Randomness and information in biological data
BIO-369

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EPFL

Lecture 3

Do you expect thermal fluctuations to be:

A. Negligible at our scale and at the cellular scale
B. Important at our scale and at the cellular scale
C. Important at our scale but negligible at the cellular scale
D. Negligible at our scale but important at the cellular scale
E. It depends

To answer, please:
- Connect to http://ttpoll.eu
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- Select your answer

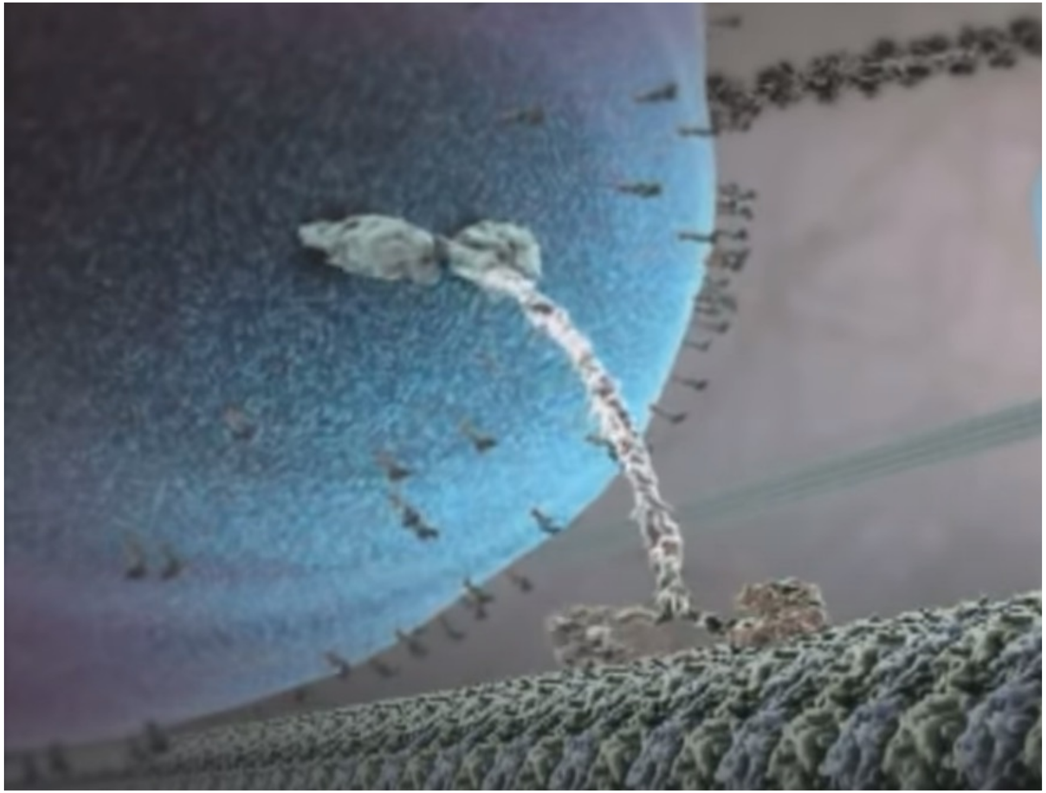
Outline of the course

Motivation

- **Thermal fluctuations are important at the cellular scale: kinesin walking on a microtubule**
  - Kinesin = motor protein, found in eukaryotic cells

  - Kinesins move along microtubule filaments *in one direction* (– → +)
  - Motion powered by the hydrolysis of ATP
  - Involved in mitosis (spindle), meiosis and transport of cellular cargo, e.g. in axons

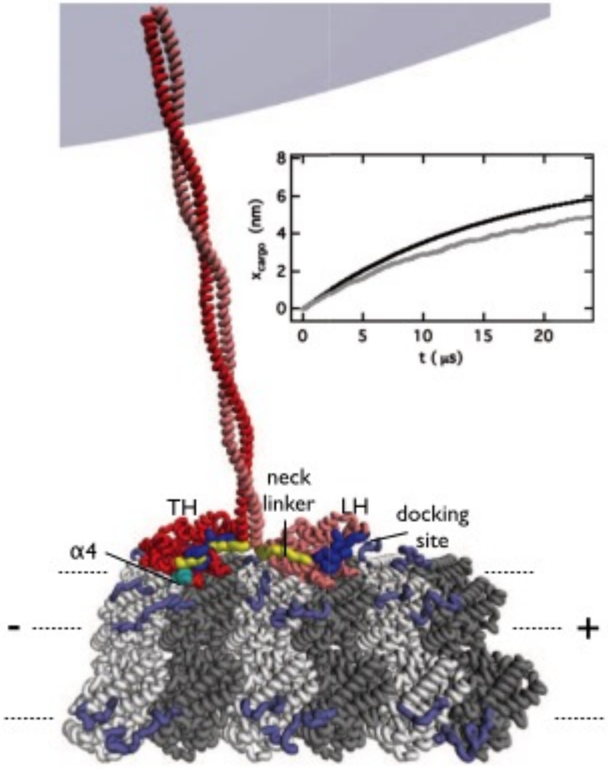
  - Speed ~40 nm/s



  - Animation
    https://www.youtube.com/watch?v=wJyUtbn0O5Y 1:14-1:25 (Harvard)

Motivation

- **Thermal fluctuations are important at the cellular scale: kinesin walking on a microtubule**
  - Brownian dynamics simulation (Zhang & Thirumalai 2012)



https://www.youtube.com/watch?v=JckOUrl3aes

Motivation

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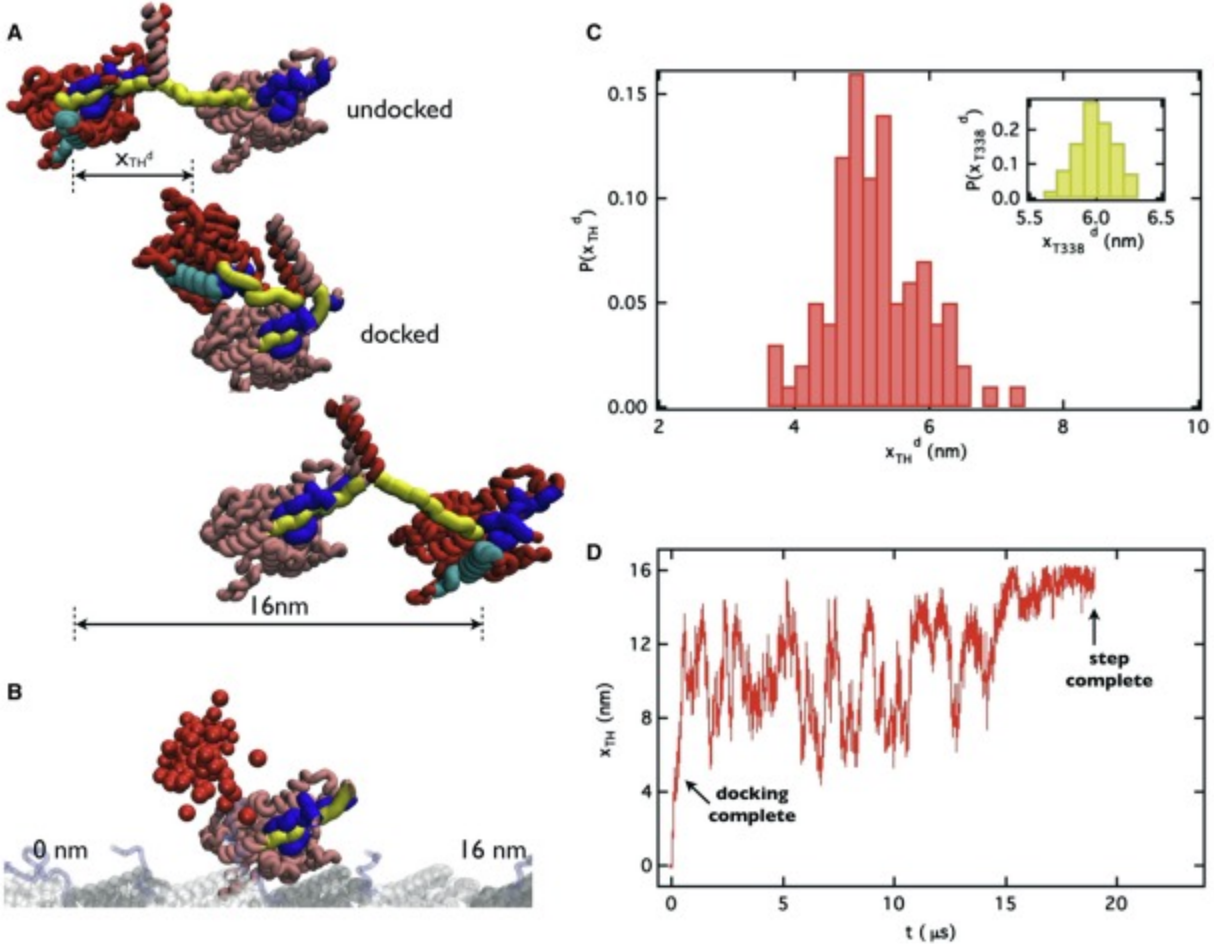

Histograms, based on 99 trajectories, of the TH (trailing head) movement

Time-dependent changes in the center of mass of the TH as a function of t for a sample trajectory

What is the unit of the Boltzmann constant k_B?

0% A. Joule (energy unit)
0% B. Kelvin
0% C. Joule / Kelvin
0% D. Joule . Kelvin
0% E. Something else

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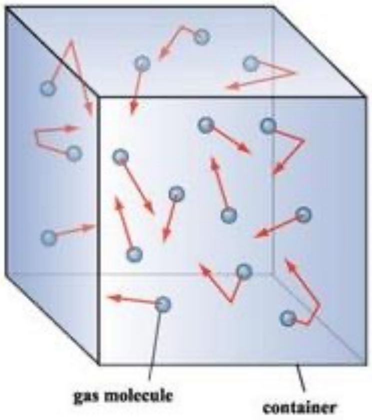
Thermal fluctuations in a gas

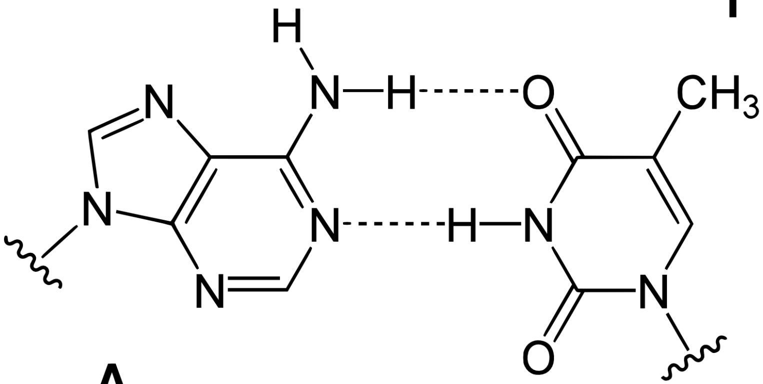
- **Random motion (microscopic) → pressure (macroscopic)**
  - Gas molecules hit the walls of the box



Hydrogen bonds

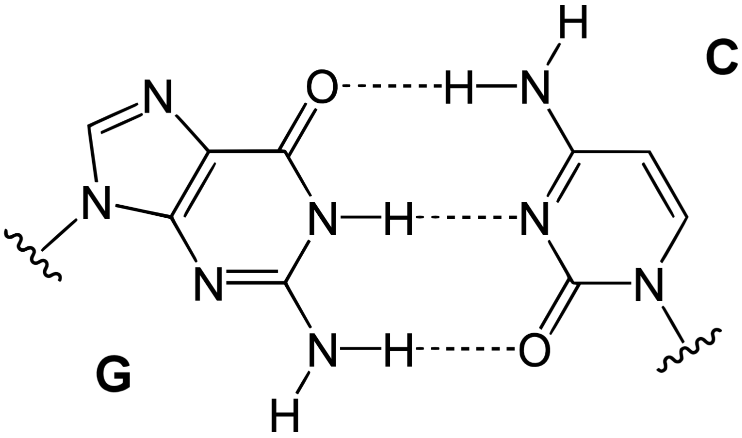
- **Watson-Crick base pairs in DNA**

T



A

C



G

Do you expect the bond between two DNA bases to be:

A. Quite robust to thermal fluctuations
B. Not so robust to thermal fluctuations
C. Completely destroyed by thermal fluctuations

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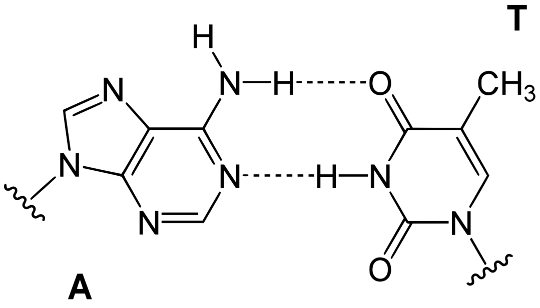
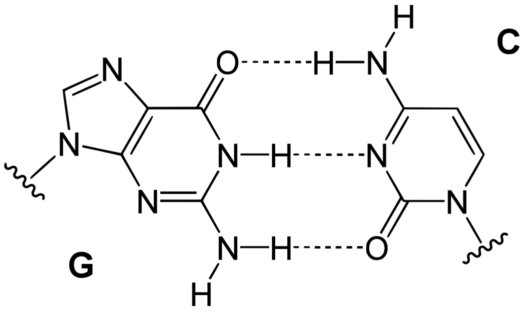
What base pair is more robust?

A. A-T
B. C-G
C. It is the same





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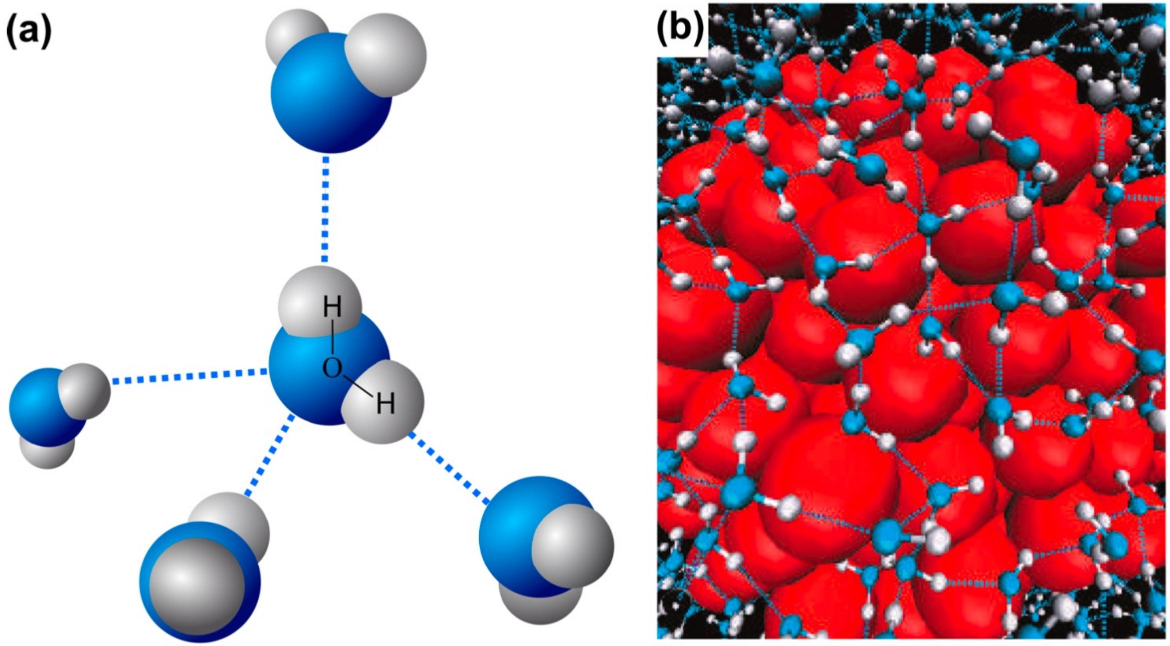
Hydrophobic interactions

- **Reorganization of dynamic hydrogen bonds between water molecules**



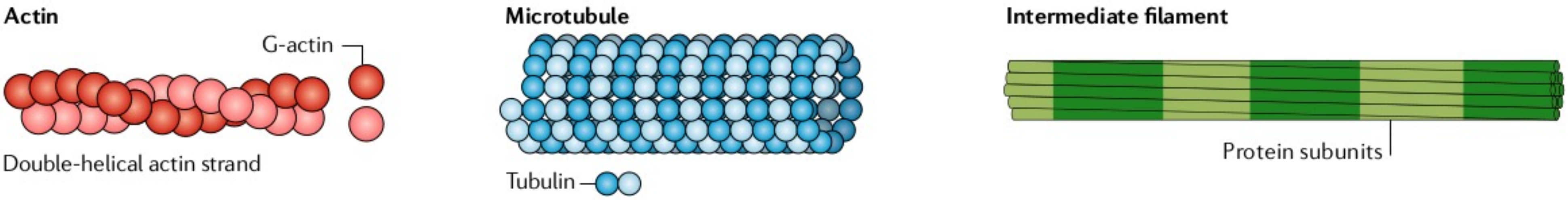
(a): In bulk water, each water molecule is able to participate in up to four hydrogen bonds
(b): Configurations of water molecules near a hydrophobic cluster (red) in a molecular dynamics simulation

Motivation

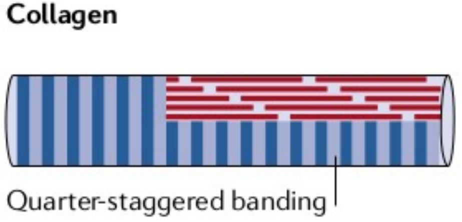
- **Importance of biopolymers and biopolymer networks in and around cells**

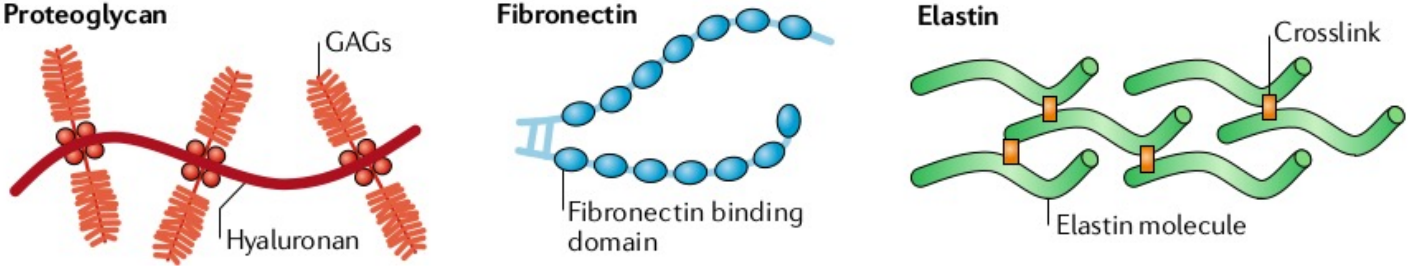
Cells and tissues are mechanically supported by biopolymer networks

- Cytoskeleton



- Extracellular matrix





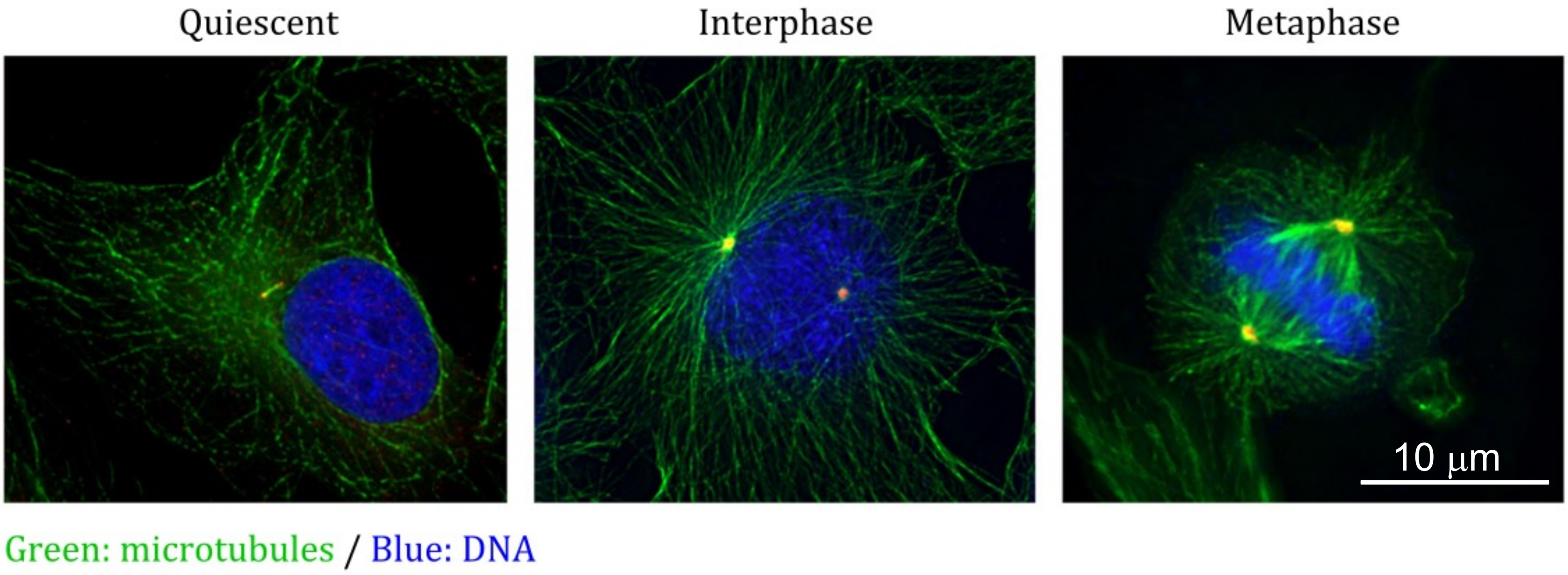
Collagen = most abundant protein in mammals

Burla et al 2019

Motivation

- **Importance of biopolymers and biopolymer networks in and around cells**

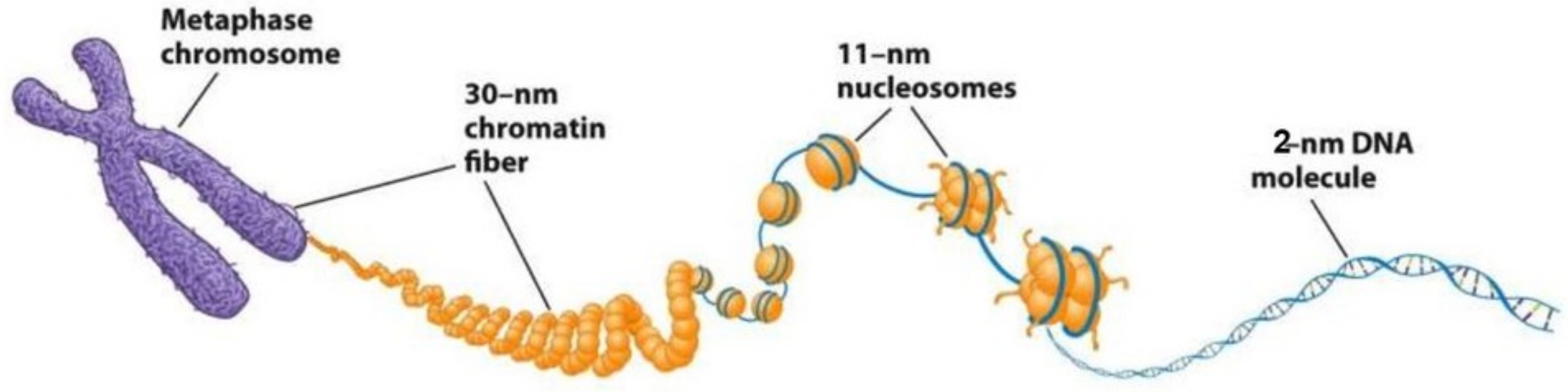
Microtubules are rigid and able to reorganize



Fu and Zhang 2019

Motivation

- **Biopolymers are also the support of genetic information**



DNA is quite flexible, and it compacts in eukaryotic cells

Remark: single proteins are also very important biopolymers, but we won't discuss them in this section (except those that form cytoskeletal protein) due to their particular 3D folding

Do you expect the persistence length of a microtubule to be:

A. Larger than that of DNA
B. Smaller than that of DNA
C. The same
D. It depends on the conditions

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Flexibility of biopolymers

- **Persistence length**

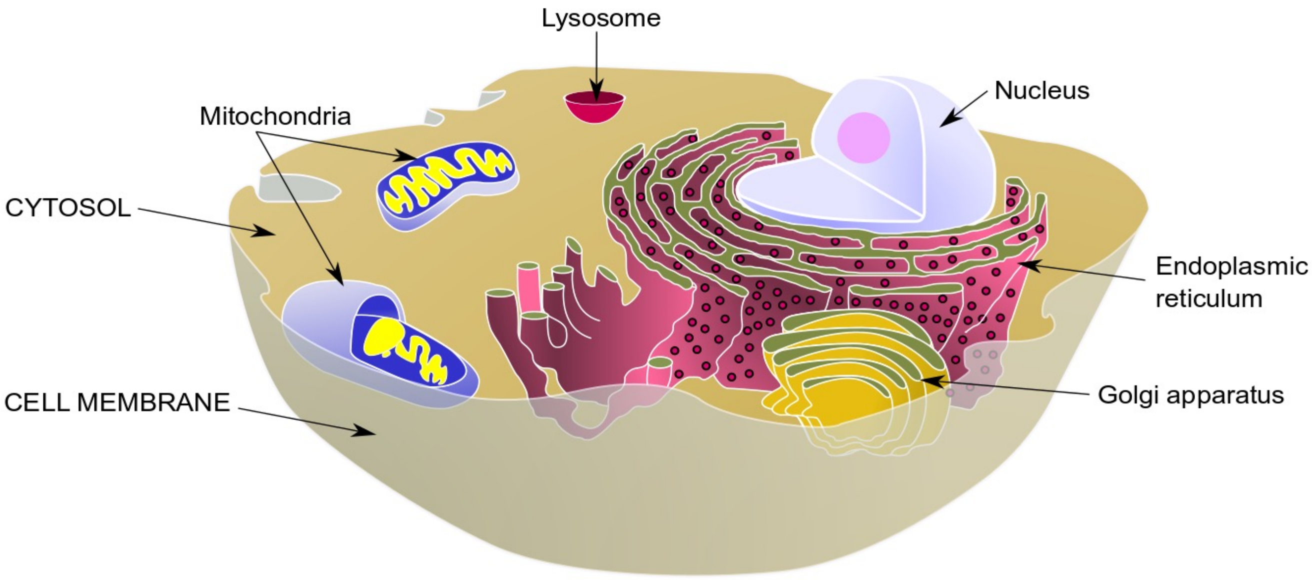
(a): total length >> persistence length

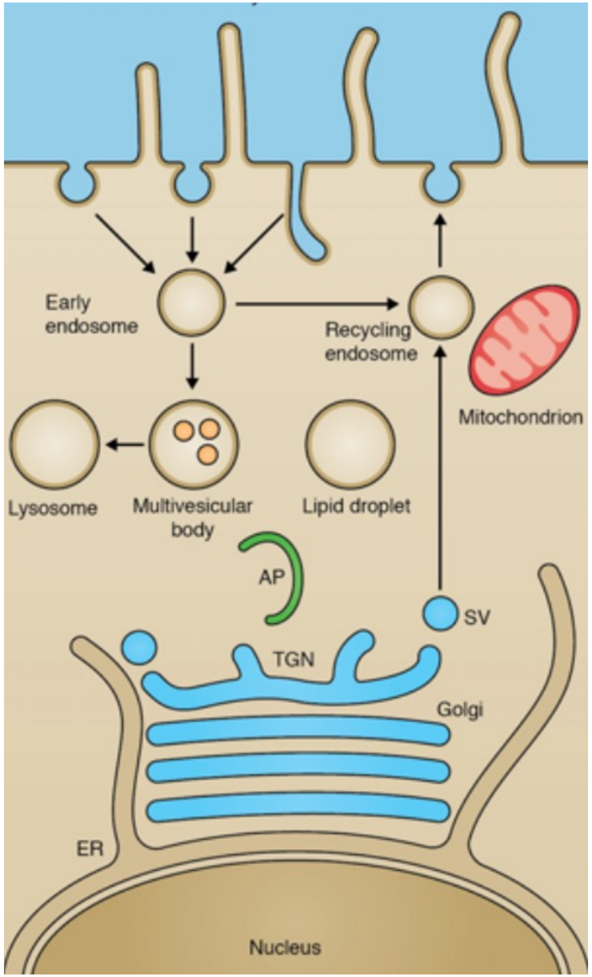
(b) total length << persistence length

(a) (b)

Motivation

- **Biomembranes are curved and constantly change shape**



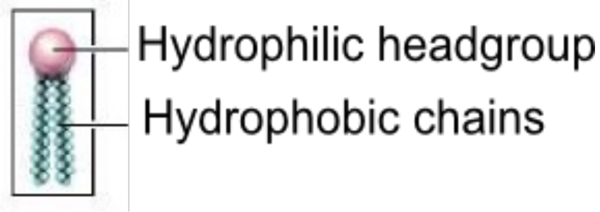


Membrane thickness: a few nm
Cell size: 1 – 100 μm

Biomembrane properties

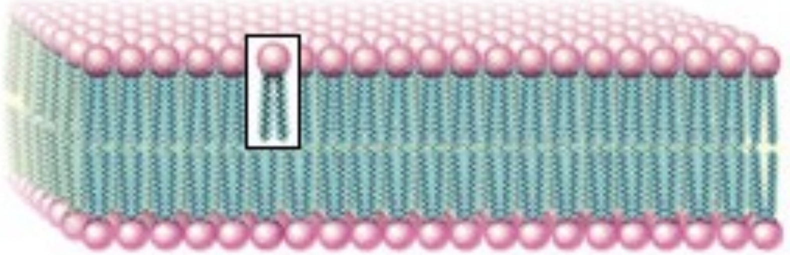
- **Basic structure**

Lipid molecule: amphiphilic

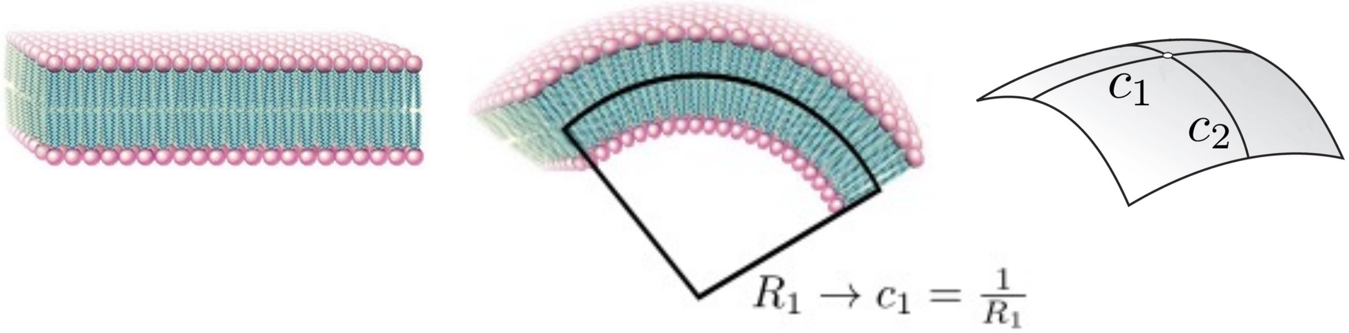


Self-assembly
in water

Lipid bilayer



- **Elasticity: bending**

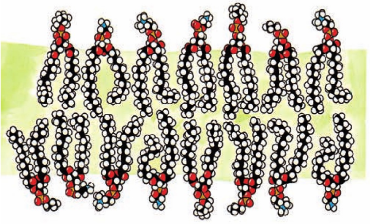


Curvature energy:

$$H = \int_A dA \, \frac{\kappa}{2} (c_1 + c_2)^2$$

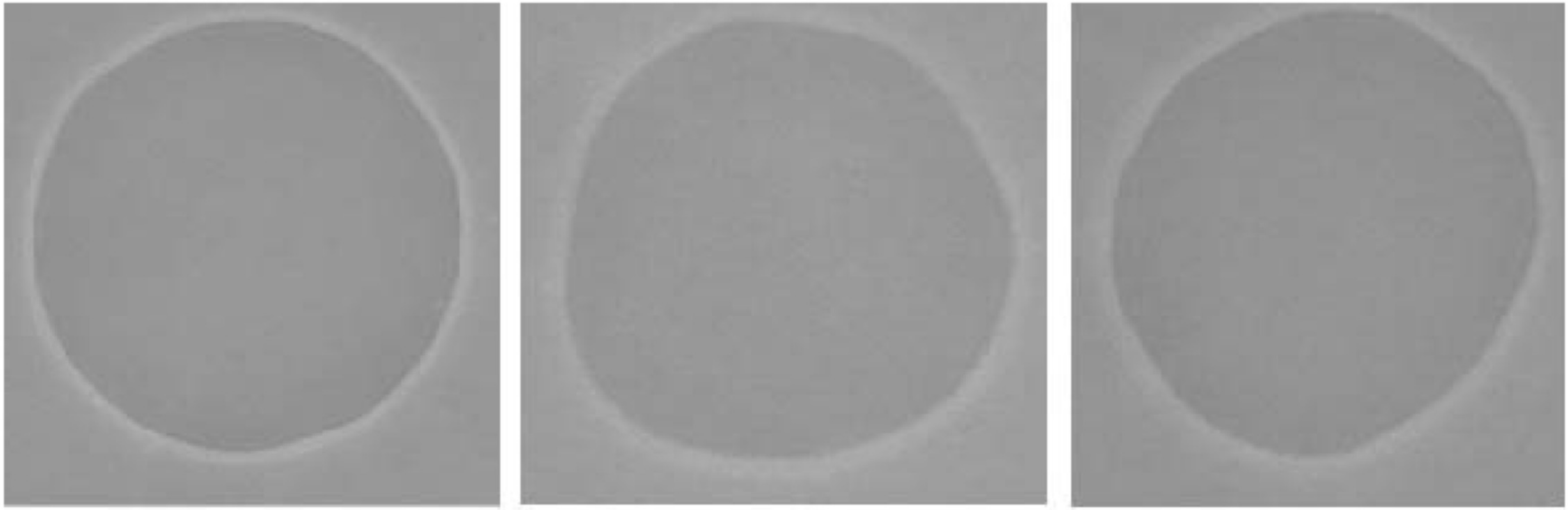
Helfrich (1973)

- **Fluidity**



Each monolayer is a 2D fluid

Flexibility of biomembranes



Snapshots of a giant unilamellar vesicle (i.e., a closed bilayer of lipids in water) of diameter 50 μm observed under the microscope at different times

Conclusion

- Thermal fluctuations have a strong impact at the microscopic scale, esp. at the cellular scale
- Importance of comparing the energy scales involved in important cell biology processes to the energy scale $k_B T$ of thermal fluctuations (Boltzmann distribution)
- Many cell biology processes, including DNA base pairing, protein-protein interactions, biopolymer and biomembrane deformations, involve energies larger than $k_B T$, but not by a lot, typically of order 10 to 20 $k_B T$ → stable to thermal fluctuations but readily deformable
- In particular, can be deformed by active processes involving ATP consumption: Hydrolysis of ATP to ADP releases an energy of 30 kJ/mol, thus for the hydrolysis of one molecule of ATP:

$$\Delta E_{\mathrm{ATP}} \approx 12\, k_{\mathrm{B}} T$$

Outline of the course