Abstract for an Invited Paper
for the MAR05 Meeting of
The American Physical Society

Exploring the protein funnel energy landscape for folding and function\textsuperscript{1}
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Globally the energy landscape of a folding protein resembles a partially rough funnel. Using minimalist model simulations together with analytical theory, we learn about good (minimally frustrated) folding sequences and non-folding (frustrated) sequences. In addition to the need to minimize energetic frustration, the fold topology also plays a major role in the folding mechanism. Some folding motifs are easier to design than others, suggesting the possibility that evolution not only selected sequences with sufficiently small energetic frustration but also more easily designable native structures. We have demonstrated for several proteins (such as CI2 and SH3) that they are sufficiently well designed (i.e., reduced energetic frustration) that much of the heterogeneity observed in their transition state ensemble (TSE) is determined by topology. Topological effects go beyond the TSE. The overall structure of the on-route and off-route (traps) intermediates for the folding of more complex proteins and protein dimers is also strongly influenced by topology. This theoretical framework, simulations of minimalist models and their connections to more computationally-expensive all-atom simulations, we are now in the process of obtaining a quantitative understanding of the folding problem, which allows for a direct comparison to a new generation of folding experiments. Connections between the folding landscape and protein function will also be discussed.

\textsuperscript{1}Center for Theoretical Biological Physics - Supported by the NSF