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 Molecular Dynamics of C-Peptide of Ribonuclease A Studied by Replica-Exchange Monte Carlo Method and Diffusion Theory

LA PENNA, Giovanni[1]; MITSUTAKE, Ayori[2]; MASUYA, Masato[3]; OKAMOTO, Yuko
([1]Natl. Res. Council, Inst. Macromol. Studies, Italy; [2]Keio Univ.; [3]Kagoshima Univ.)

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Generalized-ensemble algorithm and diffusion theory have been combined in order to compute the dynamical properties monitored by nuclear magnetic resonance experiments from efficient and reliable evaluation of statistical averages. Replica-exchange Monte Carlo simulations have been performed with a C-peptide analogue of ribonuclease A, and Smoluchowski diffusion equations have been applied. A fairly good agreement between the calculated and measured ^{1}H-NOESY NMR cross peaks has been obtained. The combination of these advanced and continuously improving statistical tools allows the calculation of a wide variety of dynamical properties routinely obtained by experiments.

I-B-2 Multi-Overlap Simulations for Transitions between Reference Configurations

BERG, Bernd A.[1]; NOGUCHI, Hiroshi; OKAMOTO, Yuko
([1]Florida State Univ.)

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We introduce a new procedure to construct weight factors, which flatten the probability density of the overlap with respect to some pre-defined reference configuration. This allows one to overcome free energy barriers in the overlap variable. Subsequently, we generalize the approach to deal with the overlaps with respect to two reference configurations so that transitions between them are induced. We illustrate our approach by simulations of the brainpeptide Met-enkephalin with the ECEPP/2 energy function using the global-energy-minimum and the second lowest-energy states as reference configurations. The free energy is obtained as functions of the dihedral and the root-mean-square distances from these two configurations. The latter allows one to identify the transition state and to estimate its associated free energy barrier.

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 Monte Carlo Simulations in Multibaric-Multithermal Ensemble

OKUMURA, Hisashi; OKAMOTO, Yuko

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We propose a new generalized-ensemble algorithm, which we refer to as the multibaric-multithermal Monte Carlo method. The multibaric-multithermal Monte Carlo simulations perform random walks widely both in volume space and in potential energy space. From only one simulation run, one can calculate isobaric-isothermal-ensemble averages at any pressure and any temperature. We test the effectiveness of this algorithm by applying it to the Lennard-Jones 12-6 potential system with 500 particles. It is found that a single simulation of the new method indeed gives accurate average quantities in isobaric-isothermal ensemble for a wide range of pressure and temperature.