

P005 A unifying model links cooperative and hierarchical folding scenarios

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Unifying the mechanisms of protein folding is currently a major challenge in protein science. Here we show that the foldon diffusion-collision (FDC) model provides a unifying framework at least for helical protein. The FDC model reconstructs the folding kinetics in terms of the minimal determinants of folding (foldons) that are detected in the protein's sequence by using a neural network. Foldons are the initiation sites of folding and their aggregation determines the rate-limiting step of the process. The FDC model is successfully applied to a variety of helical proteins (2-state and 3-state) whose folding mechanisms are known to exhibit different degrees of cooperativity. To address the unification issue we define a modularity index to rank the proteins examined according to the hierarchical (or, equivalently, cooperative) character of their own folding mechanism. The modularity index is shown to reflect the experimental characterization of the test proteins. Retrospectively, the index shows that the FDC model covers the whole gamut of folding mechanisms from cooperative to hierarchical. The cooperativity of 2-state and 3-state folders is discussed as well as the changes in cooperativity due to point mutations. The shift from cooperative to hierarchical scenarios is shown to depend critically on the number, stability, length and topology of foldons.