LECTURE 7

BB 101

MODULE: *PHYSICAL BIOLOGY*

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Review

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

In this lecture: Briefly discuss Some Aspects of Real Protein Folding

Protein folding in reality

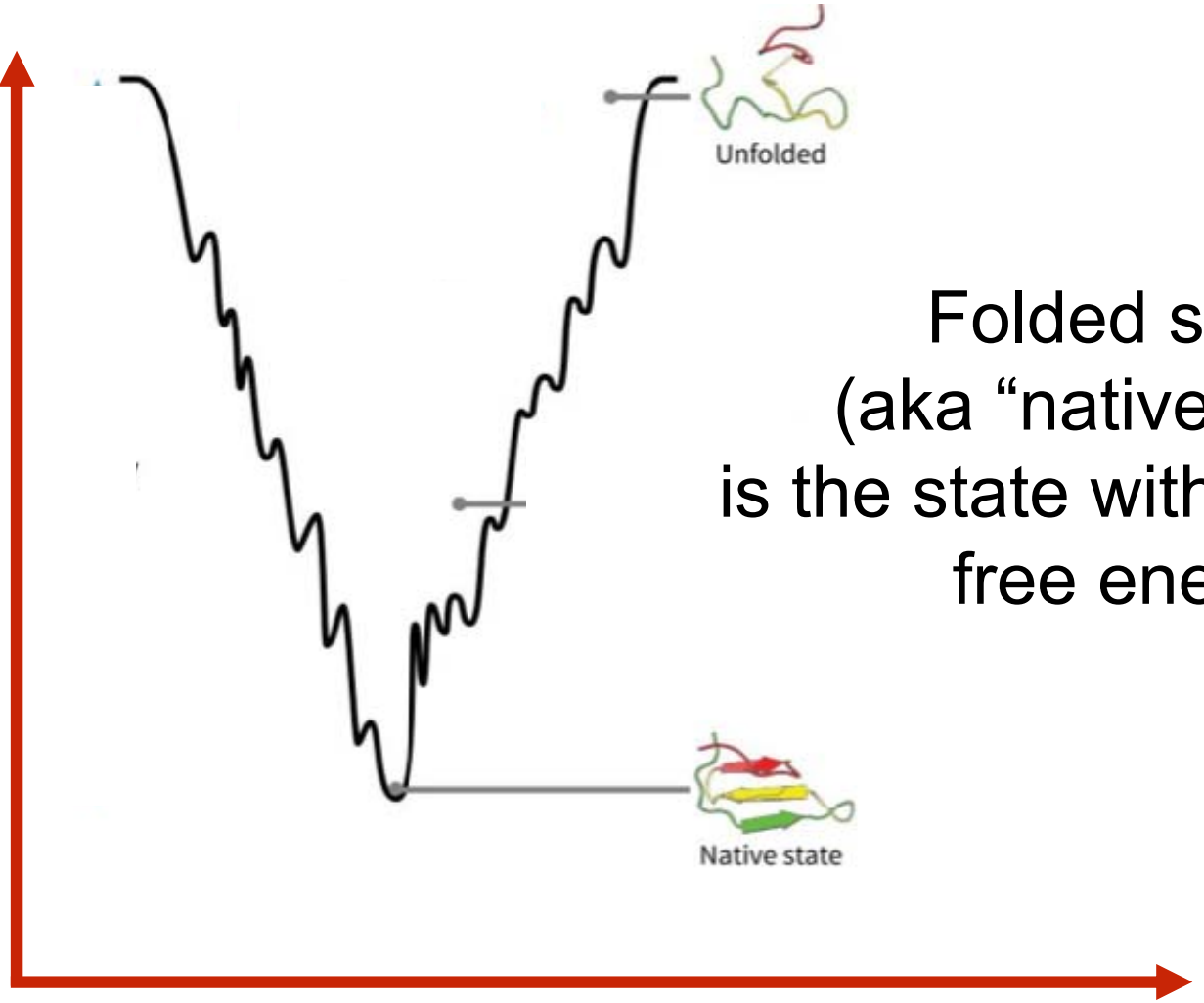
So far we considered only toy models for protein folding

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



Free energy

Folded state
(aka “native state”)
is the state with minimum
free energy

“macro-states”

Ramachandran Plot

About 50 years ago, 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

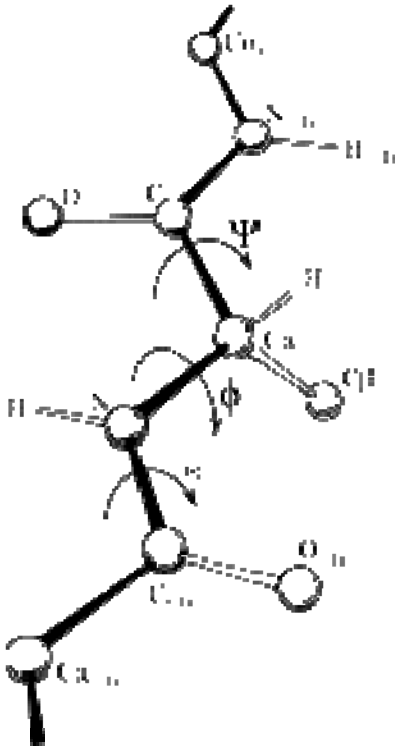
G. N. Ramachandran
(1922–2001)

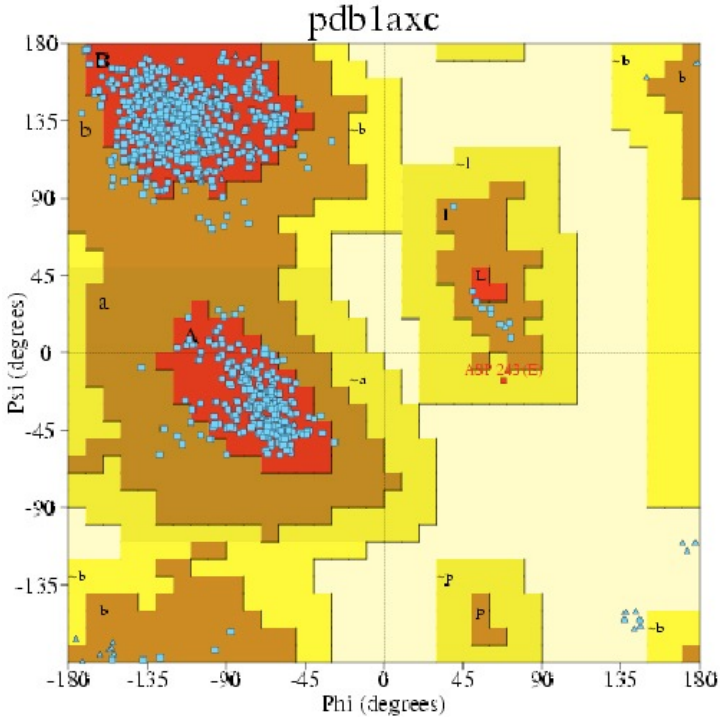
Watch movie on legacy of Prof. G. N. Ramachandran **"The Immortal Coils"**

Figure Sources: http://en.wikipedia.org/wiki/Ramachandran_plot

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

Figure Sources: http://en.wikipedia.org/wiki/Ramachandran_plot

Gene-Expression

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

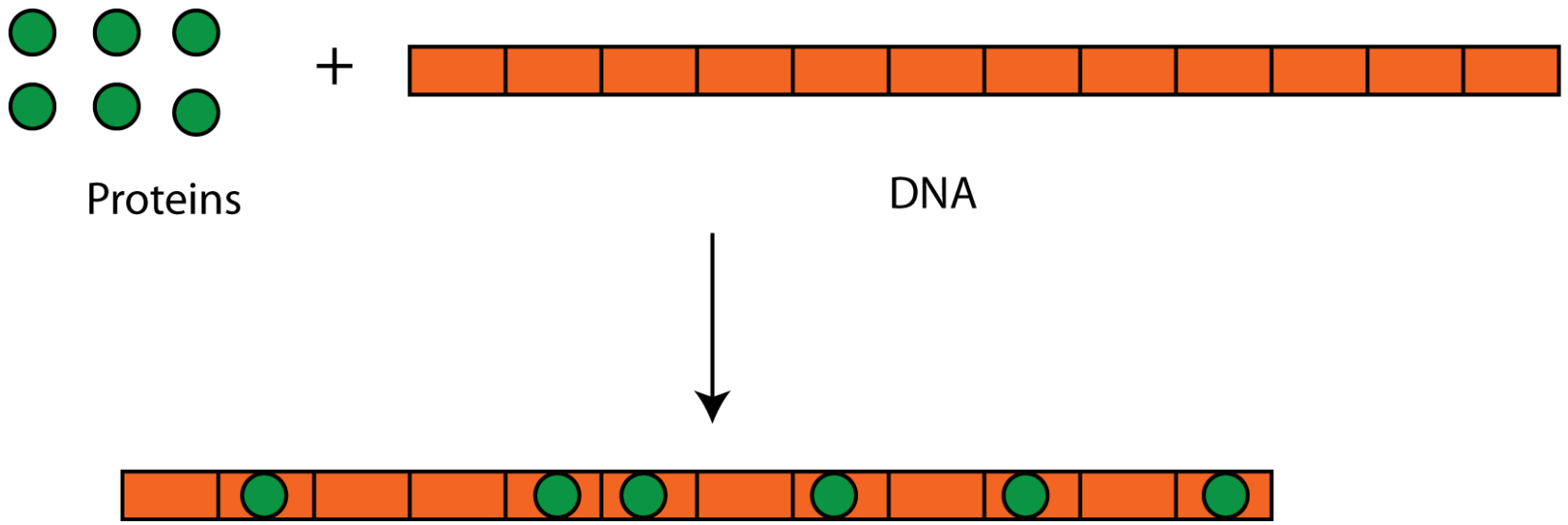
- There are many proteins involved in regulating this; these proteins bind onto DNA to regulate “gene expression” (reading of genes)

- We can again use free-energy minimization to understand Protein-DNA binding and its dynamics

Protein-DNA Binding

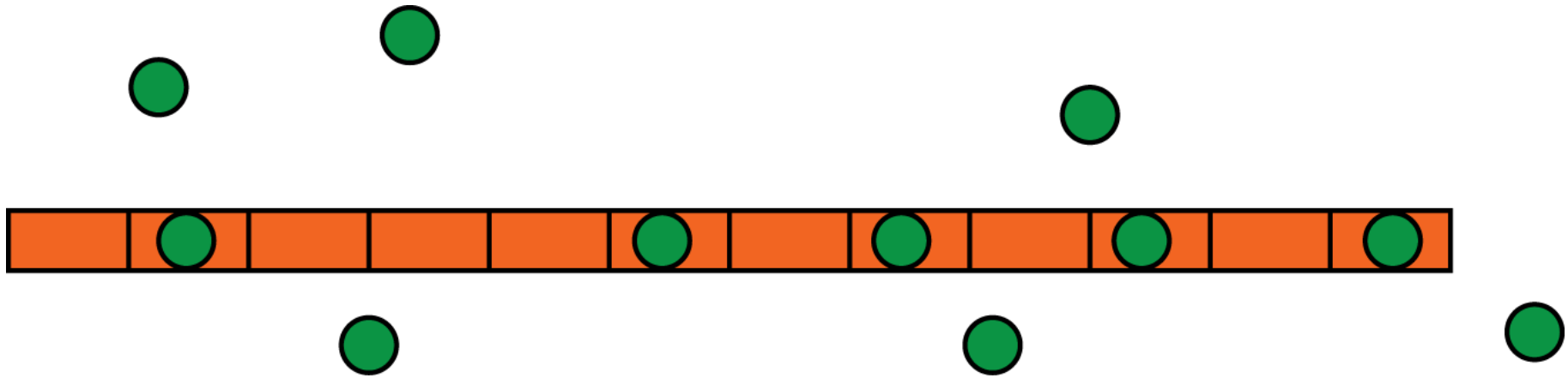
- Typically, proteins and DNA are oppositely charged

- Interaction energy favors binding; just like positive and negative charges to come together

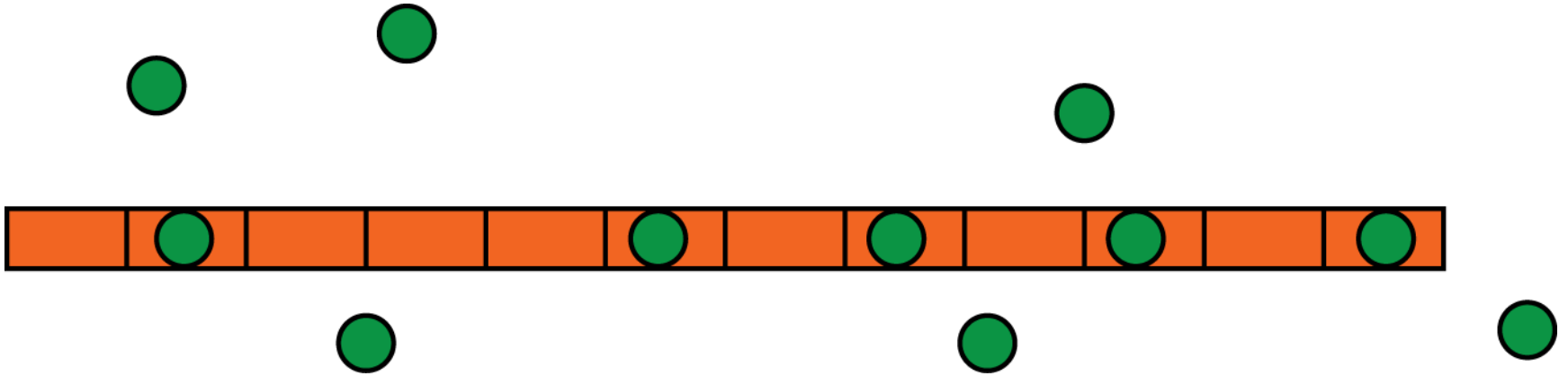


Protein-DNA Binding

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

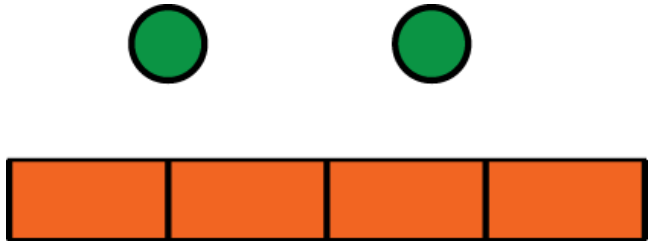


Protein-DNA Binding



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

Densityof 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

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

Use Sterling's Approximation

$$\ln p! \approx plnp \; - p$$

Protein-DNA Binding

With Stirling's approximation, one can rewrite entropy as

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

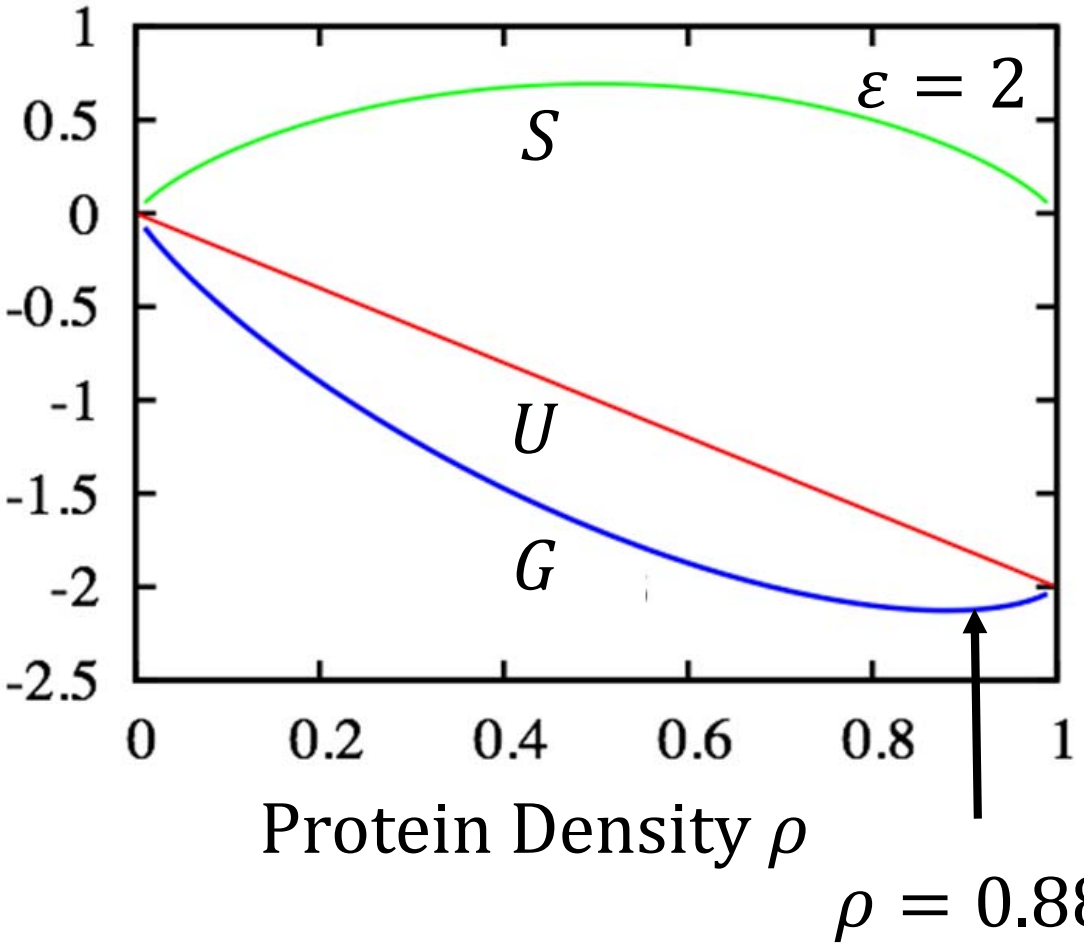
$$G = U - TS$$

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

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

Protein-DNA Binding

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



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

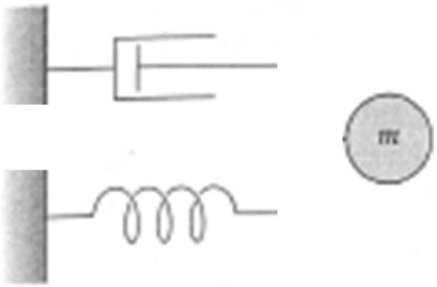
$$\rho = \frac{e^{\varepsilon}}{1 + e^{\varepsilon}}$$

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

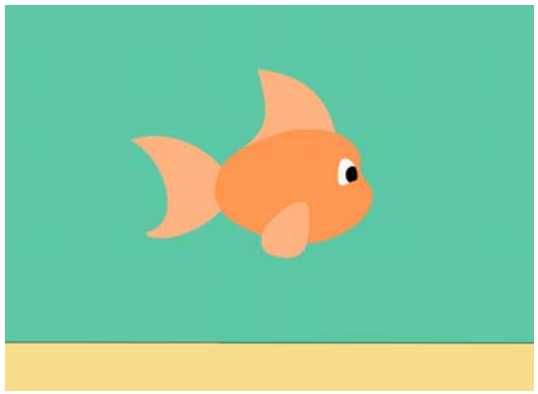
Take Home Messages

- 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 (whale)



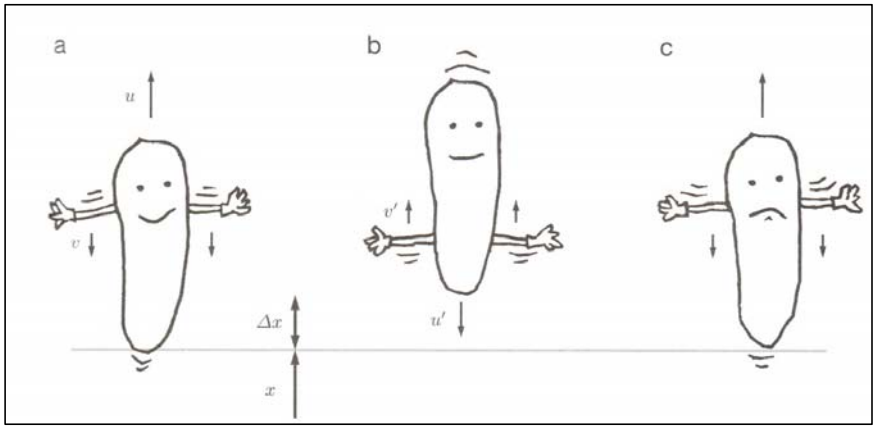
- Motion at low-Reynolds number vs motion at high Reynolds number

- 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

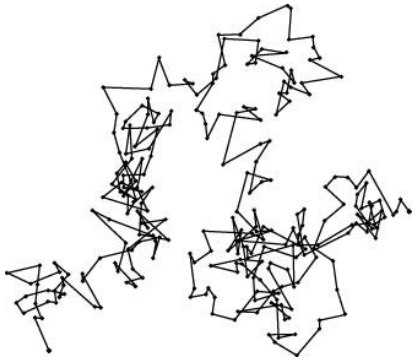


Figure Source: http://www.doc.ic.ac.uk/~nd/surprise_95/journal/vol4/ykl/report.html

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

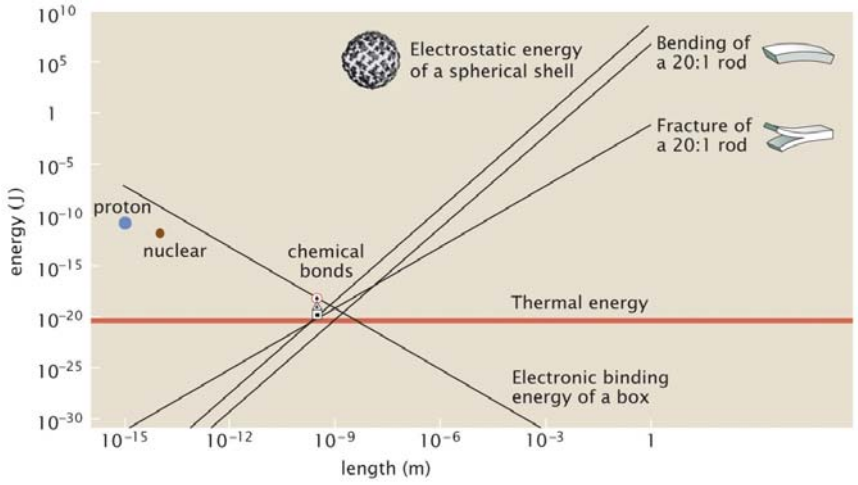
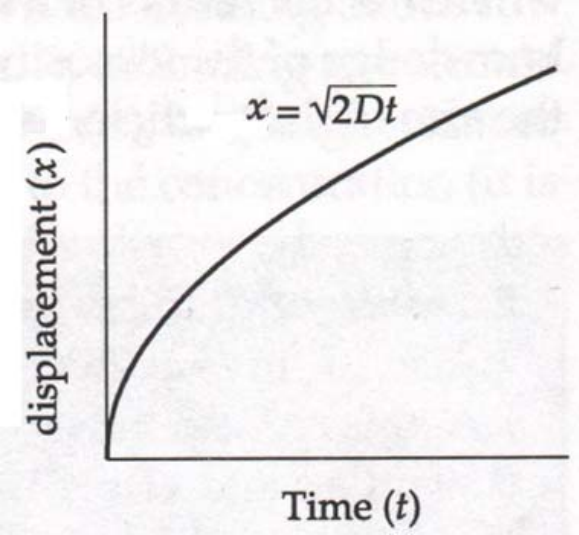


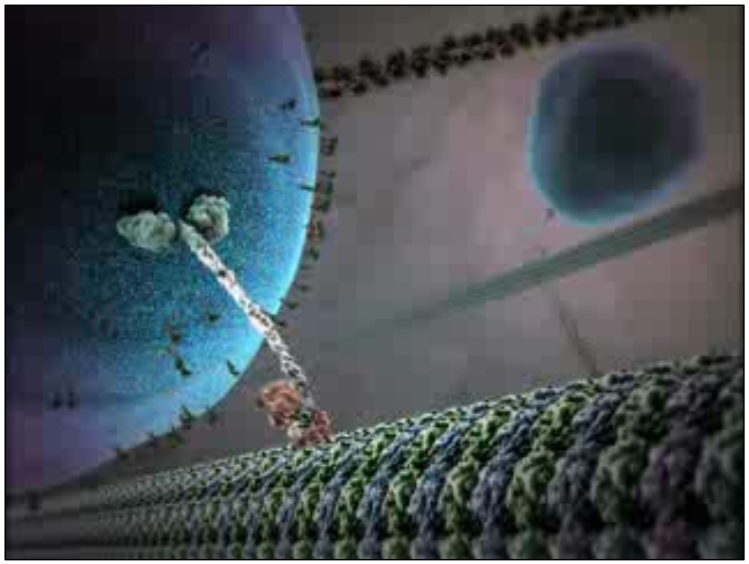
Figure 5.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Take Home Messages

- Diffusion and Diffusion Equation

- Why diffusion is not sufficient for transport



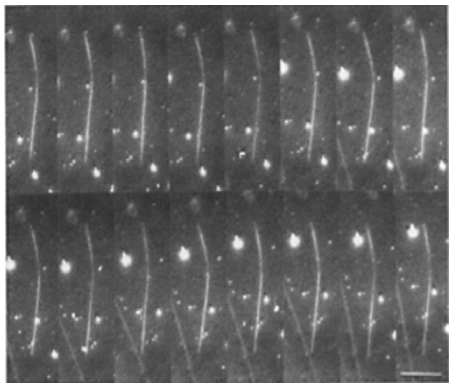


- Einstein Relation

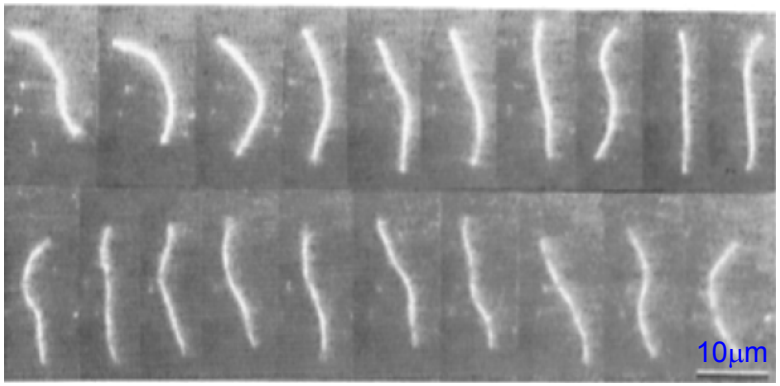
$$\gamma D = k_B T$$

Take Home Messages

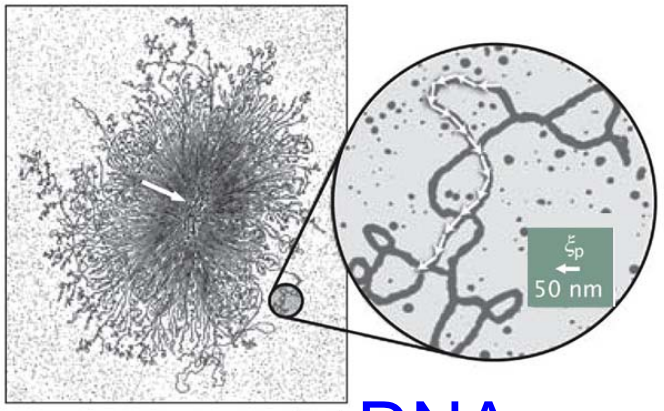
- Thermal Energy can bend the filaments



Microtubule



Actin Filaments



DNA

Figure 8.5 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

- Freely Jointed Chain (FJC) to calculate average size of the polymer
- Worm Like Chain model (WLC) to calculate energy required to bend a biofilament
- Significance of persistence length

Take Home Messages

- Microtubule and Actin filaments are polymers and can generate force

- Techniques to measure tiny forces AFM and optical Tweezers

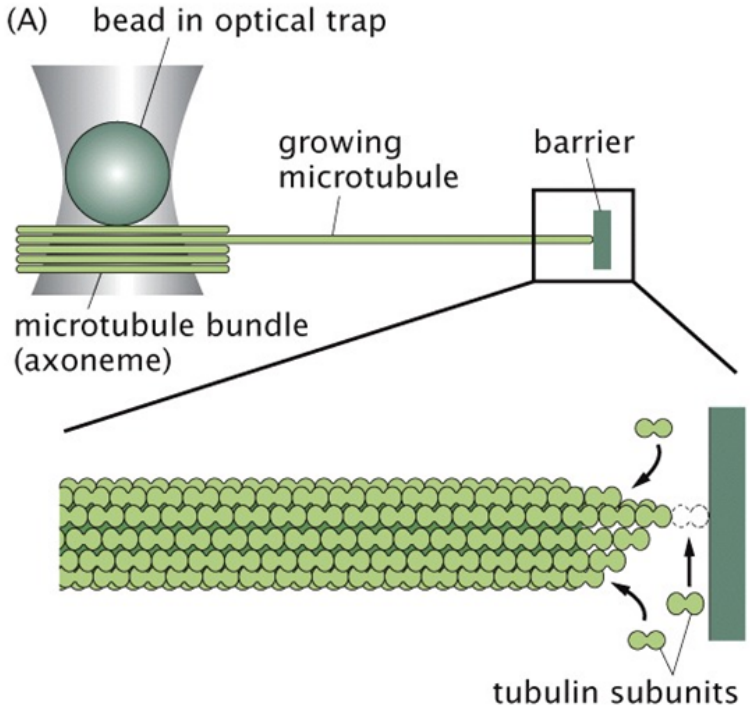


Figure 16.49 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

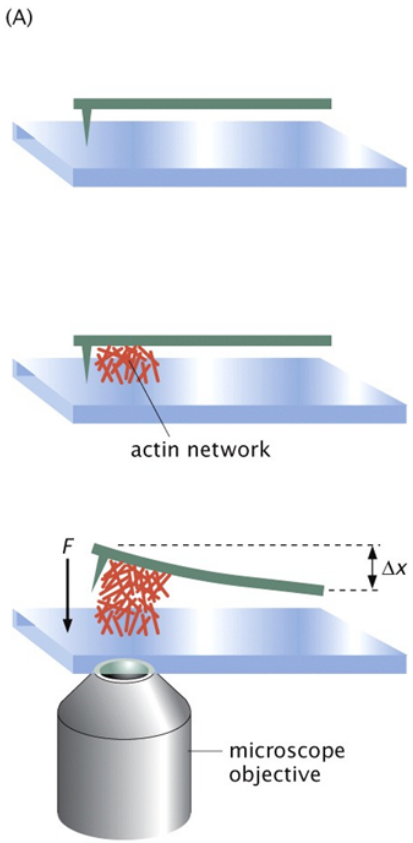


Figure 16.50 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

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!!!