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Direct application of a simple model to the quantitative analysis of experiments on an ultrafast folding protein

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A simple Ising-like statistical-mechanical model for protein folding (Henry and Eaton, *Chem. Phys.* **307**, 163-185, 2004) is used to analyze a broad set of experimental data on the ultrafast folding villin subdomain. In this model each residue in the protein sequence can adopt one of two possible microscopic states corresponding to native and non-native conformations; model protein states are identified with distinct sequences of native/non-native residues. The folding properties of the protein are determined entirely by the map of inter-residue contacts in the native structure. To compute partition functions by complete enumeration of all protein states, only those states are included that contain at most two contiguous sequences of native residues. Native contacts are only permitted between residues lying in such contiguous sequences. The stability of any state of the chain is determined by the offsetting effects of the stabilizing native contacts and the destabilizing entropy losses associated with fixing residues in the native conformation and with closing loops of nonnative residues created by contacts between distinct native sequences. In a least-squares fitting analysis, the temperature-dependent populations predicted by the model for all the protein states, combined with a simple description of the spectroscopic properties of individual states, are used to model the results of spectroscopic and thermodynamic experiments. The model reproduces the temperature dependence of the excess heat capacity, tryptophan fluorescence quantum yield, circular dichroism, and relaxation rates and amplitudes, as well as the effects of site-directed mutants on the folding rates and equilibrium constants.