I-B 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 effectsis 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.

I-B-1 Replica-Exchange Monte Carlo Simulation of a Small Peptide in Aqueous Solution Based on the RISM Theory

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We performed a replica-exchange Monte Carlo simulation of a penta peptide, Met-enkephalin, in aqueous solution that is based on the reference interaction site model (RISM) theory. The RISM theory has been developed from the statistical mechanics of molecular liquids and can calculate the solvation free energy of solure molecules,which depends on temperature. When the total energy depends on temperature, we need to modify the transition probability of replica-exchange process in replica-exchange Monte Carlo simulation. In this paper, we give the formula for the modification of this transition probability and present the results of this simulation.

I-B-2 Comparison of AMBER, CHARMM, OPLS, and GROMOS Force Fields by Generalized-Ensemble Simulations

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In order to succeed in the prediction of protein tertiary structures from the first principles, it is essential that we have an accurate potential energy function, or force field, for the protein system. Commonly used force fields are AMBER, CHARMM, OPLS-AA, and GROMOS. In the present work we try to compare these force fields. Our criterion for good force fields is whether or not molecular simulations of short peptide systems in explicit water can reproduce experimental implications of secondary structure formations such as α-helix and β-hairpin, starting from completely random initial conformations. For this purpose it is very important that we use a powerful simulation algorithm that can avoid getting trapped in states of energy local minima. Generalized-ensemble algorithms are such powerful algorithms. In particular, we use our new generalized-ensemble algorithms, replica-exchange multicanonical algorithm and multicanonical replica-exchange method. Indeed we found very different results depending on the force fields; some contradict with the experiments.

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 An Application of the Multicanonical Monte Carlo Method to the Bulk Water System

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The multicanonical algorithm is based on a non-Boltzman weight factor and produces flat probability distribution of potential energy artificially. The method allows the systemto rove through the complex potential energy surface without getting trapped in a local minimum state, and has been proven to be efficient for studying first-order phase transitions of complex systems such as spin glasses and proteins. One of the features of the method is that the expectation values of thermodynamic properties can be calculated as a function of temperature by applying the histogram-reweighting techniques to the results of one production run. In the present study, we determined the multicanonical weight factor that can produce flat probability distribution of potential energy corresponding to the temperature range from 170 to 630 K. From the peak of the heat capacity, we found a phase transition at 190 K.

The lower energy structures and oxygen-oxygen radial distribution functions imply that the structure at lower temperatures is irregular. However, the average number of hydrogen bonds per water molecule is nearly equal to four at low temperatures, which suggests the formation of amorphous ice.