2077-Pos Board B807
Generalized Scalable Multiple Copy Algorithms for Biological Molecular Dynamics Simulations in NAMD
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Computational methodologies that couple the dynamical evolution of a collection of copies, or replicas, of a system of interest offer powerful and flexible approaches to characterize complex molecular processes. Such multiple copy algorithms (MCAs) can be used to enhance sampling, compute reversible work and free energies, as well as refine transition pathways. Widely used examples of MCAs include temperature and Hamiltonian-tempering replica-exchange molecular dynamics (T-REMD and H-REMD), alchemical free energy perturbation with lambda replica exchange (FEP/-REMD), umbrella sampling with Hamiltonian replica exchange (US/*H*-REMD), and string method with swarms-of-trajectories to determine conformational transition pathways. Here, we report a robust and general implementation of MCAs for molecular dynamics (MD) simulations in the highly scalable program NAMD built upon the parallel programming system charm++. Multiple concurrent NAMD instances are launched with internal partitions of charm++ and located continuously within a single communication world. Messages between NAMD instances are passed by low-level point-to-point communication functions, which are accessible through NAMD's Tcl scripting interface. The communication-enabled Tcl scripting provides a sustainable application interface for end users to realize generalized MCAs without modifying source code. Illustrative applications of MCAs with fine-grained inter-copy communication structure, including global lambda exchange in FEP/-REMD, window swapping US/*H*-REMD in multidimensional order parameter space, and string method with swarms-of-trajectories were carried out on IBM Blue Gene/Q to demonstrate the versatility and massive scalability of the present implementation.

2078-Pos Board B808
Assessing Limitations of Elastic Network Models in Describing Equilibrium Protein Flexibility and Extensions to Predict Non-Equilibrium Unfolding Dynamics of Proteins
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Elastic network models (ENMs) are a class of harmonic models used to computationally describe biomolecular flexibility. Using ENMs, protein dynamics is often described as a collective motion of beads connected by Hookean springs for all amino acid or atom pairs whose distance is smaller than an empirically chosen cut-off distance. Despite their simplicity, ENMs show intriguing abilities to capture functionally relevant conformational changes in proteins at equilibrium. For instance, the slowest modes obtained from ENMs can map the transformation between multiple functionally relevant conformations of biomolecules captured by X-ray crystallography. Further, the directions of the slowest normal modes of proteins obtained from an ENM description show surprisingly strong correspondence with the dominant collective motions of solvated proteins from molecular dynamics trajectories which use detailed atomistic potentials. In this study we discuss some limitations of conventional ENMs in predicting relative trends in the equilibrium flexibility of ubiquitin-like proteins which share strong structural homology but have weak sequence identity. Two issues are raised: 1) the physical basis behind the empirically chosen cut-off distance for harmonic interactions and 2) the lack of relative phase information while summing the normal modes contributions to equilibrium protein flexibility. A strategy for reparameterizing the ENM based on classical molecular dynamics trajectories is proposed to overcome these limitations. We will also discuss progress in extending ENMs to predict non-equilibrium properties of biomolecules such as the unfolding force of proteins and its dependence on pulling direction, which are typically measured using single-molecule force spectroscopy.

2079-Pos Board B809
Studying Conformational Changes of Mhp1 using Unbiased All-Atom Molecular Simulations
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Mhp1 is a secondary active transporter from nucleobase/cation symporter-1 (NCS1) family. We have developed the implicit membrane-explicit membrane (IM-EX) hybrid simulation method to study conformational changes in secondary active transporters (JMB. 404:506). This novel approach starts with IM simulations and certain confirmations from the implicit simulation are placed in an explicit membrane environment to get the final conformation. Studying conformational changes of Mhp1 is an important test to our IM-EX method. Three different conformations of Mhp1 are known, i.e., inward-open, outward-occluded and outward-open. For Mhp1, the implicit simulation is applied by using SGLD-fp method (JCP. 135: 204101). The main advantage of SGLD-fp method is to overcome the energy barriers in a reasonable amount of simulation time. Then, certain conformations that show structural change during the implicit simulation are simulated with MD in an explicit membrane. Crystal structures of different conformations were used as initial conformation for SGLD-fp simulations. Glu289 was protonated based on its pKa value. The 20-ns simulation for inward-open conformation showed opening in extracellular gate but no closure for intracellular gate. In case of outward-occluded conformation, the result showed opening of EC gate while IC gate is still closed. The final structure agrees with the outward-open conformation, which means SGLD-fp method can predict conformational changes in a short time. For the outward-open conformation, simulations with SGLD-fp maintained this conformation. Protonation of other residues, choosing different initial seeds and effect of sodium and substrate are currently being studied to see how these factors affect transition between states.

2080-Pos Board B810
A New Strategy for Coarse-Grained Protein Simulations: Smoothed Energy Tables
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Coarse grained simulation methods allow the simulation of large biomolecular systems with less computational expense than the corresponding all-atom simulations. The savings come from two sources: faster computation due to a reduced number of particles, and improved sampling due to a smoother free energy surface. Many commonly used coarse-grained models suffer from serious limitations, such as being unable to properly model protein secondary structure without the addition of unphysical restraints. We have constructed a novel coarse-grained Monte Carlo method based on dividing proteins into nearly rigid fragments, constructing distance and orientation-dependent tables of the interaction energies between those fragments, and applying potential energy smoothing techniques to those tables. Preliminary results on peptides indicate that the new method is able to preserve α-helices without additional restraints. In addition, when sufficient smoothing is applied, the new method also shows an improvement in sampling per unit computation time compared to Monte Carlo simulation without tabulation or atomistic molecular dynamics.

2081-Pos Board B811
Mixed-Resolution Monte Carlo: A Tool for Sampling Proteins and Ligands
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We further develop our mixed-resolution Monte Carlo software. The code allows proteins to be modeled with arbitrary atomistic (AA) and coarse-grained (CG) regions: a focus region, such as a binding site with ligand, is modeled atomistically while the remainder is coarse-grained. A corresponding hybrid AA/CG generalized Born solvation treatment was developed [J. Chem. Theory Comp. 8:2921 (2012)]. The new package includes important improvements: (i) improved ease of initializing simulations from PDB files; (ii) improved treatment of AA/CG interface interactions using stored AA information for the CG region; and (iii) a "spotlighting" feature that enables the AA region to be re-defined on the fly to follow a ligand or mobile protein segment. The code is used to sample protein conformational flexibility and, in separate work by Palli et al., protein-ligand interactions.

2082-Pos Board B812
PB-SAM, a Novel Solution to the Poison-Boltzmann Equation for Applications in Coarse Grain Dynamics
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While molecular dynamics (MD) simulations routinely and beneficially address questions focused on detailed atomistic chemistry, structure, and kinetics over fast timescales, there exists another set of problems on the mesoscale, where limitations of size and timescales in MD are reached. These problems may be overcome by the use of coarse-grain (CG) representations, e.g. the Poisson-Boltzmann equation (PBE), of microscopic systems integrated into simulations utilizing stochastic dynamics. At supramolecular distances, electrostatic forces dominate many first interaction events. Applications of these interactions range from recognition events for biomolecular complex formation to proton transport in membranes.
A realistic simulation must include an accurate treatment of bulk electrolytes for these large-scale systems. This can be achieved using continuum