Thesis abstract

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Development of CαGō model including side-chain effect and application to analyses of folding mechanisms

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Abstract

Simplified model is required to understand a specific aspect in folding because it still remains hard to reproduce entire mechanisms of folding process with current computational technology

In the second chapter in this thesis, I attempted to improve performance of CαGō model by including two side-chain effects, heterogeneity of inter-residue interaction energies and geometrical restraints depending on effective side-chain orientations. Our model reproduced folding mechanisms resemble with the results of all-atom Gō model for protein L and protein G, and the results showed that the effect of effective side-chain orientation bring high cooperativity as topologies get complicated.

Though understanding of overview of protein folding mechanisms has been developed, details of folding processes are still not clear. For example, precise picture in each transition in the folding processes of multi-state proteins is still not clear. In this study, I attempted to analyze folding processes for multi-state proteins by means of our model.

In the third chapter, folding mechanisms of three ferredoxin-like fold proteins were analyzed. The results reproduced the differences between the three-state protein (U1A) and two-state proteins (ADA2h and S6). The results also suggested that the number of transitions is affected by the stabilities of the folding core and the difference in loop length connecting cores.

In the fourth chapter, the characteristics of independently foldable sub-structure (foldons) and the relationship between the number of foldons and the free energy profile were analyzed by applying our model to simulate many multi-state proteins. The results showed that each foldon can be partly overlapped with other foldons and discrete segments sometimes construct one foldon contrary to the original definition. It is also suggested that differences in stabilities in each foldon play a critical role for multiple transitions.