Interplay among folding, binding, and allostery of proteins

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Abstract

Despite some new discovery of protein dynamics such as the intrinsically disordered proteins, molecular dynamics for each of folding, binding, and allostery of proteins is well studied, at least for traditional proteins. However, the interplay among these three, which is quite common in nature though, has not been described as thoroughly as for isolated processes yet. This review concentrates on the recent progress in molecular dynamics (MD) simulation of this interplay mechanism, where a computational model is constructed and proved valid. However, complete experimental study is not yet implemented studying detailed interaction in molecular dynamics.

1 Introduction

Concerning study of protein dynamics, many experimental and theoretical/computational facilities have been developed. In the experimental facet, mature instruments include single-molecule force spectroscopy, solution NMR [5], CryoEM [4]. While in the theoretical/computational approach, people have developed a series of models, both all-atom and coarse-grained, in describing distinct processes of proteins, examples of which is the Off-Lattice Go Model for folding, multiple-basin model for allosteric motion, explicit and implicit ligand models for binding [2]. In biological systems, combined process of the above processes is quite common and of biological significance. In reality, models for combined processes between two of them was already developed for a relatively long time. For instance, binding process can modify energy

basin in multi-basin model [5]. However, A complete depiction of coupled processes involving all three motion of folding, binding, and allostery has been developed just recently.

2 Discussion

Recently, [3] constructed a compact model integrating all three motions — folding, binding, and allostery of proteins. For binding, they utilize the the atomic interaction-based coarse-grained (AICG) model, which captures both sequence and topological information. For allostrism, they employ the multi-basin model. And for binding of ions, they use an implicit ligand-binding model. The detailed mathematics of their model can be accessed in the SI of their original paper.Calmodulin N- and C-terminal domain are taken as the model protein. Each domain contains two EF hands for binding of Ca^{2+}, and qualitatively we know binding of ions induces a conformational transition from closed to open state.

The model is proved effective and revealed additional results in the following aspects (some of which directly quoted from [3]:

Calmodulin Domain Under Constant Mechanical Extension MD simulation gives the force trajectory agreeing with experiments and previous MD simulation results. In addition, Q value [1] trajectory indicates that there is hidden state that cannot be directly detected by force measurement.

Calmodulin Domain Near Denaturation Temperature A strong correlation between concentration of Ca^{2+} and population in different states is shown. Results suggest that one EF hand's folding can affect the stability of the other.

Interplay Among Folding, Binding, and Allostery Energy landscape profile reveals different folding pathways coupled with binding and allostery. The coupling feature can be reasoned from results including variation of the ratio of different pathways with distinct $[Ca^{2+}]$ (including the condition where Ca^{2+} is absent), and more directly from the free energy plot against Q_{open} and binding energy. Full length CaM is also studied with results consistent with experiments where a interrelation between two domains is confirmed.

On the basis of the qualitative view talked earlier, MD simulation gives a deeper insight. Statistically, binding of ions induces the opening of the protein structure but not 100% result in the opening. The interplay can be understood in a probabilistic, quantitative way.

What remains unresolved is further and more direct experimental investigation of the interplay mechanism, which should be achieved by innovation of single-molecule experimental facilities, hopefully.

References

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