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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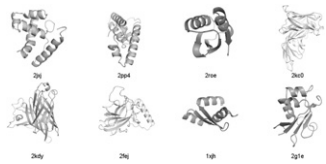
We have carried out numerical experiments to investigate the applicability of global optimization method to the NMR structure determination. Since the number of NMR observables is relatively small in the early stage of NMR structure determination process and long range NOE observables are difficult to 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