Computational Study of the Biophysics of Protein Conformational Switching

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ABSTRACT: One of the basic tenets of biophysics is that a globular protein, under physiological conditions, folds spontaneously into a unique three-dimensional structure called the native state and that it dictates the biological function of the protein. However, recent experimental observations show that some proteins can undergo drastic structural rearrangements that lead to a complete change of their native folds to alternative functional folds. In order to access the underlying biophysical principles of this conformational switch, we develop and test a generalized-ensemble algorithm for biomolecular simulations that is able to calculate the thermodynamic behavior of many sequences in a single run. By applying this method to a coarse-grained model for protein folding, we explore the folding of thousands of (model) protein sequences and find that successive point mutations can lead to abrupt fold switching. Our method helps to unravel some of the biophysical properties of mutational pathways between elementary (distinct) folds and thus provide a physical explanation of the effects of mutations in conformational switching. In addition, we employ an atomistic model to characterize the fold-switching tendency in the naturally occurring protein RfaH. Our results suggest that the all-α to all-ß fold switch of its carboxyl-terminal domain, in agreement with in vitro experiments, is thermodynamically favored. Providing a physical basis for protein fold switching, and ultimately the ability to design them, may have an extensive impact in biology and biotechnology.

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