CHEM 153A Week 3

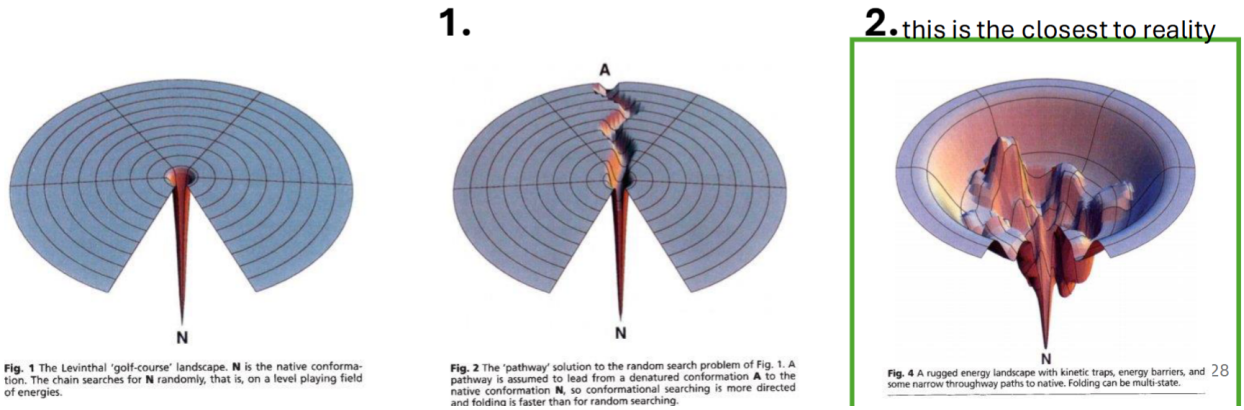
Aidan Jan

January 21, 2025

Protein Folding Continued

More Questions - Levinthal's Paradox

- Other experiments like Anfinsen's raised more questions
  - Denatured proteins refold in 0.1-1000 seconds
  - Take a hypothetical protein with 100 amino acids
  - Due to allowed rotations, amino acids can have 3 conformations
  - That's roughly 3^{100} possibilities ($\approx 5 \times 10^{47}$)
- If the protein can visit one conformation every picosecond (10^{-12} s), searching every possibility would take $5 \times 10^{47} \times 10^{-12}$ seconds, or 1.6×10^{28} years.
- This is the left diagram



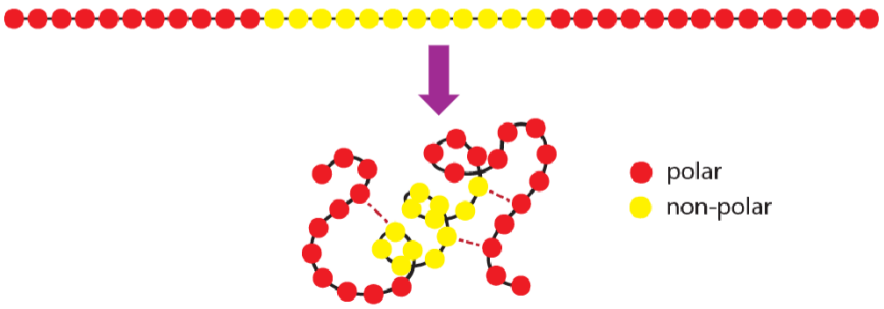
The Thermodynamics of Protein Folding

- Free Energy Funnel:
  - Unfolded states have high degree of conformational entropy, thus there is high free energy.
  - The free energy funnel shows that the closer the protein is to its **native state**, the ideal, lowest energy, folded form, the lower energy it has.
    - The middle diagram suggests that there is a pathway guiding the protein folding to the lowest energy state. This is on the right track, but is not correct.
    - The right diagram states there are multiple stable intermediates leading to the final folded protein. This is the most accurate diagram.

Hydrophobic Collapse → Molten Globule

Hydrophobic collapse is the rapid burying of hydrophobic residues in the center of the protein - they want to escape their watery environment.

- e.g., Val, Leu, Ile, etc.



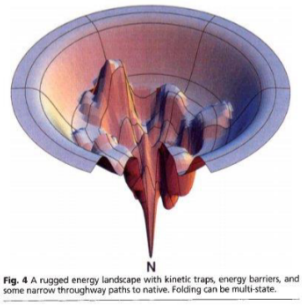
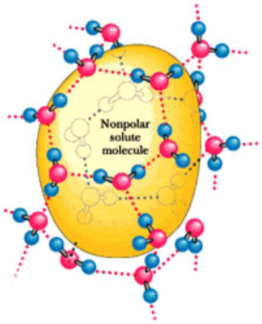
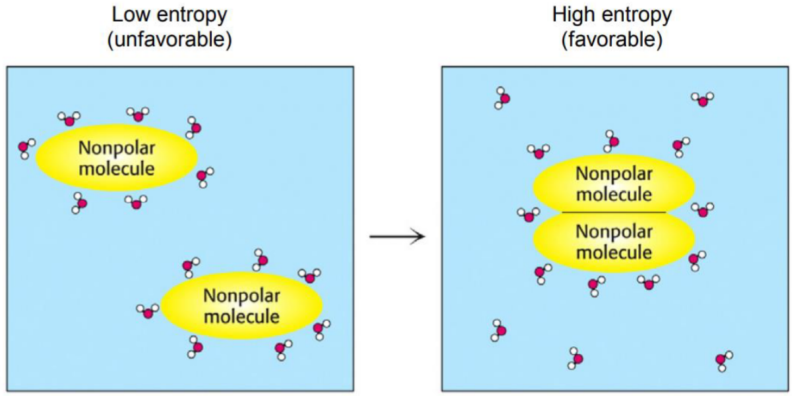


Fig. 4 A rugged energy landscape with kinetic traps, energy barriers, and some narrow throughway paths to native. Folding can be multi-state.

- Hydrophobic collapse is entropy-driven: water molecules become more ordered around hydrophobic residues, and the collapse releases that ordered water, increasing entropy.

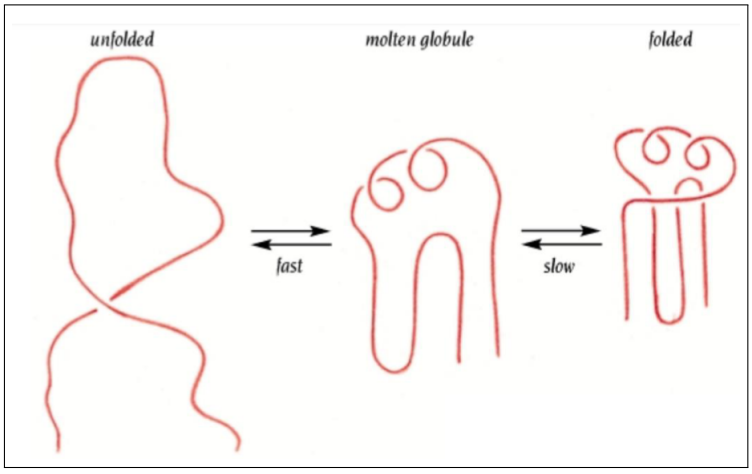


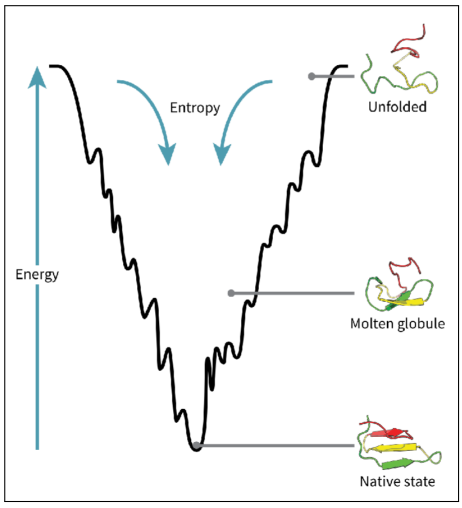
This is called a **clathrate cage**, an ordered structure formed by water when surrounding a nonpolar solute



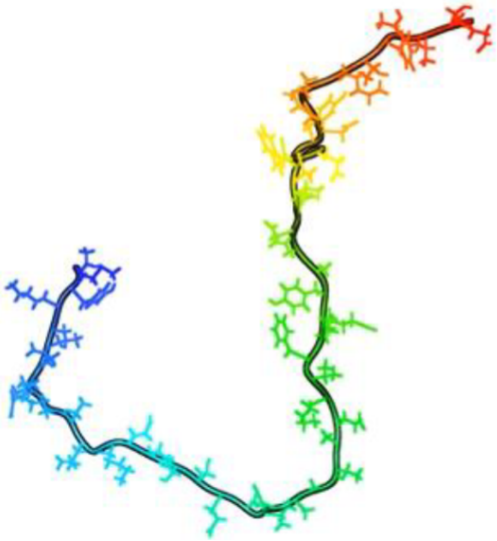
By linking up, **nonpolar molecules reduce the surface area of the cage, increasing entropy**

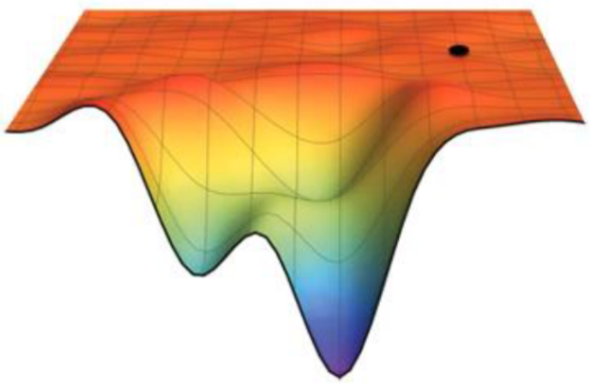
- This collapse forms the **molten globule**, an intermediate transitioning to the final form of the protein





Protein Folding and Energy Landscape





Other Significant Factors in Protein Folding

- **Chain conformational entropy** is the entropy *decrease* due to the formation of an ordered polypeptide
- **Hydrogen bonding** serves an important role, mediating interactions with the surrounding water as well as connecting the outer surface of the protein with the hydrophobic core
  - They also stabilize interactions between peptide chains (secondary structure)
  - Enthalpy decrease
- **London dispersion forces** hold together the hydrophobic core (enthalpy decrease)

Protein Structures

- **Protein segments can adopt regular secondary structures such as the α helix and the β conformation.**
- These structures are defined by particular values of ϕ and ψ and their formation is impacted by the amino acid composition on their segment.
- All of the ϕ and ψ values for a given protein structure can be visualized using a Ramachandran plot.

Secondary Structure

- **secondary structure** = describes the spatial arrangement of the main-chain atoms in a segment of a polypeptide chain
  - *regular* secondary structure = ϕ and ψ remain the sae throughout the segment
  - common types = α helix, β conformation, β turn, random coils

The α Helix is a Common Protein Secondary Structure

- α helix = simplest arrangement, maximum number of hydrogen bonds
  - backbone wound around an imaginary longitudinal axis
  - R groups protrude out from the backbone
  - Each helical turn = 3.5 residues, $\sim$5.4 Å