polymers (i.e., polymer crystal structure not maintained during simulation) and extensive class-II force fields (CFF, PCFF, COMPASS, etc.) have not been parameterized for use in proteins. We have extended the CHARMM code so as to use a dedicated class-I force field for the protein, a class-II force field (image bond extended CFF, or newly implemented PCFF) for the polymer surfaces, and tuned electrostatic and van der Waals parameters for the interphase interaction. Results will be presented on the insufficiency of class-I force field for polymers and the suitability of the use of dual (one class-I and one class-II) force fields for solid-liquid interphase interactions relevant for protein adsorption on PLA polymers.

2088-Pos Board B58

Improving Molecular Mechanics Force Fields By Comparison Of Microsecond Simulations With Nmr Experiments

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Molecular dynamics simulations and NMR spectroscopy provide complementary approaches to the study of protein structure and dynamics. We have carried out several molecular dynamics simulations of globular proteins and compared the results to a range of NMR experiments that probe the structure and dynamics of these proteins. In particular, simulations on the microsecond timescale allow full sampling of the rotamer distribution of most of the protein side chains. Comparisons with NMR data suggest that, for some residues, this distribution may be incorrectly reproduced by common force fields. We quantified these discrepancies by performing simulations of small helical peptides and comparing the side-chain rotamer distributions with those found in the Protein Data Bank. The potentially problematic residues identified with this procedure were corrected by suitable modification of the force field terms. The performance of the modified force field was evaluated against NMR spectroscopy data.

2089-Pos Board B59

Extracting The Causality Of Correlated Motions From Molecular Dynamics Simulations

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We present a new method to extract the causality of correlated motions from molecular dynamics simulations. Applications of the method to the folded DNA-bound Ets-1 transcription factor show that helix H4 responds to the motion of helix H1, and that helix HI-1 responds to the motion of helix H4. Our calculations reveal how the presence of DNA is transmitted through the protein, ultimately leading to the unfolding of HI-1 upon DNA binding.

2090-Pos Board B60

Numerical Techniques to Optimize Free Energy Estimation Using Thermodynamic Integration

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Free energy estimation using thermodynamic integration (TI) involves numerically approximating an integral based on a limited set of discrete data points. These discrete data points represent the free energy slope as a function of the switching variable lambda for TI simulations. We present several numerical techniques for generating optimal free energy estimates utilizing polynomials, instead of the often-used quadrature, to fit the data and thus reduce the bias and uncertainty of the resulting estimates. The specific techniques utilized in our current study are Lagrange and Newton interpolation, cubic spline, and polynomial regression. To further improve the overall accuracy of free energy estimates using these techniques, we also investigated the use of non-equidistant lambda values (based on Chebyshev nodes) for thermodynamic integration simulations. Our results demonstrate that the use of non-equidistant lambda values and high degrees of polynomials gives the more accurate and precise free energy estimates compared to that of trapezoidal quadrature. Regression, in particular, offers the greatest flexibility that permits the degree of polynomial to vary for any desired accuracy without imposing any limitations on the number of lambda values.

2091-Pos Board B61

Free Energy Landscape of Biomolecules from Multiple Non-Equilibrium Molecular Simulations

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Computer simulations of biomolecules, e.g. molecular dynamics (MD), have gained widespread popularity in analyzing their behavior. One of the useful applications to reveal functional mechanisms of biomolecules is free energy calculation. Most of the current free energy calculation methods, however, rely heavily on the assumption that each trajectory approximates a quasi equilibrium ensemble of a target molecule. Since its violation may cause artifacts, practical use of short independent parallel simulations performed on massive parallel computer is still limited in the case of the system with slow equilibration time such as biomolecules. Hence it is highly demanded to develop the methods without this assumptions.

We propose "Multiple Markov transition Matrix Method", an algorithm by which a stationary probability distribution is estimated from non-equilibrium multiple MD trajectories independently generated with distinct Hamiltonians. Based on the Markovity assumption, we reconstructed a Markov transition matrix from the trajectories. Combining umbrella sampling technique and maximum likelihood estimation, we developed an optimization procedure to calculate the potential of mean force (PMF). The details will be described in the presentation.

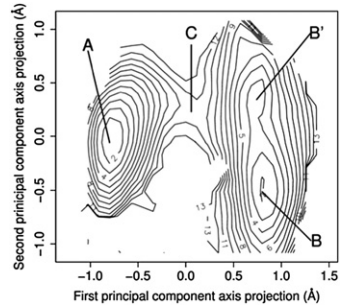

Figure 1:. Free energy landscape of Met-enkephalin calculated from non-equilibrium simulations using this method.

2092-Pos Board B62

The Extrapolated Motion Protocol For Molecular Dynamics Simulations: Predicting Large-scale Conformational Transitions In Mechanosensitive Channels

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Gating of ion channels involves large structural rearrangements and timescales posing challenges for conventional MD simulations. Forces imposed in steered MD protocols may lead to unnatural distortions, whereas near-physiological gradients produce small motions capturing just the local direction. We developed a new computationally efficient protocol allowing to 'continue' the observed small-scale motion and drive the protein along a self-chosen pathway. It was tested on bacterial channels MscL and MscS for which the initial outward motion of helices is pre-defined by membrane tension. The motion was initiated with a small (0.1-0.5 A) radial displacement of all atoms of the barrel away from the axis (step 1), followed by energy minimization (2), 1 ps relaxing MD simulation (3), and symmetry-restrained energy minimization (4). The conformational change resulting from this first cycle was linearly extrapolated with a small amplification coefficient and the three structure-relaxing steps (2-4) were repeated completing the next cycle. A sequence of 50-100 extrapolation/relaxation cycles produces a smooth pseudo-continuous trajectory revealing substantial conformational changes while preserving most of the secondary structure. The character of motion was sensitive to the amplification coefficient with 1.00 producing local oscillations, 1.05 - consistent moderate-scale motions, and 1.10 - larger transitions reaching instability. When applied to MscL, the method reproduced the characteristic iris-like gating supported by experiments. Extrapolations of the compact MscS model with reconstructed N-termini predicted barrel expansion with tilting and straightening of the kinked pore-lining helices. Extrapolations started with random thermal fluctuations produced trajectories similar to those started with a pre-conceived displacement. Open conformations of MscS reproducibly closed in extrapolations. Resting and open models of MscS based on families of extrapolated trajectories were refined in all-atom MD simulations, tested for conductance and received support by experiments.

2093-Pos Board B63

Collective variable-based calculations in NAMD

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The computational power of parallel clusters and supercomputers, and of the macromolecular simulation softwares typically used has been rapidly increasing in the recent years. One of the consequences is the higher demand for methods to analyze the dynamics and conformational space of biomolecular complexes. Several free energy calculation and enhanced sampling techniques have been developed in the past years, but only rarely they have been implemented altogether within a consistent "toolkit". Here, we introduce a new generalized interface for all those methods which rely on the definition of a set of collective variables. The code, implemented as a collective variables C++ module for NAMD (version 2.7), allows researchers in this field to choose