

PHYSICAL BIOLOGY OF THE LIVING CELL I.

MIKLÓS KELLERMAYER

Topics - semester I

Qualitative and quantitative modelling in biology (Dr. Miklós Kellermayer)	Feb. 11
Structural hierarchy of proteins (Dr. Schay Gusztáv)	Feb. 18
Stability of biological structures (Dr. Schay Gusztáv)	Feb. 25
Experimental methods to study biological structures - I (Dr. Schay Gusztáv)	Mar. 4
Experimental methods to study biological structures - II (Dr. Miklós Kellermayer)	Mar. 11
Microscopy studies of intracellular structures (Dr. Miklós Kellermayer)	Mar. 18
Formation of biological structures (Dr. Szabolcs Osváth)	Mar. 25
Dynamic intracellular protein structures (Dr. Miklós Kellermayer)	Apr. 1
Super-resolution microscopy (Dr. Szabolcs Osváth)	Apr. 8
Single molecule biological activity (Dr. Miklós Kellermayer)	Apr. 29
Visit to the research laboratories of the Dept. of Biophysics and Radiation biology of the Semmelweis University (Dr. Szabolcs Osváth)	May 6
Problem solving and consultation (Dr. Szabolcs Osváth)	May 13

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.**

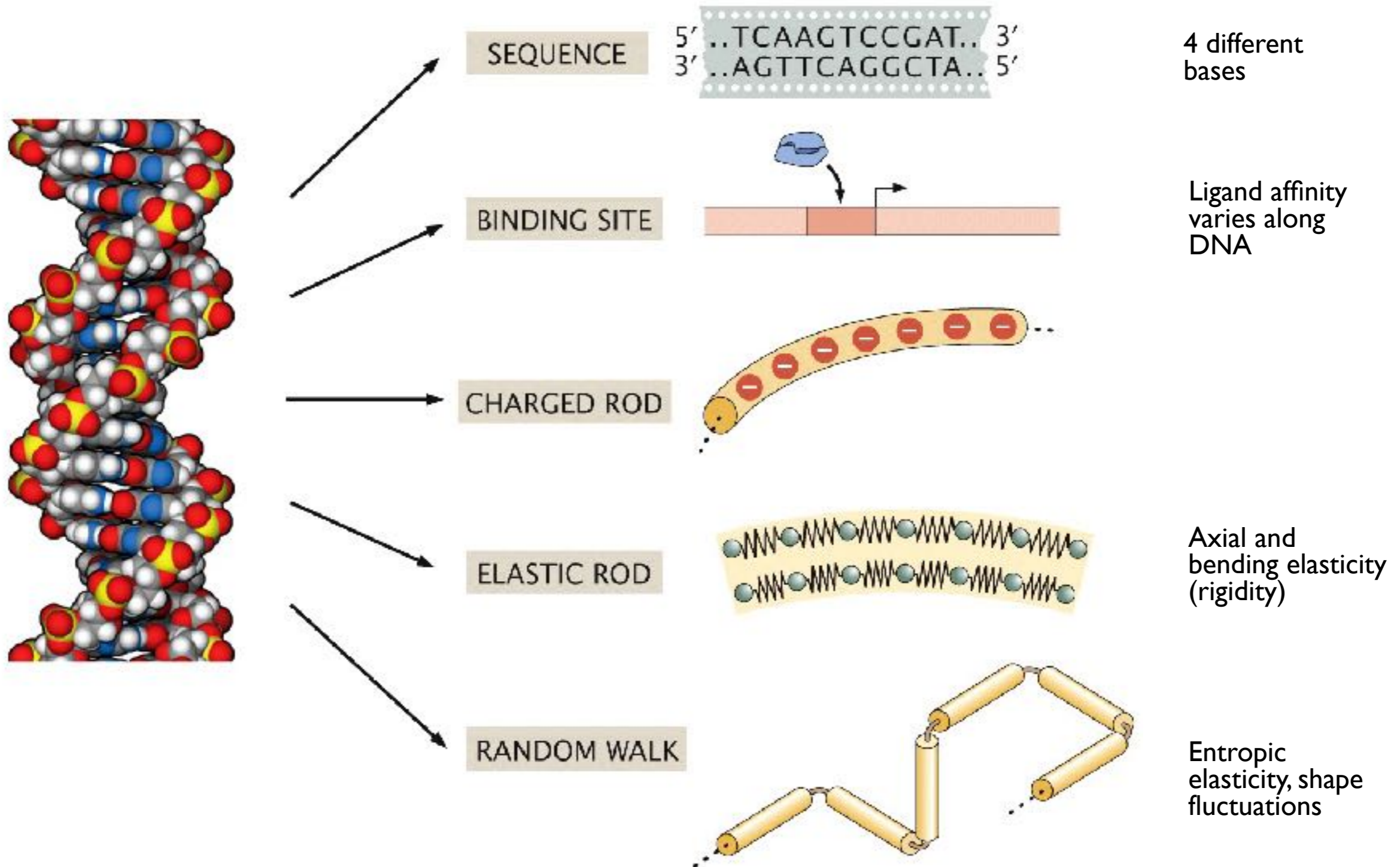
Why is life alive?

- 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”)

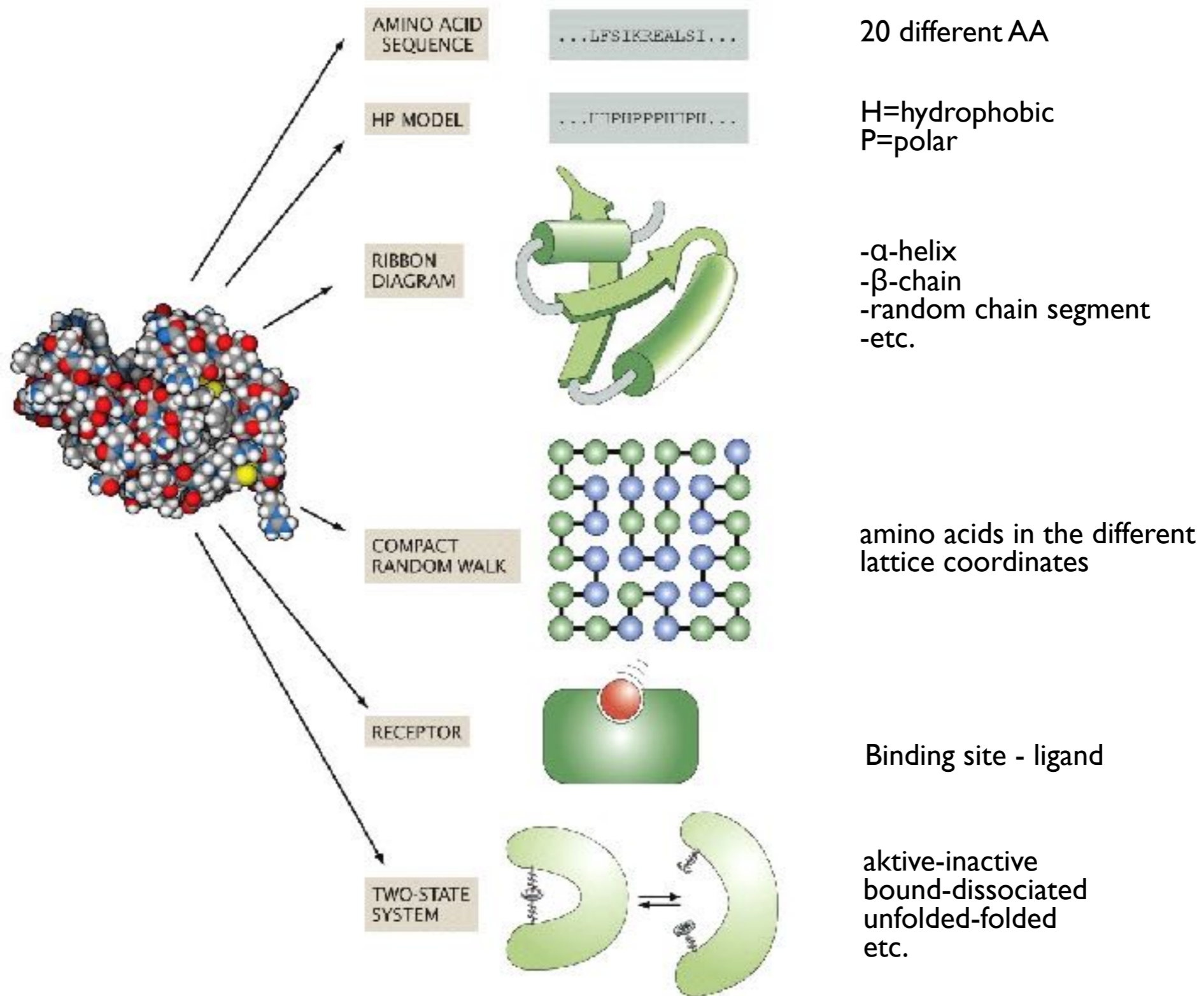
Biological model building

- 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

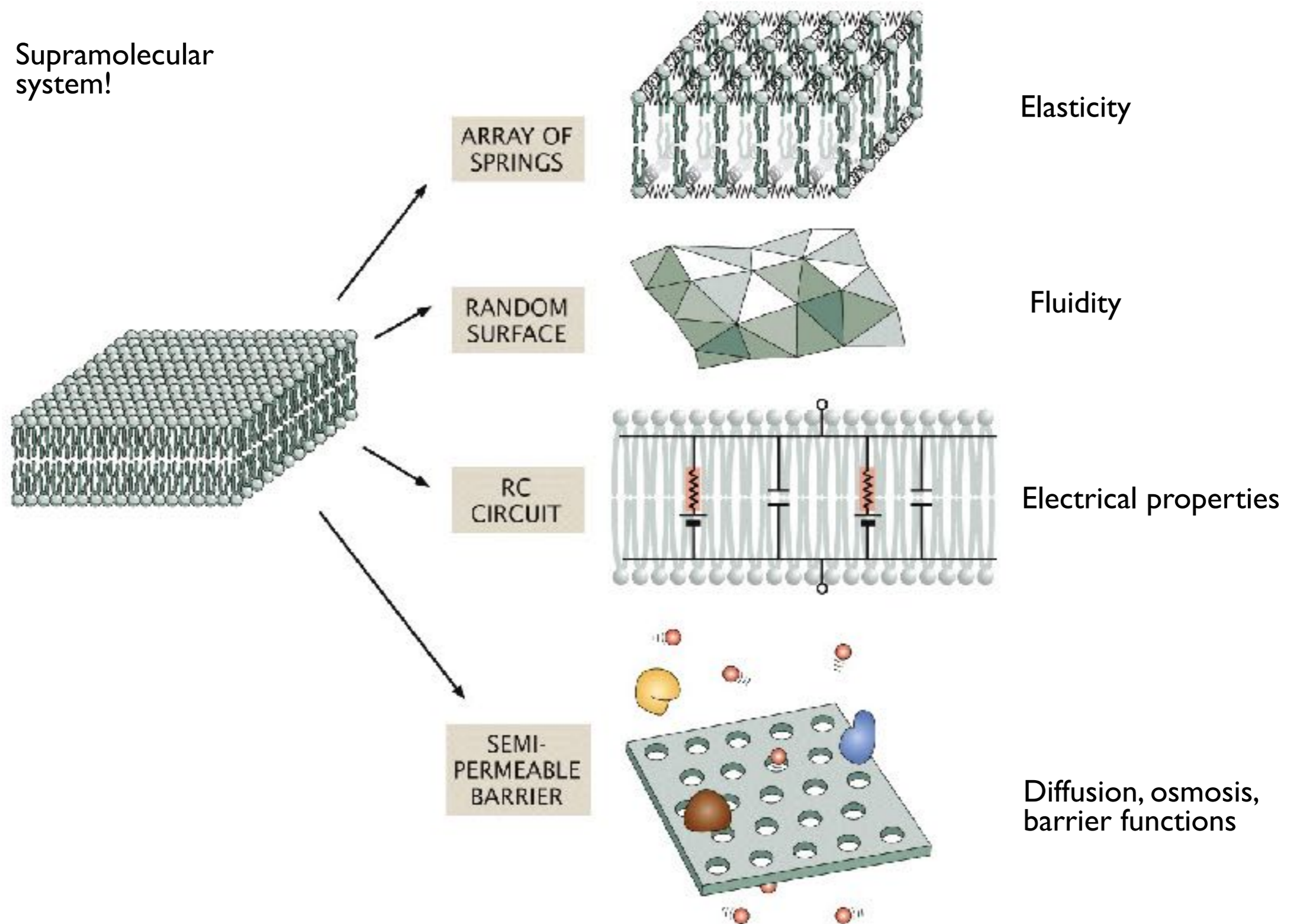


Idealization of a protein molecule

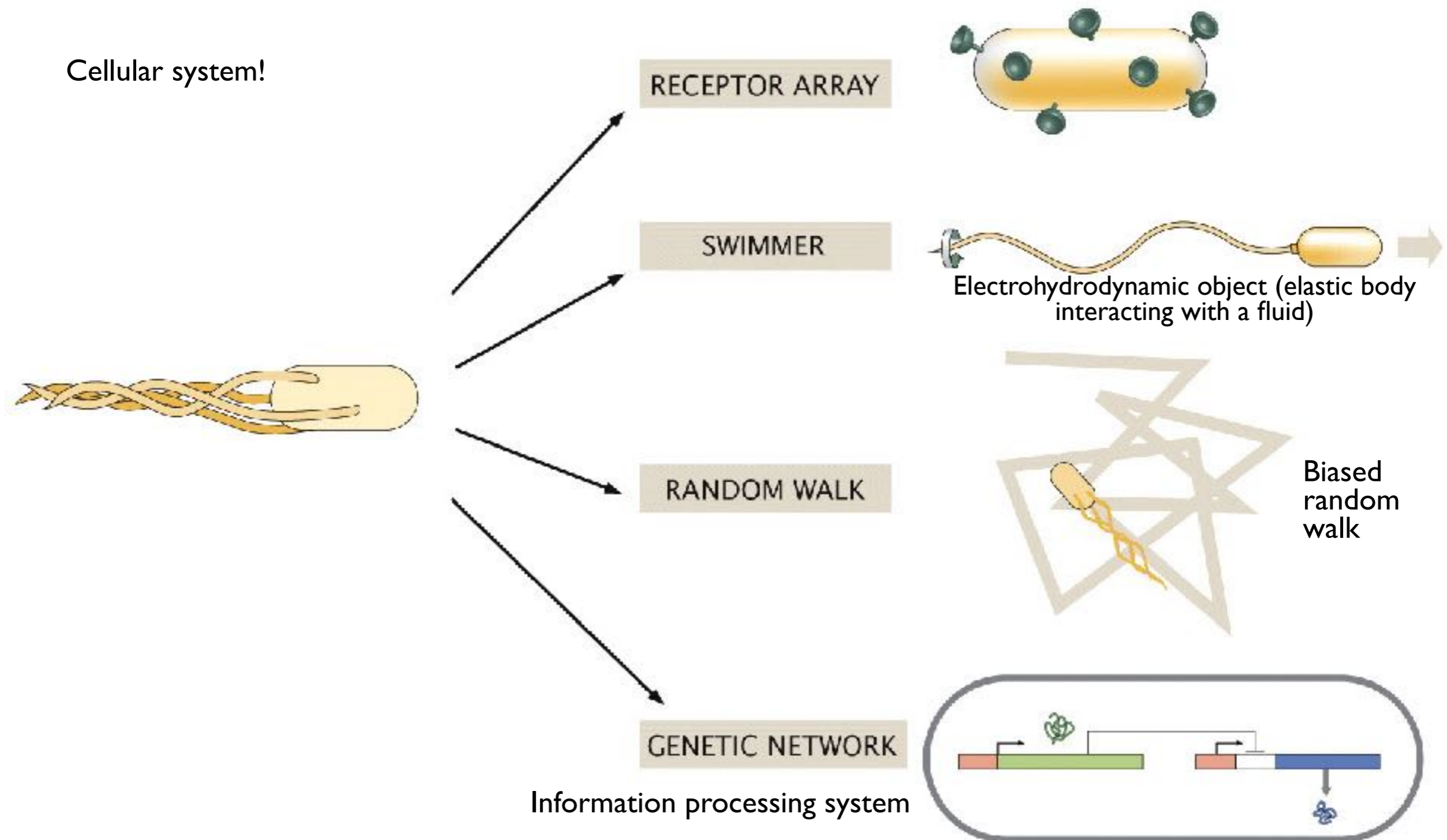


Idealization of lipids and membranes

Supramolecular system!



Idealization of an *Escherichia coli* cell

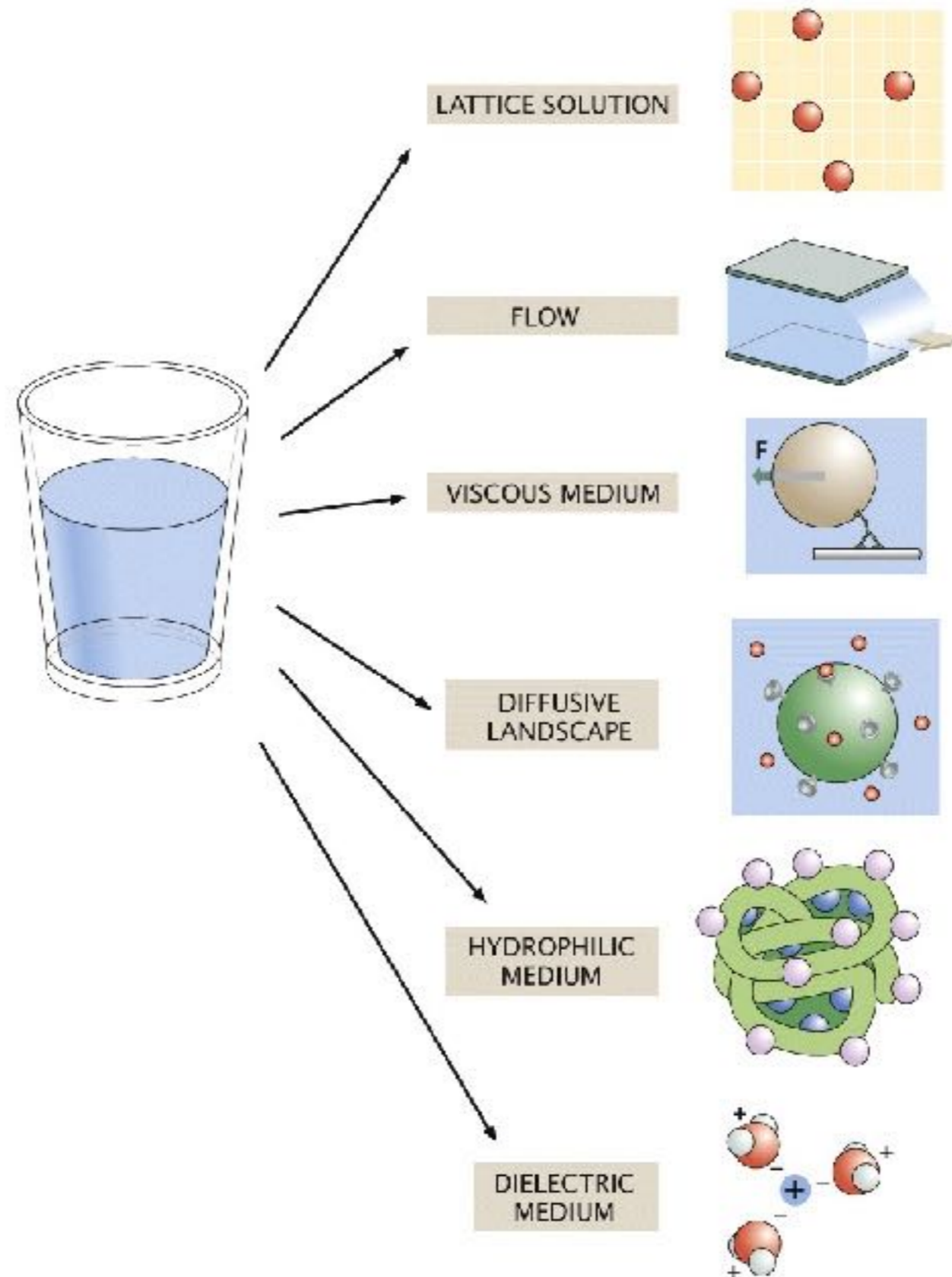


Idealization of a solution

Living cell as an
ideal solution(?)

Homogenous

Isotropic



Idealization, expansion and application of the concept of elasticity

Average deviation from equilibrium position:

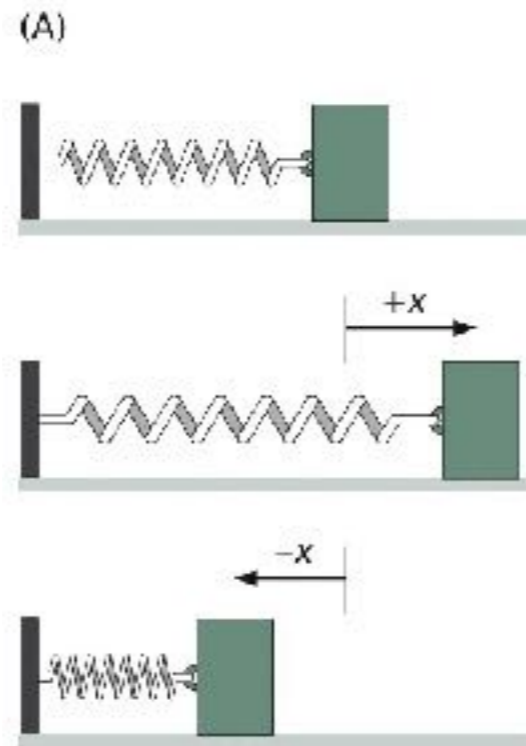
$$Energy = \frac{1}{2} \kappa x^2$$

κ : spring constant - energetic cost of deviating from equilibrium

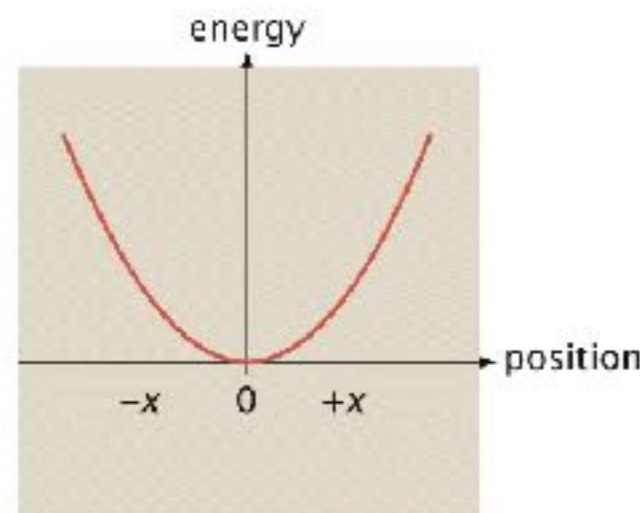
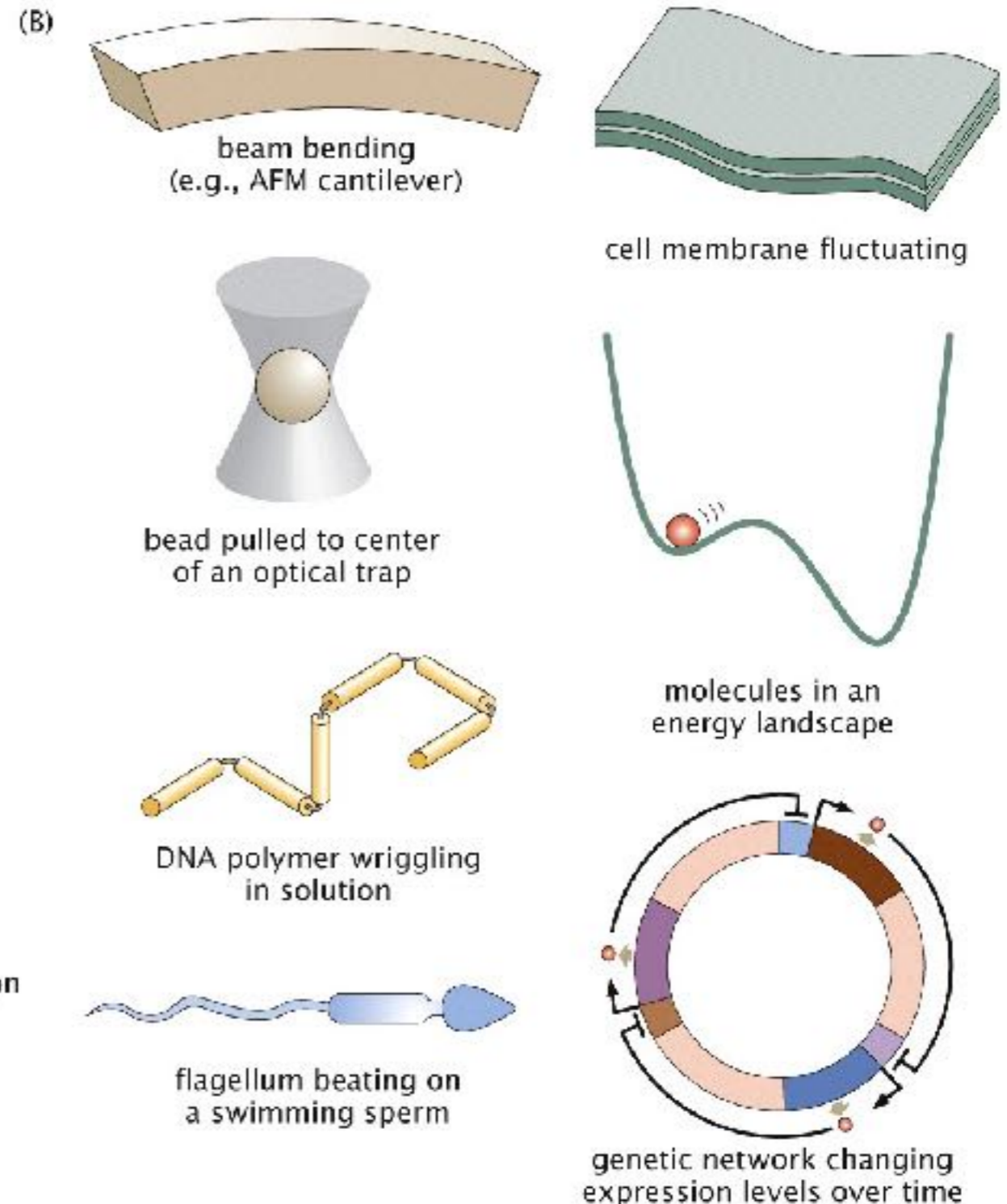
Recovery force:

$$F = -\kappa x$$

Harmonic oscillation



Biological, biophysical examples

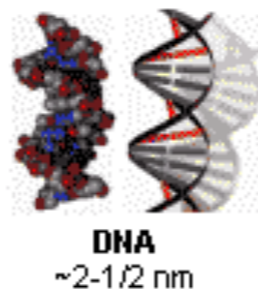
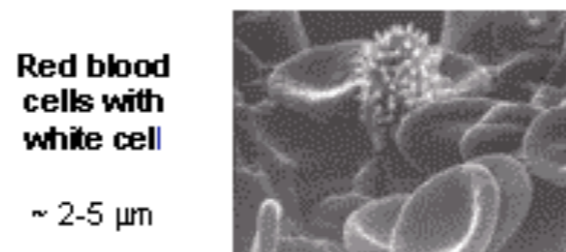
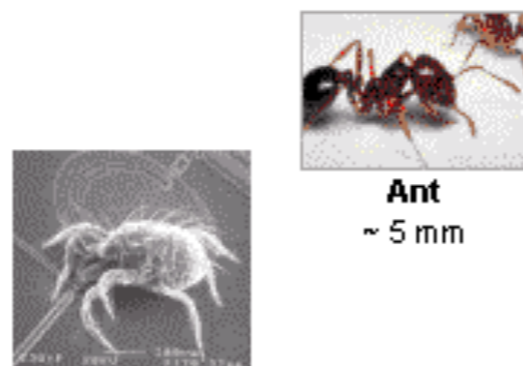


Scaling in biology

Size of biomolecular systems

Thermodynamics

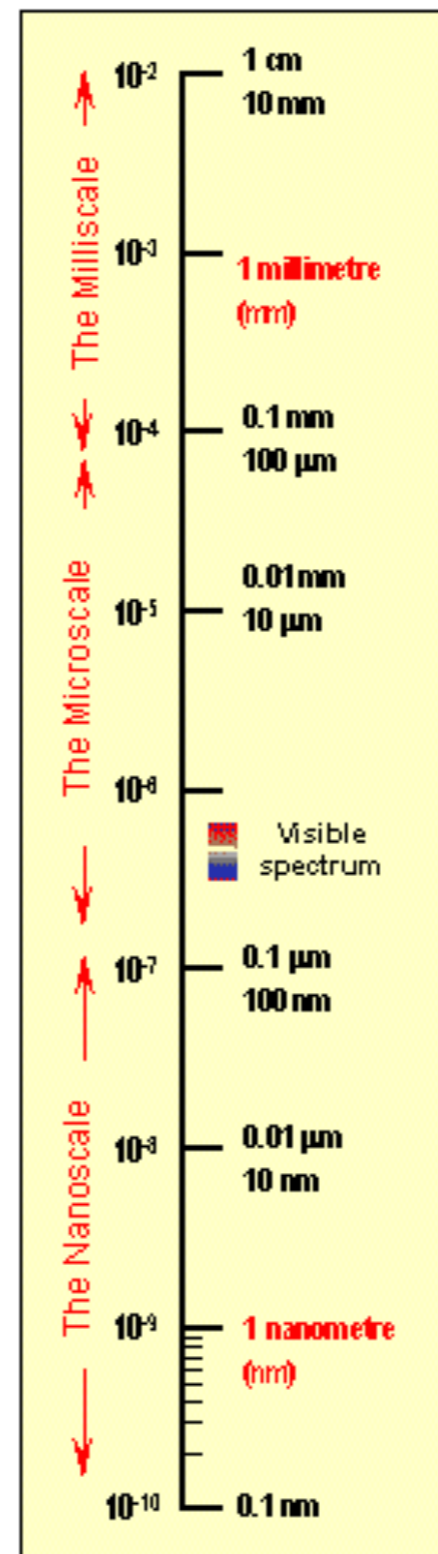
10^{23} Atoms



Mesoscale

Quantum chemistry

Quantum physics



10^{10} Atoms

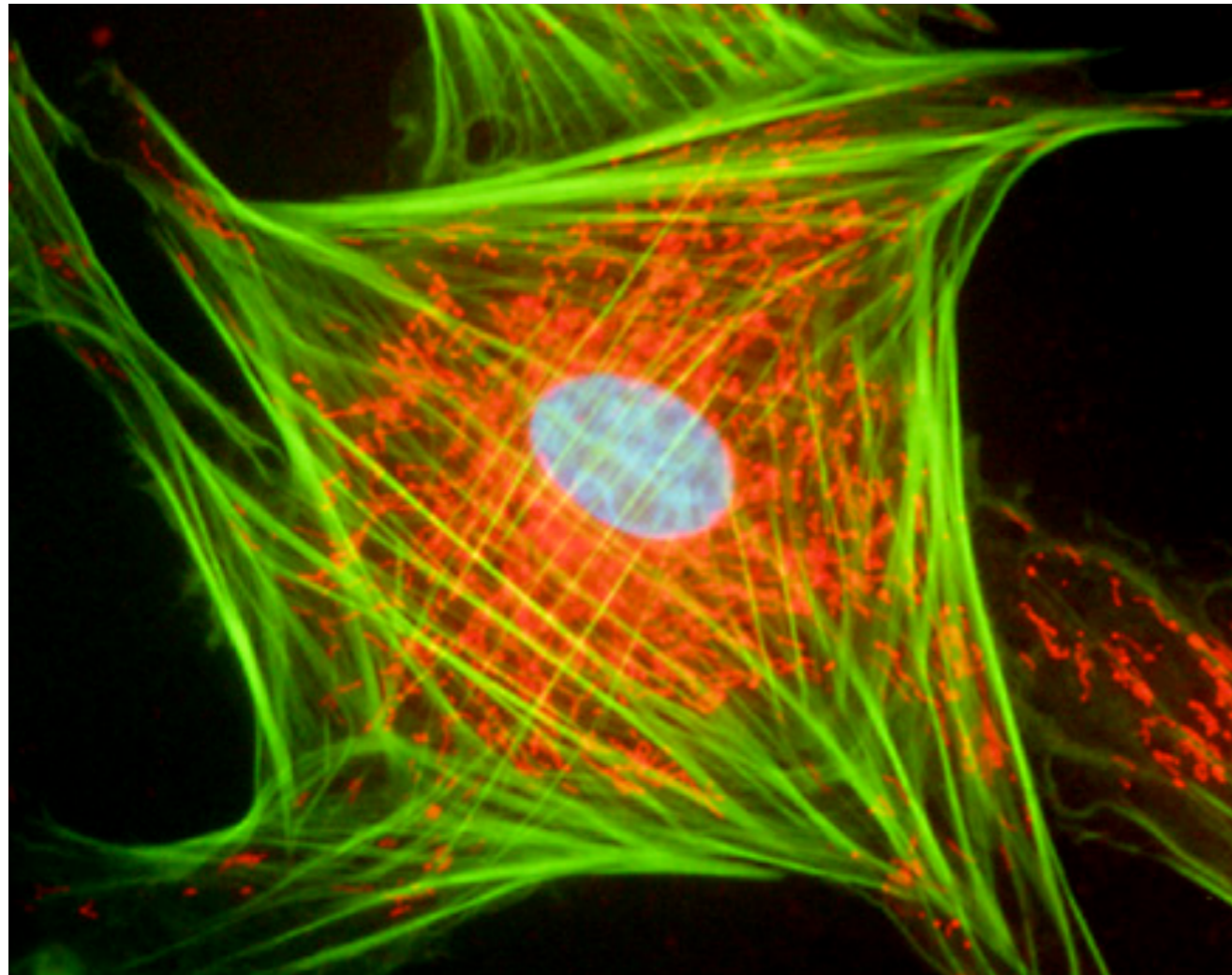
10^3 Atoms

10^1 Atoms

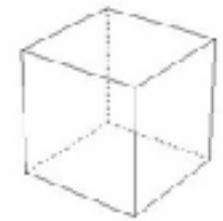
10^0 Atoms

Length scale of the living cell

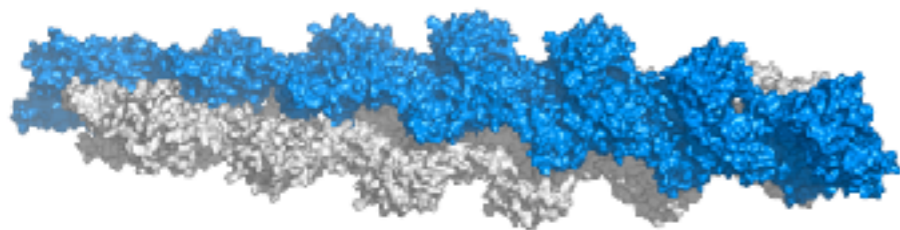
Rudolf Virchow (1855): “*Omnis cellula e cellula*”



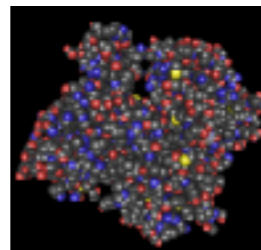
Simplified cell model:
cube



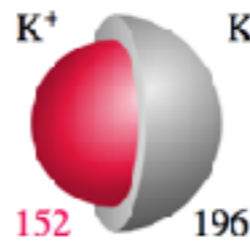
	Cell: cube with 20 μm edge	Analogue - Lecture hall: cube with 20 m edge
Size of actin molecule	5 nm	5 mm
Number of actin molecules	~500 million	~500 million
Average distance between actins	~25 nm	~25 mm
Size of potassium ion	0.15 nm	0.15 mm
Number of potassium ions	~ 10^9	~ 10^9
Average distance between K^+ ions	~20 nm	~2 cm



Actin filament (d=7 nm)



G-actin
(d=5 nm,
cc~100 μM)



Potassium ion
(d=0.15 nm,
cc~150 mM)

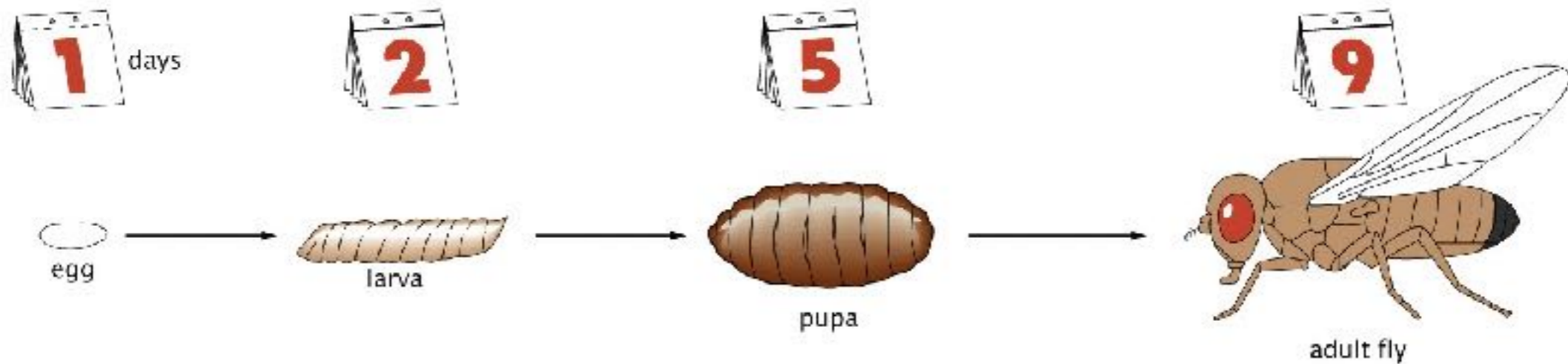
Deficiencies of the model:

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

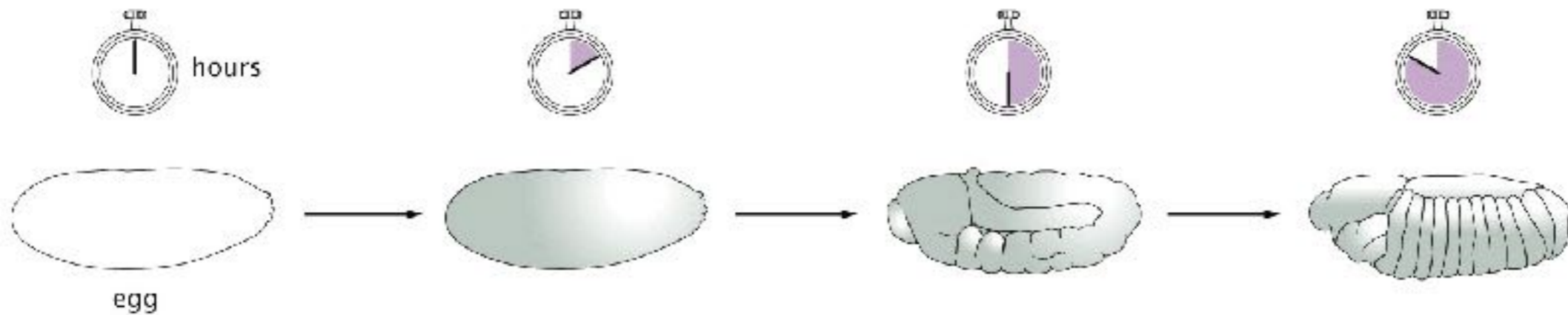
Scaling in biology

Biological time scale I.

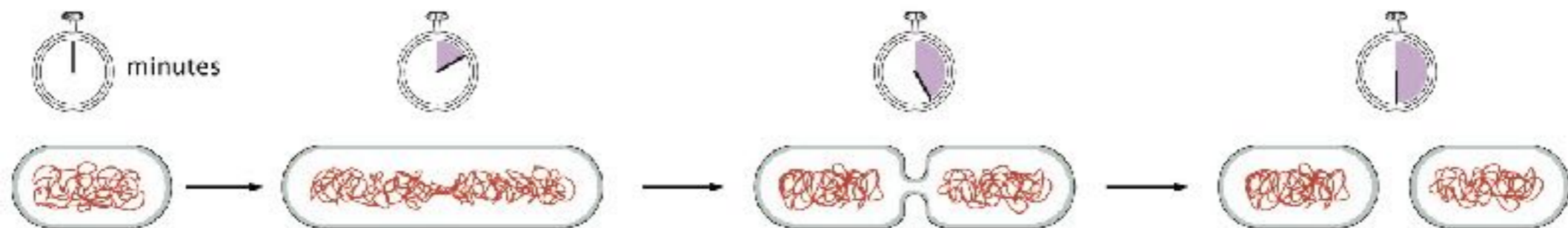
Development of *Drosophila*



Early development of *Drosophila*

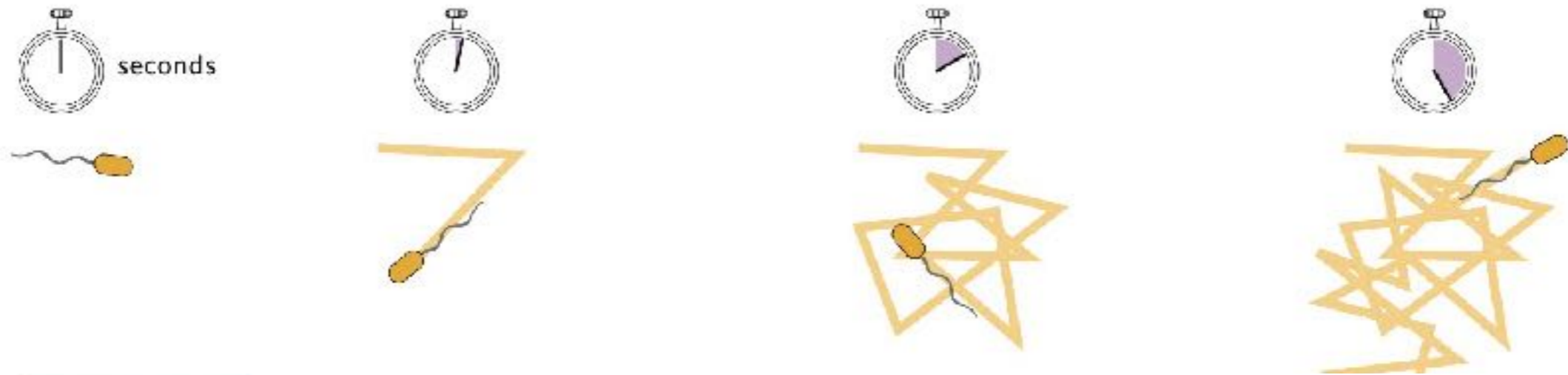


Bacterial cell division

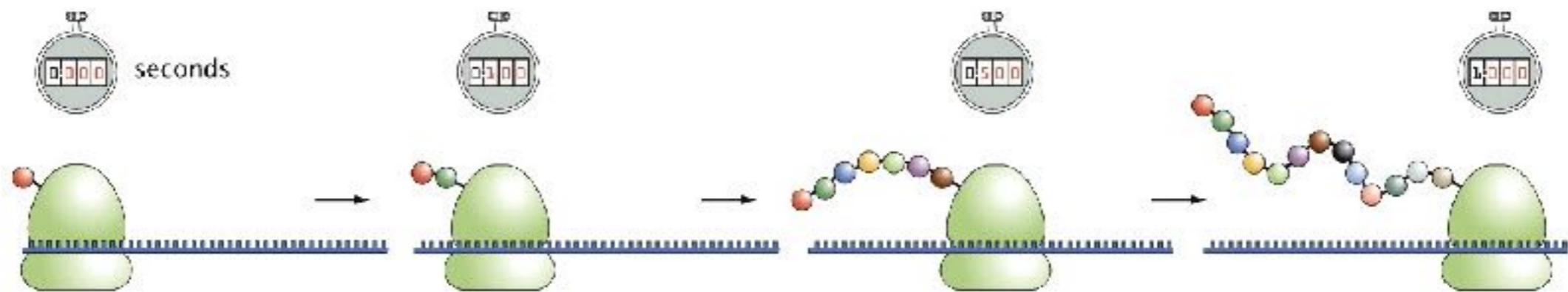


Biological time scale II.

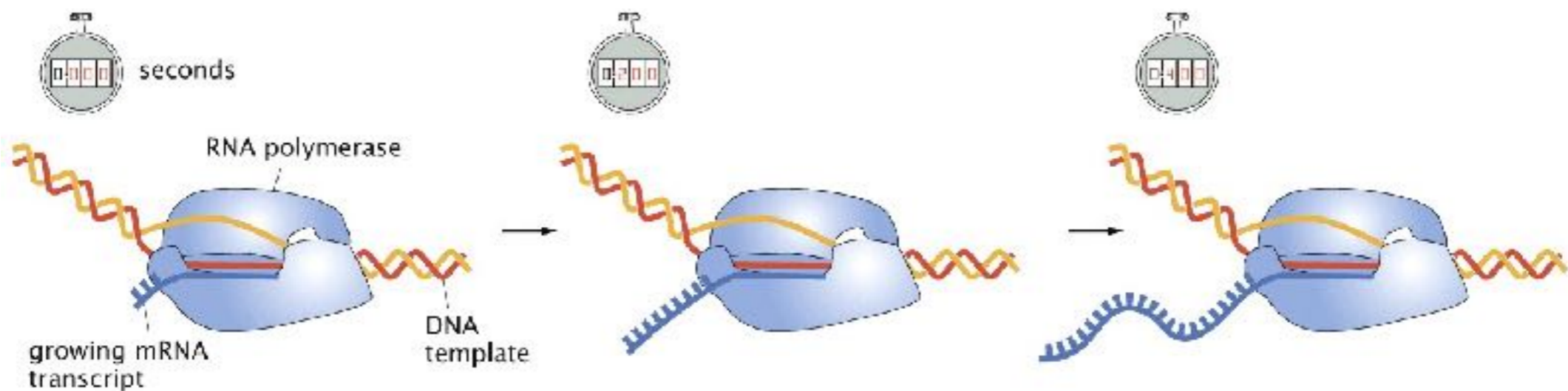
Cell movements



Protein synthesis

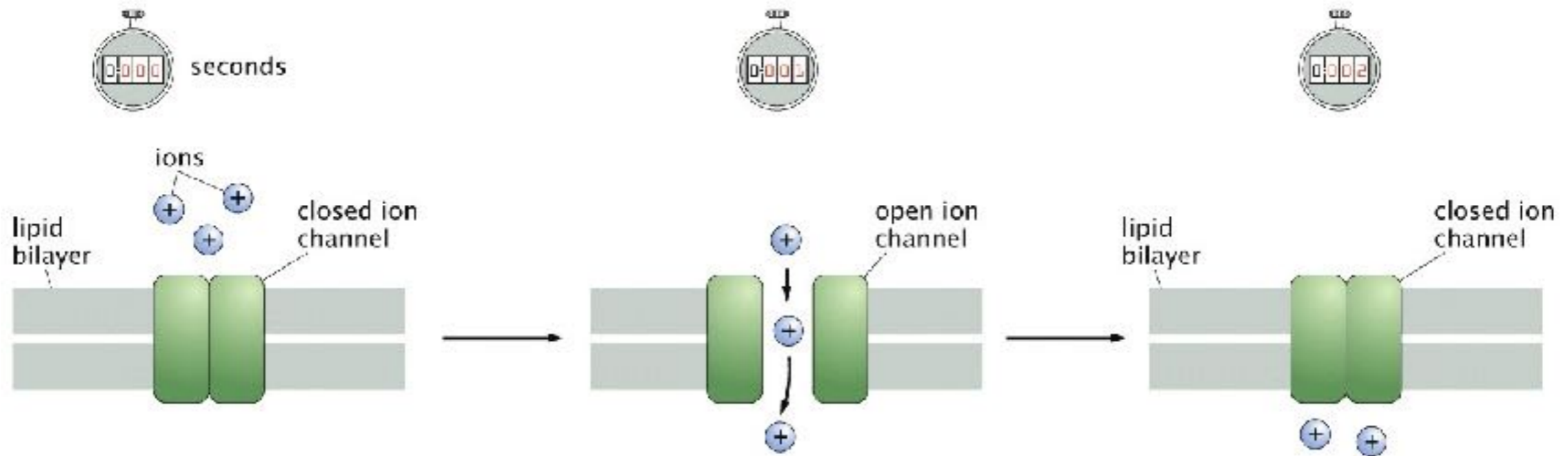


Transcription

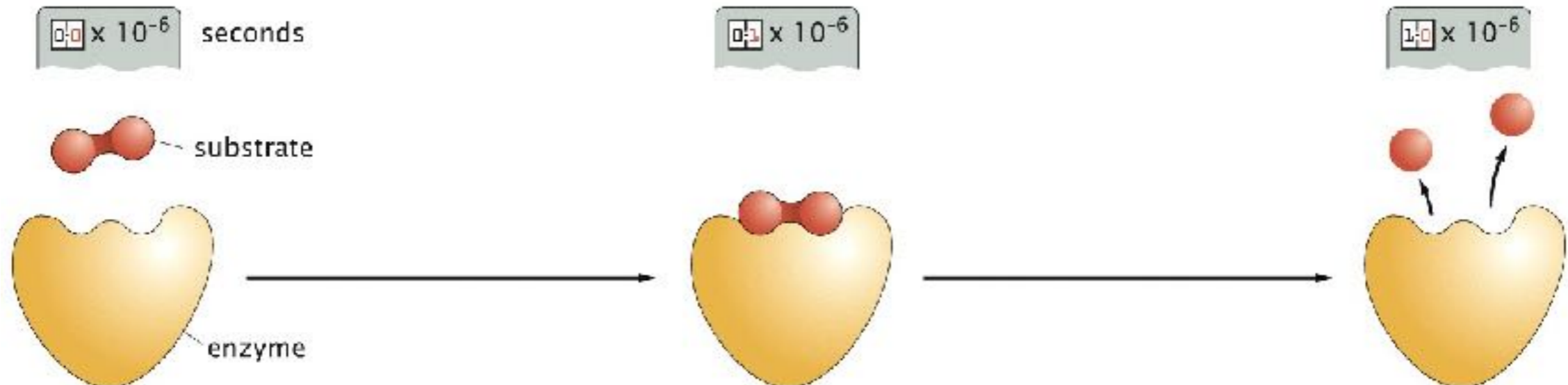


Biological time scale III.

Gating of ion channels



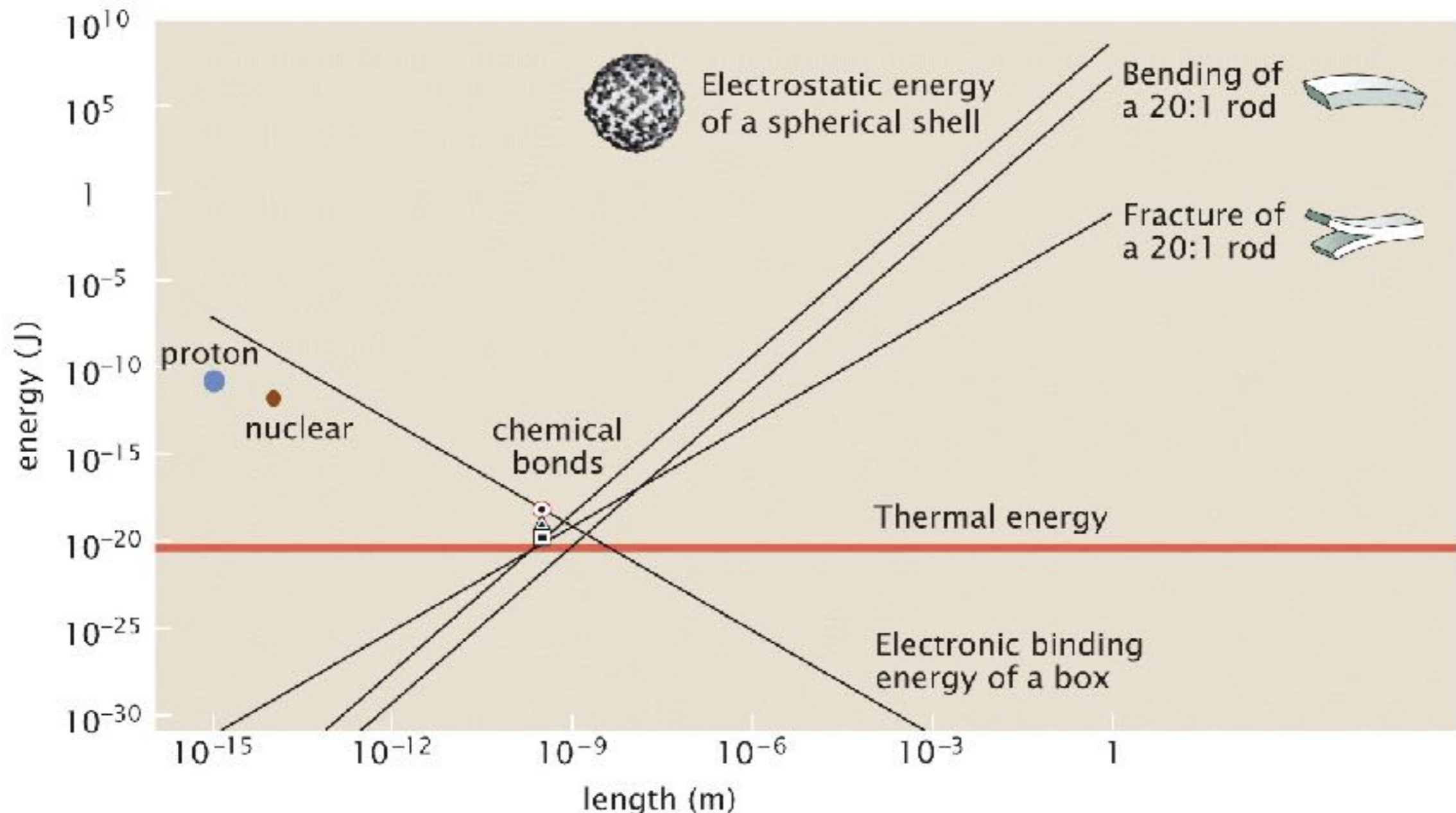
Enzyme catalysis



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

Correlation of energy and size scales

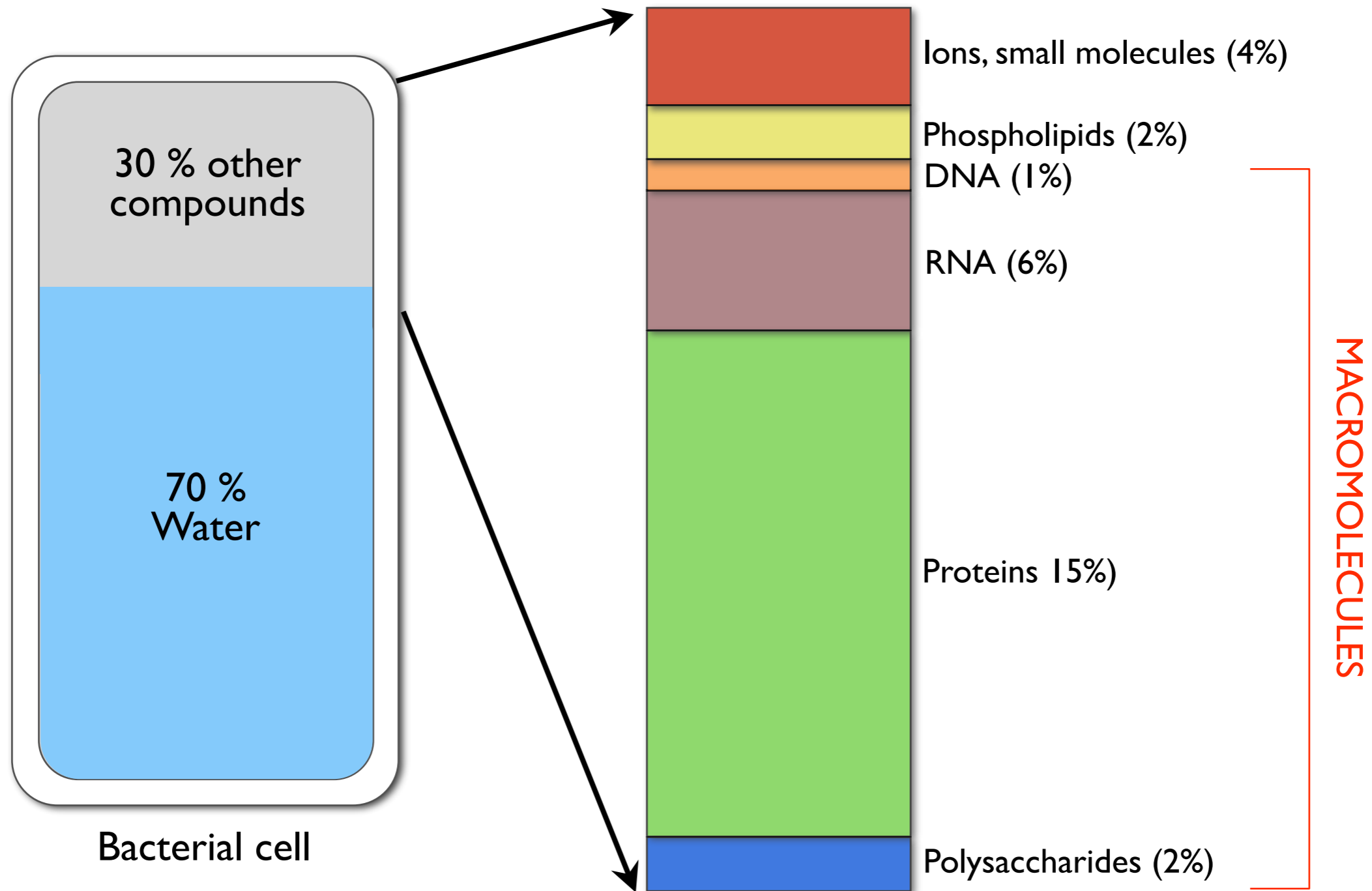
- “Deterministic” (chemical, mechanical, electromagnetic) vs. “thermal” energies
- Thermal energy unit: $k_B T = 4.1 \times 10^{-21} \text{ J} = 4.1 \text{ pNnm}$
- Relevant scaling - Boltzmann factor: $\exp(-E_{det}/k_B T)$
- Thermal energy = $k_B T = 4.1 \times 10^{-21} \text{ J} = 4.1 \text{ pNnm}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



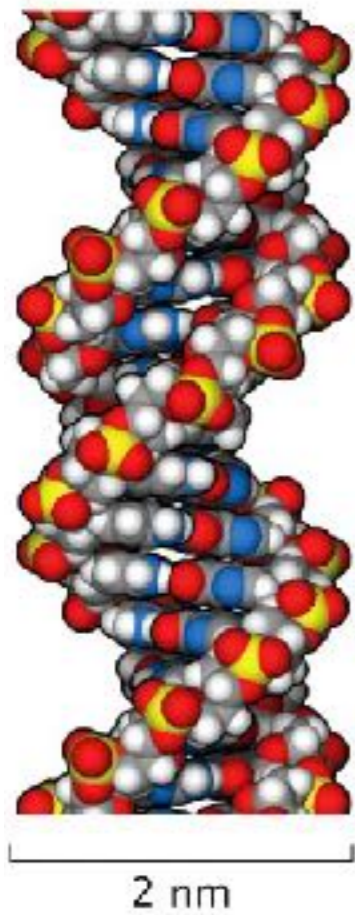
Some rules of thumb in quantitative biology

- 1 dalton (Da) = 1g/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/ μm^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 ≈ 1000 kg/ m^3
- Volume of a water molecule ≈ 0.03 nm^3
- Length of a base pair (along DNA) ≈ 0.3 nm
- Volume of a base pair ≈ 1 nm^3

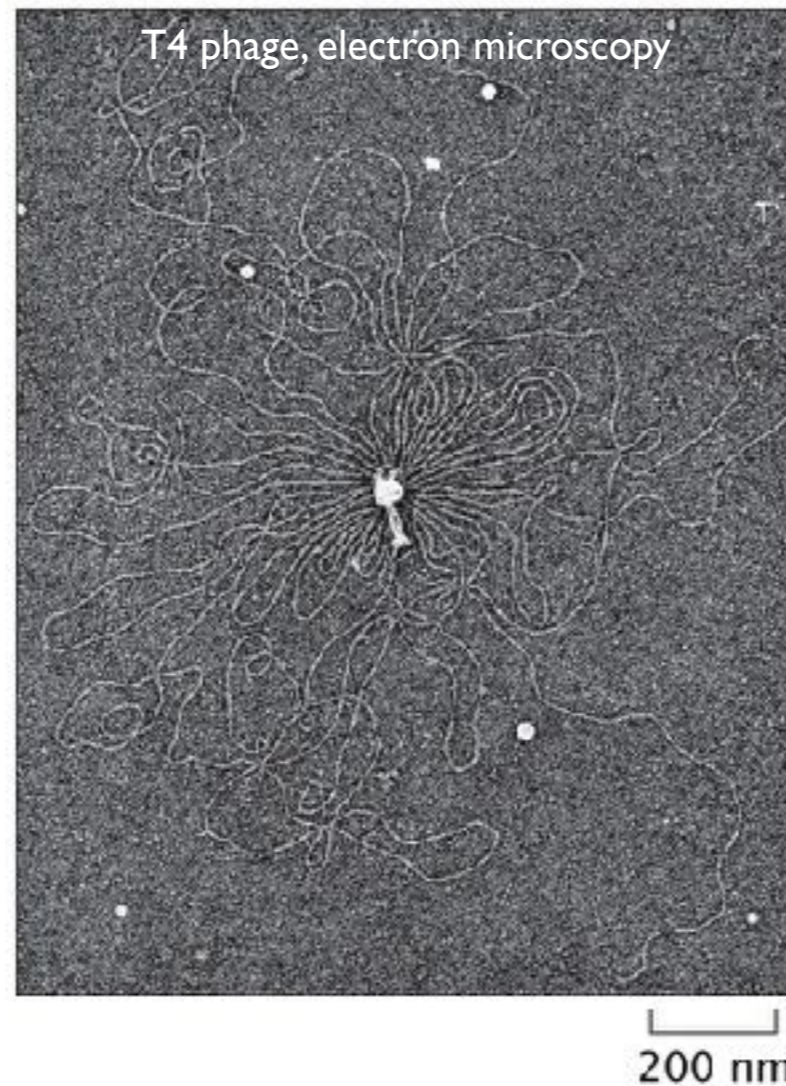
Proportion of macromolecules in the cell by mass is **large**



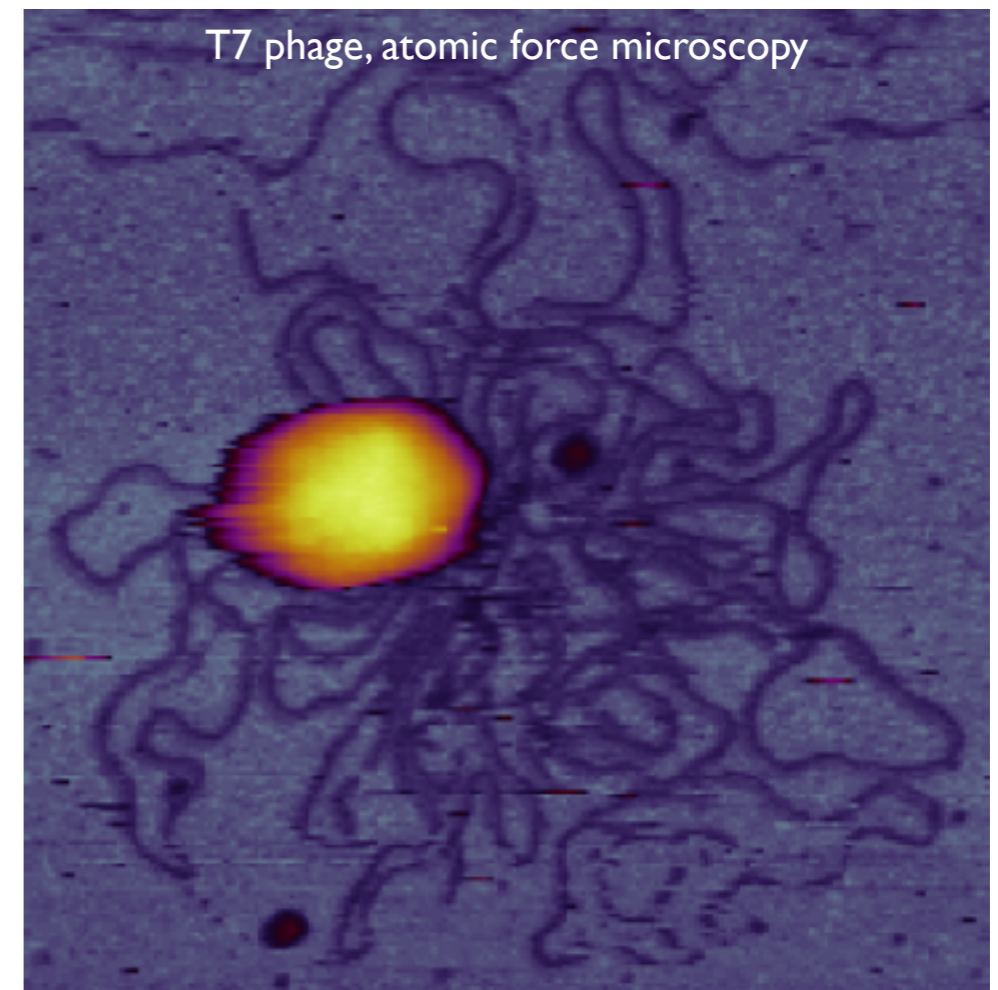
Biological macromolecules are **giant** molecules



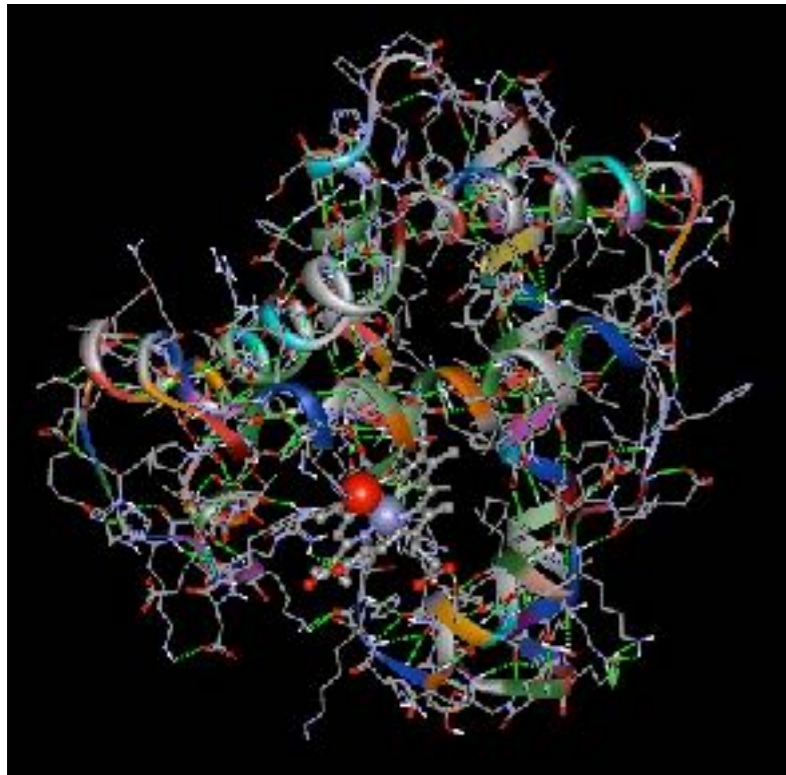
DNA double helix



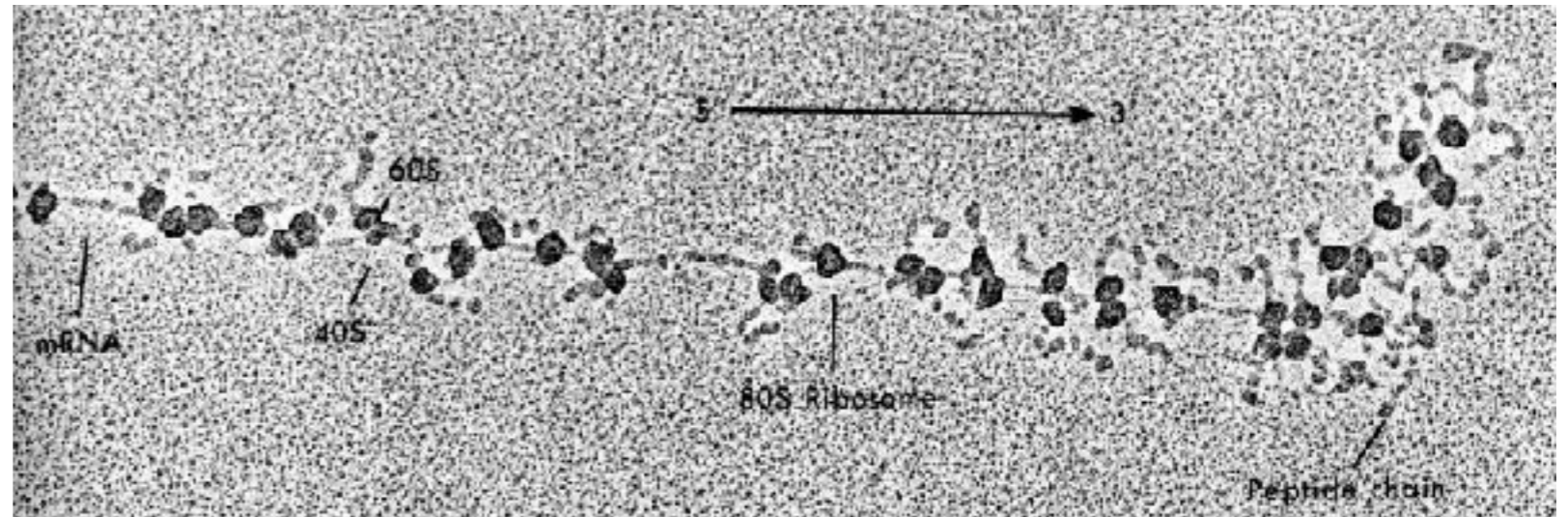
DNA released from bacteriophage head



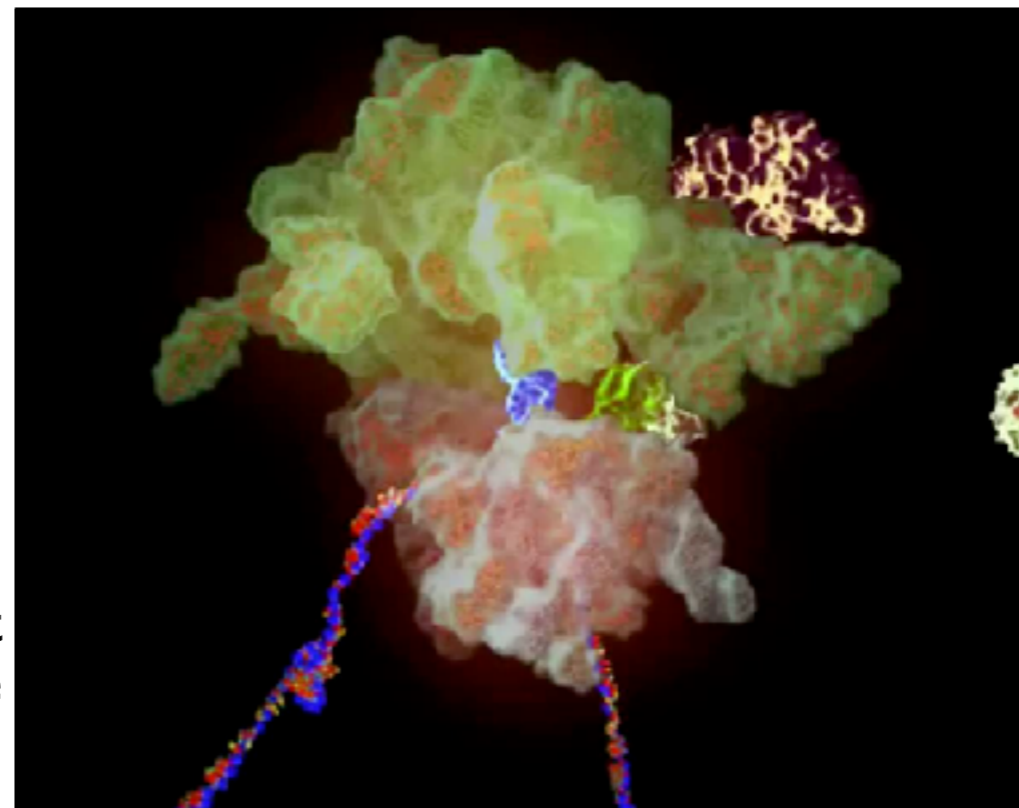
Biological macromolecules are **exciting** molecules



Structure of hemoglobin subunit



Newly synthesized protein (silk fibroin)



Folding of nascent protein (on the ribosome)

Biological macromolecules: biopolymers

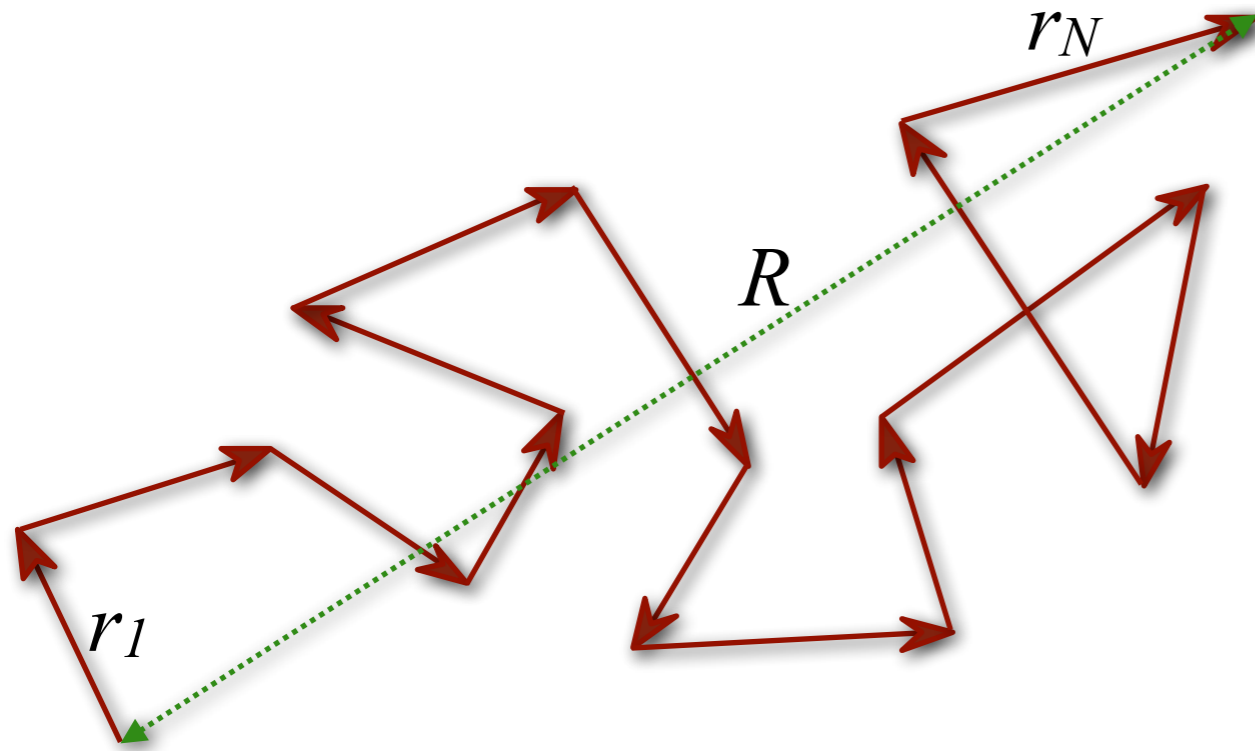
Polymers:
chains built up from monomers

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., α -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

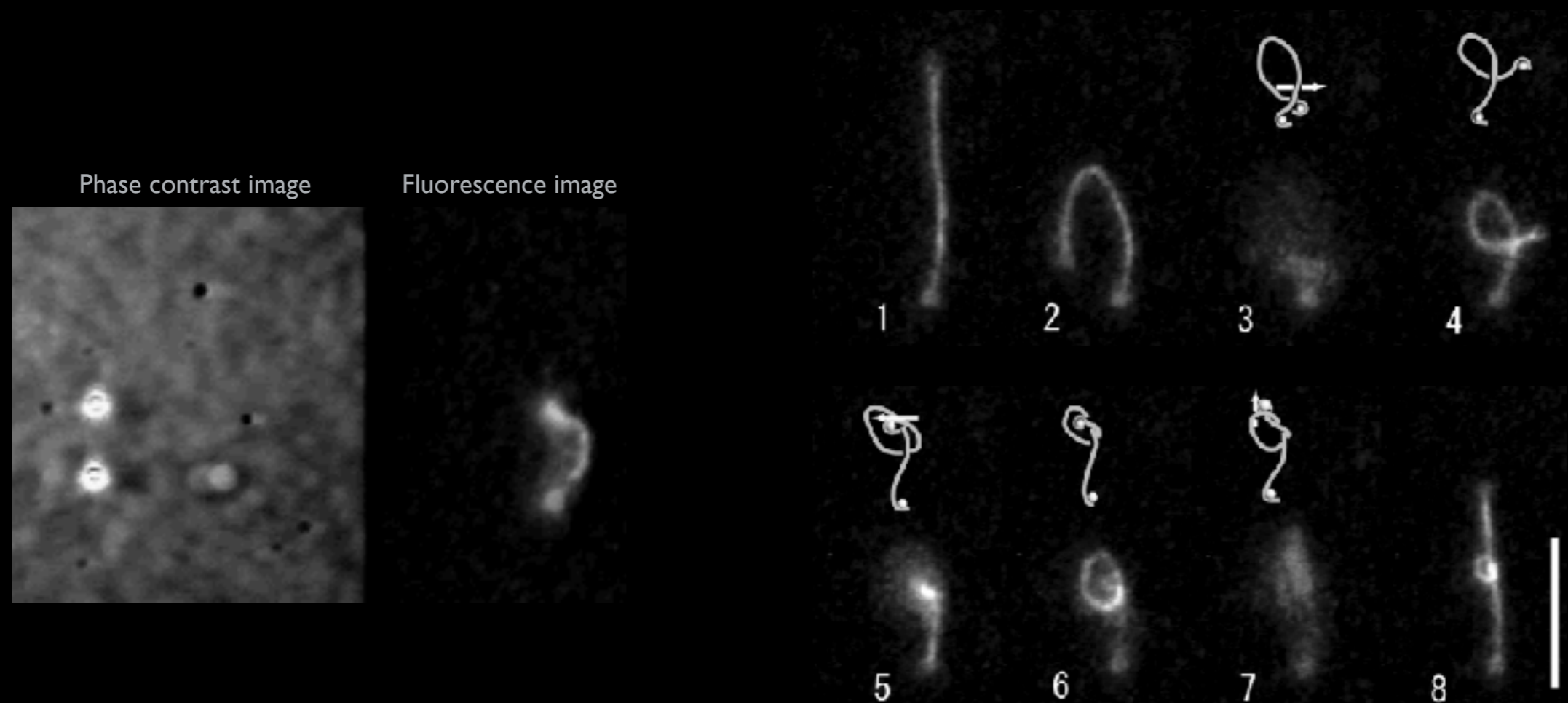
$Nl = L$ = contour length

l is related to **bending rigidity**.

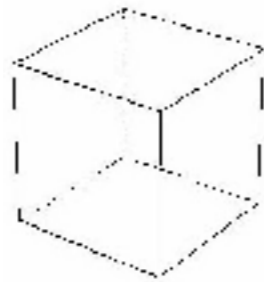
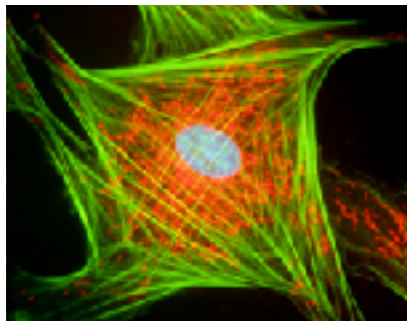
In case of Brownian-movement R = displacement, N = number of elementary steps, L = total path length, and l = mean free path length.

Visualization of a random chain

Tying a knot on a single DNA chain



Physical size of the human genome

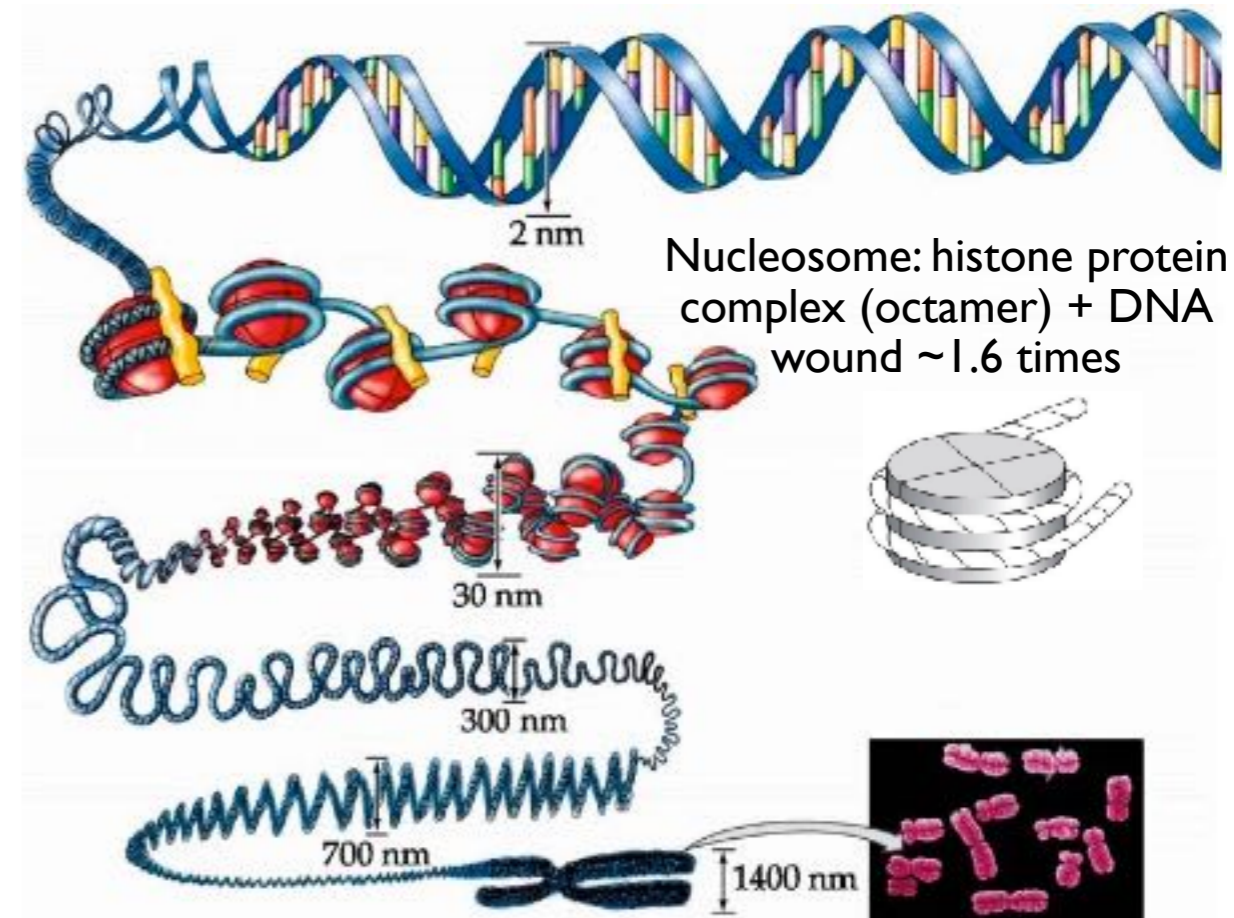


Simplified cell model: cube

Solution: DNA needs to be packed!

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

Chromosome condensation



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