RESEARCH ACTIVITIES I
Department of Theoretical Studies

I-A 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-A-1 Multicanonical Monte Carlo Simulation of a Small Peptide in Aqueous Solution Based on the RISM Theory

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We report the results of multicanonical Monte Carlo simulation of a penta peptide, Met-enkephalin, in aqueous solution that is based on the reference interaction site model theory. Averages of the energy functions, end-to-end distance, dihedral-angle distributions, and radial distribution functions are calculated as functions of temperature from a single simulation run. This is accomplished by the single-histogram reweighting techniques. It is shown that the peptide is almost fully extended in aqueous solution at all temperatures, while it forms β-turn structures in gas phase at low temperatures.

I-A-2 Replica-Exchange Multicanonical and Multicanonical Replica-Exchange Monte Carlo Simulations of a Small Peptide

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We recently developed the replica-exchange multicanonical algorithm and the multicanonical replica-exchange method for molecular dynamics simulations. In the first method, one first estimate the multicanonical weight factor from a short replica-exchange simulation, using the multiple-histogram reweighting techniques. One then performs a long multicanonical production run. The second method is a further extension of the first in which a replica-exchange production simulation is performed with each replica in multicanonical ensemble. In this article, we develope Monte Carlo versions of the two methods and show that these algorithms are very effective for simulations of a small peptide.

I-A-3 Examination of Parallel Simulated Annealing Using Genetic Crossover

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This paper proposes Parallel Simulated Annealing using Genetic Crossover (PSA/GAc). In this algorithm, there are several processes of Simulated Annealing (SA) working parallel. To exchange information between the solutions, the operation of genetic crossover is performed. Through the continuous test problems, it is found that PSA/GAc can search the solution effectively. The proposed algorithm is also applied to the prediction of protein tertiary structure. Comparing PSA/GAc to the conventional algorithm, it is also found that PSA/GAc is an effective algorithm for real world problems.

I-A-4 Solvent Effects on the Free Energy Landscape of a Short Peptide

SUGITA, Yuji; OKAMOTO, Yuko

We have studied the effects of solvent on the free energy landscape of a short peptide, Met-enkephalin, by carrying out the molecular dynamics simulations both in vacuum and in aqueous solution with explicit water molecules. The replica-exchange multicanonical algorithm, which has been recently developed by us, was employed to sample a wide conformational space. The results of the simulations were analyzed by the histogram reweighting techniques and principal component analyses. By comparing the free energy landscape in water with that in vacuum, we found that the free energy landscape is significantly changed by the solvent effects. The dependence of the free energy landscape on the different force fields is also discussed.

I-A-5 Comparison of the Numerical Efficiency of Three New Generalized-Ensemble Algorithms for Conformational Sampling of a Peptide in Explicit Water

SUGITA, Yuji; OKAMOTO, Yuko

In many systems with rough energy landscape, the conventional molecular dynamics or Monte Carlo simulation tends to get trapped in local-minimum states and cannot sample wide configurational space. To

overcome this difficulty, we have recently developed two new algorithms, namely, replica-exchange multicanonical algorithm and multicanonical replica-exchange method. In this article, we compare the numerical efficiency of these methods with that of the original replica-exchange method in simulations of a peptide with a number of explicit water molecules. We employed the average tunneling time in the energy space as a measure of the sampling efficiency. It has been shown that the sampling efficiency of the new algorithms becomes much greater than that of the original replica-exchange method.

I-B 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-B-1 Generalized-Ensemble Simulations for Systems with First-Order Phase Transition

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Replica-exchange method is a powerful generalized-ensemble algorithm that can alleviate the difficulty of getting trapped in states of energy local minima. The method, however, fails for systems with first-order phase transition. In this article we show that the recently developed algorithms, replica-exchange multicanonical algorithm and multicanonical replica-exchange method, can be successfully applied to systems with first-order phase transition. We present our results, taking the example of the two-dimensional 10-state Potts model.

I-B-2 Li_8 Cluster Structures Studied by *Ab Initio* Replica-Exchange Monte Carlo Method

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Interest in metal, semiconductor, and molecular clusters has been growing explosively in the past two decades due to the experimental advances that have facilitated the study of clusters. Furthermore, theoretical advances have enhanced the ability to interpret experimental results. Still lacking is the ability to routinely determine the structures of clusters. In the previous work, *ab initio* replica-exchange Monte Carlo method was developed and implemented to determine the global and local minimum configurations of Li_6 clusters. Gaussian98 was used for the calculations of the electronic structures. In this work, we discuss results of replica-exchange Monte Carlo simulations of Li_8 clusters.