Accelerating Chemical and Biomedical Discovery with Molecular Simulation

Dynamical Ensembles of Nucleic Acids and Their Importance for Binding, **IOAN ANDRICIOAEI** (Department of Chemistry, University of California, Irvine, Irvine, CA; andricio@uci.edu).

I will present molecular dynamics computer simulations of several examples of conformational transitions that nucleic acids and their complexes undergo upon the application of external forces and/or torques: (1) DNA supercoil relaxation by topoisomerases, (2) the condensation of DNA by dendrimers and (3) DNA ejection from viruses. Then I will showcase the use of a formalism in the theory of stochastic processes to deduce the kinetics of these transitions, from simulation trajectories or experimental single molecule recordings of the transition, under other conditions that those that are actually simulated or recorded.

Effects of Spatial Organization and Molecular Scaffoldings on the Diffusive Activity of Substrates in Enzyme Nanostructures, **CHIA-EN A. CHANG* and CHRISTOPHER ROBERTS** (Department of Chemistry, University of California, Riverside, Riverside, CA; chieanc@ucr.edu).

Many biological synthesis or metabolic processes occur within colocalized and multi-step enzyme reaction pathways with high yield and specificity. In these enzyme complexes, the relative orientation and position of the enzymes can allow for efficient diffusion of substrates between the active-sites of enzymes in the nanostructure. Taking advantage of enzyme colocalization, experimentalists synthesized a flexible DNA scaffolding for two DNA-modified enzymes: Glucose oxidase (GOx) and Horseradish peroxidase (HRP). During the catalytic oxidation of glucose, GOx reduces molecular oxygen, via a cofactor, producing H_2O_2 as a side product. As H_2O_2 is required by HRP to oxidize a substrate, GOx and HRP can share a product-reactant relationship. However, it is not understood which factors are crucial to determine the catalytic enhancement for more efficient experimental design. We therefore established a modeling platform that utilized Brownian dynamics simulations with a few different levels of coarse-grained models for computational studies. In collaboration with Prof. Ian Wheeldon at UCR, we designed the enzyme complexes based on the computational studies. The presentation will discuss the effects of position/orientation of the enzymes and the use of the DNA origami or DNA linker for potential catalysis enhancement.

AMBER 14: Peer to Peer Molecular Dynamics FTW, **SCOTT LE GRAND** (Amazon and Scatologic, Inc; varelse2005@gmail.com).

Recent code optimization targeted for AMBER 14 has improved single GPU performance by up to 30% and multi-GPU scaling by up to 70%. The latter was achieved by aggressive use of Peer-to-Peer copies and RDMA. This has unleashed new time scale regimes for sampling and simulation on low-end GPU clusters, beating every known software-based molecular dynamics codebase in existence. This talk will cover first how AMBER's already efficient single-node performance was made even more so, the challenge not only of enabling peer to peer copies between GPUs, but obtaining hardware capable of enabling it, and finally, up to the minute results using MVAPICH2 and OpenMPI for RDMA directly between GPUs on separate nodes connected by dual-line FDR Infiniband.

Protein Force Field Developments: Explicit and Implicit Strategies, **RAY LUO** (Department of Biochemistry, Molecular Biophysics and Biomedical Engineering, University of California, Irvine, Irvine, CA; ray.luo@uci.edu).

Atomistic simulations of biomolecules provide a detailed view of structure and dynamics that complement experiments. Increased conformational sampling, enabled by new algorithms and growth in computer power, now allows a much broader range of events to be observed, providing critical insights, largely inaccessible to experiments, such as characterization of the unfolded state or the transiently populated intermediates that occur during complex binding and recognition events. The Amber force field consortium have made significant inroads towards accurately representing the energetic surfaces relevant to both the native and non-native states of proteins and nucleic acids. In this talk, I will provide an overview of our latest efforts in protein force field and solvent model developments, in both atomistic and continuum representations that are widely used in bimolecular simulations.

Making Sense of Transmembrane Voltage Sensing by Voltage-Sensitive Ion Channels: Concerted Simulation and Experimental Studies, **DOUGLAS TOBIAS** (Department of Chemistry, University of California, Irvine, Irvine, CA; dtobias@uci.edu).

Voltage-gated ion channels open and close in response to changes in transmembrane potential. The details of how conformational changes in the voltage-sensing domains lead to opening/closing of the ion-conducting pore remain to be worked out. Crystal structures of the open states of voltage-gated potassium channels are available, but the structure of the closed/resting state is not known. In this talk I will report our efforts to generate a model of the resting state of the archaeal KvAP channel based on atomistic molecular dynamics (MD) simulations in explicit membrane environments, with restraints derived from experimental functional data. I will also present results from simulation studies of an isolated voltage-sensing domain in a hydrated membrane, which include validation by neutron diffraction measurements, and direct observations of elementary gating charge displacement events during a 30-microsecond MD simulation under applied transmembrane potential. Finally, I will discuss prospects for and present preliminary results on using x-ray and neutron interferometry measurements to validate and refine simulation-based models of the resting state and the voltage-sensing mechanism.

A Molecular Theory for High-throughput Prediction of Hydration Free Energies, **YU LIU, JIA FU and JIANZHONG WU*** (Departments of Chemical and Environmental Engineering and Mathematics, University of California, Riverside, Riverside, CA; jwu@engr.ucr.edu).

The classical density functional theory (DFT) is proposed as an efficient computational tool for high-throughput prediction of the solvation free energies of small molecules in liquid water at the ambient condition. With the solute molecules represented by the AMBER force field and the TIP3P model for the solvent, the new theoretical method predicts the hydration free energies of 500 neutral molecules with average unsigned errors of 0.96 kcal/mol and 1.04 kcal/mol in comparison with the experimental and simulation data, respectively. The DFT predictions are orders of magnitude faster than conventional molecular dynamics simulations and the theoretical performance can be further improved by taking into account the molecular flexibility of large solutes.