The results are interpreted under the assumption that the diffusion of the ligand can be modeled as a navigation on the PMF in which the ligand hops between the PMF local minima following the minimum free energy paths (MFEPs) with rates set by the free energy barriers that need to be crossed. We calculate all these quantities –local minima, MFEPs, barriers– with accuracy. Our results show that the positions of the local minima of the PMF are in good agreement with all the known binding cavities inside the protein, which indicates that these cavities may indeed serve as dynamical traps inside the protein and thereby influence the binding process. In addition, the MFEPs connecting the local PMF minima show a complicated network of possible pathways of exit of the dissociated CO starting from the primary docking site, in which the histidine gate is the closest exit from the binding site for the ligand but it is not the only possible one.

2960-Pos

Understanding and Optimizing the Performance of Extended Ensemble Algorithms

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There has been a lot of debate about the relative performance of different extended-ensemble methods. We discuss the relationship of different methods and argue that in the long-time limit most methods that use the same biasing parameter and target distribution should have similar dynamic behavior. Under the approximation that the bias parameter is a fast variable, we show how to analyze the performance of different methods as applied to any particular system. We present comparisons of this theory and biological simulations. We discuss how this type of analysis can be used for optimization of these types of method.

2961-Pos

Sampling Path Ensembles using the Onsager-Machlup Action with Replica Exchange

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For efficient sampling in path space at finite temperatures, we propose to combine a path sampling method, the Onsager-Machlup action method for overdamped Langevin dynamics, with a powerful generalized ensemble method, replica exchange method. We numerically demonstrate the principle and algorithm of our method using a model two dimensional system with two dominant pathways. To generate path ensembles at finite temperatures, we utilize the Fourier-path dynamics employed in the path-integral simulations. The results are compared with those derived from the direct integration of the Brownian dynamics and the equilibrium theory. We further apply this method to small biomolecular systems.

2962-Pos

Modeling Fluorescently Tagged DNA and RNA Oligonucleotides for Direct Comparison to Fluorescence-Detected Resonance Energy Transfer (FRET) Experiments

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We are developing a method for studying the structural dynamics of biomolecules which couples fluorescence spectroscopy and computational modeling, providing a more complete understanding than is possible with either technique alone. Before beginning MD simulations, force field parameters were developed for the fluorescent probes to be used in experimental studies. This was carried out by first using quantum mechanical calculations to determine low-energy conformers of the probe molecules and calculate electrostatic potentials for these conformers. The RESP charge fitting procedure was then used to derive atomic charges; all other parameters were assigned by analogy to pre-existing force field parameters. Several DNA- and RNA-fluorescent probe systems were explicitly solvated in water and equilibrated before beginning production molecular dynamics simulations. These MD simulations will be used to generate simulated fluorescence data for direct comparison to experimental bulk and single-molecule FRET data.

2963-Pos

Three-Body Expansion and Generalized Dynamic Fragmentation Improve the Fragment Molecular Orbital-Based Molecular Dynamics (fMO-MD), An *ab Initio* MD Method

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The Fragment Molecular Orbital-based Molecular Dynamics (FMO-MD) is an *ab initio* MD method suitable for simulation of large molecular systems [1]. FMO-MD was improved by the introduction of the three-body extension (FMO3, [2]) and the generalized dynamic fragmentation, namely configuration-dependent redefinition of fragments during FMO-MD. An analytical energy gradient, that is, minus the force, was derived for FMO3 and was implemented to realize FMO3-MD. An algorithm of generalized dynamic fragmentation was devised to treat each covalent-bonded and, optionally, hydrogen-bonded atom cluster as a fragment. The new algorithms were tested by performing MO-MD, based on the molecular orbital method, FMO2-MD, based on two-body extension, and FMO3-MD simulations of $(H_2O)_{32}$ and $H^+(H_2O)_{32}$. FMO3-MD gave a precision comparable to that of MO-MD, while FMO2-MD resulted in lower precision, especially in $H^+(H_2O)_{32}$. The tests also showed that the generalized dynamic fragmentation scheme treated the H^+ transfer reaction gracefully in $H^+(H_2O)_{32}$. These results of the test simulations revealed the feasibility of FMO3-MD and the generalized dynamic fragmentation.

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[2] D. G. Fedorov, K. Kitaura, J. Chem. Phys. 120 (2004) 6832, Chem. Phys. Lett. 433 (2006) 182.

2964-Pos

Coarse Grained Simulations of a Small Peptide: Effects of Finite Damping and Hydrodynamic Interactions

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In the coarse grained Brownian Dynamics simulation method the many solvent molecules are replaced by random thermal kicks and an effective friction acting on the particles of interest. For Brownian Dynamics the friction has to be so strong that the particles' velocities are damped much faster than the duration of an integration timestep. Here we show that this conceptual limit can be dropped with an analytic integration of the equations of damped motion. In the resulting Langevin integration scheme [1] our recently proposed approximate form of the hydrodynamic interactions between the particles [2] can be incorparated conveniently, leading to a fast multi-particle propagation scheme, which captures more of the short-time and short-range solvent effects than standard BD. Comparing the dynamics of a bead-spring model of a short peptide, we recommend to run simulations of small biological molecules with the Langevin type finite damping and to include the hydrodynamic interactions.

[1] Winter, Geyer, J. Chem. Phys. 131 (2009) 104102
[2] Geyer, Winter, J. Chem. Phys. 130 (2009) 114905

2965-Pos

Statistics of Single-Molecular Kinetic Transitions with Application to A-N Switching of a Pre-Unfolding GFP

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The GFP chromophore can adopt four distinct chemical substates: anionic A (deprotonated), neutral N (protonated), intermediate I (chemically similar to A), and zwitterionic Z (nonfluorescent). Two-photon fluorescence images of single GFPs revealed remarkable oscillations between A and N states immediately before unfolding. We construct a simplified model which can help us theoretically interpret and explain this behaviour based on statistics of kinetic transitions described by Master Equations, and test it in stochastic simulations.

2966-Pos

A Coarse-Grained Model Based on Morse Potential for Water and N-Alkanes

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In order to extend the time and distance scales of molecular dynamics simulations, it is essential to create accurate coarse-grained force fields, in which each particle contains several atoms. Coarse-grained force fields that utilize the Lennard-Jones potential form for pair-wise non-bonded interactions have been shown to suffer from serious inaccuracy, notably with respect to describing the behavior of water. In this paper we describe a coarse-grained force field for water, in which each particle contains four water molecules, based on the Morse potential form. By molecular dynamics simulations we show that our CSJ force field closely replicates important water properties. We also describe a Morse potential force field for alkanes and a simulation method for alkanes in which individual particles may have variable size, providing flexibility in constructing complex molecules comprised partly or solely of alkane groups. We find that in addition to being more accurate, the Morse potential also provides the ability to take larger time steps than the Lennard-Jones, because the short distance repulsion potential profile is less steep. The Morse potential is implemented in Gromacs, using a rapid table look-up capability available in that simulation package. The table look-up is about 20% slower per time step than the