Control of Biological Assembly Networks and Thermodynamics

Tetsuya J. Kobayashi

Institute of Industrial Science, the University of Tokyo

Biological systems emerge from the assembly or network of diverse components operating across multiple scales. Proteins, for instance, are organized from amino acid sequences whose specific interactions give rise to molecular functions. Similarly, chemical reaction systems can be viewed as ensembles of elementary reactions, while neural networks consist of interacting neurons that collectively process information. At a larger scale, multicellular organisms arise from the assembly of heterogeneous cell types, whose coordinated interactions underpin development, adaptation, and physiological function.

A fundamental question in biology is how the functions of these assemblies or networks are acquired, maintained, and refined through evolution. Addressing this requires a theoretical framework capable of evaluating performance, characterizing constraints, and predicting the optimal or near-optimal behaviors that emerge under evolutionary pressures with physical constraints. Such a framework must be scalable, bridging molecular assembly and biochemical regulation with collective cellular dynamics and organism-level organization.

Despite their apparent diversity, many of these systems can be formally represented as reaction networks. This abstraction provides a common mathematical language to describe how components interact and transform to generate collective biological functions. Driven by this perspective, we have been developing stochastic and thermodynamic control theories for reaction networks. Our goal is to understand how biological assemblies achieve

functional robustness in the face of noise, energetic costs, and limited resources.

In this presentation, I will introduce our recent result of the optimal control of reaction networks and discuss their application to biological assemblies. I will focus on how stochasticity, thermodynamic constraints, and network topology shape attainable functions, potentially providing a unified basis for understanding biological organization across different scales.

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Dyadic transformation dynamics govern the spatiotemporal distribution of bacterial flagella motors

Chien-Jung Lo

Institute of Physics, Academia Sinica and Department of Physics, National Central University

The distribution of cell membrane-anchored proteins is critical for cell functions. Such as bacterial flagellar motors for motility, chemoreceptors for chemotaxis, and efflux systems. Despite the technique to measure the locations of the proteins being available, there are fundamental issues to be addressed before we can proceed. First, comparing the protein distribution from cells, required proper coordinate and positioning dynamics in the growing process. A recent investigation of *E. coli* cell wall growth dynamic can be understood as a Dyadic transformation is a good example. However, the protein distribution is dynamically contributed by the newly synthesized protein intermixed with evolved existed proteins. In this presentation, I will introduce a systematic approach to investigate the bacterial flagellar motor distribution.

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Geometric Regulation of Wrinkle Patterns in Epithelial Morphogenesis

Yasuhiro Inoue

Graduate School of Engineering, Kyoto University

Epithelial morphogenesis often involves the emergence of reproducible wrinkles and folds as growing tissues release compressive stress. Although molecular prepatterns play essential roles in development, the geometry of a tissue and its surrounding environment may also determine which morphological patterns emerge. In this talk, I will present two sets of multicellular dynamics simulations that explore how geometry regulates wrinkle-pattern selection in proliferating epithelial tissues.

First, we examine a planar epithelial tissue confined between elastic walls. The distance between the tissue and the surrounding walls regulates the characteristic spacing of the folds, whereas environmental asymmetry between the apical and basal sides changes the topology of the resulting patterns. As the degree of asymmetry changes, the tissue exhibits transitions among dot-like, labyrinthine, and hole-like patterns. A reduced mechanical description derived from the energy functional reproduces the same pattern-selection behavior.

We then examine proliferating epithelial tissues on spherical and ellipsoidal surfaces. On spherical surfaces, changing the curvature induces a transition from dot-like to labyrinthine patterns. On ellipsoidal surfaces, geometric anisotropy selects both the orientation and topology of the wrinkles: prolate geometries generate Yoshimura-like zigzag folds, whereas oblate geometries generate concentric ring patterns. These distinct morphologies arise because high-curvature regions behave as effective mechanical boundaries and redirect growth-induced compression.

Together, these results suggest a common mechanical principle: cell

proliferation generates compressive stress, whereas geometry determines how that stress is released. Tissue geometry is therefore not merely a passive container but may function as a mechanical control parameter that guides and stabilizes morphogenetic pattern formation. Such geometric regulation may act together with molecular signaling to ensure robust and reproducible tissue morphogenesis.

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Spatial Logic of Cell Death: Trigger Waves in Self-Organized Cell Populations

Sheng-Hong Chen

Institute of Molecular Biology (IMB), Academia Sinica

Large-scale cell death is essential for tissue sculpting during development [1], yet how death events are coordinated across millimeter-scale tissues remains poorly understood. I will discuss our recent work revealing that ferroptosis, an iron- and lipid-peroxidation-dependent form of cell death, can propagate through cell populations as self-regenerating trigger waves of reactive oxygen species [2]. These waves arise when ferroptotic stress converts cellular redox networks into bistable media, enabling local death events to spread over long distances through coupled ROS amplification and diffusion. In the developing avian limb, ferroptosis accompanies spatially restricted tissue remodeling, suggesting that ferroptotic waves can act as a developmental sculpting mechanism.

I will then present new work showing that cellular self-organization [3] provides an additional layer of spatial control over ferroptosis propagation. In self-organized epithelial monolayers, active-nematic-like patterns of cell density and alignment encode distinct ferroptosis-sensitive and ferroptosis-resistant states: low-density, misaligned regions exhibit elevated YAP/TEAD1 activity and preferentially initiate ferroptosis, whereas high-density, aligned regions show increased NRF2 expression and form propagation-resistant boundaries. At the single-cell scale, elongation polarizes oxidizable lipids toward cell poles, biasing lipid peroxidation and ferroptosis propagation along the axis of cell alignment. Together, these mechanisms convert otherwise isotropic, unbounded ferroptotic trigger waves into anisotropic and spatially confined waves.

These findings suggest a systems-level view of regulated cell death in which biochemical feedback, lipid organization, and multicellular patterning jointly determine where cell death begins, how it spreads, and where it stops. More broadly, they raise the possibility that developmental tissues use self-

organized physical patterns, alongside genetic and morphogenetic cues, to control collective cell fate during morphogenesis and stress adaptation.

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A Mathematical Modeling of Deformable Cells in Multicellular Dynamics

Nen Saito

Life Science Center for Survival Dynamics, Tsukuba Advanced Research Alliance (TARA), University of Tsukuba

In dense tissues, cells undergo deformation in response to mechanical interactions with their neighboring cells, and this deformability plays a crucial role in determining tissue-scale mechanical properties. Simulations and theoretical studies are indispensable for understanding such collective behaviors. However, due to computational limitations, large-scale simulations of deformable cells have generally been restricted to simple convex polygonal shapes.

In this talk, I will present a novel approach [1] for simulating large populations of freely deformable cells with significantly greater computational efficiency than existing methods. We demonstrate the versatility of this approach by applying it to a variety of biologically relevant systems, including densely packed tissues, chemotaxis-guided cell assemblies, and tissues undergoing cell division. Furthermore, we show that the proposed model can be derived as a reduced representation of the well-established phase-field model, suggesting that it provides a computationally efficient alternative with broad applicability to a wide range of biological phenomena.

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Cyclic Stretch Drives Epithelial Cells to Become Taller and Narrower

Fu-Lai Wen

Department of Physics, National Central University

Tissues are composed of cells that work together to perform essential functions. In living organisms, these cells are constantly pushed and pulled by mechanical forces, yet they can maintain their structure and function. To understand how cells adapt to such mechanical stimulation, we subjected MDCK cells, a canine kidney epithelial cell line, to persistent uniaxial cyclic stretch. We found that the cells autonomously transformed from a cuboidal to a columnar shape, becoming taller and narrower. This shape transformation was accompanied by remodeling of the intracellular cytoskeleton and intercellular junctions. Using atomic force microscopy and computational modeling, we further showed that these structural changes increase tensile forces at both the apical and basal sides of the cells, driving the transition to a columnar shape. Our findings reveals a key mechanism by which epithelial cells sense dynamic forces and adapt to them.

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Building Robust Cell Assemblies at Tissue Boundaries

Daiki Umetsu

Graduate School of Biostudies, Kyoto University

The formation and maintenance of tissue boundaries are fundamental processes in the self-organization of multicellular cell assemblies. Despite the tight adhesion between neighboring cells, epithelial tissues exhibit considerable cellular fluidity driven by cell proliferation and morphogenetic rearrangements. This raises the question of how tissue boundaries are maintained despite such dynamic cellular behavior.

Using the Drosophila epithelium as a model system, we combined live imaging with mechanical perturbation experiments to investigate the physical mechanisms underlying boundary maintenance. Our studies demonstrated that a localized increase in intercellular tension plays a critical role in preventing cell mixing across tissue boundaries. In addition to tension-based regulation, we found that differences in cell-cell adhesion between neighboring cell populations actively contribute to boundary maintenance. Remarkably, this differential adhesion is mediated by a member of the Toll-like receptor (TLR) family, which is best known for its role in innate immunity.

Building on these findings, I will discuss how the mechanical regulation of cell-cell interactions contributes not only to the maintenance of multicellular organization but also to the isolation of cells that acquire inappropriate positional identities. Through this perspective, I will explore how the physical principles governing cell assembly contribute to the robustness of multicellular systems.

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Engineered nucleic-acid condensates for molecular computation

Masahiro Takinoue

Laboratory for Chemistry and Life Science, Institute of Science Tokyo

Cells process environmental information through sensing, signal transduction, gene regulation, morphogenesis, and learning via the physicochemical dynamics of molecular reactions and networks, effectively functioning as chemical information-processing machines. Recently, synthetic Biology has sought to construct cell-like systems from the bottom up as "synthetic cells," which hold promise as models for elucidating cellular function from a physical/chemical perspective, as platforms for material and pharmaceutical production, and as autonomous smart therapeutic/diagnostic devices.

Our laboratory develops synthetic cells using artificially designed DNA and RNA. By computationally optimizing the base-pairing free energy, we designed DNA/RNA nanostructures, such as 6-branched motifs, that self-assemble into liquid–liquid phase-separated droplets. Incorporating miRNA recognition sequences and dynamically associating/dissociating structural domains enables droplets capable of information processing and motile synthetic cells. We aim to extend this technology toward molecular systems with sophisticated intelligent behavior, such as immune cells, and toward molecular-AI. This presentation outlines the underlying physicochemical principles and highlights representative systems.

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Computer simulations of chromatin organization and dynamics: Influence of mechanical perturbations by subnuclear molecules and nuclear envelope features

Tetsuya Hiraiwa

Institute of Physics, Academia Sinica

Chromatin, the DNA–protein complex that stores genetic information in eukaryotic cells, forms a long polymer confined within the nucleus. Its spatial organization plays a crucial role in gene regulation and cellular function. Besides biochemical regulation, the activities of subnuclear molecules such as polymerases and topoisomerases mechanically perturb chromatin and may influence its organization and dynamics. Nuclear envelope geometry and chromatin–envelope interactions also contribute to chromatin architecture. In this presentation, we introduce our polymer-physics-based computational studies on these effects. Specifically, we present simulations of (i) chromatin organization and dynamics driven by transient catch-and-release activities of subnuclear molecules [1,2], and (ii) the influence of nuclear envelope shape and chromatin–envelope interactions on chromatin organization.

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First-hitting pathways and catalytic kernel of growing systems

Wei-Hsiang Lin

Institute of Molecular Biology, Academia Sinica

Growing systems[1,2] are commonly modeled by reaction network structures that satisfy mass conservation condition. Conceptually, we can track biomass along reaction networks and calculate the waiting time distribution for its autocatalysis. We considering a subset of nodes that control all system influxes, named as *gatekeepers*. The catalytic kernel $\alpha(\tau)$ of gatekeepers can be calculated by summing up transition delay-time distribution of all first-hitting pathways from environmental to gatekeepers.

This new formulation allows us to calculate long-term growth rate λ by the catalytic relation $\tilde{\alpha}(\lambda) = \lambda + \beta$, where $\tilde{\alpha}$ is the catalytic spectrum and β is the degradation rate of gatekeepers. Catalytic spectra are useful for comparing growing reaction networks with either distinct network topology and different parameters. It provides a rigorous framework for coarse-graining nodes and fluxes. As a real biophysically quantity, catalytic kernel can also be measured by isotope tracing experiments in the future.

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From Motions to Functional Messages: Timing/Sizing of Motions and Tracing Communication in Biomolecules

Lee-Wei Yang

Institute of Bioinformatics and Structural Biology, College of Life Science and Medicine, National Tsing Hua University

Biomolecular function emerges not only from structural architecture, but also from the timescales, amplitudes, and propagation of internal motions. This talk presents two complementary frameworks that convert molecular fluctuations into quantitative and functionally interpretable information.

From the equilibrium protein dynamics, our Molecular Timer and Sizer (MTS; Chan et al., 2020) transforms the computationally inexpensive anisotropic network model into a predictor of the absolute time and spatial extent of biomolecular motions. Principal-component timescales are defined from molecular-dynamics trajectories using autocorrelation functions, the Wiener-Khinchin theorem, and an intensity-weighted period. Fluctuation-profile matching then maps these timescales and variances onto elastic-network eigenvalues, yielding the empirical power laws

$$t(\mathrm{ns}) = 56.1\lambda_{\mathrm{ENM}}^{-1.6}, \qquad \sigma^2(\mathrm{\AA}^2) = 32.7\lambda_{\mathrm{ENM}}^{-3.0}$$

Calibrated using simulations including a 600-ns ubiquitin trajectory, the approach estimates motions in proteins and ribosomes at a computational cost more than 10^5-fold lower than all-atom simulation.

Near the equilibrium protein dynamics, our time-dependent linear response theory (td-LRT) traces nonequilibrium mechanical signals following localized impulse perturbations. Atom-specific characteristic response times are evaluated over 133 force directions and converted into an asymmetric residue-residue connection matrix, revealing signal directionality and intramolecular communication centers. In DHFR, communication scores correlate with mutation-induced activation free-energy changes, DeltaDeltaG = -RT ln(k_WT/k_mut), with correlation > 0.8 across 35 mutants at 17 sites;

disruption of key communicators reduces hydride-transfer rates by up to three orders of magnitude. Spatially clustered communicators further identified an ATG4B allosteric site 26.1 A from its catalytic center, enabling screening of 2,016 approved drugs for their potential allosteric inhibition on this cancer target.

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Clock Protein KaiC Evolving with Earth's Rotation over Billions of Years

Yoshihiko Furuike

Institute for Molecular Science

Circadian rhythm in cyanobacteria is orchestrated by three clock proteins, KaiA, KaiB, and KaiC. When mixed with ATP, these proteins autonomously undergo rhythmic assembly and disassembly with a period of around 24 hours even *in vitro*.

Our research has focused on KaiC, as two reaction cycles within its hexameric double-ring structure are the source of the rhythm. The N-terminal ring (CI) determines the period of the rhythm by hydrolyzing ATP, while the C-terminal ring (CII) sustains the amplitude through a daily phosphorylation cycle. We have investigated how modern KaiC generates time information by integrating these two reactions [1–6], and then explored when this dual-reaction system was established during Earth's geological history [7].

Fifteen crystal structures covering the day–night cycle of KaiC from *Synechococcus* uncovered that reactions in CI and CII are allosterically coordinated through secondary to quaternary structural changes and provide timing cues for KaiA and KaiB. This dual-reaction system appeared to be conserved among KaiC homologs from other cyanobacterial species.

This observation motivated us to reconstruct ancestral KaiC proteins at key nodes in the phylogenetic tree and identify the origin of the circadian rhythm. Functional analyses of ancestral KaiCs estimated to date from 3.1 to 0.1 billion years ago, together with modern KaiC homologs from 41 extant prokaryotes, revealed that modern KaiCs consistently exhibit circadian rhythms across diverse ecological environments, from tropical to near-polar regions, and that these rhythms can be traced back to an ancestral form. In particular, the ancestral KaiC from 2.2 billion years ago displayed oscillations that could be

synchronized with the faster rotational cycle of the Proterozoic Earth. Structural data obtained in crystalline and solution states revealed that the microscopic establishment of ATP-binding active sites and the macroscopic rearrangement of the hexameric architecture drove the evolution of KaiC [7–8].

Our findings suggest that the structural innovations in KaiC enabled the temporal regulation of photosynthesis and contributed to the global rise of oxygenic ecosystems on our planet.

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Elucidating Human-Specific Mechanisms of Brain Development: A Novel 2D Culture Platform for Long-Term Tracking of Single Cells

Ikuo K. Suzuki

Lab. of functional genomics for human evolution, Graduate School of Frontier Biosciences, The University of Osaka

The human brain is remarkably large and complex, a trait driven during early development by specialized stem cells that multiply and eventually turn into mature neurons. While we know this process takes longer and produces vastly more cells in humans than in other species, observing exactly how individual stem cells behave over time has remained a significant challenge because traditional three-dimensional "mini-brains" (3D organoids) are thick and opaque, leaving the internal process a "black box." To overcome this limitation, we developed a novel two-dimensional (2D) brain organoid platform that perfectly mimics the essential spatial structure and organized layers of the early developing brain while keeping the cells flat. By combining this new culture method with an automated machine-learning tracking system, we successfully recorded the real-time behaviors, divisions, and family trees (lineages) of individual neural stem cells continuously for several weeks. Comparing the early brain development of humans against chimpanzees, our continuous single-cell tracking revealed that human stem cells exhibit a highly prolonged expansion phase—dividing more times to grow the initial pool of stem cells before transitioning into mature neurons, which explains why the human brain grows so much larger. Moving forward, this high-throughput system will allow us to map gene activity directly to specific cell behaviors, enabling us to pinpoint the precise evolutionary mutations that reshaped the human brain and provide fresh insights into developmental disorders and brain diseases.

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From Variational Modeling to Constitutive Learning in Cell and Tissue Dynamics

Min-Jhe Lu

Institute of Computational and Modeling Science, National Tsing Hua University

Cell and tissue dynamics involve interfaces, intracellular condensates, and reaction–diffusion fields, from unstable vascular tumor fronts to chromosomal passenger complex (CPC) condensates on mitotic chromosomes. A central modeling question is how biochemical and mechanical states determine transport, reaction, and motion; in continuum models, these dependencies are encoded by constitutive laws.

I first consider systems whose constitutive responses are derived from physical principles. For vascular tumor growth, free-boundary laws connect nutrient transport, proliferation and death, chemotaxis, and vascular supply to linear instability, bifurcation, and nonlinear morphology [1,2]. A Cahn–Hilliard model of CPC phase separation is calibrated from condensate size and tested against cell-specific spacing and coarsening in HeLa and MCF10A-5E cells [3]. Together, these studies map biological mechanisms to quantitative observables.

I then consider unknown responses. Rather than learning a time-stepper, we retain conservation laws and kinematics and learn only the unresolved constitutive component. Tests span diffusion, Cahn–Hilliard dynamics, porous-medium transport, reaction, and coupled multispecies PDEs. This exposes a consistency condition: every Runge–Kutta stage must evaluate the constitutive response at the corresponding stage state. For smooth prescribed-field reaction–diffusion equations, freezing that response across stages reduces a nominally second-order method to first order. The framework separates two questions in data-driven PDEs: which constitutive components are identifiable from observations, and whether the learned

response is coupled consistently to the discretization.

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Toward Predictable Evolution: Low-Dimensional Evolutionary Dynamics and Steering of Bacterial Phenotypes

Chikara Furusawa

Center for Biosystems Dynamics Research, RIKEN / Universal Biology Institute, The University of Tokyo

Biological systems evolve and adapt in response to changing environmental conditions. Understanding how organisms acquire adaptive phenotypes and how their evolutionary trajectories are constrained is a fundamental question in biology. However, phenotypic plasticity and phenotypic and genetic constraints on evolution have often been studied only qualitatively.
To quantitatively investigate these properties, we performed high-throughput experimental evolution of *Escherichia coli* under diverse stress conditions using an automated cultivation system developed in our laboratory. This framework enabled systematic analysis of phenotypic and genetic changes associated with adaptation to different environmental stresses. Our analyses showed that phenotypic changes during evolution were largely confined to a relatively low-dimensional subspace [1,2], consistent with theoretical predictions that evolutionary dynamics become organized along a small number of dominant modes [3].

The emergence of such low-dimensional phenotypic dynamics suggests that evolutionary changes may be amenable, at least partly, to prediction and control. To examine this possibility, we are developing methods to predict and control phenotypic evolution within our high-throughput experimental framework. In particular, we are constructing feedback-control strategies that dynamically modify selection pressures to guide evolutionary trajectories toward target phenotypes in a multidimensional phenotypic space. Finally, I will discuss the implications of these results for phenotypic plasticity and evolvability in bacterial evolution, as well as future strategies for predicting and controlling evolutionary dynamics.

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Emergence of collective co-evolutionary dynamics in bacteria and viruses

Hong-Yan Shih

Institute of Physics in Academia Sinica

Ecosystems are generally maintained far from equilibrium by external environmental forcing and by dynamical interactions among their constituent species. A remarkable example, with major significance for the global carbon cycle, is the ecosystem formed by marine cyanobacteria among the most abundant photosynthetic organisms on Earth and their cyanophage predators. We develop a spatiotemporal stochastic model of this bacteria–virus ecosystem to investigate how collective organization can emerge from intrinsically antagonistic interactions. In the model, bacteria and viruses are coupled not only through population dynamics and infection, but also through multiscale flows of energy, nutrients, and genetic information. In particular, the oceanic photon gradient drives energy flow through photosynthesis, while phage-mediated infection generates gene flow between bacteria and viruses. We predict that the coupling between these processes can produce a collective coevolutionary state in which viral predation simultaneously imposes individual costs and generates collective benefits of the ecosystem. This state is sustained by feedbacks between ecological dynamics and evolutionary adaptation, leading to the refinement of photosynthesis-related genes and an expansion of the ecological range and stability of the ecosystem. Our results suggest that nonequilibrium antagonistic interactions, spanning genomes, populations, and environmental gradients, can drive the emergence of stable, diverse, and functionally integrated microbial ecosystems.

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Macroevolutionary pathways reveal constrained evolution of bacterial phenotypes and lifestyle strategies

Takao K. Suzuki

Department of Biochemistry and Systems Biomedicine, Juntendo University Graduate School of Medicine

Bacterial lifestyles are defined by combinations of cell morphology, motility, and spore formation. Some combinations recur across distant lineages whereas others remain rare, suggesting that evolution navigates phenotype space along constrained routes. However, the nature of these constraints and their ecological and genomic consequences remain poorly understood.

In this talk, I will present pathwayPCM, a phylogenetic comparative method that reconstructs preferred evolutionary transitions among multi-component phenotypic states as a directed, weighted network. Applying pathwayPCM to nearly 3,600 bacterial species across 40 phyla revealed recurrent but phylum-dependent pathways through combinatorial phenotype space. Phylogenetically informed gene-association and KEGG pathway enrichment analyses further identified combination-specific functional repertoires spanning environmental sensing, transport, resource utilization, and secondary metabolism.

These findings suggest that bacterial phenotypes evolve as integrated trait combinations rather than as independent features, linking macroevolutionary transition structure to ecological and genomic differentiation. I will also briefly discuss how phylogenetic comparative methods can be extended from pairwise trait associations to the analysis of transitions among multi-component states. More broadly, pathwayPCM provides a framework for connecting the assembly of complex phenotypes with the evolution of bacterial lifestyle strategies.

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Motile bacteria in 2D complex environments with liquid-liquid interfaces and self-generated heterogeneity

Joonwoo Jeong

Ulsan National Institute of Science and Technology

We employ motile bacteria as 'active colloids' in complex environments with interfaces and self-generated transient heterogeneity. First, we investigate how the active motility of these 'colloids' affects their partitioning behavior between two immiscible phases in an aqueous two-phase system. While 'dead' colloids follow the Boltzmann distribution, active motility facilitates barrier crossing. Our optical tweezer experiments, where we drag the bacteria across these interfaces, further elucidate the crossing events associated with interfacial tension. Second, we address the trap-and-escape dynamics of a 'colloid' within a soft confinement generated by another colloid. A bacterium swimming in a viscoelastic, slowly relaxing polymeric environment leaves behind a transient polymer-depleted trail that can 'trap' another swimming bacterium. Combining fluorescence optical microscopy, rheometry, and statistical analysis, we justify our observations that higher polymer concentration and a shorter time lag between the leading and trapped bacteria result in longer mean escape times.

Bacterial chemosensory arrays as molecular computing machinery

Keita Kamino

Institute of Molecular Biology (IMB), Academia Sinica

Bacterial chemosensory arrays are highly conserved macromolecular assemblies composed of chemoreceptors, the histidine kinase CheA, and the adaptor protein CheW. In the canonical membrane-bound architecture, chemoreceptors detect chemical cues and, through cooperative interactions within the array, regulate CheA kinase activity. The resulting input–output relationship has been studied most extensively in the chemotaxis pathway of Escherichia coli. Most quantitative studies, however, have examined responses to individual chemoeffectors, and our understanding of how receptor arrays integrate simultaneous inputs from multiple chemoeffectors remains incomplete. We ask what computation this molecular array performs when confronted with mixtures of chemical cues. In this talk, I will first review our recent findings on responses to single-chemoeffector inputs and then present an ongoing project investigating how the array processes multiple-chemoeffector inputs.

Non-Steady Responses of Chemotactic Drift Velocity to Continuous Ligand Concentration Variations

Cheng-Hung Chang

Institute of Physic, National Yang Ming Chiao Tung University

In contrast to traditional theoretical studies of steady chemotactic drift speed, we develop a linear-response formalism for the non-steady response of chemotactic drift velocity to time-dependent ligand gradients. In the steady limit, our formalism reduces to the drift-speed formula of Locsei, derived using a fundamentally different approach. The formalism reveals that information from the perceived chemical signal to the drift velocity passes through two cascaded convolution filters: a biochemical memory filter and an orientational relaxation filter. Time-scale analysis of these filters shows that, although the response kernel governs the transient chemotactic forcing, the overall response speed is ultimately limited by orientational relaxation. Consequently, although bacteria can retain a relatively long biochemical memory of past ligand concentrations, rotational decorrelation limits the contribution of information from the distant past to the drift velocity.

Analytical solutions are obtained for a sudden switch of the ligand gradient and a periodically rotating gradient. Numerical simulations confirm the theoretical predictions and reveal a ligand-gradient-driven convection in modulation-orientation space, reminiscent of Rayleigh-Bénard convection driven by a temperature gradient. Beyond extending classical theories of chemotactic drift (de Gennes, Schnitzer, Locsei, and others) from steady to non-steady conditions, the present framework suggests that cascaded filtering may constitute a general dynamical structure in memory-dependent physical and biological systems.

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