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

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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

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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

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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

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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

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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.