JOINT SYMPOSIUM

BETWEEN

UNIVERSAL BIOLOGY INSTITUTE
The University of Tokyo, Japan

AND

MECHANOBIOLOGY INSTITUTE
National University of Singapore

April 14 - 15, 2018

Venue:
Mechanobiology Institute
NATIONAL UNIVERSITY OF SINGAPORE

Organizers:
Masaki Sano, *Universal Biology Institute, Japan*
G.V. Shivashankar*, Mechanobiology Institute, Singapore*

Universal Biology Institute-MBI Joint Symposium

Mechanobiology Institute, National University of Singapore
April 14-15, 2018
Venue: MBI Level 5 Seminar Room

Saturday, April 14 , 2018

Time	Programme
0930-1000am	**Masaki Sano** **Dep of Physics, Graduate School of Science, The University of Tokyo, Japan** *A physical mechanism controlling collective dynamics of neural stem cells: Topological defects in nematically ordered state*
1000-1030am	**Yusuke Toyama** **Mechanobiology Institute & Department of Biological Sciences -NUS, Singapore** *Mechanobiology of apoptosis in a tissue*
1030-1100am	Coffee Break
1100-1130am	**Tetsuya Hiraiwa** **Dep of Physics, Graduate School of Science, The University of Tokyo, Japan** *Collective cell movement driven by left-right asymmetric shrinkage of cell-cell junctions*
1130am- 1200 noon	**Timothy Saunders** **Mechanobiology Institute & Department of Biological Sciences -NUS, Singapore** *Selective filopdia adhesion ensures robust cell matching in the Drosophila heart*
1200-1230 pm	**Tetsuhiro Hatakeyama** **Graduate School of Arts and Sciences, The University of Tokyo, Japan** *Reciprocity between robustness and plasticity as a universal law in biology*
1230-0200pm	Lunch
0200-0230pm	**Shuji Ishihara** **Graduate School of Arts and Sciences, The University of Tokyo, Japan** *From cell to tissue: a continuum model for epithelial tissue deformation*
0230-0300pm	**Paul Matsudaira** **Mechanobiology Institute, Centre for Bioimaging Sciences & Dept of Biological Sciences-NUS, Singapore** *The Emergency of Symmetry from Strain Maps of Zebrafish Gastrulation*
0300-0330pm	**Ronen-Zaidel Bar** **Mechanobiology Institute, Singapore** *Syncytial germline architecture is actively maintained by contraction of an internal actomyosin corset*
0330-0400pm	Coffee break
0400-0430pm	**Akihiko Nakajima** **Dep of Basic Science, Graduate School of Arts and Sciences, The University of Tokyo, Japan** *Cell-to-cell heterogeneity in spatial and temporal sensing of signals in migrating cells*
0430-0500pm	**Fumio Motegi** **Mechanobiology Institute, Singapore** *Deconstruction and reconstruction of cell polarity networks*

6.00 PM– Dinner at MBI Level 10 Lobby

Universal Biology Institute-MBI Joint Symposium

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Sunday , April 15 , 2018

Time	Programme
0930-1000am	**Yasushi Okada** **Dep of Physics, Graduate School of Science, The University of Tokyo, Japan** *Imaging based approaches to the mechanobiology of the fast axonal transport*
1000-1030am	**Alexander Bershadsky** **Mechanobiology Institute, Singapore** *Control of integrin-mediated adhesions by microtubules and actomyosin cytoskeleton*
1030-1100am	Coffee Break
1100-1130am	**Taihei Fujimori** **Dep of Basic Science, Graduate School of Arts and Sciences, The University of Tokyo, Japan** *Differential polarity - an efficient and rapid mechanism of cell sorting*
1130am-1200noon	**Virgile Viasnoff** **Mechanobiology Institute, Singapore & CNRS, France** *From Microdishes to microniches. 3D micro-environmental control around single cells. Application to single cell apico basal polarization and lumenogenesis control*
1200-1230pm	**Marius Sudol** **Mechanobiology Institute, NUS, Department of Physiology, Institute of Molecular and Cell Biology (IMCB) A*STAR, Singapore** *The role of YAP Mechano-Responder in Actin Dynamics and Metastasis is revealed by CRISPR/Cas9 Gene Editing Approach*
1230-0200pm	Lunch
0200-0230pm	**Hideo Higuchi** **Dep of Physics, Graduate School of Science, the University of Tokyo, Japan** *Unified walking model for processive motor proteins and its experimental evidences*
0230-0300pm	**Yan Jie** **Mechanobiology Institute, Department of Physics, NUS, Singapore** *Mechanical lifetime of biomolecules*
0300-0330pm	**Nen Saito** **Dep of Physics, Graduate School of Science, The University of Tokyo, Japan** *Phase field simulation for macropinocytosis of amoeboid cells*
0330-400pm	**G.V.Shivashankar** **Mechanobiology Institute & Department of Biological Sciences, NUS, Singapore & IFOM, Italy** *Mechanical control of nuclear reprogramming & cell-fate decisions*
0400-0430pm	Closing & High Tea

ABSTRACTS

A physical mechanism controlling collective dynamics of neural stem cells: Topological defects in nematically ordered state

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Mechanobiology of different cells and tissues has made great progress in recent years. However, how different types of individual motion of cells and different interactions between them create macroscopic pattern and result in functions is not yet resolved. Recently, we found a simple physical mechanism that controls macroscopic collective motions in a cultured layer of neural stem cells. In the culture of neural stem cell, as the density of cells increased by cell proliferation, elongated stem cells align their axis and pass each other. There exists no polar order but namatic order extending at least up to mm or cm order. The moving direction of each cell reversed stochastically with characteristic reversal time between 1 to 3 hours depending on its cell cycle. We found topological defects with +1/2 and -1/2 topological charge appear in this tissue. Moreover, we found that +1/2 topological defects attract cells toward the core, on the other hand -1/2 defects repels cells from the core, thus formation of 3D mound from 2D tissue is controlled by the topological defects. We also found that the phenomenon can be explained by a simple theory of active matter.

Mechanobiology of apoptosis in a tissue

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Apoptosis, or programmed cell death, is the most common mechanism of eliminating damaged or unnecessary cells during embryonic development, tissue homeostasis, and certain pathological conditions. When a cell undergoes apoptosis within a tissue, the apoptotic cell is expelled from its neighboring non- dying cells. It has been shown by many labs, including ours, that this mechanical process is driven by the formation and contraction of the actomyosin cables in the dying and the neighboring cells, and/or by the lamellipodial crawling of the neighboring cells. However, how cell mechanics arises upon apoptotic cell extrusion and feedbacks to cellular and molecular function especially in the neighboring non-dying cells is largely illusive. In this presentation, I will present our current understandings of how mechanical tension and biochemical natures are altered in the neighboring cells as a consequence of apoptosis, and how these two factors are related to each other.

Collective cell movement driven by left-right asymmetric shrinkage of cell-cell junctions

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Morphogenetic epithelial deformation occurs during embryogenesis and drives complex tissue formation. As an example, we here focus on mechanistic perspective of morphogenesis of Drosophila male Terminalia. During this process, genitalia performs 360 degrees clockwise rotation, which finally induces the dextral spermiduct looping. It is known that this rotation takes place without relying on external forcing. In this presentation, we propose a novel mechanism for collective epithelial cell movement for tissue deformation, like such genitalia rotation, due to activity of cells within the tissue. The proposed mechanism is as follows: Left-right asymmetric accumulation of myosin II, or the difference in strengths of line tensions on cell-cell junctions between the left and right inclined junctions, causes asymmetric cell intercalation within an epithelial sheet, which unidirectionally drives collective epithelial cell movement. Incorporating this mechanism in the cellular vertex model in 2D, we revealed that left-right asymmetries of line tension strength and cell intercalation can actually induce unidirectional cellular movement.

Selective Filopodia Adhesion Ensures Robust Cell Matching in the *Drosophila* Heart

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The ability to form specific cell-cell connections within complex cellular environments is critical for multicellular organisms. However, the underlying mechanisms of cell matching that instruct these connections remain elusive. Here, we quantitatively explored the dynamics and regulation of cell matching processes utilizing Drosophila cardiogenesis. We found that cell matching is highly robust at boundaries between cardioblast (CB) subtypes, and filopodia of different CB subtypes have distinct binding affinities. Cdc42 is involved in regulating this selective filopodia binding adhesion and influences CB matching. Further, we identified adhesion molecules Fasciclin III (Fas3) and Ten-m, both of which also regulate synaptic targeting, as having complementary differential expression in CBs. Altering Fas3 expression changes differential filopodia adhesion and leads to CB mismatch. Furthermore, only when both Fas3 and Ten-m are lost is CB alignment severally impaired. Our results show that differential adhesion mediated by selective filopodia binding efficiently regulates precise and robust cell matching.

Reciprocity between robustness and plasticity as a universal law in biology

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Robustness and plasticity are important characteristics in biological systems and have therefore attracted much attention from not only biologists but also physicists. Whereas robustness concerns insensitivity to perturbations, plasticity concerns the variability of external inputs. How the two phenomena are compatible with each other is an important question to be addressed.

We investigate the compatibility of the two distinguishable properties in some biological systems, e.g., circadian clocks [1, 2] and reaction-diffusion systems [3], and we found the reciprocity between robustness and plasticity as a quantitative relationship. For example, the robustness of period and plasticity of phase against environmental changes such as temperature and nutrient conditions are compatible in circadian clocks. We found a quantitative relationship between them: higher robustness in the period implies higher plasticity in the phase, where changes in period and phase follow a linear relationship with a negative coefficient.

We will introduce several examples of the reciprocity and our ongoing projects.

[1] Hatakeyama TS, Kaneko K, PNAS (2012) 109, 8109-14
[2] Hatakeyama TS, Kaneko K, PRL (2015) 115, 218101
[3] Hatakeyama TS, Kaneko K, PRE Rapid Communications (2017) 95, 030201

From cell to tissue: a continuum model for epithelial tissue deformation

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Morphogenesis is collective cellular behaviors in which both the chemical and mechanical interactions play an essential role for determining shape of tissue and bodies. Recently, mechanical force [1] and deformation [2, 3] in growing tissue were quantified in terms of stress and deformation tensors. In these quantification methods, several tens of cells are averaged in their shape and force; the scale is suitable for characterizing tissue-level deformation while keeping the information of cellular behaviors yet. To make use of these quantities, we developed a continuum model for two-dimensional epithelial tissue. The model includes a field variable M(r) representing coarse-grained cellular shape, thanks to which tissue deformation rate is decomposed into deformation originated from cellular shape change and from topological change in cell position(cell rearrangement, cell division and death). Employing free energy and thermodynamics formalism, we derived a continuum model for the epithelial tissue [4]. Furthermore, by including formalism developed in active gel theory, we introduce active terms into the model.

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

The Emergence of Symmetry from Strain Maps of Zebrafish Gastrulation

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During early embryogenesis, the metazoan body plan acquires dorsal/ventral, anterior/posterior, and left/right axis and symmetry from a radially symmetric blastula through morphogenetic events such as epiboly, convergence/extension, and ingression. We have adopted methods from plate tectonics and earth physics to characterize the collective behavior of embryonic tissues during gastrulation in terms of linear and rotational strain from the velocity field gradients of cell translocation. The linear strain maps show the emergence of axial compression and equatorial expansion along the dorsal axis that corresponds to convergence and extension as well as the early onset of somatogenesis. A significant feature of the dynamics is the presence of a stagnation point or a node of divergent migration where convergence/extension movements intersect. This stagnation point is located at/near the dorsal organizer. The linear strains are symmetric along the dorsal axis indicating that the mechanical forces are coordinated over long distances. However, a surprise is the early signature of complementary left/right symmetry during early epiboly from the plus and minus curl, rotational strain in the left and right hemisphere of the animal pole. This left/right symmetry extends to the vegetal hemisphere during the completion of gastrulation. These mechanical descriptions of the dynamics during embryogenesis are consistent with the topological constraints of dynamics covering the surface of a sphere. The nodes of zero velocity correspond to the animal/vegetal poles, dorsal stagnation point/ventral pole and can be traced to the embryonic poles/axis established by maternal factors and activation of the egg at fertilization

Syncytial germline architecture is actively maintained by contraction of an internal actomyosin corset

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Syncytial architecture is an evolutionarily-conserved feature of the germline of many species and it plays a crucial role in their fertility. However, the mechanism involved in the maintenance of syncytial organization is largely unknown. Intriguingly, in some organisms, the intercellular bridges connecting germ cells are enriched in actomyosin-related cytoskeletal proteins. Here, we investigate the role of actomyosin contractility in the maintenance of germline syncytial organization in Caenorhabditis elegans. We identify a corset-like structure made of actin, myosin and their regulators within the syncytial germline, surrounding the common rachis. Using laser microsurgery, we further demonstrate that this structure is under tension, which is higher at the distal end and lower in the proximal. Genetic and pharmacological perturbations reveal how decreasing or increasing the tension within the actomyosin corset impinges on syncytial germline structure, leading, in extreme cases, to sterility. Finally, we develop a mathematical model simulating the balance of forces within the gonad and show that contraction of the apical actomyosin corset can modulate the syncytial geometry in a manner consistent with our experimental results. Thus, our work highlights a unique tissue-level cytoskeletal structure, and explains the critical role of actomyosin contractility in the preservation of a functional germline.

Cell-to-cell heterogeneity in spatial and temporal sensing of signals in migrating cells

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Chemotaxis is a fundamental cellular process that underlies various biological phenomena ranging from multicellular development, wound healing, immune surveillance to cancer metastasis. To understand the ability of migrating cells to sense complex chemoattractant cues and migrate toward the correct direction, we developed microfluidic devices to control the concentration gradient of chemoattractant dynamically in space and time. In combination of live-cell imaging and theoretical analysis, we found that migrating Dictyostelium cells have two distinct mechanisms of direction determination; one is the gradient detection (or spatial sensing), and the other is the first-hit detection (or temporal sensing). We further developed another microfluidic chamber consisting of parallel array of linear channels of several micrometers wide for quantitative investigation of cell-to-cell variations in such behavior. In combination with live-cell confocal fluorescent imaging, the system allows one to acquire isolated and confined cell trajectories from upwards of several hundred cells in a single experimental run. By employing the device, we show that the cell polarity and spatio-temporal chemotattractrant sensing depend on cell-size and that there are distinct modes of migration.

Deconstruction and reconstruction of cell polarity networks

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Cell polarity is essential for establishing cellular structures and functions. A hallmark of polarized metazoan cells is the segregation of partitioning-defective (PAR) proteins into distinct compartments at the cell cortex. The design principle that governs local molecular interactions among PAR proteins into global cellular patterning remains elusive. Here we deconstruct the molecular circuits in the Caenorhabditis elegans cell polarity networks and reconstruct them in a non-metazoan heterologous cell system. The polarization of PAR proteins mainly relies on antagonistic phosphorylation between two complexes, Cdc42p/PAR-6/PAR-3/PKC-3 kinase and PAR-2/PAR-1 kinase. Cdc42p and PAR-3 serve as a cortical scaffold for PAR-6/PKC-3, and PAR-2 recruits PAR-1 to the cortex. Cortical PAR-3 is interfered by PKC-3 alone but is stabilized by PKC-3 associated with Cdc42p/PAR-6. Synthetic circuits among six proteins are sufficient to yield their spatial segregation into a bipolar pattern within a cell. Our findings provide the simplest network that executes spatially self-organized polarization, and will permit synthetic control of cell polarity programs in living cells.

Imaging based approaches to the mechanobiology of the fast axonal transport

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More than 30 years have passed since the identification of kinesin and cytoplasmic dynein as the motor proteins for the transport of the vesicles in the neuronal axons. Since then, many studies have clarified the various aspects of this transport machinery. However, many questions still remain to be elucidated. For example, it is still unclear how many copies of motor proteins are required for the transport of a single vesicle, and how much force is exerted. It is also yet unresolved why vesicles are transported in the axon with the maximum velocity around 5-10 μm/s, while both kinesin and dynein only moves at around 1 μm/s in vitro. These basic questions regarding the mechanical properties of the transport are not only of interest from the view point of basic biology or biophysics, but also it would have clinical implications. Some mutations in kinesin genes that slow down the motility are reported to be associated with neurodegenerative diseases such as hereditary spastic paraplegia. We have been working on the development of technologies to measure these mechanical parameters in cultured neurons, and the latest unpublished results will be discussed.

Control of integrin-mediated adhesions by microtubules and actomyosin cytoskeleton

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The interrelationship between microtubules and the actin cytoskeleton in mechanoregulation of integrin-mediated adhesions is poorly understood. Here, we show that uncoupling of microtubules from integrin adhesions by depletion or displacement of KANK family proteins connecting the adhesion protein talin with microtubule tips led to disruption of podosomes and augmentation of focal adhesions, similarly to total disruption of microtubules. Both microtubule uncoupling from adhesions and total microtubule disruption bring about a massive assembly of myosin-IIA filaments, whilst a burst of microtubule polymerization led to a transient disassembly of myosin-IIA filaments. Myosin-IIA filaments are indispensable for microtubule-dependent regulation of integrin-mediated adhesions. The myosin-IIA filament assembly depends on Rho activation by RhoGEF, GEF-H1, which is trapped by microtubules connected with integrin adhesions but released after their disconnection. Thus, microtubule capturing by integrin-mediated adhesions modulates the effect of microtubules on the actomyosin cytoskeleton. The actomyosin reorganization then remodels the adhesions, closing the regulatory loop.

Differential polarity - an efficient and rapid mechanism of cell sorting

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Precise arrangement of cell positions is fundamental to multicellular organizations, however their molecular and developmental complexity hinders exact identification of the linkage between the tissue-level macroscopic patterning and the governing rules of individual cell movement. Owing to its conditional multicellularity, such morphogenetic movements is present in one of the simplest forms in the social amoeba Dictyostelium where two cell types prestalk and prespore cells starting from random positions sort out in the aggregate to form the 'tip' which acts as a central organizer of later morphogenesis of slug and culminants. The entire dynamics are highly coordinated, robust and accompany rotational cell movements. Despite the system being the classic and well-studied, the exact navigational rules that guide the cells remains elusive. By employing microfluidics and reconstituted adhesion protein, here we show that the elemental guidance rules can be resolved from the analysis of the minimal 2-cell clusters. Our analysis revealed that there is cell-cell adhesion dependent constitutive activation SCAR/WAVE complex and dendritic actin formation at the leading edge of the cells and that this polarity is essential for the front-to-back collective movement in the cellular aggregate. Pair-wise analysis of 2-cell chimeric clusters of gene knock outs revealed that TgrB1 and TgrC1 - Ig-domain heterophillic adhesion protein must act in trans for the maintenance of cell polarity and the cell cluster. Furthermore, the TgrB1/C1-dependent polarity maintenance can be reconstituted by attaching an isolated single cell to a TgrC1-coated microsphere. In combination with the manipulation of extracellular cAMP gradients in a microfluidics chamber, we demonstrate that adhesion dependent polarity overrides chemotactic response to extracellular cAMP however this property is lost in the prestalk cells. Prestalk cells extends multiple pseusopods in addition to one at the side of TgrC1-coated microsphere. Taken together with the detailed live-cell imaging analysis of the multicellular dynamics in a confined chamber, we conclude that prespore cells exhibit monotonic rotational movements in an aggregate by contact-dependent polarity, whereas the prestalk cells deviate from the collective movement by responding to the cAMP gradient. We propose differential contact-dependent polarity as an efficient and rapid means to spatially separate cell types and that similar mechanism may underlie cell sorting events in other systems.

From Microdishes to microniches, 3D micro-environment control around single cells. Application to single cell apico basal polarization and lumenogenesis control

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The key influence of the microenvironment on cell behavior and fate is increasingly recognized. It follows that new techniques to control the 3D environment around cells are essential to understand the processes by which cells probe and respond to the cues received by their microniches. Here, we present an approach that allows transforming microwells into artificial microniches where the chemical coating, the rheological properties and the topographical properties can be differentially controlled on the top, sides and bottom of the wells and assembled in a combinatorial way. This technique is also compatible with high and super resolution imaging that allows probing the dynamics of cell cytoskeleton and regulatory proteins with unprecedented resolution down to the single molecule level in 3D. We exemplify how these *bone fide* artificial microniches can be used to induce full apico-basal polarization of single epithelial cells as well as to control intercellular stresses driving the anisotropic growth of intercellular lumens. We will detail our recent studies on the role of mechanical forces in the development of bile canaliculi in liver and explain our minimal organ approach.

Reference:
Li et al Nature Cell Biology 2016
Galland et al Nature Methods 2015
Stoecklin et al Advanced Bioengineering Systems. 2018

Short Biography

Virgile Viasnoff is a biophysicist holding a CNRS/NUS professor appointment. He is the Head of a joint CNRS/National University of Singapore lab. His group at the Mechanobiology Institute of Singapore studies how environmental sensing influences cell-cell interactions. In particular, combining microfabrication technics, original optical detection and biophysical approaches, they study the role of mechanical forces in the establishment/homeostasis/loss of epithelial polarization in the context of liver development and cancer progression.

The Role of YAP Mechano-Responder in Actin Dynamics and Metastasis is Revealed by CRISPR/Cas9 Gene Editing Approach

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YAP (Yes kinase-associated protein) is a WW domain-containing protein that acts as a potent oncogene and stemness factor. It is one of the two main effectors of the Hippo tumor suppressor pathway. YAP is a transforming gene of the chromosome 11q22 amplicon, and its expression is elevated at high frequency in human cancers, including liver, breast, ovary and stomach cancer. Our recent work showed that YAP regulates the acto-myosin network by suppressing Rho-GTPase *via* Rho-GTPase activating protein 29 (ARHGAP29) being a direct transcriptional target of YAP in human gastric cancer. We showed that YAP promoted the expression of ARHGAP29 to suppress the RhoA-LIMK-cofilin pathway, thereby destabilizing F-actin. The overexpression of YAP caused cytoskeletal rearrangement by altering the dynamics of F-actin/G-actin turnover, thus promoting migration. In a mouse model, circulating tumor cells (CTCs) exhibited an increase in ARHGAP29 RNA level compared with cells at primary tumor sites. Moreover, increased ARHGAP29 expression correlated with shortened survival of human gastric cancer patients. Importantly, we showed that ARHGAP29 is critical in regulating cancer metastasis in a mouse model of liver cancer metastasizing to lungs.

Cancer cells are generally softer than normal cells. By increasing the rigidity of cancer cells to the level of normal cells *via* novel therapeutic interventions, we could provide rather unorthodox modality to treat cancer in unison with other standard therapies.

Unified walking model for processive motor proteins and its experimental evidences

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Cytoskeletal motor proteins, kinesin-1, cytoplasmic dynein-1 and myosin-V, transport vesicles in cells. They move stepwise with regular step size in forward and backward directions along cytoskeletal filaments, actin filament and microtubules. To understand the movement of these motors with load, we constructed the simple and unified model that explains the dwell time between consecutive steps and the step ratio of the number of backward to forward steps of all three motors under the wide range of load. The model predicted the low step ratio under the assisting load and the short dwell time at super-high load, but no data of the step ratio and dwell time at those loads have been reported in kinesin-1. To confirm the model, the step ratio under the assisting load and the dwell time at high load of single molecules of kinesin were examined by measuring force and displacement measurements using optical tweezers. The results obtained fitted well to the unified model. Our model will be useful to understand the behavior of multiple motors interacting with single cytoskeletal filaments in cells.

Mechanical lifetime of biomolecules

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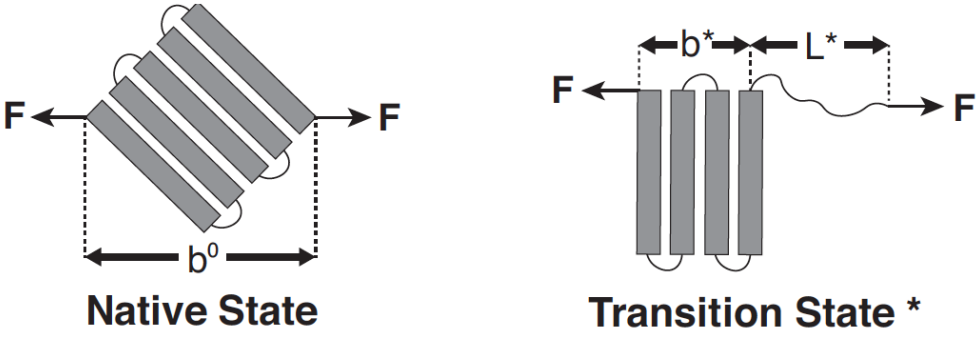
Several recent experiments have suggested that the structural-elastic properties of the native and the transition states of biomolecules are a key determinant of their mechanical stability. However, most of the current theoretical models were derived based on conformation diffusion of the molecule along a phenomenological energy surface, lacking a direct relation to the structural-elastic parameters of the molecules. Here, based on the Arrhenius law and taking into consideration of the structural-elastic properties of the native state and the transition state, we derived a simple analytical expression for the force-dependent lifetime of the native state of the molecules. We show that this model is able to fit a wide scope of experiments, and explain a variety of complex force-dependent transition kinetics observed in recent experiments. The results highlight a previously largely unrecognized structural-elastic determinant of the lifetime of biomolecules under force, and provide a new theoretical framework that can inform us the structural-elastic properties of the molecules.



Sketch of the structure of a protein domain in the native and transition states.

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4.Guo, S. et al. (2017). " Structural-elastic determination of the lifetime of biomolecules under force." Under review.

About the speaker

Jie Yan is currently a professor in the department of physics and a principal investigator in the Mechanobiology Institute, National University of Singapore. He is also a Fellow of American Physical Society and a Singapore NRF Investigator. Using single-molecule appraoch, his research aims to provide insights of the molecular mechanisms underlying a broad spectrum of biological areas such as mechanobilology, chromosome organization and DNA damage repair.

Phase field simulation for macropinocytosis of amoeboid cells

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Macropinocytosis is clathrin-independent endocytosis and allows internalization of large volume of extracellular fluid. For Dictyostelium discoideum and tumor cells, this process mediates uptake of nutrients, while it occurs for the non-specific uptake of soluble antigens in immune cells. Mechanism of macropinocytosis, especially it's dynamical aspect, remains still unclear. From theoretical perspective, we introduce phase-field model for simulation of macropinocytosis. The proposed model with the help of GPU enables us to simulate dynamics of macropinocytosis-like large membrane deformation driven by reaction and diffusion of membrane localized proteins.

Mechanical control of nuclear programming & cell-fate decisions

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In landmark experiments, exogenous biochemical factors (Yamanaka factors) were shown to induce reprogramming of somatic cells into induced Pluripotent Stem Cells (iPSC) in vitro. However, in vivo, cells undergo trans-differentiation programs in the absence of exogenous factors suggesting that the local tissue micro-environmental signals are sufficient to induce such transitions. Towards this end, I will describe our efforts to engineer microenvironment of single somatic cells and show that nuclear reprogramming can be induced by cell-mechanical constraints, with very high efficiency, and without the need for exogenous factors. The mechanical reprogramming of somatic cells and their cell-fate decisions have important implications in understanding disease models and in regenerative medicine.

http://mbi.nus.edu.sg/g-v-shivashankar/