Protein Folding Dynamics from Single Molecule Spectroscopy

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Abstract:

We use single molecule Förster resonance energy transfer (FRET) in combination with other biophysical methods to investigate the structure and dynamics of unfolded and intrinsically disordered proteins. With single molecule FRET, this question can be addressed even under near-native conditions, where most molecules are folded, allowing us to probe a wide range of denaturant concentrations and temperatures. Both distance distributions and distance dynamics are accessible in this way, providing crucial information for a quantitative physical picture of protein folding dynamics.

With these methods, both thermodynamic and structural properties of unfolded proteins can be investigated. For example, we find a compaction of unfolded proteins with increasing temperature, indicating an important role for temperature-dependent interactions within the unfolded chains. The observation of a collapse of similar extent in the extremely hydrophilic, intrinsically disordered protein prothymosin suggests that the hydrophobic effect is not the sole source of the underlying interactions. Circular dichroism spectroscopy and replica exchange molecular dynamics simulations in explicit water show changes in secondary structure content with increasing temperature and suggest a contribution of intramolecular hydrogen bonding to unfolded state collapse.

Similar approaches allow us to study intrinsically disordered proteins (IDPs), which often contain a large fraction of charged amino acids. We find that, in contrast to the compact unfolded conformations that have been observed for many proteins at low denaturant concentration, IDPs can exhibit a prominent expansion at low ionic strength that correlates with their net charge. Charge-balanced polypeptides, however, can exhibit an additional collapse at low ionic strength, as predicted by polyampholyte theory from the attraction between opposite charges in the chain. The pronounced effect of charges on the dimensions of unfolded proteins has important implications for the cellular functions of IDPs.

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