**Title: How to Model the Action of Complex Biological Systems on a Molecular Level**

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***Abstract***

Despite the enormous advances in structural studies of biological systems we are frequently left without a clear structure function correlation and cannot fully describe how different systems actually work. This introduces a major challenge for computer modeling approaches that are aimed at a realistic simulation of biological functions. The unresolved questions range from the elucidation of the basis for enzyme action to the understanding of the directional motion of complex molecular motors. Here we review the progress in simulating biological functions, starting with the early stages of the field and the development of QM/MM approaches for simulations of enzymatic reactions (1). We provide overwhelming support to the idea that enzyme catalysis is due to electrostatic preorganization and then move to the renormalization approaches aimed at modeling long time processes, demonstrating that dynamical effects cannot change the rate of the chemical steps in enzymes (2). Next, we describe the use our electrostatic augmented coarse grained (CG) model (2) and the renormalization method to simulate the action of different challenging complex systems. It is shown that our CG model produces, for the first time, realistic landscapes for vectorrial process such as the actions of F1 ATPase (3,4), F0 ATPase (5) and myosinV (6). It is also shown that such machines are working by exploiting free energy gradients and cannot just use Brownian motions as the vectorial driving force. Significantly, at present, to the best of our knowledge, these studies are the only studies that reproduced consistently (rather than assumed) a structure based vectorial action of molecular motors. We also describe a breakthrough in CG modeling of voltage activated ion channels (7). We also outline a recent simulation of the tag of war between staled elongated peptide in the ribosome and the translocon as an illustration of the power of our CG approach (8). The emerging finding from all of our simulations is that electrostatic effects are the key to generating functional free energy landscapes. Finally, we present some thought on the future of the field, taking drug resistance as an example (9)

***Biography***

Dr. Arieh Warshel, Distinguished Professor of Chemistry at the University of Southern California's Dornsife College of Letters, Arts and Sciences, was awarded a Nobel Prize in 2013 for his groundbreaking research in theoretical chemistry. Dr. Warshel holds the Dana and David Dornsife Chair in Chemistry at USC, where he has served on the faculty since 1976.

A member of the National Academy of Sciences, Dr. Warshel has pioneered computer simulations of the functions of biological molecules. He has authored nearly 400 peer-reviewed articles, including the book, *Computer Modeling of Chemical Reactions in Enzymes and Solutions* (Wiley Professional, 1991). He and his coworkers have pioneered key approaches for simulating the functions of biological molecules, including introducing molecular dynamics in biology, developing the quantum mechanical/molecular-mechanical (QM/MM) approach, introducing simulations of enzymatic reactions, pioneering microscopic simulations of electron transfer and proton transfer in solutions and in proteins, pioneering microscopic modeling of electrostatic effects in macromolecules and introducing simulations of protein folding . He and his coworkers have also elucidated recently the molecular origin of the vectorial action of molecular machines.

Dr. Warshel holds a B.Sc. Summa Cum Laude in chemistry from Technion–Israel Institute of Technology in Haifa, Israel, and both an M.Sc. and Ph.D. in chemical physics from Israel's Weizmann Institute of Science. Prior to joining USC, he was a postdoctoral scholar at Harvard University and a Senior Scientist and Associate Professor at the Weizmann Institute. In paralel he was also a European Molecular Biology Organization fellow at the Laboratory of Molecular Biology at Cambridge University.

An honorary member of the Royal Society of Chemistry (RSC), Dr. Warshel's numerous awards include the American Chemical Society's Tolman Medal, the RSC's Soft Matter and Biophysical Chemistry Award in 2012, and the Biophysical Society's Founders Award 2013.