20.2: Perspectives on Protein Folding Dynamics

These models have helped drive theoretical developments that provide alternate perspectives on how proteins fold:

State Perspective

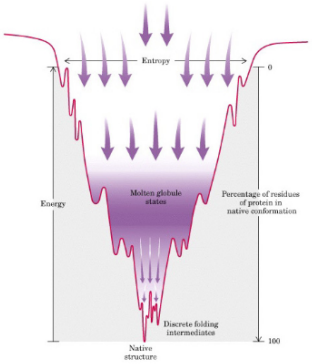
- Interchange between states with defined configurations
- What are the states, barriers and reaction coordinates?

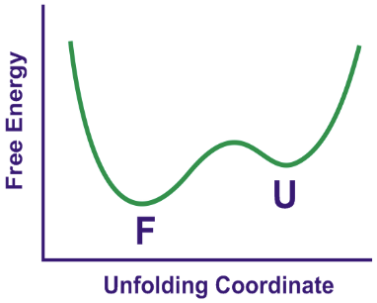
Statistical Perspective

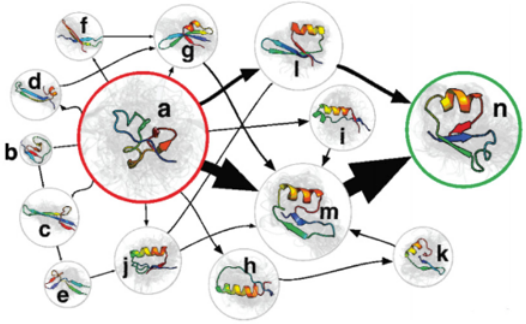
- Change in global variables
- Configurational entropy

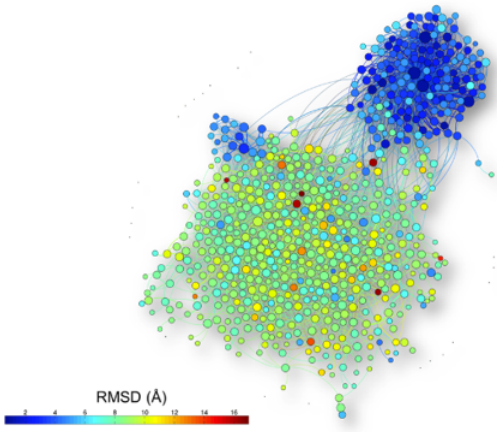
Networks

- Characterize conformational variation and network of connectivity between them.









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The statistical perspective is important. The standard ways of talking about folding is in terms of activated processes, in which we describe states that have defined structures, and which exchange across barriers along a reaction coordinate. And the emphasis is on molecularly interpreting these states. There is nothing formally wrong with that except that it is an unsatisfying way of treating problems where one has entropic barriers.

Folding Funnels and Configurational Entropy

Helps with entropic barriers[1]

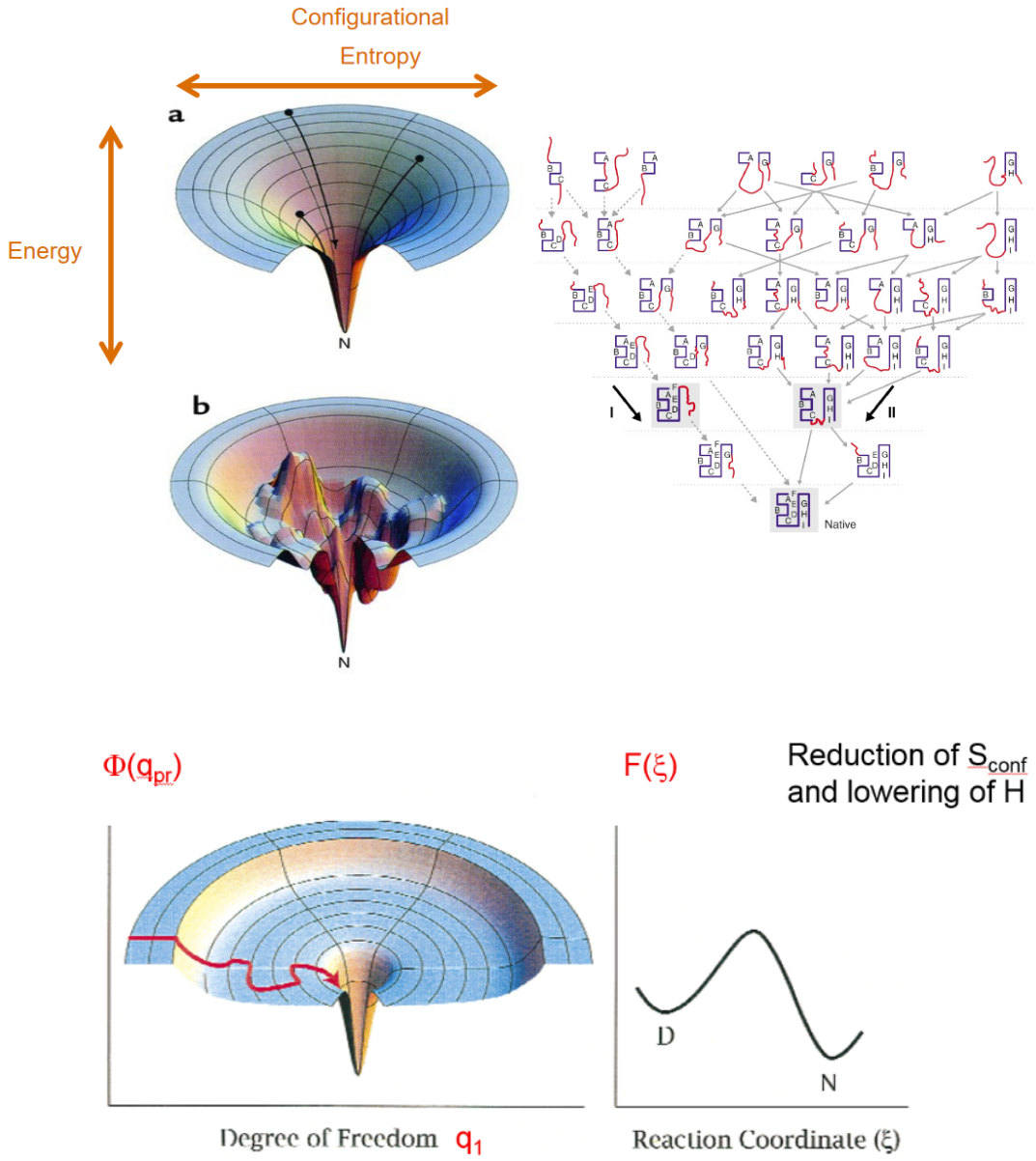

Fig. 5. (A) Energy landscape vs. (B) reaction diagram. A landscape is a free energy F_{micro} of each individual chain conformation vs. the many microscopic degrees of freedom. A reaction diagram is a free energy F_{macro} of an ensemble of molecules, and includes the chain conformational entropy. Here F_{macro} is a function of a single variable, ξ, such as a reaction coordinate. The reaction coordinate is usually not known for protein folding. The red arrow on the landscape indicates a possible micropath, an individual folding trajectory. In this case, the micropath never involves an uphill step, and yet the reaction diagram has a free energy barrier. The barrier is due to the slow entropic search of many different chains seeking the entry to the central steep funnel.

Transition State vs Ensemble Kinetics

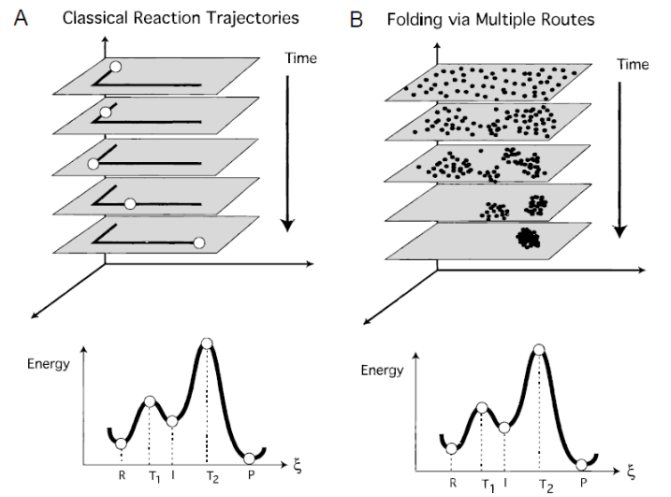

Fig. 8. A: For chemical reactions (energies $\gg kT$), the macrostates on reaction coordinate diagrams correspond to the time series of microstates on the energy landscape. B: For folding processes (energies per interaction $\approx kT$), the observed macrostates may not uniquely specify the time series of microstates on the energy landscape.

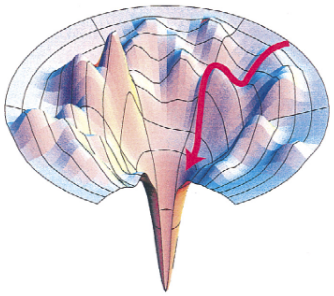

Fig. 9. An uphill micropath (red line) is surrounded by more favorable routes that do not involve uphill steps to reach the native state.

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1. K. A. Dill, Polymer principles and protein folding, Protein Sci. 8, 1166-1180 (1999).
