3322-Pos Board B427
Molecular Simulations of Sequence-Specific Association of Transmembrane Proteins in Lipid Bilayers
Manolis Doxastakis, Lorant Janosi, Anupam Prakash.
Association of membrane proteins is central in material and information flow across the cellular membranes. Amino-acid sequence and the membrane environment are two critical factors controlling association, however, quantitative knowledge on such contributions is limited. In this work, we study the dimerization of helices in lipid bilayers using extensive parallel Monte Carlo simulations with recently developed algorithms [1].
The dimerization of Glycophorin A is examined employing a coarse-grain model that retains a level of amino-acid specificity, in three different phospholipid bilayers. Association is driven by a balance of protein-protein and lipid-induced interactions with the latter playing a major role at short separations. In all bilayers, sequence-specificity is evident by the formation of a clear interface between the helices that is modulated by the lipid environment. Extracted estimates of the dimerization affinity are in excellent agreement with experimental data [2]. Following a different approach, the effect of amino-acid sequence is studied using the four transmembrane domains of the epidermal growth factor receptor family in identical lipid environments. Detailed characterization of dimer formation and estimates of the free energy of association reveal that these helices present significant affinity to self-associate with certain dimers forming non-specific interfaces. We present results that support the role of lipid-mediated contributions to such effects with major implications on protein function.
[1] Janosi L. and Doxastakis M., ''Accelerating flat-histogram methods for potential of mean force calculations'', J. Chem. Phys., 131, 054105 (2009)
[2] Janosi L., Prakash A. and Doxastakis M., ''Lipid-Modulated sequence-specific association of Glycophorin A in membranes'', Biophys. J., 99, 284-292 (2010)

3323-Pos Board B428
Low Order Physical Multipoles
Charles J. Baker, Ramu Anandakrishnan, Alexey Onufriev.
Point multipoles are a strong theoretical tool for studying fields due to a given charge distribution; they often provide simplifications that can be used to gain physical insight into systems. However, when used for practical calculations, such as the potential due to atomic charges in large biomolecules, both the required number of calculations and the complexity grows rapidly with each additional term kept in the expansion. We propose the use of physical multipoles, which consist of a set of point sources placed such that they optimally represent the multipole expansion of the original distribution. This method maintains the theoretical strength of point multipoles but allows for both fewer and simpler calculations. Most importantly, physical multipoles are always at least as accurate at describing the electrostatic potential as the corresponding point multipole of equivalent order and they can be substantially more accurate, especially in the most relevant regime where the distance from the charge distribution to the point of interest is no longer much smaller than the system size. We show that for some extreme charge distributions the RMS error in calculated potential for a physical dipole is 300-400 times lower than for point dipoles, at a distance of two system sizes from the origin. And for biologically relevant systems, such as certain amino acids, the RMS error in calculated potential for physical dipoles can be 4-5 times lower than a corresponding point dipole, at a distance of two times the size of the amino acid from its center. Thus physical multipoles offer a strong alternative to point multipoles, especially in practical computations.

3324-Pos Board B429
Multi-Scale Simulations of Proteins in Different Solvent Conditions
Dirar Homouz, Antonios Samiotakis, Margaret Cheung.
We developed a multiscale approach (MultiSCAAL) that integrates the potential of mean force (PMF) obtained from all-atomistic molecular dynamics simulations with a knowledge-based energy function for coarse-grained molecular simulation in better exploring the energy landscape of a small protein under chemical interference such as chemical denaturation. The two key features of this scheme are the Boltzmann inversion and a protein atomistic reconstruction method we previously developed (SCAAL). Using MultiSCAAL, we were able to enhance the sampling efficiency of proteins solvated by explicit water molecules. Our method has been tested on the folding energy landscape of a small protein Trp-cage with explicit solvent under 8M urea using both the all-atomistic replica exchange molecular dynamics (AA-REMD) and MultiSCAAL. We compared computational analyses on ensemble conformations of Trp-cage with its available experimental NOE distances. The analysis demonstrated that conformations explored by MultiSCAAL better agree with the ones probed in the experiments because it can effectively capture the changes in side chain orientations that can flip out of the hydrophobic pocket in the presence of urea and water molecules. In this regard, MultiSCAAL is a promising and effective sampling scheme for investigating chemical interference which presents a great challenge when modeling protein interactions in vivo.

3325-Pos Board B430
Macromolecular Crowding Effects on Multiprotein Binding Equilibria: Molecular Simulation and Theory
Jonathan Rosen, Young Chan Kim, **Jeetain Mittal**.
We present a coarse-grained model for studying the effects of macromolecular crowding on the thermodynamic and structural properties of multiprotein complexes. Residue-level interactions between proteins and crowding agents are incorporated in a recently developed transferable coarse-grained model of multiprotein complexes. The model is used to study the binding equilibrium between two protein complexes, ubiquitin/UIM and cytochrome c/cytochrome c peroxidase using replica exchange Monte Carlo simulations. We find that the change in binding free energy due to purely repulsive crowding can be quantitatively described by a scaled particle theory (SPT) model without any fitting parameters. The same SPT model can also be used to predict the effects of mixed crowding - a mixture of crowding particles with different sizes, using an additivity ansatz. We find that attractions between proteins and crowding molecules can not only change the crowding effects quantitatively but also qualitatively. For a critical attraction strength, stabilizing entropic effect due to excluded volume interactions are exactly cancelled by destabilizing enthalpic effects. We find that this critical attraction strength is largely independent of crowding packing fraction. A modified SPT model which includes the effect of protein-crowder attractions in a mean-field manner can predict the change in binding free energy due to crowding semi-quantitatively. Further, structural analysis suggests that crowding may significantly change the fraction of specific versus non-specific transient encounter complexes in a crowded environment.

3326-Pos Board B431
Classification of Projections in Single Particle Electron Microscopy using Common Line Similarity Measure
Hstau Y. Liao, Robert Langlois, Joachim Frank.
In single-particle reconstruction methods [1], projections of macromolecules lying in randomly unknown orientations are collected by a transmission electron microscope. Often, several classes of conformations or binding states coexist in the sample. To obtain structures with high accuracy, it is required to separate the classes before reconstruction of the molecules. In this work, we use a graph-theoretic criterion based on common lines, which measures both the dissimilarity between the classes and the similarity within the classes. Projections are then sorted by optimizing this measure, without need for a reference volume or for any intermediate reconstructions, as done in most classification methods.
The usefulness of this type of approach, via a combinatorial optimization of the measure, was first demonstrated in [2], but tested only on simulated projection data. We instead view the optimization as an eigen-decomposition problem, which makes it easy to account for different kinds of normalization of the measure. The work in [3] also uses eigen-decomposition, but the similarity is measured between 2D averages, and a reference volume is required to pre-sort the projections according to their angular orientation.
In this work we measure the similarity between the projection data themselves and show the results for both simulated and experimental data.
[1] J. Frank, Three Dimensional Electron Microscopy of Macromolecular Assemblies, Oxford, 2006
[2] G.T. Herman and M. Kalinowski, Classification of heterogeneous electron microscopic projections into homogeneous subsets, Ultramicroscopy 108:327-338, 2008
[3] M. Shatsky et al., Automated multi-model reconstruction from single-particle electron microscopy data, J. Struct. Biol. 170:98-108, 2010

3327-Pos Board B432
Monte Carlo Simulations of Absolute Binding Free Energy of Targeted Nanocarriers to Cell Surfaces
Jin Liu, Blaine Zern, Portonovo Ayyaswamy, David Eckmann,
Vladimir Muzykantov, Ravi Radhakrishnan.
We have developed a computational methodology based on Metropolis Monte Carlo (MC) and the weighted histogram analysis method (WHAM) to calculate the absolute binding free energy between functionalized nanocarriers (NC) and endothelial cell (EC) surfaces. The binding affinities are then calculated according to the free energy landscapes. The predictions quantitatively agree with the analogous measurements of specific antibody coated NCs (100 nm in diameter) to intracellular adhesion molecule-1 (ICAM-1) expressing EC surface in *in vitro* cell culture experiments. We then systematically explore the effects from a broad range of experimentally tunable parameters including the antibody surface coverage σ_s of NC, glycocalyx in both *in vivo* and *in vitro* conditions, shear flow and NC size. The simulation results agree remarkably well