Lecture 3: Mechanical and chemical equilibrium

Goal: Energy minimization models

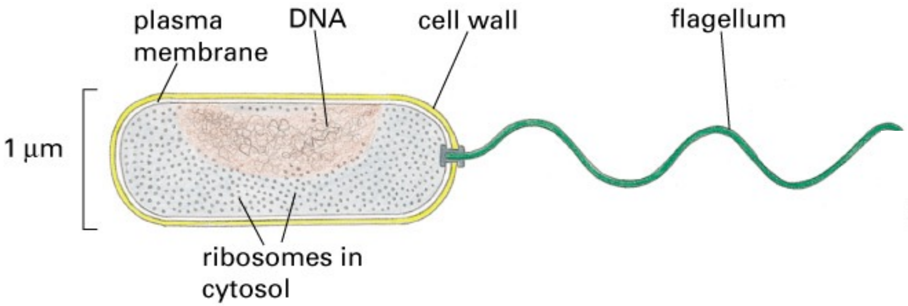
- Biological systems as minimizers
- Entropy and hydrophobicity

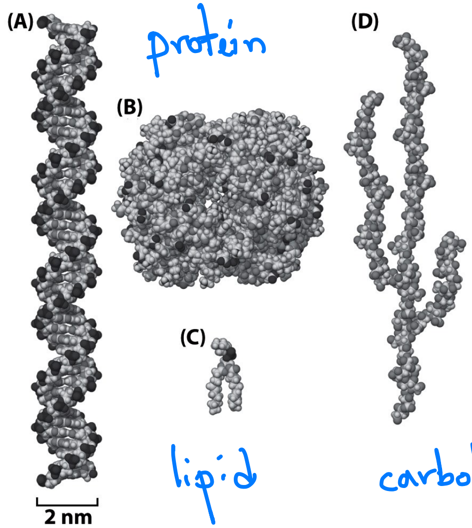
PBOC Chapter 5.2, 5.5.1

Announcement: Video-recorded lecture next week.

Basic facts about cells

Previously: *Prokaryotes and Eukaryotes*



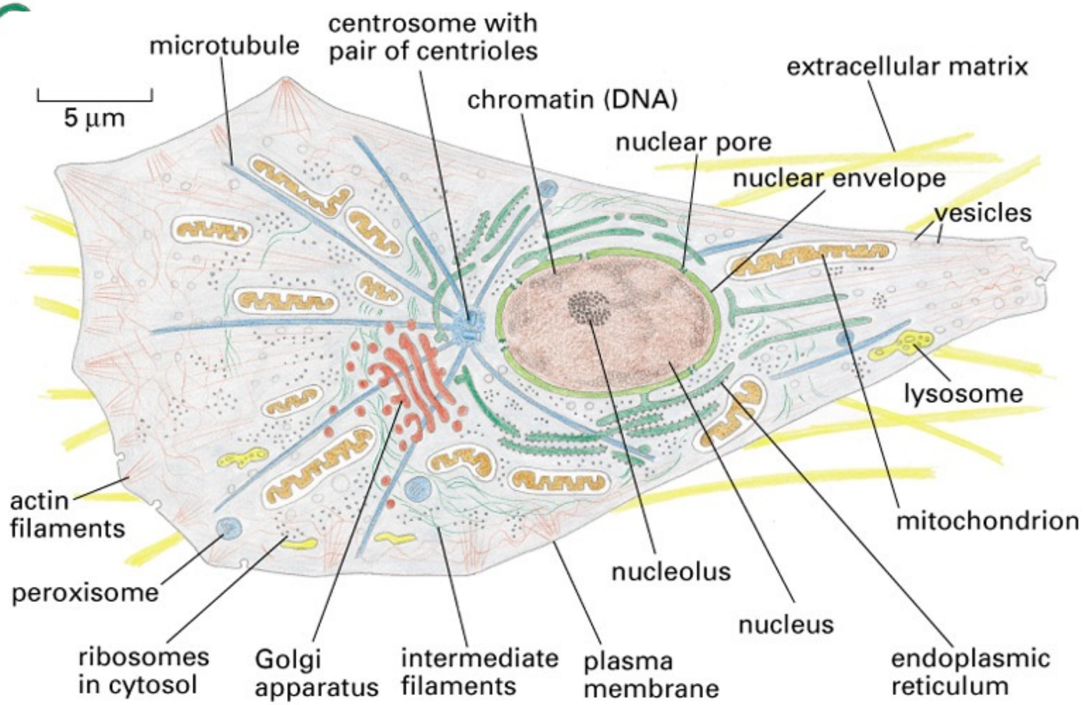


protein

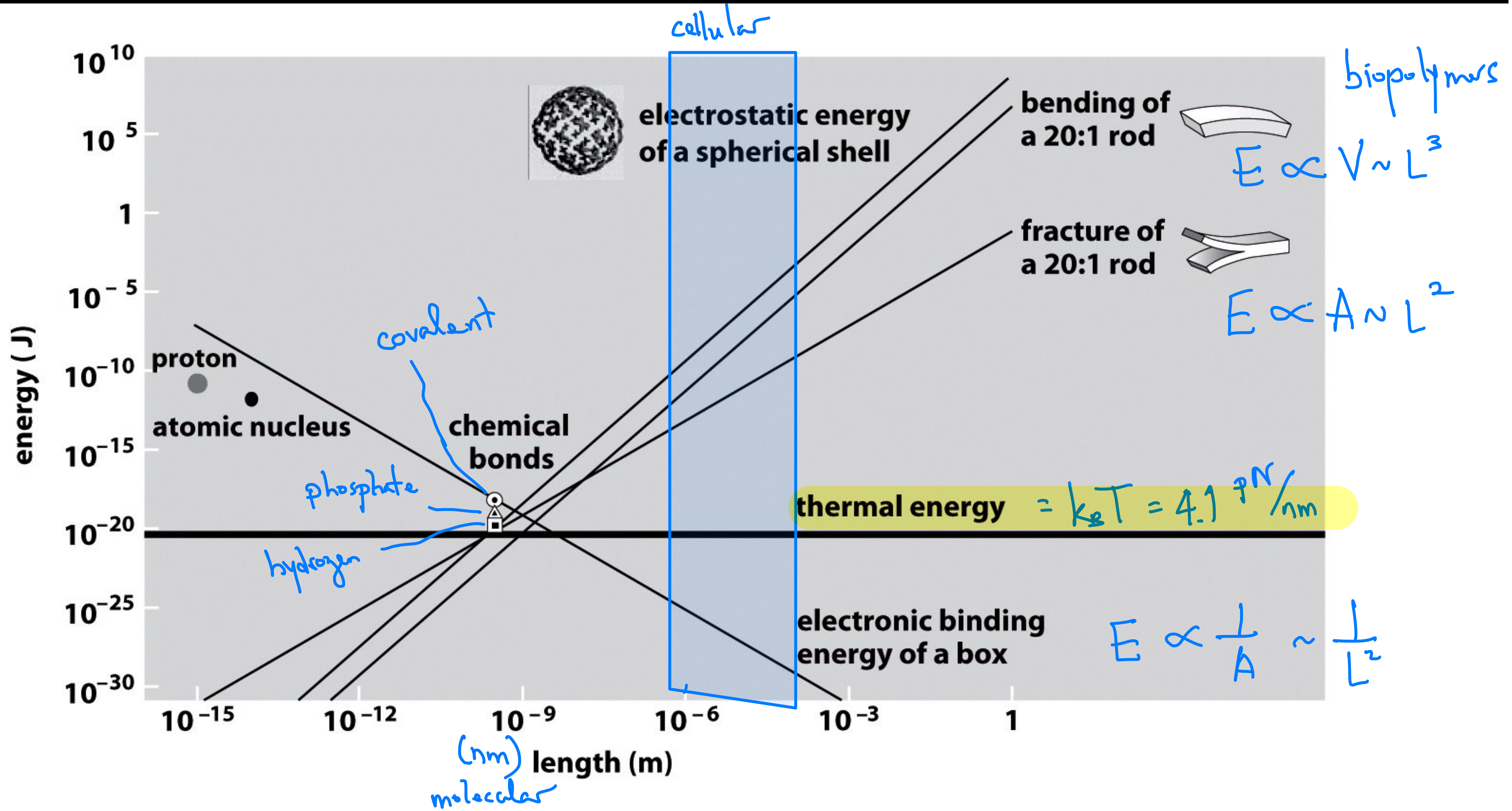
lipid

carbohydrate

DNA
(nucleic acids)



Energy in the cell



Energy in the cell

Active vs passive processes

$\gg k_B T$ $\sim k_B T$

transforming molecules, make/break covalent/phosphate bonds

steps of central dogma (transcription, translation)

transport in cell by molecular motor

constriction at cell division site

segregation of DNA into daughter cells

Non-equilibrium, consuming energy.

protein folding (hydrophobicity)

binding/unbinding processes:

ligand + protein

protein + DNA

Model using energy minimization

Biological systems as minimizers

Passive processes can be modeled by minimizing free energy

- What determines the shape of a red blood cell?
- Given a particular oxygen partial pressure in the lungs, what is the fractional binding occupancy of the hemoglobin within red blood cells?
- How much force is required to package the DNA within the capsid of a bacteriophage?
- What fraction of Lac repressor molecules in an E. coli cell are bound to DNA and what is the probability that one such molecule is bound specifically?

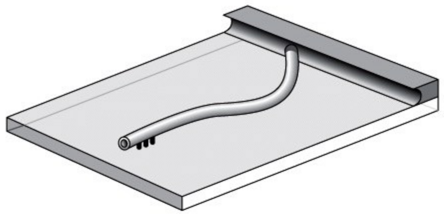
Useful simplification: many chemical and mechanical systems can be treated as if they are close to an equilibrium state.

Biological systems as minimizers

Proteins as minimizers

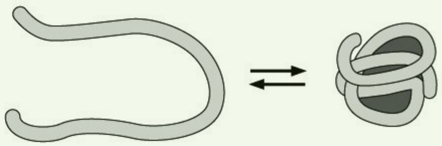
Length scale: nm

chemical bonds contribute to energy

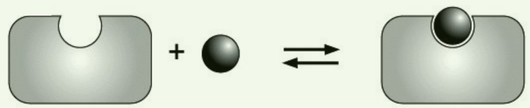


microtubule growing against a barrier

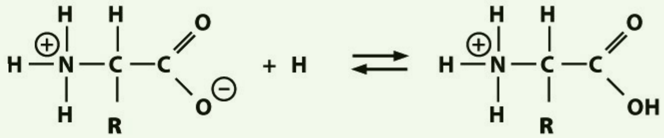
mechanical deformation contributes to energy



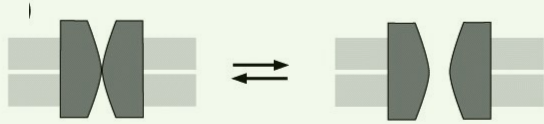
protein folding and unfolding



ligand binding and unbinding to receptor



carboxylic acid group becoming protonated and deprotonated



ion channel opening and closing

Model: write an expression for free energy, minimize.
calculate probability of finding system in a state.

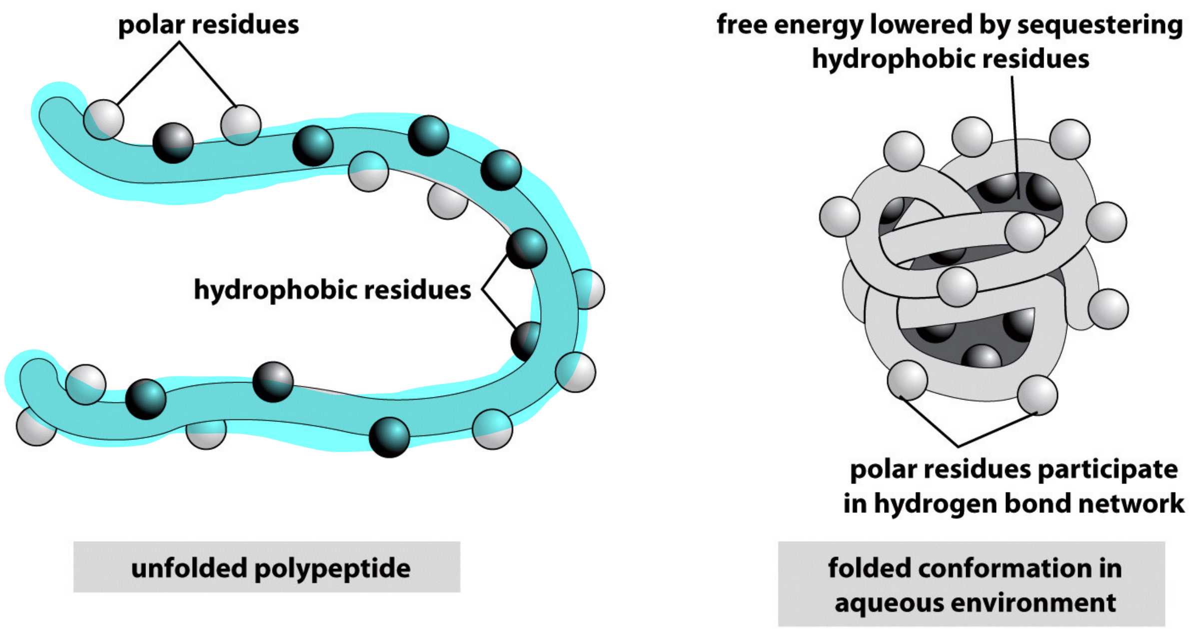
Biological systems as minimizers

How to find minimum energy states? Probabilities?

1. Identify the states.
2. Determine free energy of each state.

Biological systems as minimizers

Protein folding



Number of possible 3D conformations is so large that a random search would take a long time:

100-monomer chain
$6^{100} = 6.5 \times 10^{77}$

One structure per femtosecond
2×10^{55} years
Age of universe ~10^{10} years

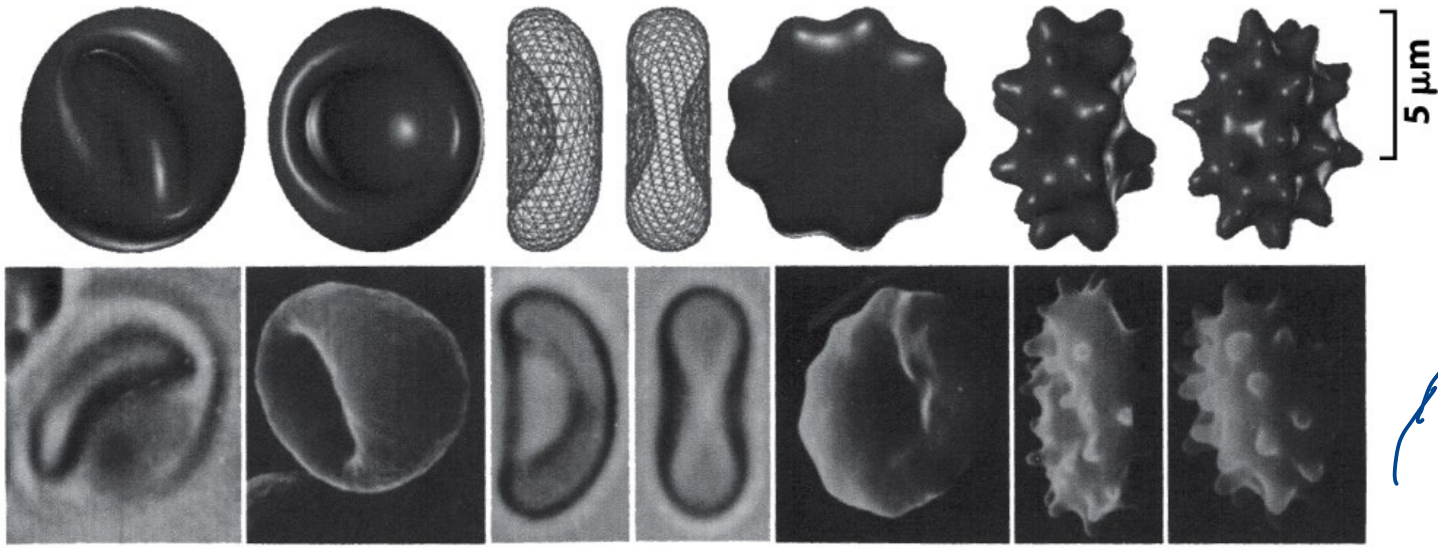
Biological systems as minimizers

Cells as minimizers

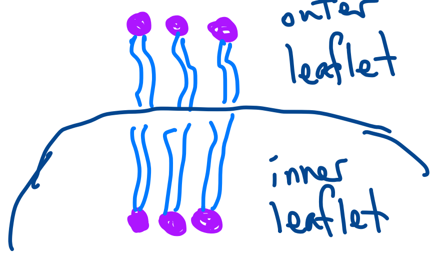
length scale: nm → μm

numerical model

experimental images



outside



inside

changes in area difference between two leaflets of bilayer

$A_{outer} - A_{inner}$

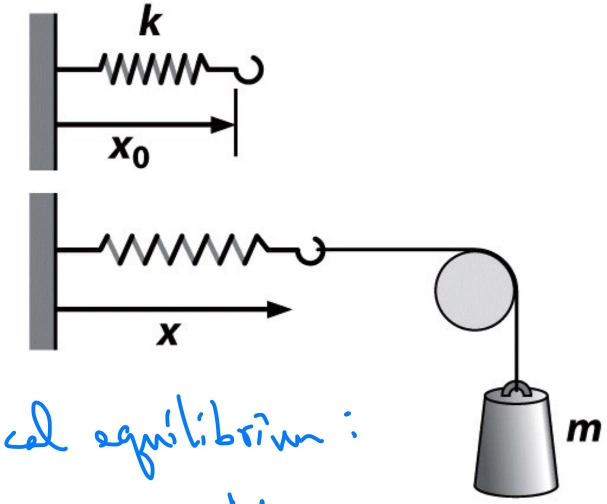
states: membrane shapes satisfying geometric constraints (constant area, constant volume)

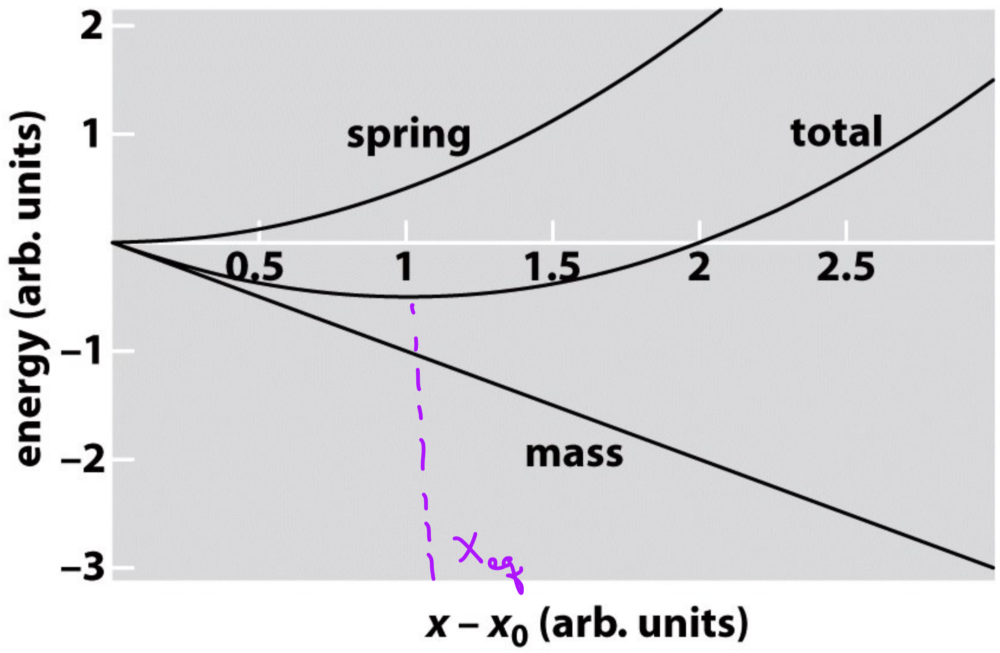
energy: mechanical (elastic) energy of deformation

Energy minimization offers a suitable model for red blood cell shape.

Biological systems as minimizers

Deformation energy: Macroscopic spring-mass system





Mechanical equilibrium:

$\sum \vec{F} = 0$ or $\frac{dU}{dx} = 0$

$$U(x) = \underbrace{\frac{1}{2}k(x - x_0)^2}_{\text{PE of spring}} - \underbrace{mg(x - x_0)}_{\text{PE of weight}}$$

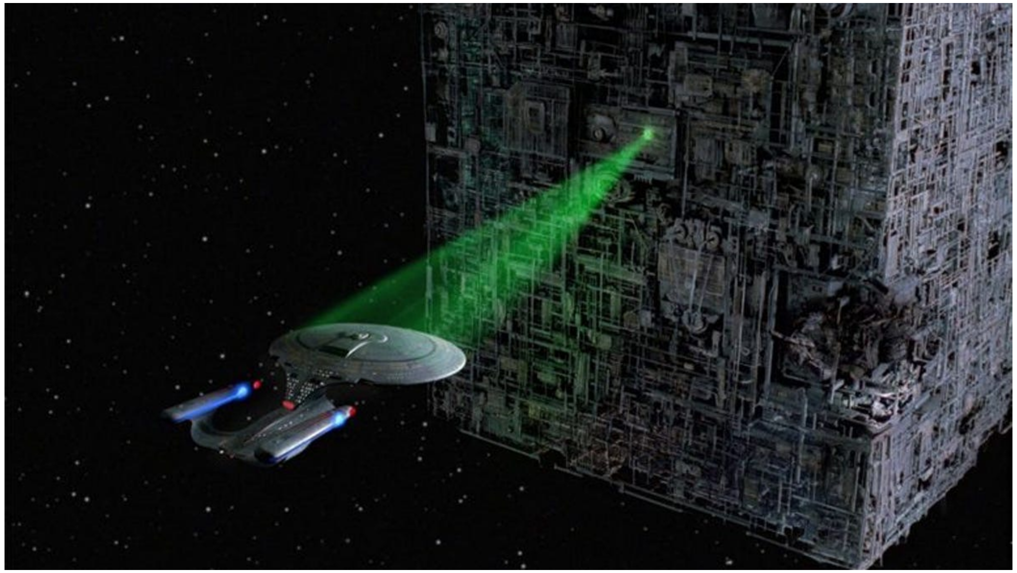
+ −

$$\frac{dU}{dx} = 0 = k(x_{eq} - x_0) - mg$$

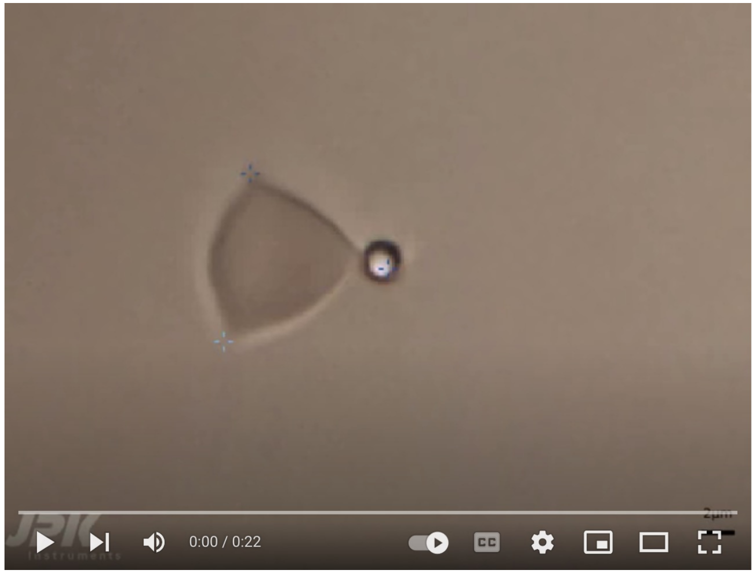
$$x_{eq} = \frac{mg}{k} + x_0$$

Biological systems as minimizers

How do we know? Force-extension mechanics



Tractor beam



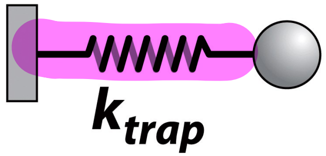
Optical tweezers

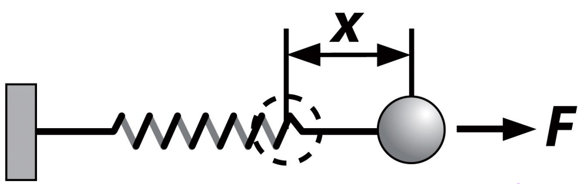
Nobel Prize 2018 Arthur Ashkin

Biological systems as minimizers

Biopolymer mechanics: optical potential well

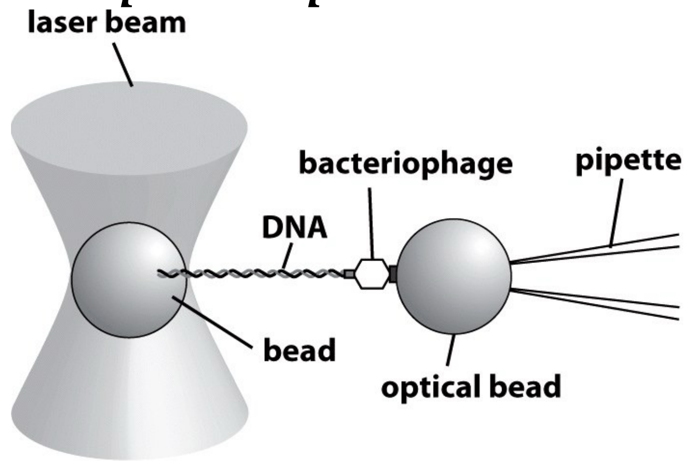
optical trap



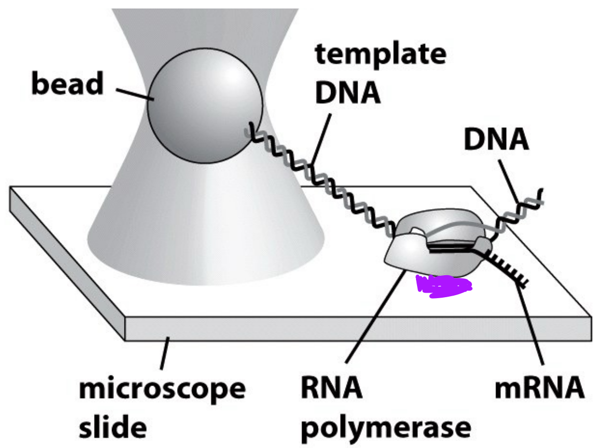


biomolecule tethered to bead

$$U(x) = \frac{1}{2} k_{trap} x^2 - Fx$$



force exerted by virus as it packages DNA

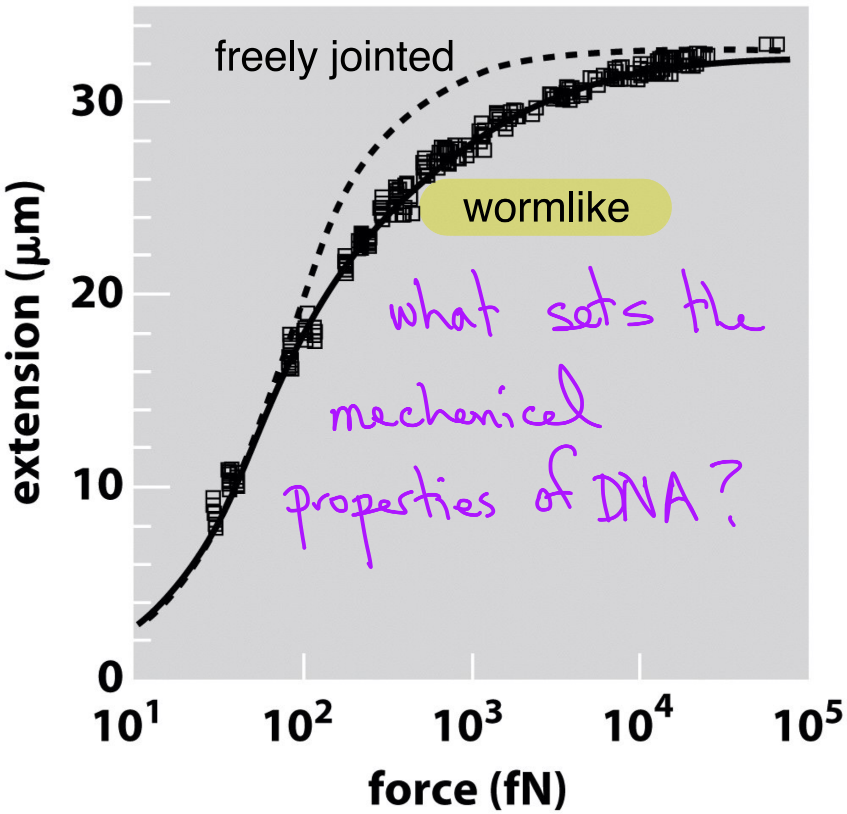


force exerted by RNA polymerase as it transcribes DNA

transcribes DNA

Biological systems as minimizers

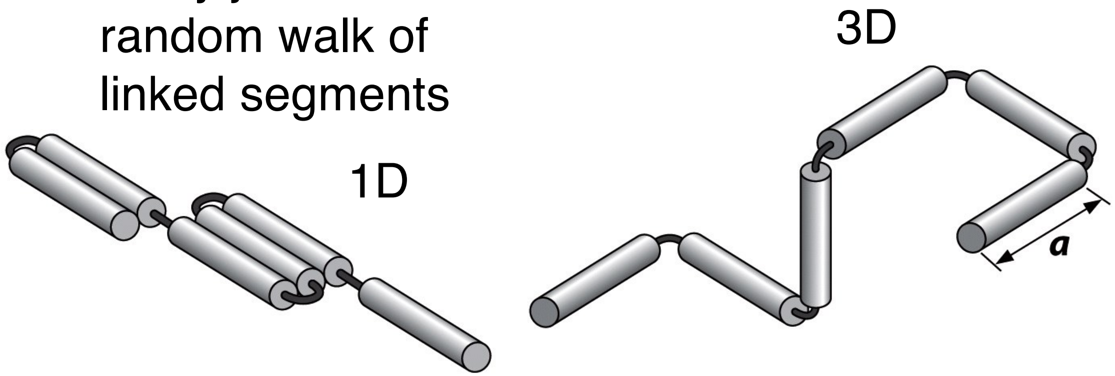
Biopolymer mechanics: optical potential well



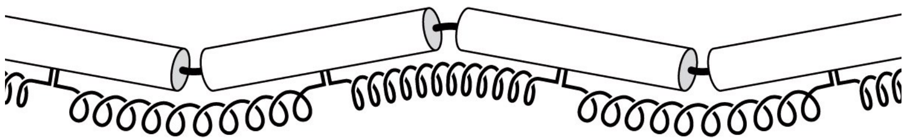
what sets the mechanical properties of DNA?

pulling on DNA

freely jointed chain:
random walk of
linked segments



wormlike chain: random walk of
linked segments with bending energy



distinguish physical polymer models.

Including entropy

Thermal fluctuations

the equilibrium state of a system is the one out of all states available to the system that minimizes the free energy

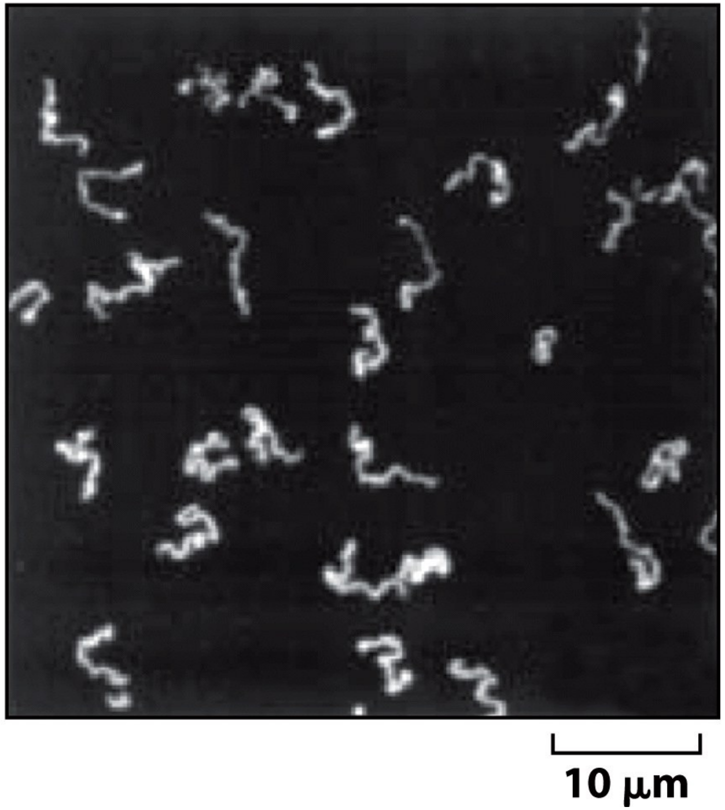
free energy = internal energy − temperature × entropy

$$G = U - TS$$

- even though it is called G, this is the Helmholtz free energy (PBoC)

Including entropy

System microstates

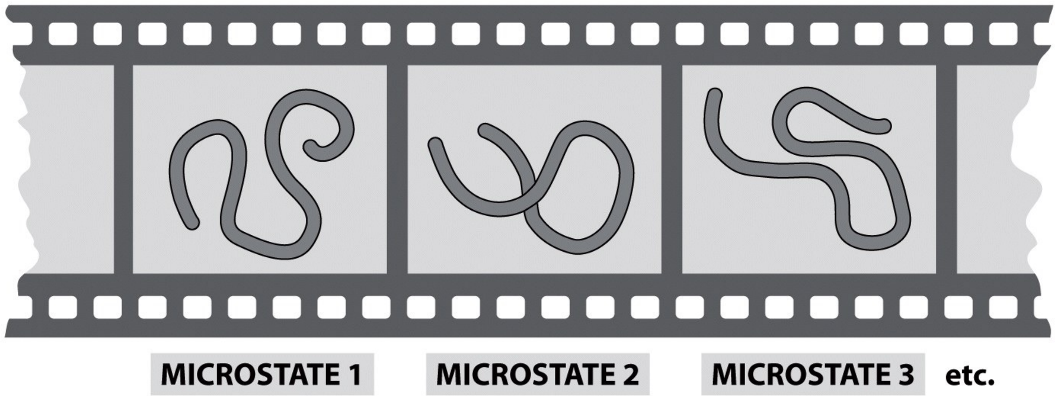


DNA conformations

$$S = k_B \ln W$$

entropy

# of accessible microstates

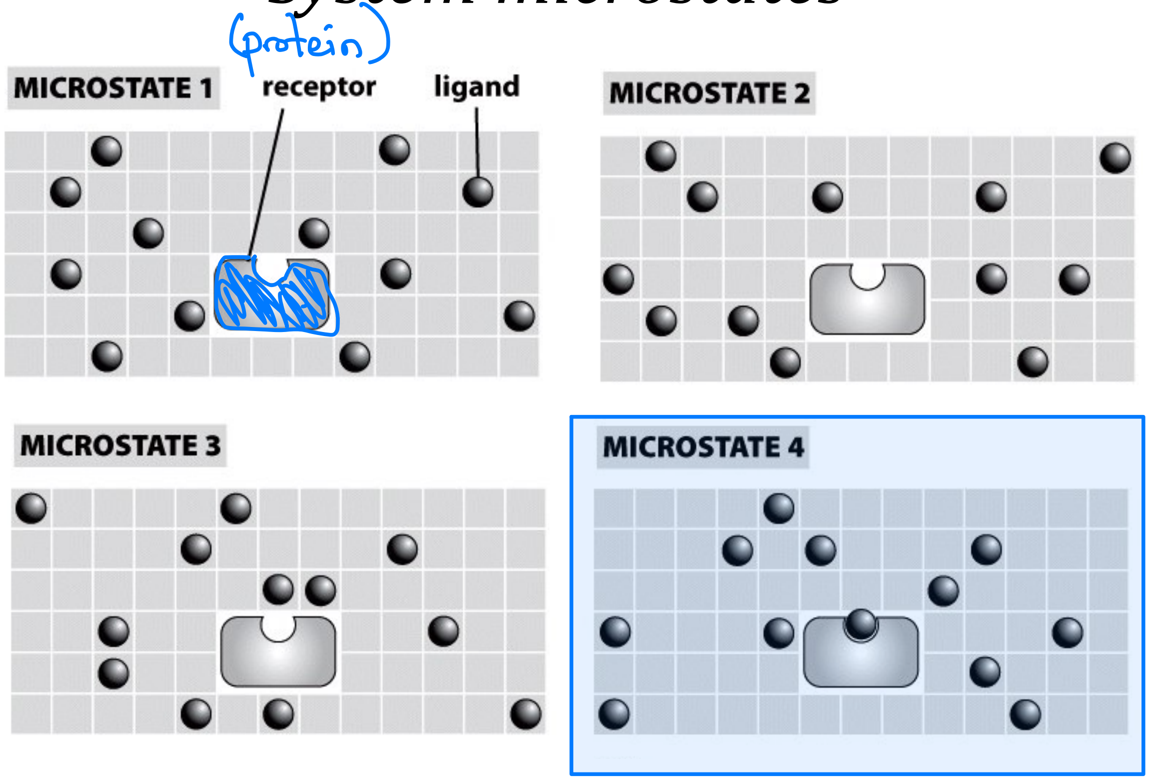


entropy is maximized by macroscopic states that have the largest number of microstates.

Including entropy

System microstates

Lattice model



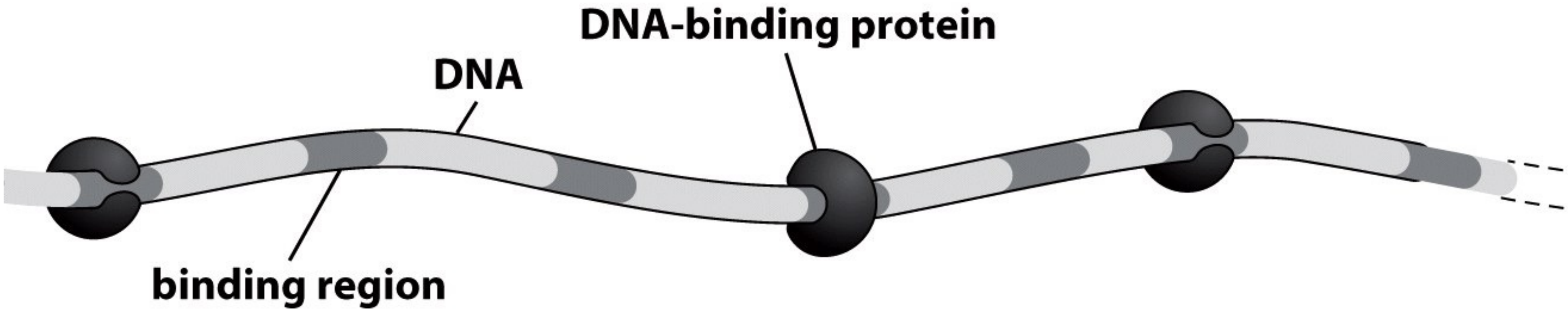
ligand is bound to protein

ligand binding to receptor protein

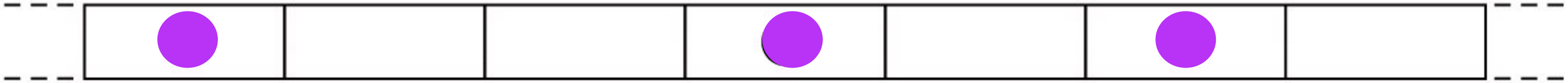
(probability depends on energy of binding, temperature of system)

Including entropy

System microstates



each box is a binding site, protein can bind DNA

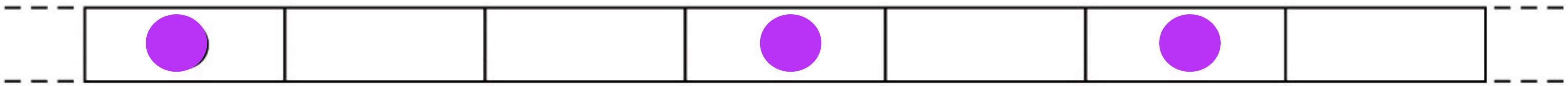


1D - **lattice model of DNA/protein complexes**

protein binding to DNA

Including entropy

System microstates



lattice model of DNA/protein complexes

N boxes, N_P proteins (indistinguishable) $N > N_P$. One protein per box.

~5-10 min.

How many accessible states? $W(N, N_P)$

Write down the entropy.

protein binding to DNA

N boxes, N_p proteins (indistinguishable)

N possible choices for where we put the first protein

$N-1$ choices for the second protein

$N-2$ choices for the third protein

number of ways to place N_p proteins:

$$N \cdot (N-1) \cdot (N-2) \ldots \cdot (N-N_p+1)$$

indistinguishability: overcounted. divide by the number of rearrangements of the N_p proteins within the occupied sites. $N_p!$

\# states: $W(N; N_p) = \dfrac{N \cdot (N-1) \cdot (N-2) \ldots \cdot (N-N_p+1)}{N_p \cdot (N_p-1) \cdot \ldots} = \dfrac{N!}{N_p!\,(N-N_p)!}$

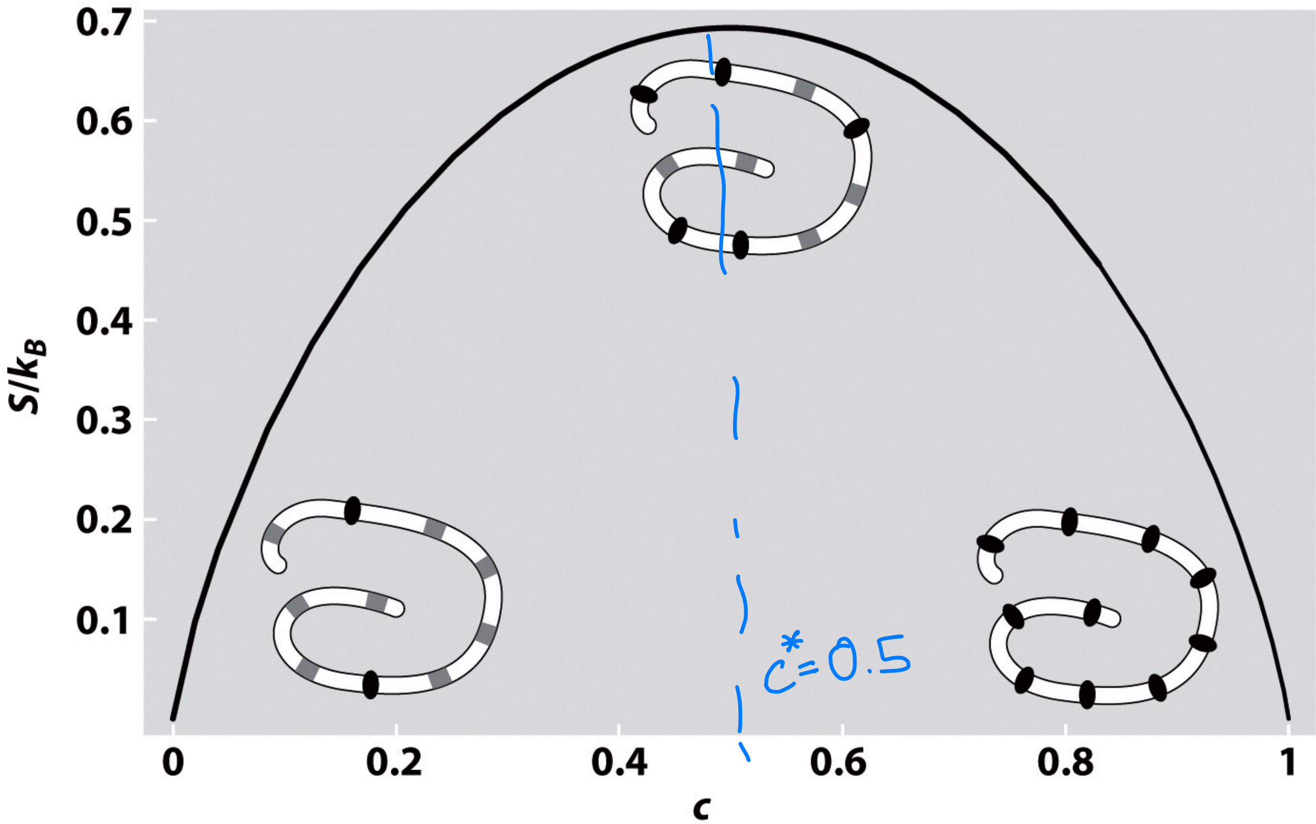
entropy: $S = k_B \ln W = k_B \ln N! - k_B \ln N_p! - k_B \ln (N-N_p)!$

Stirling approximation: $\ln N! \approx N \ln N - N$ for large N (p. 280)

$\Rightarrow$ $S = -k_B N \left[c \ln c + (1-c) \ln (1-c) \right]$ where $c = N_p / N$

Including entropy

System microstates

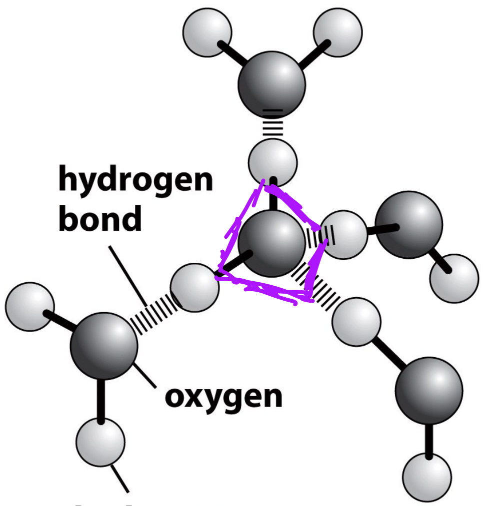


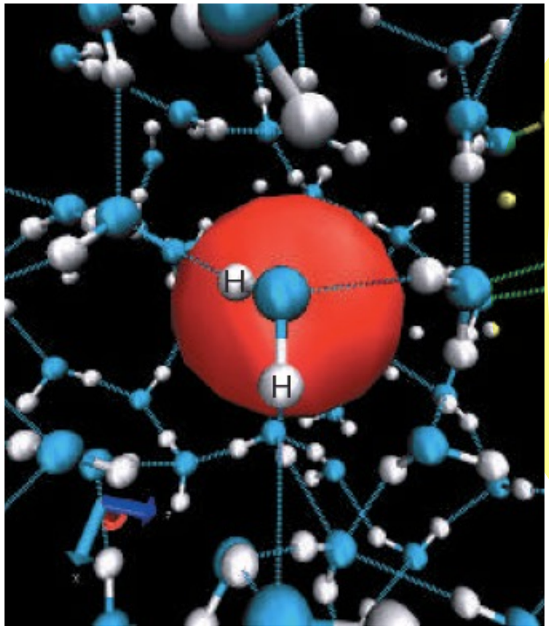
protein binding to DNA

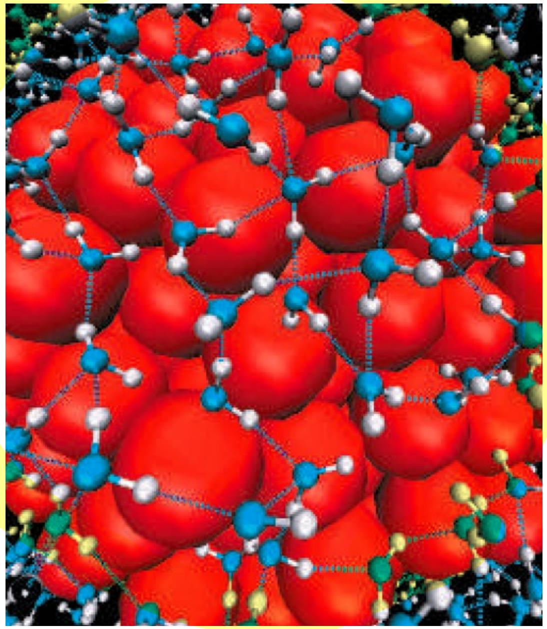
Including entropy

Hydrophobicity: Toy model

idealized H-bonding network







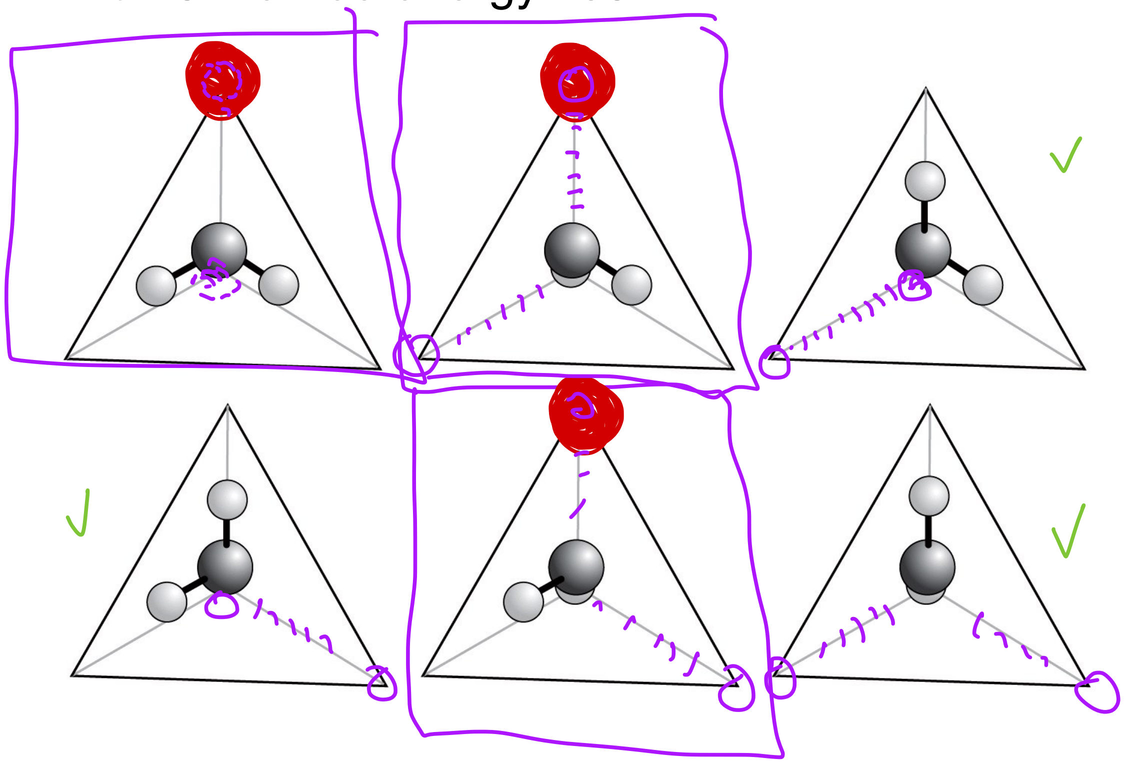
Hydrophobicity can drive molecules together.

a hydrophobic molecule prevents water molecules from hydrogen bonding

Including entropy

Hydrophobicity: Toy model

What is the free energy cost?

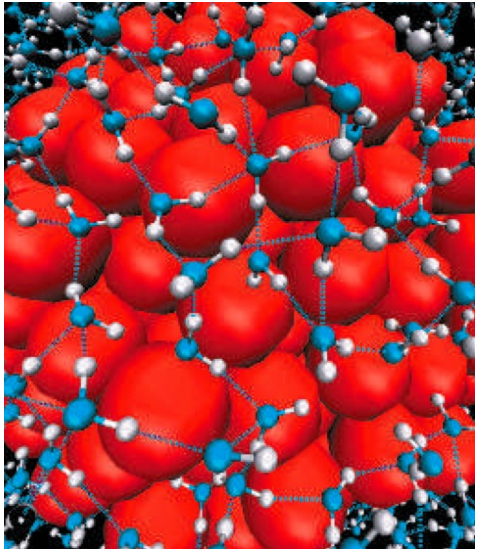


a hydrophobic molecule prevents water molecules from hydrogen bonding

Including entropy

Hydrophobicity: Toy model

What is the free energy cost? Entropy loss per H_2O molecule, assuming only microstates w/ 2 H-bon



$$\Delta S_{hydrophobic} = \underbrace{k_B \ln 3}_{\text{constrained}} - \underbrace{k_B \ln 6}_{\text{unconstrained}} = -k_B \ln 2$$

Entropic cost of hydrophobic inclusion:

$$\Delta G_s(n) = n k_B T \ln 2$$

n water molecules adjacent to hydrophobic

Assume 10 H_2O molecules / nm^2. Entropic energy per area:

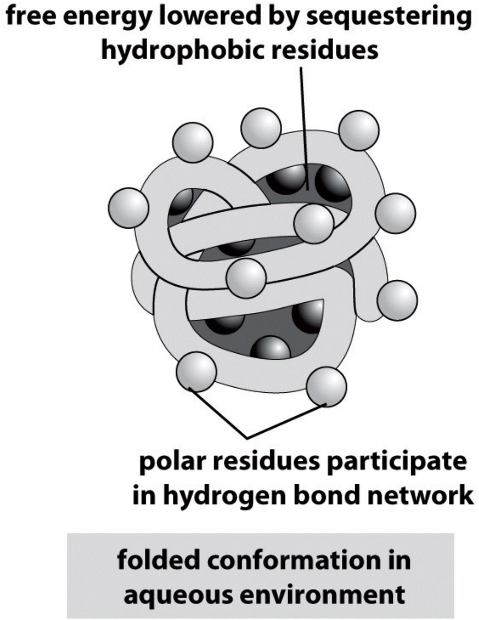
$$\frac{\Delta G_s}{A} = 10 \cdot k_B T \cdot \ln 2 = 7\, k_B T / nm^2 \Rightarrow$$

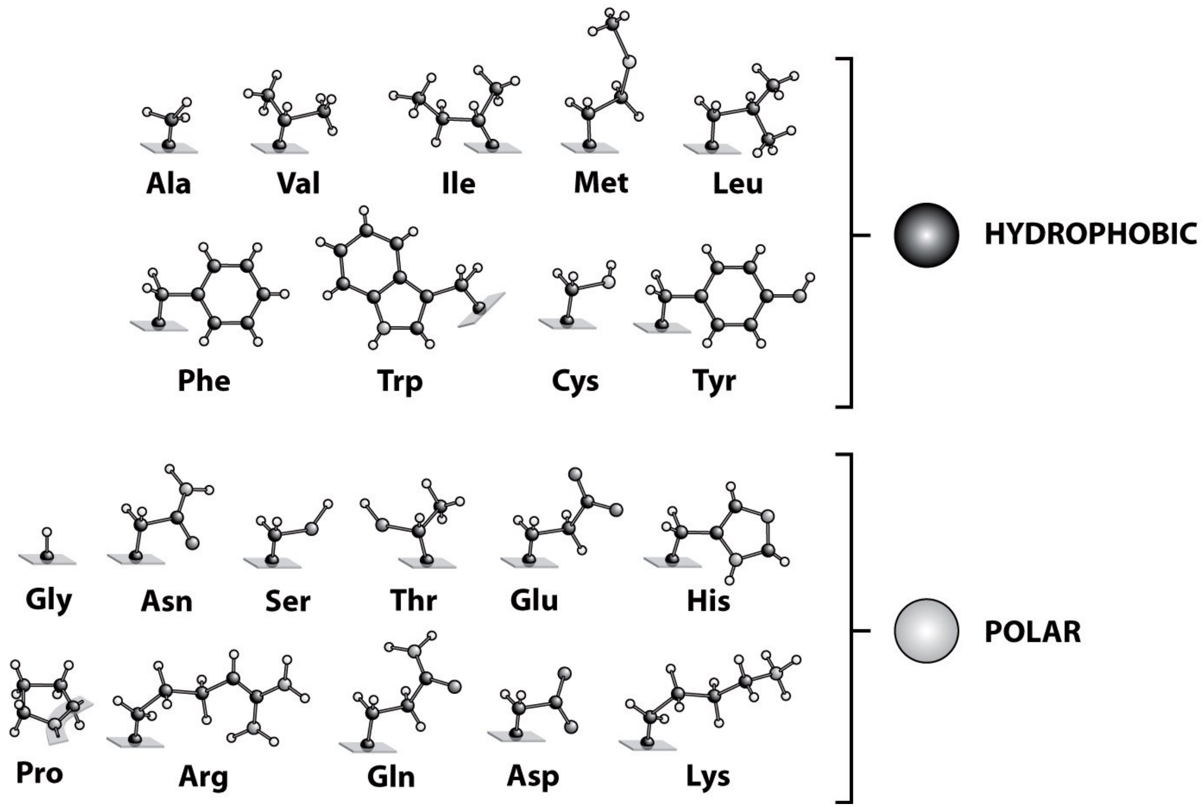
70 $k_B T$ to dissolve hydrophobic molecule $A = 10\ nm^2$

a hydrophobic molecule prevents water molecules from hydrogen bonding

Biological systems as minimizers

Protein folding: HP model





coarse-grained model

Biological systems as minimizers

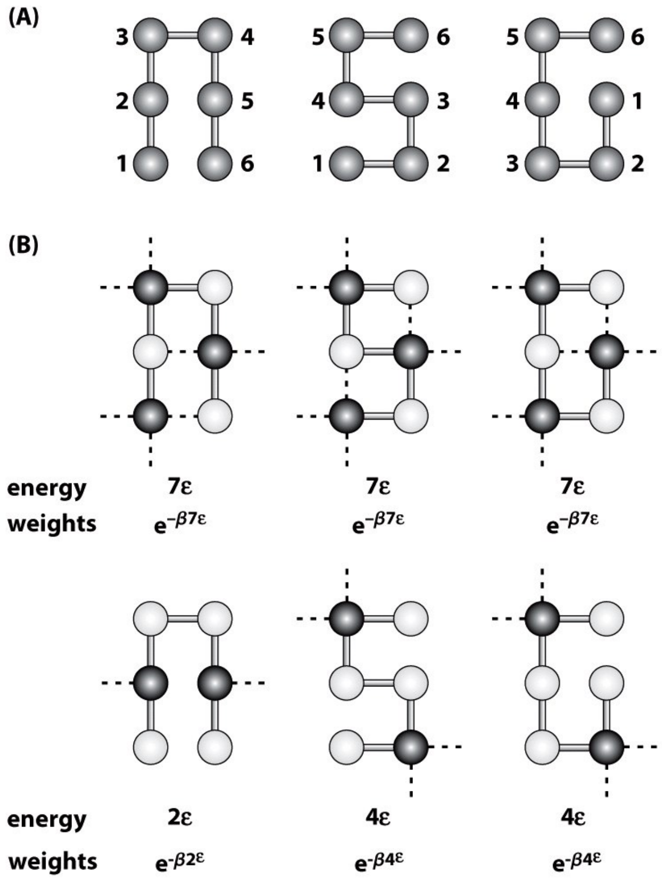
Protein folding: HP model

toy HP model:
6 monomers on a 3x2 lattice

sequences: $2^6 = 64$

sequence HPHPHP

sequence PHPPHP



states
number of unique structures: 3

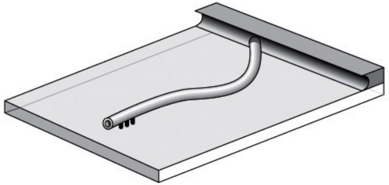
interaction model: assign **energy** penalty for H-P or H-solvent interactions (---)

Given an HP sequence, which of the possible structures minimizes the total free energy?

Biological systems as minimizers

Proteins as minimizers

mechanical energy + entropy

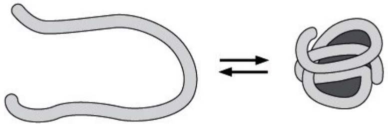


microtubule growing against a barrier

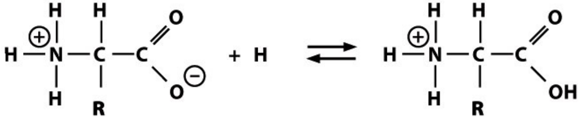
deformation contributes to energy

high entropy low energy

high energy low entropy



protein folding and unfolding



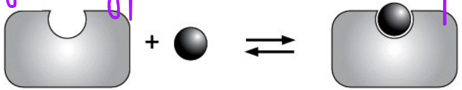
carboxylic acid group becoming protonated and deprotonated

chemical energy + entropy

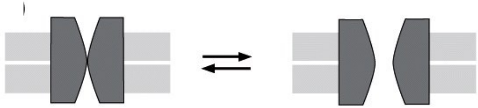
chemical bonds contribute to energy

high entropy low energy

high energy low entropy



ligand binding and unbinding to receptor



ion channel opening and closing

Lecture 3: Mechanical and chemical equilibrium

Many processes can be modeled using free energy minimization

- hydrophobic effect
- protein folding
- protein-ligand binding
- protein-DNA binding
- polymer (1D) or membrane (2D) bending

Model ingredients: energies associated with states, number of states

Lecture 4: Biological membrane elasticity

Goal: Calculate energy cost for bending membranes away from their equilibrium configurations

- The nature of biological membranes
- Springiness of membranes

PBOC Chapter 11.1, 11.2