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Dear Professor Rob deRuyter,

I am presently a post-doctoral fellow working for Professor Charles L. Brooks, III at the Scripps Research Institute (TSRI). It is my pleasure to take this opportunity to apply for a faculty position in the Biocomplexity Institute at Indiana University. Below is a brief description about my research background and training which, I believe, clearly manifest sufficient experience in both methodological developments in theoretical/computational chemistry and biology, and its applications to biological systems.

During my M.Sc. study (1994-1996) under the guidance of Professor Youngdo Won in Chemistry at Hanyang University in Seoul, I devoted most of my time to computational chemistry and studied the thermodynamic, structural, and dynamic properties of liquid alkanes and liquid acetonitrile using Molecular Dynamics (MD) simulations. I also had an opportunity to work on the biomolecular simulation program CHARMM and learn its inner workings. I started my Ph.D. study in Chemistry at University of Montreal in Montreal on February, 1997. Under the able guidance of Professor Benoît Roux, I have developed various computational methodologies to understand the underlying microscopic details of ion permeation and selectivity of biological memrbane channels. In particular, considerable efforts have been made to Poisson-Boltzmann (PB) continuum electrostatics and related methodological developments such as PB solvation forces, Poisson-Nernst-Planck (PNP) continuum electrodiffusion theory, Grand Canonical Monte Carlo - Brownian Dynamics (GCMC/BD) algorithm, Generalized Solvation Boundary Potentials (GSBP), and a general treatment of electrostatic reaction fields for Brownian dynamics simula-

tions of ion channels. I also performed a large-scale MD simulation of OmpF porin in an explicit membrane with 1 M KCl aqueous salt solution. Since June, 2000, following Professor Roux, I continued the Ph.D. study in Biochemistry at Weill Medical College of Cornell University in New York. I have focused on a theoretical study of ion permeation and selectivity in OmpF porin and its mutants using MD, GCMC/BD and PNP. After my Ph.D. study, I moved to TSRI as a post-doctoral fellow in Professor Brooks group on June, 2002. I got interested in the development and application of generalized Born (GB) electrostatics theory to the dynamics and folding of biomolecules. In particular, considerable efforts have been made to extend the method to take the influence of biological membranes into account. Applications of the membrane GB model to folding and assembly of various membrane proteins (or transmembrane domains) as well as modeling of rhodopsin, a G-protein coupled receptor (GPCR), are currently in progress.

Based on my expertise and research interests in the computational chemistry and biology, I am confident that your institute would be the most suitable place to pursue my first independent academic career. In particular, my interests in modeling of membrane proteins, protein structure refinement, and simulations of complex biological systems would well fit into the targeted areas and complement the exisiting experimental efforts on your institute as well as other departments. Lastly, I am also interested in doing my parts in teaching and, in particular, using the CHARMM program as a tool (in a class) to study macromolecules in an atomic level.

The names of **three references** are listed in my C.V. Please, feel free to email me (wonpil@scripps.edu) if you have any further questions about me. I look forward to hearing a positive response from you.

Sincerely yours,

Wonpil Im

Research Interests

Wonpil Im

Based on my expertise in both methodological developments in theorectical/computational chemistry and biology, and its applications to biological systems, my research will focus on exploring folding, assembly, and modeling of membrane proteins, structural refinement of proteins with implicit solvent models, membrane fusion, and ion channel activity in an atomic level. Owing to the fact that the size of the system of interest is often prohibitively large, methodological developments will be pursued continuously especially on the implicit solvent models. In following, I briefly describe my potential future projects.

Folding, assembly, and modeling of membrane proteins

Membrane protein folding and stability are directly governed by the unique hydrophilic and hydrophobic environment provided by biological membranes. Modeling of this heterogeneous environment has been both an obstacle and an essential requisite to experimental and computational studies on the structure and function of membrane proteins. The experimental difficulties in structural determination of membrane proteins are well manifested by only a handful of membrane-associated protein structures in PDB, compared to soluble proteins. Considering their biological importance and significant amount in known genome, i.e., 30% of all proteins, the modern computational biology should help the experiments in understanding the structure and function of membrane proteins. While the explicit water and membranes provide the most realistic environment for membrane proteins, it is not straightforward to use the same approach to folding and assembly of membrane proteins mainly due to the increased time demand of such a protocol. To circumvent the difficulty, generalized Born (GB) electrostatics theory has been recently extended to take the influence of biological membranes into account in the context of the implicit solvent model in which the average influence of both water and lipid molecules

are included implicitly. By combining this implicit membrane model with advanced computational sampling methods, like replica-exchange molecular dynamics (MD), it was able to fold and assemble helical membrane peptides correctly. The proposed method will be very useful in the study of folding and assembly of membrane proteins, and in the structure refinement and modeling of membrane proteins with a limited number of experimental observables.

Structure refinement of proteins

The structure determination of a protein is an essential step for understanding the microscopic details of its function. A protein structure can be well determined if the X-ray density map is sufficiently high enough or the NMR experimental restraints are sufficiently large enough. In either cases, there is no room for improving the quality of the structure using a better force field (i.e., molecular mechanics potential energy function plus a solvation model). In fact, most experimental structure determinations are done without electrostatic interactions mainly due to the lack of reliable solvation models. In general, it is not feasible to use explicit water molecules to take the solvation effects into account during the process of structure determinations. In particular, the structure determination by NMR requires an iterative process of assigning experiment data. I believe that the accurate implicit solvent models should play an important role in improving the quality of the structure when the experimental data is limited or during the process of NMR structure determination. The idea is not limited only to (soluble or membrane) proteins, but can be also extended to protein-DNA complexes.

Membrane fusion

Membrane fusion is one of the most fascinating and important biological events, but the detailed pictures of its energetics and dynamics are still unknown. Due to the size of the system, it is not feasible to use a tradition MD with explicit water and membranes. Here, I want to extend the usage of the GB model with explicit membranes and implicit solvent. For this aim, it it

necessary to determine adequate input atomic radii for lipid molecules. Then, stability of explicit lipid membranes and micelles in the GB model will be examined to access the quality of the (input) radii and the simulation scheme. Furthermore, this study will be also able to provide the detailed energetics and dynamics of micelle formation at difference concentrations of lipid.

Ion channel activity

Recently, I got interested in the ion channel activity of Vpu, a transmembrane protein from HIV-1. It is experimentally known that Vpu forms an oligomer (probably pentamer) and acts as ion channel, but the detailed structure of the open-state Vpu oligomer and the underlying energetics of ion permeation is not known. The aim in this project is to model the reliable Vpu oligomer using modern computational biology tools and examine the detailed energetics of ion permeation and selectivity. Moreover, the membrane GB model or (proposed) explicit membrane/implicit solvent model can be used to explore the gating events of the biologically important channel such as potassium channels and acetlycholine receptor in which the gating of the former is governed by the transmembrane potential and that of the latter by the ligand binding.

Methodological developments

I will continuously pursue methodological developments especially on the implicit solvent models to perform the proposed projects. Among those, considerable efforts will be made to improve the performance (or quality) of previously developed GB models. If necessary, the membrane GB model will be extended to incorporate the influence of head groups of lipid molecules. It will be also interesting to develop accurate and fast PB solver using the numerical integration scheme to calculate surface charges. On this other hand, I have a plan to incorporate various NMR restraints such as residual dipolar coupling in solution NMR, and ^{15}N chemical shift and ^{15}N-^{1}H dipolar coupling in solid state NMR into the biomolecular program CHARMM. The main reason of doing this is to use (or test) the constantly developed new simulation techniques in CHARMM for the structure refinement.

Statement of Teaching Philosophy

Wonpil Im

The most important role of college educators in teaching their students is to provide not only the specific knowledge and skills necessary for future professional work, but also the motivation to remain interested in the subjects they have learned to pursue further, more advanced education. I believe that this can be achieved best through an inter-disciplinary and problem-oriented teaching approach with critical emphasis on independent and analytical thoughts during the training.

Teaching inter-disciplinary subjects

Modern science requires the inter-disciplines in nature. For example, understanding a biological process in an atomic level may require not only the concepts from chemistry for explaining quantum nature of catalytic reactions along with physical insight on intermolecular interactions, but also the practical application of modern computational chemistry/biology tool along with applied mathematics as well as computer science. This may be addressed by maintaining a wide range of context for a particular subject that is being taught, either through diverse examples, demonstrating connections with other disciplines, or more directly by inter-disciplinary teaching courses. The resulting benefit for students should be a more complete understanding of science as a whole and a better ability to apply knowledge in a variety of contexts.

Teaching independent thinking

Independent and analytical thinking is practiced best in the application of learned knowledge to new problems beyond the examples that were used to illustrate a given subject. For this reason, I think that a significant portion of the time spent on science education should involve problem-solving exercises inside and outside the classroom, both, alone and in teamwork with other students.

Teaching and learning

Teaching is intimately connected with learning so that it becomes the role of the educator to facilitate learning at the same time as providing knowledge. Since learning in itself is an individual process for each student based on previous experiences, it is important to keep opening communication tools such as direct interactions with students, homework, exams, and teacher evaluation forms in order to check the progress of learning and level of understanding. I believe that the learning process can be also facilitated further if teamwork and discussions between students are encouraged. Such an intellectual exchange leads to the reflection of a learned subject from a number of different viewpoints for the benefit of all students.