I-B Prediction of Protein Tertiary Structures and Protein Folding Problem

Prediction of the three-dimensional structures of protein molecules by computer simulations is a very challenging problem in theoretical molecular science. The difficulty of the problem lies in two facts: (1) the inclusion of accurate solvent effects is non-trivial and time-consuming (2) there exist a huge number of local minima in the energy function, forcing conventional simulations to get trapped in states of energy local minima. We have been exploring the strategies that allow us to overcome these difficulties and to study the protein folding mechanism by directly folding proteins.

I-B-1 Classification and Prediction of Low-Energy Membrane Protein Helix Configurations by Replica-Exchange Monte Carlo Method

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[*J. Phys. Soc. Jpn.* **73**, 2571 (2004)]

The effectiveness of our classification and prediction method for transmembrane helix configurations of membrane proteins by replica-exchange simulations is tested with glycophorin A transmembrane dimer. Replica-exchange simulations can sample wide configurational space without getting trapped in local-minimum free energy states and we can find stable structures at low temperatures. We classify low-energy configurations into clusters of similar structures by the principal component analysis. These clusters are identified as the global- and local-minimum free energy states. Our classifications revealed that there are only two major groups of similar structures in the case of the simulation with the dielectric constant $\varepsilon = 1.0$ and five such groups in the case of $\varepsilon = 4.0$. The global-minimum free energy state in the case of $\varepsilon = 1.0$ is very close to the structure of the NMR experiments and the prediction was successful, while in the case of $\varepsilon = 4.0$ not the global-minimum but a local-minimum free energy state corresponds to the native structure. It is shown that the global-minimum free energy state at low temperatures is also the global-minimum potential energy state in both cases.

I-B-2 Combination of the Replica-Exchange Monte Carlo Method and the Reference Interaction Site Model Theory for Simulating a Peptide Molecule in Aqueous Solution

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[*J. Phys. Chem. B* **108**, 19002 (2004)]

This article reports the first attempt to combine the replica-exchange Monte Carlo method and the reference interaction site model (RISM) theory for simulating a peptide molecule in aqueous solution. The energy function is the sum of the conformational energy and the solvation free energy. The solvation free energy for a fixed conformation of the peptide molecule is calculated using the RISM theory. The replica-exchange method is modified so that the dependence of the energy function on the temperature can be incorporated. The effectiveness of the combined approach is demonstrated for Met-enkephalin in water. It is argued that the number of replicas required for a peptide molecule immersed in water is drastically reduced by employing the combined approach. Solvation properties of Met-enkephalin are discussed and the free energy surface in gas phase is compared with that in water.

I-B-3 Multi-Overlap Molecular Dynamics Methods for Biomolecular Systems

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[*Chem. Phys. Lett.* **400**, 308 (2004)]

We propose a molecular dynamics method for the multi-overlap algorithm. By utilizing a non-Boltzmann weight factor, this method realizes a random walk in the overlap space at a constant temperature and explores widely in the configurational space, where the overlap of a configuration with respect to a reference state is a measure for structural similarity. We can obtain detailed information about the free-energy landscape and the transition states among any specific reference conformations at that temperature. We also introduce a multi-dimensional extension of the multi-overlap algorithm. Appling this multi-dimensional method to a penta peptide, Met-enkephalin, we demonstrate its effectiveness.

I-B-4 Secondary-Structure Preferences of Force Fields for Proteins Evaluated by Generalized-Ensemble Simulations

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[*Chem. Phys.* **307**, 269 (2004)]

Secondary-structure forming tendencies are examined for six well-known protein force fields: AMBER-94, AMBER96, AMBER99, CHARMM22, OPLS-AA/L, and GROMOS96. We performed generalized-ensemble molecular dynamics simulations of two peptides. One of these peptides is C-peptide of ribonuclease A, and the other is the C-terminal fragment from the B1 domain of streptococcal protein G. The former is known to form α-helix structure and the latter β-hairpin struc-

ture by experiments. The simulation results revealed significant differences of the secondary-structure forming tendencies among the force fields. Of the six force fields, the results of AMBER99 and CHARMM22 were in accord with experiments for C-peptide. For G-peptide, on the other hand, the results of OPLS-AA/L and GROMOS96 were most consistent with experiments. Therefore, further improvements on the force fields are necessary for studying the protein folding problem from the first principles, in which a single force field can be used for all cases.

I-C Development of Simulation Algorithms for Complex Systems

Developing a powerful simulation algorithm that can alleviate the multiple-minima problem is important in many complex systems. We have been advocating the uses of the so-called generalized-ensemble algorithms such as multicanonical algorithm and replica-exchange method.

I-C-1 Liquid-Gas Phase Transitions Studied by Multibaric-Multithermal Monte Carlo Simulations

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[*J. Phys. Soc. Jpn.* **73**, 3304 (2004)]

We investigate the liquid-gas phase transition of a Lennard-Jones 12-6 potential system by the multibaric-multithermal Monte Carlo algorithm. The advantage of this method is that one can sample configurational space both in the gas phase and in the liquid phase from only one simulation run. Our liquid-gas coexistence data agree well with those obtained previously by other methods. We also show that this method is efficient in investigation of the transition state, which is the saddle point of a free energy surface.

I-D Other Results on Molecular Simulations

I-D-1 Comparisons between a Molecular Dynamics and Hydrodynamics Treatment of Non-Stationary Thermal Processes in a Liquid

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[*Phys. Rev. E* **70**, 061206 (2004)]

Molecular dynamics (MD) and Navier-Stokes hydrodynamics have been performed to model thermal relaxation processes arising from an initially established nonequilibrium stationary state. A nanoscale two-layer Lennard-Jones (LJ) liquid system was constructed in which the two parts were initially at a different temperature, with a narrow transitional zone between the two layers which was spatially linear in temperature. The highest temperature layer had widths of 5 or 20 LJ particle diameters. The hydrodynamics model used parameterized MD-derived transport coefficients and the LJ equation of state as input functions. The temporal and spatial temperature and density profiles produced by the two methods show good agreement, indicating that a hydrodynamics description is reliable even for non-stationary phenomena down to the scale of a few molecular diameters.