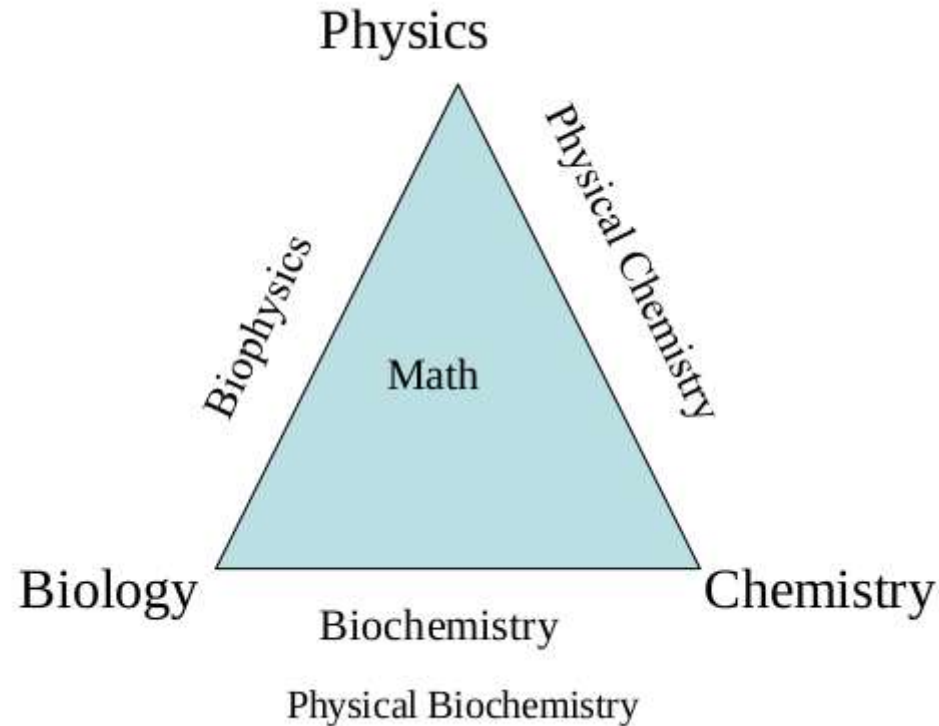


# Why biophysics and biochemistry

Systems under study

Principles  
models  
methods



# A bit of biology



Ознаки “життя”:

*отримання і перетворення енергії з середовища - метаболізм*



*самоорганізація через використання енергії – синтез, утворення макромолекулярних комплексів*



*здатність запам'ятовувати свою будову – генетичний код*

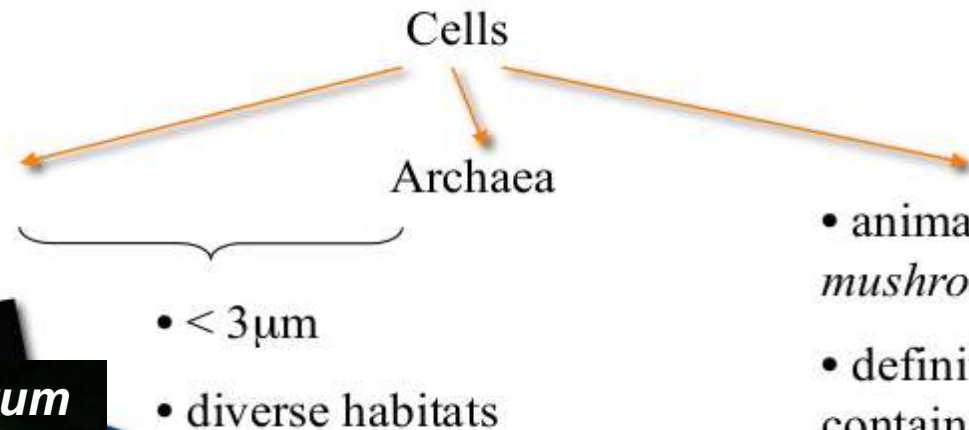
*здатність давати потомство - розмноження*

# Diversity of life forms

- Classification based on similarities and differences in ribosomal RNA seq.:

**Prokaryotes**= unicellular organisms that lack a membrane-bound nucleus, mitochondria, or any other membrane-bound organelle

**Eukaryotes**= cells with a nucleus that stores genetic information.



- animals, plants, fungi (e.g., mushrooms, mold)

- definition: a cell that contains its DNA genome within a membrane-bound nucleus

***Haloquadratum walsbyi***

Some aspects of archaeal biochemistry are unique, such as their reliance on ether lipids in their cell membranes

*Geothermal vent on the Atlantic ocean floor*

*Permafrost in Antarctica*

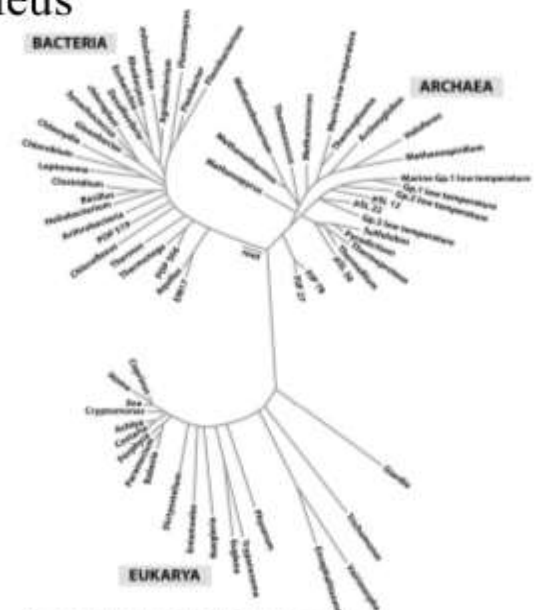


Figure 3.6 Physical Biology of the Cell (© Garland Science 2008)

# Structural hierarchy in eukaryotes

**Клітина – цеглина для всього ЖИВОГО**

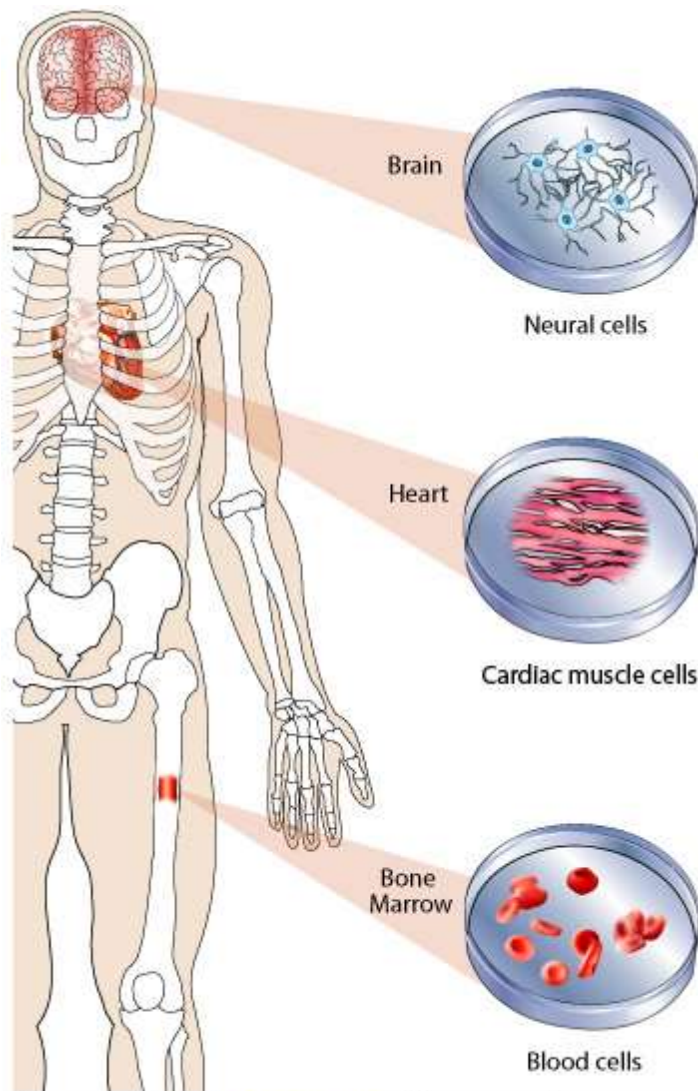
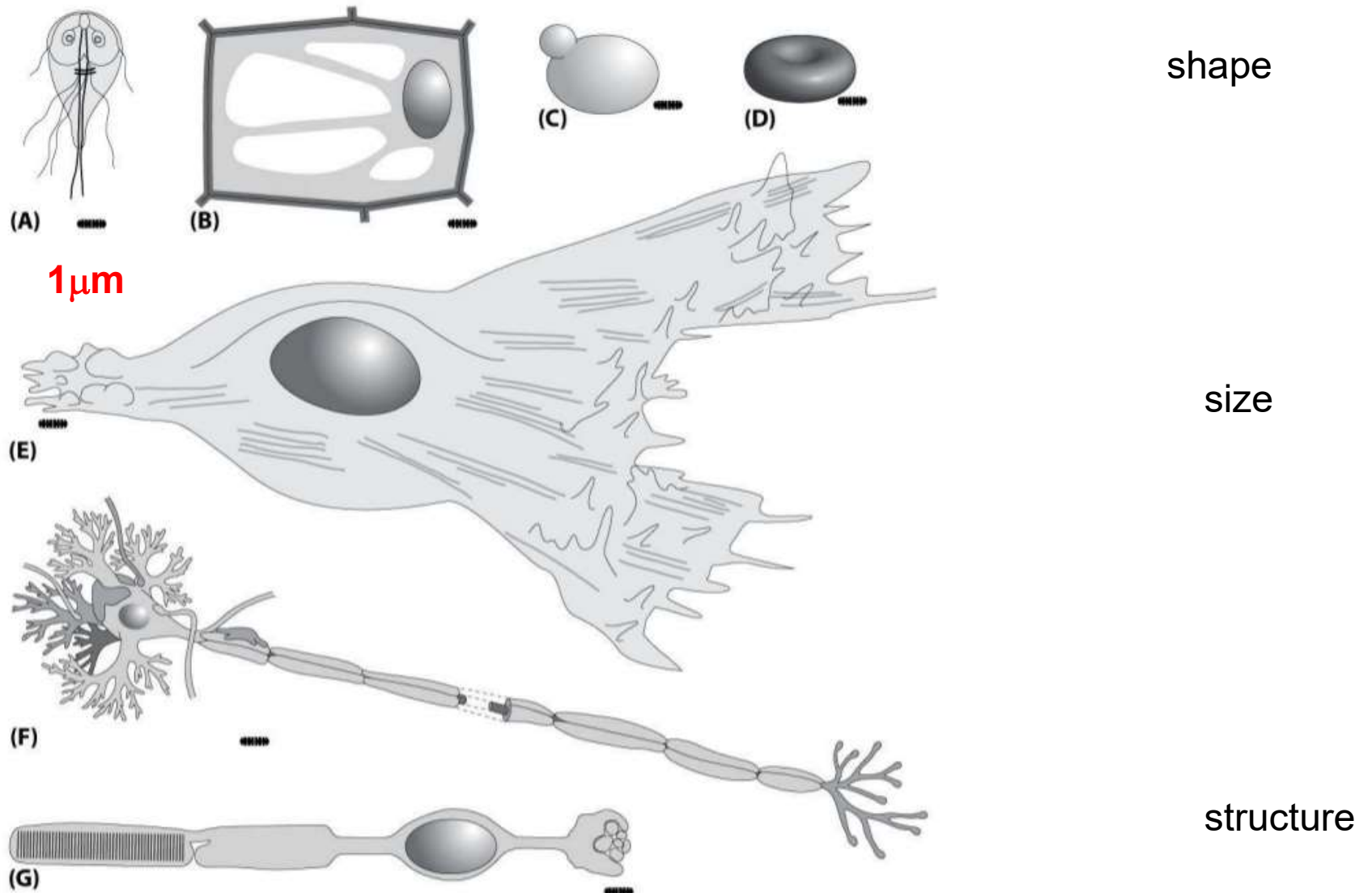


Illustration by [Cell Imaging Core](#) of the Center for Reproductive Sciences.





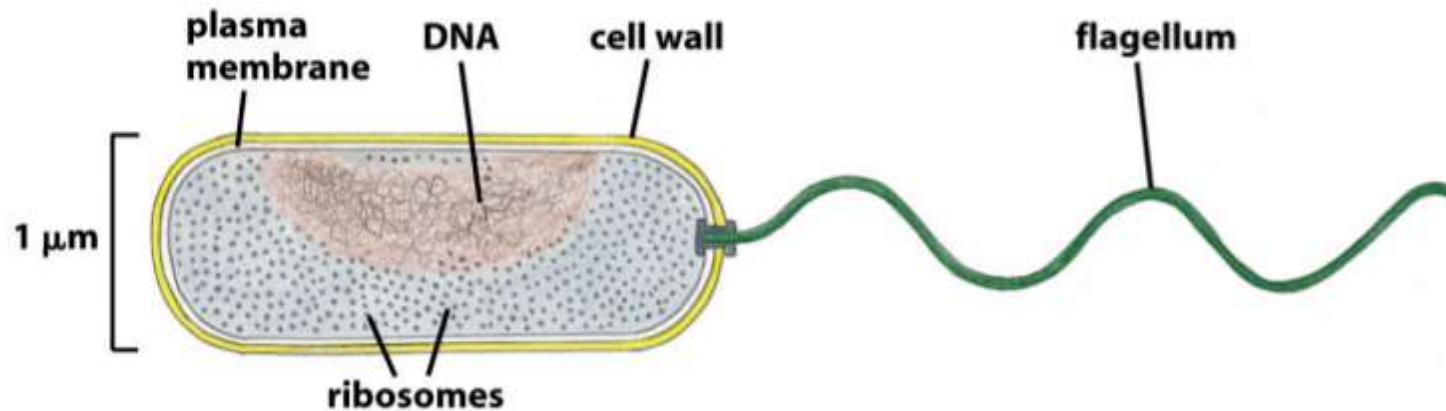
# Great diversity of cells



# Cell structure

Кишкова паличка

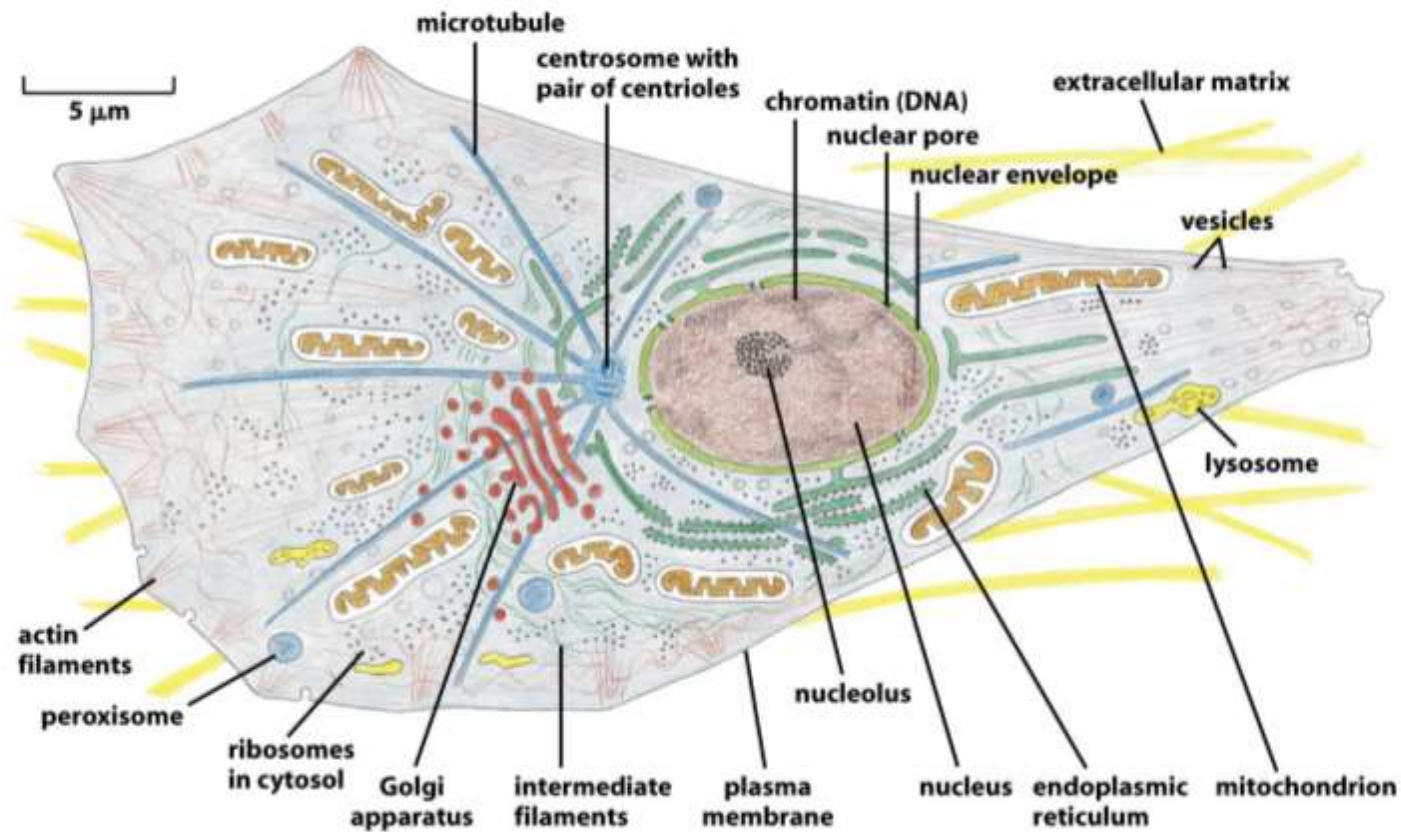
E. Coli (model prokaryotic cell)



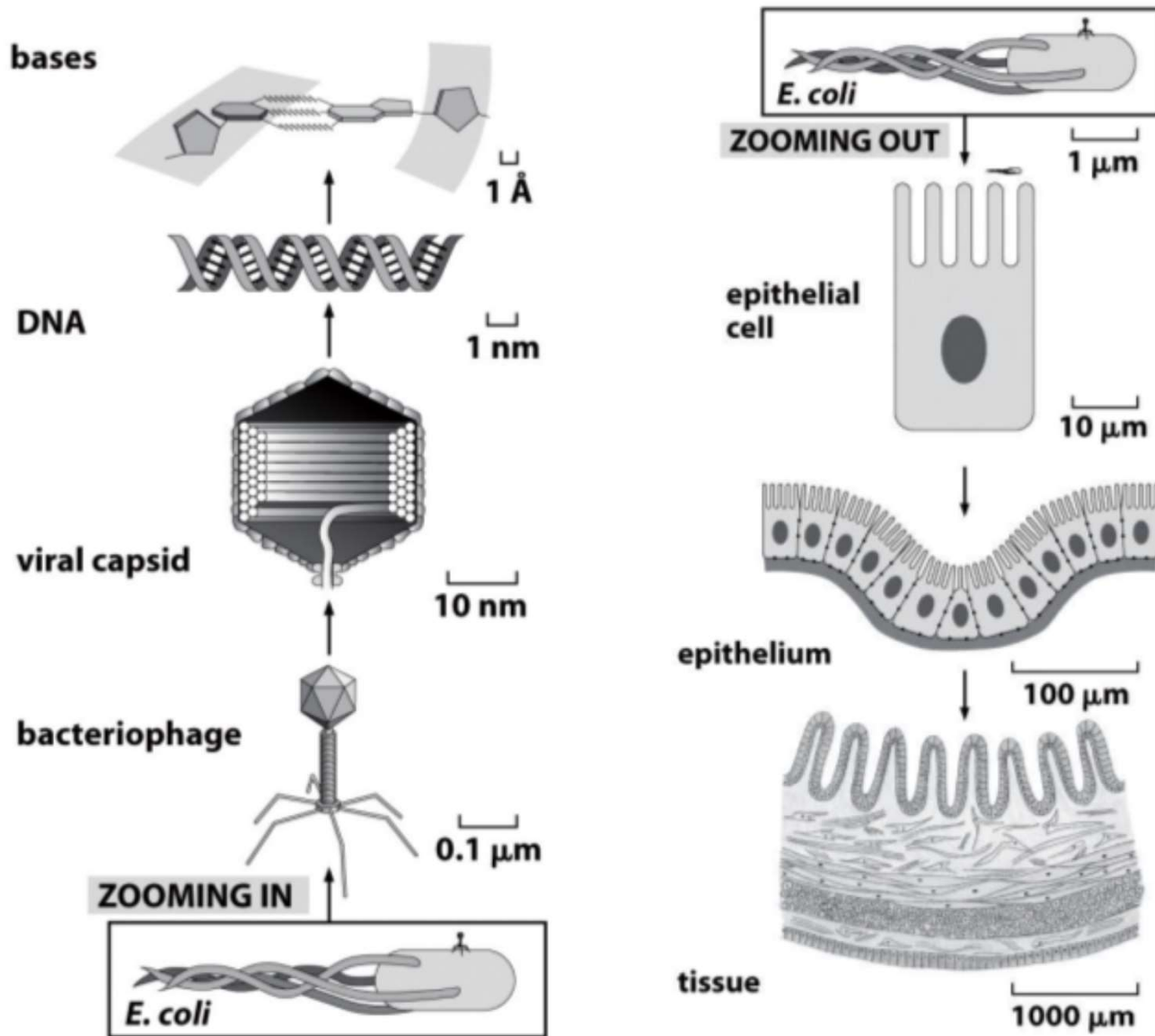
# Cell structure

Фібропласт – клітина сполучної тканини (колаген для загоювання ран)

Fibroblast (model higher eukaryotic cell)



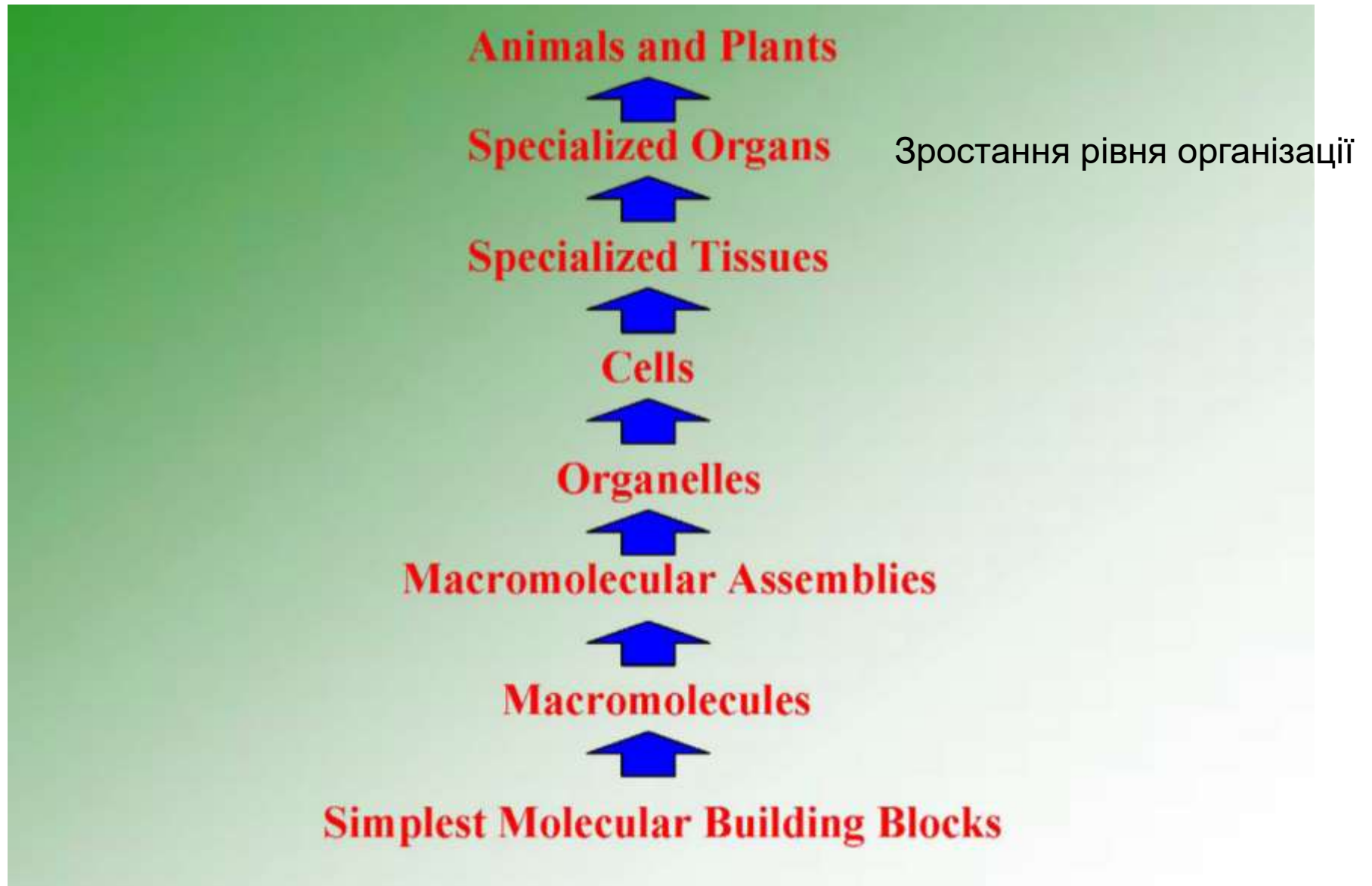
# Biological length scales



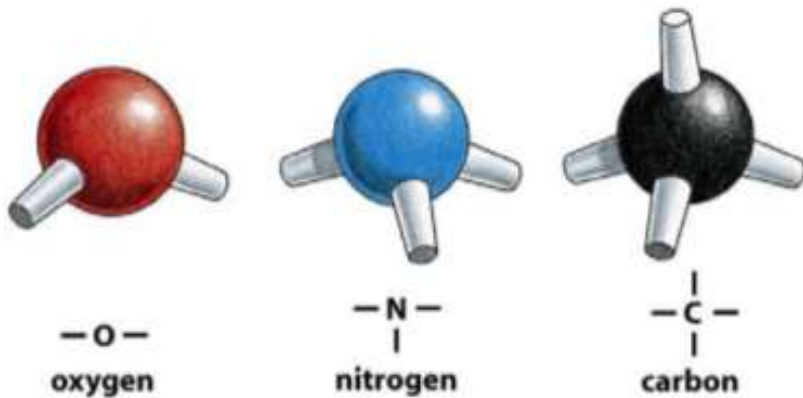
<http://learn.genetics.utah.edu/content/begin/cells/scale/>



# Hierarchical organization



# Cell atoms

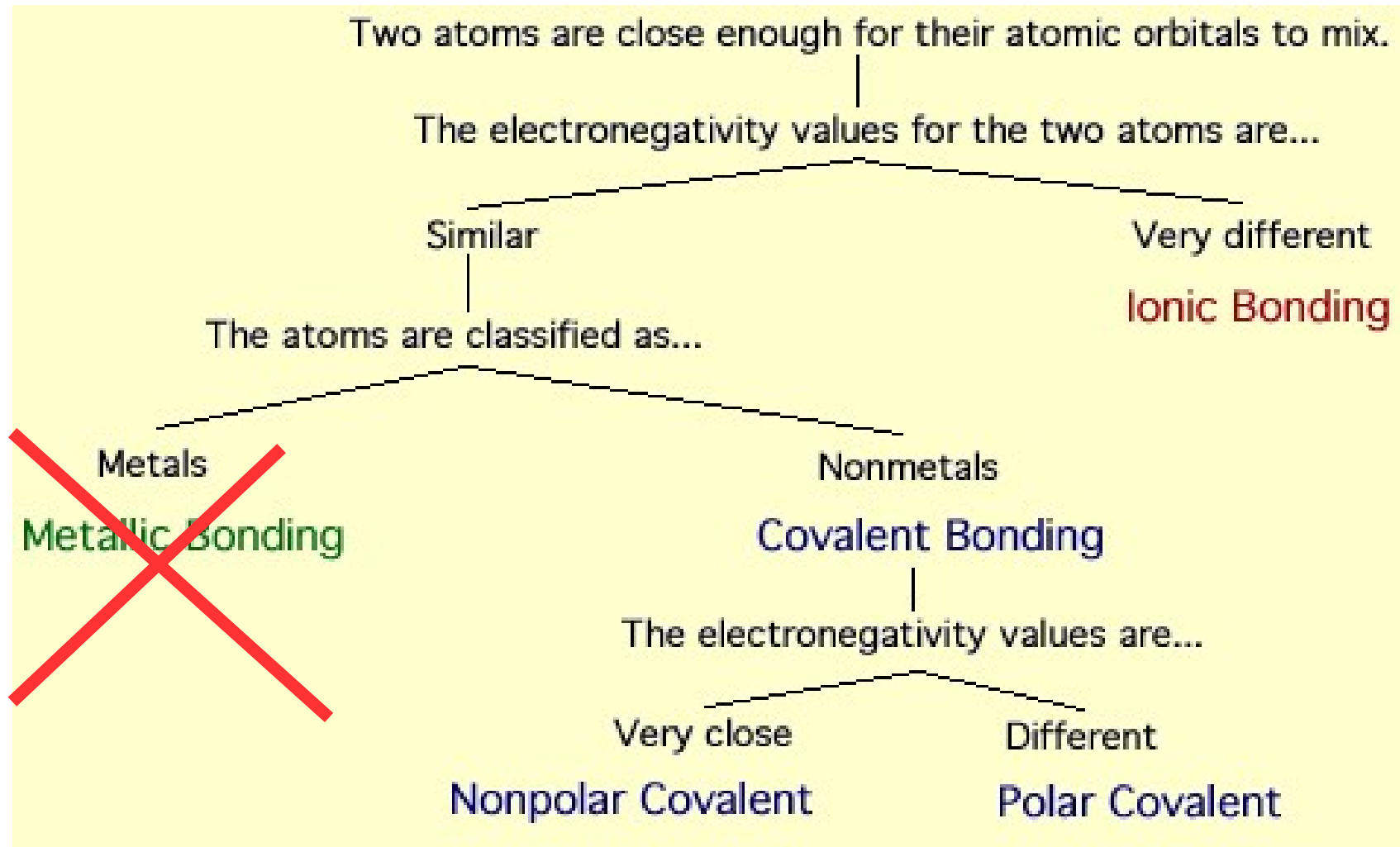


atomic number																						
1																	2					
H																	He					
1	atomic weight																					
Li	Be															B	C	N	O	F	Ne	
11	12															5	6	7	8	9		
Na	Mg															11	12	14	16	19		
23	24															Al	Si	P	S	Cl	Ar	
19	20	Sc	Ti	21	22	23	24	25	26	27	28	29	30	Ga	Ge	As	32	33	34	35	Kr	
K	Ca			V	Cr	Mn	Fe	Co	Ni	Cu	Zn								Se	Br		
39	40			51	52	55	56	59	59	64	65								79			
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te				I	Xe		
					96														127			
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn					
Fr	Ra	Ac	Rf	Ha																		

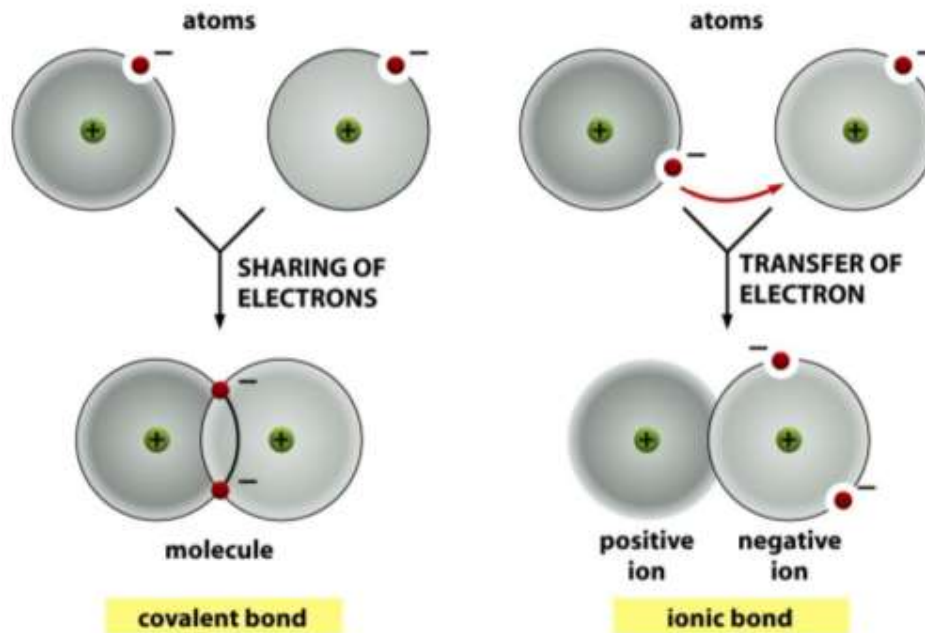
Organic Atoms (H, C, N, O)  
Ions (Na, K, Mg, Ca, P, S, Cl)

99% of cells  
0.9%

# Chemical bonds in biology

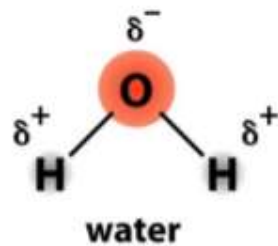


# Covalent bonds

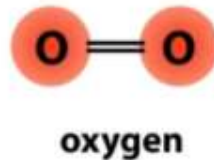


## Polar Bond

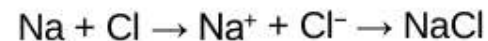
Creates permanent dipoles



## Nonpolar Bond



When [sodium](#) (Na) and [chlorine](#) (Cl) are combined, the sodium atoms each lose an [electron](#), forming cations ( $\text{Na}^+$ ), and the chlorine atoms each gain an electron to form anions ( $\text{Cl}^-$ ). These ions are then attracted to each other in a 1:1 ratio to form sodium chloride (NaCl).



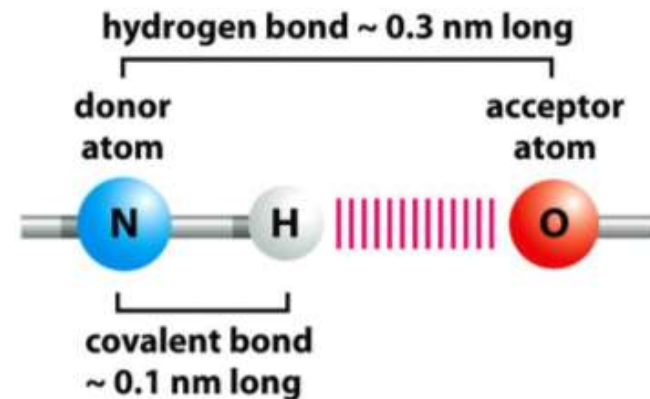


# Noncovalent bonds

## Hydrogen Bond

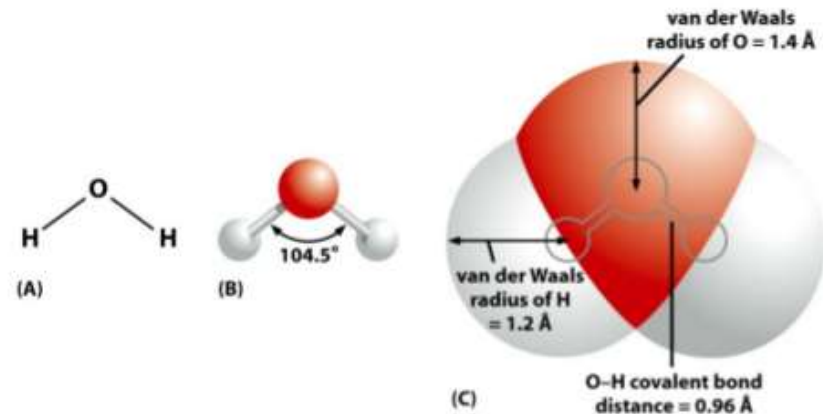
Electropositive hydrogen atom is shared by two electronegative atoms. Covalent bond is partially distorted. Interaction is weak, last a short period of time due to thermal motion.

Molecules that contain polar bonds and that can form H-bonds in water dissolve easily in water (hydrophilic). Nonpolar molecules do not dissolve in water (hydrophobic)



## Van der Waals Interaction

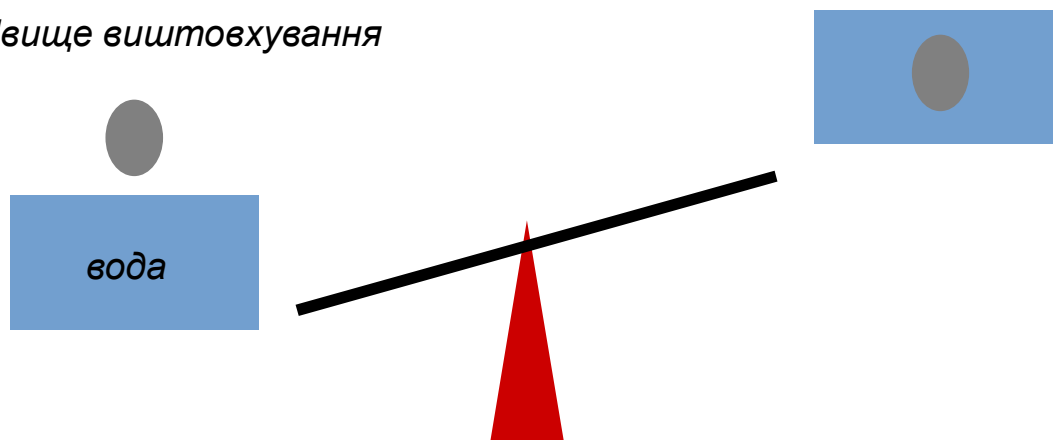
The electron cloud of an atom fluctuates, producing a flickering dipole. Such dipoles induce oppositely flickering dipoles in a nearby atom, generating a weak interaction.



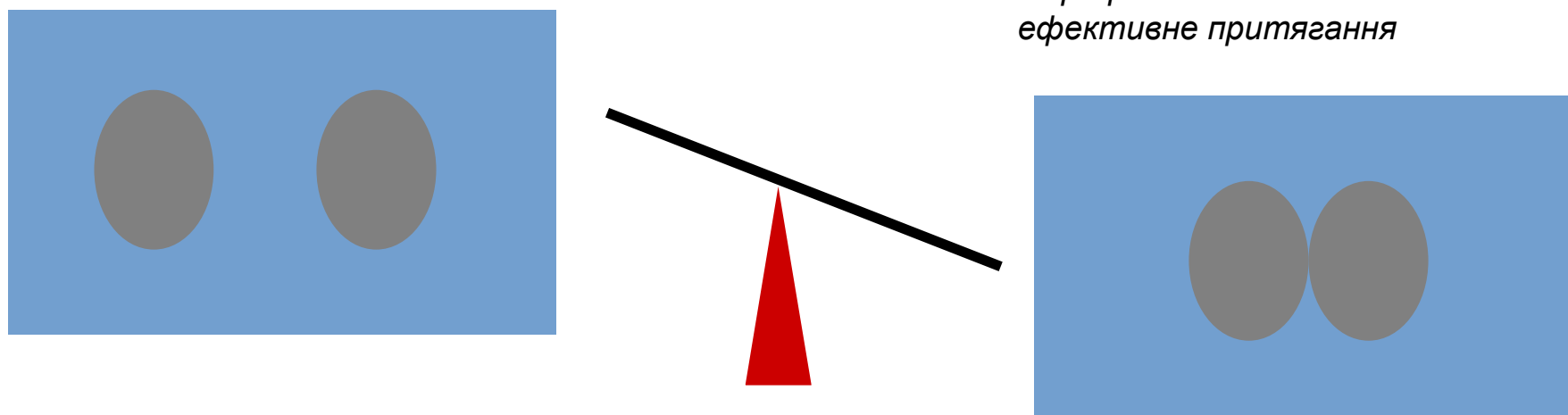
# Hydrophobic interactions

Гідрофоб – речовина яка не змішується з водою, олії, нафта та інші вуглеводні

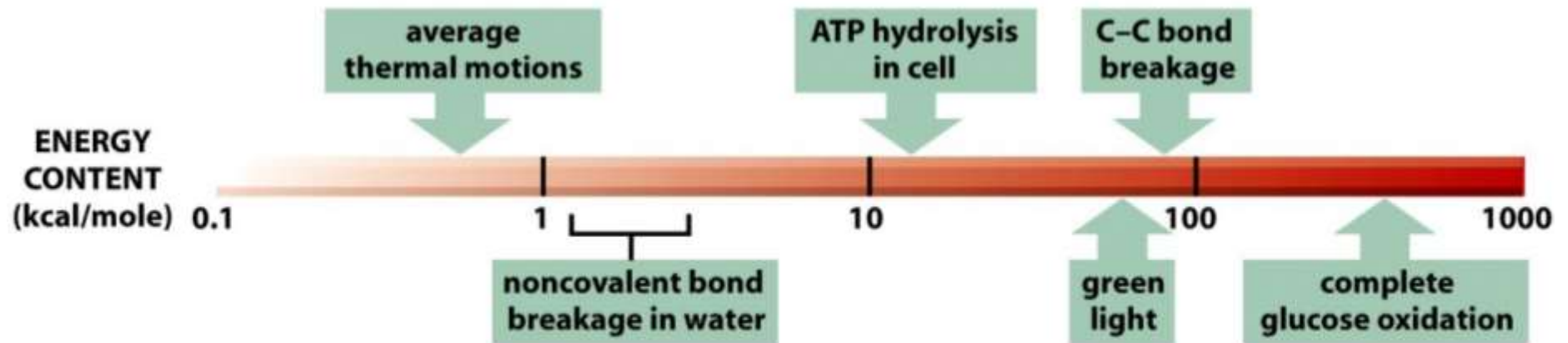
*Явище виштовхування*



*Гідрофобні частинки злипаються – ефективне притягання*



# Energy scale

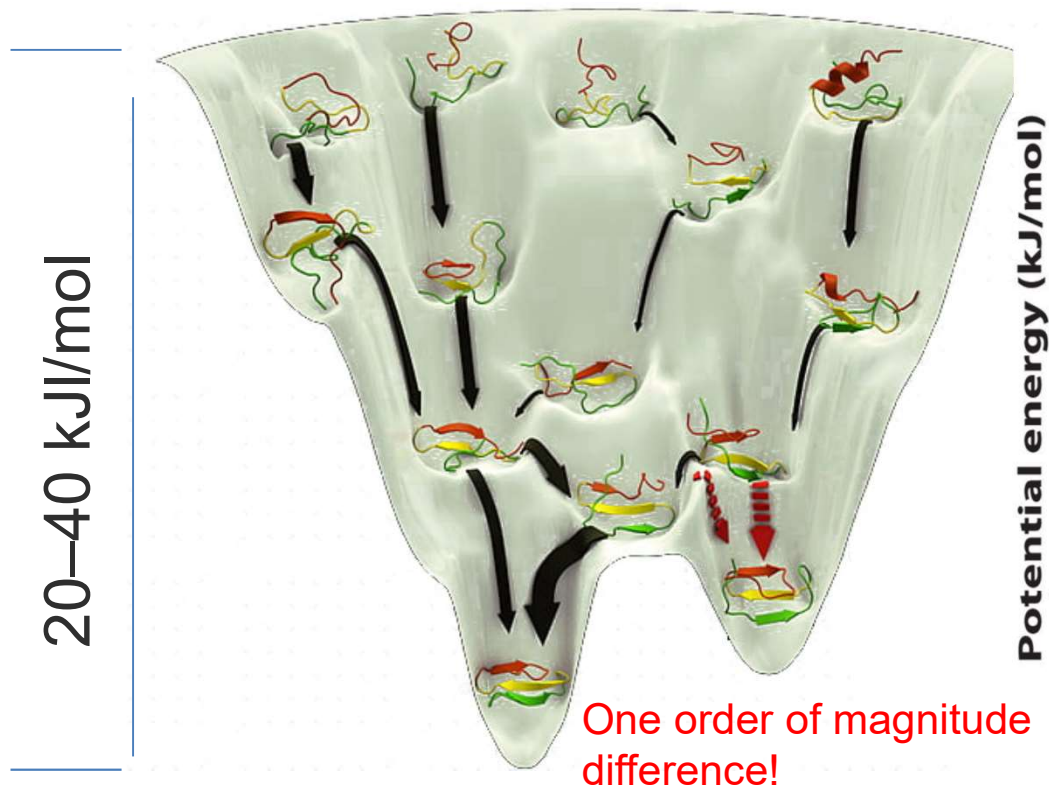


- Molecules do not fall apart by thermal agitation.
- The energy of noncovalent interactions are in the range of thermal noise in the environment.
- ATP hydrolysis energy exceeds noncovalent interactions and thermal motions
- Covalent bond energy can be used to synthesize multiple ATPs

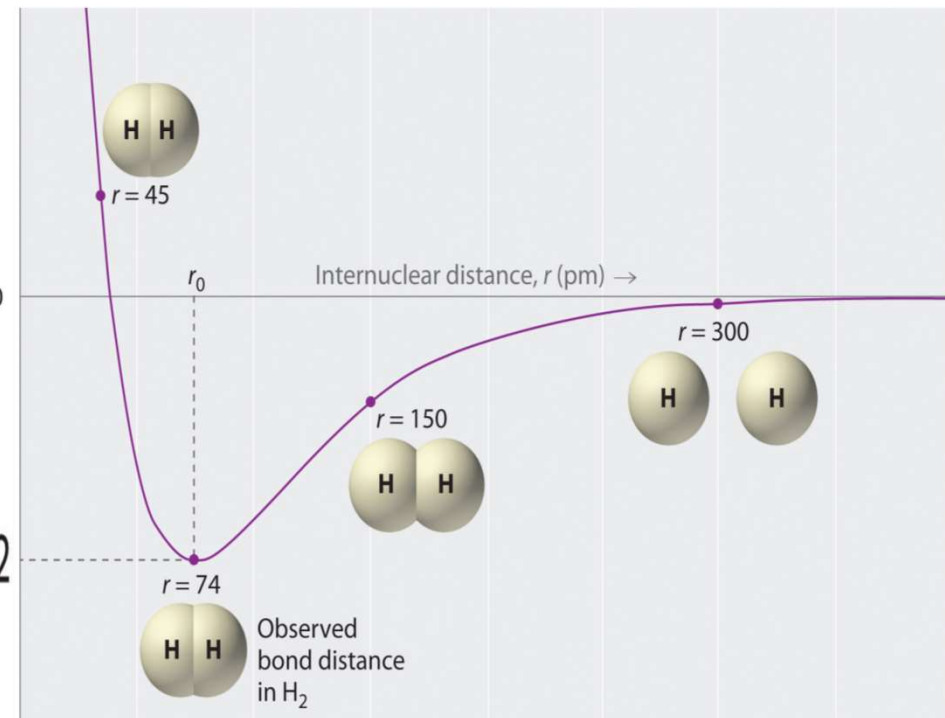
# Specifics of biological systems

1) Processes are driven by free energy not internal energy

## *Protein folding*



## *Formation of hydrogen molecule*

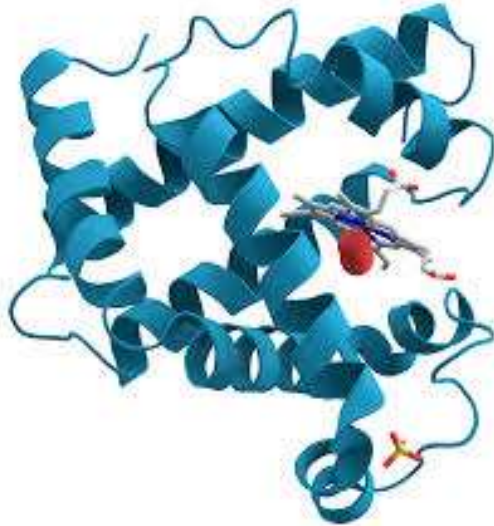


- a) Strong influence of thermal fluctuations and entropy
- b) Important role of non-covalent and solvent-mediated interactions
- c) Very little chemistry other than in enzymes



# Biological molecules

Proteins

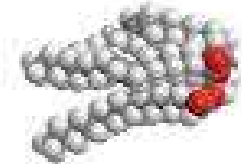


Lipids

A. Fatty acids (FA)



B. Glycerolipids (GL)



C. Glycerophospholipids (GP)



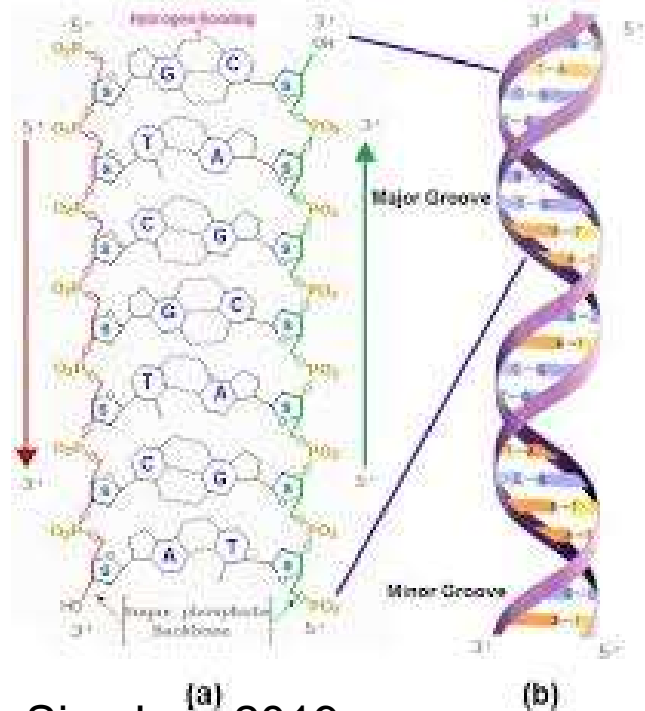
D. Sterol lipids (ST)



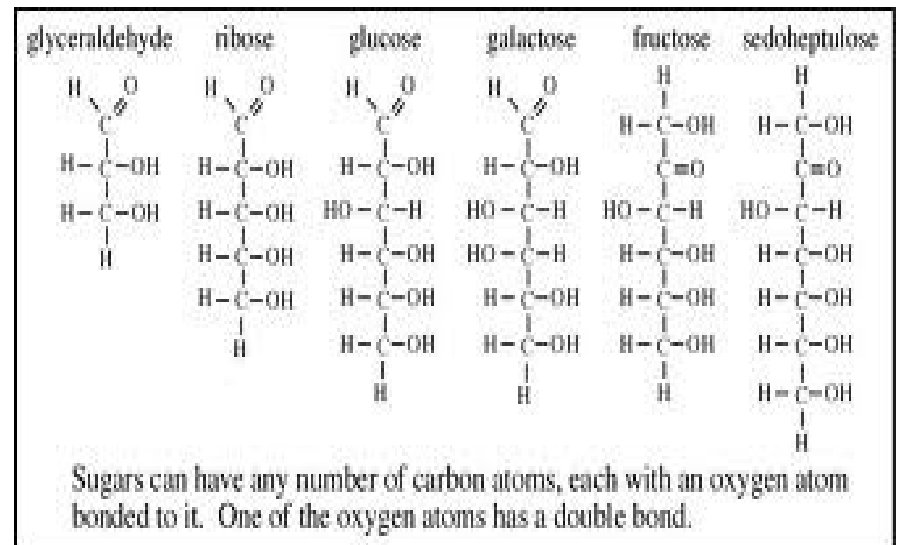
E. Sphingolipids (SP)



Nucleic acids



Sugars



## Different monosaccharides

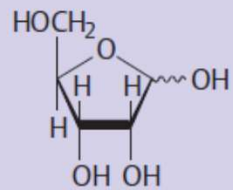
# Sugars

Carbohydrates with hydroxyl groups

*Different isomers*

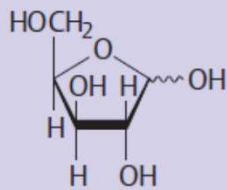
### ① Aldoses RNA

D-Ribose (Rib)

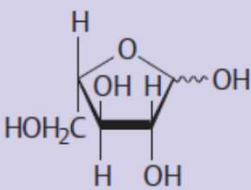


Pentoses

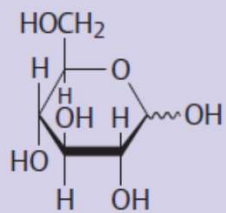
D-Xylose (Xyl)



L-Arabinose (Ara)

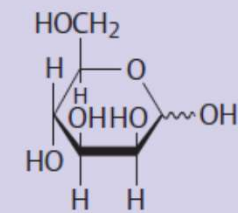


D-Glucose (Glc)

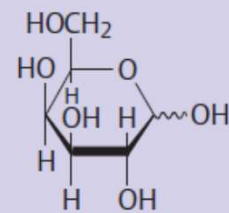


Hexoses

D-Mannose (Man)

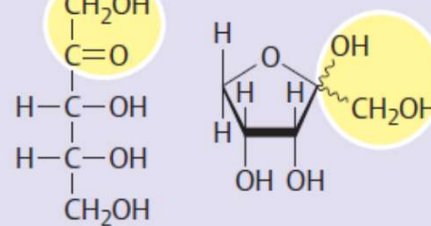


D-Galactose (Gal)

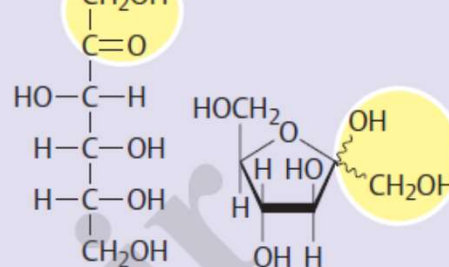


### ② Ketoses

D-Ribulose (Rub)

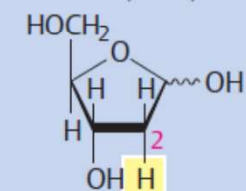


D-Fructose (Fru)

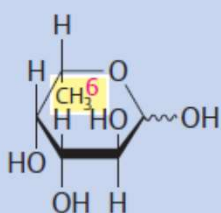


### ③ Deoxyaldoses DNA

2-Deoxy-D-ribose (dRib)

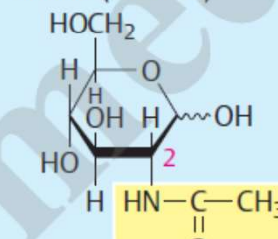


L-Fucose (Fuc)

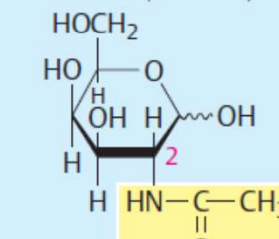


### ④ Acetylated amino sugars

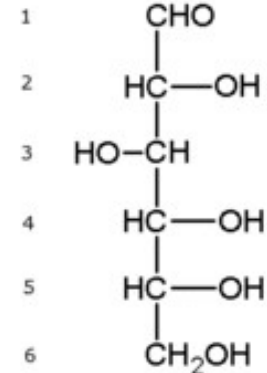
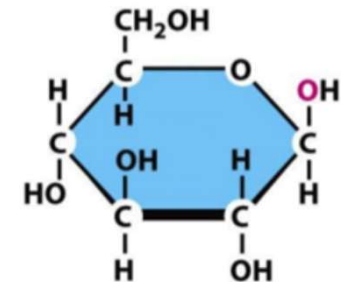
N-Acetyl-D-glucosamine (GlcNAc)



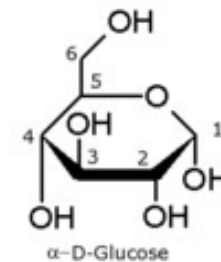
N-Acetyl-D-galactosamine (GalNAc)



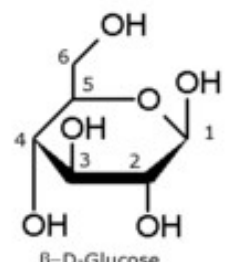
Glucose



D-Glucose



$\alpha$ -D-Glucose



$\beta$ -D-Glucose

Energy source and storage.

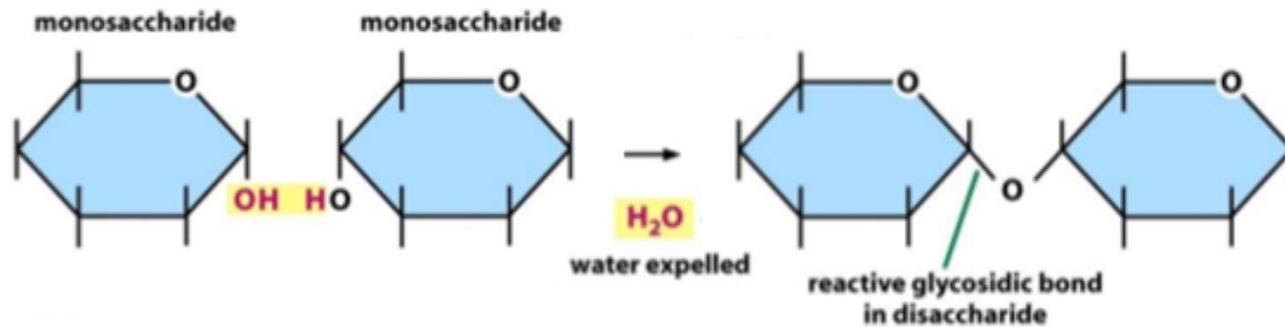
Cell wall (mechanical support)

Glycoproteins, glycolipids (surface adhesion, extracellular signaling, cell-cell interactions)

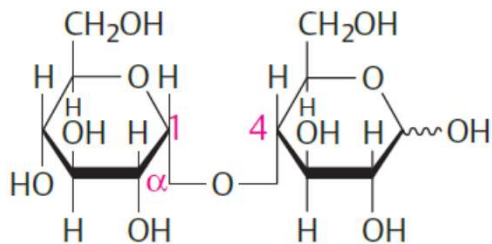
Baumketner, BioSim, Lviv 2019

# Sugars

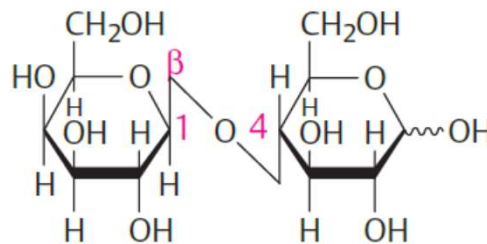
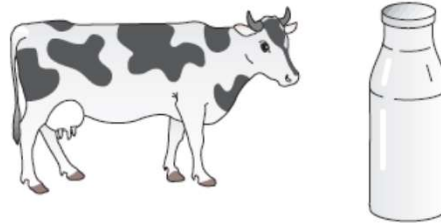
Polymerization



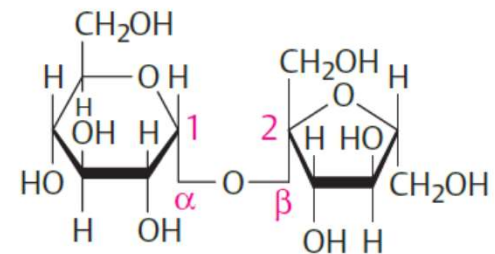
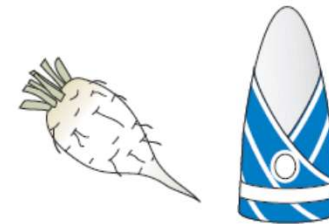
## B. Disaccharides



**1. Maltose**  
 $\alpha$ -D-Glucopyranosyl-  
 (1 $\rightarrow$ 4)-D-glucopyranose



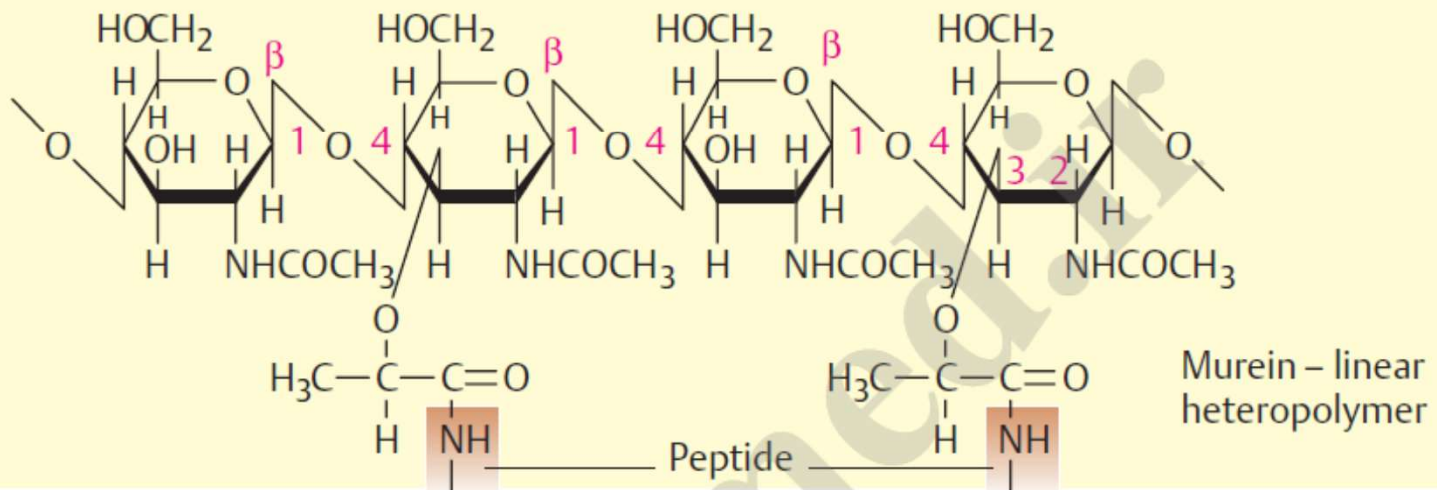
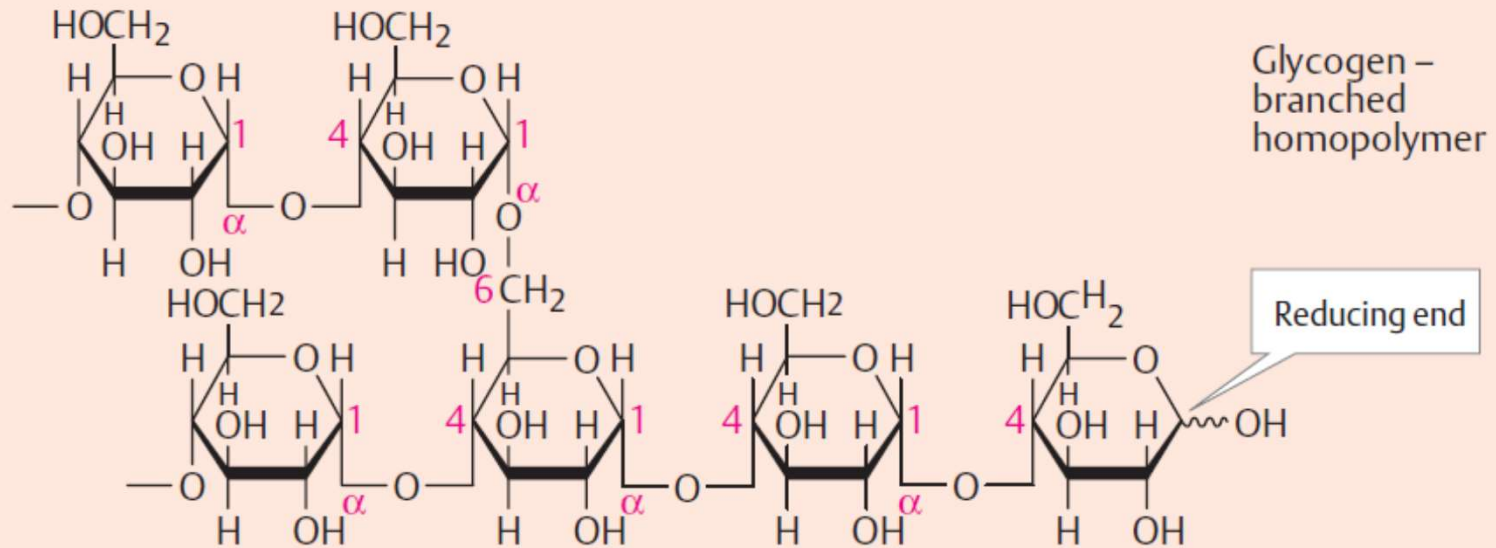
**2. Lactose**  
 $\beta$ -D-Galactopyranosyl-  
 (1 $\rightarrow$ 4)-D-glucopyranose



**3. Sucrose**  
 $\alpha$ -D-Glucopyranosyl-  
 (1 $\leftrightarrow$ 2)- $\beta$ -D-fructofuranoside

# Sugars

## A. Polysaccharides: structure





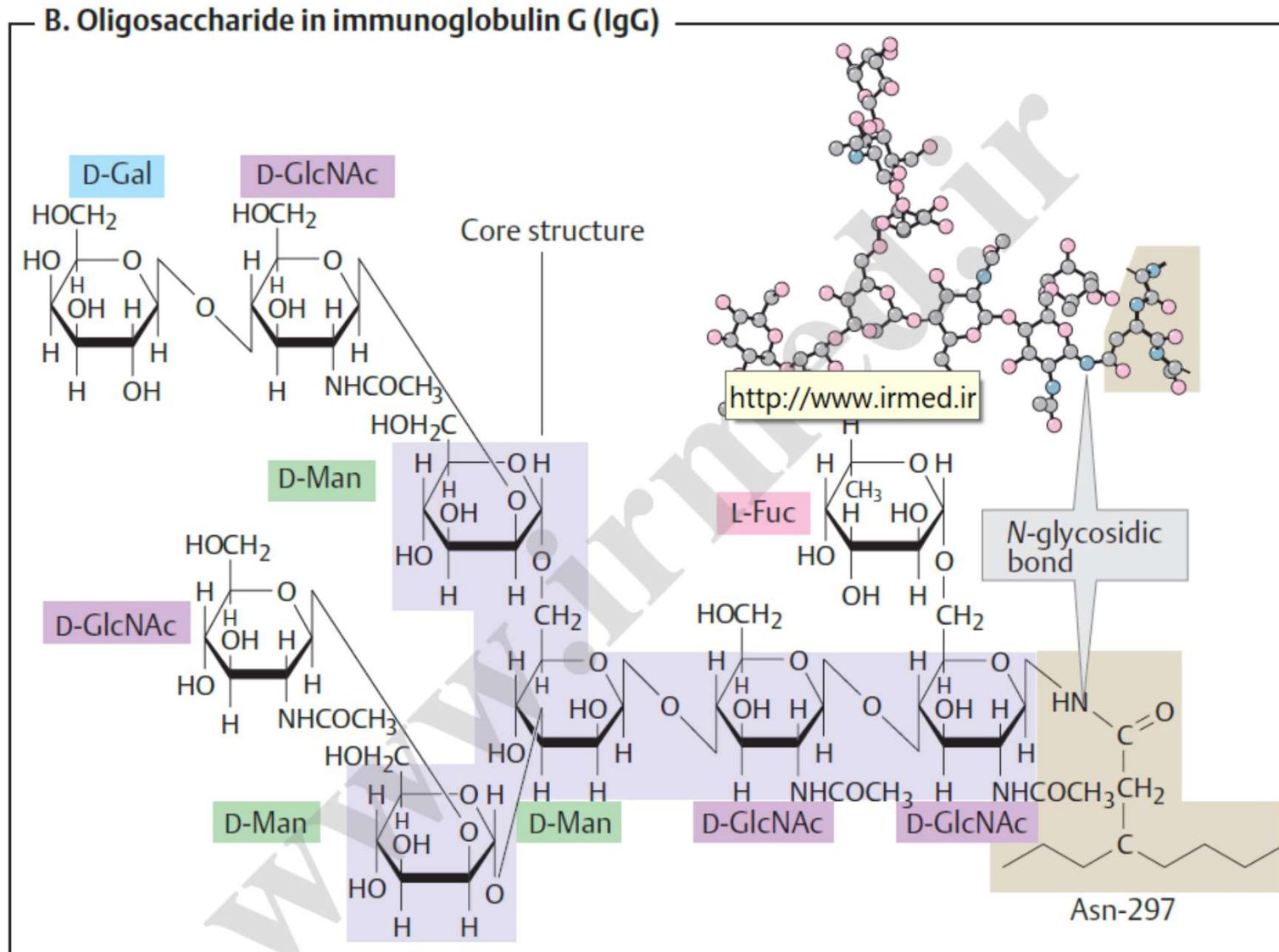
# Sugars

## B. Important polysaccharides

Poly-saccharide	Mono-saccharide 1	Mono-saccharide 2	Linkage	Branching	Occurrence	Function
<b>Bacteria</b>						
Murein Dextran	D-GlcNAc D-Glc	D-MurNAc <sup>1)</sup> —	$\beta 1 \rightarrow 4$ $\alpha 1 \rightarrow 6$	— $\alpha 1 \rightarrow 3$	Cell wall Slime	SC WB
<b>Plants</b>						
Agarose Carrageenan	D-Gal D-Gal	L-aGal <sup>2)</sup> —	$\beta 1 \rightarrow 4$ $\beta 1 \rightarrow 3$	$\beta 1 \rightarrow 3$ $\alpha 1 \rightarrow 3$	Red algae (agar) <a href="http://www.irmed.ir">http://www.irmed.ir</a>	WB WB
Cellulose Xyloglucan	D-Glc D-Glc	— D-Xyl (D-Gal, L-Fuc)	$\beta 1 \rightarrow 4$ $\beta 1 \rightarrow 4$	— $\beta 1 \rightarrow 6$ ( $\beta 1 \rightarrow 2$ )	Cell wall Cell wall (Hemicellulose)	SC SC SC
Arabinan Amylose Amylopectin Inulin	L-Ara D-Glc D-Glc D-Fru	— — —	$\alpha 1 \rightarrow 5$ $\alpha 1 \rightarrow 4$ $\alpha 1 \rightarrow 4$ $\beta 2 \rightarrow 1$	$\alpha 1 \rightarrow 3$ — $\alpha 1 \rightarrow 6$ —	Cell wall (pectin) Amyloplasts Amyloplasts Storage cells	RC RC RC RC
<b>Animals</b>						
Chitin Glycogen Hyaluronic acid	D-GlcNAc D-Glc D-GlcUA	— — D-GlcNAc	$\beta 1 \rightarrow 4$ $\alpha 1 \rightarrow 4$ $\beta 1 \rightarrow 4$ $\beta 1 \rightarrow 3$	— $\alpha 1 \rightarrow 6$ —	Insects, crabs Liver, muscle Connective tissue	SK RK SK, WB

# Sugars

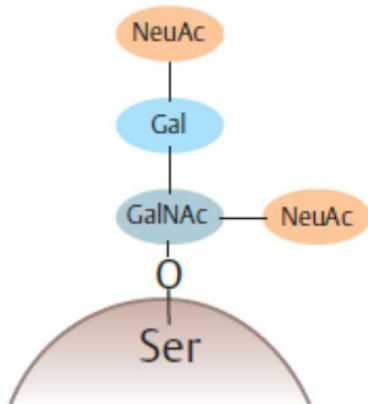
*Sugars attached to proteins=glycoproteins*



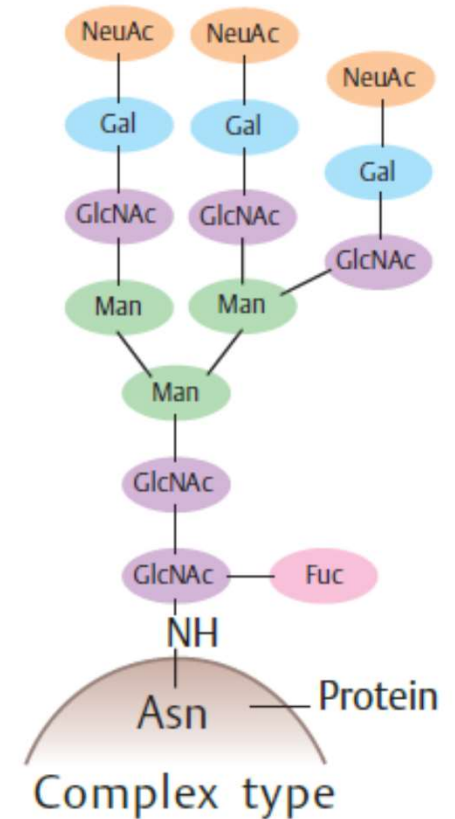
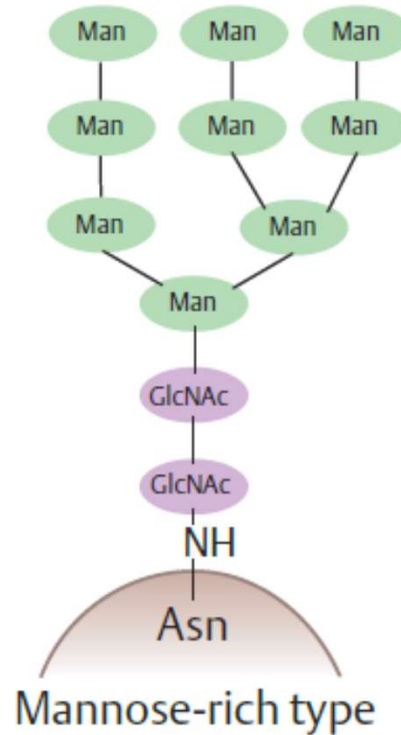
# Sugars

## C. Glycoproteins: forms

O-linked

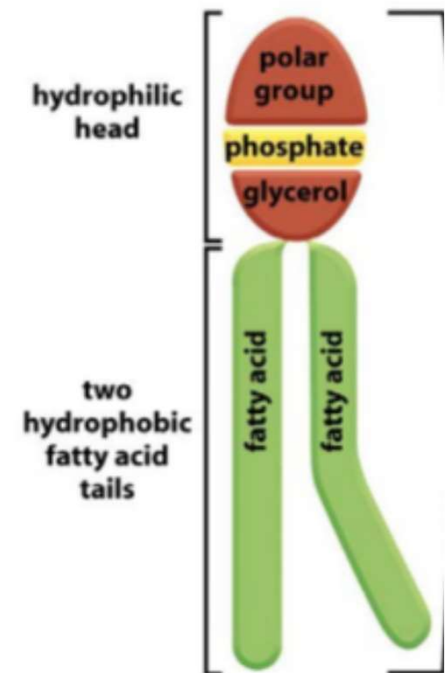
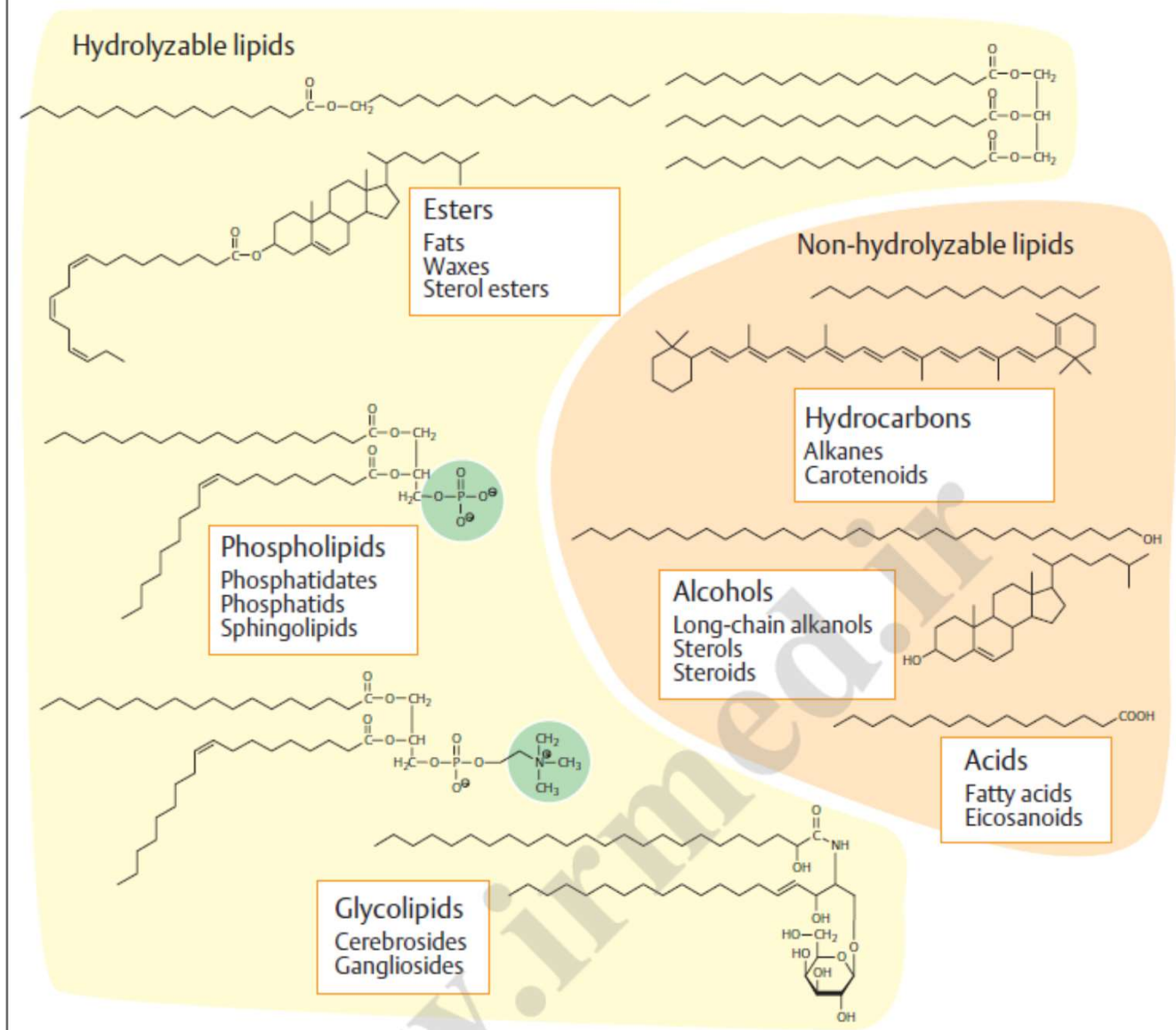


N-linked



# Lipids

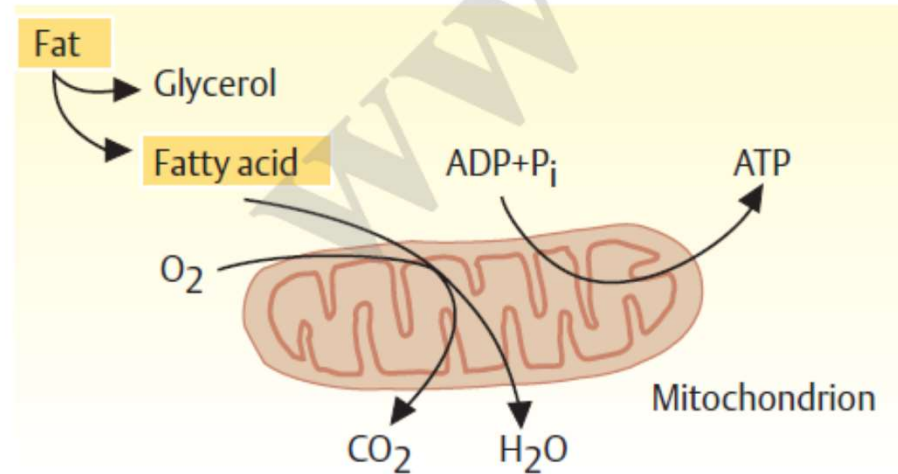
## A. Classification



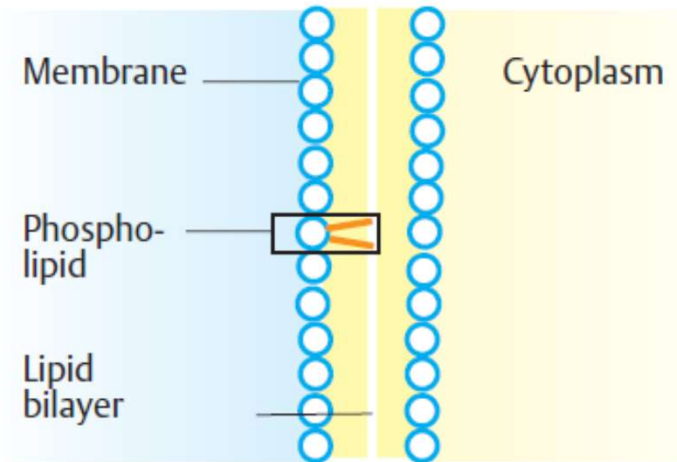


# Lipids

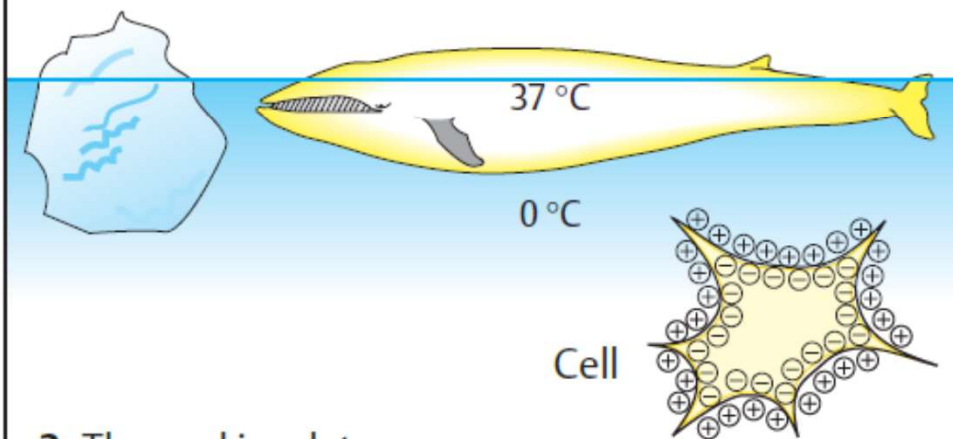
## B. Biological roles



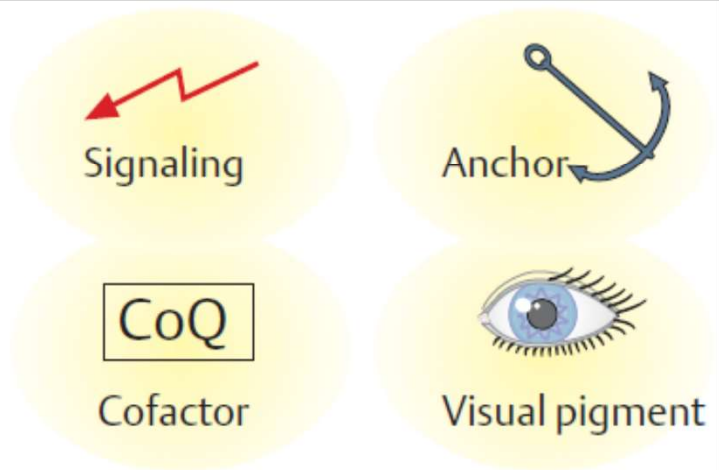
### 1. Fuel



### 2. Building block



### 3. Thermal insulator



### 4. Special tasks



# Lipids

## A. Carboxylic acids

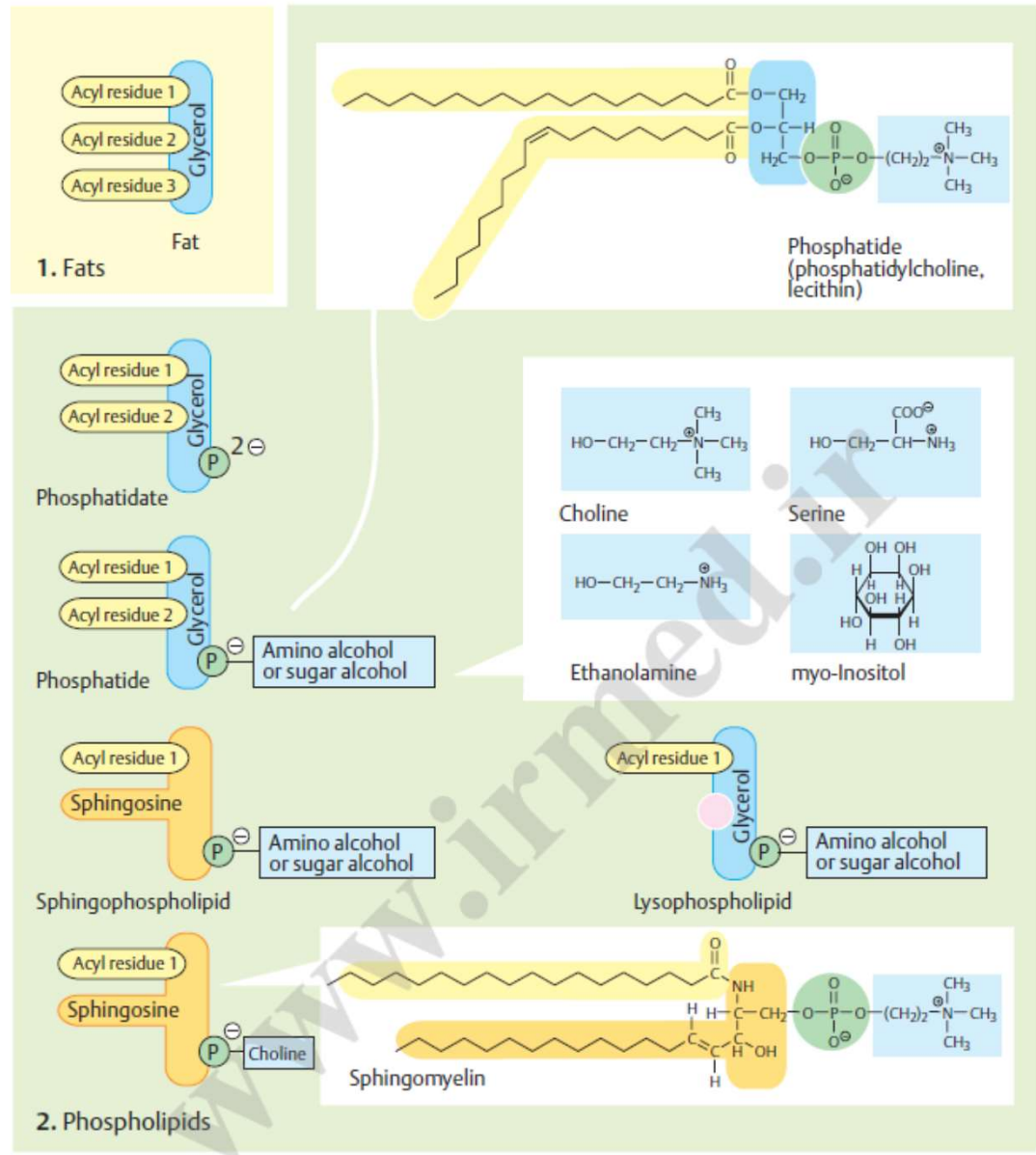
*Fatty acids*

Name	Number of carbons	Number of double bonds Position of double bonds	
Formic acid	1 : 0	●	Not contained in lipids
Acetic acid	2 : 0	●	
Propionic acid	3 : 0	●	
Butyric acid	4 : 0	●	
Valerianic acid	5 : 0	●	
Caproic acid	6 : 0	●	<chem>HOOC-CH2-CH2-CH2-CH2-CH3</chem>
Caprylic acid	8 : 0	●	Caproic acid
Capric acid	10 : 0	●	
Lauric acid	12 : 0	●	
Myristic acid	14 : 0	●	
Palmitic acid	16 : 0	●	
Stearic acid	18 : 0	●	
Oleic acid	18 : 1; 9	●	
★ Linoleic acid	18 : 2; 9,12	●	
★ Linolenic acid	18 : 3; 9,12,15	●	
Arachidic acid	20 : 0	●	
★ Arachidonic acid	20 : 4; 5,8,11,14	●	
Behenic acid	22 : 0	●	
Erucic acid	22 : 1; 13	●	
Lignoceric acid	24 : 0	●	
Nervonic acid	24 : 1; 15	●	

★ Essential in human nutrition

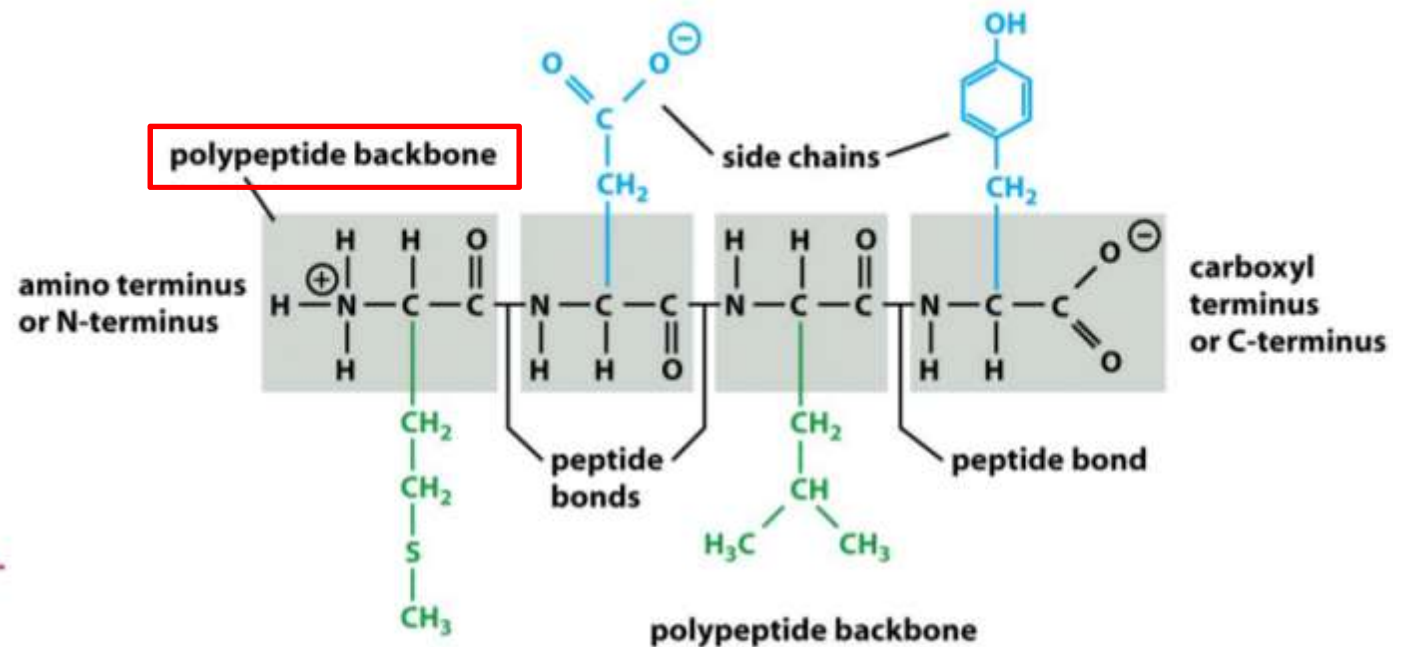
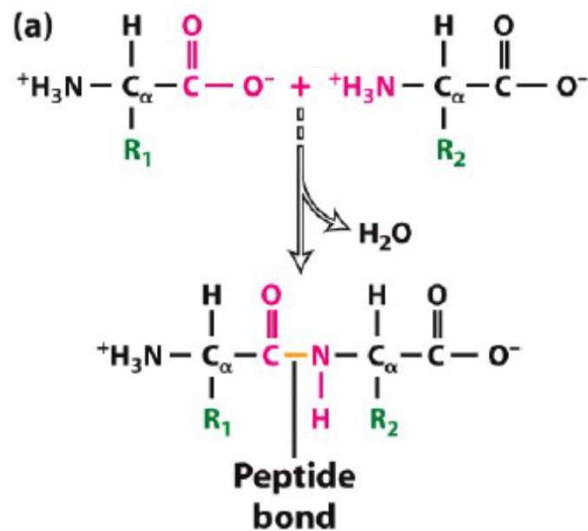
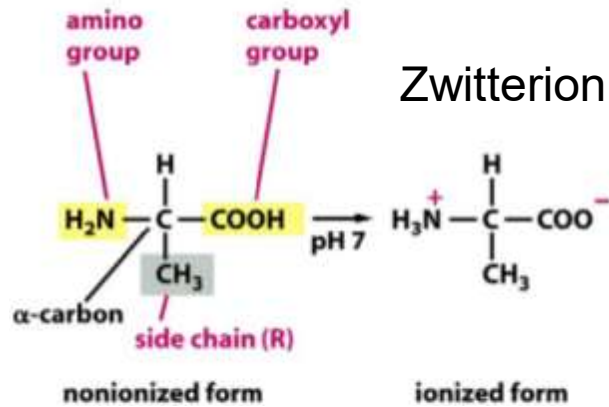
# Lipids

## A. Structure of fats, phospholipids, and glycolipids

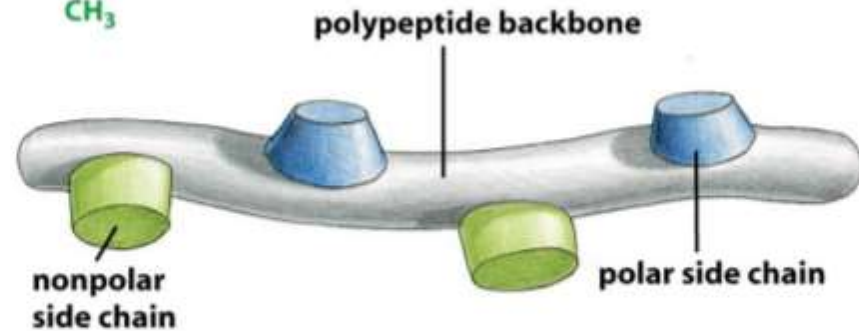


# Proteins

## Amino acid



## SCHEMATIC

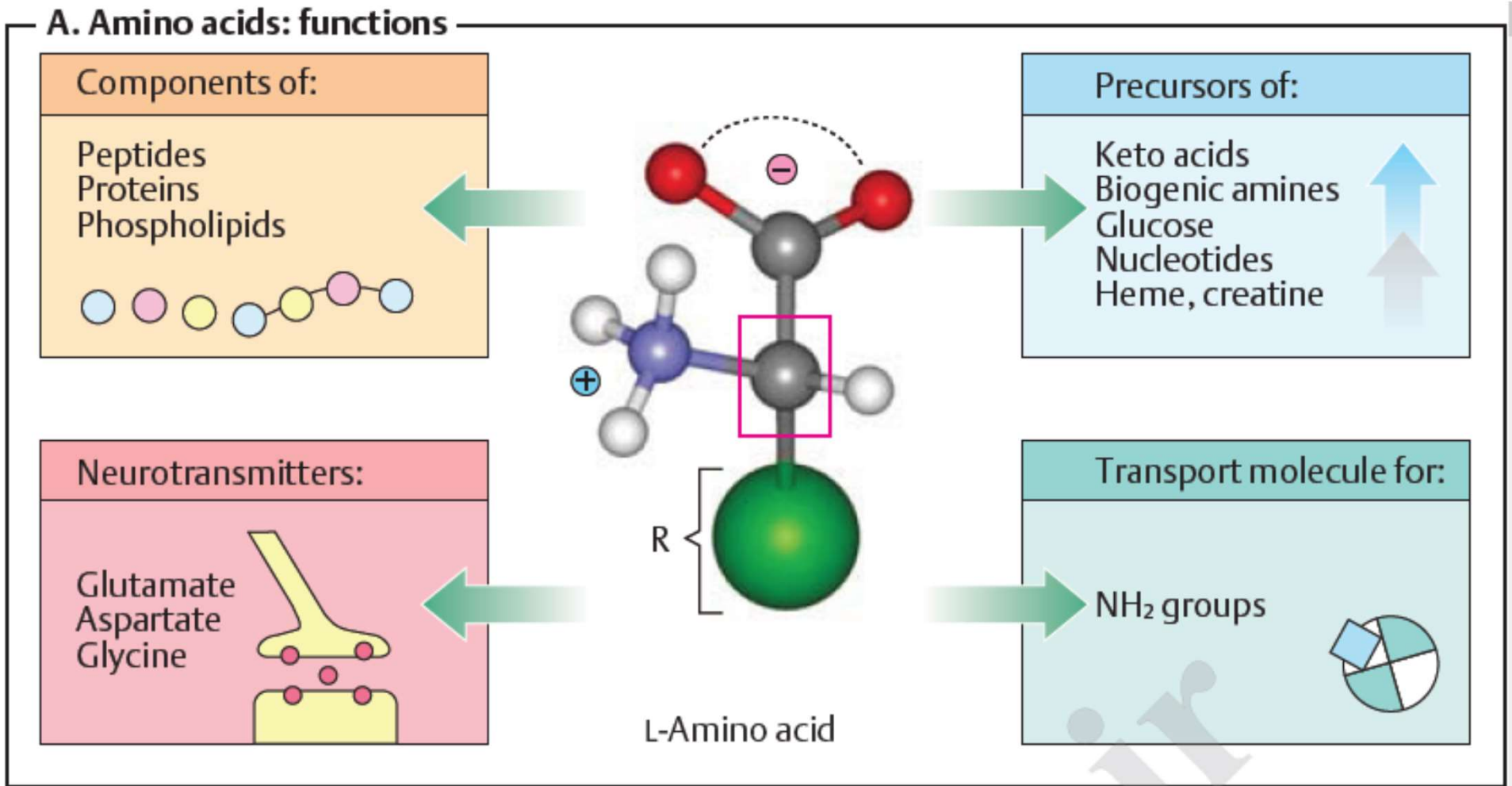


## SEQUENCE



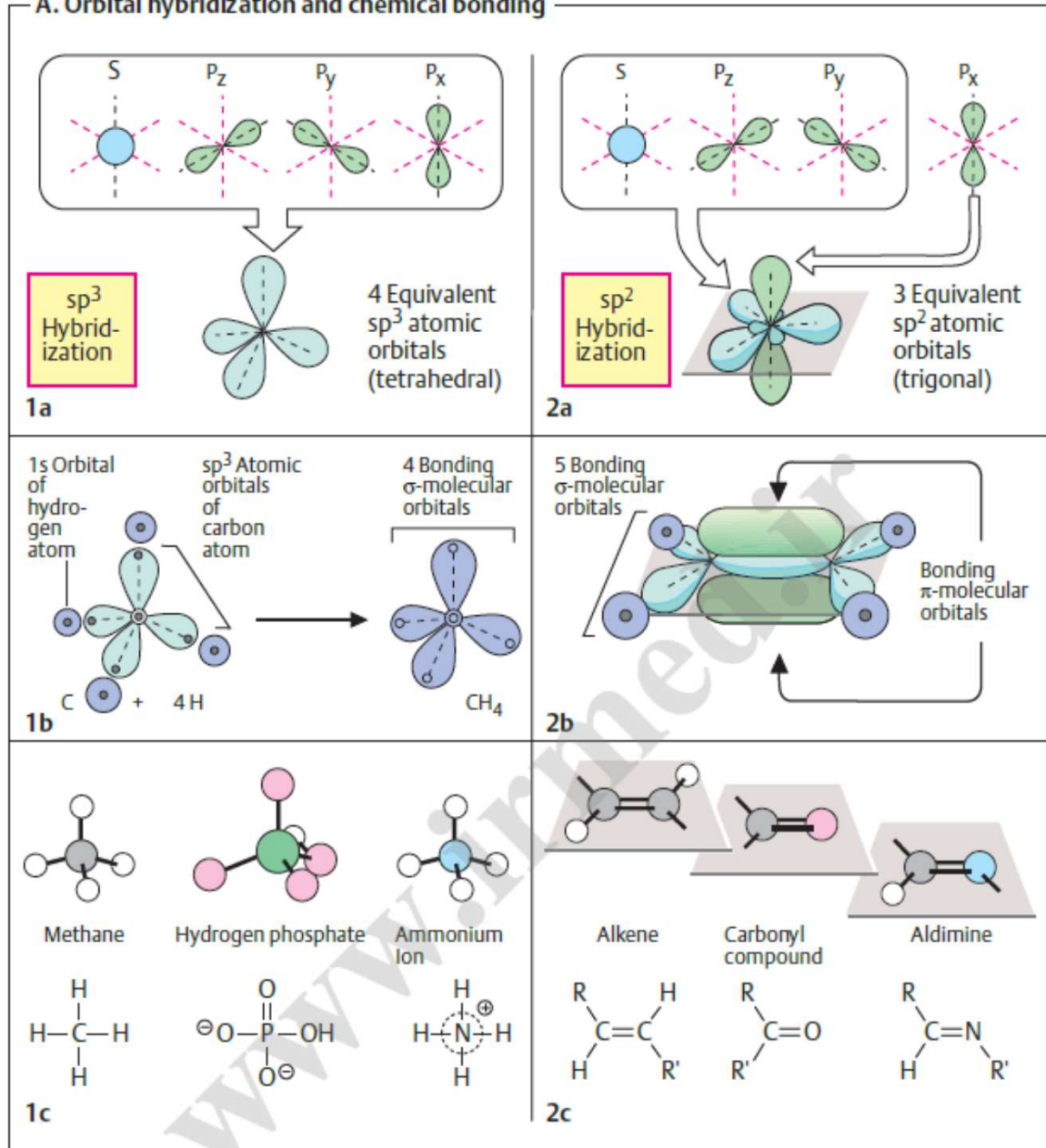
# Proteins

## A. Amino acids: functions



# Proteins

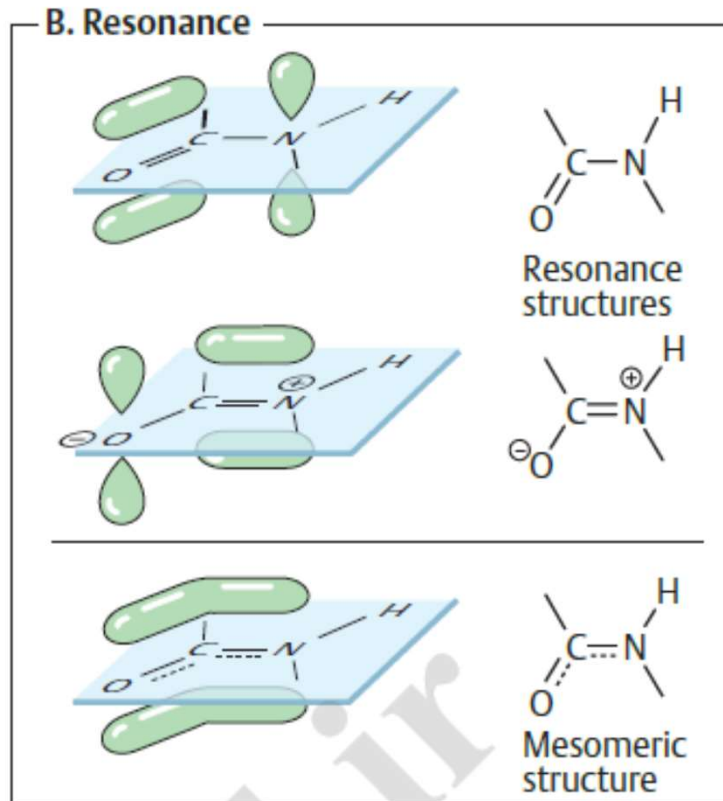
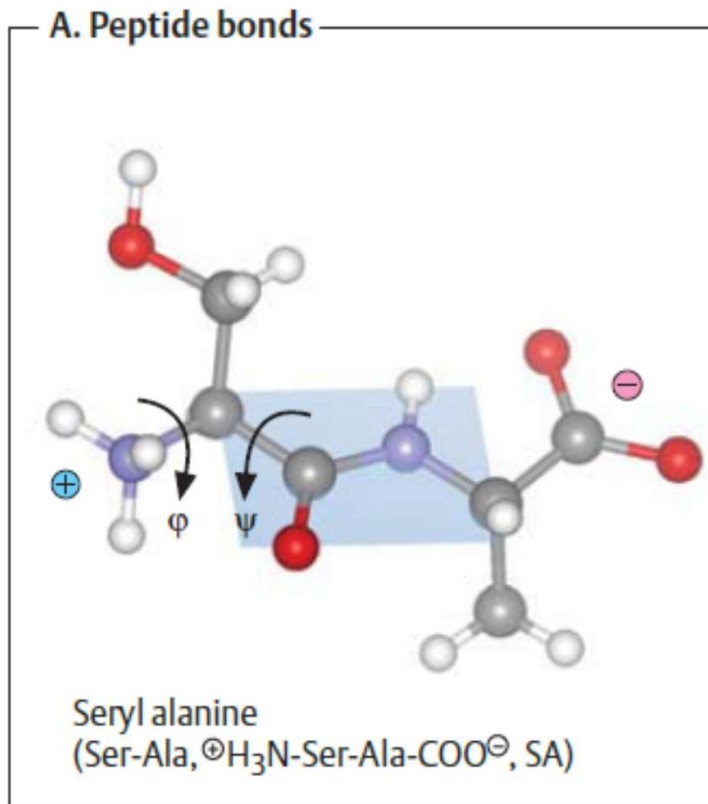
## A. Orbital hybridization and chemical bonding



*No rotation around double bonds!*



# Proteins



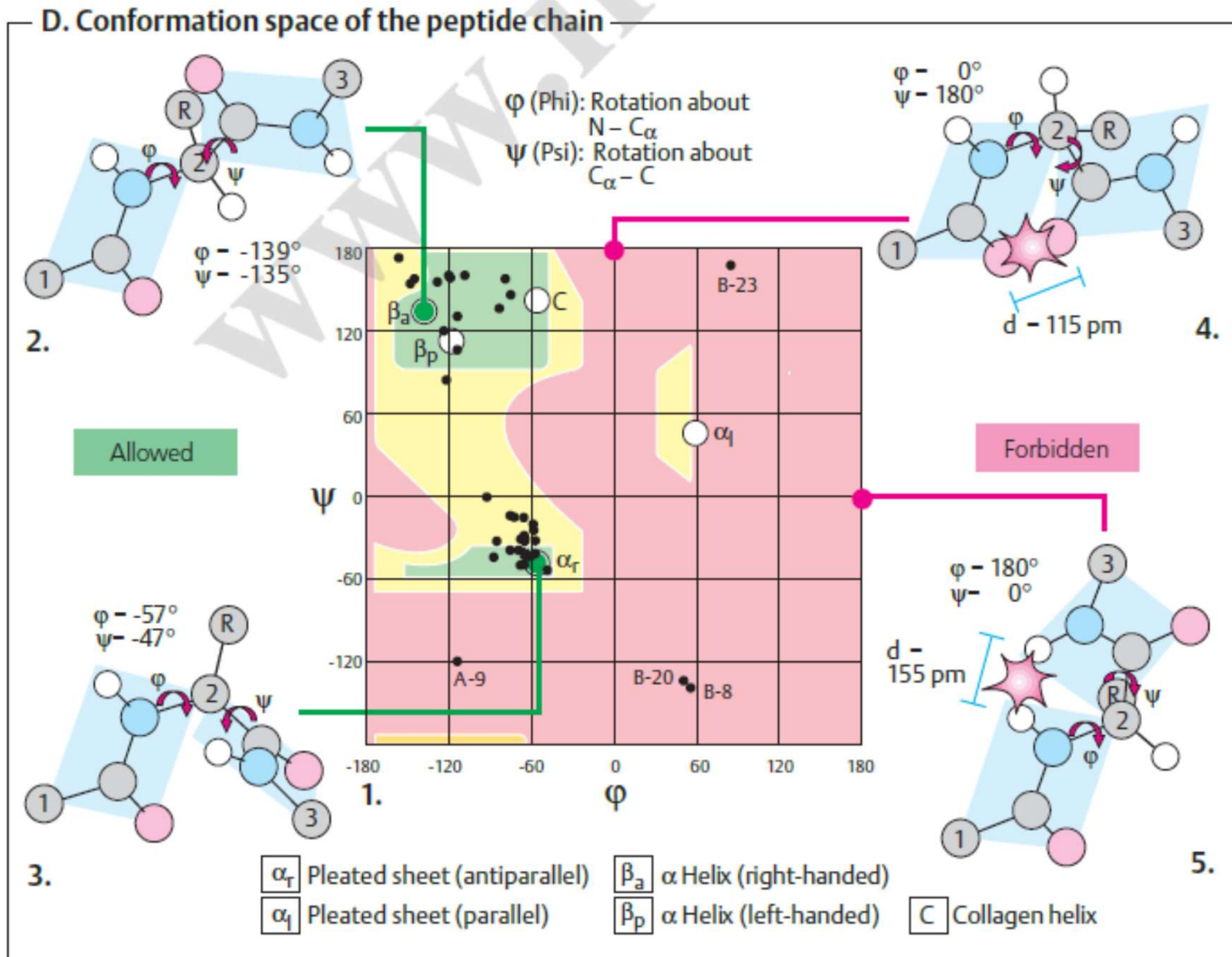
Cost of rotation  
is 90kJ/mol.  
Compare to  
2.5kJ/mol of  
thermal energy  
at 300K

*No rotation around C-N or O-C bonds.*

*The peptide bond is planar and rigid!*

*Phi/Psi angles are the only real degrees of freedom of the protein backbone*

# Ramachandran plot



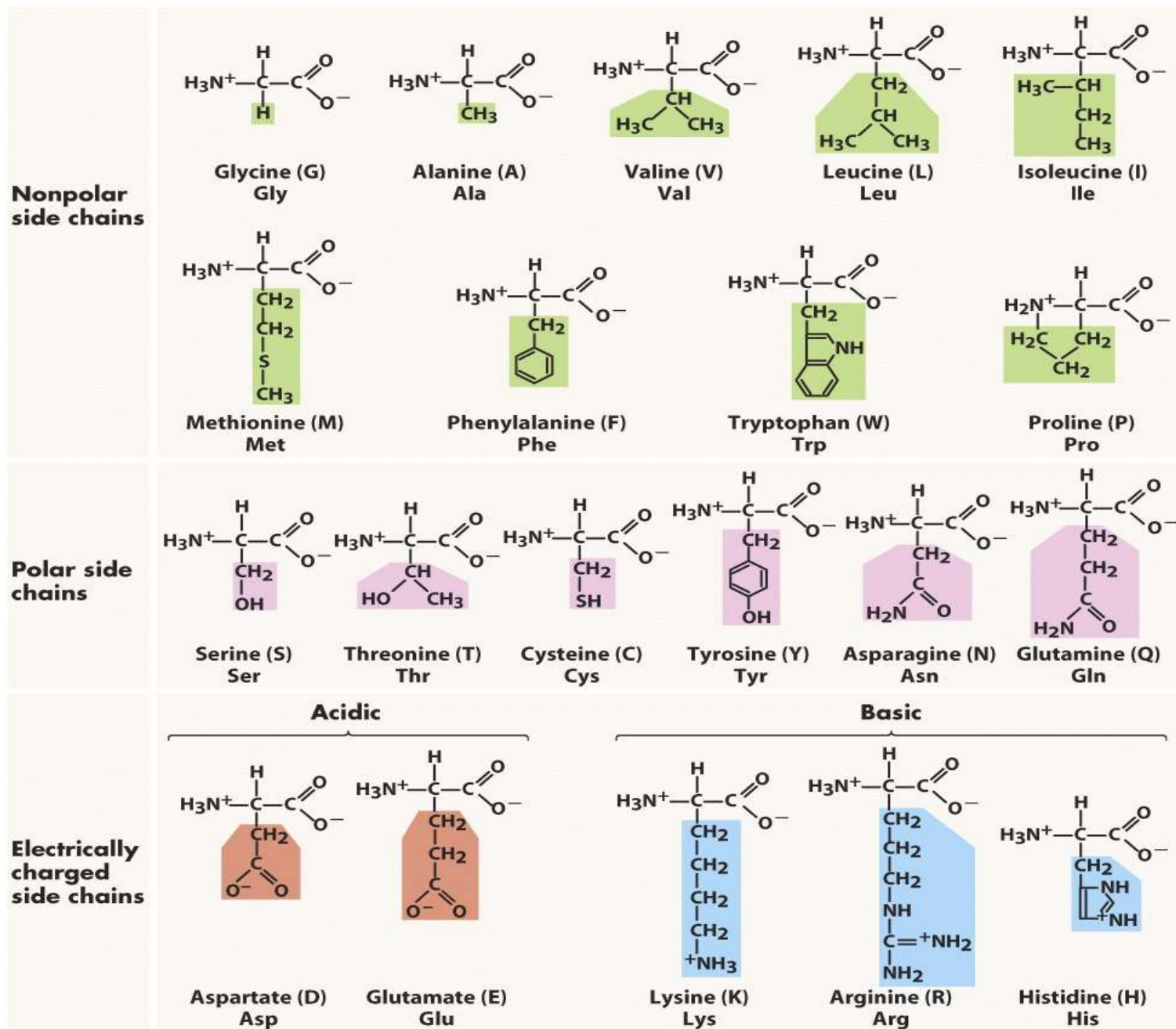
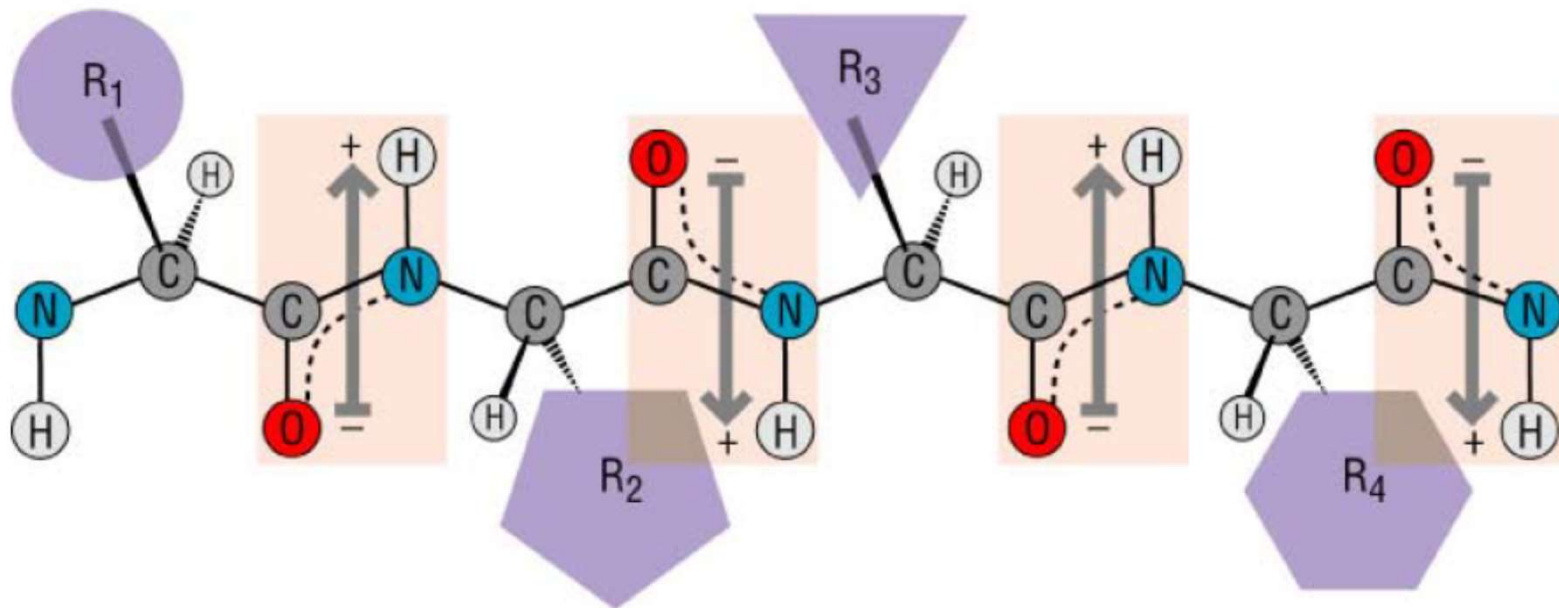


Figure 3-5 Biological Science, 2/e

© 2005 Pearson Prentice Hall, Inc.

# Primary structure



...-ASP-ALA-VAL-ILE-ASP-SER-GLU-PRO-THR-...

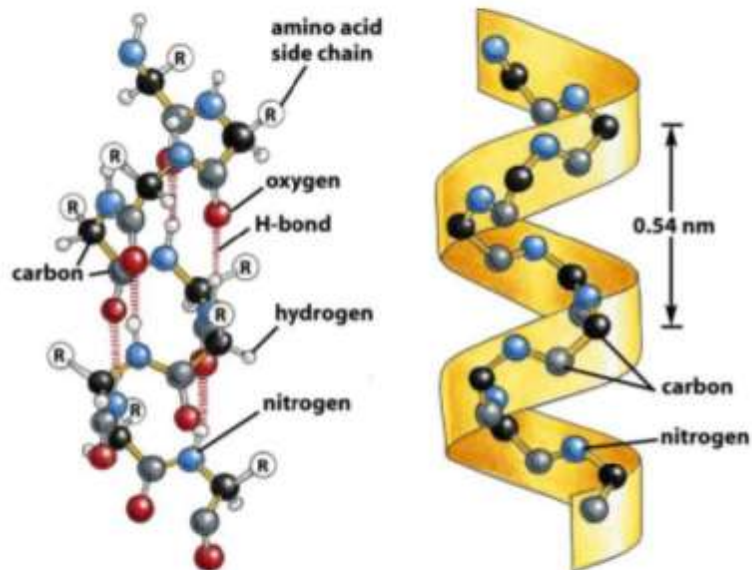
...DAVIDSEPT...



# Secondary structure

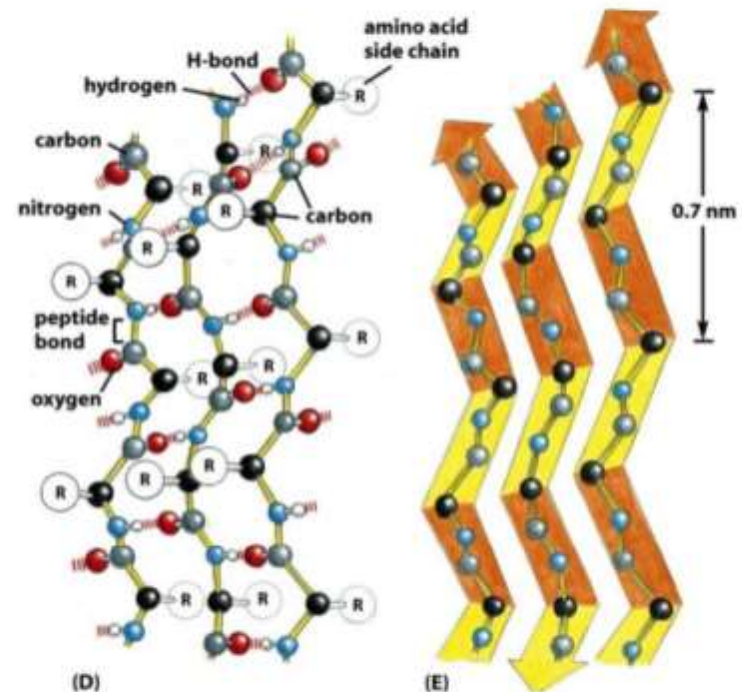
H- bonding between N-H and C=O groups without involving side chains.

## Alpha Helix



C=O of one residue bond to N-H of the fourth residue  
3.6 amino acid residues per turn.  
Helical pitch is 0.54 nm.

## Beta Sheet



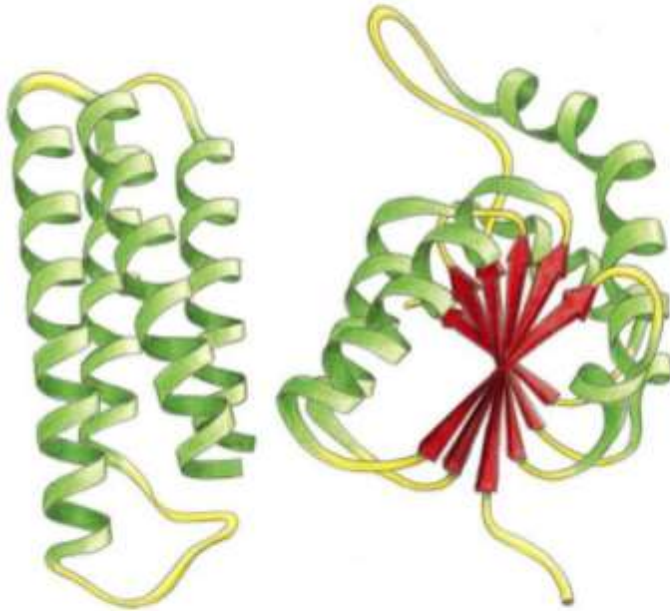
C=O of one residue bond to N-H of a residue on another strand  
0.48 nm between strands  
0.35 nm per residue



# Tertiary structure

- Helices and sheets often combine in various ways.
- Certain combinations of  $\alpha$  and  $\beta$  repeat over and over, called MOTIFS

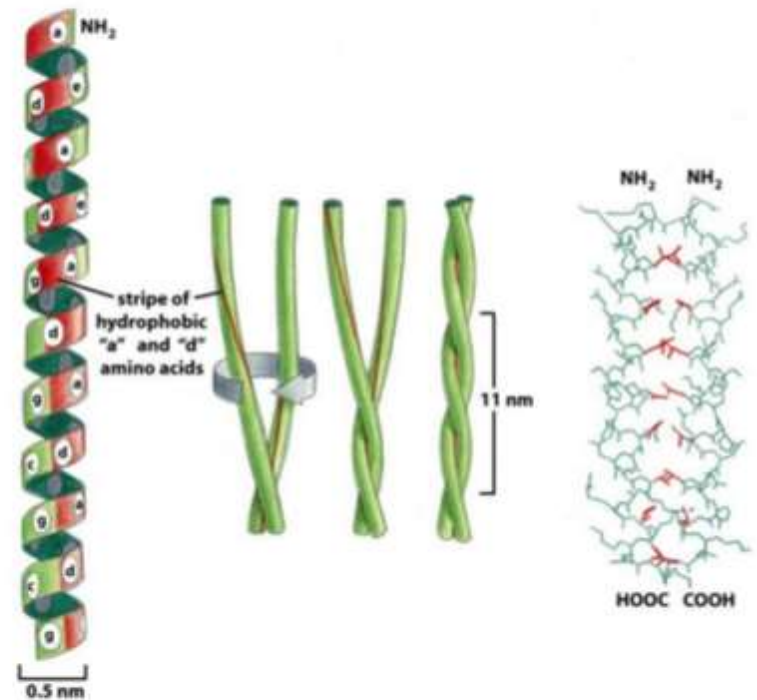
Four Helix Bundle



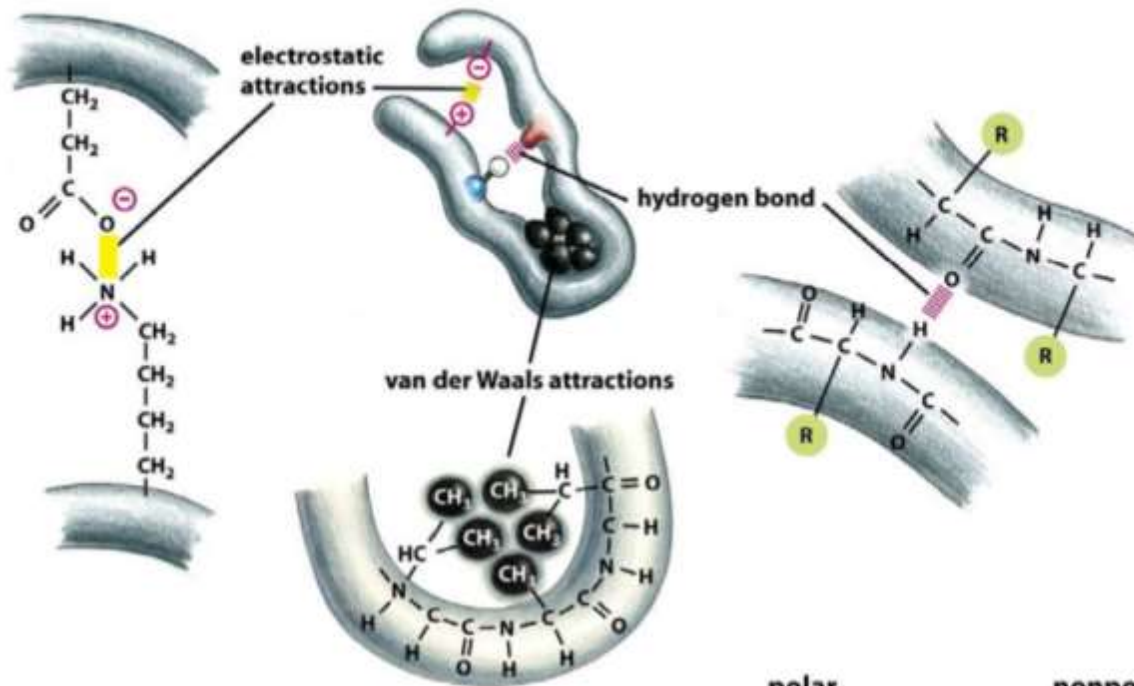
Beta Barrel



Coiled Coil



# Protein folding

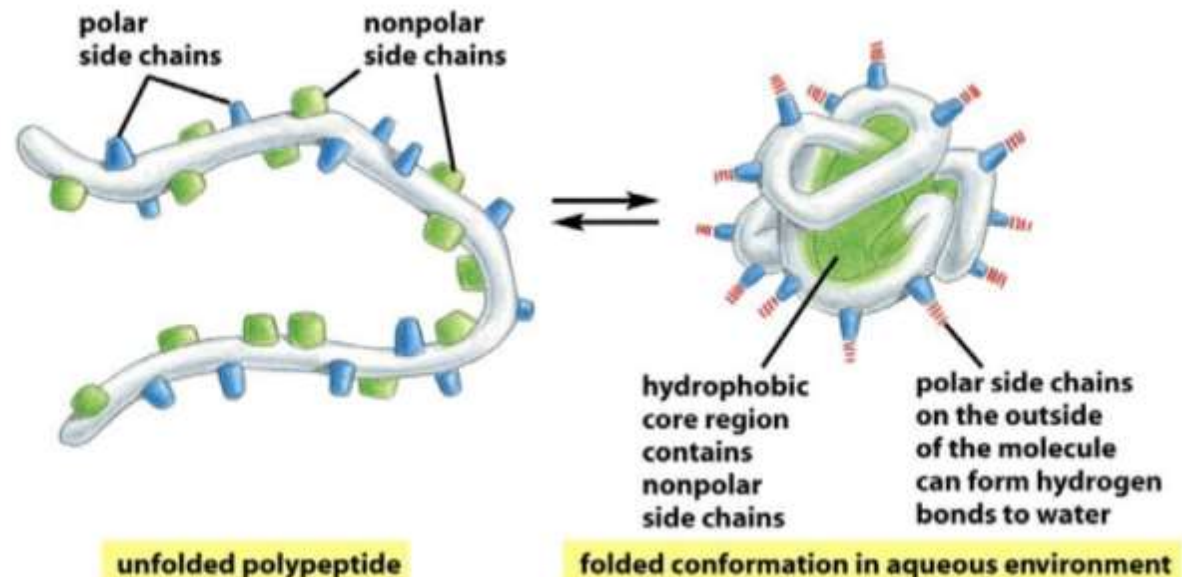


Driven by noncovalent bond formation and hydrophobic effect

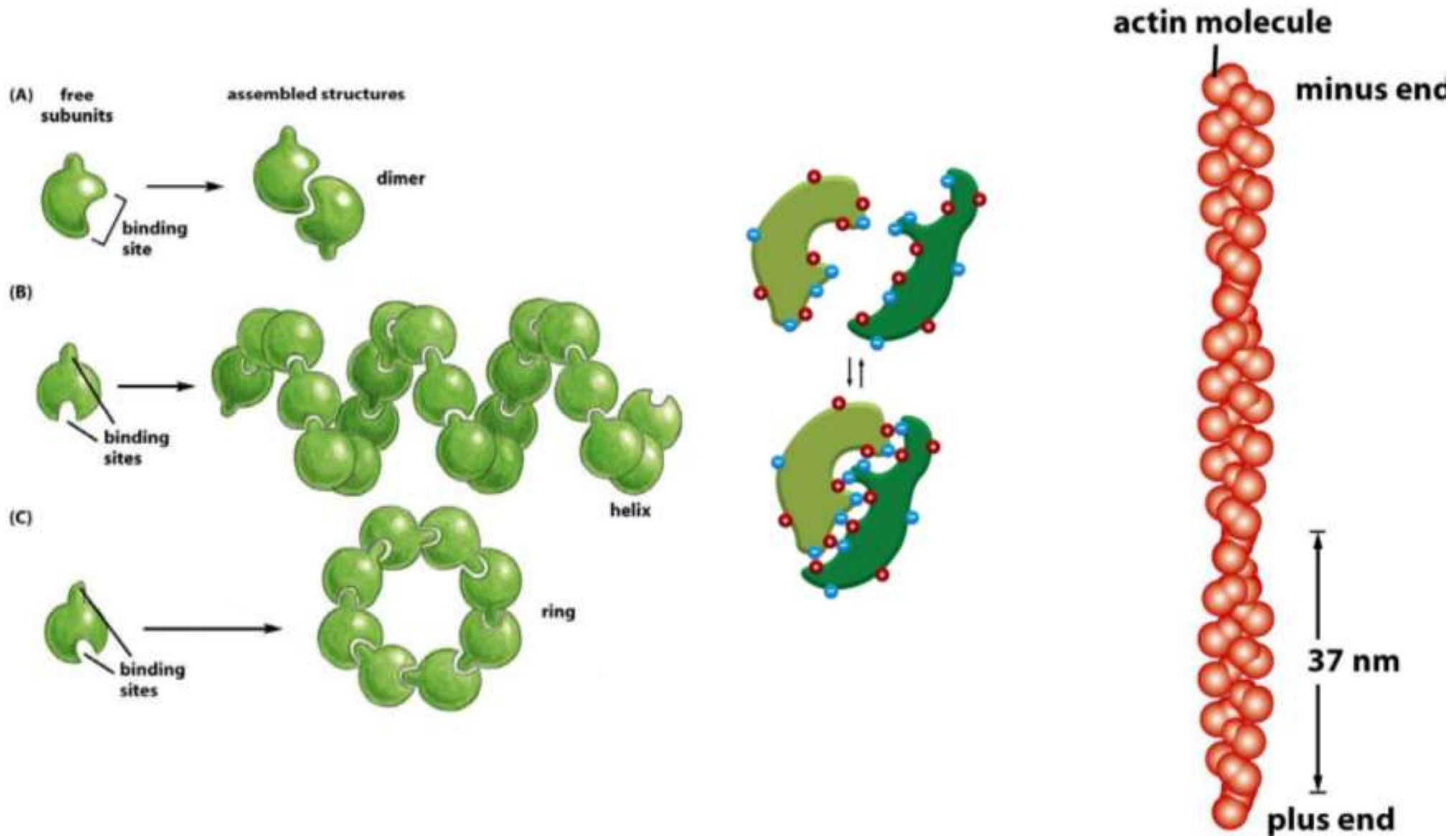
Folded state is the energetically stable state, spontaneously occurring in water.

3D shape of a protein is determined by its amino acid sequence.

Baumketner, BioSim, Lviv 2019



# Interactions between proteins

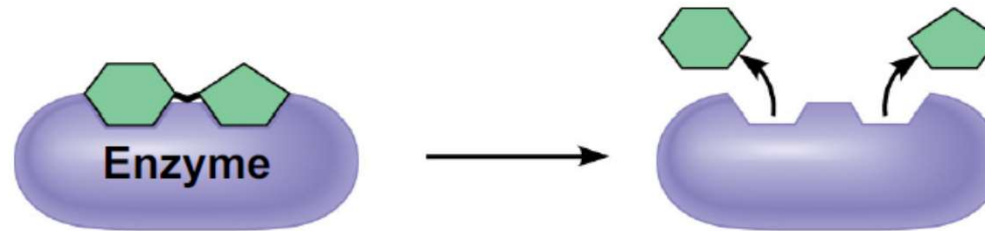


# Function of proteins

## Enzymatic proteins

Function: Selective acceleration of chemical reactions

Example: Digestive enzymes catalyze the hydrolysis of bonds in food molecules.



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- **Enzymes** are a type of protein that acts as a **catalyst** to speed up chemical reactions
- Enzymes can perform their functions repeatedly, functioning as workhorses that carry out the processes of life
- <http://www.biotopics.co.uk/other/morinf.html>

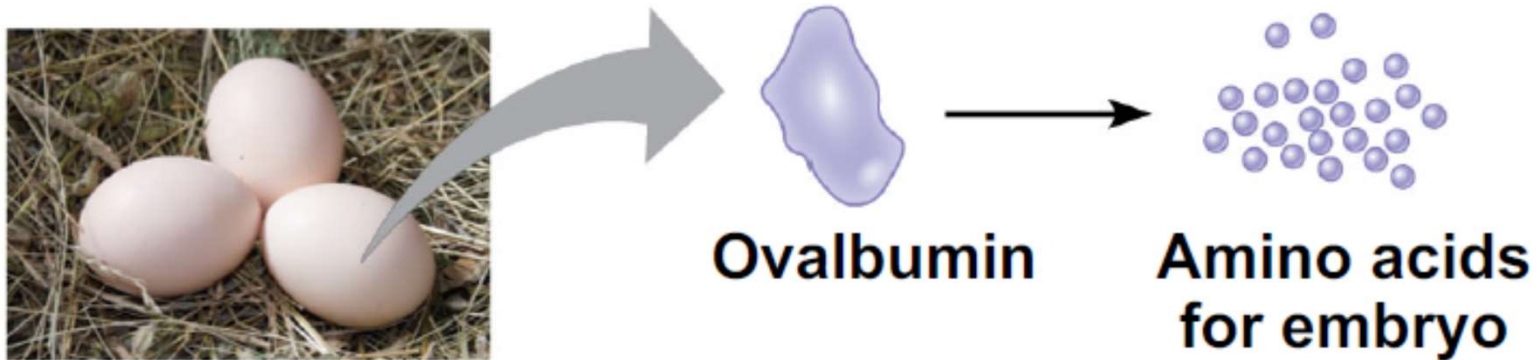


# Function of proteins

## Storage proteins

**Function:** Storage of amino acids

**Examples:** Casein, the protein of milk, is the major source of amino acids for baby mammals. Plants have storage proteins in their seeds. Ovalbumin is the protein of egg white, used as an amino acid source for the developing embryo.



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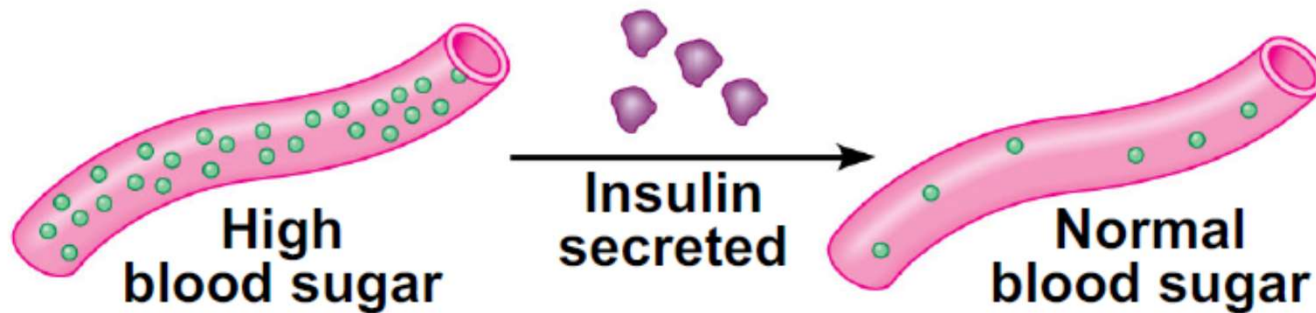


# Function of proteins

## Hormonal proteins

**Function:** Coordination of an organism's activities

**Example:** Insulin, a hormone secreted by the pancreas, causes other tissues to take up glucose, thus regulating blood sugar concentration



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Insulin protein entry:

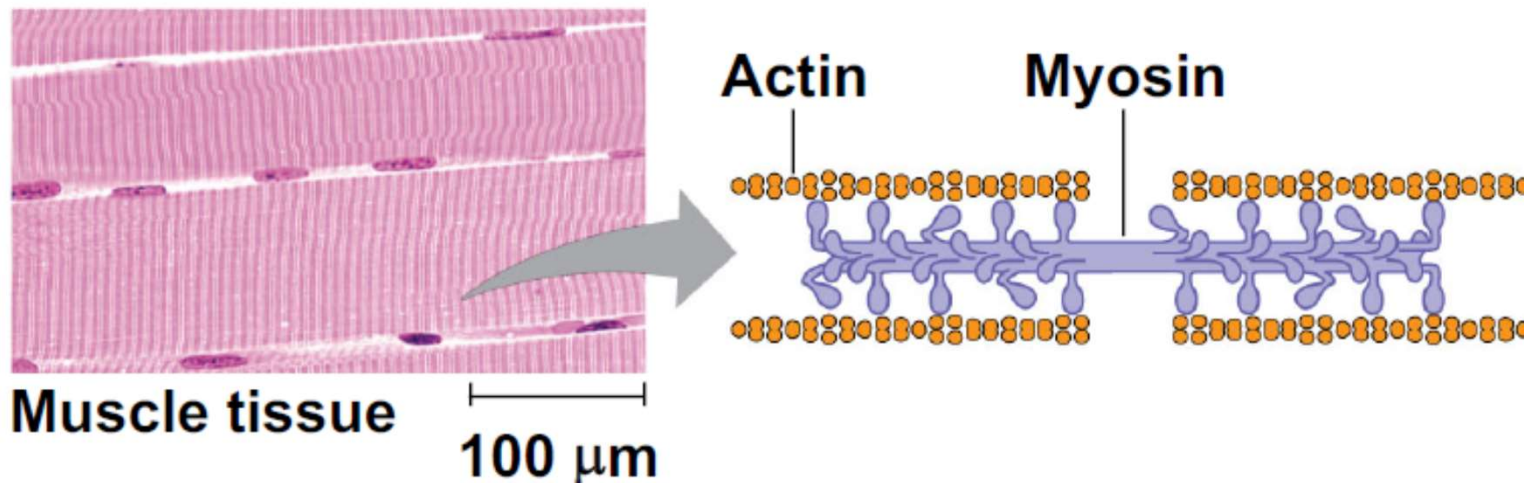
<https://www.ncbi.nlm.nih.gov/protein/AAA59172.1>

# Function of proteins

## Contractile and motor proteins

Function: Movement

Examples: Motor proteins are responsible for the undulations of cilia and flagella. Actin and myosin proteins are responsible for the contraction of muscles.

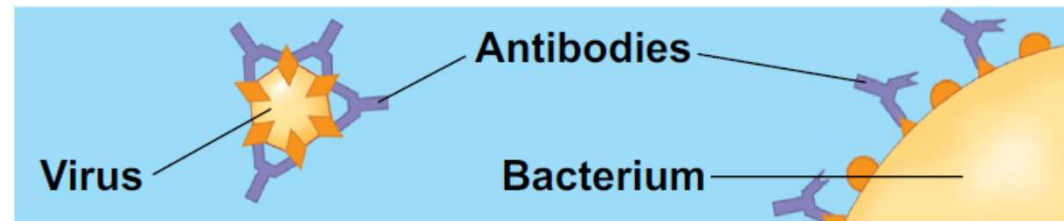


# Function of proteins

## Defensive proteins

**Function:** Protection against disease

**Example:** Antibodies inactivate and help destroy viruses and bacteria.



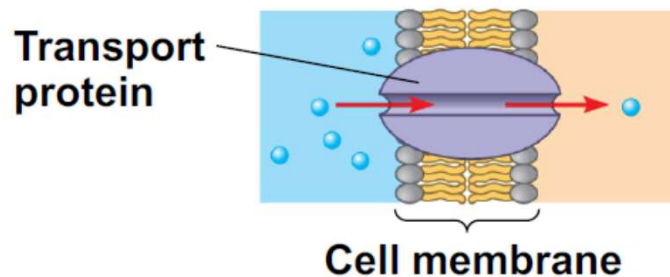
© 2011 Pearson Education, Inc.

Recognizes  
pathogen  
(antigen) via  
fragment  
antigen binding  
motif

## Transport proteins

**Function:** Transport of substances

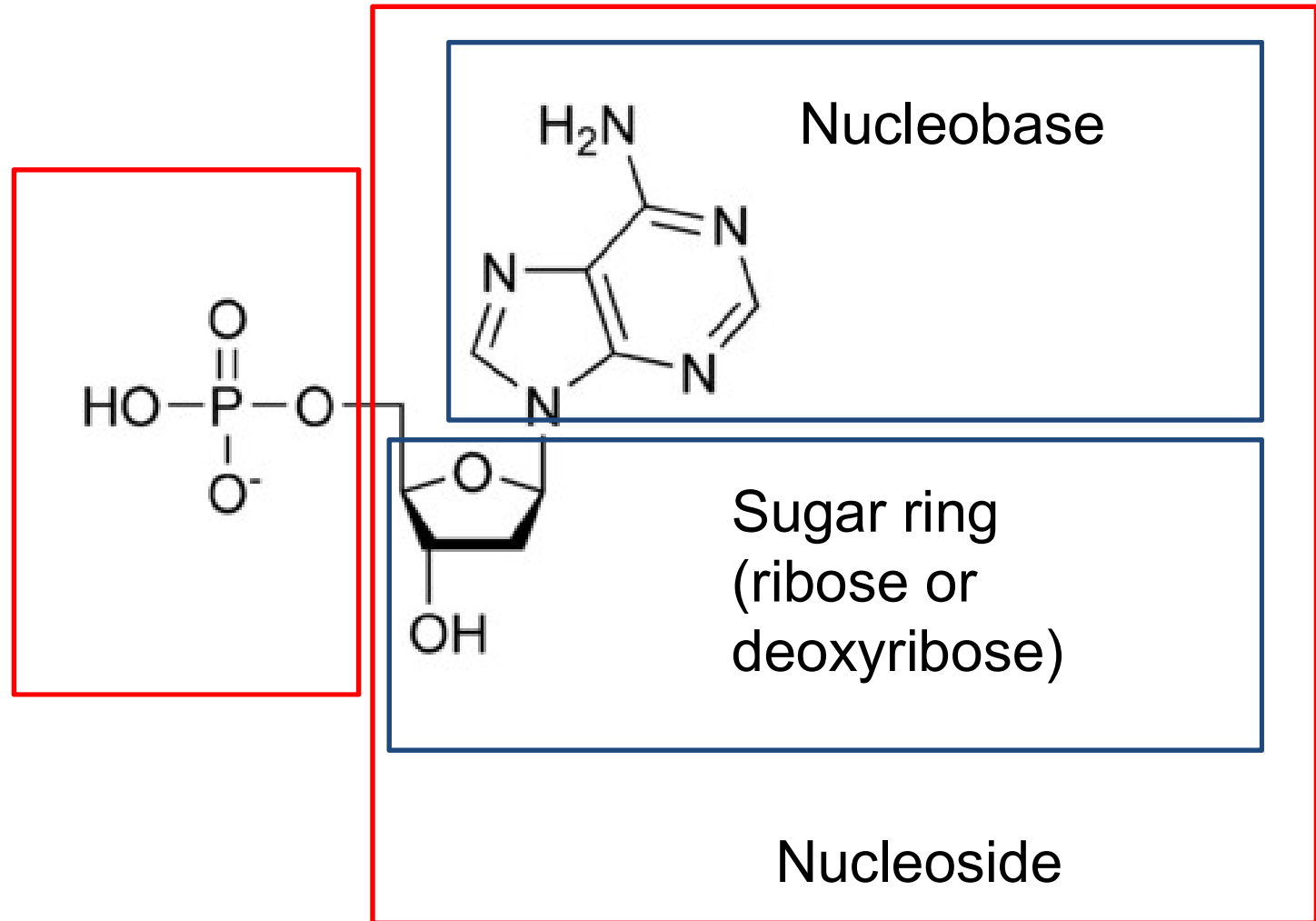
**Examples:** Hemoglobin, the iron-containing protein of vertebrate blood, transports oxygen from the lungs to other parts of the body. Other proteins transport molecules across cell membranes.



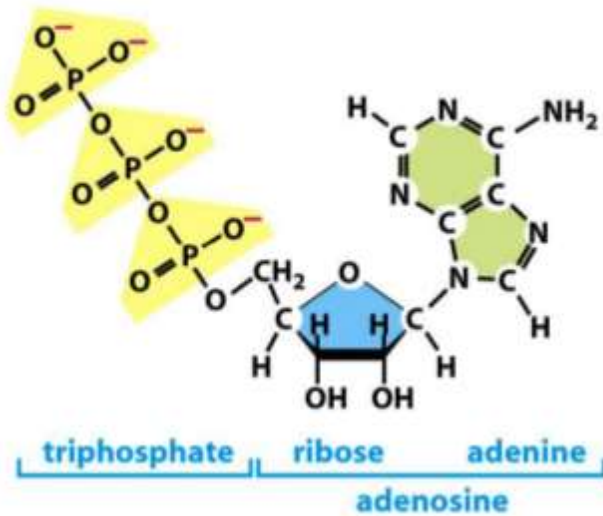
© 2011 Pearson Education, Inc.

# Nucleotides

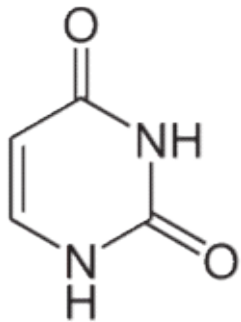
Phosphate



# Nucleic acids=poly-nucleotides



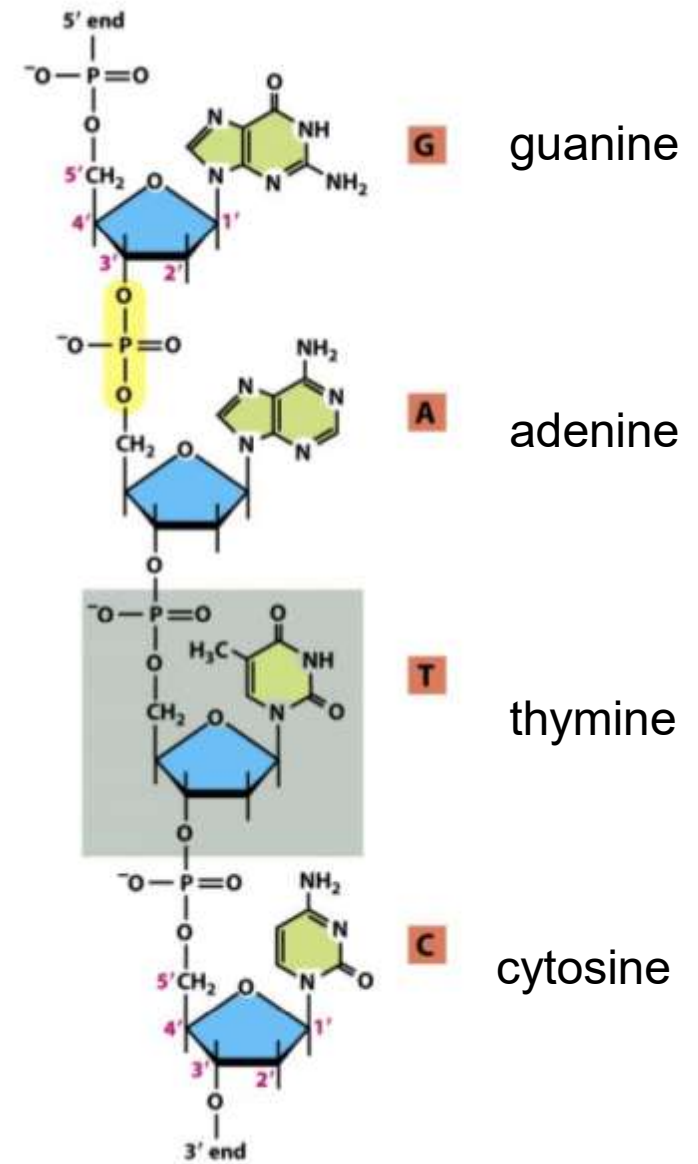
Uracil



Oligonucleotides (DNA, RNA)  
Cellular energy (ATP)

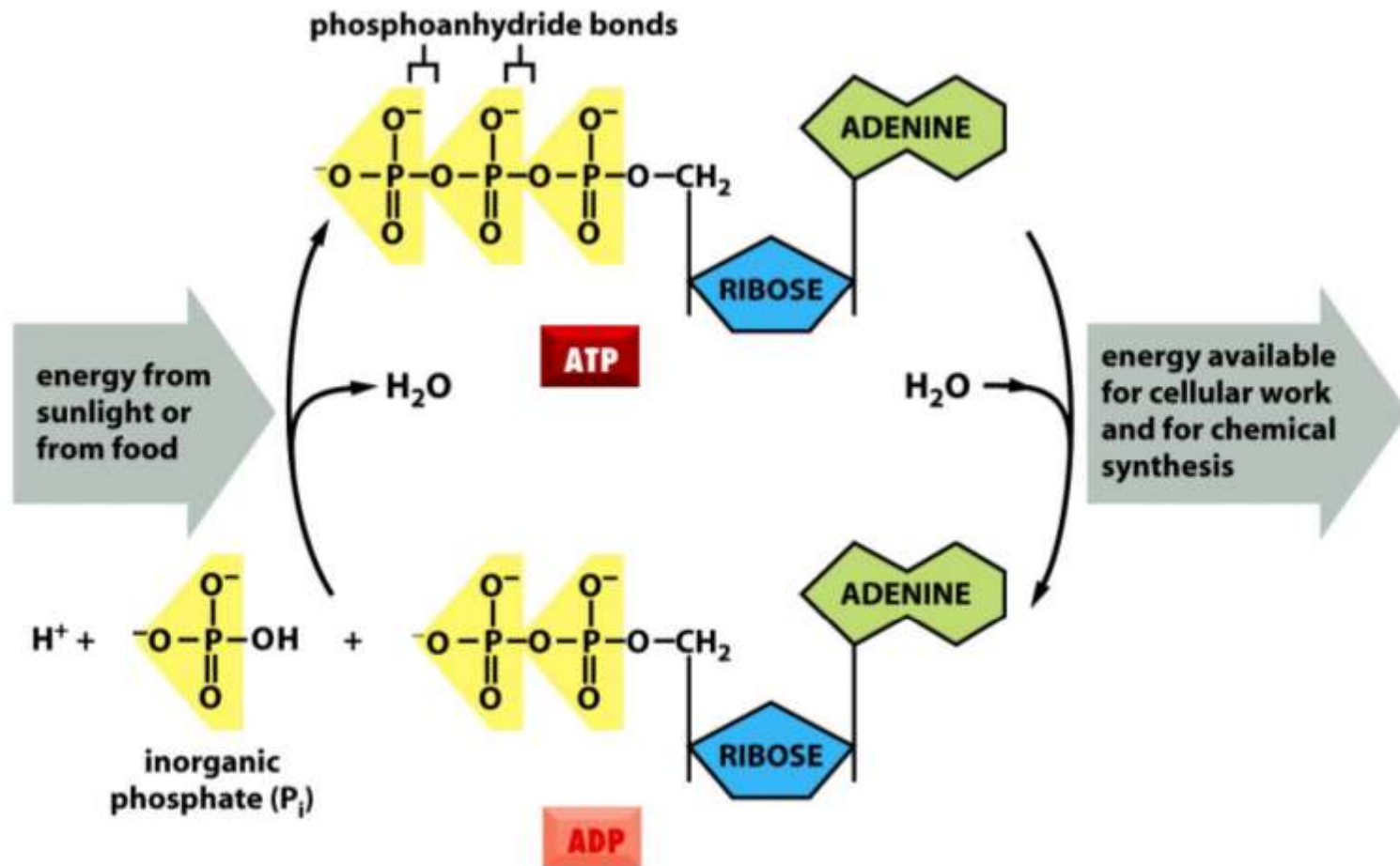
ACTGU – primary  
bases

{ ACGT - DNA  
ACGU - RNA





# ATP as energy source



# DNA structure

**AT** and **GC** pairings are possible due to HB geometry

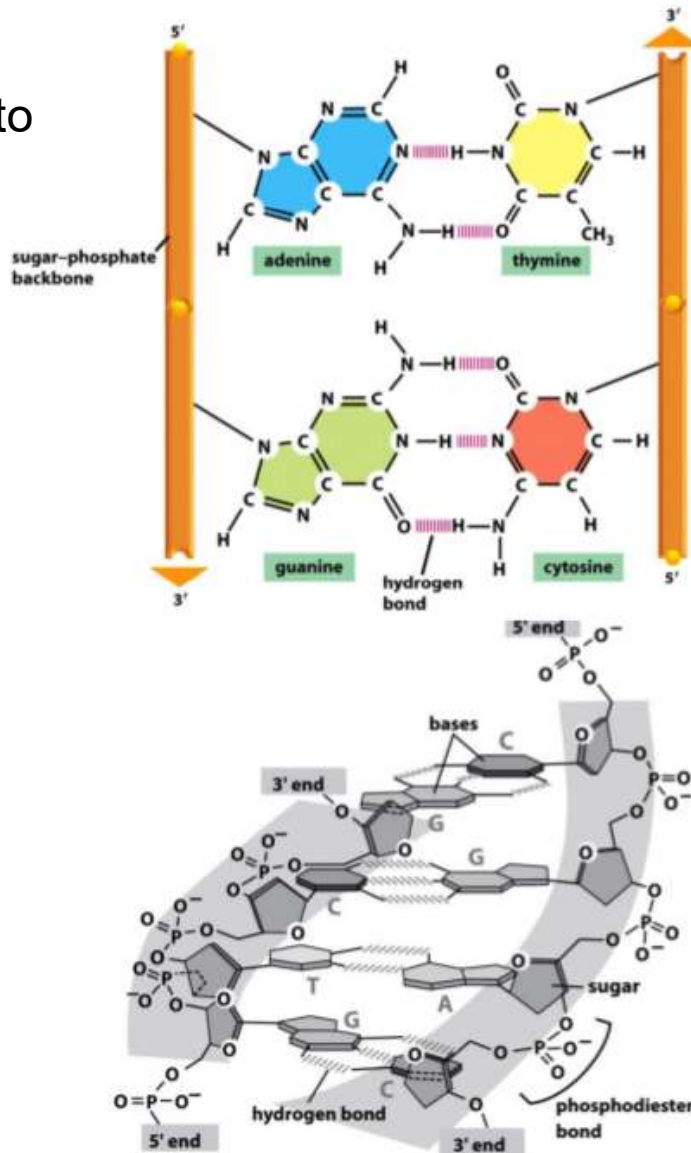
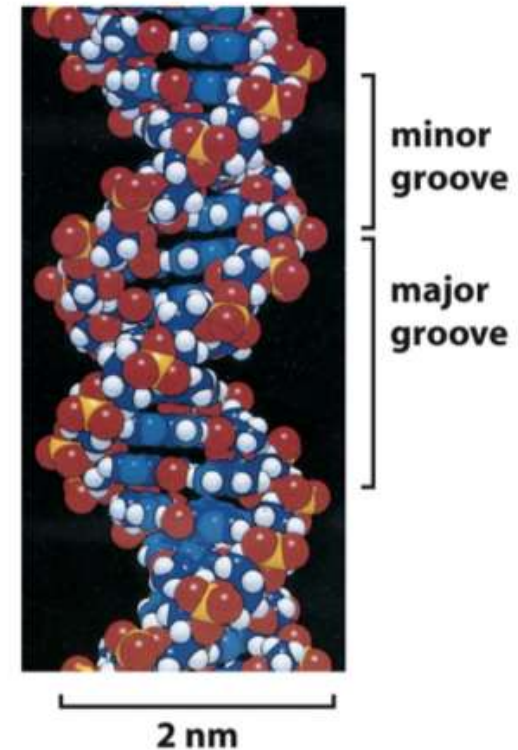


Figure 1.3b Physical Biology of the Cell (© Garland Science 2009)



- Forms a double helix.
- Each turn is made of 10 nucleotide pairs.
- 3.4 nm between adjacent nucleotide

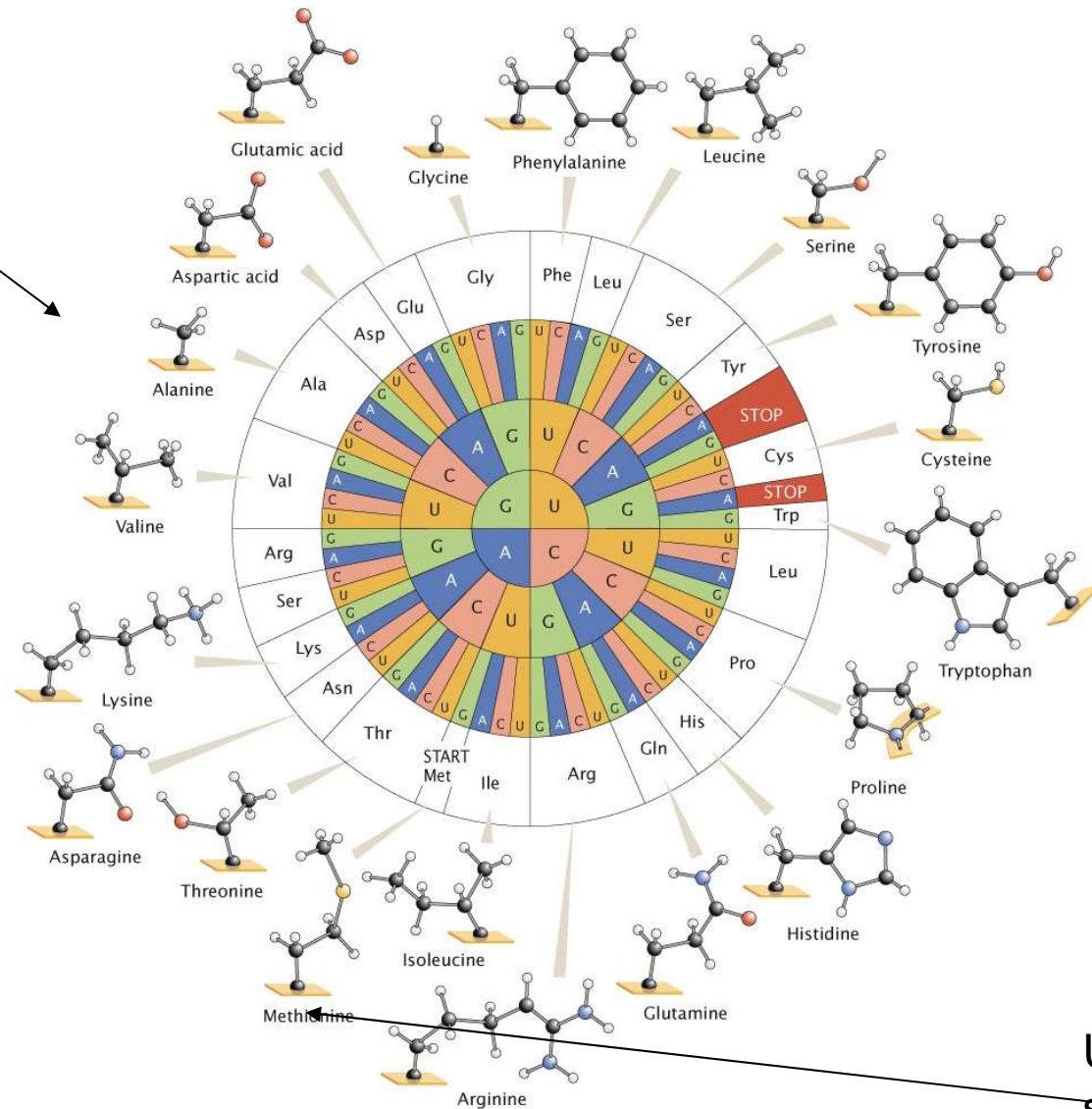
Play DNA packaging movie!

<http://www.youtube.com/watch?v=gbSIBhFwQ4s>

# Genetic code

Multiple codons  
for  
the same AA

Some codons  
are silent, or  
are they?



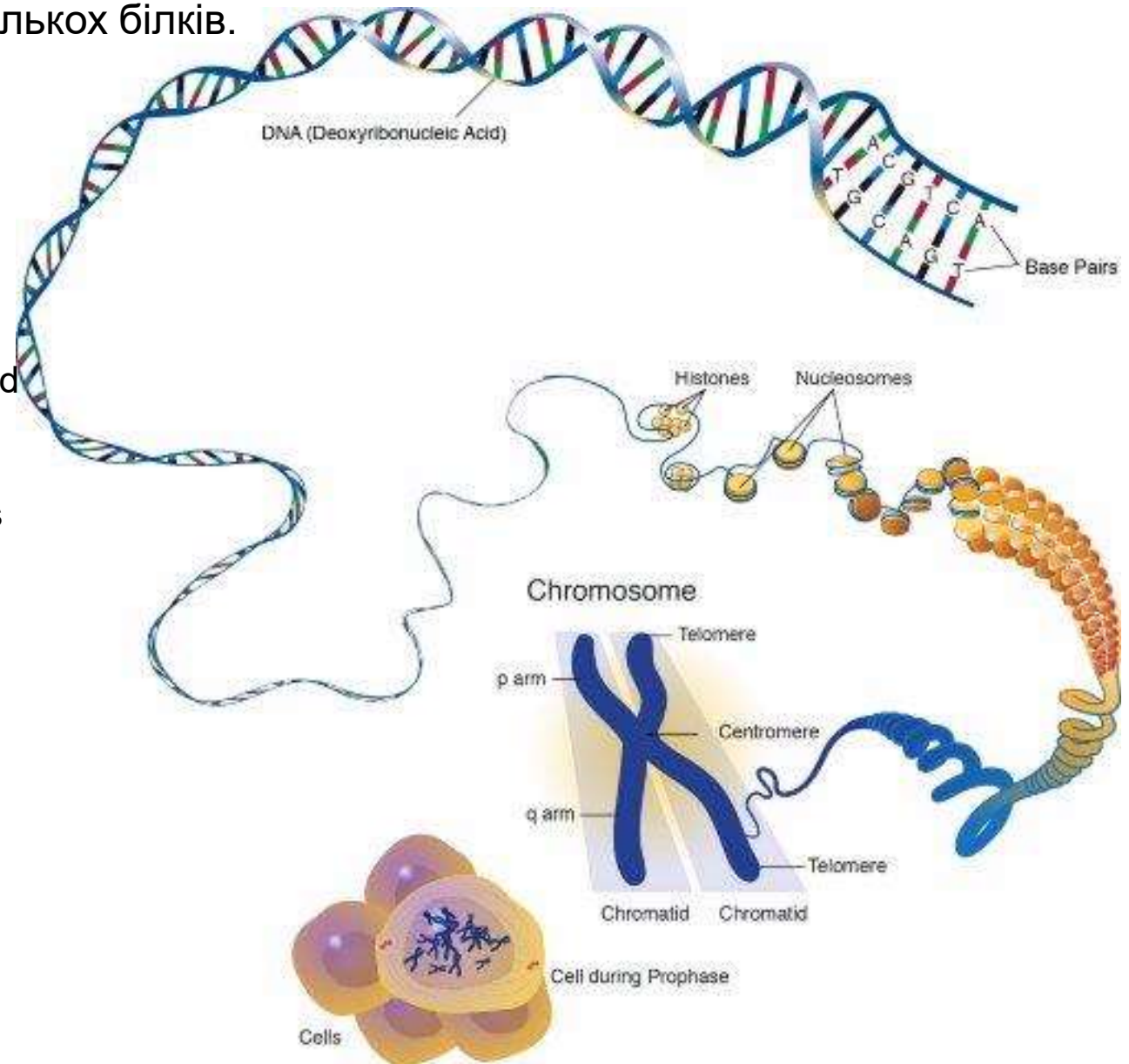
Unique  
sequences

Figure 1.4 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

# How is genetic information stored?

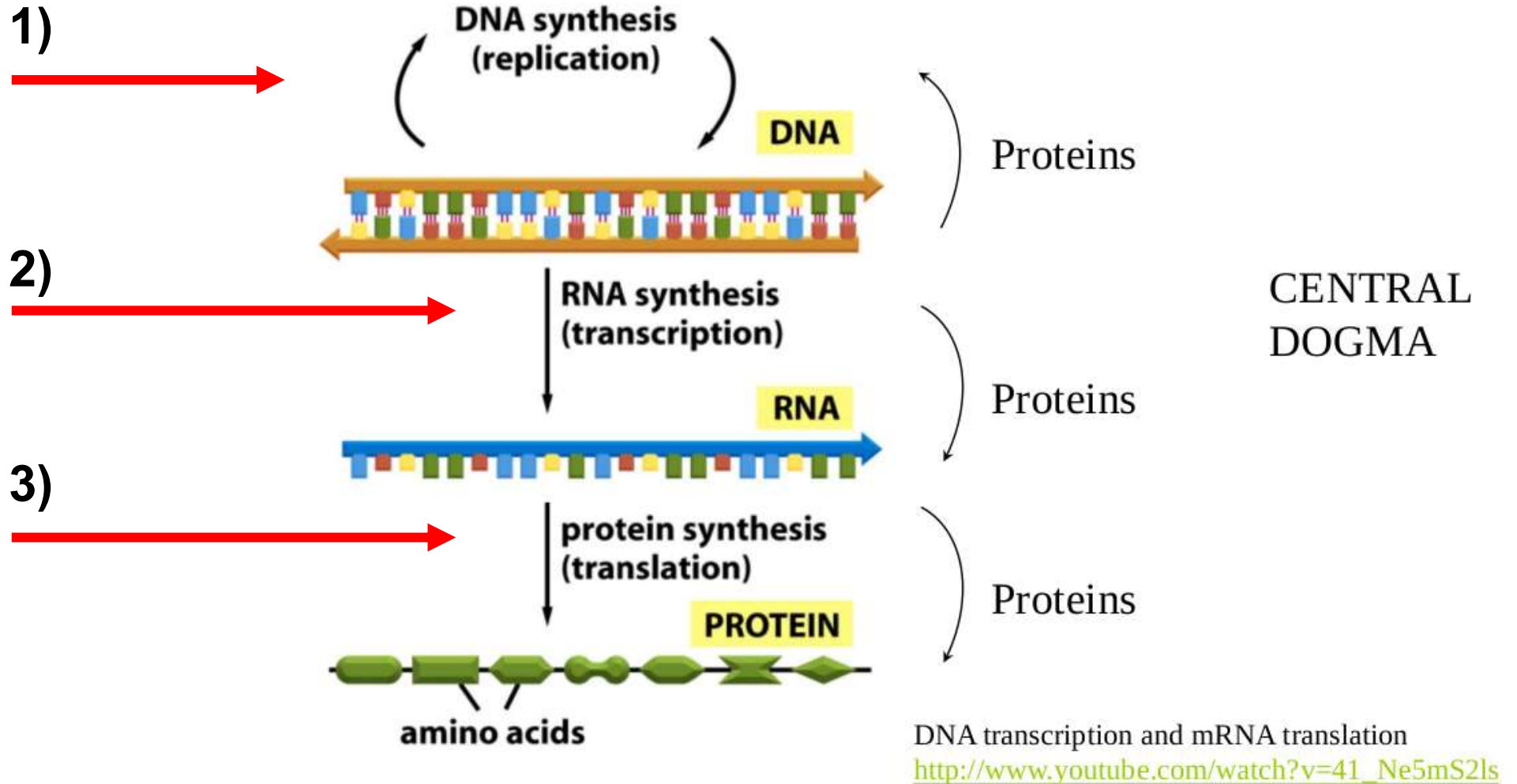
Ген – код для одного або декількох білків.

46 total chromosomes in each normal cell, grouped into 23 pairs, referred to by number  
Corresponding sets of maternal and paternal genes in each pair of chromosomes  
A specialized pair of chromosomes that determines a person's sex: females have two X chromosomes and males have one X and one Y.



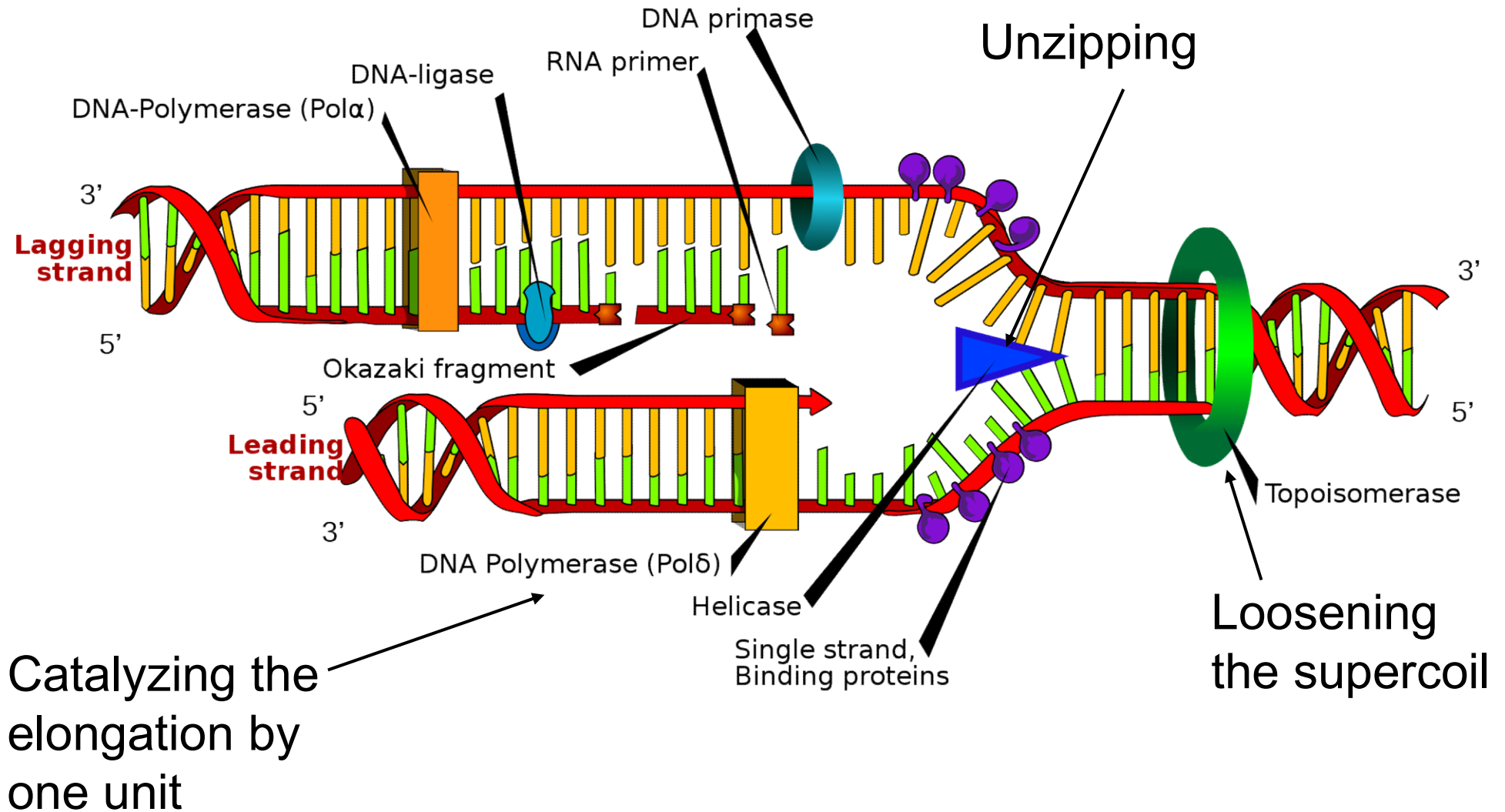


# Transcription + translation

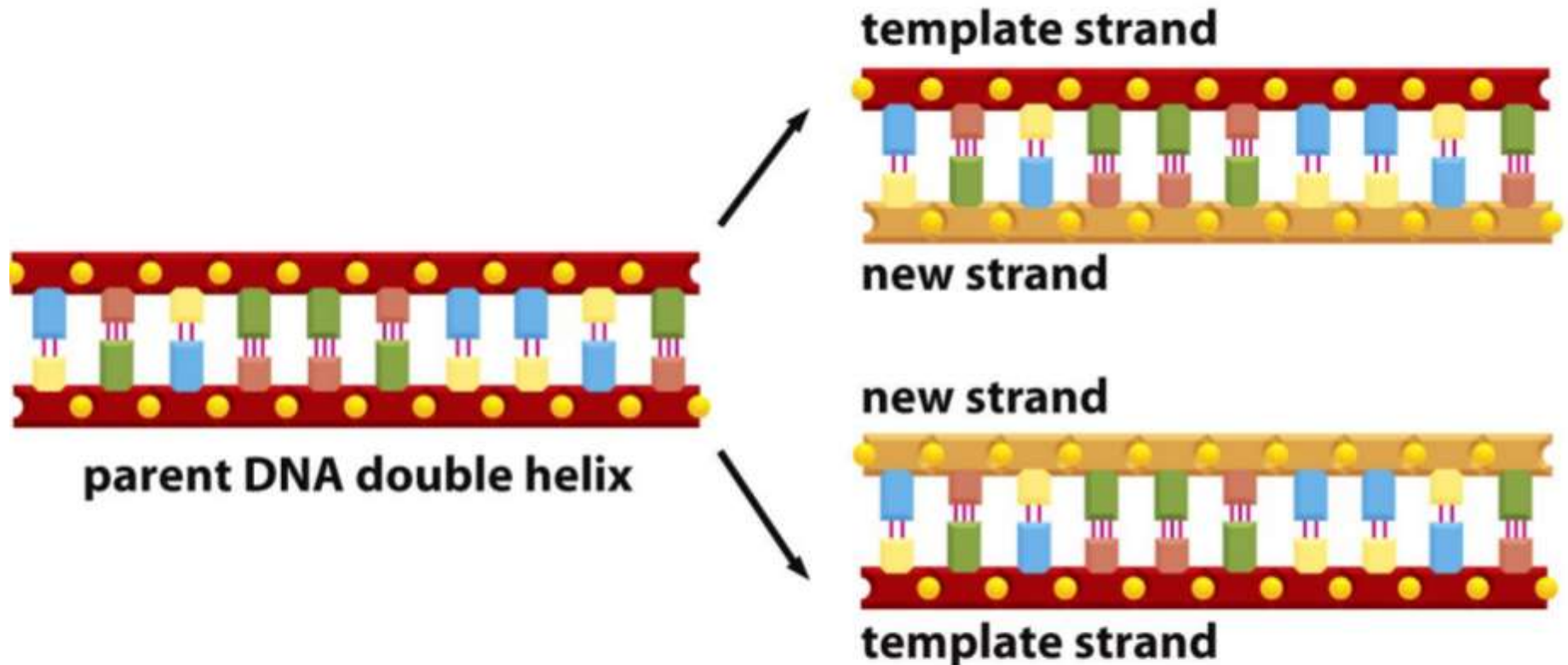




# DNA replication



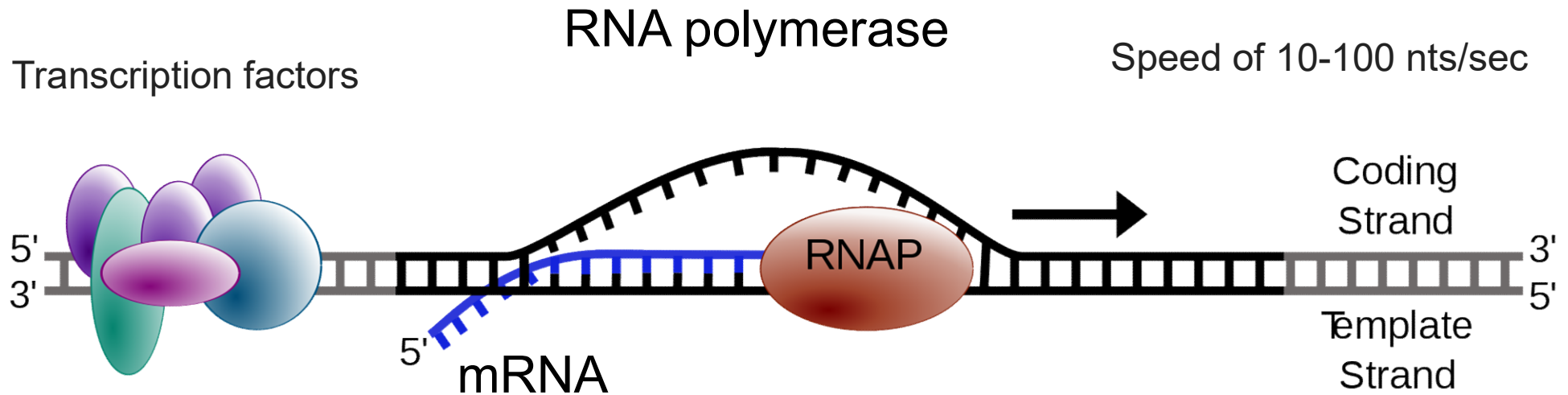
# DNA replication



Show DNA polymerase advanced

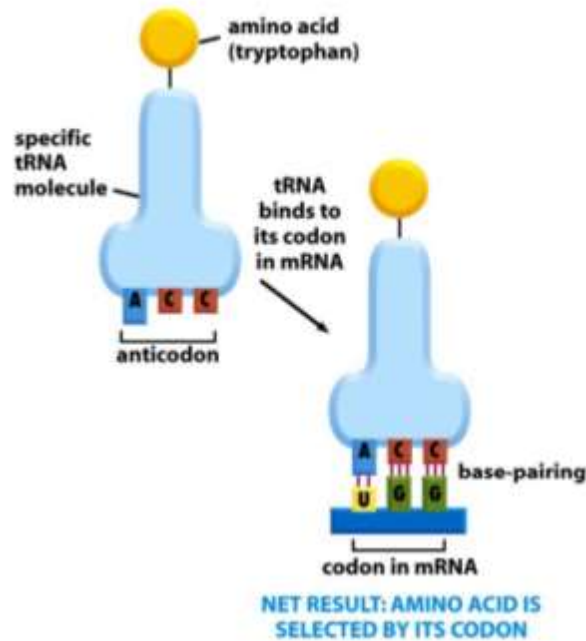
<http://www.youtube.com/watch?v=I9ArIJWYZHI&feature=related>

# Transcription

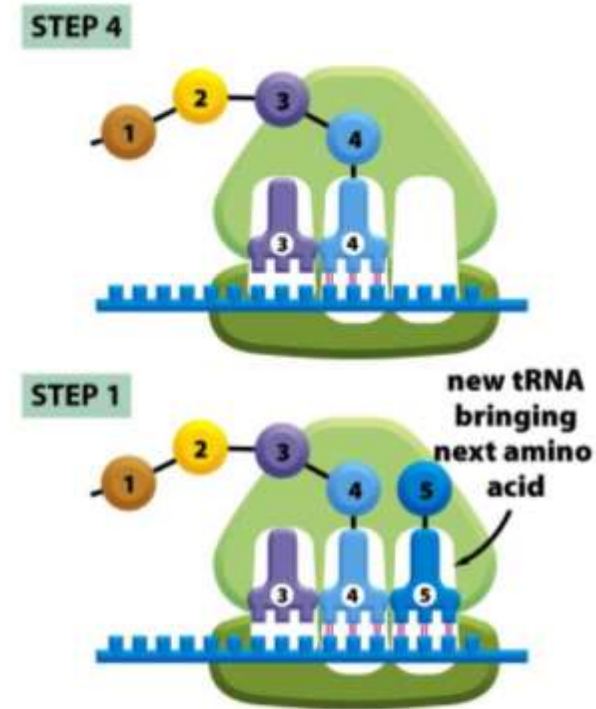
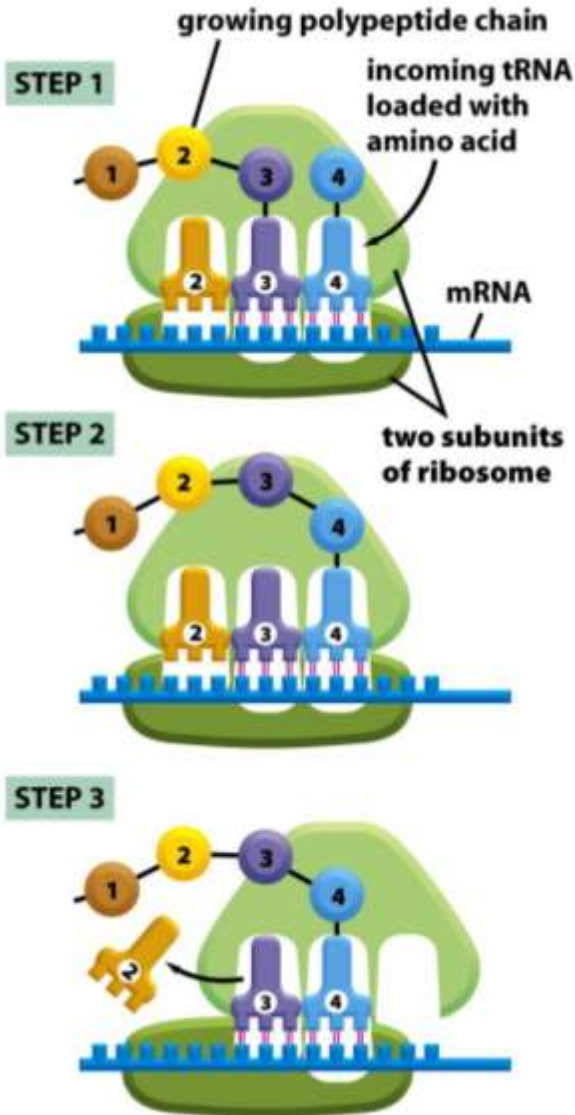


1. RNA polymerase, together with one or more general transcription factors, binds to promoter DNA.
2. RNA polymerase creates a transcription bubble, which separates the two strands of the DNA helix. This is done by breaking the hydrogen bonds between complementary DNA nucleotides.
3. RNA polymerase adds RNA nucleotides (which are complementary to the nucleotides of one DNA strand).
4. RNA sugar-phosphate backbone forms with assistance from RNA polymerase to form an RNA strand.
5. Hydrogen bonds of the RNA–DNA helix break, freeing the newly synthesized RNA strand.

# Protein synthesis=translation

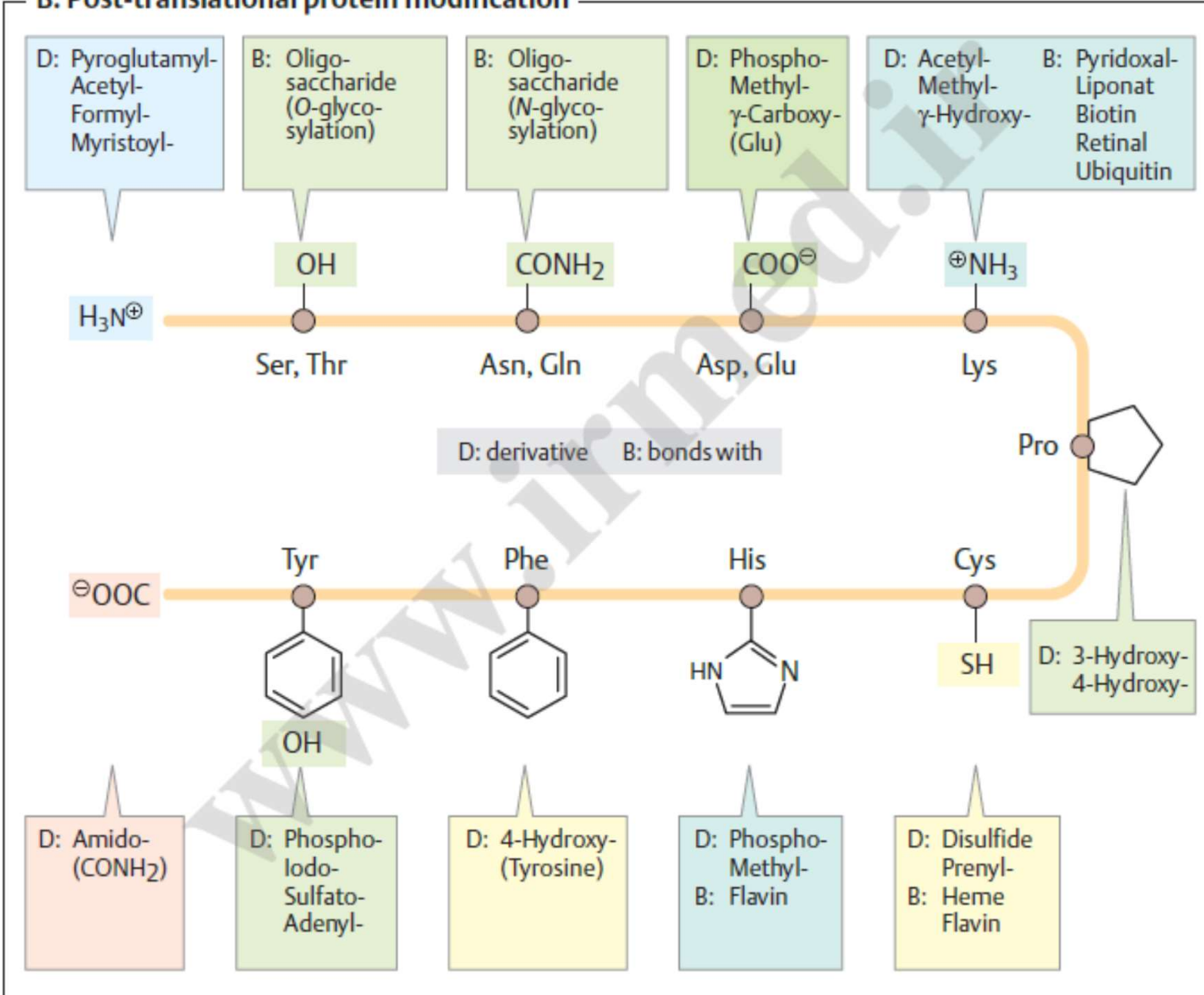


Transfer RNA (abbreviated tRNA) is an adaptor molecule composed of RNA, typically 73 to 94 nucleotides in length, that serves as the physical link between the nucleotide sequence of nucleic acids (DNA and RNA) and the amino acid sequence of proteins.



# Proteins modifications

## B. Post-translational protein modification



Modification
Phosphorylation
Acetylation
N-linked glycosylation
Amidation
Hydroxylation
Methylation
O-linked glycosylation
Ubiquitylation
Pyrrolidone carboxylic acid
Sulfation



# Абетки життя

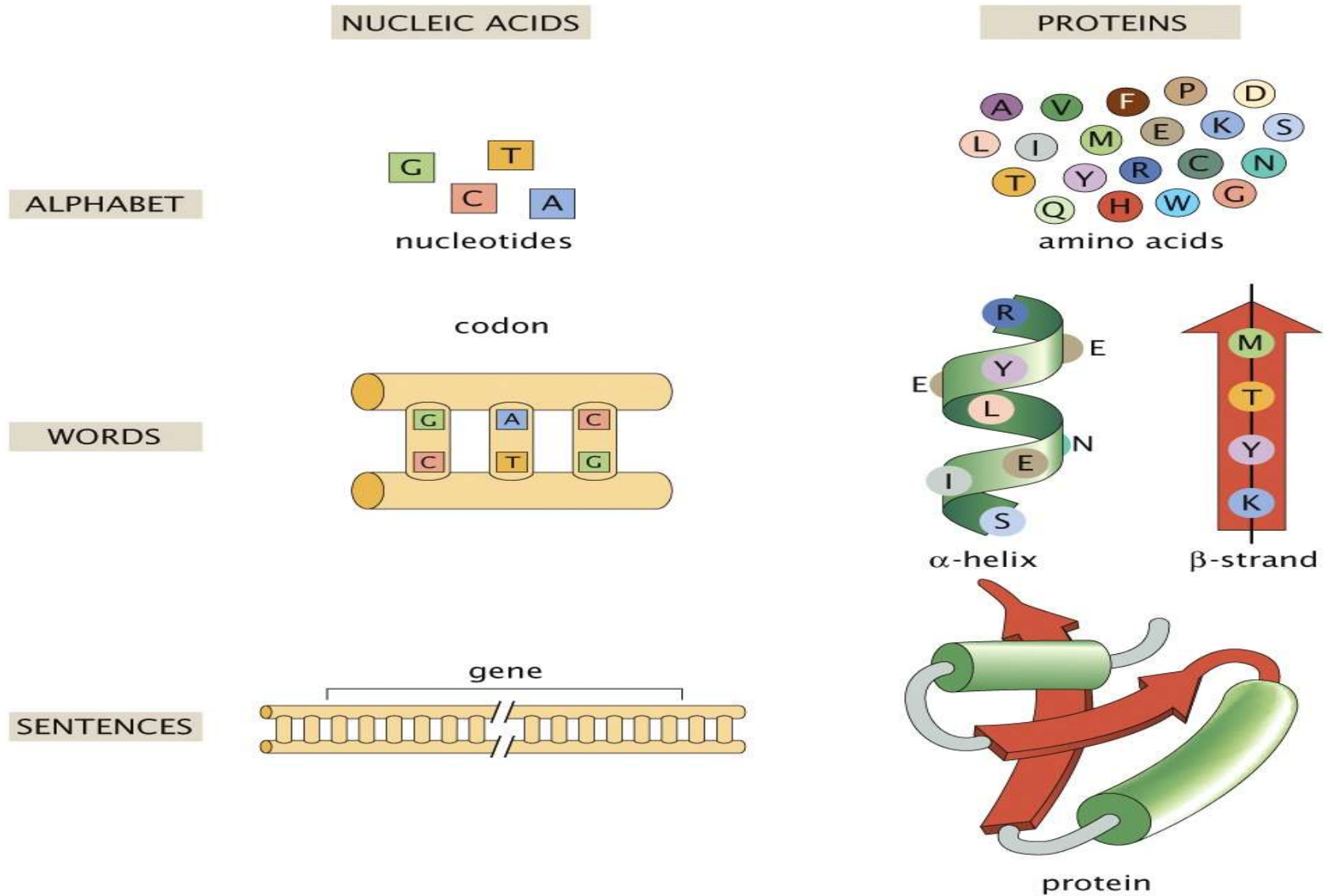
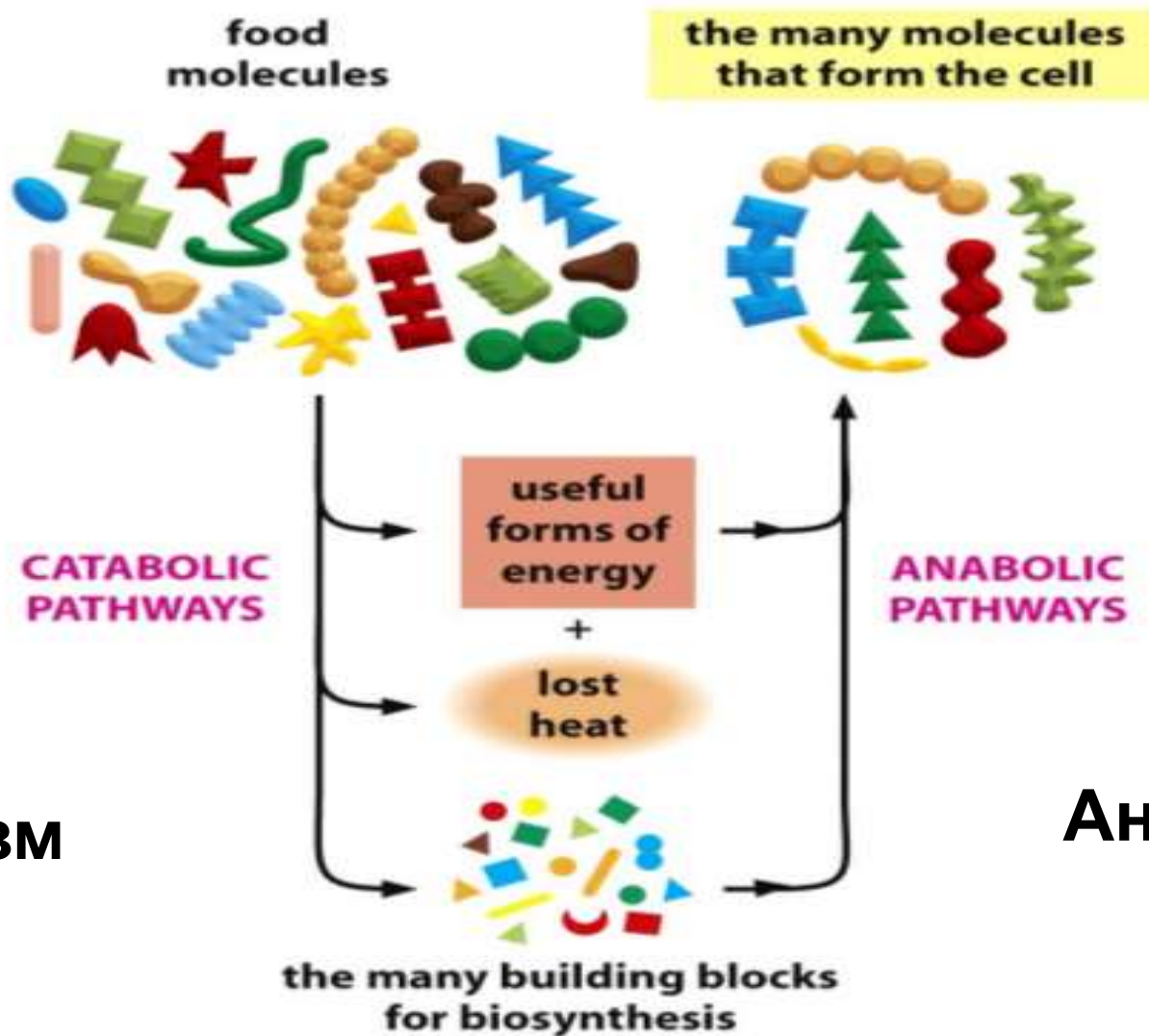


Figure 1.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

# Metabolism

Процес перетворення енергії в клітинах

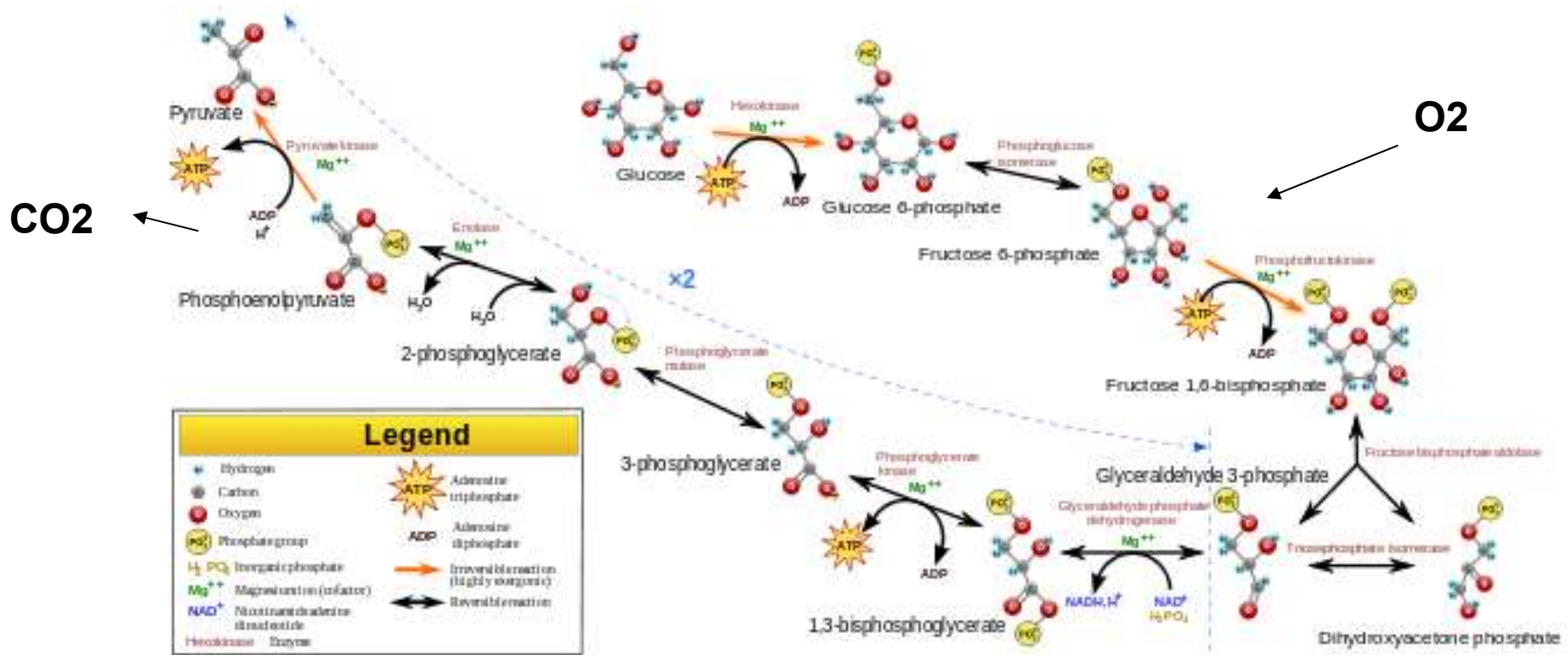


**Катаболізм**

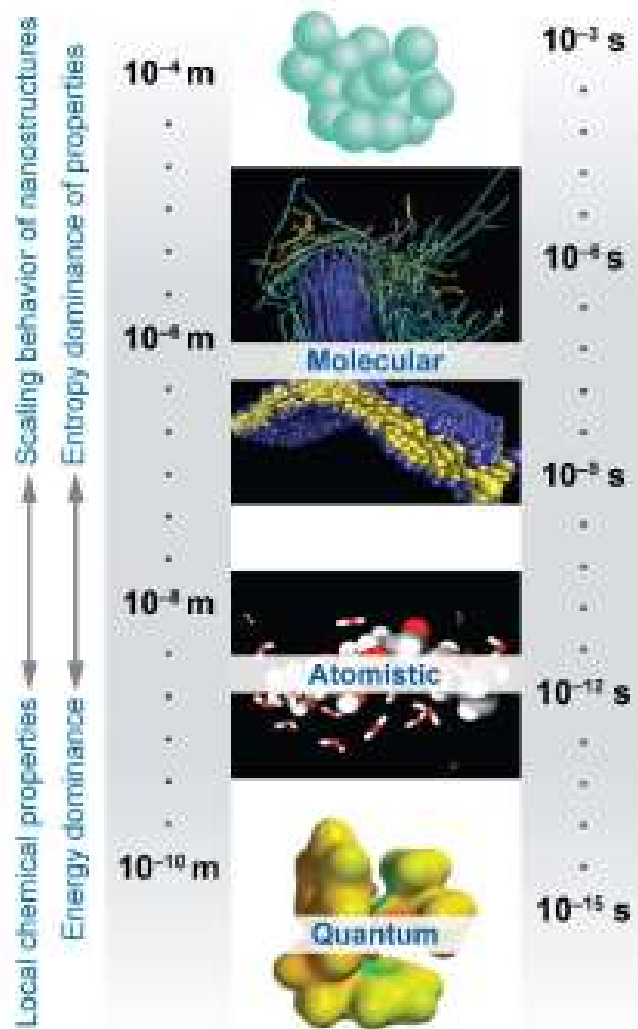
**Анаболізм**

# Приклад катаболізму: Гліколіз

Процес перетравлювання цукру (глюкози) досить складний. В результаті утворюються молекули **АТФ** та піруват. Споживається кисень для реакції оксидації та виділяється дво-окис вуглецю.



# How to model biological molecules



## MACRO

Finite-element calculations  
Continuum hydrodynamics  
Dissipative particle dynamics  
MD-MC-Lattice Boltzmann

## MESO

MC statics/dynamics  
MD, NEMD

## MICRO

Classical force field MD, MC  
Embedded atomistic-quantum methods  
Car-Parrinello MD  
Quantum MC  
Quantum chemical methods

Very little chemistry happens during the majority of all biological processes so the appropriate level of description is classical. This entails:

1) Adiabatic approximation.  
Nuclei are moving in the field created by the electrons.

2) Relaxation processes taking place on picosecond timescale and slower.

When are QM effects important?

$$\left. \begin{array}{l} h \neq 0 \\ \hbar \rightarrow 0 \end{array} \right\}$$

For harmonic oscillator, for instance:

$$\Delta E = h \nu$$



Classical	QM
$\Delta E < k_B T$	$\Delta E \gg k_B T$
$\nu \lesssim 10^{12} \text{ s}^{-1}$	$\nu \gg 10^{12} \text{ s}^{-1}$

at T=300K

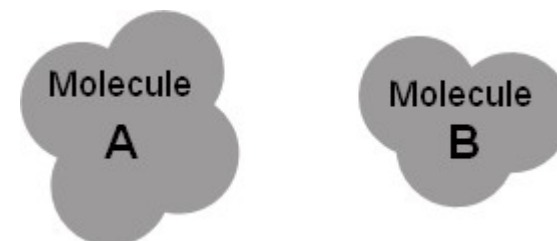
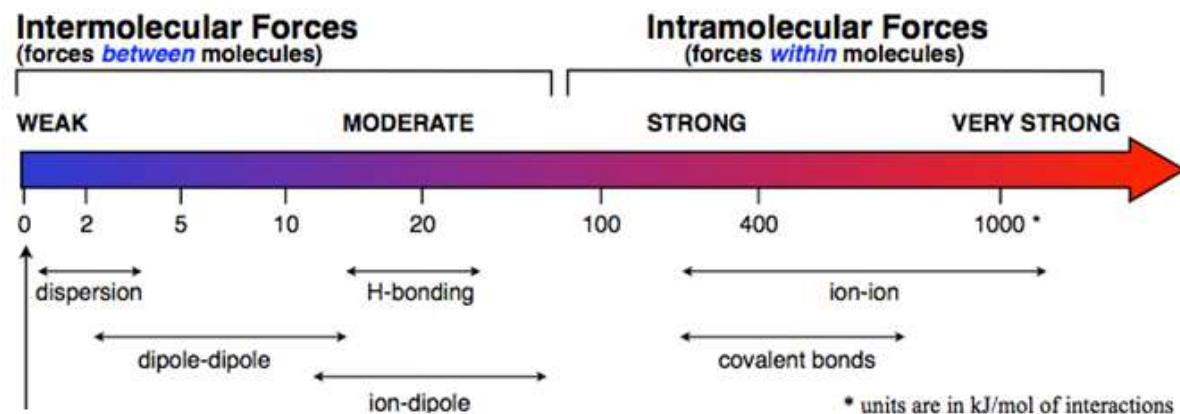


Praprotink M, et al. 2008.

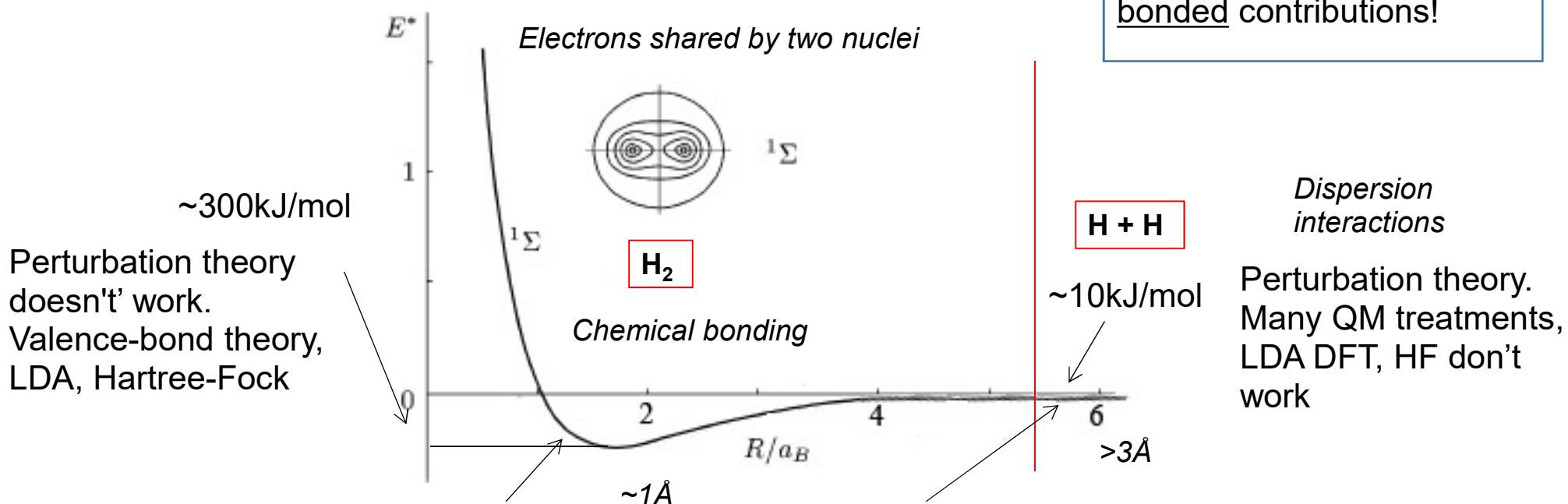
Annu. Rev. Phys. Chem. 59:545-71.



## Separation into bonded and non-bonded energy terms



Potential energy is divided into bonded and non-bonded contributions!



This part of the curve needs to be handled differently from this part!

## Non-bonded energy

### Multipole expansion for point charges

Potential energy of the set of charges  $q_i$  interacting with charge  $q$  at the origin

$$U = \sum_i^N \frac{qq_i}{|\vec{R} + \vec{r}_i|} = q \sum_i^N q_i e^{\vec{r}_i \vec{\nabla}} \frac{1}{R}$$

where  $e^{\vec{r}_i \vec{\nabla}} \frac{1}{R} = \frac{1}{|\vec{R} + \vec{r}_i|}$ ,  $e^{\vec{r}_i \vec{\nabla}} = 1 + \vec{r}_i \vec{\nabla} + \frac{1}{2} (\vec{r}_i \vec{\nabla}) (\vec{r}_i \vec{\nabla}) + \dots$  - the translation operator

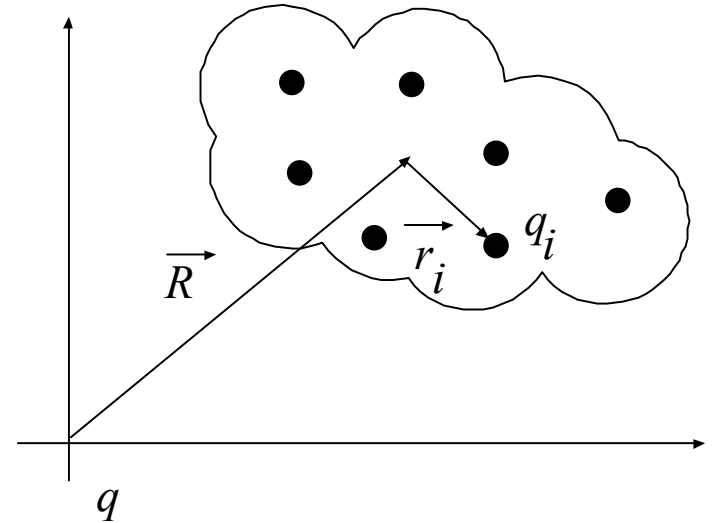
In a more compact form

$$U = q\Phi(R) = q\hat{Q} \frac{1}{R}, \quad \Phi(R) \text{ is the potential created by the charges at the origin}$$

where

$$\hat{Q} = \sum_i q_i e^{\vec{r}_i \vec{\nabla}} = \sum_i q_i (1 + \vec{r}_i \vec{\nabla} + \frac{1}{2} (\vec{r}_i \vec{\nabla}) (\vec{r}_i \vec{\nabla}) + \dots) = Q + \vec{d} \vec{\nabla} + \frac{1}{2} \sum_{\alpha\beta} Q_{\alpha\beta} \frac{\partial}{\partial X_\alpha} \frac{\partial}{\partial X_\beta} + \dots$$

$$Q = \sum_i^N q_i \quad \text{total charge} \quad \vec{d} = \sum_i^N q_i \vec{r}_i \quad \text{dipole moment} \quad Q_{\alpha\beta} = \sum_i^N q_i x_\alpha^i x_\beta^i \quad \text{quadrupole moment}$$



Potential energy then can be written as series:

$$U = q\Phi(R) = q\varphi_m(R) + q\varphi_d(R) + q\varphi_Q(R) + \dots$$

$$\varphi_m = \frac{Q}{R} \quad \text{potential created by the monopole=total charge} \quad \sim \frac{1}{R}$$

$$\varphi_d = -\frac{\vec{d}\vec{R}}{R^3} \quad \text{potential created by point dipole (at vector } -\vec{R} \text{)} \quad \sim \frac{1}{R^2}$$

$$\varphi_Q = \frac{1}{2} \sum_{\alpha\beta} Q_{\alpha\beta} \left( \frac{3X_\alpha X_\beta}{R^2} - \delta_{\alpha\beta} \right) \frac{1}{R^3} \quad \text{potential created by point quadrupole} \quad \sim \frac{1}{R^3}$$

Another way to look the interaction energy is to compute interaction of point multipoles with the field created by the charge at the origin

$$U = Q \left[ \frac{q}{R} - \vec{d}\vec{E} - \frac{1}{2} \sum_{\alpha\beta} Q_{\alpha\beta} \frac{\partial}{\partial X_\alpha} E_\beta \right]$$

potential created at the location of the charge distribution by point charge at the origin

Monopole “interacts” with the potential

$$\vec{E} = -q\vec{\nabla} \frac{1}{R} = \frac{q\vec{R}}{R^3}$$

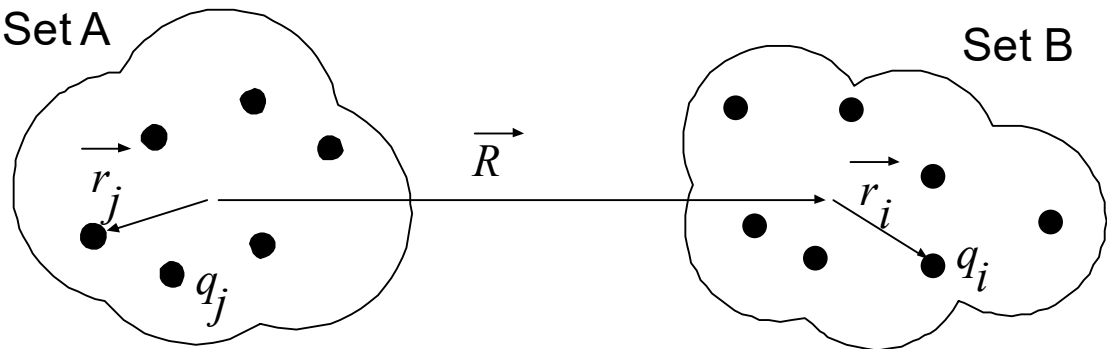
field created by the point charge at the location of the dipole

Dipole “interacts” with the field

derivatives of the electric field created by the point charge

Quadrupole “interacts” with the field derivative

Apply these formulas to two distributions of charges



To simplify things use the following abbreviations: charge dipole quadrupole octopole









Potential at site A:  
 Electric field at site A:  
 Field derivative at site A:

generated by + + + + ... at site B

$$\begin{aligned}
 U = & \begin{array}{c} \text{blue circle} \text{ red circle} \\ \frac{Q_A Q_B}{R} \end{array} + \begin{array}{c} \text{blue circle} \text{ red arrow} \\ -Q_A \frac{\vec{d}_B \vec{R}}{R^3} \end{array} + \begin{array}{c} \text{blue circle} \text{ red square} \\ \sim \frac{1}{R^3} \end{array} + \begin{array}{c} \text{blue circle} \text{ red octopole} \\ \sim \frac{1}{R^4} \end{array} + \dots \\
 & \begin{array}{c} Q_B \frac{\vec{d}_A \vec{R}}{R^3} \end{array} \begin{array}{c} \text{blue arrow} \text{ red circle} \\ + \end{array} \begin{array}{c} \text{blue arrow} \text{ red arrow} \\ + \end{array} \begin{array}{c} \text{blue arrow} \text{ red square} \\ + \end{array} \begin{array}{c} \text{blue arrow} \text{ red octopole} \\ + \end{array} \begin{array}{c} \sim \frac{1}{R^3} \\ + \end{array} \begin{array}{c} \sim \frac{1}{R^5} \\ + \end{array} \dots \\
 & \begin{array}{c} \text{blue square} \text{ red circle} \\ + \end{array} \begin{array}{c} \text{blue square} \text{ red arrow} \\ + \end{array} \begin{array}{c} \text{blue square} \text{ red square} \\ + \end{array} \begin{array}{c} \text{blue square} \text{ red octopole} \\ + \end{array} \begin{array}{c} \sim \frac{1}{R^4} \\ + \end{array} \begin{array}{c} \sim \frac{1}{R^5} \\ + \end{array} \begin{array}{c} \sim \frac{1}{R^6} \end{array}
 \end{aligned}$$

Multipole expansion  
 Interaction energy as a series in powers of  $\sim \frac{1}{R^n}$

# A table of the order of different interactions

				
	$\sim \frac{1}{R}$	$\sim \frac{1}{R^2}$	$\sim \frac{1}{R^3}$	$\sim \frac{1}{R^4}$
		$\sim \frac{1}{R^3}$	$\sim \frac{1}{R^4}$	$\sim \frac{1}{R^5}$
			$\sim \frac{1}{R^5}$	$\sim \frac{1}{R^6}$
				$\sim \frac{1}{R^7}$

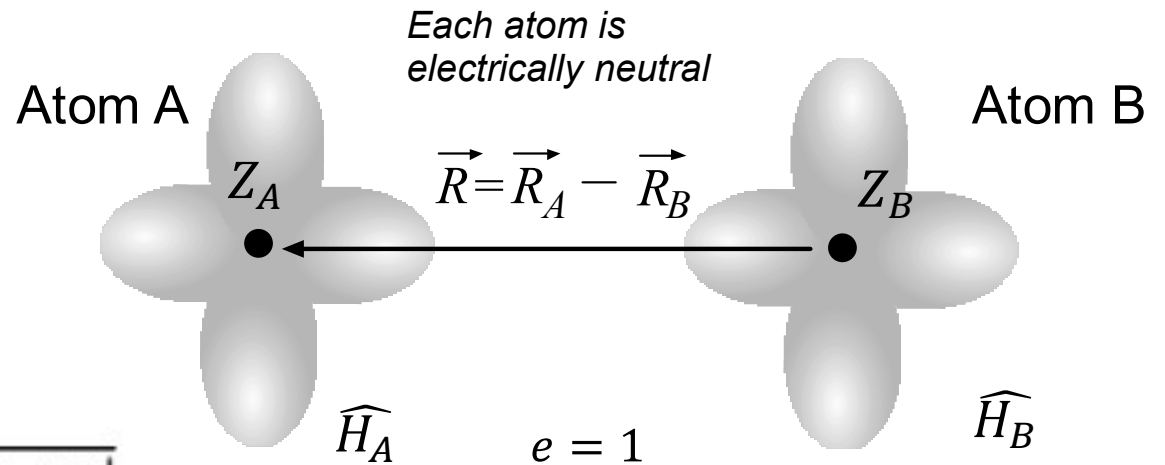


## Interaction energy between two atoms

Full Hamiltonian:

$$\hat{H} = \hat{H}_A + \hat{H}_B + \hat{U}$$

$$\hat{U} = \frac{Z_A Z_B}{|\mathbf{R}_A - \mathbf{R}_B|} + \sum_{i=1}^{Z_A} \sum_{j=1}^{Z_B} \frac{1}{|\mathbf{R}_A + \mathbf{r}_{Ai} - \mathbf{R}_B - \mathbf{r}_{Bj}|} - \sum_{i=1}^{Z_A} \frac{Z_B}{|\mathbf{R}_A + \mathbf{r}_{Ai} - \mathbf{R}_B|} - \sum_{j=1}^{Z_B} \frac{Z_A}{|\mathbf{R}_A - \mathbf{R}_B - \mathbf{r}_{Bj}|}$$



$Z_A$   $Z_B$  # of valence electrons and nuclei's charges

$|n_A\rangle$   $|n_B\rangle$  eigenfunctions

$E_n^A$   $E_n^B$  eigenvalues of energy operators

Compute the total energy by the perturbation theory:

$$E = E^{(0)} + E^{(1)} + E^{(2)} + \dots$$

$$E^{(0)} = E_0^A + E_0^B$$

ground state of individual atoms

first-order term

second-order term

$$E^{(0)} = \langle 0_A 0_B | \hat{H}_0 | 0_A 0_B \rangle$$

$$\hat{H}_0 = \hat{H}_A + \hat{H}_B$$

zero-order Hamiltonian

$\hat{U}$  perturbation term

Using the translation vector formula:

$$e^{\mathbf{r}_{Ai}\nabla} e^{-\mathbf{r}_{Bj}\nabla} \frac{1}{R} = \frac{1}{|\mathbf{R} + \mathbf{r}_{Ai} - \mathbf{r}_{Bj}|}, \quad \longrightarrow \quad \hat{U} = \sum_{i=1}^{Z_A} \sum_{j=1}^{Z_B} (e^{\mathbf{r}_{Ai}\nabla} - 1) (e^{-\mathbf{r}_{Bj}\nabla} - 1) \frac{1}{R}$$


Upon introducing charge operators:

$$\hat{Q}_A = \sum_{i=1}^{Z_A} (e^{\mathbf{r}_{Ai}\nabla} - 1)$$

Perturbation term can be written as:

$$\hat{U} = \hat{Q}_A \hat{Q}_B^+ \frac{1}{R}$$

*Multipole moments of atoms A and B*



First-order term:

$$E^{(1)} = \langle 0 | \hat{U} | 0 \rangle = \langle 0_A 0_B | \hat{Q}_A \hat{Q}_B^+ \frac{1}{R} | 0_A 0_B \rangle = \langle 0_A | \hat{Q}_A | 0_A \rangle \langle 0_B | \hat{Q}_B^+ | 0_B \rangle \frac{1}{R}$$

Let see the first few terms explicitly:

$$\hat{Q}_A = \sum_i \left( 1 + (\overrightarrow{r_i^A} \overrightarrow{\nabla}) + \frac{1}{2} (\overrightarrow{r_i^A} \overrightarrow{\nabla}) (\overrightarrow{r_i^A} \overrightarrow{\nabla}) + \dots - 1 \right) = \overrightarrow{d^A} \overrightarrow{\nabla} + \frac{1}{2} \sum_{\alpha\beta} Q_{\alpha\beta}^A \frac{\partial}{\partial x_\alpha} \frac{\partial}{\partial x_\beta} + \dots$$

$$\hat{Q}_B^+ = \sum_i \left( 1 - (\overrightarrow{r_i^B} \overrightarrow{\nabla}) + \frac{1}{2} (\overrightarrow{r_i^B} \overrightarrow{\nabla}) (\overrightarrow{r_i^B} \overrightarrow{\nabla}) + \dots - 1 \right) = -\overrightarrow{d^B} \overrightarrow{\nabla} + \frac{1}{2} \sum_{\alpha\beta} Q_{\alpha\beta}^B \frac{\partial}{\partial x_\alpha} \frac{\partial}{\partial x_\beta} + \dots$$

If atoms have non-zero charge:


$$\hat{Q}_A = Q_A + (\overrightarrow{d^A} \overrightarrow{\nabla}) + \frac{1}{2} \sum_{\alpha\beta} Q_{\alpha\beta}^A \frac{\partial}{\partial x_\alpha} \frac{\partial}{\partial x_\beta} + \dots$$

Taking the expectation value:

$$\langle 0_A | \hat{Q}_A | 0_A \rangle = \langle \vec{d}^A \rangle \cdot \vec{V} + \frac{1}{2} \sum_{\alpha\beta} \langle Q_{\alpha\beta}^A \rangle \frac{\partial}{\partial X_\alpha} \frac{\partial}{\partial X_\beta} + \dots$$

$$\langle 0_B | \hat{Q}_B^+ | 0_B \rangle = -\langle \vec{d}^B \rangle \cdot \vec{V} + \frac{1}{2} \sum_{\gamma\delta} \langle Q_{\gamma\delta}^B \rangle \frac{\partial}{\partial X_\gamma} \frac{\partial}{\partial X_\delta} + \dots$$

$$E^{(1)} = - \left( \langle \vec{d}_A \rangle \cdot \vec{V} \right) \left( \langle \vec{d}_B \rangle \cdot \vec{V} \right) \frac{1}{R} + \sum_{\alpha\beta} \langle d_\alpha^A \rangle \langle d_\beta^B \rangle \left( \frac{3X_\alpha X_\beta}{R^5} - \frac{\delta_{\alpha\beta}}{R^3} \right) \sim \frac{1}{R^3}$$



*if dipole moments are non-zero. true for molecules but not for atoms*

$$+ \frac{1}{2} \sum_{\gamma\delta} \left\{ \left( \langle \vec{d}_A \rangle \cdot \vec{V} \right) \langle Q_{\gamma\delta}^B \rangle - \left( \langle \vec{d}_B \rangle \cdot \vec{V} \right) \langle Q_{\gamma\delta}^A \rangle \right\} \frac{\partial}{\partial X_\gamma} \frac{\partial}{\partial X_\delta} \frac{1}{R} \sim \frac{1}{R^4}$$

$$+ \frac{1}{4} \sum_{\alpha\beta\gamma\delta} \langle Q_{\alpha\beta}^A \rangle \langle Q_{\gamma\delta}^B \rangle \frac{\partial}{\partial X_\alpha} \frac{\partial}{\partial X_\beta} \frac{\partial}{\partial X_\gamma} \frac{\partial}{\partial X_\delta} \frac{1}{R} + \dots \sim \frac{1}{R^5}$$

$$= \frac{C^{(3)}}{R^3} + \frac{C^{(4)}}{R^4} + \frac{C^{(5)}}{R^5} + \dots = \frac{Q_A Q_B}{R} + \frac{C^{(2)}}{R^2} + \frac{C^{(3)}}{R^3} + \frac{C^{(4)}}{R^4} + \frac{C^{(5)}}{R^5} + \dots$$

“electronic interaction energy” due to permanent multipole moments

*multipole expansion*

*expansion if atoms have uncompensated charge*

Second-order term:

$$E_n^{(2)} = \sum_{m(n \neq m)} \frac{|U_{mn}|^2}{E_n^{(0)} - E_m^{(0)}}$$

matrix element is over double indices

$$U_{mn} = \langle m_A, m_B | \hat{U} | n_A, n_B \rangle$$

Correction to the ground-state energy  
relies on the matrix entry:

$$U_{m0} = \langle m | \hat{U} | 0 \rangle = \langle m_A | \hat{Q}_A | 0_A \rangle \langle m_B | \hat{Q}_B^+ | 0_B \rangle \frac{1}{R},$$

which has to be substituted into the energy formula:

$$E_0^{(2)} = \sum_{m_A, m_B} \frac{|\langle m_A | \hat{Q}_A | 0_A \rangle \langle m_B | \hat{Q}_B^+ | 0_B \rangle \frac{1}{R}|^2}{E_0^A - E_{m_A}^A + E_0^B - E_{m_B}^B} = E_{0,ind}^{(2)} + E_{0,disp}^{(2)}$$

note that since the denominator  
is always negative and  
nominator – positive the  
correction is negative and  
corresponds to attraction

Induction energy

Summation is performed while keeping one of the  
atoms in the ground state

$$E_{0,ind}^{(2)} = \sum_{m_B} \frac{|\langle 0_A | \hat{Q}_A | 0_A \rangle \langle m_B | \hat{Q}_B^+ | 0_B \rangle \frac{1}{R}|^2}{E_0^B - E_{m_B}^B} + \sum_{m_A} \frac{|\langle m_A | \hat{Q}_A | 0_A \rangle \langle 0_B | \hat{Q}_B^+ | 0_B \rangle \frac{1}{R}|^2}{E_0^A - E_{m_A}^A}$$

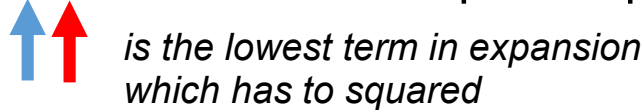
$E_{ind}(A)$                        $E_{ind}(B)$

non-zero starting from non-zero multipole.

The induction energy is non-zero starting from non-zero multipole terms.

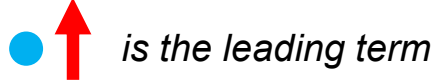
Examples:

1) Atoms have non-zero dipole in the ground state  $E_{ind}(A) \sim \left| \langle \vec{d}^A \rangle \cdot \vec{V} \langle m_B | \hat{Q}^+_B | 0_B \rangle \frac{1}{R} \right|^2 = \frac{I^{(6)}}{R^6} + \dots$



2) Atoms have non-zero charge and may or may not have dipole moment

$Q_A + \langle \vec{d}^A \rangle \cdot \vec{V} + \dots$

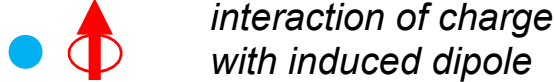


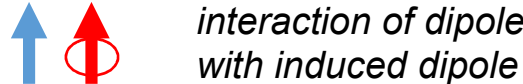
$$E_{ind}(A) \sim \left| \langle 0_A | \hat{Q}_A | 0_A \rangle \langle m_B | \hat{Q}^+_B | 0_B \rangle \frac{1}{R} \right|^2 = \left| Q_A \langle m_B | \hat{Q}^+_B | 0_B \rangle \frac{1}{R} \right|^2 = \frac{I^{(4)}}{R^4} + \dots$$

A convenient way to view induction energy is by introducing the concept of polarization. Assume that the dipole moment induced by external field can be written as:

$$\vec{\mu} = \alpha \vec{E} \quad \text{where } \alpha \text{ is the polarizability constant (tensor in general)}$$

The interaction energy of that moment with the field then is:  $E_{ind} = -\vec{\mu} \cdot \vec{E} = -\alpha E^2$

If polarization is caused by point charge,  $E \sim \frac{1}{R^2}$  and so  $E_{ind} \sim \frac{1}{R^4}$  

If polarization is caused by a point dipole  $E \sim \frac{1}{R^3}$  and so  $E_{ind} \sim \frac{1}{R^6}$  



A formal expression for the induction energy:

$$E_{ind}(A) = -\frac{1}{2} \alpha_{\alpha\beta}(A) E_{\alpha}(A) E_{\beta}(A) - \frac{1}{3} A_{\alpha,\beta\gamma}(A) E_{\alpha}(A) E_{\beta\gamma}(A) - \\ - \frac{1}{6} C_{\alpha\beta,\gamma\delta}(A) E_{\alpha\beta}(A) E_{\gamma\delta}(A) + \dots$$

molecular polarizabilities

**$\alpha, A, C$**

specific for the molecule

$$E_{\alpha}(A) = -\frac{X_{\alpha}}{R^3} Q_B + \sum_{\beta} \left( \frac{3X_{\alpha}X_{\beta}}{R^5} - \frac{\delta_{\alpha\beta}}{R^3} \right) d_{\alpha}(B) + \dots$$

electric field due to atom B

$$E_{\alpha\beta}(A) = -\left( \frac{3X_{\alpha}X_{\beta}}{R^5} - \frac{\delta_{\alpha\beta}}{R^3} \right) Q_B + \dots$$

derivative of the electric field due to atom B

### Dispersion energy

Second-order correction when the summation is performed over excited states of both atoms:

$$E_{0,disp}^{(2)} = \sum_{m_A, m_B \neq 0} \frac{|\langle m_A | \hat{Q}_A | 0_A \rangle \langle m_B | \hat{Q}_B^+ | 0_B \rangle \frac{1}{R}|^2}{E_0^A - E_{m_A}^A + E_0^B - E_{m_B}^B}$$

Keeping only the lowest-order dipolar term:  $\hat{Q}_A = \overline{d^A} \vec{V}$      $\hat{Q}_B^+ = -\overline{d^B} \vec{V}$

*Dispersion, London, van der Waals interaction*

$$E_{0,disp}^{(2)} = \sum_{m_A, m_B \neq 0} \frac{|(\langle m_A | \vec{d}^A | 0_A \rangle \vec{V})(\langle m_B | \overline{d^B} | 0_B \rangle \vec{V}) \frac{1}{R}|^2}{E_0^A - E_{m_A}^A + E_0^B - E_{m_B}^B} = \frac{D^{(6)}}{R^6}$$

*Has dipole-induced dipole interpretation. Not everyone agrees with it. See J. O. Hirschfelder; C. F. Curtiss & R. B. Bird (1954), Molecular Theory of Gases and Liquids, New York: Wiley*



*For charged systems*

$$\hat{Q}_A = Q_A + \overline{d^A} \vec{V}$$

*0 because of orthogonality condition*

$$\langle m_A | \hat{Q}_A | 0_A \rangle = Q_A \langle m_A | 0_A \rangle + \langle m_A | \overline{d^A} \vec{V} | 0_A \rangle = \langle m_A | \overline{d^A} \vec{V} | 0_A \rangle$$

so  $\sim \frac{1}{R^6}$  is genuinely the lowest order term in the dispersion interaction

*Some general properties of dispersion interactions*

*attractive regardless of molecule orientation*

*weaker than normal covalent and ionic bonds*

*strength is proportional to the polarizability of the atom*

*additive and cannot be saturated*

*short-range forces and hence only interactions between the nearest particles need to be considered*

## Extension to molecules

### Nuclear interaction

$$\frac{Z_1^A Z_1^B}{|\vec{R} - \vec{R}_1^B + \vec{R}_1^A|} + \frac{Z_1^A Z_2^B}{|\vec{R} - \vec{R}_2^B + \vec{R}_1^A|} + \frac{Z_2^A Z_1^B}{|\vec{R} - \vec{R}_1^B + \vec{R}_2^A|} + \frac{Z_2^A Z_2^B}{|\vec{R} - \vec{R}_2^B + \vec{R}_2^A|} = (\widehat{Q}_A + Z_A)(\widehat{Q}_B^+ + Z_B) \frac{1}{R}$$

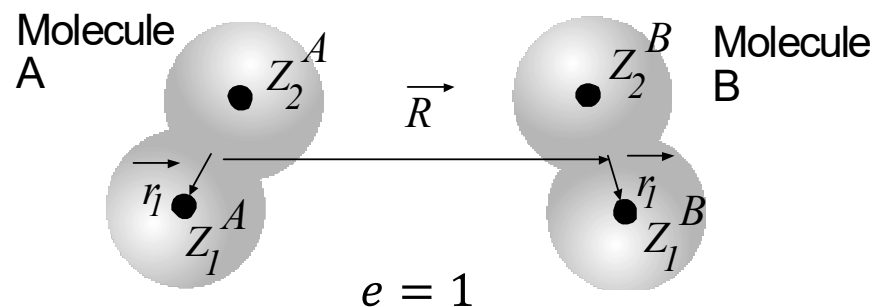
### Electrons with nuclei

$$-1 \sum_{i=1, Z_A} \left\{ \frac{Z_1^B}{|\vec{R} - \vec{R}_1^B + \vec{r}_i^A|} + \frac{Z_2^B}{|\vec{R} - \vec{R}_2^B + \vec{r}_i^A|} \right\} +$$

$$-1 \sum_{j=1, Z_B} \left\{ \frac{Z_1^A}{|\vec{R} + \vec{R}_1^A - \vec{r}_j^B|} + \frac{Z_2^A}{|\vec{R} + \vec{R}_2^A - \vec{r}_j^B|} \right\} = -\{(\widehat{Q}_A + Z_A)(\widehat{q}_B^+ + Z_B) + (\widehat{Q}_B^+ + Z_B)(\widehat{q}_A + Z_A)\} \frac{1}{R}$$

### Electrons with electrons

$$\sum_{i=1, Z_A} \sum_{j=1, Z_B} \frac{1}{|\vec{R} - \vec{r}_j^B + \vec{r}_i^A|} = (\widehat{q}_A \widehat{q}_B^+ + Z_A \widehat{q}_B^+ + Z_B \widehat{q}_A + Z_A Z_B) \frac{1}{R}$$



$$Z_A = Z_1^A + Z_2^A \quad \text{valence of molecule A}$$

$$Z_B = Z_1^B + Z_2^B \quad \text{valence of molecule B}$$

$$\widehat{Q}_A = Z_1^A e^{\vec{R}_1^A \cdot \vec{\nabla}} + Z_2^A e^{\vec{R}_2^A \cdot \vec{\nabla}} - Z_A \quad \text{nuclear "charge"}$$

$$\widehat{q}_A = \sum_{i=1, Z_A} (e^{\vec{r}_i^A \cdot \vec{\nabla}} - 1) \quad \text{electronic "charge"}$$

Full perturbation potential

$$E_{0,n}^{(1)} \neq 0, E_{0,n}^{(2)} = 0$$

$$\hat{U} = \{\widehat{Q}_A \widehat{Q}_B^+ + \widehat{q}_A \widehat{q}_B^+ - \widehat{Q}_A \widehat{q}_B^+ - \widehat{q}_A \widehat{Q}_B^+\} \frac{1}{R}$$

Additional terms:

$$E_{0,n}^{(1)} = \langle 0 | \widehat{Q}_A \widehat{Q}_B^+ | 0 \rangle \frac{1}{R} = \widehat{Q}_A \widehat{Q}_B^+ \frac{1}{R} = \frac{N^{(3)}}{R^3} + \dots$$

*multipole expansion for the nuclear subsystem.  
Starts with dipole-dipole interactions for neutral molecules*

$$E_{0,n}^{(2)} \sim \langle m_A | \widehat{Q}_A \widehat{Q}_B^+ | 0_A \rangle = \widehat{Q}_A \widehat{Q}_B^+ \langle m_A | 0_A \rangle = 0$$

*because of the orthogonality of the excited states to the ground-state wave function*

$$E_{0,c}^{(1)} = \langle 0 | \widehat{Q}_A \widehat{q}_B^+ | 0 \rangle \frac{1}{R} = \widehat{Q}_A \langle 0 | \widehat{q}_B^+ | 0 \rangle \frac{1}{R} = \frac{CN^{(3)}}{R^3} + \dots$$

$$E_{0,c}^{(2)} \sim \sum_{m \neq 0} \left| \langle 0 | \widehat{Q}_A \widehat{q}_B^+ | m \rangle \frac{1}{R} \right|^2 = \sum_{m \neq 0} \left| \widehat{Q}_A \langle 0 | \widehat{q}_B^+ | m \rangle \frac{1}{R} \right|^2 = \frac{CN^{(6)}}{R^6} + \dots$$

*cross terms.  
combined effect of electronic and nuclear permanent dipoles*

Nuclear degrees of freedom contribute additional terms to the multipole expansion corresponding to the permanent moments

Putting all summands together one arrives at the most general representation of the interaction energy between two molecules:

*both positive and negative*

$$U = \frac{Q_A Q_B}{R} + \frac{C^{(2)}}{R^2} + \frac{C^{(3)}}{R^3} + \frac{C^{(4)}}{R^4} + \frac{C^{(5)}}{R^5} + \frac{C^{(6)}}{R^6} + \dots$$

*permanent multipoles. Electronic and nuclear systems*

*electronic subsystem always negative*

$$+ \frac{I^{(4)}}{R^4} + \frac{I^{(6)}}{R^6} + \dots$$

*induction energy*

$$+ \frac{D^{(6)}}{R^6} + \dots$$

*dispersion energy*

Constants

$$C^{(i)}, I^{(i)}, D^{(i)}$$

a) Can be computed in QM studies. Difficult for large systems. Almost impossible for dispersion force.

b) Obtained by fitting. Empirical parameters



## Atom-pair potential approximation

*Proteins are modeled at the classical level. 1) Not much chemistry happens but 2) QM calculations are way too expensive*

*Interaction energy  $U(R)$  can be used to model the dynamics of the nuclei in the Born-Oppenheimer approximation. Adiabatic approximation.*

*Two options of how to proceed:*

*Option #1:*

*Assign proper (valence) charges to each nucleus and a certain number of permanent moments. These can be taken from QM calculations or some other source (from experiment in case of dipole moment for instance). The moments have to be attached to the local geometry of the molecules. As the local reference frame moves (rotates) the moments have to be recomputed.*

*Drawbacks:*

*1) Algorithms are not always straightforward to implement. It may be difficult to compute forces acting on each nucleus, especially for higher moments. See Stockmayer fluid for example. Torques are not always computed in a pairwise summation ( $i$  acting on  $j$  is not the opposite of  $j$  acting on  $i$ ).*

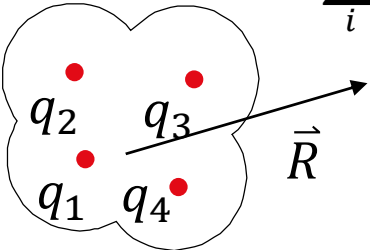
*2) The procedure is tedious and expensive. Each molecule has to have its moments recomputed at each step as it rotates in the course of the simulation.*

*3) A large amount of data needs to be stored.*

*4) A large number of parameters – dipole, quadrupole and higher moments, makes parametrization very challenging.*

## Option #2:

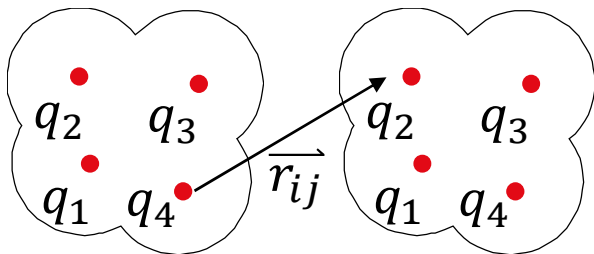
1) Assign partial charges to each nucleus. These will generate multipole series of permanent dipoles.



$$\sum_i \frac{q_i}{|\vec{R} - \vec{r}_i|} = \frac{C^{(1)}}{R} + \frac{C^{(2)}}{R^2} + \frac{C^{(3)}}{R^3} + \frac{C^{(4)}}{R^4} + \frac{C^{(5)}}{R^5} + \frac{C^{(6)}}{R^6} + \dots$$

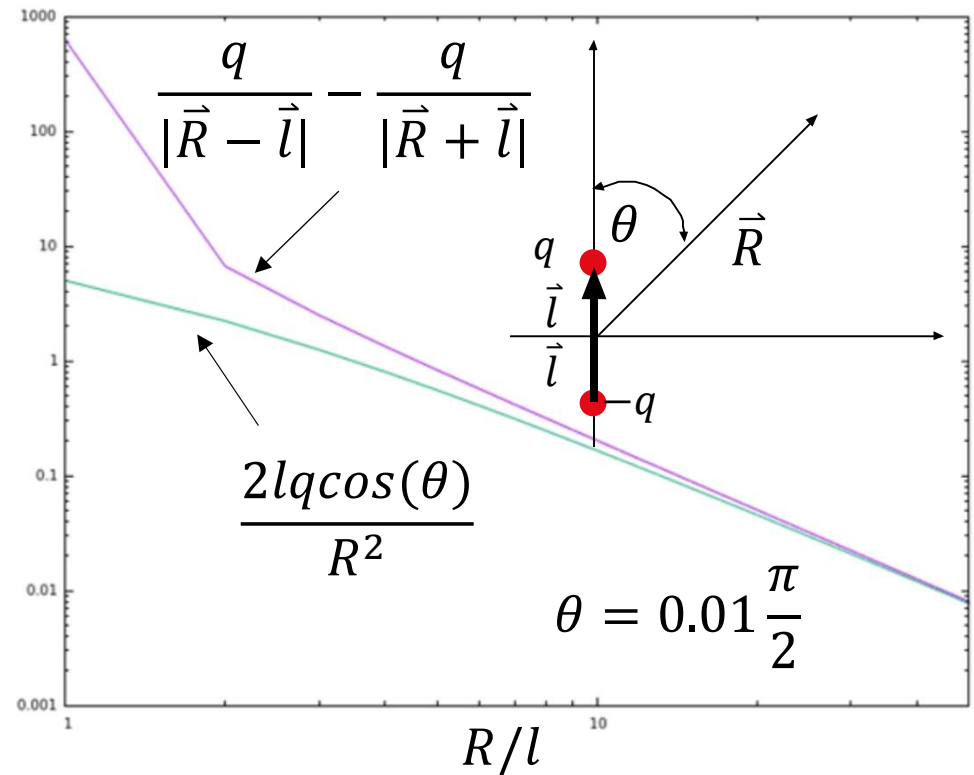
Important: the series will contain all powers of  $1/R$ , not just ones specific for a particular dipole.

2) Add polarization and dispersion interactions to each nucleus.



3) Add repulsion at short distances to prevent nuclei overlapping

Baumketner, BioSim, Lviv 2019



$$\sum_{i,j} \left( \frac{D_{ij}^{(4)}}{r_{ij}^4} + \frac{D_{ij}^{(6)}}{r_{ij}^6} + \frac{D_{ij}^{(7)}}{r_{ij}^7} + \frac{D_{ij}^{(8)}}{r_{ij}^8} \dots + \frac{D_{ij}^{(12)}}{r_{ij}^{12}} \right)$$

Parameters:  $q_1 \dots q_N$

$D_{ij}^{(n)}, n = 4, 6, 7, 8 \dots 12$  for each pair  $q_i, q_j$

## Can the atom-pair approximation work?

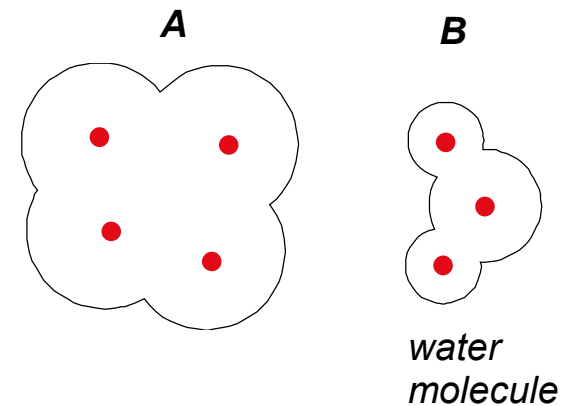
### *The method of Clementi*

- 1) Approximation: cut all terms with powers  $1/R^7$  and higher. This will lower the number of parameters
- 2) Compute potential energy for a two-molecule system in QM calculations.

**A**= amino acids and some other systems. 25 in total

**B**= water molecule

$\Delta E_{AB}(R, \theta, \varphi)$  interaction energy as a function of mutual distance and orientations. 10,000 different values



*The interaction potential*

$$\Delta E = \sum_{a(X)} \sum_{b(W)} \{c_{ab}^{(1)} / R_{ab} + c_{ab}^{(4)} / R_{ab}^4 + c_{ab}^{(6)} / R_{ab}^6 + c_{ab}^{(12)} / R_{ab}^{12}\}$$

*Results:*

- 1) Way too many parameters to perform a fit for all atoms. Introduce atom types. Typical types:  
*sp<sup>3</sup>, sp<sup>3</sup> hybridized carbon, carbon in aromatic residues etc. ~30 different classes*
- 2) Electrostatic contribution can be well approximated by charges:

$$c_{ab}^{(1)} = q_a q_b$$

3) Keeping the  $1/R^4$  term doesn't improve the quality of the fit

4) Certain rules for cross terms seem to work well. For instance:

$$c_{a(X)H(W)}^{(12)} = c_{a(X)}^{(12)} c_{H(W)}^{(12)}$$

$$c_{a(X)O(W)}^{(12)} = c_{a(X)}^{(12)} c_{O(W)}^{(12)}$$

5) Coefficients  $c_{ab}^{(6)}$  are too small and can't be determined reliably. This is the consequence of the dispersion interactions not being well described by the QM approximation.

## Conclusions

The following model of potential energy will work well for proteins:

$$U = \sum_{i,j} \left\{ \frac{q_i q_j}{r_{ij}} + c_{ij}^{(12)} / r_{ij}^{12} - c_{ij}^{(6)} / r_{ij}^6 \right\}$$

Adjustable parameters

$q_1 \dots q_N$  partial charges

$$c_{ij}^{(12)}, c_{ij}^{(6)} > 0$$

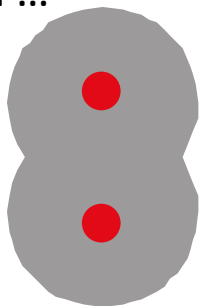
*Examples of when this approximation will fail*

oxygen, nitrogen ...

charge is zero  
at each  
nucleus  
because a) the  
molecule is  
neutral b)  
charges are  
equivalent

$$q = 0$$

$$q = 0$$



$q \neq 0$   
(for instance  
metal ion)



*Actual energy*

$$\frac{I^{(4)}}{R^4} + \dots$$



*polarization term.*

*Atom-pair model*

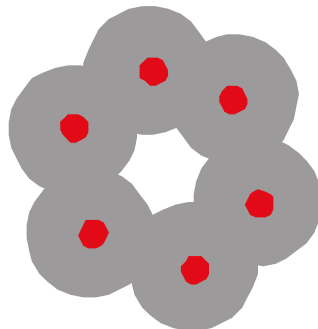
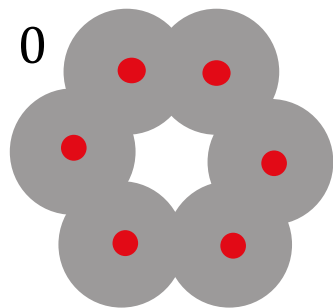
$$\frac{D^{(6)}}{R^6}$$

*dispersion term.*

benzene

Molecules that  
have zero  
charge, zero  
dipole moment  
but non-zero  
quadrupole  
moment

$$q = 0$$



*Actual energy*

$$\frac{C^{(5)}}{R^5} + \dots$$



*Atom-pair model*

$$\frac{D^{(6)}}{R^6}$$

*dispersion term.*



## Bonded energy

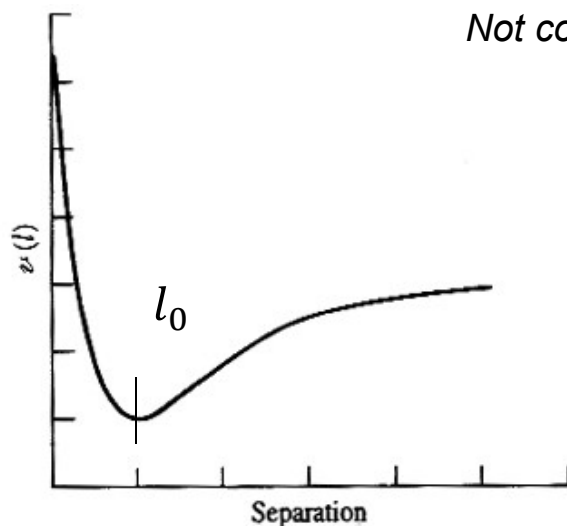
QM calculations predict certain geometry for the studied molecule. Distortions from that geometry are described by a number of potential energy terms that collectively are known as “bonded energy”

### Bond-stretching potential

Morse potential (some basis in QM calculations)

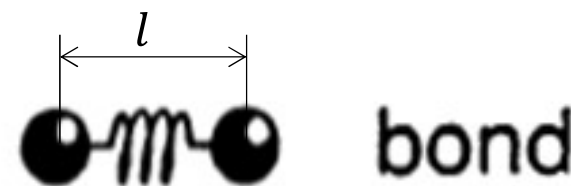
$$v(l) = D_e \{1 - \exp[-a(l - l_0)]\}^2$$

Three parameters.  
Not convenient



Bond	$l_0$ (Å)	$k$ (kcal mol <sup>-1</sup> Å <sup>-2</sup> )
Csp <sup>3</sup> –Csp <sup>3</sup>	1.523	317
Csp <sup>3</sup> –Csp <sup>2</sup>	1.497	317
Csp <sup>2</sup> =Csp <sup>2</sup>	1.337	690
Csp <sup>2</sup> =O	1.208	777
Csp <sup>3</sup> –Nsp <sup>3</sup>	1.438	367
C–N (amide)	1.345	719

Table 4.1 Force constants and reference bond lengths for selected bonds [Allinger 1977].



Harmonic approximation (typically used)

$$v(l) = \frac{k}{2} (l - l_0)^2$$

Force constant.  
Source: normal  
mode analysis of  
QM, vibrational  
spectra

Reference  
bond length.  
Source:  
crystal  
structures,  
QM  
calculations

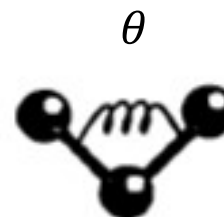
## Angle bending potential

*Harmonic approximation*

$$v(\theta) = \frac{k}{2} (\theta - \theta_0)^2$$

Force constant.  
Source: normal  
mode analysis of  
QM, vibrational  
spectra

Reference bond angle.  
Source: crystal  
structures, QM  
calculations



Angle	$\theta_0$	$k$ (kcal mol <sup>-1</sup> deg <sup>-1</sup> )
Csp <sup>3</sup> -Csp <sup>3</sup> -Csp <sup>3</sup>	109.47	0.0099
Csp <sup>3</sup> -Csp <sup>3</sup> -H	109.47	0.0079
H-Csp <sup>3</sup> -H	109.47	0.0070
Csp <sup>3</sup> -Csp <sup>2</sup> -Csp <sup>3</sup>	117.2	0.0099
Csp <sup>3</sup> -Csp <sup>2</sup> =Csp <sup>2</sup>	121.4	0.0121
Csp <sup>3</sup> -Csp <sup>2</sup> =O	122.5	0.0101

Table 4.2 Force constants and reference angles for selected angles [Allinger 1977].

*Higher-order approximations approximation:*

$$v(\theta) = \frac{k}{2} (\theta - \theta_0)^2 [1 - k'(\theta - \theta_0) - k''(\theta - \theta_0)^2 - k'''(\theta - \theta_0)^3 \dots]$$

## Dihedral angle potential

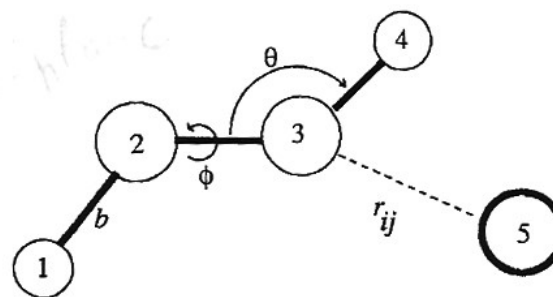
Several functional forms are in use

$$v(\phi) = \sum_{n=0}^N \frac{V_n}{2} [1 + \cos(n\phi - \gamma)]$$

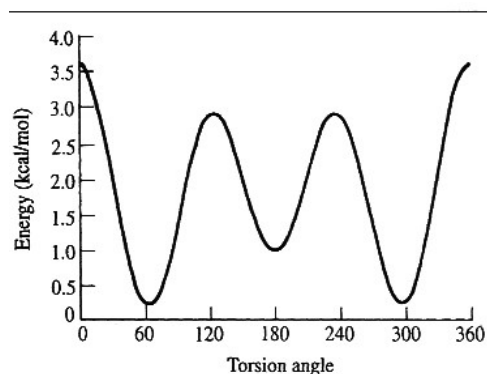
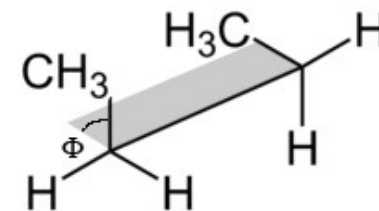
Barrier height. Provides an idea on qualitative level about the barrier to rotation around particular bond.

Multiplicity. Determines how many minima the potential has. Depends on the chemistry of the central two atoms. For  $sp^3$  atoms,  $n=3$ , giving 3 minima. For  $sp^2$  atoms,  $n=2$ , leading to 2 minima.

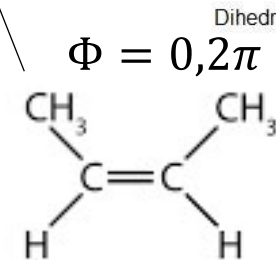
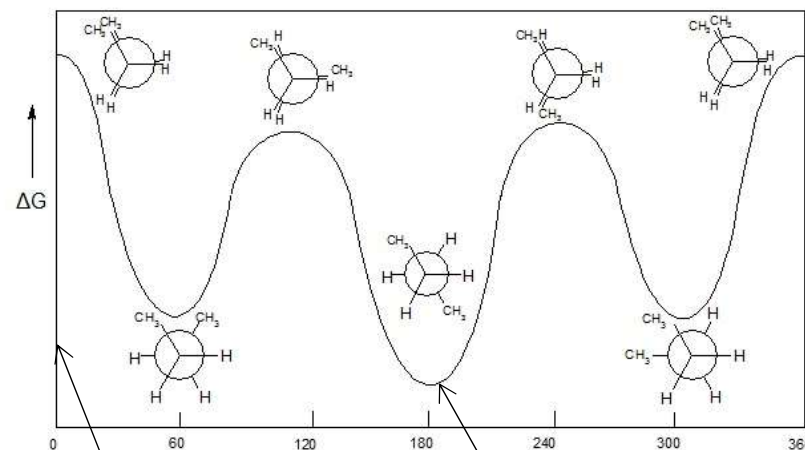
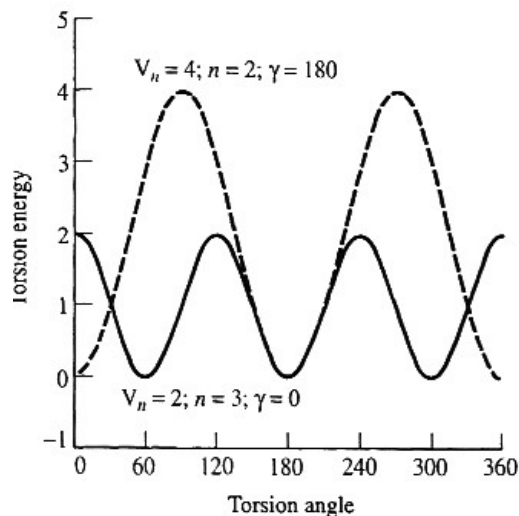
The phase factor, Determines where the potential passes through a minimum.



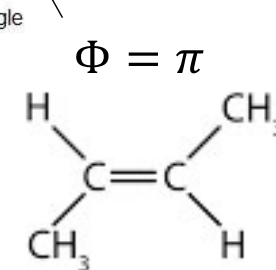
Butane



AMBER force field, with O-C-C-O torsion angle



cis-2-butene



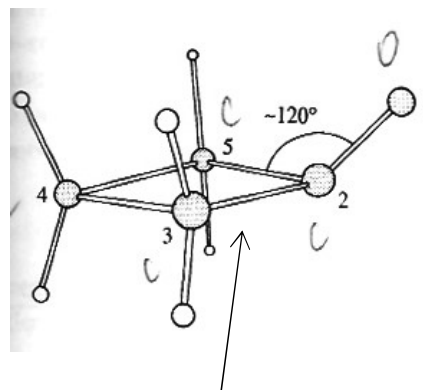
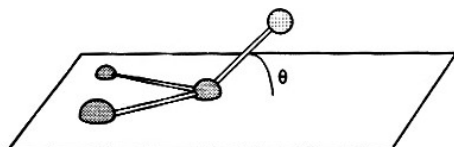
trans-2-butene

## Improper dihedrals

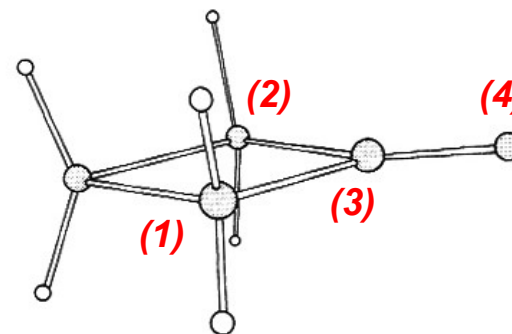
*Chemical compounds in which four non-consecutive atoms have to lie in-plane. This can't be achieved with the help bond, angle and dihedral energy alone.*

*Improper dihedral energy:*

$$v(\theta) = \frac{k}{2} \theta^2;$$

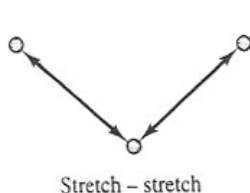


*Conformation favored by bond-angle terms*

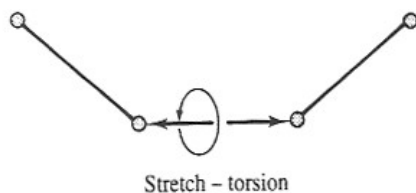


*Experimentally observed conformation. Four atoms (1)(2)(3)(4) lie in the same plane.*

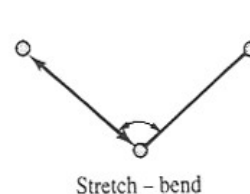
## Bonded cross-terms



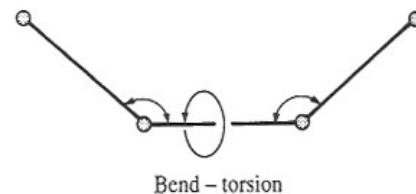
Stretch - stretch



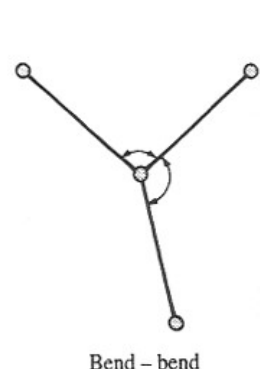
Stretch - torsion



Stretch - bend



Bend - torsion



Bend - bend

*Apply in Class II force-fields as opposed to Class I force-fields relying on fixed-charge model*

*Typically used in highly specialized force-fields such as MM2/MM3*

## Parametrization

### Partial charges

#### 1) First principle approaches:

a) *Partial charge is not an experimentally observable quantity. Can't be determined directly*

a) *In QM calculations partial charges can't be determined unambiguously. Many schemes exist. Mulliken charges are meant for intra-molecular interactions. They depend on the molecule chemistry, number of nuclei etc. Can't be used to describe interactions between molecules.*

#### 2) Fitting :

a) *Partial charges are fitted to reproduce certain thermodynamic properties of the studied system. See for instance OPLS/AA.*

b) *Partial charges are adjusted to reproduce electrostatic potential created around the molecule of interest. The latter are obtained in QM calculations. See AMBER and CHARMM.*

$$R = \sum_{i=1}^{N_{\text{points}}} w_i (\phi_i^0 - \phi_i^{\text{calc}})^2$$

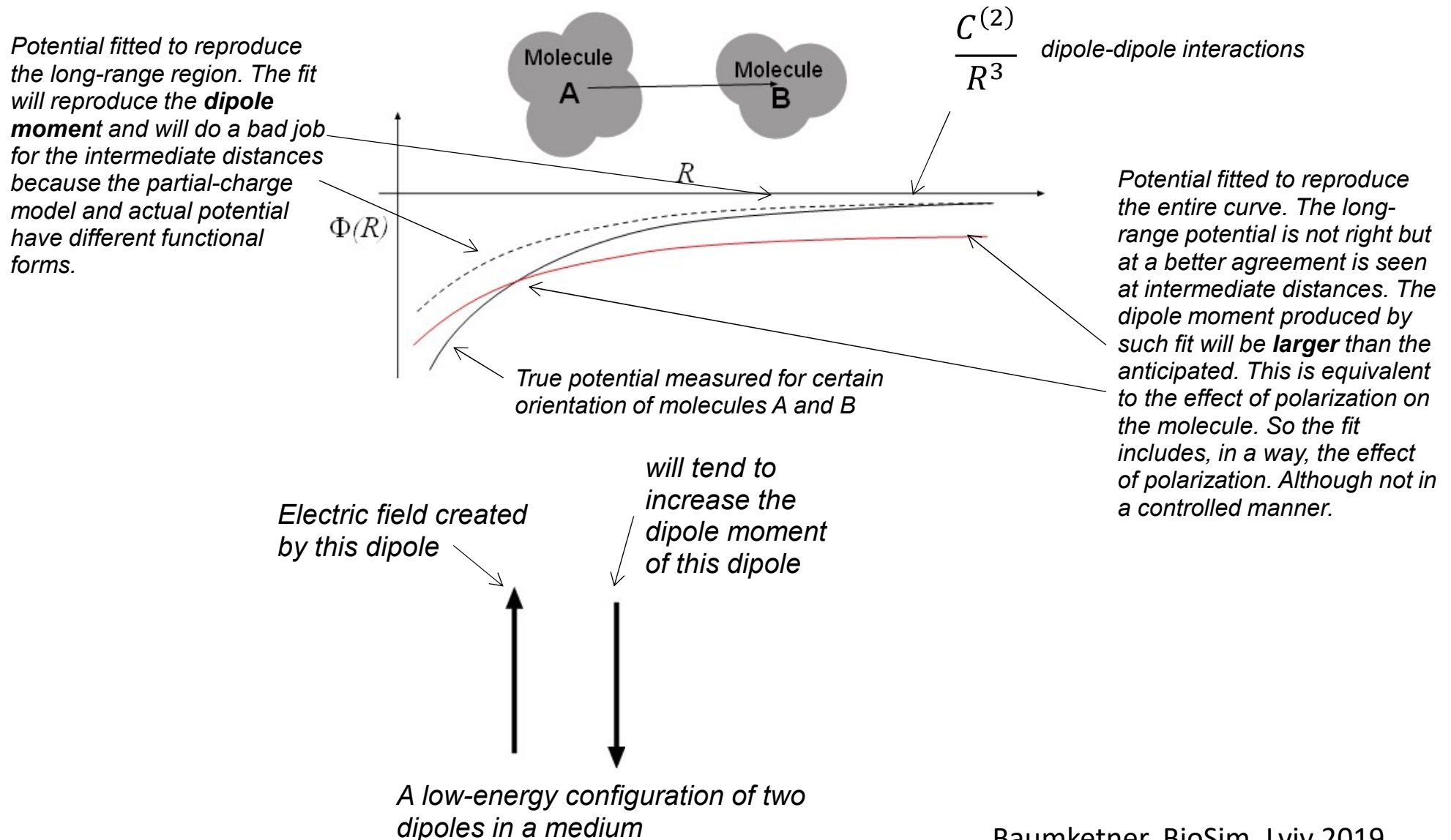
reference QM potential

partial charge potential

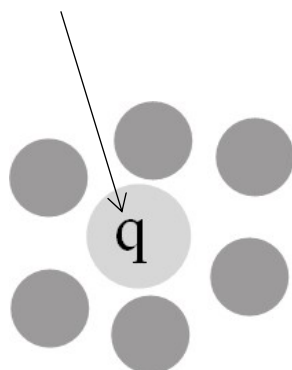
$$\phi_i^{\text{calc}} = \sum_{j=1}^{N-1} \frac{q_j}{4\pi\epsilon_0 r_{ij}} + \frac{Z - \sum_{j=1}^{N-1} q_j}{4\pi\epsilon_0 r_{iN}}$$



*In principle there is no guarantee that such fit should be successful. Much depends on how fitting is performed. In all cases errors will be present.*



c) Charges that are buried are statistically underdetermined.  
Difficult to obtain meaningful values.



Such fits lead to poor performance of the charges when they are placed in a different environment.



The problem can be addressed by introducing weight factors for the charges. Example **RESP** charges of AMBER

d) The same set of charges cannot describe the potential equally well for different configurations of the target molecules.

Some force-fields consider multiple configurations so that the fitted charge produces the best agreement for the entire ensemble of structures. See AMBER.

e) The best performing fixed-charge model produce **5-15%** relative error in electrostatic potential with respect to QM results. For comparison, polarizable force-fields can achieve less than 1% accuracy.

## Van der Waals parameters

*In almost all force-fields the vdW parameters to reproduce*

- a) *Constants in molecular crystals*
- b) *Heat of vaporization*
- c) *Liquid densities*

$$V_{LJ}(r_{ij}) = 4\epsilon_{ij} \left( \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right)$$

*Combination rules*

$$\sigma_{ij} = \sqrt{\sigma_i \sigma_j} \quad \sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j)$$
$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}$$

*Lorentz rule*

## Bonded potentials

*Bond-stretching, angle bending – normal modes, vibrational spectra. Most transferable part of force-field*

*Torsion potential.*

*QM calculations of potential energy as a function of the particular dihedral angle.*

## General scheme

*Typically, parametrization of a force-field proceeds in three steps:*

- 1) *Bond-stretching and angle-bending parameters are set. Perhaps by borrowing values from AMBER.*
- 2) *Charges are fitted*
- 3) *Vdw parameters are fitted. The rule for 1-4 interactions is set.*
- 4) *Torsion potentials are fitted on QM simulations of dipeptides.*

*These are coupled. Don't use torsion potentials obtained in one force-field in a different force-field!*

## Force-fields in general use

AMBER  
CHARMM  
OPLS

TABLE I  
Other Force Fields for Peptide and Protein Modeling

Force field	Potential type	Key references
BUFF	All Atom	Carlson, 2000
CEDAR	All Atom	Hermans <i>et al.</i> , 1984; Hu <i>et al.</i> , 2003
CVFF	All Atom	Kitson and Hagler, 1988
DISCOVER	All Atom	Maple <i>et al.</i> , 1998
ECEPP/3	All Atom, Torsional	Némethy <i>et al.</i> , 1993
ENCAD	All Atom	Daggett and Levitt, 1993; Levitt <i>et al.</i> , 1995
GROMOS87	United Atom	van Gunsteren and Berendsen, 1987
GROMOS96	United Atom	Scott <i>et al.</i> , 1999
MM2	All Atom	Lii <i>et al.</i> , 1989
MM3	All Atom	Lii <i>et al.</i> , 1991
MM4	All Atom	Langley and Allinger, 2002
MMFF	All Atom	Halgren, 1996a,b,c,d
NEMO	Polarizable	Hermida-Ramón <i>et al.</i> , 2003
PROSA	Polarizable	Stern <i>et al.</i> , 1999
SCHRODINGER	Polarizable	Kaminski <i>et al.</i> , 2002
SDFE	Polarizable	Palmo <i>et al.</i> , 2003
SIBFA	Polarizable	Gresh, 1997; Guo <i>et al.</i> , 2000
SPASIBA	All Atom	Derreumaux and Vergoten, 1995
TRIPOS	All Atom	Clark <i>et al.</i> , 1989
UCSD-WILSON	All Atom	Mackay <i>et al.</i> , 1984
UFF	All Atom	Rappé <i>et al.</i> , 1992
UPJOHN	All Atom	Oie <i>et al.</i> , 1981
YETI	United, Torsional	Vedani, 1988

# AMBER

## History

ff84                      united atom

ff94, ff96, ff99      all-atom

ff02                      polarizable

## Charges

Fitted to reproduce electrostatic potential of model peptides, ESP and then RESP charges.

In ff99 refitted using higher-order QM energies

## vdW parameters

Combination rules:  $\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}$       geometric mean  
 $\sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j)$       arithmetic mean

Density and enthalpy of vaporization of CH<sub>4</sub>, C<sub>2</sub>H<sub>6</sub>, C<sub>3</sub>H<sub>8</sub> and C<sub>4</sub>H<sub>10</sub> liquids -> sp<sup>3</sup> carbon and aliphatic hydrogen. sp<sup>2</sup> carbon and aromatic H from liquid benzene. All others borrowed from OPLS/UA

## 1-4 interactions

Scaling factor of 0.5 in ff84 and 0.83 in all-atom force fields

## Bonded

QM data and vibrational spectra

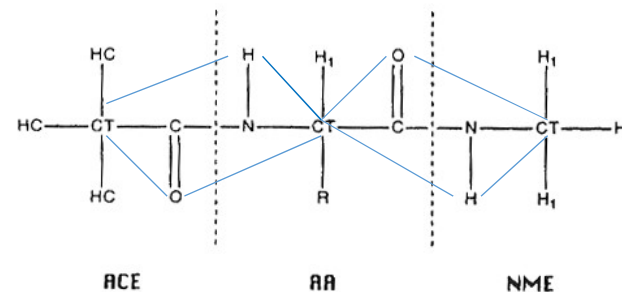
## Energy function

$$E_{\text{total}} = \sum_{\text{bonds}} K_r (r - r_{\text{eq}})^2 + \sum_{\text{angles}} K_{\theta} (\theta - \theta_{\text{eq}})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)] + \sum_{i < j} \left[ \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right]$$

RESP with the neutrality of AA enforced.

Rc=9Å, no switching

QM HF-6-31G\* set. Multiple conformations.



Alanyl and glycyl dipeptide

The side-chain is varied. QM-optimized structures for GLY and ALA

## Torsions

QM on GLY and ALA dipeptides as a function of rotation angles



# CHARMM

## History

charmm19	united atom
charmm22, charmm27	all-atom
charmm36	polarizable

## Charges

Supramolecular approach. QM energies are computed for AA-Water complexes. For neutral systems the energy is divided by 1.16. Charges are fitted to reproduce AA-Water interactions. TIP3P with non-zero vdW on H is used for water.

## vdW parameters combination rules

Density and heat of vaporization.

$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j} \quad \text{geometric mean}$$

$$\sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j) \quad \text{arithmetic mean}$$

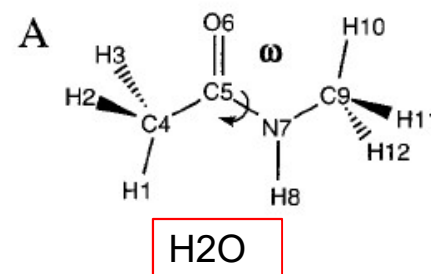
## Bonded

QM data and vibrational spectra

## 1-4 interactions

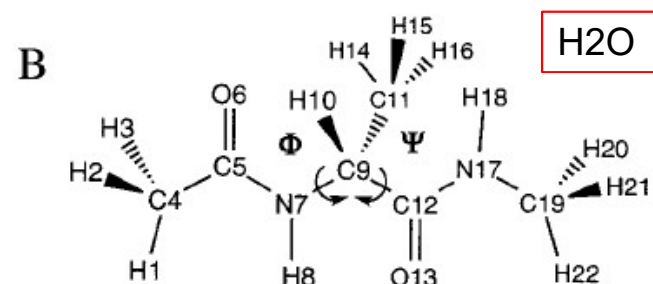
No scaling. Scaling factor of 1.0

## NMA water complexes



Backbone: QM yields geometry + force constants for bonds, angles. Water is important for geometry. Charges + vdW parameters

## Alanyl dipeptide with water



+ simulations of proteins in gas and crystal phases

↓  
ϕ, ψ  
↓

## Torsions

QM on dipeptides. Matching of energy of different minima, C7, aR etc.

# OPLS

## History

opls-UA                      united atom

opls-AA                     all-atom

## Charges

Fitted to reproduce interaction energy of model compounds with water estimated in QM simulations. Dipole moments are set about 15% larger than in gas phase to take polarization into account. TIP4P water is used in MM part, but TIP3P and SPC are also suitable. Concept of neutral groups is introduced, which reduces the number of requisite charges,.

## 1-4 interactions

Scaling factor of 0.83 in OPLS-UA and 0.5 in OPLS-AA       $R_c = 10-12\text{\AA}$       depending on the substance

## vdW parameters

Experimental density and enthalpy of vaporization in liquid state are reproduced in MC simulations of model compounds that correspond to the peptide bond and side chains .

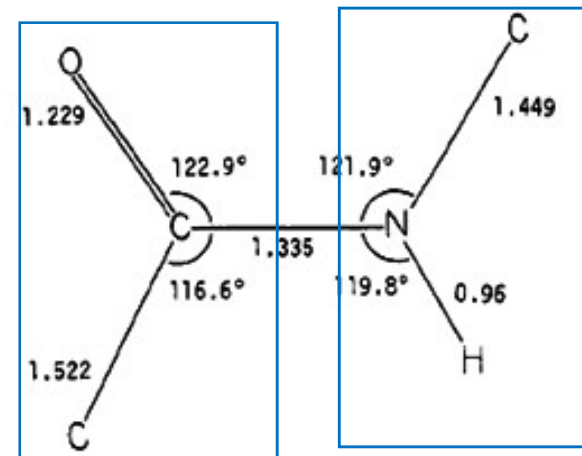
$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j} \quad \sigma_{ij} = \sqrt{\sigma_i \sigma_j} \quad \text{geometric mean}$$

## Bonded

Borrowed from AMBER94 force-field

NMA is used as the model of peptide bond. Geometry from crystal structure. Charges from solute-water interactions.

neutral block



Parameters of CH<sub>3</sub>(C-O) are taken from hydrocarbons. After charges are fitted, the number of unknown parameters is equal the number of experimental measurements

## Torsions

Adopted from AMBER94 in OPLS-UA.  
Fitted to QM energy functions computed for AA dipeptides for OPLS-AA/L

## Convergence of force-fields

*United-atom force-fields show large variation in charges:*

TABLE II

Comparison of Fixed Partial Charge Models for Serine Taken from Current and Previous Generation Protein Force Fields

	Amber 84	Amber 94/99	CHARMM19	CHARMM22/27	OPLS-UA	OPLS-AA	GROMOS96	BUFF	
Backbone	N	-0.463	-0.4157	-0.35	-0.47	-0.57	-0.50	-0.28	-0.749
	HN	0.252	0.2719	0.25	0.31	0.37	0.30	0.28	0.328
	CA	0.035	-0.0249	0.10	0.07	0.20	0.14	0.00	0.189
	HA	0.048	0.0843		0.09		0.06		0.048
	C	0.616	0.5973	0.55	0.51	0.50	0.50	0.38	0.828
	O	-0.504	-0.5679	-0.55	-0.51	-0.50	-0.50	-0.38	-0.679
	CB	0.018	0.2117	0.25	0.05	0.265	0.145	0.15	0.296
	HB	0.119	0.0352		0.09		0.06		0.006
	OG	-0.55	-0.6546	-0.65	-0.66	-0.70	-0.683	-0.548	-0.764
	HO	0.31	0.4275	0.40	0.43	0.435	0.418	0.398	0.491

*All-atom force-fields appear to converge*

## Problems, ways to improve

### Intrinsic deficiencies

The ansatz of partial charges placed at positions of nuclei not always is appropriate. It may not yield proper permanent dipoles. This can be fixed by adding more charges. Also atom-based multipole moments.

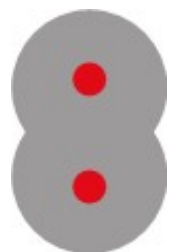
Example: nitrogen molecule

Has no dipole moment but has quadrupole moment.

Potential energy

quadrupole-quadrupole interaction

$$\sim \frac{1}{R^5}$$

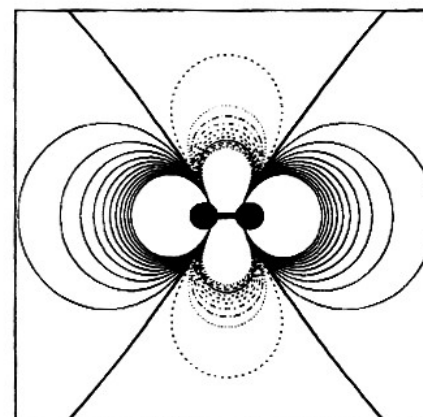


$$q = 0$$

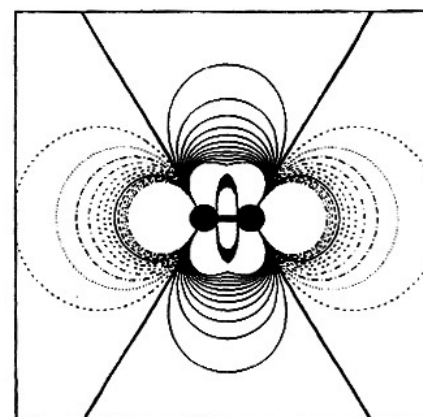
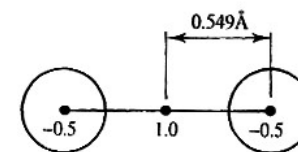
$$q = 0$$

$$\sim \frac{1}{R^6}$$

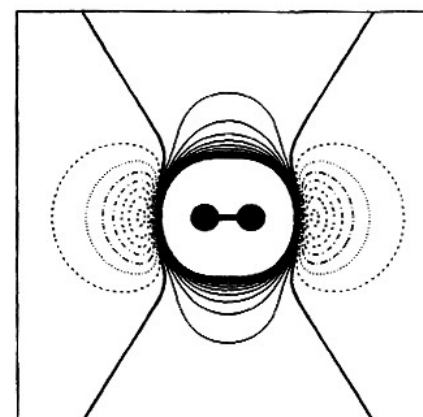
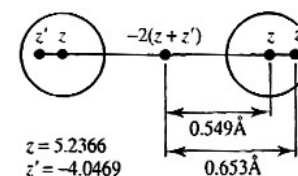
the fixed-charge model has no moments so the first term is dispersion energy



One additional charge=good



Two additional charges=better



QM potential energy map

## Problems, ways to improve

### *Polarization*

Molecules in condensed-phase environment acquire additional moments. This is a very strong effect that is seen even in molecular geometry, Polarization causes N-C distance in peptide bond to shorten while that of C-O bond to lengthen.

Table 1. Comparison of Peptide Bond Geometries from QM and Experimental Methods.

	Experimental			MP2/6-31 G(d) <sup>b</sup>		
	Gas <sup>c</sup>	Crystal <sup>d</sup>	Survey <sup>e</sup>	Gas	3H <sub>2</sub> O	H <sub>2</sub> O,2FM
Bonds						
C <sub>m</sub> —C	1.520 (5)	1.515 (3)	1.52 (1)	1.514	1.510	1.512
C—N	1.386 (4)	1.325 (3)	1.33 (1)	1.365	1.339	1.337
N—C <sub>m</sub>	1.469 (6)	1.454 (3)	1.45 (2)	1.448	1.454	1.454
C=O	1.225 (3)	1.246 (2)	1.23 (1)	1.232	1.255	1.254
Angles						
C <sub>m</sub> —C—N	114.1 (15)	116.3 (6)	116 (2)	115.3	117.1	116.6
O=C—N	121.8 (4)	121.7 (6)	123 (1)	123.1	122.1	122.6
C <sub>m</sub> —C=O	124.1	121.9 (6)	121 (4)	121.6	120.9	120.9
C—N—C <sub>m</sub>	119.7 (8)	121.3 (6)	122 (1)	122.1	121.1	121.3

Polarization is taken into account implicitly by:

- 1) Errors in QM theory
- 2) Adding water molecules to the model compounds in QM calculations
- 3) Taking molecular geometry from crystal structures
- 4) Increasing the dipole moment of studied compounds by about 15%
- 5) Optimizing dihedral angles against NMR data in liquid state or proteins in solution

Still fixed-charge force-fields are only about 5-15% accurate. The chemical accuracy of 1kCal/mol is out of reach.

## Polarization in local environment

*Better parametrization is unlikely to improve fixed-charge models by much. The fundamental problem is that they include polarization in an average sense.*

*Molecule in gas. Small dipole*

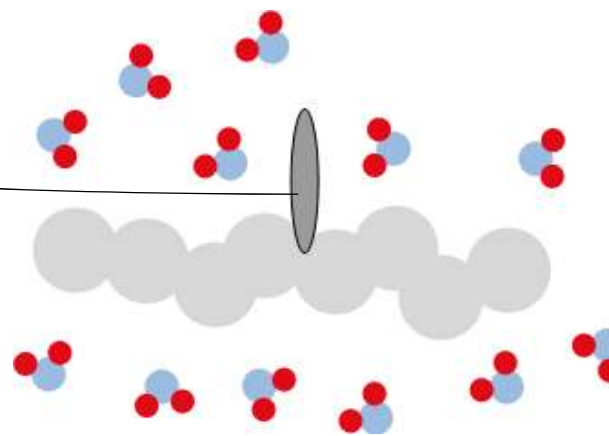
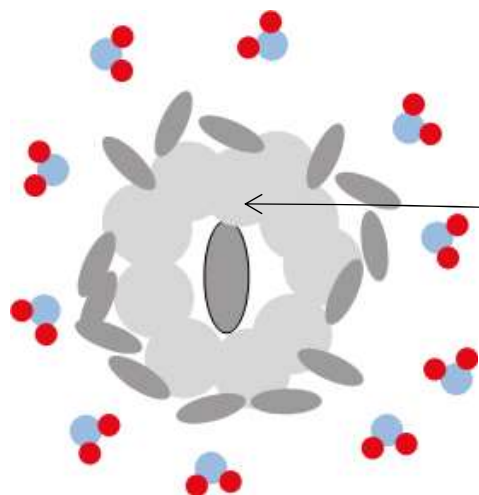


*Same molecule in polar medium, perhaps its own liquid. Increased dipole.*



*What happens during protein folding*

*The environment of target molecule changes. Could be transferred from polar medium where it's polarized to non-polar medium where it's dipole moment is small.*



*Polarization has to be included explicitly in order to make progress*

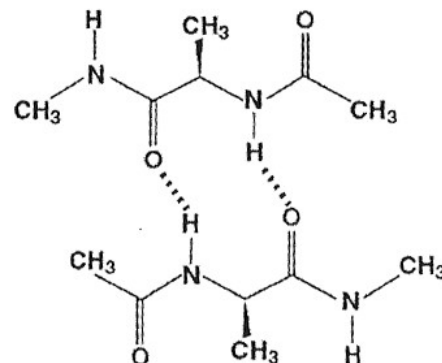
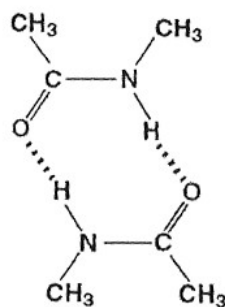
Baumketner, BioSim, Lviv 2019



## Polarizable force-fields

Three basic methods:

- 1) Fluctuating charge model
- 2) Drude oscillator
- 3) Induced dipole models



### Energy Model

### cis-NMA

### $\beta$ -sheet

### $\Delta E$

OPLS-AA	-11.5	-16.9	-5.4
CHARMM27	-11.6	-16.9	-5.3
AMBER <i>ff94</i>	-11.3	-14.8	-3.5
AMBER <i>ff02</i>	-13.5	-14.8	-1.3
AMOEBA	-18.5	-12.6	+5.9
SIBFA	-18.7	-17.1	+1.6
MP2/(CEP)4-31G+(2d)	-20.5	-17.5	+3.0
BP/DZVP ( <i>BSSE corrected</i> )	-16.2	-8.4	+7.8

Polarization seems to get the ordering of different structures right

## Two different types of physical processes, deterministic and stochastic

### Deterministic behavior:

The outcome of an experiment can be predicted exactly. Applies to many laws of physics: Newton's laws, Maxwell equations etc.

### Stochastic behavior:

The outcome of an experiment cannot be predicted exactly. This could be an intrinsic property of the physical object – quantum mechanics. Or, the lack of knowledge about the object = statistical mechanics. Fundamentally, all processes in nature are stochastic.

### Example: Dice



1) The outcome of rolling dice “experiment” consists of 6 different realizations. It can be fully described by a discrete variable  $g$  that takes on 6 values:

$$g_1, g_2, g_3, g_4, g_5, g_6$$

2) Although the laws of solid body mechanics are known, there is no way of predicting exactly the outcome of any experiment. Too many unknowns are involved: asymmetry in the mass distribution in the dice, temperature/pressure fluctuations, convection etc

For quantitative description of stochastic processes one needs the concept of distribution.

## Distributions:

Are easiest to introduce for discrete variables.

$g_1 \dots g_M$  possible realizations  
of quantity  $g$

If after  $M$  experiments value  $g_i$  is seen  
 $Mp(g_i)$  times then

$p(g_i)$  = probability distribution function

Important properties:

$p(g_i) \geq 0$ , always positive or zero

$\sum_{i=1}^M p(g_i) = 1$  has to be normalized, the  
sum is finite

Most generally:  $P(g_i) \rightarrow \frac{P(g_i)}{\sum_{i=1}^N P(g_i)}$

For continuous variables sum are replaced with integrals:

$x \in [a, b]$   $P(x)dx$  is the probability of seeing  $x$  in the interval  $[x, x+dx]$

$P(x)$  = probability distribution function

Normalization condition:  $\int_a^b P(x)dx = 1$

Averages:

By definition:

$$\langle g \rangle = \frac{1}{M} \sum_k g_k = \frac{1}{M} (g_1 + \overbrace{g_2 + g_2 + g_2}^{g_2 \text{ seen 3 times}} + g_3 + \dots) =$$

$k = \text{sum over different experiments}$

$$= \frac{1}{M} \sum_i^N M p(g_i) g_i = \sum_i^N p(g_i) g_i$$

$i = \text{sum over different realizations of variable } g$

For any function of  $g$  and normalized dist.:  $\langle f \rangle = \sum_{i=1}^M f(g_i) \cdot P(g_i)$

For any distr. funct.:  $\langle f \rangle = \frac{\sum_{i=1}^N f(g_i) P(g_i)}{\sum_{i=1}^N P(g_i)}$

Averages:  $\langle f \rangle = \int_a^b f(x) \cdot P(x) dx$

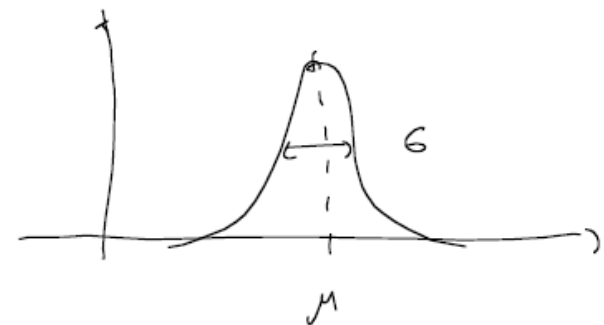
## Some basic definitions for distributions

$$\left\{ \begin{array}{ll} \mu = \int x \cdot p(x) dx & \text{mean value} \\ \sigma^2 = \int (x - \mu)^2 p(x) dx & \text{standard deviation} \\ \mu^n = \int (x - \mu)^n p(x) dx & \text{n-order moment} \\ & \text{(may or may not exist)} \end{array} \right.$$

$$\boxed{\mu, \sigma}$$

can be estimated from sampling

Geometrical interpretation



Say we have a sequence of measurements:

$$x_1, \dots, x_i, \dots, x_n$$

Average over the sample will approximate the mean value

$$\bar{x} = \frac{1}{n} \sum_{i=1}^n x_i \rightarrow \mu$$

Square deviation from the average will approximate the standard deviation:

$$s = \sqrt{\frac{1}{n-1} \sum_{i=1}^n (x_i - \bar{x})^2} \rightarrow \sigma$$

( $n-1$  comes from Bessel correction for finite  $n$ )

## Error estimate

Independent measurements

$$SE = \frac{S}{\sqrt{n}} \quad \text{sample error}$$

$$SD = \frac{S}{\sqrt{n}} \quad \text{standard error}$$

Correlated measurements

$$SE = \frac{S}{\sqrt{n}} \sqrt{\frac{1 + (n-1) \cdot \rho}{1 - \rho}}$$

$\rho = (\rho_{ij})$  correlation coefficient

$\rho = 0$  - for independent events

Examples:

$$P(x) = \frac{1}{\sqrt{2\sigma^2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2}} \quad \text{normal distribution}$$

Relative error:  $RE = \frac{SD}{\mu} \rightarrow \frac{S}{\mu} \frac{1}{\sqrt{n}}$

declines as inverse square root of the number of measurements.  $n$  must be large to achieve good accuracy

$$\sigma = \mu$$

Accuracy of SE

$n$	%
2	25
6	45

It's safe to use SE to estimate the error in the measurement for  $n > 10$

Wide distributions require larger number of steps to converge

$$RE = \frac{1}{\sqrt{n}}$$

$n$	%
100	10
10,000	1

$$\sigma = 0.1 \cdot \mu$$

$$RE = \frac{0.1}{\sqrt{n}}$$

$n$	%
100	1
10,000	0.1

## Transforming distribution functions

$X$  - is a stochastic variable characterized by  $P(x)$

$y = f(x)$  Q: what is distribution  $P(y) = ?$

From the definition of the probability distribution:

$$P(x) dx = P(y) \cdot dy \rightarrow$$

$$\rightarrow P(y) = \frac{P(x(y))}{\left| \frac{dy}{dx}(y) \right|} \quad (\text{probability density transformation theorem})$$

This can be written in a more convenient form :

$$P(y) = \frac{P(x(y))}{\left| \frac{df}{dx}(x(y)) \right|} = \int \delta(y - f(x)) P(x) dx = \langle \delta(y - f(x)) \rangle$$

change of variables rule for delta function

$$\int \delta(g(x)) f(g(x)) |g'(x)| dx =$$

$$\int \delta(u) f(u) du$$

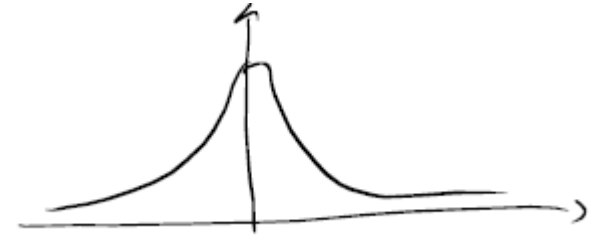
$$y' = f(x), \quad dx = \frac{dy'}{\left| \frac{df}{dx}(x(y')) \right|}$$



## Examples of probability transformations

1) Normal distribution with zero mean and  $\sigma=1$

$$p_n(x) = \frac{1}{\sqrt{2\pi}} e^{-\frac{x^2}{2}}$$



Q: what is the distribution of the linear transformation of variable  $x$ ?

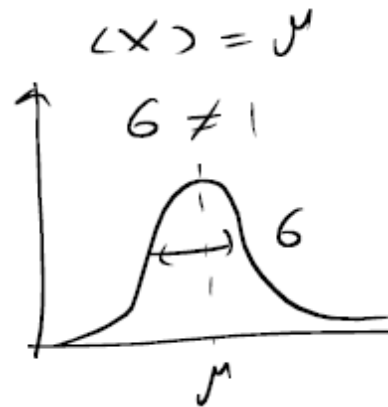
$$y = \mu + \sigma \cdot x$$

$$x = \frac{y - \mu}{\sigma} \rightarrow p_n(x(y)) = \frac{1}{\sqrt{2\pi}} e^{-\frac{(y - \mu)^2}{2\sigma^2}}$$

$$\frac{dy}{dx} = \sigma \rightarrow p(y) = \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{(y - \mu)^2}{2\sigma^2}}$$

$$y = \mu + \sigma \cdot x \rightarrow$$

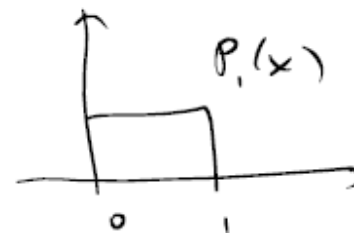
The shape of the distribution doesn't change. But now it is characterized by new mean and variance



Normal distribution with zero mean and unit standard deviation can be used to generate Gaussians with arbitrary mean and variance through linear transformation of the variable!

2) Uniform distribution:

$$P_1(x) = \begin{cases} 1 & 0 \leq x \leq 1 \\ 0 & \text{otherwise} \end{cases}$$



$$P(y) \cdot dy = P_1(x) \cdot dx$$

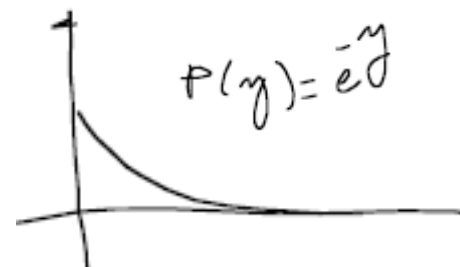
$$P(y) = \left| \frac{dx}{dy}(y) \right| \quad \text{since } P_1 = \text{const}$$

3) Exponential distribution:  $P(y) = e^{-y}$

arbitrary constant

$$\left| \frac{dx}{dy} \right| = e^{-y} \rightarrow x = e^{-y} + C \rightarrow y = -\log(x - C)$$

Set  $C = 0$  to get  $x(0) = 1, x(+\infty) = 0 \rightarrow y = -\log(x)$



4) Gaussian:  $P(y) \sim e^{-y^2}$

$$\frac{dx}{dy} \sim e^{-y^2} \rightarrow x(y) = \frac{2}{\sqrt{\pi}} \int_0^y e^{-y'^2} dy' = \text{Erf}(y), y \geq 0$$

$x(0) = 0, x(+\infty) = 1$

$y = \text{Erf}^{-1}(x)$  will generate normally distributed positive numbers.

*inversion of the error function can be costly numerically*

For negative numbers, use the property:

$$P(y) = P(-y)$$

Two random numbers  $x \in [0, 1]$

↓

$$e^{-y^2}$$

5) For distributions of arbitrary shapes: cumulative distribution transformation theorem

$P(y), y \in [y_1, y_2]$  target distribution. Define:  $F(y) = \int_{y_1}^y P(x') dx'$  cumulative dist.

$z = F^{-1}(x)$  what's dist. for this variable  $P_n(Z)$ ?  
 $\uparrow$   
 uniform  $[0,1]$

indeed, the desired distribution

$$P_n(z) dz = 1 dx \rightarrow P_n(z) = \frac{d}{dz} x(z), x(z) = F(z), \frac{dx}{dz} = \frac{dF(z)}{dz} = P(z), P_n(z) = P(z)$$

## Multivariate distributions

Multiple events can be observed simultaneously. For two variables  $x$  and  $y$  one introduces:

$\Gamma = (x, y)$  to denote a joint event

Joint distribution function  $P(x, y)$  is introduced so that  $P(x, y) dx dy$

is the probability of seeing  $x$  at  $[x, x+dx]$  and  $y$  at  $[y, y+dy]$

Distributions for individual variables:

Normalization condition:

$$P(x) = \int P(x, y) dy, P(y) = \int P(x, y) dx$$

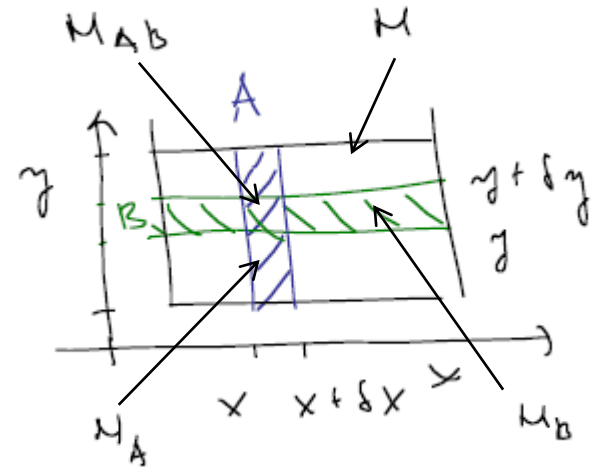
$$\int P(x, y) dx dy = 1$$

## Conditional probabilities

Assume 2-D for simplicity

Event  $A: [x, x + \delta x]$

Event  $B: [y, y + \delta y]$



$M$  = total # of 2D events

$M_A$  = # of  $A$      $M_{AB}$  = # of both  $A$  and  $B$  occurring at the same time

$M_B$  = # of  $B$

$$P(A, B) = \frac{M_{AB}}{M}$$

joint probability

Define conditional probability:

$P(A|B)$  = prob. of  $A$  once  $B$  occurred =

$$= \frac{M_{AB}}{M_B} = \frac{M \cdot M_{AB}}{M \cdot M_B} = \frac{P(A, B)}{P(B)}$$

$$\left. \begin{array}{l} \frac{P(A|B)}{P(B|A)} = \frac{P(A)}{P(B)} \end{array} \right\}$$

$$P(B|A) = \frac{M_{AB}}{M_A} = \frac{P(A, B)}{P(A)}$$

$$P(A|B) = P(B|A) \frac{P(A)}{P(B)}$$

Bayes' theorem

## Concept of independent events

Assume that event A is not conditioned upon event B. The conditional probability then is equal to the simple probability of event A:

$$P(A|B) = P(A)$$

The joint probability then becomes:

$$P(A, B) = P(A) \cdot P(B)$$

If this condition is met the events are known as independent. The distribution can be used to judge the degree of independence or correlation.

Quantitatively this can be measured by correlation coefficient:

$$\rho = \frac{\langle \Delta x \cdot \Delta y \rangle}{\sqrt{\Delta x^2} \sqrt{\Delta y^2}}$$

where  $x$  and  $y$  are two stochastic variables and

$$\Delta x = x - \langle x \rangle, \Delta y = y - \langle y \rangle$$

Case 1:  $x$  and  $y$  are independent:

$$\begin{aligned} \langle \Delta x \cdot \Delta y \rangle &= \iint (x - \langle x \rangle) \cdot (y - \langle y \rangle) \cdot p(x, y) dx dy = \\ &= \iint x \cdot y \cdot p(x) \cdot p(y) dx dy - \langle y \rangle \cdot \int x \cdot p(x) dx - \langle x \rangle \cdot \int y \cdot p(y) dy + \langle x \rangle \langle y \rangle \int p(x) \cdot p(y) dx dy = \\ &= \int x \cdot p(x) dx \int y \cdot p(y) dy - 2\langle x \rangle \langle y \rangle + \langle x \rangle \langle y \rangle = \\ &= \langle x \rangle \langle y \rangle - \langle x \rangle \langle y \rangle = 0 \end{aligned}$$

Case 2: x and y are fully correlated  $x = \alpha y$ ,  $\alpha > 0$

$$\langle \Delta x \cdot \Delta y \rangle = \alpha \cdot \langle \Delta y^2 \rangle, \quad \rho = \frac{\alpha \cdot \langle \Delta y^2 \rangle}{\sqrt{\alpha^2 \langle \Delta y^2 \rangle} \sqrt{\langle \Delta y^2 \rangle}} = 1$$

Case 3: x and y are fully anti-correlated  $x = -\alpha y$ ,  $\alpha > 0$

$$\langle \Delta x \cdot \Delta y \rangle = -\alpha \cdot \langle \Delta y^2 \rangle, \quad \rho = \frac{-\alpha \cdot \langle \Delta y^2 \rangle}{\alpha \cdot \langle \Delta y^2 \rangle} = -1$$

What multivariate distributions can be used for

Generation of normal distributions. Let x and y be random variables uniformly distributed between 0 and 1. Introduce new variables:

$$\begin{aligned} x' &= \sqrt{-2 \log(x)} \cos(2\pi y) \\ y' &= \sqrt{-2 \log(x)} \sin(2\pi y) \end{aligned} \quad x'^2 + y'^2 = -2 \log(x) \rightarrow x = e^{-\frac{1}{2}(x'^2 + y'^2)}$$



Transformation of the joint distribution function:

$$P(x) = P_1(x), P(y) = P_1(y)$$

$$P(x', y') dx' dy' = P_1(x) \cdot P_1(y) \cdot dx dy$$

$$P(x', y') \left| \frac{\partial(x', y')}{\partial(x, y)} \right| \cdot dx dy = dx dy$$

$$\longrightarrow P(x', y') = \frac{1}{\left| \frac{\partial(x', y')}{\partial(x, y)} \right|}$$

Jacobian of the transformation

$$\left( \begin{array}{l} \frac{\partial x'}{\partial x} = -\frac{1}{\sqrt{2 \log(x)}} \cdot \frac{1}{x} \cos(2\pi y) \quad , \quad \frac{\partial x'}{\partial y} = \sqrt{2 \log(x)} \cdot 2\pi \sin(2\pi y) \\ \frac{\partial y'}{\partial x} = -\frac{1}{\sqrt{2 \log(x)}} \cdot \frac{1}{x} \sin(2\pi y) \quad , \quad \frac{\partial y'}{\partial y} = -\sqrt{2 \log(x)} \cdot 2\pi \cos(2\pi y) \end{array} \right) = \frac{2\pi}{|x|}$$

$$\downarrow$$

$$P(x', y') = \frac{|x|}{2\pi}$$

$$\downarrow$$

$$P(x', y') = \frac{1}{2\pi} e^{-\frac{1}{2}(x'^2 + y'^2)} = \frac{1}{\sqrt{2\pi}} e^{-\frac{1}{2}x'^2} \cdot \frac{1}{\sqrt{2\pi}} e^{-\frac{1}{2}y'^2} = P_n(x') \cdot P_n(y')$$

two uniformly  
distributed numbers  
x and y



two normally  
distributed  
numbers x' and y'

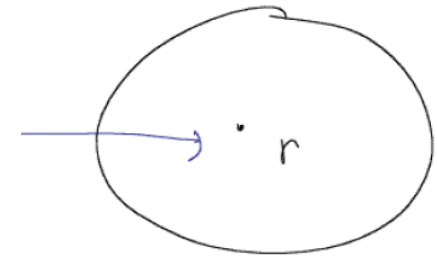
# Statistical mechanics = theory to extract macroscopic properties from microscopic variables

Microscopic description:



$$\left\{ \begin{matrix} (q_1, \dots, q_N) \\ (p_1, \dots, p_N) \end{matrix} \right\} (q, p) = r$$

2N-D phase space:



Coordinates + momenta fully define the state of a system with N degrees of freedom

Measuring property  $A(\Gamma)$  always yields time average (take pressure in tires for example):

$$A_{obs} = \langle A \rangle_{time} = \langle A(r(t)) \rangle_{time} = \lim_{t_{obs} \rightarrow \infty} \frac{1}{t_{obs}} \int_0^{t_{obs}} A(r(t)) dt$$

*real or virtual experiment* *observation time*

Observation time  $t_{obs}$  is always finite. Furthermore, in practice it is always discretized so that the integral can be carried out.:

$$t_{obs} = \delta t \cdot T_{obs} \quad - \quad T_{obs} = \# \text{ of steps/events in the observation}$$

{ *must be large enough to eliminate dependence on the initial conditions*

The expression for the observable now reads:

$$(*) A_{obs} = \langle A \rangle_{time} = \frac{1}{\tau_{obs}} \sum_{\tau=1}^{\tau_{obs}} A(\Gamma(\tau)),$$

$\tau$  is now just a blind index that enumerates all measurements

Recall how we computed averages for random variables:

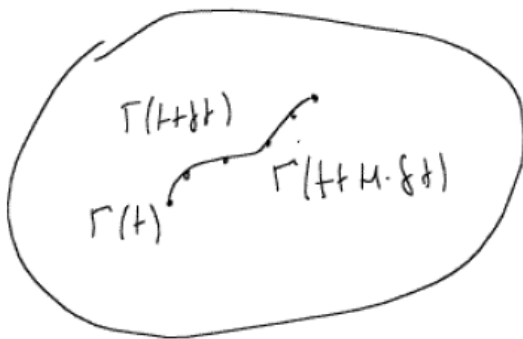
$$\langle g \rangle = \frac{1}{M} \sum_k^M g_k = \frac{1}{M} (g_1 + g_2 + g_2 + g_2 + g_3 + \dots)$$

it's the same formula

On one hand we have time evolution but on the other – different realizations of some random variables that can be described by certain distribution. Both descriptions lead to the same average. The one based on distributions is the subject of statistical mechanics.

## The concept of ensembles

### Time evolution of one system

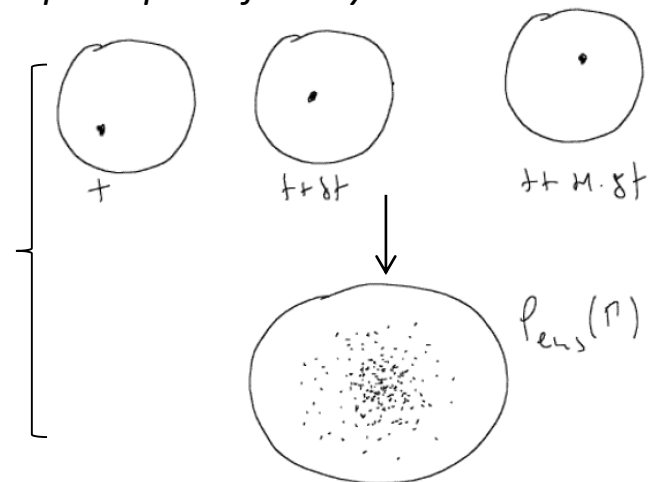


The same state point  $\Gamma$  can be visited multiple times

Ensemble = Multiple copies of the system at time  $t=0$

Points in the phase space are distributed according to certain function

$$\rho_{ens}(\Gamma) = \frac{1}{N} \sum_i \delta(\Gamma - \Gamma_i)$$



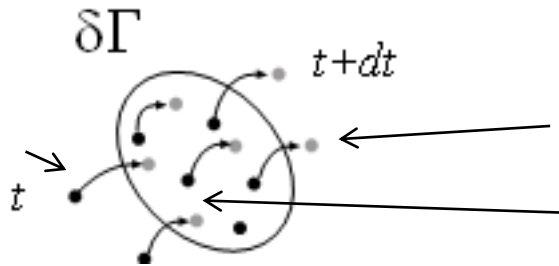
At first glance the connection between time average and ensemble average appears to be straightforward. But there are important subtleties.

Let us consider  $N$  members of the ensemble, each corresponding to a gamma point  $\Gamma_i$ . Consider that in general the distribution function may have explicit dependence on time. See what happens in a certain volume  $\delta\Gamma$  when the time changes from  $t$  to  $t+dt$ .

$$N_{points} = NP_{ens}(\Gamma, t)\delta\Gamma$$

1) Some points will enter the volume

4) None will be created or destroyed



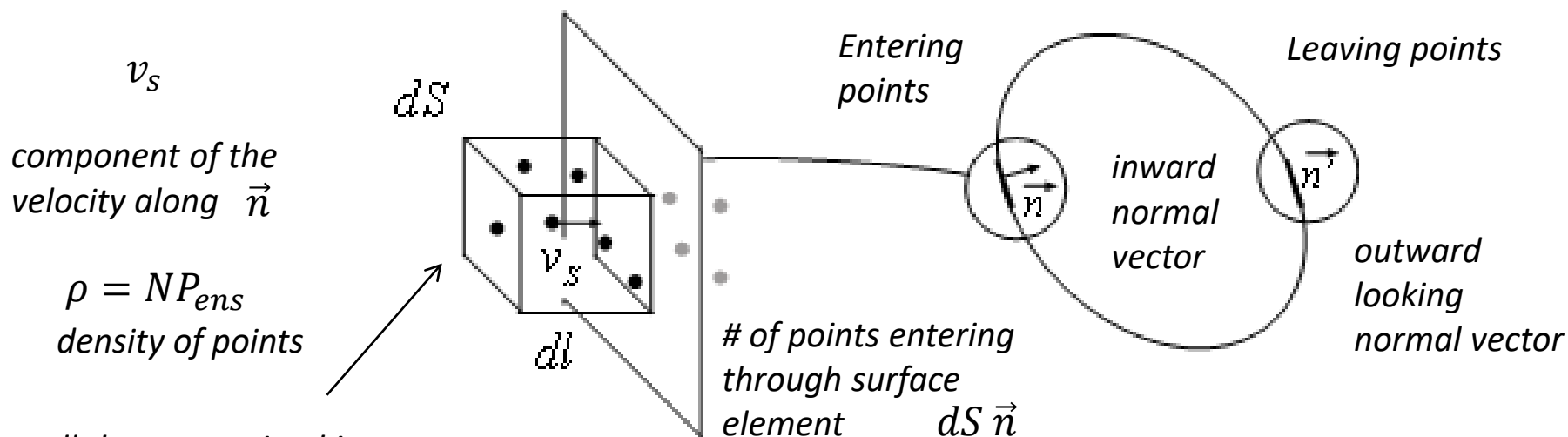
2) Some will leave it

3) Some will remain within the volume

The balance equation for the number of points:

$$\begin{array}{ccc}
 \text{change in the} & \text{difference between} & \text{sink/source term} \\
 \text{number of points} & \text{leaving/entering per} & \\
 & \text{unit time} & \\
 N\delta\Gamma \frac{\partial}{\partial t} P_{ens}(\Gamma, t) = N(\text{enter}) - N(\text{leave}) & + & F(\Gamma, t) \\
 & \uparrow & \nwarrow \\
 & \text{can be computed as} & =0, \text{ not present} \\
 & \text{surface integral of} & \\
 & \text{the flux} & 
 \end{array}$$

Let's forget about momenta in  $\Gamma$  for the moment and focus on Cartesian coordinates only



all those contained in this parallelepiped

$$N(\text{enter}) = \frac{\rho dS dl}{dt} = \frac{\rho dS v_s dt}{dt} = \vec{J} \vec{n} dS$$

$$\vec{J} = \rho \vec{v}$$

flux = the number of points passing through the boundary per unit surface area per unit time

$$N(\text{leave}) = \vec{J} \vec{n}' dS$$

surface integral of flux

divergence theorem

$$N(\text{enter}) - N(\text{leave}) = - \oint \vec{J} \vec{n}' dS = - \int (\vec{\nabla} \cdot \vec{J}) dV \approx -N(\vec{v} \cdot \vec{\nabla} P_{ens}) \delta \Gamma$$

$$\vec{J} \vec{n}' dS \text{ outward looking normal vector}$$

Putting the estimate into the balance equation:

$$N\delta\Gamma \frac{\partial}{\partial t} P_{ens}(\Gamma, t) = -N(\vec{v}\vec{\nabla} P_{ens})\delta\Gamma$$

↓

$$\frac{\partial}{\partial t} P_{ens}(\Gamma, t) + (\vec{v}\vec{\nabla} P_{ens})=0$$

↓

$$\frac{\partial}{\partial t} P_{ens}(\Gamma, t) + \dot{\vec{r}} \frac{\partial}{\partial \vec{r}} P_{ens}=0$$

If we add momenta back to the equation we will get (by analogy):

$$\frac{\partial}{\partial t} P_{ens}(\Gamma, t) + \dot{\vec{r}} \frac{\partial}{\partial \vec{r}} P_{ens} + \dot{\vec{p}} \frac{\partial}{\partial \vec{p}} P_{ens}=0$$

↓

$$\left( \frac{\partial}{\partial t} + \dot{\vec{r}} \frac{\partial}{\partial \vec{r}} + \dot{\vec{p}} \frac{\partial}{\partial \vec{p}} \right) P_{ens}(\Gamma, t) = 0$$

↓

$$\frac{dP_{ens}(\Gamma, t)}{dt} = 0 \quad \frac{d\rho_{ens}(\Gamma, t)}{dt} = 0.$$

*Liouville equation*

*The probability distribution is constant along any trajectory*



In equilibrium the probability distribution can not depend on time. Because otherwise the averages would depend on time as well. That contradicts the definition of “equilibrium”. Therefore:

$$P_{ens}(\Gamma, t) = P_{ens}(\Gamma) \longrightarrow \frac{\partial}{\partial t} P_{ens}(\Gamma, t) = 0$$

$$N(enter) - N(leave) = 0$$

*for any point in the phase space. The number of points occupying it is conserved.*

The system is evolving in is such a way that

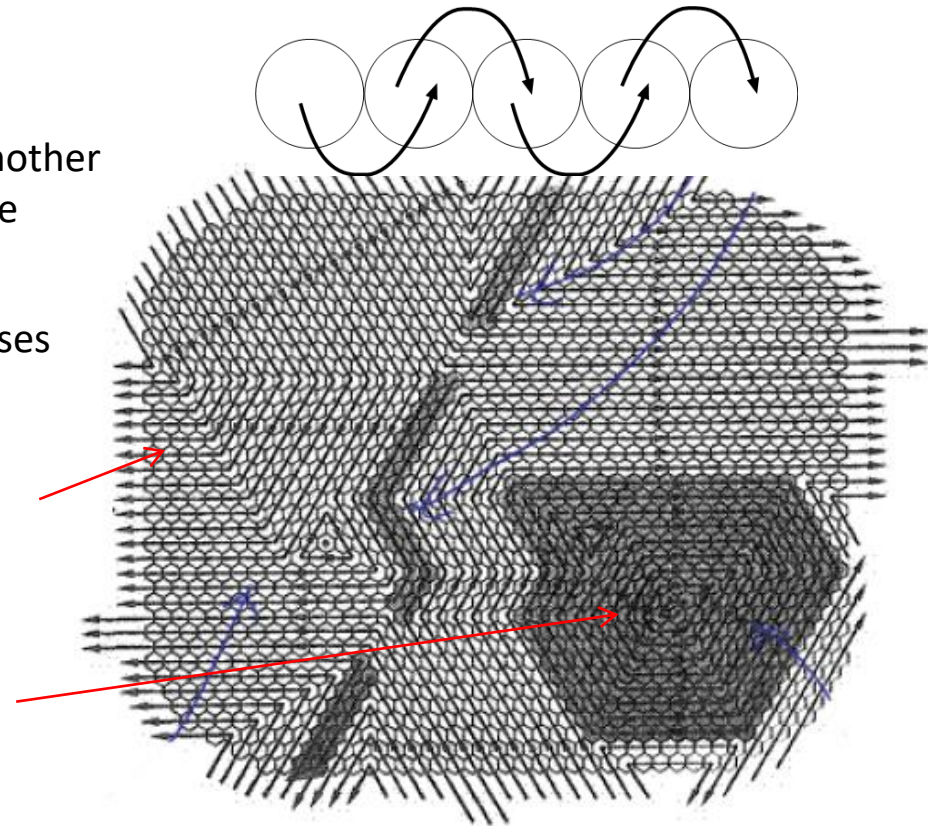
$$P_{ens}(\Gamma) = \text{const} \quad \text{at each point}$$

As one point exits certain cell in the phase space, another point immediately enters it. As a result, all points are moving in concert in what resembles a Conga line.

The line snakes around the phase space as time passes by. How this happens has important consequences.

Option 1. The snakes passes through all points available in the phase space. The entire phase space is accessible. Ergodic behavior.

Option 2. There are regions in the phase space from which the snake cannot break out. It moves in a circular manner. Non-ergodic behavior.



In ergodic systems, all phase points are visited multiple times during a simulation. Only in this case is the time average equal to ensemble average (with particular distribution function)

$$A_{obs} = \boxed{\langle A \rangle_{time} = \langle A \rangle_{ens}} = \frac{\sum_r A(r) \cdot p_{ens}(r)}{\sum_r p_{ens}(r)}$$

- 1) Determining whether or not a system is ergodic is not a trivial task. Rigorous proof exists only for a few model systems, such as coupled harmonic oscillators.
- 2) There are different reasons for non-ergodicity
  - a) Frustration – multiplicity of potential energy minima of the same depth prevents their thorough exploration
  - b) Low temperature. Creates very high barriers in the free energy landscape that can be overcome. The system becomes locked up in certain parts of the phase space. Glass transition is one example.
- 3) Certain models are known to be non-ergodic. For instance, certain lattice models of proteins
- 4) It's easy to design a non-ergodic system. All it takes is to arrange a circular movement in the phase space. Can be achieved through specific Monte Carlo moves.

## Stat mech. .vs. thermodynamics

Normalization constant of the probability distribution is not needed to compute averages. Consider

$$\rho_{ens}(\Gamma) \quad \text{and another distribution proportional to it} \quad \rho'_{ens}(\Gamma) = \alpha \rho_{ens}(\Gamma)$$

According to the definition:

$$\begin{aligned} \langle A \rangle' &= \sum_{\Gamma} A(\Gamma) \rho'_{ens}(\Gamma) / \sum_{\Gamma} \rho'_{ens}(\Gamma) = \sum_{\Gamma} A(\Gamma) \alpha \rho_{ens}(\Gamma) / \sum_{\Gamma} \alpha \rho_{ens}(\Gamma) = \\ &= \sum_{\Gamma} A(\Gamma) \rho_{ens}(\Gamma) / \sum_{\Gamma} \rho_{ens}(\Gamma) = \langle A \rangle \end{aligned}$$

But this quantity is central to establishing link between microscopic description in terms of coordinates/momenta and macroscopic description in terms of thermodynamic functions

$$Q_{ens} = \sum_{\Gamma} \rho_{ens}(\Gamma)$$

← *partition function=*  
the sum of  $\rho_{ens}(\Gamma)$   
over all possible states

$$\langle A \rangle_{ens} = \sum_{\Gamma} A(\Gamma) \rho_{ens}(\Gamma) / Q_{ens}$$
$$\Psi_{ens} = -\log(Q_{ens})$$

*Thermodynamic potential of the given ensemble*

*The function that reaches minimum in equilibrium.*

## Common ensembles

### Microcanonical ensemble (NVE)

all configurations  
with energy  $E$  are  
equiprobable

Physical equivalent= an  
isolated system

Distribution function:

$$\rho_{\text{ens}} \sim \delta(E - H(\Gamma))$$

Hamiltonian:

$$H(\Gamma) = E_k + E_p = \sum_i \frac{\vec{p}_i^2}{2m_i} + U(\vec{q}_1, \dots, \vec{q}_N)$$

Partition function:

$$Q_{NVE} = \sum_{\Gamma} \delta(E - H(\Gamma))$$

volume of the hypersurface  
that corresponds to energy  $E$

proportionality constant first introduced on the grounds of  
dimensionalities. Then recognized as the Plank constant when  
QM came about

$$Q_{NVE} = \frac{1}{N! h^{3N}} \int d\vec{p} d\vec{q} \delta(E - H(\Gamma))$$

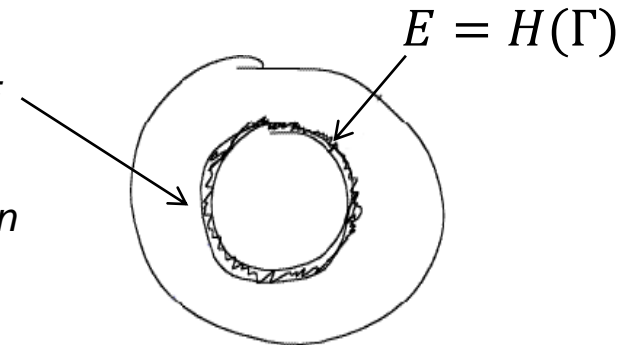
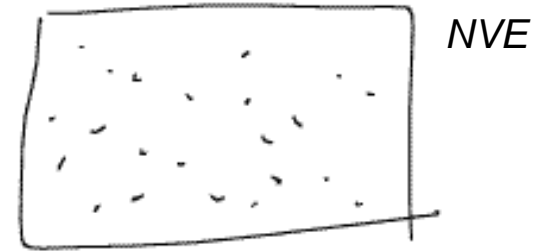
takes care of the distinguishability of the particles

Thermodynamic potential:

$$\Psi_{NVE} = -k \log(Q_{NVE}) = -S(N, V, E)$$

Boltzmann's constant

entropy



$$\begin{array}{c} \#1 \\ | \\ \#2 \end{array} = \begin{array}{c} \#2 \\ | \\ \#1 \end{array}$$

the integral counts  
these contributions  
twice

## Canonical ensemble (NVT)

### Distribution function:

$$\rho_{NVT}(\Gamma) \sim e^{-\beta H(\Gamma)}, \beta = \frac{1}{kT}$$

↑

external parameter that is associated with temperature

### Partition function:

$$Q_{NVT} = \sum_{\Gamma} e^{-\beta H(\Gamma)} = \sum_E n(E) e^{-\beta E}$$

density of states

separation of the partition function

$$Q_{NVT} = \frac{1}{h^{3N} N!} \int d\vec{p} d\vec{q} e^{-\beta H(\Gamma)} = \frac{1}{h^{3N} N!} \int d\vec{p} e^{-\beta E_K} \int d\vec{q} e^{-\beta U(\vec{q})} =$$

kinetic part

configuration integral

$$Q_{NVT}^{id} \times Q_{NVT}^{ex} \quad Q_{NVT}^{id} = \frac{V^N}{N! \lambda^{3N}}, \lambda = \sqrt{h^2 / 2\pi m k T} \quad Q_{NVT}^{ex} = \frac{Z_{NVT}}{V^N}, Z_{NVT} = \int d\vec{q} e^{-\beta U(\vec{q})}$$

### Thermodynamic potential:

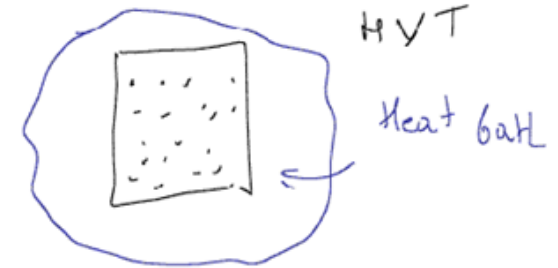
$$\Psi_{NVT} = F(N, V, T) = -kT \log(Q_{NVT}) = F_{id}(N, V, T) + F_{ex}(N, V, T)$$

Helmholtz free energy

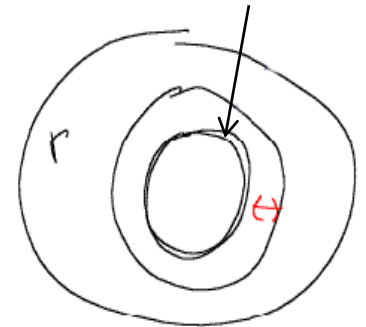
ideal gas part

excess part (due to interactions)

Physical equivalent = system exchanging heat with the environment



multiple hypersurfaces are populated with the probability  $\sim n(E) e^{-\beta E}$



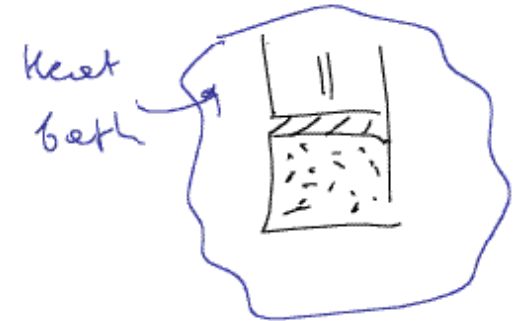
# *Isothermal-isobaric ensemble (NPT)*

*Physical equivalent= system under a piston*

Distribution function:

$$\rho_{NPT}(\Gamma) \sim e^{-\beta(H(\Gamma,V)+PV)}$$

external parameter associated with pressure



Partition function:

$$Q_{NPT} = \sum_V \sum_{\Gamma} e^{-\beta(H(\Gamma,V)+PV)} = \sum_V Q_{NVT} e^{-\beta PV}$$

*separation of the partition function*

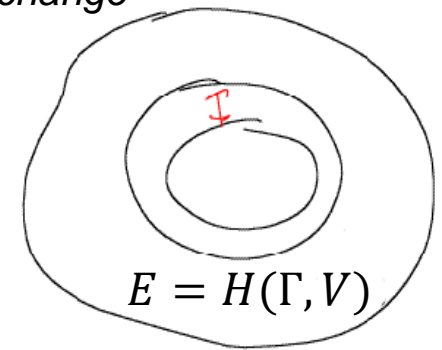
*both energy and volume are allowed to change*

$$Q_{NPT} = \frac{1}{h^{3N} N! V_0} \int dV \int d\vec{p} d\vec{q} e^{-\beta(H(\Gamma,V)+PV)} = \frac{1}{h^{3N} N! V_0} \int d\vec{p} e^{-\beta E_K} \times$$

$$\times \int dV e^{-\beta PV} \int d\vec{q} e^{-\beta U(q)} = \frac{1}{N! \lambda^{3N} V_0} Z(N, P, T)$$

$$Z(N, P, T) = \int dV e^{-\beta PV} Z_{NVT}$$

configuration integral



Thermodynamic potential:

$$\Psi_{NPT} = G(N, P, T) = -kT \log(Q_{NPT}) = G_{id}(N, P, T) + G_{ex}(N, P, T)$$

ideal gas part

excess part (due to interactions)

Gibbs free energy

(both contain contributions from configuration integral)



## Grand canonical ensemble ( $\mu VT$ )

### Distribution function:

$$\rho_{\mu VT}(\Gamma) \sim e^{-\beta(H(\Gamma, V) - \mu N)}$$

external parameter  
associated with chemical  
potential

### Partition function:

$$Q_{\mu VT} = \sum_N \sum_{\Gamma} e^{-\beta(H(\Gamma, V) - \mu N)} = \sum_N Q_{NVT} e^{\beta \mu N}$$

no separation but the kinetic part can be integrated  
explicitly

$$Q_{\mu VT} = \sum_N e^{\beta \mu N} Q_{NVT}^{id} Q_{NVT}^{ex} = \sum_N e^{\beta \mu N} \frac{1}{N! \lambda^{3N}} Z(N, V, T)$$

key property to be evaluated

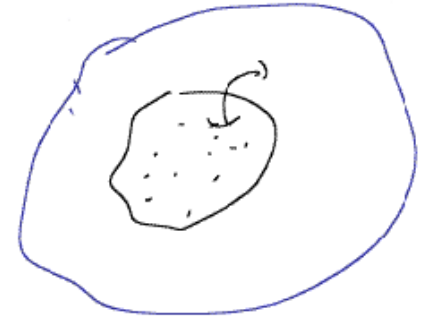
### Thermodynamic potential:

$$\Psi_{\mu VT} = \Phi_G(\mu, V, T) = -kT \log(Q_{\mu VT}) = F - \mu N = -PV$$

grand canonical  
potential

chemical potential

Physical equivalent=  
system exchanging heat  
and particles with the  
environment



energy and number of  
particles are allowed to  
change

# Summary on ensembles/thermodynamic functions

*Microcanonical (primary)*

$$\frac{S(N,V,E)}{k} = \log(Q_{NVE})$$

*entropy*

$\mu T P$  is not an ensemble. it contains only intensive variables some of which are related

*Canonical*

$$F(NTV) = -kT \log(Q(NTV)) = E - TS$$

*Helmholz free energy*

*Isobaric-isothermic*

$$G(NPT) = -kT \log(Q(NPT)) = F + PV$$

*Gibbs free energy*

*Grand canonical*

$$\Phi(\mu TV) = -kT \log(Q(\mu TV)) = F - \mu N = -PV$$

*Grand canonical or Hill free energy*

Link to thermodynamics

*Fundamental law:*

*Gibbs free energy  $\sim N$  because it's an extensive variable*

$$TdS = dU + pdV - \mu dN$$

↓

$$dF = -pdV - sdT + \mu dN \rightarrow \frac{\partial F}{\partial N} \Big|_{TV} = \mu$$

↓

$$dG = Vdp - sdT + \mu dN \rightarrow \frac{\partial G}{\partial N} \Big|_{TP} = \mu$$

$$G(NPT) = Nf(PT) \rightarrow f(PT) = \frac{\partial G}{\partial N} \Big|_{TP} = \mu$$

↓

$$G(NPT) = N\mu$$

↓

$$\Phi = F - \mu N = G - PV - \mu N = -PV$$

## Monte Carlo method

Monte Carlo – a class of algorithms that rely on random sampling to obtain numerical results

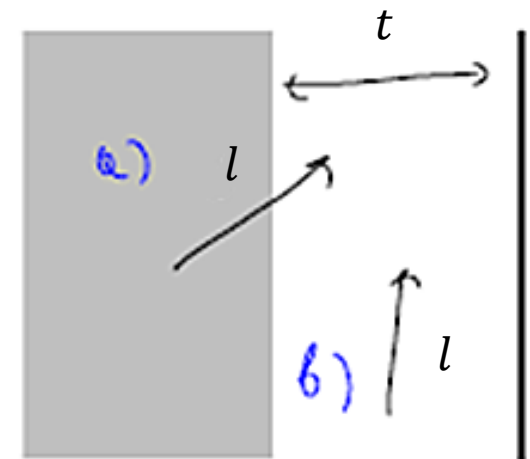
- a) *Developed by Ulam, von Nuemann and Metropolis in the 40's to model diffusion of neutrons in fissile material.*
- b) *The term is the codename coined after Monte Carlo casino where Ulam's uncle used to borrow money to gamble.*
- c) *Many flavors exist designed to address specific problems*
- d) *Use in math: applied statistics – the inference problem, integration, optimization, inverse problems etc.*
- e) *Under the name of Markov Chain Monte Carlo (MCMC), used widely in physics, chemistry, biology, finance, quantitative linguistics etc*

The main idea: use **stochastic** methods (random sampling) to solve **deterministic equations**.

How is that possible?      Why is that needed?

### Example: Buffon's needle experiment

*A needle of length  $l$  is thrown onto a striped field. What is the probability that the needle will cross the middle line?*



*Two outcomes of the experiment:  
a) Needle crosses the middle line  
b) Needle doesn't cross the line*

The state of the needle is defined by two variables:

a)  $x$  – the center of the needle

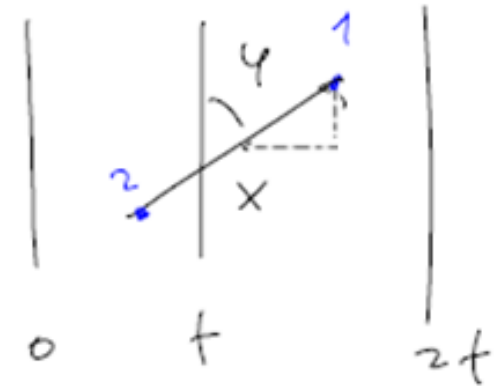
a)  $\varphi$  – the angle it makes with the vertical axis

$x$  and  $\varphi$  are random variables, independently distributed.

$P(x), P(\varphi), P(x, \varphi)$  : are all uniform distributions – no preferential  $x$  or  $\varphi$ .

$$P(x, \varphi) = \frac{1}{\pi} \cdot \frac{1}{2t}, \quad \int P(x, \varphi) dx d\varphi = 1$$

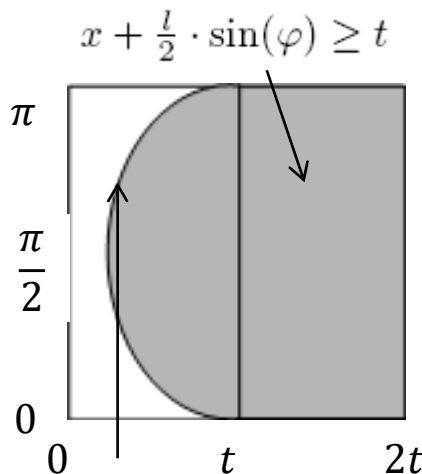
The needle crosses the line when  $x$  coordinate of points 1 and 2 satisfies the following conditions:



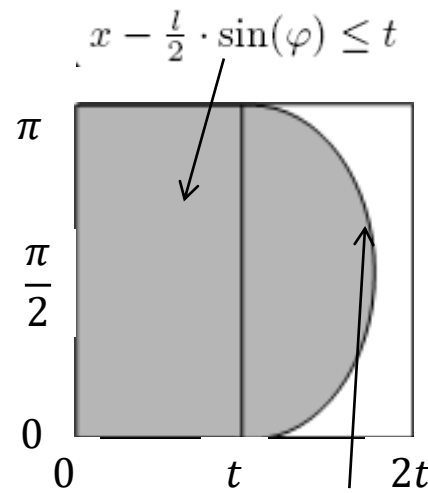
2D configuration space

$$\begin{cases} x \in [0, 2t] \\ \varphi \in [0, \pi] \end{cases}$$

①



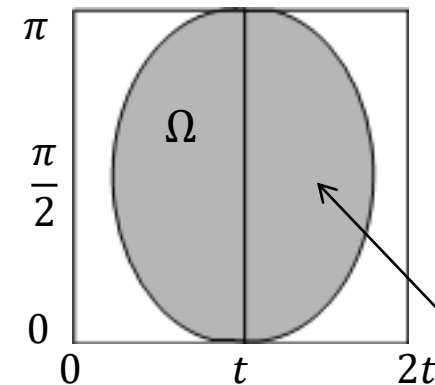
②



$$x = t - \frac{l}{2} \sin(\varphi)$$

$$x = t + \frac{l}{2} \sin(\varphi)$$

① and ②



surface area



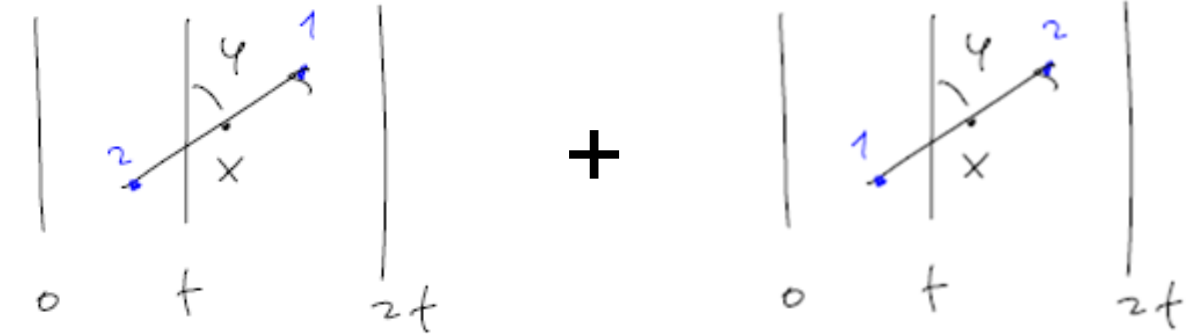
$$\begin{aligned} P_{1/2} &= \iint dx d\varphi P(x, \varphi) = \frac{1}{\pi 2t} S_c(\Omega) = \\ &= \frac{1}{\pi 2t} 2 \frac{l}{2} \int_0^\pi \sin(x) dx = \frac{2l}{\pi 2t} = \frac{l}{\pi t} \end{aligned}$$

Full probability:

$$P_{\text{crossing}} = 2P_{1/2} = \frac{2l}{\pi t}$$



$$\pi = \frac{2l}{tP_{\text{crossing}}}$$



follows from a stochastic process

deterministic result=exact number

Lazzarini's experiment: **3408** trials

$$\pi = \frac{355}{113} = 3.1415929 \quad 10^{-7} \text{ accuracy}$$

### Example: hit and miss integration

Throw particles(generate pairs of random numbers) on this square and count how many fall within the circle  $r=1$ . The goal is to compute  $\pi$ .

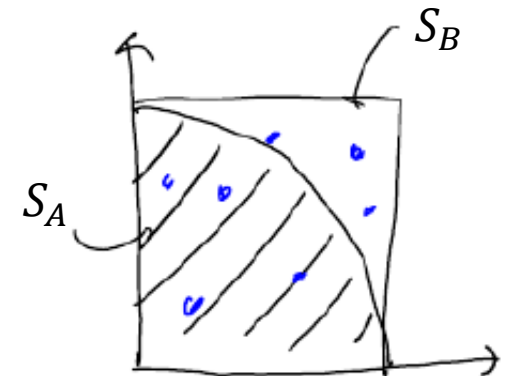
If particles are distributed uniformly then:

$P_A$  - probability to hit circle  
 $P_B$  - probability to square

$$\begin{cases} P_A \approx S_A = \frac{\pi}{4} \\ P_B \approx S_B = 1 \end{cases}$$

$$\downarrow$$

$$\frac{P_A}{P_B} = \frac{S_A}{S_B} = \frac{\pi}{4}$$



$$\begin{cases} S_A = \pi r^2 / 4 = \frac{\pi}{4} \\ S_B = r^2 = 1 \end{cases}$$

If the number of particles hitting the circle is  $n_A$  and those hitting the square is  $n_B$ :

$$\pi = \frac{4n_A}{n_B}$$

Accuracy estimates:

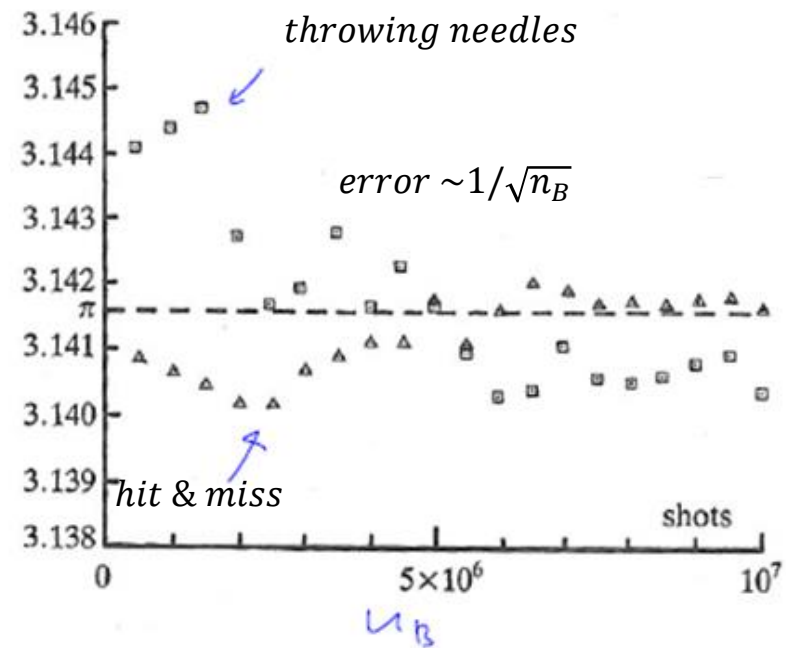
Hit & miss: **3.141 7 3** after  $10^7$  shots  
↙  $10^{-4}$  accuracy

Needles: **3.14 0 472** after  $10^7$  shots  
↙  $10^{-3}$  accuracy

Conclusion: Lazzarini was able to compute  $\pi$  with  $10^{-7}$  accuracy after  $\sim 10^4$  shots so he:

- a) cheated
- b) had a VERY lucky afternoon with numbers!

Convergence tests





## Sample mean integration

Hit & miss experiment is an example of the “sample mean” integration method.

Goal: compute  $F = \int_{x_1}^{x_2} f(x) dx$

$$\text{Rewrite } F = \int_{x_1}^{x_2} f(x) dx = \int_{x_1}^{x_2} \frac{f(x)}{\rho(x)} \cdot \rho(x) dx = \begin{cases} \rho(x) - \text{arbitrary} \\ \text{distribution} \\ \text{function} \end{cases}$$

If  $N_\tau$  trials are performed to sample random variable  $\xi$ , distributed according to  $\rho(\xi)$ , then

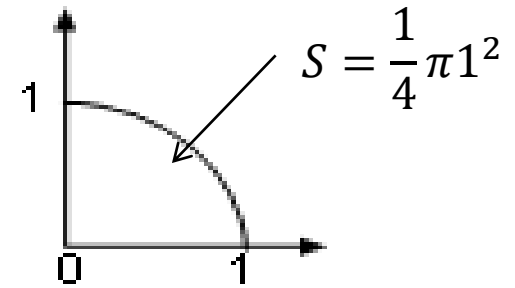
$$F = \left\langle \frac{f(\xi)}{\rho(\xi)} \right\rangle_{\text{trials}} = \frac{1}{N} \sum_i^N \frac{f(\xi_i)}{\rho(\xi_i)} \quad \leftarrow \begin{array}{l} \text{the average is} \\ \text{taken over different} \\ \text{trials} \end{array}$$

**Example:**

$$\text{uniform distribution } \rho(x) = \begin{cases} \frac{1}{x_2 - x_1} & x_2 \leq x \leq x_1 \\ 0 & \text{otherwise} \end{cases} \longrightarrow F = \frac{x_2 - x_1}{N} \sum_i^N f(\xi_i)$$

Compute  $\pi$  number by the sample mean method:

$$f(x) = \sqrt{1-x^2}, x \in [0, 1], \int_0^1 \sqrt{1-x^2} dx = \frac{\pi}{4}$$



$$\pi \approx 3.14169 \text{ for } N = 10^7$$

$10^{-4}$  accuracy

same accuracy as the hit and miss method

Simpson's integration rule:

$$\pi = 3.141593 \text{ after } 10^4 \text{ steps!}$$

$10^{-6}$  accuracy

*The stochastic method is not competitive!*

The cost of Simpson's rule (or similar quadrature method based on interpolation) is prohibitive for multi-dimensional integrals!

$$D = n \longrightarrow \int f(\vec{x}) dx_1 \dots dx_n \quad n_s - \text{number of sample points per dimension} \quad n_s^n - \text{number of function evaluations}$$

$$\begin{cases} n = 300 \\ n_s = 10 \end{cases} \quad \begin{array}{l} \text{for an ensemble of 100} \\ \text{particles} \end{array}$$

$10^{300}$  function evaluations. That's an astronomical number that no computer can handle!

For integrals of high dimensionality *stochastic* methods remain the only viable option

Two steps involved in the integration using uniform  $\rho$ :

(in math this method is known as random Monte Carlo integration)

1) Pick a point in the configuration space  $(\vec{r}_1 \dots \vec{r}_N)$  by generating  $3N$  random numbers uniformly

2) Compute the potential energy  $U(\vec{r}_1 \dots \vec{r}_N)$  and the integrand for select  $\beta$

Repeat these steps  $N_s$  times and compute the configuration integral as:

$$Z(N, V, T) = \frac{1}{N_s} \sum_{i=1}^{N_s} e^{-\beta U(\vec{r}_1(i) \dots \vec{r}_N(i))}$$

Problems with the uniform  $\rho$ :

1)  $N_s$  has to be VERY large. For most systems of practical interest in physics convergence is not attainable.

2) Ensemble averages  $\langle A \rangle = \frac{\sum A_i e^{-\beta U_i}}{\sum e^{-\beta U_i}}$  are even less accurate and in most cases meaningless

↖ a number with large uncertainty in the denominator

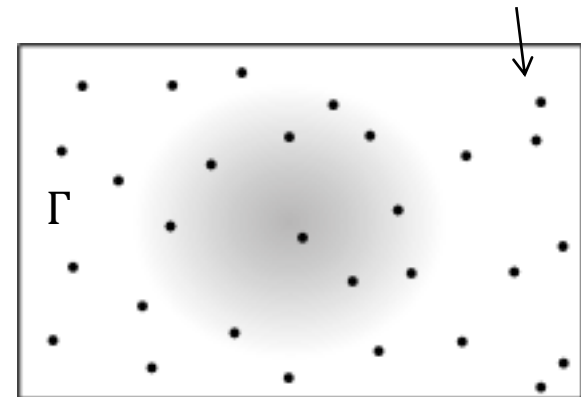
Focus on the configuration integral of the canonical ensemble.

$$Z(N, V, T) = \int e^{-\beta U(\vec{r}_1 \dots \vec{r}_N)} d\vec{r}_1 \dots d\vec{r}_N$$

↑  
Cartesian coordinates

the integral has to converge with  $N_s$

for many evaluation points  $e^{-\beta U} \sim 0$



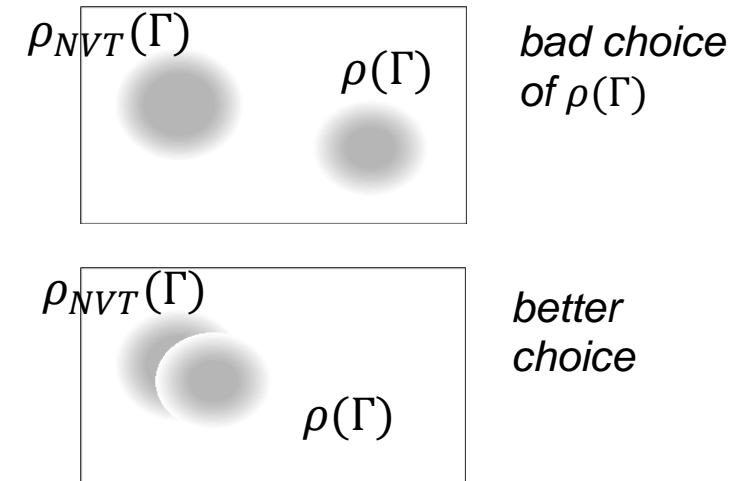
## Importance sampling

To reduce the number of zeroes choose a distribution function  $\rho(\Gamma)$  that has a strong overlap with the integrand.

For the canonical ensemble:

$$\langle A \rangle_{NVT} = \frac{\int A(\Gamma) \rho_{NVT}(\Gamma) d\Gamma}{\int \rho_{NVT}(\Gamma) d\Gamma} = \frac{\langle A \rho_{NVT} / \rho \rangle_{\text{trials}}}{\langle \rho_{NVT} / \rho \rangle_{\text{trials}}}$$

$\rho$  – sampling distribution



Specific choice  $\rho(\Gamma) = \rho_{NVT}(\Gamma)$  is known as importance sampling:

$$\left\langle \frac{\rho_{NVT}}{\rho} \right\rangle_{\text{trials}} = \langle 1 \rangle_{\text{trials}} = 1$$

$$\langle A \rangle_{NVT} = \langle A \rangle_{\text{trials}}$$

How does one generate a sequence of configurations  $\Gamma_1 \dots \Gamma_N$  that satisfy the given distribution  $\rho(\Gamma)$  ?

Answer: design a Markov chain of states whose limiting distribution is  $\rho(\Gamma)$ !

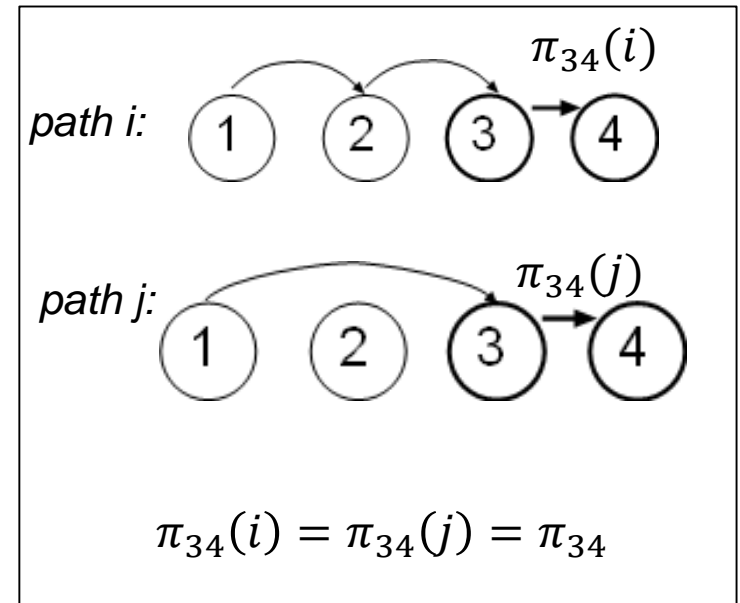
(the corresponding method is known as Markov Chain Monte Carlo (MCMC) )

# Markov chains

What does it mean “Markov chain”? Stochastic process in which:

a) there is a finite (countable) set of configurations in the phase space  $\{\Gamma_1 \dots \Gamma_N\}$ .

b) transition from state  $i$  to state  $j$  does not depend on the history prior to state  $i$ . There is no memory. Correlation only between neighboring sites.



Transition probabilities among states make a matrix  $\hat{\pi}$ :

$\pi_{mn}$  probability of making a transition from state  $m$  to state  $n$ .

$\sum_{n \neq m} \pi_{mn}$  probability of transitioning to any state

$\pi_{mm}$  probability of remaining in state  $m$ .

$$\sum_n \pi_{mn} = 1 \quad \text{consequence of the phase space finiteness}$$

How are  $\pi_{mn}$  and  $\rho(\Gamma)$  related?

**Example:** prediction of computer's up time

Computer can be either up or down. So the phase space consists of two states  $|\uparrow\rangle$  and  $|\downarrow\rangle$

*Computer has:*

60% chance of being up today if it was up the day before

*70% chance of being down today if it was down the day before*

*Transition matrix  
from day 1 to day 2*

$$\hat{\pi} = \begin{pmatrix} \pi(\uparrow\uparrow) & \pi(\uparrow\downarrow) \\ \pi(\downarrow\uparrow) & \pi(\downarrow\downarrow) \end{pmatrix} = \begin{pmatrix} 0.6 & 0.4 \\ 0.3 & 0.7 \end{pmatrix}$$

**Day 1:** computer is up,  $\rho(\uparrow) = 1, \rho(\downarrow) = 0$

**Day 2:**  $\rho(\uparrow) = 0.6, \rho(\downarrow) = 0.4$

$$\hat{\rho}(2) = (\rho(\uparrow)\rho(\downarrow)) = (0.6 \ 0.4) = \begin{pmatrix} 1 & 0 \end{pmatrix} \begin{pmatrix} 0.6 & 0.4 \\ 0.3 & 0.7 \end{pmatrix}$$

**Day 3:**  $\rho(\uparrow) = 0.6 * 0.6 + 0.4 * 0.3 = 0.48$

$$\rho(\downarrow) = 0.4 * 0.7 + 0.6 * 0.4 = 0.52$$

$$(0.48 \ 0.52) = (0.6 \ 0.4) \begin{pmatrix} 0.6 & 0.4 \\ 0.3 & 0.7 \end{pmatrix} = (1 \ 0) \begin{pmatrix} 0.6 & 0.4 \\ 0.3 & 0.7 \end{pmatrix}^2$$

$$\hat{\rho}(3) = \hat{\rho}(2) \cdot \hat{\pi} = \hat{\rho}(1) \cdot \hat{\pi} \cdot \hat{\pi} = \hat{\rho}(1) \cdot \hat{\pi}^2$$

**Day N:**

$$\hat{\rho}(N) = \hat{\rho}(1) \cdot \hat{\pi}^{N-1}$$

*probability on day N depends on probability on day 1*



Is there a limiting probability for large  $N$  in which the dependence on the initial state disappears?

$$\lim_{N \rightarrow \infty} \hat{\rho}(N) = \bar{\rho} \quad \text{does this limit exist?}$$

If it does, then the probability becomes independent of time so it is equal for day  $N+1$  and day  $N$ :

$$\hat{\rho}(N + 1) = \hat{\rho}(N) = \bar{\rho}$$

However,

$$\hat{\rho}(N + 1) = \hat{\rho}(N) \cdot \hat{\pi} \longrightarrow \bar{\rho} = \bar{\rho} \cdot \hat{\pi} \quad \text{an equation for the limiting distribution}$$

Eigenvector  
eigenvalue  
problem

$$\begin{aligned} \bar{\rho} &= \bar{\rho} \cdot \hat{\pi} \\ \rho_n &= \sum_m \rho_m \pi_{mn} \end{aligned}$$

limiting distribution  $\bar{\rho}$  is the left  
eigenvector of the transition  
matrix  $\hat{\pi}$  that corresponds to the  
eigenvalue 1

$\hat{\pi}$  is a **stochastic matrix** – its rows sum up to 1. We will also assume that it is an irreducible matrix which means that all states are accessible leading to ergodic behavior.

**Perron-Frobenius theorem** for stochastic irreducible matrices: The maximum eigenvalue is  $\lambda(1) = 1$ . It's simple (non-degenerate). Its eigenvector is real. No other real eigenvector exists.

- Consequences:
- a) limiting distribution  $\bar{\rho}$  exists
  - b) eigenvalues  $\lambda(n), n > 1$  control the convergence rate to  $\bar{\rho}$

# Application to the canonical configuration integral

The transition matrix  $\hat{\pi}$  is unknown. But we know the limiting distribution  $\rho_m = \rho_{NVT}(\Gamma_m)$

## Some rules for constructing $\hat{\pi}$

a) avoid the need to compute  $Q_{NVT} = \sum_m \rho_m$

{ not needed for averages  
may be impossible to compute if the size of the phase space is large

b) Detailed balance :  $\rho_n \pi_{nm} = \rho_m \pi_{mn}$

{ # transitioning from  $n$  to  $m$   
 $\xrightarrow{\hspace{1cm}}$   
 $\xleftarrow{\hspace{1cm}}$   
# transitioning from  $m$  to  $n$

Take the sum over  $m$ :

$$\sum_m \rho_n \pi_{nm} = \rho_n \sum_m \pi_{nm} = \boxed{\rho_n = \sum_m \rho_m \pi_{mn}} \quad \text{eigenvector condition}$$

$\rho_n$  is the desired eigenvector

A number of methods are available to build  $\hat{\pi}$  that satisfies detailed balance

Metropolis-Hastings

Wood/Glauber/Barker

Kawasaki

## Metropolis-Hastings method: asymmetrical solution

$$\begin{cases} \pi_{mn} = \alpha_{mn} & \rho_n \geq \rho_m \quad m \neq n \\ \pi_{mn} = \alpha_{mn} \cdot \frac{\rho_n}{\rho_m} & \rho_n < \rho_m \quad m \neq n \\ \pi_{mm} = 1 - \sum_{m \neq n} \pi_{mn} \longrightarrow \sum_n \pi_{mn} = 1 \end{cases}$$

$\alpha_{mn} = \alpha_{nm}$  a symmetric stochastic matrix underlying Markov chain

Proof that the solution satisfies the detailed balance:

$$\begin{aligned} & \text{ } \quad \quad \quad (n \rightarrow m \text{ for higher final } \rho) \quad \quad \quad (m \rightarrow n \text{ for lower final } \rho) \\ \rho_n \leq \rho_m: \quad & \rho_n \pi_{nm} = \rho_n \alpha_{nm} = \boxed{\rho_m} \alpha_{nm} \frac{\rho_n}{\boxed{\rho_m}} = \rho_m \boxed{\alpha_{mn} \frac{\rho_n}{\rho_m}} = \rho_m \pi_{mn} \\ \rho_n > \rho_m: \quad & \rho_n \pi_{nm} = \rho_n \alpha_{nm} \frac{\rho_m}{\rho_n} = \alpha_{nm} \rho_m = \alpha_{mn} \rho_m = \rho_m \pi_{mn} \end{aligned}$$

(n → m for lower final ρ) (m → n for higher final ρ)

Important point:  $\pi_{nm}$  depends on the ratio  $\rho_n/\rho_m$  but not on these quantities individually

One needs to know  $\rho_n$  up to a multiplicative constant to arrange a Markov chain. The normalizing factor  $Q_{NVT} = \sum_n \rho_n$  is not required.

## Symmetric solution

$$\begin{cases} \pi_{mn} = \alpha_{mn} \frac{\rho_n}{\rho_n + \rho_m} & m \neq n \\ \pi_{mm} = 1 - \sum_{n \neq m} \pi_{mn} & \alpha_{mn} = \alpha_{nm} \end{cases} \quad \text{a symmetrical stochastic matrix}$$

*Wood & Jacobson 1954*  
*Flinn & McManus 1961*  
*Glauber 1963 (Spin systems)*  
*Barker 1965 (liquids)*

Proof that the solution satisfies the detailed balance:

$$\rho_n \pi_{nm} = \rho_n \alpha_{nm} \frac{\rho_m}{\rho_n + \rho_m} = \rho_m \alpha_{mn} \frac{\rho_n}{\rho_n + \rho_m} = \rho_m \pi_{mn}$$

Which solution is better?

Statistical inefficiency to measure the rate of convergence to the limiting distribution: low inefficiency=fast convergence

$s$  is anti-correlated with the off-diagonal entries in  $\hat{\pi}$  matrix

	Asymmetrical		Symmetrical
$\rho_n \geq \rho_m$	$\alpha_{mn}$	$>$	$\alpha_{mn} \frac{\rho_n}{\rho_n + \rho_m}$
$\rho_n < \rho_m$	$\alpha_{mn} \frac{\rho_n}{\rho_m}$	$>$	$\alpha_{mn} \frac{\rho_n}{\rho_n + \rho_m}$

$$s = \frac{\tau_{run} \sigma^2(<A>_{run})}{\sigma^2(A)}$$

$$[\hat{\pi}_1]_{nm} > [\hat{\pi}_2]_{nm} \quad m \neq n$$

$$s(\pi_1) < s(\pi_2)$$

Metropolis algorithm has faster convergence rate

## MC in canonical ensemble

Let's see how Monte Carlo can be applied to simulate liquids, in particular Lennard-Jones liquid.

*Configuration space:*

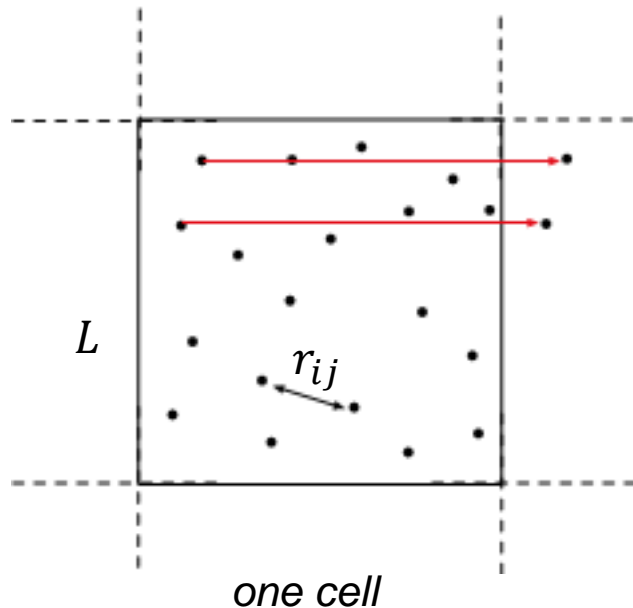
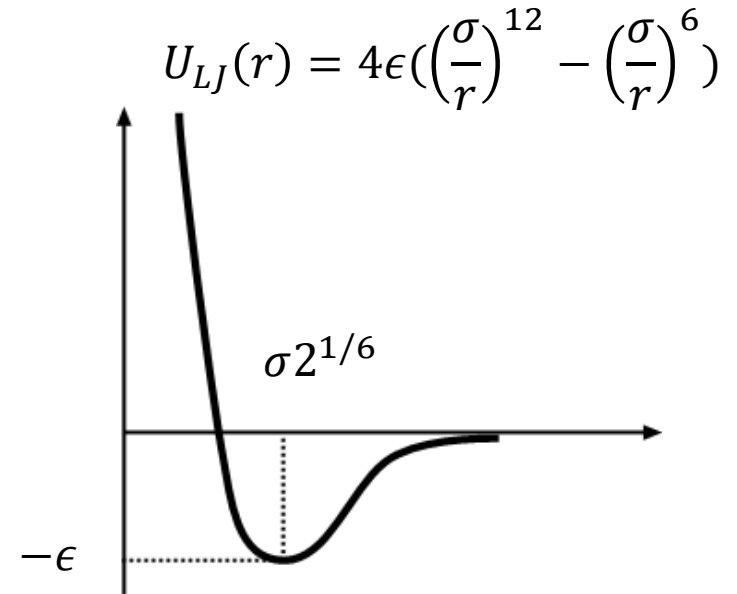
$$\Gamma = (\vec{r}_1, \dots, \vec{r}_N)$$

$$U(\Gamma) = \frac{1}{2} \sum_{i \neq j}^N U_{LJ}(r_{ij})$$

*Periodic boundary conditions (PBC) are applied to remove the surface artifacts*

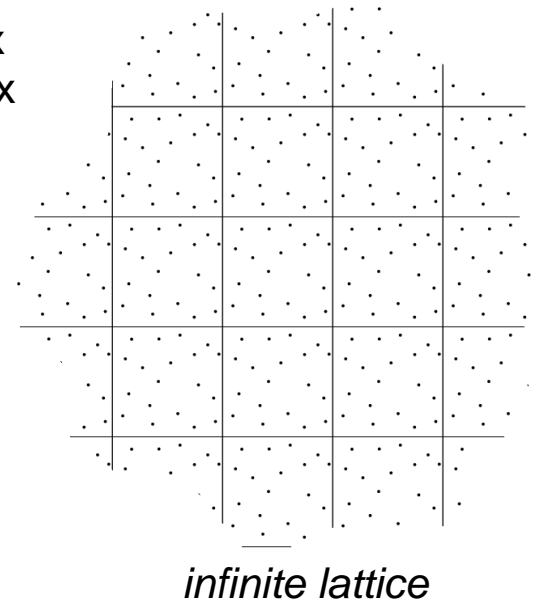
*Probability distribution:*

$$\rho_{NVT}(\Gamma) \sim e^{-\beta H(\Gamma)}, \beta = \frac{1}{kT}$$



if (x(i).ge. box) x(i)=x(i)-box  
if (x(i).lt. 0.0) x(i)=x(i)+box

*PBC*



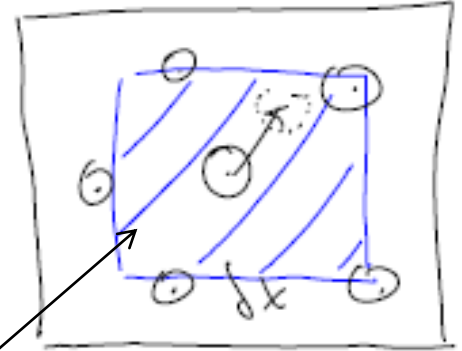
## How to design MC moves

In order to run MC one needs to select the symmetric matrix  $\hat{\alpha}$ .

For simplicity the matrix  $\alpha_{nm} = \alpha_{mn} = \alpha$  is assumed to be a constant

One possible choice for this constant is related to how new configurational states  $r_n$  are generated.

Assume new **trial** states are generated by random displacement of atom  $i$  by vector:  $\delta\vec{r} = (\xi_1\delta x, \xi_2\delta x, \xi_3\delta x)$  where  $\delta x$  is the maximum allowed displacement and  $\xi_i \in [0,1]$  are random numbers



If the initial state is  $n$ , then the final states  $m$  will make a cube with side  $\delta x$ . This cube will contain a large but finite (on computers) number of points  $N_k$ .

Any one of these points will have an  $\frac{1}{N_k}$  probability of being occupied upon transition.

Therefore random displacements occur with transition probability  $\frac{1}{N_k} = \pi_{nm} = \alpha_{nm}$

A natural choice:

$$\alpha = \frac{1}{N_k}$$

$$N_k \sim \delta x^3$$

$\left\{ \begin{array}{l} \text{so } \alpha \text{ will be set by the} \\ \text{magnitude of } \delta x \end{array} \right.$

## Simulation scheme

*The system is in an initial state  $n$ . Potential energy is available.*

- **Step 1:** *pick a random displacement vector. This will happen with probability  $\alpha$ .*
- Step 2:** *If the resulting  $\rho_m > \rho_n$ , accept the move as this means  $\pi_{nm} = \alpha$  transition probability.*
- Step 3:** *If the resulting  $\rho_m < \rho_n$ , accept the move with  $\frac{\rho_m}{\rho_n}$  probability. This means*

$$\pi_{nm} = \alpha \frac{\rho_m}{\rho_n} \quad \text{transition probability}$$

*For  $\rho_n \sim e^{-\beta E_n}$  and  $\Delta E = E_m - E_n$ , the algorithm can be written as follows:*

Accept  $\underline{n} \rightarrow \underline{m}$  move with  $\min\{1, e^{-\beta \Delta E}\}$  probability

How to decide whether a given move should be accepted or rejected based on its desired probability  $P$ ?

*The outcome is stochastic so it has to rely on a stochastic/random process. The simplest method is to flip a coin or roll a dice.*

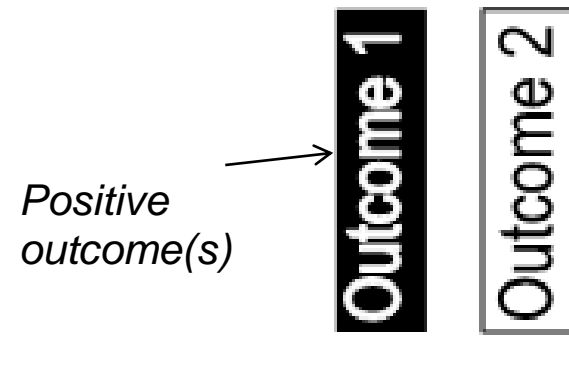


## Coin example:

*If we don't want/are unable to make a decision we leave it to chance.*

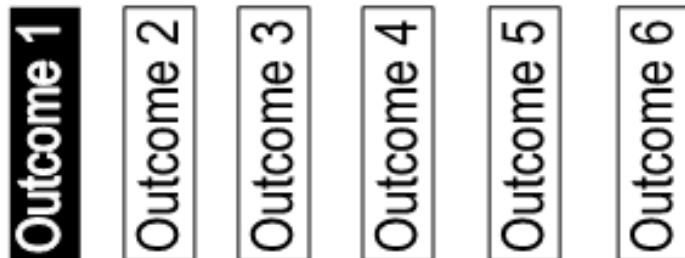
*Decision is  
made with  $P = \frac{1}{2}$*

*If we flip a coin, the positive outcome of the  
decision will have  $\frac{1}{2}$  probability*



*If we roll a dice, the positive outcome of the decision may have probability  $\frac{1}{6}$  or a number of other  
values*

$$P = \frac{1}{6}$$



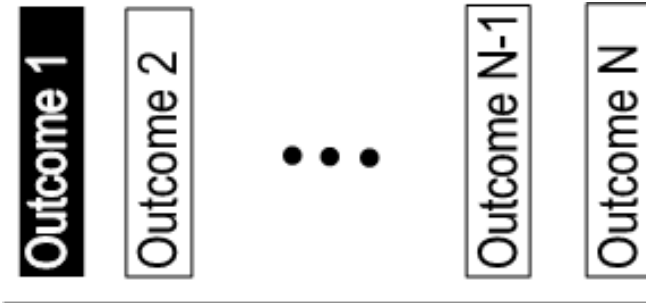
or

$$P = \frac{2}{6} = \frac{1}{3}$$



In general, a dice with  $N$  sides may encode  $N - 1$  distinct probabilities:

$$P = \frac{1}{N}$$



$$P = \frac{N - 1}{N}$$

or



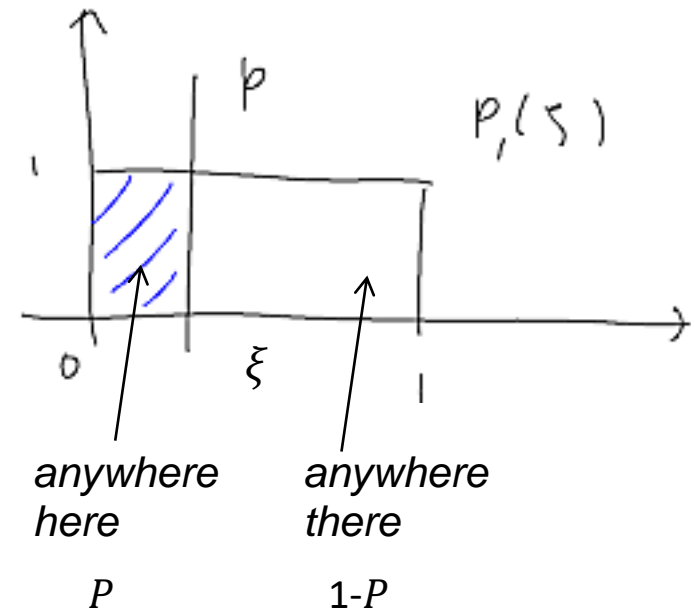
Generalization to continuous  $P$ :

$\xi \in [0,1]$  a random number

$P_1(\xi)$  uniform distribution

The event that  $\xi$  is below  $P$  will occur with  $P$  probability

Generate a random number  $\xi$ . If it is below  $P$  - accept the move, otherwise – reject it.



# Complete algorithm

→ **Step 1:** Generate new positions for particle  $k$ :

Apply PBC

$$\begin{cases} rx_{new} = rx(k) + (2 \times rand([0, 1]) - 1.0) \times dx \\ ry_{new} = ry(k) + (2 \times rand([0, 1]) - 1.0) \times dx \\ rz_{new} = rz(k) + (2 \times rand([0, 1]) - 1.0) \times dx \end{cases}$$

random number from 0 to 1

**Step 2:** Compute the resulting change in potential energy

$$\Delta E = E_m - E_n$$

$$2E = \sum_{i \neq j} U_{LJ}(r_{ij}) = \sum_{j \neq k} U_{LJ}(r_{jk}) + \sum_{k \neq j} U_{LJ}(r_{kj}) + \sum_{i \neq j, i \neq k, j \neq k} U_{LJ}(r_{ij})$$

$$2(\Delta E) = \sum_{j \neq k} U_{LJ}(r_{jk}^m) + \sum_{k \neq j} U_{LJ}(r_{kj}^m) - \sum_{j \neq k} U_{LJ}(r_{jk}^n) - \sum_{k \neq j} U_{LJ}(r_{kj}^n)$$

evaluation involves only a sum of  $O(N)$  not  $O(N^2)$

**Step 3:** If  $\Delta E < 0$ , accept the move. Otherwise, generate  $\xi \in [0, 1]$

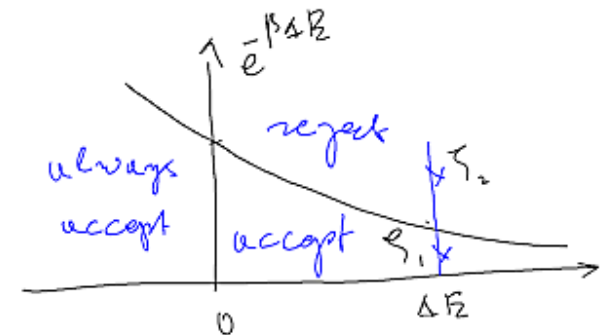
If  $\xi \leq w = e^{-\beta \Delta E}$  accept the move

If  $\xi > w$  reject the move

small  $\delta x$   $\left\{ \begin{array}{l} \text{large acceptance probability } P_{acc} \\ \text{slow movement in the phase space} \end{array} \right.$

large  $\delta x$   $\left\{ \begin{array}{l} \text{small acceptance probability } P_{acc} \\ \text{waste of computer time} \end{array} \right.$

$30\% < P_{acc} < 50\%$



Implementation example in Fortran. One particle moves at a time

```
deltaE=Enew-Eold
deltab=deltaE/(k*T)
if (deltab.le.75) then
  if (deltab.le.0.) then
    e=e+deltaE
    rx(k)=rxnew
    ry(k)=rynew
    rz(k)=rznew
    naccp=naccp+1
  else
    if (ranf().le.exp(-deltab)) then
      e=e+deltaE
      rx(k)=rxnew
      ry(k)=rynew
      rz(k)=rznew
      naccp=naccp+1
    endif
  endif
endif
ntrial=ntrial+1
```

*guard against overflow*

*don't generate the random number if  $\Delta E < 0$ . Saves time*

*generate the random number*

*reassign coordinates*

*update the counter of accepted moves*

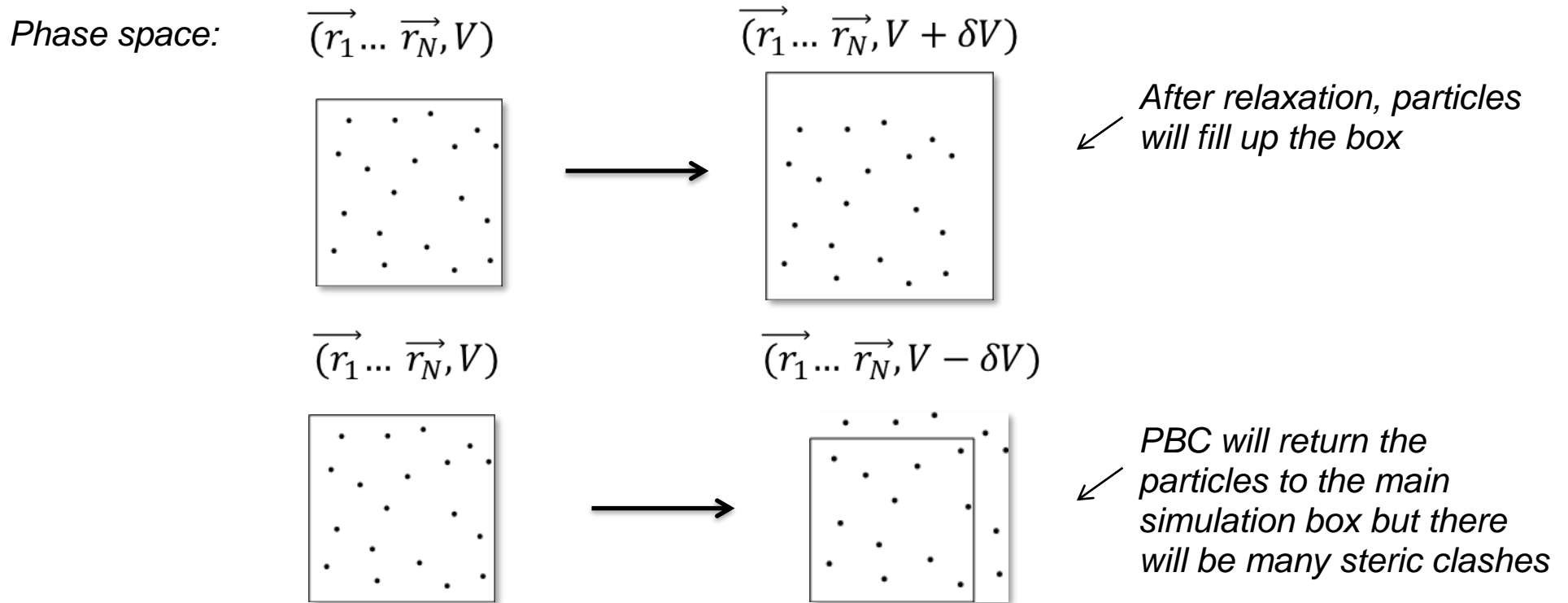
*update the counter of total trials.*

**Extensions:**

- a) multiple-particle moves
- b) all-particle moves

## Isothermal-isobaric simulations

The goal is to reproduce the NTP ensemble. Volume now has to be treated as a dynamical variable.



Alternative approach: introduce scaled coordinates

old variables:

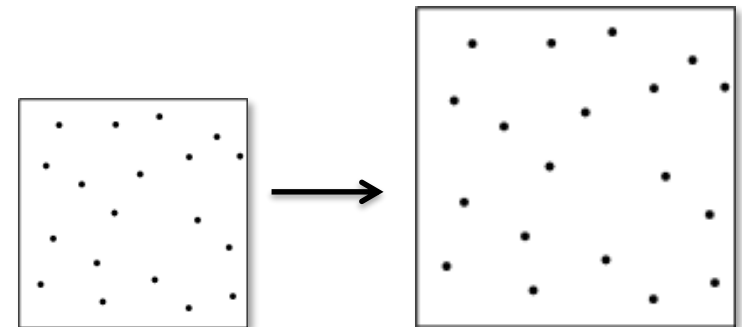
$$(\vec{r}_1 \dots \vec{r}_N, V)$$

new variables:

$$(\vec{s}_1 \dots \vec{s}_N, V)$$

$$\vec{r} = V^{\frac{1}{3}} \cdot \vec{s}, (s_x, s_y, s_z) \in [0, 1], d\vec{r}_i = V \cdot d\vec{s}_i$$

The box will experience uniform expansion or contraction



## How to compute NPT averages?

$$d\vec{r}_i = V \cdot d\vec{s}_i$$

$$\begin{aligned} \langle A \rangle_{NPT} &= \frac{\int dV e^{-\beta PV} \int d\vec{r} e^{-\beta U(\vec{r})} A(\vec{r})}{\int dV e^{-\beta PV} \int d\vec{r} e^{-\beta U(\vec{r})}} = \frac{\int dV e^{-\beta PV} V^N \int d\vec{s} e^{-\beta U(\vec{s})} A(\vec{s})}{\int dV e^{-\beta PV} V^N \int d\vec{s} e^{-\beta U(\vec{s})}} = \\ &= \frac{\int dV d\vec{s} e^{-\beta U(\vec{s})} e^{-\beta PV} e^{N \log(V)} A(\vec{s})}{\int dV d\vec{s} e^{-\beta U(\vec{s})} e^{-\beta PV} e^{N \log(V)}} = \frac{\int dV d\vec{s} e^{-\beta(U(\vec{s}) + PV - kTN \log(V))} A(\vec{s})}{\int dV d\vec{s} e^{-\beta(U(\vec{s}) + PV - kTN \log(V))}} = \langle A \rangle_{sV} \end{aligned}$$

NVT average

Sample from NVT ensemble for the extended system defined by phase space coordinates  $\Gamma = (\vec{s}_1 \dots \vec{s}_N, V)$  with the limiting distribution function:

$$\rho(\Gamma) = e^{-\beta(U(\vec{s}) + PV - kTN \log(V))}$$

### Algorithm:

Simulation is conducted as in NVT ensemble except that now we have **two types** of moves.

1) Coordinate moves:  $\vec{s}_i^m = \vec{s}_i^n + \delta x(2 \cdot \xi - 1) \quad \xi \in [0,1]$

2) Volume changes:  $V^m = V^n + \delta V(2 \cdot \xi - 1)$  ← these are expensive so should be attempted rarely

Moves accepted with the probability:

$$P = \min\{1, e^{-\beta \Delta E}\}, \Delta E = E_m - E_n + P(V_m - V_n) - kT \log\left(\frac{V_m}{V_n}\right)$$

# Grand canonical ensemble

Both coordinates and the number of particles are allowed to change

It's more convenient to introduce dimensionless coordinates as this will make distribution function dimensionless as well. This is important when comparing systems with different number of particles,  $N$  and  $N + \mu_{\text{reservoir}}$  for instance, as they have different volumes of the phase space.

Parameters of the ensemble:  $\mu, V, T$

Phase-space variables:  $(\vec{r}_1 \dots \vec{r}_N, N) \longrightarrow$  Scaled variables:  $(\vec{s}_1 \dots \vec{s}_N, N)$

Ensemble averages:

$$\vec{s}_i = V^{-1/3} \vec{r}_i$$

$$\begin{aligned} \langle A \rangle_{\mu TV} &= \sum_{N=1}^{\infty} \frac{1}{N!} e^{\beta \mu N} \frac{V^N}{\lambda^{3N}} \int d\vec{s} e^{-\beta U(\vec{s})} A(\vec{s}) / Q_{\mu VT} = \\ &= \frac{\sum_{N=1}^{\infty} \int d\vec{s} e^{-\beta(U(\vec{s}) - \mu N - kTN \log(V) + kTN \log(\lambda^3) + kT \log(N!))} A(\vec{s}; N)}{\sum_{N=1}^{\infty} \int d\vec{s} e^{-\beta(U(\vec{s}) - \mu N - kTN \log(V) + kTN \log(\lambda^3) + kT \log(N!))}} = \end{aligned}$$

de Broglie length

$$\lambda = \sqrt{h^2 / 2\pi m kT}$$

Limiting distribution in MC chain:

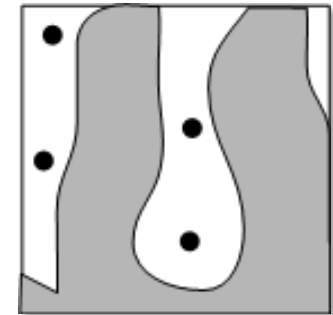
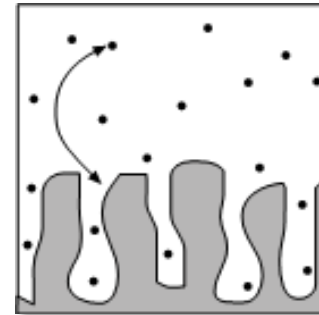
$$\rho(\vec{s}_1 \dots \vec{s}_N, N) = e^{-\beta(U(\vec{s}) - \mu N - kTN \log(V) + kTN \log(\lambda^3) + kT \log(N!))}$$

There are a number of implementations of GCMC that differ in how particles are added to/removed from the system

## Adsorption onto a porous surface

Very large system required

Focus on the surface





### Three types of moves:

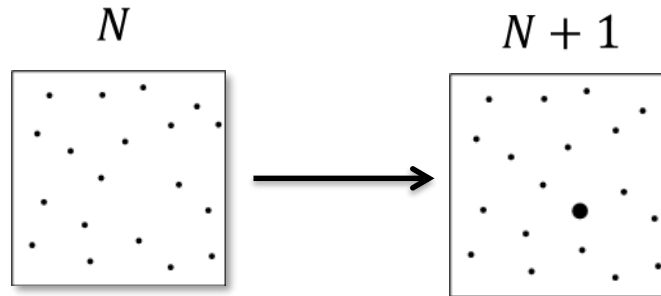
1) Coordinate moves:  $\vec{s}_i^m = \vec{s}_i^n + \delta x(2 \cdot \xi - 1) \quad \xi \in [0,1]$

$$P = \min\{1, e^{-\beta \Delta U}\}$$

for fastest convergence choose

$$P_1 = P_2 = P_3 = \frac{1}{3}$$

2) Particle creation:



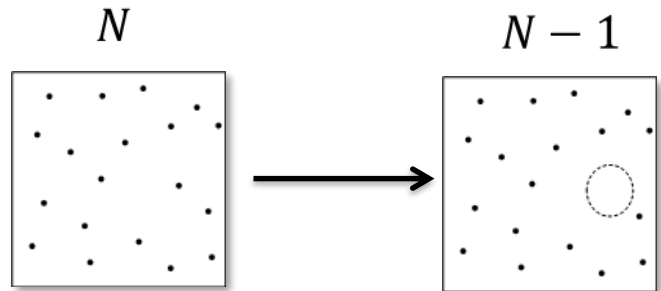
insertion at a random position. Difficult in dense fluids because of steric clashes

$$P \sim \frac{\rho_m(\vec{s}, N+1)}{\rho_n(\vec{s}, N)} = \min\left\{1, e^{-\beta \Delta U + \log \frac{zV}{N+1}}\right\}$$

$$\Delta U = U(\vec{s}, N+1) - U(\vec{s}, N)$$

$$z = e^{\beta \mu} / \lambda^3 \quad \text{activity}$$

3) Particle destruction:



deletion of a random particle. Difficult in dense fluids because the particle may experience strong attraction in the media

$$P \sim \frac{\rho_m(\vec{s}, N-1)}{\rho_n(\vec{s}, N)} = \min\left\{1, e^{-\beta \Delta U + \log \frac{N}{zV}}\right\}$$

$$\Delta U = U(\vec{s}, N-1) - U(\vec{s}, N)$$

Direct computation of free energy in GCMC:

$$A/N = \mu - \langle P \rangle_{\mu VT} V / \langle N \rangle_{\mu VT}$$

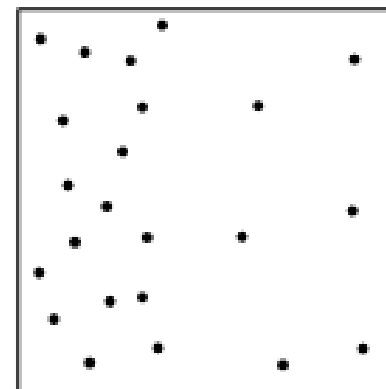
averages obtained from simulation

may not be accurate because of large fluctuation in  $\langle N \rangle$

# Gibbs-ensemble simulations

This method is designed to simulate phase equilibria.

<i>Liquid</i>	$P_l = P_g$ $T_l = T_g$ $\mu_l = \mu_g$	<i>Gas</i>
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The best choice for these experimental conditions is  $\mu_{PT}$  “ensemble”



One of the state variables has to be extensive ( $N$  or  $V$ )

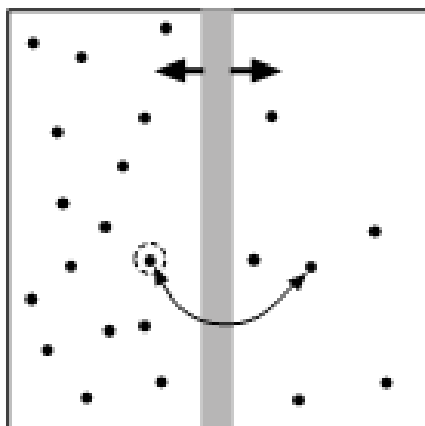
Such ensemble does not exist!

If both  $N$  and  $V$  are allowed to change a simulation box can't be defined uniquely

Consider two coupled systems with the total  $V$  and  $N$  fixed:

$$V_1 = V - V_2$$

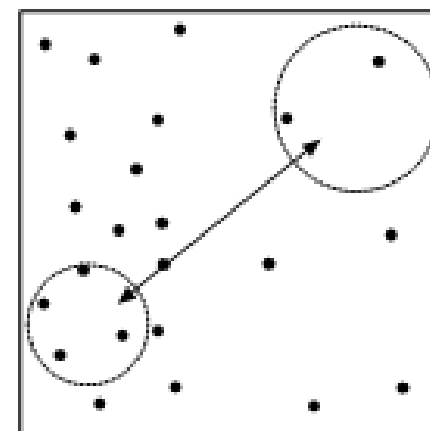
$$N_1 = N - N_2$$



$$V_2$$

$$N_2$$

Exchange of particles and volume is allowed. This enables coexistence between two phases. The advantage is that there is no interface. Molecules in system 1 and 2 do not interact with one another.



The partition function:

$$Q_G(N, V, T) = \sum_{n_1=0}^N \frac{1}{V \lambda^{3N} n_1! (N - n_1)!} \int_0^V dV_1 V_1^{n_1} (V - V_1)^{N-n_1} \times \\ \times \int ds_1^{n_1} e^{-\beta U(s_1)} \int ds_2^{N-n_1} e^{-\beta U(s_2)}$$

Variables:

$$(\vec{s}_1 \dots \vec{s}_{n_1}, n_1, V_1)$$

$$(\vec{s}_1 \dots \vec{s}_{N-n_1})$$

Distribution function:

$$\rho(n_1, V_1, s_1, s_2) = \frac{V_1^{n_1} (V - V_1)^{N-n_1}}{n_1! (N - n_1)!} e^{-\beta(U(s_1) + U(s_2))}$$

scaled coordinates of system 2  
↓

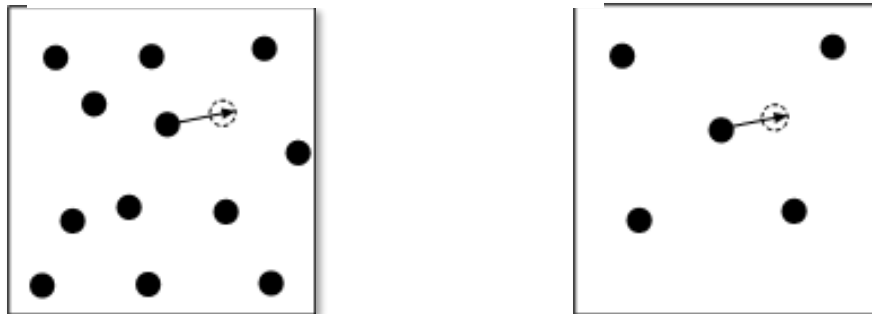
↑  
scaled coordinates of system 1

MC process that samples from that distribution:

1) Coordinate moves applied in both systems independently:

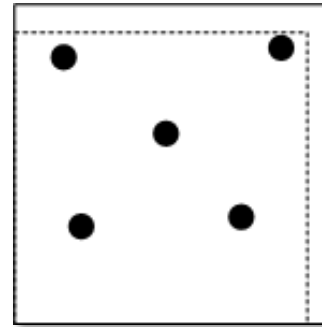
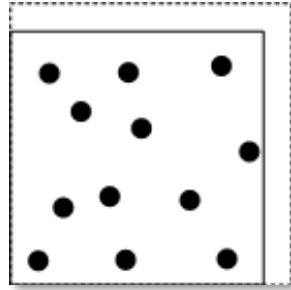
$$\vec{s}_i^m = \vec{s}_i^n + \delta x (2 \cdot \xi - 1) \quad \xi \in [0, 1]$$

$$P = \min\{1, e^{-\beta \Delta U}\}$$



2) Volume change:

$$V_1^m = V_1^n + \delta V$$



$$P < 10\%$$

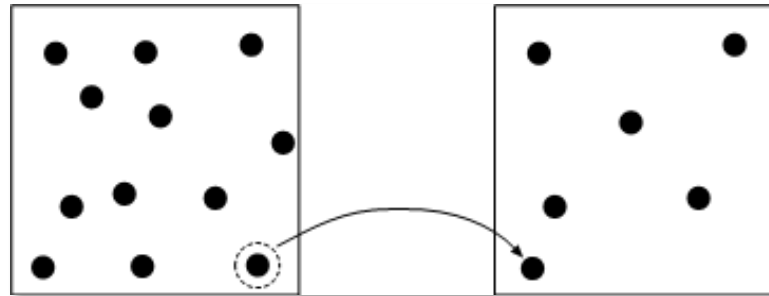
$$V_2^m = V_2^n - \delta V$$

Probability of  $n$  to  $m$  transition :

$$P = \min\left\{1, \frac{(V_1^m)^{n_1} (V - V_1^m)^{N-n_1}}{(V_1^n)^{n_1} (V - V_1^n)^{N-n_1}} e^{-\beta(\Delta U(s_1) + \Delta U(s_2))}\right\}$$

3) Particle exchange:

$$N_1^m = N_1^n - 1$$



$$P < 10\%$$

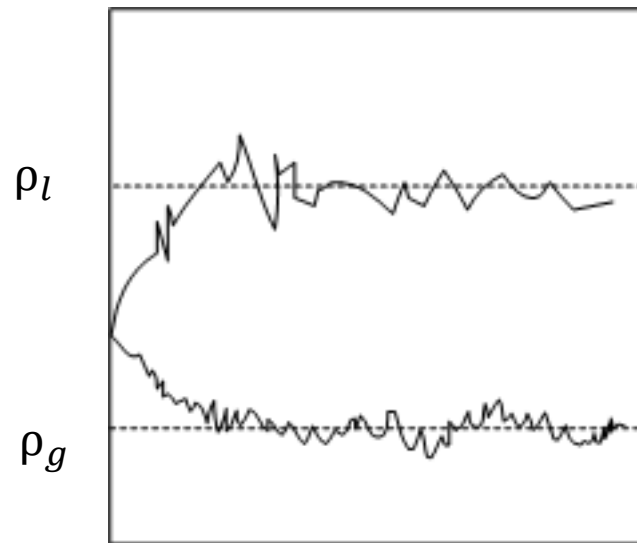
$$N_2^m = N_2^n + 1$$

Probability of  $n$  to  $m$  transition :

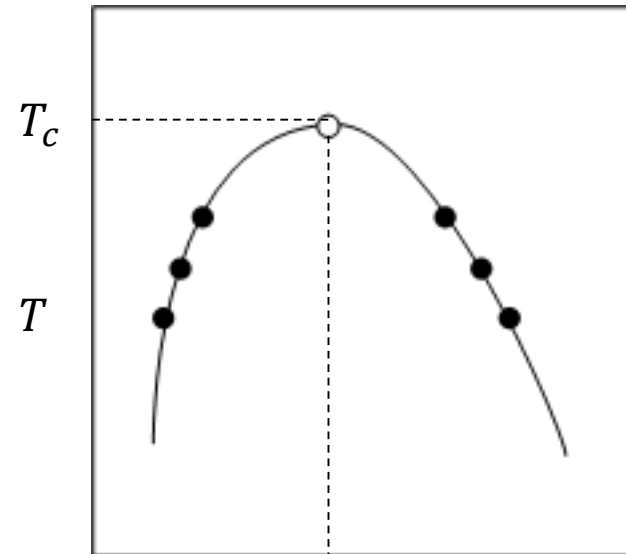
$$P = \min\left\{1, \frac{n_1(V - V_1)}{(N - n_1 + 1)V_1} e^{-\beta(\Delta U(s_1) + \Delta U(s_2))}\right\}$$

### Typical results:

*After initial relaxation, densities in the two boxes will settle down to their equilibrium values*



*MC cycles*



$\rho_c$

*In the coexistence region  $T < T_c$  there will be two distinct densities corresponding to two distinct phases.*

*In the supercritical region  $T > T_c$  there will be only one density. Boxes may have different sizes and numbers of particles.*

*Large finite size effect for gas-lattice models. Minimal effects for continuous models. Systems with  $< 100$  particles are OK for LJ model in both 2D and 3D.*

# Electrostatics in biomolecular systems

Coulomb interactions between two charges  $U_C(r) = \frac{q_1 q_2}{\epsilon}$

If cut-off  $R_c$  is introduced, as with LJ potential, the long-range correction is

$$\text{M.K.L.} \int_{R_c}^{\infty} r^2 U_C(r) dr = \text{M.K.L.} \int_{R_c}^{\infty} r^2 \cdot \frac{q_1 q_2}{\epsilon} dr - \text{Integral diverges}$$

The long-range part of the potential energy is greater than the short-range part.

Attractive forces between

two positively charged ions

Options:

I) Truncate the potential at  $R_c$

- Bad artifacts

- Wrong results even as the

limit  $R_c \rightarrow \infty$

Example: effective interaction  $w(R)$

between two iron ions.

For large  $R$ ,  $w(R) \sim \frac{q_1 q_2}{\epsilon \cdot R}$ ,  $\epsilon$  - dielectric constant

Attractive forces are seen at  $R \sim R_c$

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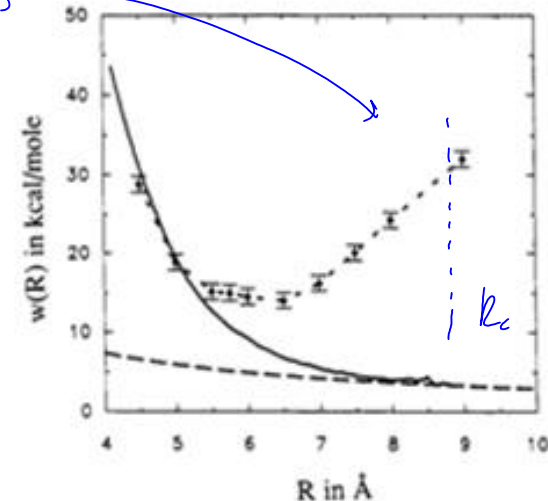
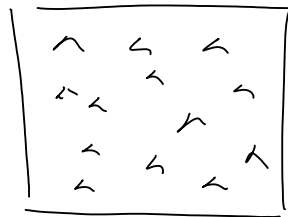


Figure 2. The potential of mean force,  $w(R)$ , for  $\text{Fe}^{2+}$ - $\text{Fe}^{2+}$  (circles) and for  $\text{Fe}^{3+}$ - $\text{Fe}^{3+}$  (solid line) in water. The former is computed from simulations with truncated interactions. The latter is computed from simulations with Ewald sums. The dashed line is the dielectric continuum potential of mean force,  $(2.5e)^2/R\epsilon$ , with  $\epsilon = 70$ . The error bars are  $\pm 1$  standard deviation. Error estimates for the solid line are of similar size (see Figure 3).

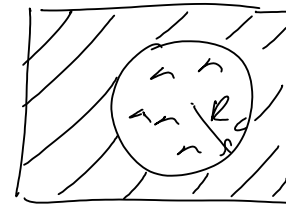
## II) Reaction field corrections (RF method)

Compute contributions of the truncated long-range part of  $U_c$  using continuum electrostatics models. For homogeneous media:

Atomic representation



continuum representation

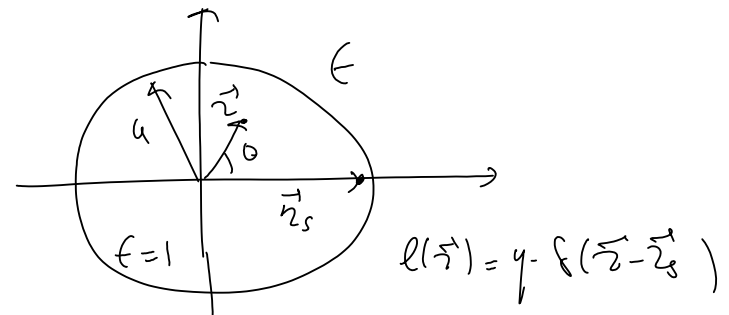


$\epsilon$  - dielectric constant of the medium

Electrostatics of charges in spherical cavities:

Poisson equation relating potential  $\Phi$  and charge density  $\rho$ :

$$\begin{cases} \Delta \Phi_I(\vec{r}) = -4\pi \rho(\vec{r}) & r \leq a \\ \Delta \Phi_{II}(\vec{r}) = 0 & r > a \end{cases}$$



Boundary conditions

$$\begin{cases} \Phi_I(r=a) = \Phi_{II}(r=a) & \text{potential is continuous at the boundary} \\ \frac{\partial \Phi_I}{\partial n}(r=a) = \epsilon \frac{\partial \Phi_{II}}{\partial n}(r=a) & \text{normal derivative, or displacement } \vec{D} = \epsilon \cdot \vec{E}, \text{ is continuous} \end{cases}$$



For the potential inside the cavity:

$$\Phi_{\text{int}}(\vec{z}) = \frac{q}{|\vec{z} - \vec{z}_s|} + \Phi_{\text{re}}(\vec{z})$$

direct Coulomb  
potential

reaction field resulting  
from the polarization of  
the dielectric medium

Workwood expansion:

$$\Phi_{\text{re}}(z, \theta) = \sum_{n=0}^{+\infty} B_n \cdot z^n \cdot P_n(\cos \theta)$$

$$B_n = q \cdot \frac{z_s^n}{a^{2n+1}} \gamma^n \left( 1 + \frac{1+\gamma}{1-\gamma+2n} \right), \quad \gamma = \frac{1-\epsilon}{\epsilon+1}$$

In the limit of small  $z$ :

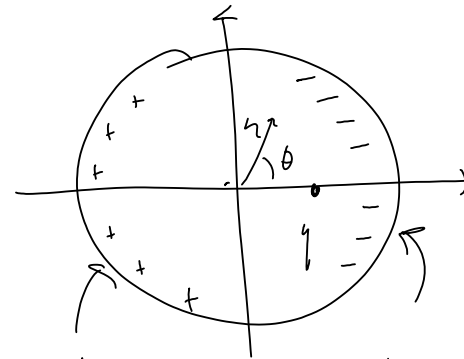
$$\Phi_{\text{re}}(\vec{z}) = -\frac{q(\epsilon-1)}{a-\epsilon} + \frac{q}{a^3} \frac{2(\epsilon-1)}{2\epsilon+1} \vec{z} \cdot \vec{z}_s + O(z^2)$$

Two important results that follow from this expansion:

1) Born solvation energy

Assume that the charge is placed at the center  $\vec{z}_s = 0$ . The reaction

potential it creates at the center is  $-\frac{q(\epsilon-1)}{a-\epsilon}$



Induced charge density that creates  
reaction potential

$P_n(x)$  - Legendre polynomials

$$P_0(x) = 1, \quad P_1(x) = x$$

$$P_2(x) = (3x^2 - 1)/2$$

It will have  $dW = \Phi_K(0) \cdot dq$  work against that potential to add fq charge at the center. The total work associated with creating charge  $q$  - charging free energy, is then:

$$\Delta G_{\text{Born}} = \int dW = - \int_0^q \frac{q(t-1)}{\epsilon \cdot t} \cdot dq = \boxed{\frac{1}{2} \frac{q^2}{\epsilon} \left( \frac{1}{\epsilon} - 1 \right)}$$

$\Delta G_{\text{Born}}(\epsilon=1) = 0$  - no charging energy in vacuum ( $\epsilon_i = \epsilon_{\text{ext}}$ )

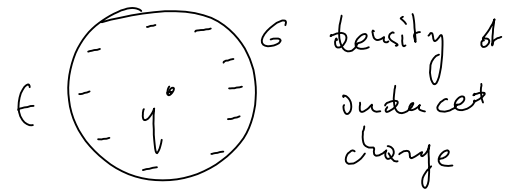
## 2) Onsager solvation of point dipoles

Place two charges  $q$  and  $-q$  at positions  $\vec{r}_s$  and  $-\vec{r}_s$  respectively. charging free energy can be computed in 2 steps!

a) Charge particle #1

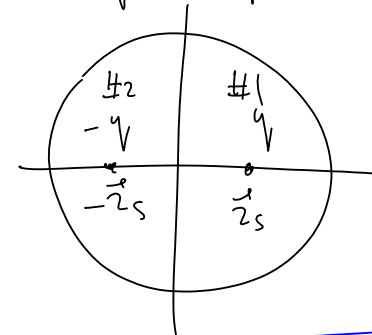
$$\begin{aligned} \Delta G_1 &= \int_0^q \Phi_K(r_s) dq = \int_0^q \left( -\frac{q(t-1)}{\epsilon \cdot t} + \frac{q}{a^3} \frac{2(1-t)}{2t+1} z_s^2 \right) dq = \\ &= -\frac{1}{2} \frac{q^2(t-1)}{\epsilon \cdot t} + \frac{1}{2} \frac{q^2}{a^3} \frac{2(1-t)}{2t+1} z_s^2 \end{aligned}$$

Born solvation energy of ions



$$\sigma = -q \left( 1 - \frac{1}{\epsilon} \right) / 4\pi a^2$$

Dipole moment  
 $\vec{M} = -q \cdot \vec{r}_s + q \cdot \vec{r}_s = 2q \cdot \vec{r}_s$



Point dipole!  $z_s \rightarrow 0, M = \text{const}$

b) charge particle ~~42~~. Work has to be done against its own reaction

field:

$$\Delta G_2 = \int_0^{-q} \left( -\frac{q(t-1)}{a-t} + \frac{q}{a^3} \frac{2(1-t)}{2t+1} z_s^2 \right) dy = -\frac{1}{2} \frac{q^2(t-1)}{a-t} + \frac{1}{2} \frac{q^2}{a^3} \frac{2(1-t)}{2t+1} z_s^2 = \Delta G_1$$

and against the reaction field created by the first particle:

$$\begin{aligned} \Delta G_3 &= \int_0^{-q} \Phi(-\vec{r}_s) dy' = \int_0^{-q} \left( -\frac{q(t-1)}{a-t} - \frac{q}{a^3} \frac{2(1-t)}{2t+1} z_s^2 \right) dy' = \\ &= \frac{q^2(t-1)}{a-t} + \frac{q^2}{a^3} \frac{2(1-t)}{2t+1} z_s^2 \end{aligned}$$

Putting three terms together:  $\Delta G = \Delta G_1 + \Delta G_2 + \Delta G_3 = \frac{2q^2}{a^3} \frac{2(1-t)}{2t+1} z_s^2$ ,  $(q z_s)^2 = \frac{M^2}{4}$

In the limit of point dipole,  $z_s \rightarrow 0$ ,  $M = \text{const}$ :

$$\Delta G_0 = \frac{1}{a^3} \frac{1-t}{2t+1} M^2$$

- higher-order terms in  $z_s$  disappear.  $\Delta G_0$  is full solvation energy

-  $\Delta G$  is dipolar approximation of the charging free energy

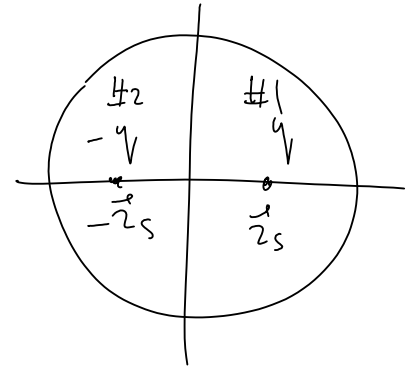
It needs to be corrected for non-point dipoles.

As with the Born energy for ions,

$\Delta G_0(t=1) = 0$  for dipoles. No charging energy in vacuum!

The charging free energy can also be interpreted as interaction of the dipole with its own reaction field. Electric field created at the center by a charge  $q$  at position  $\vec{r}_s$ :

$$\vec{E}(\vec{r}) = - \frac{\partial \Phi_R(\vec{r})}{\partial \vec{r}} = - \frac{q}{a^3} \frac{2(1-f)}{2f+1} \vec{r}_s + O(|\vec{r}|)$$



If there's more than one charge,  $q_i, \vec{r}_i$ :

$$\vec{E}(\vec{r}) = - \frac{1}{a^3} \frac{2(1-f)}{2f+1} \sum_i q_i \vec{r}_i = - \frac{1}{a^3} \frac{2(1-f)}{2f+1} \vec{M} \quad \text{dipole moment of a group of charges. The field at the center doesn't depend on their location}$$

Let's assume now that the field is created by a pair of charges  $-q, -\vec{r}_s$  and  $q, \vec{r}_s$  so that

$\vec{M} = 2q \cdot \vec{r}_s$ . Adding  $-dq$  and  $dq$  amounts of charge to these particles will cost  $d\psi = -d\vec{M} \cdot \vec{E} = -2\vec{r}_s \cdot dq \cdot \vec{E}$  electrostatic energy. Creating these charges from zero will require work:

$$\int d\psi = - \int_0^q 2\vec{r}_s \cdot \frac{1}{a^3} \frac{2(f-1)}{2f+1} \cdot 2\vec{r}_s q' \cdot dq' = - \frac{4 \cdot \vec{r}_s^2 q^2}{2} \frac{1}{a^3} \frac{2(f-1)}{2f+1} = \frac{1}{a^3} \frac{1-f}{2f+1} \cdot M^2 = \Delta f_0$$

Onsager solvation energy

Why is  $\Delta G$  called "solvation" energy?

Assume  $x$  denotes configuration of our molecule of interest. Its energy in

vacuum is  $U_v(x)$ . Probability of seeing  $x$

$$P(x) \sim e^{-\beta U_v(x)}$$

If the molecule is placed in a medium,

a solvent:

$$P(x) = \int e^{-\beta U_v(x)} \cdot e^{-\beta E(x,y)} dy / Q =$$

$$= e^{-\beta U_M(x)} / Q$$

$y$  - solvent degrees of freedom

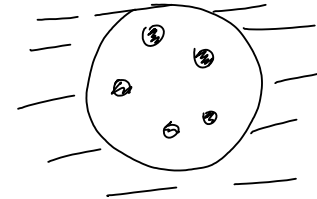
$Q$  - partition function

$U_M(x)$  - potential energy of the molecule in the medium

vacuum



medium



Introduce  $U_{eff}(x) = -kT \log \int e^{-\beta E(x,y)} dy$  - effective potential due to the medium

$$U_M(x) = U_v(x) + U_{eff}(x) \quad - \text{total potential is vacuum} + U_{eff}(x)$$

What's the physical meaning of  $U_{eff}(x)$ ?

Let's introduce a scaling variable  $\lambda$  that will "turn on" the medium:

$$Q(\lambda) = \int e^{-\beta U_v(x)} e^{-\beta \lambda \cdot E(x,y)} dy \quad - \text{partition function that depends on } \lambda$$

$$G(\lambda) = -kT \log Q(\lambda) \quad - \text{free energy.}$$

$$\lambda = 0 \quad - \text{vacuum}$$

$$\lambda = 1 \quad - \text{medium}$$

$$G_v(x) = -kT \log Q(\lambda=0) = U_v(x) - \text{vacuum,}$$

$$-kT \log \left( e^{-\beta U_v(x)} \cdot e^{-\beta U_{eff}(x)} \right) = G_v(x) + U_{eff}(x),$$

$$G_M(x) = -kT \log Q(\lambda=1) =$$

$$U_{eff}(x) = G_M(x) - G_v(x)$$

$$U_M(x) = U_v(x) + \Delta G(x)$$

free energy of turning on the medium is the effective potential:

# Effect of dielectric continuum

potential energy in vacuum

$$U_m(x) = U_v(x) + \Delta G(x)$$

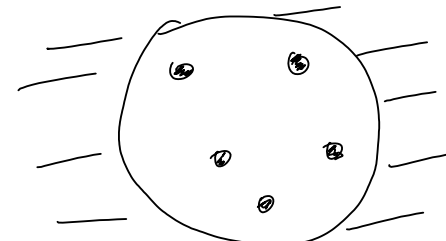
↑ potential energy in solvent  
↑ free energy difference

Vacuum

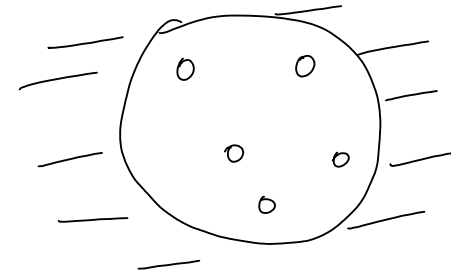


$$\Delta G_v = -U_v(x)$$

Solvent



$$\Delta G_c = \Delta G_A(x)$$

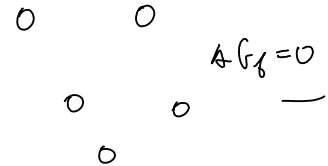


Design a charging/discharging

path: a) discharging in vacuum

b) placing neutral particles into a

cavity, c) charging the particles in the medium



$$\Delta G = \Delta G_v + \Delta G_f + \Delta G_c = \Delta G_A(x) - U_v(x)$$

total potential

inside the cavity

work against the potential

created by other particles

$$\Delta G_A(x) = \int dq \Phi = \int dy \Phi_v + \int dy \cdot \Phi_{kk} \leftarrow \text{this is what we call "charging free energy" for point dipole}$$

$$= U_v + \int dy \Phi_{kk}$$

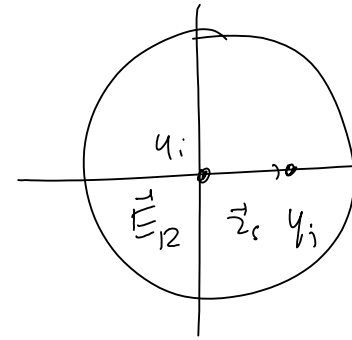
$$\Delta G = \int dy \cdot \Phi_{kk}$$

solvation energy = the energy that needs to be added to the potential in vacuo to mimic the presence of solvent

## Moving boundary reaction field method

Use the Kirkwood expansion to compute electric fields created at the center by a source charge  $q_i$ :

$$\vec{E}_E(\vec{r}=0) = -\frac{\partial}{\partial \vec{r}} \Phi_E(\vec{r}) \Big|_{\vec{r}=0} = \frac{q_i}{a^3} \frac{2(\epsilon-1)}{2\epsilon+1} \vec{r}_s$$



Force experienced by the probe charge  $q_i$  at the center due to polarization is:

$$\vec{F} = q_i \vec{E}_E(\vec{r}=0) = \frac{q_i q_i}{a^3} \frac{2(\epsilon-1)}{2\epsilon+1} \vec{r}_s \quad (\text{force from its own polarization is zero})$$

This force can be modeled by introducing an effective potential acting between particles  $i$  and  $j$ :  $U_{\text{eff}}(r_s) = \frac{q_i q_j}{a^3} \frac{\epsilon-1}{2\epsilon+1} \cdot r_s^2$

$$\vec{F}_i = -\vec{F}_j = \frac{\partial}{\partial \vec{r}_s} U_{\text{eff}}(r_s) = \frac{q_i q_j}{a^3} \frac{2(\epsilon-1)}{2\epsilon+1} \vec{r}_s$$

The total force acting between charges  $q_i$  and  $q_j$  if  $r < a$  is:

$$U_{\text{RF}}(r) = U_c(r) + U_{\text{eff}}(r) = \frac{q_i q_j}{r} + \frac{q_i q_j}{a^3} \frac{\epsilon-1}{2\epsilon+1} \cdot r^2 = \frac{q_i q_j}{r} \left( 1 + \frac{\epsilon-1}{2\epsilon+1} \left( \frac{r}{a} \right)^3 \right)$$



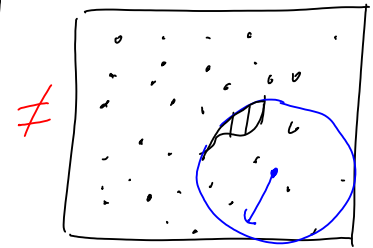
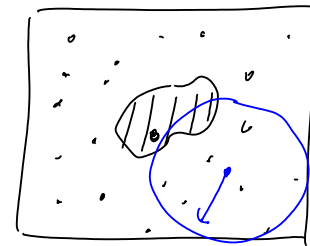
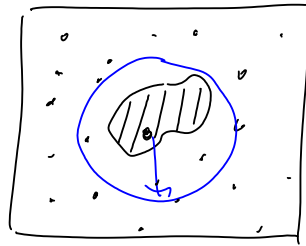
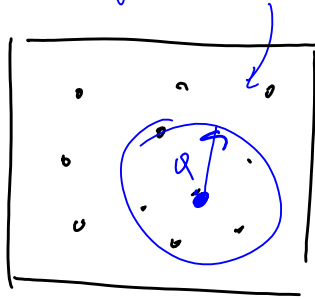
The reaction field results in a modified Coulomb potential of  $a = R_c$ .  
In all other aspects simulations are the same.

a) method is applicable to homogeneous systems only.

The area outside cut-off sphere } This approximation:  
has to be homogeneous continuum.

Applies to some  
solute atoms

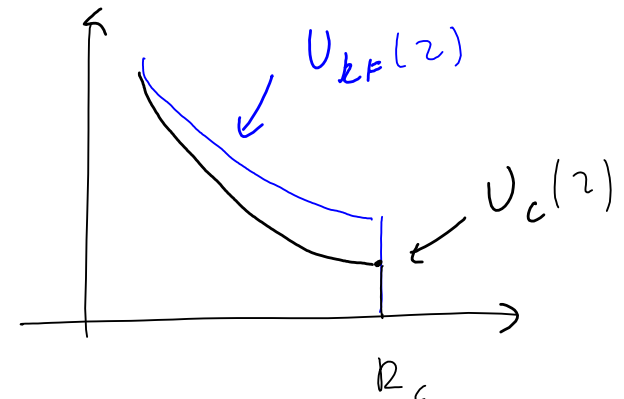
Doesn't apply to most  
solvent atoms!



b) The modified potential is still long-ranged.

$$U_{RF}(z=R_c) = \frac{q_1 q_2}{R_c} \frac{3f}{2f+1} \approx \frac{3}{2} \frac{q_1 q_2}{R_c} = \frac{3}{2} U_c(R_c)$$

The potential is still significant at the cut-off distance. The force is discontinuous at  $R_c$  as seen. This requires large  $R_c$  to minimize the contribution of the truncated part.



c) Reaction-field correction makes a big difference. Solvation of a  $\text{Na}^+-\text{Cl}^-$  ions

Truncation leads to unphysical repulsion that persists at large  $R_c$

Reaction field removes that repulsion

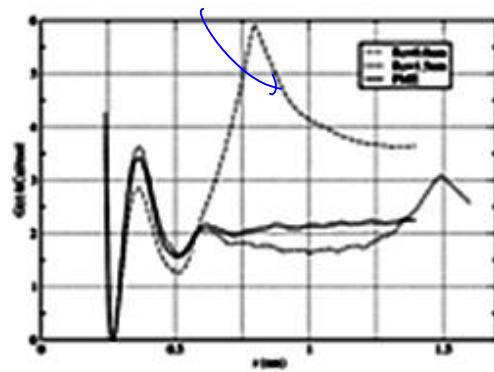


FIG. 3. Potential of mean force obtained in this work for NaCl using group-based straight cutoff method. Two values of the cutoff distance were considered,  $R_c=0.8$  nm and 1.5 nm. The distinctive feature of the obtained PMFs is a strong and unphysical maximum at  $r=R_c$ . The strength of the maximum is attenuated at larger cutoff radii.

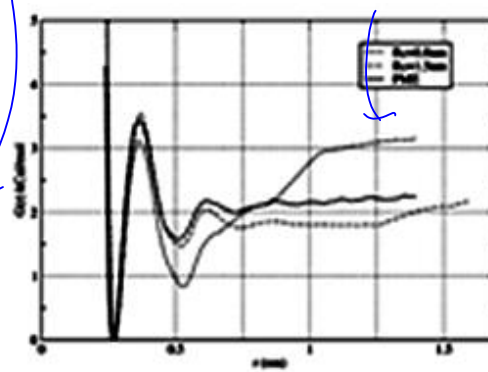
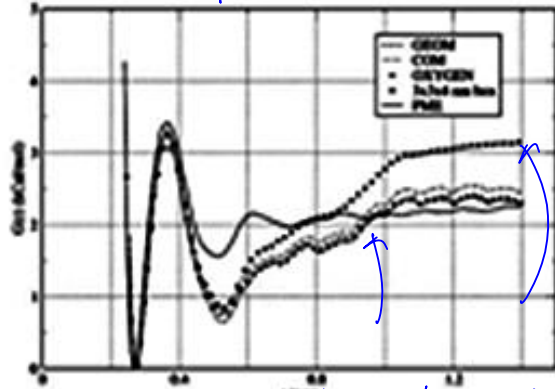


FIG. 4. Potential of mean force obtained in this work for NaCl using group-based reaction-field correction method. Two values of the cutoff distance were considered,  $R_c=0.8$  nm and 1.5 nm. Compared to Fig. 3, the unphysical maxima resulting from the potential truncation at  $r=R_c$  are gone. Significant residual errors are observed in the association energy of two ions.

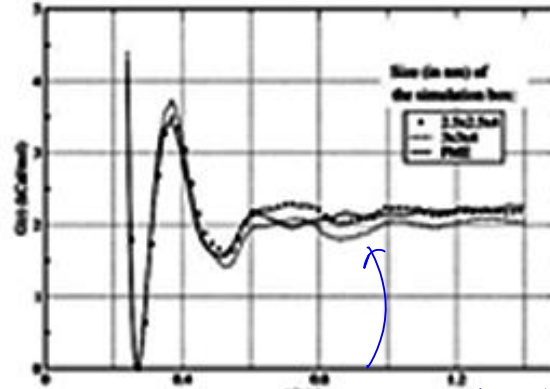
d) In molecular systems, the way truncation is implemented makes a big difference

Group-based truncation



Large error that depends on the size of the simulation box

Atom-based truncation

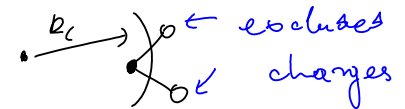


Good agreement with the lattice-sum method

Group based truncation



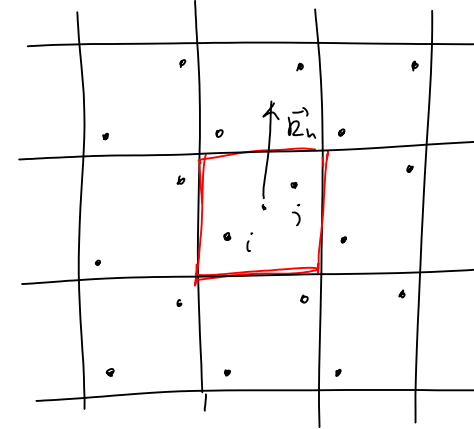
Atom-based truncation



## Ewald summation

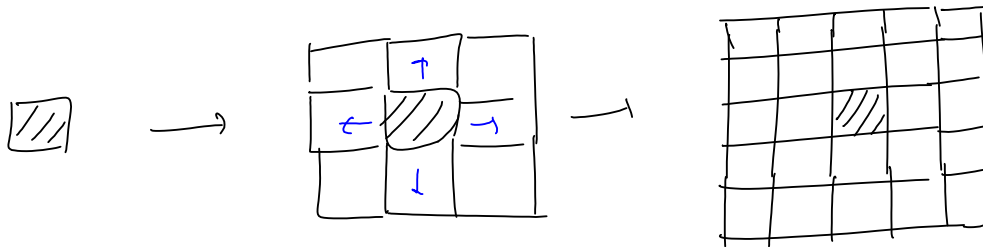
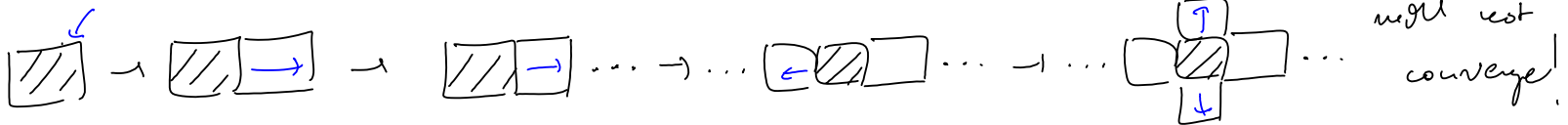
To avoid truncating the potential, consider the infinite lattice in which particles on the central simulation box interact with all their periodic images:

$$E_{\text{ES}} = \sum'_{i,j,\vec{R}_n} \frac{q_i q_j}{|\vec{r}_i - \vec{r}_j + \vec{R}_n|} \quad \text{prune term } i=j \text{ if } \vec{R}_n = 0$$



This sum is conditionally convergent, meaning the result will depend on how summation is performed. A physically appealing way is to systematically grow the lattice from all directions into infinity.

central cell

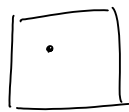


The summation can be performed directly until convergence to each atomic configuration, but this method is extremely inefficient.

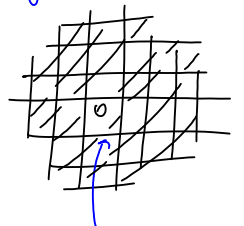
The difficulty is that for every pair of  $i$  and  $j$  atoms, an infinite (very large) number of terms have to be considered. The situation could be simplified if some of these terms were small, or were made small. This can be achieved if instead of Coulomb, some short-range potential were considered.

Each charge in the Bwald sum interacts with the outside lattice:

charge  $q_i$ :



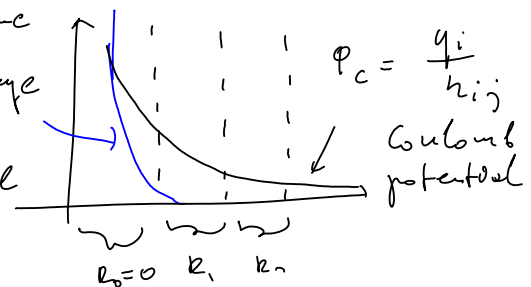
charge creating the field



$q_i$  excluded

$$\sum_{j, \vec{R}_n} \frac{q_j}{|\vec{r}_i - \vec{r}_j + \vec{R}_n|} = \sum_{j, \vec{R}_n} \Phi_c(\vec{r}_i - \vec{r}_j + \vec{R}_n)$$

$\Phi_{sc}$  - some short-range "screened" potential



Only a limited number of  $\vec{R}_n$  vectors will contribute to screened potential energy

Assume that some compensating charge distribution  $f(\vec{r})$  can be added to each  $q_i$  so that its potential becomes short-range  $\Phi_{sc}(\vec{r})$ . The potential created by that charge is  $\Phi_f(\vec{r}) = \Phi_{sc}(\vec{r}) - \Phi_c(\vec{r})$  - potential of background

$$\frac{1}{2} \sum_{i,j, \vec{R}_n} q_i \Phi_c(\vec{r}_{ij} + \vec{R}_n) = \frac{1}{2} \sum_{i,j, \vec{R}_n} q_i \Phi_{sc}(\vec{r}_{ij} + \vec{R}_n) - \frac{1}{2} \sum_{i,j, \vec{R}_n} q_i \Phi_f(\vec{r}_{ij} + \vec{R}_n)$$

↑  
Ewald energy
↑  
short-range interactions  
easy to compute
↑  
Long-range interactions

The sum on the long-range part can be supplemented by the  $i=j, \vec{k}_n=0$  term

$$\frac{1}{2} \sum_{i,j,\vec{k}_n} q_i \Phi_b(\vec{z}_i + \vec{k}_n) = \frac{1}{2} \sum_{i,j,\vec{k}_n} q_i \Phi_b(\vec{z}_i + \vec{k}_n) - \frac{1}{2} \sum_i q_i \Phi_b(0) \leftarrow \text{self-energy}$$

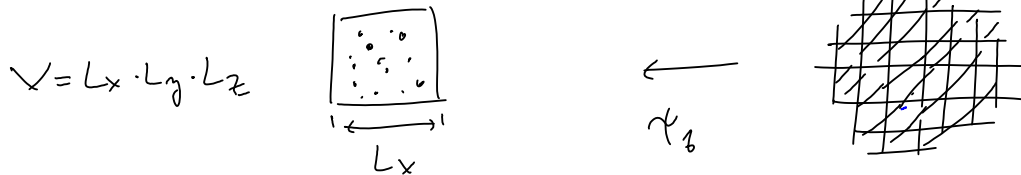
The total energy then: easy to compute

$$E_w = \frac{1}{2} \sum_{i,j,\vec{k}_n} q_i \Phi_{sc}(\vec{z}_i + \vec{k}_n) - \sum_{i,j,\vec{k}_n} q_i \Phi_b(\vec{z}_i + \vec{k}_n) + \frac{1}{2} \sum_i q_i \Phi_b(0)$$

$E_b''$  — background energy.

Charge density of the central cell  $\rho_i(\vec{z}) = \sum_i q_i \delta(\vec{z} - \vec{z}_i)$

Enlarge lattice of background charge  $\rho_b(\vec{z})$



$$E_b = \frac{1}{2} \sum_{i,j,\vec{k}_n} q_i \Phi_b(\vec{z}_i + \vec{k}_n) = \frac{1}{2} \int d\vec{z} \rho_i(\vec{z}) \cdot \Psi_b(\vec{z}) d\vec{z}, \quad \Psi_b(\vec{z}) = \sum_{j,\vec{k}_n} \Phi_b(\vec{z} - \vec{z}_j + \vec{k}_n)$$

$\Psi_b(\vec{z})$  and its associated charge contribution  $\rho_b(\vec{z})$  are related by the Poisson eq.

$$\Delta \Psi_b(\vec{z}) = -4\pi \rho_b(\vec{z})$$

Introducing Fourier transforms:

$$\begin{cases} \rho_b(\vec{z}) = \frac{1}{V} \int \rho_b(\vec{k}) e^{i\vec{k}\vec{z}} d\vec{z}, & \Psi_b(\vec{z}) = \frac{1}{V} \int \Psi_b(\vec{k}) e^{i\vec{k}\vec{z}} d\vec{z} \\ \rho_b(\vec{z}) = \sum_{\vec{k}} \rho_b(\vec{k}) e^{-i\vec{k}\vec{z}}, & \Psi_b(\vec{z}) = \sum_{\vec{k}} \Psi_b(\vec{k}) e^{-i\vec{k}\vec{z}} \end{cases}$$

Poisson equation reads:

$$\nabla^2 \psi_b(\vec{r}) = -4\pi \rho_b(\vec{r})$$

$$\vec{k} - \text{wave vector } k_i \in [-\infty, +\infty]$$

$$k_x = \frac{2\pi}{L_x} \cdot k_x, k_y = \frac{2\pi}{L_y} \cdot k_y, k_z = \frac{2\pi}{L_z} \cdot k_z$$

$$\psi_b(\vec{r}) = -\frac{4\pi \rho_b(\vec{r})}{\nabla^2} \text{ at } |\vec{r}| \rightarrow 0$$

$$\psi_b(\vec{r} \rightarrow \infty) = \int \psi_b(\vec{r}) d\vec{r} - \text{has to be finite}$$

as  $\lim_{|\vec{r}| \rightarrow 0} \frac{4\pi}{\nabla^2} \rho_b(\vec{r})$  it may become undefined.

$$E_b = \frac{1}{2} \int \rho_b(\vec{r}) \psi_b(\vec{r}) d\vec{r} = \frac{1}{2} \int d\vec{r} \sum_i q_i \delta(\vec{r} - \vec{r}_i) \psi_b(\vec{r}) = \frac{1}{2} \sum_i q_i \psi_b(\vec{r}_i) =$$

$$= \frac{1}{2} \sum_i q_i \sum_{\vec{k}} \psi_b(\vec{k}) e^{-i\vec{k} \cdot \vec{r}_i} = -\frac{1}{2} \sum_{i, \vec{k}} q_i \frac{4\pi}{k^2} \rho_b(\vec{k}) \cdot e^{-i\vec{k} \cdot \vec{r}_i}$$

$\vec{k} = 0$  needs special handling

If  $\rho_b(\vec{k})$  decays rapidly with  $|\vec{k}|$

the sum may be easy to compute

Assume that the background charge density is Gaussian. For each charge  $q_i$ :

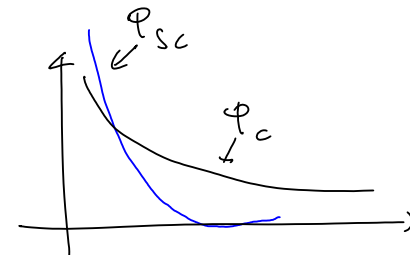
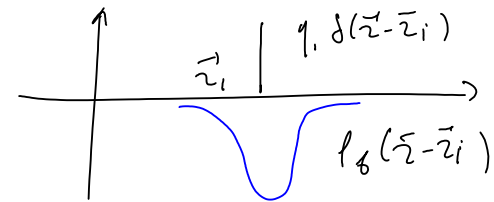
$$\rho_b^0(\vec{r}) = -q_i \left( \frac{\alpha}{\pi} \right)^{3/2} e^{-\alpha \vec{r}^2}$$

$\alpha = \text{adjustable parameter}$

$$\Delta \psi_b(\vec{r}) = -4\pi \rho_b^0(\vec{r}) \Rightarrow \psi_b(\vec{r}) = -q_i 2\sqrt{\frac{\alpha}{\pi}} \frac{1}{\alpha} \int_0^\infty e^{-\alpha x^2} dx$$

$$\psi_{sc}(\vec{r}) = \frac{q_i}{\epsilon} - q_i \sqrt{\frac{\alpha}{\pi}} \frac{2}{\alpha} \int_0^\infty e^{-\alpha x^2} dx, \text{ when } \psi_{sc}(\vec{r}) = 0$$

$$\psi_b(\vec{r} \rightarrow \infty) = -q_i 2\sqrt{\frac{\alpha}{\pi}} - \text{to be used in } E_w$$



For the infinite lattice of background charge!

$$\phi_b(\vec{z}) = \sum_{j, \vec{k}_n} \phi_b^0(\vec{z} - \vec{z}_j + \vec{k}_n) = -\left(\frac{\alpha}{\pi}\right)^{3/2} \sum_{j, \vec{k}_n} q_j e^{-\alpha(\vec{z} - \vec{z}_j + \vec{k}_n)^2}$$

$$\int_{\vec{k}_n} d\vec{z} \sum F(\vec{z} + \vec{k}_n) = \int_{\text{all space}} d\vec{z} F(\vec{z})$$

$$\phi_b(\vec{k}) = -\frac{1}{V} \left(\frac{\alpha}{\pi}\right)^{3/2} \sum_{j, \vec{k}_n} q_j \int e^{-\alpha(\vec{z} - \vec{z}_j + \vec{k}_n)^2} e^{i\vec{k} \cdot \vec{z}} d\vec{z} =$$

$$= -\frac{1}{V} \left(\frac{\alpha}{\pi}\right)^{3/2} \sum_j q_j \int_{\text{all space}} e^{-\alpha(\vec{z} - \vec{z}_j)^2} e^{i\vec{k} \cdot \vec{z}} d\vec{z} =$$

$$= -\frac{1}{V} \left(\frac{\alpha}{\pi}\right)^{3/2} \sum_j q_j \int_{\text{all space}} e^{-\alpha \cdot \vec{z}'^2} e^{i\vec{k} \cdot \vec{z}'} d\vec{z}' \cdot e^{i\vec{k} \cdot \vec{z}_j} =$$

$$\int_{V_0} e^{-\alpha(\vec{z} - \vec{k}_n)^2} d\vec{z} = \int_{V_0} e^{-\alpha \vec{z}'^2} d\vec{z}'$$

with  $\vec{z}' = \vec{z} - \vec{k}_n$  substitution

$$= \sum_j \phi_{b,j}^0(\vec{k}) \cdot e^{i\vec{k} \cdot \vec{z}_j} = -e^{-\frac{k^2}{4\alpha}} \frac{1}{V} \sum_j q_j e^{i\vec{k} \cdot \vec{z}_j}$$

$\uparrow$   
 $-q_j \cdot e^{-\frac{k^2}{4\alpha}} / V$

$$\phi_i(\vec{k}) = \frac{1}{V} \int \phi_i(\vec{z}) e^{i\vec{k} \cdot \vec{z}} d\vec{z} = \frac{1}{V} \sum_j q_j e^{i\vec{k} \cdot \vec{z}_j}$$

$$\boxed{\phi_b(\vec{k}) = -e^{-\frac{k^2}{4\alpha}} \phi_i(\vec{k})}$$

$$\epsilon_b = -\frac{1}{2} \sum_{i, \vec{k}} q_i \frac{4\pi}{k^2} \phi_b(\vec{k}) \cdot e^{-i\vec{k} \cdot \vec{z}_i} = 2\pi V \sum_{\vec{k}} \frac{1}{k^2} \phi_i(-\vec{k}) \phi_b(\vec{k}) =$$

$$= 2\pi V \sum_{\vec{k}} \frac{1}{k^2} e^{-\frac{k^2}{4\alpha}} \phi_i(\vec{k}) \cdot \phi_i(-\vec{k}) = 2\pi V \sum_{\vec{k}} \frac{1}{k^2} e^{-\frac{k^2}{4\alpha}} |\phi_i(\vec{k})|^2$$



Background charge contribution can be computed in the Fourier space:

$$E_b = \frac{1}{4\pi\epsilon_0} \sum_{\vec{k}} \frac{1}{k} e^{-\frac{k^2}{4a}} |l_i(\vec{k})|^2$$

If  $l_i(\vec{k})$  are available, the sum will be rapidly converging with  $|\vec{k}|$  due to the exponential decay of  $e^{-k^2/4a}$

$E_b$  contains one term  $\vec{k}=0$  which needs separate treatment. If we

introduce  $f(\vec{k}) = \frac{1}{k} e^{-\frac{k^2}{4a}} |l_i(\vec{k})|^2$ ,  $E_b = \frac{1}{4\pi\epsilon_0} V \cdot f(0) + \frac{1}{4\pi\epsilon_0} V \cdot \sum_{\vec{k} \neq 0} f(\vec{k})$

$$f(0) = \lim_{\vec{k} \rightarrow 0} f(\vec{k})$$

- a) Limit does not exist. The formal sum is divergent and should not be used
- b) Limit exists.  $E_b$  can be determined uniquely
- c) Limit is conditional.  $E_b$  can be determined up to a constant

Expand  $f(\vec{k})$  in powers of  $|\vec{k}|$  around  $|\vec{k}|=0$ . Choose vector  $(k_x, 0, 0)$  for simplicity:

$$l_i(\vec{k}) = \frac{1}{\sqrt{2}} \sum_j q_j (1 + i k_x \cdot x_j - \frac{1}{2} k_x^2 \cdot x_j^2 + \dots)$$

$$|l_i(\vec{k})|^2 = \frac{1}{2} \sum_{i,j} q_i (1 + i k_x \cdot x_i - \frac{1}{2} k_x^2 \cdot x_i^2 + \dots) q_j (1 - i k_x \cdot x_j - \frac{1}{2} k_x^2 \cdot x_j^2 + \dots)$$

$$|\ell(\vec{k})|^2 = \frac{1}{V^2} \left( \left( \sum_i q_i \right)^2 + k_x^2 \left( \sum_i q_i x_i \right)^2 - k_x^2 \sum_i q_i \sum_j q_j x_j^2 \right) + O(k_x^4)$$

$$G(\vec{k}) = \frac{1}{V^2} e^{-\frac{k^2}{42}} \cdot \frac{1}{k^2} \left( \left( \sum_i q_i \right)^2 + k_x^2 \left( \sum_i q_i x_i \right)^2 - k_x^2 \sum_i q_i \sum_j q_j x_j^2 \right) + O(k_x^4)$$

If  $\left[ \sum_i q_i \neq 0 \right]$  -  $\lim_{\vec{k} \rightarrow 0} G(\vec{k})$  does not exist and the Ewald sum is divergent.

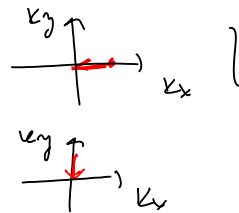
Assume charge neutral simulation cell  $\sum_i q_i = 0$ .

$$G(\vec{k}) = \frac{1}{V^2} e^{-\frac{k^2}{42}} \frac{1}{k^2} \left( k_x \sum_i q_i x_i \right)^2 = \frac{1}{V^2} e^{-\frac{k^2}{42}} \frac{1}{k^2} \left( \vec{k} \cdot \vec{M} \right)^2, \quad \vec{M} = \sum_i q_i \vec{z}_i$$

The limit depends on direction from which  $\vec{k}$  is approached! dipole moment of the simulation cell

$$\lim_{k_x \rightarrow 0} G(\vec{k}) = \frac{1}{V^2} M_x^2$$

$$\lim_{k_y \rightarrow 0} G(\vec{k}) = \frac{1}{V^2} M_y^2$$



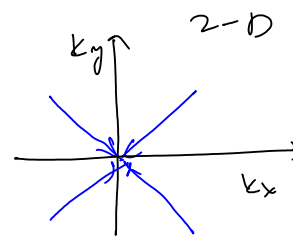
$G(\vec{k})$  is non-analytical at  $\vec{k} = 0$ . This is the consequence of Ewald summation being only conditionally convergent!

The type of summation we employed is when lattice grows in all 3 directions simultaneously. This implies that minimum  $k_x = \frac{2\pi}{L_x}$ ,  $k_y = \frac{2\pi}{L_y}$ ,  $k_z = \frac{2\pi}{L_z}$

also have to change at the same time and at the same rate:  $k_x = k_y = k_z$  (cube too)

In other words,  $\vec{k}$  should change along the diagonal to be appropriate for the chosen summation method. But there's more than 1 diagonal on the  $\vec{k}$ -space!

$f(\vec{k})$  arises in the context of Fourier transforms. There are rules in Fourier analysis for handling discontinuous functions



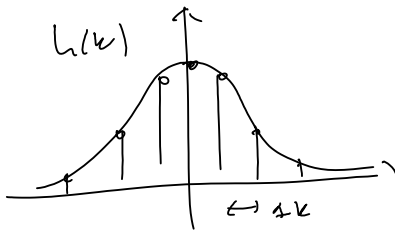
4 equivalent diagonal directions along  $\vec{k}=0$  can be reached. which one to pick!

Consider 1-D case:

$k=0$  can be reached from 2 directions

$$f(0) = \frac{1}{2\pi} \int_{-\infty}^{+\infty} f(k) e^{-ikx} dk = \frac{1}{2\pi} \left( \int_0^{+\infty} f(k) e^{ikx} dk + \int_0^{+\infty} f(k) e^{-ikx} dk \right)$$

$$\lim_{\Delta k \rightarrow 0} \frac{1}{2\pi} \sum_{k=-\infty}^{+\infty} f(k) e^{-ikx} \Delta k \rightarrow \begin{cases} \lim_{\Delta k \rightarrow 0} \frac{1}{2\pi} \left( f(0) + \sum_{k \neq 0} f(k) e^{-ikx} \right) \Delta k & f(0) \text{ is analytical} \\ \lim_{\Delta k \rightarrow 0} \frac{1}{2\pi} \left( \frac{f(+0) + f(-0)}{2} + \sum_{k \neq 0} f(k) e^{-ikx} \right) \Delta k & f(0) \text{ has a discontinuity} \end{cases}$$



$$\int_{-\infty}^{+\infty} h(k) dk - \text{errors!}$$



$$\int_{-\infty}^{+\infty} h(k) dk = \lim_{\Delta k \rightarrow 0} \left( h(0) + \sum_{k \neq 0} h(k) \right) \Delta k$$

$$\int_{-\infty}^{+\infty} h(k) dk = \lim_{\Delta k \rightarrow 0} \left( \frac{h(+0) + h(-0)}{2} + \sum_{k \neq 0} h(k) \right) \Delta k$$

The limit has to be taken on all equivalent directions and the result averaged.

In 3D there are 8 diagonals to reach  $\vec{k}=0$ . Set  $p$  a varying parameter

$\vec{k} = p/\sqrt{3} (\pm 1, \pm 1, \pm 1)$  - would give all 8 diagonals

For instance,  $\vec{k}_1 = \frac{p}{\sqrt{3}} (1, 1, 1)$ ,  $k_1^2 = p^2$ ,  $\lim_{\vec{k}_1 \rightarrow 0} G(\vec{k}_1) = \frac{1}{3k^2} (m_x^2 + m_y^2 + m_z^2)$

Taking all 8 limits:  $G(0) = \frac{1}{8} \lim_{\vec{k}_i \rightarrow 0} \sum_{i=1}^8 G(\vec{k}_i) = \frac{1}{3} \frac{1}{v^2} (m_x^2 + m_y^2 + m_z^2)$

This gives for the background energy:

$$E_b = \frac{m}{3v} \left( \sum_i q_i \vec{z}_i \right)^2 + m v \sum_{\vec{k} \neq 0} \frac{1}{k^2} e^{-\frac{k^2}{4a}} |l_i(\vec{k})|^2$$

Putting all terms together:

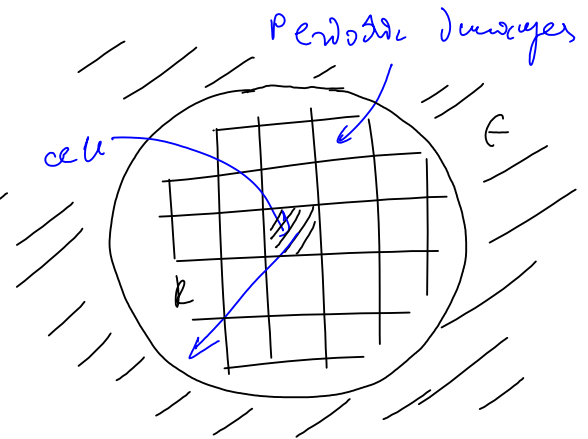
$$E_w = \frac{1}{2} \sum_{i,j,\vec{k}_u} \chi_{sc}(\vec{z}_i + \vec{k}_u) + m v \sum_{\vec{k} \neq 0} \frac{1}{k^2} e^{-\frac{k^2}{4a}} |l_i(\vec{k})|^2 - \sum_i q_i \sqrt{\frac{a}{k}} +$$

$$+ \frac{m}{3v} \left( \sum_i q_i \vec{z}_i \right)^2, \quad l_i(\vec{k}) = \frac{1}{v} \sum_i q_i e^{i\vec{k} \cdot \vec{z}_i}$$

$$\frac{m}{3v} m^2$$

Assume that the simulated system is considered in a dielectric medium and not in vacuum.

Periodic images of the central cell will gradually fill up space in approximately spherical shapes. They will generate reaction field which will contribute to the solvation free energy of the central cell  $\Delta G$ . Since in the  $R \rightarrow \infty$  limit the central cell will shrink to a point, one can use dipole approximation:



$$\Delta G = - \int_0^{\infty} d\vec{M} \cdot \vec{E}$$

$\vec{E}$  - reaction field

$d\vec{M}$  - dipole moment

$$\vec{E} = - \frac{1}{R^3} \frac{2(1-\epsilon)}{2\epsilon+1} \vec{M}_t, \quad \vec{M}_t - \text{dipole moment of the infinite lattice encapsulated inside the sphere}$$

$$\vec{M}_t = \sum_i q_i (\vec{r}_i + \vec{R}_i) = N \cdot \vec{M}, \quad \vec{M} - \text{dipole moment of the central sphere. } N - \# \text{ of images}$$

$$\frac{4\pi}{3} R^3 = N \cdot V, \quad V - \text{volume of the sm. cell.} \quad \vec{E} = - \frac{4\pi}{3} \frac{1}{V} \frac{2(1-\epsilon)}{2\epsilon+1} \vec{M}$$

$$\Delta G = \frac{4\pi}{3V} \frac{1-\epsilon}{2\epsilon+1} \vec{M}^2$$

The solvation energy can be combined with the  $\vec{v}=0$  entry to give

$$E_{\text{sw}} = \frac{1}{2} \sum_{i,j \in \text{sol}} q_i q_j \epsilon_{\text{sc}}(\vec{r}_{ij}) + 4\pi v \sum_{\vec{k} \neq 0} \frac{1}{k^2} e^{-\frac{k^2}{4\epsilon}} |l_i(\vec{k})|^2 - \sum_i q_i^2 \sqrt{\frac{\epsilon}{\pi}} +$$

$$+ \frac{4\pi}{4(2\epsilon+1)} \left( \sum_i q_i \vec{r}_i \right)^2$$

Boundary conditions:

1) "Adjusted"  $\epsilon$  should be set equal to the dielectric constant of the simulated material

2) Vacuum  $\epsilon = 1$

3) "Tourol" or metallic  $\epsilon = +\infty$ . No solvation or  $\vec{v}=0$  term

↑  
most often used. Which boundary is better is still debated

## Accuracy and complexity

one adjustable parameter -  $L$

The error is controlled by how many terms are retained in the real and inverse parts. Assume  $k_c$  cutoff is introduced for the real part, and  $n_c$  for the inverse part.  $k_c = 2\pi/L \cdot n_c$ . The error can then be estimated:

$$\left. \begin{aligned} \delta B_R &\approx Q \cdot \sqrt{\frac{k_c}{2L^3}} \frac{1}{(\beta k_c)^2} e^{-\beta^2 k_c^2} \\ \delta B_F &\approx Q \cdot \frac{\sqrt{n_c}}{\beta \cdot L^2} \frac{1}{(\pi n_c / \beta \cdot L)^2} e^{-\left(\frac{\pi n_c}{\beta} \cdot L\right)^2} \end{aligned} \right\} Q = \sum_i y_i^2$$

Both  $\delta B_R$  and  $\delta B_F$  are determined by the same function  $e^{-x^2}/x^2$ . Let's impose an accuracy  $\varepsilon = e^{-s^2}/s^2$  on both terms.

$$R_c = \frac{S}{\beta}, \quad n_c = \frac{S \cdot L^2}{\pi} \rightarrow \delta B_R \approx Q \sqrt{\frac{S}{\beta \cdot L^3}} e^{-S^2}/S^2, \quad \delta B_F = Q \sqrt{\frac{S}{2\beta L^3}} e^{-S^2}/S^2$$

$$\boxed{R_c, \varepsilon} \rightarrow S \rightarrow \begin{cases} \beta \\ n_c \end{cases}$$

↑  
these two quantities need to be fixed ahead of time



Computational effort

Total computational expense:

$$\tau = \tau_k \cdot M_k + \tau_F \cdot M_F$$

$M_k$  - number of pair interactions to be evaluated within  $k_c$

$$M_k = M_c \cdot M = \frac{4\pi}{3} \cdot k_c^3 \cdot \rho \cdot M = \frac{4\pi}{3} \frac{s^3 M^2}{\beta s \cdot L^3}$$

$M_F$  - number of terms on the Fourier series with  $k_c$  cutoff

$$M_F = M_c^* \cdot M = \frac{4}{3} \pi \frac{s^3 \beta^3 L^3}{\pi^3} M$$

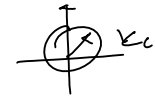
Minimize  $\tau(\beta)$ :  $\frac{\partial \tau}{\partial \beta} = 0$

$$\mathcal{L} = \left( \frac{\tau_k \tau^3 M}{\tau_F \cdot L^6} \right)^{1/6}$$

$$\tau = \frac{8 \sqrt{\tau_k \tau_F} M^{3/2} \cdot s^3}{3 \sqrt{\pi}} = \boxed{O(M^{3/2})}$$

$\tau_k$  - time needed to evaluate interactions for a pair of particles

$\tau_F$  - time needed to evaluate the Fourier part per particle and per vector  $\vec{k}$



$$M_c^* = \frac{4}{3} \pi k_c^3 / \Delta k^3$$

$$\Delta k = \frac{2\pi}{L}$$

$\tau_k / \tau_F$  ratio can be determined on short simulations

# Poisson-Boltzmann (PB) model

In canonical ensemble:

$$\rho_{NVT}(\Gamma) \sim e^{-\beta H(\Gamma)}, \beta = \frac{1}{kT}$$

Partition function:

$$Q_{NVT} = \frac{1}{h^{3N} N!} \int d\vec{p} d\vec{q} e^{-\beta H(\Gamma)} = \overset{\text{Ideal part}}{\downarrow} Q_{NVT}^{id} \times \overset{\text{excess part}}{\downarrow} Q_{NVT}^{ex}$$

$$Q_{NVT}^{id} = \frac{V^N}{N! \lambda^{3N}}, \lambda = \sqrt{h^2 / 2\pi m kT}$$

$$Q_{NVT}^{ex} = \frac{Z_{NVT}}{V^N}, Z_{NVT} = \int d\vec{q} e^{-\beta U(\vec{q})}$$

Free energy splits into two parts as well:

$$F = -kT \log Q_{NVT} = F^{id} + F^{ex}$$

Gibbs free energy:  $G = F + PV = F^{id} + F^{ex} + (P^{id} + P^{ex})V = G^{id} + G^{ex}$

Chemical potential:  $\mu = \frac{G}{N} = \mu^{id} + \mu^{ex}$  where

$$\mu^{id} = kT \log(\lambda^3) + kT \log(\rho) = kT \log\left(\frac{\rho}{n_Q}\right)$$

$n_Q = \lambda^{-3}$   $\nearrow$

$\nwarrow$  particle density

excess part due to interactions  
among particles

$$\mu^{ex} = U^{ex} - TS^{ex} + P^{ex}V$$

$\swarrow \quad \downarrow \quad \searrow$

Assume the following approximation for the ions solvated near a charged wall:

$$\mu = U^{ex} + \mu^{id} = q\varphi + kT \log\left(\frac{\rho}{n_Q}\right)$$

$\downarrow$   
*number density of ions*

*total interaction energy is approximated by the electrostatic potential. The potential needs calibration.*

*excess parts of entropy and pressure are neglected (not too bad)*

Consider system of ions confined between two surfaces. All properties depend on coordinate  $x$ .

In the state of equilibrium, or more generally stationary state, the chemical potential should not depend on  $x$  to avoid exchange of particles between different parts of the system.

$$\begin{aligned} \mu(x) &= \text{const} \\ \downarrow \\ q\varphi(x) + kT \log\left(\frac{\rho(x)}{n_Q}\right) &= \text{const} \end{aligned}$$

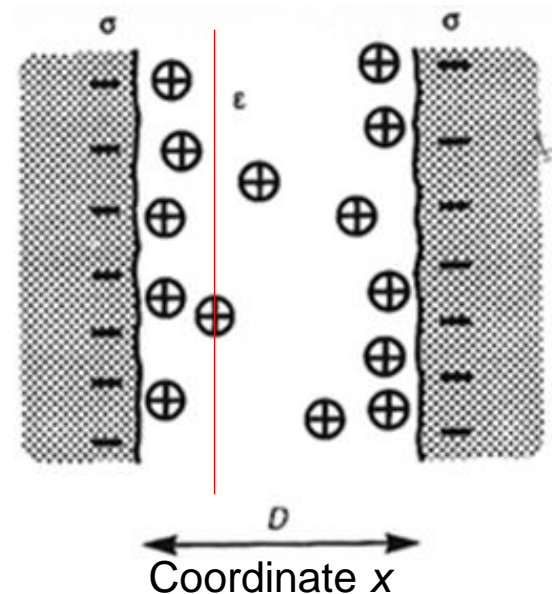
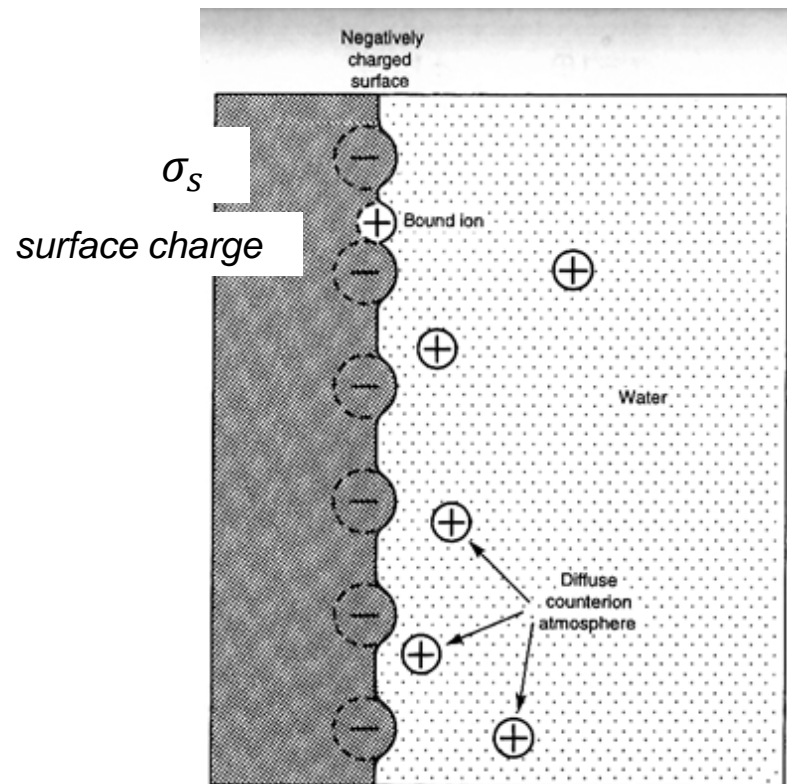
$$\downarrow$$

$$\rho(x) = \rho^0 e^{-\beta q\varphi(x)}$$

Boltzmann distribution prescribing how density of ions will change depending on the potential

$$\left\{ \begin{array}{l} \varphi(x=0) = 0 \\ \rho(x=0) = \rho^0 \end{array} \right.$$

*calibration conditions*



Density and the potential are connected by laws of electrostatics:

$$\vec{\nabla} \vec{D}(x) = 4\pi\rho_c(x)$$

*displacement created by charge distribution*  $\swarrow$   $\nwarrow$  *charge distribution*

In polarizable media:  $\vec{D}(x) = \epsilon(x)\vec{E}(x) = -\epsilon(x)\vec{\nabla}\varphi(x)$

For vacuum:  $-\vec{\nabla}\vec{E}(x) = \Delta\varphi = -4\pi q\rho(x)$   $\leftarrow$  *Poisson equation for computing potential created by charge density*

$$\frac{d^2\Delta\varphi}{dx^2} = -4\pi q\rho^0 e^{-\beta q\varphi(x)}$$

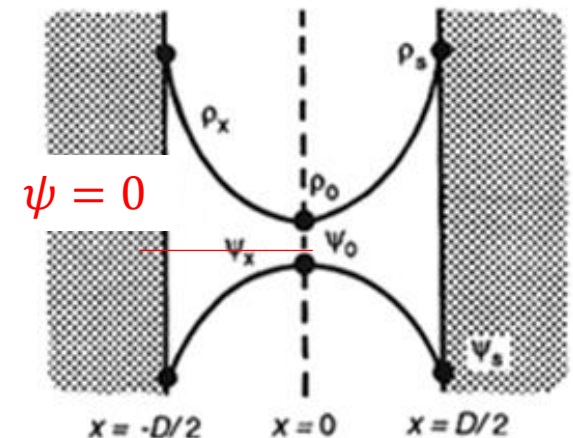
*Poisson-Boltzmann (PB) equation*

$$\varphi(x=0) = 0 \quad \sigma_s = \text{const} \quad \text{constant charge boundary condition}$$

$$\sigma_s = f(\varphi)$$

*constant "potential" boundary condition*

PB gives ion density, potential and electric field at any point within the system



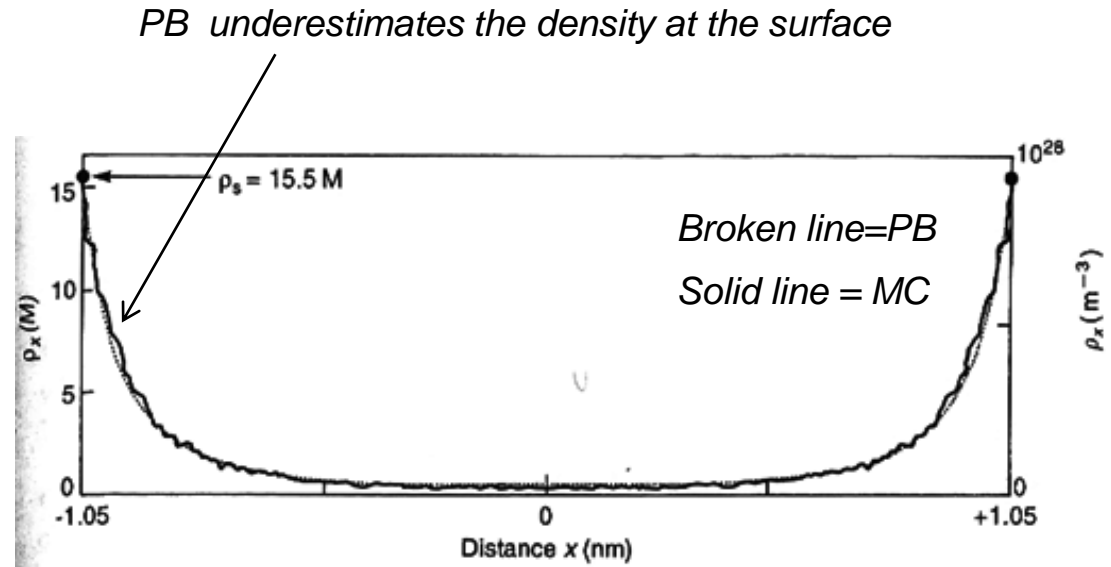
How well does the PB model work?

Analytical solution:

$$\rho(x) = \rho_0 e^{-q\beta\varphi(x)} = \rho_0 / \cosh^2(Kx)$$

$$-\frac{2K}{\beta q} \tan\left(\frac{KD}{2}\right) = \sigma_s \quad \text{equation for } K$$

The agreement is remarkably good for concentrations in the range up to 16M!



Extension to mixtures

*Assume that we have a mixture of ions with varying valency. The condition on the constancy of the chemical potential has to be satisfied for each component.*

$$\mu_i = q_i\varphi + kT \log\left(\frac{\rho_i}{n_Q}\right) \longrightarrow \rho_i(x) = \rho_i^0 e^{-\beta q_i\varphi(x)}$$

Poisson equation

$$\Delta\varphi = -4\pi \sum_i q_i \rho_i(x) \longrightarrow \Delta\varphi = -4\pi \sum_i q_i \rho_i^0 e^{-\beta q_i \varphi(x)} \quad \text{PB equation}$$

Linearize the RHS

$$e^{-\beta q_i \varphi(x)} = 1 - \beta q_i \varphi(x) + \dots$$

Zero for electrically neutral systems

$$4\pi \sum_i q_i \rho_i^0 e^{-\beta q_i \varphi(x)} = 4\pi \sum_i q_i \rho_i^0 (1 - \beta q_i \varphi(x) + \dots) = 4\pi \sum_i q_i \rho_i^0 - 4\pi \sum_i q_i^2 \rho_i^0 \beta \varphi(x) + \dots$$

$\approx -\kappa^2 \varphi$

$$\kappa = \sqrt{4\pi\beta \sum_i q_i^2 \rho_i^0} \quad \text{inverse screening length}$$

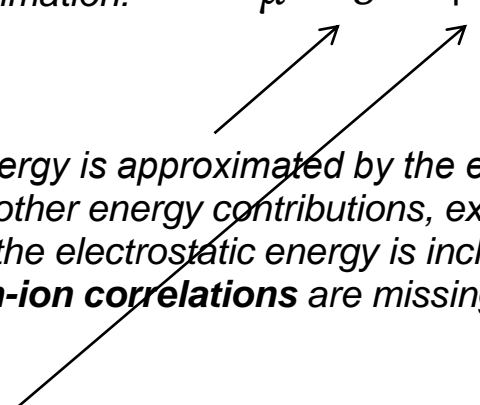
After putting everything together:

$$\Delta\varphi - \kappa^2 \varphi = 0$$

linear PB (LPB) for multicomponent systems

## Limitations of the PB model

The key approximation:

$$\mu = U^{ex} + \mu^{id} = q\varphi + kT \log\left(\frac{\rho}{n_Q}\right)$$


1) The total energy is approximated by the electrostatic component only. What's neglected:

a) other energy contributions, excluded volume, vdW etc. **The size of the ions** is missing

b) the electrostatic energy is included at the mean-field level. Approximated by the average value.

**Ion-ion correlations** are missing

2) Full entropy is approximated by its ideal part. Effect of particle-particle interactions on the excess entropy is neglected. In particular:

a) **steric effects** are missing

3) Discreetness of surface charge. May contribute additional attraction when discrete surface charges are mobile.



## How can PB model be used for biomolecules?

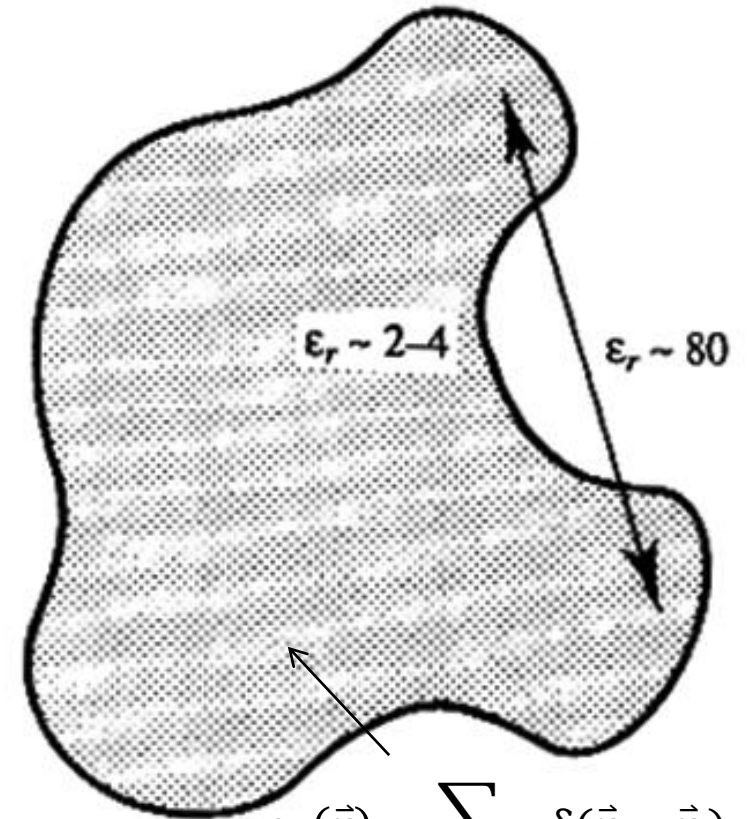
*Extension of the Poisson equation to multiple media with fixed and mobile charges:*

$$\vec{\nabla} \vec{D} = 4\pi(\rho_f + \rho_m)$$

$\nearrow$  fixed charges       $\nearrow$  mobile ions charge density

*Electric field in the continuum approximation:*

$$\begin{aligned} \vec{D}(\vec{r}) &= \epsilon(\vec{r})\vec{E}(\vec{r}) \\ \downarrow \\ \vec{\nabla}(\epsilon(\vec{r})\vec{E}(\vec{r})) &= -4\pi(\rho_f(\vec{r}) + \rho_m(\vec{r})) \\ \downarrow \\ \vec{\nabla}(\epsilon(\vec{r})\vec{\nabla}\varphi(\vec{r})) &= -4\pi(\rho_f(\vec{r}) + \sum_i q_i \rho_i^0 e^{-\beta q_i \varphi(\vec{r})}) \\ \downarrow \\ \boxed{\vec{\nabla}(\epsilon(\vec{r})\vec{\nabla}\varphi(\vec{r})) - \kappa^2(\vec{r})\varphi(\vec{r})} &= -4\pi\rho_f(\vec{r}) \end{aligned}$$



$$\rho_f(\vec{r}) = \sum_i z_i \delta(\vec{r} - \vec{r}_i)$$

sum over fixed-charge points that make up the interior of the solute molecule

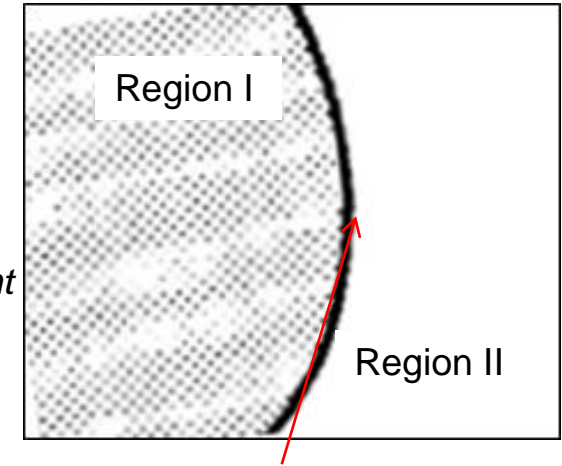
*LPB equation*

LPB can be solved numerically subject to specific boundary conditions (constant charge):

$$\left\{ \begin{array}{ll} \epsilon_I \Delta \varphi_I(\vec{r}) = -4\pi \rho_f(\vec{r}) & \varphi_I|_{\Omega} = \varphi_{II}|_{\Omega} \\ \epsilon_{II} \Delta \varphi_{II}(\vec{r}) - \kappa^2 \varphi_{II}(\vec{r}) = 0 & \epsilon_I \frac{\partial \varphi_I}{\partial n}|_{\Omega} = \epsilon_{II} \frac{\partial \varphi_{II}}{\partial n}|_{\Omega} \end{array} \right.$$

Continuity of  
potential

displacement



Boundary between two media:  $\Omega$

## Computation of the charging free energy

Recall that the potential in solvent (continuum approximation) is :

$$U_M(\Gamma) = U_V(\Gamma) + \Delta G(\Gamma) \quad \text{where}$$

$\Delta G(\Gamma)$  is the free energy associated with turning the solvent “on”.

$U_V(\Gamma)$  electrostatic energy in vacuum

Also recall that  $\Delta G(\Gamma) = \Delta G_{ch}(\Gamma) - U_V(\Gamma)$

$$\Delta G_{ch}(\Gamma) = \int dq \, \varphi$$

charging free energy. Work needed to create charge in a medium

Since the PBL equation is linear:

$$\Delta G_{ch}(\Gamma) = \frac{1}{2} \sum_i q_i \varphi_{sol}(i)$$

potential acting on charge  $q_i$  obtained  
for particular solute in solvent with  $\epsilon = 80$

Potential energy in vacuum:

$$U_V = \frac{1}{2} \sum_i q_i \varphi_{vac}(i)$$

potential acting on charge  $q_i$  in vacuum  
or solvent with  $\epsilon = 1$

Combining the formulas:

$$\Delta G(\Gamma) = \frac{1}{2} \sum_i q_i (\varphi_{sol}(i) - \varphi_{vac}(i)) = \Delta G_{PB}$$

this is the term that needs to be added to the  
potential energy in order to include the effect of  
the solvent.

The approach that combines certain force-field with PB equation for solvation energy is  
known as **PB/MM** model

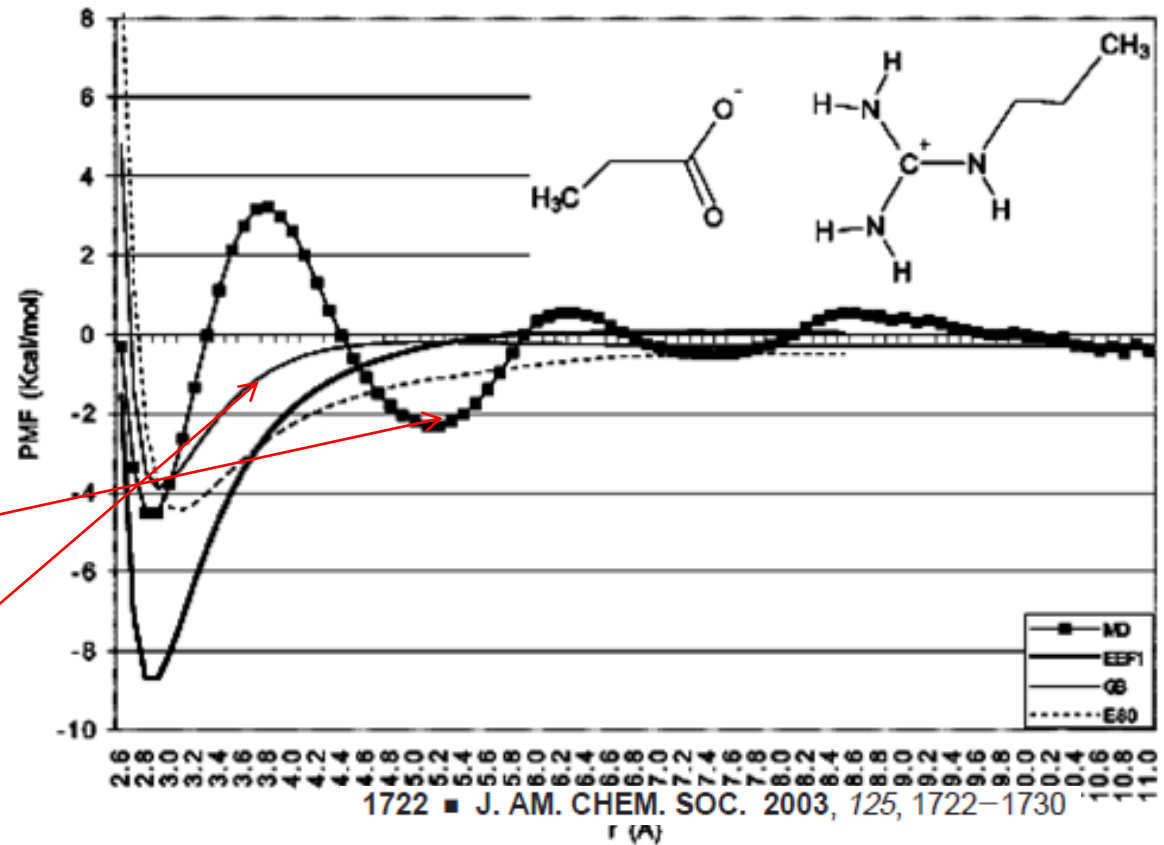
## Limitations of the PB/MM model

1) All that apply to PB equation.

2) Error due to continuum approximation for water. Model breaks down on length scales comparable to the size of water molecule.

3) Missing non-polar solvation forces

4) High computational cost



Fine structure of the potential is due to the finite size of water molecules

All implicit solvent models are missing local minima, including GB which is parameterized against PB

## Generalized Born (GB) model

Numerical solutions of PB for real molecular shapes are very costly. Much faster implicit solvation models are needed.

Draw an analogy with the Born solvation energy:  $\Delta G_{Born} = \frac{1}{2} \left( \frac{1}{\epsilon} - 1 \right) \frac{q^2}{a}$

Approximate solvation energy for a molecule:

$$\Delta G_{GB} = \frac{1}{2} \left( \frac{1}{\epsilon} - 1 \right) \sum_{i,j} \frac{q_i q_j}{f_{ij}}$$

Generalized Born (GB) model

Empirical function:

$$f_{ij} = \sqrt{r_{ij}^2 + R_i R_j} e^{-r_{ij}^2 / 4 R_i R_j}$$

Still's formula

$R_i$  is the effective Born radius for atom  $i$

If there's only one atom in the system:

$$f_{ij} = R_i, \quad \Delta G_{GB} = \frac{1}{2} \left( \frac{1}{\epsilon} - 1 \right) \frac{q_i^2}{R_i} = \Delta G_{Born}$$

Born energy for particle with radius  $R_i$

For two charges at a large separation:  $r_{12} \geq R_1, r_{12} \geq R_2, f_{ij} \approx r_{ij}$

$$\Delta G_{GB} = \frac{1}{2} \left( \frac{1}{\epsilon} - 1 \right) \frac{q_1^2}{R_1} + \frac{1}{2} \left( \frac{1}{\epsilon} - 1 \right) \frac{q_2^2}{R_2} + \left( \frac{1}{\epsilon} - 1 \right) \frac{q_1 q_2}{r_{12}}$$

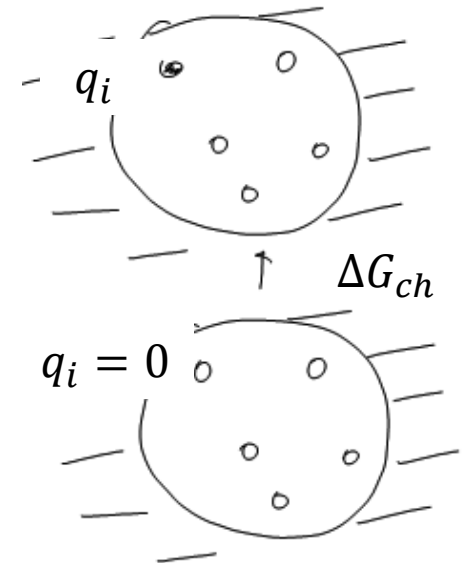
Full electrostatic interaction then is:

$$U_{ele}(r_{12}) = \frac{q_1 q_2}{r_{12}} + \Delta G_{GB} = \underbrace{\frac{1}{2} \left( \frac{1}{\epsilon} - 1 \right) \frac{q_1^2}{R_1} + \frac{1}{2} \left( \frac{1}{\epsilon} - 1 \right) \frac{q_2^2}{R_2}}_{\text{Self-energy of the two ions}} + \underbrace{\frac{q_1 q_2}{\epsilon r_{12}}}_{\text{Coulomb interaction in a continuum}}$$

To retain their physical meaning, Born radii are introduced via charging free energy:

$$R_i = \frac{2\Delta G_{ch}}{q_i^2} \frac{\epsilon}{1 - \epsilon}$$

No atoms except number  $i$  have charge



## Coulomb field approximation for the Born radii

*Another way to compute electrostatic work is via scalar product of the displacement vector with the vector of electric field:*

$$W = \frac{1}{8\pi} \int \mathbf{E} \cdot \mathbf{D} dV$$

*Assume that the displacement vector created by charge  $q_i$  retains its Coulomb form even outside of the solute molecule:*

$$\mathbf{D}_i \approx \frac{q_i \mathbf{r}}{r^3}$$

*Work needed to move charge  $q_i$  from infinity to its proper location:*

$$W = \frac{1}{8\pi} \int (\mathbf{D}/\varepsilon) \cdot \mathbf{D} dV \approx \frac{1}{8\pi} \int_{in} \frac{q_i^2}{r^4} dV + \frac{1}{8\pi} \int_{out} \frac{q_i^2}{r^4 \varepsilon} dV$$

*To compute electrostatic solvation energy one needs to subtract the same quantity evaluated at*

$$\varepsilon = 1 \longrightarrow \Delta G_{ch} = \frac{-1}{8\pi} \left( 1 - \frac{1}{\varepsilon} \right) \int_{out} \frac{q_i^2}{r^4} dV$$

*One then arrives at the following formula:*

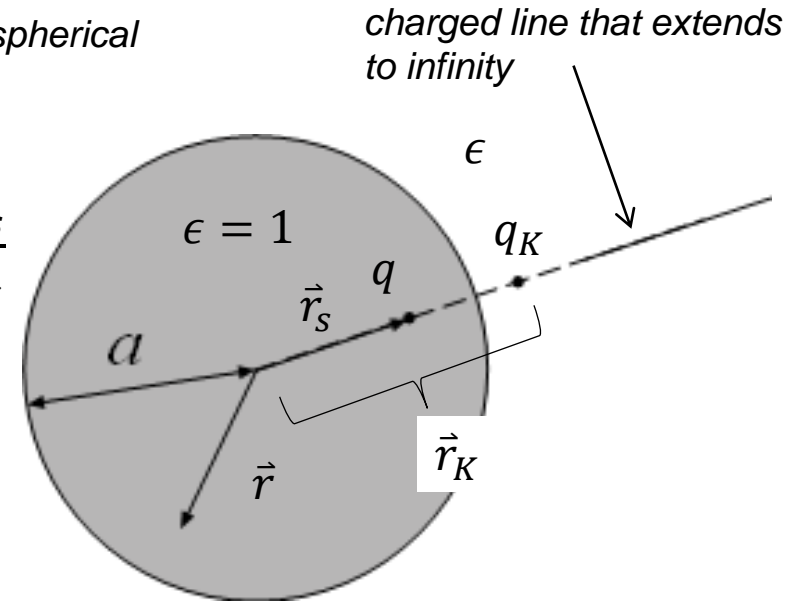
$$R_i^{-1} = \frac{1}{4\pi} \int_{out} r^{-4} dV$$



The Born radius in CF approximation can be evaluated exactly for the spherical geometry. The integral can be taken analytically to yield:

$$R_{CF} = \frac{4\pi}{\int_{out} r^{-4} dV} = 2a \left( \frac{1}{1-p^2} + \frac{1}{2p} \ln \frac{1+p}{1-p} \right)^{-1}, \quad p = \frac{r_s}{a}$$

The spherical geometry has an exact solution. In particular, the reaction field is a sum of the field created by Kelvin image and a charged ray:



$$\varphi_{RF}(\vec{r}) = \varphi_K(\vec{r}) + \varphi_{line}(\vec{r})$$

$\uparrow$  terms of order 1 and  $1/\epsilon$        $\nwarrow$  terms of orders higher than  $1/\epsilon$

Kelvin charge image.  $\vec{r}_K = \frac{q^2}{r_s}$        $q_K = \gamma \frac{a q}{r_s}$        $\gamma = \frac{1-\epsilon}{1+\epsilon}$

Reaction field at the location of the source charge:  $\varphi_{RF}(\vec{r}_s) = \frac{q_K}{r_K - r_s} = \frac{1-\epsilon}{1+\epsilon} \frac{aq}{a^2 - r_s^2}$

Charging free energy:  $\Delta G_{ch} = \int dq \varphi_{RF} = \frac{1}{2} \frac{1-\epsilon}{1+\epsilon} \frac{aq^2}{a^2 - r_s^2} = \frac{1}{2} \left( \frac{1}{\epsilon} - 1 \right) \frac{q^2}{R_K}$

GB radius in the Kelvin approximation then is:

$$R_K = \frac{1 + \epsilon}{\epsilon} a(1 - p^2) \approx a(1 - p^2) \quad \leftarrow \text{good approximation for water with } \epsilon=80$$

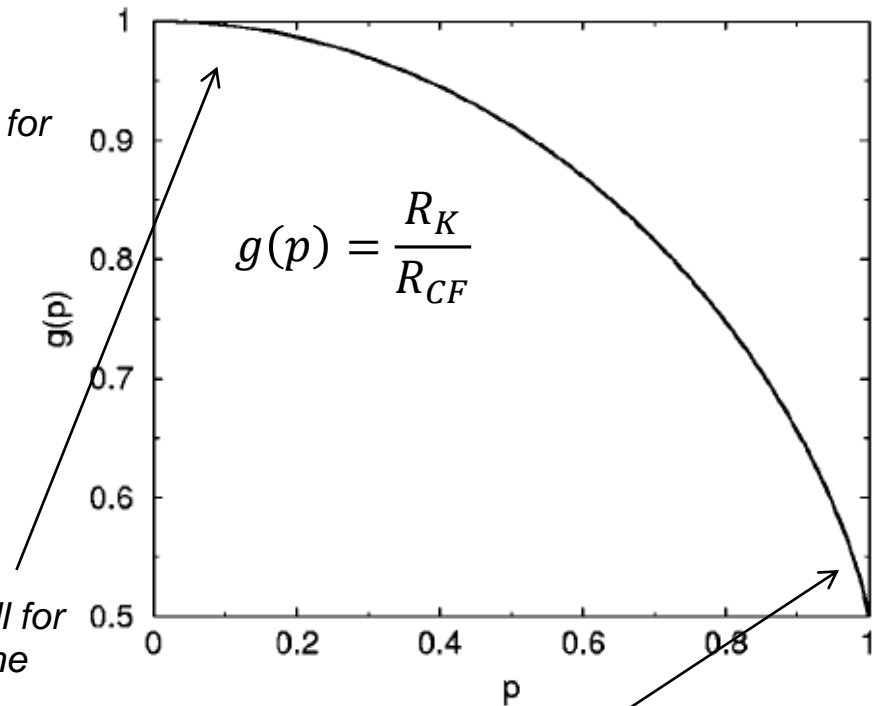
Exact radius for arbitrary dielectric constant:

$$\frac{1}{R_i} = \frac{1 - \gamma}{2} \left( \frac{1}{a(1 - p^2)} + \frac{1}{a} \sum_{n=0}^{\infty} \frac{(1 + \gamma)p^{2n}}{1 - \gamma + 2n} \right)$$

Kelvin solution also leads to a better expression for the Born energy of multi-particle systems:

$$f_{ij} = \sqrt{r_{ij}^2 + R_i R_j} \quad \leftarrow \text{Grycuk's formula}$$

$$f_{ij} = \sqrt{r_{ij}^2 + R_i R_j e^{-r_{ij}^2 / 4 R_i R_j}} \quad \leftarrow \text{Still's formula}$$



CF works well for atoms near the center of the sphere.

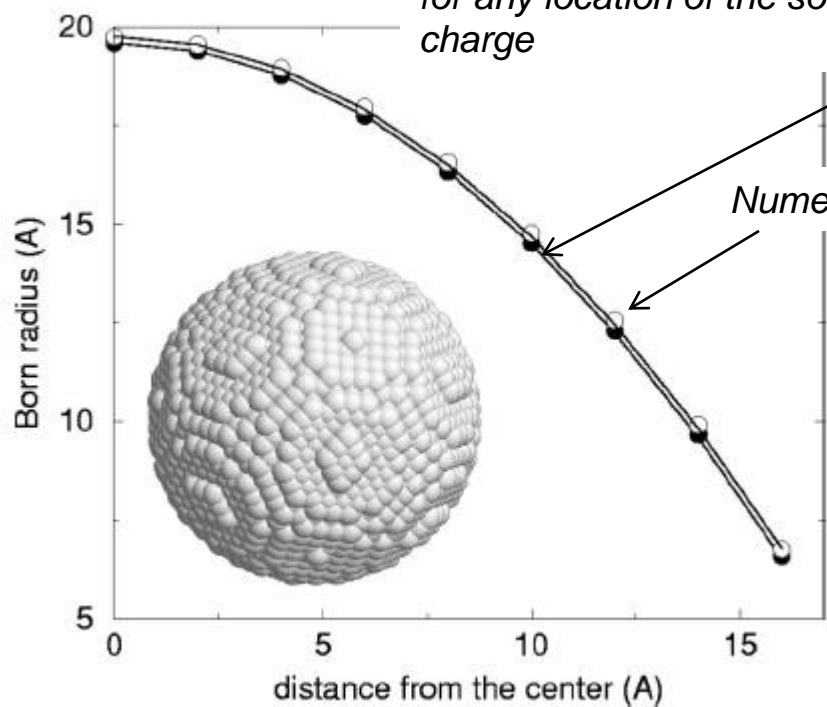
For atoms near the molecules boundary, the CF approximation overestimates the Born radius 2 times

To evaluate Born radius for non-spherical objects, an empirical formula is proposed:

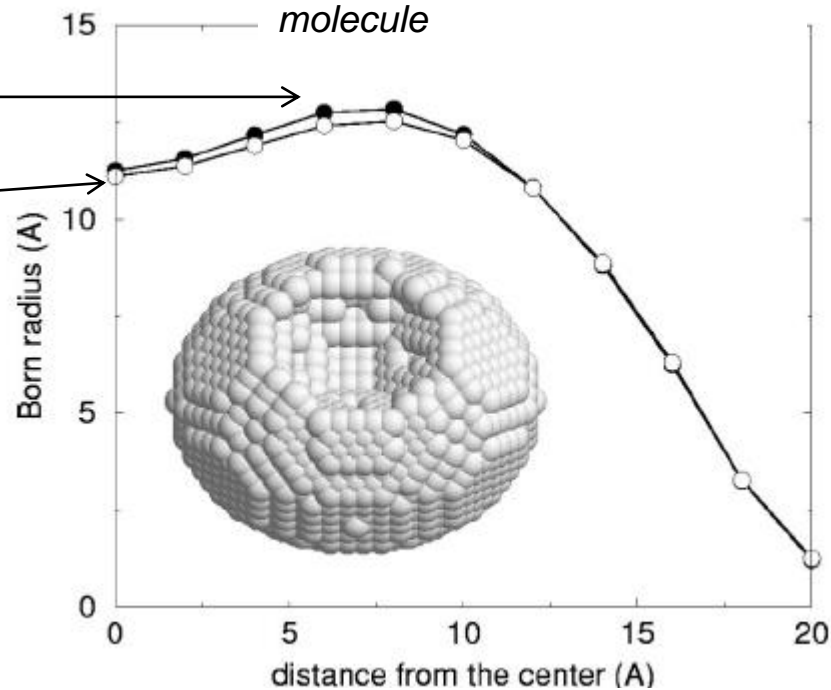
$$\frac{1}{R} = \left( \frac{3}{4\pi} \int_{\text{ex}} \frac{1}{r^6} dV \right)^{1/3}, \quad \text{this leads to } \frac{1}{a(1-p^2)} \quad \text{for a spherical molecule}$$

*this is still an approximation. Works exactly only for a sphere in high-dielectric constant medium. Perform tests for everything else!*

*Uniformly good performance for any location of the source charge*



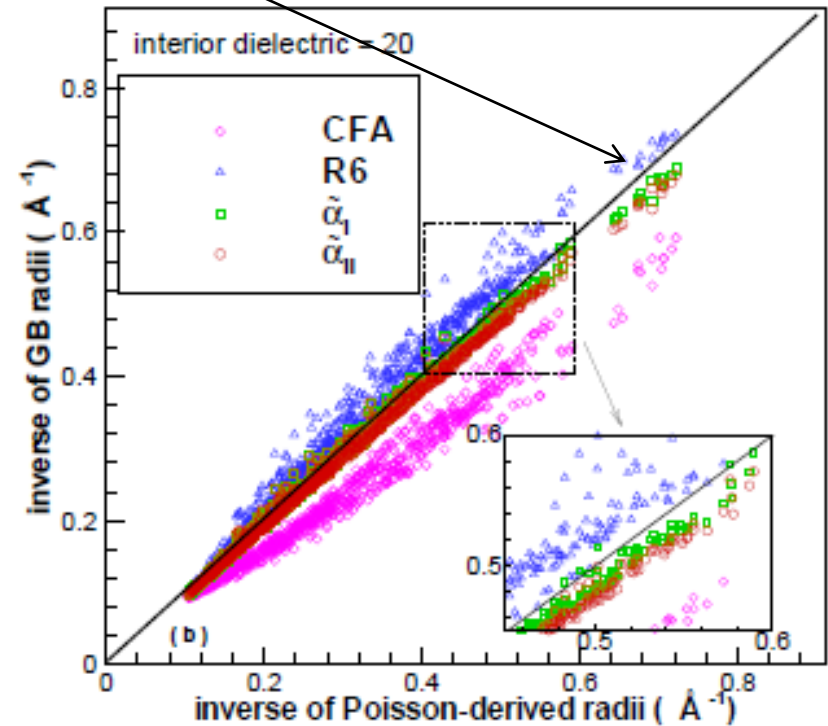
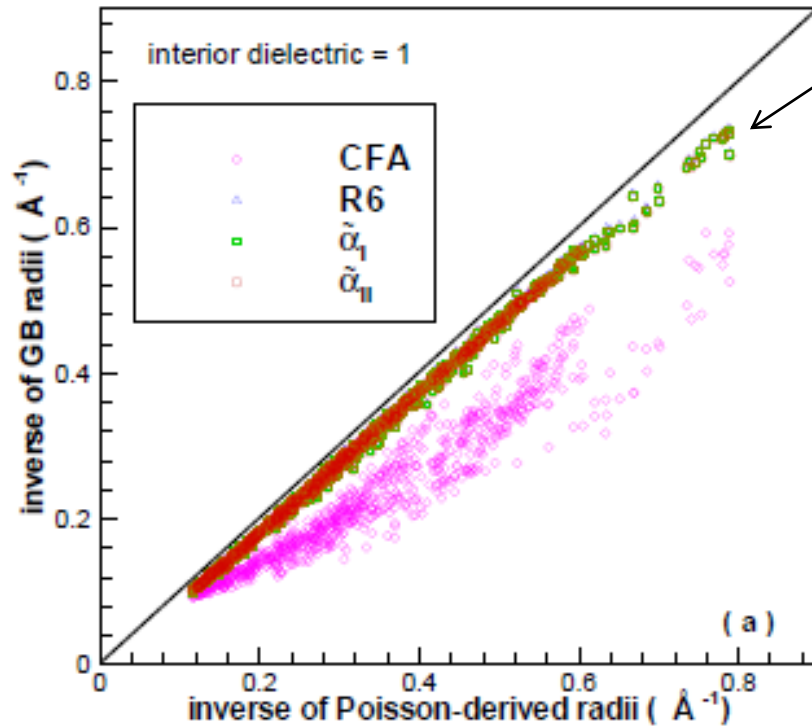
*Deterioration of quality for charges buried inside the molecule*



## Comparison for varying dielectric constant in the context of a protein

1) CFA is not accurate for any eps

2) R6 is accurate for interior dielectric of 1 but much worse for dielectric=20



3) Small shift of inverse  $R$  can improve the agreement with PB a lot. Reason – unknown

$$\frac{1}{R_i} = \frac{1}{R_i} + 0.028 \text{\AA}^{-1}$$

# Non-polar solvation

Non-polar molecules tend to minimize exposure to solvent. As a result, configurations with minimal surface area are assumed. Solvation free energy is assumed to be proportional to the surface area exposed to solvent:

solvation energy of the molecule with all non-polar groups hidden from water

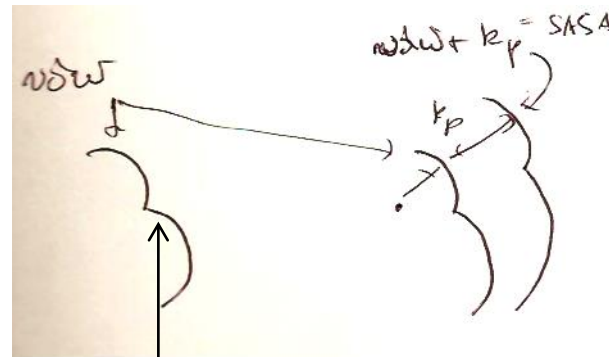
$$\Delta G_{np} = \gamma(SA) + b$$

empirical parameter. May depend on the curvature of the solvent molecule. Typical value

$$\gamma = 72 \text{ cal mol}^{-1} \text{ \AA}^{-1}$$

SASA constructed as the surface area of a figure swept by the center of a probe molecule rolled on the surface of the solute molecule

$$R_p = 1.4 \text{ \AA} \quad \text{typically used for water}$$



vdW surface = SASA with the probe radius set to zero



Molecular surface is made by the points of closest approach of the probe to the solute

- 1) Parametrizations by many groups (Sitkoff, Sheraga etc.)
- 2) Only part or the whole molecule can be treated as non-polar. Separate parameters can be introduced for polar and non-polar groups.
- 3) Several definitions of “accessible surface” are in use.

$$\Delta G = \Delta G_{PB/GB} + \gamma \Delta S$$

common models PB/SA or GB/SA

## Weighted histogram analysis method (WHAM)

Assume that we have a number  $K$  of different simulations, each performed at a separate temperature  $\beta_k, k = 1, K$

The number of sampled conformations for each temperature is  $N$

Each simulation produces an energy histogram

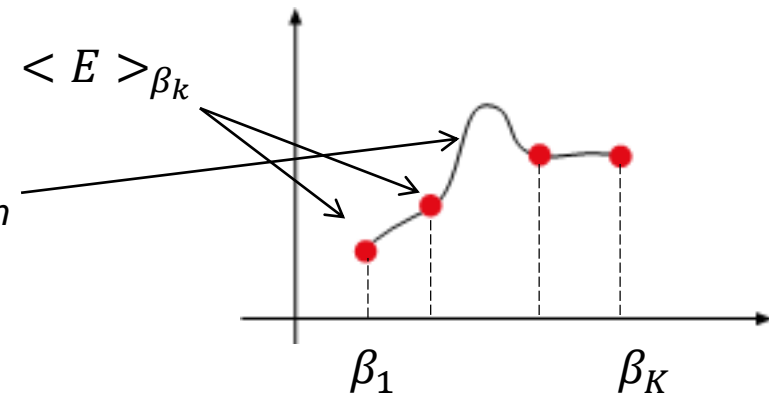
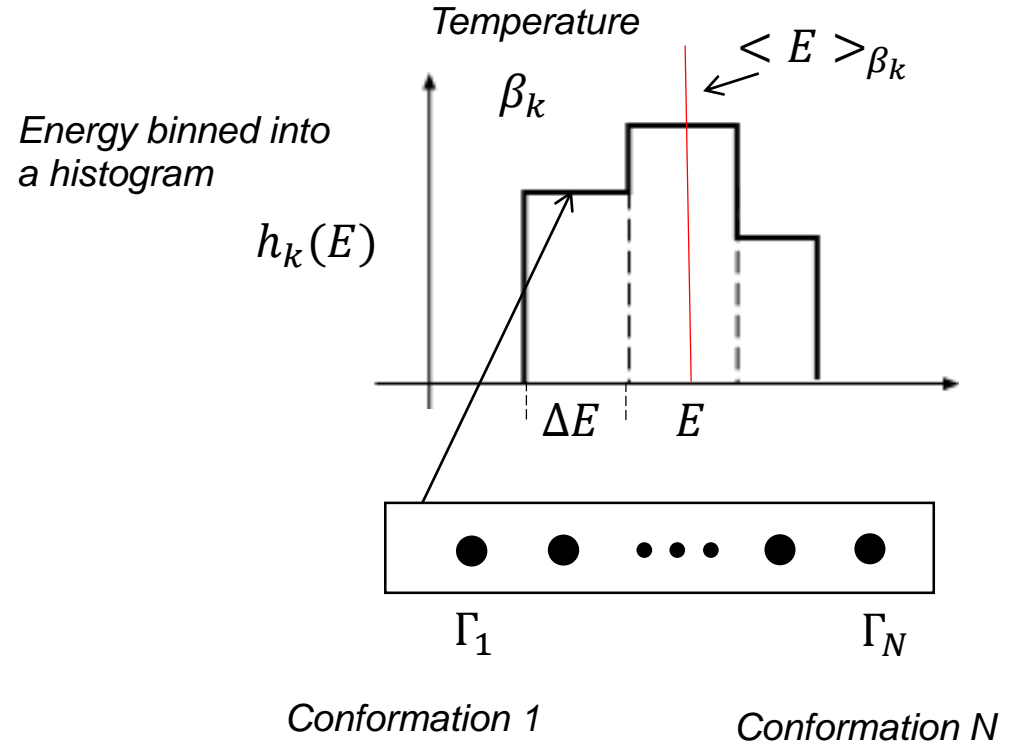
$$h_k(E)$$

where the bin size is  $\Delta E$

$$\sum_E h_k(E) = N$$

The energy can be obtained at a discrete set of temperatures

Q: How do we compute energy (and other functions) at intermediate temperatures? Is there new information hidden in these data?



*Sampled histograms can be used to estimate density of states:*

$$h_k(E) = N n_k(E) e^{-\beta_k(E-f_k)} \longrightarrow n_k(E) = \frac{h_k(E)}{N} e^{\beta_k(E-f_k)}$$

$\uparrow$   
*density of states.  
 Most accurate for  
 energy levels close  
 to  $\langle E \rangle_{\beta_k}$*

$\nearrow$   
 *$f_k$  is the free energy  
 at temperature  $\beta_k$*

*Let us combine histograms at all temperatures in order to obtain a more accurate estimate of the density of states:*

$$n(E) = \sum_{i=1}^K w_i n_i(E)$$

$\uparrow$   
*some weight  
 coefficients for each  
 temperature*

$$\sum_{i=1}^K w_i = 1$$

$\uparrow$   
*normalization condition  
 that the coefficients  
 needs to satisfy*

*If the density of states is known, energy distribution at any temperature can be computed as follows*

$$P_\beta(E) = \frac{n(E) e^{-\beta E}}{\sum_E n(E) e^{-\beta E}}$$



How to compute the weight coefficients?

Let us estimate the error in the density of states and try to minimize it. This will produce an optimal set of weights.

If we perform multiple experiments = sets of measurements, the resulting energy histograms will fluctuate. This will lead to fluctuations in the estimate of the density of states.

$$n_k(E) = \frac{h_k(E)}{N} e^{\beta_k(E-f_k)} \rightarrow \delta n_k(E) = \frac{\delta h_k(E)}{N} e^{\beta_k(E-f_k)}$$

↑  
fluctuation in the  
density of states

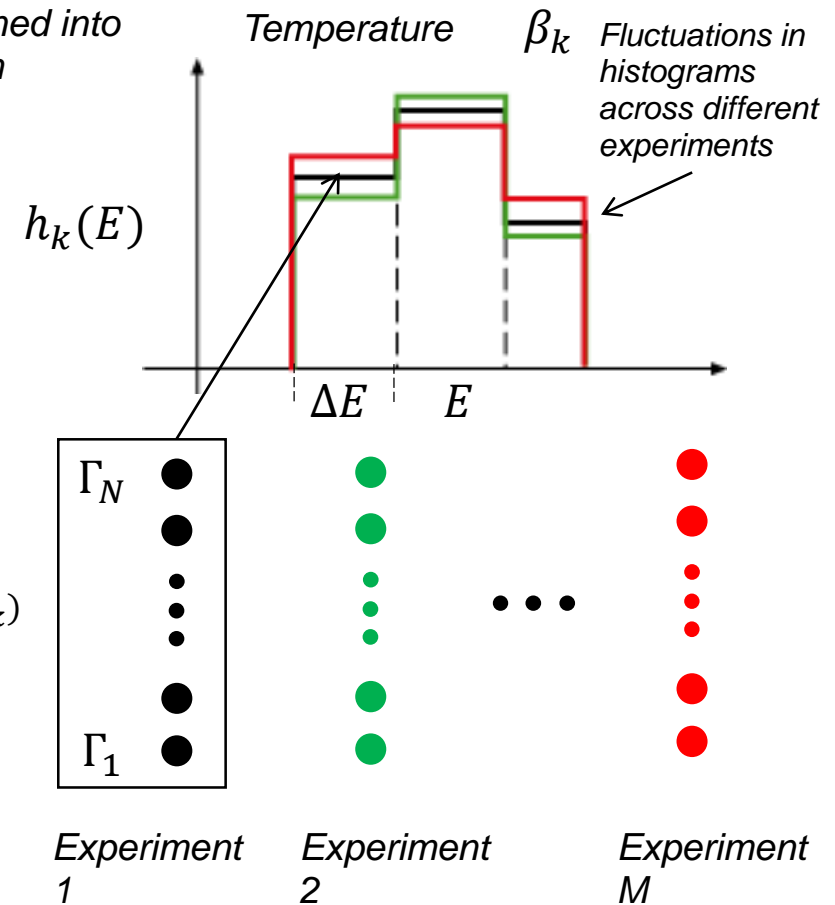
The average of fluctuations across many experiments is zero

$$\langle \delta n_k(E) \rangle_{exp} = 0$$

Fluctuation of the weighted density of states:

$$\delta n(E) = \sum_{i=1}^K w_i \delta n_i(E) \longrightarrow \langle \delta n(E) \rangle = \sum_{i=1}^K w_i \langle \delta n_i(E) \rangle = 0$$

Energy binned into  
a histogram



The error can be estimated from fluctuation squared:

$$\begin{aligned}
 (\delta n(E))^2 &= \sum_{i=1, j=1}^K w_i w_j \delta n_i(E) \delta n_j(E) \longrightarrow \langle (\delta n(E))^2 \rangle = \sum_{i=1, j=1}^K w_i w_j \langle \delta n_i(E) \delta n_j(E) \rangle = \\
 &\sum_{i=1}^K w_i^2 \langle (\delta n_i(E))^2 \rangle \quad \text{since measurements at different temperatures are uncorrelated} \longrightarrow \langle (\delta n_i(E))^2 \rangle = \delta_{ij}
 \end{aligned}$$

Average fluctuations in the density of states at fixed temperatures can be estimated as follows:

$$(\delta n_k(E))^2 = \frac{(\delta h_k(E))^2}{N^2} e^{2\beta_k(E-f_k)} \longrightarrow \langle (\delta n_k(E))^2 \rangle = \frac{\langle (\delta h_k(E))^2 \rangle}{N^2} e^{2\beta_k(E-f_k)}$$

Let us rewrite the squared fluctuation of the histogram in explicit form:

$$\langle (\delta h_k(E))^2 \rangle = \langle h_k^2(E) \rangle - \langle h_k(E) \rangle^2$$

By definition:

$$h_k(E) = \sum_{i=1}^N \delta_{E, E_i} \quad \text{where} \quad \delta_{E, E_i} = \frac{1}{2} (\Theta(E_i - E) + \Theta(E + \Delta E - E_i)) = \begin{cases} 1 & \text{if } E \leq E_i \leq E + \Delta E \\ 0 & \text{otherwise} \end{cases}$$

The square then is

$$\begin{aligned}
 \langle (h_k(E))^2 \rangle &= \left\langle \sum_{i=1, j=1}^N \delta_{E,E_i} \delta_{E,E_j} \right\rangle = \left\langle \sum_{i=1}^N \delta_{E,E_i}^2 \right\rangle + \left\langle \sum_{i \neq j}^N \delta_{E,E_i} \delta_{E,E_j} \right\rangle \\
 &\quad \downarrow \qquad \qquad \qquad \downarrow \\
 &\quad \left\langle \sum_{i=1}^N \delta_{E,E_i} \right\rangle \qquad \sum_{i \neq j}^N \langle \delta_{E,E_i} \rangle \langle \delta_{E,E_j} \rangle \\
 &\quad \downarrow \qquad \qquad \qquad \downarrow \\
 \langle h_k(E) \rangle &= Ng \qquad N(N-1)g^2 \qquad g = \langle \delta_{E,E_i} \rangle
 \end{aligned}$$

under the assumption  
that conformations  $i$   
and  $j$  are independent

number that shows how likely a  
random conformation at temperature  $\beta$   
is to have energy  $\in [E, E + \Delta E]$

For canonical distribution, quantity  $g$  can be evaluated directly:

$$g = \frac{\int_E^{E+\Delta E} \delta_{E,E_i} n(E) e^{-\beta E} dE}{\int n(E) e^{-\beta E}} \approx n(E) e^{-\beta(E-F(\beta))} \Delta E \quad \text{so} \quad \lim_{\Delta E \rightarrow 0} g = 0$$

Average square:

$$\langle h_k(E) \rangle^2 = \left\langle \sum_{i=1}^N \delta_{E,E_i} \right\rangle \left\langle \sum_{j=1}^N \delta_{E,E_j} \right\rangle = N^2 g^2$$

The difference then is

$$\langle (\delta h_k(E))^2 \rangle = \langle h_k^2(E) \rangle - \langle h_k(E) \rangle^2 = Ng + N(N-1)g^2 - N^2g^2 = Ng - Ng^2 \\ \approx Ng = \langle h_k(E) \rangle$$

if  $g^2 \ll g$  which can always be achieved by making an appropriate choice for  $\Delta E$

Going back to the estimate of error in the density of states:

$$\langle (\delta n_k(E))^2 \rangle = \frac{\langle (\delta h_k(E))^2 \rangle}{N^2} e^{2\beta_k(E-f_k)} = \frac{\langle h_k(E) \rangle}{N^2} e^{2\beta_k(E-f_k)}$$

The best estimate of the average histogram can be obtained from the improved density of states:

$$\langle h_k(E) \rangle = Nn(E)e^{-\beta_k(E-f_k)} = Ne^{-\beta_k(E-f_k)} \sum_i^N w_i n_i(E)$$

$$\langle (\delta n_k(E))^2 \rangle = \frac{n(E)}{N} e^{\beta_k(E-f_k)}$$

$$\langle (\delta h_k(E))^2 \rangle = g_k \langle h_k(E) \rangle$$

more general expression where the  $g$  factor may include the effect of energy-energy correlations

The error in the improved density of states finally:

$$\langle (\delta n(E))^2 \rangle = \sum_{i=1}^K w_i^2 \langle (\delta n_i(E))^2 \rangle = \sum_{i=1}^K w_i^2 \frac{n(E)}{N} e^{\beta_i(E-f_i)}$$

Let us consider the relative error in the density of states estimate:

$$F(w_1, \dots, w_K) = \frac{\langle (\delta n_k(E))^2 \rangle}{n(E)} + \lambda \sum_{i=1}^K w_i = \sum_{i=1}^K w_i^2 \frac{1}{N} e^{\beta_i(E-f_i)} + \lambda \sum_{i=1}^K w_i$$

Minimize the cost function:

$$\frac{\partial F(w_1, \dots, w_K)}{\partial w_l} = \frac{2w_l}{N} e^{\beta_l(E-f_l)} + \lambda = 0 \quad l = 1, K$$

$$\downarrow$$

$$w_l = -\frac{\lambda N}{2} e^{-\beta_l(E-f_l)}$$

undefined coefficient  
designed to enforce the  
normalization constraint on  
weight factors

Use the constraint to determine  $\lambda$

$$\sum_{l=1}^K w_l = -\frac{\lambda N}{2} \sum_{l=1}^K e^{-\beta_l(E-f_l)} = 1 \longrightarrow -\frac{\lambda N}{2} = \frac{1}{\sum_{l=1}^K e^{-\beta_l(E-f_l)}} \longrightarrow w_l = \frac{e^{-\beta_l(E-f_l)}}{\sum_{l=1}^K e^{-\beta_l(E-f_l)}}$$

The best estimate of the density of states:

$$n(E) = \sum_{i=1}^K w_i n_i(E) = \frac{\sum_i^K n_i(E) e^{-\beta_i(E-f_i)}}{\sum_i^K e^{-\beta_i(E-f_i)}} = \frac{\sum_i^K \overset{n_i(E) = \frac{h_i(E)}{N} e^{\beta_i(E-f_i)}}{n_i(E)} e^{-\beta_i(E-f_i)}}{\sum_i^K e^{-\beta_i(E-f_i)}} = \frac{\sum_i^K \overset{p_i(E) = h_i(E)/N}{p_i(E)}}{\sum_i^K e^{-\beta_i(E-f_i)}} \quad \text{normalized energy histogram}$$

Density of states can be evaluated from energy histograms at all temperatures and free energies.

By definition:

$$e^{-\beta_i f_i} = \sum_E n(E) e^{-\beta_i E}$$

Then one obtains a set of coupled equations:

$$n(E) = \frac{\sum_i^K p_i(E)}{\sum_i^K e^{-\beta_i(E-f_i)}} \quad (1)$$

$$e^{-\beta_i f_i} = \sum_E n(E) e^{-\beta_i E} \quad (2)$$

Reweighting: 
$$P_\beta(E) = \frac{n(E) e^{-\beta E}}{\sum_E n(E) e^{-\beta E}}$$

WHAM equations can be solved by iterations:

Step 1: Adopt some values for the free energies  $f_1 \dots f_K$

Step 2: Compute the density of states using eq. (1)

Step 3: Obtain more accurate free energy from eq. (2)

Step 4: Go back to step 1. Continue until convergence.

Non-iterative WHAM: **JCP** 135 (2011) 061103

WHAM with faster convergence: **Mol Sim** 42 (20016) 1079

Outcome:

- 1) Relative free energy for a set of temperatures.  $f_1$  has to be fixed.
- 2) Density of states so energy dist. for any temperature

Pitfalls:

- 1) Temperatures have to be narrowly spaced for energy distributions to overlap
- 2) Energy distributions have to be converged. Problems at low temperature may arise in some systems

## Two-dimensional WHAM

Imagine that it's some structural parameter  $X$  for which we seek temperature dependence.

To obtain reweighted function one needs to consider joint distribution of that parameter with  $E$

$$P_i(E, X) = \frac{n_i(E, X)e^{-\beta_i E}}{\sum_{E, X} n_i(E, X)e^{-\beta_i E}} = \underbrace{n_i(E, X)}_{\substack{\uparrow \\ \text{2D density of states}}} \underbrace{e^{-\beta_i(E-f_i)}}_{\substack{\uparrow \\ \text{free energy}}} \longrightarrow n_i(E, X) = P_i(E, X)e^{\beta_i(E-f_i)}$$

$$\sum_{E, X} P_i(E, X) = 1 \quad \swarrow \substack{\text{histograms at certain} \\ \text{temperature}}$$

$$P_i(X) = \sum_E P_i(E, X)$$

Following the WHAM procedure, build a better estimate of the density of states:

$$n(E, X) = \sum_i w_i n_i(E, X) \longrightarrow w_l = \frac{e^{-\beta_l(E-f_l)}}{\sum_{k=1}^K e^{-\beta_k(E-f_k)}}$$

2D WHAM equations:

$$n(E, X) = \frac{\sum_i^K P_i(E, X)}{\sum_i^K e^{-\beta_i(E-f_i)}}$$

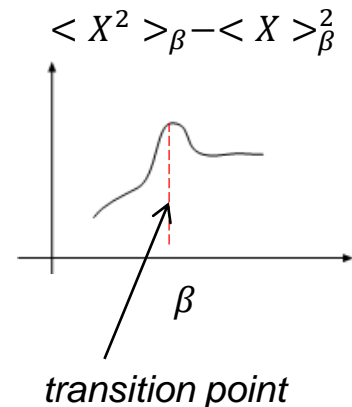
$$e^{-\beta_i f_i} = \sum_{E, X} n(E, X) e^{-\beta_i E}$$

Distribution function at any temperature by reweighting:

$$P_\beta(X) = \frac{\sum_E n(E, X) e^{-\beta E}}{\sum_{E, X} n(E, X) e^{-\beta E}}$$

$$\searrow \quad \swarrow$$

$$\langle X \rangle_\beta = \sum_X X P_\beta(X), \quad \langle X^2 \rangle_\beta = \sum_X X^2 P_\beta(X)$$



# Umbrella sampling

The idea of combining multiple trajectories can be used to obtain distributions along selected degrees of freedom with the help of biased simulations.

Recall that for a degree of freedom  $X$ :

Not normalized distribution function

$$P(X) = \sum_E P(E, X) = \frac{\sum_E n(E, X) e^{-\beta E}}{\sum_{E, X} n(E, X) e^{-\beta E}} = \frac{P_0(X)}{\sum_X P_0(X)} = P_0(X) e^{\beta F(\beta)}$$

$\uparrow$  joint normalized distribution       $\uparrow$  2D density of states       $\nearrow$  free energy at temperature  $1/\beta$

$$P_0(X) = \sum_E n(E, X) e^{-\beta E}$$

$$\sum_X P_0(X) = e^{-\beta F}$$

Imagine that we apply external potential to bias the value of coordinate  $X$  sampled in simulations

$$E \rightarrow E + \frac{\alpha}{2} (X - X_i)^2$$

$\nwarrow$  biasing "umbrella" potential

Distribution in the umbrella simulation:

$$P_i(X) = \sum_E n(E, X) e^{-\beta E} e^{-\beta \frac{\alpha}{2} (X - X_i)^2} \underset{\nearrow}{e^{f_i}} = P_0(X) e^{-\beta \frac{\alpha}{2} (X - X_i)^2} e^{f_i}$$


some normalization constant specific to  $X_i$

$$\sum_X P_i(X) = 1$$



Unbiased distribution can be recovered as follows:

$$P_0^i(X) = P_i(X) e^{\beta \frac{\alpha}{2}(X-X_i)^2} e^{-f_i} \longrightarrow \sum_X P_0^i(X) e^{-\beta \frac{\alpha}{2}(X-X_i)^2} = e^{-f_i}$$



  
 this is normalized histogram  
 from biased simulation

Let us now conduct multiple biasing simulations to obtain improved distribution:

$$P_0(X) = \sum_i w_i P_0^i(X) \quad \sum_i w_i = 1$$

Follow the WHAM procedure to estimate the error and then minimize it:

$$(\delta P_0^i(X))^2 = (\delta P_i(X))^2 e^{2\beta \frac{\alpha}{2}(X-X_i)^2} e^{-2f_i} = P_0(X) e^{\beta \frac{\alpha}{2}(X-X_i)^2} e^{-f_i}$$



$$(\delta P_0(X))^2 = \sum_i w_i^2 (\delta P_0^i(X))^2 = \sum_i w_i^2 e^{\beta \frac{\alpha}{2}(X-X_i)^2} e^{-f_i} P_0(X)$$

The function to be minimalized:

$$F = \sum_i w_i^2 e^{\beta \frac{\alpha}{2}(X-X_i)^2} e^{-f_i} + \lambda \sum_i w_i \longrightarrow w_l = \frac{e^{-\beta \frac{\alpha}{2}(X-X_l)^2 + f_l}}{\sum_i e^{-\beta \frac{\alpha}{2}(X-X_i)^2 + f_i}}$$

WHAM equations:

$$P_0(X) = \frac{\sum_i P_i(X)}{\sum_i e^{-\beta \frac{\alpha}{2}(X-X_i)^2 + f_i}}$$

$$e^{-f_i} = \sum_X P_0(X) e^{-\beta \frac{\alpha}{2}(X-X_i)^2}$$

Let  $X$  be some generalized coordinate. By definition:

$$P(X) = \int \delta(X - X(\Gamma)) e^{-\beta U} d\Gamma Z^{-1} = \frac{\int e^{-\beta U} d\Gamma_X}{\int e^{-\beta U} d\Gamma} = \frac{Z(X)}{Z}$$

$$d\Gamma = dX d\Gamma_X$$

$d\Gamma_X$  differential over variables other than  $X$  (orthogonal variables)

$$d\Gamma_1 \dots d\Gamma_N = dX \frac{\partial(\Gamma_1 \dots \Gamma_N)}{\partial(X, x_2 \dots x_N)} dx_2 \dots dx_N$$

Jacobian often difficult to evaluate

The average force that corresponds to the coordinate:

Reweightings:

$$P(X) = \frac{P_0(X)}{\sum_X P_0(X)}$$

Potential of mean force (PMF):

$$F(X) = -kT \log(P(X))$$

function that can be used as generalized potential along degree of freedom  $X$

conditional average. Coordinate  $X$  is fixed

$$\begin{aligned} \langle F_X \rangle_X &= \frac{-\int \frac{\partial U}{\partial X} e^{-\beta U} d\Gamma_X}{\int e^{-\beta U} d\Gamma_X} \\ &= \frac{1}{\beta} \frac{1}{\int e^{-\beta U} d\Gamma_X} \frac{\partial}{\partial X} \int e^{-\beta U} d\Gamma_X \\ &= \frac{1}{\beta} \frac{1}{Z(X)} \frac{\partial}{\partial X} Z(X) = -\frac{\partial}{\partial X} \log(Z(X)) \\ &= -\frac{\partial}{\partial X} \{-kT \log(P(X)) - kT \log Z\} \\ &= -\frac{\partial}{\partial X} F(X) \end{aligned}$$

“force”

“potential” that generates it

$$Z(X) = P(X)Z$$

# Free energy estimation

Key thermodynamic function that helps to describe stability of condensed matter systems

1) *Phase equilibria, transitions*

2) *Binding strength for macro complexes ...*

By definition:

$$\begin{aligned}
 & \text{Helmholtz free energy} \uparrow F(N, V, T) = -kT \log(Q_{NVT}) = F_{id}(N, V, T) + F_{ex}(N, V, T) \\
 & \text{Partition function} \swarrow \quad \text{Ideal part} \swarrow \quad \text{Excess part=due to interactions} \swarrow \\
 & Q_{NVT} = Q_{NVT}^{id} \times Q_{NVT}^{ex}, \quad Q_{NVT}^{id} = \frac{V^N}{N! \lambda^{3N}}, \quad \lambda = \sqrt{h^2 / 2\pi m k T} \\
 & F_{id}(N, V, T) = \frac{N}{\beta} \log(\rho) + \frac{N}{\beta} \log\left(\frac{1}{\lambda^3}\right) - \frac{N}{\beta}, \quad \rho = \frac{N}{V} \\
 & F_{ex}(N, V, T) = -kT \log(Q_{NVT}^{ex}) \quad Q_{NVT}^{ex} = \frac{Z_{NVT}}{V^N}, \quad \boxed{Z_{NVT} = \int d\Gamma e^{-\beta U(\Gamma)}} \\
 & \quad \quad \quad \uparrow \quad \quad \quad \swarrow \quad \quad \quad \text{3-N dimensional space} \\
 & \quad \quad \quad \text{Configuration integral}
 \end{aligned}$$

*Not formulated as an average over ensemble so difficult to estimate in simulations*

## 1) Hit and miss method

$Z_{NVT}$  is an integral in multidimensional space. The most efficient integration method is sample mean.

$$Z_{NVT} = \int e^{-\beta U(\Gamma)} d\Gamma = \left\langle \frac{e^{-\beta U(\Gamma)}}{\rho(\Gamma)} \right\rangle_{\rho} \int \rho(\Gamma) d\Gamma$$

sampling from the given distribution

The scheme can have multiple realizations:

1) Uniform distribution in the phase space  $\rho = \frac{1}{V^N}, \quad \int d\Gamma \rho(\Gamma) = 1$

$$Z_{NVT} = V^N \langle e^{-\beta U(\Gamma)} \rangle$$

Configurations are generated by randomly displacing particles anywhere in the available volume  $V$

Due to overlaps between particles, very few entries in this sum will be non-zero. The sum will never converge

## 2) Non-uniform distribution in the phase space

$$1 = \frac{\int e^{-\beta U(\Gamma)} e^{\beta U(\Gamma)} d\Gamma}{V^N} = \frac{\int e^{-\beta U(\Gamma)} e^{\beta U(\Gamma)} d\Gamma}{V^N} \frac{\int e^{-\beta U(\Gamma)} d\Gamma}{\int e^{-\beta U(\Gamma)} d\Gamma} = \frac{\langle e^{\beta U(\Gamma)} \rangle_{\rho} Z_{NVT}}{V^N}$$

$$\rho = e^{-\beta U(\Gamma)}$$

$$Z_{NVT} = \frac{V^N}{\langle e^{\beta U(\Gamma)} \rangle}$$

The sum will never converge!

The weight function is non-zero where  $U(\Gamma)$  is large and negative. But  $\exp(\beta U(\Gamma))$  is zero precisely at those points!

No overlap between the weight function and the integrand

## 2) Thermodynamic integration

### 1) Integration over density

$$dF = -PdV - SdT \longrightarrow P = -\left(\frac{\partial F}{\partial V}\right)_T$$

$$F(V) - F(V_0) = - \int_{V_0}^V P(V) dV = N \int_{\rho_0}^{\rho} d\rho \frac{P(\rho)}{\rho^2} \longleftarrow dV = -\frac{N}{\rho^2} d\rho$$

$$F(\rho) = F(\rho_0) + N \int_{\rho_0}^{\rho} d\rho \frac{P(\rho)}{\rho^2}$$

Free energy has to be known exactly for this density

Certain density for which free energy is supposed to be known

Let's pick density sufficiently low so that the system can be approximated by ideal gas

$$F(\rho_0) = F_{id}(\rho_0) = \frac{N}{\beta} \log(\rho_0) + \frac{N}{\beta} \log\left(\frac{1}{\lambda^3}\right) - \frac{N}{\beta}$$

Then the ideal part at low density can be written in terms of the ideal part at any density:

$$F_{id}(\rho_0) = \frac{N}{\beta} \log(\rho) - \frac{N}{\beta} \log(\rho) + \frac{N}{\beta} \log(\rho_0) + \frac{N}{\beta} \log\left(\frac{1}{\lambda^3}\right) - \frac{N}{\beta} = F_{id}(\rho) + \frac{N}{\beta} \log(\rho_0) - \frac{N}{\beta} \log(\rho)$$

$$F_{id}(\rho_0) = F_{id}(\rho) - \frac{N}{\beta} \int_{\rho_0}^{\rho} d\rho \frac{1}{\rho}$$

$$F(\rho) = F(\rho_0) + N \int_{\rho_0}^{\rho} d\rho \frac{P(\rho)}{\rho^2} = F_{id}(\rho) - \frac{N}{\beta} \int_{\rho_0}^{\rho} d\rho \frac{1}{\rho} + N \int_{\rho_0}^{\rho} d\rho \frac{P(\rho)}{\rho^2} = F_{id}(\rho)$$

$$+ N \int_{\rho_0}^{\rho} d\rho \frac{\beta P - \rho}{\beta \rho^2} = F_{id}(\rho) + N \int_{\rho_0}^{\rho} d\rho \frac{P^{ex}(\rho)}{\rho^2} = F_{id}(\rho) + N \int_0^{\rho} d\rho \frac{P^{ex}(\rho)}{\rho^2}$$

$$P^{ex} = P - \frac{\rho}{\beta}$$

the integral converges in the limit of low density

$$F_{ex}(\rho) = N \int_0^{\rho} d\rho \frac{P^{ex}(\rho)}{\rho^2}$$

## 2) Integration over temperature

$$Q_{NVT}^{ex} = \frac{1}{V^N} \int d\Gamma e^{-\beta U(\Gamma)} \longrightarrow \frac{\partial Q_{NVT}^{ex}}{\partial \beta} = -\frac{1}{V^N} \int d\Gamma U(\Gamma) e^{-\beta U(\Gamma)} = -\langle U \rangle Q_{NVT}^{ex}$$

$$\frac{\partial \log(Q_{NVT}^{ex})}{\partial \beta} = -\langle U \rangle(\beta) \longrightarrow \overset{-\beta F(\beta)}{\log(Q_{NVT}^{ex}(\beta))} = \log(Q_{NVT}^{ex}(\beta_0)) - \int_{\beta_0}^{\beta} d\beta \langle U \rangle$$

$$\beta F(\beta) = \beta_0 F(\beta_0) + \int_{\beta_0}^{\beta} d\beta \langle U \rangle(\beta)$$

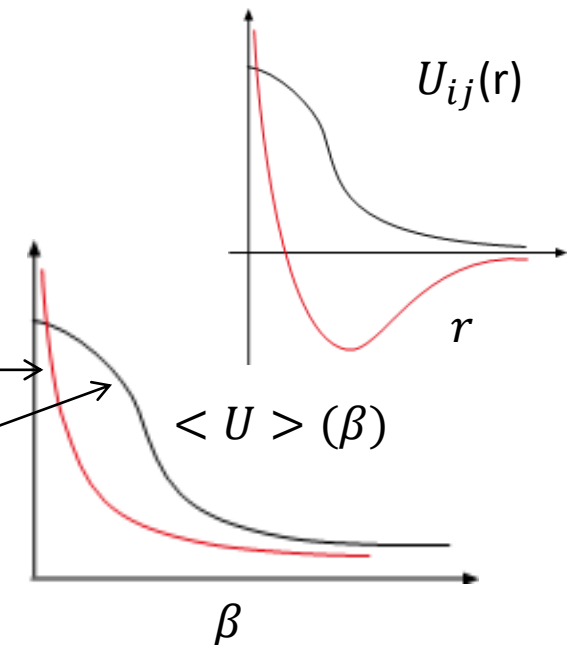
free energy difference  
between two temperatures

### a) Integration from high temperature

$$\lim_{\beta_0 \rightarrow 0} \beta_0 F(\beta_0) = 0 \quad F(\beta) = \frac{1}{\beta} \int_0^{\beta} d\beta \langle U \rangle(\beta)$$

For potentials that diverge at zero, the  
average energy will diverge at high  
temperature/low beta

For potentials bound at the origin  
the average energy will also be  
bound





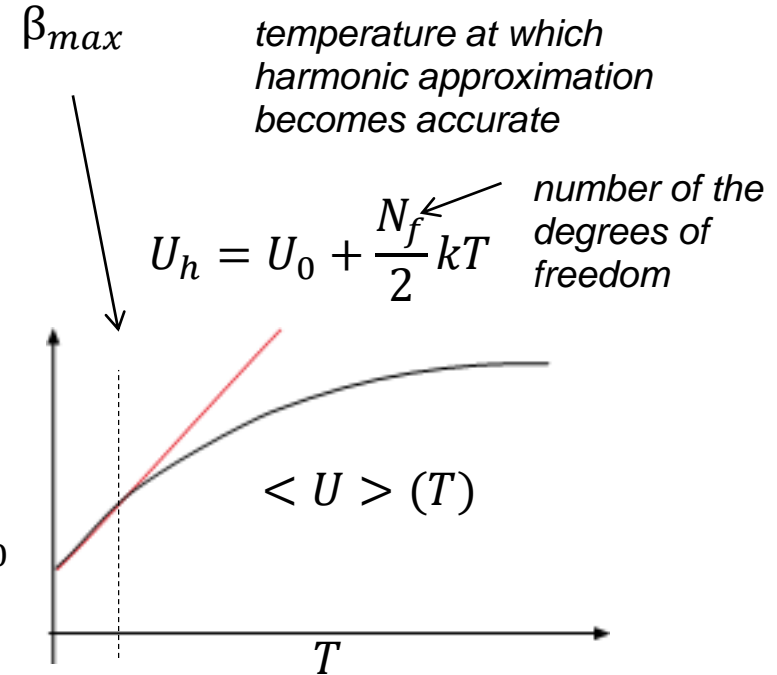
b) Integration from low temperature

$$F(\beta) = \frac{\beta_{\max}}{\beta} F_0(\beta_{\max}) - \frac{1}{\beta} \int_{\beta}^{\beta_{\max}} d\beta \langle U \rangle(\beta)$$

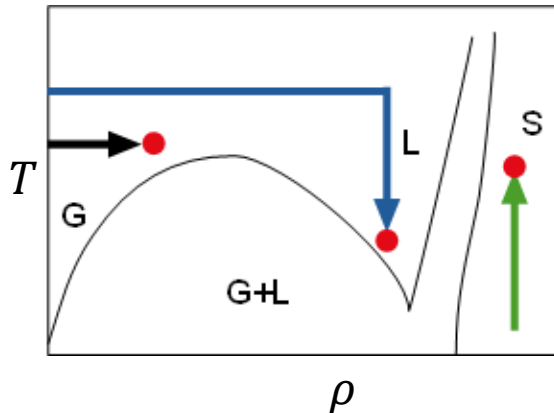
Free energy in harmonic approximation. Involves Hessian matrix. Easy to compute for a single structure, for instance in crystals. For liquids, an ensemble of local minima has to be considered

ground state energy

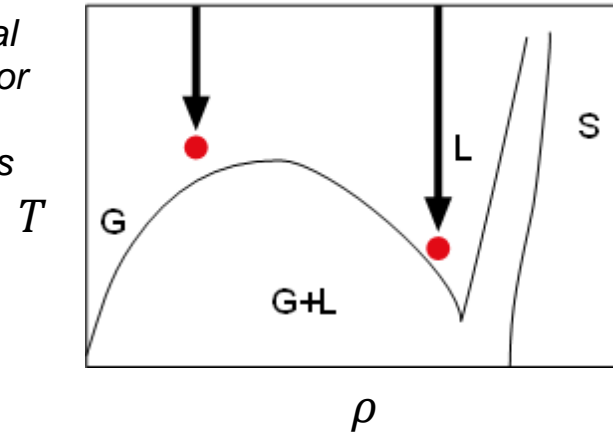
Thermodynamic integration: integration paths should not cross phase boundaries!



Suggested paths to determine absolute free energy in liquid and solid states



Additional options for bound potentials



### 3) Thermodynamic perturbation

Assume that we want to measure free energy difference between two different systems described by Hamiltonian A and B

$$Z(B) = \int d\Gamma e^{-\beta U_B(\Gamma)} = \int d\Gamma e^{-\beta U_A(\Gamma)} e^{-\beta(U_B(\Gamma) - U_A(\Gamma))} = \langle e^{-\beta \Delta U} \rangle_A Z(A)$$

$\Delta U = U_B - U_A$

$$-\beta F(B) = -\beta F(A) + \log \langle e^{-\beta \Delta U} \rangle_A$$

$$F(B) = F(A) - \frac{1}{\beta} \log \langle e^{-\beta \Delta U} \rangle_A$$

Free energy of system B is expressed in terms of free energy of system A and some average obtained in ensemble A

1) Only trajectory for one system A is required to compute free energy difference

2) Energy difference has to be small in order for the average to converge

3) A path between two states A and B can be constructed that contains intermediate states with mutual overlap

#### 4) “Artificial” thermodynamic integration

Let's consider the same problem with two different systems A and B.  $U_A$   $U_B$

Introduce a variable that transforms one system into another  $U(\lambda) = U_A + \lambda(U_B - U_A) = U_A + \lambda\Delta U$

$$U(\lambda = 0) = U_A, \quad U(\lambda = 1) = U_B$$

Partition function that depends on  $\lambda$

$$Z(\lambda) = \int d\Gamma e^{-\beta(U_A + \lambda\Delta U)} \longrightarrow \frac{\partial Z(\lambda)}{\partial \lambda} = \int d\Gamma -\beta\Delta U e^{-\beta(U_A + \lambda\Delta U)} = -\beta \langle \Delta U \rangle_\lambda Z(\lambda)$$

$$d\log(Z(\lambda)) = -\beta \langle \Delta U \rangle_\lambda d\lambda \longrightarrow \log(Z(\lambda)) = \log(Z(0)) - \beta \int_0^\lambda \langle \Delta U \rangle_\lambda d\lambda$$

$$F(B) = F(A) + \int_0^1 \langle \Delta U \rangle_\lambda d\lambda$$

*The most reliable and widely used method*

1) Integral has to be evaluated for a number of intermediate points. Each point has to be computed in a separate simulation

2) May have issues with integrand not being smooth enough

3) Applied to a large variety of tasks, for instance mutations

*Perturbation and artificial integration are equivalent when the difference between the systems is small.*

*Free energy for a small  $\lambda^*$*

$$F(\lambda^*) = F(A) + \int_0^{\lambda^*} \langle \Delta U \rangle_{\lambda} d\lambda = \boxed{F(A) + \langle \Delta U \rangle_A \lambda^*} \quad \text{if } \lambda^* \sim 0$$

*In perturbation theory:*

$$U_{B'} = U_A + \lambda^*(U_B - U_A) \longrightarrow \Delta U' = U_{B'} - U_A = \lambda^*(U_B - U_A) = \lambda^* \Delta U$$

$$F(B') = F(A) - \frac{1}{\beta} \log \langle e^{-\beta \Delta U'} \rangle_A = F(A) - \frac{1}{\beta} \log \langle e^{-\beta \lambda^* \Delta U} \rangle_A \approx \boxed{F(A) + \lambda^* \langle \Delta U \rangle_A}$$

$$\log(1 - \beta \lambda^* \langle \Delta U \rangle_A + \dots) = \beta \lambda^* \langle \Delta U \rangle_A$$

## 5) Method of Einstein crystal

*Can be used to compute absolute free energy of crystals*

*Introduce an artificial Hamiltonian that will drive the system into a state with known free energy*

$$U(\lambda) = \lambda U + (1 - \lambda)U_H$$

$$U(\lambda = 0) = U_H \quad \text{system where particles are held at their positions by harmonic potentials}$$

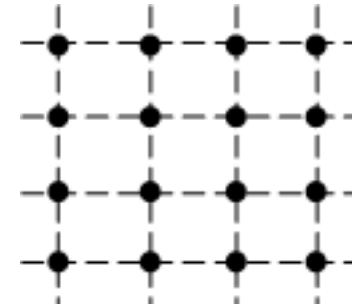
$$U(\lambda = 1) = U \quad \text{actual system}$$

$$F(\lambda) = F(0) + \int_0^\lambda \langle U - U_H \rangle_\lambda d\lambda$$

↑  
free energy of harmonic oscillator

↑  
the integrand is well behaved if particles occupy the same position at the start and the end of the integration (in both Hamiltonians)

*The system is defined by a set of positions on a lattice*



$$U_H(\Gamma) = \frac{1}{2} \alpha \sum_i^N (\vec{r}_i - \vec{r}_i^0)$$

## 6) Widom's particle insertion method

accessible in simulation through virial

Free energy can be computed from the chemical potential:  $F(NVT) = G - PV = N\mu - PV$

According to the definition:

$$G(N, TP) = N\mu \longrightarrow \mu = G(N+1, PT) - G(N, PT)$$

$$G(N, PT) = -kT \log(Q(NPT)) \longrightarrow \mu = -kT \log\left(\frac{Q(N+1, PT)}{Q(N, PT)}\right)$$

Volume distribution function:

$$P(V) = \frac{e^{-\beta PV} Z(NVT)}{\int dV e^{-\beta PV} Z(NVT)}$$

Recall the definition of the partition function in NPT ensemble:

$$Q(N, PT) = \frac{1}{N! \lambda^{3N} V_0} Z(N, PT), \quad Z(N, PT) = \int dV e^{-\beta PV} Z(NVT) \leftarrow \begin{array}{l} \text{canonical} \\ \text{configuration} \\ \text{integral} \end{array} \int dq_1 dq_2 \dots dq_N e^{-\beta U(q_1 \dots q_N)}$$

Evaluate the N+1 term first:

$$\begin{aligned} Q(N+1, PT) &= \frac{1}{(N+1)! \lambda^{3(N+1)} V_0} Z(N+1, PT) = \frac{1}{(N+1)! \lambda^{3(N+1)} V_0} \int dV e^{-\beta PV} \int dq_1 \dots dq_{N+1} e^{-\beta U} = \text{average over configurations of } N \text{ particles starting from } 2. \\ &= \frac{1}{(N+1)! \lambda^{3(N+1)} V_0} \int dV e^{-\beta PV} \int dq_1 e^{-\beta U_1} dq_2 \dots dq_{N+1} e^{-\beta U(q_2 \dots q_N)} = \frac{1}{(N+1)! \lambda^{3(N+1)} V_0} \int dV e^{-\beta PV} \int dq_1 \langle e^{-\beta U_1} \rangle Z(NVT) = \\ &\quad \text{interaction of the first particle with the remaining } N \text{ particles} \quad U_1 = U(N+1) - U(N) \quad \text{this quantity is the same for all particles and independent of their position. So the integral over } dq_1 \text{ brings } V \end{aligned}$$

$$\frac{1}{(N+1)! \lambda^{3(N+1)} V_0} \int dV e^{-\beta PV} V \langle e^{-\beta U_1} \rangle Z(NVT)$$

Similar expression for the  $N$ -particle term:

$$Q(N, PT) = \frac{1}{N! \lambda^{3N} V_0} \int dV e^{-\beta P V} Z(NVT)$$

Combining them one obtains:

$$\mu = -kT \log \left( \frac{N! \lambda^{3N}}{(N+1)! \lambda^{3(N+1)}} \frac{\int dV e^{-\beta P V} V \langle e^{-\beta U_1} \rangle Z(NVT)}{\int dV e^{-\beta P V} Z(NVT)} \right) = -kT \log \left( \frac{1}{(N+1) \lambda^3} \langle V e^{-\beta U_1} \rangle \right) =$$

average over  $PT$  ensemble with  $N$  particles

$U_1$  is evaluated by adding a particle to the system at random position

$$-kT \log \left( \frac{V}{(N+1) \lambda^3} \right) - kT \log \left( \frac{\langle V e^{-\beta U_1} \rangle}{V} \right)$$

$$\mu^{ex} = -kT \log \left( \frac{\langle V e^{-\beta U_1} \rangle}{V} \right)$$

$\mu^{id} = -kT \log \left( \frac{1}{\rho \lambda^3} \right)$

Chemical potential can be evaluated from simulations in canonical ensemble:

$$\mu^{ex} = G^{ex}(N+1, PT) - G^{ex}(N, PT) = F^{ex}(N+1, TV) - F^{ex}(N, TV) + (P^{ex}(N+1) - P^{ex}(N))V$$

$$F^{ex}(NVT) = -kT \log(Q(NVT)) \rightarrow F^{ex}(N+1, VT) - F^{ex}(N, VT) = -kT \log \left( \frac{Q(N+1, VT)}{Q(N, VT)} \right)$$

pressure evaluated in the ensemble with  $N$  particles

average in canonical ensemble with  $N$  particles

$-kT \log(\langle e^{-\beta U_1} \rangle)$

Configuration integral explicitly:

$$Q(N+1, VT) = \frac{1}{V^{N+1}} Z(N+1, VT) = \frac{1}{V^{N+1}} \int dq_1 e^{-\beta U_1} dq_2 \dots dq_{N+1} e^{-\beta U(q_2 \dots q_{N+1})} = \frac{1}{V^N} \langle e^{-\beta U_1} \rangle Z(NVT) = \langle e^{-\beta U_1} \rangle Q(NVT)$$

Pressure contribution:

$$\rho' - \rho = \frac{1}{V}$$

$$P^{ex}(N+1) = P^{ex}(\rho' = \frac{N+1}{V}) \approx P^{ex}(\rho = \frac{N}{V}) + \frac{dP^{ex}(\rho)}{d\rho} (\rho' - \rho) = P^{ex}(N) + \frac{K^{ex}}{\rho} \frac{1}{V}$$

bulk modulus

$$K^{ex} = \rho \frac{dP^{ex}(\rho)}{d\rho} = a\rho^2 + b\rho^3 + \dots$$

from virial expansion

Two terms together:

$$\mu^{ex} = -kT \log(\langle e^{-\beta U_1} \rangle) + \frac{K^{ex}}{\rho}$$

$a\rho + b\rho^2 + \dots$   
 this summand vanishes at low densities but doesn't disappear when N tends to infinity

At low densities:

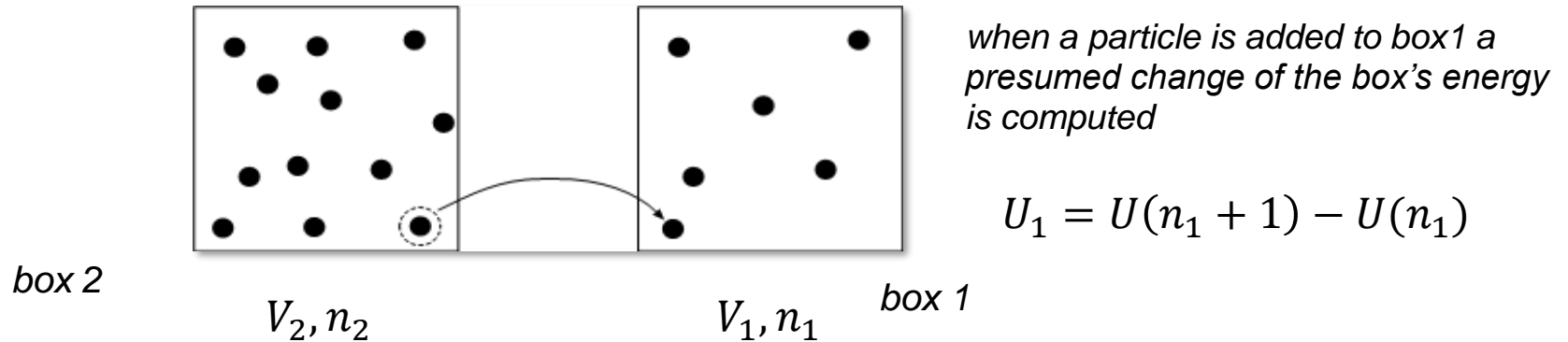
$$\mu^{ex} \approx -kT \log(\langle e^{-\beta U_1} \rangle) = F^{ex}(N+1, VT) - F^{ex}(N, VT) = \frac{F^{ex}(N+1, VT) - F^{ex}(N, VT)}{N+1 - N} \approx \frac{\partial F^{ex}(NVT)}{\partial N} \Big|_{VT} = \mu^{ex}$$

the original Widom's formula. Due to large fluctuations it applies only at low densities. So it's safe to use it there. At high densities, large variations in  $U_1$  resulting from particle overlaps hinder convergence.



## 7) Chemical potential from the Gibbs ensemble simulations

*Two boxes in GEMC simulations are maintained at constant temperature and pressure. The Widom formula for the NPT ensemble can be used to estimate chemical potential during the transfer move.*



*The volume and the number of particles change so the average includes both of them:*

$$\mu = -kT \log\left(\frac{1}{(N+1)\lambda^3} \langle V e^{-\beta U_1} \rangle\right) \longrightarrow \mu = -kT \log\left(\frac{1}{\lambda^3} \left\langle \frac{V_1 e^{-\beta U_1}}{n_1 + 1} \right\rangle\right)$$

*NPT*

*Gibbs ensemble*

1) *The identity of box 1 can't change during chemical potential evaluation. If it's vapor it has to remain vapor to the end of the simulation. Similarly for liquid. This is easy to achieve unless the system is near critical point.*

2) *If box 1 contains all particles of the system (the other box is empty) one should still attempt to add a particle to it to evaluate  $U_1$ . This step is not executed in normal GEMC.*

## 8) Multiple Bennett acceptance ratio (MBAR) method

*Imagine that we have a number of trajectories simulated at a set of temperatures. WHAM can be used to combine the energy histograms and obtain a) density of states and b) relative free energies. The relevant equations are:*

$$n(E) = \frac{\sum_i^K p_i(E)}{\sum_i^K e^{-\beta_i(E-f_i)}} \quad \swarrow \text{energy histograms}$$

$$e^{-\beta_i f_i} = \sum_E n(E) e^{-\beta_i E}$$

*Histograms are built assuming certain size of the bins  $\Delta E$ . The bin size has to be a) small so that the density of states is constant within  $[E, E + \Delta E]$  and b) large so that reasonable statistics of  $n(E)$  is obtained. The finite size of  $\Delta E$  introduces errors. If only the free energies are of interest, the error can be minimized by taking the limit  $\lim \Delta E \rightarrow 0$ . The WHAM equations then can be reduced to a simpler form.*

*Let us introduce an indicator function which is unity if energy of a given configuration  $k$  is within  $\Delta E$  of  $E$  and zero otherwise:*

$$\delta_{E,E_k} = \frac{1}{2} \left( \Theta(E_k - E) + \Theta(E + \Delta E - E_k) \right) = \begin{cases} 1 & \text{if } E \leq E_k \leq E + \Delta E \\ 0 & \text{otherwise} \end{cases}$$

The energy histogram for temperature  $i$  is

$$p_i(E) = \sum_k \delta_{E,E_k}$$

← summation runs over all sampled conformations

The density of states then can be re-written:

$$n(E) = \frac{\sum_i^K p_i(E)}{\sum_l^K e^{-\beta_l(E-f_l)}} = \frac{\sum_i^K \sum_j \delta_{E,E_j}}{\sum_l^K e^{-\beta_l(E-f_l)}}$$

for sufficiently small  $\Delta E$  the indicator function will kill the summation over  $E$

Let us substitute this expression into the second WHAM equation:

$$e^{-\beta_s f_s} = \sum_E \frac{\sum_i^K \sum_j \delta_{E,E_j}}{\sum_l^K e^{-\beta_l(E-f_l)}} e^{-\beta_s E} = \sum_i \sum_E \frac{\sum_j \delta_{E,E_j} e^{-\beta_s E}}{\sum_l^K e^{-\beta_l(E-f_l)}} = \sum_i \sum_j \frac{e^{-\beta_s E_j}}{\sum_l^K e^{-\beta_l(E_j-f_l)}}$$

← summation over all trajectories

← summation over all conformations in trajectory  $i$ .

MBAR equations

$$\beta_s f_s = -\log \left\{ \sum_i \sum_j \frac{e^{-\beta_s E_j}}{\sum_l^K e^{-\beta_l(E_j-f_l)}} \right\}$$

1) Non-linear set of equations for  $f_i$

2) Can be solved by iterations

3) No binning is required

4) Solution is not unique. Only relative free energies are obtained

General solution

↓

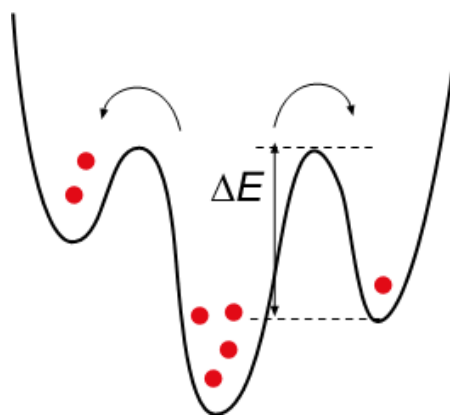
$$\beta_s f_s + A$$

Other methods:

9) *Grand canonical ensemble (covered)*

10) *Methods for approximate evaluation of the free energy: chemical Monte Carlo, lambda dynamics, linear response theory, ....*

# MC simulations in generalized (non-Boltzmann) ensembles



# Outline

- Introduction
- Generalized ensembles:
  - *multicanonical ensemble*
  - *Tsallis statistics*
  - *Wang-Landau method*
  - *1/k ensemble*
  - ***J**-walking algorithm*
  - *expanded-ensemble method*
- Replica-exchange (**REX**) approach
- Applications:
  - *replica-exchange simulations of peptide aggregation*
  - *folding of a short  $\beta$ -peptide in explicit water*

# Introduction

- Why do we need **generalized** ensembles ?
- Two ingredients of a successful simulation:

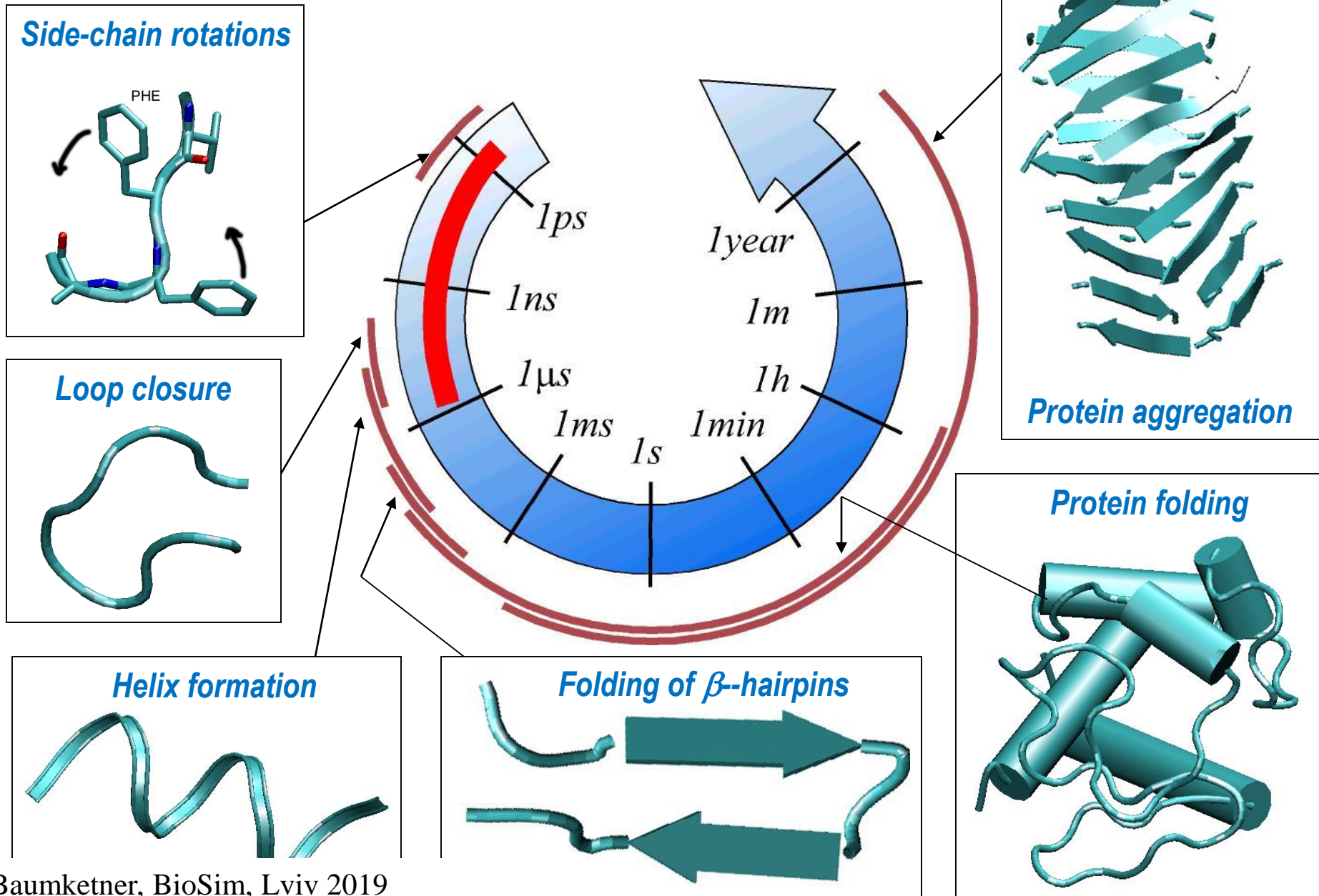
*(I) accurate representation of the **system** and **solvent***

*(II) adequate **sampling** of the conformational space*



Simulation times must be at least **10 times** longer than the relevant relaxation time !

# Time scales

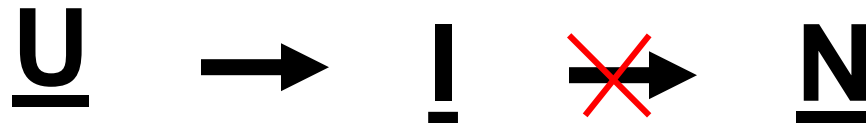




## Brute force approach

Y. Duan & P. Kollman, *Science* 282,(1998),740, “*Pathways to a protein folding intermediate observed in a 1-microsecond simulation in aqueous solution*”

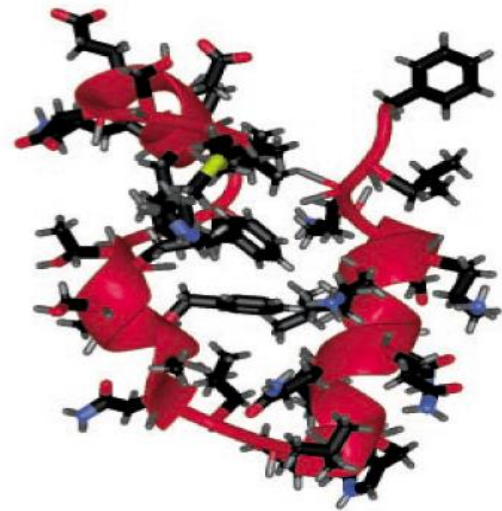
- **Villin headpiece** subdomain, 256 CPUs of Cray T3E.



RMSD~10Å



RMSD~4Å

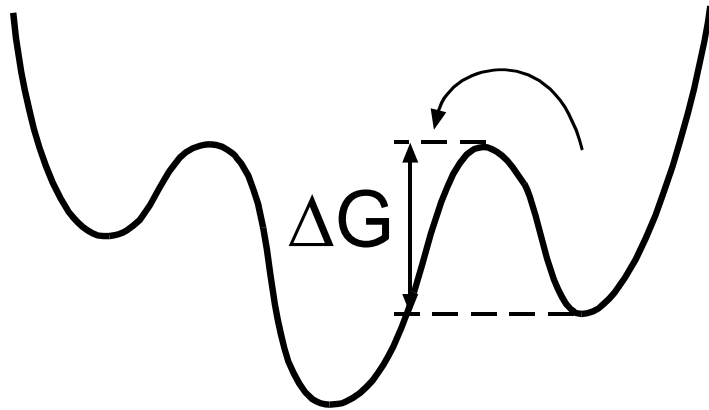


RMSD<1Å

# Rugged potential energy landscapes

- Why are the relaxation times so long ?

-number of local potential energy minima grows exponentially with  $N$



$$\tau = \tau_0 \exp(\Delta G / k_b T) \quad \tau_0 \sim 1 \text{ ps}$$

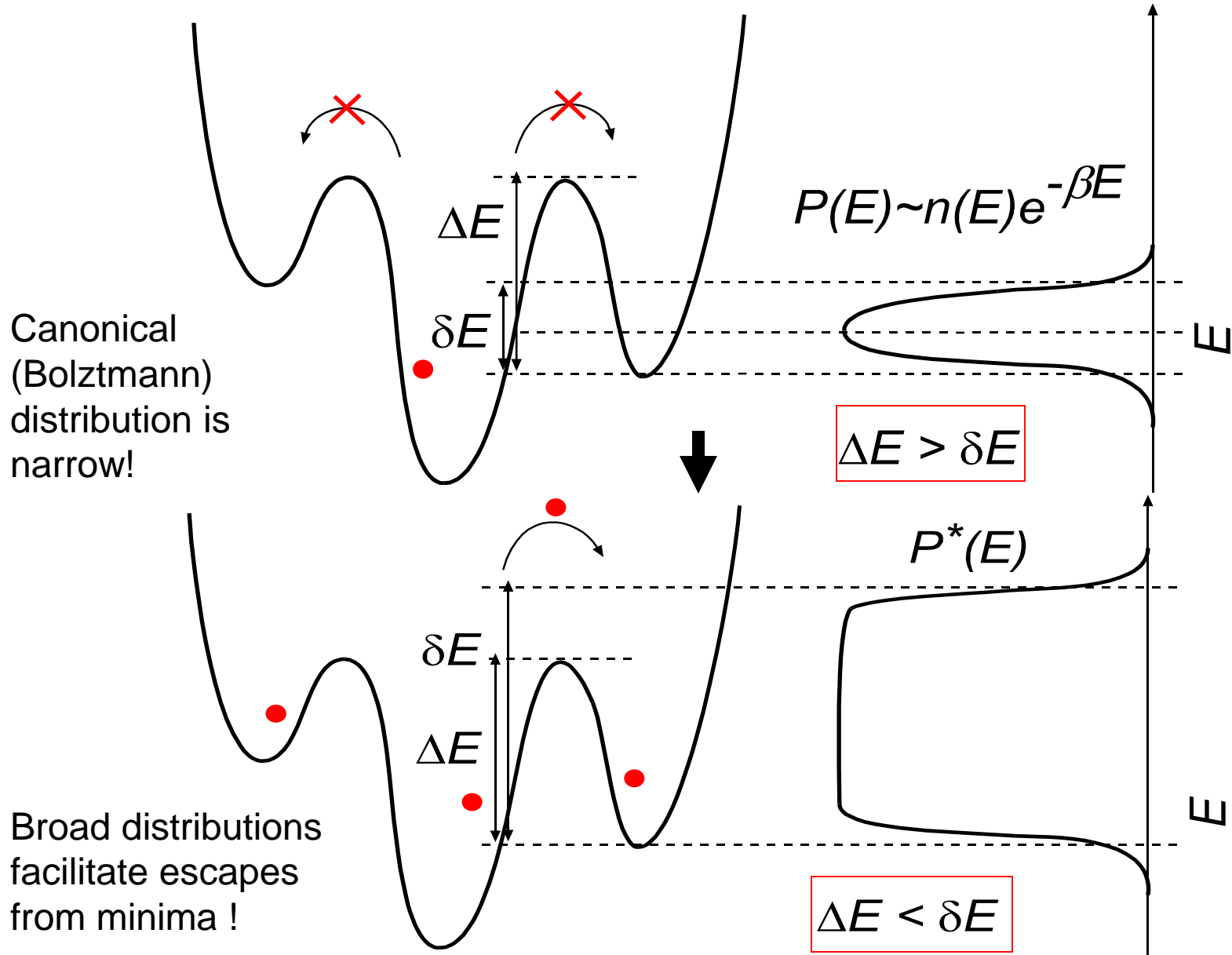
1 kcal/mol: ~1.2 ps

3 kcal/mol: ~1.5 ns

10 kcal/mol: ~1 ms and longer

-each minimum acts as a kinetic trap. The relaxation time is determined by the escape time from the minima

# Generalized ensembles



# Multicanonical ensemble

- sampling on a “deformed” potential energy surface  $W(E)$  :

$$P^*(E) \sim n(E)e^{-\beta W(E)} \quad (1)$$

- **flat** energy distribution for multicanonical ensemble:

$$P^*(E) = P_\mu(E) \sim \text{const}$$

$$W_\mu(E) = ?$$

- equation (1) can be rewritten as a non-linear equation in  $W_\mu(E)$  (*valid up to a constant which drops during normalization*):

$$W_\mu(E) = \frac{1}{\beta} [\ln n(E) - \ln P_\mu(E)] = \frac{1}{\beta} \ln n(E) \quad (2)$$

- density of states is estimated from a simulation. It depends (as a functional) on  $W_\mu(E)$  and simulation parameters:  $n(E)[W_\mu; \text{param}]$  . Simplest solution to equation (2) is given by successive iterations:

$$W_\mu^{n+1}(E) = \frac{1}{\beta} \ln n^n(E) \quad (3)$$

# Multicanonical ensemble

- final result: 
$$W_{\mu}^{n+1}(E) = W_{\mu}^0(E) + \frac{1}{\beta} \ln[P_{\mu}^0(E) \cdots P_{\mu}^n(E)] \quad (4)$$

- an example:  $W_{\mu}^0(E) = E$  , zero energy distribution  $P_{\mu}^0(E)$  is canonical and equation (4) is the standard ***multicanonical recursion***:

$$W_{\mu}^{n+1}(E) = E + \frac{1}{\beta} \ln[P_{\beta}(E) \cdots P_{\mu}^n(E)] \quad (5)$$

- canonical distribution can be recovered from  $P_{\mu}(E)$  through a reweighting procedure:

$$P_{\beta}(E) \sim P_{\mu}(E) e^{\beta(W_{\mu}(E) - E)} \quad (6)$$

- three steps of a multicanonical simulation:

- (i) generating  $W_{\mu}(E)$  in successive iterations

- (ii) equilibrium sampling

- (iii) recovering canonical expectations for various observables

# Monte Carlo studies of spin glasses

- B. A. Berg & T. Neuhaus, *PRL* 68,(1992),9, “*Multicanonical ensemble: A new approach to simulate first-order phase transitions*”
- B. A. Berg & T. Celik, *PRL* 69,(1992),2292, “*New approach to spin-glass simulations*” - multicanonical recursions
- 2D 10-state Potts model
- No exponential increase in the tunneling time between two free energy minima
- Speedup up to 2 orders of magnitude compared to standard simulations

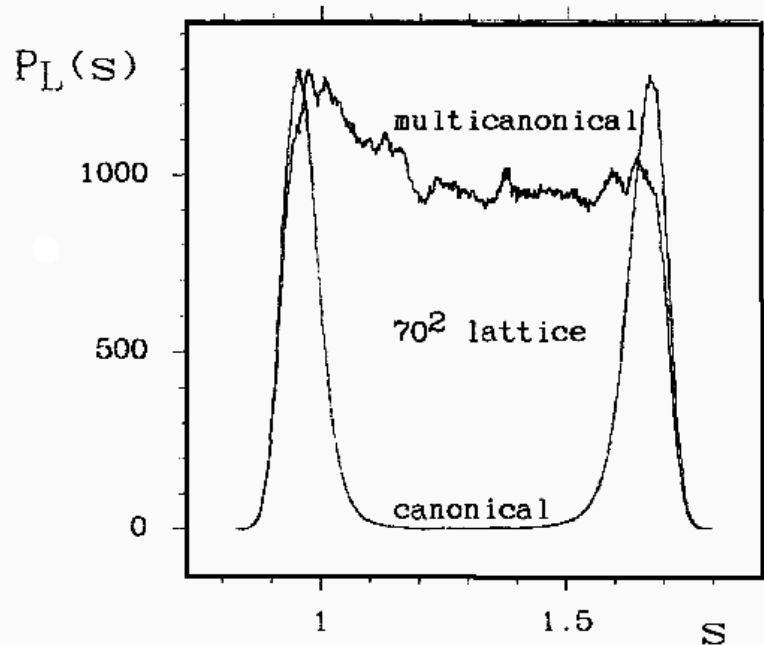


FIG. 2. Multicanonical action density distribution  $P_{70}(s)$  together with its reweighted distribution  $P_{70}(s)$ .

# Molecular dynamics simulations

- U. H. E. Hansmann, Y. Okamoto and F. Eisenmenger, *Chem. Phys. Lett* 259,(1996),321, “*Molecular dynamics, Langevin and hybrid Monte Carlo simulations in a multicanonical ensemble*”
- N. Nakajima, H. Nakamura and A. Kidera, *J. Phys. Chem. B* 101, (1997), 817, “*Multicanonical ensemble generated by molecular dynamics simulations for enhanced conformational sampling*”
- Equations of motion:

$$\dot{q}_i = \frac{dq_i}{dt} = \frac{p_i}{m_i} \quad \text{“multicanonical” force}$$

$$\dot{p}_i = f_i^\mu - \xi p_i \quad \text{factor to keep kinetic energy constant}$$

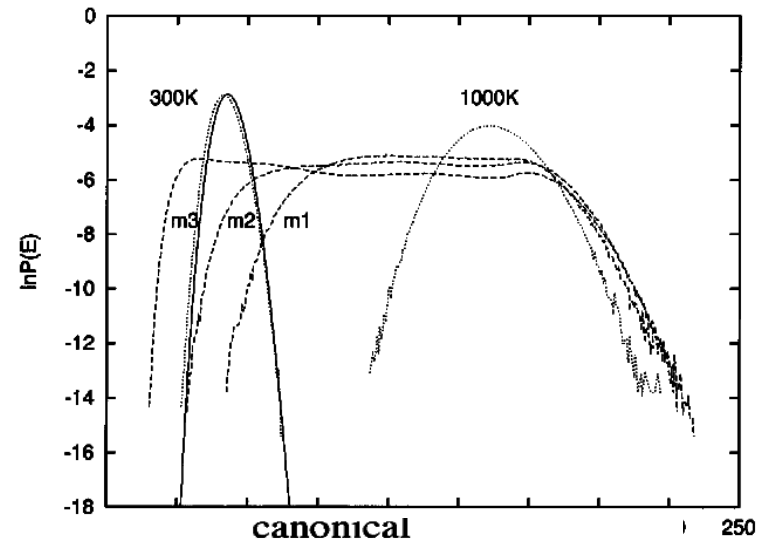
$$f_i^\mu = -\frac{\partial W_\mu(E)}{\partial q_i} = -\frac{dW_\mu(E)}{dE} \frac{\partial E}{\partial q_i} = -\frac{dW_\mu(E)}{dE} f_i$$

$$\xi = \frac{\sum f_i^\mu \cdot \dot{q}_i}{2 \sum p_i^2 / 2m_i}$$

- The only modification is in how **forces** are calculated !

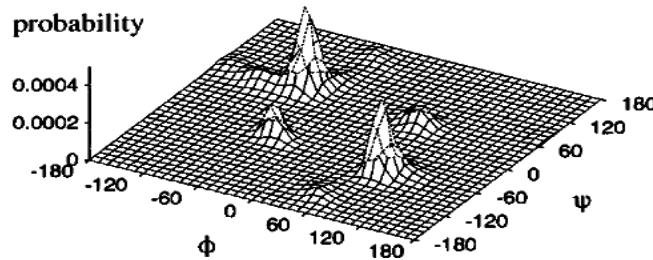
# Simulations of met-enkephalin

- The amino acid sequence of met-enkephalin is **TYR-GLY-GLY-PHE-MET**. Enkephalins belong to the family of endorphins that are expressed in reproductive organs. Their precise function is not well understood.

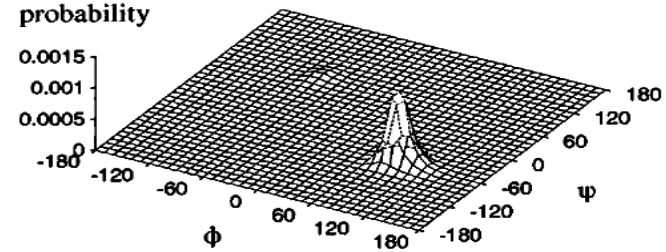


multicanonical

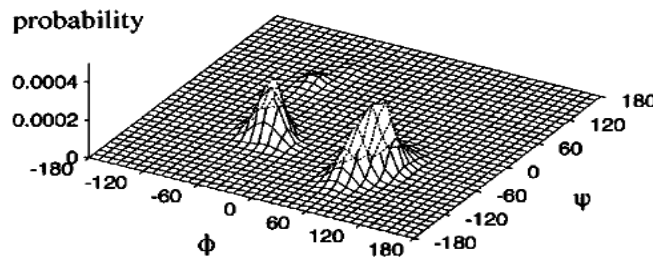
Gly2



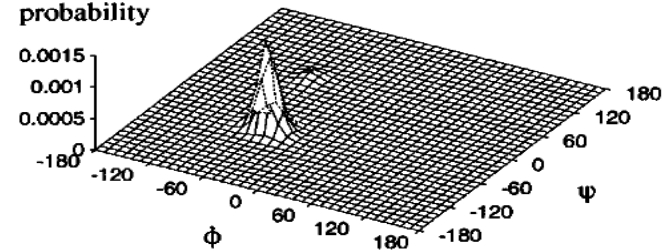
probability



Gly3



probability





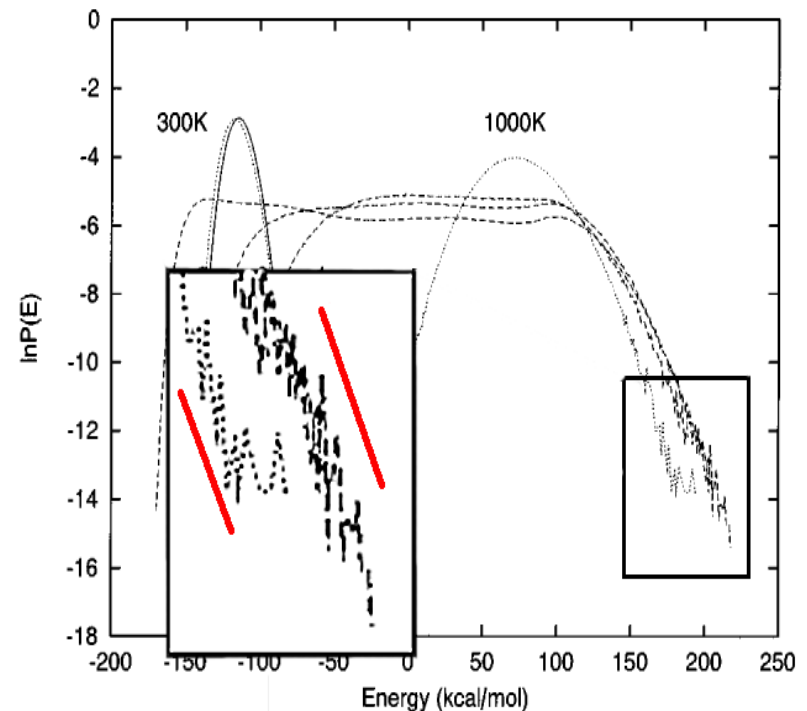
# Summary

- **Advantages:**

- (i) multicanonical simulations do not get trapped in local minima
- (ii) various thermodynamic quantities are obtained as a function of temperature from a single run. No need to run multiple simulations at different temperatures

- **Disadvantages:**

- (i) the energy transformation function  $W_\mu(E)$  is non-analytical. Several preliminary simulations are needed to generate it
- (ii) these simulations can not be run in parallel
- (iii) convergence is sensitive to the details of numerical implementation. Can be quite poor if  $P_\mu^0(E)$  is not accurately determined



# Tsallis energy transformation

- U. H. E. Hansmann & Y. Okamoto, *PRE* 56, (1997), 2228, “*Generalized-ensemble Monte Carlo method for systems with rough energy landscape*”

- **analytical** form for the multicanonical weight factor. **Non-exponential falloff** at large  $E$ :

$$w_T(E) = [1 + x\beta(E - E_0)]^{-\frac{1}{x}} \xrightarrow{x \rightarrow 0} e^{-\beta(E - E_0)}$$

- energy transformation: 
$$W_T(E) = \frac{1}{x\beta} \ln[1 + x\beta(E - E_0)]$$

- at low temperature the density of states can be calculated in harmonic approximation:

$$n(E) \sim (E - E_0)^{\frac{N_F}{2}}$$

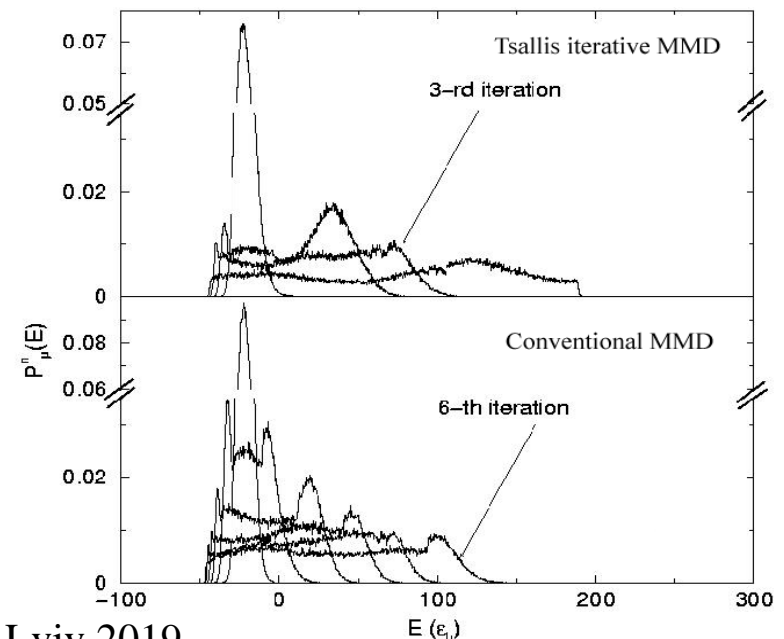
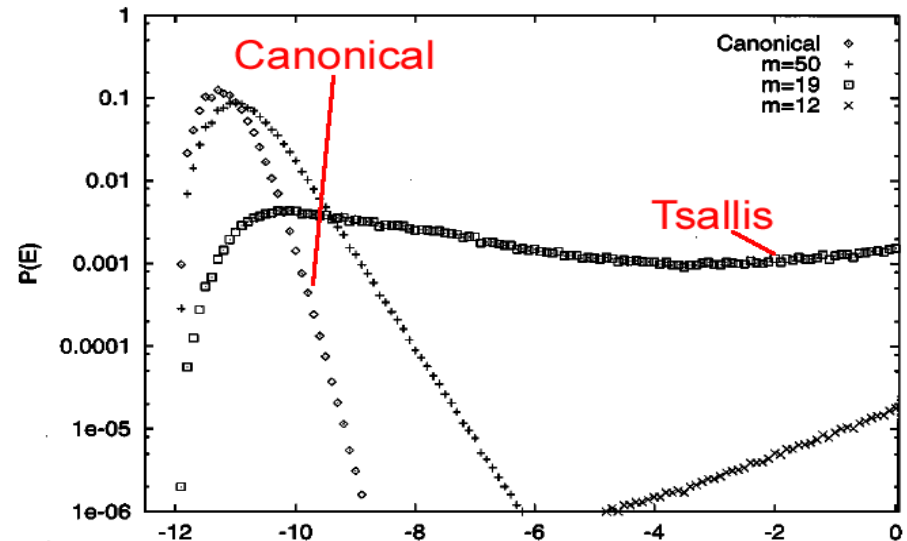
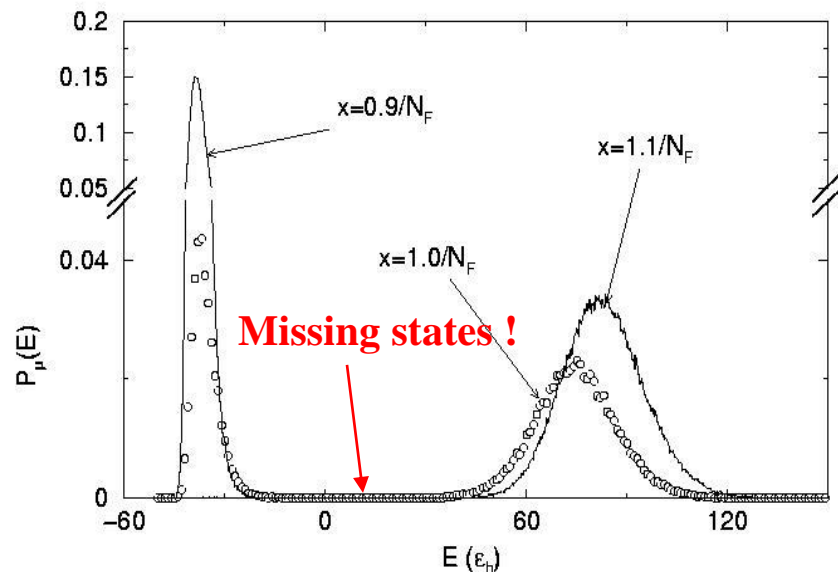
- if low-energy states are to be populated: 
$$x < x_c = 2 / N_F$$

- optimal value for  $x$ :

$$x_0 = 0.5 x_c$$

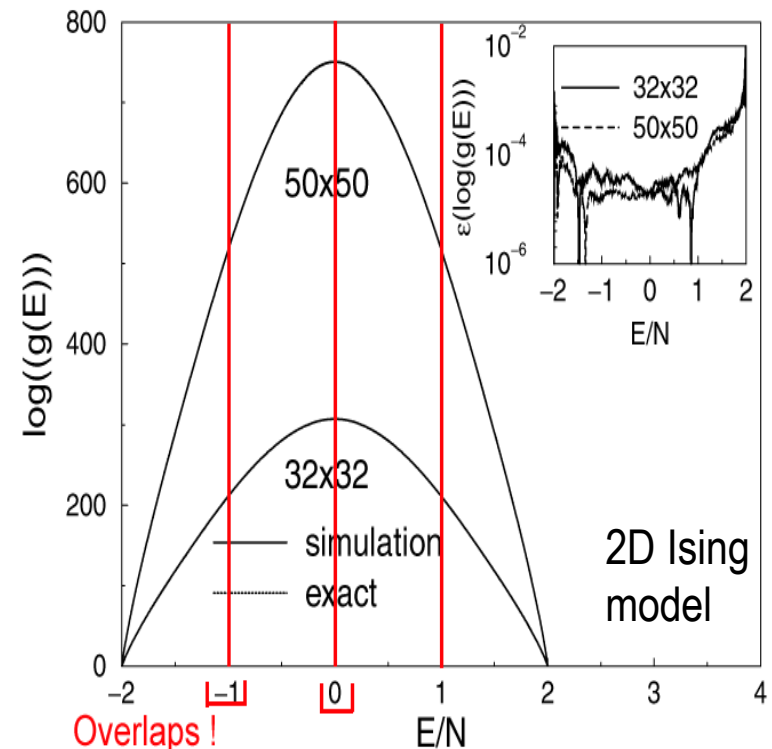
# Applications

- progressive **broadening** of the potential energy distribution of a met-enkephalin model as  $x$  is reduced
- same  $x_0$  does not work for all systems !
- simulations of **HT** protein model [AB & Y. Hiwatari, *JPSJ*, 71, (2002), 1001]. MMD iterations



# Wang-Landau method

- F. Wang & D. P. Landau, *PRL* 86, (2001), 2050, “*Efficient, multiple-range random walk algorithm to calculate the density of states*”
- Acceptance probability of a Monte Carlo move  $i \rightarrow j$ :  $\min \{ n(E_i)/n(E_j), 1 \}$
- Algorithm:
  - 0)  $n(E)=1$  for all  $E$ ,  $f \sim 3$
  - 1) every time an energy level  $E$  is visited,  $n(E)=f n(E)$
  - 2) simulation is continued until energy histogram  $H(E)$  is “flat”.  $H(E)$  for all  $E$  is not less than 80% of  $\langle H(E) \rangle$
  - 3) change the factor  $f_{i+1} = \sqrt{f_i}$
  - 4) if  $f_{i+1} > f_c (\sim 1.001)$  set  $H(E)=0$  and return to step 1
- Detailed balance is satisfied at  $f=1$
- Applicable to **large** systems. The desired energy interval can be broken into smaller pieces which are simulated in **parallel**
- Caveat: Make energy intervals large enough to avoid trapping !
- Application to proteins: [A. Cavalli et al., *Biophys J.* 88, (2005), 3158]



# 1/k ensemble

- B. Hesselbo & R. B. Stinchcombe, *PRL* 74, (1995), 2151, “*Monte Carlo simulation and global optimization without parameters*”

- Acceptance probability of a Monte Carlo move  $i \rightarrow j$  :  $\min \{ w_j / w_i, 1 \}$

*Metropolis (canonical distribution)*

$$w_i = e^{-\beta E_i}$$

*Multicanonical, Wang-Landau*

$$w_i = 1/k_i, \quad k_i = n(E_i)$$

*1/k ensemble*

$$w_i = 1/k_i, \quad k_i = \int_{E < E_i} dE n(E)$$

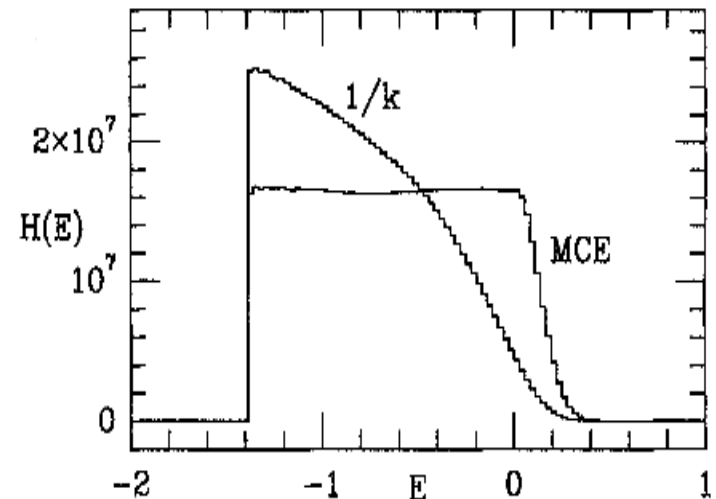
- Definitions of entropy:

$$S(E) = k \log( n(E) ) \quad S^*(E) = k \log( \int_{E' < E} dE' n(E') )$$

are equivalent in the therm. limit:

$$S^*(E) = S(E) + O(\log(N)), \quad N \rightarrow \infty$$

Differ for finite  $N$ . Energy distribution is not flat.



# J-walking algorithm

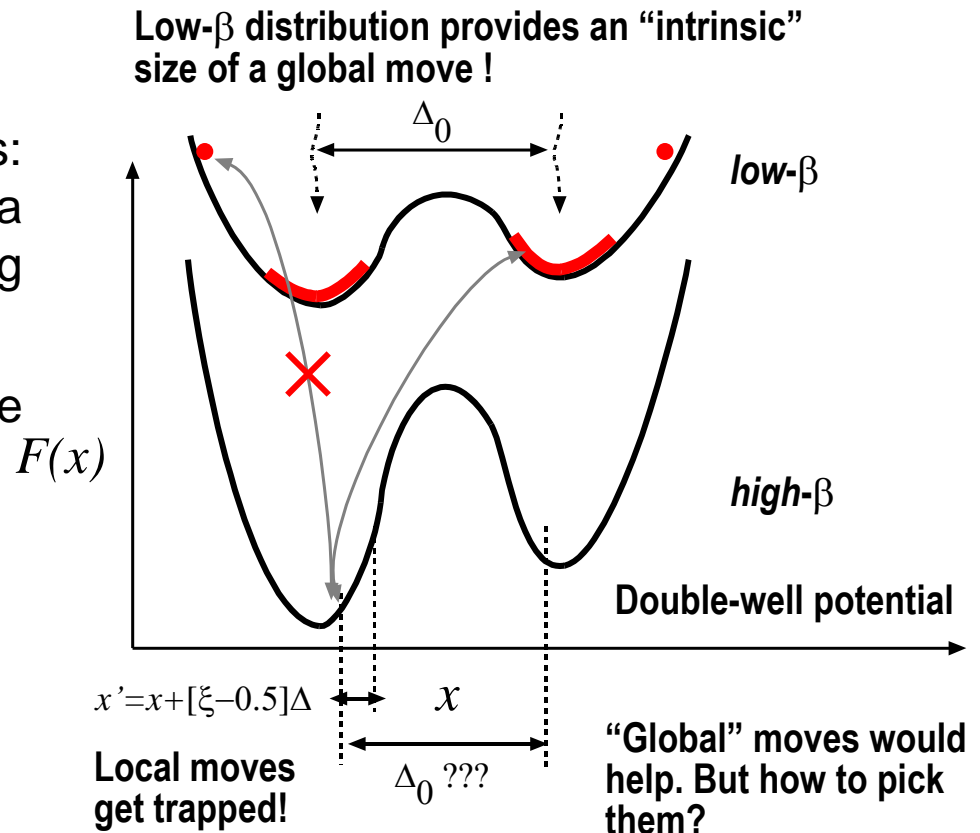
- D. D. Frantz, D. L. Freeman and J. D. Doll, JCP 93, (1990), 2769, “Reducing quasi-ergodic behavior in Monte Carlo simulations by J-walking: Applications to atomic clusters”

- It's easier to overcome potential energy barriers at **high  $T$**  (low  $\beta$ )!

- two types of Monte Carlo moves: **local** to sample free energy minima and **global** to transition among minima

- **J-walks** (global moves) are generated at high  $T$

[ too high  $T$  = low acceptance rate  
too low  $T$  = ergodicity problems



## Expanded-ensemble concept

- E. Marinari & G. Parisi, *Eur. Phys. Lett.* 19, (1992), 451, “*Simulated tempering: a new Monte Carlo scheme*”
- A. P. Lyubartsev et al., *JCP* 96, (1992), 1776, “*New approach to Monte Carlo calculation of the free energy: Method of expanded ensembles*”
- temperature  $\beta$  is treated as a **dynamical variable**. Canonical ensembles for each  $\beta$  are treated as sub-ensembles of a larger, **expanded** ensemble. Distribution function in this larger ensemble is defined through a supplementary function  $\alpha(\beta)$ :

$$P^*(\beta, \Gamma) = \frac{\exp(\beta \alpha(\beta) - \beta H(\Gamma))}{Z^*}, \quad Z^* = \sum_{\beta} \exp(\beta \alpha(\beta)) Z(\beta), \quad Z(\beta) = 1/N! \int d\Gamma \exp(-\beta H(\Gamma))$$

- probability to occupy states with temperature  $\beta$ :  $P^*(\beta) = \exp(\beta \alpha(\beta)) Z(\beta) / Z^*$
- free energy difference for two temperatures: *available from simulations*

$$\beta_2 F(\beta_2) - \beta_1 F(\beta_1) = \beta_1 \alpha(\beta_1) - \beta_2 \alpha(\beta_2) - \log \{ P^*(\beta_1) / P^*(\beta_2) \}$$

*given by the model* ↗
↓
← *main result*

# MC in expanded ensembles

- MC algorithm:

(I) Standard Metropolis moves for fixed  $\beta$ .  $p = \min \{ \exp(-\beta \Delta E), 1 \}$

(II) Temperature swaps:  $\beta_1 \rightarrow \beta_2$  with probability:

$$p = \min \{ \exp( (\beta_1 - \beta_2)E + \beta_2 \alpha(\beta_2) - \beta_1 \alpha(\beta_1) ), 1 \}$$

(III) Total time spent at each temperature is accumulated in histograms and used for estimating  $P^*(\beta)$

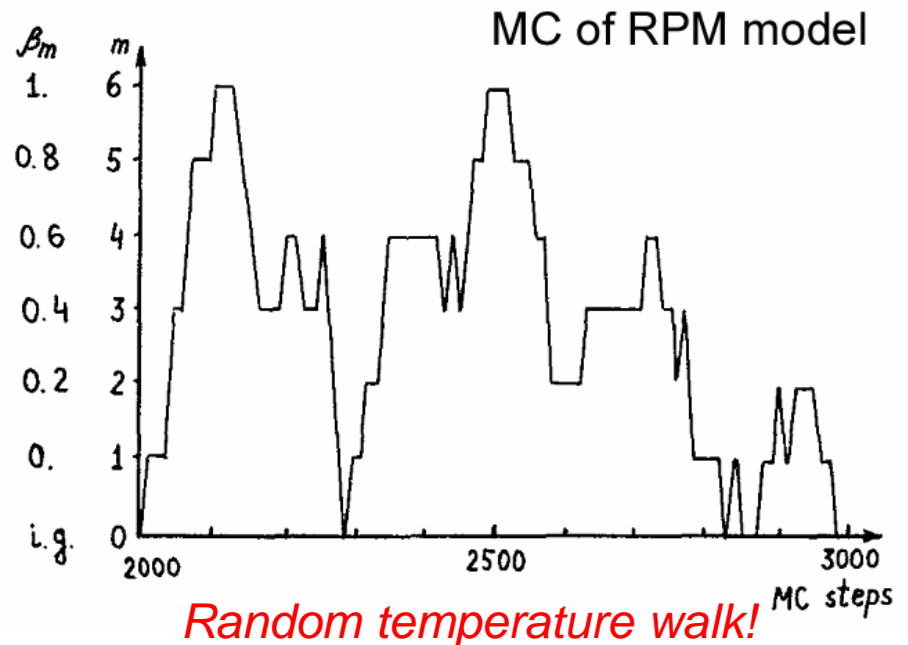
- Random walk in temperature is realized for:

$$\alpha(\beta) = F(\beta) = 1/\beta \log( Z(\beta) )$$

- $\alpha(\beta)$  are determined in successive iterations

- For each  $\beta$  canonical distributions are recovered!

- The algorithm is also known as ***simulated tempering***





## Replica-exchange algorithm

- R. H. Swendsen & J.-S. Wang, *PRL* 57, (1986), 2607, “*Replica Monte Carlo simulation of spin-glasses*”
- M. C. Tesi et al., *J. Stat. Phys.* 82, (1996), 155, “*Monte Carlo study of the interacting self-avoiding walk model in three dimensions*”
- K. Hukushima & K. Nemoto, *JPSJ*, 65, (1996), 1604, “*Exchange Monte Carlo method and application to spin glass simulations*”
- U. H. E. Hansmann, *Chem. Phys. Lett.*, 281, (1997), 140, “*Parallel tempering algorithm for conformational studies of biological molecules*”
- Y. Sugita & Y. Okamoto, *Chem. Phys. Lett.*, 314, (1999), 141, “*Replica-exchange molecular dynamics method for protein folding*”

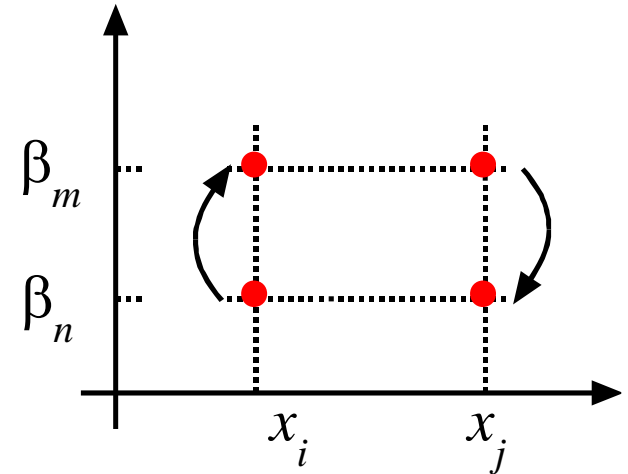
*Replica-exchange (REX) = parallel tempering = multiple Markov chain method*

# Replica-exchange algorithm

- the method is based on the **expanded-ensemble** idea  $P^*(\beta, \Gamma) \sim \exp(\beta \alpha(\beta) - \beta H(\Gamma))$
- $N$  independent replicas are considered (**parallel tempering**)
- double-jumps are attempted

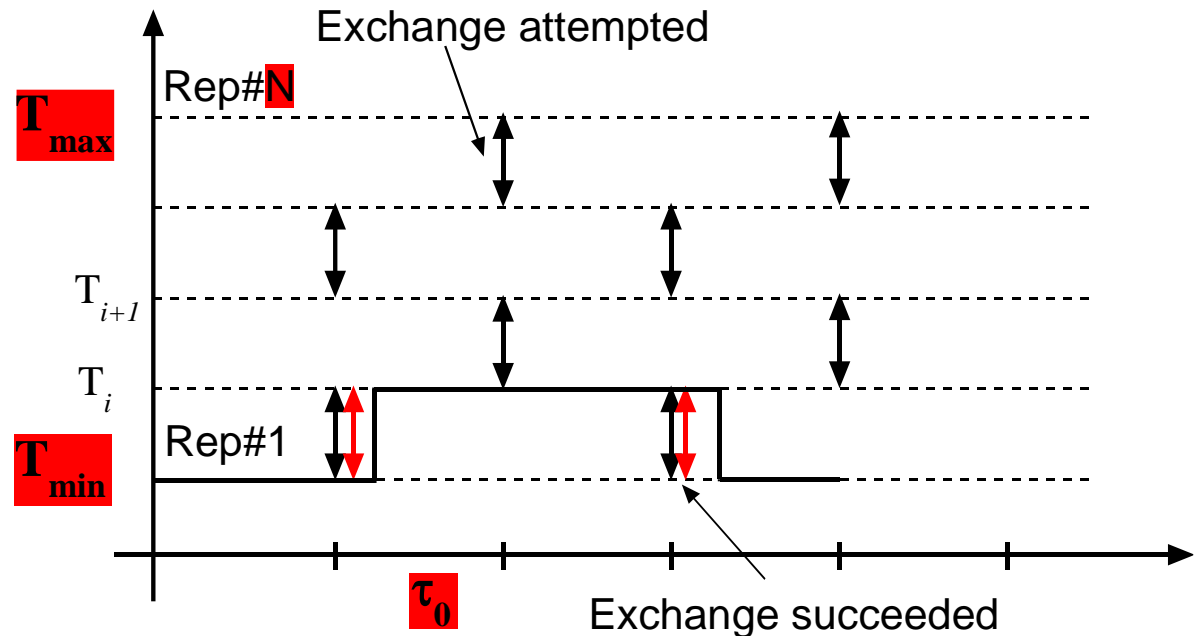
$$p = \begin{cases} e^{\Delta}, & \Delta < 0 \\ 1, & \Delta > 0 \end{cases} \quad \Delta = (\beta_m - \beta_n)(E_j - E_i)$$

$\alpha(\beta)$  drop in double jumps



- uniform distribution* over sampled temperatures (one replica per temperature condition)

- canonical distribution* for each considered temperature  $\beta$



# Practical points

- Four parameters need to be set:  $T_{\max}$ ,  $T_{\min}$ ,  $N$ ,  $\tau_0$

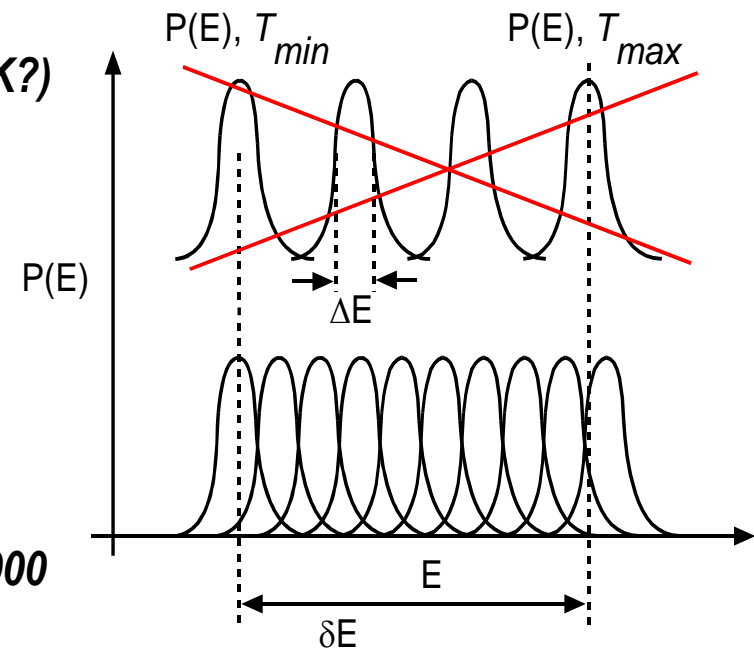
$T_{\max}$  — the higher the better (~500-700K). Typical relaxation time at this temperature should be ~1-100ps

$T_{\min}$  — the temperature of your interest (300K?)

$N$  — large enough to ensure 10-50% acceptance probability for swaps between replicas

$$N \sim \frac{\delta E}{\Delta E} \sim \frac{N_F}{\sqrt{C_v}} \sim \frac{N_F}{\sqrt{N_F}} \sim \sqrt{N_F}$$

$\tau_0$  — the longer the better. Typically 100-1000 simulation time steps



- What to look out for:

- replica-exchange acceptance ratio is more than 10%
- each replica visits  $T_{\min}$  and  $T_{\max}$  at least several times
- all **relevant** order parameters undergo sufficient relaxation

Nadler[PCL B 112 (2008)]  

$$N = 1 + 0.594 \sqrt{C} \ln T_{\max}/T_{\min}$$

# Kinetic data from REX simulations

- There is no physical kinetics in the REX simulations. A number of approaches to extract kinetic information:

*Andrec [PNAS 102 (2005) 6801]*

*van der Spoel [PRL 96 (2006) 238102]*

*Yang[JMB 372 (2007) 756]*

*Buchete[JPC B 112 (2008) 6057]*

*Muff [JPC B 113 (2009) 3218]*

*Chodera[JCP 134 (2011) 244107]*

- Most approaches rely on the following ingredients:

a) discretization of the available configuration space

{ *Very difficult to get a representative ensemble*

b) obtaining rates of transition between the identified states

{ *Most often in straight MD simulations.  
Not reliable*

c) solving master equation to generate reaction time

{ *Relies on assumption on how  
transition rates depend on temperature*

Example: ETNA of Muff and Caflisch

*Folding time for a  $\beta$ -sheet peptide predicted for varying temperature over a range that spans an order of magnitude*

# Replica-exchange flavors

- **REX** coupled with Tsallis energy deformation function: [ Hansamann, *Chem. Phys. Lett*, 281(1997) 140  
Jang et al., *PRL*, 91 (2003) 058305
- Muticanonical **REX** and **REX** multicanonical: Sugita & Okamoto, *Chem. Phys. Lett*, 329 (2000) 261
- **REX** in constant pressure (CPT) ensemble: Okabe et al. *Chem. Phys. Lett*, 335 (2001) 435
- Mutidimensional **REX**: Sugita, Kitao & Okamoto, *JCP*, 114 (2000) 6042
- *Ab initio* Monte Carlo **REX**: Ishikawa et al., *Chem. Phys. Lett.*, 333 (2001) 199
- Hamiltonian **REX**: Fukunishi, Watanabe & Takada, *JCP*, 116 (2002) 905

## Replica-exchange flavors

- **REX** coupled with RISM: Mitsutake et al., *J. Phys. Chem. B*, 108 (2004) 19002
- Local **REX**: Cheng et al., *J. Phys. Chem. B*, 109 (2005) 8220
- Non-equilibrium switches **REX**: Ballard and Jarzynski, *PNAS*, 106 (2009) 12224
- Further reading:
  - 1) Review paper by K. Tai, *Biophys. Chem.*, 107 (2004) 213
  - 2) Special issue of *J. Mol. Graph. Mod.*, 22, (2004) 317

# Multiple-histogram reweighting technique

- A. M. Ferrenberg & R. H. Swendsen, *PRL* 63, (1989), 1195, “Optimized Monte Carlo data analysis”

- Chodera et al, *JCTC* 3, (2007), 26, “WHAM for REX simulations”

- $i=1, m$  temperatures,  $N_i$  samples,  $H_i(E)$  energy histograms

$$P_i(E) = H_i(E) / N_i = n(E) \exp(-\beta_i(E - f_i))$$

- by definition, free energy:  $\exp(-\beta_i f_i) = \sum_{E_k} n(E_k) \exp(-\beta_i E_k) \frac{P(E)}{P_i(E)}$

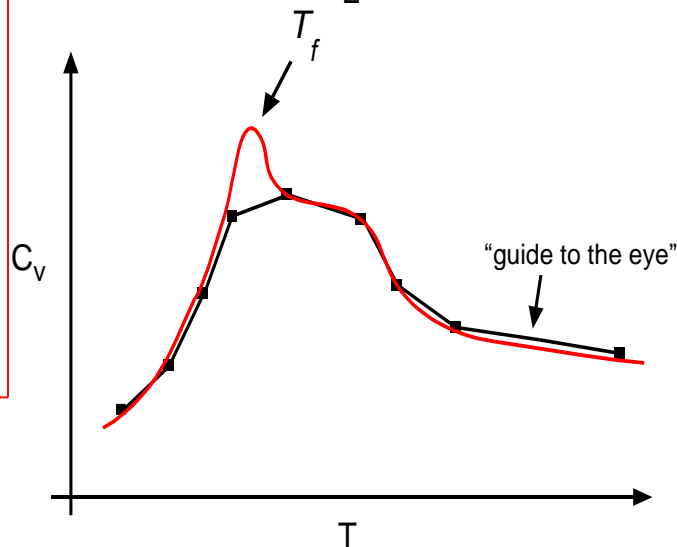
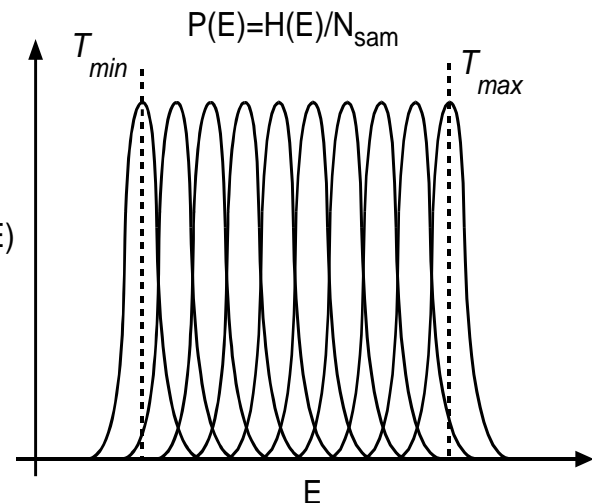
- inaccurate estimate of the density of states from simulation at temperature  $i$ :

$$n_i(E) = P_i(E) \exp(\beta_i(E - f_i))$$

- improved density of states: 
$$n(E) = \frac{\sum_i g_i n_i(E)}{\sum_i g_i}$$

- $\delta n(E)^2 / n(E)$  is minimized with respect to weighting  $g_i$  coeff.

- set of non-linear equations in  $f_i$ : 
$$n(E) = \frac{\sum_i P_i(E)}{\sum_i \exp(-\beta_i(E - f_i))}$$



# Summary

- Why is replica exchange the method of choice in biomolecular simulations?
  - Parallelism
  - No empirical parameters or fitting involved
  - Access to low free energy minima through accelerated relaxation
  - Availability of all thermodynamical properties as a function of temperature through histogram reweighting techniques