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 Optimization of Protein Force-Field Parameters with the Protein Data Bank

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[*Chem. Phys. Lett*. **382**, 626 (2003)]

We propose a novel method to optimize existing force-field parameters for protein systems. The method consists of minimizing the summation of the square of the force acting on each atom in the proteins with the structures from the Protein Data Bank. We performed this optimization to the partial-charge and torsion-energy parameters of the AMBER parm94 force field, using 100 molecules from the Protein Data Bank. We then performed folding simulations of α-helical and β-hairpin peptides. The optimized force-field parameters gave structures more consistent with the experimental implications than the original AMBER force field.

I-B-2 Prediction of Transmembrane Helix Configurations by Replica-Exchange Simulations

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[*Chem. Phys. Lett.* **383**, 397 (2004)]

We propose a method for predicting helical membrane protein structures by computer simulations. Our method consists of two parts. In the first part, amino-acid sequences of the transmembrane helix regions are obtained from one of existing WWW servers. In the second part, we perform a replica-exchange simulation of these transmembrane helices with some constraints and identify the predicted structure as the global-minimum-energy state. We have tested the second part of the method with the dimeric transmembrane domain of glycophorin A. The structure obtained from the prediction was in close agreement with the experimental data.

I-B-3 Free Energy Calculations for DNA Base Stacking by Replica-Exchange Umbrella Sampling

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[*Chem. Phys. Lett.* **385**, 1 (2004)]

We have investigated the free energy change of the stacking process of DNA dimers using molecular dynamics simulations based on replica-exchange umbrella sampling. Pairs of replicas with different umbrella potentials are exchanged in this method, which allows the simulation to sample much wider conformational space and, therefore, to yield more accurate free energy profiles than by the conventional umbrella sampling. From the free energy profiles, we observed good stacking for all DNA dimers and sequence-dependent stacking stability. This sequence dependence of the stacking free energy is in accord with the experimental results.

I-B-4 Comparisons of Force Fields for Proteins by Generalized-Ensemble Simulations

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[*Chem. Phys. Lett.* **386**, 460 (2004)]

Secondary structural characteristics of six commonly used force fields for protein systems developed by different research groups have been compared. We performed molecular dynamics simulations of an α-helical polypeptide and a β-hairpin polypeptide with explicit water molecules. Two generalized-ensemble algorithms, replica-exchange multicanonical algorithm and multicanonical replica-exchange method, for efficient sampling of configurational space have been employed. Comparisons of the secondary structure content of polypeptides for different force fields highlighted differences of their structural tendency. The results imply that α-helix is favored for AMBER94 and AMBER99 and that β-hairpin is favored for GROMOS96, while CHARMM 22, AMBER96, and OPLS-AA/L have intermediate tendency.

I-B-5 Prediction of Membrane Protein Structures by Replica-Exchange Monte Carlo Simulations: Case of Two Helices

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[*J. Chem. Phys.* **120**, 10837 (2004)]

We test our prediction method of membrane protein structures with glycophorin A transmembrane dimer and

analyze the predicted structures in detail. Our method consists of two parts. In the first part, we obtain the amino-acid sequences of the transmembrane helix regions from one of existing WWW servers and use them as an input for the second part of our method. In the second part, we perform a replica-exchange Monte Carlo simulation of these transmembrane helices with some constraints that indirectly represent surrounding lipid and water effects and identify the predicted structure as the global-minimum-energy state. The structure obtained in the case for the dielectric constant $\varepsilon = 1.0$ is very close to that from the NMR experiments, while that for $\varepsilon = 4.0$ is more packed than the native one. Our results imply that the helix–helix interaction is the main driving force for the native structure formation and that the stability of the native structure is determined by the balance of the electrostatic term, van der Waals term, and torsion term, and the contribution of electrostatic energy is indeed important for correct predictions. The inclusion of atomistic details of side chains is essential for estimating this balance accurately because helices are tightly packed.

I-B-6 Replica-Exchange Extensions of Simulated Tempering Method

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[*J. Chem. Phys.* **121**, 2491 (2004)]

In this article we consider combinations of two well-known generalized-ensemble algorithms, namely, simulated tempering and replica-exchange method. We discuss two examples of such combinations. One is the previously developed replica-exchange simulated tempering and the other is the newly developed simulated tempering replica-exchange method. In the former method, a short replica-exchange simulation is first performed and the simulated tempering weight factor is obtained by the multiple-histogram reweighting techniques. This process of simulated tempering weight factor determination is faster and simpler than that in the usual iterative process. A long simulated tempering production run is then performed with this weight factor. The latter method is a further extension of the former in which a simulated tempering replica-exchange simulation is performed with a small number of replicas. These new algorithms are particularly useful for studying frustrated systems with rough energy landscape. We give the formulations of these two methods in detail and demonstrate their effectiveness taking the example of the system of a 17-residue helical peptide.

I-B-7 Self-Assembly of Transmembrane Helices of Bacteriorhodopsin by a Replica-Exchange Monte Carlo Simulation

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[*Chem. Phys. Lett.* **392**, 168 (2004)]

We examine by a molecular simulation whether or not the transmembrane helices of bacteriorhodopsin have the ability to self-assemble into the native configuration by themselves. Starting from random initial configurations of seven transmembrane helices, the same helix arrangement as the experimental one (PDB code: 1C3W) was obtained by a replica-exchange Monte Carlo simulation. This implies that helix–helix interactions are the main driving force for the native structure formation of bacteriorhodopsin.

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 New Approach to the First-Order Phase Transition of Lennard-Jones Fluids

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[*J. Chem. Phys.* **120**, 7557 (2004)]

The multicanonical Monte Carlo method is applied to a bulk Lennard-Jones fluid system to investigate the liquid-solid phase transition. We take the example of a system of 108 argon particles. The multicanonical weight factor we determined turned out to be reliable for the energy range between 27.0 and 24.0 kJ/mol, which corresponds to the temperature range between 60 and 250 K. The expectation values of the thermodynamic quantities obtained from the multicanonical production run by the reweighting techniques exhibit the characteristics of first-order phase transitions between liquid and solid states around 150 K. The present study reveals that the multicanonical algorithm is particularly suitable for analyzing the transition state of the first-order phase transition in detail.

I-C-2 Molecular Dynamics Simulations in the Multibaric-Multithermal Ensemble

OKUMURA, Hisashi; OKAMOTO, Yuko

[*Chem. Phys. Lett.* **391**, 248 (2004)]

We propose a new generalized-ensemble molecular dynamics simulation algorithm, which we refer to as the multibaric-multithermal molecular dynamics. This is the molecular dynamics version of the recently proposed multibaric-multithermal Monte Carlo method. The multibaric-multithermal simulations perform random walks widely both in the potential-energy space and in the volume space. From only one simulation run, therefore, one can calculate isobaric-isothermal-ensemble averages in wide ranges of temperature and pressure. We test the effectiveness of this algorithm by applying it to a Lennard-Jones 12-6 potential system.

I-C-3 Monte Carlo Simulations in Generalized Isobaric-Isothermal Ensembles

OKUMURA, Hisashi; OKAMOTO, Yuko

[*Phys. Rev. E* **70**, 026702 (2004)]

We present three generalized isobaric-isothermal ensemble Monte Carlo algorithms, which we refer to as the multibaric-multithermal, multibaric-isothermal, and isobaric-multithermal algorithms. These Monte Carlo simulations perform random walks widely in volume space and/or in potential energy space. From only one simulation run, one can calculate isobaric-isothermal-ensemble averages in wide ranges of pressure and temperature. We demonstrate the effectiveness of these algorithms by applying them to the Lennard-Jones 12–6 potential system with 500 particles.