Abstract

What factors favor protein folding? This is a textbook question. Parsing the experimental free energies of folding/unfolding into diverse enthalpic and entropic components of solute and solvent favoring or disfavoring folding is not an easy task. In this study, we present a computational protocol for estimating the free energy contributors to protein folding semi-quantitatively using ensembles of unfolded and native states generated via molecular dynamics simulations. We tested the methodology on 35 proteins with diverse structural motifs and sizes and found that the calculated free energies correlate well with experiment (correlation coefficient ~ 0.85), enabling us to develop a consensus view of the energetics of folding. As a more sensitive test of the methodology, we also investigated the free energies of folding of an additional 33 single point mutants and obtained a correlation coeffiecient of 0.8. A notable observation is that the folding free energy components appear to carry signatures of the fold (SCOP classification) of the protein.