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Interplay between native state topology and sequence in two-state protein folding

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One of the outstanding questions in protein folding is why the folding into some native state topologies, e.g. all- α folds, are more sensitive to sequence variations than other, more nonlocal protein folds, such as all- β folds? To explore this question, we design and study three 35-54 amino acid sequences within a coarse-grained sequence-based model and show that they fold spontaneously into stable 3α , $4\beta+\alpha$ and β -barrel folds, respectively. Their thermodynamic behaviors, calculated using Monte Carlo techniques, exhibit features in line with experimental data including rank order of folding cooperativity and temperature-driven Hammond shifts of transition states. Using a novel generalized ensemble algorithm (A. Aina and S. Wallin, Journal of Chemical Physics 147, 095102, 2017) we then systematically study the effect of single- and double-point mutations on each of the three proteins. In total, $>2,000$ mutants are studied. We find that the proteins respond to sequence variations in a topology-dependent manner. In particular, the folding landscape of the β -barrel protein is the least perturbed of the three proteins, explaining previously observed mutational robustness of non-local folds. Moreover, we observe a link between the size of conformational fluctuations of these proteins and the divergence exhibited by their respective mutants. One consequence of such a link is that proteins with diverse folding pathways might be more sensitive to sequence variations than proteins with restricted folding pathways.

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