This Research Proposal contains following information:

Purpose of Research Proposal

The purpose of this Research Proposal is to apply for a faculty position or staff scientist position in order to conduct basic science research on membrane proteins and membrane systems in atomic details.

Research Objectives

Computer simulation on biomolecular systems plays a central role in basic science today. As an intermediary between theory and experiment, computer simulation is a very useful tool to understand molecular mechanisms via theoretical approaches and to interpret the experimental results at the microscopic level. One of the most widely used computer simulation techniques is molecular dynamics (MD) in which the time evolution of a set of interacting atoms is followed by integrating their equations of motion. In basic science research, MD simulation allows the study of the dynamics of biological systems and offers a variety of molecular modeling in visualizing function of complex biomolecules. In the pharmaceutical industry, MD simulations are commonly used to test the properties of biomolecules for drug design before synthesizing them.

The main research objective of this proposal is to understand biophysical phenomena using MD simulations. In particular, attention is mainly focused on membrane proteins and membrane systems. Membrane proteins play a vital role in many cellular and physiological processes. They are responsible for mediating materials and information signaling throughout living cells. Functionally normal membrane proteins are essential for the preservation of healthy cells and tissue function, because many diseases are closely related to their specific defect states. A large number of drugs currently in use are aimed at membrane proteins, in part, addressing their uptake and signaling functions.

Biological membranes that encapsulate the outside of the cell or separate compartments inside the cell to protect important processes and events are mainly composed of proteins and lipid bilayer. Transmembrane proteins are embedded in the lipid bilayer. The lipid molecules are amphipathic in that they have hydrophilic polar heads pointing out and the hydrophobic portion forming the core. The effect of the heterogenous and electrically complex lipid bilayer environment on membrane protein structures and their function is not well understood. Many experimental studies, in general, do not understand how the environment supports and adapts to different membrane protein conformations. To understand more about this, MD simulations on membrane proteins and membrane systems need to be performed, and results from the simulations will provide useful insights into the molecular details of protein:lipid interactions and protein dynamics.

Research Interests

Major research interests are highlighted with detailed descriptions below.

- **Ion Channels within Explicit Lipid Bilayer and Water Environment**

Ion channels are membrane proteins that control and regulate the flow of ions across biological membranes. In recent years, much progress in the determination of high resolution structure has

occurred. In particular, three dimensional structures of ion channels have provided their crystallographic snapshots (Chang et al., 1998; Doyle et al., 1998; Jiang et al., 2002, 2003; Kuo et al., 2003; Perozo et al., 2002). However, information from these static crystal structures has a weak coupling to the interpretation of their physiological functions and the dynamic behavior within surrounding environment. Dynamical events play a key role in controlling processes, which affect functional properties of ion channels.

The dynamic behavior of ion channels within their surrounding environment can be directly measured from all-atom MD simulations. In addition, results from the simulations may offer insight into defining a connection between high resolution atomic structures of ion channels and their function. However, a major obstacle of such all-atom simulation is a problem of long time-scale. In fact, simulating a large membrane protein, such as an ion channel, embedded in explicit lipid bilayer and surrounded by water molecules often involves so many atoms and is a great challenge. Although, computationally less expensive simulations with implicit solvent models, which accounts for the effects of solvent in an approximate manner (Hassan et al., 2000; Lazaridis and Karplus, 1999, 2000; Roux and Simonson, 1999; Roux et al., 2000), have provided general insight into fundamental properties of the protein dynamics in a relatively short time-scale, simulations with all-atom representations of lipid and water molecules could offer more detailed information on the structure, stability, and the dynamics of ion channels.

At present, large scale all-atom MD simulations of ion channels are still challenging, but are becoming more common with the improvement of faster hardware and algorithmic developments (Allen et al., 2000, 2003; Åqvist and Luzhkov, 2000; Bernèche and Roux, 2000, 2001, 2003; Biggin et al., 2001; Burykin et al., 2002, 2003; Capener et al., 2000; Colombo et al., 2003; Crouzy et al., 2001; Elmore and Dougherty, 2001; Guidoni et al., 2000; Gullingsrud and Schulten, 2003; Gullingsrud et al., 2001; Im and Roux, 2002; Luzhkov and Åqvist, 2001a, 2001b; Roux, 2000; Shrivastava and Sansom, 2000; Smith and Sansom, 2002; Woolf and Roux, 1997). The long-term goals are to reveal the molecular mechanisms behind ion permeation through ion channels and to determine the dynamic transition pathways between different conformational states, which large-scale conformational changes trigger the ions transport.

- **Conformational Changes and Dynamic Importance Sampling (DIMS)**

Membrane transport is mediated by some integral membrane proteins, such as ion channels, porins, transporters, and pumps. To properly conduct the function of membrane transport, membrane proteins frequently perform transitions between functional conformation states. For instance, ion channels exhibit a large-scale conformational change between open and closed states to transport or to prevent specific ions moving through a channel pore. The nature of the transitions in the conformational space may be important for understanding membrane protein folding and for rational drug design.

Determining dynamic transition pathways between functionally important conformational states in membrane proteins is of great current interest. In conventional MD simulations, however, observing the transition event that the large-scale conformational change started from is not realistic, because the molecular dynamics time-scale is so short relative to the time-scale for the large-scale conformational change. For example, sampling for the dynamic transition pathway that is associated with ion permeation is a problem of difficulty, since the typical time-scale for gating transitions of ion channels is on the order of milli-seconds. In particular, sampling would be more difficult for systems with complex environment like a membrane bilayer setting.

In order to remedy the problem, many sampling techniques defining the transition paths and the reaction rate have been proposed in the last few decades (Bolhuis and Chandler, 2000; Bolhuis et al., 2002; Chandler, 1978; Crooks and Chandler, 2001; Czerminski and Elber, 1990a, 1990b; Dellago et al., 1998a, 1998b, 1999; Fischer and Karplus, 1992; Mazonka et al., 1998; Olender and Elber, 1996). However, many approaches must require an initial definition of a reaction coordinate, indicating that sampling should start from an initial path of arbitrary quality to get a properly distributed ensemble of transition paths. This is a major disadvantage for large systems, like membrane proteins, where it is difficult to clearly define a single reaction coordinate.

To solve the problem, dynamic importance sampling (DIMS), a stochastic formulation of importance sampling techniques, is proposed (Woolf, 1998; Woolf et al., 2004; Zuckerman and Woolf, 1999). The DIMS method does not require the definition of a reaction coordinate in advance. It requires only the initial and final states as input and is capable of finding multiple reaction pathways. The method creates a set of properly weighted trajectories with their associated probabilities of occurrence, through application of weighting functions that are corrected at each time-step. The resulting set of information can be used for determination of temperature refined pathways, kinetics, and relative free energies between the defined starting and ending states.

The DIMS algorithm is now implemented in the CHARMM code for the investigation of large systems like membrane proteins. To apply DIMS techniques for membrane proteins in different conformational states, equilibrium ensembles generated from independent equilibrium simulations for systems in different states are required as the starting and ending points to determine possible dynamic pathways between transition states.

- **Stability and Formation of Small β-amyloid Fibrils on the Membrane Surface**

Protein aggregation is associated with many fatal so called “protein deposition” diseases, including Alzheimer’s disease, Parkinson’s disease, Huntington’s disease and prion diseases. An example is Alzheimer's disease (Selkoe, 1991; Simmons et al., 1994), which is characterized by the assembly of normally soluble proteins into insoluble fibril plaques in the extracellular space of brain tissue. Although extensive experimental studies (Benzinger et al., 1998, 2000; Burkoth et al., 1998; Esler et al., 1996, 2000; Lazo and Cowning, 1998; Lynn and Meredith, 2000; Sunde et al., 1997; Zhang et al., 2000) have been conducted on the fibrillization of Aβ peptide, the causes of Aβ fibril formation are largely unknown and the fundamental mechanisms underlying this aggregation are still under investigation.

The major component of these Aβ fibrils is a β–amyloid peptide, whose predominent secondary structure in the fibril is a β–sheet. Since the β–sheet motif protein is extremely difficult to study experimentally due to its insolubility, computer simulation is one of the few techniques that can

shed light on the folding and aggregation of such proteins. Current view on fibrillization of Aβ peptide from recent observations is two-fold:

(1) Fibril formation is an intrinsic property of polypeptides (Booth et al., 1997; Chiti et al., 1999). The idea here is that fibril formation is not strongly dependent upon sequence but is instead a consequence of the ability of peptides to experience hydrogen bonding and hydrophobic interactions.

(2) Small Aβ oligomers that are observed in the early stages of fibril formation (Harper et al., 1997) are now widely believed to serve as the nuclei that seed the growth of the fibrils (Pallitto and Murphy, 2001) and are the toxic species rather than the fully-formed fibrils in Alzheimers's disease (Kirkitadze et al., 2002).

From these observations, one can focus attention on ascertaining what type of conditions would cause normally soluble proteins to assemble (or aggregate) into a highly ordered structure. This is an important question because the vast majority of the so-called protein deposition diseases are caused by the aggregation of proteins into ordered aggregates called "fibrils" or "amyloid". To address this issue, detailed models of small β–amyloid fibrils on membrane surfaces using all-atom molecular dynamics simulation in conjunction with the CHARMM force field can be performed to make genuinely significant contributions to our understanding of protein aggregation, because many experimental studies did not clearly suggest the exact nature of the Aβ fibrils conformation and the β-strands arrangements (Blake and Serpell, 1996; Serpell, 2000). This would shed new light on the molecular mechanisms that drive the assembly of fibrils and determine their conformational stability.

A list of some minor research interests.

- Protein Folding and Aggregation: Discontinuous Molecular Dynamics (DMD) Simulations on Off-lattice Simplified or Intermediate Resolution Protein Models
- Equilibrium and Dynamic Phase Behaviors of Liquid Crystal in Thin Film or Slab Geometry: Lattice Spin Models with Mobile Vacancies

Research Details

- **Goals and Objectives**

There are two major goals for the Research Proposal of "Molecular Dynamics Simulations of Biomolecular Systems" and specific objectives within each of the goals.

Goal 1: To simulate membrane proteins within explicit lipid bilayer and water environment.

Objective 1: To probe the relationship between static crystal structures and the resultant dynamics of membrane proteins in connection with their functions.

Objective 2: To analyze known membrane protein structures to reveal underlying principle of membrane protein structure and stability.

Goal 2: To develop the DIMS algorithm by implementing in the CHARMM code for large biomolecular simulations.

Objective 1: To determine dynamic transition pathways between functionally important conformational states.

Objective 2: To calculate relative free energy changes and reaction rate between functionally important conformational states.

- **Methods**

The primary methods for achieving the goals and objectives of the proposal would be:

Simulation Tools

CHARMM: The CHARMM program (Brooks et al., 1983) is a research program developed at Harvard University for the energy minimization and dynamics simulation of proteins, nucleic acids and lipids in vacuum, solution or crystal environment.

NAMD: NAMD (Kalé et al., 1999) is a parallel molecular dynamics code designed

for high-performance simulation of large biomolecular systems. NAMD code can be used on small PC cluster transforming into high speed parallel platforms and allows to simulate large biomolecules in a relatively short time-sclae.

Analysis Skills

Capable of using a variety of the CHARMM analysis package.

Free energy calculation with weighted histogram analysis method (WHAM).

Density map calculation with Pymol for waters, ions, and lipid components.

Other Simulation Skills

Discontinuous molecular dynamics on simplified off-lattice protein models.

Monte Carlo simulations on lattice model of continuous spin.

Appendix A : Backgrounds - Personal Perspective

For the past 10 years, I have been engaged in a computational study for a variety of systems in the range from condensed matter physics to molecular biophysics. Through my studies at the university as a PhD student, I have made significant contributions to our understanding of thin ferromagnetic films. These materials are used in a variety of applications including sensors, actuators and magnetic media, recording heads and random access memory (RAM). In order to develop the next generation of magnetic storage materials, it is essential that we have a more thorough fundamental understanding of how the local chemical and magnetic environment near film surfaces and interfaces affects the phase transitions that they experience. As part of thesis research, I performed a series of computer simulation studies of thin ferromagnetic films that exhibit magnetization which is perpendicular to the surface. The results showed that the interface localization-delocalization transition in thin ferromagnetic Heisenberg films with competing surface forces differs from the more familiar ferromagnetic-paramagnetic transition (Jang and Grimson, 1997, 1998, 1999, 2000). Subsequent studies for the ferromagnetic systems are the nonequilibrium

dynamic phase transition (DPT). In these studies, the system under consideration is a planar thin ferromagnetic film with competing surface fields subject to a pulsed or sinusoidal oscillatory external field. Studies of the field amplitude, frequency, temperature, and exchange anisotropy dependence show distinct dynamic phase transitions (Jang and Grimson, 2001; Jang et al., 2003a, 2003b). Extensive programming language skills and analysis techniques that I acquired from the Monte Carlo studies strongly set the stage for a more complex computational study of biomolecular systems.

In the first step exploring towards biomolecules, I have focused on studying the molecular-level mechanisms behind protein folding and aggregation. In particular, the thermodynamic and kinetic properties of isolated β–sheet proteins using a discontinuous molecular dynamics (DMD) technique (Alder and Wainwright, 1959; Rapaport, 1978; Smith et al., 1996) were investigated (Jang et al., 2002a, 2002b). Understanding these β–sheet motif proteins is important in part because the abnormal fibrils found in people with Alzheimer's disease are composed of β–sheets of the β–amyloid peptide. Although, extensive experimental studies have been conducted on the fibrillization of β–amyloid, the structural details of β–amyloid fibril structure remain elusive due to insolubility of the fibrils. As a result, the exact nature of the β–sheet conformation in the β–amyloid fibril is still ambiguous. The results from the DMD simulations made important contributions to our understanding of the mechanisms of protein folding with particular focus on the role played by β–sheet proteins with different topology. The discoveries of global phase diagrams and cooperativity of kinetic pathways for isolated β–sheet proteins provided fundamental insights into the thermodynamics and kinetics of protein folding. Subsequently, I continued this work, at the forefront of protein biophysics, to study the assembly, kinetic folding pathways, and thermodynamics and stability of a β–sheet complex (Jang et al., 2004a, 2004b). The β–sheet complex, assembled from several β–sheet proteins, is a model for the small β–amyloid fibril of Alzheimer's disease. The research on computational modeling, assembly, and stability of the multiple protein systems with off-lattice models are to my knowledge among the first to show molecular mechanisms associated with the oligomer nucleation that is responsible for the seeding of the fibril growth. Further, the studies on the β–sheet complex provide significant insights to scientists interested in modeling aggregation phenomena in other systems.

In the moving towards more complex system such as a membrane protein, I simulated two conformations of wild-type bacteriorhodopsin (Jang et al., 2004c), one of the dark-adapted state and the second of an intermediate, using all-atom molecular dynamics simulation within CHARMM (Brooks et al., 1983). Bacteriorhodopsin (bR), the light-driven proton pump, is a transmembrane protein that uses large conformational changes for proton transfer during the photocycle. The simulations included all-hydrogen and all-atom representations of protein, lipid, and water and were performed for 20 ns, and the equilibrium properties and the dynamic motions of the two conformations in the lipid setting were investigated. The results from the simulations showed that the environment adjusts to these two different states and the dynamics of protein itself and solvents are closely related to the pump mechanism of bacteriorhodopsin. Determining dynamic pathways between functionally important conformational states like those found in the bacteriorhodopsin photocycle is another long-term goal. The DIMS technique (Woolf, 1998; Woolf et al., 2004; Zuckerman and Woolf, 1999) would be used to determine possible dynamic pathways between transition states. At present, the algorithm development of the DIMS code within CHARMM (Brooks et al., 1983) and its application to a small molecule, such as alanine dipeptide, are currently undertaking. In addition, to investigate the effect of the surrounding environment on membrane protein conformation, two different conformations (open and closed) of the voltage-dependent K^+ channel (Jiang et al., 2003) have been set into explicit lipid bilayer environment with ions and water molecules. All-atom molecular dynamics simulations are being conducted with a full advantage of a NAMD parallel code (Kalé et al., 1999) on PC clusters.

It is clear from my research background that I possess transcendent analytical and computational skills for the requirements of any one field as an independent scientist. Computer simulation, a tool that allows us to provide insights into biophysical phenomena that would be impossible to obtain via experiment alone, is a primary tool to conduct my research. I expect that I can make real and lasting contributions to our understanding of the properties of biomolecular systems, because I think I am creative, resourceful, knowledgeable, energetic, and have the highest standards of personal and professional integrity. For all of these reasons, I would strongly like to be a superb addition to your institute.

Appendix B : Teaching Statement

I believe learning is a process of synthesis and the main purpose of education. It is the goal of every student and the task of every teacher to increase knowledge and satisfaction in the classroom. In order to aid students in reaching their desired learning goals, the teacher should be prepared to lead students in the direction they should go to reach correct conclusions and answers, without always providing the answers themselves. The teacher always makes ready for materials thoroughly in the class and must study to keep track of new or advanced ideas before the class. In this context, I also believe teaching is a continuation of learning.

As a long-time researcher, I have been making a persistent effort to improve my learning efficiency. I understand what are the critical parts in learning new concepts and always do my utmost to absorb them into my own knowledge. I believe the most effective and successful mode of teaching is to develop the learning skill of students, since it is a tool to achieve their goals in a productive manner. Good learning skills would make it possible for the students to take an active role in their own education. I am willing to share my own experiences with students in the classroom: how to increase learning efficiency.

My objective as a teacher is to stimulate students to develop their own motivations and accomplish their own goals. I am interested in teaching students. In particular, I want to educate students about the importance of science. They should learn that science is a creative process, which helps us to explain many complex phenomena. My teaching will emphasize that science is not a symbol of complicated mathematic formula, but is a fun and interesting subject to learn the knowledge about things in nature and the universe.

With my background in physics, I can teach most undergraduate physics classes, including laboratory courses. For the more advanced classes (both graduate and undergraduate), my preference is to teach classes in the areas of condensed matter physics, solid state physics, statistical physics and thermodynamics, electromagnetic theory, electronics, and computer program language. With my background in molecular biophysics, I can also conduct classes of biological

macromolecules structure and function, biomolecular dynamics and ensembles, and biophysical chemistry.

In addition to classroom teaching, I look forward to supervising research activities of undergraduate and graduate students. I will focus on making sure that students set the direction of their own research and develop an appropriate tool to tackle the problems in their research area. I believe that this would give the students a better sense of investment within the laboratory and prepares them to direct research in their own labs.

Teaching is not just a transfer of information passively from teacher to students; it is the ultimate goal of helping students to learn, and grow, and most importantly becoming independent, self-motivated individuals. Given the opportunity, I will strive for teaching to act as a guide and facilitator and work to the best of my ability to become an inspiring and well motivated teacher.

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