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Biocomplexity Faculty Search Committee
c/o Prof. Rob de Ruyter van Steveninck
Biocomplexity Institute
Indiana University
Swain Hall West 117
Bloomington, IN 47405-7105

Dear Members of the Biocomplexity Faculty Search Committee:

I am writing to apply for the tenure-track faculty position in Biological physics at Indiana University. I am currently a postdoctoral fellow at University of Pennsylvania under the supervision of Prof. Tom C. Lubensky. I completed my physics Ph.D. under Prof. Philip A. Pincus, in the year of 2000 at University of California, Santa Barbara. I then held a postdoctoral position at College de France, Paris, in the condensed matter group headed by Prof. P.-G. de Gennes.

My research focuses on theoretical soft condensed matter physics and its overlap with cellular biology. My Ph.D. thesis is devoted to electrostatic effects in highly-charged biomolecular systems. I have made contributions to theory relating to counterion-mediated attractions, membrane rigidity of highly-charged membranes, depletion interaction mediated by semiflexible rods, and phase behaviors of nematic gels. More recently, my research has extended to the viscoelastic properties and active behavior of living cells. In particular, I have developed a phenomenological model which enables one to extract useful information about the activity of biomolecular motors from microrheological data of living cytoskeleton. I believe that one of my research strengths lies in my ability to interact closely with experimentalists and to suggest physical mechanisms to interpret their results. Indeed, some of my recent publications have resulted from fruitful collaborations with experimentalists. A summary of my previous and current work, as well as my future directions are described in the enclosed statement of my research interests.

Additionally, I have experience teaching both graduates and undergraduates. At the University of California, Santa Barbara, I had the opportunity to deliver a number of lectures in a graduate statistical physics course. I also enjoyed the role of being a teaching assistant for a number of freshman physics classes, teaching lab sections and conducting review sessions for midterms and finals. I find teaching enjoyable and look forward to preparing and to delivering good courses.

I would welcome the opportunity to continue my research and teaching in your department. Enclosed please find my curriculum vitae, which includes a list of my publications, and a statement of my research interests. The following senior scientists have agreed to serve as references: **Prof. Philip A. Pincus**, University of California, Santa Barbara, fyl@mrl.ucsb.edu; **Prof. Tom C. Lubensky**, University of Pennsylvania, tom@dept.physics.upenn.edu; **Prof. Randall D. Kamien**, University of Pennsylvania, kamien@physics.upenn.edu; **Prof. Arjun G. Yodh**, University of Pennsylvania, yodh@dept.physics.upenn.edu; **Prof. Samuel A. Safran**, The Weizmann Institute of Science, sam.safran@weizmann.ac.il; **Prof. Dov Levine**, Technion–Israel Institute of Technology, levine@tx.technion.ac.il.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

Andy W.C. Lau

Research Interests

Andy W.C. Lau

My primary research interest is theoretical soft condensed matter physics, the study of materials characterized by their ease of response to external forces and thermal fluctuations. I am particularly interested in the exciting area of its overlap with cellular biology. Indeed, the fundamental building blocks of life - the plasma membrane, the cytoskeleton, microtubule, DNA, F-actin - are all soft materials. To date, I have worked on a number of projects involving electrostatic, entropic, and elastic effects in biomolecular systems. My research interest has recently extended to viscoelastic properties of living cells and nematic gels, a simple model of actin networks in cells. Many of these activities, which were inspired by biological systems, have stimulated experimental investigations, which in turn may provide important physical insights. I believe that the prospect of analyzing biological materials using physical methods may lead to an increased understanding of the mechanism underlying their biological functions in life.

Previous and Current Work

Correlation effects in electrostatics. – Of all interactions, electrostatics is arguably the most fundamental for soft systems and it is ubiquitous in biological materials. The standard mean-field approach to charged systems is the Poisson-Boltzmann (PB) theory, or its linearized version, the Debye-Hückel theory. Although PB theory provides an adequate description for weakly charged systems, it fails for highly charged membranes and biopolymers such as DNA, and in particular, it cannot account for the counterion-mediated attractions, which are believed to play a major role in DNA condensation. I have explored this electrostatic attraction in a unified framework, based on the Wigner crystal model. In addition, I have worked out the renormalization of the bending constants of a highly charged membrane produced by charge-fluctuations. It turns out that, in contradistinction to PB prediction, a highly charged membrane can become more flexible and likely to bend. Moreover, based on a "two-fluid" model, I have predicted a novel fluctuation-induced condensation transition, in which a large fraction of counterions is condensed onto a charged plate. A particularly interesting prediction of this theory is that at physiologically relevant temperatures, monovalent and divalent counterions exhibit qualitatively distinct behaviors, as is often observed experimentally. I have also extended this condensation framework to two similarly charged plates, and found that, in addition to attraction, this system may exhibit a first-order binding transition. My recent interest in correlation effects extends to other charged systems and polyelectrolyte brushes, in particular.

Depletion interaction mediated by semiflexible rods. – Another interaction that is important in soft matter and particularly in colloidal science is the depletion attraction. Its origin is purely entropic: When two spherical particles are suspended in a solution of order-of-magnitude-smaller particles, the larger particles attract because of the gain in the available volume – hence entropy – of the smaller particles when the larger particles are close together. A recent experiment which measures the interaction potential between two spheres in a solution of semi-flexible rods (fd virus) did not agree with the "rigid-rod" theory which predicts the depletion interaction mediated by perfectly rigid rods. To explain this discrepancy, I proposed a simple bent-rod model, which relies on the assumption that if the rods are sufficiently stiff, they might be approximated by two rods of half the length attached together at a fixed angle. This model is simple enough for an analytical treatment and provides an accurate fit of the measured interaction potential.

Fluctuations of a bio-polymer in a nematic background. – The advent of single-molecule manipulation of biopolymer provides an enormous opportunity to learn about the dynamics and statistical properties of biomolecules on a single-molecule level. While most *in vitro* experiments are done in an isotropic background, many biopolymers such as the actin filaments within the sarcomere and neurofilaments within the axon actually reside in an anisotropic nematic-like environment. Together with the experimental group at UPenn, I have investigated the behaviors of single semiflexible polymers dissolved in a nematic background of fd virus. I have contributed theoretically to explain the experimental observations, and in particular, constructed a rotationally-invariant theory for a single semiflexible polymer in a nematic matrix, and calculated from it the fluctuation spectrum, which compares well with experiments.

Lyotropic nematic gels. – When rigid rods embedded in a cross-linked polymer network - nematic gels, a remarkable thing happens: there is no stress in response to a certain sets of strains. This phenomenon - soft elasticity - arises from the Goldstone mode associated with the broken rotational symmetry of the nematic state. This unique property suggests many interesting technological applications. It is also imaginable that nature has found ways to use biological version of these material, *e.g.* actin networks in the cytoskeleton, to control elastic properties of cells. Together with Tom Lubensky and David Lacoste, I have discussed the equilibrium phases and collapse transitions of a lyotropic nematic gel immersed in an isotropic solvent. Upon decreasing the quality of the solvent, we found that a lyotropic nematic gel undergoes a discontinuous volume change accompanied by an isotropic-nematic transition. We also computed phase diagrams that these systems may exhibit. In particular, we showed that coexistence of two isotropic phases, of two nematic phases, or of an isotropic and a nematic phase can occur.

Microrheology of living cells. – A physical picture of active behaviors of living cells is crucial for a more complete understanding of cellular processes such as intracellular transport of vesicles and organelles. The molecular basis of such behaviors are highly specialized protein molecules which transduce the chemical energy of a fuel molecule, ATP, to mechanical work and motion. Together with Crocker and Lubensky, I am investigating the use of the microrheology method to address mechanical and active behavior of the cytoskeleton of living cells. Microrheology has recently emerged as a powerful tool to measure the elastic moduli of complex fluids. Unlike conventional rheology measurements, it relies on the Brownian (thermal) fluctuations of micron-sized beads dispersed in the sample to assess the viscoelastic response function. As Crocker's experiment clearly demonstrated, a new theory is required in order to extend this novel technique to living cells. With Tom Lubensky, I have constructed a phenomenological theory of microrheology for active systems in general, and living cells in particular. By incorporating a non-thermal noise source arising from the presence of active elements (motors), we show that if one can quantify the rheology of a cell using a frequency-dependent shear modulus, the power spectrum of the non-thermal noise can be sensibly extracted from two-point microrheology (tracking two particles simultaneously) experiments. Experimental results of J.C. Crocker show that this power spectrum exhibits power-law behavior over a few decades.

Future Research Plan

As exemplified above, my work reflects a strong interdisciplinary interplay between physics and biology, and between theory and experiment. I believe that there is enormous potential for new physics to emerge from studies of biological systems and for physics to have a profound impact in biology. Living systems are open systems in which the flow of energy creates conditions that are different from thermodynamic equilibrium. My long-term goal is to understand biological phenomena from a non-equilibrium statistical physics point of view, which involves dynamics, noise, and nonlinearity. As is well-known, there are no general unified principles for doing statistical mechanics far from equilibrium, and one of the motivations for studying biological systems is that they are excellent systems in revealing such principles. In coming years, I would like to pursue the following research areas at the interface between biology and soft matter physics.

Dynamics of active complex fluid systems. – I plan to investigate the dynamics of a new class of non-equilibrium active complex fluid, where individual "molecules" of at least one species continuously consume and dissipate energy, creating a state that is far from equilibrium. A model system is a "bacterial bath", in which a high concentration of swimming bacteria is suspended in a liquid. This class of complex fluid is quite different from conventional equilibrium media. Indeed, preliminary experiments suggest that these systems violate the Fluctuation Dissipation Theorem. Other active systems include active gels, *e.g.* F-actin network with myosin motors, and active membranes, *e.g.* a lipid bilayer membrane with ion-pumps embedded in it. Important theoretical issues, including phase behaviors, instability, and pattern formation, require hydrodynamic and phenomenological descriptions. The aim of my work is to construct such hydrodynamical equations with non-thermal driving noise, that enable one to compute viscoelastic properties as well as fluctuations of these systems. Microrheological experiments on these active systems are now underway and will demonstrate how active behaviors are manifested in the "diffusion" of dispersed particles. My theoretical analysis will help to interpret such passive microrheology experiments.

Mechanical properties and active behavior of living cells. – A cell is a nonequilibrium soft material whose viscoelasticity arises from an intricate dynamical network of bio-polymers and its fluctuations are actively driven by ATP-consuming molecular motors. A major challenge for modern biology is to understand the interplay between these elements that are indispensable for cellular processes such as intracellular transport, cell crawling, and mechanochemical transduction. Recently, I have addressed theoretically the interpretability of an experimental method, termed two-point microrheology as applied to the cytoskeleton of living cells. Building on this successful collaboration with J. Crocker at UPenn, I will continue explore this line of research. In particular, to learn about the micro-environment of organelles inside the cytoskeleton of living cells, I will construct biologically plausible models to compute one-and two-particle correlation function, and compare the results with Crocker's one- and two-point microrheological data. This analysis will involve a "Two-fluid-like model" with non-thermal driving. For thermal systems at least, such a two-fluid model has been experimentally shown to yield information about local shear moduli of an otherwise heterogeneous soft material. I expect this calculation will be important for extracting the local properties of a living cell, including local motors activities.

Correlation effects and dynamics of charged systems. – I would like to continue to work on problems in electrostatics; there are at least two general aspects that I plan to pursue. First, I will continue the work on the fluctuation-induced counterion condensation, extending this physical picture to the important cases of charged rods and spheres, which are physical models for charged biopolymers and colloids. This work will be relevant for understanding the bundling of biopolymers induced by multivalent counterions and the aggregation of charged colloids. In addition, I plan to work on computer simulation that might be helpful to establish the fluctuation-induced counterion condensation and, in general to clarify theoretical issues which are not easily resolved experimentally or using analytical approximations. Secondly, I also plan to explore dynamics of the counterions near charged surfaces under non-equilibrium conditions, *e.g.* under flow or shear. I will use the nonlinear electro-hydrodynamical equation to compute the dynamic structure factor of the counterion density near a charged surface. This quantity is experimentally accessible and in principle reveals the underlying collective dynamics of the counterions in solutions.

I believe that the proposed research outlined above not only illuminates some fundamental issues in soft physics but also will lead to new applications in biophysics and nonlinear systems. My future research program will likely have close interaction with biologists and experimental physicists, and continue to explore other important problems at this interface.