decoupling electrostatic interactions, and similar ones for Lennard-Jones interactions, compared to state of the art soft-core transformations.

377-Pos

Hamiltonian Replica Exchange with Solute Tempering and Biasing Potentials (HREST-BP): Applications in Antibody Glycoengineering

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The glycosylation of biomolecules is essential for cell recognition and immune regulation. Intermolecular carbohydrate-carbohydrate interactions between the antibody Fc fragment and Fc receptor (FcR) are required for immune-cell activation. Further, antibody Fc glycans can be glycoengineered to enhance these interactions for applications in cancer immunotherapy: *e.g.* the removal of core fucose in the antibody Fc glycan enhances binding of the Fc fragment to the FcR and, thereby, immune-cell activity. In this work, we use molecular dynamics simulations with enhanced sampling methods—specifically, Hamiltonian replica exchange with solute tempering and biasing potentials (HREST-BP)—to determine the structural and conformational changes in such glycoengineered antibodies that initiate a potent immune response. The biasing potentials are in the form of two-dimensional grid-based correction maps (bpCMAPs) and are applied to improve the sampling efficiency along highly flexible glycosidic linkages. Through enhanced sampling of the glycan-glycan and glycan-solvent interactions *via* HREST-BP, we establish the multiscale link between the polarity of functional groups in the core sugar, solvation environment in the Fc-FcR binding pocket, and glycan flexibility, and develop broader design strategies to better modulate the immune response.

378-Pos

Using Lambda Dynamics to Study Protonation States of GLIC

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Ligand-gated ion channels have become a fascinating field of research. Their involvement in neural signalling has been the cause of a large number of studies into the behaviour of mammalian channels and their bacterial counterparts. Members of the family include the ubiquitous glycinereceptors (GlyR) and γ-aminobutyric acid receptors (GABA), among others.

The pentameric ligand gated ion channel from Gloeobacter violaceus (GLIC) is one of the more thoroughly studied members of the family. A prokaryotic channel, it has the same pentameric base structure as the rest of the family, and is activated at lower pH. The channel has been one of the first ones being successfully crystallized, with more structural information available from a number of cryo-electronmicroscopy studies under different conditions, to understand the complex gating mechanism.

Understanding the pH gating of the channel has been a challenging topic. Simulation studies using fixed protonation states have in the past used slightly different sets of protonated and de-protonated residues.

One promising approach remains the use of constant pH Molecular Dynamics (cpHMD) simulations. The issue with many of the currently used methods is that they rely on Monte-Carlo steps to change explicit protonation states, leading to inherent hysteresis when trying to model solvated systems.

We here present preliminary work using a lambda dynamics based cpHMD simulation approach. This method differs from the Monte-Carlo based methods by treating protonation as additional system variables that are integrate with the rest of the simulated system. Through this, the method avoids hysteresis from abruptly changing protonation states, while still keeping the ability to adopt to the surroundings.

We use this method to study the titration of residues involved in gating GLIC, to understand how the shifting protonation states at different external pH values affect the structure of the channel.

379-Pos

MD Simulation of Solvated DAFP-1-Ice Surface Binding using Umbrella Sampling

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The ability of antifreeze proteins (AFPs) to depress a freezing point without affecting the equilibrium melting point remains a mystery. This disparity between freezing and melting point is also known as thermal hysteresis. Previous Molecular Dynamic (MD) studies have found that the glycoprotein AFP variants bind to ice predominantly through hydrophobic resides but there are other classes of AFP without sugar structural components. DAFP-1 is an AFP found in a Dendroides canadensis species of beetle, consisting of 83 amino acid residues bound together in a helical shape by disulfide bridges, and lacking a sugar component. Using biased molecular dynamics, we are simulating DAFP-1 at ice/water interfaces and characterizing the free energy profile. This is done by rotating the protein using a biasing potential and then working backwards to the unbiased free energy using umbrella sampling. By characterizing the side chain interactions with both the water and the ice we hope to illustrate the binding interactions contributing to the freezing point depression for AFPs without sugar components. We can then use the free energy profile improve the overall understanding of AFP to thermal hysteresis.

380-Pos

Waypoint Graph Generation with Growing Neural Gases for Pathfinding Applications in Molecular Dynamics Simulations

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Path planning is a fundamental problem in the fields of autonomous robotics and molecular simulation. A large body of algorithms developed for vision-based robotic motion planning have been successfully applied to molecular pathfinding problems. We present the application of one such technique, the growing neural gas (GNG), an unsupervised machine learning procedure that estimates the optimal topological discretization of a collective variable space of arbitrary dimensionality. The GNG constructs an undirected graph representation of a probability density by utilizing a Hebb-like competitive learning rule, where individual neurons compete to represent different regions of the input space by moving and replicating in response to random samples drawn from the target density. The nodes of the resulting graph correspond to waypoint molecular states and its edges represent the potential transitions between states. Recent developments in autoencoder- and flow-based generative learning procedures have facilitated the unsupervised sampling and discovery of key collective variables in molecular systems, along which free energy differences can be calculated. Applying the GNG to such multidimensional free energy profiles allows for rapid generation of waypoint graphs within the collective variable space, which can be subsequently refined to determine optimal transition paths between selected states of interest. This proposed pipeline enables the unsupervised estimation of minimum free-energy transition paths from an initial molecular structure. We demonstrate our procedure on toy Gaussian-well systems and model molecular systems such as alanine tripeptide and show that the GNG can be a powerful tool for feature space discretization and path planning applications in molecular dynamics simulations.

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Adaptive Sampling using a Geometric Brownian Motion Model to Predict MD Trajectory Mobility on a Free Energy Surface

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We present an enhanced adaptive sampling method for swarms of Molecular Dynamics (MD) trajectories based on a mathematical model of Geometric Brownian Motion. Adaptive sampling protocols often determine the direction of trajectories in MD swarm simulation from the time evolution of collective variables (CVs) of interest extracted from multiple MD trajectories. Using dimensionality reduction projections such onto spaces such as defined by time-independent component analysis (tICA), the data are then projected onto a 2D space composed of two vectors with the slowest motion along the CVs. The trajectories are then re-initiated from the states identified in that 2D space that are the most distant from the initial conformation. This propagation approach does not prevent the system from being trapped in the local minimum, or from falling back into the initial state rather than exploring new conformational space in the re-initiated trajectories. These are important drawbacks considering that significant conformational transitions are likely rare events in large biochemical systems. We have addressed this issue by enabling the method to predict the future mobility of the trajectories from their previous motion on the tICA space. As movement on the free energy surface is commonly considered a diffusion process, we achieve this prediction by applying the geometric Brownian motion mathematical model (GBM) coupled to a Hidden Markov Model (HMM)-based event detection algorithm. We present the results from tests of this method on a variety of protein systems of different sizes, including membrane proteins (e.g., the dopamine transporter hDAT). We found that this approach improves the efficiency of configurational sampling in MD simulations with a prediction accuracy for mobile and immobile trajectories of ∼85% and ∼81%, respectively.