calculates the binding affinity of a solute molecule, its preferred spatial arrangement, lowest energy path and energy barriers along the membrane normal using solute 3D structure and pKa together with parameters of the membrane, such as surface, transmembrane potentials and pH values on both sides of the membrane. The method was tested for series of peripheral proteins, peptides and small molecules experimentally studied in lipid bilayers. Some of the results have been deposited in the Orientations of Proteins in Membranes database (http://opm.phar.umich.edu). The predicted membrane permeability of potential anticancer drugs, proapoptotic peptidomimetics correlates with their cellular activities.

2083-Pos Board B53
Generic Coarse-Grained Model for Protein Folding and Aggregation
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The complexity involved in protein structure is not only due to the rich variety of amino acids, consistent with the random heteropolymer picture, but also the weak interactions involved, comparable to thermal energy, and important cooperative phenomena. This presents a challenge in computer simulations, as it is associated with high-dimensionality and ruggedness of the free energy landscape as well as long equilibration times, frequently exceeding what can be handled in atomistic studies. We have recently developed a coarse-grained (CG) implicit solvent peptide model which has been designed to reproduce key consequences of the abovementioned weak interactions. Its intermediate level of resolution, four beads per amino acid, allows for accurate sampling of local conformations, in particular secondary structure, by designing a force field that relies on simple interactions (e.g. hydrogen bonds, hydrophobicity). A realistic ratio of alpha-helix to beta-sheet content is achieved by mimicking a nearest-neighbor dipolar interaction.
In the present study, we tune the model in order to fold helical proteins while systematically comparing the structure with NMR data. Very good agreement is achieved for proteins that have simple tertiary structures, which implies that the force field is able to reproduce important cooperativity features between amino acids. We further probe these effects by looking at peptide aggregation scenarios. Hydrophobic peptide fragments cooperatively form largescale beta-sheet structures. The model is able to reproduce features from atomistic simulations on a qualitative basis. The large-scale and long-term regime that this CG model offers, coupled with our design criteria (folding and realistic alpha/beta content), make it very suitable for many biological processes, such as misfolding and oligomerization involved in neurodegenerative diseases.

2084-Pos Board B54
Martini Force Field: Extension To Carbohydrates
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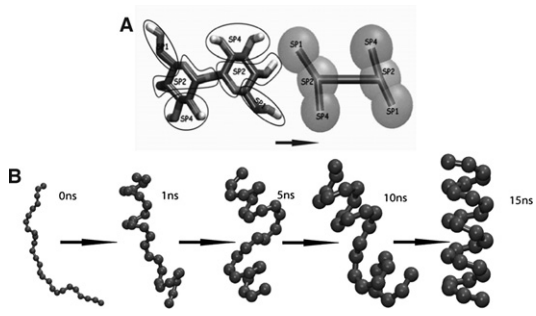
MARTINI force field: extension to carbohydrates
We present an extension of the coarse grained (CG) MARTINI force field (1) to carbohydrates. In line with the MARTINI force field development, the coarse grained model for carbohydrates has been systematically parameterized based on reproduction of experimental partitioning free energies in combination with mimicking the behaviour seen in atomistic simulations. Parameters were derived for all common mono- and disaccharides, considering the different ways of linking for monosaccharide units. The model has been tested on a number of small polysaccharides. For instance, the folding of a 26 (α 1-4) D-glucopyranose amylose chain was simulated both in a non-polar (nonane) and polar (water) environment. The folded structure is found to be similar for the CG and the all-atom model.



Coarse grain mapping of trehalose (A) and simulation of the folding of a CG 26-glucose amylose chain in nonane (B). For representation just the backbone beads are shown
The CG carbohydrate model is fully compatible with the previously parameterized lipid and protein models, and opens up the way to study a large variety of biological systems in which carbohydrates are important.
(1) S.J. Marrink, H.J. et al, JPC-B, 111:7812-7824, 2007.

2085-Pos Board B55
Scaal: A Robust, Accurate, And High-efficient All-atomistic Protein Reconstruction Method From Low-resolution Protein Models
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In the quest to develop multiscale molecular simulation methods for complex protein dynamics that fuse high-resolution and low-resolution protein representations, it is important to investigate the required information of reconstruction of all-atomistic proteins from low resolution ones with manageable uncertainly. In this paper, we introduce a robust, accurate, and fast reconstruction method (SCAAL) that produces reliable all-atomistic protein structure by taking few beads from a coarse-grained model with at least one side chain bead and one Cα bead in the backbone (Side chain-Cα Model, SCM) into accounts. Our algorithm (SCAAL) is compared with SCWRL3.0 and it excels in robustness and is more accurate in the reconstruction of large amino acids. In addition, we further test SCAAL in the reconstruction of a complete protein folding trajectory from SCM coarse-grained models. We show that the efficiency, accuracy, and robustness of SCAAL as leverage for multi-scale simulations are excellent in terms of low root mean square deviations that lie within 1Å resolution.

2086-Pos Board B56
Self-Learning Multiscale Simulation
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Molecular dynamics (MD) simulation plays more and more crucial roles in understanding the underlying molecular mechanisms of many biological processes. Unfortunately, due to the large number of degrees of freedom involved and inherently rugged energy surface, the time scale currently reachable by accurate all-atom (AA) simulation is far below typical biologically relevant time scale. Coarse graining the molecular representation can accelerate sampling, but the coarse grained (CG) simulation is unavoidably less accurate in energy estimate. To surmount these problems, a number of strategies have been proposed to integrate the AA and CG simulations, which is often called multiscale simulations. However, traditional multiscale methods heavily rely on the accuracy of the CG model. If the CG potential has its major basins different from those of AA potential, the multiscale simulation is not efficient and sometimes even bias the sampling. Here, we propose a new multiscale simulation method, self-learning multiscale molecular dynamics (SLMS-MD), which can achieve high accuracy and high sampling efficiency simultaneously. Based on the resolution exchange MD between atomistic and CG replicas, a self-learning strategy is introduced to progressively improve the initial CG potential by an iterative way based on the previously sampled CG conformations and their corresponding AA energies. The CG simulation ensures the efficient and broad sampling, and simultaneously the AA energies shape up the accuracy of the CG potential. Testing results show that the SLMS-MD can optimally combine the advantages of the AA and CG simulations, and achieve accurate and efficient multiscale simulations even when the initial CG potential is very poor. The resulting free energy converged to the exact result much faster than that by the replica exchange method. This method is generic and can be applied to many biological as well as non-biological problems.

2087-Pos Board B57
Simultaneous Use Of Class-i And Class-ii Force Fields In CHARMM For Solid-liquid Multiphase Simulation Of Protein-surface Interaction
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An appropriate understanding of conformational and behavioral changes of proteins upon their adsorption to synthetic surfaces is of crucial importance in the development of biomaterials because the changes play a governing role in determining cellular responses to implanted materials and substrates for tissue engineering. A detailed analysis of molecular behavior is key to such an understanding, and classical molecular dynamic (MD) simulation is one of the direct methods of addressing this issue. However, one of the challenges in using MD simulation is that class-I force fields (CHARMM, AMBER, OPLS, etc.) that have been parameterized for proteins are not suitable for

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.

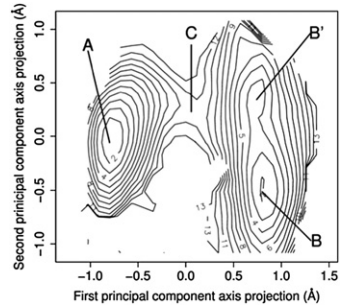

Figure 1:. Free energy landscape of Met-enkephalin calculated from non-equilibrium simulations using this method.

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