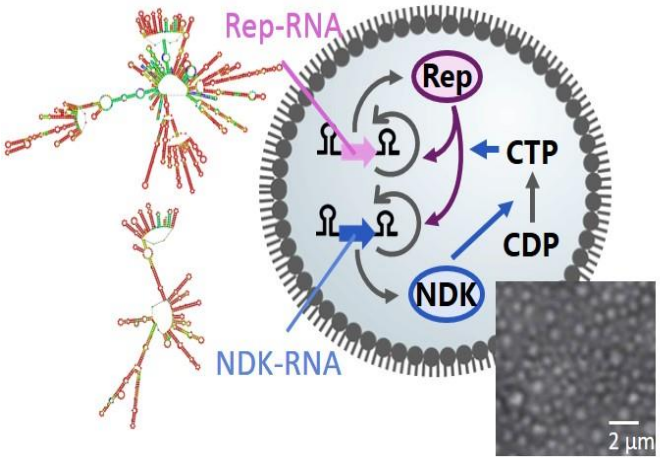


Fig. 4 Schematic representation of the translation- coupled cooperative RNA replication reaction. Rep-RNA encodes replicase, while NDK-RNA encodes nucleotide diphosphate kinase (NDK). Typical secondary structures are shown (centroid structure by Vienna RNA). The color of the structure represents the probability of base pairing (red: more probable, blue: less probable). Translated NDK catalyzes CDP to CTP conversion, producing a substrate for the RNA replication, and then the translated replicase replicates both RNAs. This system was encapsulated into microscale water-in-oil droplets. A microscopy image is shown.

II-B: Self-reproduction of supramolecular assemblies [Toyota]

Synthesis of self-reproducing self-assembly is a critical step towards the construction of chemical systems with autonomous, adaptive, and propagation properties. We have demonstrated that giant vesicles can grow and produce daughter vesicles by synthesizing and incorporating phospholipids in situ from ad-hoc precursors. Our model involves acyl chain elongation via copper(I)-catalyzed azide-alkyne [3 + 2] cycloaddition reaction or hydrolysis of amphiphilic precursors and the ensuing production of synthetic phospholipids to induce growth and division. In addition, the dynamics of giant vesicles were compatible with the encapsulation and transfer of macromolecules as large as DNA to the daughters. This chemical system provides a useful model towards the implementation of cell-like compartments capable of propagation and transport of biological materials.

・J. M. Castro, H. Sugiyama and T. Toyota. Budding and Division of Giant Vesicles Linked to Phospholipid Production. Scientific Reports, 9, 165 (2019).

・M. Matsuo, S. Ohyama, K. Sakurai, T. Toyota, K. Suzuki and T. Sugawara, A Sustainable Self-reproducing Liposome Consisting of a Synthetic Phospholipid. Chemistry and Physics of Lipids, 222, 1-7 (2019).

・M. Matsuo, Y. Kan, K. Kurihara, T. Jimbo, M. Imai, T. Toyota, Y. Hirata, K. Suzuki and T.

Sugawara, DNA Length-dependent Division of Giant Vesicle-based Model Protocell. Scientific Reports, 9, 6916 (2019).

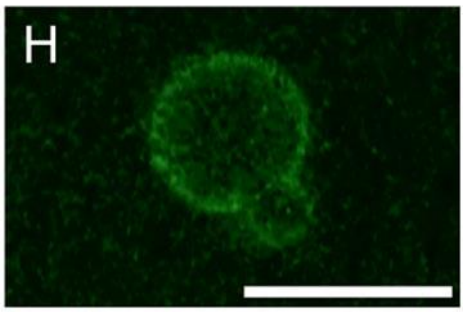


Fig.5 Localization and transport of lambda phage DNA molecules from a mature mother to its bud. Fluorescence micrographs of a GV and encapsulated DNA stained by SYBR Green I. The image was taken ca. 50 min after the mixing of a dispersion of DNA-containing immature mothers, a catalytic solution (copper (I) chloride, 10 mM; ascorbic acid, 20 mM; and deionized water) and reactive precursors LH (9 mM) and AH/Chol (9/1 mM) .Scale bar, 10 μm.

III Dynamics Research Group

Living organisms have evolved as complex systems capable of actively altering or tracking their surroundings in space and time. The Dynamics group aim to elucidate universal mechanisms in development and evolution in biological systems.

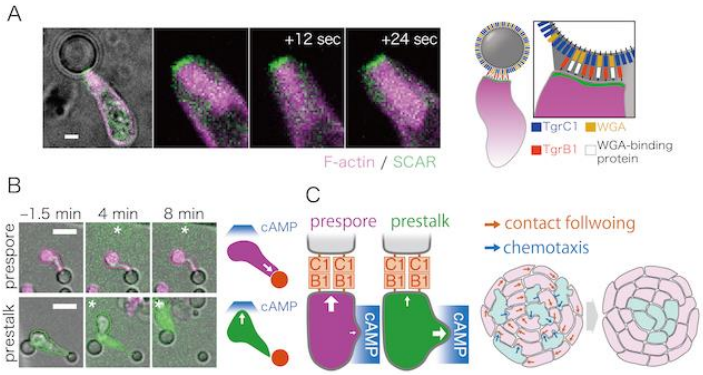
III-A Developmental process of a primitive multi-cellular system [Sawai]

A primordial example of tissue patterning by cell rearrangement is found in the social amoeba Dictyostelium discoideum where the organizing center or the “tip” self-organizes as a result of sorting of differentiating prestalk and prespore cells. By employing microfluidics and microsphere-based manipulation of navigational cues at the single-cell level, here we uncovered a previously overlooked mode of Dictyostelium cell migration that is strictly directed by cell–cell contact. The cell–cell contact signal is mediated by E-set Ig-like domain-containing heterophilic adhesion molecules TgrB1/TgrC1 that act in trans to induce plasma membrane recruitment of the SCAR complex and formation of dendritic actin networks, and the resulting cell protrusion competes with those induced by chemoattractant cAMP. Furthermore, we demonstrate that both prestalk and prespore cells can protrude toward the contact signal as well as to chemotaxis toward cAMP; however, when given both signals, prestalk cells orient toward the chemoattractant, whereas prespore cells choose the contact signal. These data suggest a model of cell sorting by competing juxtacrine and diffusive cues, each with potential to drive its own mode of collective cell migration.

・T Fujimori, A. Nakajima, N. Shimada & S. Sawai. Tissue self-organization based on collective cell migration by contact activation of locomotion and chemotaxis. Proc. Natl. Acad. Sci. USA, 116, 4291-4296 (2019)

Fig.5 Contact-mediated cell orientation in Dictyostelium. (A) Cis-acting transmembrane protein TgrB1 and TgrC1 interaction induces prolonged activation of SCAR/WAVE and actin

polymerization. (B) The resulting contact-dependent cell orientation is overridden by chemotaxis in prestalk cells but not in prespore cells. (C) A new model of how cell segregation takes place by cell-type specific preference of guidance cues. Prestalk are guided by diffusive chemoattractant and prespore by cell-cell contact.

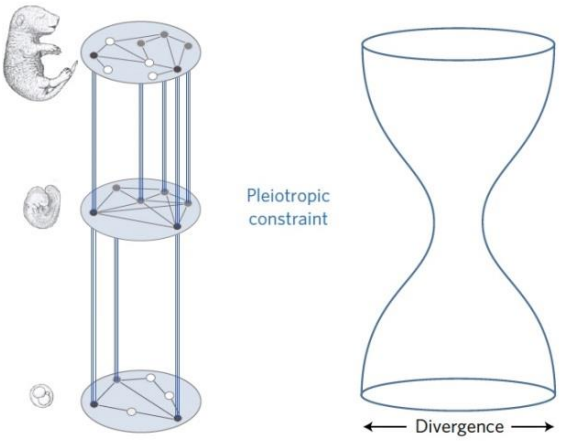


III-B Evolution

III-B-i Evolution-development relationship [Irie]

Developmental hourglass as in the figure is one of the key topics in the evolution-development. To understand it, we have focused on re-usage of genes into different biological processes. The re-usage is known to contribute to the evolution of novel phenotypes, whereas some argued that this kind of re-usage of genes in turn could lead to constrained status, or less evolvability. Here we, for the first time, obtained empirical evidences to support this double-edged sword aspect of gene recruitments. By analyzing developmental transcriptome of 8 animal (chordate) species, we found that developmental stages with more pleiotropic (genes expressed in variety of tissues and developmental stages) correlates with evolutionary conservation. This could explain why basic anatomical features such as bodyplan is highly conservative throughout evolution, because the body plan emerges during the conserved mid-embryonic stages, and the mid-embryonic stages had more pleiotropic genes than other stages. As far as we know, this is one of the few empirical evidences to support the classical notion; "more complex organisms are less evolvable".

・H. Hu, et al. (N. Irie at the last corresponding author). Constrained vertebrate evolution by pleiotropic genes. Nature Ecology & Evolution,1, 1722–1730 (2017).



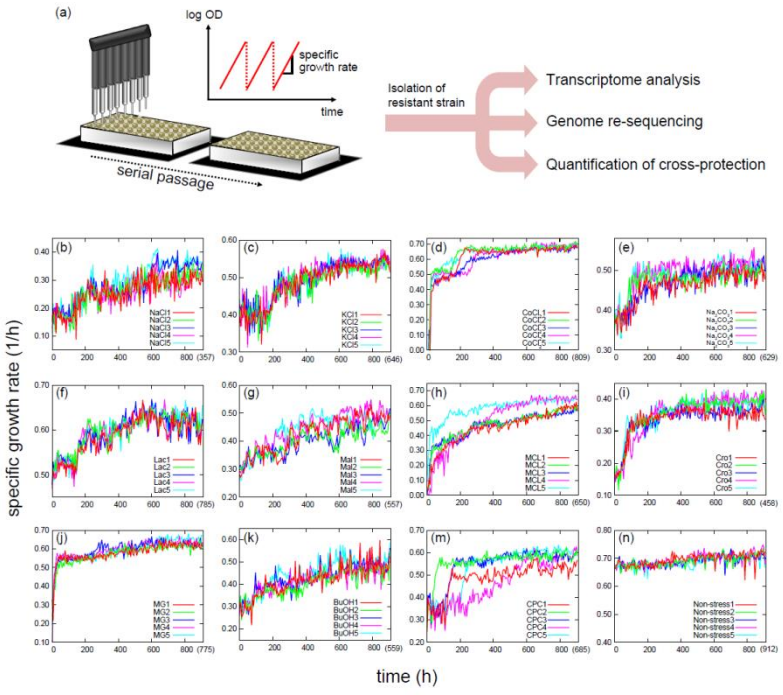
・Y. Uchida, M. Uesaka, T. Yamamoto, H. Takeda and N. Irie.Embryonic lethality is not sufficient to explain hourglass-like conservation of vertebrate embryos. EvoDevo 9:7 (2018)

Fig.6 Potential contribution of hourglass-like conservation of vertebrate mid-embryos by pleiotropic constraints. Vertebrate mid-embryonic molecular components are highly pleiotropic (grey and black circles) and

are shared (blue vertical line) by other developmental process. This 'chained' status makes it difficult for pleiotropic genes to change even at the gene regulation level, leading to conservation of a mid-embryonic developmental system that is largely composed of pleiotropic genes.

III-B-ii Bacterial evolution to environmental stresses [Furusawa]

In adaptive evolution, an increase in fitness to an environment is frequently accompanied by changes in fitness to other environmental conditions, called cross-resistance and sensitivity. Although the networks between fitness changes affect the course of evolution substantially, the mechanisms underlying such fitness changes are yet to be fully elucidated. Herein, we performed high-throughput laboratory evolution of *Escherichia coli* under various stress conditions using an automated culture system and quantified how the acquisition of resistance to one stressor alters the resistance to other stressors. We demonstrated that resistance changes could be quantitatively predicted based on changes in the transcriptome of the resistant strains. The integration of transcriptome and genome data enabled us to clarify the bacterial stress resistance mechanisms and evolutionary constraints on stress resistant evolution.



・T. Horinouchi, S. Suzuki, H. Kotani, K. Tanabe, N. Sakata, H. Shimizu, C. Furusawa. Prediction of Cross-resistance and Collateral Sensitivity by Gene Expression profiles and Genomic Mutations. Sci. Rep., 7, 14009 (2017)

Fig. 7 Laboratory evolution under environmental stress. *E. coli* cells were cultured under 11 stress conditions by using the automated culture system. Selected clones from adapted populations were sequenced, and transcriptional profiles were quantified to analyze phenotype-genotype relationships.

III-C Experiments to accelerate evolution

III-C-i Ultraviolet (UV) mutagenesis [Furusawa and Tsuru]

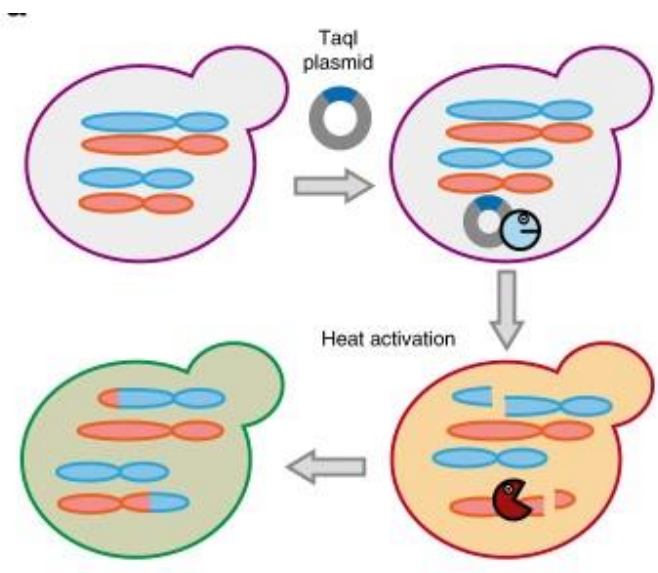
UV mutagenesis is a widely used technique to increase bacterial mutation rates in laboratory experiments. We constructed an automated UV irradiation device for microbial cell culture and demonstrated that this growth feedback control avoided extinction and enabled accumulation of mutations in bacterial genomes at a rapid rate for a long period. Whole-genome sequencing revealed the high accumulation rate, neutrality, and spectrum of UV-induced mutations. These results indicate that our automated device is useful in accelerating mutation accumulation over a long duration.

・A. Shibai, Y. Takahashi, Y. Ishizawa, D. Motooka, S. Nakamura, B.W. Ying, S. Tsuru. Mutation accumulation under UV radiation in Escherichia coli. Scientific Reports, 7, 14531, 1-12 (2017).

・A. Shibai, S. Tsuru, T. Yomo. Development of an automated UV irradiation device for microbial cell culture, SLAS Technology, 24(3), 342-348 (2018)

III-C-ii Taqing system to accelerate evolution [Ohta]

DNA double-strand break (DSB)-mediated genome rearrangements are assumed to provide diverse raw genetic materials enabling accelerated adaptive evolution; however, it remains unclear about the consequences of massive simultaneous DSB formation in cells and their resulting phenotypic impact. Here, we establish an artificial genome-restructuring technology by conditionally introducing multiple genomic DSBs in vivo using a temperature-dependent endonuclease TaqI. Application in yeast and Arabidopsis thaliana generates strains with phenotypes, including improved ethanol production from xylose at higher temperature and increased plant biomass, that are stably inherited to offspring after multiple passages. High-throughput genome resequencing revealed that these strains harbor diverse rearrangements, including copy number variations, translocations in retrotransposons, and direct end-joinings at TaqI-cleavage sites. Furthermore, large-scale rearrangements occur frequently in diploid yeasts (28.1%) and tetraploid plants (46.3%), whereas haploid yeasts and diploid plants undergo minimal rearrangement. This genome-restructuring system (TAQing system) will enable rapid genome breeding and aid genome-evolution studies.



・Muramoto N, Oda A, Tanaka H, Nakamura T, Kugou K, Suda K, Kobayashi A4, Yoneda S, Ikeuchi A, Sugimoto H, Kondo S, Ohto C, Shibata T, Mitsukawa N, Ohta K.Phenotypic diversification by enhanced genome

restructuring after induction of multiple DNA double-strand breaks. Nat Commun. 18;9(1):1995(2018)

Fig.8 Schematic diagram of the TAQing system. A TaqI-expression vector was introduced into yeast cells, followed by transient heat activation of TaqI (inactive, blue circle; active, red circle) to generate DSBs in vivo. Red and blue ovals represent homologous chromosomes.

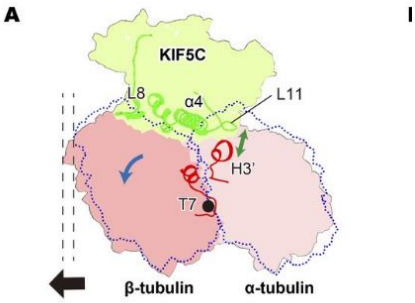
IV Measurement Group

By developing a measurement system from single-molecule to single-cell level, as well as imaging technique, we have uncovered universal characteristics therein that also contribute to biological functions.

IV-A: Molecular-level (Molecular Machine)

IV-A-i Kinesin-binding-triggered conformation switching of microtubules for polarized transport [Okada]

Kinesin-1, the founding member of the kinesin superfamily of proteins, is known to use only a subset of microtubules for transport in living cells. This biased use of microtubules is proposed as the guidance cue for polarized transport in neurons, but the underlying mechanisms are still poorly understood. Here, we report that kinesin-1 binding changes the microtubule lattice and promotes further kinesin-1 binding. This high-affinity state requires the binding of kinesin-1 in the nucleotide-free state. Microtubules return to the initial low-affinity state by washing out the binding kinesin-1 or by the binding of non-hydrolyzable ATP analogue AMPPNP to kinesin-1. X-ray fiber diffraction, fluorescence speckle microscopy, and second-harmonic generation microscopy, as well as cryo-EM, collectively demonstrated that the binding of nucleotide-free kinesin-1 to GDP microtubules changes the conformation of the GDP microtubule to a conformation resembling the GTP microtubule.



・Shima T, Morikawa M, Kaneshiro J, Kambara T, Kamimura S, Yagi T, Iwamoto H, Uemura S, Shigematsu H, Shirouzu M, Ichimura T, Watanabe TM, Nitta R, Okada Y, Hirokawa N. Kinesin-binding-triggered conformation switching of microtubules contributes to polarized transport. J Cell Biol. 217:4164-4183, 2018

Fig.9 Schematic model of the conformational changes in the

microtubule triggerd by kinesin-binding. The binding of KIF5C to ß-tubulin will push this subunit to rotate around the T7 loop, leading to the elongation of the axial pitch (top, blue and black arrows). The lattice structure of the microtubule will restrict the conformation and the arrangement of tubulin subunits so that the conformational changes of the microtubule will take place in a cooperative manner (bottom). The conformational changes of the microtubule will be recognized by the interaction between kinesin's L11-α4 junction and the H3′ helix of α-tubulin (top, green arrow).

A-ii Unified Walking Model for Dimeric Motor Proteins [Higuchi]

Dimeric motor proteins, kinesin-1, cytoplasmic dynein-1, and myosin-V, move stepwise along microtubules and actin filaments with a regular step size. The motors take backward as well as forward steps. The step ratio r and dwell time t, which are the ratio of the number of backward steps to the number of forward steps and the time between consecutive steps, respectively, were observed to change with the load. To understand the movement of motor proteins, we constructed a unified and simple mathematical model to explain the load dependencies of r and of t measured for the above three types of motors quantitatively. Our model consists of three states, and the forward and backward steps are represented by the cycles of transitions visiting different pairs of states among the three, implying that a backward step is not the reversal of a forward step. Each of r and t is given by a simple expression containing two exponential functions. We reanalyze the data to obtain r and t of native dynein to make up the insufficient data to fit them to the model. Our model successfully describes the behavior of r and t for all of the motors in a wide range of loads from large assisting loads to superstall loads.

• K. Sasaki, M. Kaya, and H. Higuchi. A unified walking model for dimeric motor proteins Biophys. J.115, 1-12 (2018.11)

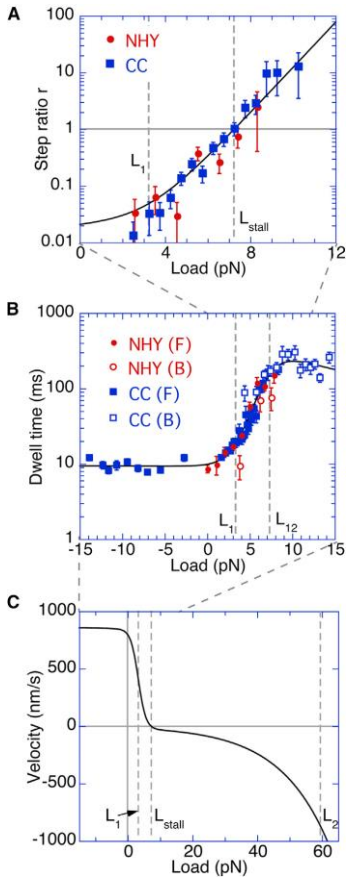


Fig.10 Dependencies of the (A) step ratio r, (B) dwell time t, and (C) velocity v on the load L for kinesin. The experimental data (symbols) were compared with the theory (solid lines)

*Other studies include discovery and analysis of Tetrahon, novel type of mobile element was isolated from the genome of medaka fish [Yajima group] and live-cell single-molecule imaging of the cytokine receptor MPL [Funatsu group].

IV-B: Cell-level [Wakamoto]

IV-B-i Single-cell measurement on cell growth-division process: (in partial collaboration with Theory group)

Cellular populations in both nature and the laboratory are composed of phenotypically heterogeneous individuals that compete with each other resulting in complex population dynamics. Predicting population growth characteristics based on knowledge of heterogeneous single-cell dynamics remains challenging. By observing groups of cells for hundreds of generations at single-cell resolution, we reveal that growth noise causes clonal populations of Escherichia coli to double faster than the mean doubling time of their constituent single cells across a broad set of balanced-growth conditions. We show that the population-level growth rate gain as well as age structures of populations and of cell lineages in competition are predictable. Furthermore, we theoretically reveal that the growth rate gain can be linked with the relative entropy of lineage generation time distributions. Unexpectedly, we find an empirical linear relation between the means and the variances of generation times across conditions, which provides a general constraint on maximal growth rates. Together, these results demonstrate a fundamental benefit of noise for population growth, and identify a growth law that sets a "speed limit" for proliferation.

・M. Hashimoto, T. Nozoe, H. Nakaoka, R. Okura, S. Akiyoshi, K. Kaneko, E. Kussell, Y. Wakamoto, Noise-driven growth rate gain in clonal cellular populations. PNAS 113, 3251-3256 (2016).

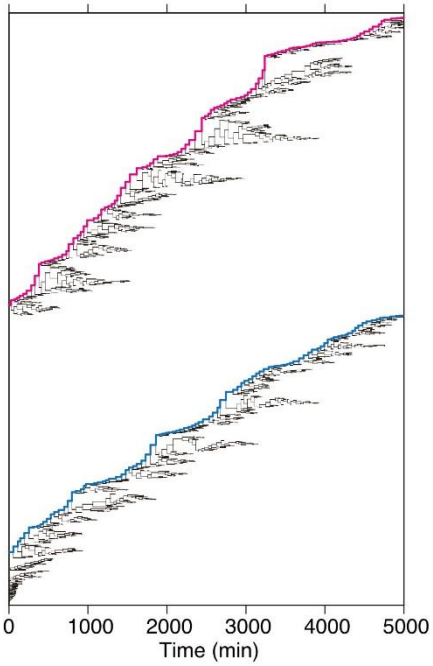


Fig.11 Single-cell lineage trees for E. coli growing in a constant environment. E. coli cells were cultured in a custom microfluidic device, dynamics cytometer, for 5000 min under the constant flow of a culture medium. The bifurcation indicates cell division, and the endpoints the flow-out of the cells from the observation channel in the device. The magenta and cyan lines show the single-cell lineages that lasted in the observation channel throughout the observation.

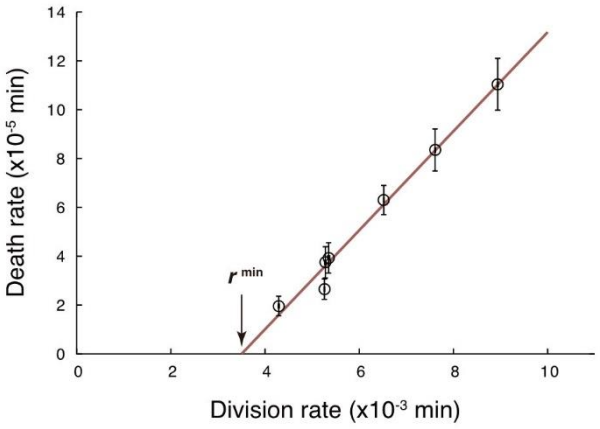
IV-B-ii Trade-off between aging and growth

Replicative aging has been demonstrated in asymmetrically dividing unicellular organisms, seemingly caused by unequal damage partitioning. Although asymmetric segregation and inheritance of potential aging factors also occur in symmetrically dividing species, it nevertheless remains controversial whether this results in aging. Based on large-scale single-cell lineage data obtained by time-lapse microscopy with a microfluidic device, in this

report, we demonstrate the absence of replicative aging in old-pole cell lineages of Schizosaccharomyces pombe cultured under constant favorable conditions. By monitoring more than 1,500 cell lineages in 7 different culture conditions, we showed that both cell division and death rates are remarkably constant for at least 50–80 generations. Our measurements revealed that the death rate per cellular generation increases with the division rate, pointing to a physiological trade-off with fast growth under balanced growth conditions.

・H. Nakaoka, Y. Wakamoto, Aging, mortality, and the fast growth trade-off of Schizosaccharomyces pombe. PLoS Biology 15, e2001109 (2017).

Fig.12 The linear relationship between division rate and death rate of S. pombe under several steady growth conditions. S. pombe cells were cultured in a microfluidic device, mother machine, and we quantified the division rate and the death rate in each condition. The red line is the linear regression for the relation. The positive x-intercept, r^(min), indicates the division rate below which the death rate becomes zero.



IV-B-iii Raman spectroscopy to characterize cellular states

Raman microscopy is an imaging technique that has been applied to assess molecular compositions of living cells to characterize cell types and states. However, owing to the diverse molecular species in cells and challenges of assigning peaks to specific molecules, it has not been clear how to interpret cellular Raman spectra. Here, we provide firm evidence that cellular Raman spectra and transcriptomic profiles of Schizosaccharomyces pombe and Escherichia coli can be computationally connected and thus interpreted. We find that the dimensions of high-dimensional Raman spectra and transcriptomes measured by RNA sequencing can be reduced and connected linearly through a shared low-dimensional subspace. Accordingly, we were able to predict global gene expression profiles by applying the calculated transformation matrix to Raman spectra, and vice versa. Highly expressed non-coding RNAs contributed to the Raman-transcriptome linear correspondence more significantly than mRNAs in S. pombe. This demonstration of correspondence between cellular Raman spectra and transcriptomes is a promising step toward establishing spectroscopic live-cell omics studies.

・K. J. Kobayashi-Kirschvink, H. Nakaoka, A. Oda, K. F. Kamei, K. Nosho, H. Fukushima, Y. Kanesaki, S. Yajima, H. Masaki, K. Ohta, Y. Wakamoto, Linear Regression Links Transcriptomic Data and Cellular Raman Spectra. Cell Systems 7, 104-117.E4 (2018).

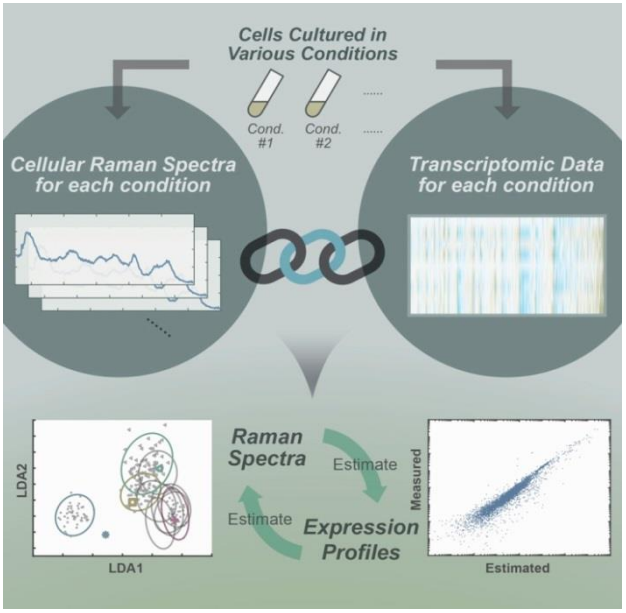


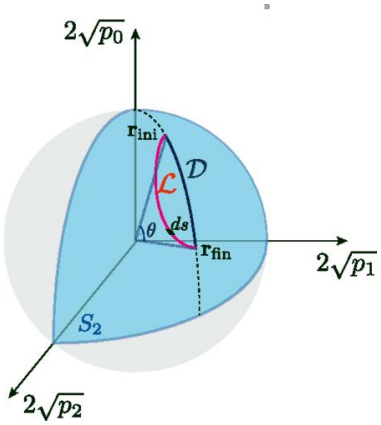
Fig. 13. characterization of cellular states

V. Information Integration Group

Information is essential to biological systems. To aim at understanding information process in biology, we developed information theory for thermodynamics and replicating system. Furthermoe, by considering the interacting units with processing information, we study the collective behaviors of active agents.

V-A Information geometry for thermodynamics [Ito]

We have discussed several relationships between thermodynamics and information theory, which are applicable to information processing in biological systems. Especially, we have studied relationships between thermodynamics and information geometry, to understand trade-off relationships between thermodynamic cost and the accuracy of biological systems. These trade-off relationships are called as thermodynamic uncertainty relationships (TURs), which are classical thermodynamic generalizations of the uncertainty relationship in quantum mechanics. We illustrate these trade-off relationships by using the enzyme reaction and autocatalytic reaction. We have also derived a generalization of the second law of thermodynamics with information theory based on the projection theorem in information geometry, and a generalization of the Glansdorff-Prigogine criterion for stability. These results reveal deep connections between thermodynamics and geometry.



・S. Ito ”Stochastic thermodynamic interpretation of information geometry" Physical Review Letters 121, 030605 (2018).

Fig.14 Schematic of the statistical manifold in information geometry. To consider the geodesic length D, the square of line element ds^2, and the length L, we have obtained the trade-off relationship between thermodynamic cost and the speed of the transition in biochemical reaction, such as the enzyme reaction.

V-B Information Theory for a system with replication and evolution[Kobayashi]

Based on the experimental result by Wakamoto's group, we have derived and developed information-theoretic reformulation of evolutionary processes by using pathwise formulation. From this approach, we have obtained fluctuation relations for fitness of a phenotypically heterogeneous population in a stochastically changing environment. We also developed methods to analyze cellular lineages obtained by long-term tracking experiments of microbial growth. We have also made information-theoretic approach to immunology, including the proposal of reinforcement learning framework for T cells.

・Y. Sughiyama, and T. J. Kobayashi. Fitness response relation of a multitype age-structured population dynamics. Phys. Rev. E, 99, 012413 (2019)

V-C Collective behavior of active units

V-C-i collective dynamics of active agents [Ikegami]

We explored the possibility of large-scale Alife models. In particular, taking the example from Cohen's LIFE and from Craig's boid model, we search for the emergent phenomena in large scales. By simulating the swarm size up to 500,000 agents by utilizing the GPGPU technique, a qualitative change in swarm formation was found in larger swarms. The concept of top-down causation will be discussed based on these simulation results.

・T. Ikegami et al.,: Life as an emergent phenomenon: studies from a large-scale boid simulation and web data, Phil.Roy.Soc.,375, pp.1-15, 2017

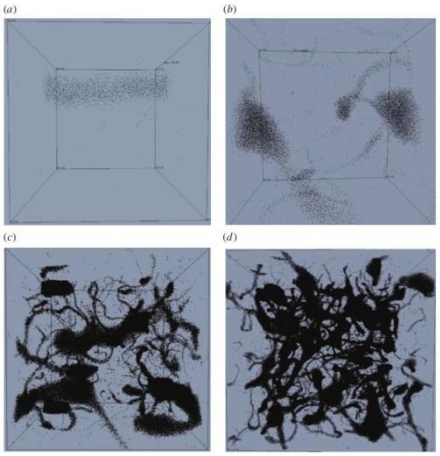


Fig. 15 Large-scal boid simulation

V-C-ii Collective dynamics in neural progenitor cell cultures [Sano and Kawaguchi]

We reported on the collective dynamics of cultured murine neural progenitor cells (NPCs or neural stem cells) that give rise to cells in the central nervous system. At low densities, NPCs moved randomly in an amoeba-like fashion. However, NPCs at high density elongated and aligned their shapes with one another, gliding at relatively high velocities. Although the direction of motion of individual cells reversed stochastically along the axes of alignment, the cells were capable of forming an aligned pattern up to length scales similar to that of the migratory stream observed in the adult brain. The two-dimensional order of alignment within the culture showed a liquid-crystalline pattern containing interspersed topological defects with winding numbers of +1/2 and−1/2 (half-integer due to the nematic feature that arises from the

head–tail symmetry of cell-to-cell interaction). We identified rapid cell accumulation at +1/2 defects and the formation of threedimensional mounds. We propose a generic mechanism for the instability in cell density around the defects based on the active matter model.

"Kyogo Kawaguchi, Ryoichiro Kageyama, Masaki Sano, Topological defects control, Nature 545, 327-331 (2017).

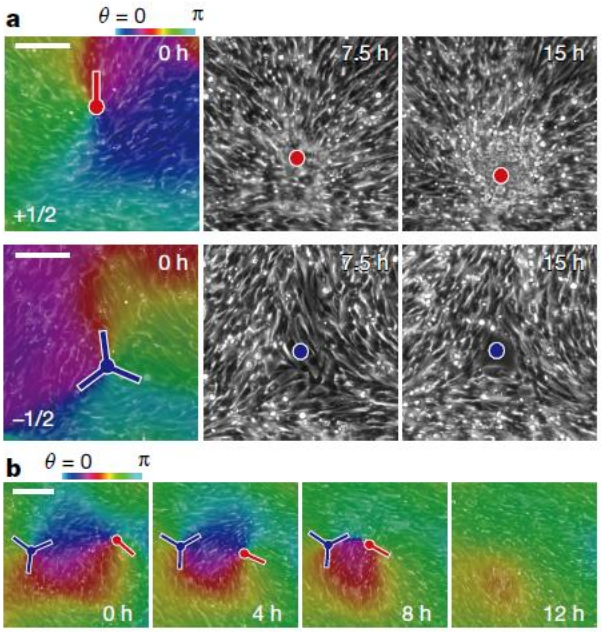


Fig. 16. Collective dynamics of neural progenitor cell.

*Other studies include small-volume effect for information processing in spine [Kuroda group] and regulation of locomotion through feedback circuits in Drosophila larvae [Nose group].

3 UBI Activities and Future plan

3.1 Annual activities

Speakers are invited for the UBI-seminar (Number of UBI-seminar: 6 times in 2016 fiscal year, 8 times in 2017, 18 times in 2018, 12 times in April-Nov. 2019). About half of seminars (21 times out of 44) were presented in English by speakers from abroad. UBI also had Internal research seminar in which two young speakers presented their recent works every month. In May, Joint symposium between biophysics course in department of physics and UBI is held for students and young scientists. In August, UBI members have lectures for junior and senior high school students at Open Campus.

3.2 International meetings

UBI had International meetings including workshop and symposium. International Symposium on Universal Biology was held in November 2016 at The University of Tokyo. LMU (Germany)-UBI Joint Workshop on Statistical and Biological Physics was held in October 2018 at The University of Tokyo. 1st and 2nd Joint Symposium between Mechanobiology (National University of Singapore) and UBI were held in April 2018 and September 2019 at National University of Singapore and The University of Tokyo, respectively. Joint UBI-NanoLSI (Kanazawa University) workshop, Trends in Molecular Biophysics of Living Cells, was held in November 2019 at Kanazawa University.

3.3 Special education for freshman and sophomore (学部 1，2 年生に対する全学体験ゼミ)

UBI prepared special experience curriculum for freshman and sophomore. About 20 students took the curriculum every semester. Each student belongs to one of the laboratories in UBI members (one or two students in each lab.) and performed basic research works. Some students continued the works and presented their works at internal and international academic conferences. A few students published the original papers. Especially, senior student, Yamagishi, who published one paper and submitted another during the undergraduate student, won the highest award among The University of Tokyo President's awards (only one student wins this award every year).

3.4 Budget

UBI is run basically on the University budget. The University budgets were 55 (2016), 55 (2017), 58 (2018) and 59 (2019) million yen. Full time members (専任教員) have acquired external funds; 10 (2017), 27 (2018) and 62 (2019) million yen. (1 million yen ≒ 9 thousands US dollar)

3.5 Future plan

3.5.1 Future plan of research works

Elucidating the underlying mechanisms universal to all living organisms is one of the ultimate purposes of biological research. By further developing measurement tools, machine learning, we aim at establishing a research field to understand universal features in life, together with developing a theory under the spirit of physics. For it we gather scientists in university of field across broad disciplines. We keep five groups we have set up. The research plan for each group is presented below, whereas we expand tight collaboration among the groups.

Theory Group

We have uncovered some universal statistical laws on adaptation and evolution, suggesting that robust biological systems that include a huge number of components are described by few macroscopic variables. With collaboration with experimental groups, we identify how such dimension reduction is shaped through evolution. Then we intend to explore the possibility of macroscopic description a la thermodynamics in physics. By also resorting to single-cell measurement developed by Wakamoto's group, we intend to extract 'equation of state' of a cell, described by few degrees of freedom such as growth-rate, activity, and so forth. With such macroscopic potential theory, we describe robustness and plasticity in biological systems quantitatively, and how robustness (to noise and environmental changes) and plasticity (dynamic transferability between various states) are compatible in biological systems. We explore a theory for multicellular system, to characterize development that involves both chemical and mechanical interactions. Equations to govern multi-cellular development will be formulated in collaboration with Dynamics group.

Synthesis Group

The analysis-by-synthesis approach (i.e., synthesize an entity first, and then analyze) is an effective strategy for studying complex systems such as living organisms, because deductive analysis of such a system from first principles is often difficult. The ultimate goal of the group is the synthesis of replicating cells that can evolve. For it, we aim at (1) construction of vesicle that grow and divide (2) in-vitro and in-vesicle reaction systems of multiple components that include metabolism and synthesis of enzymes and DNA, and membrane (3) understanding physics of chemistry of intracellular processes that sustain themselves and (4) reconstruction of cellular functions and biological phenomena,. In collaboration with Theory group and Measurement group, we unveil universal characteristics that minimal cells have to satisfy.

Dynamics Group

Living organisms are complex with hierarchy in space and time. Cells form a community by secreting metabolites whereas they move to form a multicellular organism. The Dynamics group aim to elucidate the physical and evolutionary mechanisms by which such complex dynamics in cells and multicellular tissues are formed. Through detailed quantitative analysis

and modeling of basic spatiotemporal dynamics in movement, deformation, polarization, and division of a single cell and tissues in addition to genome-wide comparisons, the group will explore common logics across the seemingly diverse type of molecule or species of organism, in collaboration with all other groups. This will also uncover reversibility/irreversibility in the differentiation from pluripotent stem cells. Next, in collaboration with Theory group, universal laws in phenotypic evolution will be explored, which describe constraint and direction in evolution.

Measurement Group

We seek to quantitatively understand the structures and functions of cells and life. We will develop high-resolution high-throughput measurement of molecular and cellular processes, and whole organisms, with developing novel techniques based on physics. Then, reduction techniques from high-dimensional data will be developed together with Theory and Information groups, by taking advantage of machine learning, statistical physics and information theory. We will uncover how biological adaptation and function are represented in high-dimensional cellular states.

Information

Matter, energy, force, space, and time are the fundamental constituent concepts of physics. In order to understand life, however, it is imperative to add the concept of information. We will formulate non-equilibrium thermodynamics in terms of information and apply the information thermodynamics to biological processes such as signaling, axis and adaptation. Learning and evolution are formulated in terms of information. Together with Theory and Synthesis groups, we also study the origin of information needed for life system, i.e., by investigating how life, a mere aggregation of matter, acquires and generates information. The study of the group will also cover 1) relationship between information and matter/energy; 2) concerted spatio-temporal dynamics of information and life; 3) relationship between information and evolution dynamics; 4) the origin of biological autonomy and self-reference. The studies of the group will allow for development of new information control techniques and learning algorithms.

3.5.2 Future plan of UBI organization.

Full-time members (専任教員)

UBI has three full-time PI and two assistant professors in 2016-2018 and two PI and four assistant professors in 2019. To strengthen the research work and organization of UBI, UBI plan to acquire PI position(s) who studies the boundary field of biology and theoretical biophysics.

Collaboration beyond the research field

To explore the universal biology as the new field, collaboration and discussion beyond the

research areas is crucial. The discussion and collaboration between UBI members were fruitful to explore the new field, because UBI members were graduated from many departments, physics, biology, biochemistry, chemistry, medicine and engineering. Actually, some papers described in Research Highlight were performed by the collaborations between different fields. UBI plan to encourage the collaboration and discussion with the new institute for Physics of Intelligence（知の物理学）and International Research Center for Neurointelligence in the University of Tokyo by promoting seminar and workshop.

Internationalization

The aim of UBI is to form the core of excellence to lead the worldwide works of universal biology that uncover the common and universal mechanism between living things. To reach the aim, it is important to cultivate the universal biology assiduously collaborated and discussed with researchers in top institutes in the world. UBI has a plan to cooperate with the top institutes (Institute for Advanced Study, Princeton University, USA; Institute for Universal Biology, University of Illinois at Urbana-Champaign USA; Curie Institute, France; Niels Bohr Institute, Demark; Mechanobiology Institute, National University of Singapore, Singapore). UBI members have collaborated with the researchers in the top institutes. In this plan, UBI prepares one-position for ～4 visiting professors who stay at UBI each quarter year. The visiting professors discuss and collaborate with UBI member's groups. In the other plan, UBI apply the budget from Core-to-Core Program in Japan Society for the Promotion of Science that promotes the international research works. UBI exchange students, young scientists and PIs between the institutes participating in the Core-to-Core Program.

Education

The integrated education system from freshmen in undergraduate course to students in graduate program was created by the collaboration between research groups in Komaba and Hongo Campuses. In the integrated education, students learn how to understand biological phenomenon from the viewpoint of mathematics and physics. To encourage the students in learning the universal biology, UBI plan to give the certification of completing Universal Biology program of to the students who finish the several courses related to the universal biology. UBI also plan to have a basic research seminar targeting undergraduate and master students.

4. List of Achievements

4.1 Honors, Awards and Professional Society Memberships

4.1.1 Principal Investigators

1. 竹内昌治.　UNESCO Netexplo Award winner 2019　(2019).
2. 柳澤実穂. 細胞モデルを用いたミクロな相転移現象の解明とミクロ材料創成, 大学女性協会 第20回守田科学研究奨励賞, (2018).
3. 柳澤実穂. バイオミメティックセルに関する生物物理学的研究, お茶の水女子大学 第2回保井コノ賞, (2018).
4. 岡田康志.　平成29年度 文部科学大臣表彰科学技術賞「共焦点顕微鏡をベースとした超解像顕微鏡の開発」（2017）.
5. 太田邦史.　日本遺伝学会第89回大会 Best Papers 賞受賞「昆虫武器サイズのエピゲノム制御」（2017）.
6. 菅 裕明.　日本イノベーター大賞 2016　特別賞（2016).
7. 菅 裕明.　Max Bergmann Medal 2016（2016).
8. 菅 裕明,　第22回読売テクノフォーラム・ゴールドメダル賞「特殊ペプチドを基軸とした創薬基盤技術の開発」（2016）

4.1.2 Staffs in UBI-member groups

1. 柳沼秀幸(岡田研研究員). 定量的 ATP イメージングを用いた細胞の代謝状態の空間的相関の解析、日本生物物理学会、若手奨励賞(2019).
2. 柳沼秀幸(岡田研研究員). 細胞のエネルギー状態の定量的単一細胞解析を可能にする ATP センサー蛍光タンパク質"QUEEN"、第71回日本細胞生物学会・第19回蛋白質科学会合同年会、若手優秀発表賞　(2019).
3. 中岡秀憲（若本研助教）. 大隅基礎科学創生財団 酵母コンソーシアムフェロー. (2019).
4. 小田有沙（太田研助教).　大隅基礎科学創生財団 酵母コンソーシアムフェロー. (2019)
5. 飯塚怜（船津研助教）. マイクロ・ナノデバイスと1分子検出顕微鏡を用いた生体分子の機能解析と新機能創生　日本薬学会関東支部奨励賞(2019).
6. 神谷厚輝（竹内研　協力研究員.）CHEMINAS 奨励賞（2019).
7. 本多智（豊田研助教）. 高分子形状初期化法の開発：光刺激による環状-直鎖状トポロジーの組換えを活かしたポリジメチルシロキサンの流動性制御, 第68回高分子学会年次大会, 優秀ポスター賞（一般部門）(2019).
8. 渡邊千穂（柳澤研助教）. ミクロ閉じ込めと高分子混雑が導く遅い分子拡散, 第8回ソフトマター研究会, (2018).
9. 渡邊千穂（柳澤研助教）.　Micrometric Confinement Induces Anomalous Diffusion in Semi-dilute Polymer Solution, International Symposium on Fluctuation and Structure out

of Equilibrium 2017 (SFS2017), ポスター賞, (2017).

4.2 Publications

4.2.1 Refereed Original Papers and Conference Proceedings with review

1. Naohiko Shimada, Hirotaka Kinoshita, Takuma Umegae, Satomi Azumai, Nozomi Kume, Takuro Ochiai, Tomoka Takenaka, Wakako Sakamoto, Takayoshi Yamada, Tadaomi Furuta, Tsukuru Masuda, Minoru Sakurai, Hideo Higuchi, and Atsushi Maruyama. Cationic Copolymer-Chaperoned 2D–3D Reversible Conversion of Lipid Membranes Advanced Materials (2019)
2. Takumi Washio, Seine A. Shintani, Hideo Higuchi, Seiryo Sugiura and Toshiaki Hisada. Effect of myofibril passive elastic properties on the mechanical communication between motor proteins on adjacent sarcomeres. Scientific Reports 9:9355 (2019).
3. Y. Li, H. Kokubu, and K. Aihara. Explicit Transversality Conditions and Local Bifurcation Diagrams for Bogdanov - Takens Bifurcation on Center Manifolds. Physica D, Vol.39, pp.52-65 (2019).
4. T. Miyaji, N. Sviridova, K. Aihara, T. Zhao, and A. Nakano. Human Photoplethysmogram through the Morse Graph: Searching for the Saddle Point in Experimental Data, Chaos, Vol.29, No.4, 043121 (2019).
5. K. Koizumi, M. Oku, S. Hayashi, A. Inujima, N. Shibahara, L. Chen, Y. Igarashi, K. Tobe, S. Saito, M. Kadowaki, and K. Aihara. Identifying Pre-disease Signals before Metabolic Syndrome in Mice by Dynamical Network Biomarkers, Scientific Reports, Vol.9, Article No.8767, pp.1-11 (2019).
6. H. Tamura, Y. Katori, K. Aihara. Possible Mechanism of Internal Visual Perception: Context-dependent Processing by Predictive Coding and Reservoir Computing Network, Journal of Robotics, Networking and Artificial Life, Vol.6, No.1, pp.42-47 (2019).
7. M Meijers, S Ito, PR Wolde. The behaviour of information flow near criticality. arXiv preprint arXiv:1906.00787 (2019).
8. S. Ito. Thermodynamics of information geometry as a generalization of the Glansdorff-Prigogine criterion for stability. arXiv preprint arXiv:1908.09446 (2019).
9. Kaneshiro J, Okada Y, Shima T, Tsuji M, Imada K, Ichimura T, Watanabe TM. Second harmonic generation polarization microscopy as a tool for protein structure analysis. Biophys Physbiol. 16: 147-157, 2019
10. Wang C, Taki M, Sato Y, Tamura Y, Yaginuma H, Okada Y, Yamaguchi S. A. photostable fluorescent marker for the superresolution live imaging of the dynamic structure of the mitochondrial cristae. Proc Natl Acad Sci U S A. 116(32):15817-15822, (2019)
11. Tanaka H, Okazaki T, Aoyama S, Yokota M, Koike M, Okada Y, Fujiki Y, Gotoh Y. Peroxisomes control mitochondrial dynamics and the mitochondrion-dependent apoptosis pathway. J Cell Sci. 132(2019)
12. Kono K, Yoshiura S, Fujita I, Okada Y, Shitamukai A, Shibata T, Matsuzaki F.

Reconstruction of Par-dependent polarity in apolar cells reveals a dynamic process of cortical polarization. eLife 8: e45559, (2019)
13. Lu CH, Tang WC, Liu YT, Chang SW, Wu FCM, Chen CY, Tsai YC, Yang SM, Kuo CW, Okada Y, Hwu YK, Chen P, Chen BC. Lightsheet localization microscopy enables fast, large-scale, and three-dimensional super-resolution imaging. Commun Biol. 2:177, (2019)
14. Li J, Suda K, Ueoka I, Tanaka R, Yoshida H, Okada Y, Okamoto Y, Hiramatsu Y, Takashima H, Yamaguchi M. Neuron-specific knockdown of Drosophila HADHB induces a shortened lifespan, deficient locomotive ability, abnormal motor neuron terminal morphology and learning disability. Exp Cell Res. pii:S0014-4827(19)30149-1, (2019)
15. N. Takeuchi, K. Kaneko. The origin of the central dogma through conflicting multilevel selection. Proc. R. Soc. B. 286: 20191359 (2019)
16. A.Kamimura, K. Kaneko. Molecular Diversity and Network Complexity in Growing Protocells. Life. 9, 53 (2019)
17. A.Kamimura, Y.J. Matsubara, K. Kaneko, and N. Takeuchi. Horizontal transfer between loose compartments stabilizes replication of fragmented ribozymes. PLoS Comp. Biol. e15, e1007094 (2019)
18. E.Nakamura and K. Kaneko. Statistical Evolutionary Laws in Music Styles. Scientific Reports (2019).
19. Tottori T, Fujii M, Kuroda S. Robust information transmission in noisy biochemical reaction. Phys. Rev. E,(2019)
20. Ohta, K., Ichihashi, N. Liposome fragment-mediated introduction of multiple plasmids into Bacillus subtilis. Biochemistry and Biophysics Reports, 18, 100646 (2019).
21. Kamiura, R., Matsuda, F., Ichihashi, N. Survival of membrane-damaged Escherichia coli in a cytosol-mimicking solution. J Biosci Bioeng, in press (2019).
22. Ueda, K., Mizuuchi, R., Matsuda, F., Ichihashi, N. A fusion method to develop an expanded artificial genomic RNA replicable by Qß replicase. Chembiochem, 20, 2331-2335 (2019).
23. S. Senmatsu, R. Asada, T. Abe, CS. Hoffman, K. Ohta, K. Hirota. lncRNA transcriptional initiation induces chromatin remodeling within a limited range in the fission yeast fbp1 promoter.Sci Rep. 9: 299 (2019).
24. Takashi Ikegami, Yasuhiro Hashimoto and Mizuki Oka. Open-Ended Evolution and a Mechanism of Novelties in Web Services. Artificial Life, 25:2, pp.168-177 (2019).
25. Norihiro Maruyama, Daichi Saito, Yasuhiro Hashimoto, Takashi Ikegami. Dynamic organization of flocking behaviors in a large-scale boids model. Journal of Computational Social Science, pp.1-8 (2019).
26. Otto E Rossler, Lisa-Ruth Vial, Frank Kuske, August Nitschke, Takashi Ikegami and Andrei Ujica. Brain Equation and Personogenesis. Clinics in Pediatrics, vol.2, pp.1-11 (2019).
27. Olaf WItkowski and Takashi Ikegami. How to Make Swarms Open-Ended? Evolving Collective Intelligence Through a Constricted Exploration of Adjacent Possibles.

arXiv:1903.08228 (2019).
28. Y. Yoon, J. Park, A. Taniguchi, H. Kohsaka, K. Nakae, S. Nonaka, S. Ishii and A. Nose. System level analysis of motor-related neural activities in larval Drosophila. J Neurogenet. 33, 179-189. (2019).
29. H. Kohsaka, M. Zwart, A. Fushiki, R. Fetter, J. Truman, A. Cardona and A. Nose. Regulation of forward and backward locomotion through intersegmental feedback circuits in Drosophila larvae. Nat. Commun. 10(1):2654. (2019).
30. Abe K, Shimada A, Tayama S, Nishikawa H, Kaneko T, Tsuda S, Karaiwa A, Matsui T, Ishitani T, and Takeda H. Horizontal Boundary Cells, a Special Group of Somitic Cells, Play Crucial Roles in the Formationof Dorsoventral Compartments in Teleost Somite. Cell Reports.27, 928-939 (2019).
31. S. Kohyama, N. Yoshinaga, M. Yanagisawa, K. Fujiwara, N. Doi. Cell-sized confinement controls generation and stability of a protein wave for spatiotemporal regulation in cells., eLife, 8:e44591 (2019).
32. A.Sakai, N. Hiro-oka, S. Sasaki, S. Kidoaki, M. Yanagisawa. Lipid membrane effect on the elasticity of gelatin microgel prepared inside lipid microdroplets. Journal of the Society of Rheology Japan (Nihon Reoroji Gakkaishi), vol. 47, p. 55-59(2019).
33. K. Koyanagi, K. Kudo, M. Yanagisawa. Sol–Gel coexisting phase of polymer microgels triggers spontaneous buckling. Langmuir, vol.35, p. 2283-2288(2019).
34. Yusuke Hirata, Yuya Morimoto, Eunryel Nam and Shoji Takeuchi. Portable biohybrid odorant sensors using cell-laden collagen micropillars. Lab on a Chip. vol.19(11), pp.1971-1076, (2019).
35. Masahide Gotanda, Koki Kamiya, Toshihisa Osaki, Norihisa Miki, and Shoji Takeuchi. Automatic Generation System of Cell-Sized Liposomes. Sensors and Actuators B: Chemical. vol. 292, pp. 57-63, (2019).
36. Akiyo Yokomizo, Yuya Morimoto, Keigo Nishimura, Shoji Takeuchi. Temporal observation of adipocyte microfiber using anchoring device. Micromachines. Vol. 10, No. 6, 358 (10 pages), (2019).
37. Dong-Chel Shin, Yuya Morimoto, Jun Sawayama, Shigenori Miura, Shoji Takeuchi. Centrifuge-based step emulsification device for simple and fast generation of monodisperse picoliter droplets. Sensors and Actuators B: Chemical. vol. 301, 127164 (6 page), (2019).
38. Koki Kamiya, Toshihisa Osaki, and Shoji Takeuchi. Formation of vesicles-in-a-vesicle with asymmetric lipid components using a pulsed-jet flow method. RSC Advances. Vol.9, pp.30071-30075, (2019).
39. T. Maeda, T. Horinouchi, N. Sakata, A. Sakai, C. Furusawa. High-throughput identification of the sensitivities of an Escherichia coli ΔrecA mutant strain to various chemical compounds. Jour. Antibiot. 72(7), 566 (2019).
40. C.Furusawa, T. Horinouchi, T. Maeda. Toward prediction and control of antibiotic-resistance evolution. Curr. Opin. Biotech. 54, 45-49 (2019).

41. A.Shibai, T. Maeda, M. Kawada, H. Kotani, N. Sakata, C. Furusawa. Complete Genome Sequences of Three Star-Shaped Bacteria, Stella humosa, Stella vacuolata, and Stella Species ATCC 35155. Microbiol. Resour. Announc. 8(32), e00719 (2019).
42. Hasegawa S., Susaki E.A., Tanaka T., Komaba H., Wada T., Fukagawa M., Ueda H.R., Nangaku M. Comprehensive three-dimensional analysis (CUBIC-kidney) visualizes abnormal renal sympathetic nerves after ischemia/reperfusion injury. Kidny Int. 96, 129-138 (2019).
43. Puelles V.G., Fleck D., Ortz L., Papadouri S., Strieder T., Böhner A.M.C., van der Wolde J.W., Vogt M., Saritas T., Kuppe C., Fuss A., Menzel S., Klinkhammer B.M., Müller-Newen G., Heymann F., Decker L., Braun F., Kretz O., Moeller M.J. Novel 3D analysis using optical tissue clearing documents the evolution of murine rapidly progressive glomerulonephritis. Kidny Int. 96, 505-516 (2019).
44. J. M. Castro, H. Sugiyama and T. Toyota. Budding and Division of Giant Vesicles Linked to Phospholipid Production. Scientific Reports, 9, 165 (2019).
45. S. Honda, H. Takagi, M. Oka and T. Toyota. Topology - Reset Execution: Repeatable Postcyclization Recyclization of Cyclic Polymers. Angewandte Chemie International Edition, 58, 144-148 (2019).
46. H. Morohashi, M. Imai and T. Toyota. Construction of a Chemical Motor-Movable Frame Assembly Based on Camphor Gains using 3D Printed Water-Floating Models. Chemical Physics Letters, 721, 104-110 (2019).
47. M. Matsuo, S. Ohyama, K. Sakurai, T. Toyota, K. Suzuki and T. Sugawara. A Sustainable Self-reproducing Liposome Consisting of a Synthetic Phospholipid. Chemistry and Physics of Lipids. 222, 1-7 (2019).
48. M. Matsuo, Y. Kan, K. Kurihara, T. Jimbo, M. Imai, T. Toyota, Y. Hirata, K. Suzuki and T. Sugawara. DNA Length-dependent Division of Giant Vesicle-based Model Protocell. Scientific Reports, 9, 6916 (2019).
49. Y. Fujimoto, K. Kaneko. Functional Dynamics by Intention Recognition in Iterated Games. New J. Phys. 21, 023025 (2019).
50. S. Yamamoto, Y. Iwamaru, Y. Shimizu, Y. Ueda, M. Sato, K. Yamaguchi and J. Nakanishi. Epidermal growth factor-nanoparticle conjugates change the activity from anti-apoptotic to pro-apoptotic at membrane rafts, Acta Biomater., 88, 383-391 (2019).
51. S.R. Fleming, T.E. Bartges, A.A. Vinogradov, C.L. Kirkpatrick, Y. Goto, H. Suga, L.M. Hicks, A.A. Bowers. lexizyme-enabled benchtop biosynthesis of thiopeptides. Journal of the American Chemical Society (2019)
52. T.P. Christoph Nitsche, Paul Varava, Mithun C. Mahawaththa, Mila M. Leuthold, Christian D. Klein, Hiroaki Suga and Gottfried Otting. De Novo Discovery of Nonstandard Macrocyclic Peptides as Noncompetitive Inhibitors of the Zika Virus NS2B-NS3 Protease. ACS Med. Chem. Lett., (2019).
53. R. Takatsuji; K. Shinbara; T. Katoh; Y. Goto; T. Passioura; R. Yajima; Y. Komatsu; H. Suga.

Ribosomal synthesis of backbone-cyclic peptides compatible with in vitro display. Journal of the American Chemical Society, (2019).

54. Y. Yin; Q. Fei; W. Liu; Z. Li; H. Suga; C. Wu. Chemical and Ribosomal Synthesis of Topologically Controlled Bicyclic and Tricyclic Peptide Scaffolds Primed by Selenoether Formation.Angewandte Chemie, (2019).
55. A.A. Vinogradov; Y. Yin; H. Suga. Macrocyclic Peptides as Drug Candidates: Recent Progress and Remaining Challenges.Journal of the American Chemical Society, (2019).
56. Yohsuke Fukai, Masaki Sano. Large-scale flow out of spatiotemporal chaos in electroconvection of cholesteric liquid crystal. Bulletin of the American Physical Society American Physical Society (2019).
57. Takaki Yamamoto, Masaki Sano. Hydrodynamic rotlet dipole driven by spinning chiral liquid crystal droplets. Physical Review E American Physical Society(2019)
58. Norihiro Maruyama,Daichi Saito, Yasuhiro Hashimoto, Takashi Ikegami. Dynamic organization of flocking behaviors in a large-scale boids model, journal of Computational Social Science. pp 1-8(2019)
59. Otto E Rossler, Lisa-Ruth Vial, Frank Kuske, August Nitschke, Takashi Ikegami and Andrei Ujica. Brain Equation and Personogenesis. Clinics in Pediatrics, vol.2 pp.1-11.(2019)
60. Tetsuya Hiraiwa. Two types of exclusion interactions for self-propelled objects and collective motion induced by their combination. Physical Review E Vol.99, p.012614 (2019).
61. Shotaro Tsuji and Kazuyuki Aihara. A Fast Method of Computing Persistent Homology of Time Series Data, Proceedings of 2019 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP 2019), pp.3462-3466 (2019).
62. Farad Khoyratee, Stephany Mai Nishikawa, Zhongyue Luo, Soo Hyeon Kim, Sylvain Saighi, Teruo Fujii, Yoshiho Ikeuchi, Kazuyuki Aihara, Timothee Levi. Biomimetic Spiking Neural Network (SNN) Systems for 'in vitro' Cells Stimulation, Proceedings of IEEE International Symposium on Circuits and Systems, 18880988, pp.1-5 (2019).
63. Tottori T, Fujii M, Kuroda S. NMDAR-Mediated Ca2+ Increase Shows Robust Information Transfer in Dendritic Spines Biophys. J. 116, 1748-1758 (2019)
64. Seohyun Lee, Hyuno Kim, Masatoshi Ishikawa, and Hideo Higuchi. 3D Nanoscale Tracking Data Analysis for Intracellular Organelle Movement using Machine Learning Approach. International conference on Artificial Intelligence in Information and Communication. 181-184 (2019)
65. Takami Maekawa, Koki Kamiya, Tooru Takahashi, Kentaro Kaji, Yukio Tezuka, Toshihisa Osaki, Shoji Takeuchi, and Takashi Kondoh. TMC6 : A Novel Salt Taste Receptor in Mice. Florida, USA. (2019).
66. Tetsuya Yamada, Koki Kamiya, Toshihisa Osaki, Shoji Takeuchi. ARTIFICIAL CELL MEMBRANE SYSTEM FOR ODORANT SENSOR: DEVELOPMENT OF SOLUTION EXCHANGE DRIVEN BY SUPERABSORBENT POLYMER FOR REPEATABLE

DETECTION. SOEN 2019 (18th International Symposium on Olfaction and Electronic Nose). pp.28-30. Fukuoka, Japan, (2019).
67. Keisuke Sugahara, Sho Takamori, and Shoji Takeuchi. PAIRING AND ELECTROFUSION OF LIPOSOMES IN A DYNAMIC MICROARRAY DEVICE. Transducers2019. pp.482-483. Berlin, Germany, Jun, (2019).
68. Yoshihisa Ito, Toshihisa Osaki, Koki Kamiya, Tetsuya Yamada, Norihisa Miki, and Shoji Takeuchi. QUAD LIPID BILAYER MODULE WITH 1-GΩ SERIES RESISTORS. Transducers 2019 – EUROSENSORS XXXIII. pp6-8. Berlin, Germany(2019).
69. Hironori Sugiyama, Toshihisa Osaki, Shoji Takeuchi, Taro Toyota. Microfluidic trapping and observation of size-sorted liposomes prepared by water-in-oil emulsion transfer method. ACS Fall 2019 National Meeting & Expo. San Diego, USA, (2019).
70. S. Nagata, S. Takeuchi. ORGANOID ENGINEERING: FIBROUS NEURAL ORGANOID FORMATION USING MICROFLUIDIC DEVICE. the 4th AIBBC, Mombasa, Kenya, (2019).
71. Yasuaki Ishii, Yusuke Hirata, Yuya Morimoto, Ai Shima and Shoji Takeuchi. Centimeter-sized Tissue with Perfusable Channels toward Cultured Steak. MicroTAS2019. Basel, SWITZERLAND (2019).
72. M. Kato-Negishi, J. Sawayama, S. Takeuchi. FIBER-SHAPED 3D TISSUE IN 96 WELL PLATE FOR HIGH-THROUGHPUT DRUG SCREENING. MicroTAS2019. Basel, SWITZERLAND (2019).
73. Yugi K., Kuroda S. Metabolism as a signal generator across trans-omic networks at distinct time scales,Curr. Opin. Sys. Biol. 8, 59-66 (2018).
74. Ueno A, Omori Y, Sugita Y, Watanabe S, Chaya T, Kozuka T, Kon T, Yoshida S, Matsushita K, Kuwahara R, Kajimura N, Okada Y, Furukawa T. Lrit1, a retinal transmembrane protein, regulates selective synapse formation in cone photoreceptor cells and visual acuity. Cell Reports 22, 3562-3573 (2018).
75. Ohashi, K., Fujii, M., Uda, S., Kubota, H., Komada, H., Sakaguchi, K., Ogawa, W., Kuroda, S. Increase in hepatic and decrease in peripheral insulin clearance characterize abnormal temporal patterns of serum insulin in diabetic subjects. NPJ Syst. Biol. 4, 14 (2018).
76. Seohyun Lee, Hyuno Kim, Hideo Higuchi. Focus Stabilization by Axial Position Feedback in Biomedical Imaging Microscopy. IEEE Sensors Applications Symposium 2018, 309-314 (2018).
77. Atsushi Kamimura, Kunihiko Kaneko. Exponential growth for self-reproduction in a catalytic reaction network: relevance of a minority molecular species and crowdedness. New Journal of Physics 20, 035001 (2018).
78. K. Tokuyama, Y. Toya, T. Horinouchi, C. Furusawa, F. Matsuda, H. Shimizu,Application of adaptive laboratory evolution to overcome a flux limitation in an Escherichia coli production strain. Biotechnology and Bioengineering, 1-10 (2018).
79. C. Furusawa, T. Horinouchi, T. Maeda. Toward prediction and control of antibiotic-

resistance evolution. Current Opinion in Biotechnology 54, 45-59 (2018).
80. Takaki Yamamoto and Masaki Sano,Theoretical model of chirality-induced helical self-propulsion,Phys. Rev. E 97, 012607/1-11 (2018).
81. T. Hirasawa, M. Saito, K. Yoshikawa, C. Furusawa. Integrated Analysis of the Transcriptome and Metabolome of Corynebacterium glutamicum during Penicillin-Induced Glutamic Acid Production. Biotechnology Journal 1700612, 1-11 (2018).
82. Daiki Nishiguchi, Junichiro Iwasawa, Hong-Ren Jiang and Masaki Sano. Flagellar dynamics of chains of active Janus particles fueled by an AC electric field. New Journal of Physics 20, 015002/1-14 (2018).
83. A. Germond, T. Ichimura, T. Horinouchi, H. Fujita, C. Furusawa, T. M. Watanabe. Raman spectral signature reflects transcriptomic features of antibiotic resistance in Escherichia coli. Communications Biology, 1:85 (2018).
84. .K. Okamoto, A. Germond, H. Fujita, C. Furusawa, Y. Okada, T. M. Watanabe. Single cell analysis reveals a biophysical aspect of collective cell-state transition in embryonic stem cell differentiation. Sci. Rep., 8(1):11965 (2018).
85. C.Furusawa and K.Kaneko. Formation of dominant mode by evolution in biological systems. Phys. Rev. E, 97(4), 042410 (2018).
86. K.Tokuyama, Y.Toya, T.Horinouchi, C.Furusawa, F.Matsuda, H.Shimizu. Application of adaptive laboratory evolution to overcome a flux limitation in an Escherichia coli production strain. Biotechnol. Bioeng. 115(6):1542-1551 (2018).
87. T.Hirasawa,M.Saito,K.Yoshikawa,C.Furusawa, H.Shimizu. Integrated Analysis of the Transcriptome and Metabolome of Corynebacterium glutamicum during Penicillin-Induced Glutamic Acid Production,Biotechnol. Jour., 1700612 (2018).
88. Y.Fujimoto, K.Kaneko. Functional Dynamics by Intention Recognition in Iterated Games. New J. Phys. 21, 023025 (2018).
89. M.Inoue, K.Kaneko. Cooperative reliable response from sloppy gene-expression dynamics. EPL, 124, 38002(2018).
90. Y. J. Matsubara and K. Kaneko. Kinetic selection of template polymer with complex sequences. Phys. Rev. Lett. 121, 118101 (2018).
91. A.Kamimura and K. Kaneko. Exponential growth for self-reproduction in a catalytic reaction network: relevance of a minority molecular species and crowdedness.New J. Phys. 20, 035001 (2018).
92. T.Kohsokabe and K. Kaneko. Boundary-Induced Pattern Formation from Uniform Temporal Oscillation. Chaos 28, 045110 (2018).
93. K.Kaneko and C.Furusawa. Macroscopic Theory for Evolving Biological Systems Akin to Thermodynamics. Ann. Rev. Biophys, 47, 273-290 (2018).
94. V. Nier, G. Peyret, J.d'Alessandro, S.Ishihara, B. Ladoux, and P. Marcq. Kalman inversion stress microscopy. Biophys. J. 115, 1808-1816 (2018).
95. Shima T, Morikawa M, Kaneshiro J, Kambara T, Kamimura S, Yagi T, Iwamoto H, Uemura

S, Shigematsu H, Shirouzu M, Ichimura T, Watanabe TM, Nitta R, Okada Y, Hirokawa N. Kinesin-binding-triggered conformation switching of microtubules contributes to polarized transport. J Cell Biol. 217:4164-4183, (2018).

96. Hayashi K, Tsuchizawa Y, Iwaki M, Okada Y. Application of the fluctuation theorem for non-invasive force measurement in living neuronal axons. Mol Biol Cell, 29:3017-3025, (2018).
97. Gzrybowski M, Taki M, Senda K, Sato Y, Ariyoshi T, Okada Y, Kawakami R, Imamura T, Yamaguchi. S.A highly photostable near-infrared labeling agent based on a phospha-rhodamine for long-term and deep imaging. Angew. Chem. 57:10137-10141, (2018).
98. Komatsu N, Terai K, Imanishi A, Kamioka Y, Sumiyama K, Jin T, Okada Y, Nagai T, Matsuda M.A platform of BRET-FRET hybrid biosensors for optogenetics, chemical screening, and in vivo imaging. Scientific Reports 8: 8984, (2018).
99. K. Sasaki, M. Kaya, and H. Higuchi.,A unified walking model for dimeric motor proteins Biophys. J.115, 1-12 (2018).
100. Yoshimi Kinoshita, Taketoshi Kambara, Kaori Nishikawa1, Motoshi Kaya and Hideo Higuchi. Step Sizes and Rate Constants of Single-headed Cytoplasmic Dynein Measured with Optical Tweezers. Sci. Rep. 16333 (2018).
101. Seohyun Lee, Hyuno Kim, Hideo Higuchi. Numerical method for vesicle movement analysis in a complex cytoskeleton network. Opt. Express 26, 16236-16239 (2018).
102. K. J. Kobayashi-Kirschvink, H. Nakaoka, A. Oda, K. F. Kamei, K. Nosho, H. Fukushima, Y. Kanesaki, S. Yajima, H. Masaki, K. Ohta, Y. Wakamoto. Linear Regression Links Transcriptomic Data and Cellular Raman Spectra. Cell Systems 7(1), 104-117.E4 (2018).
103. Hiroshi Yamaguchi, Toshiyuki Oda, Masahide Kikkawa, Hiroyuki Takeda. Systematic studies of all PIH proteins in zebrafish reveal their distinct roles in axonemal dynein assembly. eLife, 7. pii: e36979(2018).
104. Yui Uchida Y, Masahiro Uesaka, Takayoshi Yamamoto, Hiroyuki Takeda, Naoki Irie. Embryonic lethality is not sufficient to explain hourglass-like conservation of vertebrate embryos. EvoDevo, 9(7)(2018).
105. Inoue Y., Kumagai M., Zhang X., Saga T., Wang D., Koga A. , Takeda H. Fusion of piggyBac-like transposons and herpesviruses occurs frequently in teleosts.Zoological Letters, 4:6 (2018).
106. Umeda M., Tsunekawa C., Senmatsu S., Asada R., Abe T., Ohta K., Hoffman CS., Hirota K. Histone Chaperone Asf1 Is Required for the Establishment of Repressive Chromatin in Schizosaccharomyces pombe fbp1 Gene Repression. Mol Cell Biol. 38(18) pii: e00194-18 (2018).
107. Kobayashi-Kirschvink KJ, Nakaoka H., Oda A., Kamei KF., Nosho K., Fukushima H., Kanesaki Y., Yajima S., Masaki H, Ohta K., Wakamoto Y. Transcriptomes and Raman spectra are linked linearly through a shared low-dimensional subspace. Cell Systems

7:104-117.e4. (2018).
108. Muramoto N., Oda A., Tanaka H., Nakamura T., Kugou K., Suda K., Kobayashi A., Yoneda S., Ikeuchi A., Sugimoto H., Kondo S., Ohto C., Shibata T., Mitsukawa N., Ohta K.,Phenotypic diversification by enhanced genome restructuring after induction of multiple DNA double-strand breaks. Nature Comm., 9: 1995 (2018).
109. Yamada S., Kugou K., Ding DQ., Fujita Y., Hiraoka Y., Murakami H., Ohta K., Yamada T. The conserved histone variant H2A.Z illuminates meiotic recombination initiation. Curr. Genetics 64: 1015-1019 (2018).
110. Okamoto Y, Iwasaki WM, Kugou K, Takahashi KK, Oda A, Sato K, Kobayashi W, Kawai H, Sakasai R, Takaori-Kondo A, Yamamoto T, Kanemaki MT, Taoka M, Isobe T, Kurumizaka H, Innan H, Ohta K, Ishiai M, Takata M. Replication stress induces accumulation of FANCD2 at central region of large fragile genes. Nucleic Acids Res., 46: 2932-2944 (2018).
111. Yamada S., Kugou K., Ding DQ., Fujita Y., Hiraoka Y., Murakami H., Ohta K., Yamada T. The histone variant H2A.Z promotes initiation of meiotic recombination in fission yeast. Nucleic Acids Res., 46: 609-620 (2018).
112. Adachi A., Senmatsu S., Asada R., Abe T., Hoffman C.S., Ohta K. Hirota K. Interplay between ADCRs and histone acetylation regulates the formation of accessible chromatin in fission yeast fbp1 upstream regulatory region. Genes & Genetic Systems, 92: 267-276 (2018).
113. Goto T, Ito Y, Michiue T. Roles of Xenopus chemokine ligand CXCLh (XCXCLh) in early embryogenesis.Dev. Growth Differ. 60: 226-238. (2018).
114. Hirano S, Yamamoto T, Michiue T. FRET-based tension measurement across actin-associated mechanotransductive structures using Lima1. Int. J. Dev. Biol. 62:631-636. (2018)
115. Watanabe T, Yamamoto T, Tsukano K. Hirano S. Horikawa A, Michiue T. Fam46a regulates BMP-dependent pre-placodal ectoderm differentiation in Xenopus.Development 145: pii:dev166710. (2018)
116. Soeda S, Yamada-Nomoto K, Michiue T, Ohsugi M. RSK/MASTL pathway delays meiotic exit in mouse zygotes to ensure paternal chromosome stability.Dev. Cell. 47: 363-376. (2018)
117. K. Nishio; R. Belle; T. Katoh; A. Kawamura; T. Sengoku; K. Hanada; N. Ohsawa; M. Shirouzu; S. Yokoyama; H. Suga. Thioether Macrocyclic Peptides Selected against TET1 Compact Catalytic Domain Inhibit TET1 Catalytic Activity.Chembiochem. a European journal of chemical biology, 19, 979-985 (2018)
118. T. Passioura; B. Bhushan; A. Tumber; A. Kawamura; H. Suga. Structure-activity studies of a macrocyclic peptide inhibitor of histone lysine demethylase 4A. Bioorganic & medicinal chemistry, 26, 1225-1231 (2018)
119. J.M. Rogers; S. Kwon; S.J. Dawson; P.K. Mandal; H. Suga. I. Huc. Ribosomal synthesis and folding of peptide-helical aromatic foldamer hybrids. Nature chemistry, 10, 405-412 (2018)

120. T. Katoh; H. Suga. Ribosomal Incorporation of Consecutive beta-Amino Acids. Journal of the American Chemical Society, 140, 12159-12167 (2018).
121. J.M. Bacusmo; A.B. Kuzmishin; W.A. Cantara; Y. Goto; H. Suga; K. Musier-Forsyth Quality control by trans-editing factor prevents global mistranslation of non-protein amino acid alpha-aminobutyrate. RNA Biol, 15, 576-585 (2018)
122. T.E. McAllister; T.L. Yeh; M.I. Abboud; I.K.H. Leung; E.S. Hookway; O.N.F. King; B. Bhushan; S.T. Williams; R.J. Hopkinson; M. Munzel; N.D. Loik; R. Chowdhury; U. Oppermann; T.D.W. Claridge; Y. Goto; H. Suga; C.J. Schofield. A. Kawamura Non-competitive cyclic peptides for targeting enzyme-substrate complexes. Chemical science, 9, 4569-4578 (2018)
123. H. Suga. Max-Bergmann award lecture:A RaPID way to discover bioactive nonstandard peptides assisted by the flexizyme and FIT systems Journal of peptide science : an official publication of the European Peptide Society, 24, (2018)
124. K. Tajima; T. Katoh; H. Suga. Genetic code expansion via integration of redundant amino acid assignment by finely tuning tRNA pools. Current opinion in chemical biology, (2018)
125. N.K. Bashiruddi; U. Matsunaga; M. Nagano; J. Takagi; H. Suga. Facile Synthesis of Dimeric Thioether-Macrocyclic Peptides with Antibody-like Affinity against Plexin-B1. Bioconjugate Chem, 29, 1847-1851 (2018)
126. Y. Goto; H. Suga. Engineering of RiPP pathways for the production of artificial peptides bearing various non-proteinogenic structures. Current opinion in chemical biology, 46, 82-90 (2018)
127. T. Passioura; W. Liu; D. Dunkelmann; T. Higuchi; H. Suga. Display Selection of Exotic Macrocyclic Peptides Expressed under a Radically Reprogrammed 23 Amino Acid Genetic Code. Journal of the American Chemical Society, 140, 11551-11555 (2018)
128. T. Passioura; K. Watashi; K. Fukano; S. Shimura; W. Saso; R. Morishita; Y. Ogasawara; Y. Tanaka; M. Mizokami; C. Sureau; H. Suga; T. Wakita. De Novo Macrocyclic Peptide Inhibitors of Hepatitis B Virus Cellular Entry. Cell chemical biology, 25, 906(2018).
129. T. Kusakizako; Y. Tanaka; C.J. Hipolito; H. Suga; O. Nureki. Crystallographic Analysis of MATE-Type Multidrug Exporter with Its Inhibitors. Methods Mol Biol. 1700, 37-57 (2018).
130. Y. Iwane; T. Katoh; Y. Goto; H. Suga. Artificial Division of Codon Boxes for Expansion of the Amino Acid Repertoire of Ribosomal Polypeptide Synthesis. Methods Mol Biol. 1728, 17-47 (2018).
131. Y. Goto; H. Suga. Artificial In Vitro Biosynthesis Systems for the Development of Pseudo-Natural Products. B Chem Soc Jpn, 91, 410-419 (2018)
132. J.M. Rogers; T. Passioura; H. Suga. Nonproteinogenic deep mutational scanning of linear and cyclic peptides. Proc Natl Acad Sci USA, 115, 10959-10964 (2018)
133. W. Miao; K. Sakai; R. Imamura; K. Ito; H. Suga; T. Sakuma; T. Yamamoto; K. Matsumoto. MET Activation by a Macrocyclic Peptide Agonist that Couples to Biological Responses Differently from HGF in a Context-Dependent Manner. Int J Mol Sci, 19, 3141 (2018)

134. K. W. Decoene, W. Vannecke, T. Passioura, H. Suga,A. Madder. Pyrrole-Mediated Peptide Cyclization Identified through Genetically Reprogrammed Peptide Synthesis. Biomedicines, 6, 99 (2018)
135. Y. Huang,M. M. Wiedmann, H. Suga. RNA Display Methods for the Discovery of Bioactive Macrocycles. Chem Rev, (2018)
136. W. Miao; K. Sakai; N. Ozawa; T. Nishiuchi; Y. Suzuki; K. Ito; T. Morioka; M. Umitsu; J. Takagi; H. Suga; K. Matsumoto. Cellular signaling and gene expression profiles evoked by a bivalent macrocyclic peptide that serves as an artificial MET receptor agonist. Sci Rep, 8, 16492 (2018)
137. H. Hirose; C. Tsiamantas; T. Katoh; H. Suga. In vitro expression of genetically encoded non-standard peptides consisting of exotic amino acid building blocks,Curr Opin Biotechnol, 58, 28-36 (2018)
138. M.E. Otero-Ramirez; T. Passioura; H. Suga. Structural Features and Binding Modes of Thioether-Cyclized Peptide Ligands.Biomedicines, 6, (2018)
139. T. Watahiki, T. Nomoto, L. Chiari, T. Toyota, and M. Fujinami, Experimental investigation of the self-propelled motion of a sodium oleate tablet and boat at an oil-water interface. Langmuir 34, 5487-5494 (2018)
140. S. Honda and T. Toyota. Photocontrolled network formation and dissociation with coumarin end-functionalized branched poly(dimethyl siloxane)s. Polymer 148, 211-216 (2018)
141. S. Konno, T. Banno, H. Takagi, S. Honda and T. Toyota. Irreversible Aggregation of Alternating Tetra-Block-Like Amphiphile in Water. PLOS ONE 13, e0202816 (2018).
142. Kawata, K., Yugi, K., Hatano, A., Kokaji, T., Tomizawa, Y., Fujii, M., Uda, S., Kubota, H., Matsumoto, M., Nakayama, K.I., and Kuroda, S. Reconstruction of global regulatory network from signaling to cellular functions using phosphoproteomic data Genes to Cells 24, 82-93. (2018)
143. Inoue, H., Kunida, K., Matsuda, N., Hoshino, D., Wada, T., Imamura, H., Noji, H., and Kuroda, S. Automatic Quantitative Segmentation of Myotubes Reveals Single-cell Dynamics of S6 Kinase Activation Cell Struct. Funct. 43, 153-169 (2018)
144. Kubota, H., Uda, S., Matsuzaki, F., Yamauchi, Y., and Kuroda, S. In Vivo Decoding Mechanisms of the Temporal Patterns of Blood Insulin by the Insulin-AKT Pathway in the Liver. Cell Sys. 7, 1-11 (2018)
145. J. Park, S. Kondo, H. Tanimoto, H. Kohsaka and A. Nose. Data-driven analysis of motor activity implicates 5-HT2A neurons in backward locomotion of larval Drosophila.Sci Rep. (1):10307 (2018)
146. John Brumley, Charles Taylor, Reiji Suzuki, Takashi Ikegami, Victoria Vesna, Hiroo Iwata.Bird Song Diamond in Deep Space 8k. AI & Society (2018).
147. Y.Nakanishi-Ohno and K.Hukushima. Data-driven diagnosis for compressed sensing with cross validation. Physical Review E, 98, 052120 (2018)

148. R.Tamura and K.Hukushim. Bayesian optimization for computationally extensive probability distributions. PloS one 13 (3), e0193785 (2018)
149. Y.Mizuno and K.Hukushima. Power-law decay in the nonadiabatic photodissociation dynamics of alkali halides due to quantum wavepacket interference. J. Chem. Phys. 149 (17), 174313(2018)
150. S.Takabe, T.Maehara and K.Hukushima. Typical approximation performance for maximum coverage problem. Physical Review E 97 (2), 022138 (2018)
151. T. Komori, A. Shibai, H. Saito, Y. Akeno, A. Germond, T. Horinouchi, C. Furusawa and S. Tsuru. Enhancement of K - strategy evolution in histidine utilization using a container with compartments. Volume23, Pages 893-903 (2018)
152. Tetsuya Hiraiwa and Roland Netz. Systematic bottom-up theory for the viscoelastic response of worm-like-chain networks.Europhysics Letters Vol.123, p.58002 (2018).
153. Hiroki Kojima, Tom Froese, Mizuki Oka, Hiroyuki Iizuka andTakashi Ikegami. T. A Sensorimotor Signature of the Transition to Conscious Social Perception: Co-regulation of Active and Passive Touch.Frontiers in psychology 8, 1778 (2017).
154. Sinapayen, L.,Ikegami. T. Online fitting of computational cost to environmental complexity: Predictive coding with the ε-network. Proceedings of the 14th European Conference on Artificial Life 2017 14, 380-387 (2017).
155. bibitem{a2}Doi, I., Ikegami, T., Masumori, A., Kojima, H., Ogawa K., Ishiguro, H. A new design principle for an autonomous robot Proceedings of the 14th European Conference on Artificial Life 2017. 14, 490-466 (2017).
156. Masumori, A., Sinapayen, L., Ikegami, T. Learning by Stimulation Avoidance Scale to Large Neural Networks. Proceedings of the 14th European Conference on Artificial Life 2017. 14, 275-282 (2017).
157. Masumori, A., Maruyama, N., Mita, T., Bakkum, D., Frey, U., Takahashi, H., Ikegami, T. Learning by Stimulation Avoidance in Cultured Neuronal Cells. The 2nd International Symposium on Swarm Behavior and Bio-Inspired Robotics (SWARM 2017), 275-282 (2017).
158. Maruyama, N., Hashimoto, Y., Mototake, Y., Saito, D. Ikegami, T Revisiting Classification of Large Scale Flocking. The 2nd International Symposium on Swarm Behavior and Bio-Inspired Robotics(SWARM 2017) , 307-310 (2017)
159. Hashimoto, Y., Ikegami, T.Novelty production in tagging crowds. The 2nd International Symposium on Swarm Behavior and Bio-Inspired Robotics (SWARM 2017)311-312 (2017).
160. Motoshi Kaya, Yoshiaki Tani, Takumi Washio, Toshiaki Hisada and Hideo Higuchi. Coordinated force generation of skeletal myosins in myofilaments through motor coupling, Nature Communications 8, 16036 (2017).
161. Akira Adachi, Satoshi Senmatsu, Ryuta Asada, Takuya Abe, Charles S. Hoffman, Kunihiro Ohta, Kouji Hirota,Interplay between chromatin modulators and histone acetylation regulates the formation of accessible chromatin in the upstream regulatory region of fission yeast fbp1. Genes & Genetic Systems 92(6): 267-276, (2017).

162. Eng Kuan Moo, Daniel R.Peterson, Timothy R. Leonard, Motoshi Kaya and Walter Herzog,In vivo muscle force and muscle power during near-maximal frog jumps.,PloS one (2017).
163. Lana Sinapayen, Atsushi Masumori, Takashi Ikegami, Learning by Stimulation Avoidance: A Principle to Control Spiking Neural Networks Dynamics., PLoS One 12(2), e0170388 (2017).
164. Takumi Washio, Toshiaki Hisada, Seine A. Shintani and Hideo Higuchi,Analysis of spontaneous oscillations for a three state power stroke model,Physical Review E. 95, 022411 (2017).
165. Takaho Tsuchiya, Masashi Fujii, Naoki Matsuda, Katsuyuki Kunida, Shinsuke Uda, Hiroyuki Kubota, Katsumi Konishi, Shinya Kuroda,System identification of signaling dependent gene expression with different time-scale data,PLOS Computational Biology 13（12）, e1005913 (2017).
166. Napo K. M. Cheung, Ryohei Nakamura, Ayako Uno, Masahiko Kumagai, Hiroto S. Fukushima, Shinichi Morishita, Hiroyuki Takeda,Unlinking the methylome pattern from uncleotide sequence, revealed by large-scale in vivo genome engineering and methylome editing in medaka fish,PloS Genetics 13, e1007123 (2017).
167. Suguru Takagi, Benjamin T. Cocanougher, Sawako Niki, Dohjin Miyamoto, Hiroshi Kohsaka, Hokuto Kazama, Richard D. Fetter, James W. Truman, Marta Zlatic, Albert Cardona and Akinao Nose. Divergent connectivity of homologous command-like neurons mediates segment-specific touch responses in Drosophila. Neuron 96(6), 1373-1387 (2017).
168. James R. Krycer, Katsuyuki Yugi, Akiyoshi Hirayama, Daniel J. Fazakerley, Lake-Ee Quek, Richard Scalzo, Satoshi Ohno, Mark P. Hodson, Satsuki Ikeda, Futaba Shoji, Kumi Suzuki, Westa Domanova, Benjamin L. Parker, Marin E. Nelson, Sean J. Humphrey, Nigel Turner, Kyle L. Hoehn, Gregory J. Cooney, Tomoyoshi Soga, Shinya Kuroda and David E. James,Dynamic metabolomics reveals that insulin primes the adipocyte for glucose metabolism,Cell Reports 21(12), 3536-3547 (2017).
169. Takayuki Katoh, Yoshihiko Iwane, Hiroaki Suga, Logical engineering of D-arm and T-stem of tRNA that enhances d-amino acid incorporation., Nucleic Acids Research 45, 12601-12610 (2017).
170. Ryan Kniewel, Hajime Murakami, Yan Liu, Masaru Ito, Kunihiro Ohta, Nancy M. Hollingsworth and Scott Keeney. Histone H3 threonine 11 phosphorylation is catalyzed directly by the meiosis-specific kinase Mek1 and provides a molecular readout of Mek1 activity in vivo. GENETICS 207, 1313-1333 (2017).
171. Chiba K, Chien K, Sobu Y, Hata S, Kato S, Nakaya T, Okada Y, Nairn AC, Kinjo M, Taru H, Wang R, Suzuki T.,Phosphorylation of KLC1 modifies interaction with JIP1 and abolishes the enhanced fast velocity of APP transport by kinesin-1 ,MOLECULAR BIOLOGY OF THE CELL 28, 3857-3869 (2017).
172. Kazuki Ichikawa, Shingo Tomioka, Yuta Suzuki, Ryohei Nakamura, Koichiro Doi, Jun

Yoshimura, Masahiko Kumagai, Yusuke Inoue, Yui Uchida, Naoki Irie, Hiroyuki Takeda, Shinich Morishita, Centromere evolution and CpG methylation during vertebrate speciation , Nature Communications 1833, 1-11 (2017).

173. Tsukasa Kusakizako,Yoshiki Tanaka, Christopher J. Hipolito, Hiroaki Suga, Osamu Nureki, Crystallographic analysis of MATE-type multidrug exporter with its inhibitors., Methods Mol Biol. 1700, 7-57 (2017).
174. Jo Marie Bacusmo, Alexandra B. Kuzmishin, William A. Cantara, Yuki Goto, Hiroaki Suga, Karin Musier-Forsyth,Quality control by trans-editing factor prevents global mistranslation of non-protein amino acid α-aminobutyrate,RNA Biol., 1-10 (2017).
175. Ryo Yokota, Yuki Kaminaga, Tetsuya J. Kobayashi. Quantification of Inter-Sample Differences in T-Cell Receptor Repertoires Using Sequence-Based Information. Frontier Immunology 8, 1500 (2017).
176. T. S. Hatakeyama, C. Furusawa. Metabolic dynamics restricted by conserved carriers: Jamming and feedback. PLOS COMPUTATIONAL BIOLOGY 13-11, e1005847 (2017).
177. K. Tanabe, N. Sakata, H. Shimizu, C. Furusawa. Prediction of Cross-resistance and Collateral Sensitivity by Gene Expression profiles and Genomic Mutations. SCIENTIFIC REPORTS 7, 14009 (2017).
178. Sanki Tashiro, Yuki Nishihara, Kazuto Kugo,u Kunihiro Ohta, Junko Kanoh. Subtelomeres constitute a safeguard for gene expression and chromosome homeostasis. Nucleic Acids Research 45, 10333-10349 (2017).
179. Haiyang Hu, Masahiro Uesaka, Song Guo, Kotaro Shimai, Tsai-Ming Lu, Fang Li, Satoko Fujimoto, Masato Ishikawa, Shiping Liu, Yohei Sasagawa, Guojie Zhang, Shigeru Kuratani, Jr-Kai Yu, Takehiro G. Kusakabe, Philipp Khaitovich, Naoki Irie. the EXPANDE Consortium,Constrained vertebrate evolution by pleiotropic genes. Nature Ecology & Evolution 1, 1722-1730 (2017).
180. Ryohei Nakamura, Ayako Uno, Masahiko Kumagai, Shinichi Morishita &Hiroyuki Takeda. Hypomethylated domain-enriched DNA motifs prepattern the accessible nucleosome organization in teleosts. Epigenetics & Chromatin 110, 44 (2017).
181. Ryuta Asada Miki Umeda Akira Adachi Satoshi Senmatsu Takuya Abe Hiroshi Iwasaki Kunihiro Ohta Charles S. Hoffman Kouji Hirota. Recruitment and delivery of the fission yeast Rst2 transcription factor via a local genome structure counteracts repression by Tup1-family corepressors. Nucleic Acids Res. 45, 9361-9371 (2017).
182. Takayuki Katoh, Yoshihiko Iwane & Hiroaki Suga. tRNA engineering for manipulating genetic code. RNA Biol. 2017 Jul 19, 1-8 (2017).
183. Yusuke Inoue, Tomonori Saga, Takumi Aikawa, Masahiko Kumagai, Atsuko Shimada, Yasushi Kawaguchi, Kiyoshi Naruse, Shinichi Morishita, Akihiko Koga, Hiroyuki Takeda. Complete fusion of a transposon and herpesvirus created the Teratorn mobile element in medaka fish. Nature Communications 15, 551 (2017).
184. Shuji Ishihara, Philippe Marcq, and Kaoru Sugimura. From cells to tissue: A continuum

model of epithelial mechanics. Physical Review E 96, 022418/1-14 (2017).
185. Byung-Sik Shin, Takayuki Katoh, Erik Gutierrez, Joo-Ran Kim, Hiroaki Suga, Thomas E. Dever, Amino acid substrates impose polyamine, eIF5A, or hypusine requirement for peptide synthesis, Nucleic Acids Res. 45(14), 8392-8402 (2017).
186. Masahiko Ueda, Nobuto Takeuchi, Kunihiko Kaneko. Stronger selection can slow down evolution driven by recombination on a smooth fitness landscape. PLoS ONE 12(8), e0183120 (2017).
187. Nobuto Takeuchi, Paulien Hogeweg, Kunihiko Kaneko. The origin of a primordial genome through spontaneous symmetry breaking. Nature Communications 8, 250 (2017).
188. Kwesi Teye, Koji Hashimoto. Sanae Numata, Kunihiro Ohta, Marek Haftek,Takashi Hashimoto. Altmetric: 1More detailArticle－OPENMultimerization is required for antigen binding activity of an engineered IgM/IgG chimeric antibody recognizing a skin-related antigen. Scientific Reports 7, 8212 (2017).
189. T. Horinouchi, A. Sakai, H. Kotani, K Tanabe, C. Furusawa, Improvement of isopropanol tolerance of Escherichia coli using adaptive laboratory evolution and omics technologies, JOURNAL OF BIOTECHNOLOGY 255, 47-56 (2017).
190. Yu Sakurai , Wataru Mizumura, Manami Murata, Tomoya Hada, Shoshiro Yamamoto, Kenichiro Ito, Kazuhiro Iwasaki, Takayuki, Katoh, Yuki Goto, Asako Takagi, Michinori Kohara, Hiroaki Suga, and Hideyoshi Harashima. Efficient siRNA delivery by lipid nanoparticles modified with a nonstandard macrocyclic peptide for EpCAM-targeting. Mol. Pharmaceutics 14 (10), 3290-3298 (2017).
191. Louise J. Walport, Richard Obexer, HiroakiSuga. Strategies for transitioning macrocyclic peptides to cell-permeable drug leads. Curr Opin Biotechnol. 48, 242-250 (2017).
192. Eric M. Danhart, Marina Bakhtina, William A. Cantara, Alexandra B. Kuzmishin, Xiao Ma, Brianne L. Sanford, Oscar Vargas-Rodriguez, Marija Košutić, Yuki Goto, Hiroaki Suga, Kotaro Nakanishi, Ronald Micura, Mark P. Foster and Karin Musier-Forsyth. Conformational and chemical selection by a trans-acting editing domain. Proc Natl Acad Sci U S A 114(33), E6774-E6783 (2017).
193. Hirotaka Matsumoto, Hisanori Kiryu, Chikara Furusawa, Minoru S. H. Ko, Shigeru B. H. Ko, Norio Gouda, Tetsutaro Hayashi, Itoshi Nikaido,SCODE: an efficient regulatory network inference algorithm from single-cell RNA-Seq during differentiation. BIOINFORMATICS 33-15, 2314-2321 (2017).
194. Tadasu Nozaki, Ryosuke Imai, Mai Tanbo, Ryosuke Nagashima, Sachiko Tamura, Tomomi Tani, Yasumasa Joti, Masaru Tomita, Kayo Hibino, Masato T. Kanemaki, Kerstin S. Wendt, Yasushi Okada, Takeharu Nagai, Kazuhiro Maeshima. Dynamic Organization of Chromatin Domains Revealed by Super-Resolution Live-Cell Imaging. MOLECULAR CELL 67, 282-293 (2017).
195. Tetsuya Hiraiwa, Erina Kuranaga and Tatsuo Shibata. Wave propagation of junctional remodeling in collective cell movement of epithelial tissue: Numerical simulation study.

frontiers in Cell and Developmental Biology 5, 66/1-15 (2017).
196. Yuma Fujimoto, Takahiro Sagawa, Kunihiko Kaneko. Hierarchical prisoner's dilemma in hierarchical game for resource competition. New Journal of Physics 19, 073008 (2017).
197. Tetsuya J. Kobayashi, Yuki Sughiyama. Information thermodynamic structure in population dynamics in fluctuating environment. Physical Review E 96, 012402 (2017).
198. Masashi K. Kajita, Kazuyuki Aihara, Tetsuya J. Kobayashi. Balancing specificity, sensitivity, and speed of ligand discrimination by zero-order ultraspecificity. Physical Review E 96, 012405 (2017).
199. Nozaki T, Imai R, Tanbo M, Nagashima R, Tamura S, Tani T, Joti Y, Tomita M, Hibino K, Kanemaki MT, Wendt KS, Okada Y, Nagai T, Maeshima K. Dynamic Organization of Chromatin Domains Revealed by Super-Resolution Live-Cell Imaging. MOLECULAR CELL 67, 282-293 (2017).
200. Kazuki Harada, Tetsuya Kitaguchi, Taichi Kamiya, Kyaw Htet Aung, Kazuaki Nakamura, Kunihiro Ohta and Takashi Tsuboi. Lysophosphatidylinositol-induced activation of the cation channel TRPV2 triggers glucagon-like peptide-1 secretion in enteroendocrine L cells. J. Biol. Chem. 292, 10855-10864 (2017).
201. Yusuke Himeoka, Kunihiko Kaneko. Theory for transitions between log and stationary phases: universal laws for lag time. Physical Review X 7, 021049 (2017).
202. Hidenori Nakaoka, Yuichi Wakamoto, Aging, mortality, and the fast growth trade-off of Schizosaccharomyces pombe, PLoS Biology 15, e2001109 (2017).
203. M. Yoshida, S. G. Reyes, S. Tsuda, T. Horinouchi, C. Furusawa,L. Cronin. Time-programmable drug dosing allows the manipulation, suppression and reversal of antibiotic drug resistance in vitro. NATURE COMMUNICATIONS 8, 15589 (2017).
204. A.Germond, V. Kumar, T. Ichimura, J. Moreau, C. Furusawa, H. Fujita. Raman spectroscopy as a tool for ecology and evolution. JOURNAL OF THE ROYAL SOCIETY INTERFACE 14, 131 (2017).
205. Keita Kamino, Yohei Kondo, Akihiko Nakajima, Mai Honda-Kitahara, Kunihiko Kaneko, and Satoshi Sawai. Fold-change detection and scale-invariance of cell-cell signaling in social amoeba. Proceedings of the National Academy of Sciences of the United States of America 114(21), E4149-E4157 (2017).
206. Xiao Song, Lu-yi Lu, Toby Passioura, Hiroaki Suga. Macrocyclic peptide inhibitors for the protein-protein interaction of Zaire Ebola virus protein 24 and karyopherin alpha 5. Org Biomol Chem 15(24), 5155-5160 (2017).
207. S. Suzuki, T. Horinouchi, C. Furusawa. Acceleration and suppression of resistance development by antibiotic combinations. BMC GENOMICS 18, 328 (2017).
208. Kyogo Kawaguchi, Ryoichiro Kageyama ,Masaki Sano. Topological defects control collective dynamics in neural progenitor cell cultures. Nature 545, 327-331 (2017).
209. Shintaro Yamada, Mika Okamura, Arisa Oda, Hiroshi Murakami, Kunihiro Ohta and Takatomi Yamada. Correlation of meiotic DSB formation and transcription initiation

around fission yeast recombination hotspots. GENETICS 206, 801-809 (2017).
210. Akane Kawamura, Martin Munzel, Tatsuya Kojima, Clarence Yapp, Bhaskar Bhushan, Yuki Goto, Anthony Tumber, Takayuki Katoh, Oliver N. F. King, Toby Passioura, Louise J. Walport, Stephanie B. Hatch, Sarah Madden, Susanne Muller, Paul E. Brennan, Rasheduzzaman Chowdhury, Richard J. Hopkinson, Hiroaki Suga , Christopher J. Schofield. Highly selective inhibition of histone demethylases by de novo macrocyclic peptides. Nat Commun. 8, 14773 (2017).
211. Takaki Yamamoto and Masaki Sano. Chirality-induced helical self-propulsion of cholesteric liquid crystal droplets. Soft Matter 13, 3328-3333 (2017).
212. Hao Yu, Patricia Dranchak, Zhiru Li, Ryan MacArthur, Matthew S. Munson, Nurjahan Mehzabeen, Nathan J. Baird, Kevin P. Battalie, David Ross, Scott Lovell, Clotilde K. S. Carlow, Hiroaki Suga. James Inglese, Macrocycle peptides delineate locked-open inhibition mechanism for microorganism phosphoglycerate mutases. Nat Commun 8, 14932 (2017).
213. Takashi Amoh, Keiji Murakami, Reiko Kariyama, Kenji Hori, Yasuhiko Irie, Darija Viducic, Katsuhiko Hirota, Jun Igarashi, Hiroaki Suga, Hiromi Kumon, Yoichiro Miyake. A pseudomonas aeruginosa quorum-sensing autoinducer analog enhances the activity of antibiotics against resistant strains. J Med Invest 64(1.2), 101-109 (2017).
214. Tetsuhiro S. Hatakeyama, Kunihiko Kaneko. Robustness of spatial patterns in buffered reaction-diffusion systems and its reciprocity with phase plasticity. Physical Review E, Rapid Communication 95, 030201(R) (2017).
215. Richard Obexer, Louise J. Walport, Hiroaki Suga. Exploring sequence space: harnessing chemical and biological diversity towards new peptide leads. Curr Opin Chem Biol. 38, 52-61 (2017).
216. Yui Uchida, Masahiro Uesaka, Takayoshi Yamamoto, Hiroyuki Takeda and Naoki Irie. Embryonic lethality is not sufficient to explain hourglass-like conservation of vertebrate embryos. EvoDevo 9:7, 1-11 (2017).
217. Jonathan T.Young, Tetsuhiro S. Hatakeyama, Kunihiko Kaneko. Dynamics Robustness of Linear Signaling Cascades. PLOS Computational Biology 13, e1005434 (2017).
218. Nen Saito, Kunihiko Kaneko. Embedding dual function into molecular motors through collective motion. Scientific Reports 7, 44288 (2017).
219. Seino A.K. Jongkees, Sami Caner, Christina Tysoe, Gary D. Brayer, Stephen G. Withers, Hiroaki Suga. Rapid discovery of potent and selective glycosidase-inhibiting de novo peptides. Cell Chem Biol 24(3), 381-390 (2017).
220. Masashi Fujii, Kaoru Ohashi, Yasuaki Karasawa, Minori Hikichi and Shinya Kuroda. Small-Volume effect enables robust, sensitive, and efficient information transfer in the spine. Biophysical Journal 112, 813-826 (2017).
221. Yohei Murakami, Masanori Koyama, Shigeyuki Oba, Shinya Kuroda and Shin Ishii. Model-based control of the temporal patterns of intracellular signaling in silico. Biophysics and Physicobiology 14, 29-40 (2017).

222. Katsuyuki Yugi and Shinya Kuroda. Metabolism-Centric Trans-Omics. Cell Systems 4(1), 19-20 (2017).
223. H. Shimizu, C. Furusawa, T. Hirasawa, K. Yoshikawa, Y. Toya, T. Shirai, F. Matsuda. Omics-Integrated Approach for Metabolic State Analysis of Microbial Processes: Innovationsand Future Directions. Applied Bioengineering -, 213-236 (2017).
224. Toby Passioura, Hiroaki Suga. A RaPID way to discover nonstandard macrocyclic peptide modulators of drug targets. Chem Commun (Camb) 53(12), 1931-1940 (2017).
225. Sughiyama Y, Kobayashi TJ. Steady-state thermodynamics for population growth in fluctuating environments, Physical Review E 95, 012131 (2017).
226. Koichi Kosodo, Taeko Suetsugu, Tetsuya J. Kobayashi, Fumio Matsuzaki. Systematic time-dependent visualization and quantitation of the neurogenic rate in brain organoids. Biochemical and Biophysical Research Communications 483, 94-100 (2017).
227. Taro Toyota, Taisuke Banno, Juan M. Castro, and Masayuki Imai. Locomotion and transformation of underwater micrometer-sized molecular aggregates under chemical stimuli. J. Phys. Soc. Jpn. 86, 101006 (2017).
228. S. Suzuki, T. Horinouchi, C. Furusawa. Expression profiling of antibiotic resistant bacteria obtained by laboratory evolution. Methods Mol Biol. 1520, 263-279 (2017).
229. C. Furusawa. Analysis of Drug Resistance Using Experimental Evolution. Yakugaku Zasshi 137, 373-376 (2017).
230. Shingo Suzuki, Takaaki Horinouchi, Chikara Furusawa. Expression profiling of antibiotic resistant bacteria obtained by laboratory evolution. Methods in Molecular Biology 1520, 263-279 (2017).
231. Takahiro Kohsokabe, Kunihiko Kaneko. Boundary-Induced Pattern Formation from Temporal Oscillation: Spatial Map Analysis. Europhysics Letters 116, 48005/1-6 (2017).
232. Takumi Washio, Seine A. Shintani, Hideo Higuchi and Toshiaki Hisada. Analysis of spontaneous oscillations for a three state power stroke model. Physical Review E 95, 022411 (2017).
233. Ryohei Seki, Cai Li, Qi Fang, Shinichi Hayashi, Shiro Egawa, Jiang Hu, Luohao Xu, Hailin Pan, Mao Kondo, Tomohiko Sato. Haruka Matsubara, Namiko Kamiyama, Keiichi Kitajima, Daisuke Saito, Yang Liu, M. Thomas P. Gilbert, Qi Zhou, Xing Xu, Toshihiko Shiroishi, Naoki Irie, Koji Tamura, Guojie Zhang. Functional roles of aves class-specific cis-regulatory elements on macroevolution of bird-specific features. Nature Communications 8, 14229 (2017).
234. Taro Ozaki, Kona Yamashita, Yuki Goto, Morito Shimomura, Shohei Hayashi, Shumpei Asamizu, Yoshinori Sugai, Haruo Ikeda, Hiroaki Suga, Hiroyasu Onaka. Dissection of goadsporin biosynthesis by in vitro reconstitution leading to designer analoges expressed in vivo. Nature Communications 8, 14207 (2017).
235. S. A. K. Jongkees, S. Umemoto, Hiroaki Suga. Linker-free incorporation of carbohydrates into in vitro displayed macrocyclic peptides. Chemical Science 8, 1474-1481 (2017).

236. Takayuki Katoh, Kenya Tajima, Hiroaki Suga. Consecutive Elongation of D-Amino Acids in Translation. Cell Chemical Biology 24, 46-54 (2017).
237. Tomoyuki Mano, Jean-Baptiste Delfau, Junichiro Iwasawa, and Masaki Sano. Optimal run-and-tumble based transportation of a Janus particle with active steering. Proceedings of the National Academy of Sciences 114(13), E2580-E2589 (2017).
238. Daiki Nishiguchi, Ken H. Nagai, Hugues Chate, and Masaki Sano. Long-range nematic order and anomalous fluctuations in suspensions of swimming filamentous bacteria. Physical Review E 95, 020601(R) /1-6 (2017).
239. Masashi Fujii, Kaoru Ohashi, Yasuaki Karasawa, Minori Hikichi, Shinya Kuroda. Small-volume effect enables robust, sensitive, and efficient information transfer in the spine. Biophysical Journal 112, 813-826 (2017).
240. Hideki Terajima, Hikari Yoshitane, Haruka Ozaki, Yutaka Suzuki,Shigeki Shimba, Shinya Kuroda, Wataru Iwasaki and Yoshitaka Fukada. ADARB1 catalyzes circadian A-to-I editing and regulates RNA rhythm. Nature Genetics 49, 146-151 (2017).
241. Katsuyuki Yugi,Shinya Kuroda. Metabolism-Centric Trans-Omics. Cell Systems 4, 19-20 (2017).
242. Teruyuki Matsunaga, Hiroshi Kohsaka, and Akinao Nose. Gap junction-mediated signaling from motor neurons regulates motor generation in the central circuits of larval Drosophila. The Jounal of Neuroscience 37(8), 2045-2060 (2017).
243. Lana Sinapayen, Atsushi Masumori, Takashi Ikegami. Learning by Stimulation Avoidance: A Principle to Control Spiking Neural Networks Dynamics. PLoS One 12(2), e0170388 (2017).
244. Yoichi Kosodo, Taeko Suetsugu, Tetsuya J. Kobayashi, Fumio Matsuzaki. Systematic time-dependent visualization and quantitation of the neurogenic rate in brain organoids. Biochemical and Biophysical Research Communications 483, 94-100 (2017).
245. Yuki Sughiyama, Tetsuya J. Kobayaashi. Steady-state thermodynamics for population growth in fluctuating environments. Physical Review E 95, 012131 (2017).
246. Aleksandr Drozd,Olaf Witkowski,Satoshi Matsuoka,Takashi Ikegami. Critical Mass in the Emergence of Collective Intelligence: a Parallelized Simulation of Swarms in Noisy Environments. Artificial Life and Robotics 21, 317-323 (2016).
247. Taylor, T., Bedau, M., Channon, A., Ackley, D., Banzhaf, W., Beslon, G., Dolson, E., Froese, T., Hickinbotham, S., Ikegami, T., McMullin, B., Packard, N., Rasmussen, S., Virgo, N., Agmon, E., Clark, E., McGregor, S., Ofria, C., Ropella, G., Spector, L., Stanley K. O., Stanton, A., Timperley, C., Vostinar, A., Wiser, M. Open-Ended Evolution: Perspectives from the OEE Workshop in York. Artificial Life 22, 408-423 (2016).
248. Olaf Witkowski, Takashi Ikegami. Emergence of Swarming Behavior: Foraging Agents Evolve Collective Motion Based on Signaling. PLOS ONE 11, 1-26 (2016).
249. Takashi Ikegami, Naoto Horibe, M Hanczyc. Potential Memory Effects in Self-Moving Oil Droplets. INTERNATIONAL JOURNAL OF UNCONVENTIONAL COMPUTING 11,

345-355 (2016).

250. Do Won Hwang, Namryeong Bahng, Kenichiro Ito, Seunggyun Ha, Mee Young Kim, Eunji Lee, Hiroaki Suga, Dong Soo Lee. In vivo targeting of c-Met using a non-standard macrocyclic peptide in gastric carcinoma. Cancer Lett 385, 144-149 (2016).
251. Chikara Furusawa, Tomoyuki Yamaguchi. Robust and accurate discrimination of self/non-self antigen presentations by regulatory T cell suppression. PLoS One 11(9), e0163134 (2016).
252. Shingo Suzuki, Takaaki Horinouchi, Chikara Furusawa. Phenotypic changes associated with the fitness cost in antibiotic resistant Escherichia coli strains. Molecular Biosystems 12(2), 414-20 (2016).
253. Kenji Shinoda and Kunihiko Kaneko. Chaotic Griffiths Phase with Anomalous Lyapunov Spectra in Coupled Map Networks. Physical Review Letters 117, 254101/1-6 (2016).
254. Jumpei F Yamagishi, Nen Saito, Kunihiko Kaneko. Symbiotic Cell Differentiation and Cooperative Growth in Multicellular Aggregates. PLOS Computational Biology 12(10), e1005042/1-17 (2016).
255. Tomoki Kurikawa, Kunihiko Kaneko. Dynamic Organization of Hierarchical Memories. PLoS ONE 11, e0162640/1-19 (2016).
256. Nen Saito, Yuki Sughiyama, and Kunihiko Kaneko. Motif analysis for small-number effects in chemical reaction dynamics. The Journal of Chemical Physics 145, 094111/1-7 (2016).
257. Yohei Saito, Yuki Sughiyama, Kunihiko Kaneko, and Tetsuya J. Kobayashi. Discreteness-induced transitions in multibody reaction systems. Physical Review E 94, 022140/1-8 (2016).
258. Atsushi Kamimura, Kunihiko Kaneko. Negative scaling relationship between molecular diversity and resource abundances. Physical Review E 93, 062419/1-13 (2016).
259. Benjamin Pfeuty and Kunihiko Kaneko, Requirements for efficient cell-type proportioning: regulatory timescales, stochasticity and lateral inhibition. Physical Biology 13, 026007/1-9 (2016).
260. Nobuto Takeuchi, Kunihiko Kaneko, Paulien Hogeweg. Evolutionarily stable disequilibrium: endless dynamics of evolution in a stationary population. Proceedings of the Royal Society B 283, 20153109 (2016).
261. Yusuke Himeoka and Kunihiko Kaneko. Enzyme oscillation can enhance the thermodynamic efficiency of cellular metabolism: consequence of anti-phase coupling between reaction flux and affinity. Physical Biology 13, 026002/1-12 (2016).
262. Morito Sakuma, Sayaka Kita, and Hideo Higuchi. Quantitative evaluation of malignant gliomas damage induced by photoactivation of IR700 dye. Science and Technology of Advanced Materials 22, 473-482 (2016).
263. Gaigai Yu, Hiroyuki Onodera, Yuki Aono, Fuun Kawano, Yoshibumi Ueda, Akihiro Furuya, Hideyuki Suzuki, and Moritoshi Sato. Optical manipulation of the alpha subunits of

heterotrimeric G proteins using photoswitchable dimerization systems. Scientific Reports 6, 35777 (2016).

264. Fuun Kawano, Risako Okazaki, Masayuki Yazawa, and Moritoshi Sato. A photoactivatable Cre?loxP recombination system for optogenetic genome engineering. Nature Chemical Biology 12, 1059-1064 (2016).
265. Keiji Fushimi, Takahiro Nakajima, Yuki Aono, Tatsuro Yamamoto, Ni-Ni-Win, Masahiko Ikeuchi, Moritoshi Sato and Rei Narikawa. Photoconversion and fluorescence properties of a red/green-type cyanobacteriochrome AM1_C0023g2 that binds not only phycocyanobilin but also biliverdin. Frontiers in Microbiology 7, 588 (2016).
266. Mikihiro Hashimoto, Takashi Nozoe, Hidenori Nakaoka, Reiko Okura, Sayo Akiyoshi, Kunihiko Kaneko, Edo Kussell, and Yuichi Wakamoto. Noise-driven growth rate gain in clonal cellular populations. PNAS 113, 3251-3256 (2016).
267. Maroš Pleška, Long Qian, Reiko Okura. Tobias Bergmiller, Yuichi Wakamoto, Edo Kussell, and Călin C. Guet, Bacterial autoimmunity due to a restriction-modification system. Current Biology 26, 404-409 (2016).
268. Ayako Uno, Ryohei Nakamura, Tatsuya Tsukahara, Wei Qu, Sumio Sugano, Yutaka Suzuki, Shinichi Morishita, and Hiroyuki Takeda. Comparative analysis of genome and epigenome in the closely related medaka species identifies conserved sequence preferences for DNA hypomethylated domains. Zoological Science 33, 368-365 (2016).
269. Takane Ozawa, Tomoko Mizuhara, Masataka Arata, Masakazu Shimada, Teruyuki Niimi, Kensuke Okada, Yasukazu Okada, and Kunihiro Ohta. Histone deacetylases control module-specific phenotypic plasticity in beetle weapons. PNAS 113, 15042?15047 (2016).
270. Koji Hashimoto, Kohei Kurosawa, Akiho Murayama, Hidetaka Seo, and Kunihiro Ohta. B Cell-Based Seamless Engineering of Antibody Fc Domains. PLoS One 11, e0167232 (2016).
271. Naomichi Takemata and Kunihiro Ohta. Role of non-coding RNA transcription around gene regulatory elements in transcription factor recruitment. RNA Biology 14, 1-5 (2016).
272. Yoshito Hirata, Arisa Oda, Kunihiro Ohta, and Kazuyuki Aihara. Three-dimensional reconstruction of single-cell chromosome structure using recurrence plots. Scientific Reports 6, 34982 (2016).
273. Atsuko Miki, Josephine Galipon, Satoshi Sawai, Toshifumi Inada, and Kunihiro Ohta. RNA decay systems enhance reciprocal switching of sense and antisense transcripts in response to glucose starvation. Genes to Cells 21, 1276-1289 (2016).
274. Naoyoshi Kumakura, Hiroka Otsuki, Masaru Ito, Mika Nomoto, Yasuomi Tada, Kunihiro Ohta, and Yuichiro Watanabe. Arabidopsis AtRRP44 has ribonuclease activity that is required for cell viability. Plant Biotechnology 33, 77-85 (2016).
275. Risa Mitsumori, Tomoe Ohashi, Kazuto Kugou, Ayako Ichino ,Kei Taniguchi, Kunihiro Ohta, Hiroyuki Uchida, and Masaya Oki. Analysis of novel Sir3 binding regions in Saccharomyces cerevisiae. The Journal of Biochemistry 160, 11-17 (2016).
276. Naomichi Takemata, Arisa Oda, Takatomi Yamada, Josephine Galipon, Tomoichiro

Miyoshi, Yutaka Suzuki, Sumio Sugano, Charles S. Hoffman, Kouji Hirota,and Kunihiro Ohta. Local potentiation of stress-responsive genes by upstream noncoding transcription. Nucleic Acids Research 44 , 5174-5189 (2016).

277. Sanki Tashiro, Tetsuya Handa, Atsushi Matsuda, Takuto Ban, Toru Takigawa, Kazumi Miyasato, Kojiro Ishii, Kazuto Kugou, Kunihiro Ohta, Yasushi Hiraoka, Hisao Masukata and Junko Kanoh. Shugoshin forms a specialized chromatin domain at subtelomeres that regulates transcription and replication timing. Nature Communications 7, 10393 (2016).
278. Atsuko Miki, Josephine Galipon, Satoshi Sawai, Toshifumi Inada, and Kunihiro Ohta. RNA decay systems enhance reciprocal switching of sense and antisense transcripts in response to glucose starvation. Genes to Cells. Genes to Cells 21, 1276-1289 (2016).
279. Akihiko Nakajima, Motohiko Ishida, Taihei Fujimori, Yuichi Wakamoto, and Satoshi Sawai,The Microfluidic lighthouse: an omnidirectional gradient generator,Lab on a Chip 16, 4382-4394 (2016). Satoshi Kuwana, Hiroshi Senoo, Satoshi Sawai, and Masashi Fukuzawa. A novel, lineage-primed prestalk cell subtype involved in the morphogenesis of D. discoideum. Developmental Biology 416, 286-299 (2016).
280. Fumihito Fukujin, Akihiko Nakajima, Nao Shimada, and Satoshi Sawai. Self-organization of chemoattractant waves in Dictyostelium depends on F-actin and cell?substrate adhesion. Journal of The Royal Society Interface 13 (2016).
281. Akihiko Nakajima, Satoshi Sawai. Dissecting Spatial and Temporal Sensing in Dictyostelium Chemotaxis Using a Wave Gradient Generator. Methods in Molecular Biology 1407, 107-122 (2016).
282. Naohiro Terasaka, Kazuki Futai, Takayuki Katoh, Hiroaki Suga. A human microRNA precursor binding to folic acid discovered by small RNA transcriptomic SELEX. RNA 22(12), 1918-1928 (2016).
283. Yukiko Matsunaga, Nasir K. Bashiruddin, Yu Kitago, Junichi Takagi, Hiroaki Suga. Allosteric inhibition of a semaphorin 4D receptor plexin B1 by a high affinity macrocyclic peptide. Cell Chemical Biology 23, 1341-1350 (2016).
284. Yuki Goto, Hiroaki Suga. A post-translational cyclodehydratase, PatD, tolerates sequence variation in the C-terminal region of the substrate peptides. Chemistry Letters 45, 1247-1249 (2016).
285. Kazuki Futai, Naohiro Terasaka, Takayuki Katoh, Hiroaki Suga. tRid, an enabling method to isolate previously inaccessible small RNA fractions. Methods 106, 105-111 (2016).
286. Takayuki Katoh, Ingo Wohlgemuth, Masanobu Nagano, Marina V. Rodnina, and Hiroaki Suga. Essential structural elements in tRNA(Pro) for EF-P-mediated alleviation of translation stalling. Nature Communications 7, 11657 (2016).
287. Yoshihiko Iwane, Azusa Hitomi, Hiroshi Murakami, Takayuki Katoh, Yuki Goto, and Hiroaki Suga. Expanding the amino acid repertoire of ribosomal polypeptide synthesis via the artificial division of codon boxes.Nature Chemistry 8(4), 317-325 (2016).

288. Taisuke Banno, Yuki Tanaka, Kouichi Asakura, Taro Toyota. Self-propelled oil droplets and their morphological change to giant vesicles induced by a surfactant solution at low pH. Langmuir 32, 9591-9597 (2016).
289. Taisuke Banno, Arisa Asami, Naoko Ueno, Hiroyuki Kitahata, Yuki Koyano, Kouichi Asakura, Taro Toyota. Deformable self-propelled micro-object comprising underwater oil droplets. Scientific Reports 6, 31292 (2016).
290. Yuno Natsume, Taro Toyota. Appearance of crystalline pattern for colloidal particles encapsulated in giant vesicles. Transactions of the Materials Research Society of Japan 41, 147-149 (2016).
291. Masahito Hayashi, Masayoshi Nishiyama, Yuki Kazayama, Taro Toyota, Yoshie Harada. Kingo Takiguchi,Reversible morphological control of tubulin-encapsulating giant liposomes by hydrostatic pressure. Langmuir 32, 3794-3802 (2016).
292. Yuki Kazayama, Tetsuhiko Teshima, Toshihisa Osaki, Shoji Takeuchi, Taro Toyota. Integrated microfluidic system for size-based selection and trapping of giant vesicles. Analytical Chemistry 88, 1111-1116 (2016).
293. Kazuma Gotoh, Tomonori Nomoto, Taro Toyota, Masanori Fujinami. Effects of halide ions on the acceptor phase in spontaneous chemical oscillations in donor/membrane/acceptor systems. Journal of Colloid and Interface Science 462, 351-358 (2016).
294. Yuno Natsume, Taro Toyota. Asymmetrical polyhedral configuration of giant vesicles induced by orderly array of encapsulated colloidal particles. PLOS ONE 11, e0146683 (2016).
295. Tetsuya Hiraiwa, and Guillaume Salbreux. Role of Turnover in Active Stress Generation in a Filament Network. Physical Review Letters 116, 188101 (2016).
296. Takao Ohta, Mitsusuke Tarama and Masaki Sano. Simple model of cell crawling. Physica D 318-319, 3-11 (2016).
297. John J. Molina, Kotaro Otomura, Hayato Shiba, Hideki Kobayashi, Masaki Sano, and Ryoichi Yamamoto. Rheological evaluation of colloidal dispersions using the smoothed profile method: formulation and applications. Journal of Fluid Mechanics 792, 590-619 (2016).
298. Masaki Sano and Keiichi Tamai. A Universal Transition to Turbulence in Channel Flow. Nature Physics 12, 249-253 (2016).
299. Takanori Sano, Kentaro Kawata, Satoshi Ohono, Katsuyuki Yugi, Hiroaki Kakuda,Hiroyuki Kubota, Shinsuke Uda, Masashi Fujii, Katsuyuki Kunida, Daisuke Hoshino, Atsushi Hatano, Yuki Ito, Miharu Sato, Yutaka Suzuki, Shinya Kuroda. Selective control of up-regulated and down-regulated genes by temporal patterns and doses of insulin. Science Signaling 9, ra112 (2016).
300. Takamasa Kudo, Shinsuke Uda, Takaho Tsuchiya, Takumi Wada, Yasuaki Karasawa, Masashi Fujii, Takeshi H. Saito, Shinya Kuroda. Laguerre filter analysis with partial least square regression reveals a priming effect of ERK and CREB on c-FOS induction. PLoS

ONE 11, e0160548 (2016).

301. Sarah Filippi, Chris P. Barnes, Paul D.W. Kirk, Takamasa Kudo, Katsuyuki Kunida, Siobhan S. McMahon, Takaho Tsuchiya, Takumi Wada, Shinya Kuroda, and Michael P.H. Stumpf. Robustness of MEK-ERK dynamics and origins of Cell-to-Cell variability in MAPK signaling. Cell Reports 15, 2524-2535 (2016).
302. Eri Hasegawa, James W. Truman, and Akinao Nose. Identification of excitatory premotor interneurons which regulate local muscle contraction during Drosophila larval locomotion. Scientific Reports 6, 30806 (2016).
303. Aleksandr Drozd, Olaf Witkowski, Satoshi Matsuoka, Takashi Ikegami. Critical Mass in the Emergence of Collective Intelligence: a Parallelized Simulation of Swarms in Noisy Environments. Artificial Life and Robotics 21, 317-323 (2016).
304. Tim Taylor, Mark Bedau, Alastair Channon, David Ackley, Wolfgang Banzhaf, Guillaume Beslon, Emily Dolson, Tom Froese, Simon Hickinbotham, Takashi Ikegami, Barry McMullin, Norman Packard, Steen Rasmussen, Nathaniel Virgo, Eran Agmon, Edward Clark, Simon McGregor,Charles Ofria, Glen Ropella, Lee Spector, Kenneth O. Stanley, Adam Stanton, Christopher Timperley, Anya Vostinar, and Michael Wiser. Open-Ended Evolution: Perspectives from the OEE Workshop in York, Artificial Life 22, 408-423 (2016).
305. Olaf Witkowski, Takashi Ikegami. Emergence of Swarming Behavior: Foraging Agents Evolve Collective Motion Based on Signaling. PLoS ONE 11(4), e0152756 (2016).
306. Julien Hubert and Takashi Ikegami, How long did it last? Memorizing interval timings in a simple robotic task, Proceedings of the Artificial Life Conference 2016, 406-407 (2016).
307. Martin Biehl, Takashi Ikegami. Daniel Polani. Towards information based spatiotemporal patterns as a foundation for agent representation in dynamical systems. Proceedings of the Artificial Life Conference 2016, 722-729 (2016).
308. Yohei Saito, Yuki Sughiyama, Kunihiko Kaneko, Tetsuya J. Kobayashi, Discreteness-induced transitions in multibody reaction systems, Physical Review E 94, 22140 (2016).
309. Yukinobu Arata, Michio Hiroshima, Chan-Gi Pack, Ravikrishna Ramanujam, Fumio Motegi, Kenichi Nakazato, Hitoshi Sawa, Tetsuya J. Kobayashi, Tatsuo Shibata, and Yasushi Sako,Cortical. Polarity of the RING Protein PAR-2 Is Maintained by Exchange Rate Kinetics at the Cortical-Cytoplasmic Boundary. Cell Reports 16, 2156-2168 (2016).
310. Tetsuya J. Kobayashi, Ryo Yokota, Kazuyuki Aihara. Feedback Regulation and its Efficiency in Biochemical Networks. Journal of Statistical Physics 162. 1425-1449 (2016).

4.2.2 Books and Reviews

1. Ichihashi, N. What can we learn from the construction of in vitro replication systems? Ann NY Acad Sci, 1447, 144-156 (2019).
2. 市橋伯一. 「リボソームの in vitro 進化技術の開発」生物工学 2019 年 8 月号 97 巻 481-484(2019)

3. 金子邦彦, 古澤力. 「適応と進化におけるマクロ現象論――表現型変化の低次元拘束と揺らぎ–応答関係」日本物理学会誌, 第 74 巻 第 3 号, 137 (2019)
4. 金子邦彦. 普遍生物学: 物理に宿る生命、生命の紡ぐ物理. 東京大学出版会 (2019)
5. 樋口秀男. 「ファイマンラチェット-生体分子の運動の理解にむけて-」数理科学 56, 34-39 (2019)
6. 亀井健一郎、小林鉱石、中岡秀憲、若本祐一. 「細胞のラマンスペクトルから遺伝子発現プロファイルを推定する新手法」バイオサイエンスとインダストリー77, 17-21 (2019)
7. Tetsuya Hiraiwa, Fu-Lai Weng, Tatsuo Shibata and Erina Kuranaga, Mathematical Modeling of Tissue Folding and Asymmetric Tissue Flow during Epithelial Morphogenesis,Symmetry Vol.11, p.113 (2019).
8. 金本理奈, 石原秀至.「弱点克服 物理数学」東京図書(2019)
9. 樋口秀男. 「ファイマンラチェット-生体分子の運動の理解にむけて-」数理科学 56 , 34-39 (2019)
10. H. Higuchi and C. Shingyoji. Measuring the Motile Properties of Single Dynein Molecules. Chaper 5 In Handbook of dynein 2nd eds. Hirose and Amos ed. Pan Stanford Publishing.(2019)
11. 池上高志. 分担執筆、iHuman 有機体 -人間 -機械の未来、学芸みらい社 (2019)
12. 渡邊千穂, 柳澤実穂. 「リポソームの応用における基本課題と対策 : 膜構造と閉じ込め」膜誌, 44, 234-238 (2019)
13. 渡邊千穂, 柳澤実穂. 「高分子混雑とミクロな閉じ込めが導く分子拡散」 C&I Commun. 44, 1 (2019)
14. 森本雄矢・竹内昌治（共著）. 骨格筋研究を核とした筋スマート社会、第 5 章 7 身体運動を再現するバイオハイブリッドロボット、CMC リサーチ、pp.241-247、2019
15. 三浦重徳、竹内昌治（共著）. マイクロ流体デバイスを用いたヒト胎盤バリアチップの開発、特集「マイクロフルイディクスの DDS 研究への応用」、じほうビジネスサービス Drug Delivery System、第 34 巻 4 号 pp.261-267、(2019)
16. 金子邦彦, 古澤力. 適応と進化におけるマクロ現象論--表現型変化の低次元拘束と揺らぎ-応答関係--, 日本物理学会誌 74(3), 137-145 (2019)
17. Ukai H., Sumiyama K., Ueda H.R. Next-generation human genetics for organism-level systems biology. Curr. Opin. Biotechnol. 58, 137-145 (2019)
18. Millius A., Ode K.L., Ueda H.R. A period without PER: understanding 24-h rhythms without classic transcription and translation feedback loops. F1000Res. 8, 499 (2019)
19. 村上達哉, 上田泰己. 見る脂質のページ〈透明化による全細胞解析〉第 5 回 一細胞解像度脳アトラスによる全脳全細胞解析. Lipid 30, 122-127, (2019)
20. 杉村薫、石原秀至.「細胞と組織をつなぐ新しいクラスの連続体モデル」生体の科学 70, (2019)

21. （分担執筆）豊田太郎，池田 将，本多 智. セル・リポソーム・ヒドロゲルを基盤とする医療分子ロボット, 分子ロボティクス概論（村田　智　編），第 6 章　6.2 ，CBI 学術出版，pp.263-273 (2019).
22. 澤井哲，藤森大平.　「集団運動による自己組織的パターン形成」実験医学 37, 2180-218337 (2019)
23. K. Kaneko, C. Furusawa, Macroscopic Theory for Evolving Biological Systems Akin to Thermodynamics, Annual Rev. Biophys., 47, 273-290 (2018)
24. T. Horinouchi, T. Maeda, C. Furusawa, Understanding and engineering alcohol-tolerant bacteria using OMICS technology, World Jour. Microb. Biotech., 34(11), 157 (2018)
25. 樋口秀男.　「ファイマンラチェット-生体分子の運動の理解にむけて-」数理科学 56 ，34-39 (2019)
26. 佐藤守俊.「バイオ医薬品創出の基盤技術であるゲノム編集を自由自在に光操作する」
27. 入江直樹.　「動物学の百科事典」　公益社団法人日本動物学会 , 3-20, ファイロティピック段階 (2018)
28. 小田有沙、太田邦史.『制限酵素を用いた新しいゲノム改良技術　～大規模ゲノムシャフリング「TAQing システム」』、バイオサイエンスとインダストリーVol.76 No.5 (2018)
29. 神野圭太，近藤洋平，澤井哲.　「スケール不変な細胞間シグナリング」生物物理 58(6) 316-318 (2018)
30. 本多 智, 豊田太郎.「光で流動・非流動状態を制御する高分子材料ーナマコをヒントに生みだされた 次世代の新素材」化学 73, 40-44 (2018)
31. 豊田太郎.「ジャイアントベシクルの基礎と細胞構成系・再構成系への展開」Molecular Electronics and Bioelectronics 29, 12-15 (2018)
32. H. Sugiyama and T. Toyota. Toward Experimental Evolution with Giant Vesicles. Life 8, 53 (2018)
33. 高木優、能瀬聡直.　「ショウジョウバエ幼虫の行動制御回路」　月刊臨床神経科学 36(8), 903-906 (2018)
34. S. Takagi and A. Nose Circuit architecture for somatotopic action selection in invertebrates. Neurosci Res. 2019 Mar;140:37-42. doi: 10.1016/j.neures.2018.08.008. Epub (2018)
35. 永井健、平岩徹也、太田隆夫.「アクティブソフトマターの動的秩序」固体物理 (8 月号 通巻 630 号) 423-434 頁 (2018) .
36. 平岩徹也.「アクトミオシン細胞骨格のダイナミクスと力学の数値シミュレーション」 分子シミュレーション研究会会誌「アンサンブル」20, (No. 3, 7 月号 通巻 83 号) 167-172 頁 (2018). 担執筆, 定量生物学（小林徹也 編）, 化学同人, 2018
37. 金子邦彦.（分担執筆）、第 13 章　生命システムの物理ーゆらぎ、安定性、可塑性ー（『現代物理の展望』放送大学教育振興会（2019）
38. .杉村薫, 石原秀至.「組織の力・応力の定量生物学」小林徹也編　定量生物学 第 7 章 化学同人 (2018)

39. 岡田康志.　超解像・一分子イメージングによる分子動態の計測、森泰生、尾藤晴彦編、脳神経化学、第 30 章、319－329、化学同人、(2018)
40. 若本 祐一.（分担執筆）, 細胞成長・増殖の定量生物学. 第 5 章 In 定量生物学 - 生命現象を定量的に理解するために. 化学同人 (2018)
41. 太田邦史.「生命多元性原理」入門　講談社メチエ (2018)
42. 澤井哲, 中島昭彦.「這いまわる細胞の走化性に関する定量生物学」『定量生物学 －生命現象を定量的に理解するためにー』（小林徹也 編）第 6 章 p.93-107. 化学同人 (2018)
43. T. Toyota, T. Banno and K. Asakura. Synthetic approaches to control self-propelled motion of micrometre-sized oil droplets in aqueous solution. Chapter 5 In Self-organized Motion: Physicochemical Design based on Nonlinear Dynamics. Nakata, Pimienta, Lagzi, Kitahata, Suematsu ed. RSC Publishing (2018)
44. 古澤力, 前田智也, 堀之内貴明.　ラボ内での全自動進化実験システムの構築,実験医学別冊「あなたのラボに AI×ロボットがやってくる（夏目徹 編）(2017).
45. 石原秀至、澤井哲.　細胞内反応場のゆらぎと細胞運動,パリティ 32, 22-25 (2017).
46. 岡田康志.　超解像顕微鏡によるライブイメージング,生体の科学 68(5), 378-379 (2017).
47. 小田有沙，平田祥人，太田邦史，合原一幸. .Hi-C という染色体の立体パズルを解く,実験医学最強のステップ UP シリーズ シングルセル解析プロトコール 別冊, 313-318 (2017).
48. 畠山哲央,　金子邦彦. .生体リズムの頑健性と可塑性,生物物理 57, 186-190 (2017).
49. 小澤高嶺　太田邦史,「昆虫の形態の多様性とエピゲノム」?子供のころの疑問を明らかに,生物の科学　遺伝 4, 314-318 (2017).
50. 岡田康志, 超解像顕微鏡で観える生物現象,医学の歩み 262(5), 573-579 (2017).
51. 大橋郁、藤井雅史、小川渉、*黒田真也. 血糖値恒常性システムの数理モデル解析,実験医学 35（5）, 830-833 (2017).
52. 岡田康志. ライブイメージングのための高速超解像蛍光顕微鏡法,O plus E 39(2), 74-178 (2017).
53. 能瀬聡直、高坂洋史、伏木彬. 光によるショウジョウバエ中枢回路の機能解剖,生体の科学 68(5), 478-479 (2017).
54. 岡田康志. 共焦点顕微鏡の光学系を用いた超解像顕微鏡法,顕微鏡 52(2), 62-66 (2017).
55. 岡田康志.　超解像顕微鏡研究の最前線,顕微鏡 52(2), 61 (2017).
56. 中岡秀憲, 梅谷実樹, *若本祐一. 細胞レベルの環境応答と選択の計測,化学と生物.
57. 豊田太郎, 風山祐輝, 大崎寿久, 竹内昌治. ジャイアントベシクルのダイナミクスと人工細胞型センサーへの展開,分析化学 65, 715-727 (2017).
58. 古澤力, 鈴木真吾, 堀之内貴明. 大腸菌進化実験を用いた遺伝子発現量からの抗生物質耐性メカニズムの解析,バイオサイエンスとインダストリー 74(2), 138-140 (2016).
59. 高井啓.　岡田康志,3 色の高輝度発光タンパク質プローブの開発と応用,Journal of Japanese Biochemical Society 88(5), 669-673 (2016).

60. 岡田康志. 超解像蛍光顕微鏡法の現状と生体イメージングへの応用,レーザー研究 44(10), 643-647 (2016).
61. 岡田康志. 超解像蛍光顕微鏡,Clinical Neuroscience 34(6), 638-642 (2016).
62. 佐藤守俊. CRISPR-Cas9 システムの光操作技術,実験医学増刊号「All about ゲノム編集」 34, 47-52 (2016).
63. 豊田太郎, 本多智. 合成両親媒性分子で創る細胞様システム,生物物理 56, 165-167 (2016).
64. 佐野雅己. 現象のモデル化と数理モデルの普遍性,数理科学 631, 1-4 (2016).
65. 秋山泰身, 小林徹也. システム生物学と免疫系の自己-非自己識別,医学の歩み 259, 839-842 (2016).

4.3 Outreach

1. 古澤研、岡田研、樋口研、伊藤研。高校生のための東京大学オープンキャンパスにて展示、東京大学(2017.8, 2018.8, 2019.8)
2. 岡田康志「生物の普遍性を探る～生きているってどういうこと？」高校生のための東京大学オープンキャンパス、東京大学(2019.8.8)
3. 樋口秀男「生物の普遍性を探る～生体運動に見られる普遍性～」高校生のための東京大学オープンキャンパス、東京大学(2019.8.8)
4. 津留三良「生物の普遍性を探る～サイコロを巧みに使う生き物たち～」高校生のための東京大学オープンキャンパス、東京大学(2019.8.8)
5. 池上高志　シンポジウム「深層学習時代に認知科学の歴史と価値を見つめなおす主観を扱う科学としての認知モデリングの未来」　一般・研究者静岡大学　(2019.9.6)
6. 池上高志　NIKKEI AI/SUM 2019 「アプライド AI サミット～AI と人・産業の共進化」　招待講演　一般　東京丸の内ビルディングス　(2019.4.22-24)
7. 樋口秀男　講義「がんを知り，がんを治す」沼津西高校生　（東大）　(2019.10.25)
8. 茅元司　KISTEC 理科実験室「きん肉が動く仕組みをさぐろう！」小中学生対象（神奈川県立産業技術総合研究所）(2019.2.23)
9. 竹内研究室　東大と女子美のコラボ企画『サイエンス×アートプロジェクト 2019』女子美術大学　アート･デザイン表現学科　メディア表現領域 3 年生／ヒーリング表現領域 3 年生　計 14 名　(2019.6.20)
10. 石原秀至　第２回数理生物学若手の回夏の学校「細胞集団のダイナミクス: 濃度、極性、ネマティックス」若手の回参加者（約 30 名）　(総合研究大学院大学葉山キャンパス) (2019.8.29)
11. 豊田太郎，教養学部進学選択シンポジウム「私はどのようにして進路を決めたか」，キャリアビルディング，教養学部前期課程生（約 70 名），東京大学（駒場 I キャンパス），(2019.4.15)
12. 岡田康志「神経細胞の中のミクロの「宅配便」」「世界一おもろい授業」（体験型イベント）理化学研究所　生命システム研究センター（QBIC）対象者：一般（主に子ども）(2016.11.19)

13. 岡田康志　最先端イメージング技術で探る神経細胞の中の「宅配便」の仕組み（無料講演）千里ライフサイエンス新適塾「脳はおもしろい」第 14 回会合場所：千里ライフサイエンスセンタービル 6 階対象者：一般(2016.9.13)
14. 樋口秀男「がんを知り，がんを治す」（講義）場所：東京大学本郷キャンパス対象者：沼津西高校生約 80 名(2016.10.16)
15. 佐野雅己「物理学とはなんだろうか？－高校生に理系をすすめる 7 つの理由―」（講義）東大理学部高校生のための冬休み講座 2016 場所：東京大学理学部化学科講堂対象者：一般中高生(2016.12.27)
16. 佐野雅己「自己組織化とは何か？－ゆらぎと秩序の法則―」（講義）東大エグゼクティブ・マネジメント・プログラム「東大 EMP 第 16 期」場所：伊藤国際学術研究センター対象者：社会人(2016.11.25)
17. 佐野雅己「生命現象における普遍性とは何か？」（講義） 第 56 回生物物理若手の会「夏の学校」場所：支笏湖ユースホステル対象者：学生、大学院生（生物物理学会若手の会）(2016.9.3)
18. 佐野雅己「物理学とはなんだろうか？」（講義）東京大学オープンキャンパス場所：東京大学理学部 1 号館対象者：一般中高生(2016.8.3)
19. 佐野雅己「自己組織化とは何か？－ゆらぎと秩序の法則―」（講義）東大エグゼクティブ・マネジメント・プログラム「東大 EMP 第 15 期」場所：伊藤国際学術(2016.7.2)

Individual reports of UBI members belonging to
Department of Physics, Graduate School of Science
(2012~2019)

Full-time members　(専任)

・Chikara Furusawa

・Sosuke Ito

古澤　力、 Chikara Furusawa

1 Education and Professional Experiences

Education

1995	B.S. (Physics)	Meiji University
1997	MSc. (Physics)	The University of Tokyo
2000	Ph.D. (Physics)	The University of Tokyo

Professional Appointments

1999−2001	JSPS Research Fellow	The University of Tokyo
2001−2003	Special Postdoctoral Scientist	RIKEN
2003−2012	Associate Professor	Osaka University
2011−	Team Leader	RIKEN
2016−	Professor	The University of Tokyo

2 Research Highlights

Highlights of our research achievements are as follows:

(1) A dynamical system model of stem cell differentiation: One important issue in developmental biology is the understanding of differences between multipotent stem cells from differentiated cell types. We have performed computer simulations of the developmental process to screen for the gene regulatory networks that can generate cell-type diversity through stem cell differentiations. We found that those stem cells that both proliferate and always differentiate exhibit oscillatory expression dynamics, and that regulating the differentiation frequency of these stem cells causes a robust number distribution of cell types. These findings can explain the recently observed heterogeneity and dynamic equilibrium of the cellular states in stem cells (Furusawa and Kaneko, Science 2012; Suzuki, Furusawa and Kaneko, PLoS One 2012).

(2) Study on the emergence of low-dimensional dominant mode in evolutionary dynamics: A reduction in high-dimensional phenotypic states to a few degrees of freedom is essential to understand biological systems. In this study, we show evolutionary robustness causes such reduction which restricts possible phenotypic changes in response to a variety of environmental conditions. To examine if such dimension reduction is a result of evolution, we analyzed a cell model?with a huge number of components, that reproduces itself via a catalytic reaction network?and confirmed that common proportionality in the concentrations of all components is shaped through evolutionary processes. We found that the changes in concentration across all components in response to environmental and evolutionary changes are constrained to the changes along a small number of "dominant modes," within a huge-dimensional state space. From these observations, we propose a theory in which such constraints in phenotypic changes are achieved both by evolutionary robustness and plasticity and formulate this proposition in terms of dynamical systems (Furusawa and Kaneko, Phys Rev. E 2018; Kaneko and Furusawa, Annu. Rev.

Biophys. 2018). Accordingly, broad experimental and numerical results on phenotypic changes caused by evolution and adaptation are coherently explained.

(3) Phenotype-genotype analysis of bacterial adaptive evolution: Technological advances enabled us to quantify the phenotypic and genetic changes in their adaptive evolution. Here, to analyze nature of phenotypic and genetic changes in microbial adaptive evolution, we performed laboratory evolution experiments of E. coli under addition of various antibiotics and obtained drug-resistant strains (Suzuki et al., Nature Comm. 2014). The results of phenotypic and genotypic analyses demonstrated that the resistance to antibiotics can be quantitatively predicted by expression levels of small number genes, which suggested that the expression changes were restricted to a low dimensional dynamics which is consistent with the phenomenological laws mentioned above. The existence of an epigenetic memory that has a much longer time-scale than their generation time and contributes to the adaptive phenotypic changes was also suggested (Horinouchi et al., BMC Evo. Biol. 2015).

3 Selected Papers

- C. Furusawa and K. Kaneko, Science **338**, 215 (2012)
  This paper has been cited 138 times.
- S. Suzuki et al., Nature Comm. **5**, 5792 (2014)
  This paper has been cited 133 times.
- C. Furusawa and K. Kaneko, Phys. Rev. Lett. **108**, 208103 (2012)
  This paper has been cited 38 times.
- T. Miyamoto et al., PLoS Comp. Biol. **11**(8), e1004476 (2015)
  The paper has been cited 32 times.
- S. Ohno et al., Bioinformatics **30**(7), 981-7 (2014)
  The paper has been cited 31 times.

4 Honors, Awards and Professional Society Memberships

2012, Chikara Furusawa, Fermentation and Metabolism Research Award, Japan Bioindustry Association.

2012, Chikara Furusawa, Outstanding Paper Award, The Biophysical Society of Japan.

5 Research Plan

Future research plans are as follow:

(1)High-throughput bacterial experimental evolution under various conditions: Our theoretical and computational analyzes suggested that a phenotype of replicating cells are restricted to relatively low-dimensional dynamics. To verify the theoretical predictions and to unveil universal laws of adaptive evolution, we are planning to perform a systematic experimental evolution of E. coli cells under hundreds of stress conditions. For this purpose, we have developed an automated system for experimental evolution. This system enables us to maintain thousands of independent culture series in a fully automated manner (Horinouchi et al., Jour. Lab Auto. 2014), which is the most high-throughput system for laboratory evolution at present. We will perform a genome-wide analysis of phenotypic and genotypic changes occurred during the adaptive evolution experiments. By integrating these high-dimensional data, we will analyze the structure and dimensionality of "possible phenotype/genotype space" in the high-dimensional state space of *E. coli*, by using appropriate machine learning methods. We expect that the comprehensive analysis of phenotype-genotype mapping during the adaptive evolutions will provide the nature of phenotypic and genotypic plasticity.

(2) Analysis of interplay between adaptive dynamics at different time-scales: The process of adaptive evolution is maintained by cellular dynamics of different time-scales. These include expression dynamics, epigenetic dynamics, and evolutionary dynamics with genomic alternations. For robust adaptive evolution, the appropriate interplay between the dynamics of different time-scales should be critical. In this study, by using the theoretical analysis computational model of replicating cells, we will analyze how such dynamics interplays between different time-scale maintains robustness and plasticity in biological systems, and how such dynamics can be represented by a small number of macroscopic variables. Furthermore, based on the high-dimensional data acquired of phenotypic and genetic changes in bacterial adaptive evolution mentioned above, we are planning to decode the macroscopic state variables representing plasticity and robustness. We expect the construction of a macroscopic state theory will provide an effective method for the prediction and control of adaptive evolution in biological systems.

(3) Understanding the plasticity and robustness of multicellular systems: Recently, high-dimensional quantifications of biological dynamics, such as single-cell RNA-Seq analysis of developmental process (e.g., Wagner et al., Science 2018) have become possible. Although such large-scale data have enough information to describe plasticity and robustness of complex cellular dynamics, methods for analyzing such high-dimensional data of biological dynamics are still in developmental stages. Here, by using such high-dimensional data of developmental dynamics, we will decode a small number of essential degrees of freedom representing stem cell differentiation dynamics. Furthermore, we will reconstruct an epigenetic landscape represented by the essential degrees of freedom, which controls the differentiation dynamics of stem cells, as proposed by Waddington. The landscape should dynamically change via cell-cell communications. Analyzing the dynamics of the landscape helps us understand how phenotypic plasticity (e.g., fluctuations and oscillations in the expression dynamics) and cell-cell communication coordinate robust developmental processes. Based on this understanding, we will develop a method that can control the cellular state by modifying the landscape using chemical or physical perturbations.

6 Publications and Patents

< Refereed Original Papers >

[1] C. Furusawa and K. Kaneko: A Dynamical-Systems View of Stem Cell Biology, Science **338**, 215 (2012).

[2] T. Hirasawa, J. Kim, T. Shirai, C. Furusawa, H. Shimizu: Molecular Mechanisms and Metabolic Engineering of Glutamate Overproduction in Corynebacterium glutamicum, Subcell. Biochem. **64**, 261-81 (2012).

[3] S. Ohno, C. Furusawa, H. Shimizu: In silico screening of triple reaction knockout Escherichia coli strains for over production of useful metabolites., J. Biosci. Bioeng. **115**(2), 221-8 (2012).

[4] C. Furusawa, K. Kaneko: Adaptation to optimal cell growth through self-organized criticality, Phys. Rev. Lett. **108**, 208103 (2012).

[5] Y Usui, T. Hirasawa, C. Furusawa, N. Yamamoto, H. Mori, and H. Shimizu: Investigating the effects of perturbations to pgi and eno gene expression on central carbon metabolism in Escherichia coli using 13C metabolic flux analysis, Microb. Cell Fact. **11**(1), 87 (2012).

[6] S. Chatsurachai, C. Furusawa and H. Shimizu: An in silico Platform for Heterologous Pathway Design to Produce Nonnative Metabolites, BMC Bioinformatics **13**(1), 93 (2012).

[7] S.A. Mahmud, T. Hirasawa, C. Furusawa, K. Yoshikawa, H. Shimizu: Understanding the mechanism of heat stress tolerance caused by high trehalose accumulation in Saccharomyces cerevisiae using DNA microarray, J Biosci Bioeng **113**(4), 526-8 (2012).

[8] Y. Ida, C. Furusawa, T. Hirasawa, H. Shimizu: Stable disruption of ethanol production by deletion of the genes encoding alcohol dehydrogenase isozymes in Saccharomyces cerevisiae, Jour. Biosci. Bioeng. **113**(2), 192-5 (2012).

[9] T. Hirasawa, M. Takekuni, K. Yoshikawa, A. Ookubo, C. Furusawa, H. Shimizu: Genome-wide identification of the targets for genetic manipulation to improve L-lactate production by Saccharomyces cerevisiae by using a single-gene deletion strain collection, Jour. Biotech. **168**(2), 185-93 (2013).

[10] C. Furusawa, K. Kaneko: Epigenetic feedback regulation accelerates adaptation and evolution, PLoS One **8**(5), e61251 (2013).

[11] S. Chatsurachai, C. Furusawa, H. Shimizu: ArtPathDesign - Rational heterologous pathway design system for the production of nonnative metabolites, Jour. Biosci. Bioeng. **116**(4), 524-7 (2013).

[12] K. Yoshikawa, T. Hirasawa, K. Ogawa, Y. Hidaka, T. Nakajima, C. Furusawa, H. Shimizu: Integrated transcriptomic and metabolomic analysis of the central metabolism of Synechocystis sp. PCC 6803 under different trophic conditions, Biotech. Jour. **8**(5), 571-80 (2013).

[13] Y. Ida, T. Hirasawa, C. Furusawa, H. Shimizu: Utilization of Saccharomyces cerevisiae recombinant strain incapable of both ethanol and glycerol biosynthesis for anaerobic bioproduction, J. Biosci. Bioeng. **97**(11), 4811-9 (2013).

[14] N. Ono, S. Suzuki, C. Furusawa, H. Shimizu, T. Yomo: Development of a physical model-based algorithm for the detection of single-nucleotide substitutions by using tiling microarrays, PLoS One **8**(1), e54571 (2013).

[15] C. Furusawa, T. Horinouchi, T. Hirasawa, H. Shimizu: Systems Metabolic Engineering: The Creation of Microbial Cell Factories by Rational Metabolic Design and Evolution, Adv. Biochem. Eng. Biotechnol. **131**, 1-23 (2013).

[16] N. Saito, S. Ishihara, K. Kaneko: The Baldwin effect under multi-peaked fitness landscapes: Phenotypic fluctuation accelerates evolutionary rate, Physical Review E, **87**, 052701 (2013).

[17] N. Saito, M. Kikuchi: Robustness Leads Close to the Edge of Chaos in Coupled Map Networks: toward the understanding of biological networks, New Journal of Physics, **15** 053037 (2013).

[18] Y. Matsumoto, Y. Murakami, S. Tsuru, B.W. Ying, T. Yomo: Growth rate-coordinated transcriptome reorganization in bacteria, BMC Genomics **14**(808), 1-10 (2013).

[19] S. Suzuki, T. Horinouchi, C. Furusawa: Prediction of antibiotic resistance by gene expression profiles, Nature Comm. **5**, 5792 (2014).

[20] K. Tokuyama, S. Ohno, K. Yoshikawa, T. Hirasawa, S. Tanaka, C. Furusawa, H. Shimizu: Increased 3-hydroxypropionic acid production from glycerol, by modification of central metabolism in Escherichia coli, Microb. Cell Fact **13**, 64 (2014).

[21] N. Okahashi, S. Kajihata, C. Furusawa, H. Shimizu: Reliable Metabolic Flux Estimation in Escherichia coli Central Carbon Metabolism Using Intracellular Free Amino Acids, Metabolite **4**(2), 408-20 (2014).

[22] T. Nakajima, S. Kajihata, K. Yoshikawa, F. Matsuda, C. Furusawa, T. Hirasawa, H. Shimizu: Integrated Metabolic Flux and Omics Analysis of Synechocystis sp. PCC 6803 under Mixotrophic and Photoheterotrophic Conditions, Plant Cell Physiol. **55**(9), 1605-12 (2014).

[23] S. Kajihata, C. Furusawa, F. Matsuda, H. Shimizu, OpenMebius: An Open Source Software for Isotopically Nonstationary (13)C-Based Metabolic Flux Analysis, Biomed. Res. Int. **2014**, 627014 (2014).

[24] Y. Yamauchi, T. Hirasawa, M. Nishii, C. Furusawa H. Shimizu: Enhanced acetic acid and succinic acid production under microaerobic conditions by Corynebacterium glutamicum harboring Escherichia coli transhydrogenase gene pntAB, Jour. Gen. Appl. Microbiol. **60**(3), 112-8 (2014).

[25] S. Ohno, H. Shimizu, C. Furusawa: FastPros: screening of reaction knockout strategies for metabolic engineering, Bioinformatics **30**(7), 981-7 (2014).

[26] T. Horinouchi, T. Minamoto, S. Suzuki, H. Shimizu, C. Furusawa: Development of an Automated Culture System for Laboratory Evolution, Jour. Lab. Automation **19**(5), 478-82 (2014).

[27] T. Hirasawa, Y. Ida, C. Furusawa, H. Shimizu: Potential of a Saccharomyces cerevisiae recombinant strain lacking ethanol and glycerol biosynthesis pathways in efficient anaerobic bioproduction, Bioengineered **5**(2), 123-8 (2014).

[28] N. Saito, S. Ishihara, K. Kabeko: Evolution of Genetic Redundancy : The Relevance of Complexity in Genotype-Phenotype Mapping, New Journal of Physics, **16**, 063013 (2014).

[29] B.W. Ying, S. Tsuru, S. Seno, H. Matsuda, T. Yomo: Gene expression scaled by distance to the genome replication site, Molecular BioSystems **10**(3), 375-9 (2014).

[30] Y. Akeno, B.W. Ying, S. Tsuru, T. Yomo: A reduced genome decreases the host carrying capacity for foreign DNA, Microbial Cell Factories **13**(49), 1-9 (2014).

[31] K. Nishimura, S. Tsuru, H. Suzuki, T. Yomo: Stochasticity in gene expression in a cell-sized compartment, ACS Synthetic Biology **4**(5), 566-76 (2014).

[32] Y. Ishizawa, B.W. Ying, S. Tsuru, T. Yomo: Nutrient-dependent growth defects and mutability of mutators in Escherichia coli, Genes to Cells **20**(1), 68-76 (2014).

[33] M. Yoshida, S. Tsuru, N. Hirata, S. Seno, H. Matsuda, B.W. Ying, T. Yomo: Directed evolution of cell size in Escherichia coli, BMC Evolutionary Biology **14**(257), 1-12 (2014).

[34] K. Yoshikawa, S. Aikawa, Y. Kojima, Y. Toya, C. Furusawa, A. Kondo, and H. Shimizu: Construction of a genome-scale metabolic model of Arthrospira platensis NIES-39 and metabolic design for cyanobacterial bioproduction, PLoS One **10**(12), e0144430 (2015).

[35] C. Furusawa and K. Kaneko: Global relationships in fluctuation and response in adaptive evolution, Jour. Roy. Soc. Interface **12**(109), 20150482 (2015).

[36] T. Horinouchi, S. Suzuki, T. Hirasawa, N. Ono, T. Yomo, H. Shimizu, and C. Furusawa: Phenotypic convergence in bacterial adaptive evolution to ethanol stress, BMC Evo. Biol. **15**, 180 (2015).

[37] B.W. Ying, Y. Matsumoto, K. Kitahara, S. Suzuki, N. Ono, C. Furusawa, T. Kishimoto, and T. Yomo: Bacterial transcriptome reorganization in thermal adaptive evolution, BMC genomics **16**(1), 802 (2015).

[38] T. Miyamoto, C. Furusawa, and K. Kaneko: Pluripotency, Differentiation, and Reprogramming: A Gene Expression Dynamics Model with Epigenetic Feedback Regulation, PLoS Comp. Biol. **11**(8), e1004476 (2015).

[39] K. Kaneko, C. Furusawa, T. Yomo: Universal Relationship in Gene-Expression Changes for Cells in Steady-Growth State, Physical Review X **5**, 011014 (2015).

[40] S. Suzuki, T. Horinouchi, C. Furusawa: Suppression of antibiotic resistance acquisition by combined use of antibiotics, Jour. Biosci. Bioeng. **120**(4), 467 (2015).

[41] K. Kajihata, F. Matsuda, M. Yoshimi, K. Hayakawa, C. Furusawa, A. Kanda, H. Shimizu: 13C-based metabolic flux analysis of Saccharomyces cerevisiae with a reduced Crabtree effect, Jour. Biosci. Bioeng. **120**(2), 140 (2015).

[42] Y. Murakami,Y. Matsumoto, S. Tsuru, B.W. Ying,T. Yomo: Global coordination in adaptation to gene rewiring, Nucleic Acids Research **42**(2), 1304-16 (2015).

[43] T. Kishimoto, B.W. Ying, S. Tsuru, L. Iijima, S. Suzuki, T. Hashimoto, A. Oyake, H. Kobayashi, Y. Someya, D. Narisawa, T. Yomo: Molecular Clock of Neutral Mutations in a Fitness-Increasing Evolutionary Process, PLoS Genetics **11**(7), 1-18 (2015).

[44] B.W. Ying, T. Honda, S. Tsuru, S. Seno, H. Matsuda, Y. Kazuta, T. Yomo: Evolutionary Consequence of a Trade-Off between Growth and Maintenance along with Ribosomal Damages, PLoS ONE **10**(8), 1-19 (2015).

[45] S. Tsuru, Y. Ishizawa, A. Shibai, Y. Takahashi, D. Motooka, S. Nakamura, T. Yomo: Genomic confirmation of nutrient-dependent mutability of mutators in Escherichia coli, Genes to Cells **20**(12), 972-81 (2015).

[46] R. Baumstark, S. Hanzelmann, S. Tsuru, Y. Schaerli, M. Francesconi, F.M. Mancuso, R. Castelo, M. Isalan: The propagation of perturbations in rewired bacterial gene networks, Nature Communications **6**(10105), 1-11 (2015).

[47] N. Saito, Y. Sughiyama and K. Kaneko: Motif Analysis for Small-Number Effects in Chemical Reaction Dynamics, Jour. Chem. Phys. **145**, 094111 (2016).

[48] C. Furusawa and T. Yamaguchi: Robust and Accurate Discrimination of Self/Non-Self Antigen Presentations by Regulatory T Cell Suppression, PLoS One **11**(9), e0163134 (2016).

[49] S. Suzuki, T. Horinouchi and C. Furusawa: Phenotypic changes associated with the fitness cost in antibiotic resistant Escherichia coli strains, Mol. Biosys **12**(2), 414-20 (2016).

[50] J. F. Yamagishi, N. Saito and K. Kaneko: Symbiotic Cell Differentiation and Cooperative Growth in Multicellular Aggregates, PLoS Comput. Biol. **12**(10), e1005042 (2016).

[51] N. Saito and K. Kaneko: Embedding dual function into molecular motors through collective motion, Scientific Reports **7**, 44288 (2017).

[52] H. Shimizu, C. Furusawa, T. Hirasawa, K. Yoshikawa, Y. Toya, T. Shirai and F. Matsuda: Omics-Integrated Approach for Metabolic State Analysis of Microbial Processes: Innovations and Future Directions, Appl. Bioeng. **5**, 213-236 (2017).

[53] S. Suzuki, T. Horinouchi and C. Furusawa: Expression profiling of antibiotic resistant bacteria obtained by laboratory evolution, Meth. Mol. Biol. **1520**, 263-279 (2017).

[54] H. Matsumoto, H. Kiryu, C. Furusawa, M. SH. Ko, S. BH. Ko, N. Gouda, T. Hayashi and I. Nikaido: SCODE: An efficient regulatory network inference algorithm from single-cell RNA-Seq during differentiation, Bioinformatics **33**(15), 2314-2321 (2017).

[55] S. Suzuki, T. Horinouchi and C. Furusawa: Acceleration and Suppression of Resistance Development by Antibiotic Combinations, BMC Genomics, **18**(1), 328 (2017).

[56] M. Yoshida, S. G. Reyes, S. Tsuda, T. Horinouchi, C. Furusawa and L. Cronin: Time-programmable drug dosing allows the manipulation, suppression and reversal of antibiotic drug resistance *in vitro*, Nature Comm. **8**, 15589 (2017).

[57] A. Germond, V. Kumar, T. Ichimura, J. Moreau, C. Furusawa, H. Fujita, T. M. Watanabe: Raman spectroscopy as a tool for ecology and evolution, Jour. Roy. Soc. Interface **14**(131) 20170174 (2017).

[58] T. Horinouchi, A. Sakai, H. Kotani, K Tanabe, C. Furusawa: Improvement of isopropanol tolerance of Escherichia coli using adaptive laboratory evolution and omics technologies, Jour. Biotech **255**, 47-56 (2017).

[59] T. Horinouchi, S. Suzuki, H. Kotani, K. Tanabe, N. Sakata, H. Shimizu, C. Furusawa: Prediction of Cross-resistance and Collateral Sensitivity by Gene Expression profiles and Genomic Mutations, Sci. Rep. **7**(1), 14009 (2017).

[60] T. S. Hatakeyama, C. Furusawa: Metabolic dynamics restricted by conserved carriers: Jamming and feedback, PLoS Comp. Biol. **13**(11), e1005847 (2017).

[61] A. Shibai, Y. Takahashi, Y. Ishizawa, D. Motooka, S. Nakamura, B. W. Ying, S. Tsuru: Mutation accumulation under UV radiation in Escherichia coli, Sci. Rep. **7**(1), 14531 (2017).

[62] S. Takano, B.J. Pawlowska, I. Gudelj, T. Yomo, S. Tsuru: Density-Dependent Recycling Promotes the Long-Term Survival of Bacterial Populations during Periods of Starvation, mBio **8**(1), 1-14 (2017).

[63] C. Furusawa, T. Horinouchi, T. Maeda: Toward prediction and control of antibiotic-resistance evolution, Curr. Opin. Biotechnol. **54**, 45-59 (2018).

[64] K. Kaneko and C. Furusawa: Macroscopic Theory for Evolving Biological Systems Akin to Thermodynamics, Annu. Rev. Biophys. **47**, 273-290 (2018).

[65] C. Furusawa and K. Kaneko: Formation of Dominant Mode by Evolution in Biological System, Phys. Rev. E **97**(4), 042410 (2018).

[66] K. Tokuyama, Y. Toya, T. Horinouchi, C. Furusawa, F. Matsuda, H. Shimizu: Application of adaptive laboratory evolution to overcome a flux limitation in an Escherichia coli production strain, Biotechnol. Bioeng. **115**(6), 1542-1551 (2018).

[67] T. Hirasawa, M. Saito, K. Yoshikawa, C. Furusawa, H. Shimizu: Integrated Analysis of the Transcriptome and Metabolome of Corynebacterium glutamicum during Penicillin-Induced Glutamic Acid Production, Biotechnol. Jour. **13**(5), e1700612 (2018).

[68] A. Germond, T. Ichimura, T. Horinouchi, H. Fujita, C. Furusawa, T. M. Watanabe: Raman spectral signature reflects transcriptomic features of antibiotic resistance in Escherichia coli, Comm. Biology **1**, 85 (2018).

[69] K. Okamoto, A. Germond, H. Fujita, C. Furusawa, Y. Okada, T. M. Watanabe: Single cell analysis reveals a biophysical aspect of collective cell-state transition in embryonic stem cell differentiation, Sci. Rep. **8**(1), 11965 (2018).

[70] T. Komori, A. Shibai, H. Saito, Y. Akeno, A. Germond, T. Horinouchi, C. Furusawa, S. Tsuru: Enhancement of K-strategy evolution in histidine utilization using a container with compartments, Genes Cells **23**(10), 893-903 (2018).

[71] A. Shibai, S. Tsuru, T. Yomo: Development of an Automated UV Irradiation Device for Microbial Cell Culture, SLAS Technol. **10**, 1-7 (2018).

[72] T. Maeda, T. Horinouchi, N. Sakata, A. Sakai, C. Furusawa: High-throughput identification of the sensitivities of an Escherichia coli ΔrecA mutant strain to various chemical compounds, Jour. Antibiot.**72**(7), 566 (2019).

[73] C. Furusawa, T. Horinouchi, T. Maeda: Toward prediction and control of antibiotic-resistance evolution, Curr. Opin. Biotech. **54**, 45-49 (2019).

[74] A. Shibai, T. Maeda, M. Kawada, H. Kotani, N. Sakata, C. Furusawa: Complete Genome Sequences of Three Star-Shaped Bacteria, Stella humosa, Stella vacuolata, and Stella Species ATCC 35155, Microbiol. Resour. Announc.**8**(32), e00719 (2019).

[75] T. Yamaguchi, S. Teraguchi, C. Furusawa, H Machiyama, T. M. Watanabe, H. Fujita, S. Sakaguchi, T. Yanagida: Theoretical modeling reveals that regulatory T cells increase T cell-interaction with antigen-presenting cells for stable immune-tolerance, Int. Immunol. in press.

[76] A. Shibai, K. Satoh, M. Kawada, H. Kotani, I. Narumi, C. Furusawa: Complete Genome Sequence of a Radioresistant Bacterial Strain, Deinococcus grandis ATCC 43672, Microbiol. Resour. Announc., in press.

＜Review Papers＞

[77] K. Yoshikawa, C. Furusawa, T. Hirasawa, and H. Shimizu: Design of Superior Cell Factories Based on Systems Wide Omics Analysis, Systems Metabolic Engineering p. 57-81 (edited by C. Wittmann and S. Y. Lee), Springer (2012).

[78] C. Furusawa, T. Horinouchi, T. Hirasawa, and H. Shimizu: Systems Metabolic Engineering: The Creation of Microbial Cell Factories by Rational Metabolic Design and Evolution, Adv. Biochem. Eng. Biotechnol. **131**, 1-23 (2013).

[79] 堀之内貴明, 古澤力: 適応進化はどのように起こるのか?〜進化実験によるアプローチ〜, 細胞工学 **33**(6), 666-669 (2014).

[80] 古澤力: 微生物の実験室進化, 生体の科学 **65**(5), 452-453 (2014).

[81] Y. Iba, N. Saito: A. Kitajima: Multicanonical MCMC for Sampling Rare Events, Annals of the Institute of Statistical Mathematics, **66**, issue3, (2014)

[82] 堀之内貴明, 鈴木真吾, 古澤力: 微生物の適応進化過程の理解とその応用, 生物工学会 **93**(9), 536-538 (2015).

[83] 古澤力, 鈴木真吾, 堀之内貴明: 大腸菌進化実験を用いた遺伝子発現量からの抗生物質耐性メカニズムの解析, バイオサイエンスとインダストリー **74**(2), 138-140 (2016).

[84] C. Furusawa: Analysis of Drug Resistance Using Experimental Evolution, Yakugaku Zasshi **137**(4), 373-376 (2017).

[85] T. Horinouchi, T. Maeda, C. Furusawa: Understanding and engineering alcohol-tolerant bacteria using OMICS technology, World Jour. Microb. Biotech. **34**(11), 157 (2018).

[86] 金子邦彦, 古澤力: 適応と進化におけるマクロ現象論–表現型変化の低次元拘束と揺らぎ-応答関係–, 日本物理学会誌 **74**(3), 137-145 (2019).

＜Books＞

[87] 古澤力: 進化学に残された謎：複数の形質が絡み合う進化プロセスはどのように可能か？, 進化の謎をゲノムで解く（長谷部光泰 編）, 学研メディカル秀潤社　(2015).

[88] 古澤力, 前田智也, 堀之内貴明: ラボ内での全自動進化実験システムの構築, 実験医学別冊「あなたのラボに AI ×ロボットがやってくる（夏目徹 編）, 羊土社 (2017).

[89] 古澤力: 進化実験の定量生物学, 定量生物学（小林徹也　編）, 化学同人 (2018).

＜Patent Applications＞

[90] R. Fujii, T. Shirai, T. Araki, K. Amano, Y. Matsumoto, T. Tateno, N. Takebayashi, T. Morishige, H. Takahashi, M. Wada, H. Shimizu, C. Furusawa, T. Hirasawa, T. Hidesaki, A. Endo, D. L. Jurgenlohmann, A. Madhavan, S. S. Chong: Microorganism having carbon dioxide fixation pathway introduced thereinto. Patent Application WO2013018734

[91] K. Amano, T. Shirai, H. Takahashi, J. Hirano, Y. Matsumoto, N. Takebayashi, M. Wada, H. Shimizu, C. Furusawa, T. Hirasawa: Isopropyl alcohol-producing bacterium having improved productivity by gntr destruction, United States Patent Application 201302808044

[92] Y. Matsumoto, J. Hirano, T. Morishige, T. Shirai, H. Takahashi, K. Amano, N. Takebayashi, M. Wada, H. Shimizu, C. Furusawa, T. Hirasawa: Highly Productive Isopropyl Alchol-Producing Bacterium, United States Patent Application 20130005008

[93] 白井智量, 古澤力, 堀之内貴明, 折下涼子, 阪田奈津枝, 田辺久美, 小谷葉月: メタクリル酸耐性微生物及びその製造方法, 特願 2016-230548

7 Invited Presentations at International Conferences

[1] Chikara Furusawa: Oscillatory protein expression dynamics generates robust and irreversible differentiation dynamics of stem cells, iCeMS Symposium on Theoretical and Computational Biology, Kyoto (2013).

[2] Chikara Furusawa: Oscillatory protein expression dynamics generates robust and irreversible differentiation dynamics of stem cells, 8th Asian Biophysics Association (ABA) Symposium, Jeju (2013).

[3] Chikara Furusawa: Oscillatory Protein Expression Dynamics Generates Robust and Irreversible Differentiation Dynamics of Stem Cells, The 4th Symposium on Systems and Synthetic Biology(TriSys), Hong-Kong (2013).

[4] Chikara Furusawa: Oscillatory protein expression dynamics generates robust and irreversible differentiation of stem cells, 3rd International Conference on Tissue Science & Regenerative Medicine, Valencia (2014).

[5] Chikara Furusawa: Creating stress tolerant bacterial cells by experimental evolution, 5th Asian Symposium on Innovative Bio-production and Biorefinery, Tainan (2014).

[6] Chikara Furusawa: Toward Understanding of Adaptive Evolution: Computational Analysis and Experimental Evolution, QBiC Symposium: High-dimensional data for the design principles of life, Osaka (2015).

[7] Chikara Furusawa: Phenotypic Convergence in Experimental Evolution of Antibiotic Resistant Bacteria, 2nd Symposium on Complex Biodynamics & Networks, Tsuruoka (2015).

[8] Chikara Furusawa: Toward Understanding of Adaptive Evolution: High-throughput Laboratory Evolution and Computational Analysis, International Symposium on Universal Biology, Tokyo (2016).

[9] Chikara Furusawa: Toward Understanding of Adaptive Evolution: Theoretical Analysis and Microbial Laboratory Evolution, 5th International Symposium of the Mathematics on Chromatin Live Dynamics, Hiroshima (2017).

[10] Chikara Furusawa: Phenotypic diversity and constraints in microbial adaptive evolution, Les Houches School “Evolution of Diversity”, France (2018).

[11] Chikara Furusawa: High-throughput Laboratory Evolution of E. coli to Unveil Phenotypic Plasticity and Constraint, 1st Asia Evo., China (2018).

[12] Chikara Furusawa: High-throughput laboratory evolution of E. coli: toward understanding of phenotypic plasticity and constraint, Euro EvoDevo2018, Ireland (2018).

[13] Chikara Furusawa: High-throughput Laboratory Evolution of E. coli to Unveil Phenotypic Plasticity and Constraint, 46th Naito Conference, Sapporo (2018).

[14] Nen Saito: Self organization via membrane deformation and reaction diffusion: 3D modeling for macropinocytosis of ameboid cell, LMU-UT Joint Workshop ,Tokyo (2018).

8 Teaching Accomplishment

8.1 Organization of Professional Societies

2011-, 古澤力, 分野別専門委員会, 日本生物物理学会

8.2 Organization and Advisory of Conferences

2012, Chikara Furusawa, Organizing committee, QBiC Symposium: High-dimensional data for the design principles of life

2016, Chikara Furusawa, Organizing committee, International Symposium on Universal Biology

9 Outreach

2012, 古澤力, 「生きているって何だろう？」, 平成２３年度西宮湯川記念こども課外教室, 西宮市立甲東小学校

2012, 古澤力, 細胞が語り合う『言葉』を理解する ～計算機シミュレーションによる生命システムの解析～, オープントラカレ講座（ヒッポファミリークラブ主催）

2013, 古澤力, 「生きているって何だろう？」, QBiC サイエンスカフェ（理化学研究所・神戸研究所一般公開）

2014, 古澤力, 生物らしさの理解へ向けて：ゆらぎと進化について, オープントラカレ講座（ヒッポファミリークラブ主催）

10 Committee Service

10.1 University Committees

理学系研究科物理学専攻サブコース主任, 2017 年 –

11 Internationalization Statistics

	Number	Country
Foreign students advised		
Bachelor Course	3	India, USA
Master Course	0	
Doctor Course	0	
Foreign researchers hosted	0	
Students sent abroad	1	France
Researchers sent abroad	0	
Foreign visitors	5	France, Germany, Denmark, UK

伊藤　創祐 (生物普遍性研究機構)、 **Sosuke Ito**

1 Education and Professional Experiences

Education

2010	B.S. (Physics)	The University of Tokyo
2012	MSc. (Physics)	The University of Tokyo
2015	Ph.D. (Physics)	The University of Tokyo

Professional Appointments

2012−2015	JSPS Research Fellowships for Young Scientists (DC1)	The University of Tokyo
2015−2017	JSPS Research Fellowships for Young Scientists (PD)	Tokyo Institute of Technology
2017−2018	Assistant Professor	Hokkaido University
2018−	PRSETO researcher	JST
2018−	Lecturer	The University of Tokyo

2 Research Highlights

We have mainly discussed connections between thermodynamics and information theory which are applicable to biochemical systems. Based on thermodynamics for stochastic processes (stochastic thermodynamics), we have newly found several relationships between thermodynamics and information theory for mesoscopic systems such as chemical reaction in biological cells and the Brownian particles. We here show research highlights of our recent results as follows.

We have generalized the second law of thermodynamics for autonomous information processing, which can solve the paradox of the Maxwell's demon. For example, we have used the Bayesian network to describe the complex information processing and generalized the second law of thermodynamics with information flow on this network [7]. In this generalization, information flow is quantified by the transfer entropy and the directed information which are well known measures of causal information flow. Then, our result gives a thermodynamic interpretation of the transfer entropy and the directed information.

We have also discussed an application of this generalized second law to the biochemical signal transduction of *E. coli* bacterium chemotaxis [5]. In this application, we focus on the information flow from the kinase activity (CheA) and the methylation level of the receptor in *E. coli* cell. As a result, we can quantitatively show that the generalized second law gives the informational bound of the robustness of the sensory adaptation.

We have additionally obtained several thermodynamic and informational results related to this generalized second law of thermodynamics with information flow. For example, the second law of thermodynamics has been generalized not only for the Bayesian network, but also for the Markov jump process [6]. We then have obtained the generalization of the Onsager reciprocal relationship for autonomous information processing with information flow for the Markov jump process [2]. We have also proposed informational and thermodynamic measure of causality based on the generalization of the second law of thermodynamics, that is called as the backward transfer entropy [3].

Recently, we have consider another type of relationship between thermodynamics and information theory based on geometry. To consider a differential geometric theory of information well known as information geometry, we have tried to construct information geometric theory of thermodynamics which are applicable to biochemical systems. For example, we have obtained a classical thermodynamic generalization of the uncertainty relationship between energy and speed (the quantum speed limit) [1]. This uncertainty relationship is applicable to the biochemical reaction such as the enzyme reaction.

3 Selected Papers

- S. Ito and T. Sagawa, Physical Review Letters, 111, 180603 (2013)
  This paper has been cited 123 times in Google scholar.
- S. Ito and T. Sagawa, Nature communications, 6, 7498 (2015)
  The paper has been cited 80 times in Google scholar. This work has been highlighted in natureasia.com as a featured paper.
- N. Shiraishi, S. Ito, K. Kawaguchi, T. Sagawa, New Journal of Physics 17, 045012 (2015)
  The paper is an invited paper. The paper has been cited 40 times in Google scholar.
- S. Ito, Scientific reports 6, 36831 (2016)
  The paper has been cited 18 times in Google scholar.
- S. Ito, Physical Review Letters, 121, 030605 (2018)
  The paper has been cited 12 times in Google scholar.

4 Honors, Awards and Professional Society Memberships

2015 The Research Award for Ph. D. Students of Faculty of Science, The University of Tokyo
2015 11th Early Career Award in Biophysics in Japan
2017 11th Young Scientist Award of the Physical Society of Japan

5 Research Plan

In a near future, we would like to develop a fundamental theory of thermodynamics with information geometry as a general framework to understand a thermodynamic aspect of information processing in living systems. To clarify the deep connection between information geometry and thermodynamics, we can consider biological systems in information geometry, which is used in the fields of the artificial intelligence, the machine learning, and neural networks. We would like to understand the design principle of living systems as a machine of information transmission driven by thermodynamic resources.

To develop it, we will reconsider several laws of thermodynamics and recent results of thermodynamics with information, from a view point of information geometry at first. To reconsider it,

we have obtained several relationships between thermodynamics and information geometry. For example, we will reconsider the thermodynamic theory of stability well known as the Glansdorff-Prigogine criterion for stability from a view point of information geometry. This theory is the old theory in 1970s, but it can be generalized in a modern form based on our theory of information geometry and thermodynamics.

Moreover, we would like to make a fundamental theory of the phase transition, dynamical system of chemical reaction, and chaos based on thermodynamics of information geometry. This fundamental theory would help to understand biological systems, which is constructed by dynamical system of chemical reactions. We would like to reconsider informational aspects of the well known phenomena from a view point of information geometry.

We also would like to make a statistical method to measure informational and thermodynamic quantities from biological experimental data, e. g., the statistics of trajectories of time series such as the FRET signal and the motion of colloidal particles. For example, we would like to make a method to measure several informational and thermodynamic quantities such as the mutual information, the transfer entropy, the integrated information, the entropy production, the partial entropy production, dynamic information flow, thermodynamic efficiency, the Fisher information and efficiencies of thermodynamic uncertainty relationships.

Based on the above plan, we would like to ask a fundamental question, i.e., how biological system can reduce thermodynamic cost and maintain an efficient system. The answer of this question would reveal the universality of living things.

6 Publications and Patents

< Refereed Original Papers >

[1] S. Ito, Phys. Rev. Lett. 121, 030605 (2018)

[2] S. Yamamoto, S. Ito, N. Shiraishi and T. Sagawa, Phys. Rev. E 94, 052121 (2016)

[3] S. Ito, Sci. Rep. 6, 36831 (2016)

[4] N. Matsumoto, K. Komori, S. Ito, Y. Michimura and Y. Aso, Phys. Rev. A 94, 033822 (2016)

[5] S. Ito and T. Sagawa, Nat. Commun. 6, 7498 (2015)

[6] N. Shiraishi, S. Ito, K. Kawaguchi and T. Sagawa, New J. Phys. 17, 045012 (2015)

[7] S. Ito and T. Sagawa, Phys. Rev. Lett. 111, 180603 (2013)

[8] K. Ashida, K. Hotta and K. Oka, iScience 19, 191 (2019)

[9] K. Ashida, T. Kato, K. Hotta and K. Oka, Neuroscience letters 706 68 (2019)

[10] K. Ashida and K. Oka, Biochemical and biophysical research communications 508, 690 (2019)

[11] T. Yoshimizu, H. Shidara, K. Ashida, K. Hotta and K. Oka, The Journal of experimental biology 221, 182790 (2018)

< Conference Proceedings >

< Review Papers >

[12] S. Ito, BUSSEI KENKYU DENSHIBAN, 6(4), 064232 (2017)

[13] S. Ito and T. Sagawa, NIHON BUTSURI GAKKAISHI, 72, 9 (2017).

[14] S. Ito, SEIBUTSU BUTSURI, 56, 232 (2016).

< Books >

[15] S. Ito, "Information Thermodynamics on Causal Networks and its Application to Biochemical Signal Transduction", Springer, 2016. (ISBN: 978-981-10-1664-6)

[16] S. Ito and T. Sagawa, "Information flow and entropy production on Bayesian networks" As a chapter of M. Dehmer, F. Emmert-Streib, Z. Chen, X. Li, Y. Shi (Eds.), "Mathematical Foundations and Applications of Graph Entropy", Wiley, 2016. (ISBN: 978-3-527-33909-9)

< Patent Applications >

7 Invited Presentations at International Conferences

[1] S. Ito, "Thermodynamics of information geometry", Data analysis and machine learning in dynamical systems, Tokyo, Japan, May. 27-29, 2019.

[2] S. Ito, "Stochastic thermodynamics of information", Frontiers of complex systems science: soft matters, statistical physics, and big data, Taipei, Taiwan, Jan. 22-23, 2018.

[3] S. Ito, "Thermodynamics of information on biochemical signaling networks", Deciphering complex energy landscape and kinetic network from single molecules to cells: a new challenge to make theories meet experiments, Dijon, France, Sep. 3-8, 2017.

[4] S. Ito, "Information flow and entropy production on Bayesian networks", Data Science Challenges: a Complex Systems Perspective, Torino, Italy, Oct. 14-17, 2015.

[5] S. Ito, "Maxwell's demon in biochemical signal transduction with feedback loop: the role of information flow in biological communication", Conference on Sensing, Information and Decision at the Cellular Level, Trieste, Italy, Jul. 14-17, 2015.

[6] S. Ito, "Maxwell ' s demon in biochemical signal transduction with feedback loop", Focus Meeting of the Kyoto Winter School for Statistical Mechanics, Kyoto, Japan, Feb. 16-17, 2015.

[7] S. Ito, "Information thermodynamics reveals the robustness of biochemical signal transduction", Bridging the gap between matter and life -Discussion with Prof. Albert Libchaber-, Tokyo, Japan, Jun. 6, 2014.

[8] S. Ito, "Information Thermodynamics on Causal Networks", Frontier of Statistical Physics and Information Processing -Perspectives from Nonequilibrium Behaviors-, Kyoto, Japan, Jul. 11-14, 2013.

8 Teaching Accomplishment

9 Contribution to Academic Community

9.1 Editorial Activities

9.2 Organization of Professional Societies

9.3 Organization and Advisory of Conferences

10 Outreach

- 2013 年 8 月 8 日　東京大学理学部オープンキャンパス 2013 講演会「情報と物理　ギャンブルの情報理論から最新の熱力学まで 」
- 2015 年 6 月 30 日　プレスリリース: 大腸菌に潜む「マクスウェルのデーモン」の働きを解明 ―情報と熱力学の融合による生体情報処理の解析への第一歩―
- 2015 年 7 月 15 日　拓く研究人-81- 「日本学術振興会特別研究員 伊藤創祐氏」 日刊工業新聞
- 2015 年 9 月 20 日　第 2 回ぶつりがく徒のつどい 「確率的な熱力学と「情報」」
- 2018 年 3 月 2 日 企業での一般公開セミナー: “Stochastic thermodynamics of information”, ARAYA Seminar, ARAYA Inc.
- 2018 年 7 月 19 日　プレスリリース: 情報の幾何学から熱力学的な不確定性原理を発見 生体内の “ ゆらぐ化学反応 ” による情報伝達の普遍的な理解へ
- 2018 年 7 月 30-31 日　夢・化学 21 北海道大学化学系への二日体験入学「サイコロから学ぶ化学反応-化学反応の熱力学理論-」
- 2019 年 8 月 8 日　東京大学理学部オープンキャンパス 2019 「生物の普遍性を探る」

11 Committee Service

11.1 External Committees

11.2 University Committees

12 Internationalization Statistics

	Number	Country
Foreign students advised		
Bachelor Course	0	
Master Course	0	
Doctor Course	0	
Foreign researchers hosted	0	
Students sent abroad	0	
Researchers sent abroad	0	
Foreign visitors	1	Germany

Individual reports of UBI members belonging to
Department of Physics, Graduate School of Science
(2012~2019)

Concurrent members (兼任)

Hideo Higuchi

Yasushi Okada

Akinao Nose

樋口 秀男、 Higuchi Hideo

1 Education and Professional Experiences

Education

1981	B.S. (Physics)	Waseda University
1983	MSc. (Physics)	Waseda University
1988	Ph.D. (Physics)	Waseda University

Professional Appointments

1983−1992	Assistant Professor	The Jikeikai University School of medicine
1992−1997	Group reader	JST ERATO Yanagida Biomotoron project
1997−2004	Associate Professor	Tohoku University
2004−2008	Professor	Tohoku University
2008−present	Professor	The University of Tokyo

2 Research Highlights

Human and mammalian bodies have a structural hierarchy in order of bio-molecule, cell, organ and body. Therefore, to understand each hierarchy and relationship between hierarchy. we investigated the dynamic function of purified protein molecule by single molecule technology, the function of molecules or organelle in cell and the vesicle movement of neutrophil in mouse.

Single Molecules: Cytoplasmic dynein is a molecular motor moving toward the minus end of microtubules. The swing of the dynein linker is supposed to be cruicial to walking of dynein. However, there is no measurement of the displacement generated by the swing. We investigated the displacement of microtubules driven by the swing of single molecules of single-headed dynein by optical tweezers [Kinoshita et al. Scientific Rep 2018]. The displacement of swing by dynein was 8.3 nm which is close to tubulin spacing in microtubule, indicating that dynein is able to walk only by the swing of dynein lever.

Model for single molecules: We constructed the unified mathematical model for processive molecular motors, dynein, kinesin and myosin-V. Our model consists of three states, and the forward and backward steps are represented by the cycles of transitions visiting different pairs of states among the three states [Sasaki et al. Biophys. J. 2018]. Our model successfully describes the behavior of step ratio of forward to backward steps and the stepping time for all of the motors in a wide range of loads from large assisting loads to superstall loads.

Multiple molecules: To understand the molecular mechanism of muscle contraction, we measured forces generated by synthetic myofilaments, in which 17 myosin molecules interact with single actin filament [Kaya et al. Nature Comm. 2017]. We found the synchronization of myosin power stroke that helps generation of large force.

Vesicle transport in cells: The transports of vesicles in cells are driven by the motor proteins. To understand the trajectory form of the transport, we tracked the vesicles by labeling it with fluorescence quantum dots [Opt. Exp. 2018]. We found an acute rotational movement of an endocytic vesicle with a pitch of 1 micrometer along microtubules in cells. It is expected that vesicles

encountered any obstacles and rotated to avoid it. We also found that the vesicle transport is an excellent indicator of cell activity. Vesicle movement in cells was decreased with increase in the cell damage induced by reactive oxygen species (ROS) of fluorescence dye [Sakuma et.al. Sci. Technol. Adv. Mater. 2016]. The motilities of kinesin and dynein were also reduced by the ROS. We evaluated quantitatively cell damage or cell activity by calculating the vesicle motility which reflects activity of the motor proteins.

Vesicle transport in mouse: Neutrophils play an essential role in the innate immune response. We developed a new non-invasive technique for the in vivo imaging of neutrophils labeled with quantum dots. The quantum dots were endocytosed into vesicles in the neutrophils, allowing us to track the vesicles at 80 frames/s with ∼20 nm accuracy [Kikushima et al. Scientific Rep. 2013]. Intriguingly, the vesicles containing quantum dots were transported at higher speed than the in vitro velocity of a molecular motor such as kinesin or dynein.

3 Selected Papers

- K. Sasaki, M. Kaya, and H. Higuchi. A unified walking model for dimeric motor proteins Biophys. J.115, 1-12 (2018)
  This work proposes the unified working model that explained movement of many molecular motors.

- Motoshi Kaya, Yoshiaki Tani, Takumi Washio, Toshiaki Hisada and Hideo Higuchi. Coordinated force generation of skeletal myosins in myofilaments through motor coupling. Nature Communications 8,16036 (2017)
  The paper has been cited 22 times for two years. This work solved the mechanism of spontaneous oscillation of cardiomyocyte.

- Takumi Washio, Toshiaki Hisada, Seine A. Shintani and Hideo Higuchi. Analysis of spontaneous oscillations for a three state power stroke model. Physical Review E. 95, 022411(2017)
  This work solved the mechanism of spontaneous oscillation of cardiomyocyte.

- Kohsuke Gonda, Minoru Miyashita, Hideo Higuchi, Hiroshi Tada, Tomonobu M Watanabe, Mika Watanabe, Takanori Ishida, Noriaki Ohuchi. Predictive diagnosis of the risk of breast cancer recurrence after surgery by single-particle quantum dot imaging. Scientific Reports 5, 14322 (2015).
  In this paper, we developed a useful monoclonal antibody (Inventers of Patent, Gonda, Higuchi, Ohuchi, Takeda) that was sold commercially (Novus Biologicals).

- Kenji Kikushima, Sayaka Kita and Hideo Higuchi* A non-invasive imaging for the in vivo tracking of high-speed vesicle transport in mouse neutrophils. Scientific reports 3:1913 (2013)
  This is the first report of noninvasively imaging of vesicles in mice.

4 Honors, Awards and Professional Society Memberships

5 Research Plan

We plan to verify the unified model for motor proteins by experiment, extend the skeletal myosin work to cardiac one, investigate the beating mechanism of sperm flagella and verify the generality of vesicle fluctuation method for index of cell activity.

Experimental evidence for the unified model: The unified mathematical model for processive molecular motors predicted the behavior of step ratio of forward to backward steps and the stepping time for kinesin, dynein and myosin-V in a wide range of loads from large assisting loads to superstall loads. However, experimental data is limited in the range of load and some data had large errors. It is, therefore, crucial to clarify the step ratio and dwell time of motors under a wide range of load. We will measure stepping motion of single molecule of motors at high temporal resolution to obtain the data with small errors.

Cyclic force generation of cardiac myosin: Molecular structure of cardiac muscle is the similar to that of skeletal muscle, while cyclical contraction of cardiac muscle is clearly different from skeletal one. We will elucidate the molecular mechanism of how dynamics of cardiac myosin molecules contributes to heart function by measuring forces of synthetic β-cardiac myosin filaments using optical tweezers. In preliminary work, the stepping ratio of cardiac myosin is much lower than that of skeletal myosin and the peak forces generated by cardiac myofilaments were 2 times higher than those observed in skeletal myofilaments. We will reveal the function of cardiac myosin specialized for cyclical contraction.

Beating mechanism of sperm flagella: The beating of sperm flagella is generated by axonemal dynein with regulation. The knowledge of the beating mechanism is still very limited at molecular level. We plan to measure force generation of dynein attached on a doublet microtubule to understand the collective force generation of an ensemble of dynein in axoneme, bundle of doublet microtubules and single doublet microtubule. In the preliminary work, the force generated by dynein ensemble was $\sim$15 pN perm of double. The 15pN will be generated $\sim$3 dynein molecules as reported value of purified dynein. The dynein containing in doublet per onem is $\sim$100. These indicate that only 3% of dynein generates force. We will understand how such low population of dynein generates beating motion.

Generality of vesicle fluctuation method: We evaluated quantitatively cell damage or activity by calculating the vesicle motility or fluctuation for two kinds of cells. We do not know the vesicle fluctuation is general index for cell activity. We plan to verify generality of the vesicle fluctuation for general cells (cancer cells, frog cells and yeast) and damages (heat, pH, toxin and ROS).

6 Publications and Patents

＜ Refereed Original Papers ＞

[1] Kon T, Oyama T, Shimo-Kon R, Imamula K, Shima T, Sutoh K, and Kurisu G The 2.8 A crystal structure of the dynein motor domain, Nature, Epub ahead of print(2012)

[2] Jinha A., Ait-Haddou R., Kaya M. and Herzog W. Response to Letter to the Editor regarding Jinha et al. A task-specific validation of homogeneous non-linear optimization approaches Journal of Theoretical Biology 306, 145. (2012)

[3] Arslam Y. Z., Jinha A., Kaya M. and Herzog W. Prediction of muscle forces using static optimization for different contractile conditions. Journal of Mechanics in Medicine and Biology 13, 1350022-1-13. (2013)

[4] Yasuhiro Suzuki, Chandra Nath Roy, Warunya Promjunyaku, Hiroyasu Hatakeyama, Kohsuke Gonda, Junji Imamura, Biju Vasudevan Pillai, Noriaki Ohuchi, Makoto Kanzaki , Hideo Higuchi, and Mitsuo Kaku. Single quantum dot tracking reveals that an individual multivalent 2 HIV-1 Tat-protein transduction domain can activate machinery for 3 lateral transport and endocytosis. Mol. Cell Biol. 33: 3039-3049 (2013).

[5] Kaya. M. and H. Higuchi. Stiffness, working stroke and force of single myosins in skeletal muscle: Elucidation of these mechanical properties by non-linear elasticity. Cell and Mol. life Sci. 70: 4275-4292 (2013)

[6] Kikushima Kenji, Kita Sayaka and Higuchi Hideo. A non-invasive imaging for the in vivo tracking of high-speed vesicle transport in mouse neutrophils. Scientific Reports 3:doi:10.1038/srep01913 (2013).

[7] Ryoma Nakao, Kenji Kikushima, Hideo Higuchi, Nozomu Obana, Nobuhiko Nomura, Bai DongYing, Makoto Ohnishi, and Hidenobu Senpuku. Novel Approach for Purification and Selective Capture of Membrane Vesicles of Periodontopathic Bacteria, Porphyromonas gingivalis. PLos One. May9e95137 (2014)

[8] Ichimura T., T. Jin, H. Fujita, H. Higuchi and T.M. Watanabe. Nano-scale measurement of biomolecules by optical microscopy and semiconductor nanoparticles. Frontiers in Physiology. 00273 (2014)

[9] Kohsuke Gonda, Minoru Miyashita, Hideo Higuchi, Hiroshi Tada, Tomonobu M Watanabe, Mika Watanabe, Takanori Ishida, Noriaki Ohuchi. Predictive diagnosis of the risk of breast cancer recurrence after surgery by single-particle quantum dot imaging. Scientific Reports 5, 14322 (2015)

[10] Chikako Shingyoji, Izumi Nakano, Yuichi Inoue and Hideo Higuchi. Dynein arms are strain-sensitive direction-switching force generators. Cytoskeleton 72:388-401 (2015) doi: 10.1002/cm.21232.

[11] Naoaki Bekki and Seine A. Shintani “Simple Dispersion Equation Based on Lamb-Wave Model for Propagating Pulsive Waves in Human Heart Wall” J. Phys. Soc. Jpn. Publication Center for Pure and Applied Physics, 84, 124802-1-6 (2015)

[12] Naoaki Bekki, Seine A. Shintani, Shin'ichi Ishiwata and Hiroshi Kanai “A Model for Measured Traveling Waves at End-Diastole in Human Heart Wall by Ultrasonic Imaging Method” J. Phys. Soc. Jpn. Publication Center for Pure and Applied Physics, 85, 044802-1-6 (2016)

[13] Morito Sakuma, Sayaka Kita and Hideo Higuchi. Quantitative evaluation of malignant gliomas damage induced by photoactivation of IR700 dye. Science and Technology of Advanced Materials. 17, 473-482 (2016)

[14] Eug Kuan Moo, Daniel R Peterson, Timothy R Leonard, Motoshi Kaya, Walter Herzog. In vivo muscle force and muscle power during near-maximal frog jumps. PLoS One. Mar 10;12(3): e0173415 (2016)

[15] Katsuhiko Sato, Koutaro Nakagome, Seine A. Shintani, Fuyu Kobirumaki-Shimozawa, Norio Fukuda, Kazuya Suzuki, Jun Takagi, Yuta Shimamoto and Takeshi Itabashi., “Dynamic properties of bio-motile systems with a liquid-crystalline structure”, Molecular Crystals and Liquid Crystals, 647,127-150(2016)

[16] Seiichi Tsukamoto, Teruyuki Fujii, Kotaro Oyama, Seine A. Shintani, Togo Shimozawa, Fuyu Kobirumaki-Shimozawa, Shin ' ichi Ishiwata and Norio Fukuda, " Simultaneous imaging of local calcium and single sarcomere length in rat neonatal cardiomyocytes using yellow Cameleon-Nano140 " J. Gen. Phys. 148, 341-355 (2016)

[17] Koutaro Nakagome, Katsuhiko Sato, Seine A. Shintani and Shin ' ichi Ishiwata, " Model simulation of the SPOC wave in a bundle of striated myofibrils ", Biophysics and Physicobiology, 13, 217-226 (2016)

[18] Naoaki Bekki, Seine A. Shintani, Shin ' ichi Ishiwata and Hiroshi Kanai, " A model for Measured Traveling Waves at End-Diastole in Human Heart Wall by Ultrasonic Imaing Method ", 85, 044802 (2016)

[19] Takumi Washio, Seine A. Shintani, Hideo Higuchi and Toshiaki Hisada. Analysis of spontaneous oscillations for a three state power stroke model. Physical Review E. 95, 022411 (2017).

[20] Togo Shimozawa, Erisa Hirokawa, Fuyu Kobirumaki-Shimozawa, Kotaro Oyama, Seine A. Shintani, Takako Terui, Yasuharu Kushida, Seiichi Tsukamoto, Teruyuki Fujii and Shin ' ichi Ishiwata, " In vivo cardiac nano-imaging: A new technology for high-precision analyses of sarcomere dynamics in the heart ", Prog. Biophys. Mol. Bio. 124, 31-40 (2017)

[21] Motoshi Kaya, Yoshiaki Tani, Takumi Washio, Toshiaki Hisada and Hideo Higuchi*. Coordinated force generation of skeletal myosins in myofilaments through motor coupling. Nature Communications 8,16036 (2017)

[22] Takumi Washio, Toshiaki Hisada, Seine A. Shintani and Hideo Higuchi. Analysis of spontaneous oscillations for a three state power stroke model. Physical Review E. 95, 022411(2017).

[23] Eng Kuan Moo, Daniel R.Peterson, Timothy R. Leonard, Motoshi Kaya and Walter Herzog In vivo muscle force and muscle power during near-maximal frog jumps. PLoS One. Mar 10;12(3): e0173415 (2017)

[24] Seohyun Lee, Hyuno Kim, Hideo Higuchi. Focus Stabilization by Axial Position Feedback in Biomedical Imaging Microscopy IEEE Sensors Applications Symposium pp. 309-314 (2018)

[25] K. Sasaki, M. Kaya, and H. Higuchi. A unified walking model for dimeric motor proteins Biophys. J.115, 1-12 (2018)

[26] Yoshimi Kinoshita, Taketoshi Kambara,Kaori Nishikawa, Motoshi Kaya and Hideo Higuchi. Step Sizes and Rate Constants of Single-headed Cytoplasmic Dynein Measured with Optical Tweezers. Sci. Rep. 16333 (2018)

[27] Seohyun Lee, Hyuno Kim, Hideo Higuchi. Numerical method for vesicle movement analysis in a complex cytoskeleton network. Opt. Express 26, 16236-16239 (2018)

[28] Seohyun Lee, Hyuno Kim, Masatoshi Ishikawa, and Hideo Higuchi. 3D Nanoscale Tracking Data Analysis for Intracellular Organelle Movement using Machine Learning Approach. International conference on Artificial Intelligence in Information and Communication (IEEE -ICAIIC) (2019)

[29] Naohiko Shimada, Hirotaka Kinoshita, Takuma Umegae, Satomi Azumai, Nozomi Kume, Takuro Ochiai, Tomoka Takenaka, Wakako Sakamoto, Takayoshi Yamada, Tadaomi Furuta, Tsukuru Masuda, Minoru Sakurai, Hideo Higuchi, and Atsushi Maruyama. Cationic Copolymer-Chaperoned 2D–3D Reversible Conversion of Lipid Membranes Advanced Materials190432,1-7(2019)

[30] Takumi Washio, Seine A. Shintani, Hideo Higuchi, Seiryo Sugiura and Toshiaki Hisada. Effect of myofibril passive elastic properties on the mechanical communication between motor proteins on adjacent sarcomeres. Scientific Reports 9:9355 (2019)

[31] Seohyun Lee, Hyuno Kim, Hideo Higuchi, and Masatoshi Ishikawa. Optical flow of vesicles: computer vision approach for endocytosis of Nano Particles in a living cell. SPIE Photonics West In press (2020)

[32] Seohyun Lee and Hideo Higuchi. 3D rotational motion of an endocytic vesicle on a complex microtubule network in a living cell. Biomed. Opt. Exp. In press.

＜**Books**＞

[33] Y Toyoshima and H. Higuchi “Motile and Enzymatic properties of native dynein molecules” in Handbook of Dynein. K. Hirose and LA Amos ed. (2012)

[34] Shima T, Sutoh K, and Kon T　Chapter3, Functional Analysis of the Dynein Motor Domain, Handbook of Dynein, Pan Stanford Publishing (2012)

[35] 樋口秀男、権田幸祐　「量子ドットを用いたがん細胞の単一分子イメージング」　分担執筆 NTS 出版　バイオマテリアル　(2012)

[36] 茅元司，樋口秀男 ビジュアルレビュー：筋肉の巧みな収縮メカニズム．感染. 疫 42-2，28-35. (2012)

[37] 樋口秀男、神原丈敏　「歩行型分子モーター、ダイニン」　パリティ　(2013)

[38] 樋口秀男　「普遍生物学」生物物学会誌　巻頭言 55,285. (2015)

[39] 新谷正嶺、戸次直明、福田紀男、石渡信一、樋口秀男「心筋細胞に備わった昇温誘起の高速サルコメア振動」国士舘大学紀要　情報科学　第 37 号 (2015)

[40] 樋口秀男　「石渡牧場」早稲田応用物理会, 理会会報 27, (2016)

[41] 戸次直明、新谷正嶺「レイリーラム方程式の心室中隔壁への応用」国士舘大学紀要　情報科学　第 37 号 (2016)

[42] 新谷正嶺、戸次直明、樋口秀男、福田紀男、石渡信一「心筋細胞に備わった温度依存の高速自励振動特性」統計数理研究所共同研究リポート「動的生体情報の現状と展望」　21-27(2016)

[43] 茅　元司　第 11 章　少数の機能を知る（93-111 頁）「少数性生物学」永井健治・冨樫祐一編　日本評論社 (2016)

[44] 木下慶美「Opinion- 研究の現場から ～研究交流から共同研究への実現に向けた挑戦～」，羊土社『実験医学』34 (3) (2016)

[45] 新谷正嶺「第 3 回少数性生物学トレーニングコース　参加者の声」少数性生物学 NEWS LETTER Vol. 5 (2016)

[46] 新谷正嶺「温めた心筋細胞に備わった収縮リズムの周期安定化の仕組みについて」国士舘大学紀要　情報科学　第 38 号 (2017)

[47] 樋口秀男　「生物物理学と他の領域をゆらぐ」　東大理学部ニュース 48　（2017）

[48] 戸次直明、石井啓翔、城戸真弥、新谷正嶺、鷲尾巧「心臓壁に対する非線形波動モデルを目指して」国士舘大学紀要　情報科学　第 38 号 (2017)

[49] 樋口秀男　数理科学　「ファイマンラチェット-生体分子の運動の理解にむけて-」633, 34-39　（2018）

[50] H. Higuchi and C. Shingyoji. Measuring the Motile Properties of Single Dynein Molecules Chaper 5 In Handbook of dynein 2nd. Hirose and Amos ed. Pan Stanford Publishing　(2019)

＜**Patent Applications**＞

[51] USA patetnt Kohsuke Gonda, Hideo Higuchi, Noriaki Ohuchi, Motohiro Takeda, Cancer cell migration and cancer cell invasion inhibitor. #8674079. March 3, 2014.

7 Invited Presentations at International Conferences

[1] Motoshi Kaya (2012) Application of optical tweezers to understand molecular mechanism of muscle contractions. International Symposium on Nanomedicine, Nagoya University, Japan (Mar. 2012)

[2] Higuchi H. and M Kaya Single molecule biophysics in an in vivo and in vitro. Japan-Taiwan joint symposium. Kyoto, Japan (Feb. 2012)

[3] Kaya, M. Force generation mechanism of single skeletal myosin molecules in myofilaments. The 50th Annual Meeting of the Biophysical Society of Japan, Nagoya University, Japan (Sep.2012)

[4] Kikushima k. A non-invasive method for the in vivo tracking of high-speed vesicle transport in mouse neutrophils. 6th International Symposium of Nanomedicine Tottori (Nov.2012)

[5] Higuchi H., Kikushima K., and Kita S. Single molecule biophysics toward in vivo. The 4th Taiwan-Japan Symposium on Nanomedicine. Taipei,Taiwan (Jan.2013)

[6] Higuchi H., Kikushima K., and Kita S. Single molecule biophysics toward in vivo. 2nd Tokyo U-Korea U Joint Symposium. Soul, Korea (2013.3)

[7] Higuchi H and T. Nomura. “Understanding of hierarchy in muscle contraction.” The international Symposium on multi-scale muscle mechanics. Session Moderator. Yokohama, Japan (Mar.2013)

[8] Kaya, M. Molecular level on muscle contraction. The international Symposium on multi-scale muscle mechanics. Session Moderator. Yokohama, Japan (Mar.2013)

[9] Hideo Higuchi, Kenji Kikushima, Sayaka Kita: Noninvasive in vivo imaging of neutrophil and tumor in mouse auricles. Dynein 2013 International Workshop, Kobe , Japan (Nov.2013)

[10] Hideo Higuchi, Kenji Kikushima and Sayaka Kita “Noninvasive in vivo imaging of neutrophil and tumor in mouse auricles” Molecules view The International Symposium on Multi-Scale Muscle Mechanics. ,Kitakyusyu Fukuoka, Japan (Nov.2013)

[11] Hideo Higuchi, Kenji Kikushima and Sayaka Kita. Biophysics toward noninvasive imaging. International Symposium on Nanomedicine molecular Science,Nagoya, Japan (Jan.2014)

[12] Hideo Higuchi and Norio Fukuda. Symposium on Biophysics toward In Vivo work. Biophysical society of Japan,Kyoto, Japan (Oct.2013)

[13] Motoshi Kaya, Hideo Higuchi Mokecular properties and dynamics of single skeletal myosins designed for force generations in ensemble of myosin molecules.Biophysical society of Japan,Kyoto, Japan (Oct.2013)

[14] Kenji Kikushima,Sayaka Kita,Hideo Higuchi,A non-invasive technique for the in vivo tracking of high-speed versicle transport in mouse neutrophils Symposium on Biophysics toward In Vivo work.Biophysical society of Japan,Kyoto, Japan (Oct.2013)

[15] Motoshi Kaya,Intermolecular cooperativity of skeletal myosins in myofilaments. Gordon Research Conference (Muscle & Molecular Motors), Mount Snow Resort West Dover, VT USA (Jul.2014)

[16] Hideo Higuchi, Kenji Kikushima and Sayaka Kita Noninvasive in vivo imaging of neutrophil and tumor in mouse auricles. A3 Foresight Symposium on Nanomedicine,Sendai, Japan (Sep.2014)

[17] Hideo Higuchi, Kenji Kikushima and Sayaka Kita. Noninvasive in vivo imaging of neutrophil and tumor in mouse auricles. 8th Internal Symposium on Nanomedicine ,Matsushima, Japan (Dec.2014)

[18] Hideo Higuchi Noninvasive in-vivo imaging of neutrophil and tumor cells in mouse auricles. PacifiChem Hawai USA (Dec.2016)

[19] Hideo Higuchi「Toward Medical Biophysics」3rd international nanomedicine symposium. Univ Tokyo , Japan (Nov.2015)

[20] Motoshi Kaya. Molecular mechanism of efficient muscle contraction revealed by single molecule approach. 5th Asian and Pacific-Rim Symposium on Biophotonics (Pacifico Yokohama) , Japan (Apr.2015)

[21] Hideo Higuchi: Motility of motor proteins, myosin, kinesin and dynein. Cooperation in Physics Workshop: LMU-UT　Univ Tokyo, Japan (Feb.2016)

[22] Seohyun Lee, Motoshi Kaya, Kohsuke Gonda, Hideo Higuchi. Trafficking of Endocytic Vesicles on Cytoskeleton in LiveCancer Cells. A3 Foresight 9th Meeting.　Yokohama, Japan (Sep.2017)

[23] Yongtae Hwang, Hideo Higuchi. Motoshi Kaya. Property of Cardiac Myosin Assemble Measured by Optical Trapping. A3 Foresight 9th Meeting. Yokohama, Japan (Sep.2017)

[24] Yoshimi Kinoshita, Hideo Higuchi. Step sizes and rate constants of single-headed dynein measured by optical tweezers, International Workshop Dynein 2017, International Conference Center,　Awaji Yumebutai, Japan （Oct.2017）

[25] Chikako Shingyoji, Hiroshi Yoke,Yasuhide Izawa, Izumi Nakano,Yuichi Inoue, Hideo Higuchi. Mechanical activity of dynein and its dynamical regulation underlying oscillatory movement of sperm flagella. International Workshop Dynein 2017, International Conference Center, Awaji Yumebutai, Japan （Oct.2017）

[26] Morihito Sakuma,Yuichi Kondo and Hideo Higuchi. Damage of cancer cells evaluated by intensity fluctuation of images under phase contrast microscope. 11th International Symposium on Nanomedicine. University of Tohoku, Japan (Dec.2017)

[27] S. Shintani, T. Washio, Y. Hwang, M, Kaya and H. Higuchi. Molecular mechanism of self-oscillatory contraction of cardiac muscle. Internatinal Symposium on Nanomedicine. Ube Yamaguchi, Japan (Dec.2018)

[28] Hideo Higuchi, Yuichi Kondo and Kazuo Sasaki. Unified walking model for processive motor proteins and its experimental evidences Joint symposium between UBI and MBI in NUS Natinal university of Singapore. Singapore (Apr.2018)

[29] Yongtae Hwang. Collective behaviors of cardiac myosin molecules for effective cardiac function. LMU-UT Joint Workshop on Statistical and Biological Physics,Germany (Oct.2018)

[30] Motoshi Kaya. Keynote lecture: Reverse stroke of cardiac myosin is essential for heart function: lessons from skeletal myosin. The 4th Rocky Mountain satellite Muscle Symposium. Canmore. Canada (Jul.2019)

[31] Motoshi Kaya. Function of cardiac myosin essential for heart contraction. 2nd East Asian Symposium On Single-Molecule Biological Sciences. Seoul. Korea (Jul.2019)

[32] Hideo Higuchi and Kazuo Sasaki Universal walking model for processive motor proteins. Joint Workshop between NanoLSI (Kanazawa University) and Universal biology institute (The University of Tokyo). Kanazawa. Japan (Sep.2019)

[33] Motoshi Kaya, Yongtae Hwang and Hideo Higuchi. Reverse stroke of cardiac myosin revealed by single molecule microscopy is essential for heart function. 2nd Joint Symposium between mechanobaiology institute and Universal biology institute. Tokyo. Japan (Sep.2019)

8 Teaching Accomplishment

- 菊島健児　「量子ドットを用いたマウス耳介内における白血球内小胞運動の非侵襲イメージング」ナノ学会　若手優秀発表賞 (2012. 6)
- 新谷正嶺：日本生物学会優秀ポスター賞、日本時間生物学会 (2016.11.12)
- 張致遠「超解像イメージ法を用いた骨格筋ミオシン分子動態の直接計測」、第 54 回日本生物物理学会年会学生賞、つくば、(2016.11.25 − 11.27)
- 近藤雄一　「広い負荷領域におけるキネシン 1 分子のステップ運動」ナノ学会　Young best presentation award　(2018.5.12)
- Hwang Yongtae　Collective behaviors of cardiac myosins for effective cardiac function. 第 56 回生物物理学会　発表奨励賞　(2018.9.15)
- 上道　雅仁　Traction Force of Neural Stem Cells under Collective Migration was Modeled using the Orientation Field of Cell Alignment　第 57 回生物物理学会年会　学生発表賞　(2019.9.27)

9 Contribution to Academic Community

- Vice president of the society of Nano Science and Technology (2016-present)
- Session chair of nanomedicine and nanobiology in the society of Nano Science and Technology (2009-2016)

9.1 Editorial Activities

9.2 Organization of Professional Societies

9.3 Organization and Advisory of Conferences

- Member of advisory committee of ISSPIC (International Symposium on Small Particles and Inorganic Clusters) 2013−2014
- Organizer of 3rd International symposium on Nanomedicine molecular Science.
- Organizer of 2nd joint symposium between Mechanobiology Institute (National University of Singapore) and Universal Biology Institute (Univ. Tokyo) 2019

10 Outreach

- 樋口秀男「細胞の謎をさぐる」東大理学部高校生のための夏休み講座 2013　東大（本郷）東京 (2013.7.25)　（対象　高校生・中学生）
- 喜多清 日本免疫学会主催「免疫ふしぎ未来 2013」協力員 日本科学未来館 (2013.8.11)
- 喜多清　小学校 5 年生への理科の講義（ガン研究の紹介と発生についてとキャリア教育も兼ねて）つくばみらい市立　小絹小学校 約 100 名 (2014.7.14)
- 樋口秀男　高校生に対する講義「傷を治す白血球と分子の活躍」 沼津西高校生約 90 名、東大 (2014.10.20)
- 樋口秀男　講義「傷を治す白血球と分子の活躍」 沼津西高校 1，2 年生　（東大）(2015.10.19)
- 喜多清　出前講義　「最先端 がん細胞のナノイメージングと生き物の誕生～研究の仕事～」茨城県つくばみらい市市立小絹小学校 5 年生 (2015.7.9)
- 樋口，齋藤，佐久間，茅，喜多．沼津西高生へ講義および実験の実演 (2016.10.17)
- 喜多清　出前授業「理科関係のお仕事（研究の仕事とは？）& 生き物の誕生」茨城県つくばみらい市市立小絹小学校 5 年生（2017.2.3）
- 樋口秀男，喜多清，Hwang Yongtae，Seohyun Lee．沼津西高校生に対する模擬講義「がんを知り，がんを治す」および実験の実演　（2017.10.16）
- 喜多清 : 茨城県つくばみらい市市立小絹小学校 5 年生対象の出前講義　研究の仕事とは」～最先端　がん細胞をナノサイズで観察する研究～（2017.7.4）
- 樋口秀男　東京大学　「生命現象の普遍性」理学部公開講演会　(東大)　(2018.3.28)
- 樋口秀男　講義「がんを知り，がんを治す」 沼津西高校生約 45 名　（東大）　(2018.10.15)
- 茅　元司　2019 年 第 3 回 KISTEC 理科実験室　「きん肉が動く仕組みをさぐろう！」　小学生 3 年生～中学 2 年生 37 名（かながわサイエンスパーク、溝の口）(2019.2.23)
- 茅元司　KISTEC 理科実験室「きん肉が動く仕組みをさぐろう！」小中学生対象（神奈川県立産業技術総合研究所）(2019.2.23)
- 樋口秀男　講義「がんを知り，がんを治す」 沼津西高校生　（東大）　(2019.10.25)

11 Committee Service

- 医療分野研究成果展開事業　審査委員 (2018)
- JST　さきがけ　審査委員長 (2018)
- JST　ICORP　事後審査委員長 (2015-2016)

11.1 External Committees

11.2 University Committees

- President of Universal Biology Institute (Graduate School of Science)　2018 年 −present
- 理学系研究科キャンパス将来計画員会　委員
- 理学系研究科バイオサイエンス委員会　委員
- 理学系研究科男女共同参画委員会　委員

12 Internationalization Statistics

	Number	Country
Foreign students advised		
Bachelor Course	0	
Master Course	2	Korea
Doctor Course	2	Korea
Foreign researchers hosted	0	
Students sent abroad	2	USA, Germany
Researchers sent abroad	2	USA, Switzerland
Foreign visitors	9	Germany, USA, Singapole, France

岡田　康志、 **Yasushi Okada**

1 Education and Professional Experiences

Education

1993	B.S. (Medicine)	The University of Tokyo
2011	Ph.D. (Medicine)	The University of Tokyo

Professional Appointments

1994−1997	JSPS Research Fellow (DC1)	The University of Tokyo
1995−2011	Assistant Professor	The University of Tokyo
2011−	Team Leader	RIKEN
2016−	Professor	The University of Tokyo

Visiting, Guest Appointments

2012−	Guest Professor	Osaka University
2017−	Visiting Professor	Kobe University
2018−	VIsiting Professor	National Institutes of Natural Sciences

2 Research Highlights

We are trying to understand the dynamics of the protein molecules working in the living cells, especially motor proteins undergoing the intracellular transport. For that purpose, we have been working on the development of the imaging technologies as well as their biological applications.

2.1 Development of imaging technologies

2.1.1 Super-resolution microscope

For the development of the microscopes, we have been working on the super-resolution microscope for the observation of the fast dynamics in the living cells. Our original super-resolution microscope, the spinning-disk super-resolution microscope or SDSRM [19] has enabled us to observe dynamic processes of fine structures in living cells at 100 frames per sec per plane.

Special fluorescent dyes are required for the further improvement in the spatial resolution. We are, therefore, collaborating with chemists for the development of new fluorescent dyes suitable for the super-resolution live-cell imaging. For example, HMSiR is a self-blinking dye which is ideal for the single molecule localization microscopy [23, 5]. PREX710 is an extremely photostable near infrared dye, and is very suitable for the long-term in vivo imaging and single-molecule imaging [11]. MitoPB Yellow stains the inner membrane of mitochondria specifically and is very suitable for the super-resolution STED imaging. The inner membrane structure or cristae was clearly observed in living cells [2].

2.1.2 Improvement of single-molecule imaging optics for living cells

Total internal reflection fluorescence (TIRF) optics has been widely used for single-molecule imaging but it has several drawbacks. It illuminates the sample from one side. Thus, the generated evanescence field is highly polarized and only half of the fluorescent molecules are excited. Secondly, the excitation laser is focused to a single point on the back focal plane of the objective lens. Thus, the area of homogeneous illumination is limited and can be sensitive to the speckle pattern noise, which collectively results in a small field of view. Moreover, the power of the excitation laser cannot be increased, because the focused laser beam can damage the objective lens. We have developed a new illumination optics which we call as the ring-TIRF system. The excitation laser beam is shaped as an annular ring pattern on the back focal plane of the objective lens, so that the sample is illuminated homogeneously from all directions. Thus, a homogeneous large field of view without polarization bias is achieved. Furthermore, the introduction of a higher power laser enabled us to accelerate the frame rate of the single molecule imaging to 1000 frames/sec.

The ring-TIRF microscope was successfully applied for the live cell super-resolution imaging of the structure and the dynamics of the genome DNA in the nucleus [16], the dynamics of the transcription factors such as nanog, and the measurement of the protein-protein interaction kinetics in the cytoplasm of living cells.

2.2 Study of axonal transport

The axonal transport is one of the most sophisticated intracellular transport system. We have been working on this sytem for more than 20 years, but still many basic questions have remained unanswered. For example, it has not been clear how many molecules of motor protein are required to transport a single cargo vesicle in the axon. We have solved this question by applying the fluctuation theorem of non-equilibrium statistical physics [9].

We have also examined the navigation mechanisms in this transport system. A neuron typically has a single axon and more than dozens of dendrites, but the axonally transported cargos are transported into the axon. We have identified that the microtubules, the rail polymer for the transport, can take two different conformations. Binding of kinesin-1, the motor protein for the axonal transport, triggers the cooperative conformational changes in the microtubule, which serves as the road sign for the following kinesins [8].

3 Selected Papers

- S. Hayashi & Y. Okada, Molecular Biology of the Cell, 26: 1743-1751 (2015)
  This work was selected and highlighted as the cover for this issue. Commendation for Science and Technology was awarded to this work by MEXT.
- C. Wang et al., Proceedings of the National Academy of Science USA. 116: 15817-22 (2019)
  This works was highlighted in PNAS, Scientific American and other news media.
- K. Hayashi et al., Molecular Biology of the Cell, 29: 3017-3025 (2018)
  A successful combination of physics theory and biological experiments.

- S. Uno et al., Nature Chemistry 6: 681-689 (2014)
  This paper is cited 131 times.
- T. Shima et al., Journal of Cell Biology 217: 4164-4183 (2018)
  This paper got 2 recommendations in F1000Prime.

4 Honors, Awards and Professional Society Memberships

2017 Commendation for Science and Technology by MEXT.

5 Research Plan

5.1 Development of imaging technologies – Molecular resolution at sub-millisecond frame rates

Bridging the gap between the molecular and the cellular levels is one of the BDR missions. The current spatial resolution of our microscope is still much larger than molecules. Furthermore, the molecules in the cell are moving very rapidly, so that the imaging speed should be increased proportionally to the increased spatial resolution. We are, therefore, starting the development of several new microscopes. One is to track the trajectories of a single fluorescent molecule at 10,000 frames per second or more. This frame rate is required to measure the dynamics of protein molecules in the cytoplasm. Conventional single-molecule imaging could only observe the protein molecules bound to some fixed structures such as membranes or cytoskeleton. The development of photostable fluorescent dye is required to track the molecule for longer time at this frame rate, and we will continue the current collaboration with chemists.

The third key emerging technology for imaging is the computational image processing. Machine-learning or neural-network based image processing technologies would enable us to overcome the conventional limits of the optics or the fluorescent dyes/molecules. Through the STEPS program, we have started collaboration with computer scientists in Moscow Univ.

5.2 Study of axonal transport – Physics in the crowded environment of living cytoplasm

The results of the force estimation from the fluctuation theorem [9] indicated that more than 1000x stronger drag force is exerted on the axonally transported vesicles from the crowded cytoplasm than in vitro. However, the velocity is even faster in vivo than in vitro, though kinesin has been shown to slow down in the crowded solution in vitro. Our working hypothesis is that this apparent paradox might be resolved through the understanding of the crowded environment of the cytoplasm of living cells. The new microscope discussed in the previous section was primarily designed for this study. Here, the theoretical physics would play important roles. Our force measurement is dependent on the modern theory of non-equilibrium physics. The movement of the molecular motor can be theoretically analyzed by using the information thermodynamics. The

characterization of the crowded environment of the cytoplasm and its interaction with kinesin would require new theory of non-equilibrium information thermodynamics. So we have started a new collaborative project along with theoretical physicists. The project has been approved by MEXT and supported by Grant-in-Aid for Scientific Research on Innovative Areas.

6 Publications and Patents

＜ Refereed Original Papers ＞

[1] Kaneshiro J *et al.* Biophys Physbiol. 16: 147-157, 2019

[2] Wang C *et al.*, Proc Natl Acad Sci U S A. 116:15817-15822, 2019.

[3] Tanaka H *et al.*, J Cell Sci. 132: jcs224766, 2019.

[4] Kono K *et al.*, eLife 8: e45559, 2019.

[5] Lu CH *et al.*, Commun Biol. 2:177, 2019.

[6] Li J *et al.*, Exp Cell Res. pii:S0014-4827: 30149-1, 2019.

[7] Hasegawa S *et al.*, Sci. Rep 9: 5099, 2019.

[8] Shima T *et al.*, J Cell Biol. 217:4164-4183, 2018

[9] Hayashi K *et al.*, Mol Biol Cell. 29:3017-3025, 2018

[10] Okamoto K *et al.*, Sci Rep. 8:11965, 2018

[11] Gzrybowski M *et al.*, Angew. Chem. 57:10137-10141, 2018.

[12] Komatsu N *et al.*, Scientific Reports 8: 8984, 2018.

[13] Takeshima T *et al.*. Journal of Microscopy. 2018.

[14] Ueno A *et al.*, Cell Rep. 2018 Mar 27;22(13):3548-3561.

[15] Chiba K *et al.*, Mol Biol Cell, 28:3857-3869, 2017

[16] Nozaki T *et al.*, Mol Cell. 67:282-293, 2017

[17] Minegishi K *et al.*, Dev Cell. 40:439-452, 2017

[18] Chinen T *et al.*, Nat Commun. 6:8722, 2015

[19] Hayashi S & Okada Y. Mol. Biol. Cell., 26:1743-51, 2015

[20] Takai A *et al.*, Proc. Natl. Acad. Sci. U S A. 112:4352-6. 2015

[21] Ohyanagi T *et al.*, Chem. Commun., 51(80):14836-9. 2015

[22] Okada Y & Nakagawa S. Methods Mol. Biol., 1262:21-35. 2015

[23] Uno S *et al.*, Nat. Chem., 6: 681-689, 2014

[24] Chiba K *et al.*,Mol Biol Cell, 25: 3569-3580, 2014

[25] Hayashi K *et al.*, Euro Phys J, E 36: 136, 2013

[26] Sato Y *et al.*, Sci Rep. 3:3436, 2013

[27] Ota S *et al.*, Genes Cells, 18: 450-458, 2013

[28] Hisano Y *et al.*, Biol Open, 2, 363-367, 2013

[29] Sakuma T *et al.*, Genes Cells, 18: 315-326, 2013

[30] Yajima H *et al.*, J Cell Biol 198: 315-322, 2012

＜ Review Papers ＞

[31] 岡田康志、超解像顕微鏡の原理と応用、病理と臨床 37: 580-587, 2019

[32] 岡田康志、共焦点顕微鏡の光学系を用いた超解像顕微鏡法、顕微鏡 52(2):62-66, 2017

[33] 岡田康志、超解像顕微鏡研究の最前線、顕微鏡 52(2):61, 2017

[34] 岡田康志、超解像顕微鏡で観える生物現象、医学の歩み 262(5): 573-579, 2017

[35] 岡田康志、超解像顕微鏡によるライブイメージング、生体の科学、68(5): 378-379, 2017

[36] 岡田康志、ライブイメージングのための高速超解像蛍光顕微鏡法、O plus E、39(2): 174-178, 2017

[37] 高井啓、岡田康志、3 色の高輝度発光タンパク質プローブの開発と応用、Journal of Japanese Biochemical Society 88:669-673, 2016

[38] 岡田康志、超解像蛍光顕微鏡法の現状と生体イメージングへの応用、レーザー研究 44:643-647, 2016

[39] 岡田康志、「超解像蛍光顕微鏡」、Clinical Neuroscience 34(6): 638-642, 2016

[40] 岡田康志、シャッター速度世界一の超解像蛍光顕微鏡、OplusE 2015 年 8 月号

[41] 岡田康志、藤田克昌、清末優子、2014 年ノーベル化学賞 : 超解像蛍光顕微鏡法の開発、実験医学 32:3074-3076, 2014

[42] 岡田康志、ノーベル化学賞：超解像蛍光顕微鏡法の開発、パリティ 29:37-39, 2014

[43] 岡田康志、ゲノム編集革命、現代化学 2014 年 8 月号 p 22-27

[44] 岡田康志、はじめての超解像イメージング、実験医学 32:2623-2629, 2014

[45] 岡田康志 、超解像光学顕微鏡によるイメージング、パリティ28:25-30, 2013

[46] 川原敦雄、岡田康志、TALEN による遺伝子改変ゼブラフィッシュの作成、細胞工学 32:558-563, 2013

[47] 岡田康志、ライブイメージングのための超解像顕微鏡、光技術コンタクト 51:4-12, 2013

[48] 岡田康志、ライブセルイメージングのための超解像蛍光顕微鏡法、バイオイメージング 21: 100-101, 2012

＜Books＞

[49] 岡田康志、超解像・一分子イメージングによる分子動態の計測、森泰生、尾藤晴彦編、「脳神経化学」、第 30 章、319 - 329、化学同人、2018

[50] 岡田康志 [編・著]「初めてでもできる！超解像イメージング」羊土社、2016

＜Patent Applications＞

[51] 岡田康志、池田一穂　DNA 結合タンパク質ドメインの改変による高活性 TALE タンパク質、特願 2013-167144

[52] 林久美子、岡田康志　力測定方法、力測定装置、力測定システム、力測定プログラム及び記録媒体、特願 2017-210698

[53] 岡田康志、有吉哲郎　蛍光発生核酸分子、及び標的ＲＮＡの蛍光標識方法、特願 2018-226743

[54] 岡田康志、稲生大輔　ＤＮＡ結合タンパク質、及びゲノムＲＮＡ立体構造の標識方法、特願 2019-074004

7 Invited Presentations at International Conferences

[1] Okada Y. “Dissecting molecular mechanisms by optical microscopy in living cells and in vitro.” Cold Spring Harbor Conferences Asia, Cross-scale biological structure 2019.

[2] Okada Y. “Super-resolution live-cell imaging 2019: new optics, new dyes, and new algorithms.” The 46th Annual Meeting of Microscopical Society of Canada, 2019

[3] Okada Y. “Mechanisms of axonal transport investigated by high-speed and high-resolution imaging.” 15th Annual German-Japanese Colloquium, 2019

[4] Okada Y. “Live cell imaging technologies for single-cell analysis How can imaging meets genomics ” Human Genome Meeting 2018

[5] Okada Y. “Development and application of high-speed super-resolution and single-molecule imaging for cell biology studies’ ’SPIE BioS、2018

[6] Okada Y. “Development and application of high-speed super-resolution and single-molecule microscopes for nanomedicine” International Symposium on Nanomedicine (ISNM2017), 2017

[7] Okada Y. “Imaging technologies for single cell analysis” Human Cell Atlas Asia Meeting, 2017

[8] Okada Y. “Current limitations in super-resolution fluorescence microscopy for biological specimens: how deep can we go from the cover glass?” Biomedical Imaging and Sensing Conference 2017 (BISC2017), 2017

[9] Okada Y. “Regulation of the conformational polymorphism of microtubule and its physiological role in the regulation of kinesin-based intracellular transport”, IGER International Symposium on “Now in actin study: Motor protein research reaching a new stage”, 2016

[10] Okada Y. “Development and application of high-speed super-resolutoin microscope” The 31st International Congress on High-Speed Imaging and Photonics, 2016

[11] Okada Y. “Neuronal Biophysics”, Discussion Leader, Gordon Research Conference, “Single Molecule Approaches to Biology”, 2016

[12] Okada Y. “Development and application of spinning disk super-resolution microscope for the high spatio-temporal resolution imaging of dynamic cellular components in living cells” The 43rd Annual Meeting of Microscopical Society of Canada, 2016

[13] Okada Y. “Dissecting kinesin regulation through single molecule in cellulo measurements” Janelia Conference, 2015

[14] Okada Y. “Ultrafast superresolution fluorescence imaging with spinning disk confocal microscope optics” 9th Asian Biophysics Association Symposium, 2015

[15] Okada Y. “Atomic mechanism for the intracellular navigation of molecular motor, kinesin.” Joint Weizmann-MBI Mechanobiology Conference, Singapore, 2013

[16] Okada Y. “Structural basis for the polarized axonal transport by kinesin-1” The 4th Taiwan-Japan Symposium on Nanomedicine, 2013

[17] Okada Y. “Structural basis for the polarized axonal transport by kinesin-1” UK-Japan Symposium for Mechanochemical Cell Biology, 2012

[18] Okada Y. “From single molecule to in vivo imaging” Leica Meets Science, 2012

8 Teaching Accomplishment

2019	Early Carrier Award, the Biophysical Society of Japan	Hideyuki Yaginuma.
2019	Young Scientist Award, Japanese Society for Cell Biology	Hideyuki Yaginuma.
2018	Young Scientist Award, Japanese Society for Cell Biology	Tetsuro Ariyoshi.
2015	Young Scientist Award, Japanese Society for Cell Biology	Akira Takai.

9 Contribution to Academic Community

9.1 Editorial Activities

Associate Editor, Cell Structure and Function 2014−

9.2 Organization of Professional Societies

Representative of the Japanese Society of Microscopy 2017−
Exective board member of Japan Society of Cell Biology 2016−

9.3 Organization and Advisory of Conferences

Committee chair for Naito Conference 2021
President, the 73rd Annual Meeting of the Japan Society for Cell Biology 2021
Organizing committee member, the 57th Annual Meeting of the Biophysical Society of Japan 2019
Program committee member, Joint Annual Meeting of 71st JSCB and 19th PSSJ, 2019
Executive committee member, the 61st Symposium of the Japanese Society of Microscopy, 2018
Session organizer, Gordon Conference on “Single molecules approaches to biology” 2016
Organizer, QBiC International symposium 2016
Organizer, RIKEN Symposium, the 4th Molecular Motor Meeting, 2014

10 Outreach

一般講演会：
「生物の普遍性を探る〜生きているってどういうこと？」、高校生のための東京大学オープンキャンパス、2019 年
「神経細胞の中のミクロの「宅配便」」、理研・生命システム研究センター一般公開「世界一おもろい授業」2016 年
「最先端イメージング技術で探る神経細胞の中の「宅配便」の仕組み」新適塾「脳はおもしろい」2016 年
「ライブイメージングのための高速超解像顕微鏡の開発と応用」、理研理事長懇談会、2015 年
「細胞の中の宅配便を光で見て、理解して、操作する」、東京大学物性研一般講演会、2015 年
「小さな分子モーターの大きな働き」理研神戸研一般公開講演会、2012 年

マスメディア：
サイエンス ZERO「青色 LED だけじゃない！ノーベル賞特集」2014 年

Web メディア・動画：
テルモ生命科学芸術財団　生命科学 DOKIDOKI 研究室　第 42 回「細胞内のモーター分子の動きをとことん見つめ生命の謎に迫る」
YouTube 理研チャネル 60 秒でわかる？　「キネシンは、なぜ迷子にならない？」
理学系研究科 YouTube チャネル 研究室の扉「生きたミトコンドリアの内部構造を鮮明に見る」

11 Committee Service

11.1 External Committees

Research Area Advisor, PREST “Quantum Bio”, JST 2017−2022

11.2 University Committees

理学系研究科技術委員会 委員　2018 年 –
Community office member of IRCN 2019−
卓越大学院運営委員 2019 年 –

12 Internationalization Statistics

	Number	Country
Foreign students advised		
Bachelor Course	6	USA, Denmark
Master Course	3	Germany, Russia
Doctor Course	1	UK
Foreign researchers hosted	6	Singapore, Finland
Students sent abroad	2	USA, Germany
Researchers sent abroad	0	
Foreign visitors	20	USA, Singapore, UK, France, Germany, Sweden, Taiwan

能瀬　聡直、 Akinao Nose

1 Education and Professional Experiences

Education

1984	B.S. (Science)	Kyoto University
1986	MSc. (Physics)	Kyoto University
1989	Ph.D. (Physics)	Kyoto University

Professional Appointments

1989−1989	Postdoctoral Researcher	Kyoto University
1989−1993	Postdoctoral Researcher	University of California at Berkeley, U.S.A.
1993−1998	Research Associate	National Institute for Basic Biology
1998−2007	Associate Professor	The University of Tokyo
2007−	Professor	The University of Tokyo

2 Research Highlights

We are interested in the mechanisms of how the neural circuits develop and function to generate specific behavior, by using the nervous system of the fruit fly Drosophila as a model. In this organism, the relative simplicity and highly sophisticated genetic techniques allow one to identify and manipulate specific neurons. To dissect the circuit logic, we use a variety of genetic and biophysical techniques. For example, we use calcium imaging to record the activity of specific population of neurons. By using optogenetics, we manipulate the activity of specific neurons with light at high resolution. Connectomics (reconstruction from 3D electron microscopy images) allows determination of neuronal wiring diagrams at the cellular and synaptic level. Recent research highlights are summarized below.

(1) Circuit mechanisms for motor pattern generation: Animals move by adaptively coordinating the sequential activation of muscles. We aim to reveal novel circuit mechanisms for the propagation of muscle contraction, using the peristaltic locomotion of Drosophila larvae as a model. One circuit motif we identified was a feed-forward circuit, which consists of an intersegmental chain of synaptically connected neurons, alternating excitatory (a27h) and inhibitory (GDL), necessary for wave propagation and active in phase with the wave (Fushiki et al., eLife, 2016). Another circuit motif was a feed-back motif that mediates phase-coupled delay in motor activation. The central component of the circuit is a pair of higher-order premotor excitatory interneurons (Ifb-fwd) present in each abdominal neuromere that intersegmentally provides feedback to the adjacent neuromere during motor propagation (Kohsaka et al., Nat. Comm., 2019).

(2) Circuit mechanisms for action selection: How animals adaptively respond to sensory stimuli by choosing an ethologically relevant behavior is a fundamental question in neuroscience. We investigate this problem by using the body-location specific tactile responses in Drosophila larvae. Larvae escape by backward locomotion when touched on the head, while they crawl forward

when touched on the tail. We identify a class of segmentally repeated second-order somatosensory interneurons, that we named Wave, whose activation in anterior and posterior segments elicit backward and forward locomotion, respectively. Anterior and posterior Wave neurons extend their dendrites in opposite directions to receive somatosensory inputs from the head and tail, respectively. Downstream of anterior Wave neurons, we identify premotor circuits including the neuron A03a5, which together with Wave, is necessary for the backward locomotion touch response. Thus, Wave neurons match their receptive field to appropriate motor programs by participating in different circuits in different segments (Takagi et al., Neuron, 2017).

3 Selected Papers

- Kohsaka H, Takasu E, Morimoto T and *Nose A. A Group of Segmental Premotor Interneurons Regulates the Speed of Axial Locomotion in Drosophila Larvae, ***Current Biology*** **24**, 2643-2651 (2014).
  (Journal Impact Factor 9.1, Citation 32)

- Fushiki, A., Zwart M.F., Kohsaka, H., Fetter, R.D., *Cardona, A., *Nose, A. A circuit mechanism for the propagation of waves of muscle contraction in Drosophila. ***eLife*** **10**, 7554/eLife.13253 (2016).
  (Journal Impact Factor 7.6, Citation 48, Introduced by an "INSIGHT" article of the journal)

- Takagi S, Cocanougher BT, Niki S, Miyamoto D, Kohsaka H, Kazama H, Fetter RD, Truman JW, Zlatic M, Cardona A, *Nose A. Divergent Connectivity of Homologous Command-like Neurons Mediates Segment-Specific Touch Responses in Drosophila. ***Neuron*** **96**(6):1373-1387 (2017).
  (Journal Impact Factor 14.4, Citation 10)

- Matsunaga T, Kohsaka H, *Nose A. Gap junction-mediated signaling from motor neurons regulates motor generation in the central circuits of larval Drosophila. ***J Neurosci.*** **37**: 2045-2060 (2017).
  (Journal Impact Factor 6.0, Citation 12, selected as a "featured article" in the issue of the journal)

- Kohsaka H, Zwart M, Fushiki A, Fetter R, Truman J, Cardona A, *Nose A. Regulation of forward and backward locomotion through intersegmental feedback circuits in Drosophila larvae. ***Nat. Commun.*** **10**(1):2654. (2019).
  (Journal Impact Factor 11.9, Citation 0)

4 Honors, Awards and Professional Society Memberships

Member: The Biophysical Society of Japan
Member: Society for Neuroscience
Member: The Japan Neuroscience Society
Member: Japanese Society of Developmental Biologists
Member: The Molecular Biology Society of Japan

5 Research Plan

We focus on the "small-scale neurocircuity" in the larvae of fruitfly and try to understand the logic of brain information processing. We try to identify neural circuits that function as units of brain information processing and analyze their structural and functional connectivity by cellular imaging, optogenetics, connectomics and mathematical modeling. We use machine learning and other computational methods to analyze the dynamics of population activity of neurons. We also study how neural circuits form during development via activity-dependent processes such as the sensory feedback.

6 Publications and Patents

＜Refereed Original Papers＞

[1] Fukui A, Inaki M, Tonoe G, Hamatani H, Homma M, Morimoto T, Aburatani H and *Nose A. Lola regulates glutamate receptor expression at the Drosophila neuromuscular junction. Biology Open 1, 362-375 (2012).

[2] Matsunaga T, Fushiki A, Nose A, *Kohsaka H. Optogenetic Perturbation of Neural Activity with Laser Illumination in Semi-intact Drosophila Larvae in Motion. J Vis Exp. 2013 Jul 4;(77), e50513 (2013).

[3] Fushiki A, Kohsaka H, *Nose A. Role of sensory experience in functional development of Drosophila motor circuits. PLoS One. 2013 Apr 19;8(4), e62199 (2013).

[4] Okusawa S, Kohsaka H, *Nose A. Serotonin and downstream leucokinin neurons modulate larval turning behavior in Drosophila. J Neurosci. 34, 2544-2558 (2014).

[5] Kohsaka H, Takasu E, Morimoto T and *Nose A. A Group of Segmental Premotor Interneurons Regulates the Speed of Axial Locomotion in Drosophila Larvae, Current Biology 24, 2643-2651 (2014).

[6] Itakura Y, Kohsaka H, Ohyama T, Zlatic M, *Pulver SR, *Nose A. Identification of Inhibitory Premotor Interneurons Activated at a Late Phase in a Motor Cycle during Drosophila Larval Locomotion. PLoS One 3, e0136660 (2015)

[7] Fushiki, A., Zwart M.F., Kohsaka, H., Fetter, R.D., *Cardona, A., *Nose, A. A circuit mechanism for the propagation of waves of muscle contraction in Drosophila. eLife 10, 7554/eLife.13253 (2016) doi: 10.7554/eLife.13253.

[8] Hasegawa E, Truman JW, *Nose A. Identification of excitatory premotor interneurons which regulate local muscle contraction during Drosophila larval locomotion. Sci Rep. 2016; 6: 30806 (2016) doi: 10.1038/srep30806.

[9] Matsunaga T, Kohsaka H, *Nose A. Gap junction-mediated signaling from motor neurons regulates motor generation in the central circuits of larval Drosophila. J Neurosci. 37: 2045-2060 (2017)

[10] Takagi S, Cocanougher BT, Niki S, Miyamoto D, Kohsaka H, Kazama H, Fetter RD, Truman JW, Zlatic M, Cardona A, *Nose A. Divergent Connectivity of Homologous Command-like Neurons Mediates Segment-Specific Touch Responses in Drosophila. Neuron 96(6):1373-1387 (2017)

[11] Park J, Kondo S, Tanimoto H, Kohsaka H, *Nose A. Data-driven analysis of motor activity implicates 5-HT2A neurons in backward locomotion of larval Drosophila. Sci Rep. 2018 Jul 9;8(1):10307 (2018)

[12] Yoon Y, Park J, Taniguchi A, Kohsaka H, Nakae K, Nonaka S, Ishii S, Nose A. System level analysis of motor-related neural activities in larval Drosophila. J Neurogenet. 33, 179-189. (2019) doi: 10.1080/01677063.2019.1605365.

[13] *Kohsaka H, Zwart M, Fushiki A, Fetter R, Truman J, Cardona A, *Nose A. Regulation of forward and backward locomotion through intersegmental feedback circuits in Drosophila larvae. Nat. Commun. 10(1):2654. (2019) doi: 10.1038/s41467-019-10695-y.

＜Review Papers＞

[14] Kohsaka H, Okusawa S, Itakura Y, Fushiki A and Nose A. Development of larval motor circuits in Drosophila. Develop.Growth Differ. 54, 408-419 (2012).

[15] Nose A. Generation of neuromuscular specificity in Drosophila: novel mechanisms revealed by new technologies. Front Mol Neurosci. 5, 62 (2012).

[16] 高坂洋史、能瀬聡直　ショウジョウバエを用いたオプトジェネティクス研究、in オプトジェネティクス、エヌ・ティー・エス、141-153 (2013).（著書、分担執筆、査読なし）

[17] 能瀬聡直 文部科学省科学研究費・新学術領域研究「メゾスコピック神経回路から探る脳の情報処理基盤」がめざすもの　生体の科学 64(1), 80-87 (2013).

[18] 能瀬聡直 ショウジョウバエ幼虫を用いて定型運動の制御機構を探る 細胞工学 33, 249-254 (2014).

[19] Kohsaka, H. and Nose, A. Optogenetics in Drosophila. (a book chapter in ”Optogenetics ”), Springer Verlag (2015).

[20] 能瀬聡直、高坂洋史、伏木彬　光によるショウジョウバエ中枢回路の機能解剖　生体の科学 68(5):478-479 (2017).

[21] *Kohsaka H, Guertin PA, Nose A. Neural circuits underlying fly larval locomotion. Current Pharm. Design. 23:1-12 (2017).

[22] 高木優、能瀬聡直　ショウジョウバエ幼虫の行動制御回路　月刊　臨床神経科学 36(8):903-906 (2018). 中外医学社

[23] Takagi S, Nose A Circuit architecture for somatotopic action selection in invertebrates. Neurosci Res. 2019 Mar;140:37-42. doi: 10.1016/j.neures.2018.08.008. Epub 2018 Aug 18.

＜**Books**＞

[24] 高坂洋史、能瀬聡直： ショウジョウバエを用いたオプトジェネティクス研究、「オプトジェネティクス」、エヌ・ティー・エス、141-153 (2013).（分担執筆）

[25] Kohsaka, H. and Nose, A. Optogenetics in Drosophila. (a book chapter in ”Optogenetics”), Springer Verlag (2015).

7 Invited Presentations at International Conferences

[1] 能瀬聡直：Optogenetic dissection of motor circuits that regulate larval locomotion in Drosophila、新学術領域「メゾ神経回路」第 1 回公開国際シンポジウム、 2012.7.7、東京

[2] 能瀬聡直、高坂洋史、高木俊輔：Optogenetic dissection of motor circuits in Drosophila larvae、「第 35 回日本神経科学大会」シンポジウム、 2012.9.18、名古屋

[3] Nose, A. ：Optogenetic dissection of motor circuits that regulate larval peristalsis in Drosophila, ”Behavioral Neurogenetics of Drosophila Larva” meeting at Janelia Farm,2012.9.30〜10.3, 米国

[4] Nose, A. ：Optogenetic dissection of the neural circuits that regulate rhythmic movement in Drosophila larvae, Symposium on Sensory Systems and Neural Circuits, 2013.2.12, 東京

[5] Nose, A. ：Optogenetic dissection of the neural circuits that regulate rhythmic movement in Drosophila larvae, The University of Tokyo - Korea University The 2nd Joint Workshop on Bio-Soft Matter, 2013.3.1, Seoul, Korea

[6] Nose, A. ：Functional dissection of the central circuits that regulate larval locomotion, Behavioral Neurogenetics of larval Drosophila: Molecules, Circuits, Computation and Robotics, 2014.3.10, Atami

[7] Nose, A. ：Functional dissection of the central circuits that regulate Drosophila larval locomotion, ESF-EMBO Flies, worms and robots: combining perspectives on minibrains and behaviours, 2014.11.11, Sant Feliu, Spain

[8] Nose, A.: Neuronal dynamics underlying motor decision making, Cooperation in Physics Workshop: LMU-UT , 2016.2.29-3.1, Tokyo, Japan

[9] Nose, A., Kohsaka, H., Yoon, Y., Takagi, S., Hiramoto, A., Ohura, S. and Niki, S.: Circuit mechanisms that regulate motor pattern in larval Drosophila. Behavioral Neurogenetics of Drosophila Larva, 2016 10.25 Janelia Farm Research Campus, USA.

[10] Nose, A. : Genomic and connectomics analysis of the motor circuits in larval Drosophila, NSF Workshop: Comparative Principles of Brain Architecture and Functions 2016.11.18, Marriott Marquis San Diego Marina, USA

[11] Nose, A. : Circuit mechanisms of action selection in Drosophila larvae, Systems biology of the brain “Reconstructing the connectome of the fruit fly larva” : CUSO Staromics PhD-program Workshop, 2017.9.11, University of Fribourg, Switzerland

[12] X. Zeng, T. Kawasaki, K. Inada, H. Kazama and A. Nose : Embryonic development of the motor circuits in Drosophila: emergence of coordinated neural activities and the role of sensory feedback, Behavioral Neurogenetics of Drosophila Larva, 2018.10.10, University of Edinburgh, UK

[13] Nose, A. : Regulation of motor circuit development by proprioceptive feedback, 2019 ASIA-PACIFIC DRORSOPHILA NEUROBIOLOGY CONFERENCE, 2019.1.18, Institute of Molecular Biology, Academia Sinica, 台湾

[14] Nose, A. : Functional connectomics of motor circuits in Drosophila larvae, Max Planck / HHMI Connectomics Conference Berlin 2019, 2019.4.16, Harnack-Haus of the Max Planck Society, Berlin

[15] Xiangsunze Zeng, Tappei Kawasaki, Kengo Inada, Hokto Kazama, Akinao Nose : Embryonic development of the motor circuits in Drosophila: emergence of coordinated neural activities and the role of sensory feedback, NEURO2019, 2019.7.27, TOKI MESSE , Niigata

8 Teaching Accomplishment

東京大学

理学部物理学科　講義　「生物物理学」　2012−2015, 2019
新領域創成科学研究科　大学院講義　「複雑生命現象論」　2012, 2014, 2016, 2019
理学系研究科　物理学専攻　大学院講義　「生物物理学 III」 2012, 2014, 2016 （上記、新領域講義と共通）
理学部物理学科　講義　「生物物理学特論　II」　2016−2018
理学系研究科　物理学専攻　大学院講義 「生物物理学 II」2016−2018 （上記、学部講義「生物物理学特論　II」と共通）
理学部物理学科　「物理学ゼミナール」2011, 2014, 2017
理学部　クラスター講義　2014

他大学

基盤医学特論講義、名古屋大学環境医学研究所、2012 年度
集中講義、学習院大学、2013 年度
神経科学序説、横浜市立大学、2014 年度
集中講義、学習院大学、2015 年度
集中講義、学習院大学、2017 年度
集中講義、学習院大学、2019 年度
Lecturer; Developmental Biology Course, 2012 at OIST （沖縄科学技術大学院大学）
Lecturer; Developmental Biology Course, 2013 at OIST （沖縄科学技術大学院大学）
Lecturer; the Collaborative lnternational Undergraduate Workshop at OIST、2015 年度、（沖縄科学技術大学院大学）

9 Contribution to Academic Community

9.1 Editorial Activities

N/A

9.2 Organization of Professional Societies

文部科学省科学研究費補助金　新学術領域研究　「メゾスコピック神経回路から探る脳の情報処理基盤」領域代表　2010−2015

9.3 Organization and Advisory of Conferences

Co-organizer, International Symposium on “Neuronal circuits at the intersection of theory and experiment”, Tokyo, Japan, 2012

Program Committee, The 35th Annual meeting of the Japan Neuroscience Society, Nagoya, Japan, 2012
Local Organizing Committee, 16th International Conference on Retinal Proteins (ICRP), Nagahama, Japan, 2014
Co-organizer, International Symposium on “Neuronal Circuits: Cutting edge approaches to the complexity”, Kyoto, Japan, 2013
Co-organizer, Conference on“Behavioral Neurogenetics of larval Drosophila: Molecules, Circuits, Computation and Robotics”, Atami, Japan, 2014
Co-organizer, Janelia Research Conference on“Behavioral Neurogenetics of Drosophila Larva”, Ashburn, USA, 2016
Co-organizer, Conference on “Behavioral Neurogenetics of Drosophila Larva”, Edinburgh, UK, 2018
Local Organizing Committee, 19th International Conference on Retinal Proteins (ICRP), Shima, Japan, 2020

10 Outreach

プレスリリース

「動物の動く速さをコントロールする。– 動物の運動速度を支える神経回路の解明 –」2014.10.16
「臨機応変」を配線する – 動物の行動選択を担う神経回路メカニズムの解明 –」2017.12.1
「前に行ったり、後ろに行ったり ～ 1 つの神経回路が異なる動きを効率よく生み出すしくみ～」 2019.6.17

ホームページ

http://bio.phys.s.u-tokyo.ac.jp/

11 Committee Service

11.1 External Committees

領域アドバイザー、戦略的創造研究推進事業（さきがけ）研究領域「脳神経回路の形成・動作と制御」、2009−2017 年
外部評価委員会、新潟大学脳研究所、2012 年
専門委員、日本学術振興会　科学研究費委員会（基盤・社会脳科学 A)、2012−2014 年
評価者、文部科学省　科学研究費補助金の評価（審査)、2012-2013 年
専門委員、文部科学省　科学研究費　新学術領域研究専門委員会（メゾ神経回路)、2012 年
英国 Welcome Trust Henry Dale Fellowship 審査委員

第 1 段審査担当委員、科学研究費補助金（基盤研究等）、脳科学、基盤・社会脳科学 2013−2014 年度
外部評価委員会、沖縄科学技術大学院大学、2014 年
運営会議委員、基礎生物学研究所、2015−2019 年
領域アドバイザー、JST 戦略的創造研究推進事業（さきがけ）　研究領域「生命機能メカニズム解明のための光操作技術」、2016−2020 年
書面審査員・書面評価員、日本学術振興会　特別研究員等審査会専門委員及び国際事業委員会、2016−2017 年
点検評価委員会、基礎生物学研究所、2017−2018 年
外部評価者、JST 戦略的創造研究推進事業（さきがけ）　研究領域「多細胞システムにおける細胞間相互作用とそのダイナミクス」、2019 年

11.2 University Committees

新領域創成科学研究科複雑理工学専攻・入試委員、2014 年度
全学　教員懲戒委員会　委員、2016 年度
新領域創成科学研究科・研究教育改善室長、2017−2018 年度

12 Internationalization Statistics

	Number	Country
Foreign students advised		
Bachelor Course	0	
Master Course	5	China, Korea
Doctor Course	5	China, Korea
Foreign researchers hosted	0	
Students sent abroad	5	USA
Researchers sent abroad	2	USA
Foreign visitors	5	USA