Lecture 11:
Protein Folding & Stability

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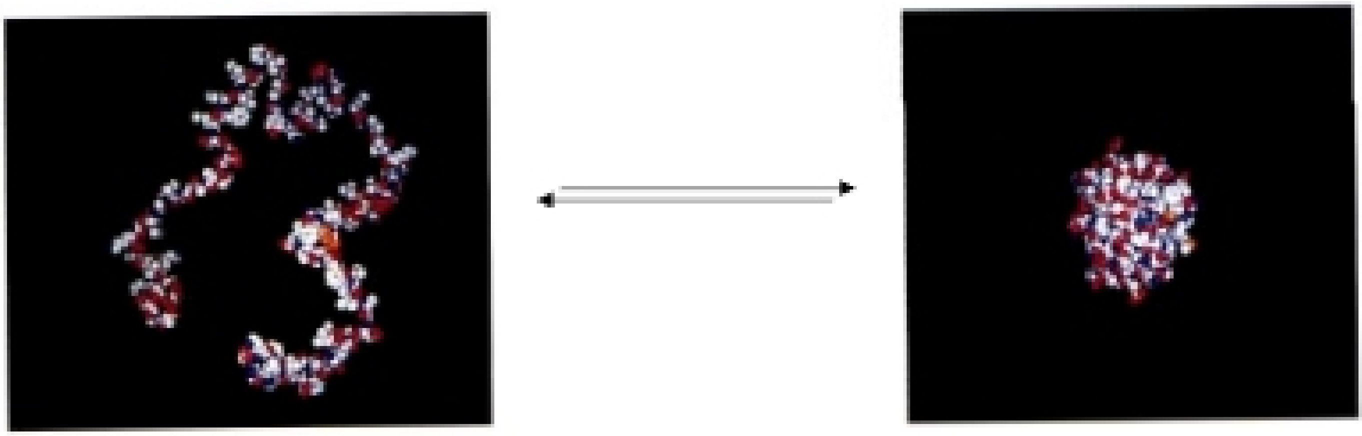
How do we go from an unfolded polypeptide chain to a compact folded protein?



(Folding of thioredoxin, F. Richards)

Protein Folding: What we know

Structure - Function

1). Amino acid sequence dictates structure.
2). The native structure represents the lowest energy state for a protein (physiological conditions).
3). Proteins are densely packed as small organic crystals.

Protein Folding

4). A protein cannot sample all possible conformations in finding its native structure (Levinthal's paradox).
5). Protein folding *in vitro* is a good model for *in vivo* folding.
6). Protein folding is a cooperative process, usually between N <--> U states.
7). Intermediates with non-native structure can exist is some protein folding pathways.
8). The molten globule is likely to be an intermediate on protein folding pathways.

The Future of Folding

9). The protein folding problem will be solved within 5 years (Walter Gilbert, 1988)
10). Designed proteins usually turn out to be molten globules.
11). We will eventually be able to predict protein structure from sequence.

Anfinsen's protein folding experiment

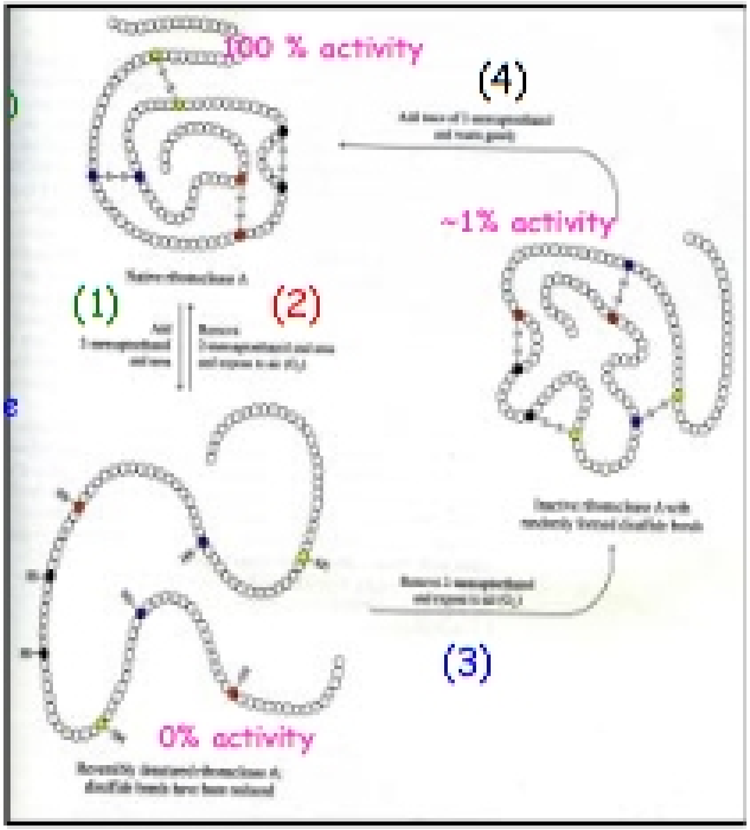
Ribonuclease A

124 aa, pancreatic enzyme

1916-1995

Anfinsen's experiment: sequence dictates structure `57:

Nobel Prize in 1972



(1) a. Reduce protein (β-ME destroys disulfides)
b, Unfold protein in urea

(2) Remove urea - allow protein to refold
Remove β-ME- allow disulfide to reoxidize

(3) Remove β-ME - allow disulfides to reoxidize
Remove urea - alllow protein to refold

(4) Add trace β-ME, warm
~10 hrs ==> 100% ACTIVITY
Add trace β-ME + cytosolic* fraction
~2 minutes ==>100% ACTIVITY

Protein folding

Thermodynamic component: The native structure represents the lowest energy state for a protein

Kinetic component: A protein cannot sample all possible conformations in finding its native structure