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**Protein Folding Transition Paths: Single Molecule Experiments, Theory and Simulations**

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The transition-path is the tiny fraction of an equilibrium, single-molecule trajectory when the transition over a free-energy barrier occurs between two states. In the case of protein folding, the distribution of transition paths contains all of the mechanistic information on how a protein folds and unfolds. Transition path distributions can now be predicted for fast folding proteins by all-atom molecular dynamics simulations and by an Ising-like theoretical model [1,2]. Experimental information on transition paths should provide the most demanding test of both simulations and theoretical models. However, transition-paths for barrier crossings have never been observed experimentally for any molecular system in solution. Because it is a single molecule property, even determining the average transition-path time is challenging. In this presentation, I will discuss how we use measurements of Foerster resonance energy transfer in single molecule fluorescence experiments and a photon-by-photon analysis to measure average transition path times for proteins of different topology and folding rate coefficients using the Gopich/Szabo maximum likelihood method [3.4]. These results, which are surprisingly interesting, are just the first, but important, steps toward measuring intra-molecular distances during individual transition paths. [1] Best, R.B.; Hummer, G.; Eaton. W.A. Native contacts determine protein folding mechanisms in atomistic simulations." Proc. Natl. Acad. Sci. USA 2013, 110, 17874; [2] Henry, E.R.; Best, R.B.; Eaton, W.A. Comparing a simple theoretical model for protein folding with all-atom molecular dynamics simulations. Proc. Natl. Acad. Sci. USA 2013,110, 17880; [3] Chung, H.S.; McHale, K.; Louis, J.M.; Eaton, W.A. Single-molecule fluorescence experiments determine protein folding transition path times. Science 2012, 335, 981; [4] Chung, H.S.; Eaton, W.A.Single molecule fluorescence probes dynamics of barrier crossing. Nature 2013, 502, 685.