Research Interests & Projects

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My research will focus on the applications of theoretical/computational methods to chemical and physical problems in biology and material science. Specific research interests and projects are

- development of efficient and reliable tools for membrane protein modeling and studies of insertion, folding, and assembly of membrane proteins/peptides
- NMR & X-ray structure refinement of proteins and protein-DNA complexes using implicit solvent models
- ion channel activities such as ion permeation, selectivity, and gating at molecular level
- membrane fusion with simplified lipid molecules

In addition, significant efforts will be continually made to theoretical and methodological developments with particular emphasis on implicit solvent models, which is necessary for efficient modeling of large biological systems. In the following, I briefly describe the proposed research objectives with specific aims.

1. Membrane protein modeling: insertion, folding, and assembly

While explicit water and membranes provide the most realistic environment for membrane proteins [1], it is not straightforward to use such an approach to study insertion, folding, and assembly of membrane proteins/peptides mainly due to the prohibitive computational cost. To circumvent this problem, I have recently extended the generalized Born (GB) electrostatics theory to take into account the average influence of both water and biological membranes implicitly [2,3]. Combined with advanced computational sampling methods such as replica-exchange (REX) molecular dynamics (MD), the efficacy of the implicit membrane GB model has been demonstrated in the folding and assembly of simple transmembrane (TM) helices [3], de novo folding of a complex fd coat protein and calculations of its solid-state NMR properties [4], and exploring interfacial folding and membrane insertion of WALP and TMX series peptides [5]. I plan to further develop the implicit membrane model by incorporating the influence of head groups of lipid molecules (explicitly and implicitly) as well as the lipid-protein dispersion interactions, which are absent in the present model. These efforts will be complimented with continued studies of insertion, folding, and assembly of other important membrane proteins/peptides such as bacterial toxin, antimicrobial peptides, membrane fusion peptides, sarcolipin (SLN), phospholamban (PLN), virus protein "u" (Vpu) of HIV-1, and F_0 subunit of F_0/F_1 ATP synthases. The ultimate goal is to develop a suite of efficient and reliable modeling tools for studying complex membrane protein systems. These tools will potentially lead to the

design of de novo membrane peptides to block certain target proteins/peptides that cause various human diseases. Given the difficulties in determining membrane proteins/peptides structure as well as the biological importance and significant presence of these biopolymers in known genomes, the proposed research will be very helpful in providing important and unique insights toward their structures and functions, and in assisting experimental investigations. In addition, the developed methodology can be utilized to study the insertion and assembly of organic nanotubes for biotechnological applications.

2. NMR & X-ray structure refinement of proteins

Determining the atomic three-dimensional structure of a protein, typically by X-ray or NMR, is an essential step toward understanding the microscopic details of its functions. Biomolecules mostly exist in aqueous solution and thus solvation plays an essential role in their structures and functions. Nonetheless, solvation has not been taken into account in these processes mainly due to the lack of efficient solvation models. The X-ray and NMR communities have traditionally exploited rather simple non-bonded potential functions, typically in the absence of electrostatic interactions. Clearly, if the structure can be determined unambiguously with high-resolution X-ray density maps or redundantly large NMR restraints, there is little room for improving the quality of a protein structure even with an accurate force field with a reliable and efficient solvation model. Consequently, the modern molecular force field has been mostly used to "polish" the final structures with the full strength of experimental restraints just before the publications. However, there are a number of situations in which experimental restraints are limited, and thus useful higher resolution structural models are difficult to obtain. As demonstrated by my colleagues and I, an efficient and reliable continuum solvation model can be combined with advanced sampling techniques to significantly improve the quality of the structure [6] and to reliably generate native-like initial folds [7] when experimental NMR restraints are limited. I plan to combine the implicit solvent/membrane GB model with 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, to provide a useful tool for NMR structure refinements in ordered and disordered phases. Continued efforts will be made to applying the developed methodology to soluble and membrane proteins and protein-DNA complexes. Since the electron density maps can be considered as restraints to confine certain atom or residue in a specific region, the same idea can be applied to X-ray structure determination as well in situations where the resolution is not high enough. I plan to incorporate the implicit solvent/membrane GB model into widely used programs (such as CNS or REFMAC) by X-ray crystallographers. Then, I will develop a protocol to maximize the efficacy of the implicit solvent in improving the quality of the X-ray structures. The ultimate goal in the proposed NMR & X-

ray structure refinement project is to provide useful structural models in the context of limited restraints.

3. Ion channel activities: ion permeation, selectivity, and gating

Identification of the molecular interactions governing ion conduction through biological pores (ion channels) is one of the most important goals of modern electrophysiology. I have been involved in theoretical and methodological developments of various permeation models such as the Grand Canonical Monte Carlo – Brownian Dynamics (GCMC/BD) algorithm [8] and Poisson-Nernst-Plank continuum electrodiffusion theory [9]. These methods have been successfully applied to exploring ion permeation and selectivity of the OmpF porin [9] and recently the □–hemolysin channel [10]. Based on recent advances in the study of ion permeation [11], my particular interest is to explore the ion channel activities of virus protein "u" (Vpu) and phospholamban (PLN) together with folding and assembly of these proteins. Vpu is a transmembrane (TM) protein of 81 amino acids from HIV-1 and shows ion channel activities by forming an oligomer (probably pentamer). As a regulator of Ca^{2+} ATPase (i.e., a Ca^{2+} pump), PLN is a small TM protein of 52 amino acids that also acts as ion channel in a pentameric form. However, the detailed atomic structures of the open and closed states of these proteins are not known. The proposed research will provide structural models and detailed energetics of ion permeation and selectivity of these proteins. These studies will also make it possible to further examine the potential (Vpu-targeting) drugs for HIV and the activity of the Ca^{2+} pump that is controlled by both the association/dissociation of pentameric PLN and those of monomeric PLN and Ca^{2+} ATPase. The research project is not limited to biological membrane channels, but can be extended to organic nanotubes such as pore-forming cyclic peptides. Examining channel activities of such nanotubes will lead me to redesign them with specific functions for biotechnological applications. In addition, I plan to utilize the membrane GB model or simplified coarse-grained lipid molecules or combined model (proposed below) to explore the gating events of biologically important channels such as potassium channels and acetylcholine receptor in which gating of the former is governed by the TM potential and that of the latter by ligand binding.

4. Membrane fusion

Membrane fusion is one of the most fascinating and important biological events, but the detailed energetics and processes are largely unknown yet [12]. Due to the size of the vesicular system, it may not be feasible to use traditional MD techniques with explicit water and membranes. I plan to develop various simplified coarse-grained lipid molecules that contain a few atoms to capture the necessary features of realistic membranes and micelles. The simulations with fully atomistic

models will be exploited to test and optimize such coarse-grained models. It should be possible to combine them with the implicit GB model to take into account solvation efficiently. By determining appropriate input atomic radii for the lipid molecules, the stability of explicit lipid membranes and micelles in the GB model will be examined to access the quality of simplified lipid molecules and the (input) radii. The developed coarse-grained lipid models can be used to explore (protein-mediated) membrane fusion and related energetics. In addition, the membrane GB model can be combined with such simplified models to incorporate the influence of the different head groups for the study of membrane insertion and ion channel activities.

5. Theoretical & methodological developments

Theoretical and methodological developments will be continually pursued in order to perform the proposed projects, with particular interests in

- improvement of the performance and quality of existing GB models
- incorporation of the influence of head groups of lipid molecules as well as the lipid-protein dispersion interactions into the membrane GB model
- utilizing the GB formalism for efficient and reliable calculations of reaction field energy in the study of ion channel activities
- development of fast and accurate Poisson-Boltzmann (PB) solver by calculating induced surface charges using the numerical integration scheme
- incorporation of 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 to exploit the new simulation techniques constantly developed in CHARMM for the structure refinement
- incorporation the implicit solvent/membrane GB model into widely used programs (such as CNS or REFMAC) by X-ray crystallographers

- References

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Teaching Philosophy & Interests

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The two most important roles of college educators are to provide the specific knowledge and skills necessary for future professional work of their students, and the motivation for them to remain interested in the subjects they have been taught and thus to pursue 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 thinking during the training.

1. Teaching inter-disciplinary subjects

Modern science is inter-discipline in nature. For example, understanding a biological process at an atomic level may require not only the concepts from chemistry to explore the quantum nature of catalytic reactions and to provide physical insight regarding intermolecular interactions, but also the practical application of modern computational chemistry/biology tools 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 is a more complete understanding of science as a whole and a better ability to apply knowledge in a variety of contexts.

2. Teaching independent thinking

Independent and analytical thinking is practiced best through the application of learned knowledge to new (research-oriented) 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.

3. 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 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 also be 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.

4. Teaching interests

The 2004 CTBP Summer Workshop in which I participated as lecturer and helper provided me an opportunity to be involved in inter-disciplinary and problem-oriented teaching. In addition to regular courses in your existing curriculum, I am willing to contribute my specialty (solvation & continuum electrostatics) to the existing inter-disciplinary core course or to develop such a course. In particular, I would like to create a problem and research-oriented biomolecular modeling course that introduces basic molecular mechanics, minimization and dynamics, explicit and implicit solvation, continuum electrostatics, statistical mechanics, and free energy calculations with practical examples. The biomolecular simulation package CHARMM in whose developments I have been involved can be used for the practical exercises. I believe that such courses will help further enhance the strength of the department.