



KATEDRA FYZIKÁLNÍ CHEMIE
UNIVERZITY PALACKÉHO V OLOMOUCI



INSTITUTE OF MOLECULAR AND
TRANSLATIONAL MEDICINE



6th Advanced

in silico Drug Design

KFC/ADD

Molecular Modelling intro

Karel Berka



EMBL-EBI



UP Olomouc, 30.1.-3.2. 2023



INSTITUTE OF PHYSICS
National academy of Sciences of Ukraine



ÚOCHB AV
ČR
IOCB PRAGUE

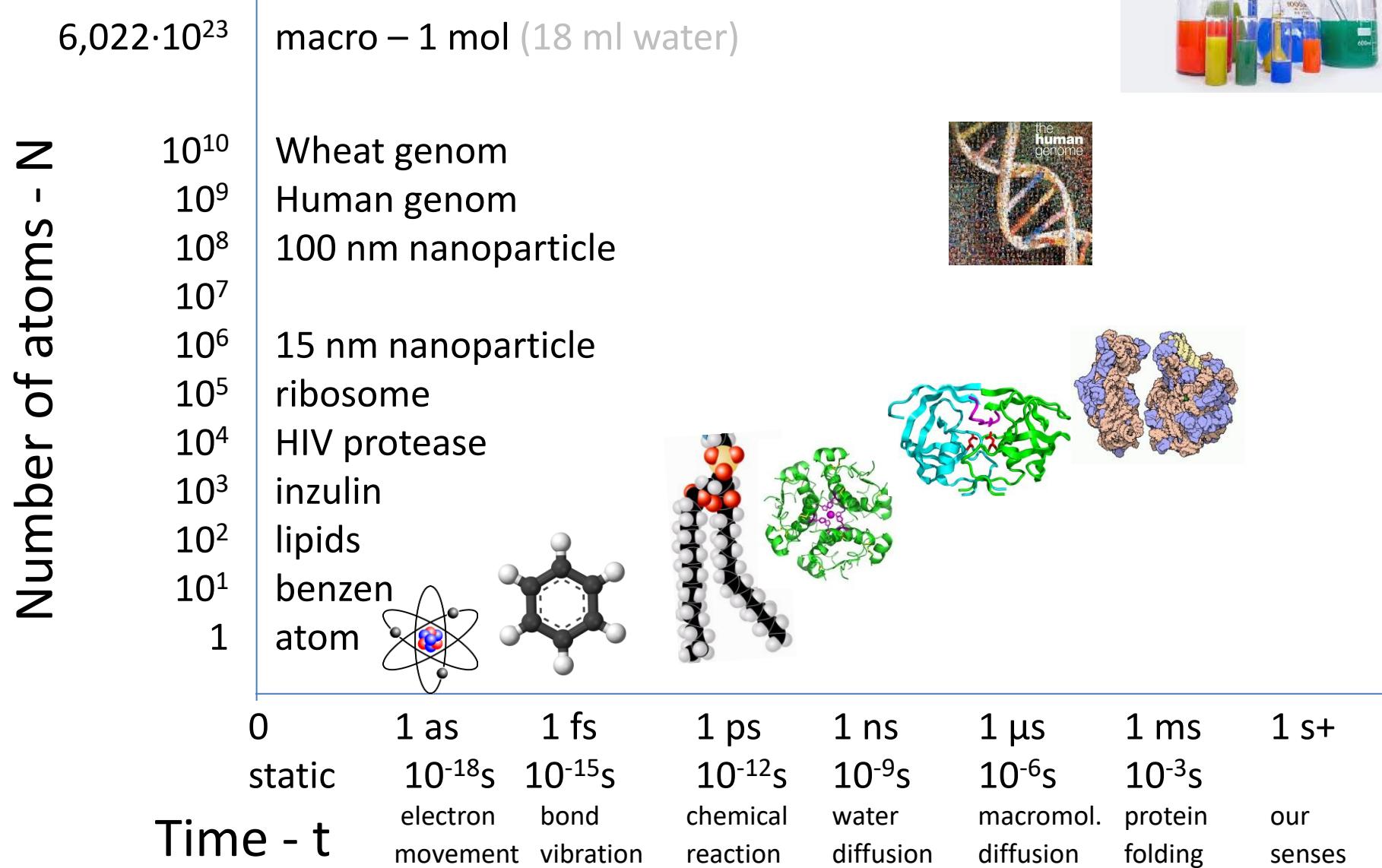


Motto

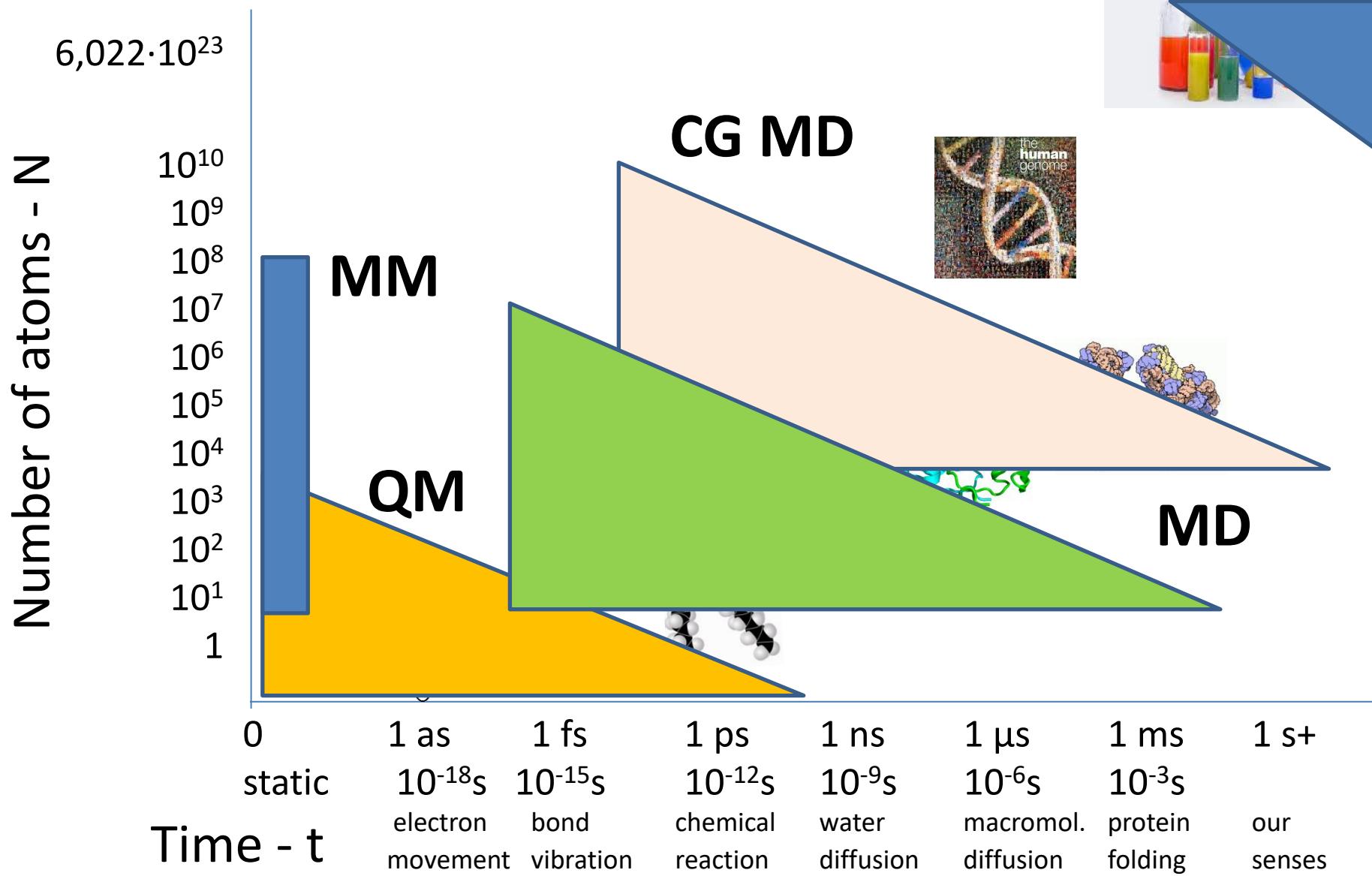
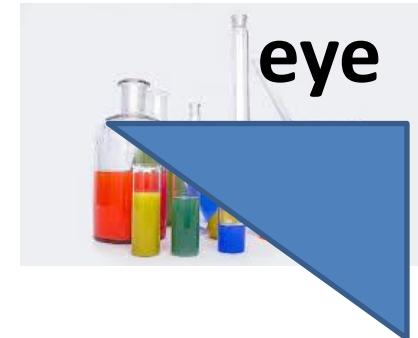
- *A theory is something nobody believes, except the person who made it*
- *An experiment is something everybody believes, except the person who made it*

Albert Einstein

Scale of Matter

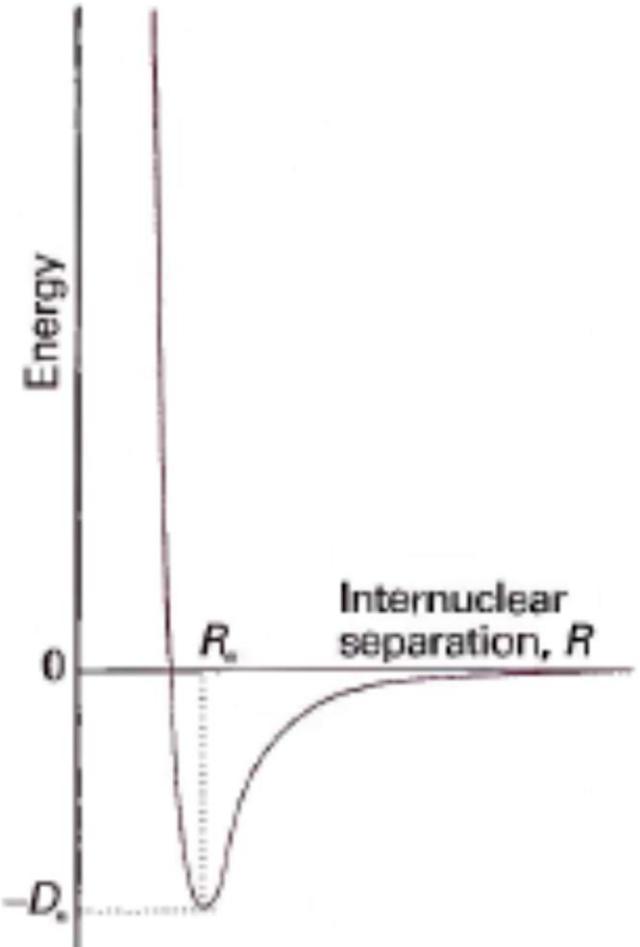


Scale of Matter



MOLECULAR INTERACTIONS

Covalent and Noncovalent Interactions



Different origin

Covalent Interactions – overlap of orbitals

Noncovalent Interactions – electric properties of molecules

Different properties ($\Delta G = \Delta H - T\Delta S$)

ΔE (kcal/mol)	R (Å)	ΔS entropy
-----------------------	---------	--------------------

Cov.Int. - ~ 100	1.2 - 1.6	not important
------------------	-----------	---------------

NoC.Int - ~ 1 – 5	2.0 - 5.0	key property
-------------------	-----------	--------------

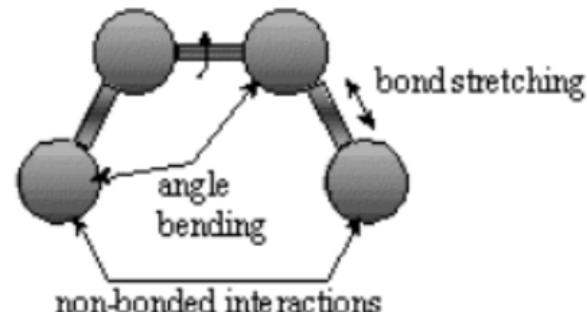
Molecular Mechanics

total energy is function of atom positions

$$E = f(\mathbf{R}) = E_{covalent} + E_{noncovalent}$$

$$E_{covalent} = E_b + E_a + E_t$$

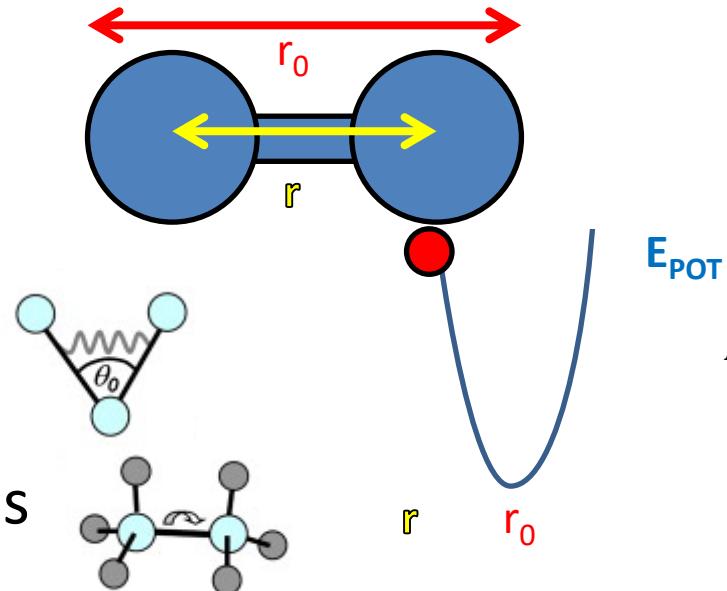
$$E_{noncovalent} = E_c + E_{vdw}$$



.....

Molecular Mechanics

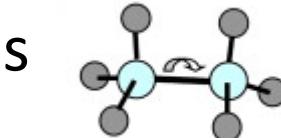
- Atoms „balls on springs“
- Bonds



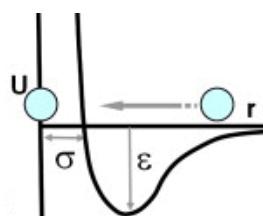
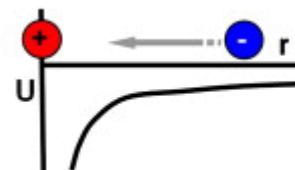
$$E_{POT} = f(x)$$

$$E_{POT} = \frac{1}{2}k(r - r_0)^2$$

- Angles
- Dihedrals

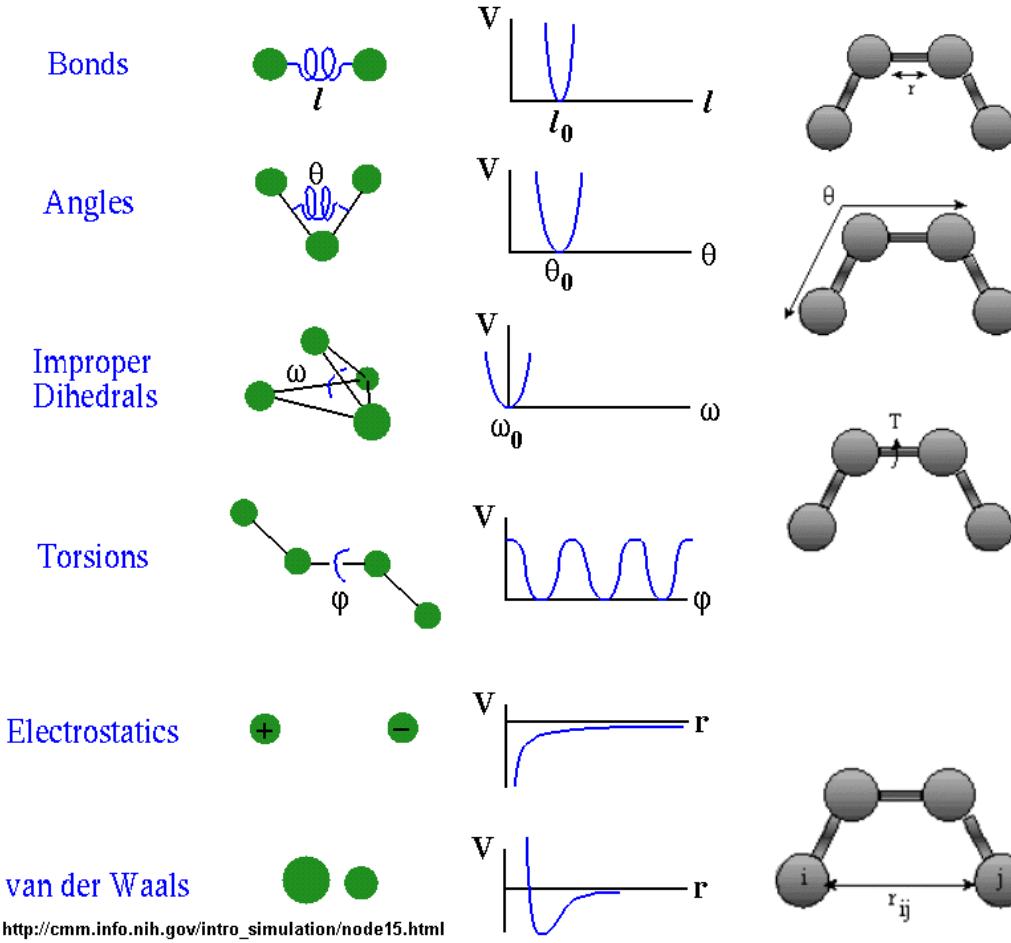


- Elektrostatic interactions
- vdW interactions



Force-field

Empirical Potential Energy Function



$$E_b = \frac{k_r}{2} (r - r_0)^2$$

$$E_a = \frac{k_\theta}{2} (\theta - \theta_0)^2$$

$$E_t = \frac{k_\theta}{2} (1 + \cos(n\phi - \phi_0))$$

$$E_c = \frac{1}{4\pi\epsilon_0\epsilon_r} \frac{q_i q_j}{r_{ij}}$$

$$E_{vdw} = -2\epsilon_{ij} \left(\frac{r_{ij}^*}{r_{ij}} \right)^6 + \epsilon_{ij} \left(\frac{r_{ij}^*}{r_{ij}} \right)^{12}$$

Bonds

Angles

Dihedral angles

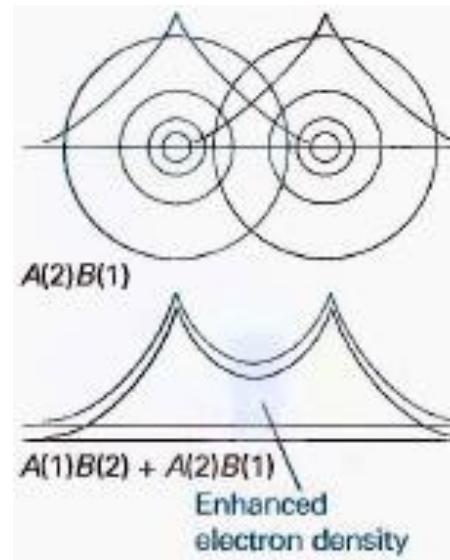
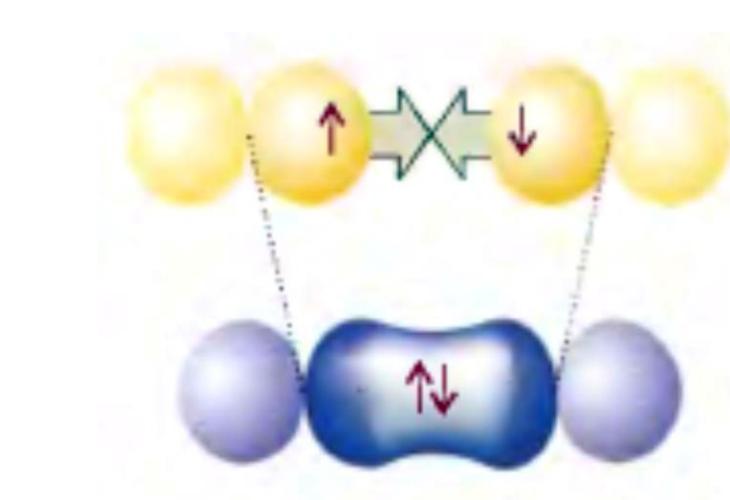
Improper torsions

COVALENT INTERACTIONS

Covalent bond

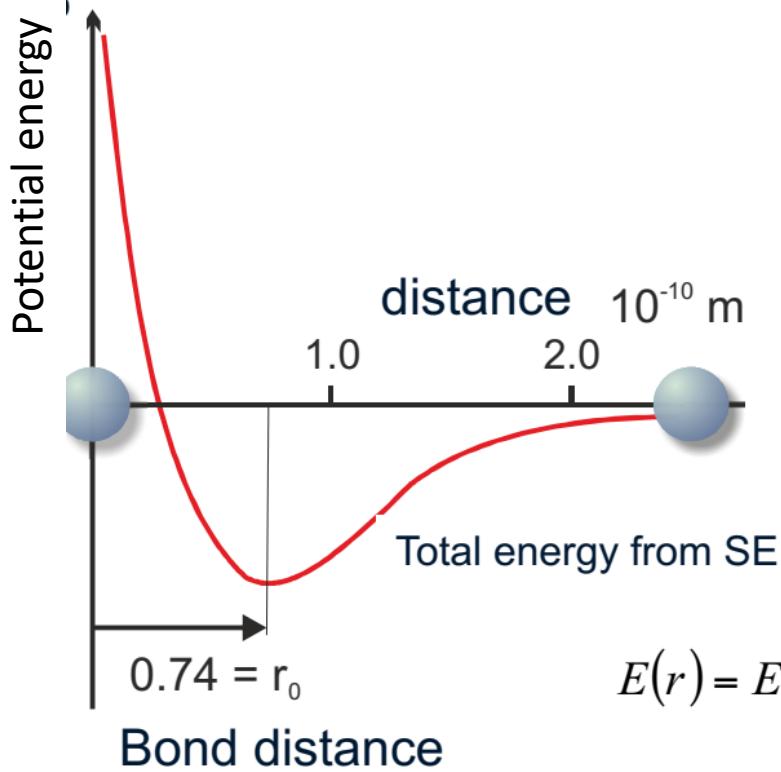
Sharing of noncomplete electron orbitals

- gives valence electron configuration with greater stability than in isolated atoms



Internal electrons are intact

Covalent Bond



Behavior close minimum

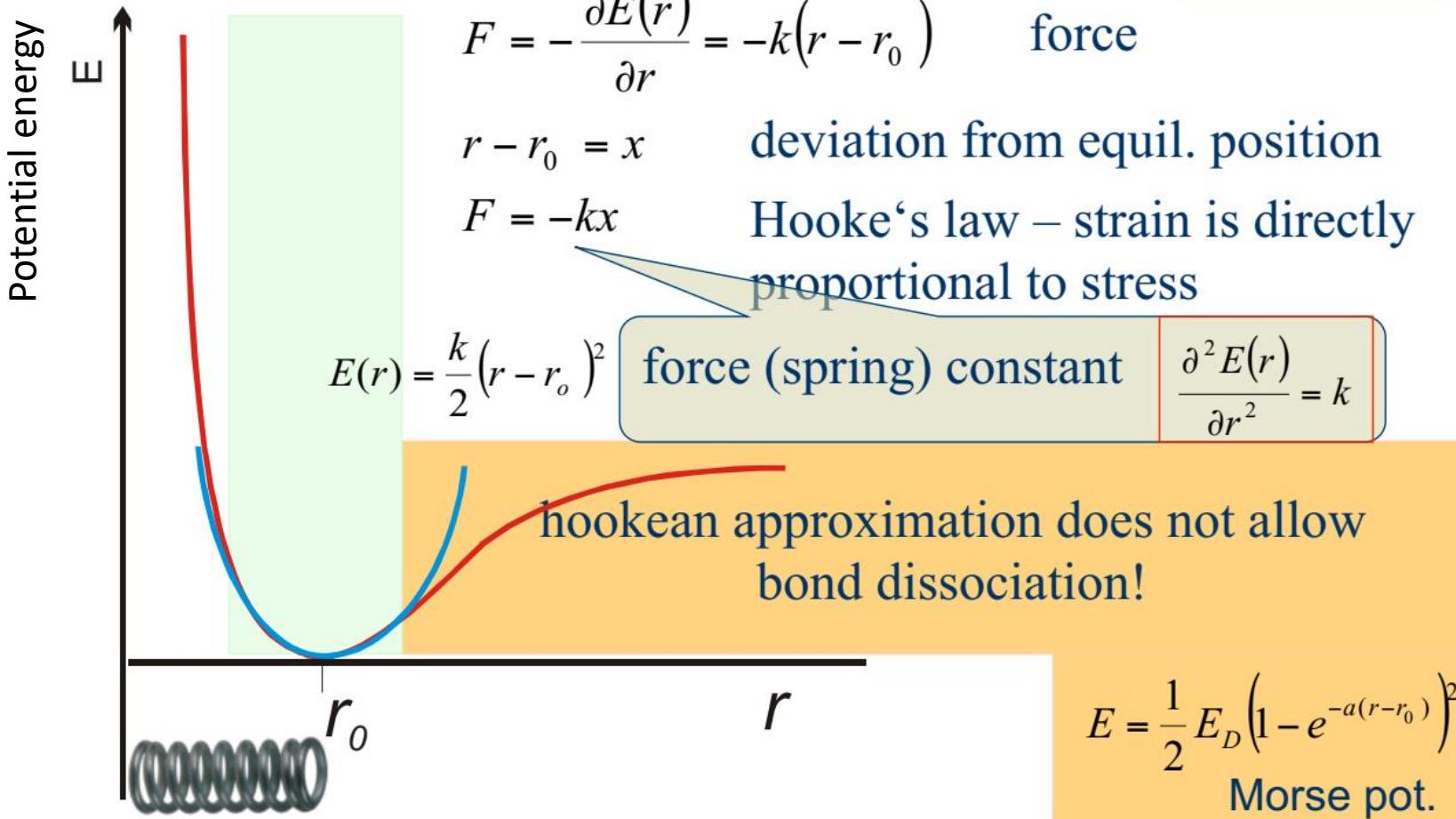
Taylor expansion

$$f(x) = \sum_{n=0}^{\infty} \frac{f^{(n)}(a)}{n!} (x - a)^n.$$

$$E(r) = E(r_0) + \frac{1}{1!} \frac{\partial E(r_0)}{\partial r} (r - r_0) + \frac{1}{2!} \frac{\partial^2 E(r_0)}{\partial r^2} (r - r_0)^2 + \dots$$

$$E(r) = \frac{1}{2} \frac{\partial^2 E(r_0)}{\partial r^2} (r - r_0)^2$$

Bond as a spring



Bond types

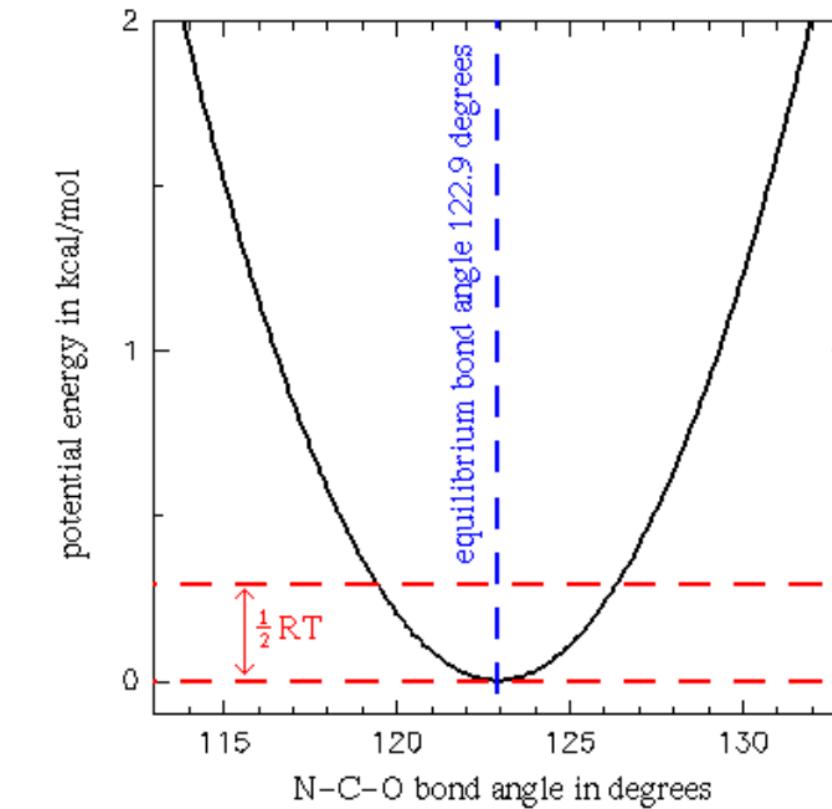
- various covalent bonds have various:
 r_0 , bond distance (X-ray)
 k , force constant (IR)
 - similar bonds share similar behavior in all molecules, insensitive to environment
 - Parameters are transferable => force fields
 - AMBER, CHARMM, MARTINI, MMFF94, OPLS...
- | molecule | $k / \text{N}\cdot\text{m}^{-1}$ | r_0 / pm |
|--------------------------|----------------------------------|-------------------|
| H_2 | 510 | 74.1 |
| H^{35}Cl | 478 | 127.5 |
| H^{79}Br | 408 | 141.4 |
| H^{127}I | 291 | 160.9 |

Angle bending

$$E = \frac{k_\theta}{2} (\theta - \theta_0)^2$$

$$k_\theta = 80 \text{ kcal/mol.deg}^2$$

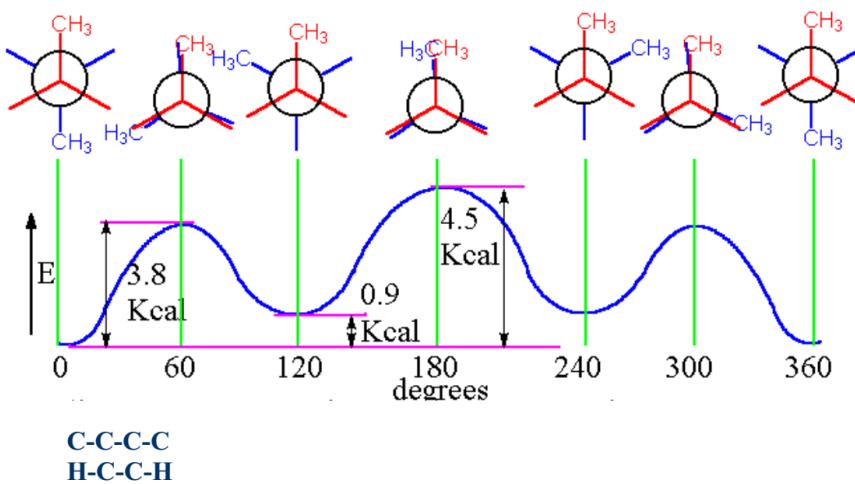
$$\theta_0 = 122.9^\circ$$



© O. S. Smart, 1995

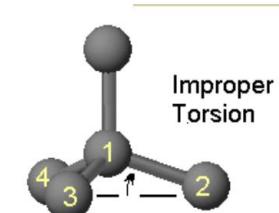
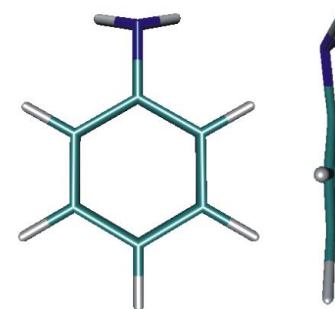
Torsions/Dihedrals

Proper dihedrals



Improper Torsions

geometry of aminogroup



AMBER
2-3-1-4
phase 180°
 $n = 2$

CHARMM

$$E = \frac{k_\omega}{2} (\omega - \omega_0)^2$$

Electrostatic
Induction
Dispersion
Hydrophobic
Specials – Hydrogen bonding, Halogen bonding

NONCOVALENT INTERACTIONS

Motto:

*Not **despite** the weakness
but **because** of weakness
the noncovalent
interactions play a key role
in biodisciplines*

Pavel Hobza



Pavel Hobza
(1946)

Noncovalent interactions

Chemistry - liquids

Physics - existence of molecular crystals

Biology - dominant

- molecular recognition

- macromolecular structure and function

On the one hand, they should be strong enough to ensure the preferential binding but on the other hand they should be weak enough to allow disruption of bonding

J. Watson on role of noncovalent interactions in DNA

Types of noncovalent interactions

Coulombic (Electrostatic) (+,-) $\sim r^{-1} - r^{-3}$

perm.multipole-perm.multipole

Induction (polarization) (-) $\sim r^{-5}$

perm.multipole-ind.multipole

London dispersion (-) $\sim r^{-6}$

inst.multipole-inst.multipole

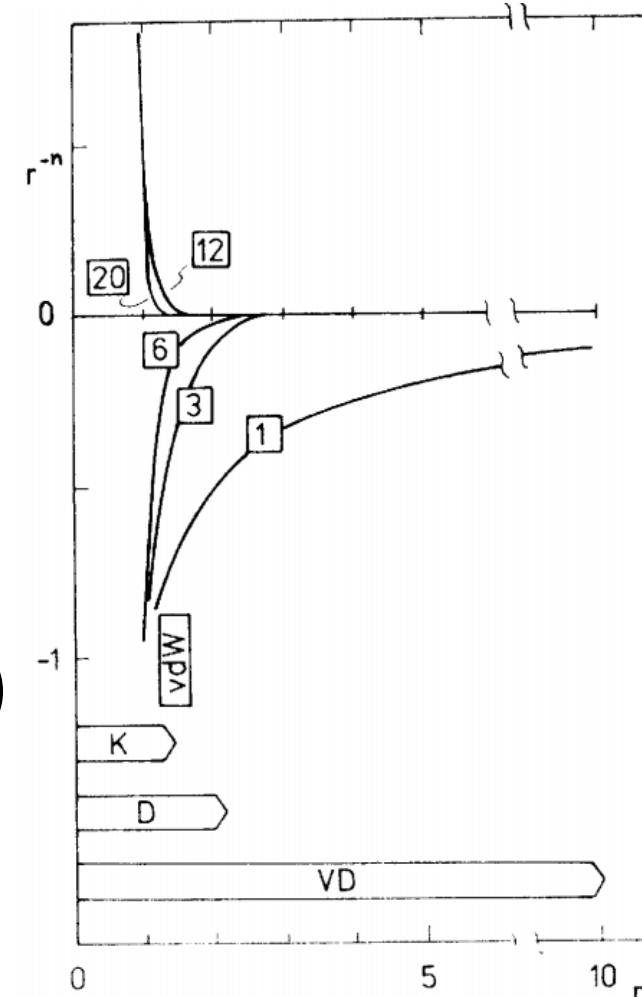
Repulsion (+) $\sim e^{-\alpha r}(r^{-12})$

(Pauli) electron exchange

$$\Delta E = E^E + E^I + E^D + E^R$$

(+) – repulsive

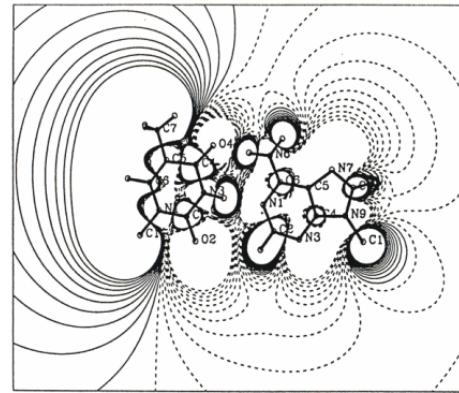
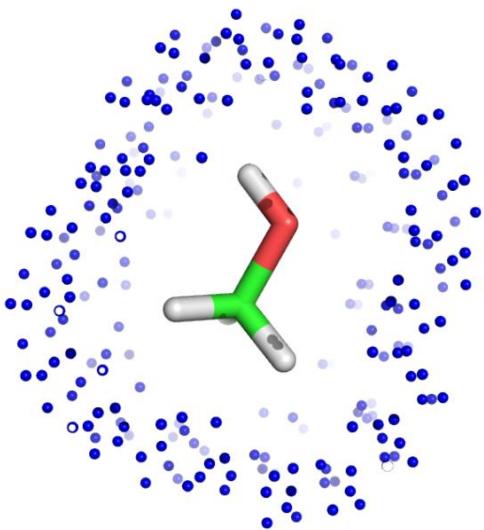
(-) - attractive



Coulombic Interaction

- Coulomb law
- Atomic centered partial charges
 - RESP (Restrained ElectroStatic Potential fit)
- EEM methods – quicker empirical

$$E = \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{r}$$



$$\chi^2 = \chi_{esp}^2 + \chi_{resp}^2 + \lambda g(q_i)$$

$$\chi_{esp}^2 = \sum_i (V_i - \hat{V}_i)^2, \hat{V}_i = \sum_j \frac{q_j}{r_{ij}}$$

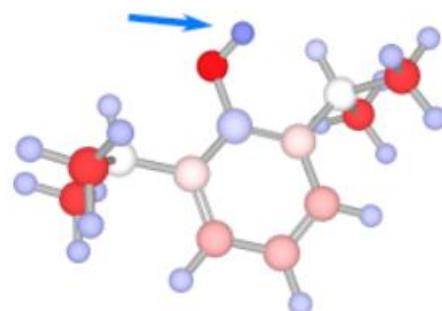
$$\chi_{resp}^2 = a \sum_j ((q_j^2 + b^2)^{1/2} - b)$$

Empirical charge calculator

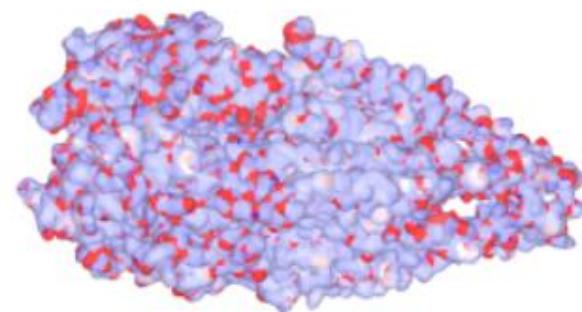
Atomic Charge Calculator II

- 20 empirical methods
- Handles large proteins and small molecules

Dissociating hydrogens → pKa



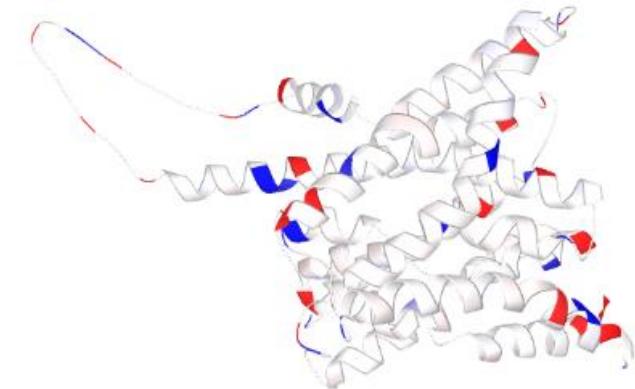
Transmembrane protein



αCharges

- SQE+qp empirical charges – similar to QM
- On AlphaFoldDB structures

PIN proteins



Web: <https://acc2.ncbr.muni.cz/>

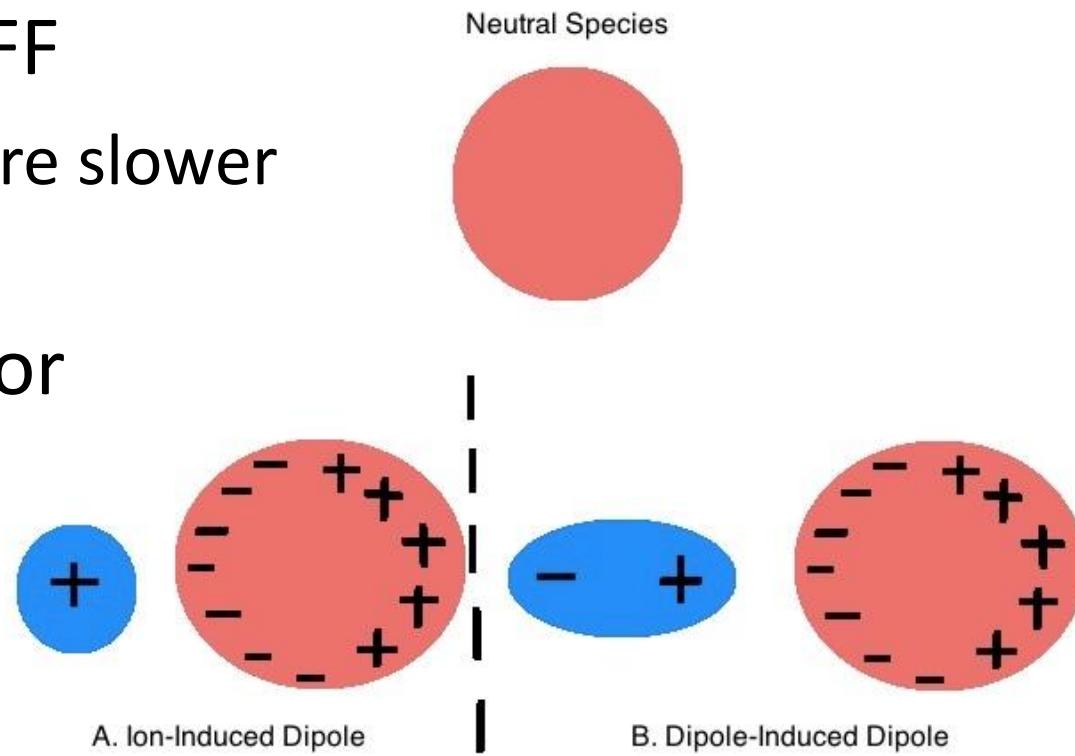
Command-line: <https://github.com/krab1k/ChargeFW2>

API: <http://78.128.250.156/>

<https://alphacharges.ncbr.muni.cz/>

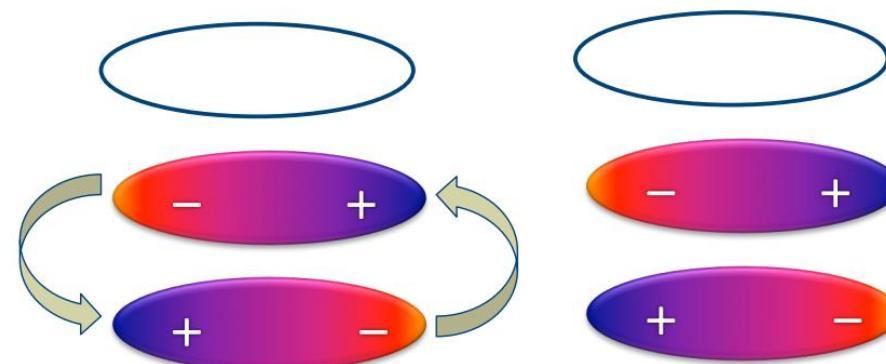
Induction/Polarization

- Around ions -> induced charges
- Usually neglected in FF
 - FF with polarization are slower (Drude CHARMM)
- Might be important for chemical reactions
 - QM/MM



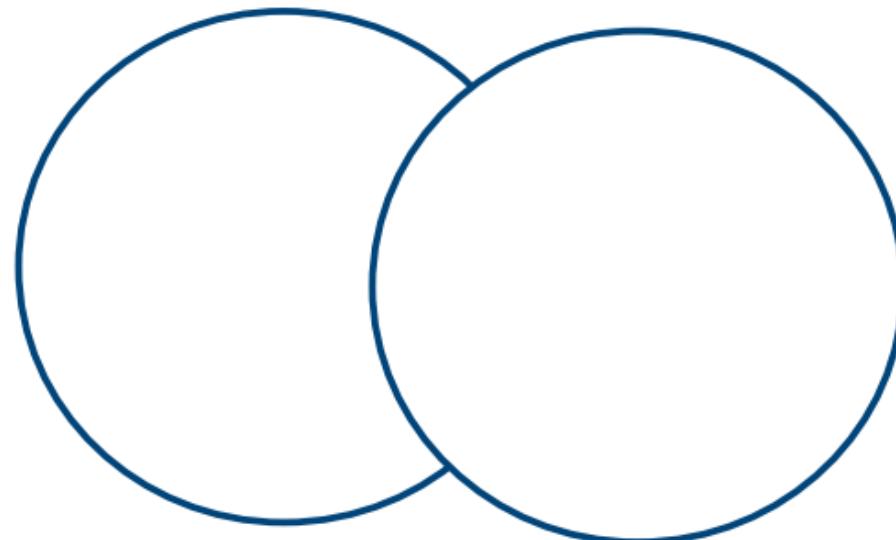
London Dispersion

- Instantaneous correlation between electrons induces polarization
- Always attractive



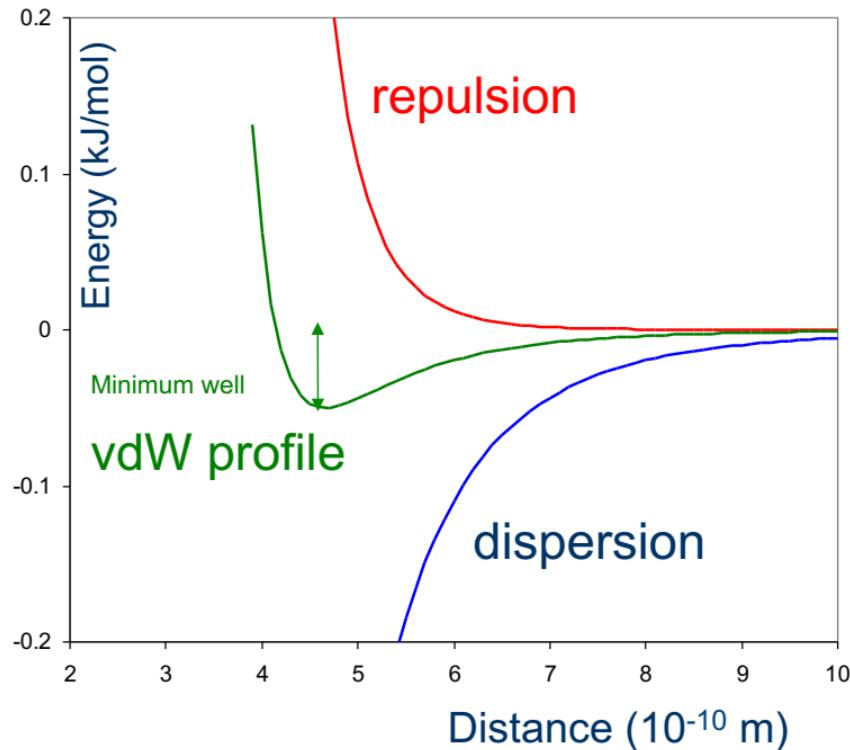
(Pauli) Repulsion

- Increases exponentially with occupied electron orbital overlap
- Usually combined with dispersion



Van der Waals term

- Lennard-Jones Potential



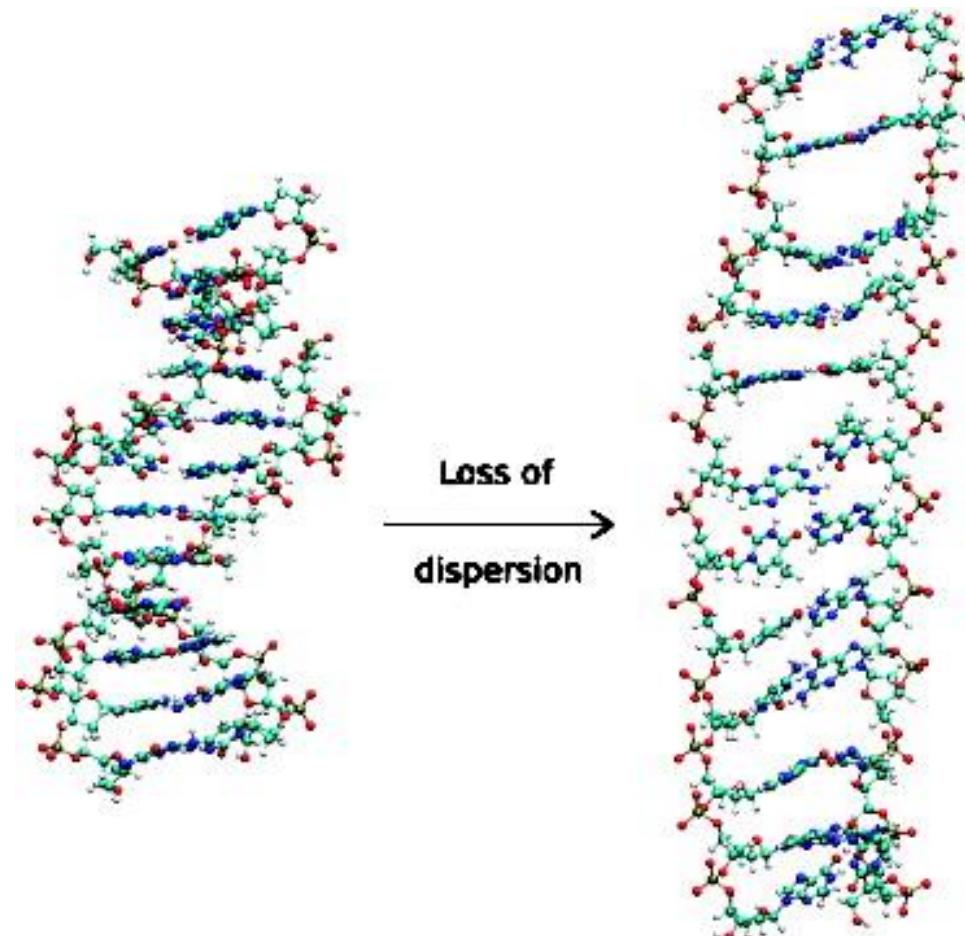
$$u(r) = 4\epsilon \left(\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right) = \epsilon \left(\left(\frac{\sigma_{vdw}}{r} \right)^{12} - 2 \left(\frac{\sigma_{vdw}}{r} \right)^6 \right)$$

Why is LJ potential 12-6 computationally effective?
Enumeration of square is quick
 $r^{-12} = (r^{-6})^2$.
Repulsion increases exponentially!

Dispersion bound complexes

	$-\Delta E$ (kcal/mol)
Dimers of rare gasses	1 – 2
Benzen dimer (T, PD)	2.5
Stacked DNA bases	10 – 15
Intercalator...WC DNA base pair	30 - 50

DNA with and without dispersion interaction



Černý, J., Kabeláč, M., Hobza, P., J. Am. Chem. Soc., **2008**, 130, 16055

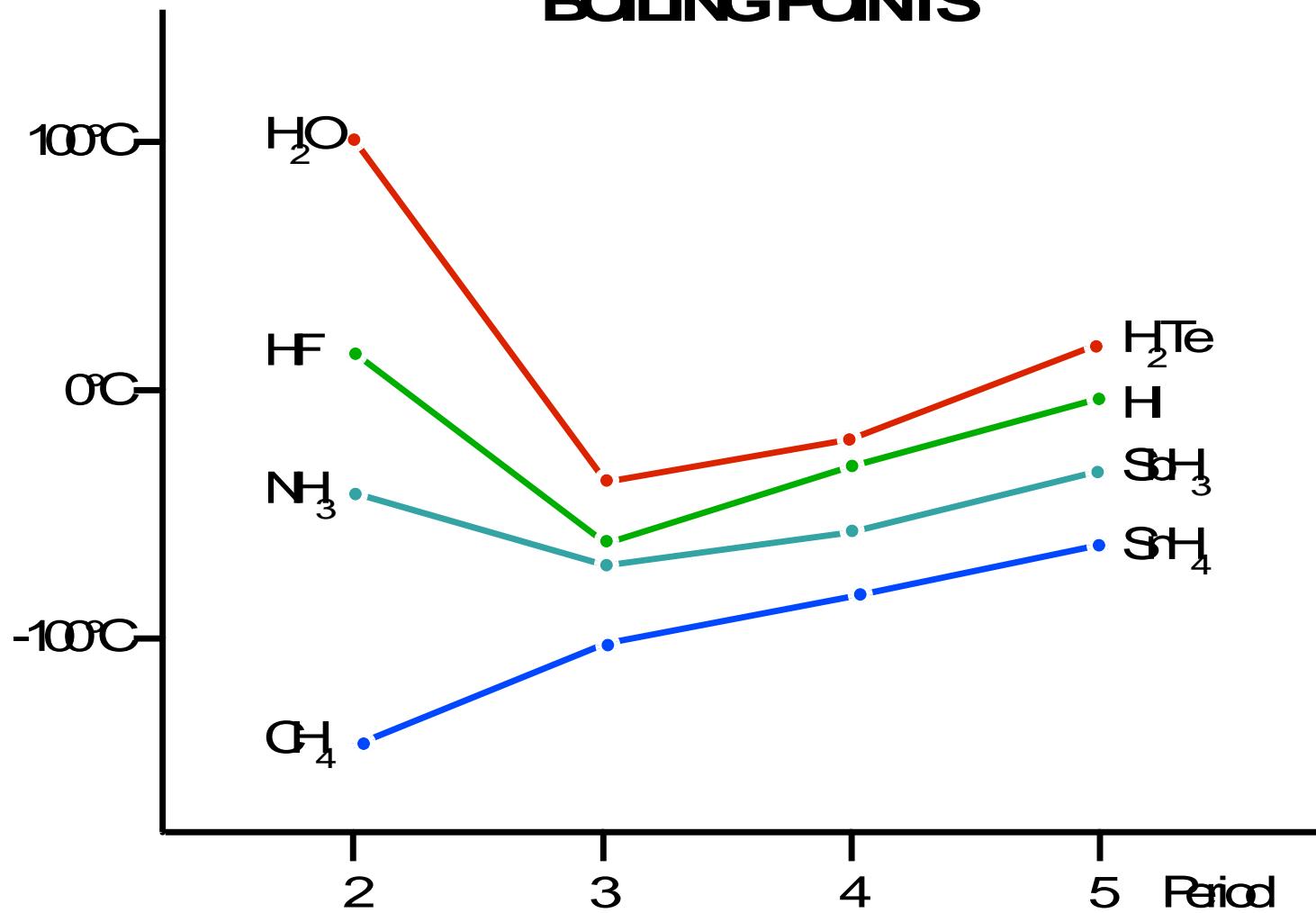
Special types of noncovalent interactions

- ◆ H-bonds (bridges); blues-shifting H-bond
- ◆ Salt bridges
- ◆ π - π , d- π interactions
- ◆ Van der Waals forces
- ◆ Halogen bond
- ◆ Dihydrogen bonds
- ◆ *Hydrophobic effect*

MESS!

Hydrogen bond

BALING PAINTS



Electrostatic Origin of H-bonding



X-H elongates

Elongation of X-H bond increases dipole of donor

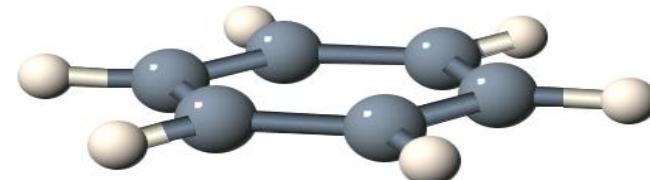
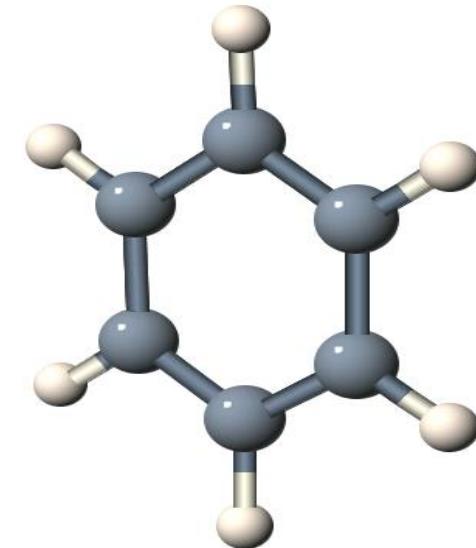
→ ↑ dipole-dipole electrostatic energy

→ ↑ attraction

→ red shift in IR spectrum (longer vibrations)

Improper blue-shifting H-bonding

- *P.Hobza et al.: JPCA 102, 2501 (1998)*
benzene...H-X
(X=CH₃, CCl₃, C₆H₅)
- *P.Hobza, Z.Havlas: Chem. Rev. 100, 4253 (2000)*
improper, blue-shifting hydrogen bond



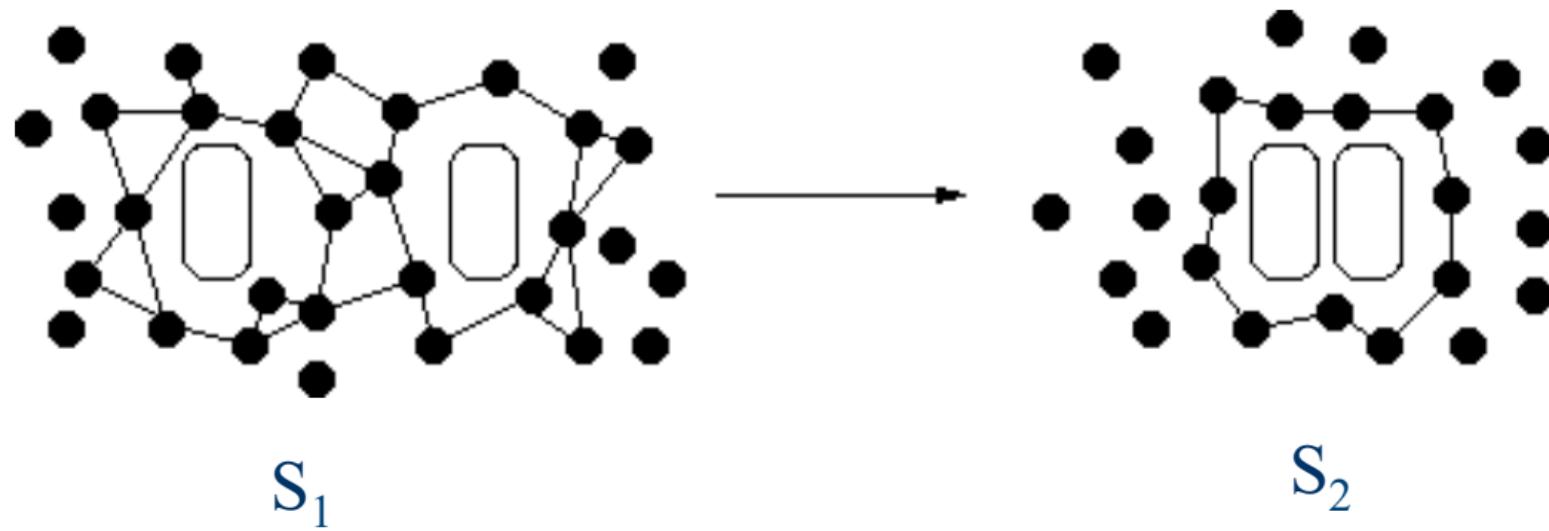
H-bonds

X-H...Y

<i>H-bond</i>	<i>improp. H-bond</i>
Elongation X-H	Shortening X-H
red shift ν	blue shift ν
\uparrow intensity	\downarrow intensity
$\text{H}_2\text{O} \dots \text{HOH}$	$\text{H}_2\text{O} \dots \text{HCX}_3$ (X=F,Cl,Br,I)

Hydrophobic interaction

- Interactions water-waters (~ 5 kcal/mol/atom) are stronger than between nonpolar organic compounds and water (~ 1 kcal/mol/atom)

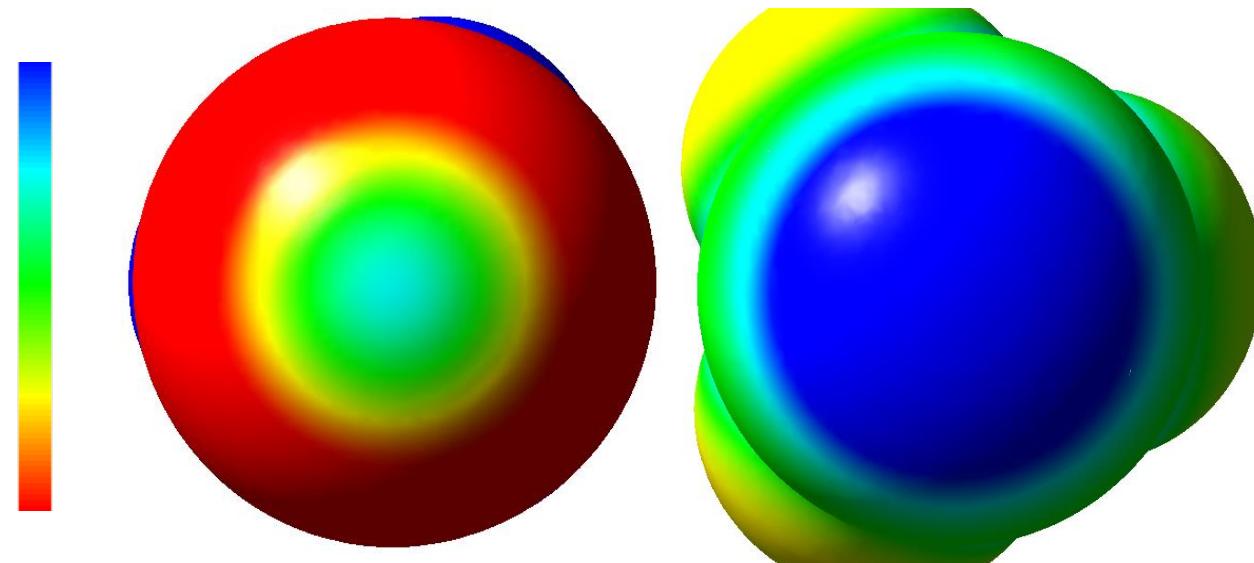


- Entropically advantageous

Halogen bond

C-X...Z-Y

(X=Cl, Br, I; Z=N, O)



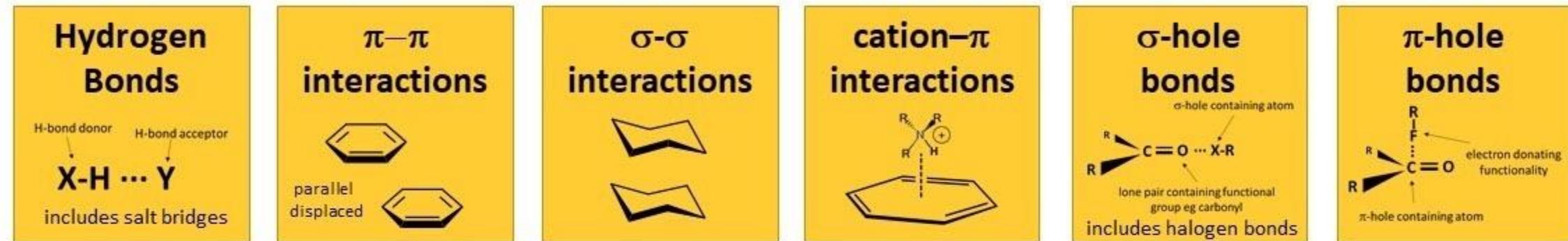
Electrostatic potential for H₃CBr and F₃CBr

Blue – positive, red – negative potential

Strength of Noncovalent interactions

Type of bond	dE (kcal/mol/at.)	Note
Covalent	40-160	C-C is stable bond
Ionic-ionic	~100	Unstable in water
Ionic-dipole	~40	Destroys salt-bridges
Dipole-dipole	1-10	Brings organization
H-bond	~5	Drives hydrophobic effect
VdW	~1	Everything sticks together-> large contact area can be enough

The Six Interaction Classes: Frequencies & Strength

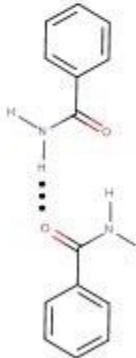


Frequency in
Protein-Ligand
complexes¹

~80% ~10% ~7% ~2% ~0.3% ~0.1%

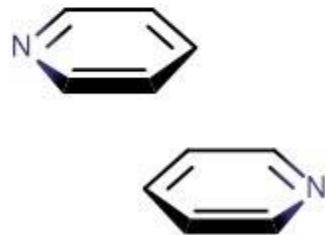
benzamide dimer

$\epsilon = -6.4$ kcal/mol



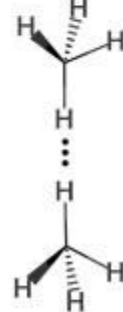
pyridine dimer

$\epsilon = -3.8$ kcal/mol



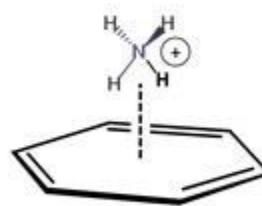
methane dimer

$\epsilon = \sim -0.5$ kcal/mol



methylammonium...benzene

$\epsilon = -19$ kcal/mol



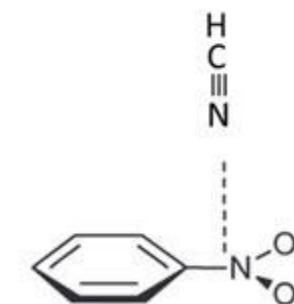
iodobenzene...pyridine

$\epsilon = -2.9$ kcal/mol



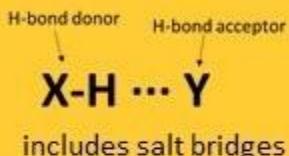
nitrobenzene...N≡CH

$\epsilon = -2.3$ kcal/mol



Gas phase
energy
examples

Hydrogen
Bonds



$\pi-\pi$
interactions



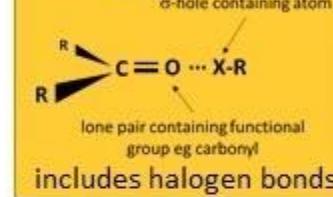
$\sigma-\sigma$
interactions



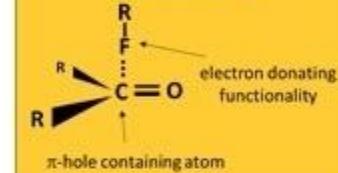
cation- π
interactions



σ -hole
bonds

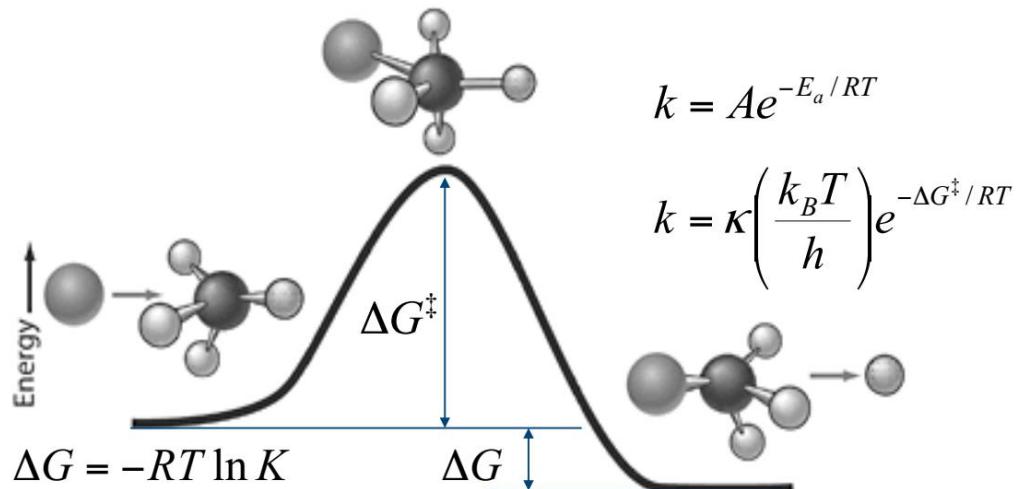
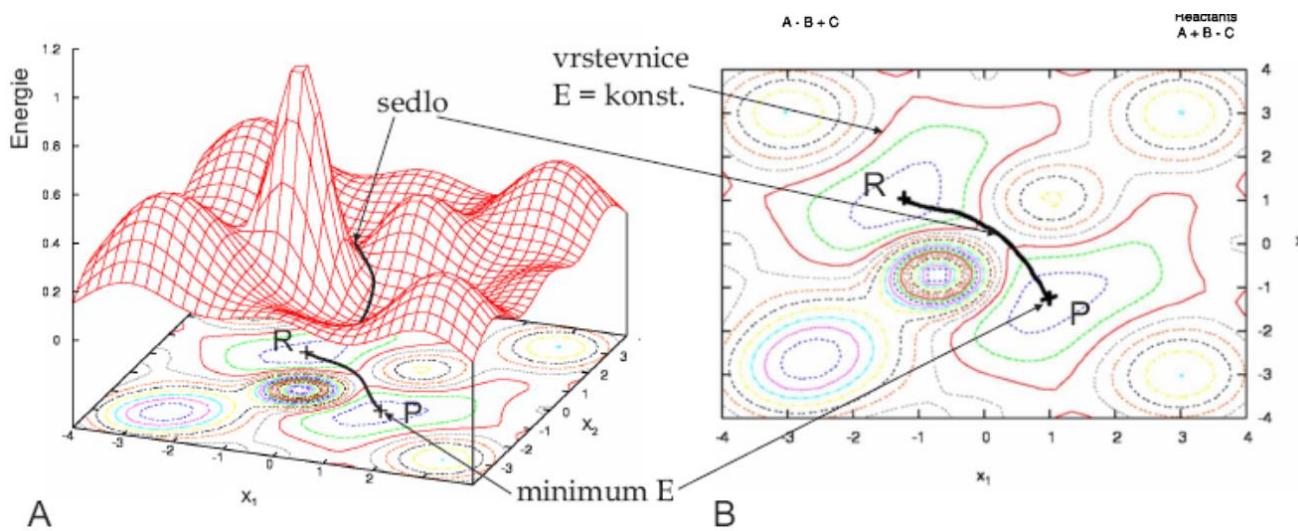


π -hole
bonds



1. de Freitas, Renato Ferreira, and Matthieu Schapira. "A systematic analysis of atomic protein-ligand interactions in the PDB." *Medchemcomm* 8.10 (2017): 1970-1981.

Potential Energy Surface and its exploration



- Minimization
 - Simplex, newton, conjugated gradients
 - Reach closest local minimum
- Grid-based methods
 - Torsional driving
 - Hard to define in multivariable space
- Stochastic
 - Monte Carlo, Simulated Annealing, Genetic algorithms
 - Not always converging to same solution
- Advanced MD sampling techniques
 - Umbrella sampling, METAdynamics, ...
 - Often require Collective variable definition

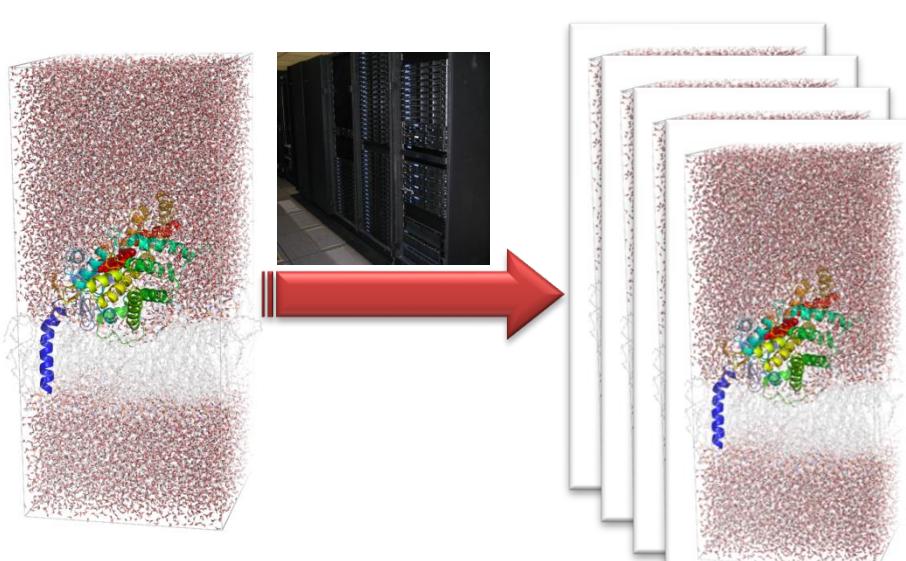
MOLECULAR DYNAMICS

Molecular dynamic simulations

$$\mathbf{x}_i = \mathbf{x}_i^0 + \mathbf{v}_i^0 \Delta t + \frac{1}{2} \mathbf{a}_i^0 \Delta t^2$$

$$\mathbf{F}_i = m_i \mathbf{a}_i = m_i \frac{\partial^2 \mathbf{r}_i}{\partial t^2}$$

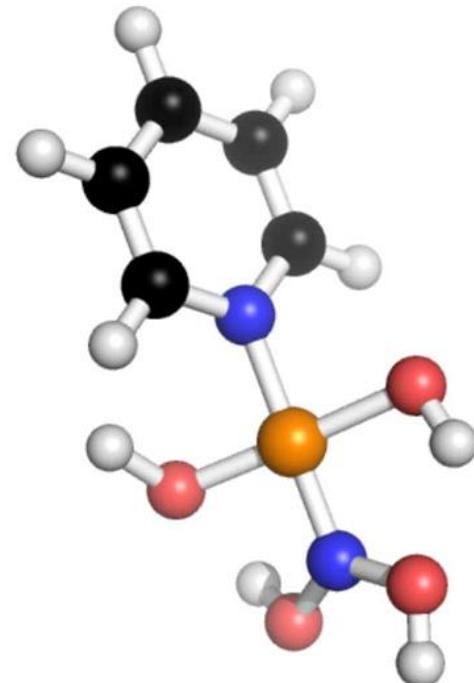
$$\mathbf{F}_i = -\frac{\partial E}{\partial r_i} \frac{\mathbf{r}_i}{r_i}$$



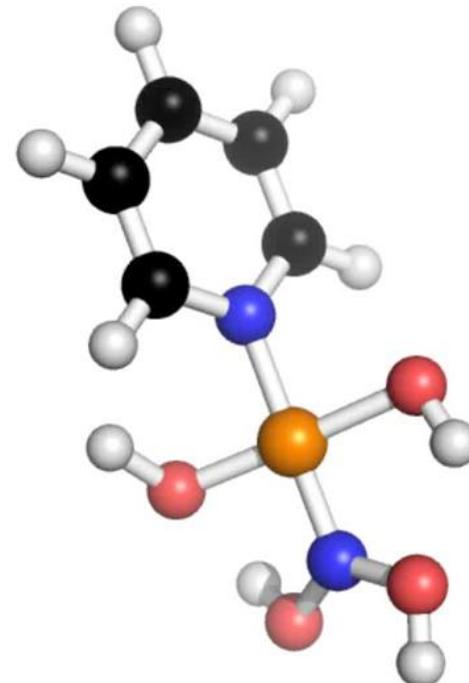
- Positions are calculated from previous step
 - Position
 - Velocity
 - Acceleration
- Acceleration (Force) is derivative of Energy of interactions – potential -> force field
- Atomic resolution
- Sub-ps time resolution ($\Delta t = 2$ fs)
- Large data ($1 \mu s = 10^9$ fs)

MM vs MD

- Molecular Mechanics



- Molecular Dynamics

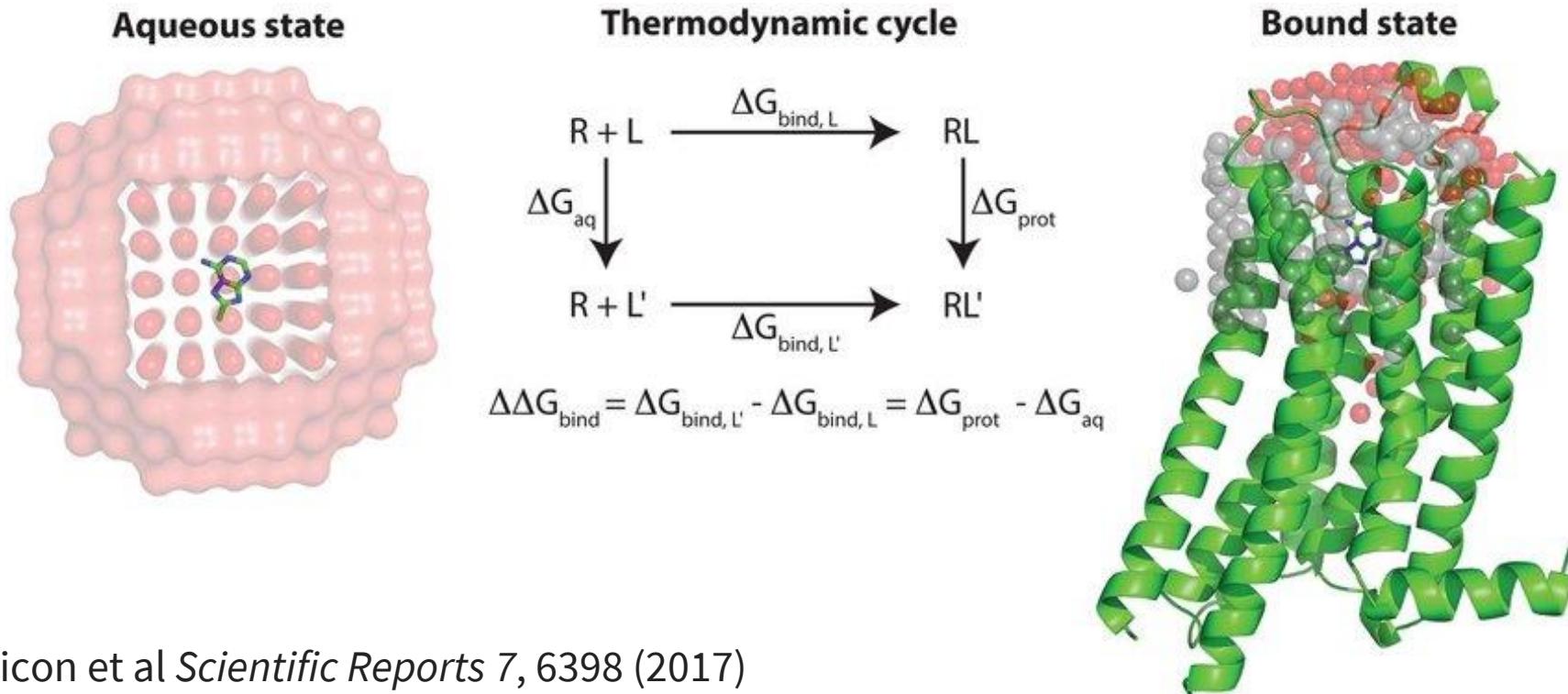


Important parameters

- Force field
 - Polarizable:
 - AMOEBA, Amber02, CHARMM, Drude, CHEQ,...
 - Atomistic:
 - **Amber**, CHARMM, GROMOS, OPLS-AA, MMFF, OpenFF, ...
 - Coarse grain:
 - MARTINI, UNRES, SIRAH, Go, ...
- Time step
 - 1fs (optimization), 2fs (atomistic), 5fs (virtual sites), 20fs (coarse grain)...
- Temperature termostats
 - Berendsen, Nose-Hoover, **V-rescale**, Andersen, Langevin
- Pressure barostats
 - isotropic x anisotropic (membranes)
 - Berendsen, Andersen,
- Periodic box size and shape

MD usability

- Account for flexibility of receptor
- Optimization of structure
- Include solvent effect
- Include induced fit effect
- Confirm poses – refinement
- Calculate more accurate $\Delta G_{\text{binding}}$
- Alchemical $\Delta\Delta G$ values



TAKE HOME MESSAGE

Take Home Message

- Molecular mechanics is an approximation of molecular interactions
- Error-cancelation in most terms
- Noncovalent interactions are strong in weakness
- Chemistry is hiking on potential energy surface
- Molecular dynamics gives additional information

