PROTEIN FOLDING - SEEING IS DECEIVING

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Abstract

This Perspective is intended to raise questions about the conventional interpretation of protein folding. According to the conventional interpretation, developed over many decades, a protein population can visit a vast number of conformations under unfolding conditions, but a single dominant native population emerges under folding conditions. Accordingly, folding comes with a substantial loss of conformational entropy. How is this price paid? The conventional answer is that favorable interactions between and among the side chains can compensate for entropy loss, and moreover, these interactions are responsible for the structural particulars of the native conformation. Challenging this interpretation, the Perspective introduces a proposal that high energy (i.e., unfavorable) excluding interactions winnow the accessible population substantially under physical-chemical conditions that favor folding. Both steric clash and unsatisfied hydrogen bond donors and acceptors are classified as excluding interactions, so called because conformers with such disfavored interactions will be largely excluded from the thermodynamic population. Both excluding interactions and solvent factors that induce compactness are somewhat non-specific, yet together they promote substantial chain organization. Moreover, proteins are built on a backbone scaffold consisting of a-helices and strands of b sheet, where the number of hydrogen bond donors and acceptors is exactly balanced. These repetitive secondary structural elements are the only two conformers that can be both completely hydrogen-bond satisfied and extended indefinitely without encountering a steric clash. Putting the "bottom line" at the top: *it is likely that hydrogen-bond satisfaction represents a largely overlooked parameter in protein folding models.*

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