BIOENGINEERING AND BIOMEDICAL ENGINEERING RESEARCH SEMINAR

COOPERATIVITY, NONNATIVE INTERACTIONS, AND EVOLUTIONARY SWITCHES IN PROTEIN FOLDING

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The Levinthal paradox of protein folding is commonly perceived as stating the impossibility of folding by a completely random search. Often missed, however, is the historical context: The question raised by Levinthal was in response to the experimental discovery of two-state, switch-like cooperative folding in the late 1960s, rather than to the problem of conformational search per se. The physical implication of this understanding on the notion of a funnel-like energy landscape will be discussed. Principles governing cooperative folding can be gleaned from coarse-grained models. Bacterial colicin-immunity proteins Im7 and Im9 are homologous, but they fold by different mechanisms. Im7 tends to fold in a three-state manner via an intermediate but Im9 folding is two-state-like. Our model rationalizes these observations by suggesting that non-native effects in Im7 folding are caused by a higher local hydrophobicity concomitant with a lower local native contact density. How novel folds of proteins may evolve will then be addressed by modeling the folding behaviors of twelve well-characterized GA/GB sequences covering a switch from an all-alpha GA fold to an entirely different four-beta + alpha GB fold. In agreement with experiment, our model exhibits conformational switching from GA to GB upon a single L45Y substitution in the GA98 mutant. The fold preference shows a gradual sequence-dependent change in our model, in line with the latent evolutionary potential concept. Our theoretical findings thus provide a consistent physical picture for rationalizing and predicting non-native effects and conformational switches in protein folding.

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1:00-2:00 PM
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