

# MEDICAL PHYSICS AND STATISTICS

MIKLÓS KELERMAYER

## SEMESTER LECTURES

Structural organization of biomolecules.

Condensed matter.

Liquid crystals, lipids.

Biostatistics I.

Biostatistics II.

Ultrasound.

Magnetic resonance imaging.

Equilibrium thermodynamics.

Transport phenomena.

Diffusion, osmosis.

Blood circulation, cardiac function.

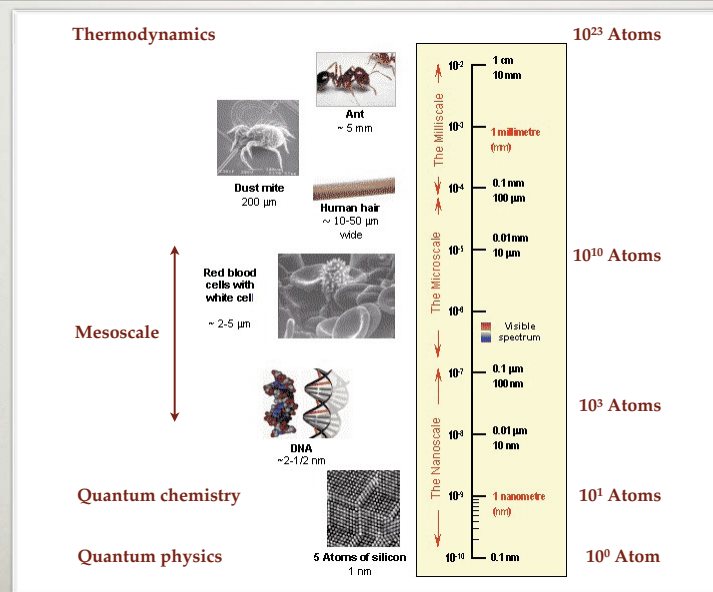
Bioelectric processes.

Sensory function. Vision and hearing.

Biophysics of motion.

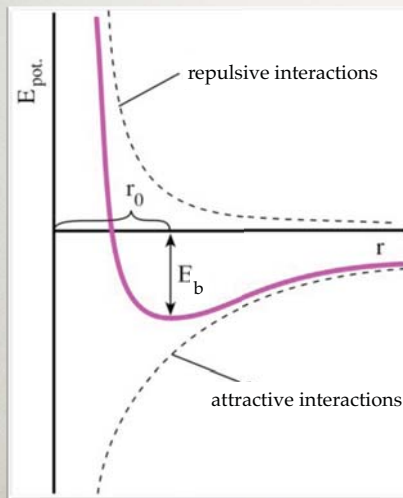
Complexity

## DIMENSIONS OF LIVING SYSTEMS



## STRUCTURAL ORGANIZATION OF BIOMOLECULES

# ATOMIC INTERACTIONS



$r$  = distance  
 $r_0$  = bond length  
 $E_b$  = bond energy (negative):  
 equivalent to the (positive) energy to be  
 invested for bond rupture.

Interaction-free condition:  
 $E_{pot} = 0$   
 $r = \infty$

$$E_{pot} = E_{attr} + E_{rep} = -\frac{A}{r^n} + \frac{B}{r^m}$$

# TYPES OF BONDS

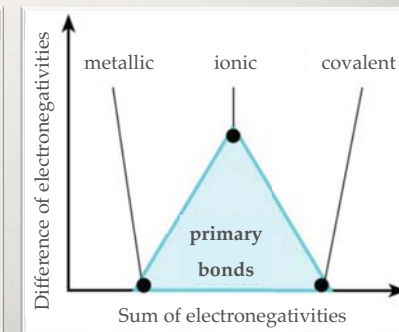
According to **location**: intramolecular, intermolecular

According to **bond energy** ("strength"): strong (primary), weak (secondary)

**Electronegativity ( $\chi$ )**: ability of an atom to attract electrons towards  
 itself in a covalent bond. Sum of ionization energy and electron affinity.  
 [Linus Pauling (1901-1994), Nobel Prize (1954 chemistry, 1962 peace)]

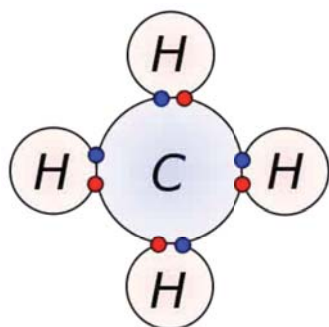


H 2.20																		
Li 0.98	Be 1.57											B 2.04	C 2.55	N 3.04	O 3.44	F 3.98	Ne 4.79	
Na 0.93	Mg 1.31											Al 1.61	Si 1.90	P 2.19	S 2.56	Cl 3.16	Ar 3.64	
K 0.82	Ca 1.00	Sc 1.36	Ti 1.54	V 1.63	Cr 1.66	Mn 1.55	Fe 1.83	Co 1.88	Ni 1.91	Cu 1.90	Zn 1.65	Ga 1.81	Ge 2.01	As 2.18	Se 2.55	Br 2.96	Kr 3.63	
Rb 0.82	Sr 0.95	Y 1.22	Zr 1.33	Nb 1.6	Mo 1.16	Tc 1.9	Ru 2.2	Rh 2.26	Pd 2.20	Ag 1.93	Cd 1.69	In 1.78	Sn 1.96	Sb 2.05	Te 2.1	I 2.66	Xe 3.2	
Cs 0.79	Ba 0.89			Hf 1.3	Ta 1.5	W 2.36	Re 1.9	Os 2.2	Ir 2.20	Pt 2.28	Au 2.54	Hg 2.00	Tl 1.62	Pb 2.33	Bi 2.02	Po 2.0	At 2.2	Rn 3.4
Fr 0.7	Ra 0.9			Rf 1.3	Db 1.5	Sg 2.36	Bh 1.9	Hs 2.2	Mt 2.20	Ds 2.28	Rg 2.54	Uub 2.00	Uut 1.62	Uuq 2.33	Uup 2.02	Uuh 2.0	Uus 2.2	Uuo 3.4
*																		
	La 1.1	Ce 1.12	Pr 1.13	Pd 1.14	Pm 1.13	Sm 1.17	Eu 1.2	Gd 1.1	Tb 1.22	Dy 1.22	Ho 1.23	Er 1.24	Tm 1.25	Yb 1.26	Lu 1.27			
**	Ac 1.1	Th 1.3	Pa 1.5	U 1.38	Np 1.36	Pu 1.28	Am 1.1	Cm 1.26	Bk 1.3	Cf 1.3	Es 1.3	Fm 1.3	Md 1.3	No 1.3	Lr 1.3			



# COVALENT BOND

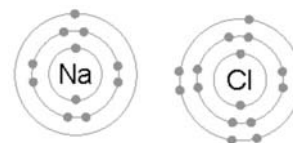
Sharing of pairs of electrons between atoms, or between atoms and  
 other covalent bonds. Attraction-to-repulsion stability that forms  
 between atoms when they share electrons.



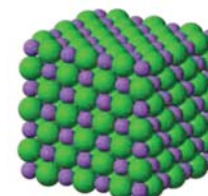
- Bond energy: several eV (strong).
- Valence electrons contribute to molecular orbitals.
- Molecular geometry determined by symmetry of atomic electron states.
- Pure covalent bond is rare, electrostatic effects often arise.

# BONDS BASED ON CHARGE-CHARGE INTERACTIONS

## Ionic bond

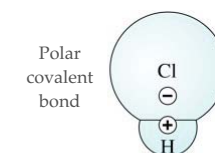


Bond energy: 2-3 eV  
 Large difference between  
 electronegativities  
 Multi-ion crystals

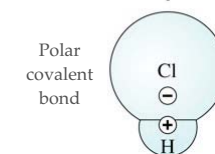


## Electrostatic interaction

Bond energy: ~0.2 eV



Dipole-dipole interaction





# VAN DER WAALS INTERACTION

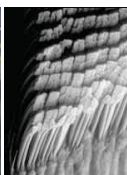
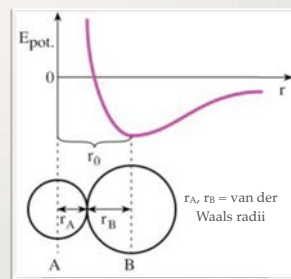
- Attractions between atoms, molecules, and surfaces (weak).
- Caused by correlations in the fluctuating polarizations of nearby particles.
- Dispersion forces, London forces.



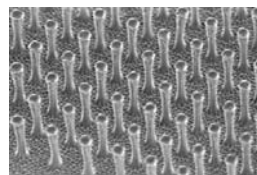
Jan Diderik van der Waals  
(1837-1923), Nobel prize 1910



Fritz London (1900-1954)



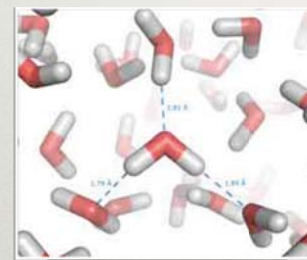
Gecko foot stickiness:  
Bristles (setae) coupled in parallel



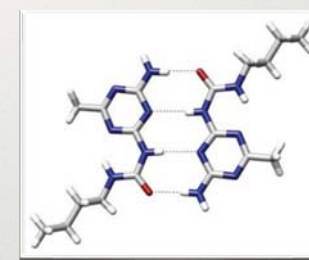
Artificial gecko foot

# HYDROGEN BOND

- Attractive force between the hydrogen attached to an electronegative atom of one molecule and an electronegative atom of a different molecule.
- Results from a dipole-dipole force with a hydrogen atom bonded to nitrogen, oxygen or fluorine. Must not be confused with a covalent bond to hydrogen.
- Energy:  $\sim 0.2$  eV.



Snapshot from a simulation of liquid water.



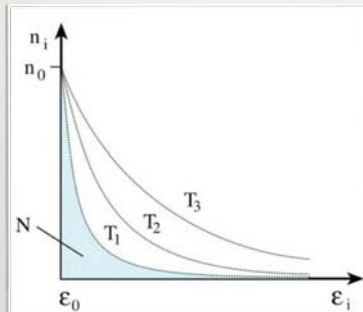
Intermolecular hydrogen bonding in a self-assembled dimer.

# BOLTZMANN DISTRIBUTION

- Universal organizing principle in ensembles.
- Describes the probability for the distribution of the states of a system.  
(Distribution of "microscopic states" across "macroscopic states".)



Ludwig Boltzmann (1844-1906)



$$\frac{n_i}{n_0} = e^{-\frac{\epsilon_i - \epsilon_0}{k_B T}}$$

- $\epsilon_i$  = energy states
- $\epsilon_0$  = lowest-energy state
- $n_0$  = number of particles in the lowest-energy state
- $n_i$  = number of particles in the  $\epsilon_i$  energy state
- $k_B$  = Boltzmann's constant (relates units of temperature to units of energy)
- $T$  = absolute temperature
- $N$  = total number of particles

## 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

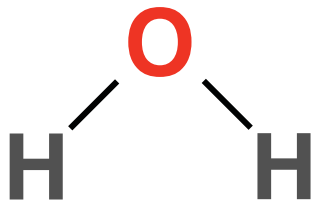
## WATER

- 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.

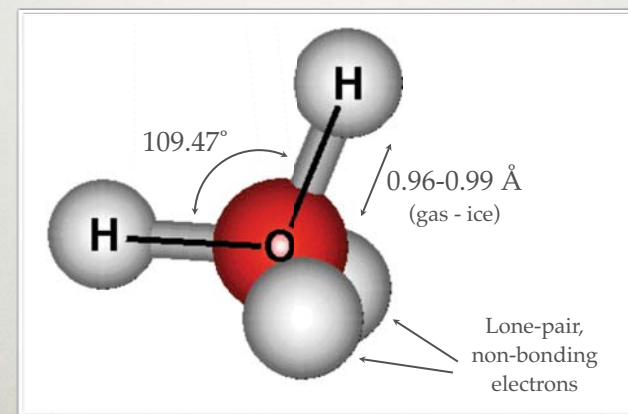
One of the smallest molecules:  
barely larger than a single atom

Oxygen:  $2s^2p^4$



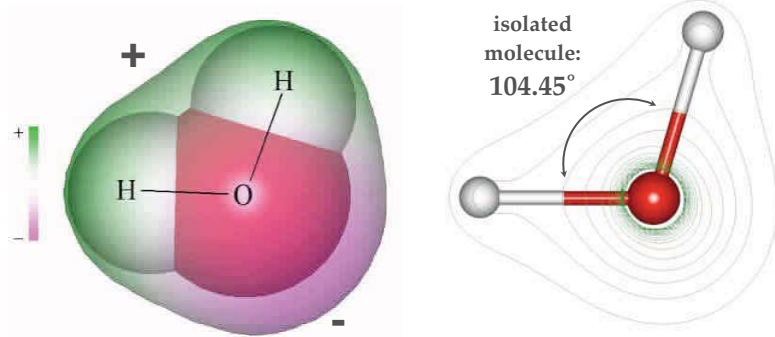
### STRUCTURE OF THE WATER MOLECULE II.

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



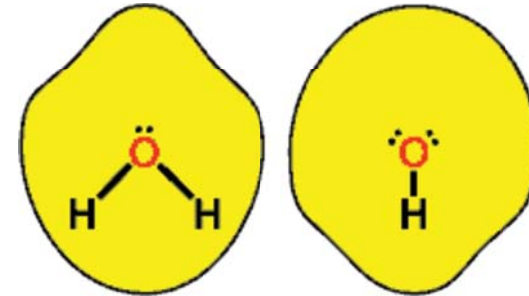
### STRUCTURE OF THE WATER MOLECULE III.

Large constant dipole moment



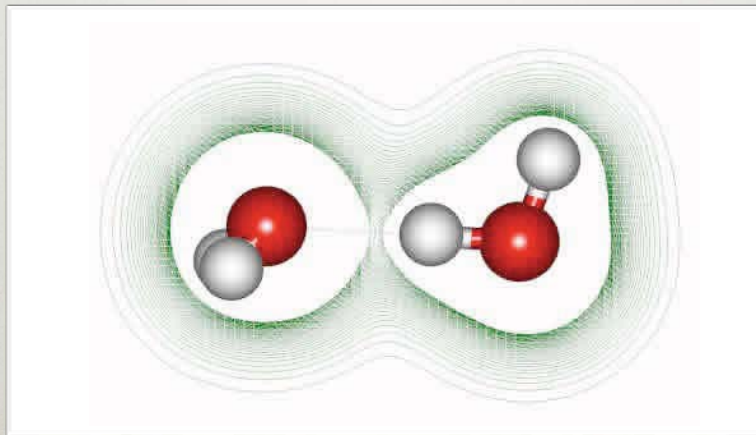
### STRUCTURE OF THE WATER MOLECULE IV.

van der Waals radius:  $\sim 3.2 \text{ \AA}$   
non-spherical shape

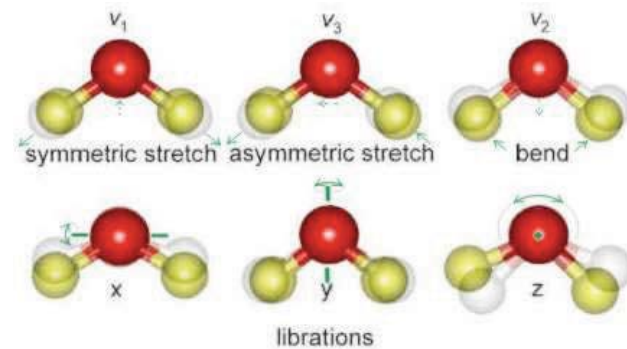


### STRUCTURE OF THE WATER MOLECULE V.

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



### ROTATIONAL AND VIBRATIONAL MOTION OF THE WATER MOLECULE

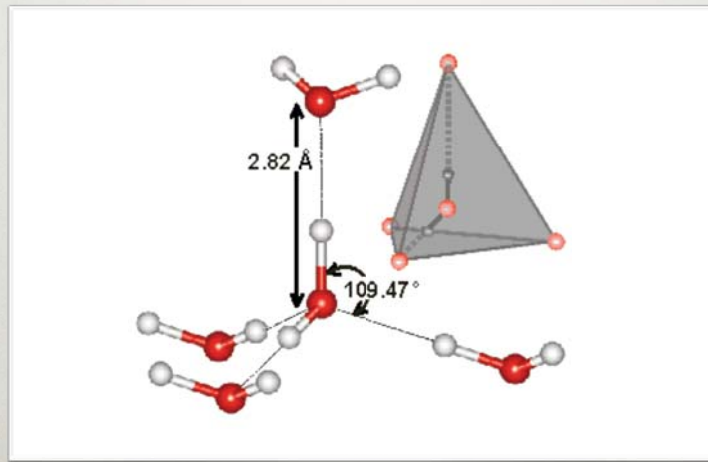


Absorption in the infrared and red spectral region ->  
"blue" color of natural waters



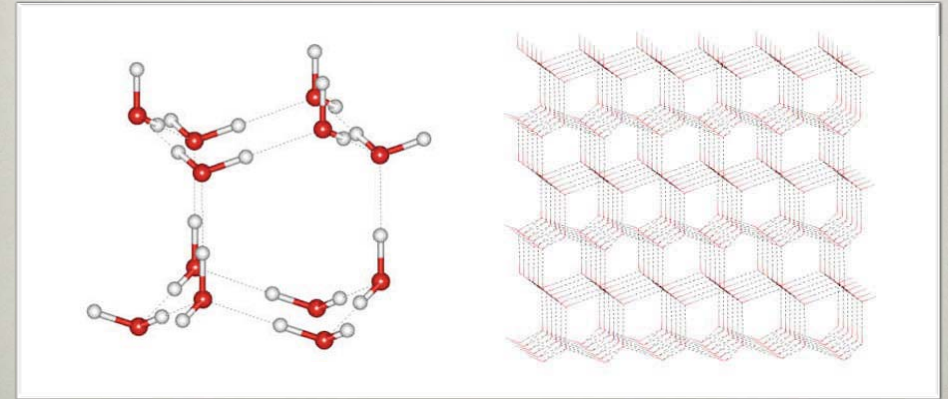
## HYDROGEN BONDING IN WATER

Formation of pentameric water



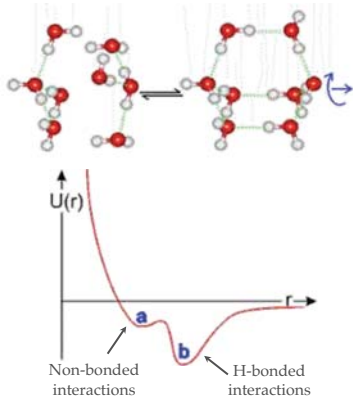
## STRUCTURE OF ICE

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

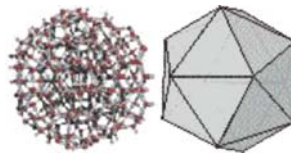


## STRUCTURE OF LIQUID WATER

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



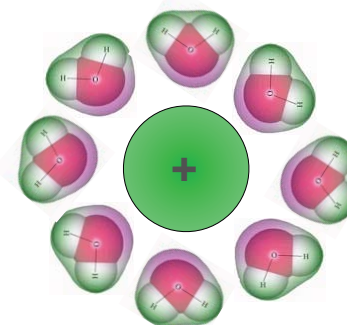
From clusters to networks:  
280 molecules form  
icosahedral structure



Spatial networks:  
May explain anomalous  
properties of water

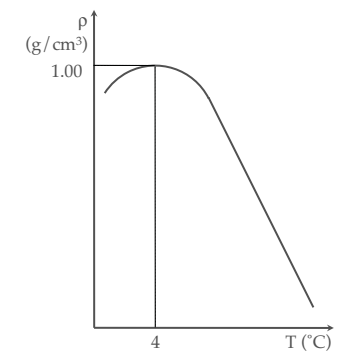
## PHYSICAL PROPERTIES OF WATER I.

Large dipole moment:  
Very good solvent  
Electrolyte solutions



Microwave oven!

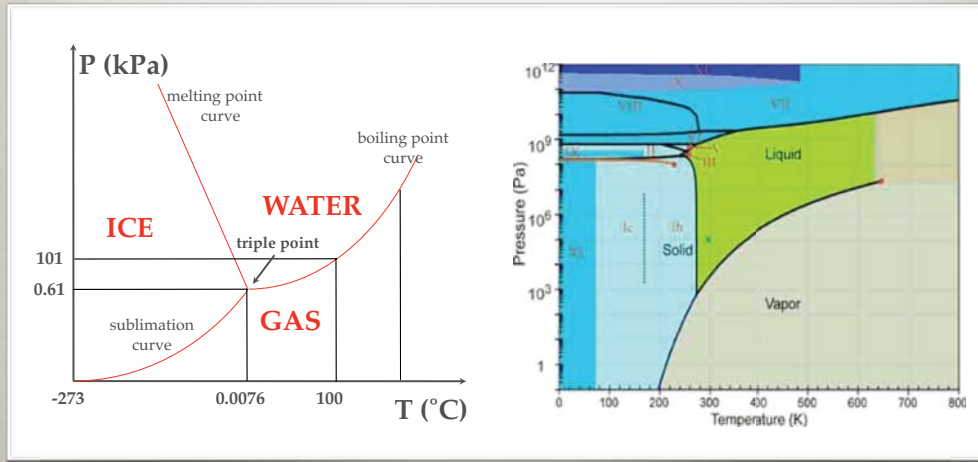
Anomalous density-  
Temperature function



Life in the frozen lake!

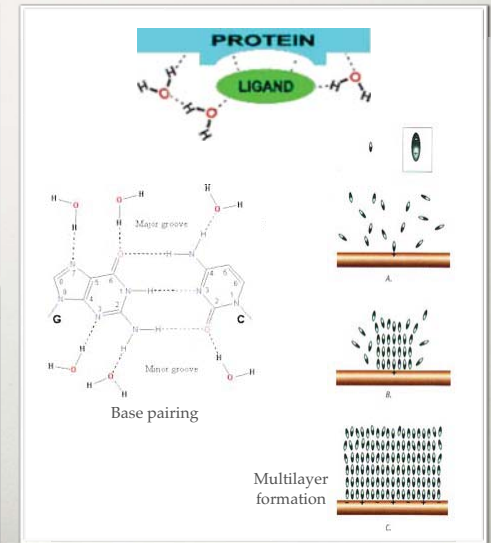
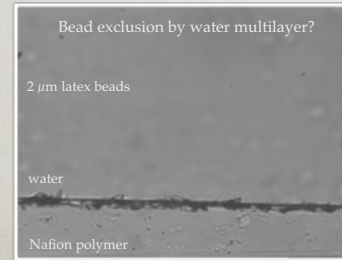
## PHASE DIAGRAM

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



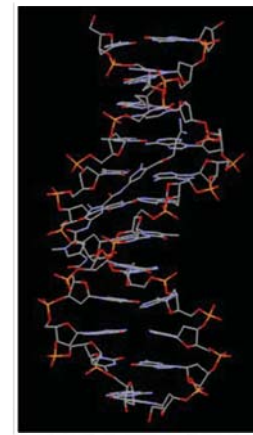
## HYDRATION

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

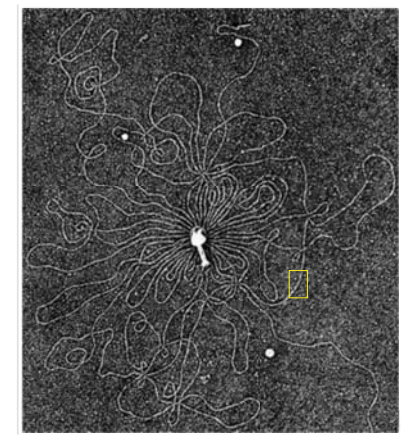


# MACROMOLECULES

# BIOLOGICAL MACROMOLECULES ARE GIANT MOLECULES

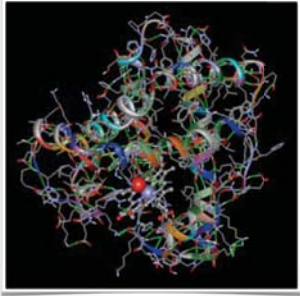


DNS double helix

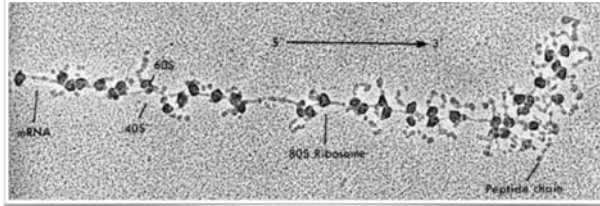


DNA released from bacteriophage head

## BIOLOGICAL MACROMOLECULES ARE EXCITING MOLECULES

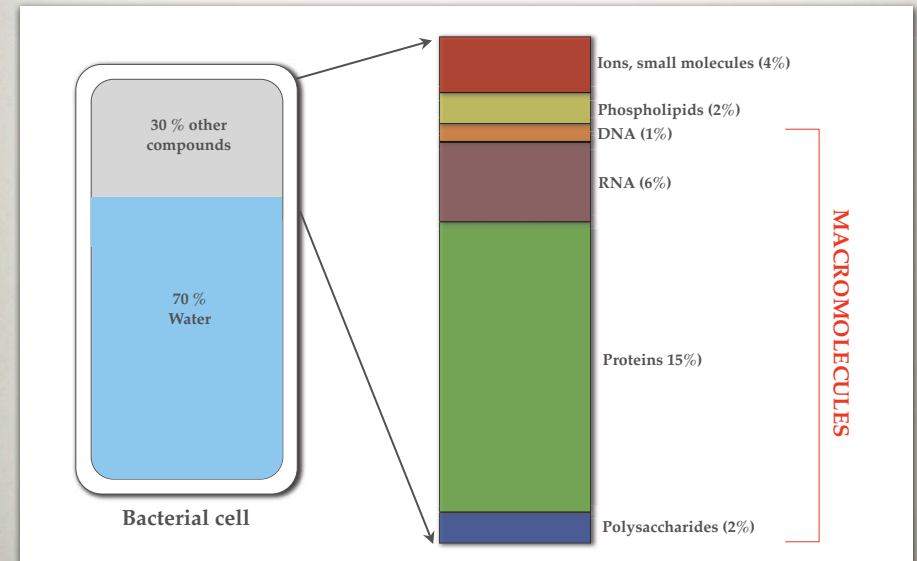


Structure of hemoglobin subunit



Newly synthesized protein (silk fibroin)

## PROPORTION OF MACROMOLECULES IN THE CELL BY MASS IS **LARGE**



## BIOLOGICAL MACROMOLECULES: BIOPOLYMERS

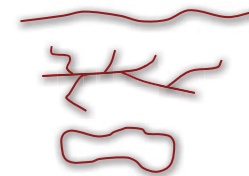
Polymers:  
chains built up from monomers

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

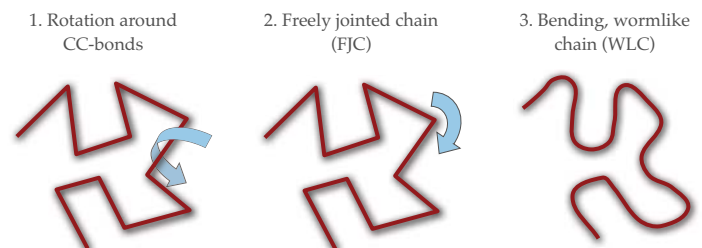
Biopolymer	Monomer	Bond
Protein	Amino acid	Covalent (peptide bond)
Nucleic acid (RNA, DNA)	Nucleotide (CTUGA)	Covalent (phosphodiester)
Polysaccharide (e.g., glycogen)	Sugar (e.g., glucos)	Covalent (e.g., $\alpha$ -glycosidic)
Protein polymer (e.g., microtubule)	Protein (e.g., tubulin)	Secondary

## SHAPE OF POLYMERS

1. Linear
2. Branched
3. Circular



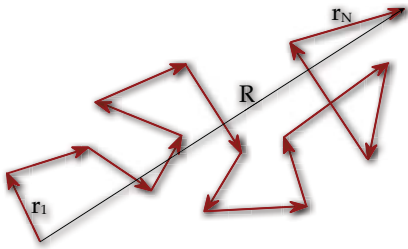
Shape of polymer chain changes dynamically. Possible mechanisms:





## 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  
 $l = |r_i|$  = correlation length  
 $r_i$  = elementary vector  
 $Nl = L$  = contour length  
 $l$  is related to **bending rigidity**.

## MECHANICS OF POLYMERS

### Entropic elasticity

Thermal fluctuations of the polymer chain



Configurational entropy (orientational disorder of elementary vectors) increases.



The chain shortens.

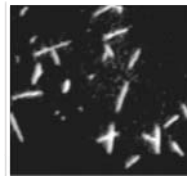


## BIOPOLYMER ELASTICITY

$l$  = correlation length  
 $L$  = contour length

**Rigid chain**  
 $l \gg L$

Microtubule



**Semiflexible chain**  
 $l \sim L$

Actin filament



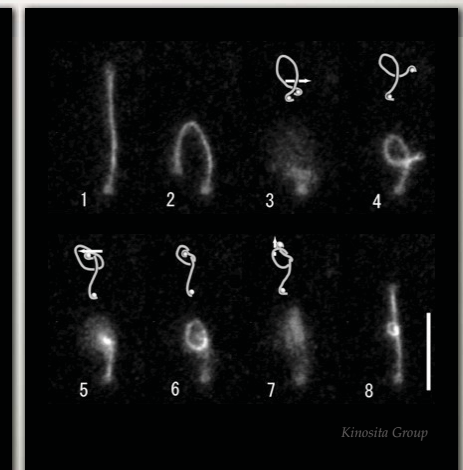
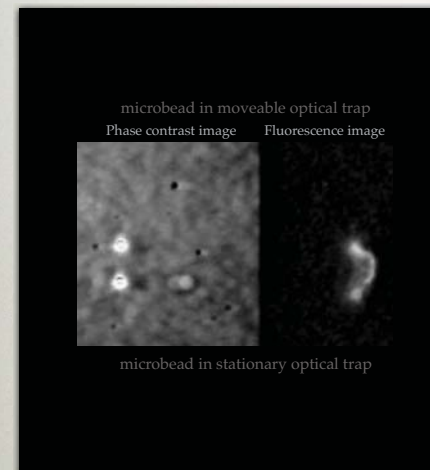
**Flexible chain**  
 $l \ll L$

DNA



## VISUALIZATION OF BIOPOLYMER ELASTICITY

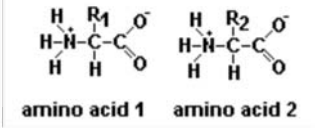
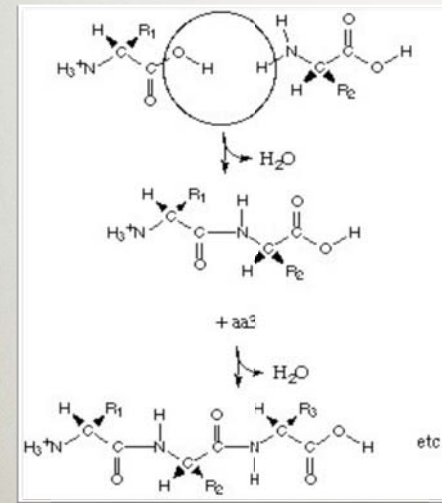
Tying a knot on a single DNA molecule



Kinosita Group

# PROTEIN FOLDING

## THE PEPTIDE BOND

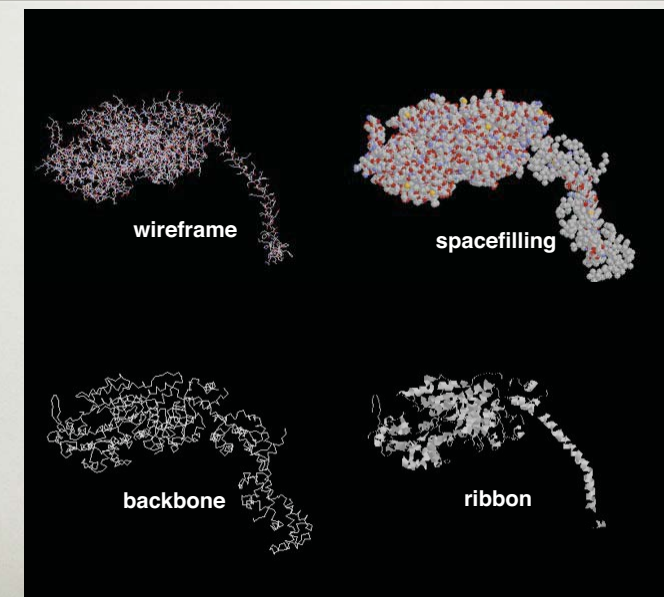


Condensation reaction  
followed by the release of water

## PROTEIN STRUCTURE

Primary	Secondary	Tertiary
Amino acid sequence	<p><math>\alpha</math>-helix <math>\beta</math>-sheet <math>\beta</math>-turn</p> <p><math>\alpha</math>-helix: •right handed •3.4 residue/turn •H-bridges</p> <p><math>\beta</math>-sheet: •parallel or antiparallel •H-bridges between distant residues</p>	<p>3D structure of single-chain protein</p>

## DISPLAY OF PROTEIN STRUCTURE



## 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)

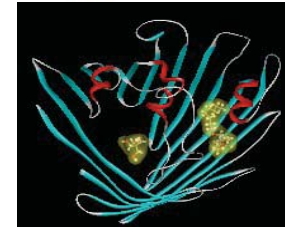
## PROTEIN STRUCTURE CLASSES

1. All alpha



calmodulin

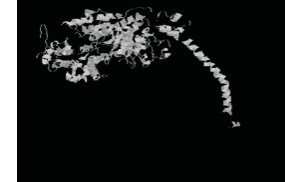
2. All beta



porin

(3. Alfa-beta)

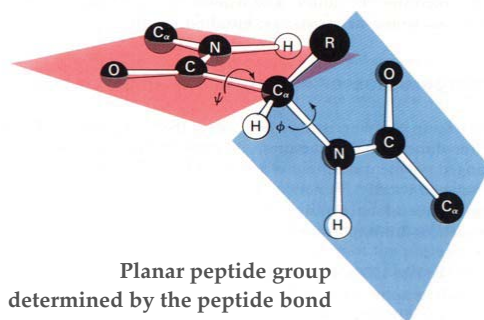
4. Multidomain



myosin

## LEVINTHAL'S PARADOX:

ARE ALL CONFORMATIONS EXPLORED BY THE PROTEIN MOLECULE?



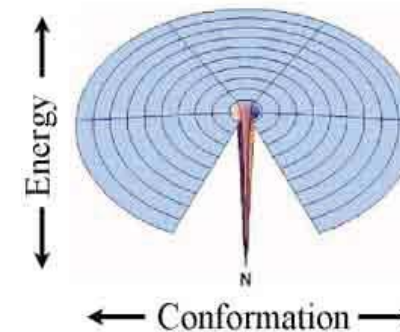
Number of possible protein configurations:

$$i^n$$

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

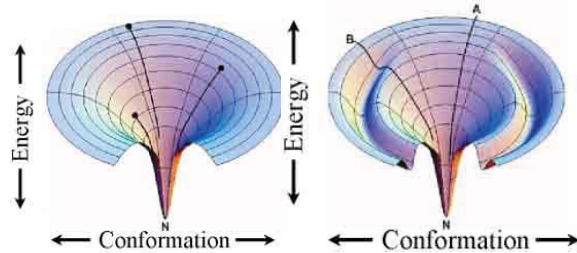
## LEVINTHAL'S PARADOX:

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)

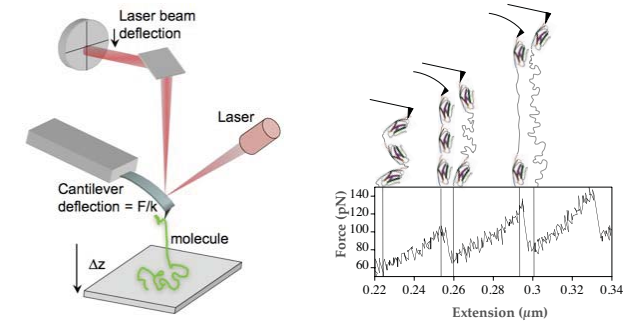


Beta-fibrils:  
Insoluble  
aggregates

## METHODS OF PROTEIN UNFOLDING (DENATURATION)

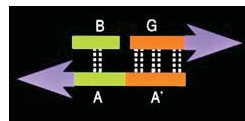
- Heat
- Chemical agent
- Mechanical force

Mechanical unfolding of a single protein with atomic force microscope



## MECHANICAL UNFOLDING OF A BETA-SHEET PROTEIN

Steps of computer-simulated domain unfolding



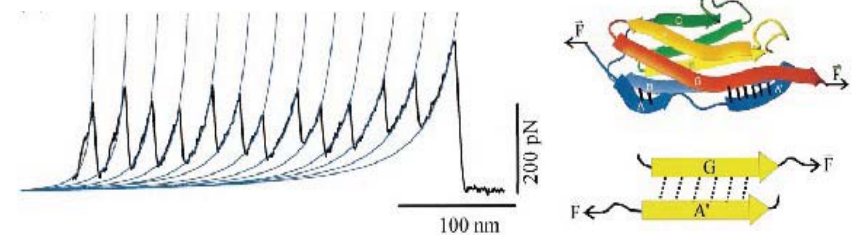
Basis of mechanical  
stability:

H-bridges between the  
first and last  $\beta$ -strands  
of the domain

## MECHANICAL UNFOLDING OF TITIN I27 DOMAIN

Mechanical stability provided by shear pattern of H-bond patch

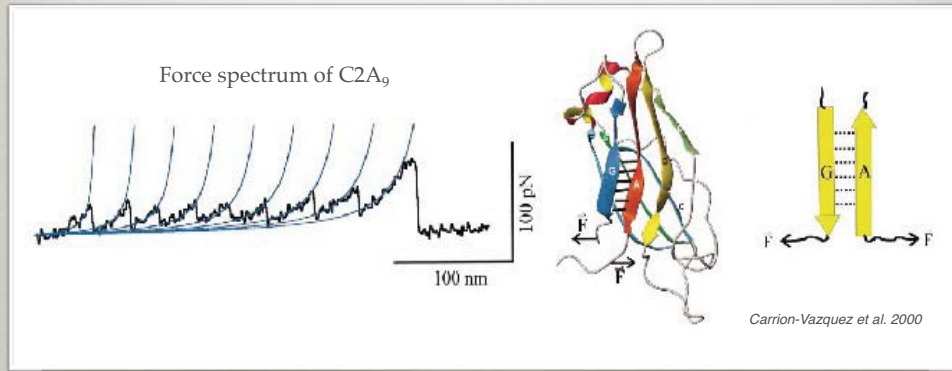
Force spectrum of I27<sub>12</sub>



Carrión-Vázquez et al. 2000

# MECHANICAL UNFOLDING OF C2A DOMAIN

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

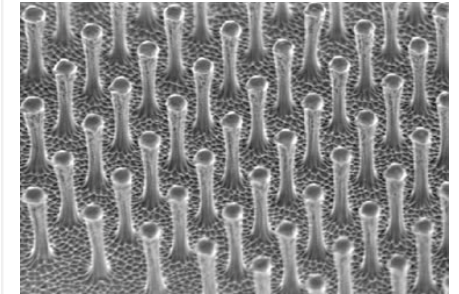
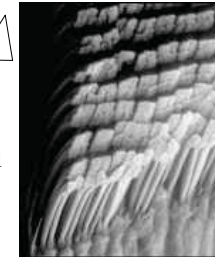


# MECHANICAL STABILITY IN PROTEINS

## PRINCIPLE OF PARALLEL BOND COUPLING



Gecko foot stickiness:  
Bristles (setae)  
coupled in parallel



Artificial gecko foot