

# PHYSICAL BIOLOGY OF THE LIVING CELL I.

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# Topics - semester I

<b>Qualitative and quantitative modelling in biology</b> (Dr. Miklós Kellermayer)	Feb. 17
<b>Structural hierarchy of proteins</b> (Dr. Schay Gusztáv)	Feb. 24
<b>Stability of biological structures</b> (Dr. Schay Gusztáv)	Mar. 3
<b>Experimental methods to study biological structures - I</b> (Dr. Schay Gusztáv)	Mar. 10
<b>Experimental methods to study biological structures - II</b> (Dr. Miklós Kellermayer)	Mar. 17
<b>Microscopy studies of intracellular structures</b> (Dr. Miklós Kellermayer)	Mar. 24
<b>Formation of biological structures</b> (Dr. Szabolcs Osváth)	Mar. 31
<b>Dynamic intracellular protein structures</b> (Dr. Miklós Kellermayer)	Apr. 7
<b>Super-resolution microscopy</b> (Dr. Szabolcs Osváth)	Apr. 28
<b>Single molecule biological activity</b> (Dr. Miklós Kellermayer)	May. 5
<b>Visit to the research laboratories of the Dept. of Biophysics and Radiation biology of the Semmelweis University (Dr. Szabolcs Osváth)</b>	May 12
<b>Problem solving and consultation</b> (Dr. Szabolcs Osváth)	May 19

# Physical biology

- Today not only qualitative observations, but quantitative measurements are made (biological data → quantitative data).
- From quantitative data, quantitative models are built.
- Quantitative models are expected to provide with experimentally testable predictions.

*“Make things as simple as possible, but not simpler.”*

*Albert Einstein*

# Premises of model building

- What facts are available?
  - a. Facts observable by anyone  
(e.g., the cell contains proteins)
  - b. Facts accepted after extensive experimental testing  
(e.g., proteins are synthesized on the ribosome)
  - c. Speculative statements  
(e.g., mitochondria are descendents of ancient bacteria)
- Is the problem interesting or important?
- Biological entities must not violate the laws of physics and chemistry.

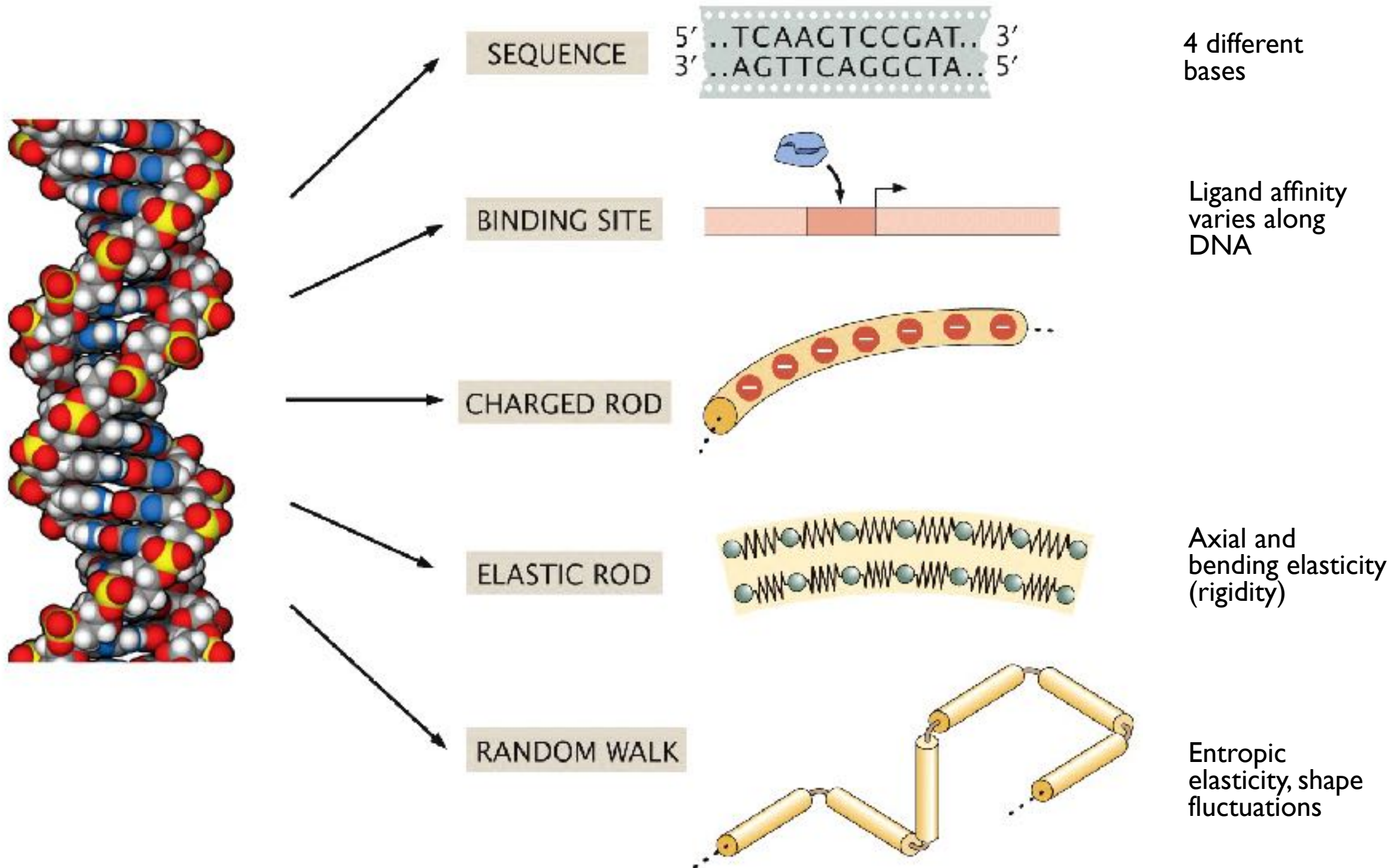
# Why is life alive?

- Life is described through a collection of qualitative approximations
  - e.g., growth, energy utilization/transformation, reproduction
- The living cell is built of surprisingly few elements
- The cell contains structurally and functionally specialized macromolecules
  - proteins, nucleic acids, carbohydrates, lipids
  - macromolecules are formed by a combinatorial assembly of units
  - macromolecules encode information (in different “languages”)

# Biological model building

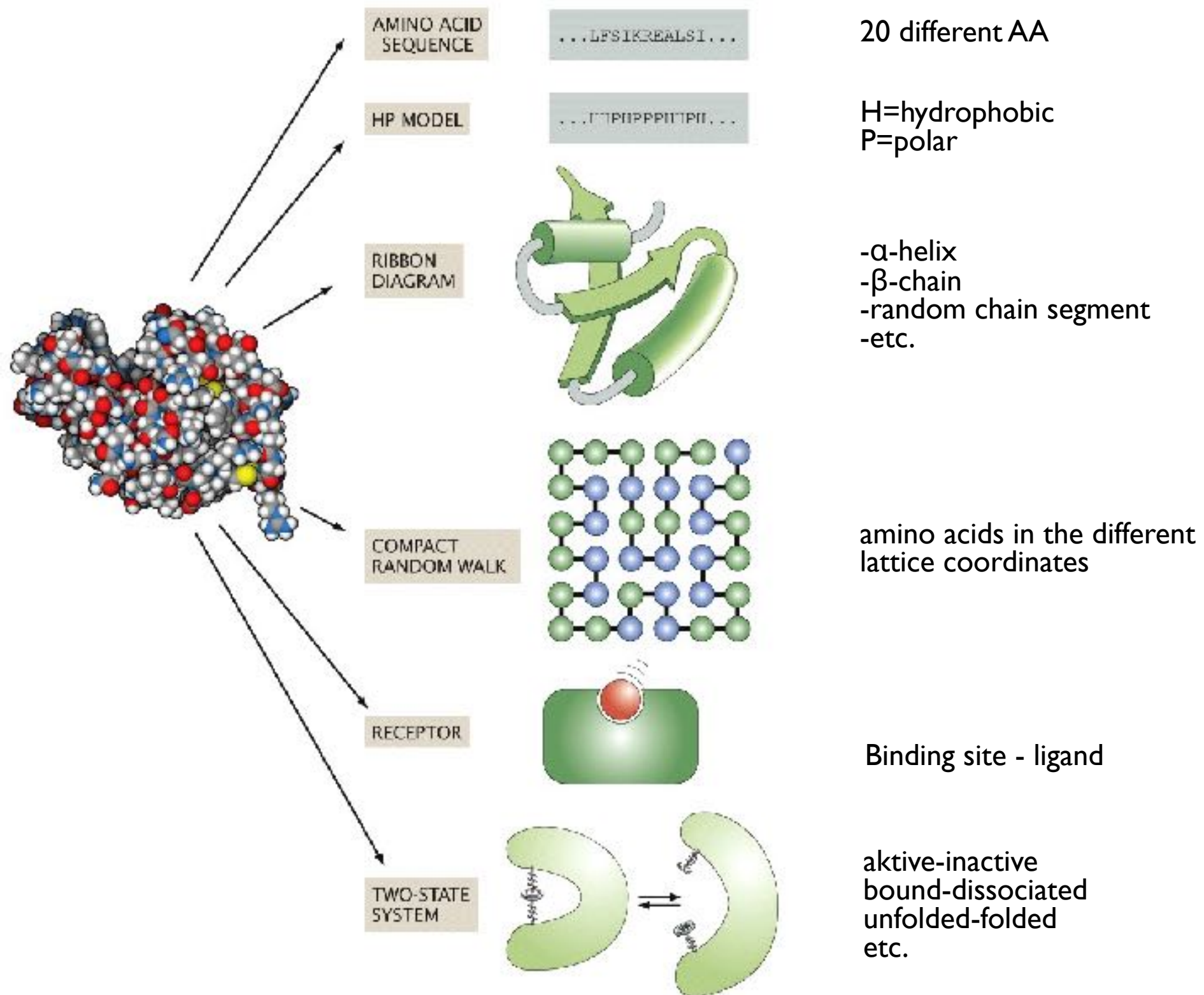
- Abstraction
- Simplification
- We cannot attain a complete atomic description of the macromolecules
- Projections are made, which reflect a certain property of the macromolecule
- Idealization

# Idealization of the DNA molecule





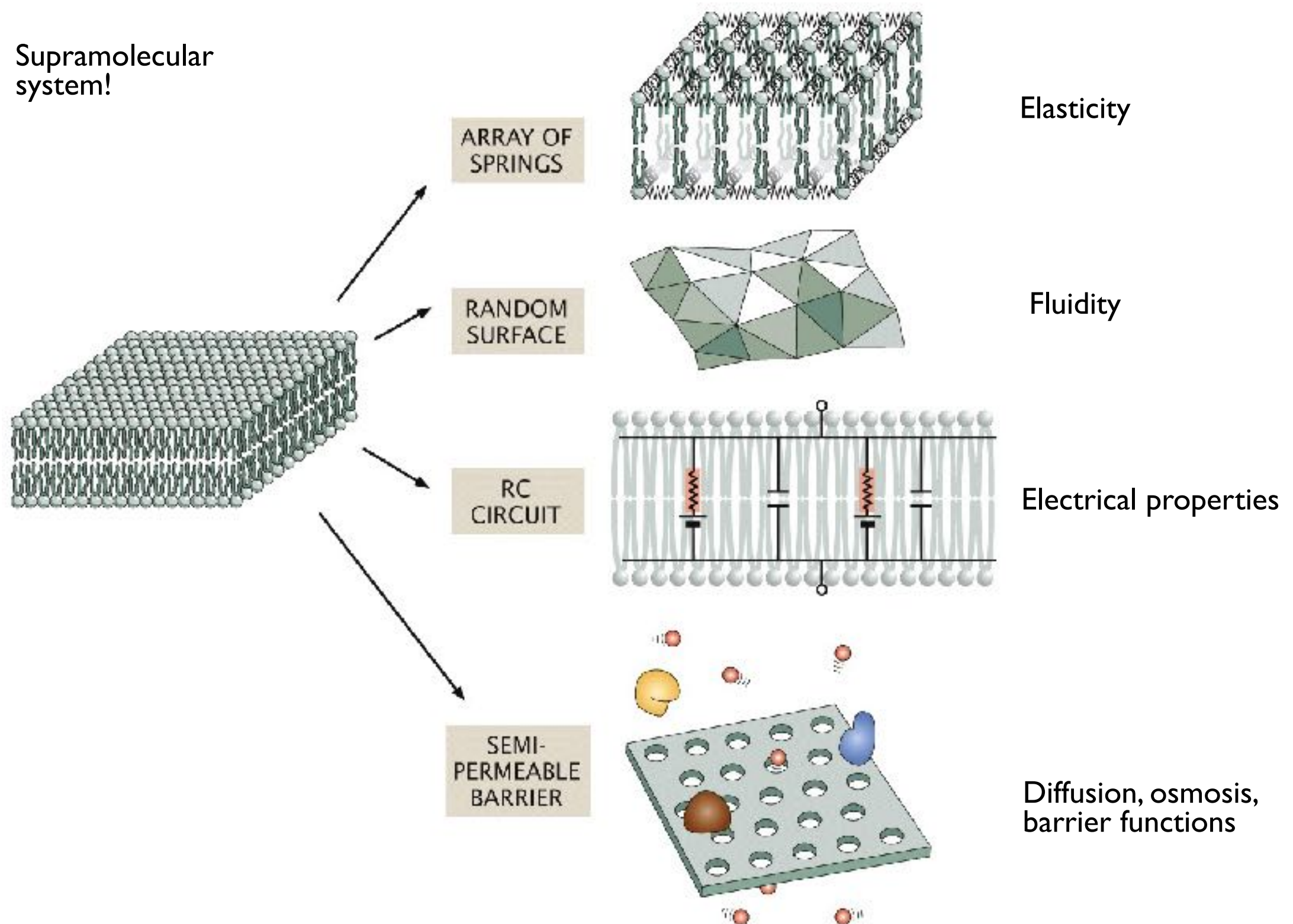
# Idealization of a protein molecule



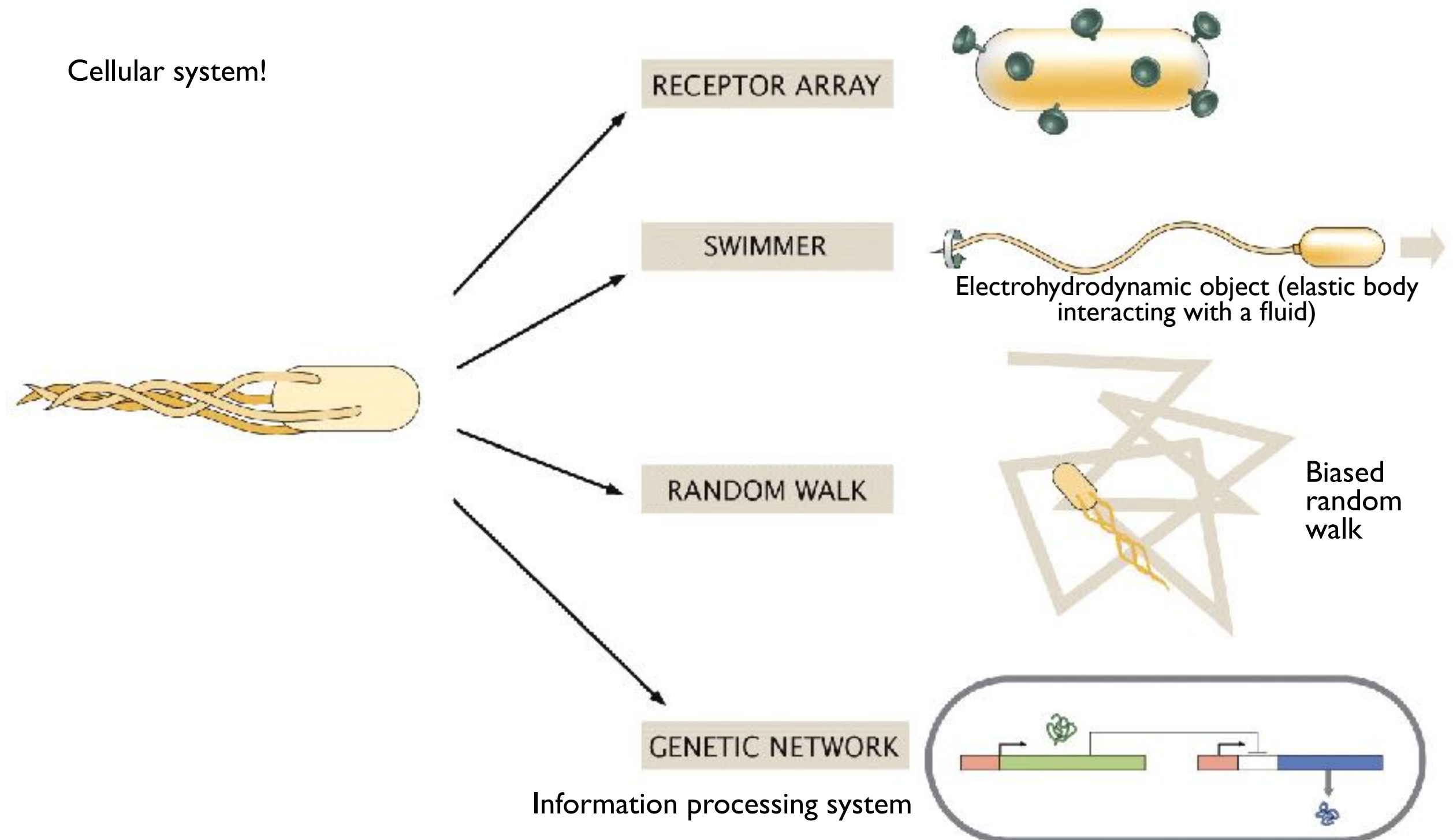


# Idealization of lipids and membranes

Supramolecular system!



# Idealization of an *Escherichia coli* cell

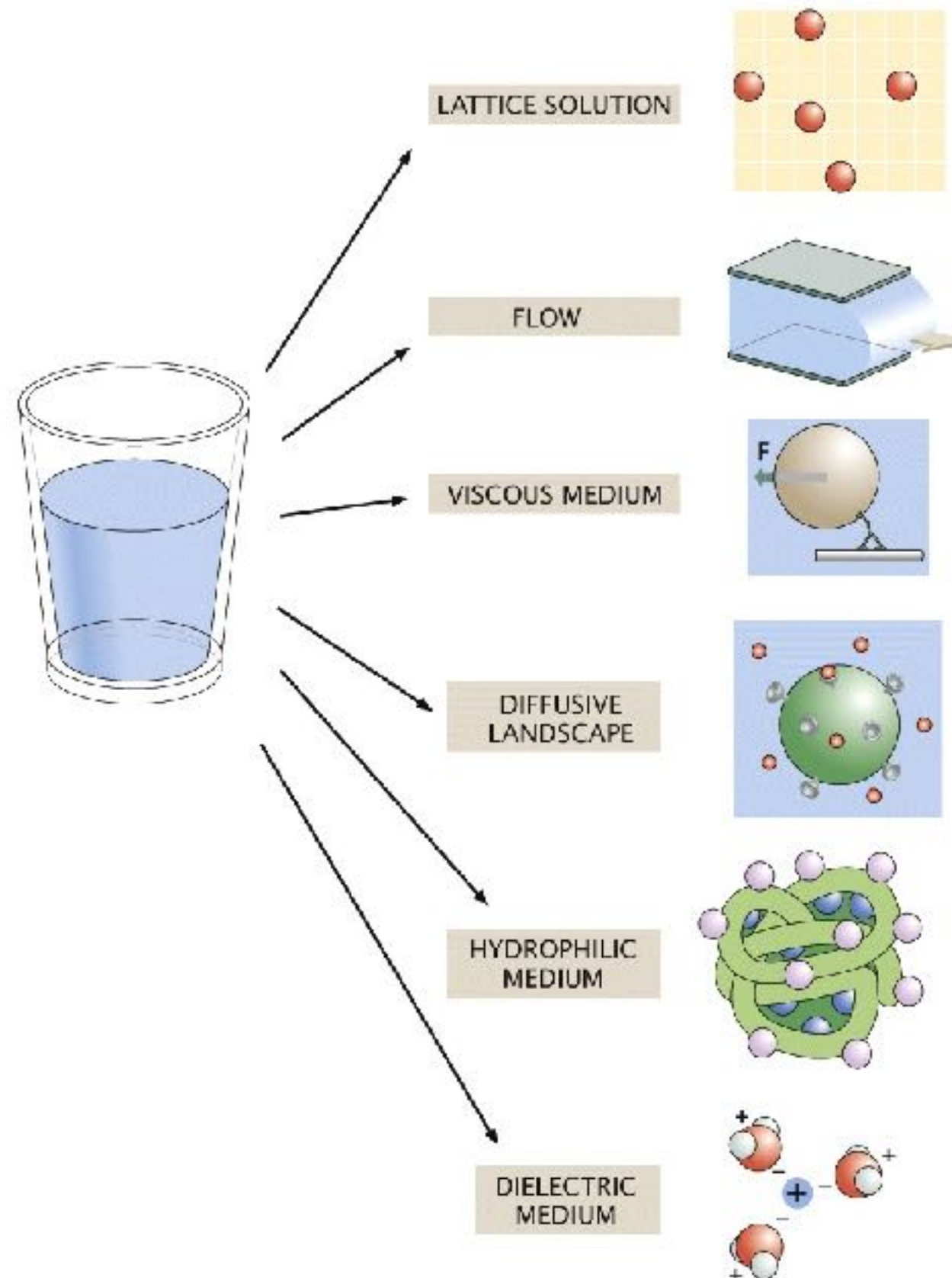


# Idealization of a solution

Living cell as an  
ideal solution(?)

Homogenous

Isotropic





# Idealization, expansion and application of the concept of elasticity

Average deviation from equilibrium position:

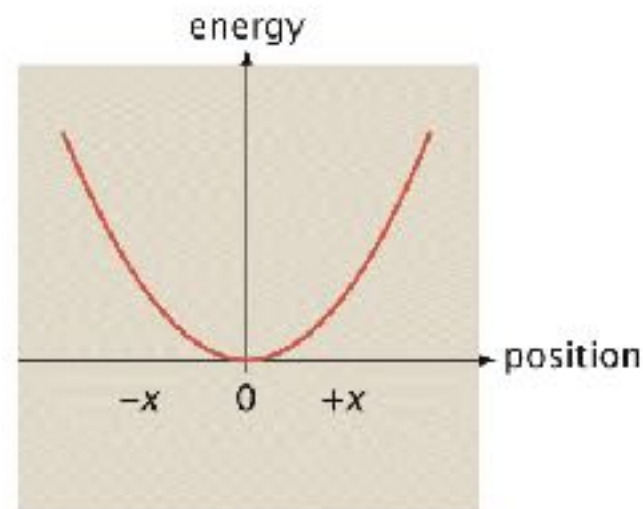
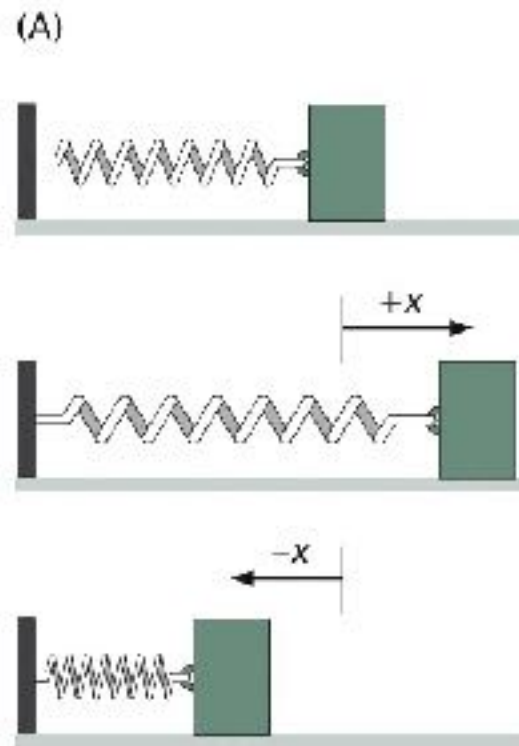
$$Energy = \frac{1}{2} \kappa x^2$$

$\kappa$ : spring constant - energetic cost of deviating from equilibrium

Recovery force:

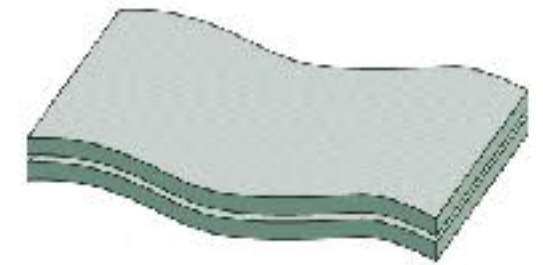
$$F = -\kappa x$$

Harmonic oscillation



Biological, biophysical examples

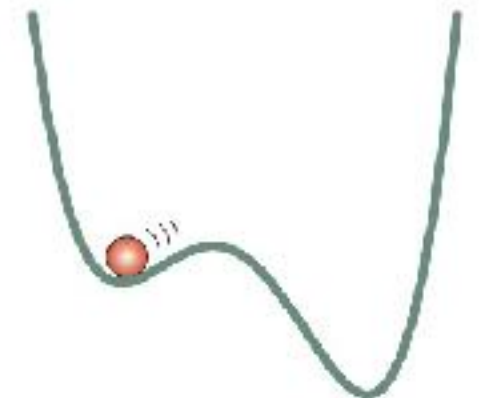
(B)



cell membrane fluctuating



bead pulled to center of an optical trap



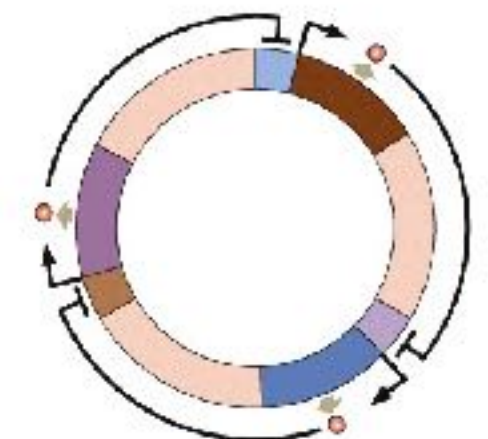
molecules in an energy landscape



DNA polymer wiggling in solution



flagellum beating on a swimming sperm



genetic network changing expression levels over time

# Scaling in biology

## Size of biomolecular systems

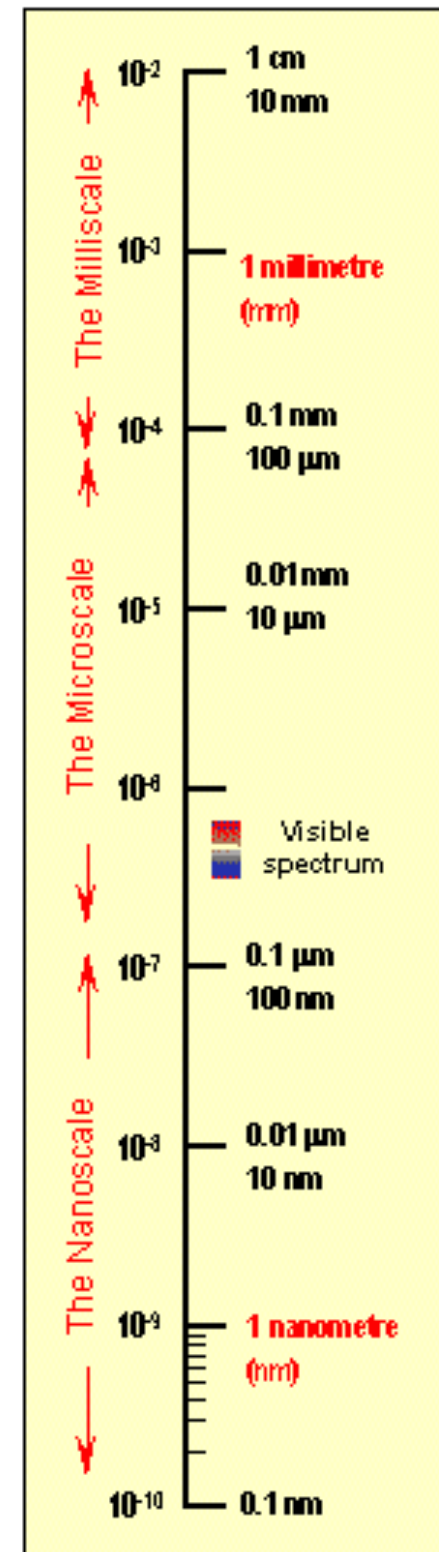
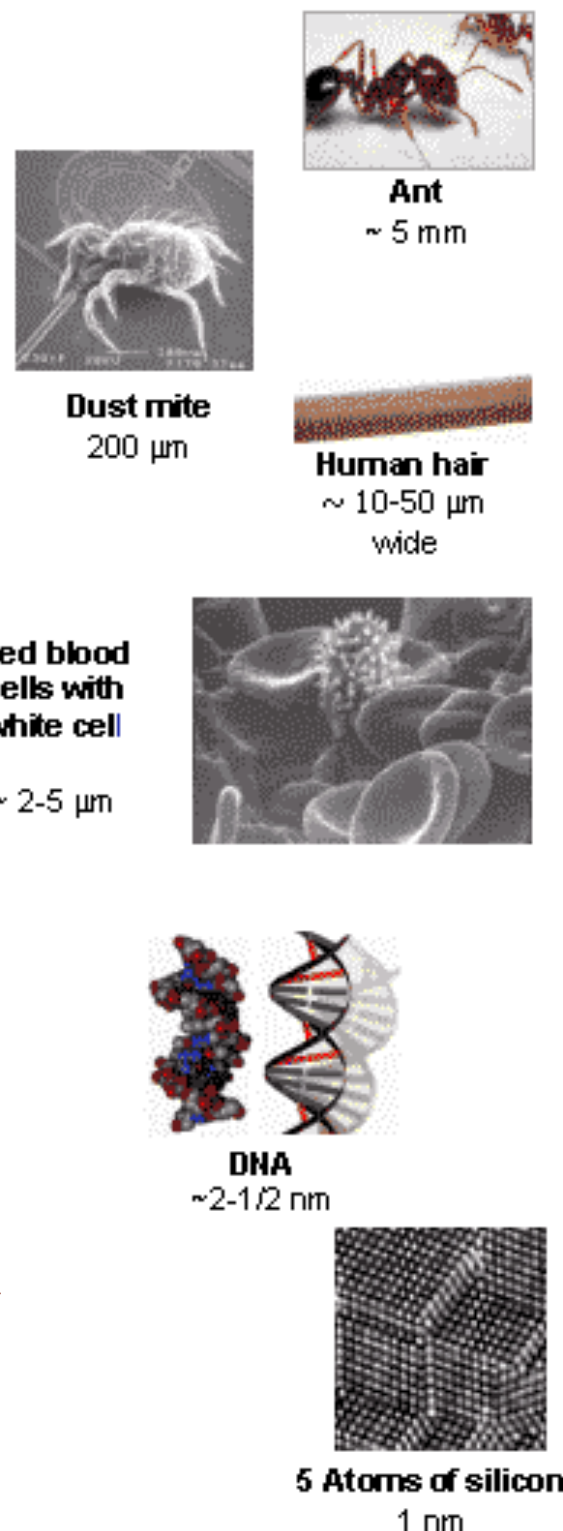
Thermodynamics

$10^{23}$  Atoms

Mesoscale

Quantum chemistry

Quantum physics



$10^{10}$  Atoms

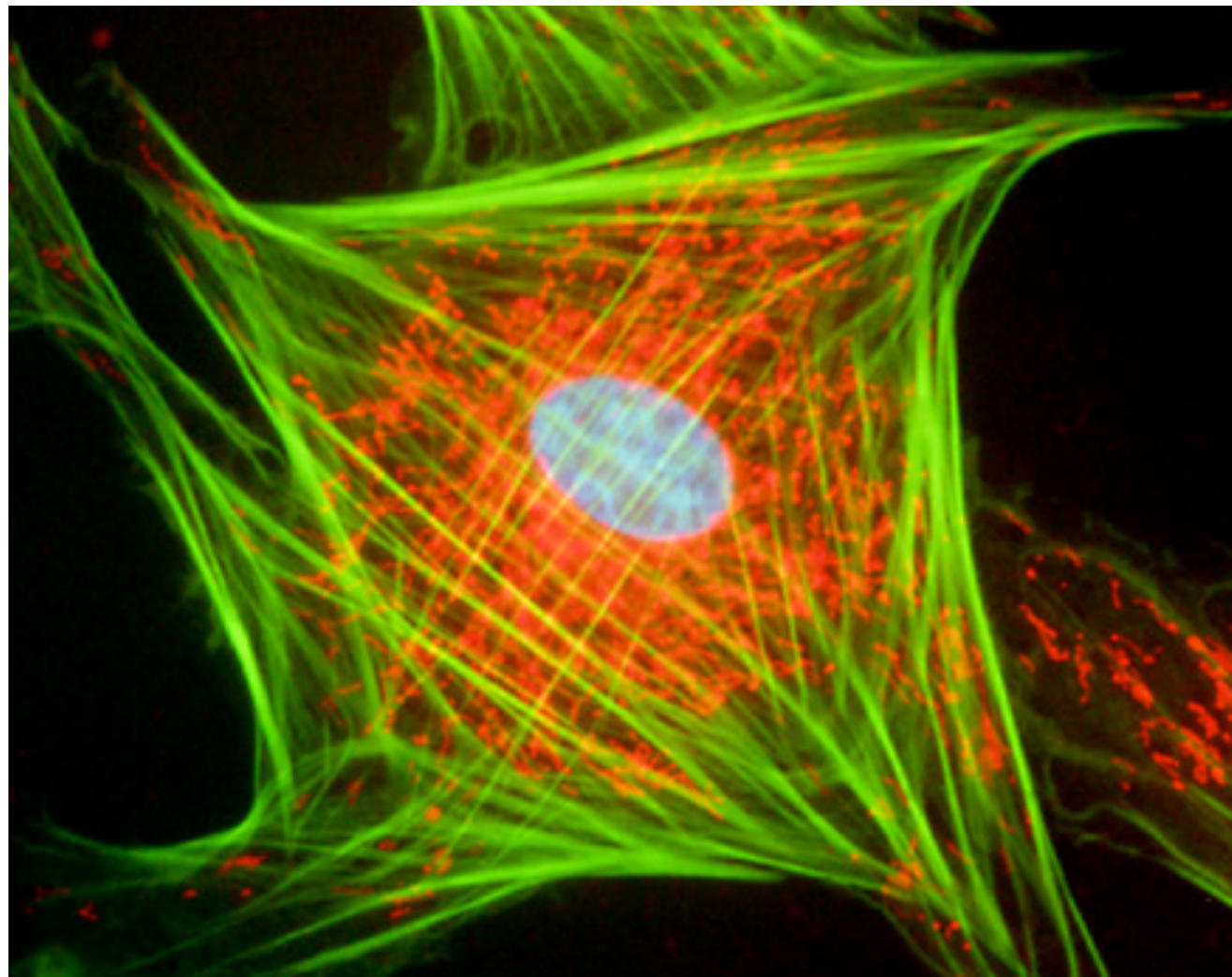
$10^3$  Atoms

$10^1$  Atoms

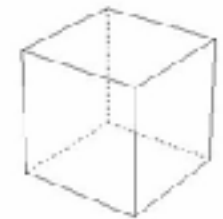
$10^0$  Atoms

# Length scale of the living cell

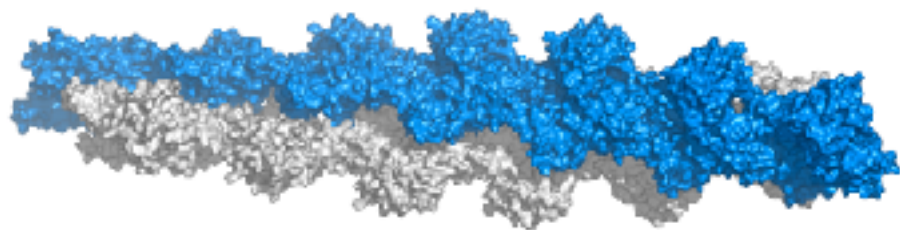
Rudolf Virchow (1855): “*Omnis cellula e cellula*”



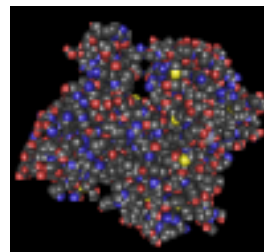
Simplified cell model:  
cube



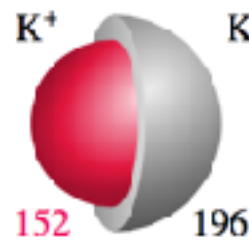
	<b>Cell:</b> cube with 20 $\mu\text{m}$ edge	Analogue - <b>Lecture hall:</b> cube with 20 m edge
Size of actin molecule	5 nm	5 mm
Number of actin molecules	~500 million	~500 million
Average distance between actins	~25 nm	~25 mm
Size of potassium ion	0.15 nm	0.15 mm
Number of potassium ions	~ $10^9$	~ $10^9$
Average distance between $\text{K}^+$ ions	~20 nm	~2 cm



Actin filament ( $d=7$  nm)



G-actin  
( $d=5$  nm,  
 $cc \sim 100 \mu\text{M}$ )



Potassium ion  
( $d=0.15$  nm,  
 $cc \sim 150$  mM)

Deficiencies of the model:

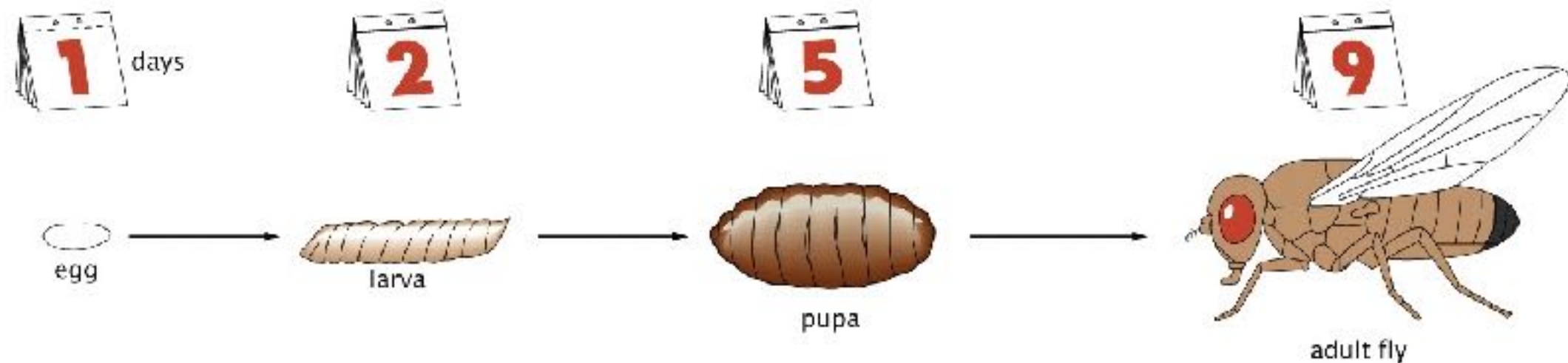
- concentrations vary locally
- dynamics: constant motion and collisions
- interactions, many types due to dynamics



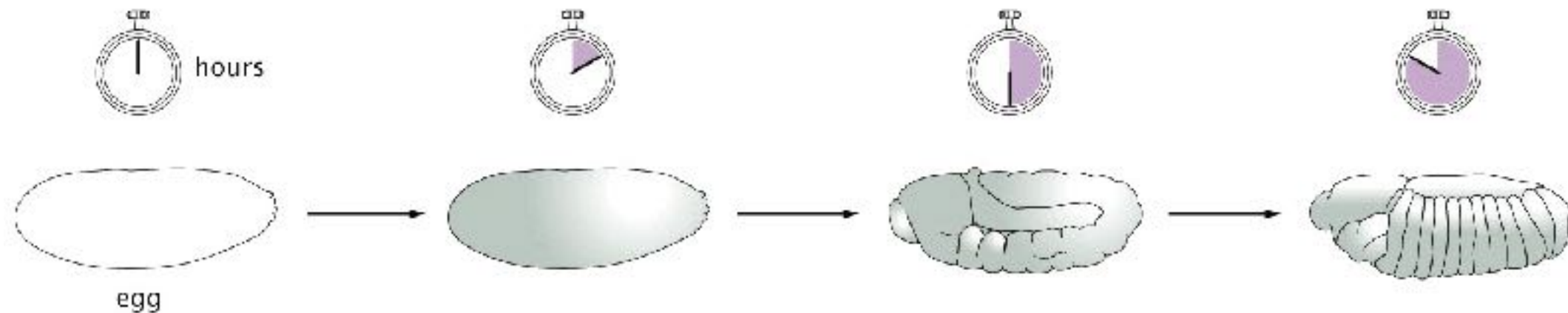
# Scaling in biology

## Biological time scale I.

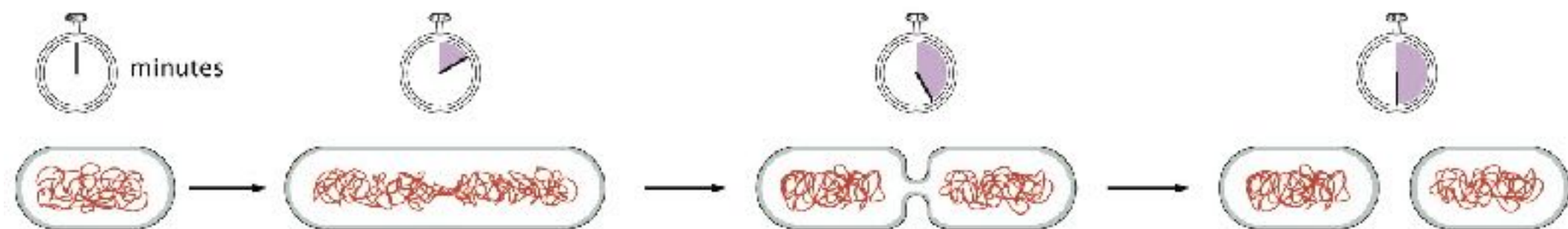
Development of *Drosophila*



Early development of *Drosophila*

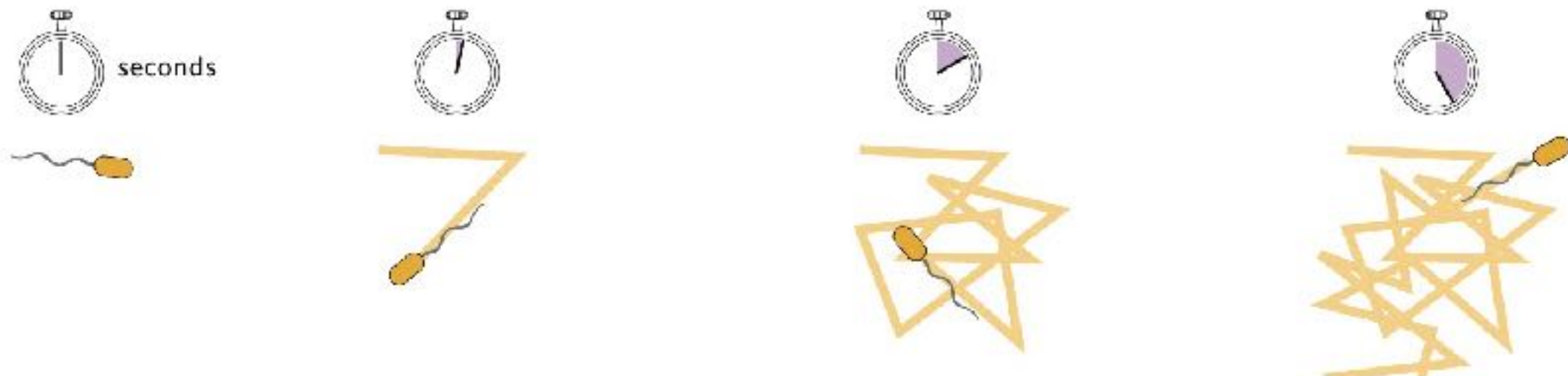


Bacterial cell division

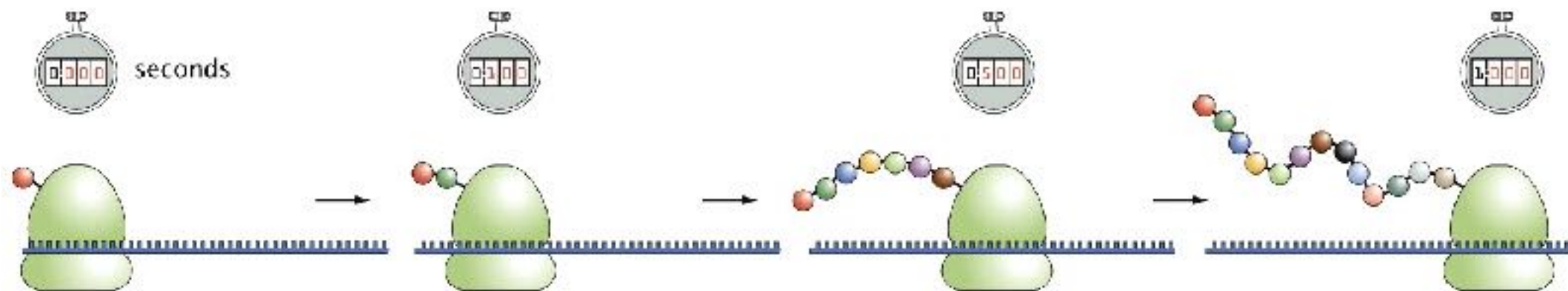


# Biological time scale II.

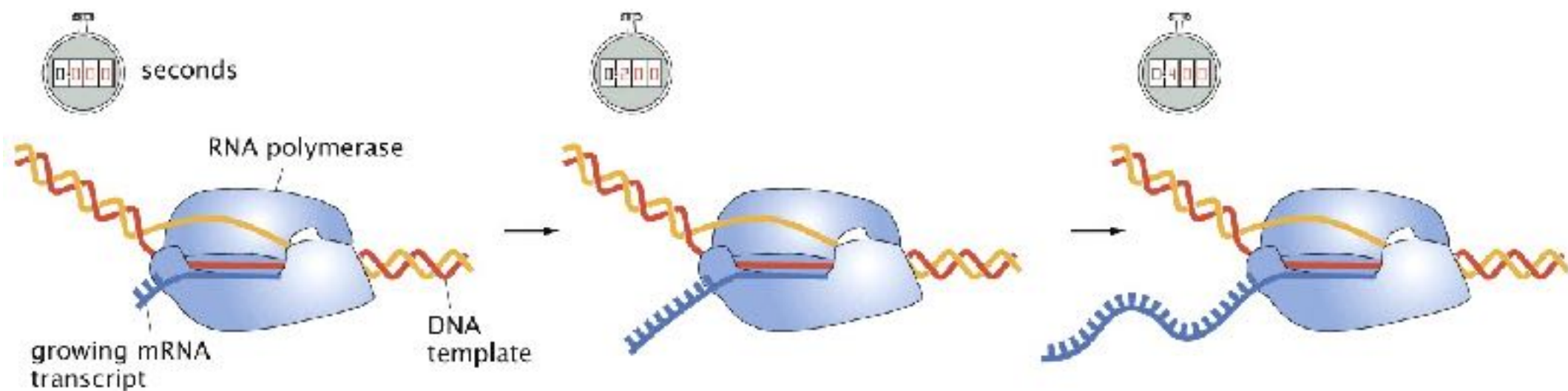
## Cell movements



## Protein synthesis

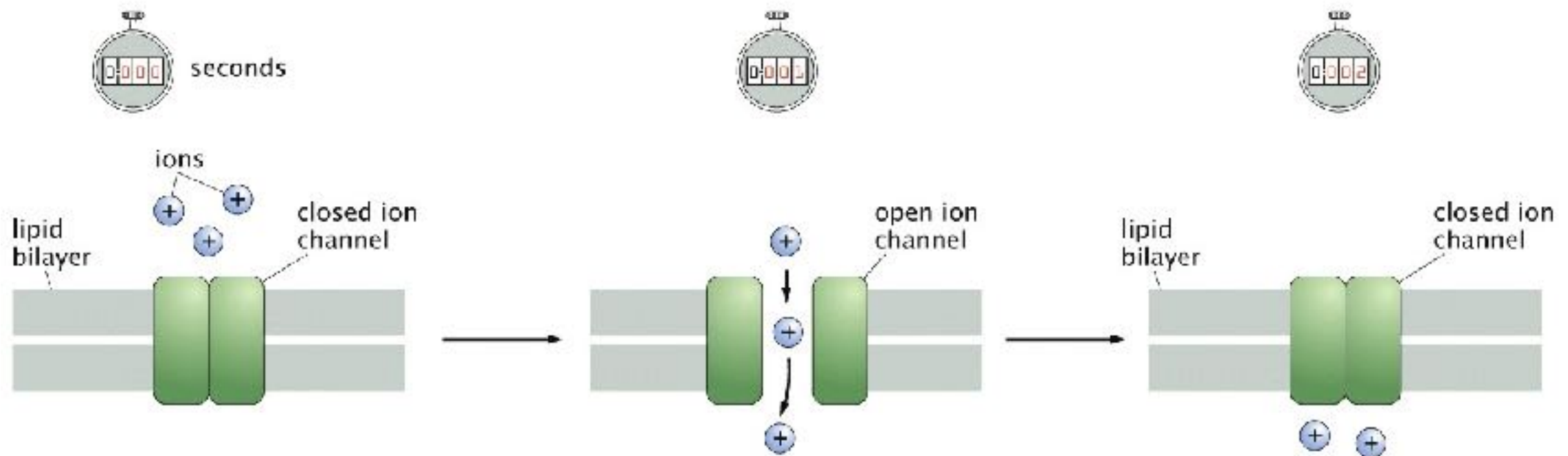


## Transcription

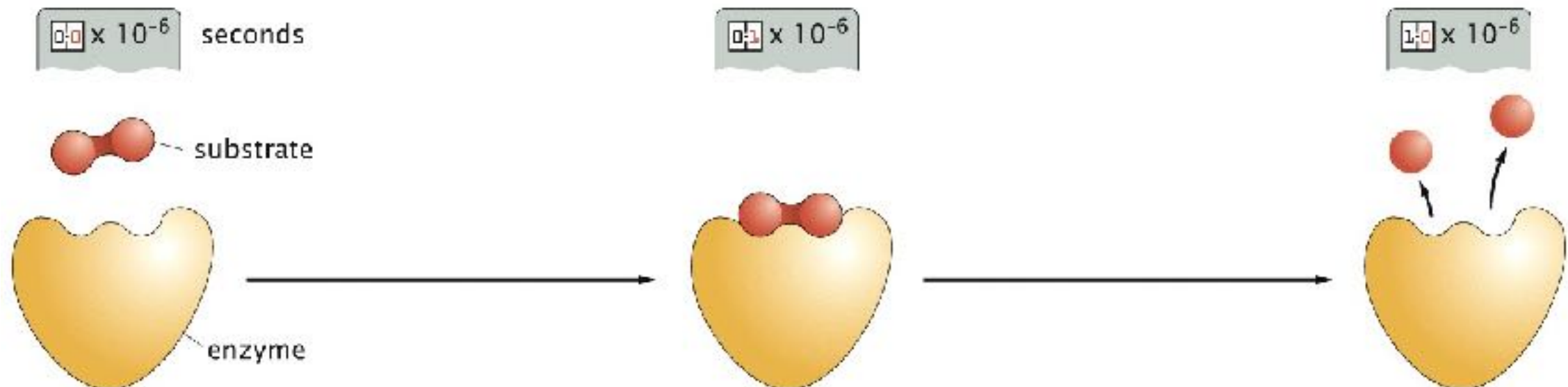


# Biological time scale III.

## Gating of ion channels



## Enzyme catalysis

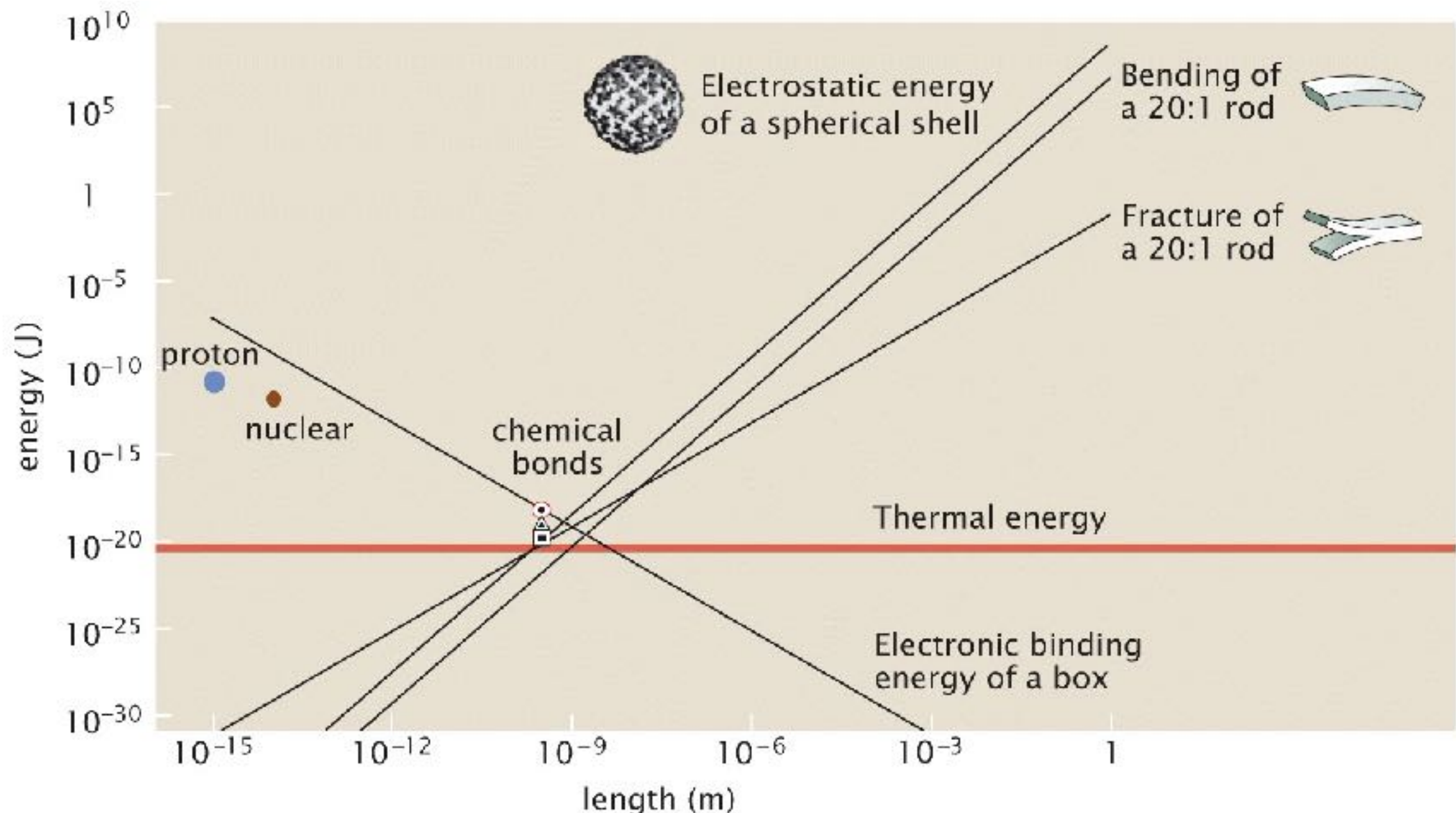


Furthermore, light absorption  $10^{-15}$  s!



# Correlation of energy and size scales

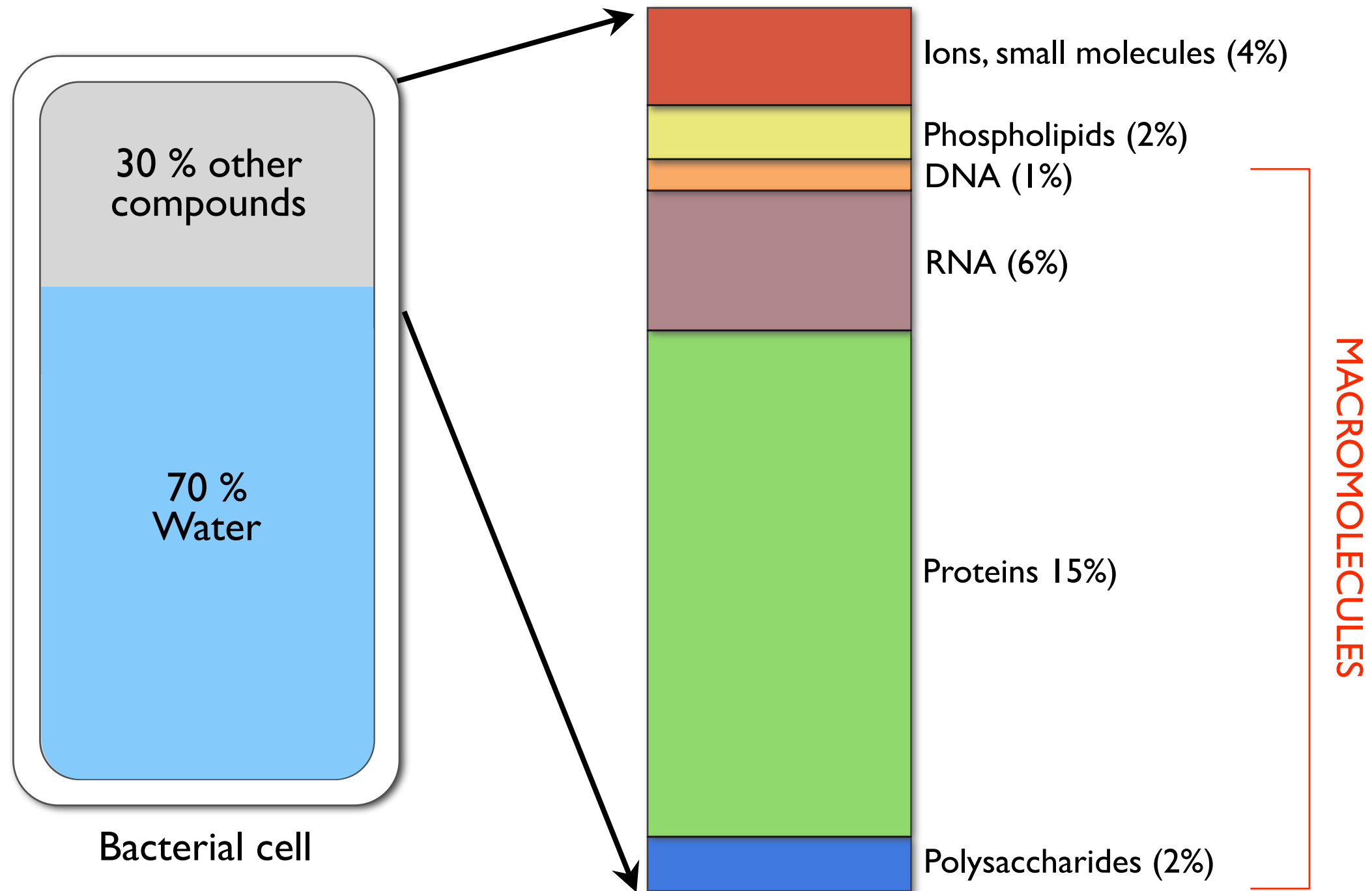
- “Deterministic” (chemical, mechanical, electromagnetic) vs. “thermal” energies
- Thermal energy unit:  $k_B T = 4.1 \times 10^{-21} \text{ J} = 4.1 \text{ pNnm}$
- Relevant scaling - Boltzmann factor:  $\exp(-E_{det}/k_B T)$
- Thermal energy =  $k_B T = 4.1 \times 10^{-21} \text{ J} = 4.1 \text{ pNnm} = 0.6 \text{ kcal/mol} = 2.5 \text{ kJ/mol}$   
(biochemical reactions) = 25 meV (charge transfer)



# Some rules of thumb in quantitative biology

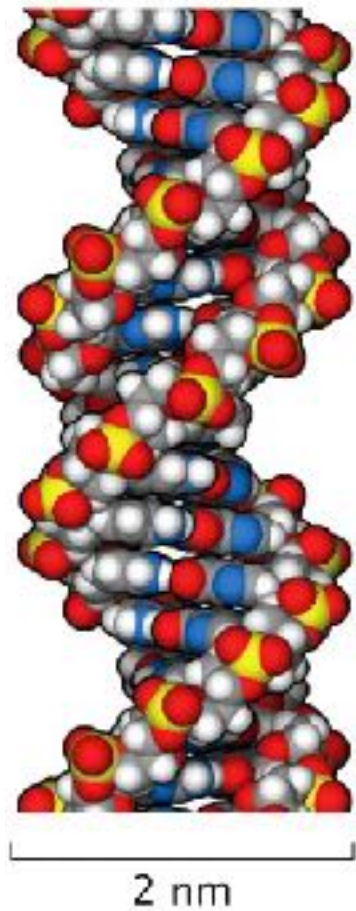
- 1 dalton (Da) = 1 g/mol  $\approx 1.6 \times 10^{-24}$  g
- 1 nM  $\approx 1$  molecule/bacterium  $\approx 10^3$ - $10^4$  molecule/eukaryotic cell
- 1 M  $\approx 1/\text{nm}^3$
- Cellular protein concentration  $\approx 2$ -4 million/ $\mu\text{m}^3$
- 1 mg of 1 kb DNA fragment  $\approx 1$  pmol  $\approx 10^{12}$  molecules
- Mean distance between molecules at 1 M concentration  $\approx 1$  nm
- Molecular mass of a typical amino acid  $\approx 100$  Da
- Water concentration/density  $\approx 55$  M  $\approx 1000$  kg/ $\text{m}^3$
- Volume of a water molecule  $\approx 0.03$   $\text{nm}^3$
- Length of a base pair (along DNA)  $\approx 0.3$  nm
- Volume of a base pair  $\approx 1$   $\text{nm}^3$

# Proportion of macromolecules in the cell by mass is **large**

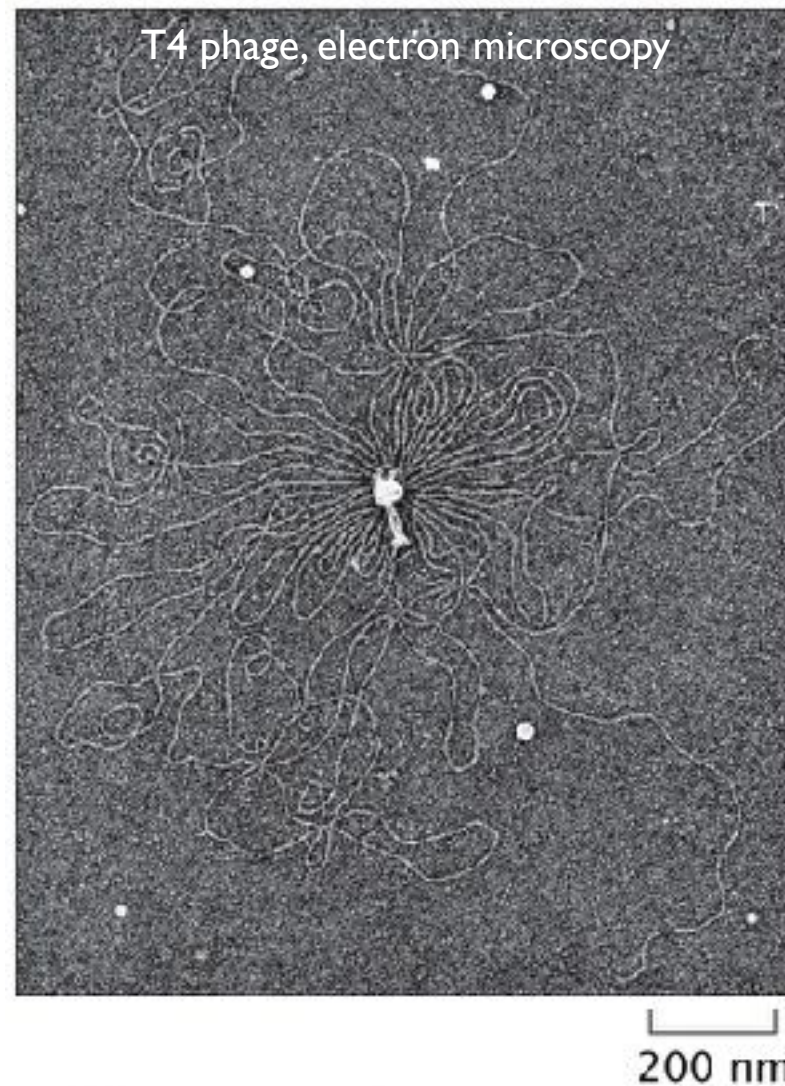




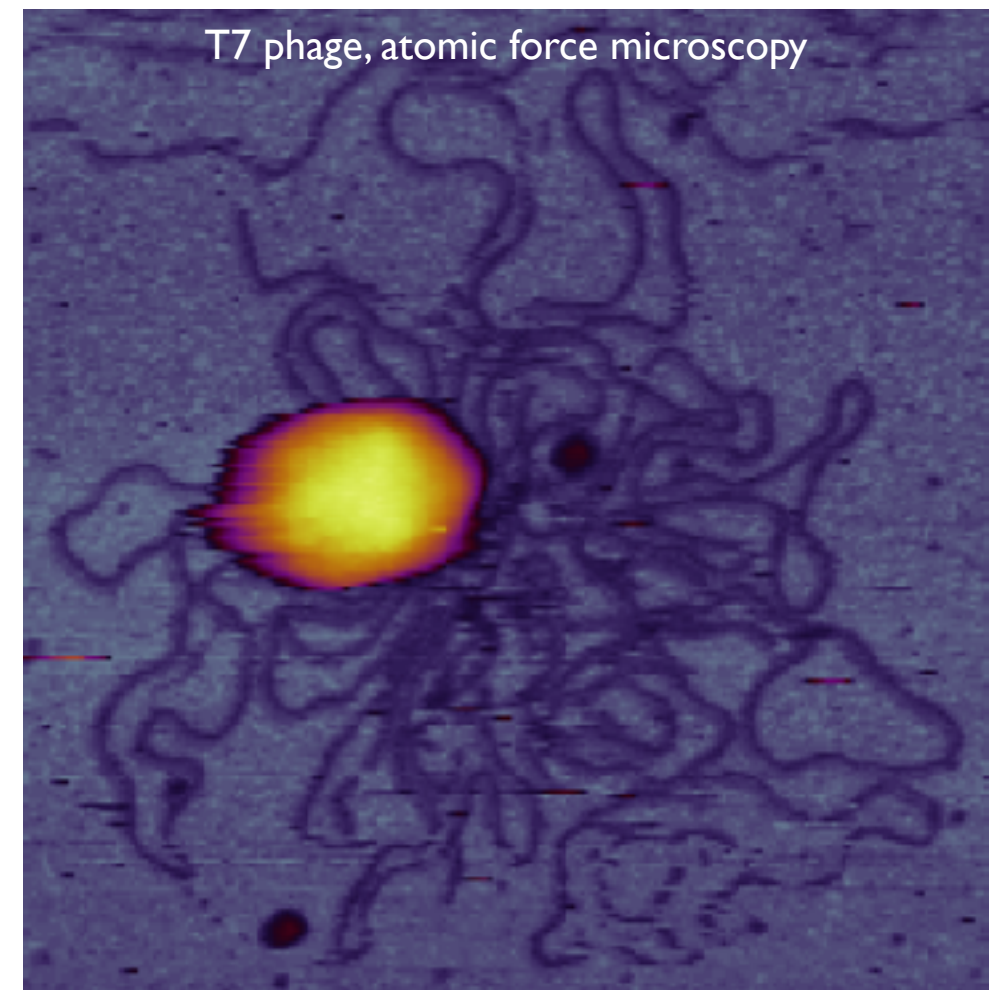
# Biological macromolecules are **giant** molecules



DNA double helix

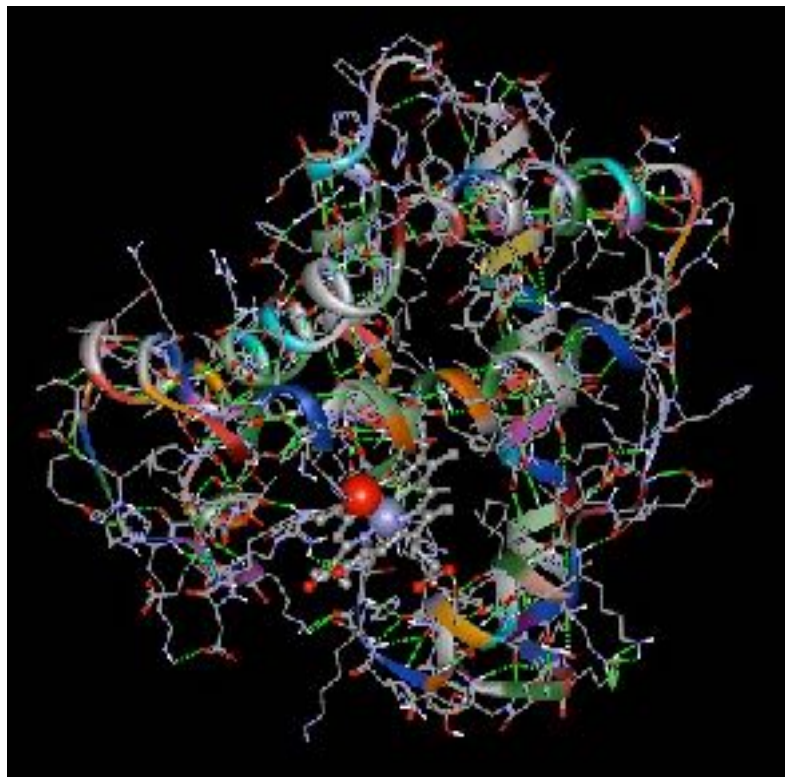


DNA released from bacteriophage head

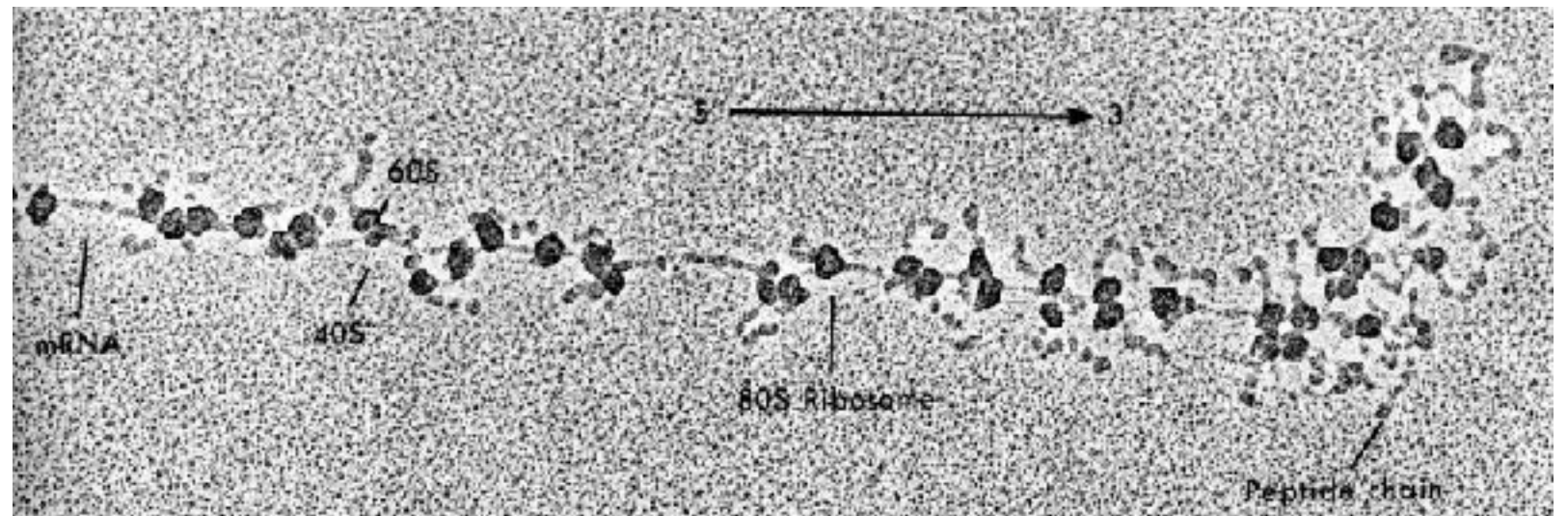




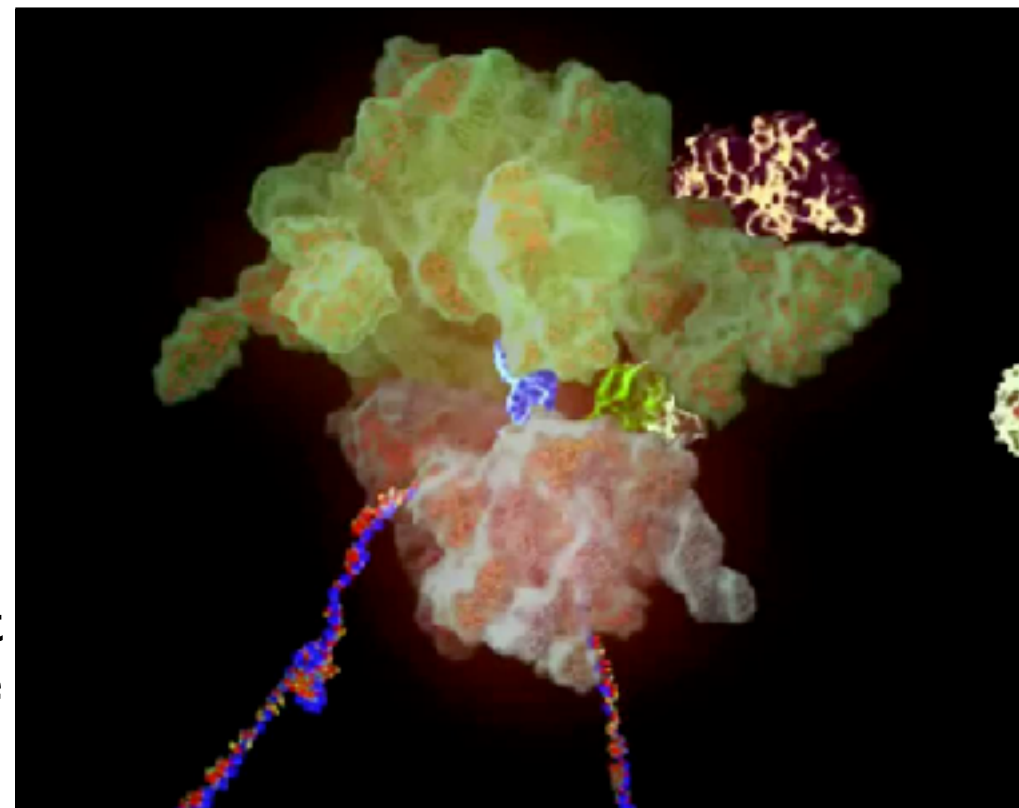
# Biological macromolecules are **exciting** molecules



Structure of hemoglobin subunit



Newly synthesized protein (silk fibroin)



Folding of nascent protein (on the ribosome)

# Biological macromolecules: biopolymers

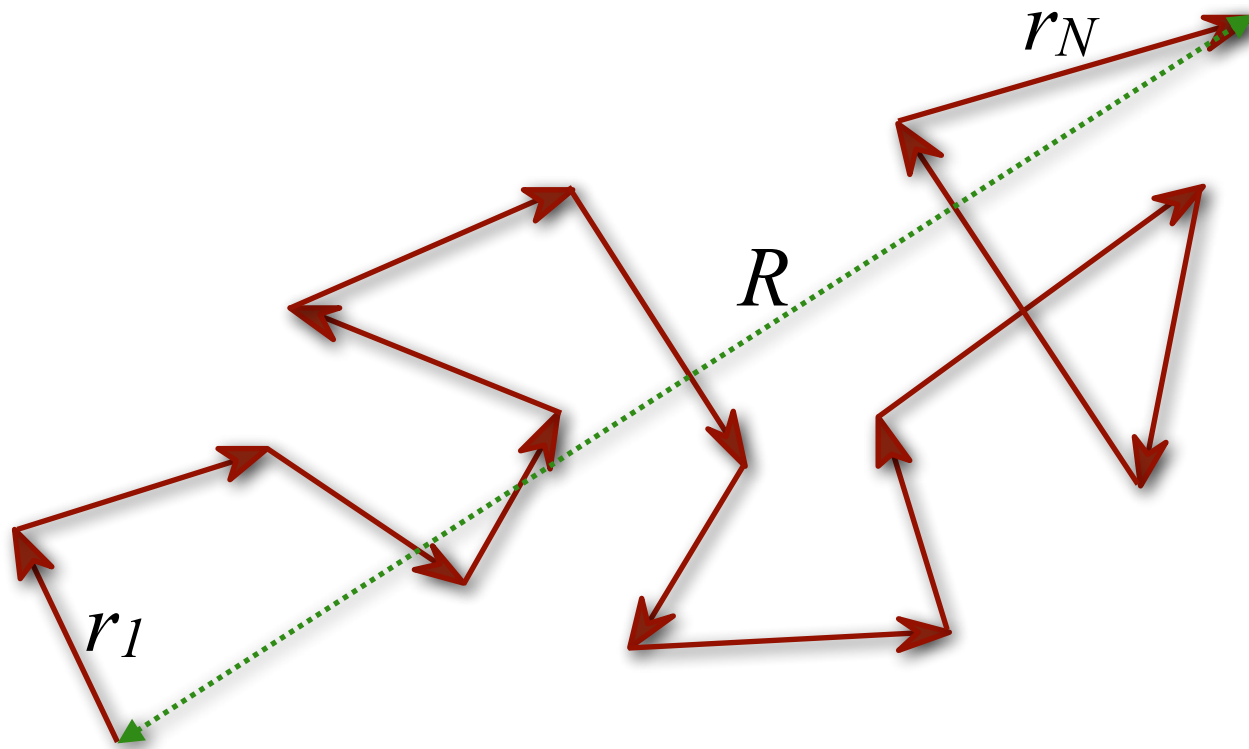
Polymers:  
chains built up from monomers

Number of monomers:  $N \gg 1$ ;  
Typically,  $N \sim 10^2 - 10^4$ ,  
but, in DNA, e.g.:  $N \sim 10^9 - 10^{10}$

Biopolymer	Monomer	Bond
Protein	Amino acid	Covalent (peptide bond)
Nucleic acid (RNA, DNA)	Nucleotide (CTUGA)	Covalent (phosphodiester)
Polysaccharide (e.g., glycogen)	Sugar (e.g., glucose)	Covalent (e.g., $\alpha$ -glycosidic)
Protein polymer (e.g., microtubule)	Protein (e.g., tubulin)	Secondary

# Shape of the polymer chain resembles random walk

Brownian-movement -  
“random walk”



“Square-root law”:

$$\langle R^2 \rangle = Nl^2 = Ll$$

$R$  = end-to-end distance

$N$  = number of elementary vectors

$l = |\vec{r}_i|$  = correlation length

$r_i$  = elementary vector

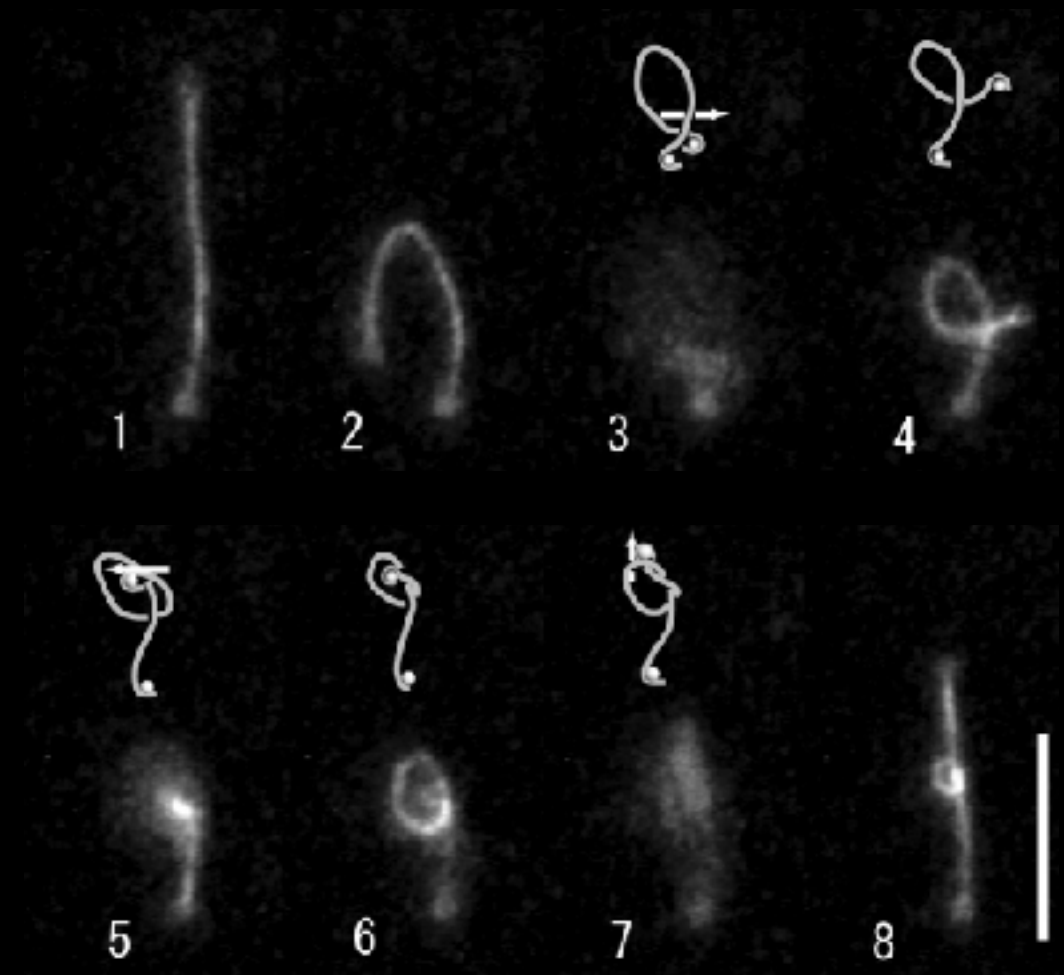
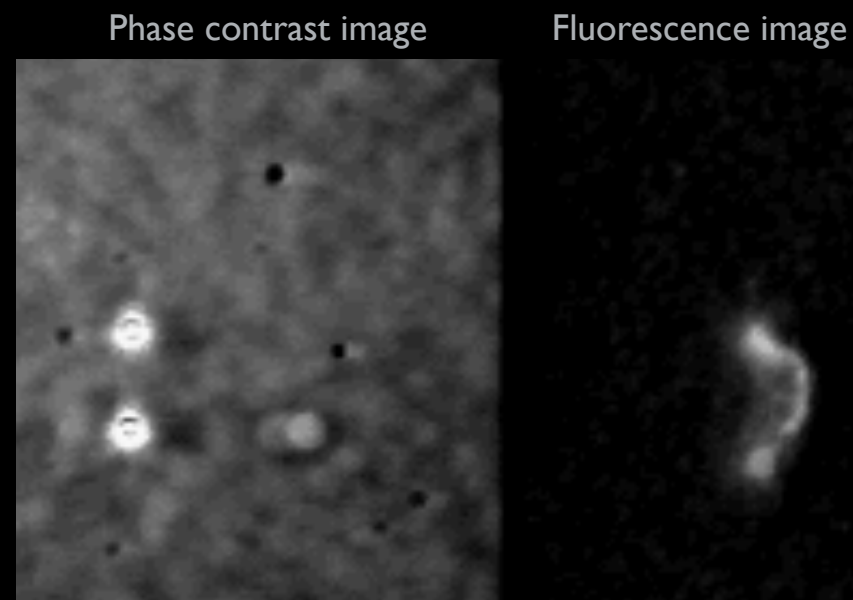
$Nl = L$  = contour length

$l$  is related to **bending rigidity**.

In case of Brownian-movement  $R$  = displacement,  $N$  = number of elementary steps,  $L$  = total path length, and  $l$  = mean free path length.

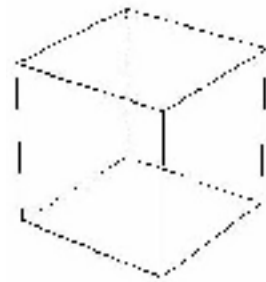
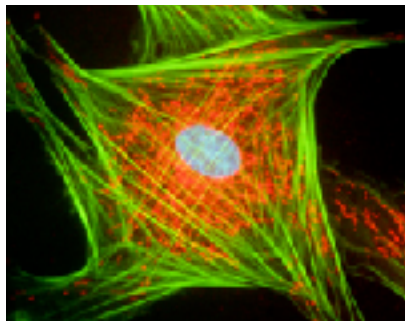
# Visualization of a random chain

## Tying a knot on a single DNA chain





# Physical size of the human genome

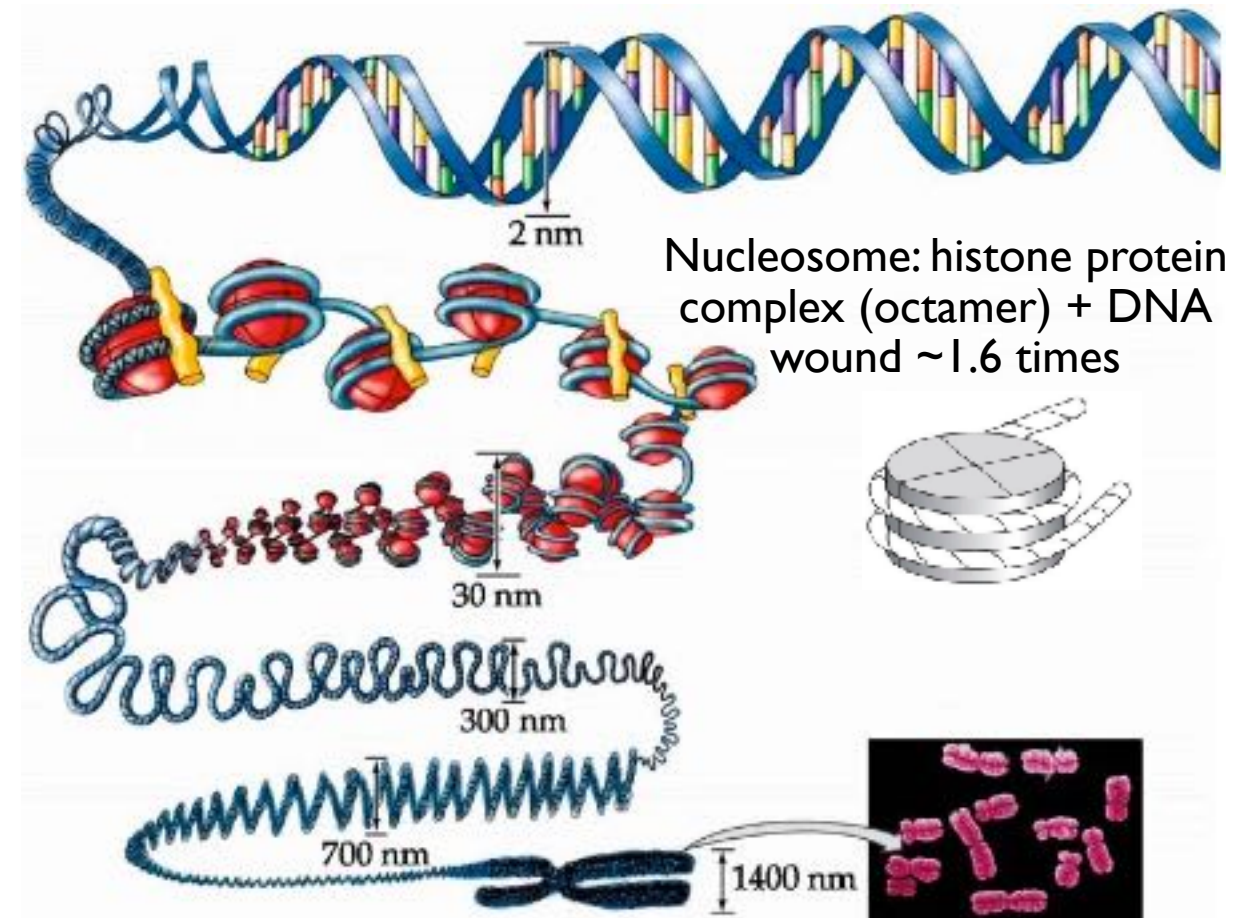


Simplified cell  
model: cube

**Solution:** DNA needs  
to be packed!

	<b>Cell:</b> 20 $\mu\text{m}$ edge cube	Analog - <b>Lecture hall:</b> 20 m edge cube
DNA thickness	2 nm	2 mm
Full length of human DNA	$\sim 2$ m	$\sim 2000$ km (!!!) (Perimeter of Hungary: $\sim 2200$ km)
Persistence length of dsDNA ( $L_P$ )	$\sim 50$ nm	$\sim 50$ cm
Mean end-to-end length $\sqrt{\langle R^2 \rangle} = \sqrt{L_C L_P}$	$\sim 350$ $\mu\text{m}$ (!)	$\sim 350$ m (!)
Radius of gyration ( $R_G$ ) $R_G = R/\sqrt{6}$	130 $\mu\text{m}$	130 m
Volume of fully compacted DNA	$\sim 2 \times 2 \times 2$ $\mu\text{m}^3$	$\sim 2 \times 2 \times 2$ $\text{m}^3$ (= 8 $\text{m}^3$ )

## Chromosome condensation



- **Condensins** play a role in high-order DNA packaging
- DNA chain: complex linear path with roadblocks!