I-D Prediction of Protein Tertiary Structures from the First Principles

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 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.

I-D-1 Helix-Coil Transitions of Amino-Acid Homo-Oligomers in Aqueous Solution Studied by Multicanonical Simulations

MITSUTAKE, Ayori; OKAMOTO, Yuko

[*J. Chem. Phys.* **112**, 10638 (2000)]

Helix-coil transitions of homo-oligomers in aqueous solution are studied by multicanonical Monte Carlo simulations. The solvation effects are represented by the sum of the terms that are proportional to the solvent-accessible surface area of the atomic groups. Homo-oligomers of length 10 are considered for three characteristic amino acids, alanine, valine, and glycine, which are helix former, helix indifferent, and helix breaker, respectively. We calculated as a function of temperature the distributions of the backbone dihedral angles, the average values of total energy, and its component terms of the homo-oligomers. It is shown that for homo-alanine the helix-coil transition exists and that the transition temperature in water is considerably lower than in gas phase, which implies that the effects of solvation tend to reduce helical content. Moreover, the helix propagation parameter *s* and nucleation parameter σ of the Zimm-Bragg model were calculated. The *s* values that were obtained from the simulations in aqueous solution are in remarkable agreement with the experimental results.

I-D-2 Multidimensional Replica-Exchange Method for Free Energy Calculations

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[*J. Chem. Phys.* **113**, 6042 (2000)]

We have developed a new simulation algorithm for free energy calculations. The method is a multidimensional extension of the replica-exchange method. While pairs of replicas with different temperatures are exchanged during the simulation in the originalreplica-exchange method, pairs of replicas with different temperatures and/ or different parameters of the potential energy are exchanged in the new algorithm. This greatly enhances the sampling of the conformational space and allows accurate calculations of free energy in a wide temperature range from a single simulation run, using theweighted histogram analysis method.

I-D-3 Replica-Exchange Multicanonical Algorithm and Multicanonical Replica-Exchange Method for Simulating Systems with Rough Energy Landscape

SUGITA, Yuji; OKAMOTO, Yuko

[*Chem. Phys. Lett.* **329**, 261 (2000)]

We propose two efficient algorithms for configurational sampling of systems with rough energy landscape. The first one is a new method for the determination of the multicanonical weight factor. In this method a short replica-exchange simulation is performed and the multicanonical weight factor is obtained by the multiple-histogram reweighting techniques. The second one is a further extension of the first in which a replica-exchange multicanonical simulation is performed with a small number of replicas. These new algorithms are particularly useful for studying the protein folding problem.

I-D-4 Multicanonical Algorithm Combined with the RISM Theory for Simulating Peptides in Aqueous Solution

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[*Chem. Phys. Lett.* **329**, 295 (2000)]

This letter contributes to the development of the first-principles prediction methods for peptide and protein conformations in aqueous solution. We report results of the first attempt to combine the multicanonical algorithm for extensive sampling of the phase space and the reference interaction site model theory for incorporating solvent effects. Met-enkephalin in aqueous solution is chosen as an example system. Averages of the energy functions, end-to-end distance, and dihedral-angle distributions are calculated as functions of temperature.

I-D-5 A pH-dependent Variation in α-Helix Structure of the S-peptide of Ribonuclease A Studied by Monte Carlo Simulated Annealing

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[submitted for publication]

Low-energy conformations of the S-peptide fragment (20 amino-acid residues long) of ribonuclease A were studied by Monte Carlo simulated annealing. The obtained lowest-energy structures have a-helices with different size and location, depending distinctively on the energy functions that allow for protonation and deprotonation of acidic amino-acid residues. The simulation started from completely random initial conformation and was performed without any bias towards a particular structure. The most conspicuous a-helices arose from the simulation when both Glu 9 and Asp 14 were assumed to be electrically neutral, whereas the resulting conformations became much less helical when Asp 14 rather than Glu 9 was allowed to have a negative charge. Together with experimental evidence that the a-helix in the S-peptide is most stable at pH 3.8, we consider the carboxyl group of Asp 14 should be protonated at this weakly acidic condition to facilitate the helix formation. In contrast, a negative charge at Asp 14 appears to function in support of a view that this residue is crucial to helix termination owing to its possibility to form a salt bridge with His 12. These results indicate that the conformation of the S-peptide depends considerably on the ionizing state of Asp 14.

I-E 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-E-1 Replica-Exchange Monte Carlo Methods for the Isobaric-Isothermal Ensemble

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[submitted for publication]

We propose an extension of Replica-Exchange Monte Carlo (REMC) method for canonical ensembles to isothermal-isobaric ensemble as an effective method to search for stable states quickly and widely in complex configuration space. We investigated the efficiency of the new method on a benchmark testing system which consists of 256 Lennard-Jones particles. The new method enables one to shorten dramatically the relaxation time of phase change from liquid structure to crystal structure in comparison with the conventional Monte Calro method.

I-E-2 Ab Initio Replica-Exchange Monte Carlo Method for Cluster Studies

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[*Chem. Phys. Lett.* **333**, 199 (2001)]

We have developed and implemented an algorithm for ab initio replica-exchange Monte Carlo simulations based on an ab initio correlated electronic structure theory. The many-body interactions in metal, semiconductor and molecular clusters are described by ab initio correlated method at the level of second-order Moller-Plesset perturbation theory. The replica-exchange Monte Carlo procedure allows for an efficient sampling of the global and low-lying local minima in a single simulation run, and thus, is ideally suited for locating energy minima of complex systems which possess a number of local minima. We have successfully applied the replica-exchange Monte Carlo method to the geometry optimization of the Li_6 cluster.