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

Dear Prof. Ruyter,

I would like to apply for the junior faculty position in Biocomplexity Institute at Indiana University. I am a university postdoctoral fellow in Department of Physics at The Ohio State University. My research interests are problems in statistical physics. My current research has mainly focused on theoretical approaches for biological systems. I hope I can collaborate with Prof. Beggs, Prof. Glazier, and Prof. Setayeshgar in your institute.

Please find the enclosed *Curriculum Vitae*, statement of *Research Plan*, and *Teaching Interests*. I look forward to your reply.

Yours sincerely

Ha Youn Lee

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Research Plan

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I. INTRODUCTION

My long-term research plan aims to understand complex biological systems through two important tools: statistical physics and computational modeling based on biological data. Currently we are observing a huge generation of biological data such as the complete genome of many organisms from bacteria to human, the structures of some RNA and numerous proteins, and the expression profiles of genes by chip technology. Converting this enormous data to useful biological knowledge requires a new paradigm, systems biology. Systems biology is the study of living organisms in terms of their underlying systematic structure rather than simply their individual molecular components. A *system* can be anything from a gene regulatory network to a cell, a tissue, an entire organism, or an ecosystem. Based on investigations of all interacting components simultaneously, we can have a systematic view of the biological function of each element. The integrated understanding for biological systems is necessary for meaningful prediction of biological functions under specific conditions. Hence my long-term research goal is to develop novel models to predict the behavior of complex biological systems and to apply these models to problems in medical research.

Based on my research experiences which have been focused on interdisciplinary subjects between statistical physics and other fields such as the immune system, the visual cortex, mirotubules and molecular motors, and traffic flow, I am currently interested in three areas. The first one is establishing an integrated view of the immune system which consists of many interacting ingredients: peptides, proteins, and cells. I will apply the concept of systems biology to describe immune responses by quantitative modeling. I know my effort will improve the scope and power of current drug and vaccination, for example, to conquer AIDS disease, destroy tumors and prevent autoimmune disease. I have a plan for incorporating the current tremendous genome-related discoveries into a systematic description of immune responses. The second one is investigating the mechanism of cell motility. The motility of the cell is essential for immune responses, wound healing, and more generally many kinds of

cellular processes. Within past 10 years, the biochemical mechanism of cell motion has been actively investigated. The most important ingredient of cell motion is actin filament polymerization, which involves many kinds of actin associated proteins. To understand the cell motility, *in vitro* biomimetic experiments using beads or phospholipid bilayer vesicles with cell extract or purified proteins have been performed. I will make a statistical physics model to describe the results of biomimetic experiments. The third area of my interests is applying well established methods in bioinformatics to interesting problems such as RNA editing and predicting peptide sequences that bind to specific MHC molecules. Furthermore, I will invent new algorithms to describe important subjects in bioinformatics by incorporating approaches of statistical physics.

II. RESEARCH PROJECTS

My research interests cover a broad area. Here I have chosen three examples of my short-term research projects.

1. T cell proliferation model based on gene analysis

Goals: *Predicting T cell repertoire dynamics based on gene analysis in order to develop a novel vaccine strategy for HIV virus*

The immune system is our primary defense against pathogenic organisms. Like the nervous system, the immune system performs pattern recognition tasks, learns, and retains a memory of the antigens that it has fought. Immunological memory is carried by antigen-specific T and B cells. The immune response develops in time and the description of its time evolution is an interesting problem in dynamical systems. I will make a systematic approach for the dynamics of T cell immune response. An integrated model study is expected to predict rather complicated immune responses, for example, those to mixtures of related viruses.

I have experience in such systematic approach to immune responses from my work, describing B cell responses as localization in the antibody sequence space, which has been published in Physical Review Letters. This work related with flu vaccination has attracted popular press interests of nationwide distributors, such as those of ABC and NBC.

My research is motivated by an experiment by Busch and Parmer that displays that

diversity reduction in T cell repertoire genes accompanies the T cell affinity maturation after an infection. I will investigate the quantitative relationship between the T cell division rate and the affinity of T cell to the specific antigen. To explore the relationship, I will establish a collaboration with an experimental group who can analyze the detailed dynamics of T cell repertoire genes after an infection. Once the assumption that the affinity is the key factor for T cell division rate is proven by the experiment, I will invent a T cell repertoire proliferation model based on that.

By analyzing the dynamics of T cell proliferation, I will describe the experimentally confirmed original antigenic sin in T cell responses. Original antigenic sin means that vaccination by one type of the virus creates memory immune cells that can increase susceptibility to future exposure to a related but different virus. Original antigenic sin is initially observed in influenza and subsequently seen in dengue, HIV, and malaria. Especially, HIV virus is characterized by high mutation rate, which results in the generation of many related viruses. To prevent the original antigenic sin by HIV vaccination, a cocktail of related viruses is considered as a novel concept for HIV vaccination. I expect that my model for the dynamics of T cell repertoire can provide a vaccination strategy optimizing both the distance among viruses and the number of viruses.

2. Symmetry breaking by actin polymerization

Goals: *Understanding and predicting the phenomenon of symmetry breaking by actin polymerization and the nature of the phase transition*

Cell motion is a very complex process involving various biochemical elements. Eukaryotic cells move in response to internal and external stimuli. A major ingredient for cell motility is actin polymerization, the addition of actin monomers to actin filaments. Understanding of the molecular basis of actin driven cell motility was enhanced by the discovery that *Listeria* (one of intracellular bacterial pathogens) use the actin machinery to move. It was revealed that *Listeria* need only a few actin associated proteins for the polymerization.

Recently, a biomimetic motility assay studied mechanism of force generation. Numerous biomimetic experiments have observed that actin polymerization induces a uniform speed or stepping motion of beads coated uniformly with an actin-catalysis protein. Initially, a small bead with a scale of μm diameter is surrounded by symmetrical clouds of actin

filaments. After a transient time, the bead displays a uniform directional motion involving the formation of actin filament tails in the opposite direction of the motion. Here the most interesting phenomenon is symmetry breaking, the attainment of a directional motion from a stationary state.

My research project is making a macroscopic approach to understand this symmetry breaking. Following Prof. Kardar's suggestion, I will study macroscopic equations consisting of actin filament density, the effective force by actin filaments, and the speed of the bead. Through analytical and numerical analysis, I will obtain the phase diagram of the motion in the space of model parameters which can be related physical quantities such as the bead diameter, ActA(or WASP) density, and the capping protein density. I expect that the phase diagram itself and the nature of phase transition can be compared with experimental observations including the relation between the speed of the bead and ActA(or WASP) protein concentration, bead size dependence, and the effect of capping proteins.

To establish a collaboration with experimental groups, I've met with Dr. Upadhyaya in Prof. Van Oudenaarden group in MIT. Through the collaboration with Dr. Upadhyaya, I will suggest an experimental design for specific measurements and elaborate the macroscopic equations by comparisons with experimental results. In addition to the phenomenon of symmetry breaking, I will also investigate the phase transition, observed in the experiment, from uniform velocity motion to stepping motion as the diameter of a bead increases. Also I will study the motion of various shapes of objects such as ellipse and rod, caused by actin polymerization.

3. RNA editing

Goals: *Identifying genes in the mitochondrial sequence and unraveling the mechanism underlying the RNA editing*

A basic principle of molecular biology is that the primary sequence of RNA faithfully reflects the sequence of the DNA from which it is transcribed. This concept has been challenged recently by the discovery of RNA editing, broadly defined as any process that changes the nucleotide sequence of an RNA molecule from that of the DNA template encoding it. RNA editing occurs in a diverse span of organisms, including the Ebola virus, Drosophila melanogaster, and humans.

Current computational approaches to the identification of genes, such as de novo gene finding programs and sequence alignment programs, fail for organisms that perform RNA editing. To reveal RNA editing mechanism, I will study a computational transfer matrix algorithm, the hidden Markov model for RNA editing which was developed by Prof. Bundschuh. The Hidden Markov model for nucleotide sequences yields the optimal interpretation of the genomic sequence as coding for the query protein with RNA editing. Thus the model specifically predicts the optimal positions for the RNA editing sites.

First I will concentrate on the mitochodrium of Physarum polycephalum where the insertion of single C is the most prevalent RNA editing. After predicting the editing sites for the rps12 gene in Physarum using the nucleotide hidden Markov model, my plan is identifying genes which were not present on other mitochondrial genomes using a de novo gene finding algorithm including C insertions. Here examples of novel genes include genes of the RNA editing machinery itself. The prediction by the model study should be examined through experimental confirmation of editing sites and I will incorporate experimental statistics into the hidden Markov model itself.

The computational approach using hidden Markov models can be extended to various RNA editing patterns such as uridine insertion and deletion editing in kinetoplastid mitochondria, C to U editing in plant mitochondria, and A to I editing in hepatitis delta virus. Hence I will generalize the hidden Markov model with single C insertion and systematically establish hidden Markov models incorporating different characteristics of RNA editing mechanisms in different organisms.

Teaching Interests and Philosophy

Ha Youn Lee

I have two main teaching principles: for students to have fun and to think about the value of science. I will try hard to motivate students to explore various problems in physics. From my experience, the motivation generally comes from fun. Learning science, especially physics indeed involves genuine fun in different levels: it makes us to realize the principles of our daily life tools and electronics; it guides us to current technology and development; and it stimulates our imagination and curiosity for interactions of ultimate elements of universe. I have a plan for introducing different levels of fun in each course of physics. To teach this way, I will study not only innovative methods from physics education but also frontier advances in various areas of physics. Doing science may come from natural desire for knowledge, however, science has a huge impact on the society. I will encourage students to have both pride and responsibility as scientists.

I would be happy to teach any physics courses at undergraduate or graduate levels. Especially, I am interested in developing and teaching new courses in biophysics. Based on the courses which I audited such as *statistical physics in biology* by Prof. Kardar at MIT and *cellular and molecular immunology* by a group of professors including Prof. Sheridan at OSU, I will develop a course which describes methods of statistical physics used in biological systems. The biophysics course is characterized as an interdisciplinary one which covers physics, biology, and chemistry. If the situation allows, I will establish a joint department course with professors in biology and chemistry. This kind of trial can help students both to understand the subject better by learning from experts and to communicate more effectively among students from distinct backgrounds and interests. For an advanced level of course, I will suggest students to make small groups which can do small research by themselves. I learned this idea from the course, *statistical physics in biology* by Prof. Kardar I will encourage students to apply the methods learning from the course to the real problems which can be identified by group discussions. I can also provide a course of computational physics which I taught for one semester at University of Seoul in Korea as a lecturer. That course was for physics undergraduate students and I taught C programings for numerical integrations and Monte-Carlo simulations to solve problems in physics.

I believe that as a female scientist I can offer special guidance to female undergraduate and graduate students. When I worked at MIT as a postdoctor, I regularly attended "MIT graduate women in physics" meeting where female graduate students discuss their work and statistics and status of female physicist in United States. I was impressed by how female students strength their motivations by mutual communication. Especially, several MIT female faculty members gave advises and guidances based on their experiences. I will help to organize a female student meeting and attend the meeting frequently. Also I will teach women students based on their characteristics. According to Prof. Conrad at Columbia University, women have a tendency to use more words relative to equations. This tendency can count against them on exams. I will stimulate women students to generate a new idea by in-depth communication and encourage them to develop their mathematical skills.