

Short Announcements

1st Quiz today: 15 minutes

Homework 3: Due next Wednesday.

Next Lecture, on Visualizing Molecular Dynamics (VMD) by Klaus Schulten

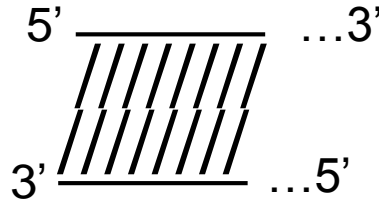
Today's Lecture: Protein Folding, Misfolding, Aggregation

Quiz

You have 15 minutes to answer the following questions

1. Starting with double-stranded DNA, explain step-by-step, the process of making RNA and a protein. Tell about what are (thermodynamically) stable molecules and how to make them chemically reactive, including small molecules or other molecules/proteins which need to interact with them. [You may use drawing in your explanation.]

dsDNA



The Protein Energy Landscape

Largely from Martin Gruebele, Chemistry, Physics UIUC
Also from Maria Spies, Biochemistry, UIUC

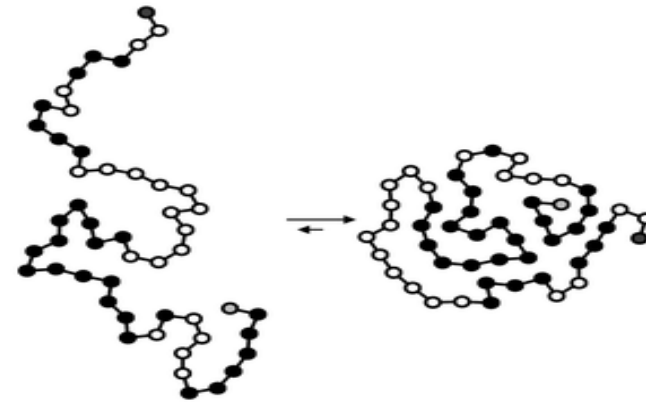
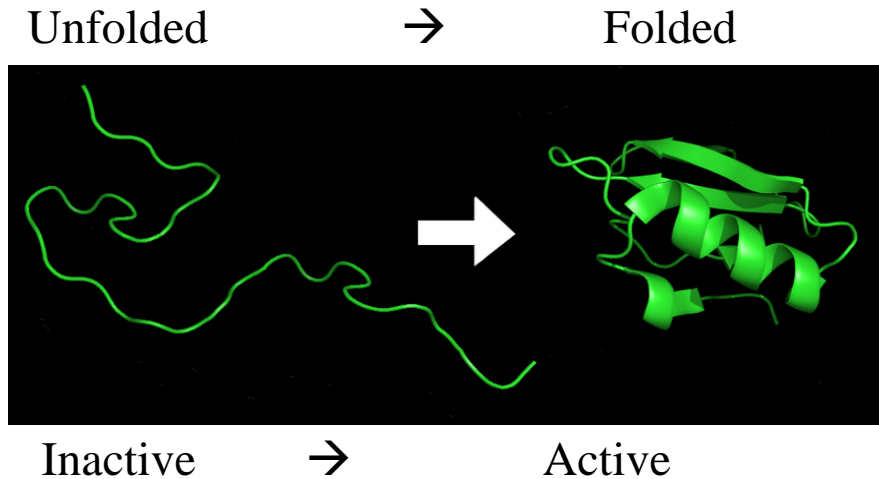
Protein Folding Summary

- Proteins can fold and do so fairly fast (< second).
- In most cases, don't need help. In complicated cases (big proteins, very crowded conditions such as in a cell) proteins get help: proteins called chaperones.
- ΔG is almost always small: (5-10 kT—few H-bonds).
E goes down; S goes down. They compensate.
- Kinetics – fast cause not huge barriers. (Detailed calculations necessary.)
- Protein Funnel is a good model.

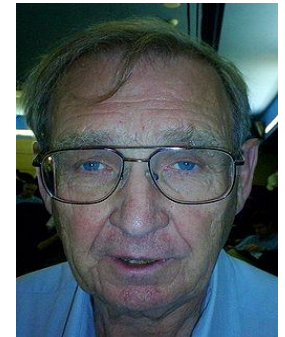
How does a Protein go from unfolded to folded

a) at all; b) in 1 msec; c) with no chaperones?

(Helping proteins)



Hans Frauenfelder,
founder of biological
physics.



Main driving forces:

- 1) Shield hydrophobic (black spheres) residues/a.a. from water;
- 2) Formation of intramolecular hydrogen bonds.

Active areas: 4 centuries on it

Predicting tertiary structures from primary sequence still not solved!

Difficulty relating to experimental observations.

Levinthal's Paradox

Protein folding – the process that results in acquisition of the native structure from a completely or partially unfolded state



Protein folding cannot proceed by purely random search among ALL possible conformations:

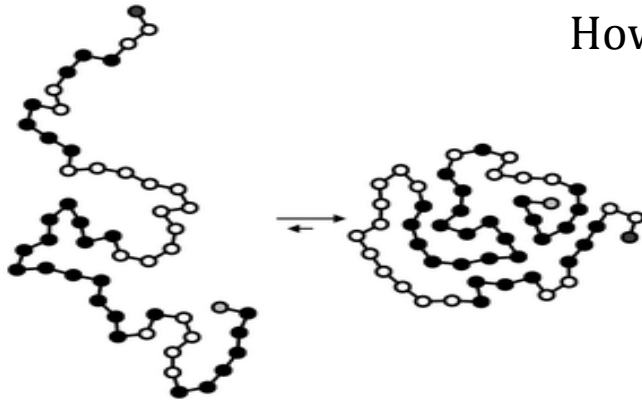
Imagine:

100 aa protein (M.W. 10kDaltons– very small)

Let's say 3 configurations for each step☐

How Many possible configurations? → 3^{100}

It takes at minimum 10^{-15} sec for each step:
(time scale required for bond rotation)

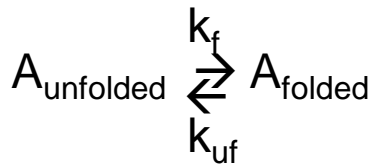


How long to fold?

→ longer than the age of the universe!!!

Proteins: A short, hard life.

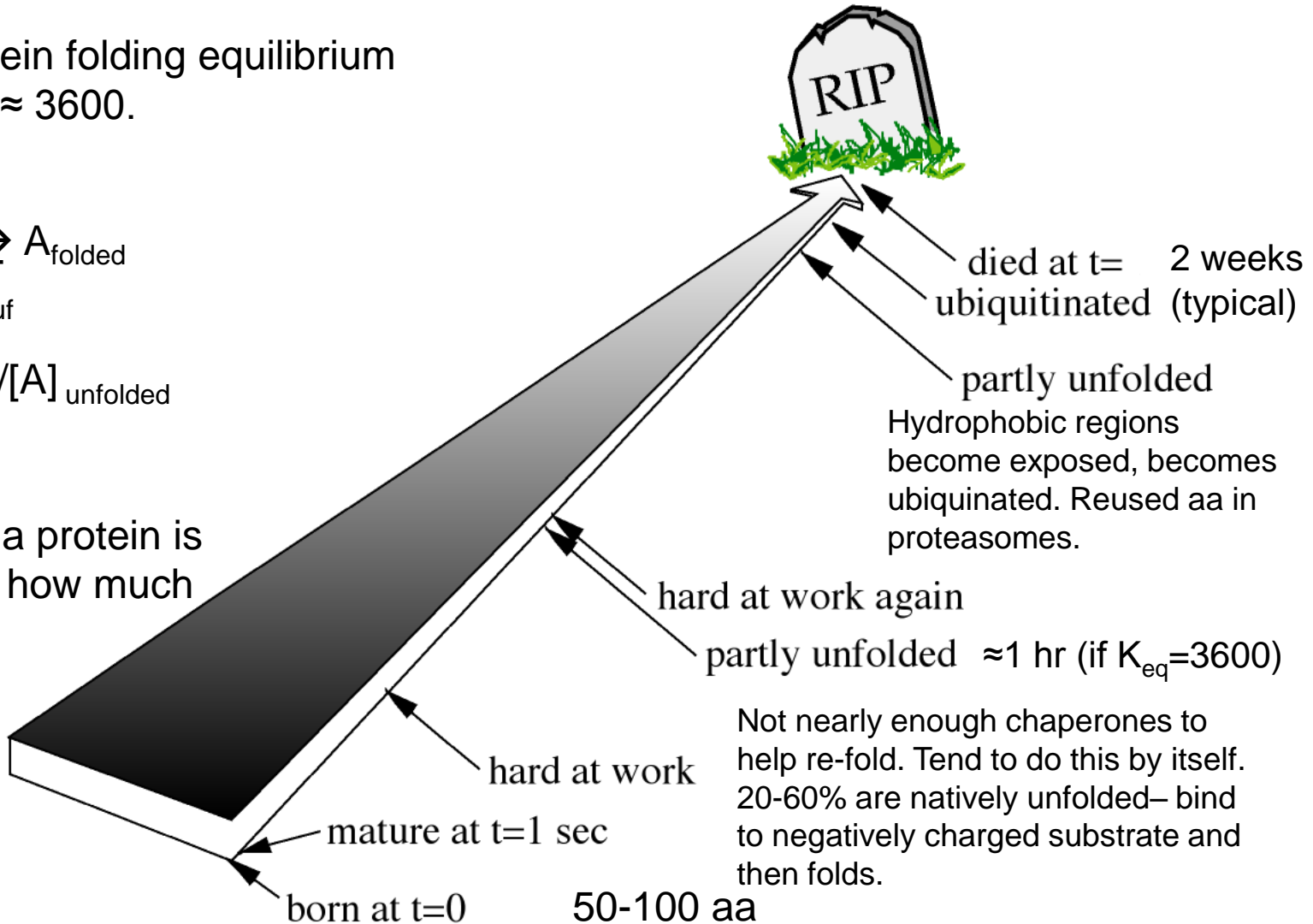
A typical protein folding equilibrium constant $K_{eq} \approx 3600$.



$$K_{eq} = [A_{\text{folded}}] / [A_{\text{unfolded}}]$$

$$= k_{\text{f}} / k_{\text{uf}}$$

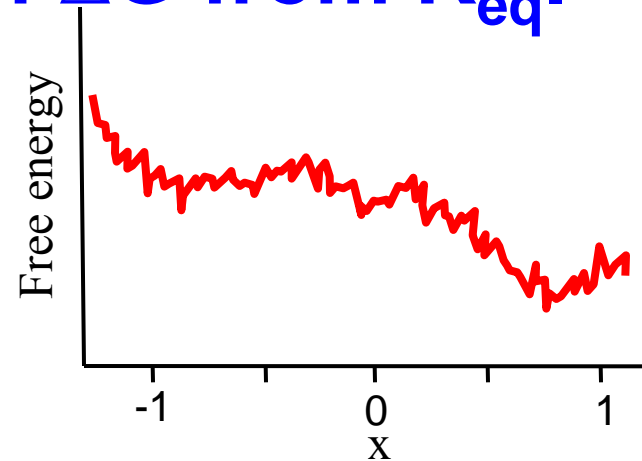
This means a protein is unfolded for how much time/day?
24 sec/day
once/hr!



Simple Calculation of ΔG from K_{eq} .

$$K_{eq} = \exp(-\Delta G/kT) = 1000$$

$$\text{Therefore } \Delta G = 7 k_B T$$

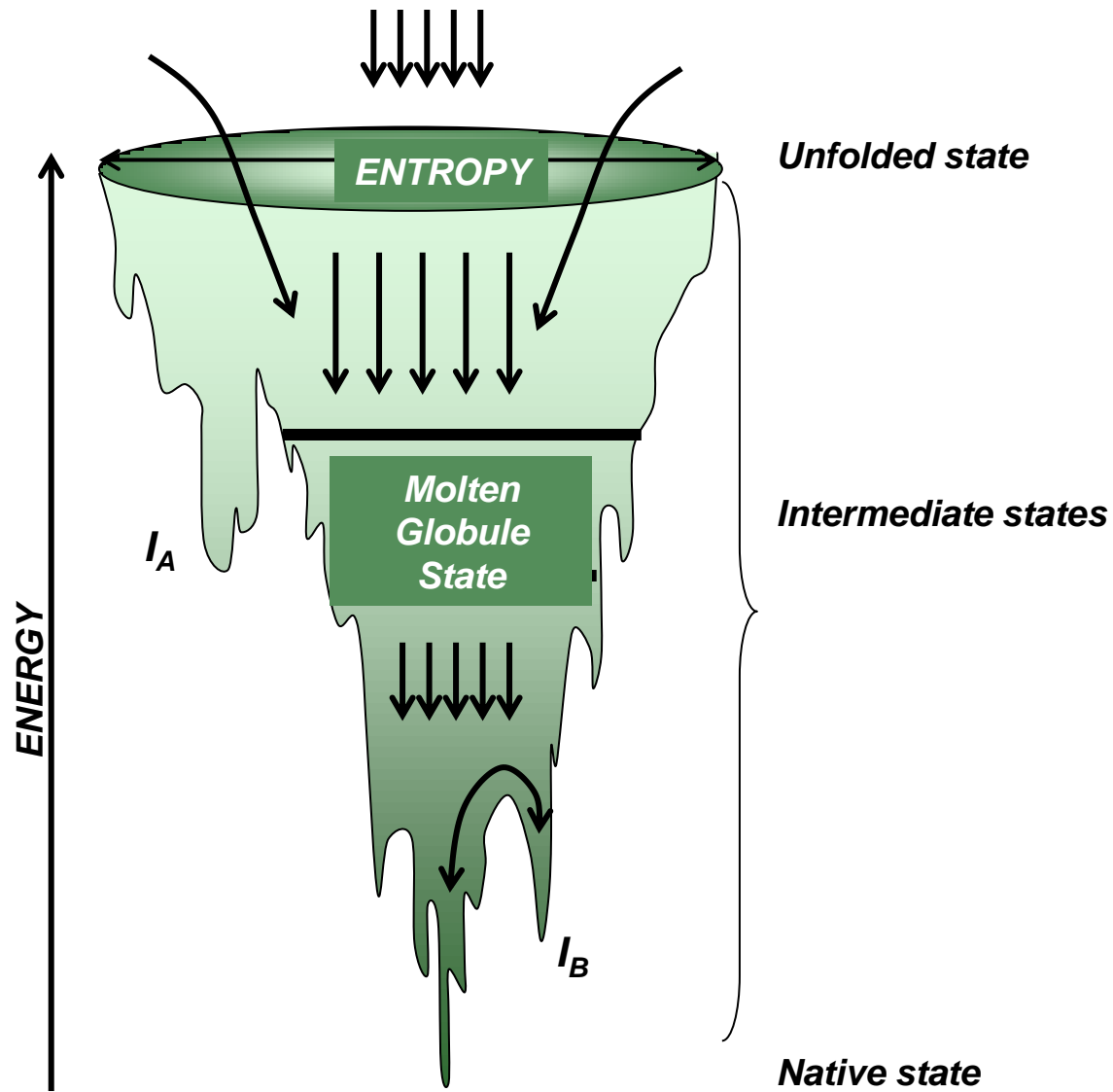


That's equivalent to just a couple of Hydrogen bonds.
 ΔG is (almost flat).

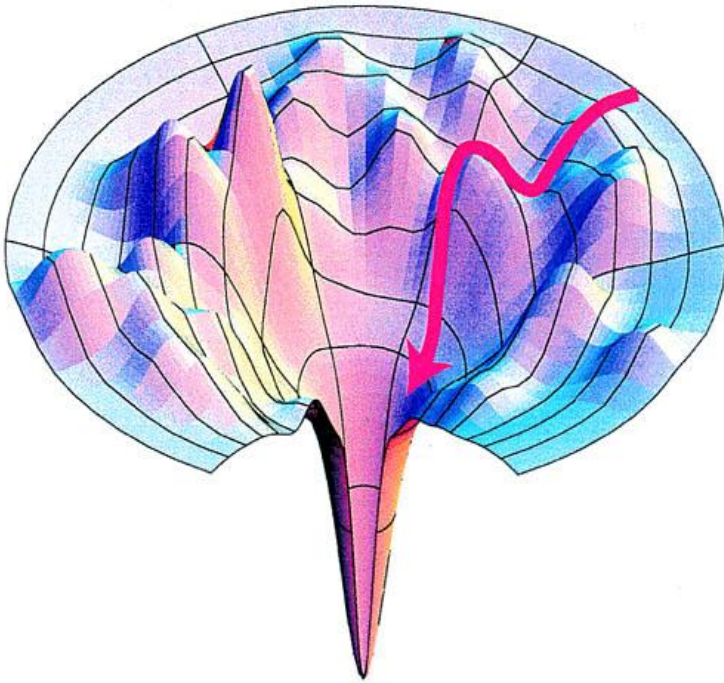
What about ΔE , ΔS ? (Recall: $\Delta G = \Delta E - T\Delta S$)

If ΔS is large and ΔE is large, then ΔG can be small.
This is what happens: ΔE , $T\Delta S \approx -100$'s kJ/mole
(Lots of bonds form but loss of a lot of entropy)

Protein folding: the energy landscape theory

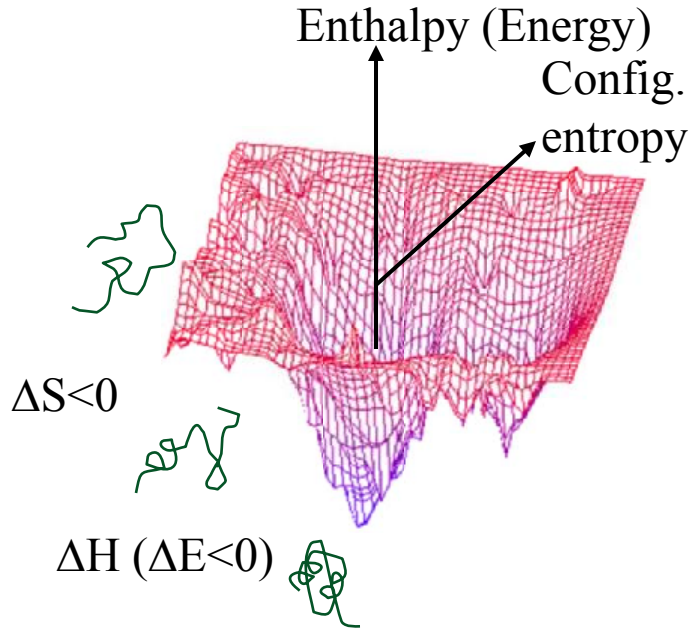


Protein folding: the energy landscape theory

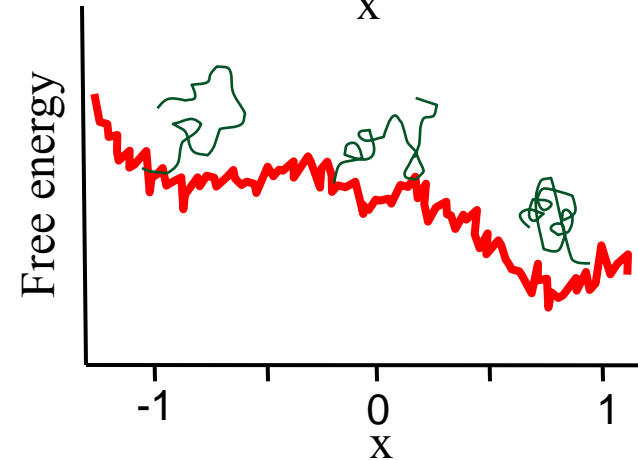
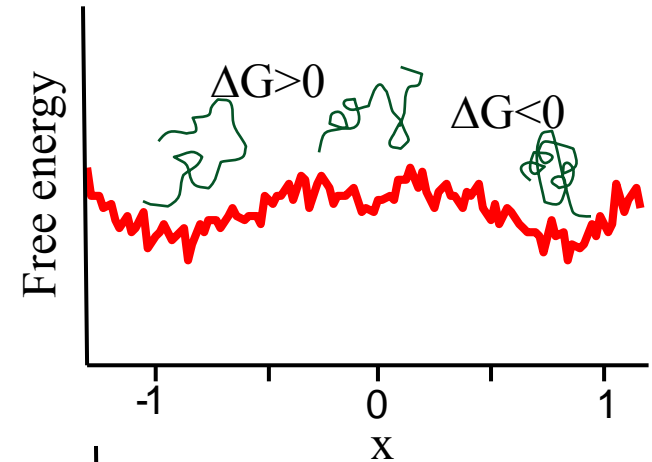


- 1. Fast – (on a ms timescales for single domains). Unfolded proteins “roll downhill” towards smaller populations of conformations.**
- 2. Highly cooperative – intermediates are rarely observed**
- 3. Heterogeneity of the starting points – each unfolded molecule has different conformation and different path downhill the folding funnel**
- 4. In many cases is coupled to translation**

Energy Funnel and Free Energy Surface



$$\Delta G = \Delta H - T \Delta S$$



Work of: Wolynes , Bryngelson, Onuchic,
Luthey-Schulten, Dill, Thirumalai

Example: the lattice model

A simplified model of protein folding:

Only 2-D motion allowed; only 90° motion.

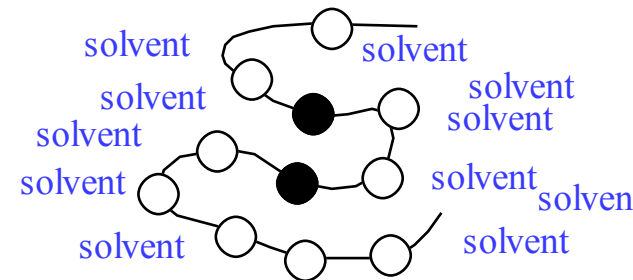
(Real proteins are 3D; are not restricted to 90° rotation.)

- 6-mer peptide (2 hydrophobic and 4 hydrophilic amino acids)
- Each amino acid is represented as a bead
 - Black bead: hydrophobic (H)
 - White bead: hydrophilic (P)
- Bonds represented by straight lines
- H-H (=1000J = 1/3 kT) and P-P (=250J) bonds favorable
- Single 90° rotation per time step allowed.

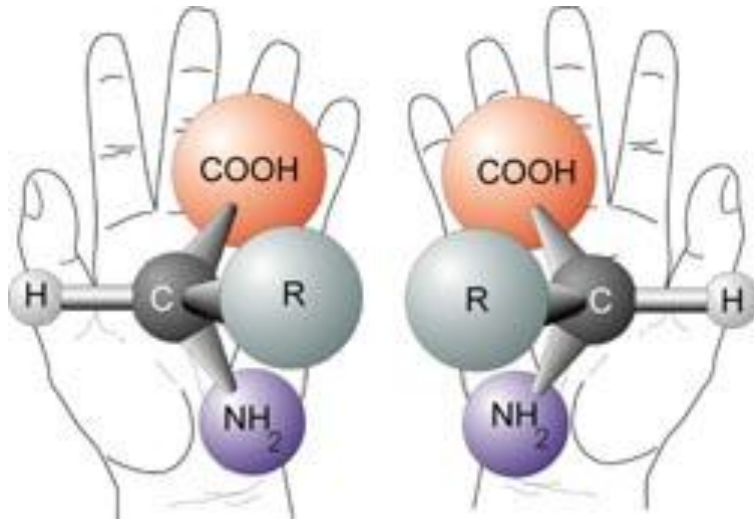
Note: Proteins fold; Peptides don't fold
Peptides have too few H-H and P-P to fold stably.



Core and surface



Chirality in Amino acids

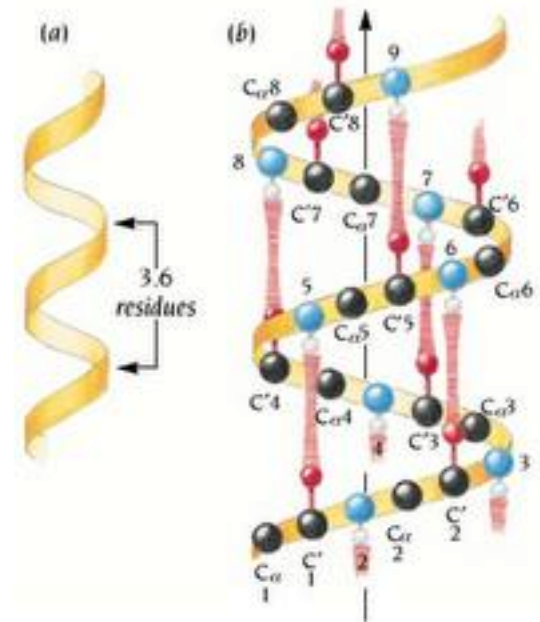


Although most amino acids can exist in both left and right handed forms, Life on Earth is made of left handed amino acids, almost exclusively.

Why? Not really known. Meteorites have left-handed aa.

http://en.wikipedia.org/wiki/File:Chirality_with_hands.jpg

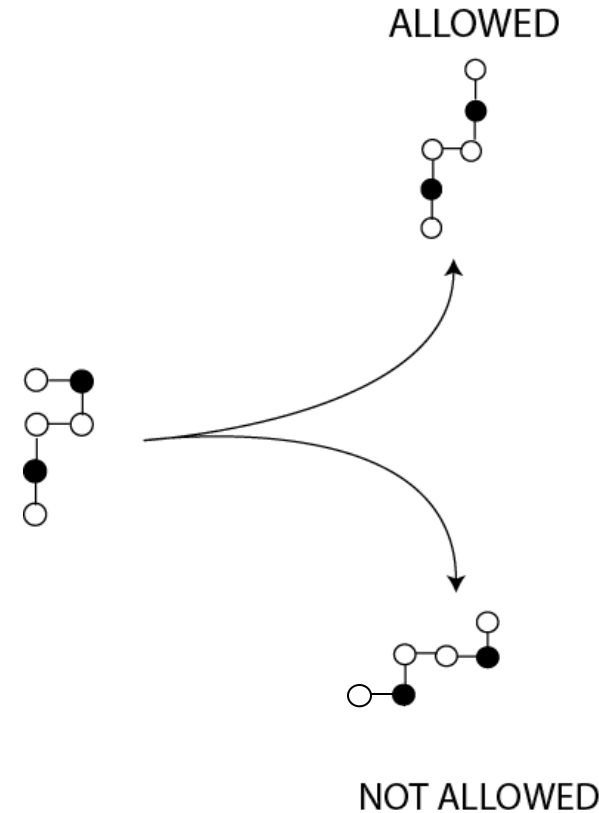
Alpha helix is a right-handed coil, with left-handed amino acids. (There is steric hinderance for a left-handed helix from left-handed amino acids.) Similar for β -sheets.



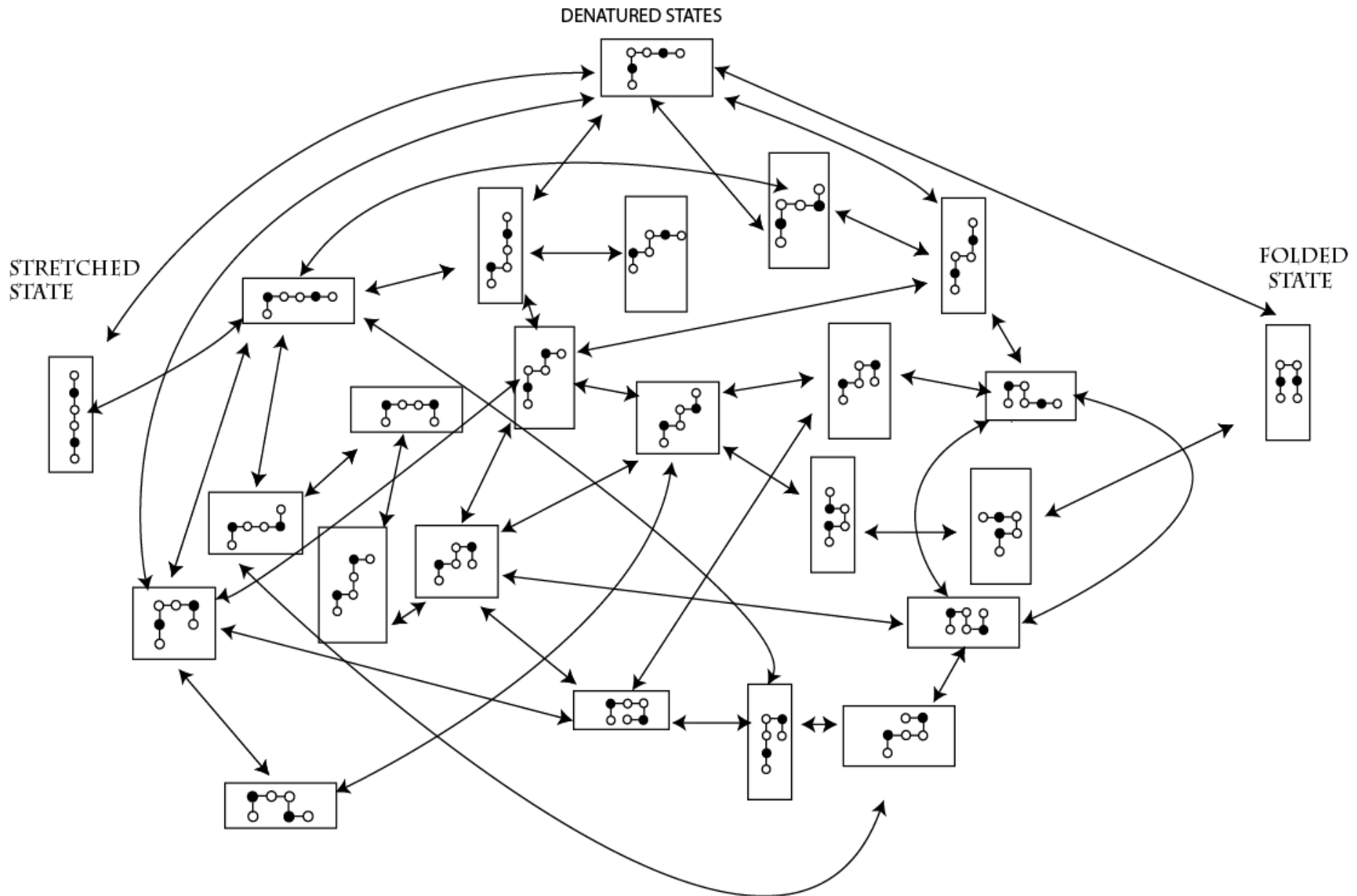
- In 2D: To avoid issues with chirality, all molecules are made so that the first two amino acids go upwards.
- Also, the first kink always goes to the right.

Rotation rules under Lattice Model

- 2-D model - no rotations allowed.
[Don't allow over-counting: horizontal = vertical configuration]
- Molecules are only allowed to change in a single "kink" in 90° increments per time.

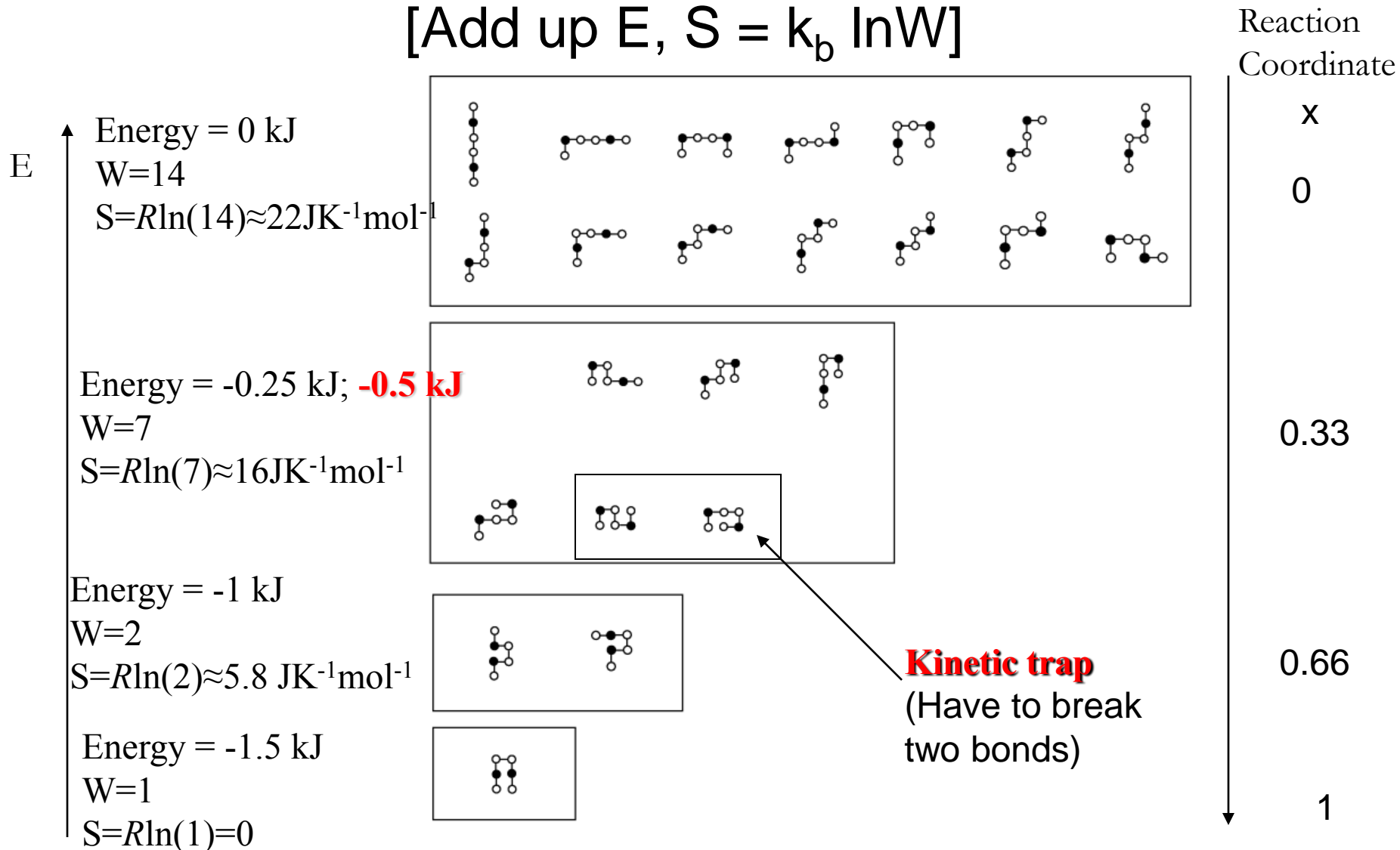


The Journey



Conformation Analysis

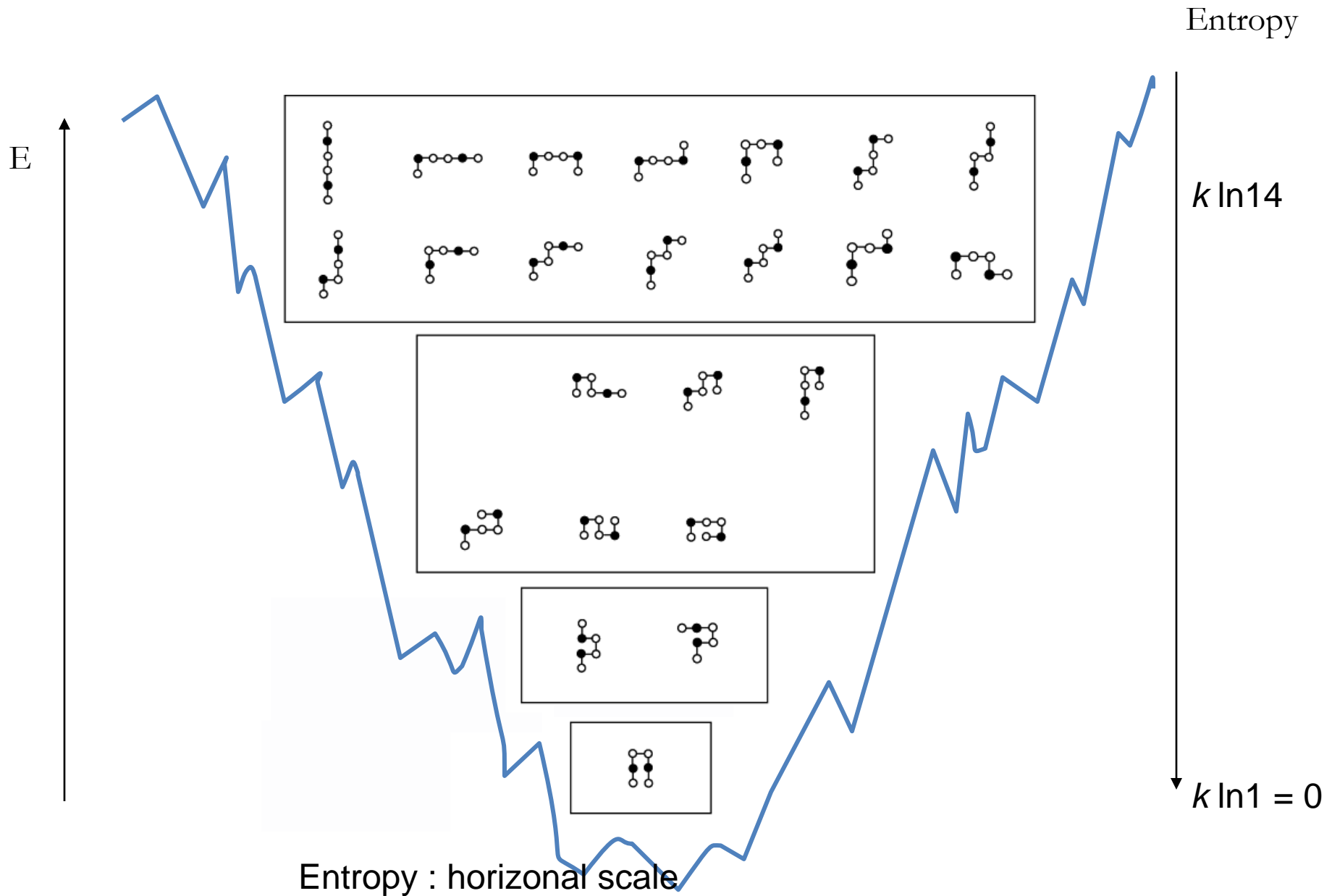
[Add up E, $S = k_b \ln W$]



Note: Only nearest neighbors that count

Molecular Dynamics has actually taken over to make it more realistic

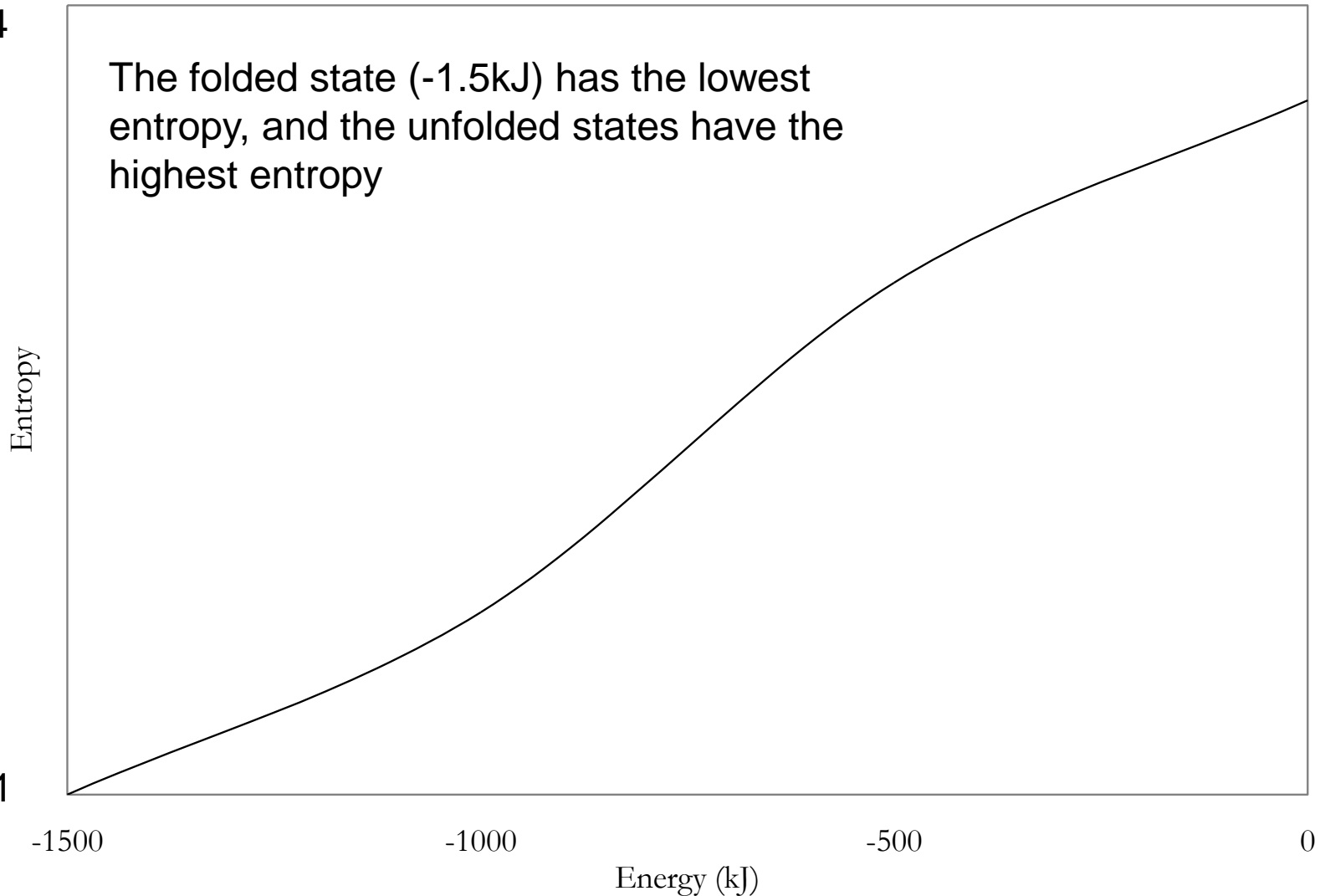
The Protein Folding funnel



Entropy vs. Energy

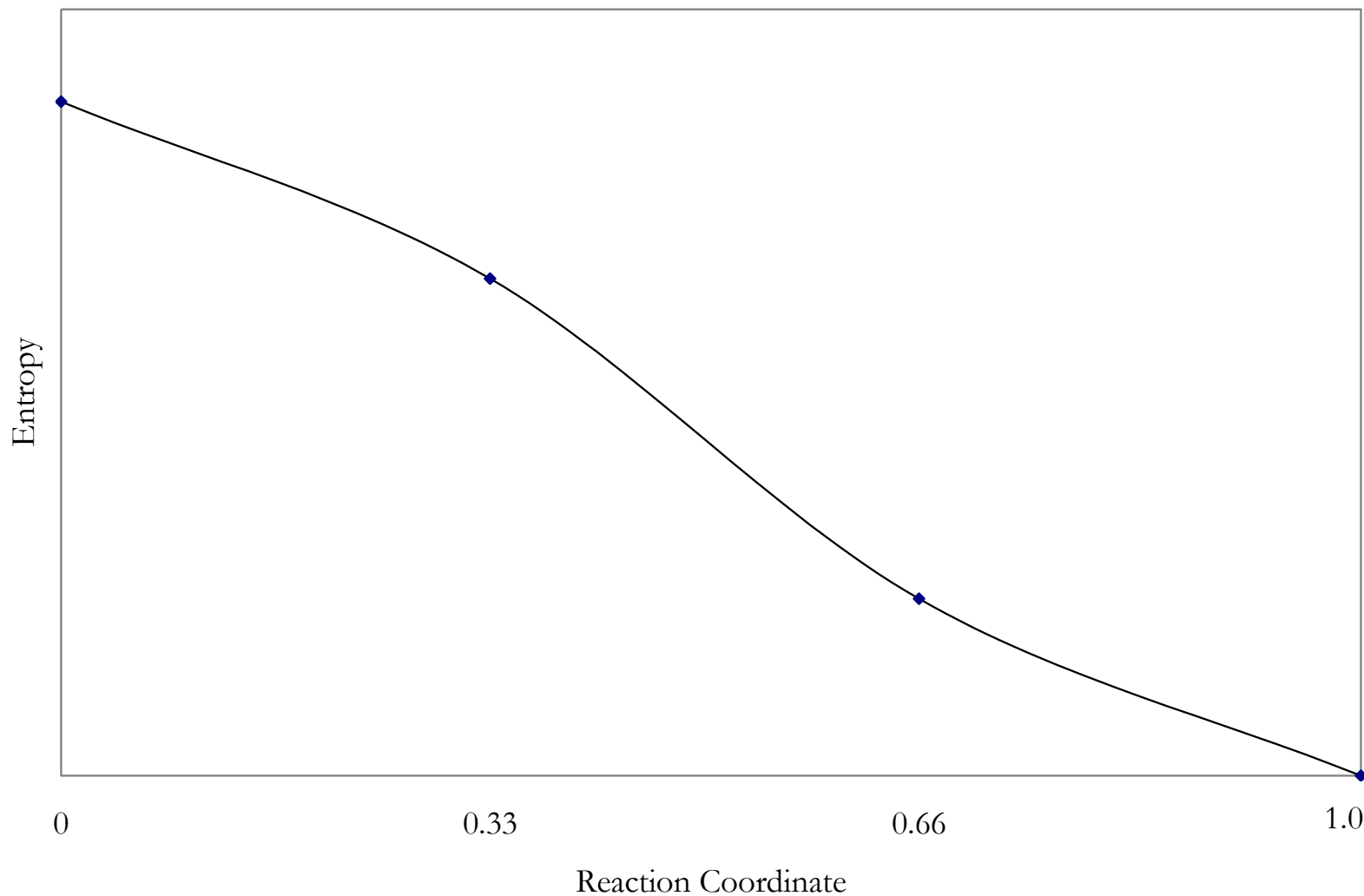
(correlated monotonic function)

Ln 14

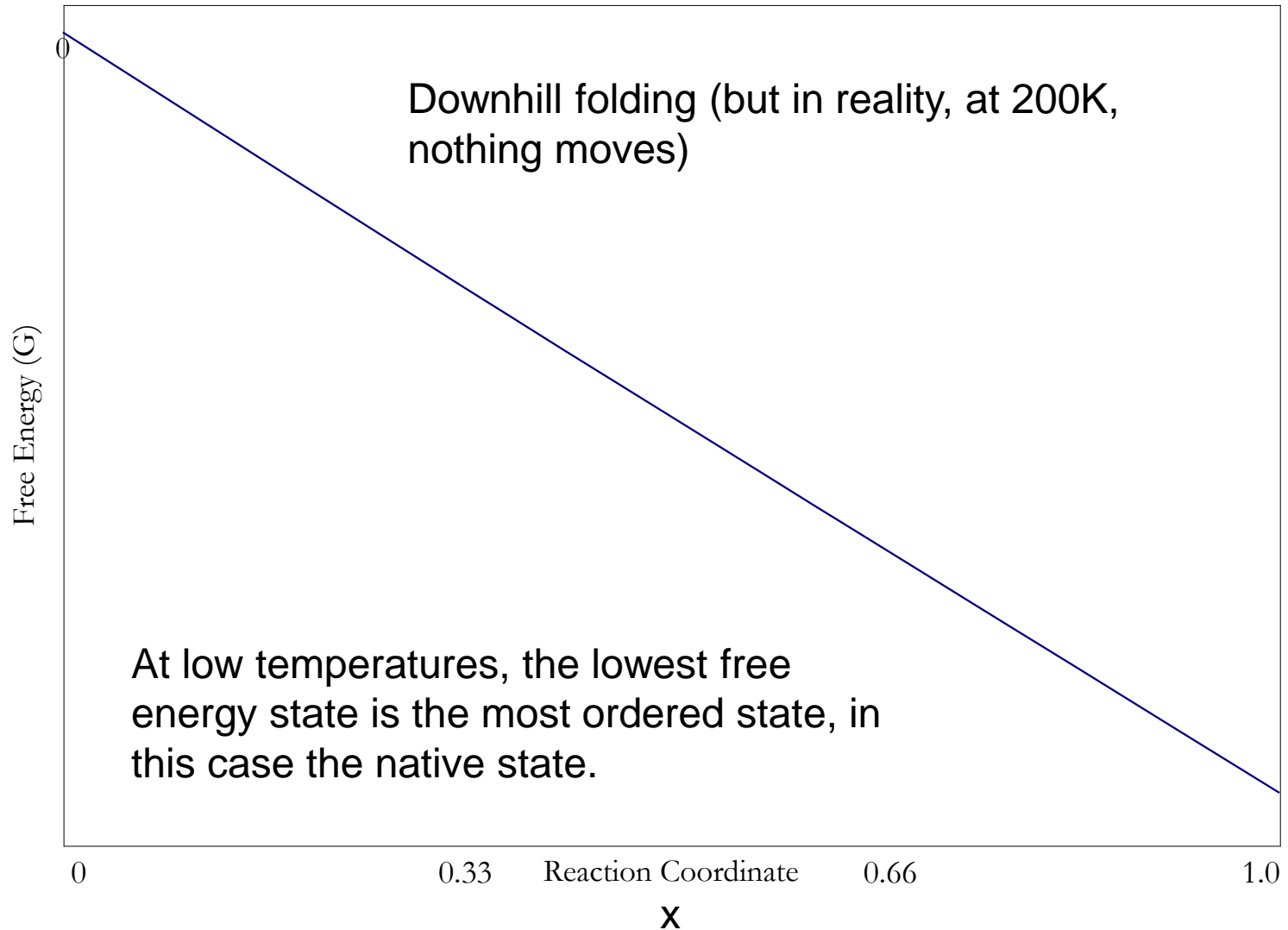


Ln 1

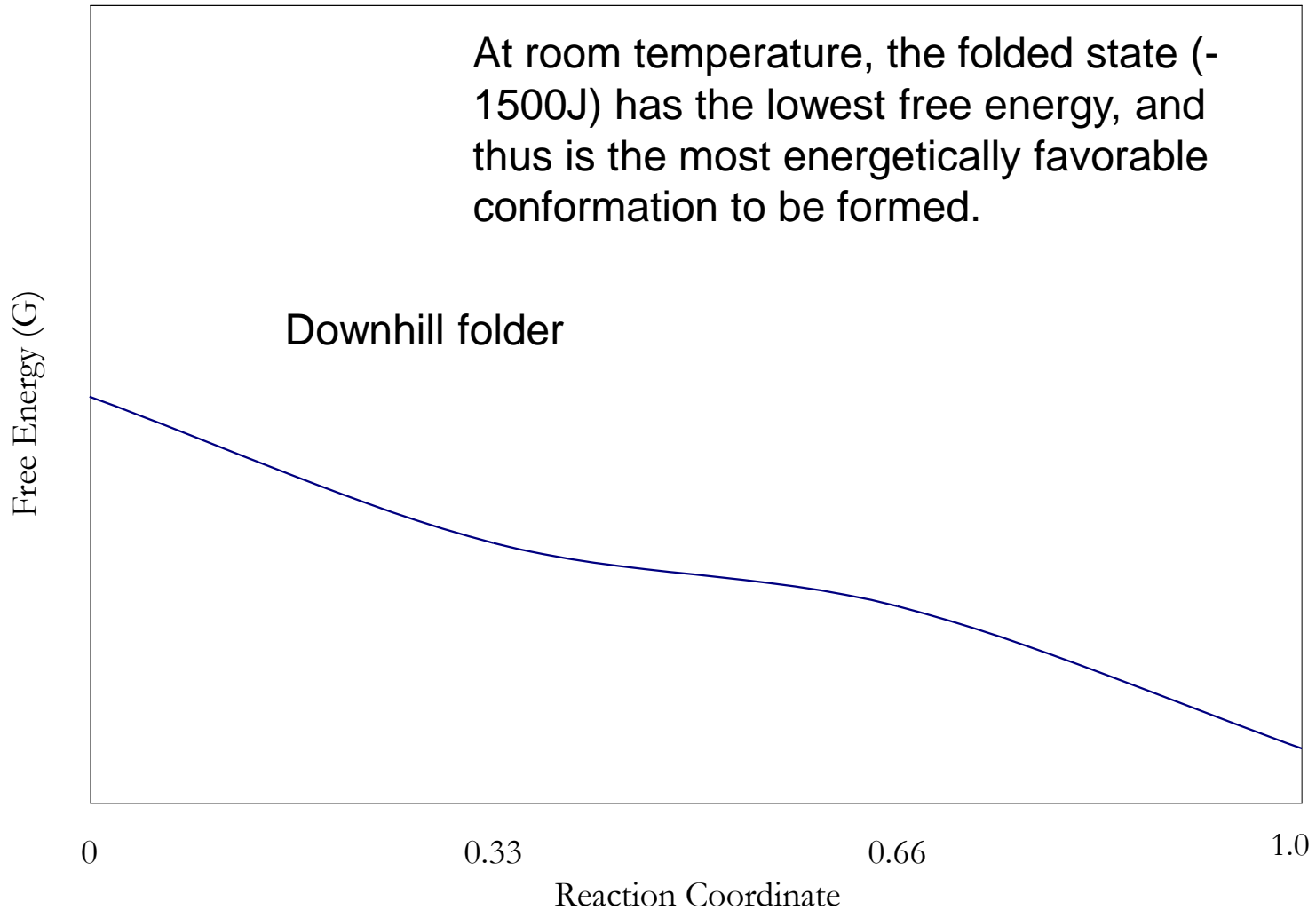
Entropy vs. Reaction Coordinate



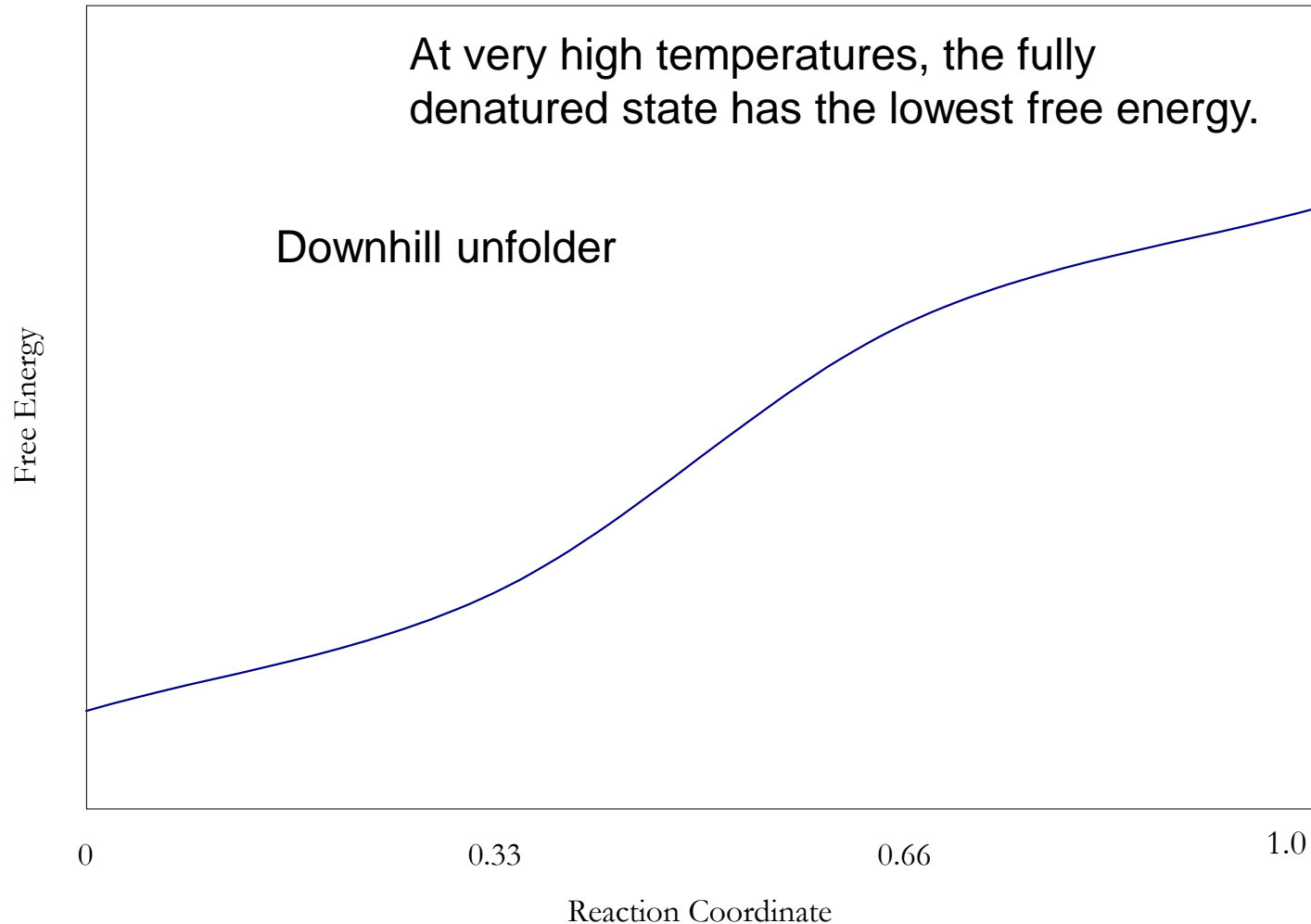
Free Energy Analysis (200K)



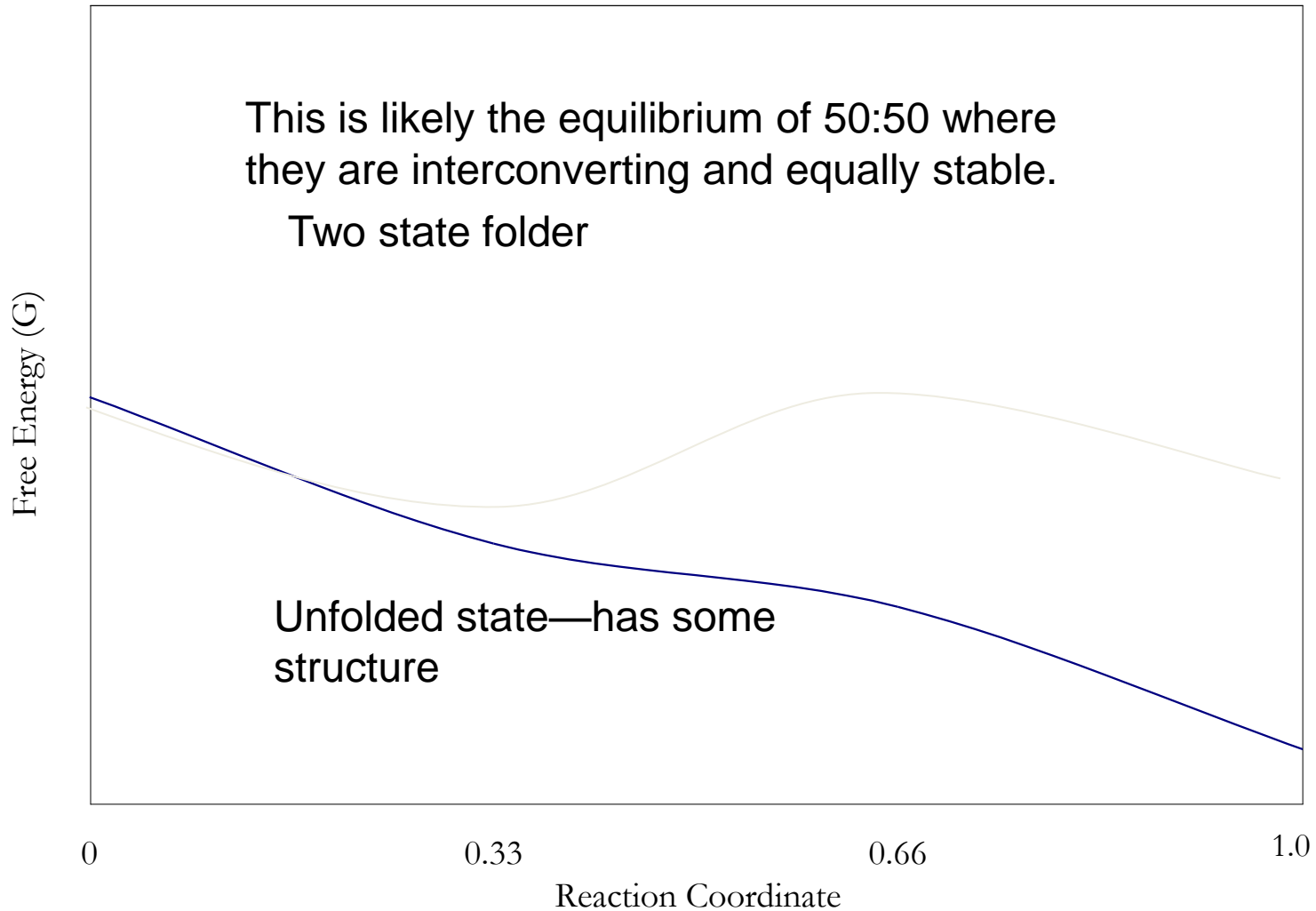
Free Energy Analysis (298K)



Free Energy Analysis (2000K)



Free Energy Analysis (360 K)



Summary of Protein Folding

Proteins can fold.

Don't need chaperones.

ΔG is always about zero.

Kinetics – fast cause not huge barriers

Class evaluation

1. What was the most interesting thing you learned in class today?
2. What are you confused about?
3. Related to today's subject, what would you like to know more about?
4. Any helpful comments.

Answer, and turn in at the end of class.