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Predicting Aggregation Propensity from Low-Temperature Conformational Fluctuations

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Abstract : There have been rapid advances in the upstream processing of protein therapeutics, which has shifted the bottleneck to downstream purification and formulation. Finding liquid formulations with shelf lives of up to two years is increasingly difficult for some of the newer therapeutics, which have been engineered for activity, but their formulations are often viscous, can phase separate, and have a high propensity for irreversible aggregation1. We explore means to develop improved predictive ability from a better understanding of how protein-protein interactions on formulation conditions (pH, ionic strength, buffer type, presence of excipients) and how these impact upon the initial steps in protein self-association and aggregation. In this work, we study the initial steps in the aggregation pathways using a minimal protein model based on square-well potentials and discontinuous molecular dynamics. The effect of model parameters, including range of interaction, stiffness, chain length, and chain sequence, implies that protein models fold according to various pathways. By reducing the range of interactions, the folding- and collapse- transition come together, and follow a single-step folding pathway from the denatured to the native state2. After parameterizing the model interaction-parameters, we developed an understanding of low-temperature conformational properties and fluctuations, and the correlation to the folding transition of proteins in isolation. The model fluctuations increase with temperature. We observe a low-temperature point, below which large fluctuations are frozen out. This implies that fluctuations at low-temperature can be correlated to the folding transition at the melting temperature. Because proteins “breath” at low temperatures, defining a native-state as a single structure with conserved contacts and a fixed three-dimensional structure is misleading. Rather, we introduce a new definition of a native-state ensemble based on our understanding of the core conservation, which takes into account the native fluctuations at low temperatures. This approach permits the study of a large range of length and time scales needed to link the molecular interactions to the macroscopically observed behaviour. In addition, these models studied are parameterized by fitting to experimentally observed protein-protein interactions characterized in terms of osmotic second virial coefficients.

Keywords : protein folding, native-ensemble, conformational fluctuation, aggregation
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