Research interests and accomplishments

Before describing my future research plans, I find it helpful to describe my research accomplishments and interests briefly. The main theme of my research is structure-function relationship of membrane proteins and membrane processes. I have investigated these topics through application of molecular modeling and computer simulation techniques to atomic-resolution models of membrane proteins of known structure. The techniques that I have primarily employed in my research are classical molecular dynamics (MD) simulation, different levels of quantum mechanical (QM) calculations, and combined classical and quantum mechanical (QM/MM) calculations. Two families of membrane proteins have been the primary foci of my research during the last 8 years: *retinal proteins* and *aquaporin water channels*. The following paragraphs summarizing my major discoveries and accomplishments regarding the function of these proteins are by no means comprehensive, and I would be happy to provide more details.

Retinal proteins. I have studied three members of this family: the bacterial proton pump *bacteriorhodopsin*, the visual receptor *rhodopsin*, and the bacterial *sensory rhodopsin II*. All members of this family use a polyene chromophore with a highly delocalized electronic structure, retinal, to detect and absorb light. I have analyzed these proteins at three different levels: **1)** a detailed analysis of the chromophore's structure and its electronic properties; **2)** interaction between the chromophore and its embedding protein; and **3)** modeling of retinal proteins in biological membranes. The results of my research on retinal proteins have been published in 16 papers.

In a comprehensive QM study of an exhaustive set of retinal analogues, I demonstrated how various structural elements may affect the excitation energy and isomerization barriers of retinal, both being critical in the biological function of all retinal proteins, and how the interplay of the structure and the proton affinity of the molecule may explain the coupling of isomerization and proton transfer events in a protein. I was among the first researchers to propose through calculations a twisted structure for the protein-bound form of the chromophore and its implication in the selectivity of the photoinduced isomerization reaction. The first complete structural model of bacteriorhodopsin in membrane, the so-called *purple membrane*, was modeled and simulated by us and was featured in an invited paper with the cover page in JPC in 2001. I conducted the first MD simulation of chromophore isomerization in rhodopsin, the human visual receptor and the only G-protein coupled receptor (GPCR) of known structure. The results of the study established the mechanism by which light energy is stored in the receptor, and clearly demonstrated how retinal isomerization is coupled to different events in proteins with different biological functions. Finally, I participated in a series of advanced QM/MM studies that revealed what mechanisms are employed by different retinal proteins to tune the maximal absorption of their common chromophore in order to maximize the gain of energy from ambient light and to protect the cell from harmful sources of light (the study was featured on the cover page of JPC in 2001). Probably the most outstanding QM/MM study is the first report of the excited state dynamics of retinal isomerization inside a protein that provided an unprecedented level of detail regarding the primary photoinduced event in retinal proteins.

Aquaporin water channels. The investigation of aquaporins' structure-function relationship and discoveries made by computational modeling approaches regarding the physical basis of their selective function is my most significant accomplishment and most important contribution to biological sciences. I strongly believe that this project represents one of the most successful biomolecular modeling projects ever conducted for a membrane protein, both in terms of the extent and the significance of the obtained results. The results of my studies of aquaporins, which started only in 2001, have appeared in more than 10 papers in high-profile journals. I successfully

explained the functional implication of the conserved protein architecture in the whole family of aquaporins based on extensive MD simulations of these channels in lipid bilayers. Due to its significant structural biological implication, the study was featured on the cover page of the *Structure* magazine. For the first time, full permeation of materials across biological membranes was described by our equilibrium and non-equilibrium MD simulations. The most outstanding result of my studies was the discovery of a novel mechanism against proton transfer in biological channels, which had not been previously observed in any other molecular system. This study, which appeared in one of the April issues of *Science* in 2002, revealed how aquaporins manage to allow water molecules to pass, but block water-mediated proton transfer, a quality that had puzzled scientists since the discovery of these channels. Using non-equilibrium simulations, we described the energetics associated with transport of linear sugar molecules through aquaporins (*PNAS, 2002*). The obtained energy profile led to the discovery of the fact that the channel has a very asymmetric shape and alignment inside the membrane. Through a devised novel methodology, we were also able to provide a simulation setup very similar to experiments through which the diffusion and osmotic permeability of water channels can now be calculated from MD simulations and compared directly to experiments.

Research plans

In view of the basic and essential roles of membrane proteins in the physiology of all living cells, and their significance in pathophysiology of diseases and pharmacological interventions, I intend to keep the focus of my research on membrane proteins. Naturally, I would welcome and actively seek collaboration with other faculty members on different protein systems, should the opportunity arise. Given the significant progress in structure determination of membrane proteins, and the availability of more powerful computers, I strongly believe that theoretical and computational biophysical studies are in a unique position to revolutionize our level of understanding of the function of these proteins in living organisms. We have documented examples of such successful cases.

I plan to work mainly on two membrane systems/processes: *G-protein coupled receptors* and *membrane transport*. To be more specific, my short-term research plans would be the study of activation of G-proteins, and simulation of transport of materials through lipid bilayers and through membrane channels.

I hope to continue working on the complex of rhodopsin and its G-protein, *transducin*, and understand how conformational changes induced by the chromophore's isomerization in the receptor can be transmitted to the transducer molecule, which is located inside the cell. In order to understand this communication, one would need to first characterize the nature of the complex between the two proteins. As a matter of fact, I have already established a collaboration with crystallographers working on wild type and mutant forms of transducin to understand the details of interaction between the receptor and its G-protein.

In the second category, I am very interested in investigating the mechanism of permeation and selectivity of transport of materials across biological membranes. In particular, I have recently concentrated more on the dynamics of ion permeation and, more importantly, on the selectivity mechanisms employed by ion channels. The problem is a very interesting one, but requires a careful treatment and analysis of electrostatic interactions and forces in the membrane and in the pore region of the channel, as well as an adequate description of bulk solvation and dielectric effects. Certainly, a combination of QM calculations and MD simulations need to be applied to understand the mechanisms involved. I am currently studying permeation of small substrates, such as O_2, CO_2, and NH_3, through pure lipid bilayers and through channels. Moreover, I have become interested in the mechanisms of ligand-gating and voltage-gating of membrane channels.

I am currently collaborating with our experimental colleagues at UIUC on nicotinic acetylcholine receptor.

I think that the two classes of projects described above are both very exciting applications of computational methodologies to biological problems that are highly relevant to basic cellular processes. Since GPCRs and membrane transport are very critical elements in physiology and pathophysiology of human beings, I believe there is high probability in obtaining external funding for these projects, e.g., through the NIH or pharmaceutical companies. The mechanisms employed by membrane proteins are of great potential also in design of nanostructures and nanodevices. My successful studies of nanotubes as models for water channels, and designing decorated nanotubes to reproduce selectivity mechanism of biological water channels are good example of such potential applications in nanotechnology.

The main objective of computational and theoretical biophysical studies is to gain insight into the mechanisms of biological processes and to answer biological questions. The presently available computational modeling techniques have reached a rather advanced and fairly mature level and can be successfully applied to diverse biological problems. The main challenge now is to define a computationally tractable problem of biological significance. A very critical step of a successful theoretical biophysical research project is finding an important biological problem that can be addressed by computational methodologies, and designing a computational approach that can address the problem. These two requirements, which are by nature closely coupled to each other, demand a high level of understanding of the biology and biochemistry of the biological systems and experience in application of computational methods to such problems. Through my vast research experience, I have acquired a very good sense in applying computational methodologies to biological problems. With my strong background in chemistry, biochemistry, and pharmacology, and my experience in studying several different biological systems with various computational methodologies, I have attained a high level of proficiency in posing the right biological questions for computational studies.

I view collaborations, especially with experimental colleagues, an absolute necessity for my research, a great opportunity to learn from one another, and a great pleasure. I have had and continue to keep up a high level of interaction with other researchers in different fields. In fact, my most successful projects have been those with both a theoretical and an experimental component. Therefore, I will seek collaborations with other colleagues on campus on various protein systems. Although I have been mainly working on membrane proteins, simulation of globular proteins poses a less challenging problem, and I can integrate it into my research program without difficulty.

Upon request, I would be happy to discuss my research plans in more detail.

Teaching philosophy

I view teaching a major mission of higher education organizations in our community. I firmly believe that there should be a strong connection and overlap between teaching and research activities, and that they can promote each other very effectively. Teaching is a field of inquiry and the teacher should be dedicated to and feel responsible for it. I believe that an effective teacher must have a good understanding of the subject and the underlying theory. It is his/her responsibility to stay current in the field by reading new books and literature, by participating in classes and workshops, and by actively engaging in research and mentoring students. Interaction with students can strongly motivate teachers to improve and augment their own knowledge.

In both my teaching and mentoring experiences, I have found it very enjoyable and rewarding to closely interact with students with fresh and young minds, and to be able to transfer my knowledge to them, both in the classrooms and in the lab. I believe that teaching is a process of encouraging students to make connection between their experiences and the subject matter. In order to be an effective teacher, we must be aware of what students know when they come into the classroom, so that we can add to that knowledge and build on it.

I believe that the main goal of a teacher in the classroom should be to teach the students how to think, and how to find, access, and then process information and materials. In order to be an effective teacher of thinking, the teacher must observe when the student attempts to think. Therefore, one should try not to use the whole time of the classroom for lecturing, but leave at least a part, preferably a major part, of the classroom activity for students to apply newly learned concepts. Obviously, a given body of information can be conveyed more permanently and effectively to the students if they are actively engaged in thinking about it. Students should be actively involved in the class by asking questions, thinking out loud, and voicing mental corrections to the teacher's statements.

I believe that the quality and the content of the teaching materials should be continuously improved through incorporating recent literature on the subject and the results of one’s own research. My experience in doing so for a half-semester, graduate biophysics course at the UIUC campus (www.ks.uiuc.edu/~emad/BIOPHYS490M/) proved very successful. In that course, integrating interactive molecular visualization had a tremendous effect on the quality and the effectiveness of the presentations as well as on the enthusiasm of students. I would like to create a course, or even a program in computational biology in which application of molecular modeling and other computational methodologies to chemical and biological problems will be presented and promoted. I would like to also develop interactive teaching materials in which structure-function relationships of various macromolecular systems, particularly proteins, are presented to students, as well as to other researchers who may be interested in the systems, in an interactive manner, namely in the form of a series of text tutorials in which pre-defined representations of special features of a protein and dynamic trajectories that students can work with interactively are used to walk the students through the complex structure of a macromolecule and its relation to function. Given the availability of an increasing number of 3D structures for proteins, and the current power of personal computers, the new materials will be a very effective medium for teaching structure-function relationship of macromolecules.