Novel Scenarios of Protein Unfolding in the Presence of an External Force: Experiments and Simulations

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Single molecule force spectroscopy studies of protein folding dynamics have yielded unprecedented insight into the mechanisms of the folding reaction. Still, they usually allow for a very limited description of the process of interest (e.g. based on the reaction coordinate that is probed experimentally). Molecular simulations --even using very simplified models-- can give a much-enriched view of the underlying molecular events. I will explain the observations on a prototypical two-state folding protein, the cold shock protein, that in the AFM turns out to exhibit multiple intermediate states [1]. Using a very simple topology based model for the protein we show that in fact, this should not come as a surprise. Indeed, force can selectively stabilize different protein intermediates and act in a very different way compared to that of chemical denaturants[2].

[1] J. Schöenfelder, R. Pérez-Jiménez & V. Muñoz, A simple two-state protein unfolds mechanically via multiple heterogeneous pathways at single-molecule resolution, *Nat. Commun.* (2016) 7, 11777.
[2] D. De Sancho & R. B. Best, Reconciling Intermediates in Mechanical Unfolding Experiments with Two-State Protein Folding in Bulk, *J. Phys. Chem. Lett.* (2016) 19, 3798-3803.