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Hue Sun Chan
Departments of Biochemistry, of Molecular Genetics, and of Physics, University of Toronto

Principles of Protein Folding: Insights from Coarse-Grained Modeling

The Levinthal paradox of protein folding is commonly perceived as a statement about the impossibility of folding by a completely random conformational search. Often missed in such narratives is the fact that 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 implication of this understanding on the notion of a funnel-like energy landscape will be discussed. Comparisons between theory and experiment on cooperative folding indicate a prominent role of desolvation barriers. Investigations into the role of desolvation in protein folding also resolves an apparent inconsistency between experimental observations of enthalpic folding barriers and the theoretical funnel picture of folding. Examples will be given to illustrate how important folding principles have been gleaned from studies using native-centric models, including a critical assessment of the diffusion perspective of folding and the concept of preequilibrium, and how nonnative interactions may be treated as a perturbation in essentially the same theoretical framework.

Hue Sun Chan was born in Hong Kong and received his B.Sc. in physics from the University of Hong Kong in 1981 and his Ph.D. in physics from the University of California at Berkeley in 1987. He is currently Professor of Biochemistry, Molecular Genetics and Physics at the University of Toronto. Before taking up his appointment at the University of Toronto in 1998, he was Associate Adjunct Professor in the Department of Pharmaceutical Chemistry at the University of California at San Francisco (UCSF). He was trained as a theoretical particle physicist at the University of California at Berkeley (1981-1987). However, since his postdoctoral years at UCSF (1987-1989), his research interest has turned to theoretical and computational biophysics. His current research interests include protein folding, role of solvation in the properties of biomolecules, protein-protein interactions involving intrinsically disordered proteins, molecular evolution, and DNA topology. Prof. Chan is a member of the Editorial Board of Proteins: Structure, Function, and Bioinformatics. He has published about 115 scientific papers which have received over 8,500 citations.