their separation in the sequence, is a critical feature of successful distance restraints selection. Sequence coverage, a measure of the representation of the entire sequence, was identified as another important feature. For the use of experimental restraints to be practical, restraint patterns must be optimized to limit the number of measurements required to produce quality models and increase the throughput of the technique. The focus of this work is the creation of an algorithm that predicts from primary sequence a set of distance measurements that would most effectively guide tertiary structure prediction. For our prediction algorithm, we have developed four individual terms that approximate these features: sequence separation, label density, secondary structure placement, and secondary structure connections. We used these terms to generate patterns of distance measurements in T4 Lysozyme, simulated these distance measurements from the crystal structure (2LZM), and ran restraint-based folding with Rosetta. We observed a significant improvement in RMSD distribution when using the optimized restraint patterns when compared to both randomized patterns and folding without restraints.

1.Alexander, N., Bortolus, M., Al-Mestarihi, A., Mchaourab, H., Meiler, J. *Structure.* De novo high-resolution protein structure determination from sparse spin-labeling EPR data. **16**, 181-195 (2008).

2955-Pos

Simulaid: a Simulation Facilitator and Analysis Program

Mihaly Mezei.
Mount Sinai School of Medicine, New York, NY, USA.

The poster describes the program Simulaid that performs a large number of simulation-related tasks: interconversion and modification of structure and trajectory files, optimization of orientation, and a variety of analysis functions. It can handle structures and (in most cases) trajectories in a variety of the popular formats: PDB, Charmm CRD, Amber, Macromodel, Gromos/Gromacs, InsightII, Tripos' .mol2 (only input) and the MMC.

Analysis features range from simple distance calculations and hydrogen-bond analysis to calculation of 2-D RMSD maps (both as text file with the data and as a color-coded matrix) and cross RMSD maps between trajectories as well as clustering based on RMSD maps; analysis of torsion angles, Ramachandran angles, proline kink angles, pseudorotational angles; as well as novel analyses, e.g., analysis based on circular variance. Torsion angle evolutions are presented in dial plots. The complete list of features will be presented, including the theory behind them (whenever applicable) and examples of typical plots will be shown. Several of these features are unique to Simulaid.

2956-Pos

Development and Applications of a Novel QM/MM Hybrid Molecular Dynamics Calculation System on Highly Parallel Supercomputer Systems

Masaru Tateno, Yohsuke Hagiwara, Jiyoung Kang.
University of Tsukuba, Tsukuba Science City, Japan.

Quantum mechanical (QM) calculation is now an important tool for investigations of functional mechanisms of biological macromolecules based on their three dimensional and electronic structures. However, the system size which QM calculations can treat is usually up to a few hundred atoms, whereas those of most biological systems of interests are in the range of 1,000 to 1,000,000 including surrounding solvent water. To overcome these difficulties, quantum mechanics/molecular mechanics (QM/MM) calculation has been used as an efficient method, in which the system is divided into QM and MM regions; the active sites to be investigated are assigned as the QM regions, which are described quantum mechanically, and the other regions of the macromolecular systems are assigned as the MM regions, which are described molecular mechanically. To date, many works for developments of efficient/accurate algorithms and their implementations/applications have been performed for QM/MM calculations.

In this study, we have developed an interface program to connect conventional but highly-parallelized QM and MM calculation engines running on massively-parallel supercomputers with more than thousands of CPUs. We connected AMBER and GAMESS for molecular dynamics (MD) and QM calculation engines, respectively, which enabled us to perform high-performance QM/MM hybrid MD simulations. Actually, we have evaluated the accuracy and performance of the present system on our supercomputers, the PACS-CS system (14.34 TFlops) and the T2K Tsukuba system (95.39 TFlops) in the Center for Computational Sciences, University of Tsukuba, by comparing the calculated results with experimental data with respect to a metalloprotein (the Cu-bound active center is assigned as the QM region). Furthermore, we have applied it for investigations of environmental effects on the electronic structure of a protein-DNA complex and the reaction mechanisms of cytochrome *c* oxidase.

2957-Pos

Rapid and Accurate Binding Free Energy Prediction for Inhibitor-Bound HIV-1 Enzymes

Peter V. Coveney, David W. Wright, S. Kashif Sadiq.
UCL, London, United Kingdom.

Medical practitioners have limited ways of matching a drug to the unique genetic profile of a virus population as it mutates within a patient under drug-related selective pressure. Currently, knowledge based decision support software based on existing clinical records and associated viral genotypic data is used to aid inhibitor selection. In the instance of the emergence of drug resistance and associated treatment failure, the ineffective treatment may be minimized by selection of the next most appropriate drug regimen. The latest generation of petascale computational resources offer the potential to enhance these systems by using predictive modelling to explain and quantify the effects of resistance mutations. We show here that it is possible to quantitatively predict the differences in strength of inhibitors binding to wildtype and mutant HIV-1 proteases using the established MM-PBSA free energy calculation methodology.

Excellent agreement between simulation and experimental results have been achieved for both absolute and relative binding affinities in a series of resistant HIV-1 protease mutants bound to the inhibitor lopinavir using an ensembles of 50 simulations. By utilising ensembles of short simulations we achieve both efficient sampling of phase space and reduced turn around times. This combination allows simulations to be performed on a timescale relevant to medical practitioners. Preliminary results indicate that our methodology is also be applicable to other drug and enzyme combinations.

Our studies are facilitated by the Binding Affinity Calculator (BAC), which performs the rapid and automated construction, deployment, implementation and post processing of simulations across multiple supercomputing grid-based resources. BAC has been integrated with the ViroLab Virtual Laboratory suite of decision support and research tools. This provides a user friendly interface designed to encourage users outside the existing academic research community to perform molecular level simulations.

2958-Pos

Biased Motion and Molecular Motor Properties of Molecular Spiders

Laleh Samii[1,2], Martin J. Zuckermann[1,2], Gerhard A. Blab[1], Heiner Linke[3], Nancy R. Forde[1].
[1]Department of Physics, Simon Farser University, Burnaby, BC, Canada, [2]IRMACS, Simon Fraser University, Burnaby, BC, Canada, [3]The Nanometer Structure Consortium and Division of Solid State Physics, Lund University, Lund, Sweden.

Molecular spiders are synthetic molecular motors featuring multiple legs that each can interact with a substrate through binding and cleavage. Experimental studies suggest the motion of the spider in a matrix is biased towards uncleaved substrates, and that spider properties such as processivity can be altered by changing the binding strength of the legs to substrate [R. Pei *et al.*, *J. Amer. Chem. Soc.***128**, 12693 (2006)]. We investigate the origin of biased motion and molecular motor properties of bipedal spiders using Monte Carlo simulations. Our simulations combine a realistic chemical kinetic model, hand-over-hand (HOH) or inchworm (IW) modes of stepping, and the use of a 1D track. We find that substrate cleavage and spider detachment from the track are both contributing mechanisms to population bias but are not necessary for biased motion on an asymmetric track. We investigate the contributions of stepping mechanism to speed, randomness parameter, processivity, coupling and efficiency, and comment on how these molecular motor properties can be altered by changing experimentally tunable kinetic parameters. We then consider the more general case where steps can occur by any mechanism, subject to steric constraints. We compare these results with the above for bipedal spiders and then simulate quadrupedal spiders to investigate the effect of leg number on motor performance.

2959-Pos

Mapping Co Diffusion Paths in Myoglobin with the Single Sweep Method

Luca Maragliano[1], **Grazia Cottone**[2], Giovanni Ciccotti[3], Eric Vanden-Eijnden[4].
[1]University of Chicago, Chicago, IL, USA, [2]University of Palermo, Palermo, Italy, [3]University of Rome, Rome, Italy, [4]New York University, New York, NY, USA.

The pathways of diffusion and escape of a CO molecule inside and out a myoglobin protein are investigated. Specifically, the three-dimensional potential of mean force (PMF or free energy) of the CO molecule position inside the protein is calculated by using the single-sweep method in concert with fully resolved atomistic simulations in explicit solvent.

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

Hugh Nymeyer, David R. Arthur.
Florida State University, Tallahassee, FL, USA.

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

Hiroshi Fujisaki[1], Akinori Kidera[1], Motoyuki Shiga[2].
[1]RIKEN, Wako, Japan, [2]JAEA, Higashi-Ueno, Japan.

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

Amy L. Speelman, Arcelia S. Ortega, David A. Paul, Bryan A. Leland, Brent P. Krueger.
Hope College, Holland, MI, USA.

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

Yuto Komeiji[1], Yuji Mochizuki[2], Tatsuya Nakano[3].
[1]AIST, Tsukuba, Japan, [2]Rikkyo Univ, Tokyo, Japan, [3]NIHS, Tokyo, Japan.

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

Uwe Winter, **Tihamer Geyer**.
Saarland University, Saarbrücken, Germany.

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

Hanbing Lin, Jian-min Yuan.
Drexel University, Philadelphia, PA, USA.

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

See-Wing Chiu[1], H. Larry Scott[2], Eric Jakobsson[1].
[1]University of Illinois, Urbana, IL, USA, [2]Illinois Institute of Technology, Chicago, IL, USA.

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