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December 25, 2004

Re: Faculty Search
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 Prof. Rob de Ruyter van Steveninck:

Please accept this application for the advertised assistant professor position in the research area of Computational Biology and Biomechanics. I have enclosed the copies of my CV, research and teaching statement.

Over the course of my academic career, I have experienced a wide range of professional activities including research in computational biology and engineering. The biological systems that I have studied include biomolecule, biomembrane, cell, soft tissue and organ. Biological systems function on multiple scales, and my studies involve the application of the principles of biochemistry, biophysics, molecular dynamics, continuum mechanics, computer science and engineering. My research goal is to develop and apply multiscale computational models to investigate the functional mechanisms of biological systems. The study could have applications in molecular therapy, biomolecular, cellular and tissue engineering.

With my education and training in interdisciplinary research fields, I hope to find a faculty position that will allow me to use my research background to establish an interdisciplinary research program. In addition, I look forward to the opportunity to develop and enhance the graduate and advanced undergraduate curricula at the interface of engineering and the life sciences.

Thank you for your consideration of this application.

Sincerely,

Yuhua Song

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RESEARCH PLANS

MULTISCALE MODELING OF BIOLOGICAL SYSTEM

The goal of my research is to develop and apply multiscale computational models to investigate the functions of biological systems by employing theory and techniques from engineering, biophysics, biochemistry, and computer science. This research will help to understand the underlying biomolecular, biomembrane, cellular, and tissue function mechanisms which are important in disease and healing processes. Such insights could have applications in molecular therapy and functional tissue engineering. One specific focus of my work will be multiscale modeling of biological membrane systems. Studies will include small molecule interactions with a biomembrane, and the molecular basis of mechanotransduction for a mechanosensitive ion channel and focal adhesion. Another focus of my research will be multiscale modeling of the response of ligament tissue and its constituent collagen protein to applied mechanical force. To accomplish this goal, I plan to combine the strengths of atomic level molecular dynamics and continuum level finite element methods to model these biological systems, and develop algorithms to interface biological simulations at microscopic, mesoscopic and macroscopic levels.

Study the effect of cholesterol on biological membrane. One of my future research efforts will be the integration of molecular dynamics simulation techniques with continuum finite element simulation to study the effect of cholesterol on a biomembrane. Cholesterol is a major component of the animal plasma membrane, and through its structural characteristics (see Figure 1) cholesterol plays an important role for membrane properties, including enhancement of the permeability-barrier properties of the lipid bilayer [1]. Studies have shown that some pathological phenomena are directly related to cholesterol distribution. Compromised central nervous system function and acanthocytic red blood cells are correlated with a reduction in the transbilayer cholesterol distribution across the cell membranes [4]. Cholesterol distribution within the plane of membrane is important for the function of the CXCR4 protein receptor, which is involved in HIV infection [5]. Although pathological phenomena have been linked to cholesterol, molecular mechanisms for its interaction with the lipid bilayer, its effect on protein receptors in the biomembrane, and its effect on macroscopic membrane properties are still not well known. While molecular dynamics (MD) simulations of cholesterol interaction with different types of lipids at different concentrations have been performed [6, 7], the physiological asymmetric cholesterol distribution across cell surface plasma membrane and uneven distribution within the plane of biomembrane bilayer have not been simulated in these studies. In addition, cholesterol's effect on phenomenological properties such as the transbilayer fluidity gradient, membrane rigidity, and geometric shape change in connection with pathological phenomena have not been reported. The atomic level simulation of the effect of cholesterol on protein receptors has not been fully investigated. I plan to study the interaction of cholesterol with a lipid bilayer, its effect on kinetic, structural, mechanical and electrostatic properties of the

Figure 1. Cholesterol in a lipid bilayer [1]

lipid bilayer, and its effect on the conformational change of protein receptors with equilibrium and nonequilibrium molecular dynamics (MD) simulations. Furthermore, I will investigate cholesterol's effect on macroscopic deformation and stress/strain distribution of the lipid bilayer and protein receptor with continuum finite element analysis. Composition dependent properties of the lipid bilayer will be obtained from the MD simulations. The MD simulation systems will be set up to mimic both the physiological and the pathological distribution of cholesterol within the membrane. With mechanical properties and an initial configuration of the lipid bilayer obtained from MD simulations, the deformation and stress/strain distribution of the lipid bilayer under an external force will be analyzed with the finite element method. The bulk modulus and viscosity parameters are the important bridging factors from microscopic simulation to continuum level simulation. The strain field obtained from finite element analysis will be used as input for the nonequilibrium MD simulation to further study the interaction of cholesterol with the lipid bilayer and its effect on protein receptors under the external force. Results from MD simulation and finite element analysis will form a closed feedback loop for multiscale modeling of the effect of cholesterol on the biomembrane. The interfacing technique between MD simulation and finite element analysis will be based on the work by Ayton et al. [11-13] and will be further developed. Modeling results will be compared to experimental results to understand the effect of cholesterol on properties of the biomembrane, and to unravel the molecular mechanism of pathological phenomena in which cholesterol plays an important role.

Understand action mechanism of mechanosensitive ion channel in the biomembrane. Mechanotransduction in the biomembrane plays an important role in response to the stimuli such as sound, touch, and pressure. Some excellent candidates for the mechanotransduction study are the transmembrane mechanosensitive (MS) ion channels, which play a critical role in transduction of mechanical strain into an electrochemical response to enable the cell to respond to external stimuli [14]. While structures of MS ion channels have been studied [3, 15], the molecular mechanism for MS ion channel action in response to mechanical stress is not well known. A large conductance MS ion channel (MscL) from *Mycobacterium tuberculosis* (Tb-MscL), whose structure is well characterized [3], will be studied. Tb-MscL is composed of a transmembrane domain and a cytoplasmic domain (Figure 2). In response to mechanical force, protein conformational change is thought to control ion flux through the cell membrane. I plan to study this induced conformational change with a nonequilibrium MD simulation and a combination of MD and continuum finite element simulations. There will be two methods included to implement this objective. The first method will study protein conformational change induced by external force applied on the lipid bilayer with nonequilibrium MD simulation. The system used for nonequilibrium MD simulation will be first equilibrated with equilibrium MD simulation. Due to the high computational cost of MD simulations, a limited section of lipid bilayer can be included in the simulation, which limits the analysis of the conformational change of Tb-MscL in response to forces applied to distal portions of the lipid bilayer. The second method will combine MD simulation and

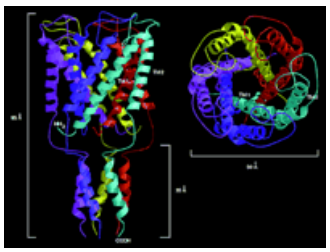


Figure 2. Structure of the homopentameric mechanosensitive ion channel from *M. tuberculosis* [3]

finite element analysis to study protein conformational change for a larger system. Equilibrium and non-equilibrium MD simulations will be used to obtain mechanical and viscosity properties for both the lipid bilayer and Tb-MscL protein. The equilibrated system from MD simulation will be duplicated to obtain a larger system according to the periodic boundary condition in the MD simulation. This expanded system will be used as the initial configuration for continuum finite element analysis. Both the Tb-MscL protein and lipid bilayer will be treated as continuum and discretized with the method developed for complex molecular geometry meshing [16]. For the finite element analysis of the deformation, stress/strain distribution for the lipid bilayer and Tb-MscL protein in response to the external force, a viscoelastic constitutive equation will be used for both bilayer and Tb-MscL protein. The contact between lipid bilayer and Tb-MscL protein will be treated as nonlinear contact. With the contact stress between Tb-MscL and lipid bilayer as the external force applied on the protein, a nonequilibrium MD simulation will be used to further analyze the conformational change of Tb-MscL with the consideration of atomic detail of protein. In the nonequilibrium MD simulation, lipid bilayer will be treated as continuum dielectric materials, which will reduce the computational cost of the analysis of for a larger lipid bilayer system. Results from this study will elucidate the action mechanism of MscL protein in response to mechanical stress.

Understand the molecular basis of mechanotransduction of focal adhesion. Focal adhesion is the link between the extracellular matrix and cytoskeleton, and is formed by the transmembrane protein integrin linking extracellular matrix proteins to the cytoskeleton (Figure 3). Extensive study has indicated that focal adhesion plays an important role in normal physiological processes such as embryonic development, tissue regeneration, and wound healing, as well as in pathological processes such as tumor cell invasion and thrombosis [17]. Mechanical force can be transmitted across the membrane through focal adhesion [18] and regulate signal pathways. One recent review reported that under external force, any of the proteins in the focal adhesion might partially unfold to expose binding sites or change conformation and generate a chemical signal. It is also possible that the force is further transmitted through focal adhesion to a distant part of the cell to initiate a signal [19]. Although there are some experimental data to support these speculations, the molecular mechanism is still being investigated. I plan to study the molecular basis of the mechanotransduction of focal adhesions by focusing on the protein conformational change under external force applied on the protein with molecular dynamics method. This information could offer the binding possibilities between proteins and the binding status of the protein complex, which might be related to the triggering of chemical signal transmission in the cell. The proteins for the focal adhesion pathway that I will focus on include extracelluar fibronectin protein, transmembrane integrin protein and intracellular focal adhesion kinase (FAK) protein. Fibronectin is structurally well known and found in all vertebrates, integrin is the key component of focal adhesion, and FAK has been reported to promote cell migration and invasion [21]. Docking techniques [20] will be adopted to obtain protein complex in the focal adhesion. In this study, nonequilibrium MD simulation will be used to study the conformational change of the three proteins induced by

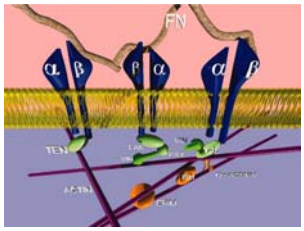
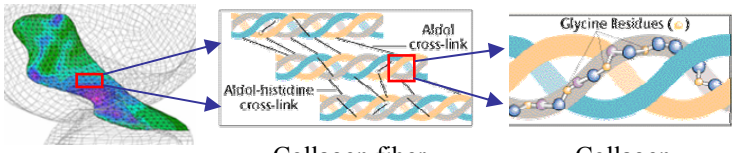


Figure 3. Integrin (blue) links cytoskeleton to extracellular matrix to form focal adhesion [2]

the external force. For the transmembrane integrin protein, the conformational change will be simulated in the system with integrin embedded in the lipid bilayer. Docking technique will be also used to find the possible binding site between fibronectin and integrin and between integrin and FAK with the changed conformation. Conformational change of protein complex in focal adhesion especially for the change of binding site in the protein complex in response to an external force will be also investigated with nonequilibrium MD simulation. Results from this study could offer some insights for the molecular basis of the mechanotransduction of focal adhesion.

Multiscale modeling of the ligament. Functional tissue engineering for ligament healing and regeneration is an emerging and promising field [22]. For this process, it is necessary to understand the underlying mechanism from the molecular, cellular, and tissue levels. Ligament system hierarchy is shown in Figure 4. Collagen is the major protein in the extracelluar matrix and is a major component of the ligament [23]. Collagen plays important roles not only in the structural and mechanical properties of the ligament, but also for signal transmission pathways. Collagen has also served as a carrier for drug delivery [24], and the kinetics of drug release can be influenced by modification of the matrix. In the functional tissue engineering field, mechanical stimulation of the tissue to study its biological reaction has been a focus [25]. However, the molecular mechanism underlying mechanical stimulation of tissue still remains unclear. I plan to use multiscale modeling to study the response of ligament tissue and its constituent collagen protein and collagen fibers to applied mechanical force. As the main component of ligament, collagen structure is well characterized. Collagen properties will be obtained with equilibrium and nonequilibrium MD simulations [13]. Different nonequilibrium MD simulations will be conducted with tension force, shear force, and compression force as perturbation force separately. Collagen fibers are formed and strengthened by the collagen protein molecules with intramolecular and intermolecular cross linking [23]. Computational costs of MD simulation have limited its application to large time and length scales. The deformation of collagen fibers under mechanical force will be studied with the continuum finite element method using the collagen properties obtained from MD simulations. The intramolecular and intermolecular cross linking between collagen will be treated as springs. The stress/strain applied on the collagen fiber will be obtained from the analysis of the ligament. Continuum finite element analysis of the ligament has been extensively studied [26, 27], although the constitutive equation for the ligament still needs improvement. For the finite element analysis, ligament will be treated as an incompressible elastic material, and geometry of the ligament will be obtained from MRI/CT images. The stress/strain within the ligament will be analyzed in response to different loading conditions. With the stress/strain distribution obtained from collagen fiber analysis, the collagen protein conformational change will be studied with nonequilibrium MD simulation. This information could offer insight about possible binding sites of collagen with the transmembrane protein integrin at different loading conditions. The formed focal adhesion could transmit the external force



Ligament Collagen fiber Collagen

http://www.mun.ca/biology/scarr/Collagen_structure.htm

Figure 4. System hierarchy for ligament

information into the cell, and might trigger the signal transmission pathways. The properties of collagen obtained from molecular dynamics simulation can also serve to improve the constitutive equation for the ligament to obtain a more realistic stress/strain distribution within the ligament under external loads. The results from this study will help elucidate the molecular mechanism for the mechanical stimulation of tissue, and could help to optimize the mechanical conditions for the healing and regeneration process of ligament. Results from this study will benefit the computational biology, computational biomechanics and functional tissue engineering fields.

With my education and training in interdisciplinary research fields, I look forward to collaborating with faculty from engineering, computer science, biology, biophysics, biochemistry and clinical study disciplines to explore the best interface of engineering and the life sciences. I am also looking forward to mentoring students from different backgrounds, guiding their understanding of methods and theory in multiple research fields, and motivating their interest in science and research.

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TEACHING INTEREST AND PHILOSOPHY

Yuhua Song

Teaching and mentoring students are greatly rewarding activities. I highly value the opportunity to teach students and share their excitement for learning. Through the course of mentoring students I gain a more critical perspective and deepen my own scientific understanding. Teaching is full of challenges and responsibilities, and I plan to implement effective teaching strategies to maximize student's comprehension of course materials. Teaching, together with research, will be an integral part of my future academic career.

My teaching interests are in the areas of computational biology and biomechanics. I am also interested in developing and enhancing graduate and advanced undergraduate curricula at the interface of engineering and the life sciences, especially for the development and application of multiscale computational modeling for biological systems.

To be an effective teacher, I will focus on the following aspects.

1. A multimedia teaching approach and practical examples will be integrated with courses to make abstract concepts easily understood to students. Course content will include applications at the forefront of current scientific events and will help define future career directions for students in order to motivate students to actively think and participate in the course.
2. I will incorporate problem-based learning and hands-on experimentation in the course to facilitate learning by doing. Carefully chosen homework will be assigned to facilitate the students' understanding of the materials.
3. I will also combine text book materials with journal articles and seminars to emphasize the relevance of course materials to current scientific advances. This approach helps literature searching, reading, and critical thinking skills that are important for the students' future career development.
4. I will integrate research projects into advanced courses. Including research projects as coursework will help emphasize understanding and application rather than memorization. The application of course material directly to a research project can also increase student interest and self-motivation for study.
5. I will actively interact with students, and utilize comments and suggestions to improve effective teaching skills.

The above serves as an outline for how I will interface my teaching and research to have the greatest impact on student development.