論文の内容の要旨

論文題目

Exploration of free energy profiles of proteins

with enhanced sampling methods

（エンハンスドサンプリング手法を用いたタンパク質の自由エネルギー地形の探索）

氏　　名　　近藤　寛子

Molecular dynamics (MD) simulation is a powerful tool for analyzing the dynamic and thermodynamic properties that are experimentally inaccessible. However, the time scale of biologically significant events, such as the protein folding and conformational transition of proteins, substantially exceeds the time scale that can be achieved with MD simulation. Although special purpose computers have recently enabled the micro- to millisecond scale simulation of proteins, the millisecond scale is difficult to achieve with general-purpose computers and not even sufficient for studying biological phenomena. Therefore, it is important to develop enhanced sampling methods, which form one approach that can be used to investigate protein function. A difficulty in calculating the free energy landscape of biomolecules lies in the sampling of their rugged energy surface and the determination of appropriate reaction coordinates. The complex energy surface of biomolecules prevents sampling of the broad conformational space, by trapping the system in local minima. Solving the problem of "local minimum trapping" would enable the exploration of free energy landscapes along certain appropriate reaction coordinates. This would, in turn, help us gain a better understanding of the thermodynamical properties of proteins.

Here three studies involving computer simulations were conducted to accelerate conformational sampling and explore the free energy landscape of proteins. The first study was aimed at calculating the

free energy landscape along reaction coordinates appropriate in protein functions. The following two studies aimed to develop efficient sampling methods to overcome difficulties experienced in the first study.

In the first study, entitled "**Free energy landscapes of protein domain movements upon ligand binding**" (Chapter II), we investigated the mechanism by which conformational transitions are induced in proteins upon ligand binding, by exploring the free energy profiles of two types of proteins. Free energy profiles were calculated using the umbrella sampling method, resulting in an observed difference between the free energy profiles of the apo- and holostates. However, high computational costs and the inaccuracy of free energy calculations owing to insufficient sampling were identified as the main difficulties in conducting further studies. The next two studies focused on developing a method for enhancing conformational sampling.

In one of these two studies, entitled "**Enhanced exchange algorithm without detailed balance condition for replica exchange method**," describes a methodological study conducted to enhance sampling efficiency. In this study, we proposed and validated a new algorithm for the exchange process in the replica exchange method (REM), whose application is described in Chapter IV. We developed exchange criteria that do not fulfill the detailed balance condition, unlike existing algorithms for the efficient exchange between replica pairs. Test simulations of the alanine dipeptide and chignolin confirmed the correctness and improved sampling efficiency of our method.

Chapter IV, entitled "**Improvement of sampling efficiency through combined use of molecular dynamics simulations with implicit and explicit solvent models**", we attempted to improve the sampling efficiency of simulations with an explicit solvent model by adopting the results obtained from those with an implicit solvent model. In this study, REM for conformational sampling was used, as it does not require the determination of reaction coordinates. With advances in computing power, REM has increasingly been used for biomolecular simulations. Conformational sampling of a small protein, chignolin, was performed to examine the efficiency of the new method. The results of the new method revealed a significant reduction in the computational cost compared with that of conventional temperature REM.