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**Kinetics of an ultrafast folding protein analyzed with a free energy surface model<sup>1</sup>**

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Both theoretical and simulation studies have been successful in describing the kinetics of protein folding as diffusion over a one-dimensional free energy barrier, using an order parameter such as the number of ordered residues or the number of native inter-residue contacts as the reaction coordinate. In contrast, experimental results have been analyzed almost exclusively in terms of chemical kinetic schemes, with rate coefficients for transitions between well-defined thermodynamic states. We find that the two-phase relaxation kinetics of the ultra-fast folding villin subdomain following a laser temperature jump cannot be explained by a three-state kinetic model, but is readily explained by diffusion on a one-dimensional, temperature-dependent free energy profile that has a low free energy barrier separating folded and unfolded states. This analysis demonstrates the advantage of physical kinetics compared to chemical kinetics in understanding complex dynamics of protein folding, and should enable a closer connection between experiment and both theory and simulations.

<sup>1</sup>with Jan Kubelka and James Hofrichter