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.

[1] Y. Komeiji et al., Chem. Phys. Lett. 372 (2003) 342., J. Comput. Chem. 30 (2009) 40.
[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 incorporated 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 standard Lennard-Jones, but is more than compensated for by the longer time step possible, so that overall simulation times are shorter when using the Morse potential. We suggest that the Morse potential form should be considered as an alternative for the Lennard-Jones form for coarse-grained molecular dynamics simulations. We are working on coarse-grained force fields for amphipathic molecules and for ions, and will provide a progress report on that work in this presentation.

2967-Pos
Optimizing the State Identities in Markov Models of Macroscopic Ion Channel Activity

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Ion channel kinetics are often modeled and simulated using Markov models, where rate constants provide the probability of transitioning between a defined connectivity of closed and open states. Usually, the connectivity and state identities (open versus closed) are set by the modeler and an optimization routine is used to search for the rate constants with which the model best matches the experimental activity. Here we present a novel approach for ion channel model specification where a genetic algorithm (GA) is used to optimize both the rate constants between state transitions as well as the identities of the states. Specifically, the GA chooses which states are open and which are closed. Including the state identities as free parameters improves efficiency by concomitantly searching multiple models within one optimization routine instead of individually fitting each model. Using this approach, we correctly identified models ranging from three to seven states that were used to simulate macroscopic concentration response relationships. We then fit experimental macroscopic $GABA_A$ receptor activity to seven models, ranging from three to eight states, where seven-state models with three open and four closed states provided the best fits. This approach may be particularly useful for fitting macroscopic data where the number of closed and open states is not delineated by dwell-time distributions, as with single-channel analysis, and provides an alternative where fewer constraints and assumptions are made of the ion channel models.

2968-Pos
Parameter Refinement, Optimization, and Extension of the Absinth Implicit Solvation Model

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Computer simulations of biomolecules offer detailed insight into the molecular driving forces and mechanisms of fundamental biological processes such as protein folding and aggregation. Such studies present a challenge to biophysicists since most systems of interest possess a large number of degrees of freedom which must be rigorously sampled.

The ABSINTH model (Vitalis & Pappu, J. Comput. Chem.,30:673-700) attempts to address this challenge by coarse-graining the solvent degrees of freedom. This leads to considerable simulation speed-up and allows for the study of previously inaccessible length and timescales in silico. The unique aspect of the model lies in the parsing of biomolecules into solvation groups which have experimentally known free energies of solvation (FES). These reference FES are used directly to compute the mean-field interaction of the solvation group with the solvent milieu. This avoids decomposition of the FES into polar and non-polar components, as is done in the Poisson-Boltzmann/Generalized Born formalism.

The ABSINTH model has been successfully used to describe polymeric properties and aggregation behavior of archetypal intrinsically disordered protein systems. Valuable insights into the aggregation mechanism of polyglutamine and the Huntingtin N-terminal domain along with the phase behavior of highly charged protamines were all made possible by this model, which gave readouts that were quantitatively comparable to experimental studies. The central assumption in the model is that the FES of the solvation groups is additive upon concatenation and this appears to be valid when sidechain behavior dominates the system, as is the case of those systems mentioned above. Polyglycine poses a particular challenge, as the additivity assumption makes the backbone appear overly hydrophilic. Here, we describe extensions and corrections made to the ABSINTH model to better describe backbone solvation equilibria.

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2969-Pos
Biomolecular Coarse-Grained Simulation Program CafeMol

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Our group are developing biomolecular coarse-grained (CG) simulation program, which we call CafeMol. CG molecular dynamics (MD) simulation is able to reach much larger time- and spatial- resolution than conventional all-atom MD simulation. Thus, CG model have been used for long time simulation of biomolecular system, such as protein folding, DNA duplex melting, and self-assembly of lipid bilayer. CafeMol includes CG- protein, nucleotide, lipid models. We are developing to applicable protein-nucleotide and protein-lipid system.

For protein model, we use off-lattice Go model and multi-basin model. Go model is minimal model for representing funnel-like energy landscape of protein folding, and multi-basin model, is extension of Go model, can treat large conformational change. CG DNA chain is repeat of three bead, which are represent base, sugar, and phosphate, respectively. This model distinguishes major- and minor- groove of DNA duplex. CG lipid molecules are composed of several beads. These lipid molecules self-assemble into bilayer vesicle. Now, CafeMol beta-version is released at http://www.cafemol.org/, which includes only CG protein model and attaches source code, manual, and some examples.

2970-Pos
Multi-Scale, Integrative Model Development using High-Performance Computer Architectures

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In the field of biophysical modeling, it has often been desirable to build models that can run in real-time on a standard desktop workstation, but this is becoming more difficult to achieve. The complexity of molecular model components is increasing. Models of protein kinetics are evolving into large Markov chains where there were once a handful of Hodgekin-Huxley gating variables or algebraic equations. Additionally, models are integrating more modules for many aspects of cellular regulation, greatly increasing the number of states and expanding the range of relevant timescales. These models achieve mechanistic accuracy at the cost of greatly increased computation. Approximations may be made to decrease simulation time, but with some sacrifice of simulation accuracy. A simplified model of cardiac excitation-contraction (EC) coupling such as the coupled L-type Ca2+ channel-Ryanodine Receptor (LCC-RyR) model can provide a reasonable facsimile of EC coupling gain by modeling only a single LCC-RyR pair per cardiac dyad, far less than what is observed experimentally. To produce more detailed output the number of channels modeled per dyad can be increased, leading to an exponential growth in the number of states and compute time.

Increased computing power is becoming more readily available in the form of multi-core processors, cluster computing, and general purpose graphics processing units (GPUs.) As the cost of such advanced computation decreases, the added benefit of including the fully detailed biophysical mechanisms in these models outweighs the computational cost of maintaining the model's complexity. The methods used here show how implementation of the coupled LCC-RyR model on the parallel GPU architecture can lead to significant speedup in simulation time. Use of the GPU also provides a beneficial scaleup in performance as models comprised of more states can be simulated on a larger machine in less time.

2971-Pos
Finite Element Modeling of Cell-Matrix Adhesive Interaction

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Finite Element Modeling of Cell-Matrix Adhesive Interaction

When cells adhere to extracellular matrix (ECM) or other bioactive surfaces (substrates), the bond formation is mediated by the bindings of cell receptors, which can diffuse along the cell membrane surface, to immobilized ligands in ECM. Cells spread and the adhesion zone grows as bond formation at the adhesion front increases to a critical level. This process consists of multiple physical and chemical mechanisms and involves the coupling of reaction-diffusion and mechanical contact between cells and ECM. In this study, we have developed a finite element code to incorporate the kinetics of receptor-ligand interaction into the mass diffusion of cell receptor. For the mechanical interactions attributed to the cell adhesion development and spreading, this code is implemented in a commercial finite element program, through features of user subroutine provided, using its coupled diffusion-displacement solver. This can take into account the fully coupling of reaction-diffusion with mechanics of cell/substrate contact and deformation. In the finite element model, interaction forces between cell and substrate include the specific attraction due to the receptor-ligand binding and the nonspecific repulsion due to glycocalyx proteins associated with cell surface. Parametric studies are also performed to