Medical Biophysics

Introduction

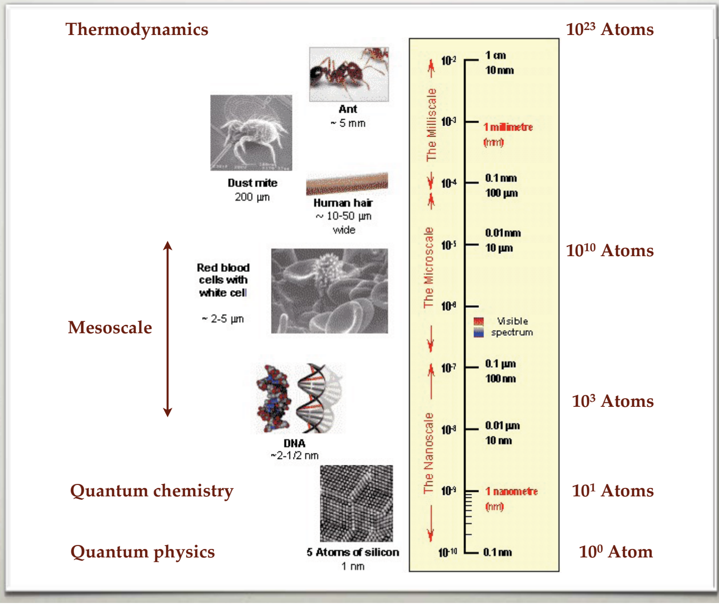
Miklós Kellermayer

Semester Lectures

Introduction. Biomolecules.
Radiations
Luminescence
X-radiation
Radioactivity, dosimetry
Sound, ultrasound
Investigation of biomolecular systems
Thermodynamics, transport phenomena
Blood circulation, cardiac function
Bioelectric processes
Sensory function. Vision and hearing.
Muscle function
Biophysics of motion.

Complexity

Dimensions of Living Systems



Foundation of Scientific Truth

„the test of any idea is the **experiment**"

Scientific method:

Observation
Consideration
Experiment

Scientific attitude:

Wondering
Critical thinking
Asking and doubting

Fundamental statements of Science

>Atomic theory<

The entire natural world is made up of particles that constantly move and attract or repel each other.

The characteristics and processes of nature can be described through the atomic particles.

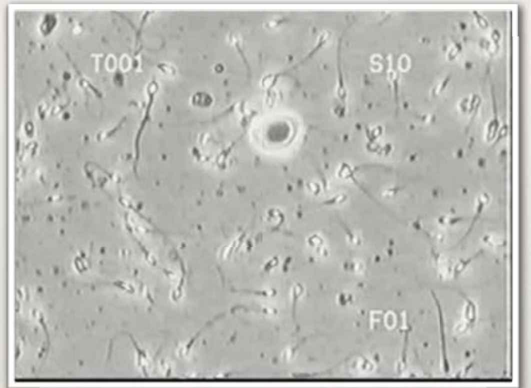
Natural laws are statistical (probabilistic). (example: eardrum)

Biophysics

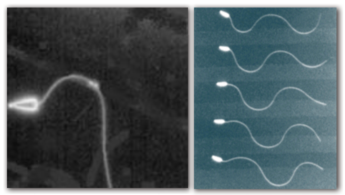
Biological processes are
Simplified,
Quantified

Objective: Physical description of biomedical phenomena

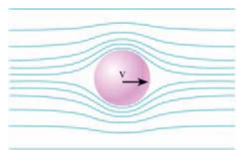
I. Physical description of biological phenomenon



Drag coefficient of the spermatocyte



Stokes' Law:

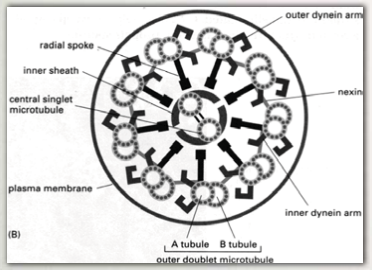


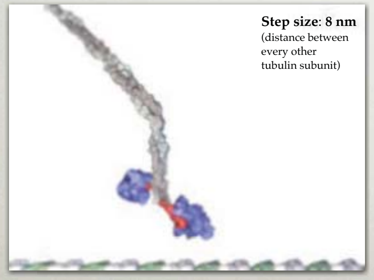
$$F = \gamma v = 6 r \pi \eta v$$

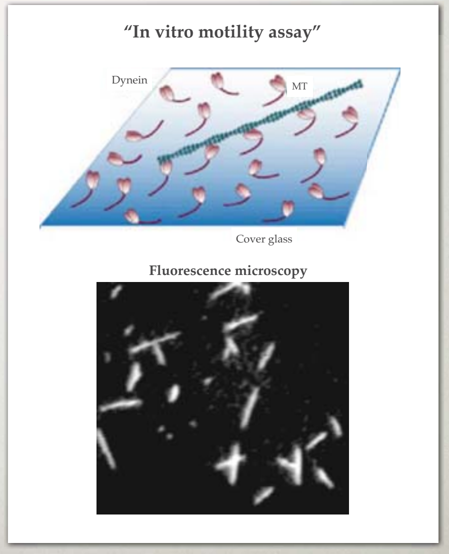
$$\gamma = 6 r \pi \eta = 6 \cdot 1.6 \times 10^{-6} (m) \cdot \pi \cdot 10^{-3} (Pas) = 3 \times 10^{-8} Ns/m$$

$$F = \gamma v = 3 \times 10^{-8} Ns/m \cdot 5 \times 10^{-5} m/s = 1.5 \times 10^{-12} N = 1.5\, pN$$

Mechanisms behind spermatocyte motility?







News Headlines

The first prize of the Idaho Falls High School Science Fair was awarded on April 26 to a student of Eagle Rock High School. The student wanted to demonstrate the extent to which the public is manipulated by vague references to science in generating environmental concern. He prepared a proposal for banning the use of the chemical *dihydrogen monoxide* and investigated whether he can convince supporters to sign it. He argued for the toxicity of the chemical based on the following:

1. the chemical induces strong perspiration and vomiting,
2. it is one of the main components of acid rain,
3. its gaseous form may cause serious burns,
4. its excessive inhalation may lead to suffocation,
5. it contributes to erosion,
6. it significantly reduces the efficiency of car brakes,
7. it has been shown to be present in cancer.

The student surveyed 50 people for support of the proposal:

Forty three (43) signed immediately.
Six (6) asked for time to think.

Only one (1) person knew that the chemical is water. . .

Biophysics of water

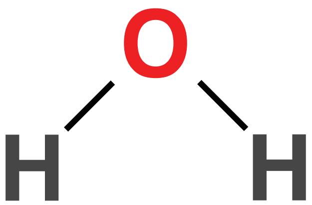
Water

- Only chemical that is liquid in nature
- Only chemical that naturally exists in all three states
- Although inorganic, extremely important for LIFE, which is organic

Structure of the water molecule I.

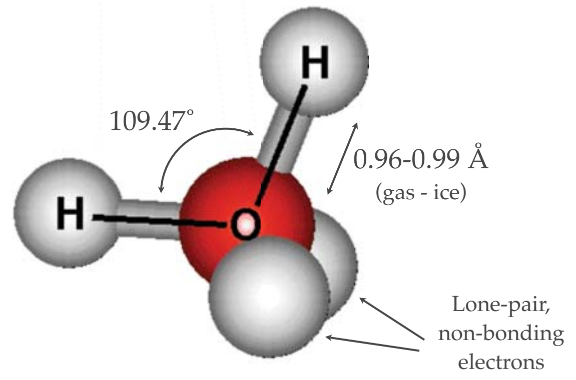
One of the smallest molecules:
barely larger than a single atom

Oxygen: $2s^2p^4$



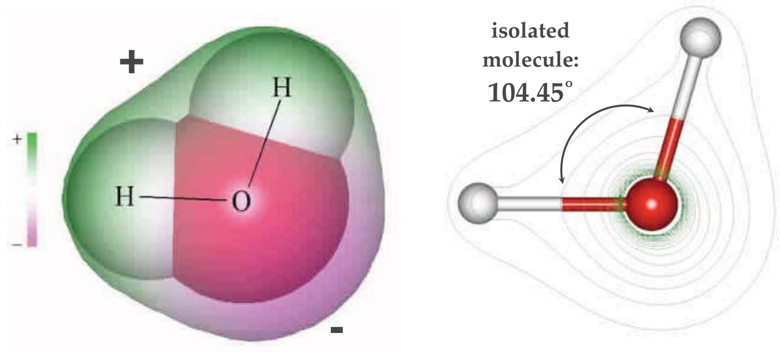
Structure of the water molecule II.

- Tetrahedral structure
- sp^3 hybridization (Hybridization: combination of states with identical principal quantum number but different symmetry)



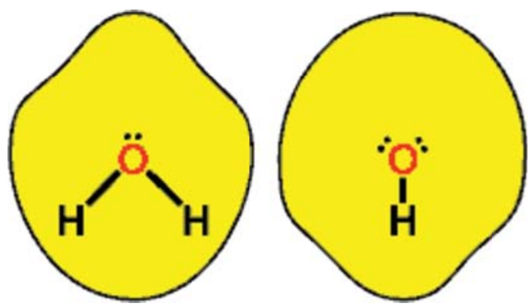
Structure of the water molecule III.

Large constant dipole moment



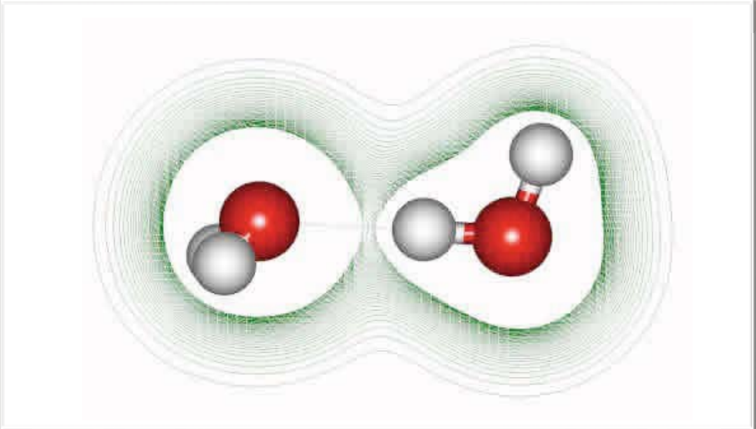
Structure of the water molecule IV.

van der Waals radius: ~ 3.2 Å
non-spherical shape

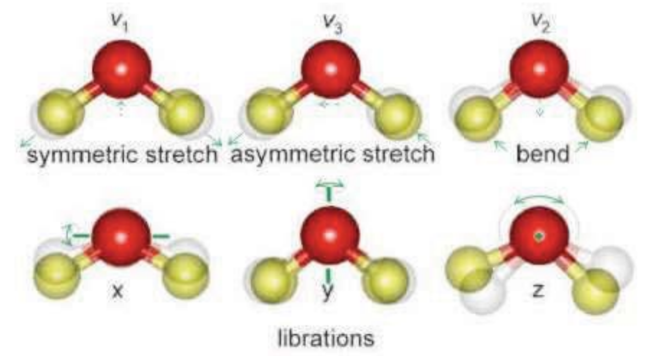


Structure of the water molecule V.

Water dimer:
H-bond between the proton and lone-pair electrons



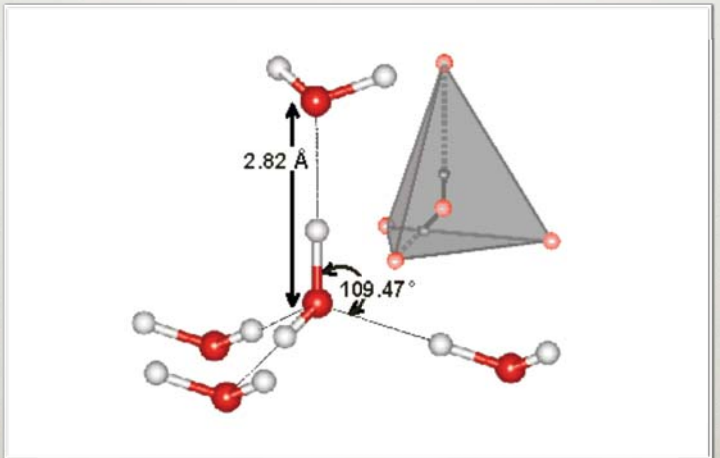
Rotational and vibrational motion of the water molecule



Absorption in the infrared and red spectral region ->
"blue" color of natural waters

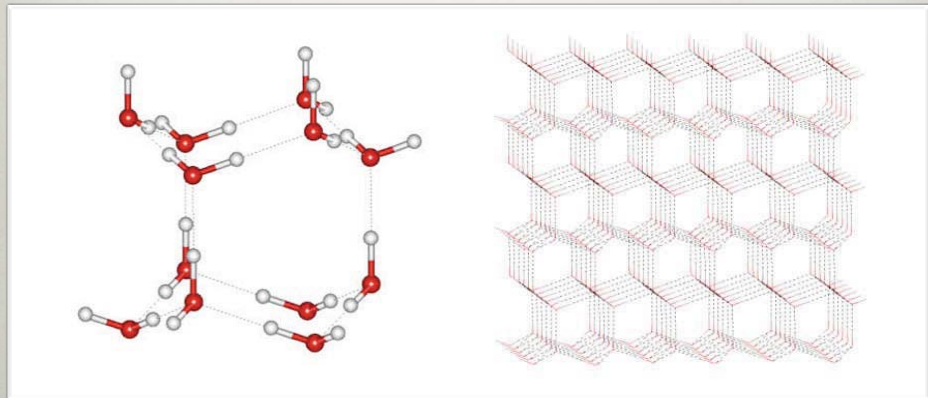
Hydrogen bonding in water

Formation of pentameric water



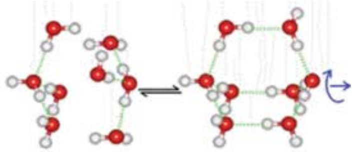
Structure of ice

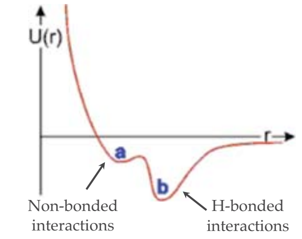
- 9 different forms
- Conventional ice: hexagonal structure
- Coordination number: 4 (each molecule coordinates another four)
  Interstitium: could incorporate a water molecule



Structure of liquid water

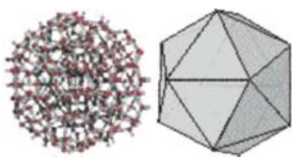
H-bridge: cohesion + repulsion
Cluster formation: bicyclo-octamer





From clusters to networks:
280 molecules form
icosahedral structure

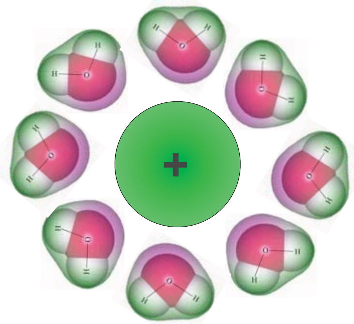
(*icosahedron*: regular polyhedron with 20 identical equilateral triangular faces)



Spatial networks:
May explain anomalous
properties of water

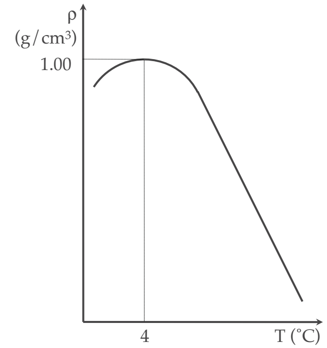
Physical properties of water I.

Large dipole moment:
Very good solvent
Electrolyte solutions



Microwave oven!

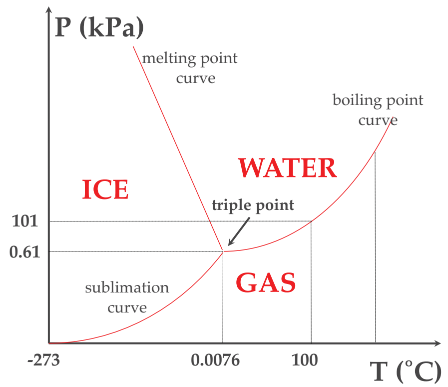
Anomalous density-
Temperature function

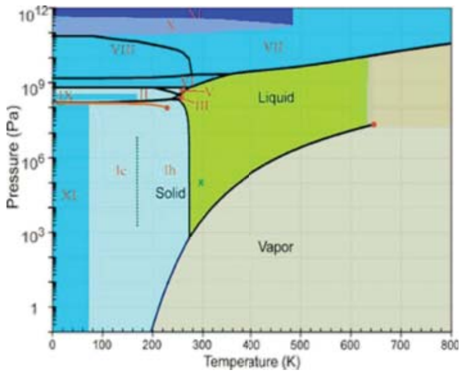


Life in the frozen lake!

Physical properties of water II.
Phase diagram

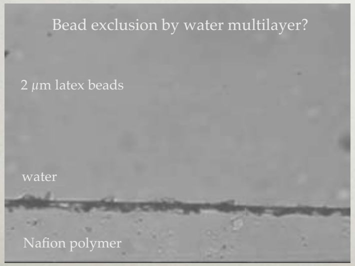
- Phase curve: two pases are in equilibrium
- Area between phase curves: a single phase is present
- Cross-section: triple point

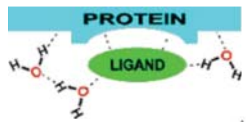


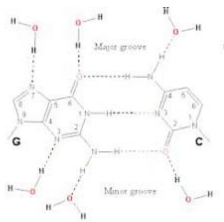


Hydration

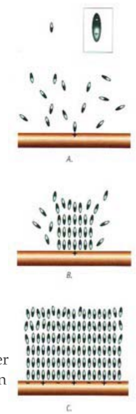
1. **Electrolyte solutions**
2. **Non-electrolyte solutions, apolar molecules**
   hydrophobic hydration
3. **Protein hydration**
   Maintenance of 3D structure
   Polarized "multilayers"
4. **Nucleic acids**
   Base pairing







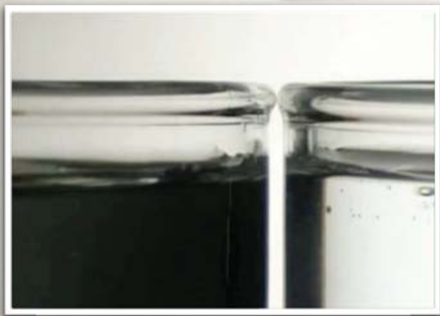
Base pairing

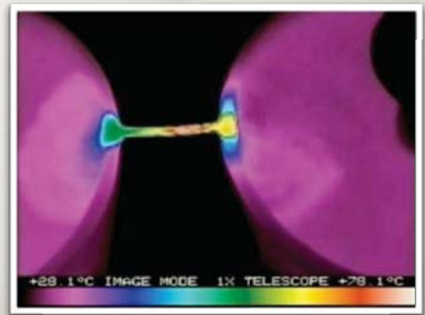


Multilayer
formation

“Floating water bridge”

5 kV

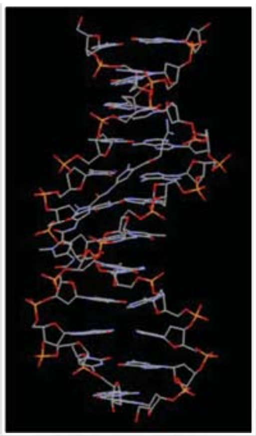




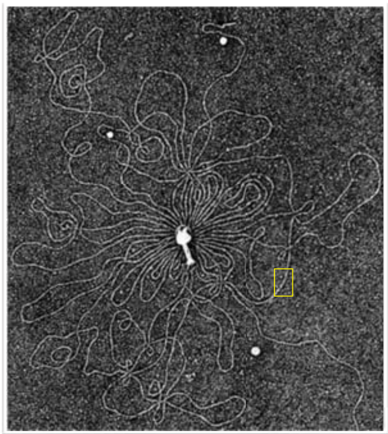
Elmar Fuchs, Wetsus

Macromolecules

Biological macromolecules are GIANT molecules

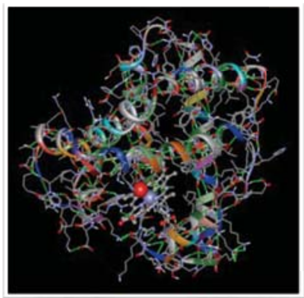


DNS double helix

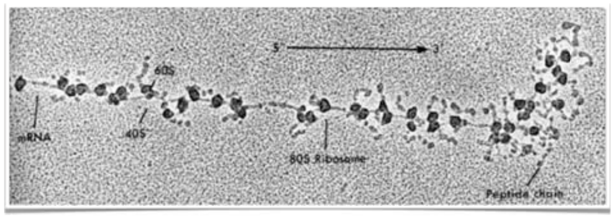


DNA released from bacteriophage head

Biological macromolecules are EXCITING molecules

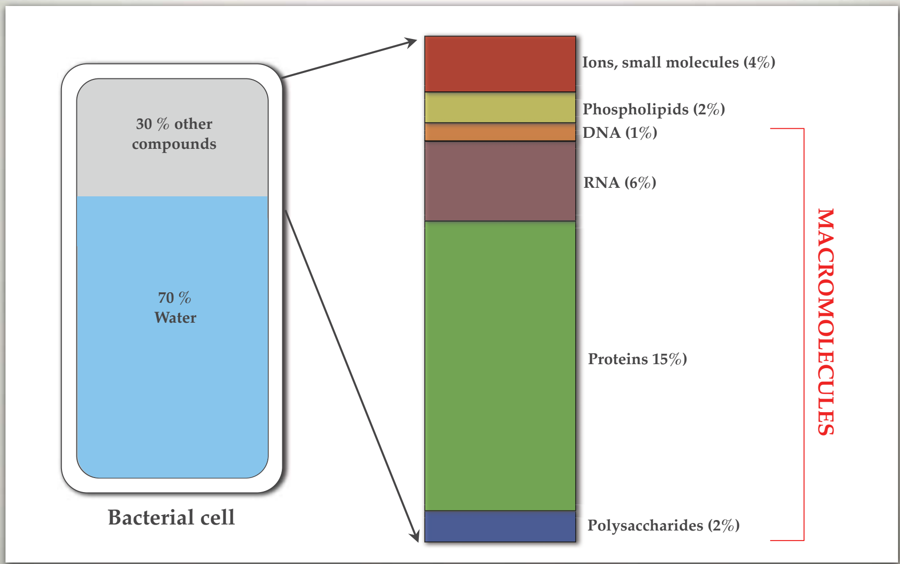


Structure of hemoglobin subunit



Newly synthesized protein (silk fibroin)

Proportion of macromolecules in the cell by mass is LARGE



Biological macromolecules: biopolyers

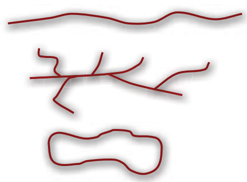
Polymers:
chains built up from monomers

Number of monomers: N>>1;
Typically, N~10^2-10^4,
but, in DNA, e.g.: N~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

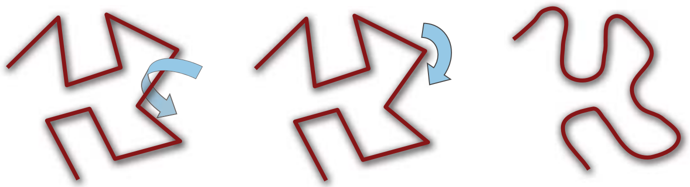
Shape of polymers

1. Linear
2. Branched
3. Circular



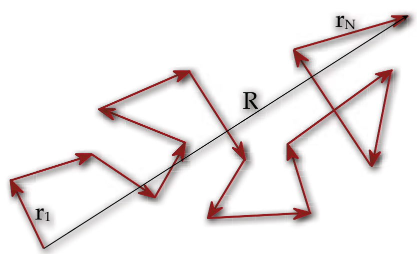
Shape of polymer chain changes dynamically. Possible mechanisms:

1. Rotation around CC-bonds
2. Freely jointed chain (FJC)
3. Bending, wormlike chain (WLC)



Shape of the polymer chain resembles random walk

Brown-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 Brown-movement R=displacement, N=number of elementary steps, L=total path length, és l=mean free path length.

Mechanics of polymers

Entropic elasticity

Thermal fluctuations of the polymer chain

Configurational entropy (orientational disorder of elementary vectors) increases.

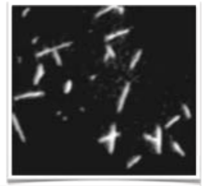
The chain shortens.

Biopolymer elasticity

l = correlation length
L = contour length

Rigid chain
$l >> L$

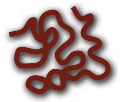
Microtubule



Semiflexible chain
$l \sim L$

Actin filament

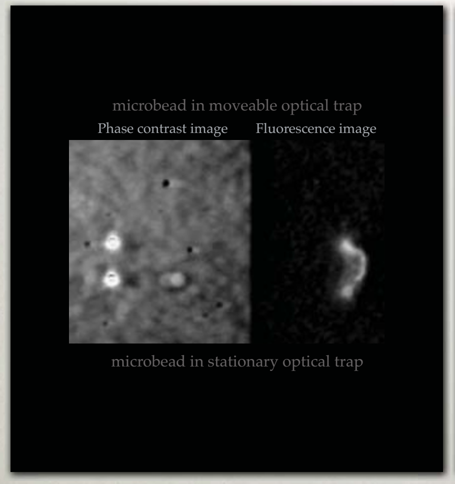
Flexible chain
$l << L$

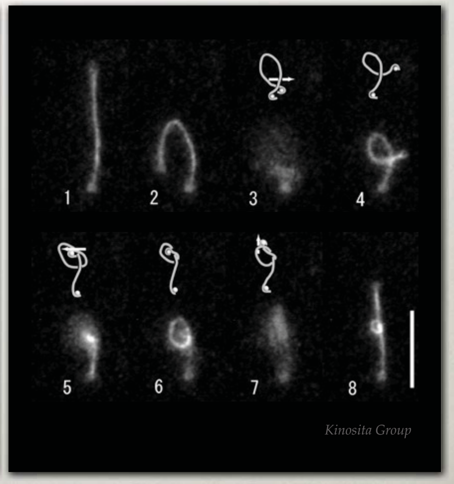


DNA

Visualization of biopolymer elasticity

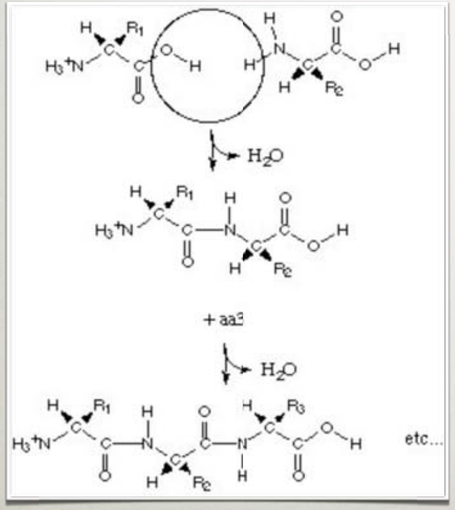
Tying a knot on a single DNA molecule

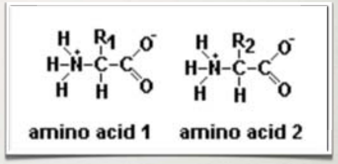




Protein folding

The peptide bond





Condensation reaction
followed by the relase of water

Protein structure

Primary

Amino acid
sequence

Secondary

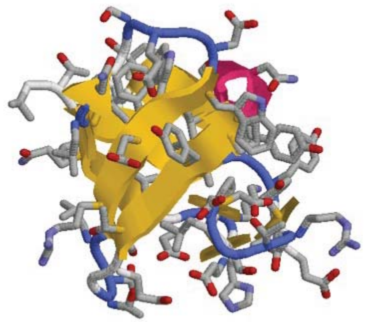
α-helix
β-sheet
β-turn

α-helix:
- right handed
- 3.4 residue/turn
- H-bridges

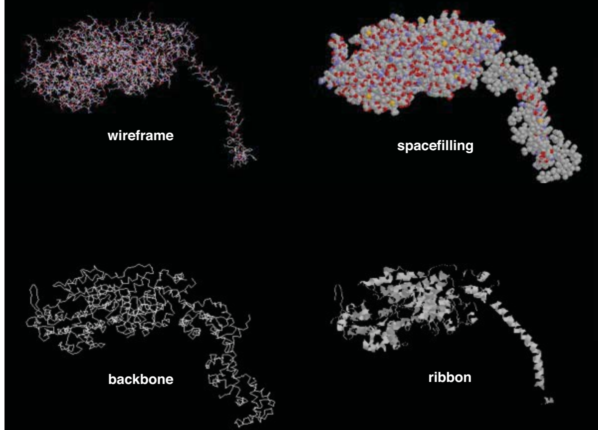
β-sheet:
- parallel or
- antiparallel
- H-bridges between distant residues

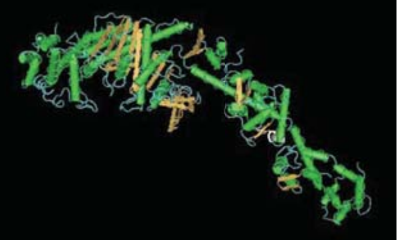
Tertiary

3D structure of
single-chain protein



Display of protein structure





Myosin S-1

Bonds holding protein structure together

1. Disulfide bridge: between cysteine residues
2. Hydrogen bond: shared proton
3. Salt bridge: between oppositely charged residues
4. Hydrophobic interaction: between hydrophobic residues
   (in the interior of the molecule)

Protein structure classes

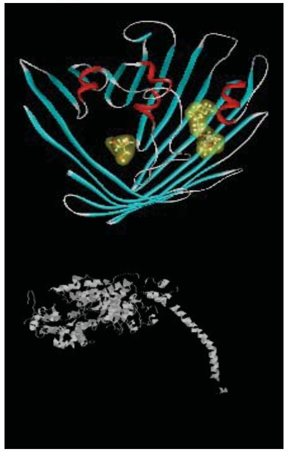
1. All alpha

calmodulin

2. All beta

(3. Alfa-beta)

4. Multidomain

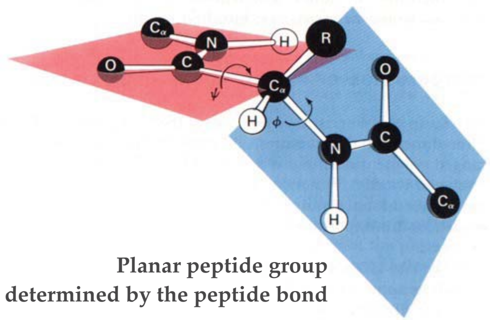


porin

myosin

Levinthal's paradox:

Are all conformations explored by the protein molecule?



Planar peptide group
determined by the peptide bond

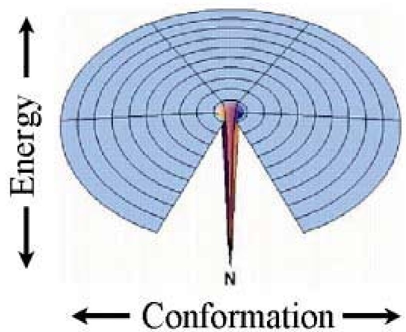
Number of possible protein configurations:

$$i^n$$

i: number of configurations related to the amino acid
n: number of amino acids

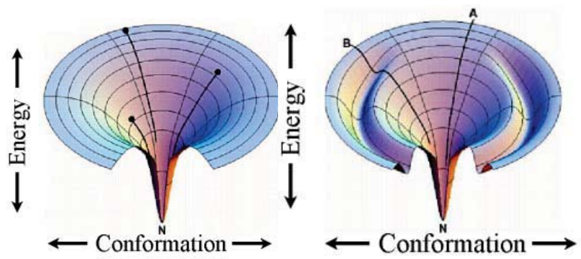
Levinthal's paradox:

Are all conformations explored by the protein molecule?



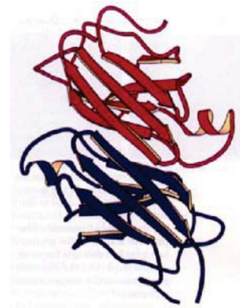
„Folding funnel"

Protein folding diseases



In the living cell, chaperones assist protein folding

Pathology:
-Alzheimer's disease,
-Familial amyloidotic neuropathy (FAP)

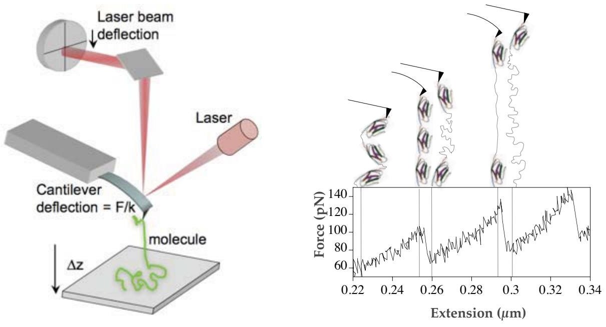


Beta-fibrils:
Insoluble aggregates

Methods of protein unfolding (denaturation)

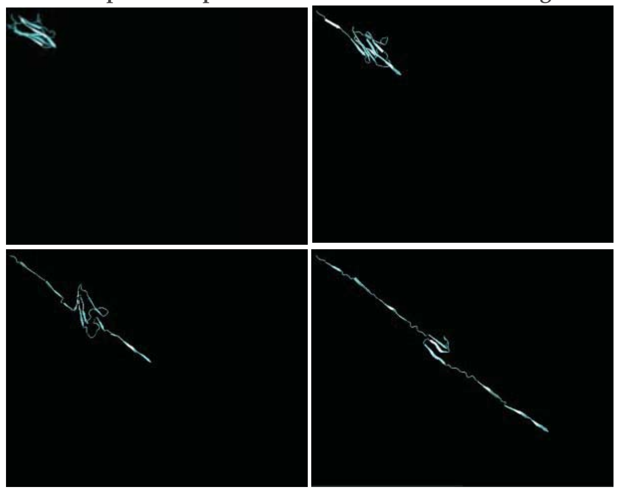
- Heat
- Chemical agent
- Mechanical force

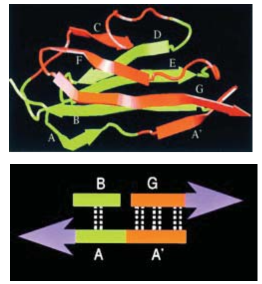
Mechanical unfolding of a single protein with atomic force microscope



Mechanical unfolding of a beta-sheet protein

Steps of computer-simulated domain unfolding





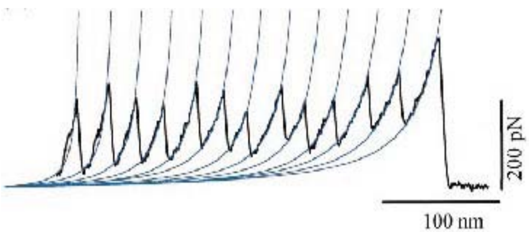
Basis of mechanical stability:

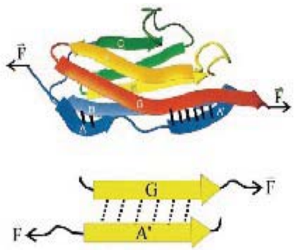
H-bridges between the first and last ß-strands of the domain

Mechanical unfolding of titin I27 domain

Mechanical stability provided by shear pattern of H-bond patch

Force spectrum of $I27_{12}$



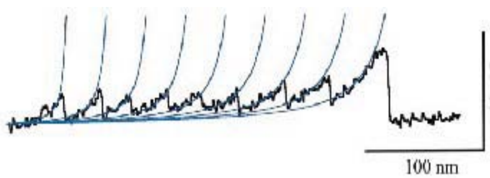


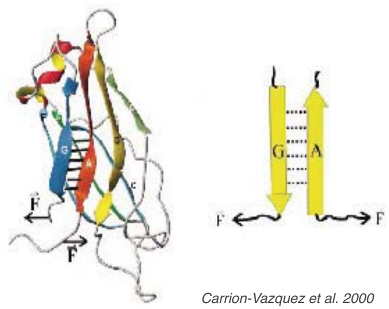
Carrion-Vazquez et al. 2000

Mechanical unfolding of C2A domain

Low mechanical stability due to zipper pattern of H-bond patch

Force spectrum of $C2A_9$

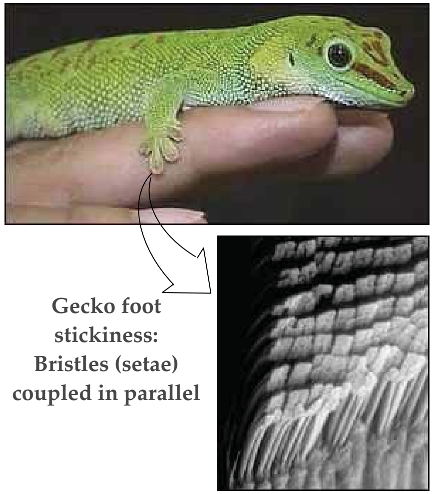




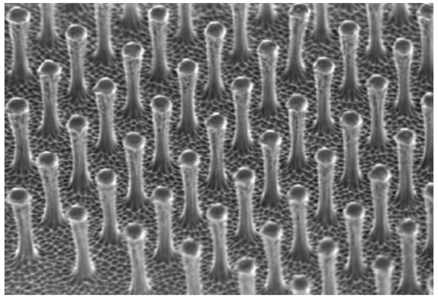
Carrion-Vazquez et al. 2000

Mechanical stability in proteins

Principle of parallel bond coupling



Gecko foot stickiness: Bristles (setae) coupled in parallel



Artificial gecko foot