Thermal versus Mechanical Unfolding of a Model Protein: Free Energy Profiles, Configurational Networks and Folding Pathways

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Force is often used as a probe to explore the free energy landscape of macromolecules such as proteins, both experimentally and computationally. Nevertheless, this mechanical load induces a privileged coordinate through which the conformational space is constraint, and the molecule evolves from the folded native structure to the unfolded one [1]. In this sense, it is unclear how the information obtained by these procedures -such as free energy barriers, transition rates or the appearance of intermediate configurations- relates to the actual behavior of the molecule in the absence of the force.

Here, we use a non-Go coarse-grained protein model (BLN46)[2] to explore these questions. We simulate the mechanical and thermal unfolding of the model protein, describing respective free energy landscapes first through one dimensional profiles onto different reaction coordinates and second with Markov State models[3, 4], that do not use any assumed order parameter. As previously described [5], BLN46 exhibits a complex mechanical unfolding mechanism, which surprisingly is not well captured by single reaction coordinates, such as the end-to-end distance or the fraction of native contacts. On the contrary, we find out that thermal unfolding occurs through a much simpler free energy landscape, which can be easily projected onto a single coordinate [6]. Although similar configurations can be compared in both scenarios, the mechanical intermediates are not visited thermally, being configurations created by the pulling force. In this sense, the conformational space visited by an unfolding protein under force is significantly different from that of a free protein, so any kinetic or even thermodynamic magnitude obtained by extrapolation at zero force should be taken with care, as the force can alter essentially the folding pathways.

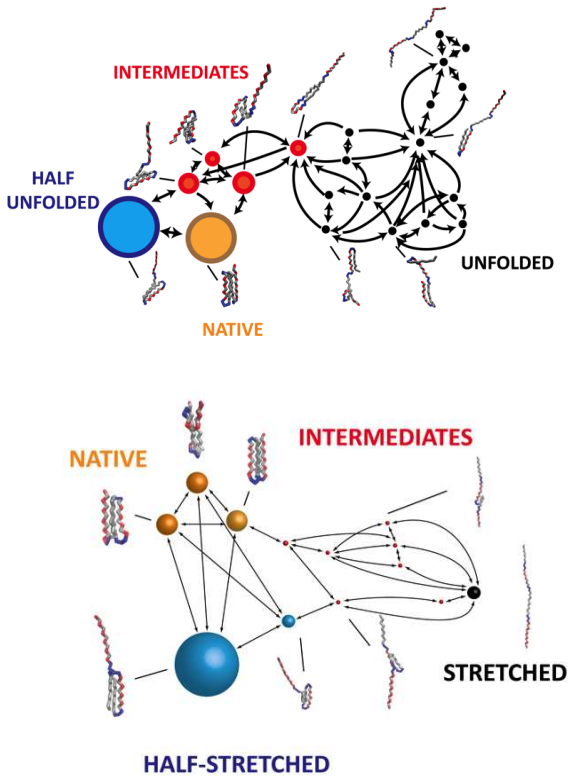

Figure 1: Compared Conformational Spaces or Thermal (top) and Mechanical (bottom) unfolding

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