Complex Intramolecular Mechanics of Protein Machines

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Protein machines perform the function through their internal motion (conformational changes). Many of them consist of two or more domains or subunits, and sometimes form a complex. Signal transduction inside the molecule or complex is essential for their concerted motion. In addition, some proteins can respond to external mechanical signals. For example, the "strain sensor" mechanism in myosins, which controls the affinity to the actin filament according to the force applied to the tail, was experimentally shown by Iwaki *et al.* [1].

Since it is difficult to trace internal motion of a whole molecule by experiments, molecular dynamics (MD) simulations are commonly used. MD simulations with external forces, called steered MD (SMD), are convenient for investigations of molecular responses to signals. However, the computational cost of all-atom MD simulations is extremely high, as the cycle-time of the machine operation is typically on the order of microseconds to seconds.

To reduce the computation, we adopted elastic network modeling (ENM) of proteins. In ENM, each amino-acid residue is represented by a point-like particle, and the interactions between them are modeled by linear (Hookean) springs. We have shown that a variety of protein machines share mechanical features that facilitate well-defined ordered motion, convenient for machine operation under fluctuations, by comparing their relaxation processes with those of artificially generated structures [2,3]. We also employed SMD simulations of ENM, to probe mechanical signal transduction in proteins. Possible mechanical transduction pathways involved in the strain sensor mechanism in myosin V [4], and nucleotide-dependent conformational transitions of G-actin [5], were suggested.

In our previous works [4,5], to probe the mechanical sensitivity, 200 simulations with randomly-chosen force directions were performed for each residue (force application point), i.e. more than 10^5 trials in total. In turn, by such a large number of trials, we can roughly survey a huge variety of proteins. Currently, Protein Data Bank (PDB) stores ca. 90,000 structural data sets. As a feasibility study of such large-scale screening, 1 SMD trial for each residue in a similar way to [4,5] was performed. We are searching for proteins particularly with a certain kind of mechanical transduction, e.g. long-ranged or one-way, to elucidate the relationship between the modality of transduction and the molecular structure.

Although ENM is rough and the results need to be confirmed by experiments or more detailed simulations, screening not only by structural features but also by the mechanical properties and dynamics —*Virtual Mechano-Proteomics*— can be a new tool to connect structural and mechanical aspects of molecular machines and reveal their operation mechanisms.

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