Anfinsen's Dogma

The native (N) state of a protein is determined by its amino acid (AA) sequence. The N state is unique, stable, and kinetically accessible. **Uniqueness** means that the free energy minimum is sharp, i.e. there's no comparable conformations (states). **Stability** means that the free energy minimum is deep, i.e. a perturbation will not unfold the proteins. **Kinetically accessible** means that the path from the unfolded (U) state to the folded N state must be smooth. **Kinetic accessibility** give rise to the **Levinthal's paradox**.

Protein-Folding Funnel

Excerpts from *Proc Natl Acad Sci USA* 103:1744– 1749, 2006

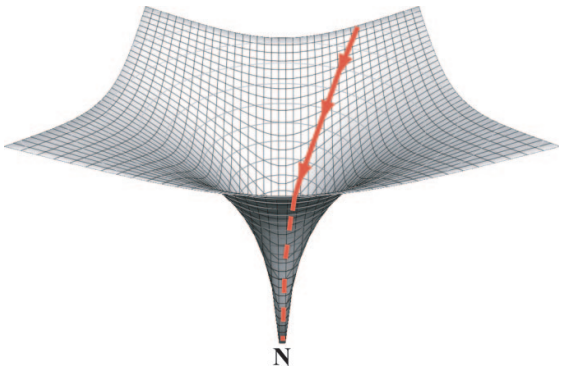
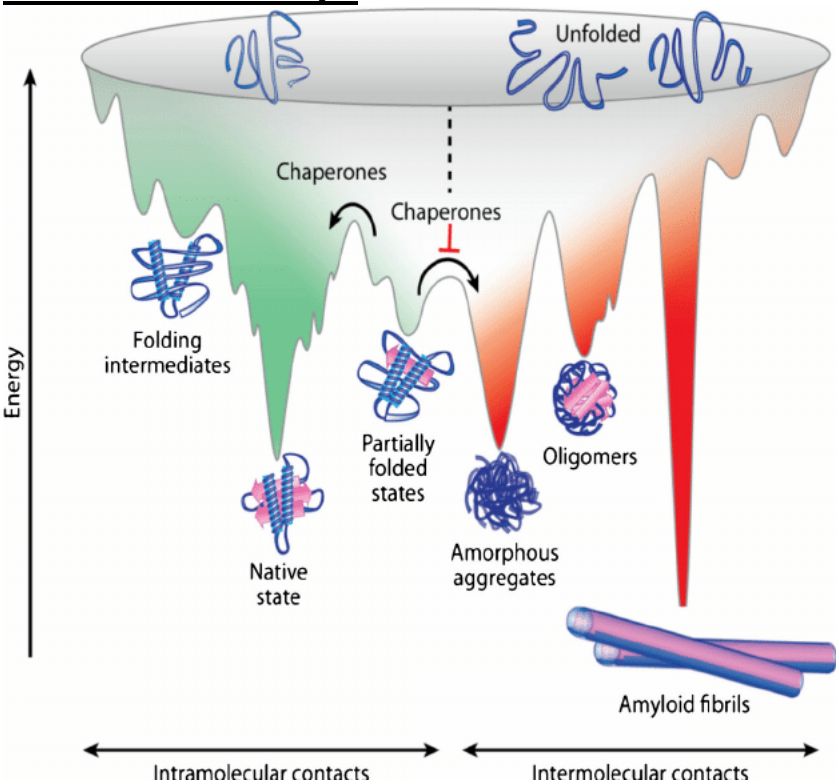


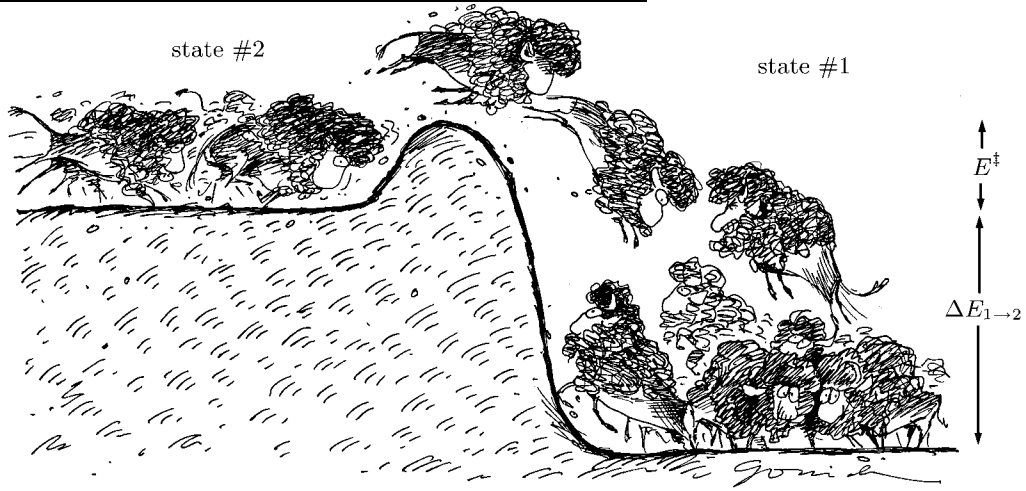
Fig. 3. A folding funnel. The funnel landscape depicts protein folding as a process that proceeds from a high entropy, disorganized state lacking in intramolecular interactions (mouth), to a low entropy, organized state with native intramolecular interactions (spout). Evolution has selected sequences that avoid frustrating traps en route from mouth to spout, smoothing what might otherwise be a rugged landscape. Under folding conditions, individual molecules can follow any route from mouth to spout, like a ball rolling down a free energy hill. One such trajectory is shown here. For a gallery of variant funnel landscapes, see ref. 126.

The Funnel Landscape Is Explicitly Sequence-Dependent. The funnel model describes the behavior of a population of proteins of identical sequence as they wend their way downhill from U to N under folding conditions. Every unique sequence has its own funnel. For example, the globin fold is attained by thousands of different known globin sequences, many of which have only a small fraction of their residues in common (34). Each such globin sequence is associated with its own characteristic folding funnel. All globin sequences are presumed to have evolved so as to adopt the globin fold and to maintain similar overall structural characteristics (35), while simultaneously avoiding frustrating traps and dead ends in transit. The need to avoid unintentional, impeding interactions has long been recognized in protein-design research, where it is called ''negative design'' (36, 37). Neither folding theorists nor protein designers can ignore the inadvertent pitfalls of frustration.

Possible Landscape



Reaction rates and Boltzman Factor



$$S_2 \Leftrightarrow S_1$$

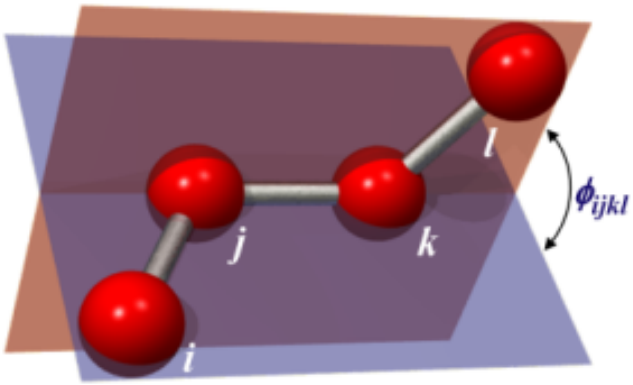
Forward $2 \to 1$, rate $k_+ \propto e^{-\frac{\Delta E^{\ddagger}}{k_B T}}$;

Reverse $2 \leftarrow 1$, rate $k_- = k_+ \propto e^{-\frac{\left(\Delta E^{\ddagger} + \Delta E\right)}{k_B T}}$

$$\Delta E = E_2 - E_1$$

The Ramachandran Plot

Preamble: Dihedral Angle ϕ_{ijkl}, defined by plane ijk, and plane jkl.



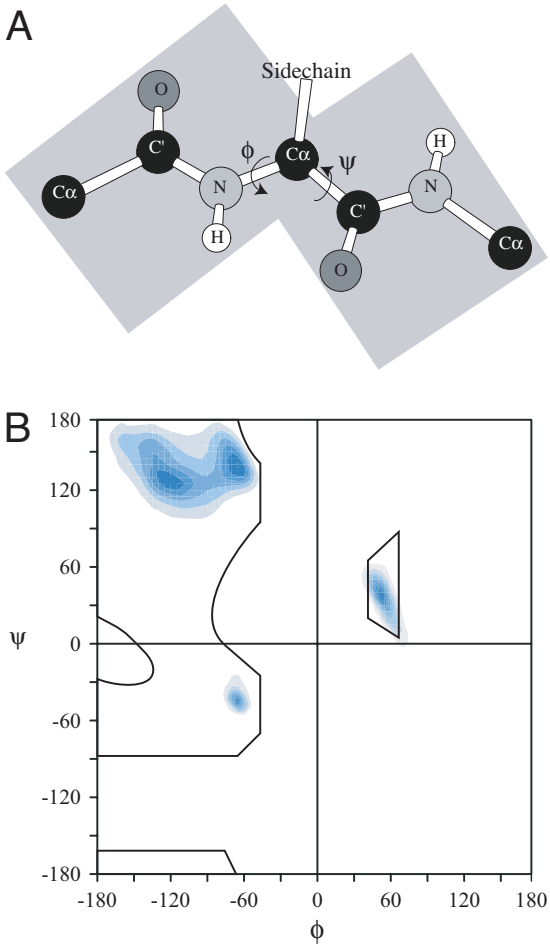


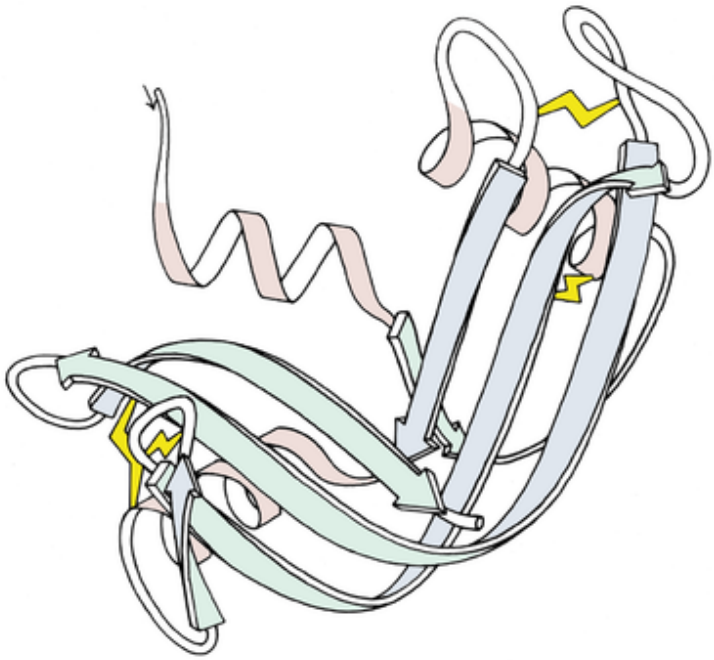
Fig. 2. The peptide unit. (*A*) Degrees of freedom. The peptide bond, Cα-N, has partial double-bond character (23), so the six backbone atoms, -Cα-CO-NH-Cα-, in the peptide unit (shaded rectangles) will be approximately coplanar. Consequently, there are two primary degrees of freedom in each pep- tide unit, the two torsion angles, ϕ and ψ (24). Assuming complete independence of these angles, there would be three staggered configurations per torsion, $3 \times 3 = 9$ conformers per peptide unit, and $9100 \sim 1095$ conformers for a 100-residue protein. (*B*) Residue ϕ, ψ distributions. Sterically allowed ϕ, ψ regions for the alanyl dipeptide, from model studies of Ramachandran and Sasisekharan (25), are shown in dark outline. Other regions are predicted to be unpopulated because their backbone torsion

2A) Definition of dihedral angle ϕ, ψ

2B) Ramachandran Plot of ϕ, ψ showing that only some values of ϕ, ψ are allowed.

New Levinthal's paradox assumes that each amino acid (AA) occupies 9 distinct conformations.

Data on RNASE A



Ribonuclease A

N = 124 AA

Folding time $t_{fold} \sim 1s$

$\Delta H = H_U - H_N = 484 \frac{kJ}{mol}$ and $\Delta S = S_U - S_N = 1.46 \frac{kJ}{K \cdot mol}$