advances on our extension of the MARTINI model to more accurately describe the internal flexibility of peptides and small proteins. The model is applied to simulations of amyloid peptides of different lengths in water. Its performance is assessed by comparing the distributions of various structural properties with their counterparts from atomistic simulations.

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2942-Pos

Biophysics of Transmembrane Pores - Interactions by Coarse-Grained Molecular Dynamics Simulation

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The hydrophobic thickness of lipid bilayers has been shown to influence the biological activity of transmembrane (TM) pores which are of central importance to the biology of cells and to a number of nanotechnological applications. Here we report on a systematic exploration of protein pores and their interactions with lipid bilayers via coarse-grained molecular dynamics (CG-MD) simulation. Until recently computational studies on these interactions have focused on simplified models. To extend to a wider range of more biologically representative models of TM pores and their interactions with lipid bilayers, CG-MD simulations were employed to initially study a set of 72 pore-lipid bilayer systems. Both main structural classes of membrane proteins (alpha-helical and beta-barrel) were represented by the eight pores investigated and the nine bilayer systems (phosphate-phosphate distances: 2.8 - 5.3 nm) sample a wide range of local hydrophobic mismatch conditions. Lipid bilayer perturbation due to pore insertion, the dependence between hydrophobic mismatch and the observed pore tilt angle, and the local de-mixing of lipid types around a pore in mixed-lipid bilayers were all analysed. The local lipid bilayer perturbation caused by the inserted pores suggests possible mechanisms for both lipid bilayer-induced protein clustering and protein-induced lipid de-mixing - both driven by the hydrophobic mismatch. This has been further investigated by a series of CG-MD simulations of multiple TM pores in large planar lipid bilayer patches. To study the impact of membrane curvature on protein-lipid interactions, analogous simulations with vesicles (diameter: 31 nm) are currently being conducted.

2943-Pos

Hybrid Simulations: Atomistic Peptides in Coarse Grained Solvent

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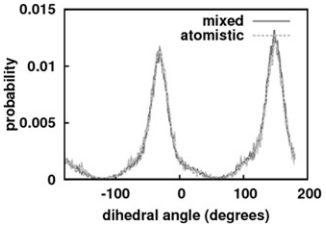
Here we present a multiscale simulation approach to study aggregation of small peptides. We develop a protocol that uses atomistic trajectories and the Iterative Boltzmann method to construct a mixed representation of the peptide/solvent system, in which the peptide is described with the united atom GROMOS forcefield and the solvent is described with effective potentials derived from atomistic radial distribution functions. For a test system composed of di-alanine peptide and octane as solvent, we show that the peptide structural properties (see figure) as well as solvation free energy obtained in the hybrid approach matches results obtained from reference atomistic simulations. Next, the model is used to calculate the potential of mean force between two peptides to evaluate how the reduced representation of the solvent influences solute aggregation properties. We show that accurate reproduction of the octane and di-alanine solvation free energy as well as careful choice of the degree of coarse-graining of the peptide-solvent interactions are important to obtain a realistic potential of mean force. Finally aggregation of many peptides is studied with this multiscale protocol. The future applications include aggregation and folding of atomistic peptides and proteins in coarse grained bilayers.



2944-Pos

Discrete Molecular Dynamics as a Tool to Test Soluble Protein Models

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Discrete molecular dynamics (DMD) has been applied in many areas of protein folding and aggregation because relatively long time scales can be simulated. Coarse-graining and implicit solvent models have been implemented to maximize its efficiency. However, there has been no rigorous evaluation with DMD on experimentally known structures. Here, we ran DMD with four-bead peptide model on X-ray structure of a human serum retinol-binding protein and NMR structure of a regulator of G-Protein signaling, and compared the results to those of simulations by NAMD (all atom molecular dynamics with explicit water). DMD showed larger root mean squared deviation (RMSD) from the starting conformation compared to NAMD though tertiary structures were mostly maintained. We developed a new implicit solvent model for DMD based on Miyazawa-Jernigan interaction pair potential that has advantage of unambiguous implementation to address dependencies in implicit solvent models. Results obtained with the Miyazawa-Jernigan implicit solvent model were comparable to those obtained with a previously used implicit solvent model based on Kyte-Doolittle hydropathy scale. We ran DMD and NAMD on incorrectly folded models. Structures of the incorrectly folded models were very poorly preserved during the DMD simulations. Both methods were able to distinguish between the correct and incorrect structures based on differences in the magnitudes of the RMSD from the starting conformation. Hence, we suggest that DMD may be useful as a tool to test soluble protein models.

2945-Pos

Determining the Molecular Basis of Disease in Single Nucleotide Polymorphism Variants using Wavelet Analysis

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Single nucleotide polymorphisms (SNPs) are the bases of a wide range of diseases and disorders, yet 3D structures and experiments often show little or no clear difference between variants, shedding little light on how a SNP leads to disease. Molecular dynamics (MD) simulations, in contrast, have shown differences between variants, but these are often very subtle and difficult to identify. Wavelet analysis is a data mining technique that has shown promise in determining the often subtle events that occur during an MD simulation. Here, we apply wavelet analysis to MD simulations of the variants of several SNPs and show how the technique can be used to isolate differences between the variants that are otherwise extremely elusive. We demonstrate that wavelet analysis can be especially useful in proteins with several mutations and show it to be a valuable technique for understanding the molecular basis of such diseases.

2946-Pos

Brownian Dynamics Simulation of FCS Measurements on Single Fluorophore-Labeled Superhelical DNA

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We investigated the dynamics of a single-fluorophore-labeled pUC18 plasmid through a Brownian dynamics algorithm, followed up by a simulation of the Fluorescence Correlation Spectroscopy (FCS) process. Recent experimental FCS measurements indicated a sensitivity of the monomer mean square displacements in DNA circles towards superhelicity. Simulations with homogeneous DNA elasticity and local straight equilibrium are not sufficient to reproduce this observed behavior. But inserting permanently bent sequences into the DNA, which favor end loop formation, caused a dependence of the calculated FCS correlation curves on superhelical density. Furthermore, our simulations allow us to take into account the orientation of the fluorophore in polarized excitation, which might explain the observed appearance of a Rouse-like regime at intermediate time scales.

2947-Pos

Investigation of Fluorescent DYE-DNA Interactions using Multidimensional Adaptive Umbrella Sampling Simulations

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Fluorescence resonance energy transfer is often used as a "molecular ruler" to measure distances between fluorescent dyes attached to a biomolecule. This technique relies on the assumption that these dyes rotate freely around the linkers that attach them to the molecule. In the case of Cy3 attached to the 5' end of DNA, it is known from NMR studies that the dye stacks on top of the first base pair, but recent fluorescence anisotropy studies show that there is still some rotation about the linker on short time scales. To explore the dynamics of this system more fully, we performed atomistic molecular dynamics simulations using GAMUS, a recently developed multidimensional adaptive umbrella sampling method. Using the method, the free energy basins of the DNA/Cy3 system were characterized in terms of five dihedral angles along the linker between Cy3 and the DNA.