

# Phys-301

## Biophysics: Physics of the Cell

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exercises (problems)



journal articles

# Overall course goals

- Understand the **organization of the cell** and its components
- Examine **universal** features/processes of cells
- Model features/processes using **physical concepts**

*Note: This course is taken by students from PH, SV, GM ...*

# Biophysics overview

## Key physical concepts behind most biophysical models:

1. Simple numerical estimates
2. Elasticity theory (1D, 2D, 3D)
3. Statistical mechanics models
4. Diffusion and random walks
5. Circuit/network theory
6. Fluid mechanics (Newtonian, Navier-Stokes) (BA5, Ramirez-San Juan)
7. Information theory, dynamical systems (MA1/3, PHYS-302, Rahi)
8. Biopolymers (MA2, PHYS-441, De Los Rios)
9. Charges in solution (Poisson-Boltzmann)
10. Rate equation models of chemical kinetics

# Course content

## Topics (lectures):

1. **Introduction to the cell** (1-3)
2. **Biological membranes** (4-5)
3. **Proteins** (6-7)
4. **Dynamics** (8-9)
5. **Genomes** (10-13)

## Course components:

1. **Introduction to systems and concepts**
2. **Description of observations and measurements**
3. **Estimates of relevant numbers / development of quantitative models**
4. **Analysis of research articles**

## Why is the course designed this way?

Introduce fundamental topics in cellular biophysics

Develop skills in model building

Practice reading to find information, provide context

Consider uncertainties of unsolved problems

# Course structure

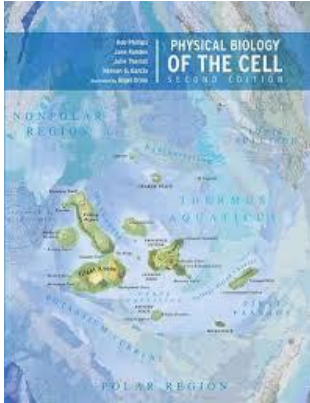
- One lecture and one exercise session per week.
  - (C) Mon, 13:15-15:00 (SM).
  - (E) Mon, 15:15-16:00 (SR or NM)
- Your role:
  - Read weekly before the course from PBOC (~1-2 hours)
  - Attempt the exercises/article before the exercises (~1-2 hours)
- Lectures will introduce and develop topics
- Exercises: problem solving or analyzing journal articles
- Written final exam

## **Resources:**

- Moodle
- Lecture slides (TAKE NOTES)
- Bionumbers website <https://bionumbers.hms.harvard.edu/search.aspx>
- Physical Biology of the Cell by Rob Phillips, Jane Kondev and Julie Theriot.
- Selected journal articles

# Your roles

# 1. Before class: read PBoC, glossary, attempt weekly assignment



### Exercise set II

### 1. A feeling for the numbers: molecular

**a)** Estimate the mass of a "typical" amino acid explaining how many of each type of atom are in each. List the 3 key amino acids: glycine, proline, arginine.

**b)** On the basis of your result for part (a), estimate the mass of a protein (reported in kDa) based on the number of amino acids in myosin II and G-actin and compare these proteins. \*Use the Pubmed protein database. <http://www.scripps.edu/~cdputnam/pr>

c) Estimate the size of the same proteins, proteins  $R_g = 0.395 \cdot M^{1/3} + 7.257$  [1], where radius of gyration in Angstrom (the root  $r$  from their common center of mass). Rewrite between mass and  $R_g$ .

[1] Narang et al. *Phys. Chem. Chem. Phys.*,  
2. Areas, volumes and diffusion in orga

**a)** Estimate the area of the ER (endoplasmic reticulum) form. Use a model for its structure of 1a, and estimated values for  $a$  and  $d$  bases (scale bar = 1  $\mu\text{m}$ ).

### A quantitative model for m low-energy intermediates

[illegible]

**I**n biological membrane fusion, the lipid bilayers of two distinct

■ Membranes become one, and initially separated aqueous compartments become continuous. Even though biological fusion is mediated by proteins, the lipids must transiently leave their lamellar orientations for lipid merger to occur. It is generally thought that the lipid rearrangements of biological fusion proceed in two stages. In the first, the contacting membranes (referred to as "oil" droplets here) are bridged, but the distal (distant "true") leaflets have not yet merged, a stage known as hemifusion. In the second, the distal leaflets merge and, in so doing, generate a pore. The pore is then enlarged by the merging process as often observed in Erythrocytes within an extended hemifusion diaphragm, electron microscopy indicates that pores, in fact, form at different, but ordered, lipid sites (27).

The transition/interactions of *cn* monofaunas during hominization will expose hydrophilic portions of the lipids to water. Because of the hydrophobic nature of the lipids, the monofauna and water, the sites of hydrophobic regions exposed to water must be kept small to help provide a maximum number of disordered lipid tails. The basis of such reasoning, more than 20 years ago is a truism, that is, "A stick is not a stick if it is too long." The lipid monolayer (3) is a stick as treated when the *cn* monofaunas heal and merge, the train monofaunas have not yet come into contact. The monofauna are not yet healed, the monofauna are still two separate monofaunas and found to be rather large for monofaunas of *non spontaneous* curvature (4, 5). Because the two train monofaunas must contact each other after the stick is healed, the monofaunas must be small enough so that for the train monofaunas to come into contact was calculated (3). This latter bonding energy was found to be inordinately large, more than 100 kT. These unrealistically large predicted energies must be reduced to a more realistic value. The energy of fusion has not yet been achieved. In addition, the physics responsible for pore formation from the point of stick formation were not accounted for in the prior quantitative theoretical treat-

## 2. During lecture: take notes, do in-class exercises

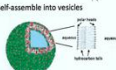
# BIOLOGICAL MEMBRANES

① Self-Assembly & Hydrophobic effect

Spontaneous organization


We say that "Living things tend to be complex and highly organized" (def. life). However, this is also true for some non-living systems. For instance, BIOLOGICAL MEMBRANES self-assemble with a little bit of energy.

- made of small ( $< 1$  kDa) amphiphilic molecules called lipids
- self-assemble into vesicles



Spontaneous Organization

Liquid phases



cell mass =  $1 \text{ pg} = 10^{-12} \text{ g}$

protein mass  $\approx 1.5 \times 10^{-13} \text{ g}$

in cytoplasm  $\approx 10^{-13} \text{ g}$

in membrane  $\approx 5 \times 10^{-14} \text{ g}$

mean protein size = 300 amino acids

mean amino acid mass = 100 Da

$1 \text{ Da} = 1.6 \times 10^{-24} \text{ g}$

Number of proteins in cell?

$$\frac{\text{mass of proteins}}{\text{mass of one protein}} = \frac{1.5 \times 10^{-13} \text{ g}}{300 \text{ amino acids}}$$
$$= \frac{1.5 \times 10^{-13} \text{ g}}{300 \text{ aa} \cdot \frac{100 \text{ Da}}{\text{aa}} \cdot \frac{1.6 \times 10^{-24} \text{ g}}{\text{Da}}}$$
$$= \frac{1.5 \times 10^{-13}}{5 \times 10^{-20}} \text{ proteins}$$

$\approx 3 \times 10^6 \text{ proteins}$

**3. After lecture: participate in exercise session, complete weekly assignment, compare with posted solutions (Wednesday each week)**

# Lecture 1 outline

## Today's goal: Introductions

- Physical biology of the cell
  - The stuff of life
  - Model building in biology
  - Quantitative models and the power of idealization
- atoms / molecules  
electrical / mechanical
- philosophy / approach  
components: biomolecules  
physical models for different components  
examples

PBOC Chapter 1

# Physical biology of the cell

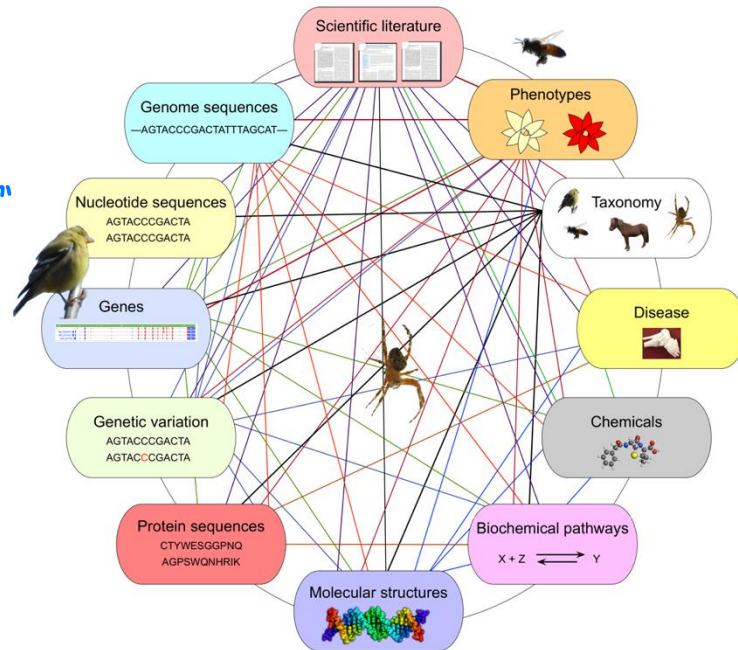
... all observation must be for or against  
some view if it is to be of any service!

*Darwin*

lots of data!

lists of constituents: "ome"

- genome (genetic sequences)
- proteome (proteins)
- biome (organisms)



Good models overlook  
some of the details,  
while keeping enough  
to make useful  
predictions.



# The stuff of life

What is life?



- grow
- move
- reproduce
- consume energy
- die
- respond to stimuli

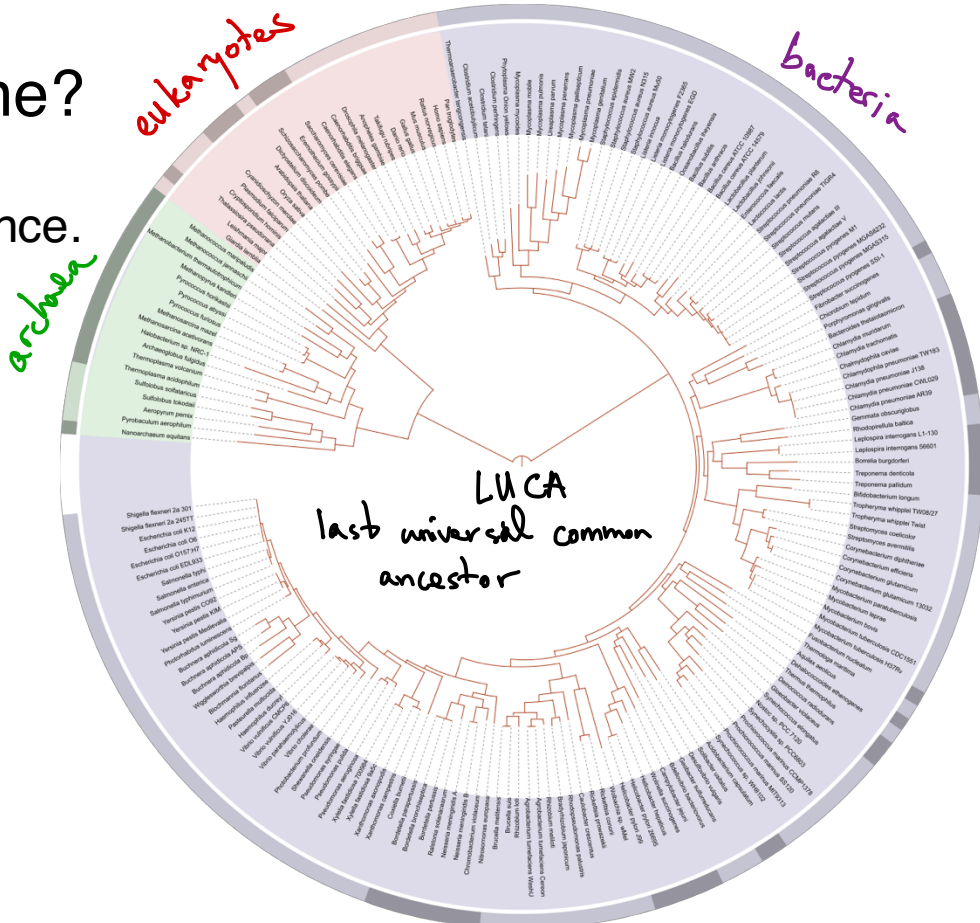
# The stuff of life

## Why is it so difficult to define?

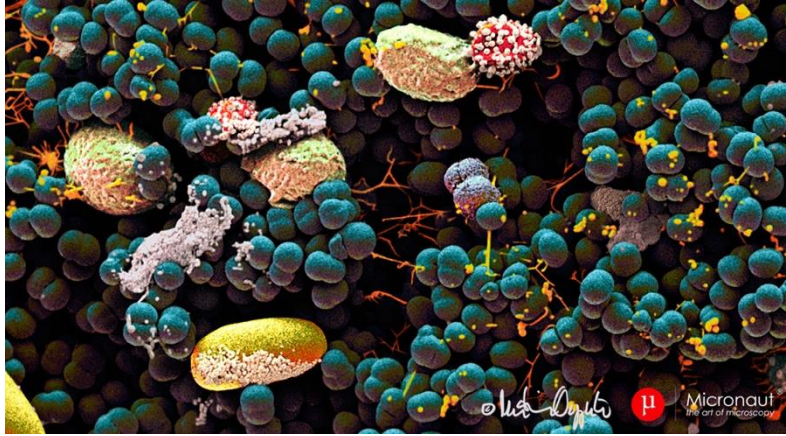
Life is a process, not a pure substance.  
A great diversity of life exists.

phylogenetic classification: evolutionary history, encoded in genes

NASA: life is a self-sustaining chemical system capable of Darwinian evolution

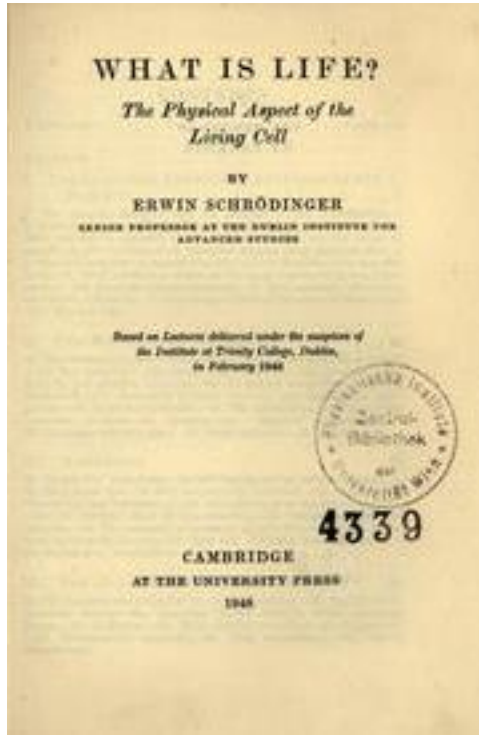


# LIFE ADAPTS/EVOLVES TO ENVIRONMENTAL NICHE





# The stuff of life



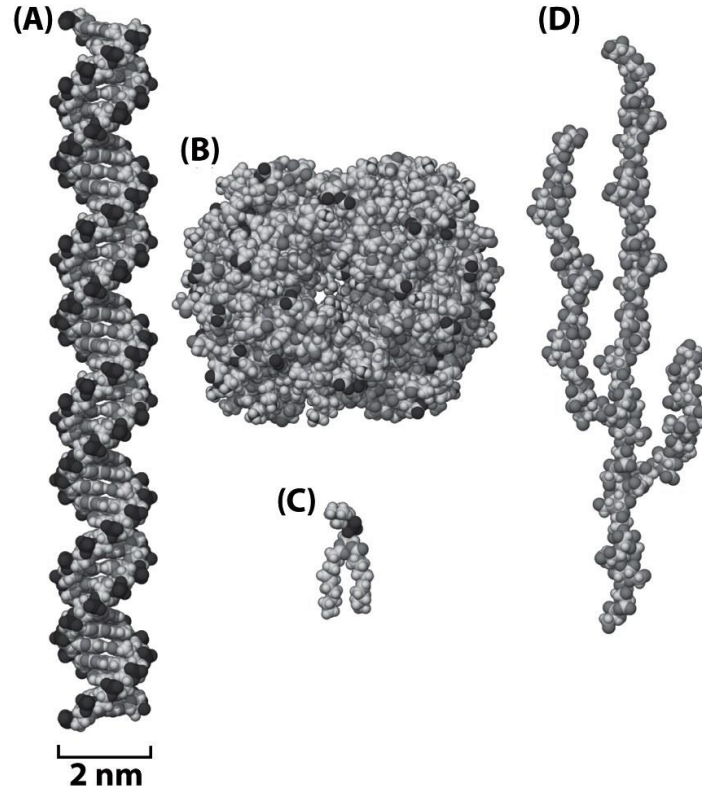
When is a piece of matter said to be alive? When it goes on "**doing something**," ... for a much longer period than we would expect an inanimate piece of matter to "keep going" under similar circumstances. When a system that is not alive is isolated or placed in a uniform environment, all motion usually comes to a standstill very soon as a result of various kinds of friction; differences of electric or chemical potential are equalized, substances which tend to form a chemical compound do so, temperature becomes uniform by heat conduction. After that the whole system fades away into a dead, inert lump of matter. A permanent state is reached, in which no observable events occur. *The physicist calls this the state of thermodynamical equilibrium, or of "maximum entropy."*

"What is life", 1944, Schrödinger

# The stuff of life

What macromolecules are cells made of?

Four main  
bio-macromolecules



Name the molecule  
What are its parts?  
What are its units?  
What is it used for?

# The stuff of life

What macromolecules are cells made of?

Name the molecule

What are its parts?

What are its units?

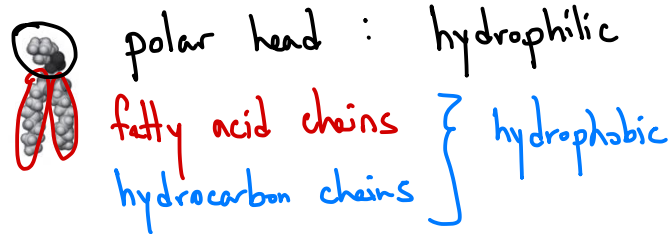
What is it used for?

lipid (phospholipid)

hydrophilic / hydrophobic

chain length, saturation of bonds in chains

cell membrane, compartmentalize (cell, organelles)



# The stuff of life

What macromolecules are cells made of?

(we aren't going to study this one)

Name the molecule

What are its parts?

What are its units?

What is it used for?

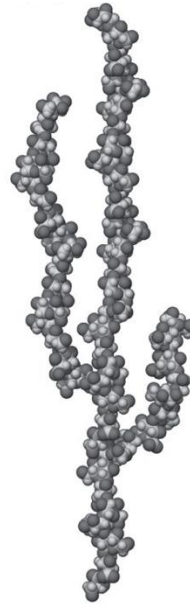
carbohydrate

carbon, hydrogen, oxygen

$(C_mH_2O)_n$  chain length  $n$

energy storage, cell surface

selectivity, cell walls



# The stuff of life

What macromolecules are cells made of?

Name the molecule  
What are its parts?  
What are its units?  
What is it used for?



DNA

bases / nucleotides (A, T, G, C)

base pairs

encoding genetic information



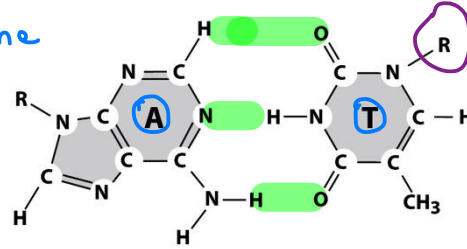
# The stuff of life

What macromolecules are cells made of?

Name the molecule  
What are its parts?  
What are its units?  
What is it used for?



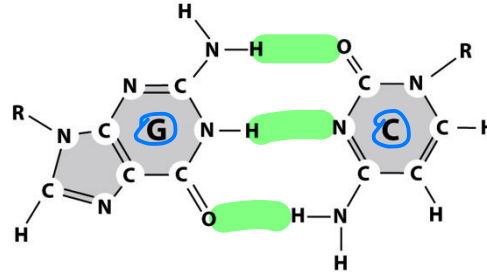
adenine



ribose

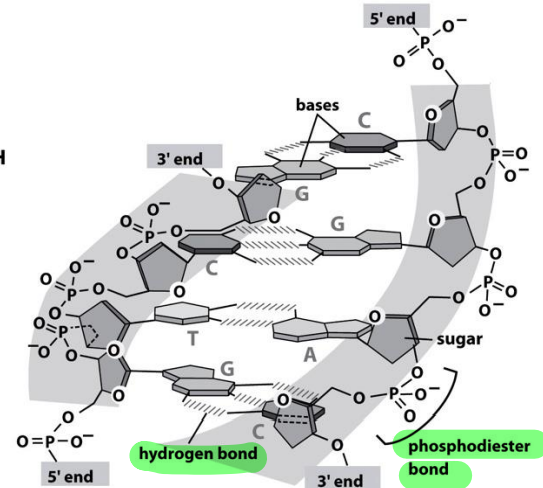
thymine

base pairs



guanine

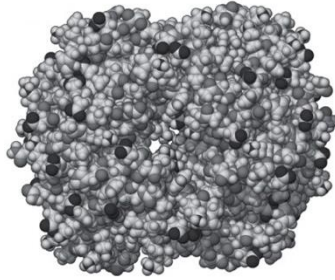
cytosine



# The stuff of life

What macromolecules are cells made of?

Name the molecule  
What are its parts?  
What are its units?  
What is it used for?



protein (hemoglobin)  
amino acids  
Daltons (unified atomic mass unit)  
 $\frac{1}{12}$  mass of  $C_{12}$  atom  
enzymes (catalyze processes) or  
structural (mechanical properties)  
bind ligands/ions (sensors, carriers)

structural motifs: alpha helices, beta sheets

# The stuff of life

Nucleic acids and proteins are polymer languages

DNA

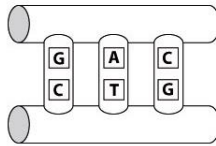
NUCLEIC ACIDS

four natural

G T  
C A  
nucleotides

ALPHABET

codon (3 bp)

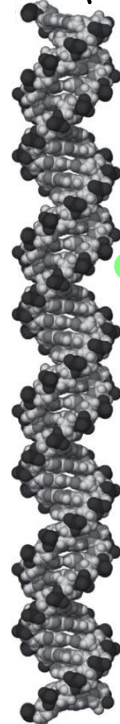
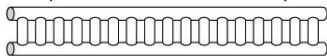


WORDS

DNA is read as codons

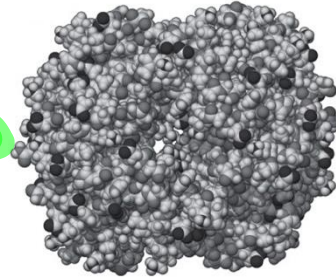
string of codons, may encode a protein

SENTENCES



2 nm

protein



protein

ribosome  
translation

DNA → mRNA

RNA polymerase  
transcription

How many?

$$4^3 = 64$$

ALPHABET

structural  
motifs

WORDS

folded  
protein

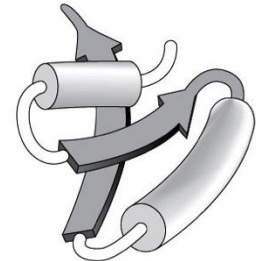
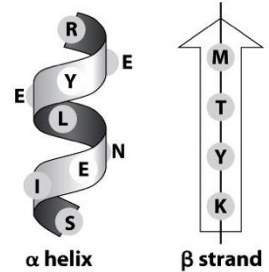
SENTENCES

codon → amino acid

PROTEINS

A V F P D  
L I M E K S  
T Y R C N  
Q H W G  
amino acids

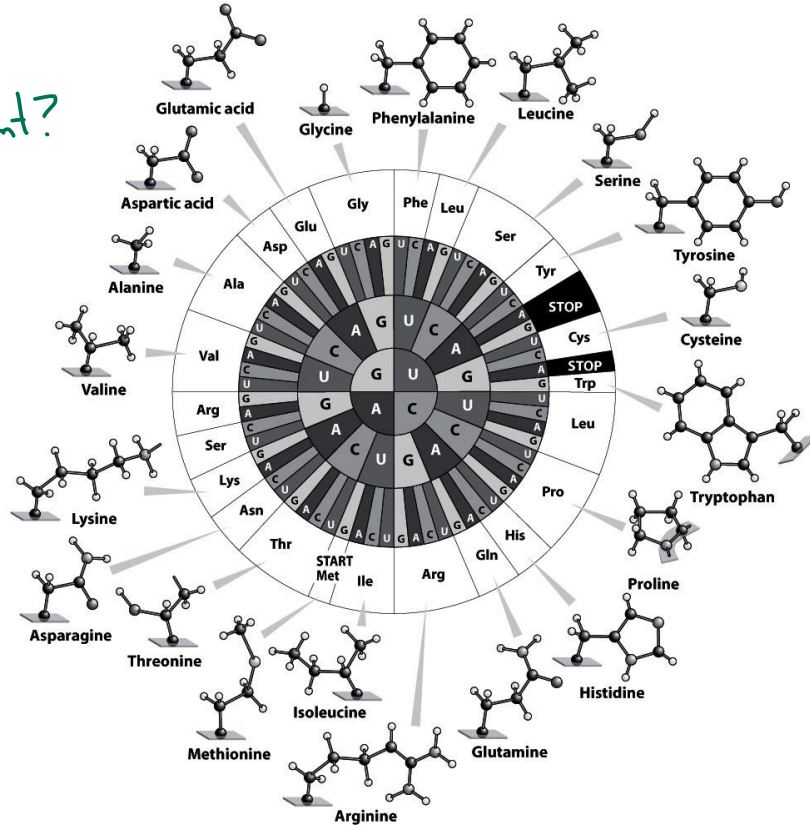
20  
natural  
amino acids



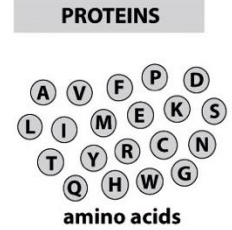
# The stuff of life

What macromolecules are cells made of?

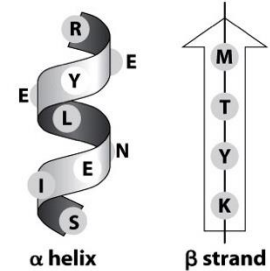
Why redundant?  
Robustness



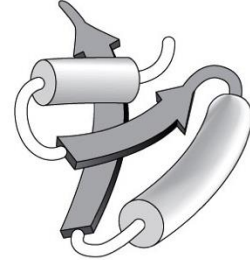
ALPHABET



WORDS

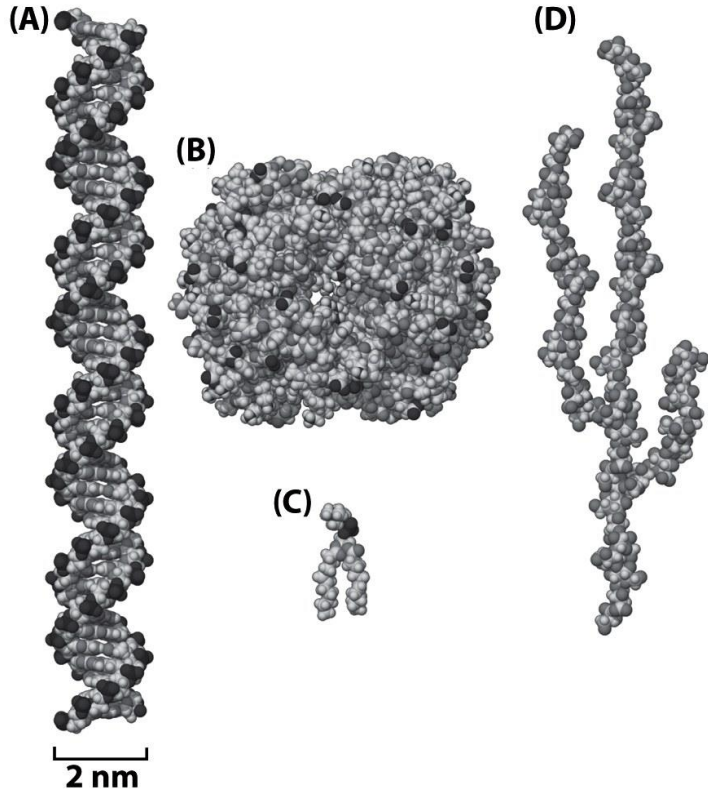


SENTENCES



# The stuff of life

What macromolecules are cells made of?



Advantages:

- Each class can be assembled by the cell from a small set of simpler subunits
- Combinatorial assembly gives rise to diversity
- Limited repertoire of chemical reactions needed
- Facilitates existence of food chain

# Model building

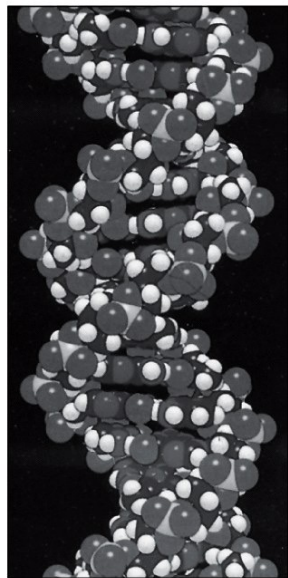
What is a model?

- Overlook / coarse grain some details, keep enough to make prediction
- Explain / capture existing phenomena  $\rightarrow$  extrapolable to predict

Main challenge: what to simplify, what to keep complex

# Model building

DNA

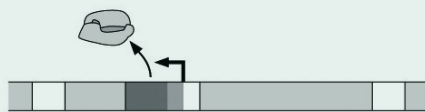


SEQUENCE

5' ..TCAAGTCCGAT.. 3'  
3' ..AGTTCAGGCTA.. 5'

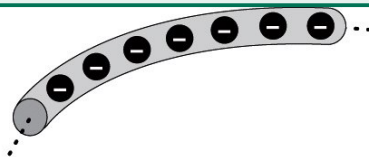
information carrier → model evolution

BINDING SITE



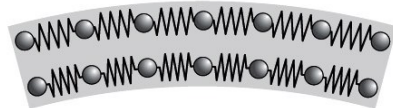
gene regulation → model gene expression  
through binding

CHARGED ROD



electrostatics

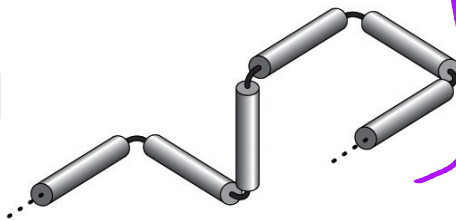
ELASTIC ROD



bending elasticity

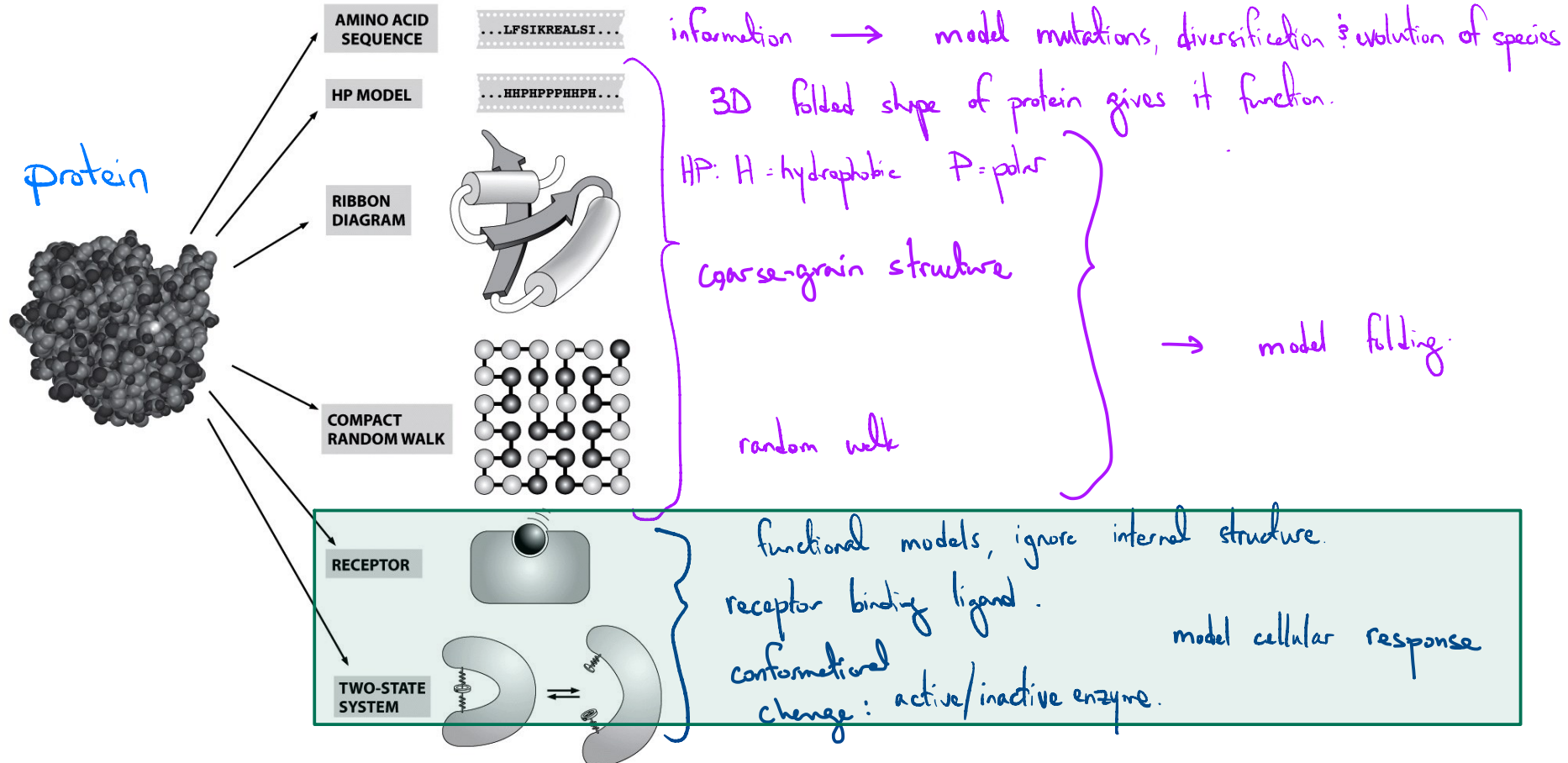
model mechanics  
and structure

RANDOM WALK



polymer

# Model building

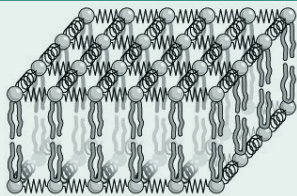




# Model building

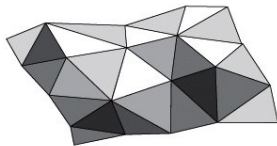
lipid  
bilayer membrane

ARRAY OF  
SPRINGS



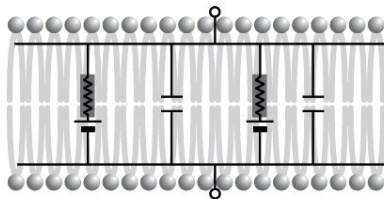
mechanics. → model deformations under applied force,  
energy to create different shapes

RANDOM  
SURFACE



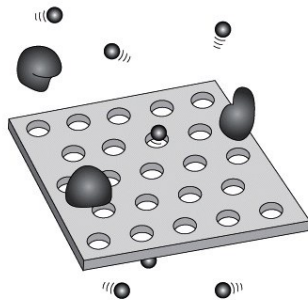
interaction surface. → model binding

RC  
CIRCUIT



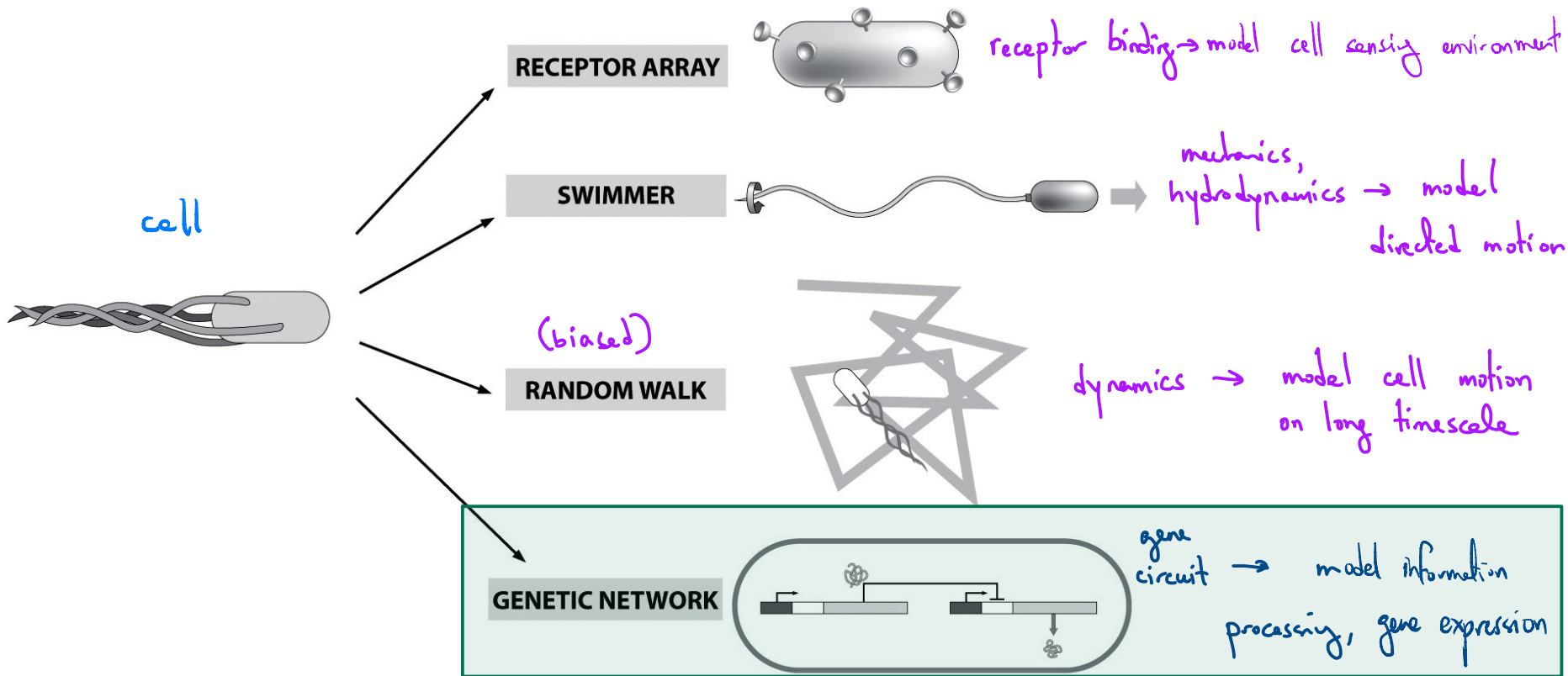
electrical properties. → model voltage across membrane.

SEMI-  
PERMEABLE  
BARRIER



transport properties → model transport of material  
(ions, molecules)

# Model building



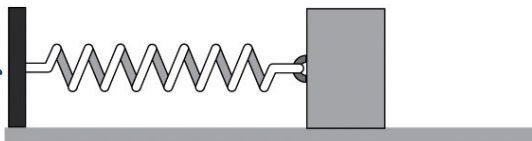
# Quantitative models and the power of idealization

Simple spring model

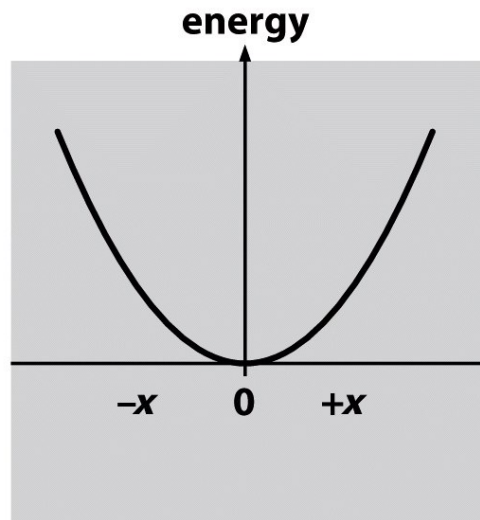
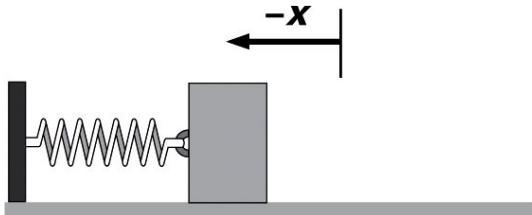
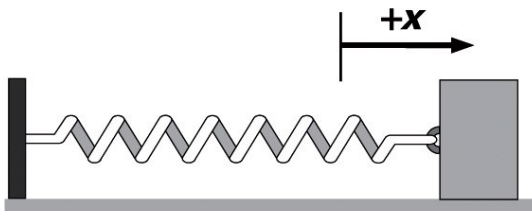
*Example: Potential energy landscape*

linear

force-displacement



$$F = -kx$$



potential energy

$$U = \frac{1}{2} kx^2$$

free energy minimization

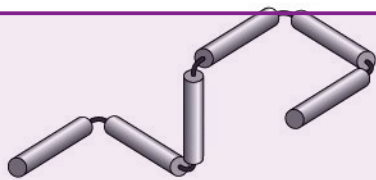
oscillation when energy  
is added

# Quantitative models and the power of idealization

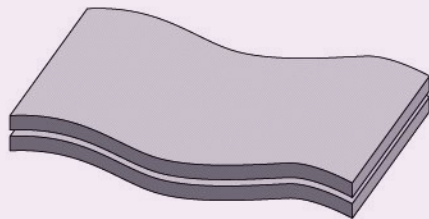
Analogs in biophysics

measure mechanics of biological systems

*Example: Potential energy landscape*



DNA polymer wiggling in solution



cell membrane fluctuating

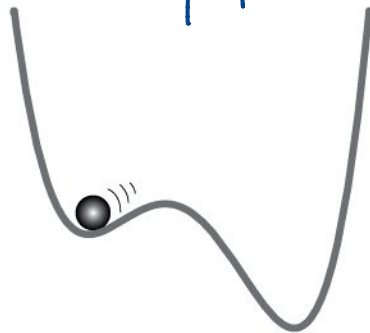


bead pulled to center of an optical trap



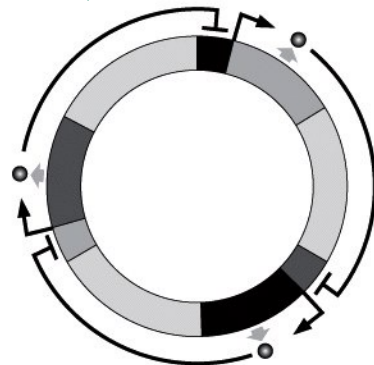
flagellum beating on a swimming sperm

probability  $p(E)$



molecules in an energy landscape

dynamics  
 $c_1(t)$ ,  $c_2(t)$ ,  $c_3(t)$



genetic network changing expression levels over time

oscillatory solutions to differential eqns

# Quantitative models and the power of idealization

## Numerical estimates

Phillips Numbers Snapshot  
BioNumbers website

Quantity of interest		Symbol	Rule of thumb				
<i>E. coli</i>	Cell volume	$V_{E. coli}$	$\approx 1 \mu\text{m}^3$	DNA	Length per base pair	$l_{bp}$	$\approx 1/3 \text{ nm}$
	Cell mass	$m_{E. coli}$	$\approx 1 \text{ pg}$		Volume per base pair	$V_{bp}$	$\approx 1 \text{ nm}^3$
	Cell cycle time	$t_{E. coli}$	$\approx 3000 \text{ s}$		Charge density	$\lambda_{DNA}$	$2 \text{ e}/0.34 \text{ nm}$
	Cell surface area	$A_{E. coli}$	$\approx 6 \mu\text{m}^2$		Persistence length	$\xi_P$	$50 \text{ nm}$
	Genome length	$N_{bp}^{E. coli}$	$\approx 5 \times 10^6 \text{ bp}$				
	Swimming speed	$v_{E. coli}$	$\approx 20 \mu\text{m/s}$				
Yeast	Volume of cell	$V_{yeast}$	$\approx 60 \mu\text{m}^3$	Amino acids and proteins	Radius of "average" protein	$r_{protein}$	$\approx 2 \text{ nm}$
	Mass of cell	$m_{yeast}$	$\approx 60 \text{ pg}$		Volume of "average" protein	$V_{protein}$	$\approx 25 \text{ nm}^3$
	Diameter of cell	$d_{yeast}$	$\approx 5 \mu\text{m}$		Mass of "average" amino acid	$M_{aa}$	$\approx 100 \text{ Da}$
	Cell cycle time	$t_{yeast}$	$\approx 200 \text{ min}$		Mass of "average" protein	$M_{protein}$	$\approx 30,000 \text{ Da}$
	Genome length	$N_{bp}^{yeast}$	$\approx 10^7 \text{ bp}$		Protein concentration in cytoplasm	$C_{protein}$	$\approx 300 \text{ mg/mL}$
Organelles	Diameter of nucleus	$d_{nucleus}$	$\approx 5 \mu\text{m}$	Lipid bilayers	Characteristic force of protein motor	$F_{motor}$	$\approx 5 \text{ pN}$
	Length of mitochondrion	$l_{mito}$	$\approx 2 \mu\text{m}$		Characteristic speed of protein motor	$v_{motor}$	$\approx 200 \text{ nm/s}$
	Diameter of transport vesicles	$d_{vesicle}$	$\approx 50 \text{ nm}$		Diffusion constant of "average" protein	$D_{protein}$	$\approx 100 \mu\text{m}^2/\text{s}$
Water	Volume of molecule	$V_{H_2O}$	$\approx 10^{-2} \text{ nm}^3$		Thickness of lipid bilayer	$d$	$\approx 5 \text{ nm}$
	Density of water	$\rho$	$1 \text{ g/cm}^3$		Area per molecule	$A_{lipid}$	$\approx \frac{1}{2} \text{ nm}^2$
	Viscosity of water	$\eta$	$\approx 1 \text{ centipoise}$ $(10^{-2} \text{ g}/(\text{cm s}))$		Mass of lipid molecule	$m_{lipid}$	$\approx 800 \text{ Da}$
	Hydrophobic embedding energy	$\approx E_{hydr}$	$25 \text{ cal}/(\text{mol } \text{\AA}^2)$				

# Lecture 2 outline

## Goal: Size and contents of cells

- An ode to *E. coli*
- Cells and the structures within them

PBOC Chapter 2.1, 2.2