Cooperativity, Non-cooperativity and Barriers in Protein Folding

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Many small single-domain proteins with ~ 60-100 amino acid residues undergo cooperative, switch-like folding/unfolding transitions with very low populations of intermediate, i.e., partially folded, conformations. This phenomenon is referred to as cooperative folding. For most natural proteins, cooperativity is likely an evolved trait to guard against disease-causing aggregation. From a biophysical standpoint, cooperativity is a remarkable molecular-recognition feat that has not yet been achieved by de novo experimental design. Therefore, knowing the biophysical basis of folding cooperativity is central to addressing many questions in protein folding and design and to progress in understanding diseases of misfolding. However, folding cooperativity is not readily accounted for by common notions about driving forces for folding. I will discuss how commonprotein chain models with pairwise additive interactions are insufficient to account for the folding cooperativity of natural proteins, and how models with nonadditive local-nonlocal coupling are able to rationalize cooperative folding rates that are well correlated with native topology. For even smaller proteins with ~ 40 residues such as BBL and an NTL9 fragment, our modeling investigations indicate that the difference in their apparent folding cooperativities is at least partly related to their different native topologies. The traditional formulation of folding transition states entails a macroscopic folding free energy barrier with both enthalpic and entropic components. I will explore the microscopic origins of these thermodynamic signatures in terms of conformational entropy as well as desolvation (dewetting) effects.

Intriguingly, the existence of significant enthalpic folding barriers raises fundamental questions about the validity of the funnel picture of protein folding, because such enthalpic barriers appear to imply that there are substantial uphill moves along a microscopic folding trajectory. Using results from extensive atomic simulations, I will show how the paradox can be resolved by a dramatic entropy-enthalpy compensation at the rate-limiting step of folding. In this perspective, the height of the enthalpic barrier is seen as related to the degree of cooperativity of the folding process.

References:
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