FREE ENERGY, KINETICS AND MECHANISMS OF PROTEIN SELF-ASSEMBLY

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Detailed understanding of protein self-assembly (e.g folding, binding, fibril and virus formation) requires knowledge of the free energy landscape, kinetics and mechanisms of these complex processes. Molecular simulation can yield such information directly, for instance by constructing a so-called Markov state model consisting of a coarse-grained network of metastable states between which transitions occur. Analysis of such a network using Markov theory or transition path theory leads to a description of the free energy, kinetics and mechanisms. However, in general, the direct construction of such a network is extremely inefficient, since the time wasted in a metastable state grows exponentially with its stability. Using a network version of transition path sampling, called /single replica transition interface sampling/, we can efficiently sample the entire network. We apply this method to the folding of small model proteins, as well as to diffusive assembly of coarse-grained patchy particles. For the folding of Trp-cage and Villin headpiece we show that we predict experimental timescales and free energies, as well as novel intermediates. For the patchy particle assembly we investigate the influence of rotational diffusion on the network assembly. While changing the diffusion does not alter the free energy landscape, it does change the kinetics, and the mechanism of formation. This suggests a new handle for controlling the self-assembly.

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