

BB 101

MODULE: *PHYSICAL BIOLOGY*

Ambarish Kunwar

Lab No. 204

Department of Biosciences and Bioengineering
IIT Bombay

akunwar@iitb.ac.in

<http://www.bio.iitb.ac.in/~akunwar/>

Review

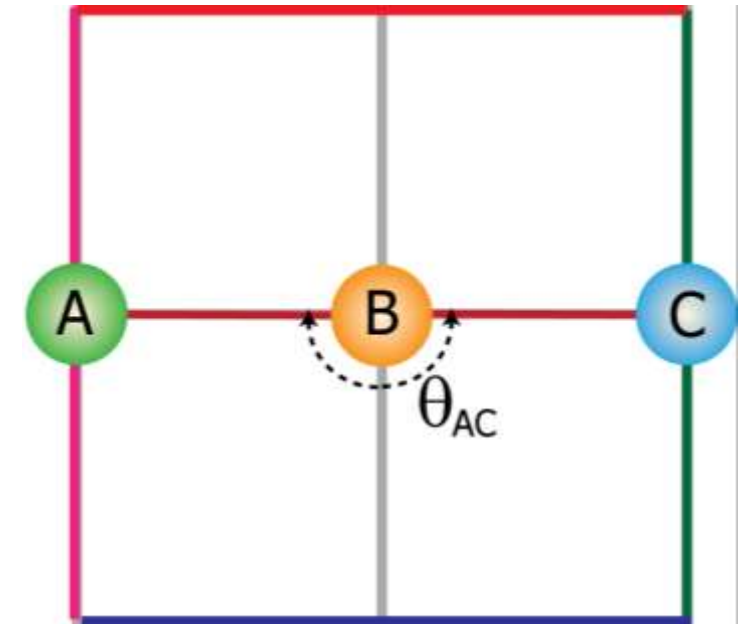
- Proteins and their structures
- Proteins are free energy minimizers
- Microstate and Macrostate
- Relations $G = H - TS$, $G = -k_B T \ln Z$ and $S = k_B \ln W$
- HP models of protein folding

Another Toy Models of Protein Folding

- Consider a protein consisting of three amino acids A, B and C connected with bonds of equal length
- This protein is placed on a square grid such that only A and C are free to rotate in a plane due to thermal energy such that the bonds are always aligned along the grid lines
- Bending energy of the protein is given by

$$\epsilon = A(1 + \cos\theta_{AC})$$

- What is the energy of the straight conformation?
- What is the energy of the bent conformations?



Colored lines denote that space is inhomogeneous

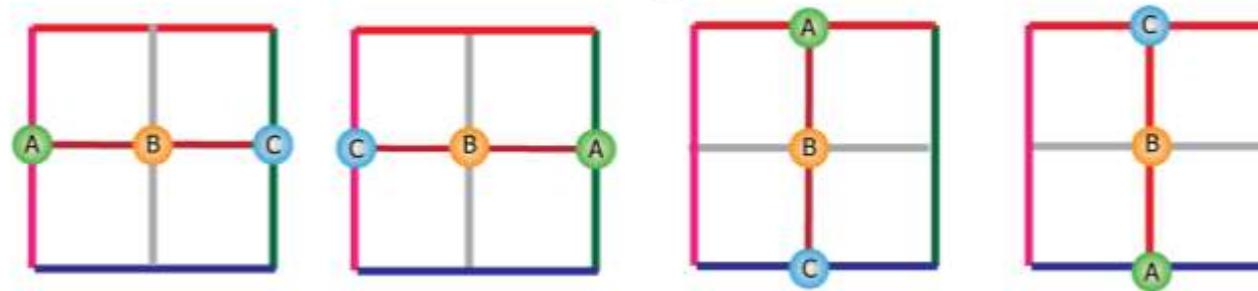
What will be the structural state of the protein when A is small and when A is large?

Bent or straight?

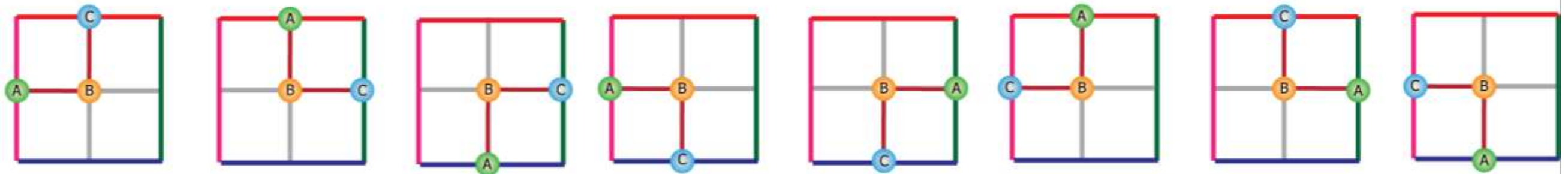
Classical Mechanics: It will be found in straight state

Number of Straight and Bent conformations

Straight



Bent

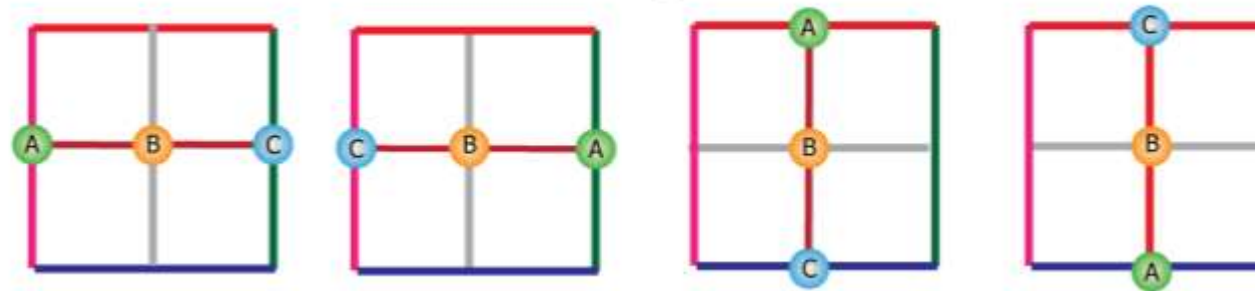


- No. of straight conformations=4
- No. of bent conformations=8

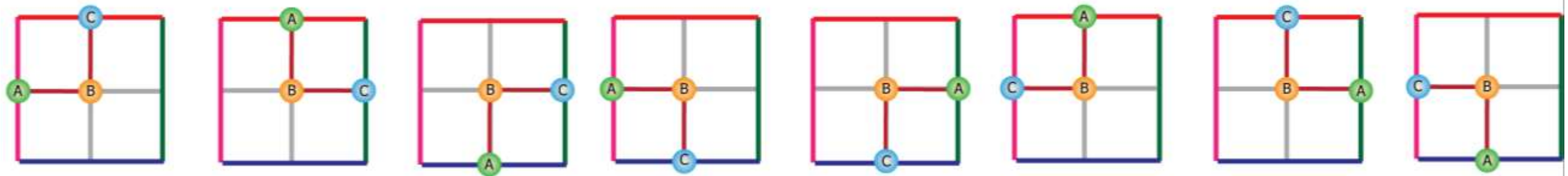
Calculate Average Bending Energy

$$\epsilon = A(1 + \cos\theta_{AC})$$

Straight



Bent



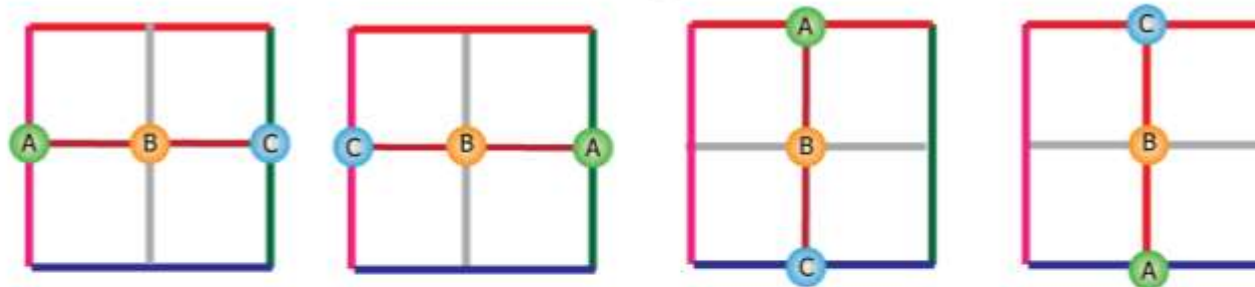
$$\epsilon_{Straight} = 0$$

$$\epsilon_{bent} = A$$

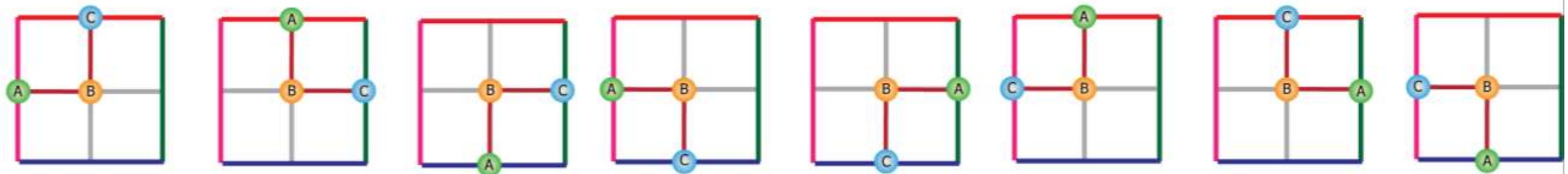
Calculate Entropy

$$S = k_B \ln W$$

Straight



Bent



$$W_{\text{Straight}} = 4$$

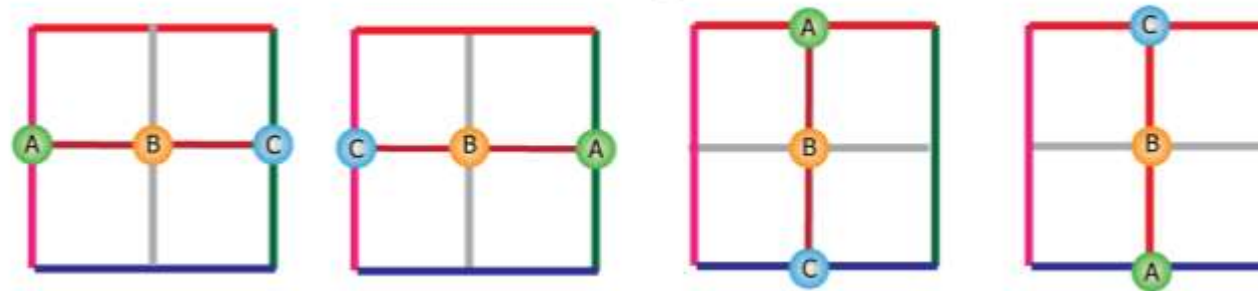
$$S_{\text{Straight}} = k_B \ln 4 = 1.4 k_B$$

$$W_{\text{Bent}} = 8$$

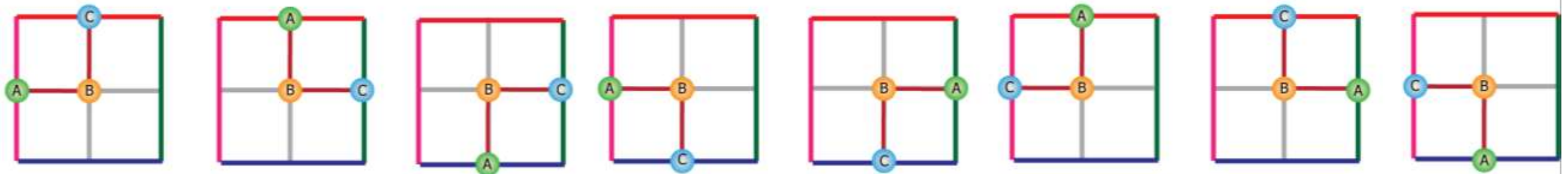
$$S_{\text{Bent}} = k_B \ln 8 = 2.1 k_B$$

Calculate Free Energy

Straight



Bent



$$G_{straight} = 0 - 1.4 k_B T$$

$$G_{bent} = A - 2.1 k_B T$$

Bent or Straight

$$G_{Straight} = 0 - 1.4 k_B T$$

$$G_{bent} = A - 2.1 k_B T$$

- When $A = 0.1 k_B T$ bent structure is preferred
- However, when $A = 1.5 k_B T$, straight structure is preferred

Protein folding in reality

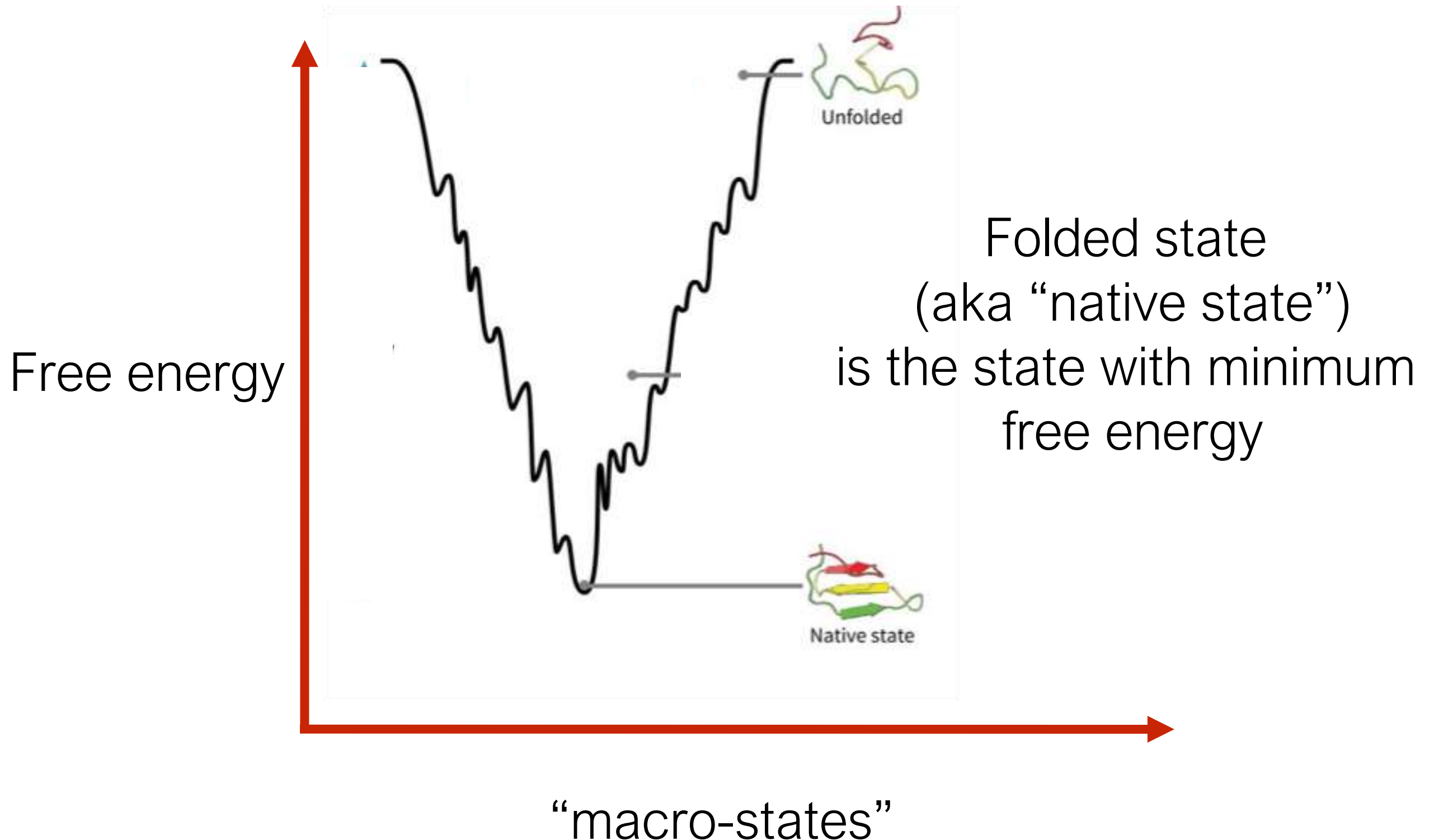
So far we considered only toy models for protein folding

However, in reality

- Protein monomers have many types of interaction: electrostatic, bending, Van der Waals etc
- Protein monomers interact with water (hydrophobic/hydrophilic)
- Energy/Enthalpy is more complicated than simple bending example we discussed
- One has to worry about entropy of the whole system (protein monomers+water+other ions like Na^+ and Cl^-)

Protein folding in reality

Typical proteins “see” such a free energy landscape



Protein folding in reality

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NIH Center for Macromolecular Modeling and Bioinformatics
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presents

Six Microseconds of Protein Folding

Video Source: <https://www.youtube.com/watch?v=sD6vyfTtE4U>

Molecular Dynamics (MD) Simulations

- Calculates **motion of atoms** in a molecular assembly **using Newtonian dynamics** to determine the net force and acceleration experienced by each atom.
- Newton's law of motion: $\mathbf{F} = m\mathbf{a}$ where $\mathbf{F} = -\frac{dU(\mathbf{r})}{d\mathbf{r}}$

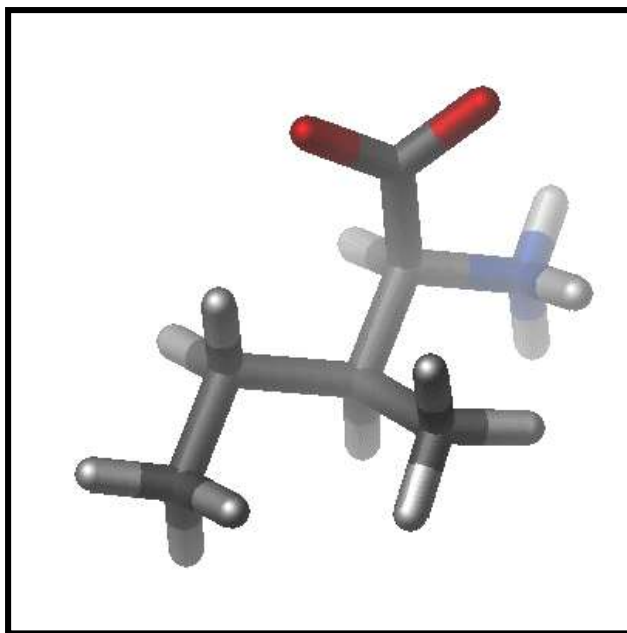


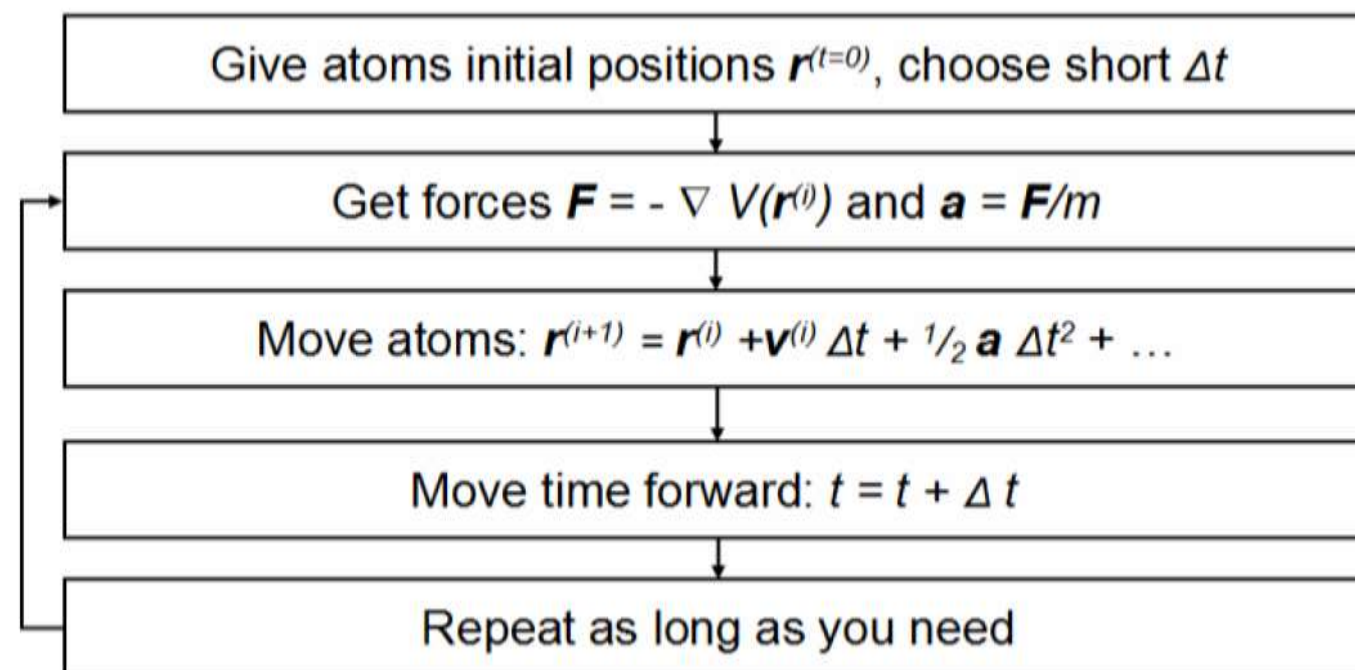
Figure taken from a talk by Dr. Suman Chakrabarty, National Chemical Laboratory, Pune, India

$$U(\mathbf{r}) = U_{\text{bonded}} + U_{\text{non-bonded}}$$

$$U_{\text{bonded}} = U_{\text{bond}} + U_{\text{angle}} + U_{\text{torsion}}$$

$$U_{\text{non-bonded}} = U_{\text{VDW}} + U_{\text{electrostatic}}$$

$$\Delta t \sim 10^{-15} \text{ s (fs)}$$



Ramachandran Plot

Prof. G. N. Ramachandran, an Indian Physicist, made a famous discovery on proteins

Ramachandran and his colleagues said that, due to various constraints of arrangements of atoms in 3D, neighboring amino acids (protein monomer) in a protein can't fold into any shape — there are some constraints that their arrangements have to satisfy



Ramachandran Plot

Watch movie on legacy of Prof. G. N. Ramachandran https://www.youtube.com/watch?v=T_YgWjoaLXQ



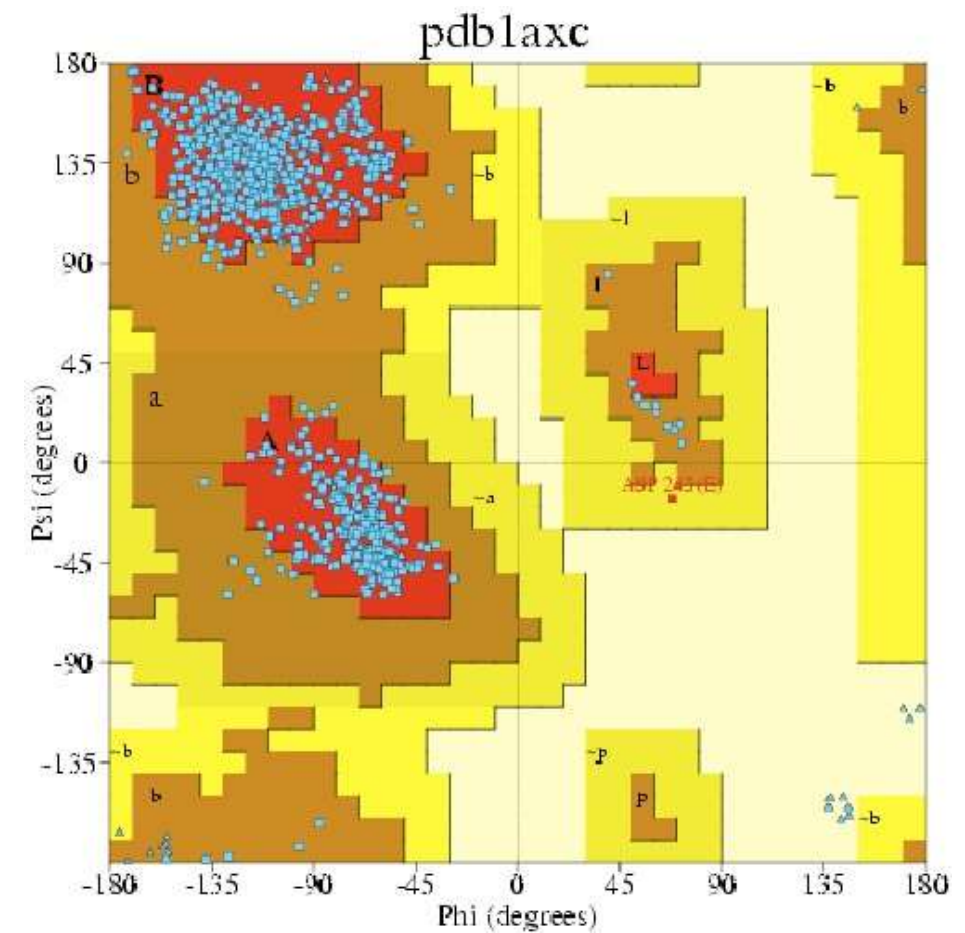
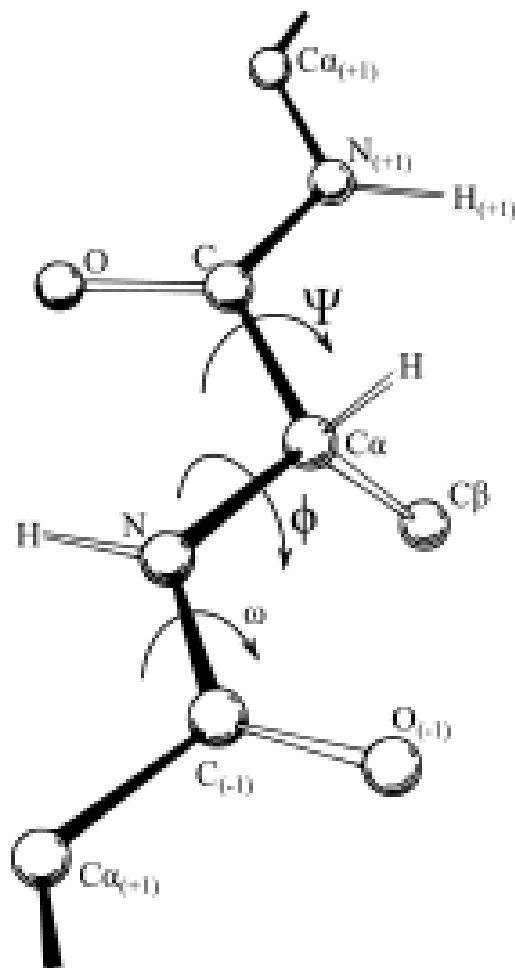
Ramachandran Plot

Watch movie on legacy of Prof. G. N. Ramachandran https://www.youtube.com/watch?v=T_YgWjoaLXQ



Ramachandran Plot

The set of “allowed” angles can be plotted: This plot is called the “Ramachandran Plot”



The red, brown, and yellow regions represent the favored, allowed, and "generously allowed" regions

Gene-Expression



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Figure Source: <https://downloads.safariltd.com/images/1000x1000/safariltd-human-organs-689304-1.jpg>

All cells of a human body have EXACTLY the same DNA i.e. cells that form your eye, cells that form your kidney, cells that form your bone

Gene-Expression

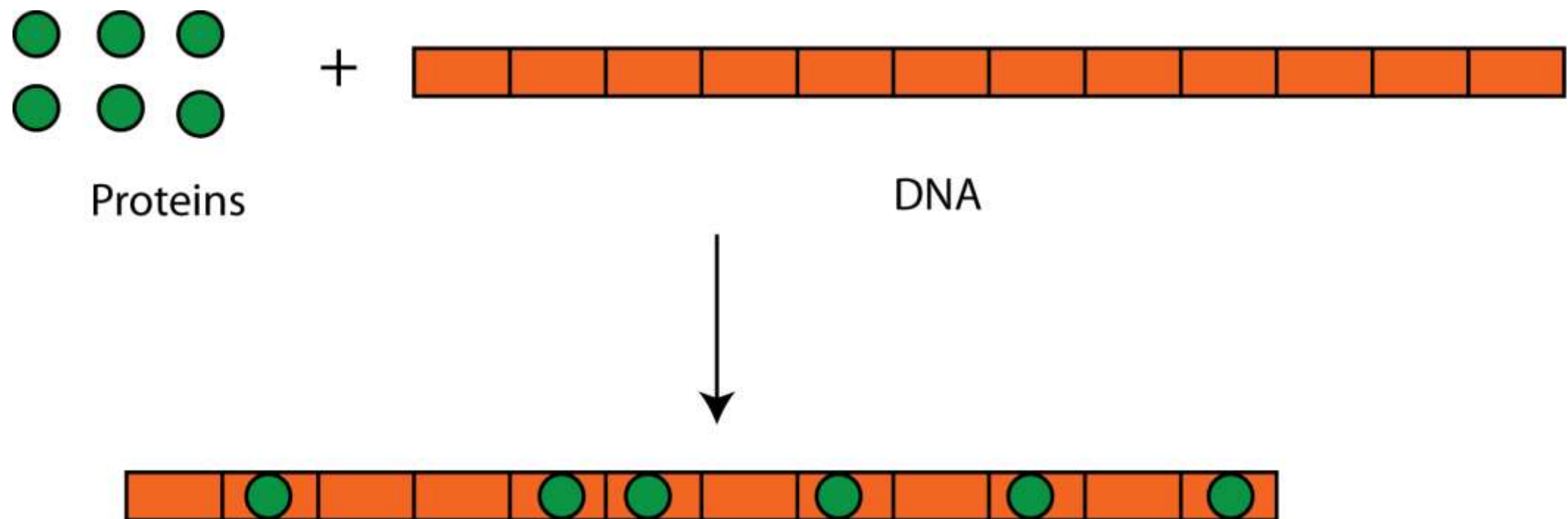
- Same “genetic code” but works differently, how?
- We roughly know that each cell uses slightly different parts of DNA i.e. Cells in your eye “expresses” (reads) a set of different “genes” from cells in your skin

Gene-Expression

- Cells can “regulate” packaging and reading of DNA depending on many factors, including the external environment
- There are many proteins involved in regulating this; these proteins bind onto DNA to regulate “gene expression” (reading of genes)
- We can again use free-energy minimization to understand Protein-DNA binding and its dynamics

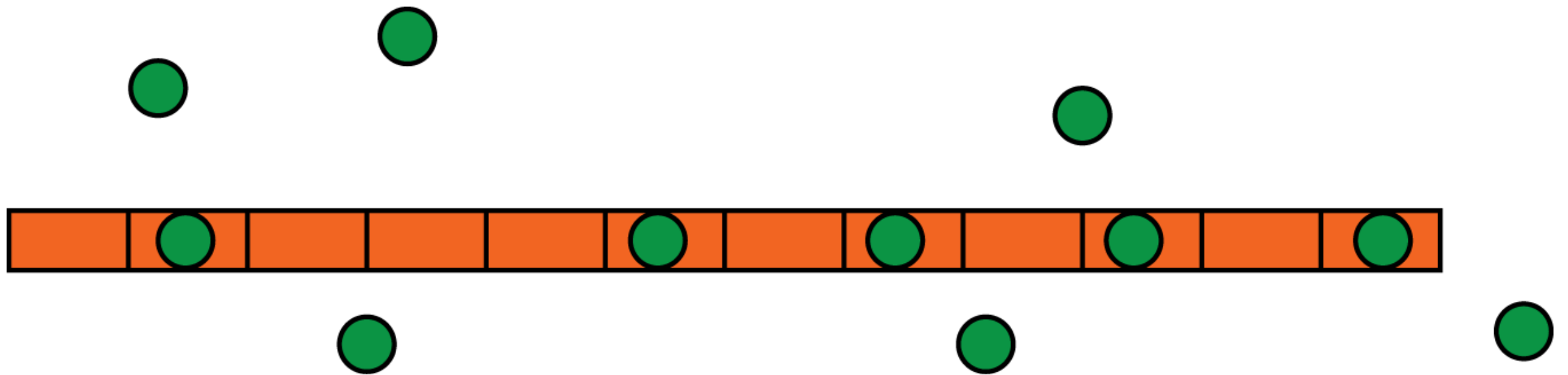
Protein-DNA Binding

- Typically, proteins and DNA are oppositely charged
- Interaction energy favors binding; just like positive and negative charges to come together

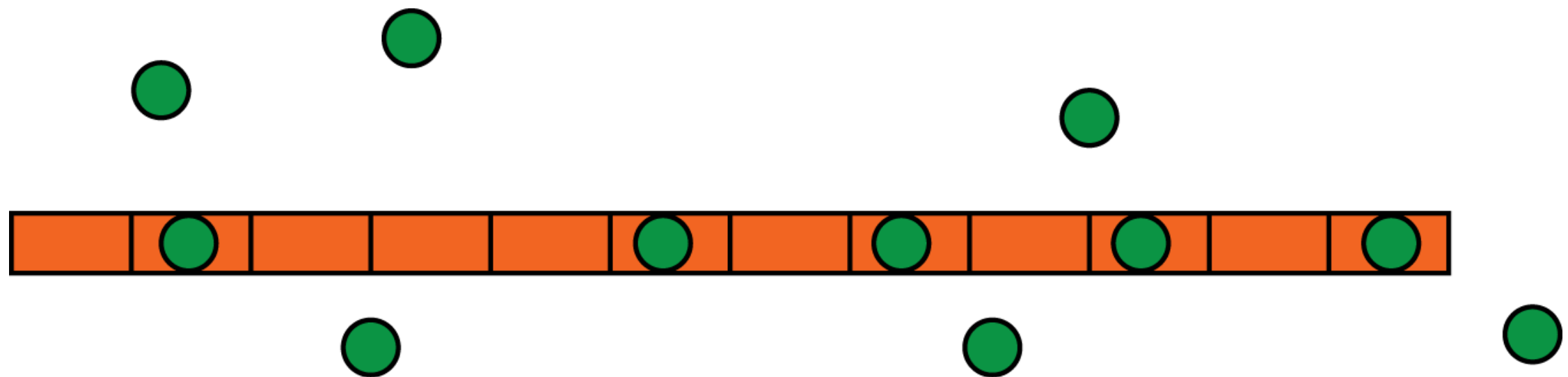


Protein-DNA Binding

Imagine a DNA with N binding sites (locations) where a certain protein can bind with high affinity

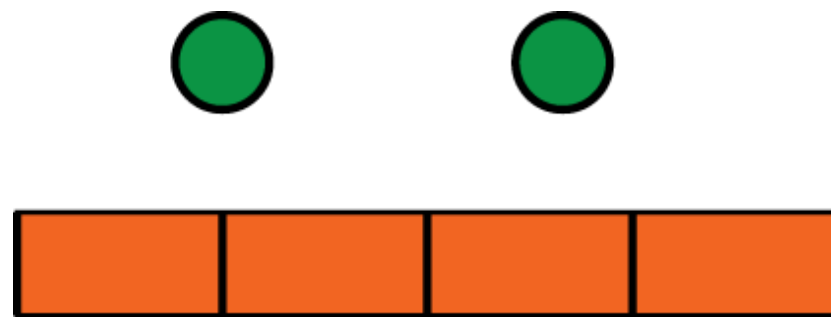


Protein-DNA Binding



If you do an experiment, how many of those “locations” will be occupied by proteins?

Protein-DNA Binding



Imagine a “state” with m proteins bound. ($m < N$)

In this picture $m=2$, $N=4$

Protein-DNA Binding

- Assume each protein binding gives a constant energy change $-\varepsilon k_B T$
- If m proteins are bound then What is the total energy change?

Protein-DNA Binding

$$U = -m\varepsilon k_B T = -N\rho\varepsilon k_B T$$

In other words, ε is the binding energy of a protein

Density of proteins

$$\rho = \frac{m}{N}$$

Protein-DNA Binding

Imagine a “macro-state” with m proteins bound. ($m < N$)

What is the entropy?

Protein-DNA Binding

“m” proteins, “N” binding locations

Number of arrangements (“micro-states”)?

Let's calculate this for $m=2$, $N=4$

Protein-DNA Binding

“m” proteins, “N” binding locations

Number of arrangements (number of “micro-states”)

$$W = \frac{N!}{m! (N - m)!}$$

Protein-DNA Binding

$$S = k_B \ln W = k_B \ln \left(\frac{N!}{m! (N - m)!} \right)$$

Use Sterling's Approximation

$$\ln p! \approx p \ln p - p$$

Protein-DNA Binding

With Stirling's approximation, one can rewrite entropy as

$$S = -k_B N [\rho \ln \rho + (1 - \rho) \ln(1 - \rho)]$$

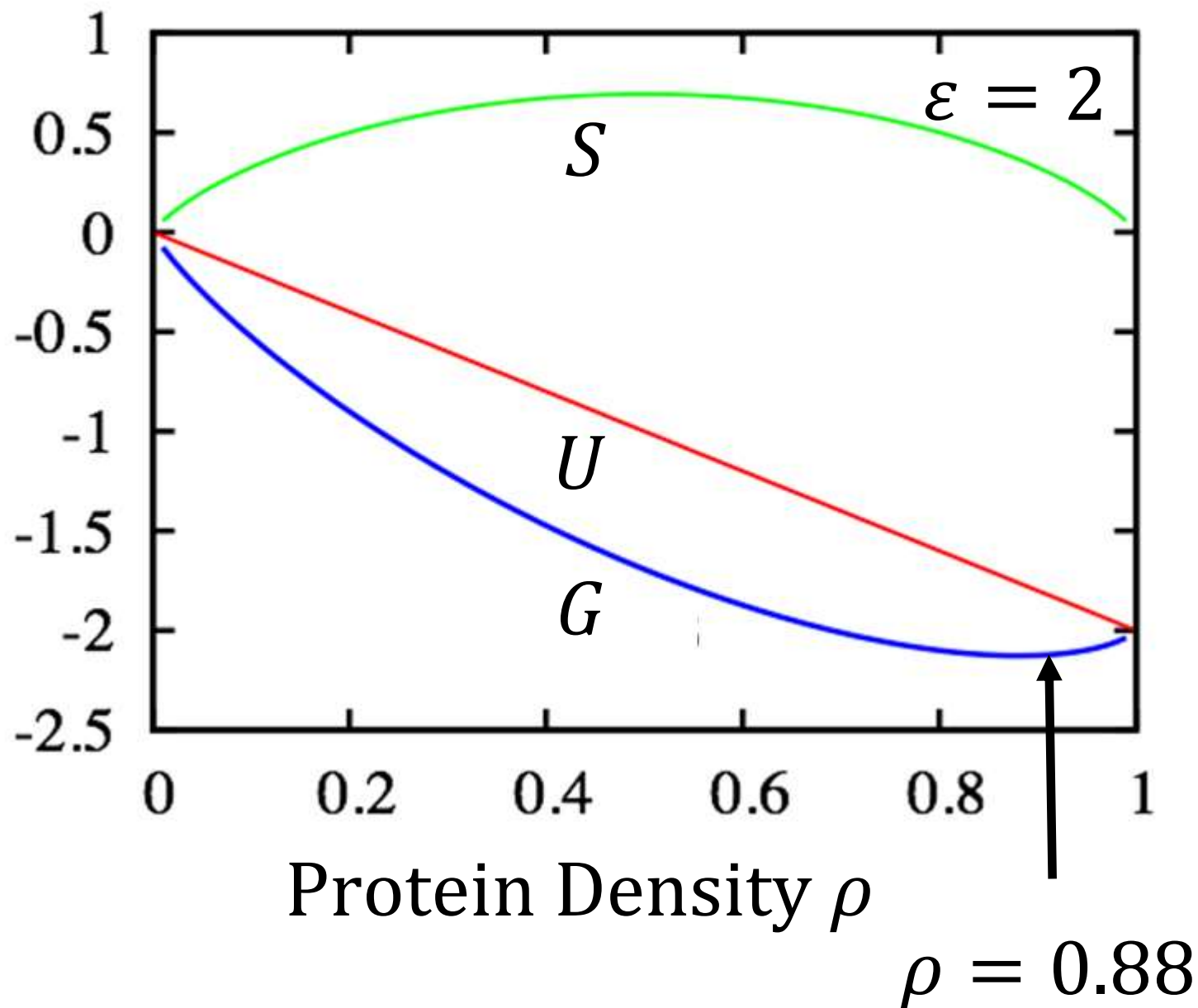
$$G = U - TS$$

$$G = -N\rho\varepsilon k_B T - k_B T N [\rho \ln \rho + (1 - \rho) \ln(1 - \rho)]$$

$$\frac{G}{Nk_B T} = -\rho\varepsilon - \rho \ln \rho + (1 - \rho) \ln(1 - \rho)$$

Protein-DNA Binding

The protein-DNA system would like to go to its minimum free energy “macro-state”



$$\frac{\partial G}{\partial \rho} = 0$$

$$\rho = \frac{e^{\epsilon}}{1 + e^{\epsilon}}$$

Summary So far..

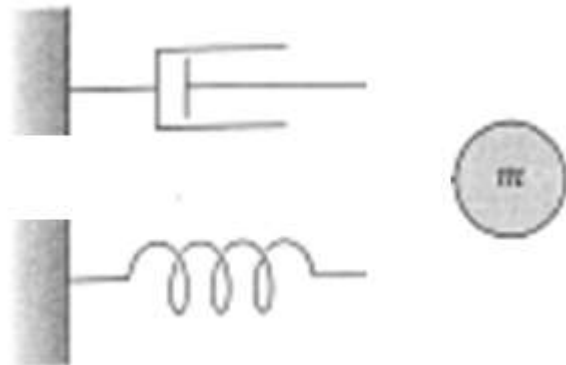
- Proteins that bind on to the DNA control the “gene” expression in each cell
- Protein-DNA system minimizes its free energy
- Number of proteins bound to DNA will depend on the free energy of the protein-DNA system

Summary of Lecture 6

- Toy models of Protein-folding
- Ramachandran Plot
- Toy Model for Protein-DNA binding
- A simple model of Protein-DNA binding

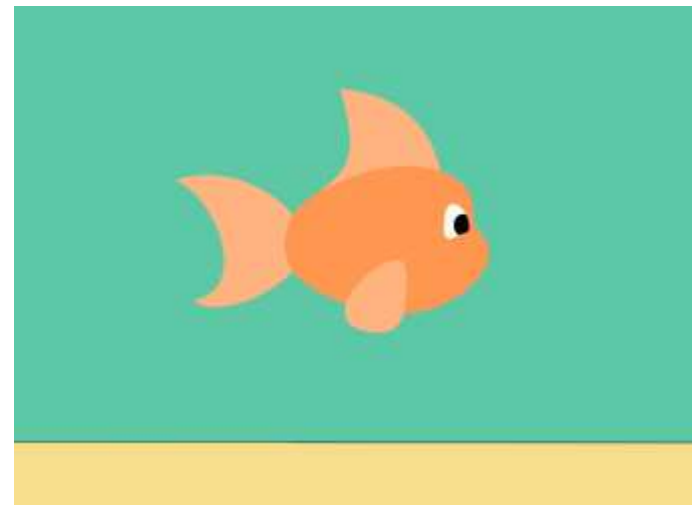
Take Home Messages

- You can use combination of mass, spring and dashpots to understand some biological phenomenon-bacterial swimming and sedimentation of proteins



Take Home Messages

- Swimming of a bacteria is different from swimming of a fish

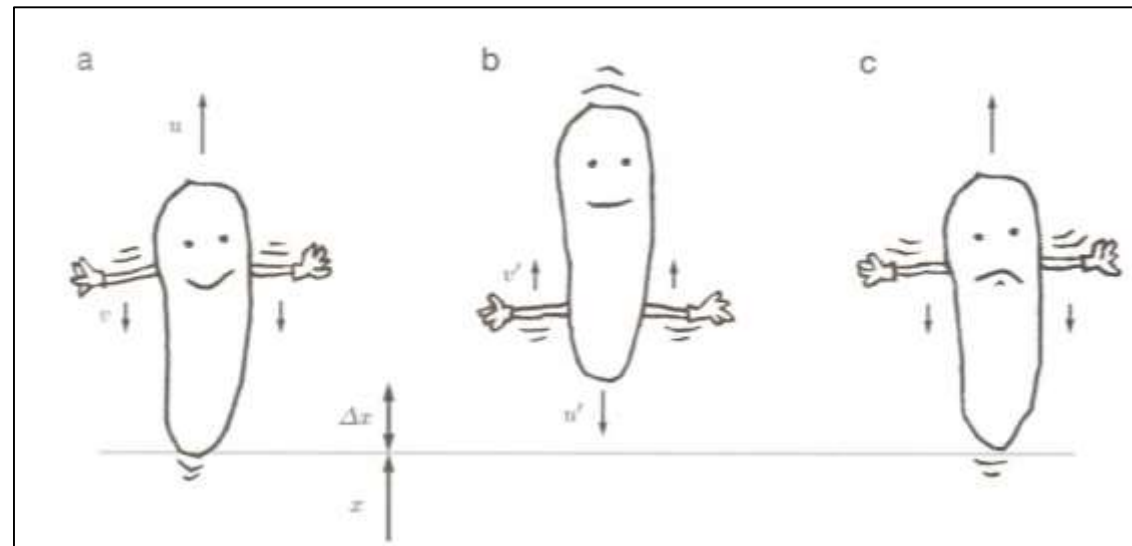


- Motion at low-Reynolds number vs motion at high Reynolds number
- Motion at low-Reynolds number is dominated by viscous forces

Take Home Messages

- A low-Reynolds number microorganism can't swim by executing *geometrically reciprocal motion*

The Scallop Theorem



Take Home Messages

- Thermal forces and Brownian motion

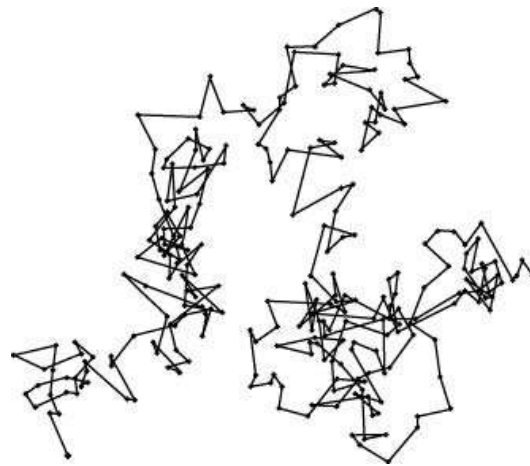


Figure Source: http://www.doc.ic.ac.uk/~nd/surprise_95/journal/vol4/ykl/report.html

- Thermal energy is comparable with other deterministic energy at molecular scales

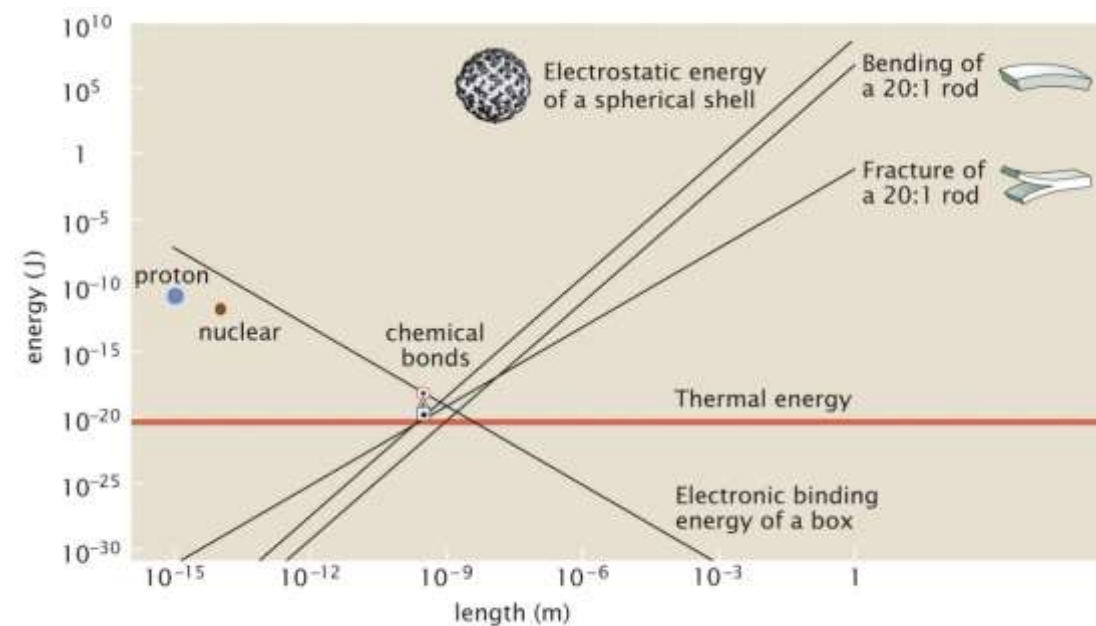
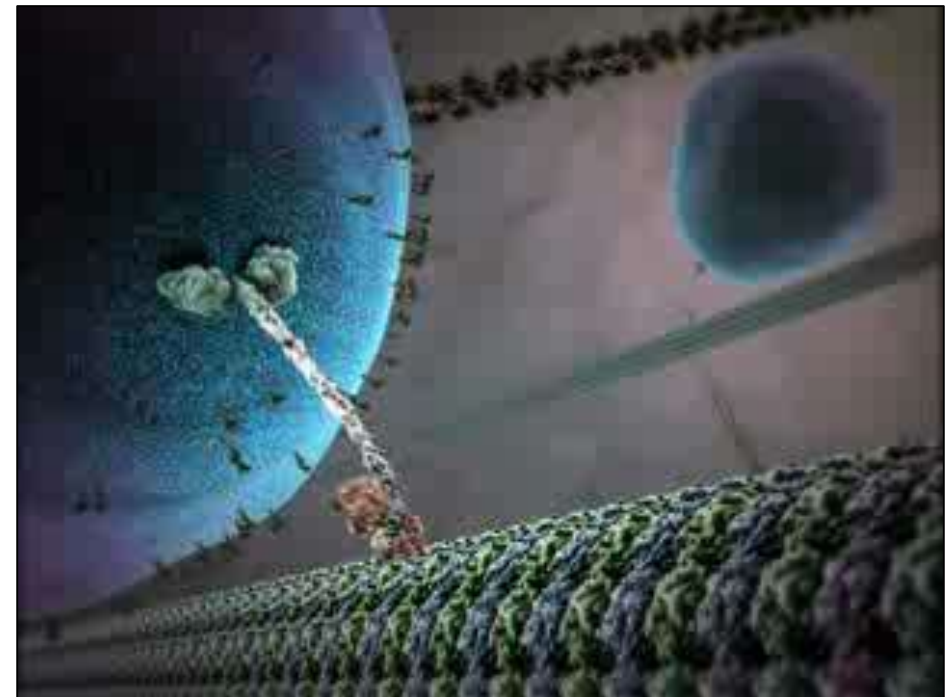
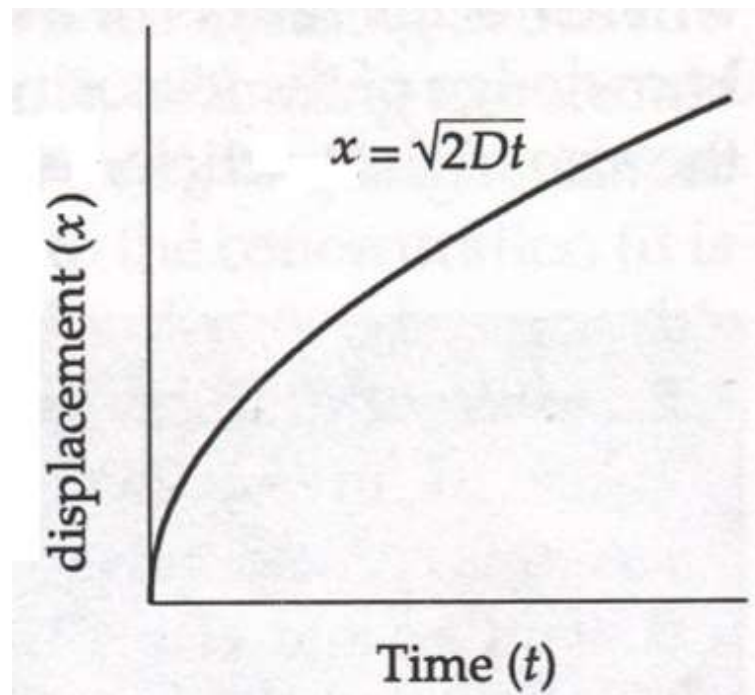


Figure 5.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Take Home Messages

- Diffusion and Diffusion Equation
- Why diffusion is not sufficient for transport



- Einstein Relation $\gamma D = k_B T$
- Reaction-Diffusion System

Take Home Messages

- In presence of thermal energy, biological systems minimize free energy
- Concept of Macro-state and Micro-states
- How to calculate Entropy from Micro-states
- Toy models of Protein-folding and Ramachandra Plot
- Toy Model for Protein-DNA binding

End of Physical Biology Module

Physical biology or Biophysics exciting !!!

**you realized that we can use the
physics and mathematics you
learned, to think about
biological problems!**

End of Physical Biology Module

**Every time you see a biological phenomenon,
think how to use your science/engineering
knowledge to understand it**

**We know very little about what is going on in
many biological processes**

***So, there is a great opportunity for you to
go and make important discoveries!!!***

Thank you!!!