How Long Does it Take a Protein to Fold?

Levinthal Paradox

The number of non-native configurations outnumber native configuration(s) by such a large amount, that proteins will cannot fold on a reasonable time scale, if the search in configuration space is unbiased.

An Order-of-Magnitude Argument

Consider a 60 residue protein:
Assume 10 conformers/amino acid in the unfolded state:
\[ \rightarrow 10^{60} \text{ non-native configurations} \]
Assume \( 10^{-11} \) seconds per configuration
\[ \rightarrow 10^{49} \text{ seconds to search all configurations. } (10^{42} \text{ years}) \]

* A very long time to find the folded state.*
How Long Does it Take a Protein to Fold?

Experimental Measurements indicate milliseconds to seconds

*Single Molecule Measurements can distinguish the Native from Unfolded States by FRET*
Microfluidic Mixer:
Protein denatured in 4 M GdmCl
Rapidly diluted with buffer to start folding

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Conclusion: *The search of configuration space is not unbiased.*
Folding Model derived from simulation and experiment

**Horizontal Scale:**
Entropy (number of configurations)

**Vertical Scales:**
1. Energies of the configuration
2. Extent of structure formation:
   a. $Q = \text{fraction of native state contact formed}$
   b. $A = \text{number of native state bond angles formed}$

**Distinct Structural States/Folding Stages:**
1. Unfolded
2. Molten Globule
3. Transition State/Glass Transition
4. Discrete folding intermediates
5. Native structure

Fig. 1. Schematic of the folding funnel for a fast-folding 60-residue helical protein according to Onuchic et al. (2). The width of the funnel represents entropy, and depth, the energy. The flow of the molecule through the molten globule, folding bottleneck, or transition state ensemble and a glass transition region where discrete pathways emerge are indicated. The fraction of native contacts correctly made, $Q$, is indicated for each collection of states.

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