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November 9, 2005

Systems Biology/Microbiology Faculty Search
Department of Biology,
Indiana University
Jordan Hall 142, 1001 E 3rd St
Bloomington IN 47405-7005

Dear Prof. Brun,

I am writing to apply for the advertised faculty position in Systems Biology and Microbiology at the Indiana University, Bloomington.

As my CV indicates, I am a theoretical and computational biophysicist. My work has spanned from complex fluids at the macroscopic level (foam rheology and membrane dynamics), biological pattern formation and morphogenesis at the cell/tissue level (e.g. Myxobacteria fruiting body formation), self-assembly of lipids and other macromolecules (e.g., membrane inclusions) at the molecular level, to most recently modeling cancer development with an integrative multiscale approach that encompasses cell cycle regulation, cell dynamics, and extracellular chemical dynamics. These seemingly diverse fields are actually a unified set of problems that aim to understand cell interaction and the resulting cell-cell organization from a physicist's point of view. I believe my research interests overlap with many of the projects/interests in your department (e.g., Kearns, Velicer, Saxton, Nephew, and Brun, just to name a few). Trained as a theoretical physicist, armed with mathematical modeling and computational skills, I wish to expand into areas where my research would make the most impact, which include cancer development and biofilm formation. I view my strongest ability as building mathematical or physical models for complex systems based on experiments.

I believe the funding climate for the types of research I am doing and am interested in is very good, and the combination of my physicist's approach and biological/biomedical interests is perfectly situated for the money. I expect that I will find both NSF and NIH funding rapidly.

I have mentored many undergraduate and graduate students in the past 5 years. Currently I also supervise 2 postdocs, 3 graduate students, and 5 undergraduate students. I enjoyed the mentoring experience and look forward to more interactions with students in the future.

I would be very delighted if you consider me for an open position in your faculty. Attached are my CV with a publication list, a statement of research, a statement of teaching, and some supplementary material. I have requested six recommendation letters from

Dr. James Mac Hyman – Los Alamos National Lab, hyman@lanl.gov, (505) 667-6294,
Prof. James Glazier – IU Bloomington, glazier@indiana.edu, (812) 855-3735,

Prof. Mark Alber – Notre Dame, malber@nd.edu, (574) 631-8371,
Prof. Francois Graner – Grenoble, francois.graner@ufj.grenoble.fr, +33 4 76 51 47 74,
Prof. Dale Kaiser – Stanford, kaiser@pmgm2.stanford.edu, (650) 725-7657, and
Dr. James Freyer – Los Alamos National Lab, freyer@lanl.gov, (505) 667-8229, respectively.

Please feel free to contact me or my references if you require further information.

Sincerely,

Yi Jiang

Research Statement

Yi Jiang

My research interests lie in the interface between physics and biology. I develop theoretical models to help understand cell-cell interaction and the resulting cell organization. My strength is building phenomenological mathematical and physical models to study complex biological problems. Tools I use include particle based models (molecular dynamics and coarse-grained molecular dynamics), rule based models (cellular automata), continuous methods (partial differential equations based on continuous mechanics and statistical physics), and integrated, multiscale, hybrid methods.

A. Past Research

- Complex fluid, cellular materials
  (with James Glazier, Francois Graner)

Cellular materials, such as foams, emulsions and colloidal suspensions, can support finite stresses like a solid but yield and flow like a fluid under sufficiently large shear. This transition from solid-like to fluid-like behavior depends sensitively on the microscopic structure and interactions at the cell level. My interests in these materials reside mainly in the mechanisms through which microscopic interactions and disorder give rise to macroscopic properties. We have studied the effects of coarsening, liquid drainage, and flow properties of fluid foams.

By studying the dynamical response of liquid foams under shear in an driven large-Q Potts model, I have succeeded in connecting the highly nonlinear macroscopic rheology of this cellular materials to the microscopic properties such as topological defect structures, structural disorder, and dynamics of local cell organization. The classical elasticity describes elastic solids and the classical hydrodynamics describe simple fluids. To extend both successful theories to more general materials, which display both elastic and fluid properties, we have introduced a descriptor generalizing the classical strain to include plastic deformations: the "statistical strain", based on averages on the fabric tensor describing the microscopic details. With this statistical analysis, we have shown that a two-dimensional foam steadily flowing through a constriction has the elastic properties of a (linear and isotropic) continuous medium. This new descriptor is a major step toward deriving the constitutive relationship for foams.

- Dictyostelium morphogenesis
  (with Herbert Levine, James Glazier)

Dictyostelium discoideum is a classic model for biological pattern formation. Its life cycle shows the transition from solitary amoebae to the multicellular fruiting body. Guided by the diffisible signal cAMP, the cells aggregate to form a multicellular mound, in which cells differentiate into two major types. Subsequently, the initially randomly distributed pre-stalk cells sort to the top of the aggregate to form a cylindrical nipple-like

tip. This tip controls all morphogenetic movements during later multicellular development until the formation of the fruiting body. How do the cells sort in the mound? I used a cellular model to examine two possible mechanisms of cell organization, differential cell adhesion and chemotaxis. The simulations showed that without chemotaxis, pre-stalk cells move to the surface of the mound but form no tip. With chemotaxis to an outgoing circular wave only, a tip forms but contains both pre-stalk and pre-spore cells. Only for a narrow range of relative strengths between differential adhesion and chemotaxis, can both mechanisms work in concert to form a tip which contains only pre-stalk cells. The model explained several experimental puzzles.

- Membrane Dynamics
  (with Turab Lookman, Avadh Saxena, Jack Douglas)

When the membrane is composed of more than one species of lipid molecules, phase segregation of different lipids can induce dramatic shape changes. I used tools from statistical mechanics and computer simulations to model shape transformations of vesicles. I treated the membranes as elastic layers and studied how the phase-separation of different components of membranes affect the shapes. Within a coupled-field Ginsburg-Landau model, I have solved analytically for the equilibrium solutions and numerically for the time evolution of the preferential phase separation to different curvatures. The results were reproduced recently in experiments by an MIT group.

B. Present Research

- Tumor growth and angiogenesis
  (with James Freyer, Trachette Jackson, Lisett de Pillis)

The microenvironment inside a tumor is complex and adaptive, involving spatial and temporal variations in nutrient and waste gradients, cellular physiology, metabolism, the expression patterns of genes and proteins as well as the malignant progression. The sum of all these elements defines the response of a tumor to treatment. The multicellular tumor spheroid system has been a primary example of in vitro models of the tumor microenvironment, which has provided numerous insights into tumor dynamics and progression. I have developed a multiscale model to study spheroid tumor growth, which includes at the intracellular level a protein expression network that regulates the cell cycle, at the cellular level a cellular dynamics description, and at the extracellular level the reaction-diffusion dynamics of chemicals. This integrated multiscale model provides a realistic representation of both structure and dynamics over a large range of time and length scales. Our simulations showed excellent comparisons with spheroid experiments (from Freyer's lab).

With Freyer, we are currently trying to systematically compare simulations with experiments of different chemical environments to validate model parameters, simulate new experimental conditions and predict spheroid growth under new conditions. We are also extending the model to match experiments of different cell lines, and hypothesize the

differences between the cell lines tested; and suggesting new experiments to test hypothesis based on the model.

With Jackson, I am developing a model for angiogenesis in a similar multiscale framework. We model the development of a new blood vessel at the level of vascular endothelial cells. In response to angiogenic factors (e.g., VEGF) secreted from a near by tumor, endothelial cells sprout from an existing vessel, proliferate and migrate the normal tissue toward an avascular tumor. We include an intracellular signaling pathway (the VEGF-IL8 pathway) for endothelial cells, detailed cell-matrix interactions, matrix-VEGF interactions, and VEGF dynamics. Preliminary results show promising sprout extension rate and patterns that match experimental observations.

With de Pillis, I am leading a student team (Harvey Mudd math clinic project) studying the avascular tumor growth by introducing blood vessels to a tumor. We are also interested in studying the effects of chemotherapy on vascular tumor growth.

The eventual goal of this research is to develop a comprehensive and predictive tumor model that helps understanding the tumor biology and can be used as a prognostic tool.

- Myxobacteria development
  (with Mark Alber, Dale Kaiser)

Myxobacteria are one of the prime model systems for studying cell-cell interaction and cell organization preceding differentiation. Myxobacteria are social bacteria which swarm, feed and develop cooperatively. When starved, myxobacteria self-organize into a three dimensional fruiting body structure through a complex multi-step process. Understanding the formation of fruiting bodies in myxobacteria would provide a new insight since collective myxobacteria motion depends on contact-mediated signaling, unlike the more familiar chemotaxis as in Dictyostelium.

With Alber's group, we have developed a series of lattice-gas cellular automata models with extended cell representation, based entirely on local cell-cell interaction and cell motility, to model the different stages of fruiting body formation. We have successfully modeled rippling, aggregation due to alignment, and formation of cell mound due to jamming. We are currently modeling the fruiting body formation with cells differenciating from rod-like motile cells to spherical non-motile spores. We are also modeling myxobacteria swarming. The goal is to model the entire fruiting body formation of myxobacteria and examine the mechanisms for such collective cell organization. We are very close to achieving this goal. Kaiser's lab provides the necessary experimental guidance and correspondence for our models.

- Bone remodeling
  (with Juan Restrepo, Rustum Choksi)

Human bones are dynamic tissues that are remodeled constantly through processes that remove existing bone and deposit new bone. I aim to create more informative---and

ultimately more medically useful---models of bone dynamics by developing a three level approach. The first is the microscopic level that incorporates the bone cells and signaling molecules, coupled to external mechanical stimulus. The second is the intermediate level that examines the effects of remodeling on the individual beams of spongy bone. The third is the macroscopic level of the whole bones in terms of how bone structure changes affect bone's mechanical properties. My current focus is the first level modeling using a set of continuous equations to investigate how mechanical stress/strain could influence the average bone porosity.

I have developed a system of integral-differential equations, which is a constitutive model including a number of relevant mechanical and biological processes. The model aims to address differences in the remodeling behavior as a volume element of bone is placed in disuse or overload. With Restrepo and Choksi, we show numerical results that, consistent with clinical observations, both disuse and overload result in bone loss. I also show that a short-term disuse (e.g. 6 months under microgravity) could have a long-term effect on bone loss, and exercise can greatly reduce the damage. The model can be used to examine the various exercise routines proposed for astronauts, for example. We are currently trying to improve the model by including a more realistic description for damage removal.

- Membrane Dynamics
  (with Pawel Weronski, Jinsuo Zhang, Steen Rasmussen, Andrew Shreve, John McCaskill)

I continue to study lipid membrane dynamics, with a focus in the nano-bio initiative at Los Alamos. Using atomic scale molecular dynamics (with Weronski), we study the partition of inclusion molecules (e.g., PNA and DNA) in lipid bilayers. Using a coarse-grained molecular dynamics, dissipative particle dynamics (with Zhang), we study the aggregation dynamics of lipids into various structures, including micelle, tubule, vesicle and bilayers; we also study the phase separation dynamics with two-phase lipid and three-phase lipid/water/oil mixtures. I have developed a Brownian dynamics model for the complexation of polyelectrolytes with counter ions; will model this complexation in an anchored lipid bilayer (in connection with experiments in Shreve's lab). I have also developed a system of equations that couple the description of phase separation and membrane elasticity to hydrodynamics, to study the effects of flow field on a phase separating vesicle in a microfluidic channel (experiments in McCaskill's lab).

C. Future Research

I plan to focus my research in areas where the potential breakthrough could make the most impact.

- Cancer development and therapeutic strategies

The resent and spectacular surge in the understanding of the processes that act at multiple scales to drive the advancement of cancer is allowing novel mathematical models of

tumorigenesis to be developed. The combination of a data-rich experimental system with sophisticated mathematical modeling holds the promise of an improved basic understanding of cancer malignant progression and therapeutic response in humans. The complex cascade of events that leads to vascular tumor growth involves the cooperative interactions of cells with their microenvironment. Although the full picture is still developing, the time for innovative modeling involvement is now. I plan to expand my integrated multiscale approach in this area to model the development of cancer from initiation to metastasis, with an emphasis on examining different therapeutic strategies.

- Biofilm formation

Biofilm forms when bacteria adhere to surfaces in aqueous environments and excrete a slimy substance that can anchor them to all kinds of material surfaces, and is a major economical problem. Conventional methods of killing bacteria are often ineffective with biofilm bacteria. New strategies based on a better understanding of how bacteria attach, grow, and detach are urgently needed by many industries from environmental to medical. I will further expand my models of cell-cell interaction and motility to develop a multiscale mathematical and computational model of bacterial aggregation in biofilm.

- Immune system model

When an infectious disease emerges, how can we rapidly assess the risk of the disease and decide the appropriate public health intervention measures? This question is very complex yet very important, especially in light of the current bird flu worries and potential bio-terror threat. I plan to develop a hybrid, cellular automata based human immune system model that takes into account the cell-cell interaction as well as the molecular level regulations. The model will be able to simulate different infection scenarios as a 'war-game'. I will particularly focus on the response of different immunocompromised cases, for I believe the immunocompromised subpopulation might offer the first clues to an emerging disease.

D. Summary

Although the above topics span a diverse array of systems, I view them as a *unified* whole within the framework of mathematical modeling of cell-cell interaction and the resulting organization at various scales, accessible both theoretically and experimentally, and important in their applications and their potential for new and exciting developments in biology and biomedical fields.

At the interface between physics/mathematics and biology, I have found my "niche" in building models for complex physical/biological systems. An important way to enhance this ability, I believe, is to have close connections with experimentalists, to find the most interesting and important problems where modeling can make an impact, and to have the experimental support to guide and validate the models. In all the projects I work on, I have tried to strengthen the ties with the experimentalists, which has been very productive and rewarding.

Teaching Statement

Yi Jiang

I have been extensively involved in teaching and mentoring of various forms in the past 16 years. It started with the tutoring of high school students in my freshman year, which lasted through the rest of my undergraduate years. In the graduate school of Notre Dame, I had worked as a teaching assistant for both undergraduate and graduate classes for 4 semesters, and have taught physics labs and delivered lectures to the premed students. Since joining Los Alamos National Lab in 1998, I have mentored 8 undergraduate students, 4 Ph.D. students and 2 postdoctoral research associates, and I have taught in Los Alamos Summer School for five consecutive years from 2000 to 2004. In 2004, I received the Outstanding Mentor Award from the Los Alamos National Lab for my excellent performance in mentoring. Drawing from my own extensive experiences as a teacher, as well as a student, and my constant contacts with many teaching professionals, I have identified following principles as the key to successful teaching: interest in teaching and students, an interactive teaching style, encouragement of creative thinking and problem solving, and a positive relationship with students.

First and foremost, I believe a teacher must enjoy teaching in order to teach well. In fact, I derive great pleasure from seeing students' face lid-up when their questions are resolved and obstacles overcome, and I find great satisfaction and fulfillment in helping students to gain new skills and knowledge, witnessing them moving up in the professional ladders. A good teacher also should be constantly aware of students' interests and needs, and understand their perspectives. With all my previous students, I have always worked hard to cultivate their desires and passions for learning, and inspire their fascinations for new knowledge and discoveries. And I also do my best to tailor teaching materials to suit student's specific conditions and special needs.

In actual lecturing, I like to employ interactive teaching method. I like to be the director, and students the actors, instead of me being the story teller and students the passive listeners and note-takers. I will provide key guidance for the students to "perform" the thinking and understanding themselves. Only when they actively participate in the role, they will really start to absorb, think, question and understand, and be able to apply their understandings to solve new problems. Also during the lecturing, other than leading students from one topic to the next, I also like to emphasize how each topic fits together and always get students back to the big picture. Whenever possible I will use the simplest example to illustrate the abstract concepts. And I would always try to avoid my lecture speed being dictated by my own mental flow; rather I would observe the students' response and try to synchronize the lecturing with students' mental dynamics.

The training of creative thinking and problem solving has always been a major component of my teaching. Good students rely less on memorizing formulas and more on understanding. They are more confident and are more likely to try applying methodical tools beyond just solving the assigned homework. Whenever possible I always like to provide exercises in class to improve the creative thinking and problem

solving skills. And I always encourage my graduate and undergraduate students to participate in real research and have hands-on experience in solving real problems.

I have enjoyed a trusting and friendly relationship with my advisors during my student years, which have shown me how such a positive relationship facilitates effective teaching and learning, and creates a pleasant working environment. As a teacher myself, I have tried to friendly and approachable to all my students. In addition to teaching them knowledge in specific subjects, I have tried to cultivate their appreciation for intellectual activities and enjoyment in learning, which I believe will nourish an individual for a much longer journey. For the selected group of students under my supervision, I have tried to build a research group that encourages communications and collaborations, and emphasize scientific ethics. I also made strong efforts to expose them to a wide range of research areas and to the larger research community, which will help them to develop successful careers in the future.

In addition to the classical physics and mathematics courses, I also can I develop the curriculum for interdisciplinary students, and offer courses such as mathematical biology, computational biology, and biophysics, at both introductory and advanced levels.