Computational Methods II

2948-Pos

Analysis of Spatio-Temporal Dynamics by Artificial and Real FRAP Data

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In the current paper we introduce a novel approach for the analysis of fluorescence recovery after photobleaching (FRAP) data. By using a (semi-) analytical solution for reaction diffusion equations, allowing for multiple diffusion, we start from the assumption that all involved molecular fractions, whether bound or unbound, could be mobile with different diffusion coefficients. The Laplace transformed equation of the analytical solution is found and inverted numerically using the Stehfest algorithm. For fitting purposes the Simulated Annealing strategy proves to be a better alternative to the conventionally used Levenberg-Marquardt algorithm.

We asses performance of our model by fitting different analytical solutions to artificial FRAP data as well as by applying our approach to FRAP data on yellow protein labelled aryl hydrocarbon receptor (transiently transfected into mouse hepatoma cells) comparing the results to previously introduced models. Subsequently we test the capability of our fitting algorithm for identifying the characteristics of binding and diffusion (i.e. number of binding partners, percentage of bound and unbound fraction, binding and diffusion constants).

Our new approach provides a constistent extension of so far existing models by allowing for multiple diffusion which might be needed to describe intracellular processes in which assumption of only one mobile molecular fraction is not valid.

2949-Pos

In Silico Investigation of the Molecular Effects Caused by Missense Mutations in Spermine Sythase Gene Associated with Human Mental Retardation

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It was shown that a particular mental retardation disorder, the Snyder-Robinson syndrome, is caused by missense mutations in spermine sythase gene that encodes a protein (SMS) of 529 amino acids. The human SMS forms a homo-dimer and each subunit includes two important functional domains: the N-terminal domain which is important for dimerization, and the C-terminal domain which includes active site for spermine synthesis. Three missense mutations, G56S, I150T and V132G in SMS that were identified to cause the disease, were investigated *in silico* to reveal the molecular effects causing the malfunction of SMS. It was done by performing single-point energy calculations, molecular dynamics simulations and pKa calculations to reveal the effects of these mutations on SMS's stability, flexibility and interactions. It is demonstrated that although most of the missense mutations are conservative mutations, they can still significantly affect wild type properties of SMS protein. The analysis of the pKa's of ionizable groups showed that despite that mutations do not involve titratable groups they affect the ionization properties of neighboring residues. The major effect was associated with the internal protein dynamics and mutants were predicted to be more flexible than the wild structure. The stability of the SMS domains and the home-dimer were calculated to be sensitive to the mutations and the effect depends on the location of mutation site with respect to the surface of the protein. The results indicate that the disease is caused by diverse molecular mechanisms depending on the site of mutation and amino acid type substitution and can be revealed only by a detailed structure-based analysis.

2950-Pos

NMR Structure Determination by Conformational Space Annealing

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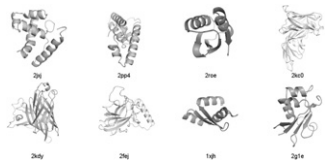
We have carried out numerical experiments to investigate the applicability of global optimization method to the NMR structure determination. Since the number of NMR observables is relatively small in the early stage of NMR structure determination process and long range NOE observables are difficult to obtain, advanced sampling techniques are greatly in need to generate valid NMR structures from a small number of experimental restraints. By utilizing conformational space annealing method, we have determined solution NMR structures from NOE distance and backbone dihedral restraints. Several solution NMR structures are determined starting from fully randomized conformations. We have evaluated them by measuring the qualities of determined structures, such as structure convergence of ensemble, Ramachandran preferences, clash scores, and the total NOE violation. These qualities are compared to those from the corresponding PDB structures.



2951-Pos

Library-Based Monte Carlo as a Convenient Platform for Variable-Resolution Protein Models

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We recently developed the library-based Monte Carlo (LBMC) which exploits pre-calculated libraries of molecular fragments, such as amino acids. We now use LBMC as the foundation for a variable-resolution platform for protein modeling. The unique feature of this platform is the capability to track coordinates of all atoms at no run-time cost, while turning on only desired interactions. More accurate interactions can be used in some parts of the protein (e.g., a binding site) and more approximate in others, depending on the problem. This strategy permits model tuning/simplification to the point where good statistical sampling can be achieved. We hope our platform will prove useful for estimating protein-ligand binding affinities.

2952-Pos

Efficient Equilibrium Sampling of All-Atom Peptides using Library-Based Monte Carlo

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We applies our previously developed library-based Monte Carlo (LBMC) to equilibrium sampling of several implicitly solvated all-atom peptides. LBMC performs equilibrium sampling of molecules by utilizing pre-calculated statistical libraries of molecular-fragment configurations and energies. For this study we employed the OPLS-AA forcefield with residue-based fragments. Two solvent models were employed, a simple uniform dielectric and the Generalized Born/Surface Area (GBSA). The efficiency of LBMC was compared to standard Langevin dynamics (LD) for tetraalanine, Met-Enkephalin and octaalanine. Based on several statistical analyses of the trajectories, we find that LBMC is more than 100 times faster than LD for our systems.

2953-Pos

Elastic and Morphological Properties of Porous Biomaterials

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The relationship between effective elastic moduli and morphological properties of microstructured or porous biomaterials including bone, wood, biomineralised skeletons of crustaceans, biopolymer networks and cubic lipid mesophases remains an open question. We compute effective elastic moduli and morphological properties of ordered porous media models based on triply-periodic minimal and constant mean-curvature surfaces of cubic symmetry.

Bulk and shear moduli are computed using voxel-based finite-element method considering the solid fraction to be a homogeneous linear elastic solid. For structures with varying volume fraction of the solid fraction, the effective bulk and shear moduli of the microstructures can be related to the porosity by a power law with fractional exponent. For fixed volume fraction of 50%, we find that within classes of geometrically similar structures the effective bulk modulus decreases with increasing heterogeneity of the domain thickness of the solid fraction which is quantified by using euclidean distance maps and percolation critical radii. On the other hand, we find significant differences between the elastic moduli of topologically distinct classes of structures. In particular, a porous medium where the solid fraction comprises a thick warped sheet separating two hollow labyrinthine network domains has larger bulk modulus than a medium where both the solid and the void fraction are represented by congruent labyrinthine domains.

2954-Pos

Optimal Selection of EPR Distance Restraints for Global Folding of Protein Structure

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Experimental restraints are critical to the expansion of *de novo* proteinfolding as restraints limit the conformational search space and increase the proportion of quality models. Our laboratory has shown that only a small percentage of randomly selected distance restraints, obtained from EPR analysis of spin labeled protein, are responsible for the improvements in model quality associated with restraint-based folding (1). Furthermore, we demonstrated that information content, a ratio of geometric distance between residues and

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.