Principles of Protein Folding: Insights from Coarse-Grained Modeling

The Levinthal paradox of protein folding is commonly perceived as a statement about the impossibility of folding by a completely random conformational search. Often missed in such narratives is the fact that the question raised by Levinthal was in response to the experimental discovery of two-state, switch-like cooperative folding in the late 1960s, rather than to the problem of conformational search per se. The implication of this understanding on the notion of a funnel-like energy landscape will be discussed. Comparisons between theory and experiment on cooperative folding indicate a prominent role of desolvation barriers. Investigations into the role of desolvation in protein folding also resolves an apparent inconsistency between experimental observations of enthalpic folding barriers and the theoretical funnel picture of folding. Examples will be given to illustrate how important folding principles have been gleaned from studies using native-centric models, including a critical assessment of the diffusion perspective of folding and the concept of preequilibrium, and how nonnative interactions may be treated as a perturbation in essentially the same theoretical framework.

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