

Workshop Schedule

Events for:
Monday, December 3rd - Friday, December 7th

Monday, December 3rd

8:00am **Breakfast - Simons Center Cafe**

8:45am **Workshop Begins**

9:00am **Martin Gruebele - SCGP 102**

Title: Folding and protein interactions inside the cell

Abstract: While many proteins are highly stable, or interact with others at the nanomolar affinity level, many others are not. Intrinsically disordered proteins are marginally stable, and many protein-protein associations such as chaperoning are weak. One of the reasons is that the intracellular environment can thus exert control over such interactions, for instance by fine-tuning temperature, ATP concentration or free volume inside the cell. I will discuss experimental examples, as well as some molecular dynamics simulations of a model cytoplasm to highlight the kinds of interactions that can be fine tuned by the cell, as well non-specific 'sticking' interactions that arise. The latter are important because they could be a starting point for evolved functional interactions.

9:45am **Pierre Gaspard - SCGP 102**

Title: Kinetics and thermodynamics of DNA replication and other molecular information processes

Abstract: More than 50 years have passed since the discovery of DNA structure and its role in coding genetic information. Yet, the kinetics and thermodynamics of genetic information processing in DNA replication, transcription, and translation remain poorly understood. Challenging issues arise from the facts that DNA and RNA sequences form disordered chains for the motion of polymerases or ribosomes, while thermal fluctuations is at the origin of copying errors. Recent advances show that these issues can be addressed in terms of so-called iterated function systems, which provide an exact mathematical solution to the kinetic equations of such processes. Remarkably, the iterated function systems determine the effects of sequence heterogeneity and copying errors. In particular, the local velocities of polymerases or ribosomes along the template sequence may have a fractal or continuous distribution. Furthermore, the growth of the copy can be linear or sublinear in time, and driven either by a favorable free-energy landscape, or by the entropic effect of copying errors in an adverse free-energy landscape. In this regard, the thermodynamic entropy production depends on the rate of copying errors. These links between molecular information processing and the second law of thermodynamics shed a new light on genetic drift, mutations, and evolution.

10:30am **Coffee Break**

11:00am **Marlan Scully - SCGP 102**

Title: QUANTUM THERMODYNAMICS: From black mold to black holes

Abstract: Quantum mechanics and thermodynamics are a powerful combination having applications from biology to general relativity. I got interested in the issue via Schrödinger's comments on life and negentropy, which I applied to the quantum heat engine . Later work along these lines involved the quantum photocell and photosynthetic extensions . Experimental work stimulated by these studies included new forms of coherent Raman spectroscopy for detection of, e.g., anthrax, black mold, etc. It is interesting that the same quantum thermodynamic tools are useful in the general relativistic study of Unruh-Hawking radiation , which will be sketched as time allows.

11:45am **Shaul Mukamel - SCGP 102**

Title: Novel spectroscopic probes of conical intersections, chirality and photosynthetic charge and energy transfer with quantum and x-ray light

Abstract: Ultrafast nonlinear x-ray spectroscopy is made possible by newly developed free electron laser and high harmonic generation sources. The attosecond duration of X-ray pulses and the atomic selectivity of core X-ray excitations offer a uniquely high spatial and temporal resolution. We demonstrate how stimulated Raman detection of an X-ray probe may be used to monitor the phase and dynamics of the nonequilibrium valence electronic state wavepacket created by e.g. photoexcitation, photoionization and Auger processes. Conical intersections (CoIn) dominate the pathways and outcomes of virtually all photophysical and photochemical molecular processes. Despite extensive experimental and theoretical effort, CoIns have not been directly observed yet and the experimental evidence is being inferred from fast reaction rates and some vibrational signatures. Novel ultrafast X ray probes for these processes will be presented. Short X-ray pulses can directly detect the passage through a CoIn with the adequate temporal and spectral sensitivity. The technique is based on a coherent Raman process that employs a composite femtosecond/attosecond X-ray pulse to directly detect the electronic coherences (rather than populations) that are generated as the system passes through the CoIn. Applications will also be made for time- resolved diffraction, X ray sum frequency generation, and detecting molecular chirality. Conventional nonlinear spectroscopy uses classical light to detect matter properties through the variation of its response with frequencies or time delays. Quantum light opens up new avenues for spectroscopy by utilizing parameters of the quantum state of light as novel control knobs and through the variation of photon statistics by coupling to matter. Entangled- photon pairs are not subjected to the classical Fourier limitations on their joint temporal and spectral resolution. Low intensity requirements for multi- photon processes make them ideally suited for minimizing damage in imaging applications. We show how the unique temporal and spectral features of entangled light may be used to reveal properties of multiexcitons in photosynthetic aggregates. Simulations demonstrate that they provide unique control tools for two-exciton states in the bacterial reaction center of *Blastochloris viridis*. Population transport in the intermediate single-exciton manifold is suppressed by the absorption of photon pairs with short entanglement time, thus allowing the manipulation of the distribution of two-exciton states. The quantum nature of light is essential for achieving this degree of control, which cannot be reproduced by stochastic or chirped light. Classical light is fundamentally limited by the frequency-time uncertainty, whereas entangled photons have independent temporal and spectral characteristics not subjected to this uncertainty. In another application of quantum light, the exciton relaxation dynamics of light-harvesting complex II (LHCII) in an optical cavity is manipulated and detected by multidimensional photon coincidence counting. This technique reveals the dynamics in both single and double excitation bands. We study how the cavity polariton dynamics are affected by coupling to photon modes and molecular vibrations described by a realistic spectral density at 77 K. Without the cavity, the energy transfer pathways are not resolved due to the line broadening caused by fast exciton dephasing. The strong coupling to cavity photons results in well-resolved polariton modes. The hybrid (matter and field) nature of polaritons slows down their energy transfer rates. Finally we show how Raman processes involving femtosecond X ray pulses can be used to monitor and coherently control long-range electron Transfer in Azurin.

12:30pm **Lunch Break - Simons Center Cafe**

2:00pm **Chris Jarzynski - SCGP 102**

Title: Non-equilibrium thermodynamics of nanoscale systems

Abstract: Thermodynamics provides a robust conceptual framework and set of laws that govern the exchange of energy and matter. Although these laws were originally articulated for macroscopic objects, it is hard to deny that nanoscale systems also exhibit "thermodynamic-like" behavior - for instance, biomolecular motors convert chemical fuel into mechanical work. To what extent can the laws of thermodynamics be "scaled down" to apply to individual microscopic systems, and what new features emerge at the nanoscale? I will review some of the challenges and recent progress associated with answering these questions, with a particular focus on non-equilibrium behavior, fluctuations, and strong system-bath coupling.

2:45pm **Felix Ritort - SCGP 102**

Title: Experimental Measurement of Information-Content in Mutational Ensembles

Abstract: Biology is intrinsically noisy at all levels, from molecules to cells, tissues, organs, communities and ecosystems. While thermodynamic processes in ordinary matter are driven by free-energy minimization, living matter and biology delineate a fascinating nonequilibrium state predominantly governed by information flows through all organizational levels. Whereas we know how to measure energy and entropy in physical systems we have poor knowledge about measuring information-content in general. Recent developments in the fields of stochastic thermodynamics and thermodynamic-information feedback combined with single molecule experiments show the way to define information-content in nonequilibrium systems. In this talk I will introduce a mutational ensemble of DNA hairpin folders and show how to measure information-content in this context. A definition of information-content applicable to generic disordered populations is proposed. Results are experimentally verified in single molecule pulling experiments.

3:30pm **Coffee Break**

4:00pm **Pieter Ten Wolde - SCGP 102**

Title: Optimal Cellular Information Transmission

Abstract: Experiments in recent years have vividly demonstrated that living cells can measure chemical concentrations with remarkable accuracy. Importantly, these concentrations often vary on the timescale of the response of the system. In this talk, I will discuss the optimal design of cell sensing systems. I will show that not only receptors and readout molecules fundamentally limit the accuracy of sensing, but also time and power; each of these resources imposes a fundamental sensing limit, which cannot be enhanced by raising another resource. This observation leads to a novel design principle for the optimal allocation of cellular resources in systems that need to detect time-varying signals. I show that the chemotaxis system of the bacterium *E. coli* obeys this design principle.

4:45pm **Steve Presse - SCGP 102**

Title: Understanding Life One Photon at a Time

Abstract: Monitoring life in action as it occurs in real time within the cellular cytoplasm at the relevant single molecule scale remains an important challenge. In order to see life occur and monitor specific biomolecules as they diffuse and assemble in the cytoplasm we create contrast with the cellular background by fluorescently labeling such biomolecules. Yet the diffraction limit of light keeps us from peering into length scales comparable to those of single molecules. In fact typical diffraction limited point spread functions of light-emitting biomolecules can be two orders of magnitude greater in size than the biomolecules themselves. For this reason, it has so far been impossible to clearly distinguish biomolecules within a few tens of nanometers of each other if they are simultaneously emitting light. In other words, it is difficult to monitor life unfold. The 2014 Chemistry Nobel Prize was therefore awarded for separating signals from particles in time that cannot otherwise be separated in space to localize biomolecular structures to a precision beyond the diffraction limit. However this process is slow and thus we compromise temporal resolution by separating signal in time. Here we present new Mathematics that make it possible to consider complex dynamical signals from which we can build a story of life in action starting from single, or very few, photons. The methods we present--motivated by the tools of Bayesian nonparametrics—show us how to achieve diffraction-limited tracking from signal previously considered insufficient. If time allows, we will discuss extensions of our methods to inferring diffusional dynamics from single photon arrivals from confocal imaging methods.

Tuesday, December 4th

8:00am **Breakfast - Simons Center Cafe**

8:30am **Ken Dill - SCGP 102**

Title: Maximum Caliber: an inference principle for nonequilibrium statistical mechanics.

Abstract: Maximum Caliber is a principle for inferring pathways and rate distributions of kinetic processes. The structure and foundations of MaxCal are much like those of Maximum Entropy for static distributions. We have explored how MaxCal may serve as a general variational principle for nonequilibrium statistical physics -- giving well-known results, such as the Green-Kubo relations, Onsager's reciprocal relations and Prigogine's Minimum Entropy Production principle near equilibrium, but is also applicable far from equilibrium. I will also discuss some applications, such as finding reaction coordinates in molecular simulations.

9:15am **Joe Howard - SCGP 102**

Title: Oscillatory enthalpic changes during early embryogenesis driven by the cell cycle

Abstract: To probe the energetic costs associated with embryogenesis, we repurposed an isothermal calorimeter to measure the heat flow between developing zebrafish embryos and the surrounding medium. During reductive cleavage, when the number of cells increases rapidly due to synchronized divisions while the total embryo volume remains fixed, we made the unexpected discovery that the heat flow oscillated with a period matching that of the cell cycle. The oscillations were blocked by inhibitors of the cdk1-cyclin, which drives the cell cycle, but persisted even when DNA synthesis, mitosis and cell division were all blocked. We propose that the phosphorylation and dephosphorylation reactions catalyzed by the cell cycle oscillator, the biochemical network controlling mitotic entry and exit, impose a high energetic cost that is necessary for the accurate and robust timing of cell proliferation during development.

10:00am **Coffee Break**

10:30am **Jose Onuchic - SCGP 102**

Title: Towards Decoding the Metabolic Plasticity in Cancer: Coupling of Gene Regulation and Metabolic Pathways

Abstract: It has been becoming clear that both glycolysis and oxidative phosphorylation (OXPHOS) play critical roles in various types of cancer. This study aims to decipher the genetic and metabolic regulation of glycolysis and OXPHOS in cancer. In particular, through coupling a gene regulatory network model with the metabolic pathways it controls, we establish a theoretical framework to study the interplay between glycolysis and OXPHOS. Our model demonstrates a direct association between the activities of AMPK and HIF-1, master regulators of OXPHOS and glycolysis respectively, with the activities of three metabolic pathways: glucose oxidation, glycolysis and fatty acid oxidation (FAO). Moreover, cancer cells are able to acquire a hybrid metabolic state characterized by high AMPK/HIF-1/OXPHOS/glycolysis activities. Guided by the model, we develop metabolic pathway signatures to quantify the activities of glycolysis, FAO and the citric acid cycle of tumor samples by evaluating the expression levels of enzymes involved in the corresponding processes. By applying the pathway signatures and our previously defined AMPK/HIF-1 signatures, we confirmed their association and the existence of a hybrid metabolic phenotype at both the tumor level and the single cell level. The association of AMPK/HIF-1 activity with metabolic pathway activity, predicted by the model and verified by analyzing the gene expression and metabolite abundance data of patient samples and single cells, was further validated by in vitro studies of aggressive triple negative breast cancer cell lines. In summary, we demonstrate a direct association of the AMPK/HIF-1 activity with metabolic pathway activity and investigate the existence of a aggressive hybrid metabolic phenotype.

11:15am **Jin Wang - SCGP 102**

Title: Quantifying landscape and flux for nonequilibrium biological systems

Abstract: We established a theoretical framework for studying the dynamics and thermodynamics of nonequilibrium physical and biological systems. We identify the main driving force for the nonequilibrium systems as the landscape gradient and rotational flux. We found that landscape and flux can be quantified and are critical for the global dynamics and thermodynamics of the nonequilibrium systems. We uncovered that these driving forces are crucial in determining the functions of cell cycle, differentiation/development, cancer, neural networks, evolution and ecology. We demonstrated that the landscape and flux can be quantified experimentally in self repressor/lambda phage and single molecule enzyme dynamics respectively.

12:00pm **Lunch Break - Simons Center Cafe**

1:00pm **SCGP Weekly Talk - Peter G. Wolynes - 102**

Title: Functional Biology: Landscape Physics-A Little Bit Beyond Equilibrium

Abstract: While structural biology is clearly governed by energy landscapes of systems that are very near to equilibrium, it is not clear how far the notion of landscapes can be pushed as we delve further into cellular function. I will discuss three complex problems of functional biology: cytoskeleton dynamics, gene regulation, and chromosome dynamics. In all of these cases, landscape ideas provide a zeroth order approximation to the main phenomena, but the limitations of the ideas also begin to emerge.

2:00pm **Coffee Break**

3:00pm **Jacques Prost - SCGP 102**

Title: Tissues as Active Systems

Abstract: After introducing the notion of homeostatic pressure, I will subsequently introduce dynamical equations, which exhibit fluid like behavior on time scales long compared to duplication and apoptosis times, in the vicinity of homeostatic conditions. Subsequently, I will describe stress-clamp experiments, which provide numbers on the effects of stress on cell division and apoptosis and introduce the idea of "active" tissue, which allows us to understand some aspects of experimental results. Then I will describe a dynamical transition in nematic epithelia which we predicted about ten years ago in the context of active gels: a nematic epithelial tissue placed on stripes of different width, switches from a perfectly quiescent state to a spontaneously shearing state, simply by changing the stripe width! Eventually, I will shortly give some conjectures about long time electric effects on polar tissues.

3:45pm **Thierry Emonet - SCGP 102**

Title: Exploiting fluctuations to climb gradients faster

Abstract: Countless organisms use a run-and-tumble strategy to navigate gradients. The classical drawback of this approach is that runs in the wrong direction are wasteful. We show analytically that organisms can overcome this fundamental limitation by exploiting the non-normal dynamics and intrinsic nonlinearities inherent to the positive feedback between motion and sensation. This mechanism drives large asymmetric fluctuations and circulatory fluxes in the organism's behavioral phase space, not described by mean field theory, that selectively amplify runs in the correct direction and result in fast "ratchet-like" gradient climbing.

Wednesday, December 5th

8:00am **Breakfast - Simons Center Cafe**

9:00am **Herbert Levine - SCGP 102**

Title: Cellular Pattern Formation via Notch Signaling

Abstract: One of the best-studied intercellular signaling systems used in developmental biology relies on the Notch pathway. In its canonical form, this pathway leads to lateral inhibition and thereby to spatial organization of differentiated tissue. During cancer progression, this pathway can shift to a lateral induction mode that may play a key role in metastasis. Here we survey various models of the Notch pathway and place its dynamics within the general mathematical framework of non-equilibrium pattern formation. We argue that the results may be helpful in resolving outstanding issues regarding pattern regularity and pattern flexibility.

9:45am **Ao Ma - SCGP 102**

Title: Dynamic instability from non-equilibrium structural transitions on the energy landscape of microtubule

Abstract: Microtubule is a major component of the cytoskeleton and is vital to numerous cellular processes. All the functions of microtubules are driven by dynamic instability; its mechanism, however, has remained unresolved for over thirty years due to conceptual difficulties inherent in the dominant GTP-cap paradigm. Here we present a new conceptual framework: dynamic instability is non-equilibrium structural transitions on the energy landscape of microtubule and is determined by its topology (e.g. basins, barriers), which we infer from steric constraints of tubulin structures and the geometry of microtubule lattice. From the resulting energy landscape emerges a physically rigorous structural mechano-chemical model that, for the first time, unifies all the phenomena of dynamic instability (e.g. growth, shortening, catastrophe, rescue and pausing at both plus and minus ends) and enables us to reproduce them in kinetic simulations.

10:30am **Coffee Break**

11:00am **Jean Francois Joanny - SCGP 102**

Title: Physical properties of suspensions of active particles

Abstract: In this talk, we discuss unexpected physical effects associated to non-equilibrium fluctuations in solutions of active particles. In the first part, we consider mixtures of active (high effective temperature) and passive (low effective temperature) particles and we present a kinetic theory in the dilute limit. Our theory is a non-equilibrium analog of a second order virial expansion. At a finite density, we show that the solution can phase separate into two phases each containing mostly one type of particles (active or passive). In this second virial approximation, we can introduce non-equilibrium "chemical potentials" whose gradients govern diffusion fluxes and a nonequilibrium "osmotic pressure," which governs the mechanical stability of the interface between the two phases. We also discuss the phase diagram and the surface tension between two phases at equilibrium. In the second part, we investigate non-interacting Ornstein-Uhlenbeck particles (OUP), which are self-propelled in a viscous medium by a force, correlated over a finite time. In one dimension, we study the steady state of a single OUP in a harmonic potential and use the result to explore more complex geometries. In a "Casimir"-like setup involving two narrowly-spaced walls, we describe a particle-trapping phenomenon, which leads to a repulsive effective interaction between the walls. In a two-dimensional annulus geometry, we observe net stresses which resemble the Laplace pressure of equilibrium statistical physics.

11:45am **Karsten Kruse - SCGP 102**

Title: Accuracy of position determination in Ca^{2+} signaling

Abstract: Living cells respond to spatially confined and transient signals. Intracellular signal transmission often involves the release of second messengers like Ca^{2+} . They eventually trigger a physiological response, for example, by activating kinases. Here, we investigate theoretically how positional information can be accurately read out by protein phosphorylation in spite of rapid second messenger diffusion. We find that accuracy is better for kinases that need to bind to a membrane before activation compared to cytosolic kinases. We show that our findings can explain some salient features of the ubiquitously expressed conventional protein kinase $\text{C}\alpha$.

12:30pm **Lunch Break - Simons Center Cafe**

2:00pm **Cristina Marchetti - SCGP 102**

Title: Topology and dynamics in active and living matter

Abstract: Topology underlies much of our understanding of equilibrium matter in terms of defects in ordered media and topologically protected states. In active systems composed of individually powered units, such as bacterial suspensions or epithelial cell layers, topological phenomena can take on new and surprising roles. In this talk I will highlight topological phenomena in active fluids with polar and nematic liquid crystalline order. I will show how broken time-reversal symmetry due to the active drive allows polar flocks on a curved surface to support topologically protected sound modes. In active nematics, activity instead causes topological disclinations to become spontaneously motile, driving a non-equilibrium variant of the Berezinskii-Kosterlitz-Thouless transition and novel phases of defect order and chaos. Such topological phenomena offer intriguing possibilities for biology.

2:45pm **Kim Sneppen - SCGP 102**

Title: Theoretical Tool Bridging Cell Polarities with Development of Morphologies

Abstract: Despite continual renewal and damages, a multicellular organism is able to maintain its complex morphology. How is this stability compatible with the complexity and diversity of living forms? Looking for answers at protein level may be limiting as diverging protein sequences can result in similar morphologies. Inspired by the progressive role of apical- basal and planar cell polarity in development, we propose that stability, complexity, and diversity are emergent properties in populations of proliferating polarized cells. We support our hypothesis by a theoretical approach, developed to effectively capture both types of polar cell adhesions. When applied to specific cases of development - gastrulation and the origins of folds and tubes - our theoretical tool suggests testable predictions pointing to the strength of polar adhesion, restricted directions of cell polarities, and the rate of cell proliferation to be major determinants of morphological diversity and stability.

3:30pm **Coffee Break**

4:00pm **Mehran Kardar - SCGP 102**

Title: Affinity maturation of antibodies and the puzzle of HIV low spike density

Abstract: Affinity maturation (AM) is the process through which the immune system evolves antibodies (Abs) which efficiently bind to antigens (Ags), e.g. to spikes on the surface of a virus. This process involves competition between B-cells: those that ingest more Ags receive signals (from T helper cells) to replicate and mutate for another round of competition. Modeling this process, we find that the affinity of the resulting Abs is a non-monotonic function of the target (e.g. viral spike) density, with the strongest binding at an intermediate density (set by the two-arm structure of the antibody). We argue that, to evade the immune system, most viruses evolve high spike densities (SDs). This is indeed the case, except for HIV whose SD is two orders of magnitude lower than other viruses. However, HIV also interferes with AM by depleting T helper cells, a key component of Ab evolution. We find that T helper cell depletion results in high affinity antibodies when SD is high, but not if SD is low. This special feature of HIV infection may have led to the evolution of a low SD to avoid potent immune responses early on in infection.

4:45pm **Dave Thirumalai - SCGP 102**

Title: From caging to super-diffusive behavior in tumor growth

6:00pm **Conference Dinner**

Thursday, December 6th

8:00am **Breakfast - Simons Center Cafe**

9:00am **Rama Ranganathan - SCGP 102**

Abstract: Proteins can fold spontaneously into well-defined three-dimensional structures and can carry out complex biochemical reactions such as molecular recognition, catalysis, and allosteric communication. The precision required for these properties is somehow achieved while also preserving evolvability - the capacity for adaptive variation in response to ever-changing selection pressures. How are proteins built in Nature to support all of these properties? In the past, we have taken a statistical genomics approach to this question, deducing the pattern of constraints on amino acid residues in proteins through analysis of amino acid coevolution a protein family. This approach reveals a novel decomposition of proteins into sparse groups of collectively-evolving amino acids termed "protein sectors", embedded within an environment of weaker, more local interactions. The sectors comprise contiguous networks of amino acids within the tertiary structure that often connect distant functional surfaces - a basis for allosteric communication. We are now developing new approaches for (1) understanding the physics of sectors, and (2) defining how the dynamics of the evolutionary process controls the emergence of this structural architecture in proteins.

9:45am **Ting Lu - SCGP 102**

Title: Bottom-up Assembly of Microbial Communities: Modeling, Analysis and Engineering

Abstract: Microbial communities are fundamentally important to the environment, agriculture and human health. To realize their potential for various applications, one major challenge is to uncover the basic rules underlying community organization that is often heterogeneous in space and time. Using synthetic consortia as model systems, we recently investigated two questions relating to microbial social interactions: First, how do the modes of interaction contribute to community dynamics? Second, how does the spatial scale of interaction determine ecosystem behaviors during range expansion? Combining modeling with experiment, our studies help to reveal the roles of microbial interactions in controlling community assembly, and also provide insights into the creation of synthetic communities for future applications.

10:30am **Coffee Break**

11:00am **Michael Shelley - SCGP 102**

Title: Self-Organization and Mechanics in the Cell

Abstract: The inside of a cell is an active place, with molecular machines busy positioning subcellular organelles, organizing themselves within membranes, or remodeling chromatin in the nucleus. I will discuss how mathematical modeling and large-scale simulations have interacted with experimental measurements and perturbations of such motor-driven biomechanical processes within the cell. This includes how the spindle finds its place in the cell, which is best treated as complex mechanical systems that works with transitory elements, and how motor activity and hydrodynamic interactions may underlie an apparently self-organizing dynamics of chromatin in the nucleus.

11:45am **Massimiliano Esposito - SCGP 102**

Title: Thermodynamics of open chemical reaction networks: Energy and information transduction in biology

Abstract: Open chemical reaction networks (CRNs) play a central role in biology, in particular for metabolism. I will show how open CRNs can be seen as thermodynamic machines transducing energy and information far from-equilibrium. More specifically, the following questions will be addressed: What is minimal chemical work needed to bring a CRN into a given nonequilibrium state? What is a thermodynamically meaningful notion of information in a CRN? How does the topology of a CRN affects its dissipation? How can one coarse grained the description of a CRN without altering its thermodynamics? . How can one account for fluctuations and spatial inhomogeneities?

12:30pm **Lunch Break - Simons Center Cafe**

2:00pm **Andre Levchenko - SCGP 102**

Title: The decision landscapes in living cells

Abstract: Live cells routinely make decisions that are informed by external stimuli and endogenous noisy regulatory networks. At this point, we lack a coherent understanding of how these decisions are made, although we have developed mechanistic descriptions of various instances of decision making processes in specific systems. In this talk, using the recent experimental and modeling analyses of cell migration, proliferation and death conducted at our lab, I will suggest a methodology for quantitative understanding of cellular decision making. I will also demonstrate that this method has a powerful predictive power, with particular applications to therapeutic interventions in cancer and other complex diseases. This approach can be extended to other systems and can lay the foundations for a more integrative analysis of cell function.

2:45pm **Kingshuk Ghosh - SCGP 102**

Title: Truth is in the Disorder and Noise

Abstract: In this talk we will argue the importance of noise and disorder to learn and advance design principles in Biology. First, we will briefly discuss how stochastic time trajectories mimicking experiment can be used to build and infer models of genetic networks. Next, we will show the importance of the disordered state in two problems in protein science. We will address a long-standing question in protein science: how do thermophilic proteins -- extracted from organisms that live at high temperature -- can withstand temperatures much higher than their mesophilic counterparts, obtained from organisms that live near room temperature. This extreme thermal tolerance in thermophilic (folded) proteins is particularly intriguing given they share high structural and sequence similarity with their mesophilic counterparts. Supported by polymer physics theory and all-atom simulations, we will show charge patterning in the folded and unfolded ensemble is key to understand this puzzle. We will further demonstrate the important role of charge patterning to model conformational heterogeneity in the Intrinsically Disordered proteins (IDP), an emerging class of proteins that completely lack folded state. Specifically, we will show how subtle mutations or post-translational modifications in conjunction with slight changes in temperature and/or salt concentration can significantly alter IDP conformations, giving us new insights to design and manipulate charges.

3:30pm **Workshop Discussions**

4:30pm **Laufer Center Gathering**

Friday, December 7th

8:00am **Breakfast - Simons Center Cafe**

9:00am **Jason Wagoner - SCGP 102**

Title: The biological catch bond suppresses fluctuations in nonequilibrium systems

Abstract: Some cell processes must be sensitive to an external signal while also keeping fluctuations low. These features would violate an equilibrium fluctuation-dissipation relationship and can only be found in nonequilibrium systems that dissipate energy. Here, we show that the biological catch bond--a bond that has increasing lifetime with respect to increasing bond force--is a mechanism that suppresses fluctuations in several such systems. An example is a myofilament, where, during muscle contraction, the mean number of myosin-actin bonds must steeply increase with respect to applied tension, but the fluctuations around this mean must also be kept low. Similar requirements are found in the other processes, like the adhesion of leukocytes or platelets to a blood vessel wall. We show the precise role of the catch bond in these systems with a nonequilibrium fluctuation-dissipation relation, which can be broken into additive equilibrium and violation components. The catch bond gives a strong violation component by inducing a correlation between the mesostate of interest (the number of bonds) and the extent to which transitions in and out of this mesostate break detailed balance.

9:45am **Coffee Break**

10:15am **Hong-Yan Shih - SCGP 102**

Title: Emergence of a stable nonequilibrium bacteria-phage collective state from multi-scale feedback

Abstract: Ecosystems are generally maintained out of equilibrium by driving forces from the environment and dynamical ecological interactions. Population fluctuations lead to the violation of detailed balance. A remarkable example of this, with great significance for the functioning of the planet's global carbon cycle, is the world's most abundant organism marine cyanobacteria *Prochlorococcus* spp. and its phage predators. We develop a spatio-temporal stochastic model for this ecosystem and predict that a collective state emerges through couplings between energy flow from the photon gradient and gene flow between bacteria and viruses. This state represents a dynamic balance between individual sacrifice and collective benefits. The consequences are the improvement of photosynthesis genes and the enlargement of the range and stability of the ecosystem. This mechanism shows that non-equilibrium antagonistic interactions between organisms, on scales ranging from genomes to the environment, can drive the emergence of collective stability and diversity in ecosystems.