CEITEC
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Chemo part of Glycoinformatics: Molecular Modeling

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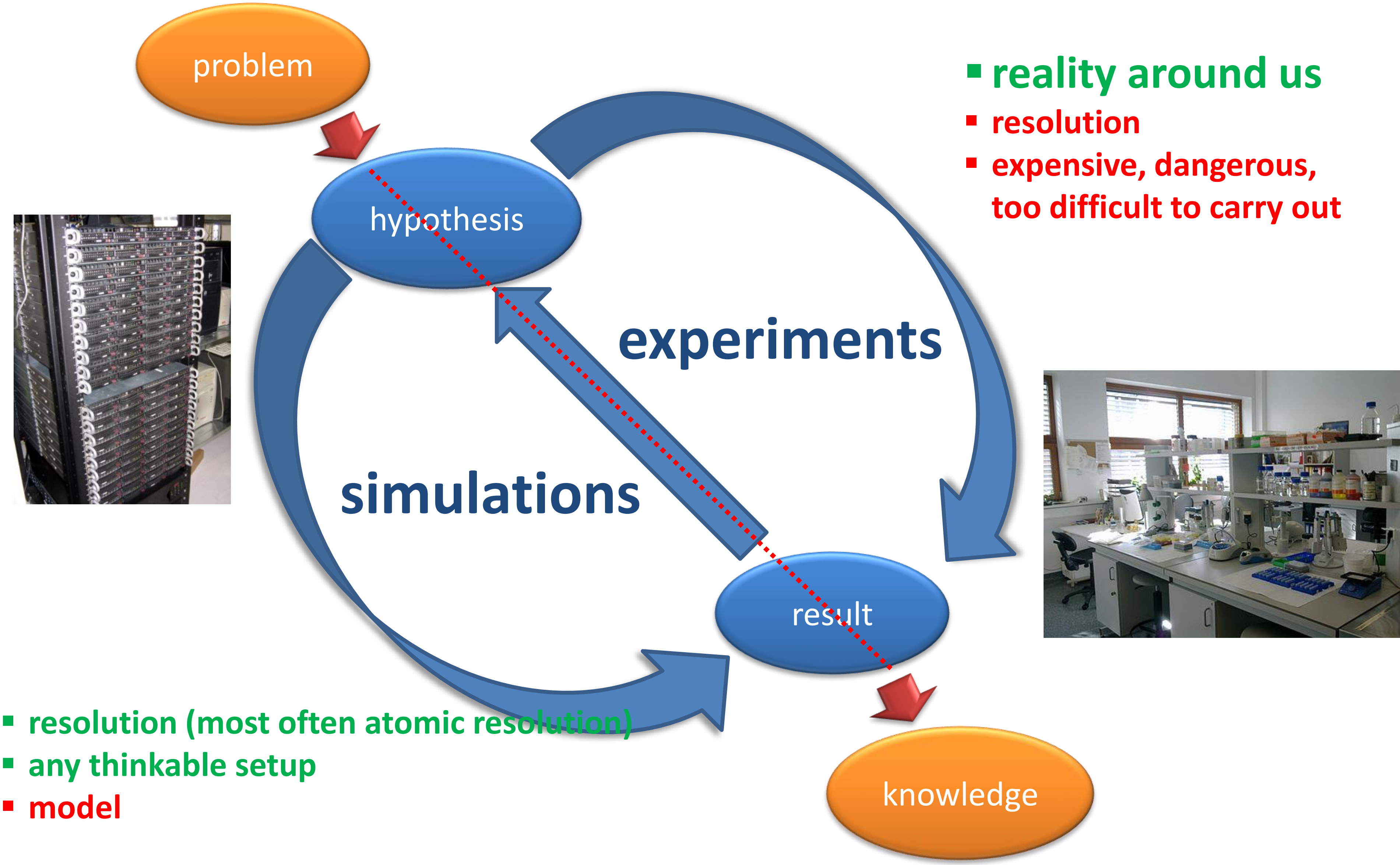
Experiment vs Simulations

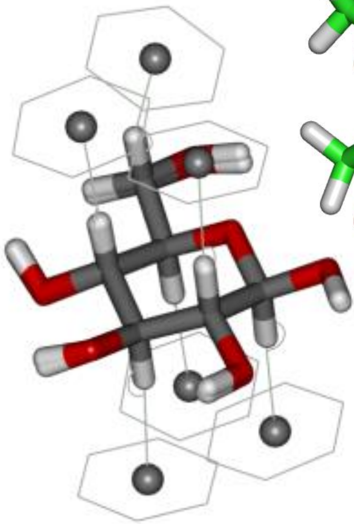


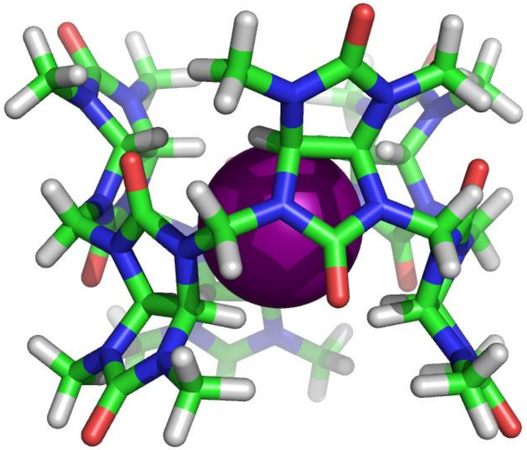
- reality around us
- resolution
- expensive, dangerous, too difficult to carry out

- resolution (most often atomic resolution)
- any thinkable setup
- model

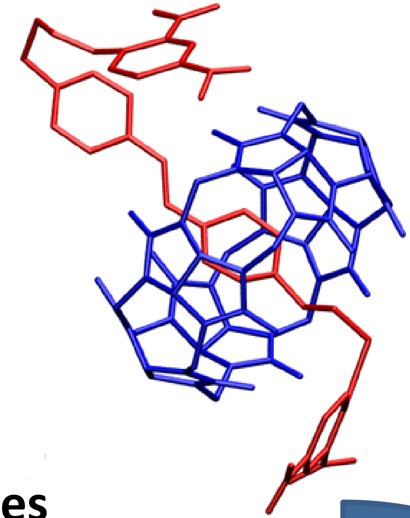
What can be studied?

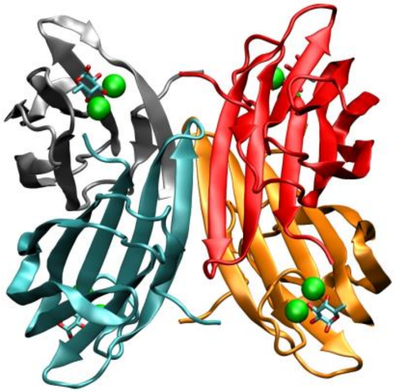
atomic resolution

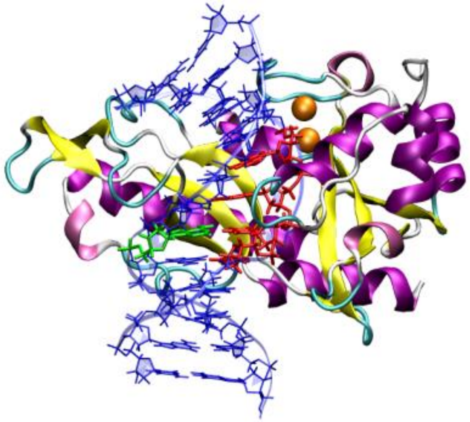




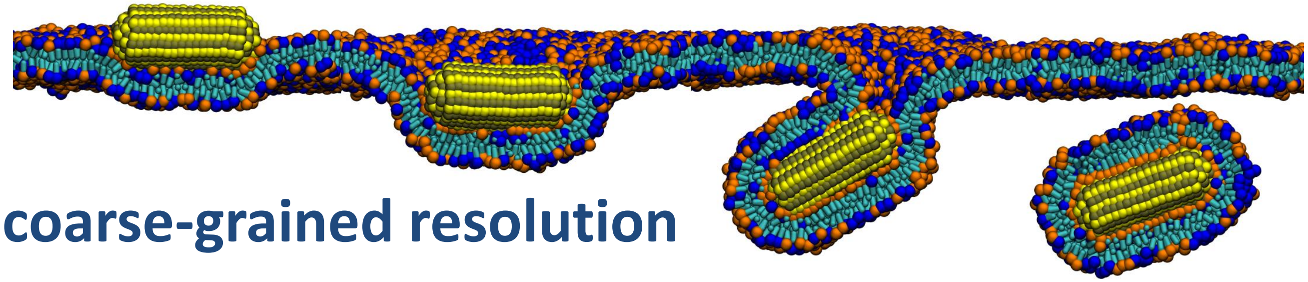
"small" complexes





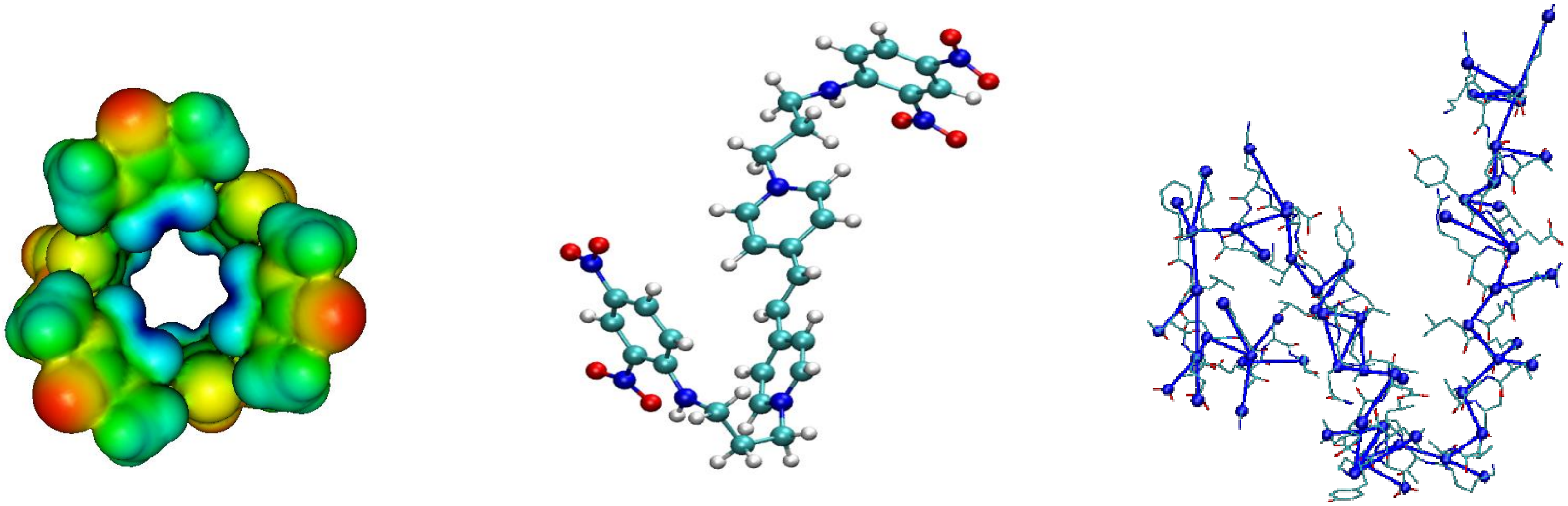


biomolecular systems



coarse-grained resolution

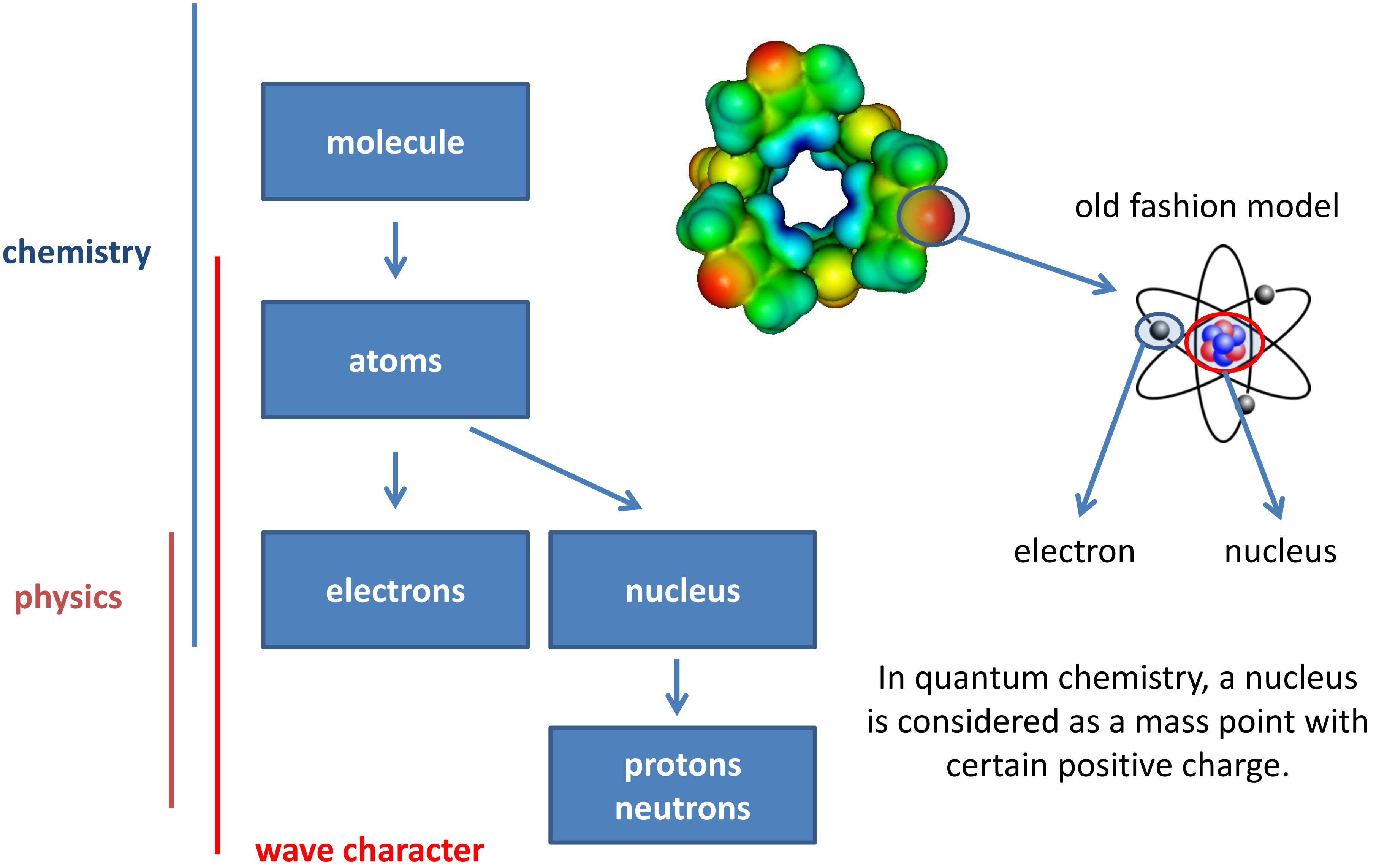
Levels of Theory



Quantum Mechanics	Molecular Mechanics	*Coarse-grained* Mechanics
Atomic Resolution		Bead Resolution
reactivity	conformational movement	domain movement, folding
up to 1'000 atoms	up to 1'000'000 atoms	up to 1'000'000 beads
up to 100 ps	up to µs	up to ms

Quantum Mechanics

Composition of Molecules



chemistry

physics

wave character

molecule

atoms

electrons

nucleus

protons
neutrons

old fashion model

electron

nucleus

In quantum chemistry, a nucleus is considered as a mass point with certain positive charge.

Schrödinger Equation

Due to **wave character of particles** (electrons and nuclei) it is necessary to solve the **Schrödinger equation**. Its **time dependent** version is however very difficult to solve and moreover it **does not provide** any information about **energy** of studied system due to the uncertainty principle. This can be overcome by neglecting time and introducing so called stationary states.

The **time-independent** Schrödinger equation:

(positions of electrons **and** nuclei)

$$\boxed{\hat{H}\psi_k(\mathbf{r}) = E_k\psi_k(\mathbf{r})}$$

Hamilton operator
(it defines a **system**, etc. number of particles and their mutual interactions)

wavefunction
(it determines a **state** of the system)

\+

the **energy** of state

Solutions are couples: ψ_k a E_k. They represents full description of **allowed system stationary states** and their energies.

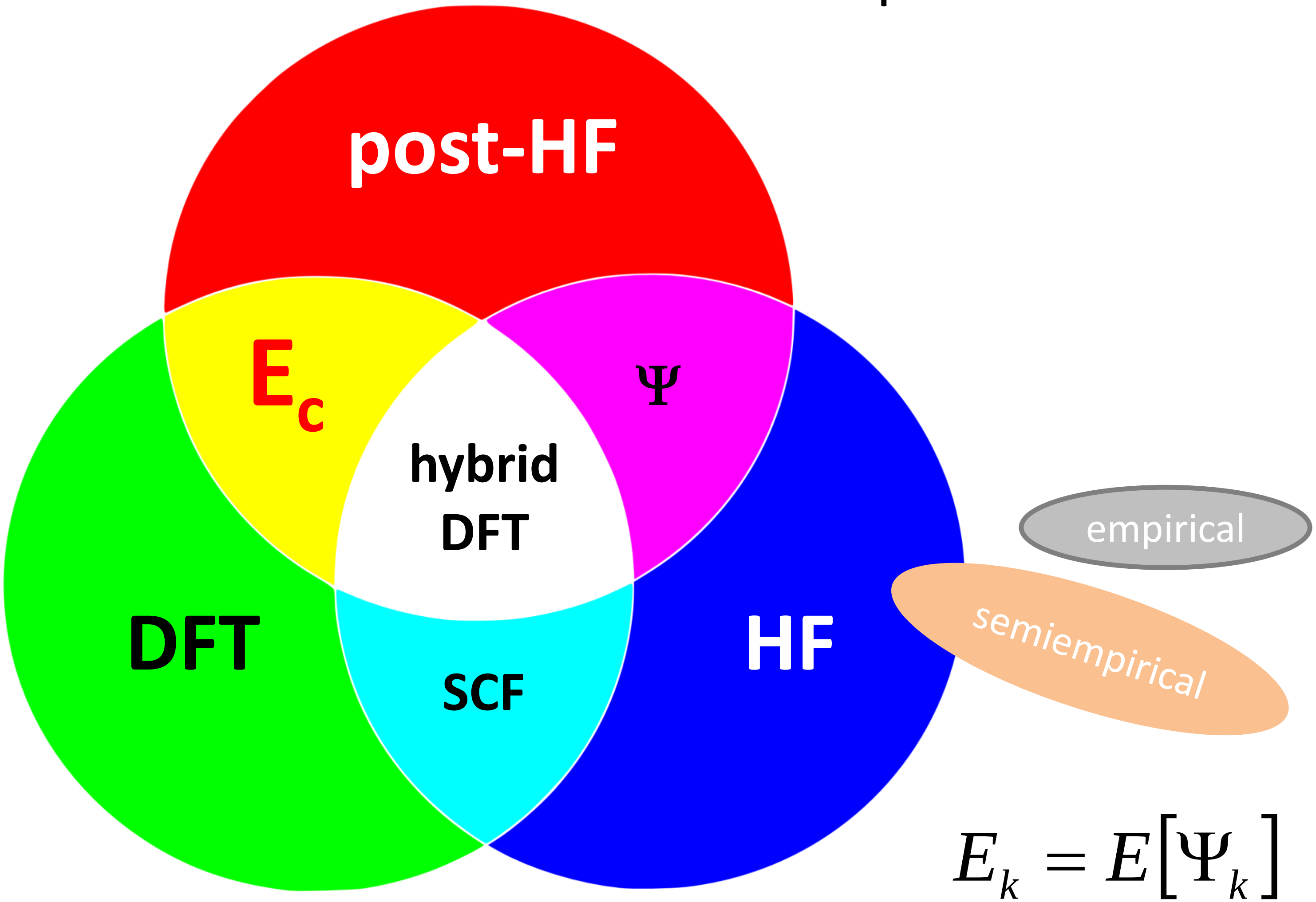
Basic Approximations

Even **time-independent** Schrödinger equation is very difficult to solve for "large" molecular systems (two and more atoms, two and more electrons). Therefore several fundamental approximations were introduced in the past:

- **Born-Oppenheimer approximation** – separation of motions of nuclei and electrons, which provides energy of the system as a function of atomic coordinates (PES - **potential energy surface**)
- **One-electron approximation** – it allows to solve SE of many-electron systems at all but it also introduces a **significant error** that is called the **correlation energy**
- **MO-LCAO** – approximate description of one-electron wavefunction as a linear combination of atomic orbitals (basis functions). It can provide an exact solution in the limit of **complete basis set**.

Classifications of Methods

variational + perturbation



$$E_k = E[\rho_k]$$

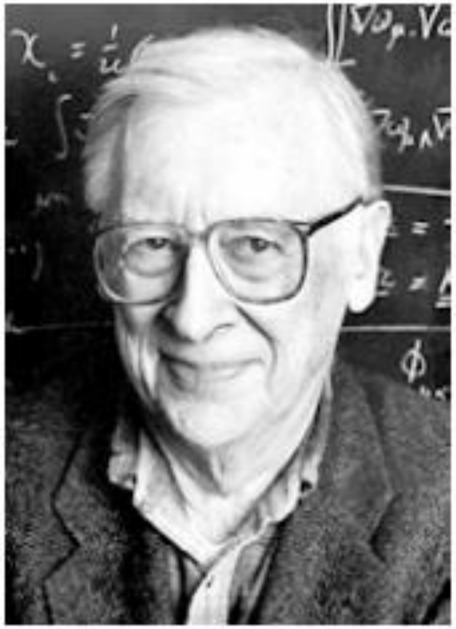
$$E_k = E[\Psi_k]$$

variational

Andrew Gilbert

The Nobel Prize in Chemistry 1998

Walter Kohn



John A. Pople

The Nobel Prize in Chemistry 1998 was divided equally between **Walter Kohn** "for his development of the **density-functional theory**" and **John A. Pople** "for his development of **computational methods in quantum chemistry**"

http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1998/

Computational Complexity

			Methods	
Formal Scaling	**HF**	**CI metods**	**MP metods**	**CC metods**
N^4 -> N^2 -> N^1	HF, DFT			
N^5			MP2	CC2 (iterative)
N^6		CISD	MP3, MP4(SDQ)	CCSD (iterative)
N^7			MP4	CCSD(T), CC3 (iterative)
N^8		CISDT	MP5	CCSDT
N^9			MP6	
N^{10}		CISDTQ	MP7	CCSDTQ (iterative)

Legend

HF – Hartree-Fock method

DFT – density functional theory methods
CI – configuration interaction methods
MP - Møller–Plesset perturbation methods
CC – coupled cluster methods

N – number of basis functions

$$N \approx N_A \overline{N_{BF}}$$

Methods highlighted in the box can provide results, which include part of omitted correlation energy.

Complexity & Accuracy

	Methods			
Formal Scaling	**HF**	**CI metods**	**MP metods**	**CC metods**
N^4 -> N^2 -> N^1	HF, DFT			
N^5			MP2	CC2 (iterative)
N^6		CISD	MP3, MP4(SDQ)	CCSD (iterative)
N^7			MP4	CCSD(T), CC3 (iterative)
N^8		CISDT	MP5	CCSDT
N^9			MP6	
N^{10}		CISDTQ	MP7	CCSDTQ (iterative)

N – number of basis functions

$$N \approx N_A \overline{N_{BF}}$$

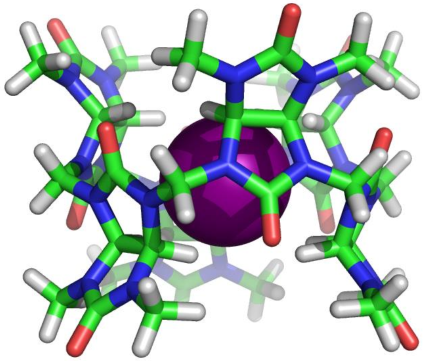
Coupled cluster methods are able to reach **chemical accuracy** but only for small molecules.
On currently available hardware, it is possible to apply the CCSD(T) method to systems containing up to **50 atoms**.

Accuracy

Small Numbers from Big Numbers

RI-BLYP-d3/def2-TZVPP (vacuum)

```
BU6/I(-) -4152.181032604 Hartree
BU6      -3854.321084579 Hartree
I(-)      -297.740268591 Hartree
         ----------------
             -0.119679434 Hartree
                  ~ -75.1 kcal/mol
```



bambus[6]uril/anion interaction
(139 atoms)

"Chemical" Accuracy

error < 1 kcal mol^{-1}

Accuracy

Small Numbers from Big Numbers

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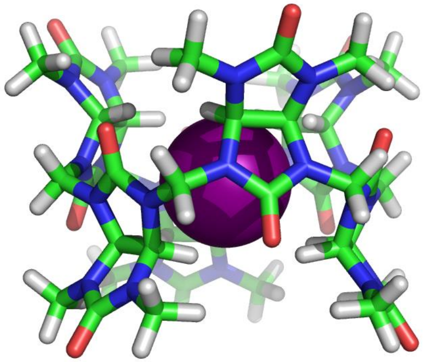


bambus[6]uril/anion interaction
(139 atoms)

"Chemical" Accuracy

error < 1 kcal mol^{-1}

Take Home Message

Quantum Mechanics

- **due to dual character** (particles/waves) of electrons and nuclei, any chemical system has to be described by the **Schrödinger equation** (SE)
- albeit very simple notation of SE, its **analytical** solution is not impossible even for simple chemical systems (two and more electrons)
- **several approximations** were introduced that make **numerical** solution of SE possible but some of them introduces very **serious errors** (correlation energy)
- it is possible to fix these errors but procedures are very **computationally demanding** even for small systems (up to 50 atoms)
- once **approximate solution** of SE is known then **any property** (including energy) can be easily obtained from **wavefunction of given state**
- SE is naturally able to describe **chemical reactions**

Molecular Mechanics

Can we make calculations faster?

Molecular Mechanics

Schrodinger equation - quantum mechanical description

$$\hat{H}\psi_k^{\mathbf{R}}(\mathbf{r}_e) = \boxed{E_k(\mathbf{R})}\psi_k^{\mathbf{R}}(\mathbf{r}_e)$$

approximation
electron motions is omitted
(electron motions is implicitly included in empirical parameters)

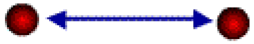
$$E_k(\mathbf{R}) = \underbrace{E_{bonds} + E_{angles} + E_{torsions}}_{\text{bonded contributions}} + \underbrace{E_{ele} + E_{vdw} + \ldots}_{\text{non-bonded contributions}}$$

Classical physics - mechanical description

Bonded Contributions

Bonds

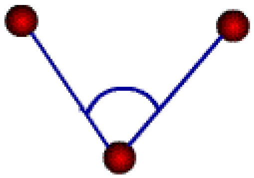
$$E_{bonds} = \sum_{b=1}^{bonds} \frac{1}{2} K_b (d_b - d_{b0})^2$$



Bond stretching

Angles

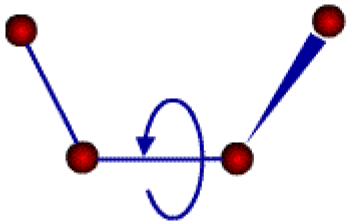
$$E_{angles} = \sum_{a=1}^{angles} \frac{1}{2} K_a (\theta_a - \theta_{a0})^2$$



Angle Bending

Torsion angles

$$E_{torsions} = \sum_{t=1}^{torsions} \sum_{n} \frac{V_{t,n}}{2} \left(1 + \cos\left[n\varphi_t - \delta_{t,n}\right]\right)$$



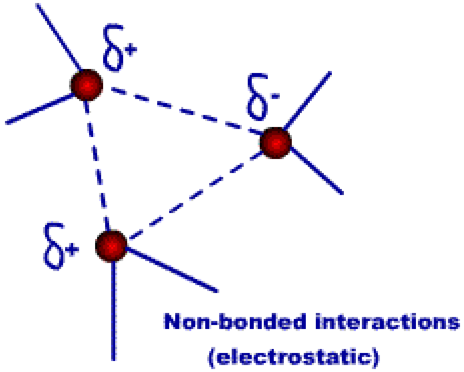
Bond rotation (torsion)

🟥 **empirical parameters**

Non-bonded Contributions

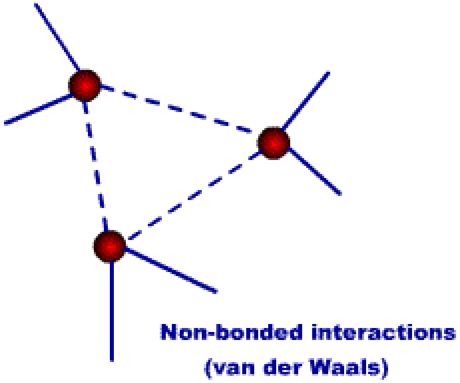
Electrostatic interactions

$$E_{ele} = \sum_{i=1}^{N} \sum_{j=i+1}^{N} \frac{1}{4\pi\varepsilon_o} \frac{q_i q_j}{r_{ij}}$$



van der Waals interactions

$$E_{ele} = \sum_{i=1}^{N} \sum_{j=i+1}^{N} 4\varepsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right]$$



PME – particle meshed Ewald (N $\log_2$ N)

N – number of atoms

🟥 **empirical parameters**

Take Home Message

Molecular Mechanics

- based on **classical mechanics**, **accuracy is compromised**
- **empirical parameters (parameter set, force field)** derived from experimental or high-level QM calculations are required
- **parameter transferability problems**, parameters are derived for limited set of systems (proteins, nucleic acids, lipids, saccharides, etc), no general parameter set yet
- **very fast calculations** of systems containing up to millions of atoms
- electrons are not explicitly accounted in the theory thus it is **not possible** to describe **chemical reaction** (exceptions: ReaxFF, EVB)
- suitable for study of **conformational changes and structure**

Potential Energy Surface

Configuration Space

$$\boxed{E(\mathbf{R})}$$

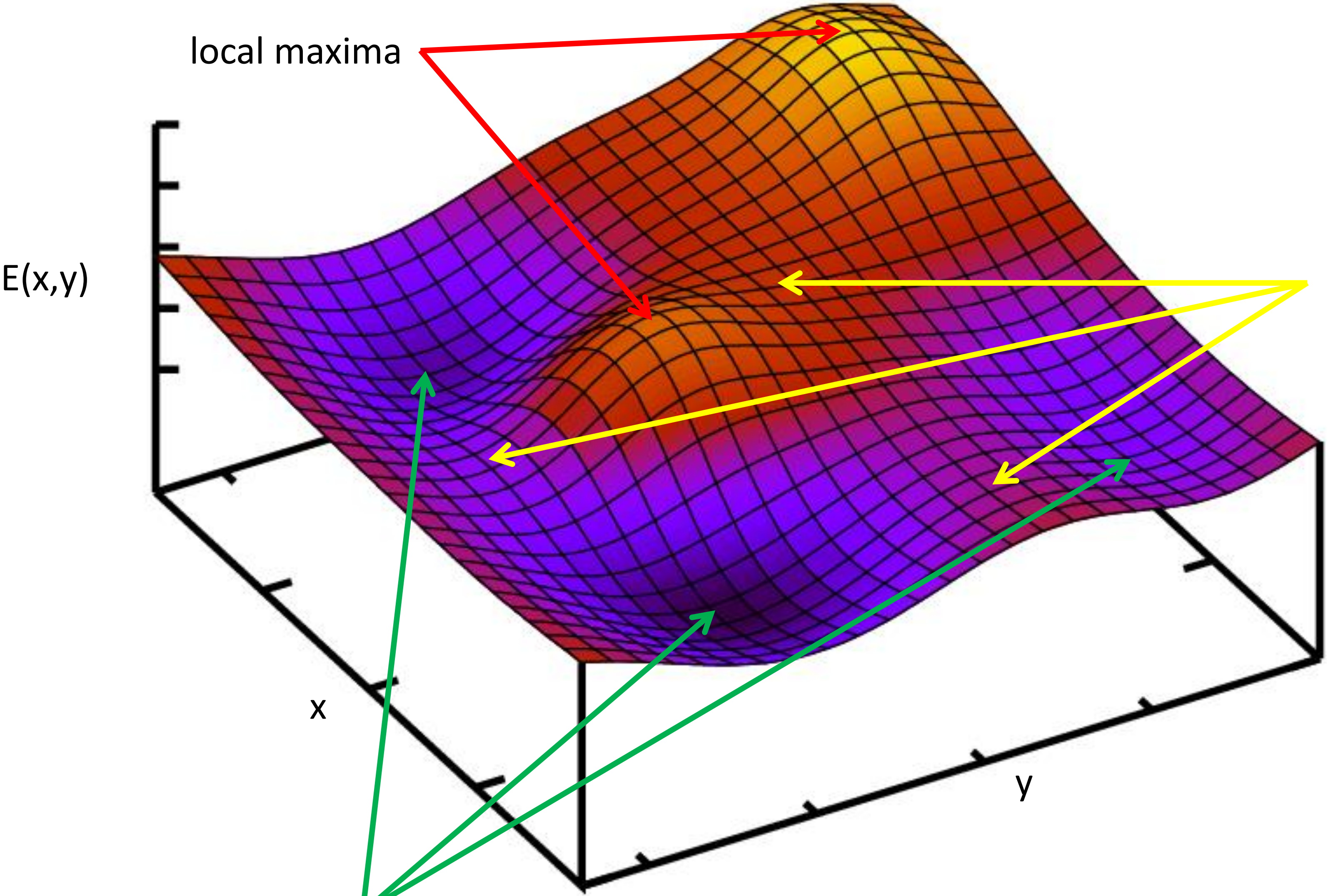
R = point in 3N-dimensional space (N is number of atoms)

$$\mathbf{R} = \{\underline{x_1, y_1, z_1}, x_2, y_2, z_2, \ldots, x_N, y_N, z_N\}$$

Cartesian coordinates
of the first atom

Individual points form the **configuration space**.
Every point in the configuration space represents
a **unique structure** of studied system.

Two-dimensional Case



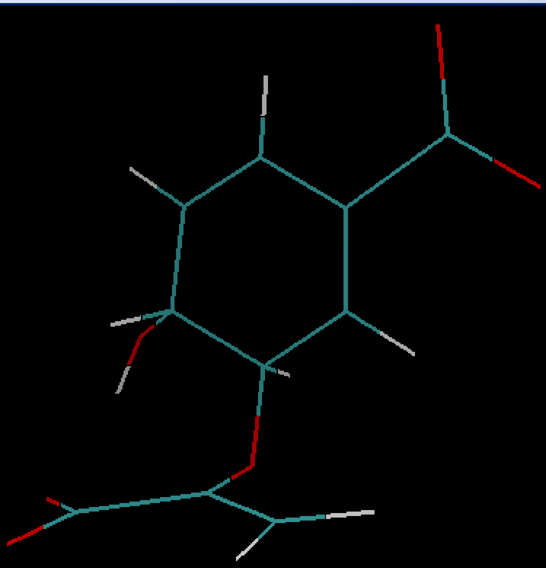
local maxima

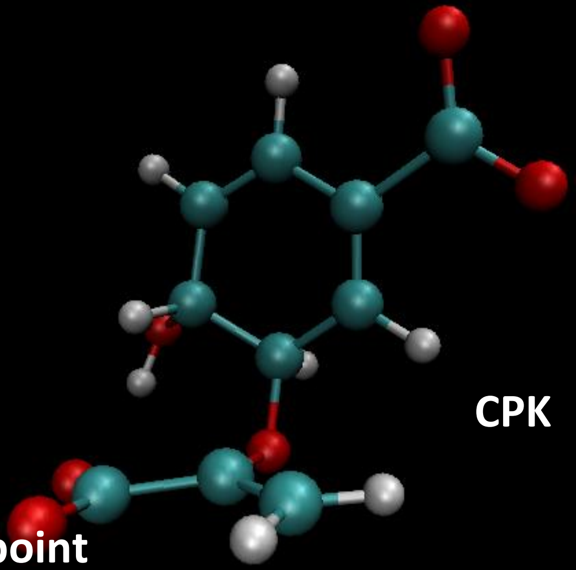
saddle points

local minima

Models – small molecules

lines

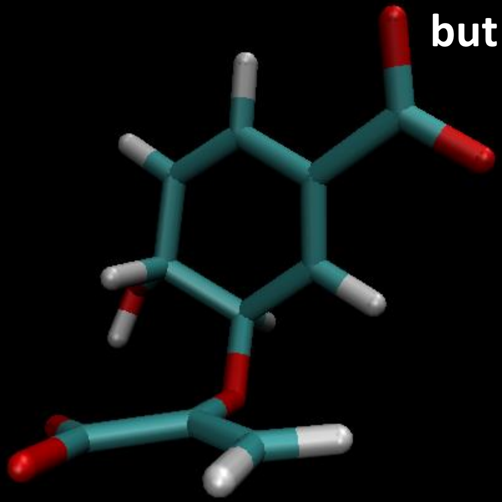


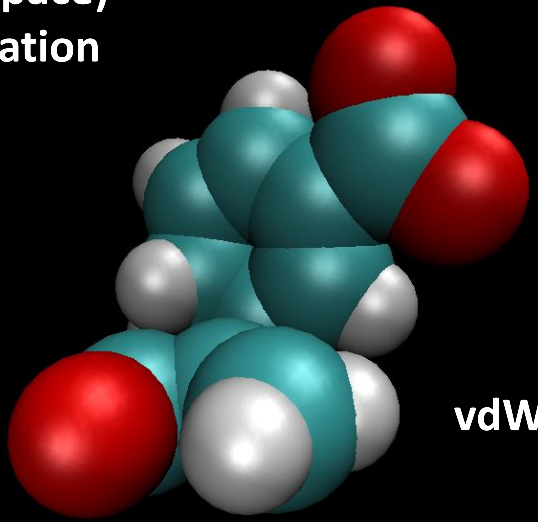


CPK model

the same structure (point in the configuration space) but different visualization

tubes

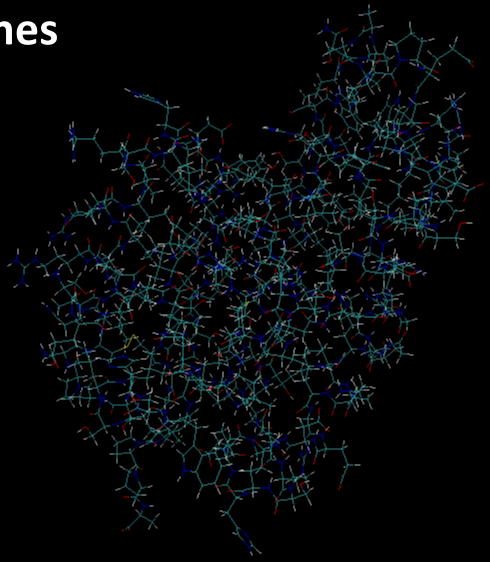




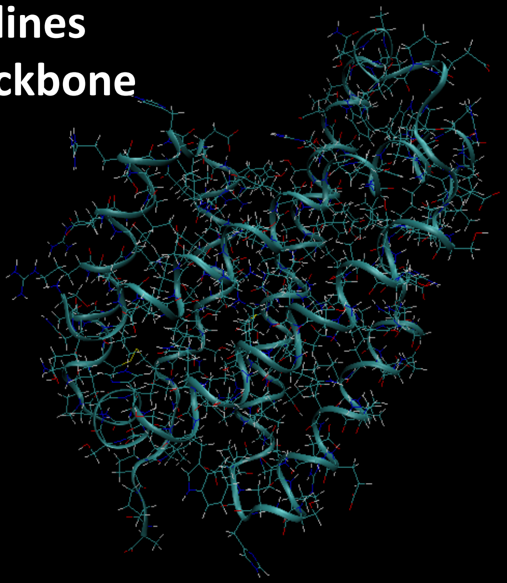
vdW model

Models – biomolecules

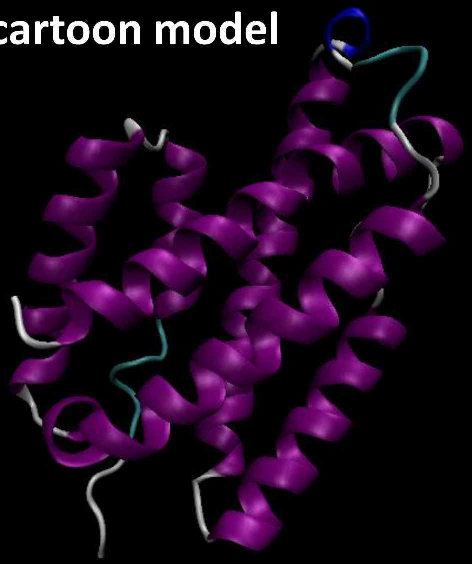
lines



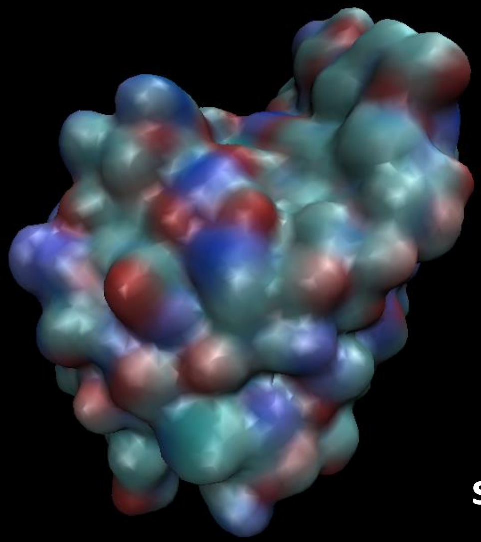
lines
backbone



cartoon model



the same structure (point in the configuration space) but different visualization



surface

Different visualization models are used to depict various structural features or internal properties of molecules or molecular assemblies, which then improve perceptions of studied systems/problems.

Take Home Message

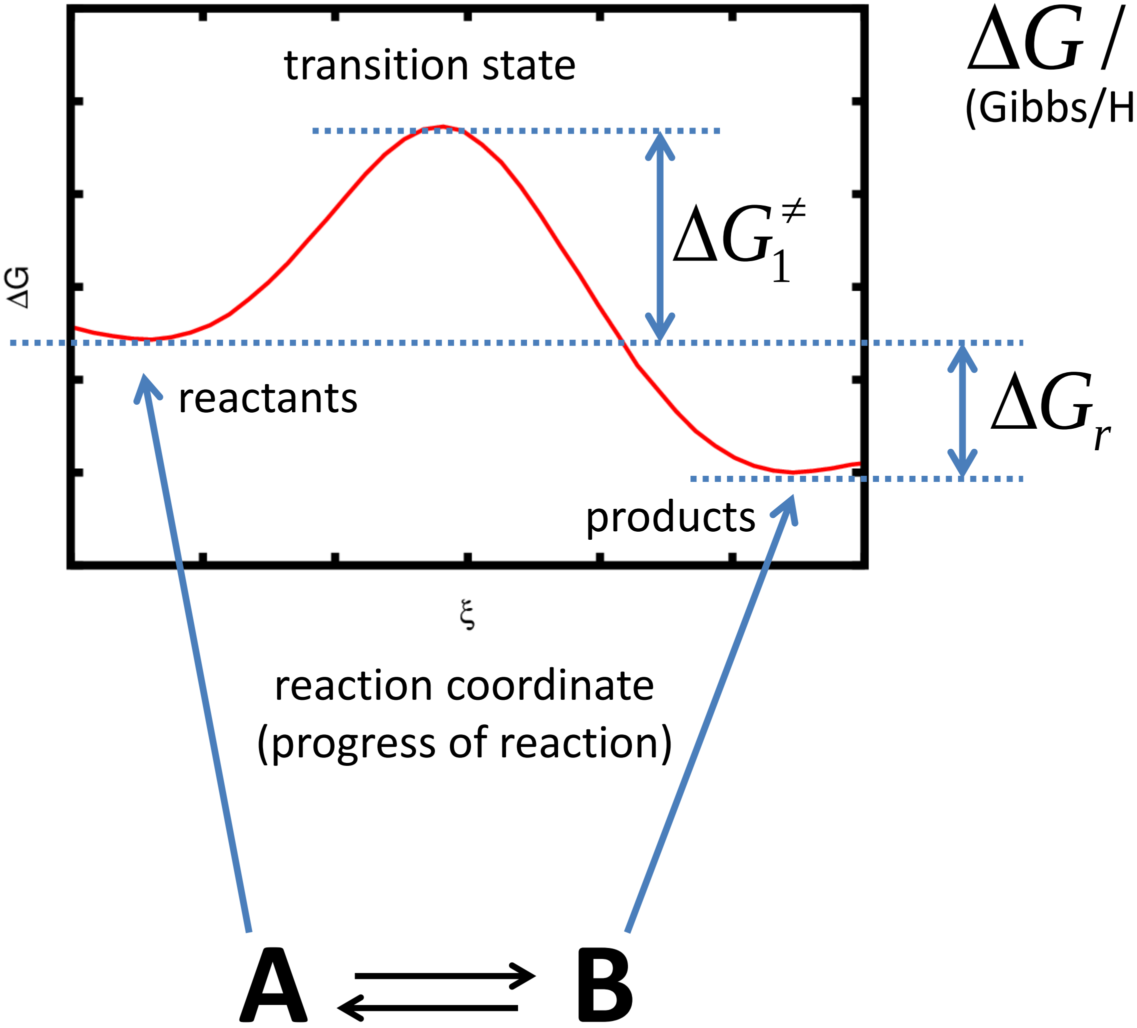
Potential Energy Surface

- stationary points (**local minima** and **saddle points**) are very important for description of reactivity and kinetics of small molecular systems
- stationary points represents **unique structures** of molecular system

Macroscopic Systems

Back to origin of our interest ...

Thermodynamics & Kinetics



$\Delta G / \Delta A$ is change of the free energy (Gibbs/Helmholtz energy)

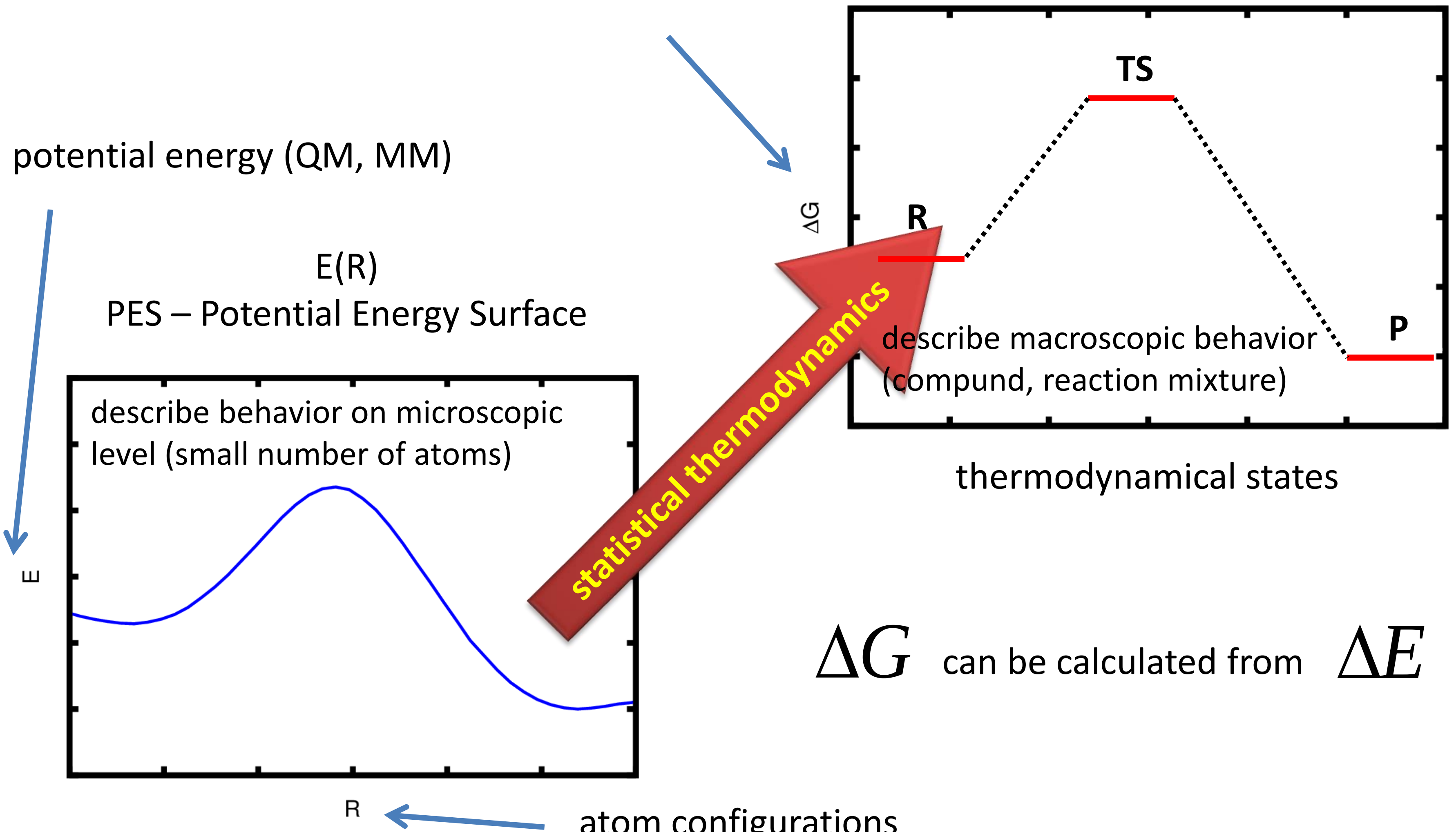
$$k = \kappa \frac{k_B T}{h} e^{-\frac{\Delta G^{\neq}}{RT}}$$

rate constant

equilibrium constant

$$\Delta G_r = -RT \ln K$$

PES vs Free Energy



Gibbs (free) energy

potential energy (QM, MM)

E(R)
PES – Potential Energy Surface

describe behavior on microscopic level (small number of atoms)

describe macroscopic behavior (compund, reaction mixture)

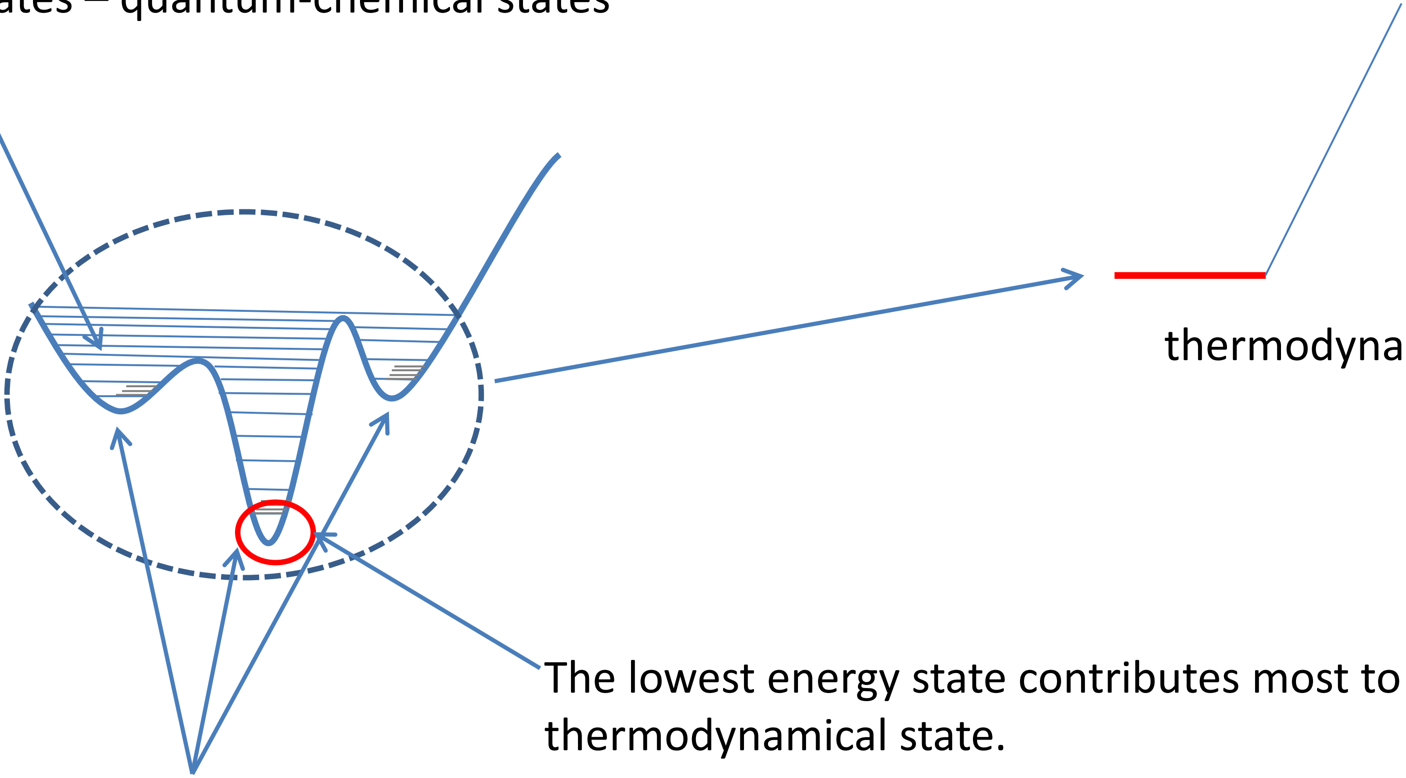
thermodynamical states

ΔG can be calculated from ΔE

atom configurations

Thermodynamical vs QM state

Thermodynamical state (macro state) **is assemble of quantum-chemical states** (microstates), which are energetically accessible under given conditions (temperature, pressure).



microstates – quantum-chemical states

thermodynamical state

The lowest energy state contributes most to the thermodynamical state.

etc conformations

Molecular Dynamics

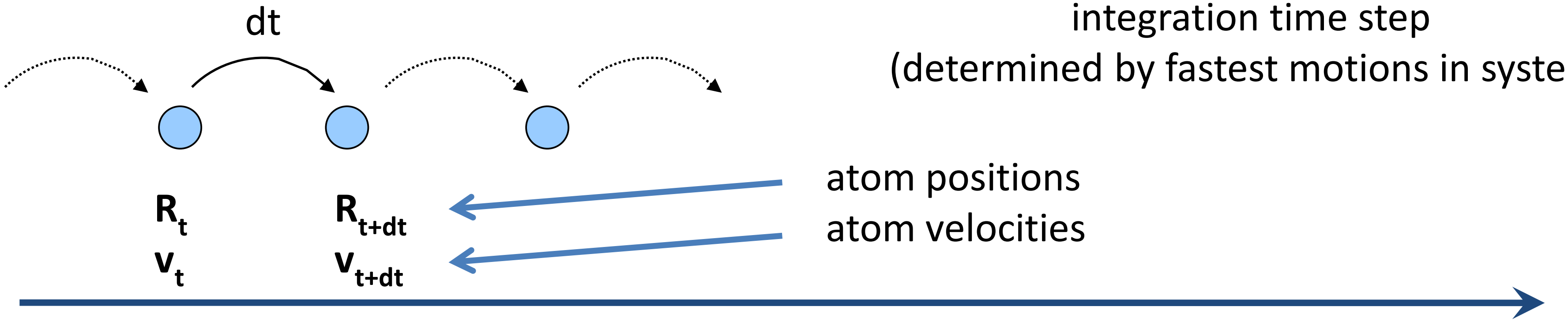
How to get thermodynamical parameters of complex systems ...

Molecular Dynamics

Evolution of system in time

dt = 1fs

integration time step
(determined by fastest motions in system)



dt

$\mathbf{R}_t$
$\mathbf{v}_t$

$\mathbf{R}_{t+dt}$
$\mathbf{v}_{t+dt}$

atom positions
atom velocities

trajectory

Equation of Motions

$$-\frac{\partial^2 E(\mathbf{R})}{\partial \mathbf{r}_i^2} = m_i \frac{d^2 \mathbf{r}_i}{dt^2}$$

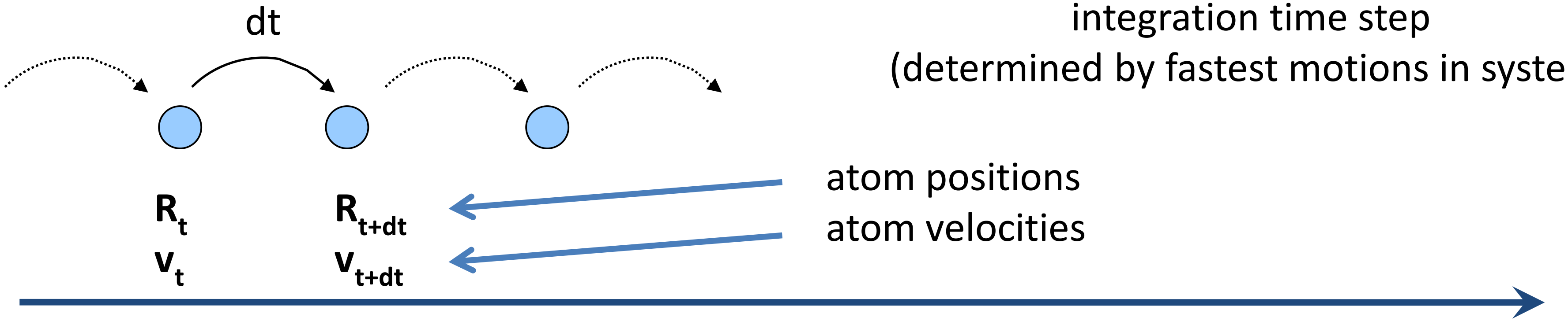
$$\boxed{\mathbf{F}_i = m_i \mathbf{a}_i}$$

Molecular Dynamics

Evolution of system in time

dt = 1fs

integration time step
(determined by fastest motions in system)



trajectory

Sampling problem

1 μs = 10^9 fs

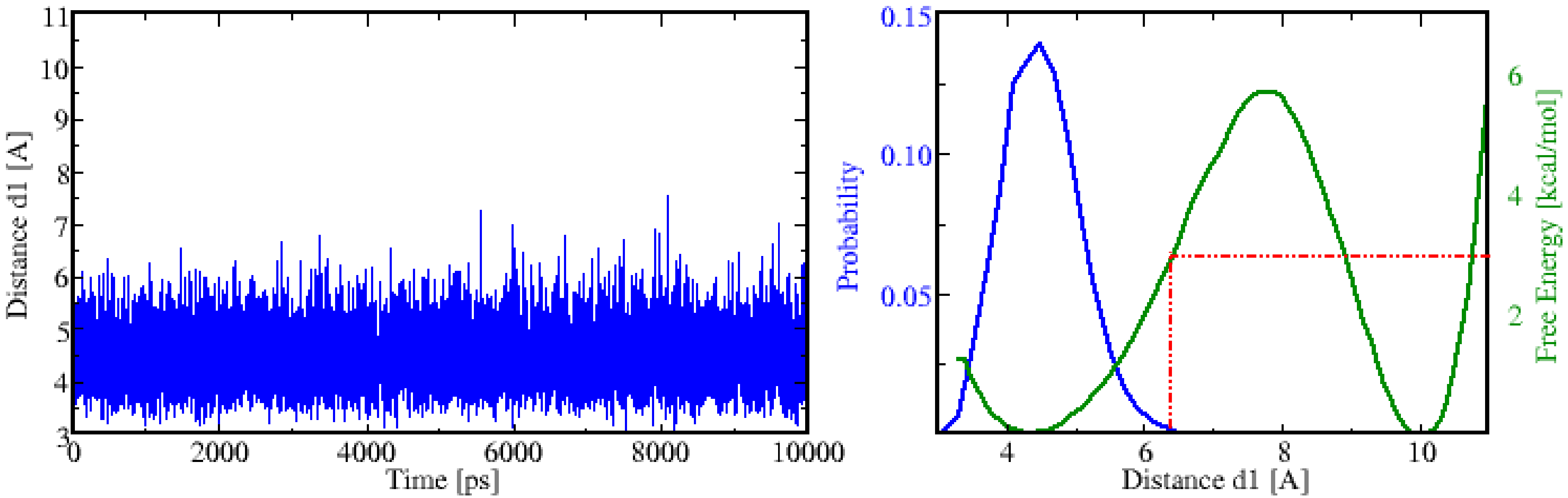
1631 atoms, AMBER, GPU acceleration

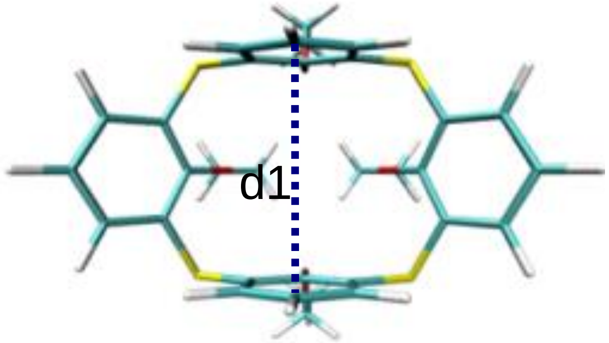
1 step ~ 1 ms CPU/GPU time
10^9 steps ~ 12 days CPU/GPU time

Characteristic timescales:

- Protein folding (ms)
- Chemical reactions (ms, s, h)

Sampling Problem





10 ns long simulation is able to discover free energy landscape with depth only about **3 kcal/mol**.

Free Energy Calculations

A system has to be **biased** achieving efficient sampling in the region of interest. We need to know how to obtain the **unbiased free energy** from such biased simulation.

Available methods:

- ***constrained dynamics***

  system is biased by constraining reaction coordinate
- ***adaptive biasing force***

  system is biased by force which is opposite to potential of mean force
- ***umbrella sampling***

  system is biased by restraining reaction coordinate
- ***metadynamics***

  system is biased by Gaussian hills, which fill free energy landscape

Free Energy Calculations

Alchemical Transformation

one system is slowly changed to another one (changes are very often unrealistic, atoms are created and/or annihilated)

what: mostly *changes* in binding free energies:

how: thermodynamic integration (TI), free energy perturbation (FEP)

Potential of Mean Force

system is changed along reaction coordinate

what: free energy of conformation changes, **reaction free energies**

how: constrained dynamics, adaptive biasing force, umbrella sampling, metadynamics, steered dynamics

End-points Methods

free energy of every state is calculated independently

what: mostly binding free energies

how: MM/XXSA; XX=PB, GB, LRA

Multiscale Methods

Coarse-grained Simulations

How to study really very large molecular assemblies?

System Simplification

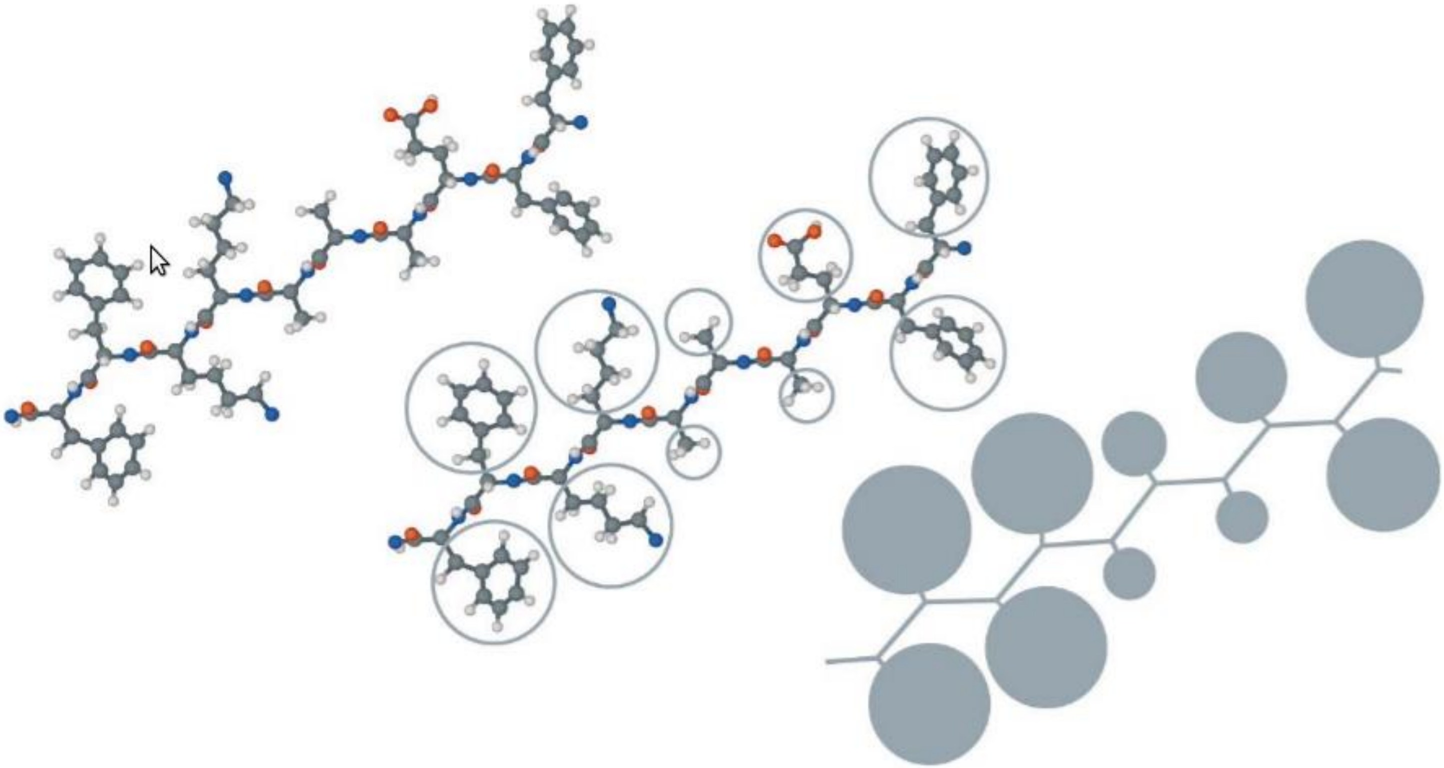
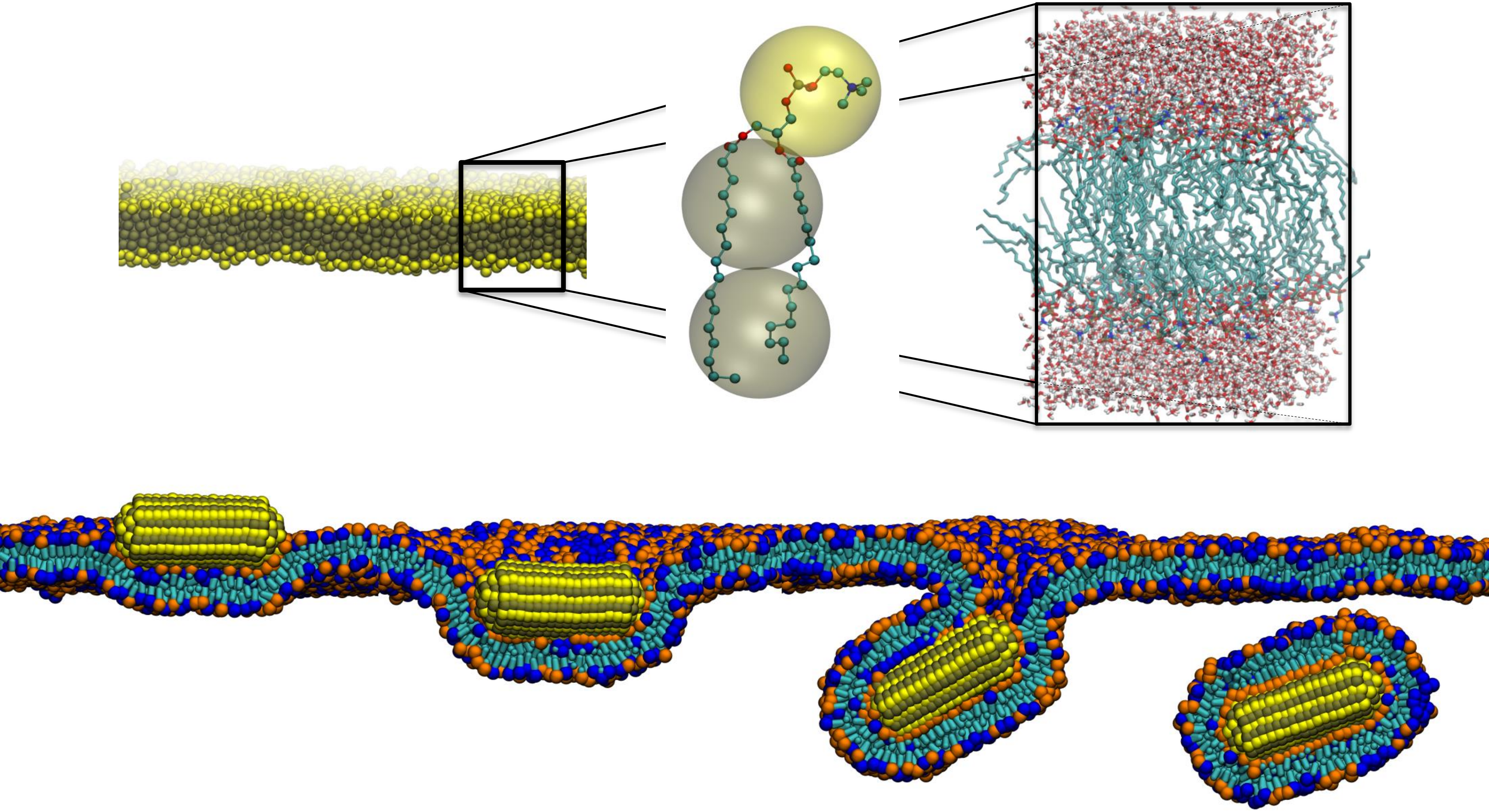


Figure 4. The detailed structure of a polypeptide chain (top) is simplified by assigning each amino acid residue with an interaction volume (middle) and the resulting string-of-pearls like structure (bottom) is used for the simulation.

System Simplification



Multiscale Methods

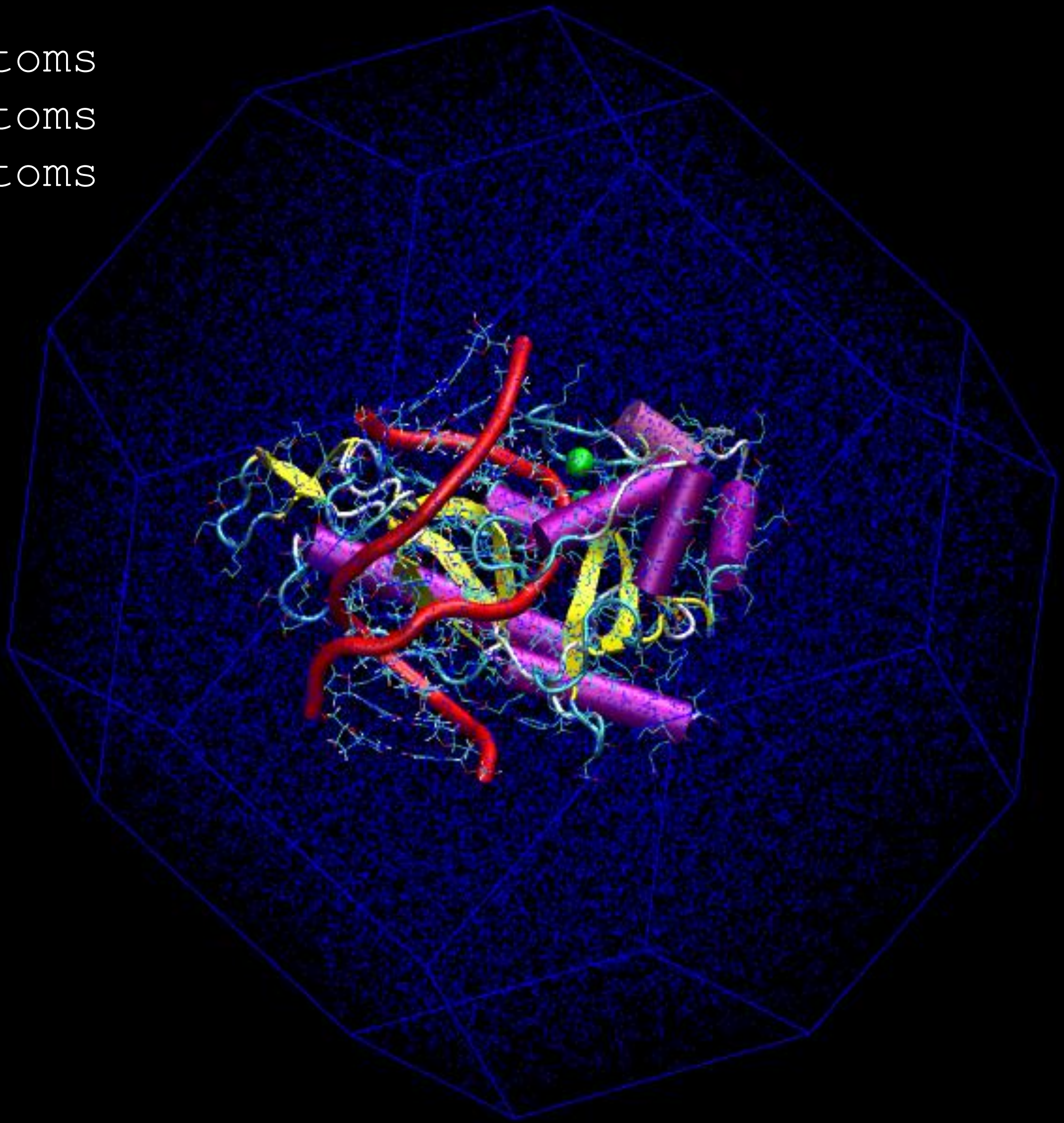
QM/MM Methods

How to describe reactivity occurring in biomolecules (enzymes)?

Enzymatic Reactions

```
Enzyme: ~4,300 atoms
Water: ~42,000 atoms
Total: ~46,500 atoms
```

MutH



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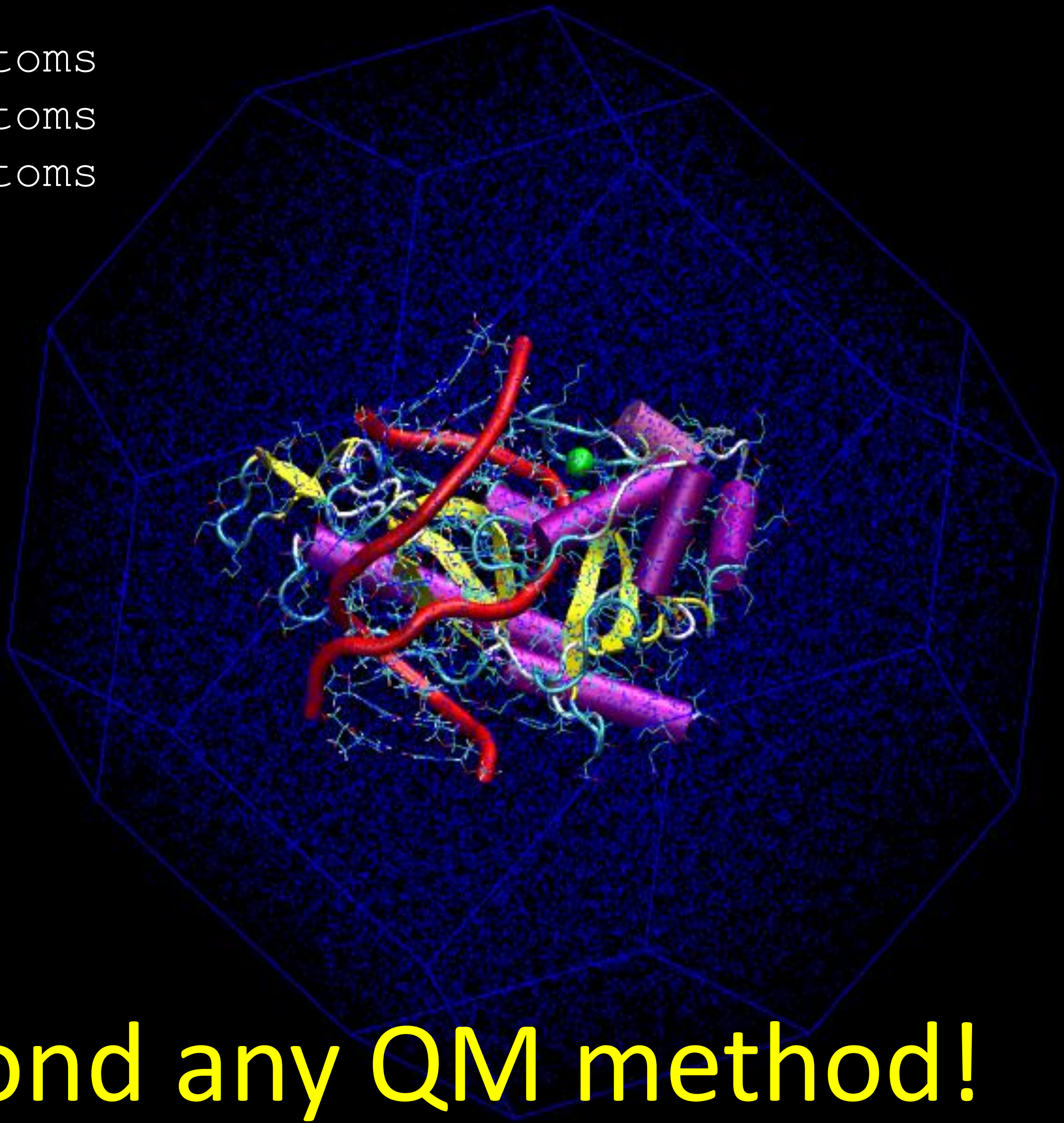
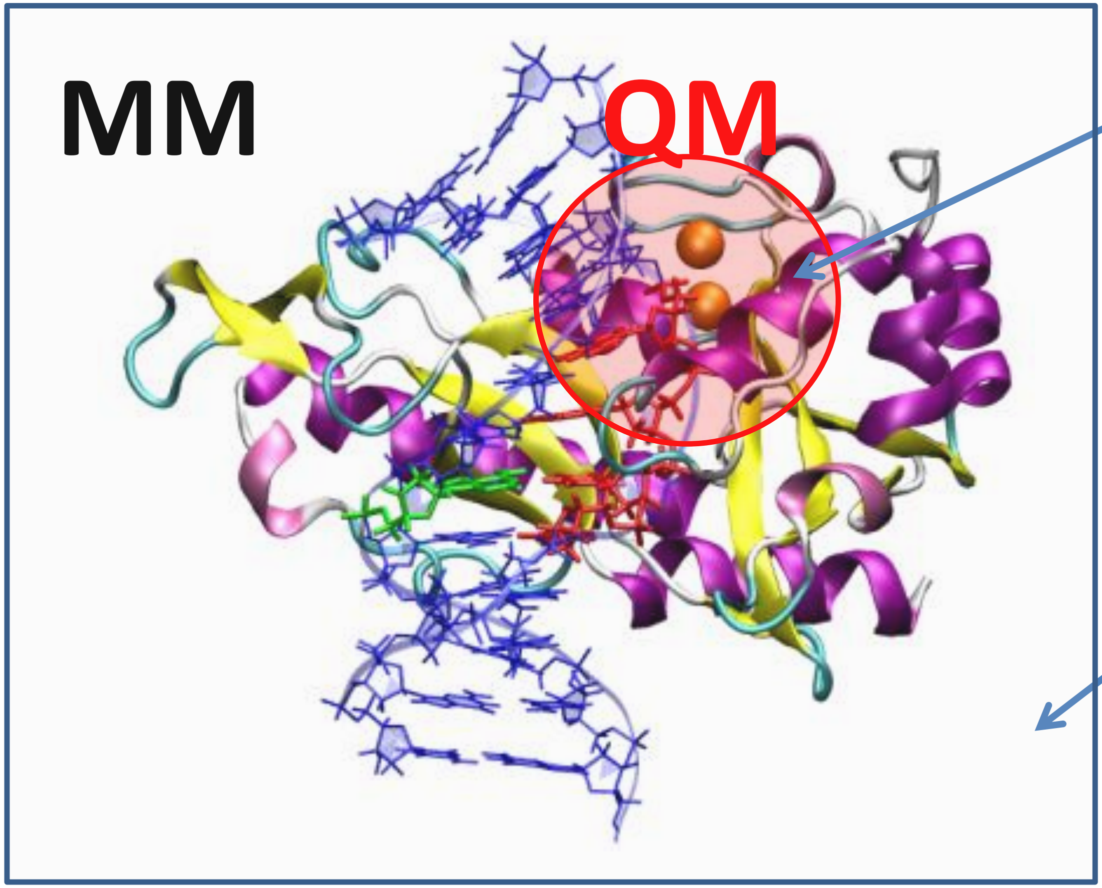


Beyond any QM method!

Enzymatic Reactions



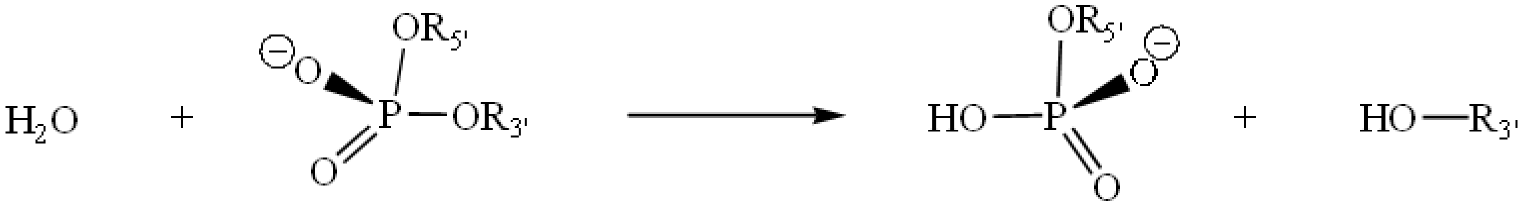
QM

active site only
tens to hundreds atoms

MM

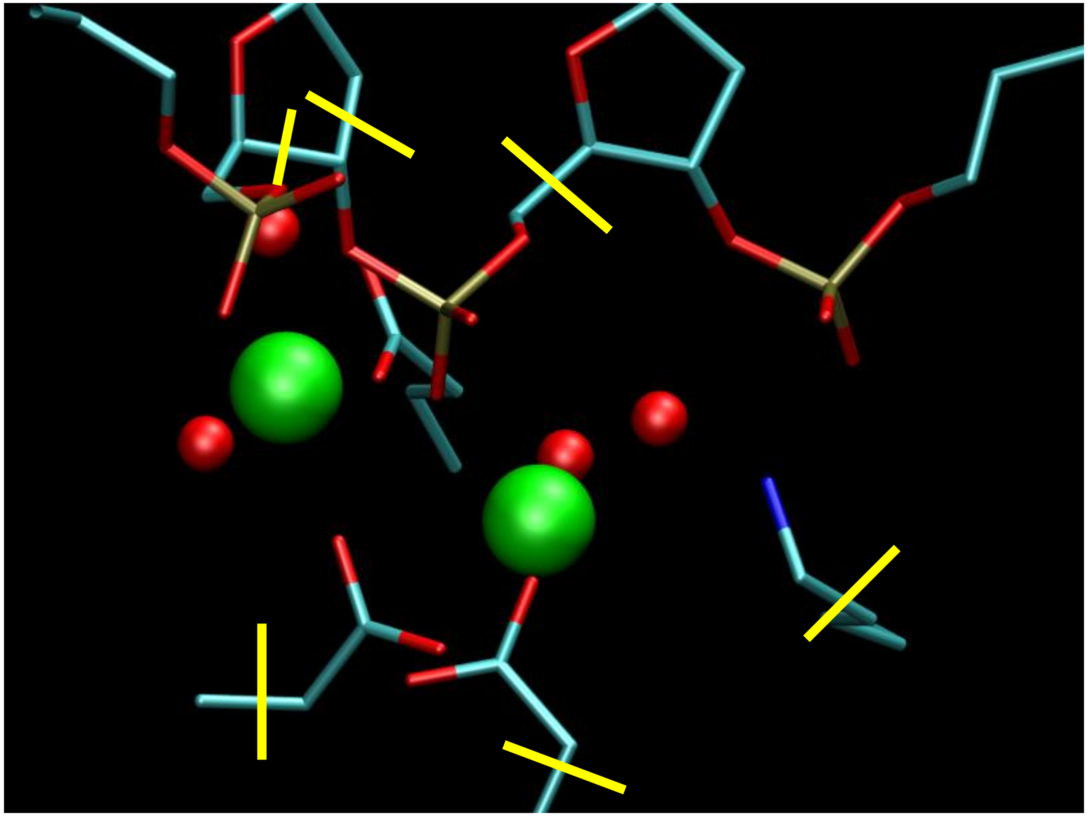
rest of enzyme
solvent (water)

Catalyzed reaction – hydrolysis of phosphodiester bond



$$H_2O + {}^{\ominus}O-P(=O)(OR_{5'})-OR_{3'} \longrightarrow HO-P(=O)(O^{\ominus})(OR_{5'}) + HO-R_{3'}$$

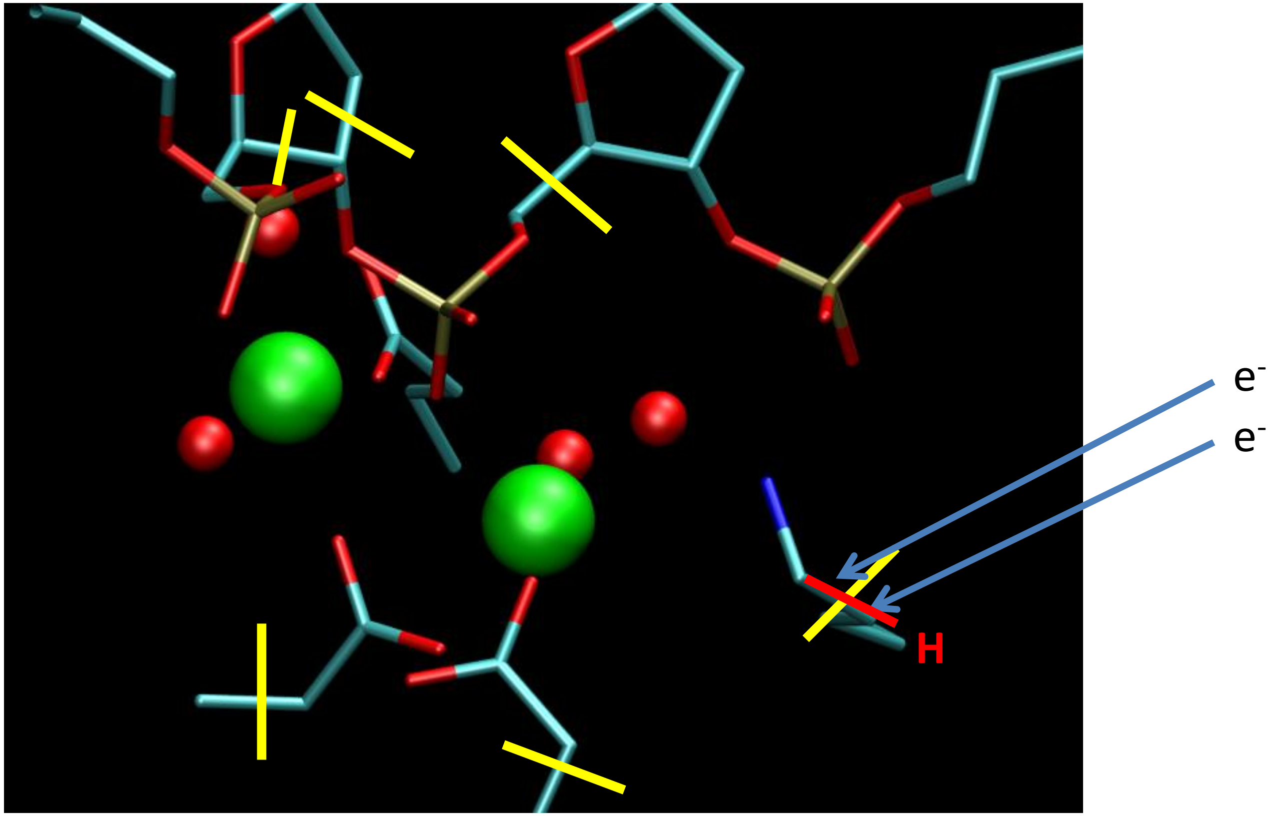
Hybrid QM/MM – boundary problem



Link atoms

- **how to cut covalent bonds?**
- tension at boundary due to incompatible precision of QM and MM potentials
- MM atoms cannot be polarized by QM zone but QM atoms can be (over)polarized by MM atoms

Hybrid QM/MM – boundary problem



Link atoms

- **how to cut covalent bonds?**
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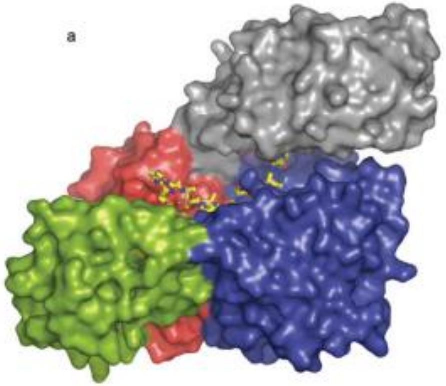
Introduction - OGT glycosyltransferase

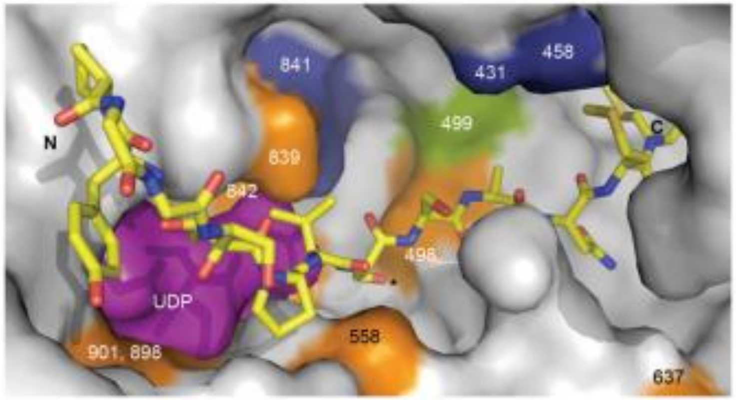
- Uridine diphospho-*N*-acetylglucosamine: polypeptide β-N-acetylaminyltransferase; PDB ID: 3PE4
- Enzymatic transfer of N-acetylglucosamine molecule on Ser/Thr residue of protein
- Inverting glycosyltransferase of the GT-B family
- Post-translational modification: first reported in 1984

UDP-GlcNAc + OH-Ser/Thr (peptide) ⟶ Peptide-GlcNAc + UDP

Donor Acceptor



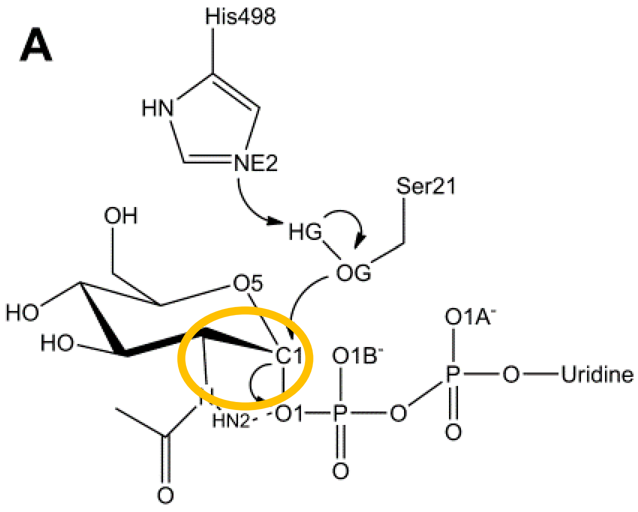
OGT Crystal Structure **(Walker et al, 2011)**



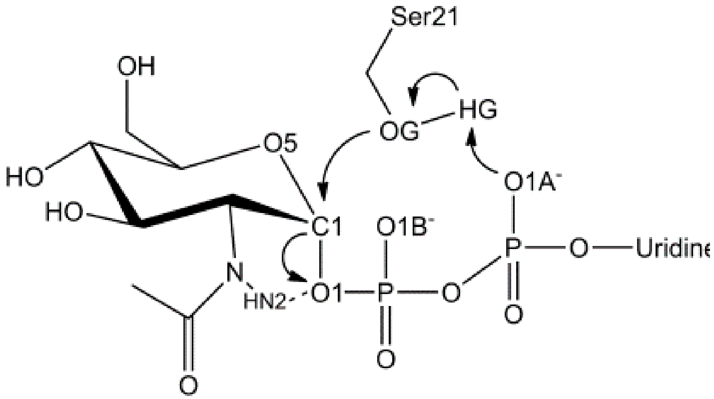
OGT Catalytic Site

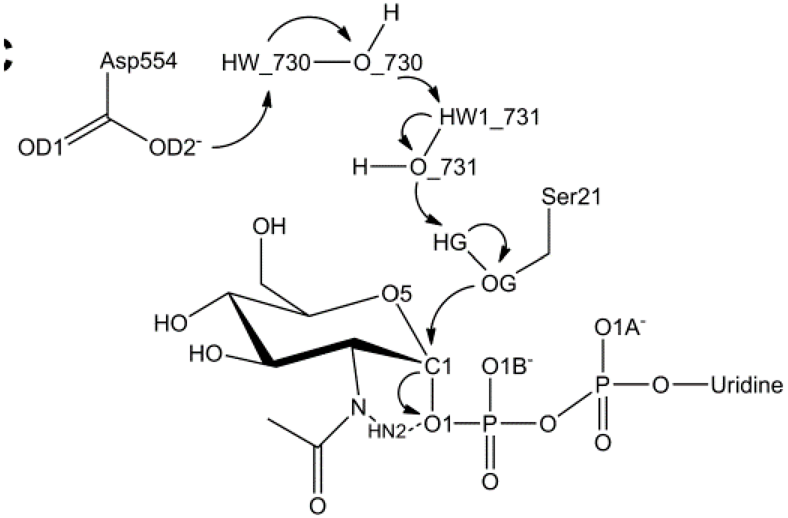
Different Mechanisms Proposed for OGT

1. **His498 as catalytic base (M$_{His}$)**
   (Lazarus et al. 2011
   Tvaroska et al. 2012)



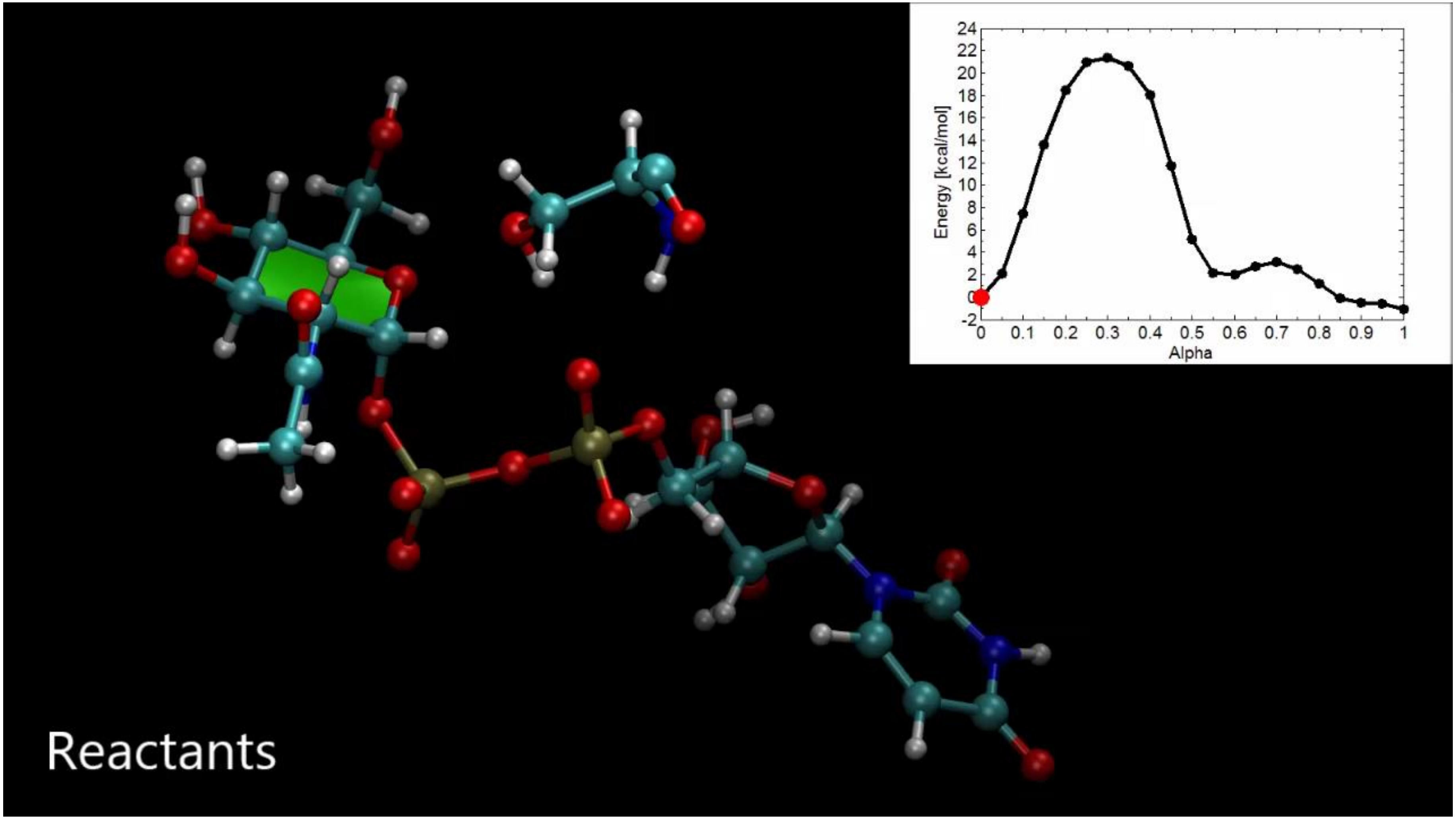
2. **α-phosphate as base (MPO4)**
   (Schimpl et al. 2012)





3. **Water molecule for shunting**
   proton to ASP554 (MAsp)
   (Lazarus et al. 2012)

Most Probable Reaction Path – M_{PO4}



Nobel Laureates in Chemistry 2013

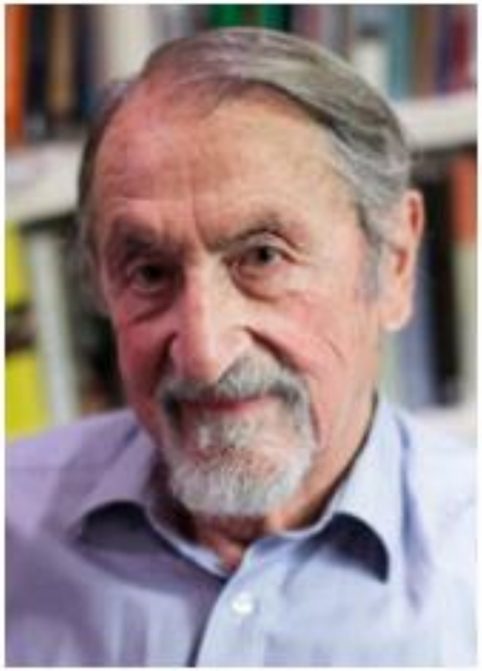


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Photo: Wikimedia Commons

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University of Southern California, Los Angeles, CA, USA

http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2013/

Take Home Message

Figure 2. Newton and Schrödinger's cat. Previously, classical physics and quantum chemistry belonged to rivalling worlds. The Nobel Laureates in Chemistry 2013 have opened a gate between those worlds and have brought about a flourishing collaboration.

- study of chemical reactions occurring in very large molecular assemblies is possible by QM/MM methods ("routine" calculations)
  - enzymatic reactions (drug development)
  - catalysis in solid state (zeolites, industry)
- many unresolved issues (QM accuracy, MM polarization, boundary problems , ...)

Acknowledgement

Thank you for your attention !

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