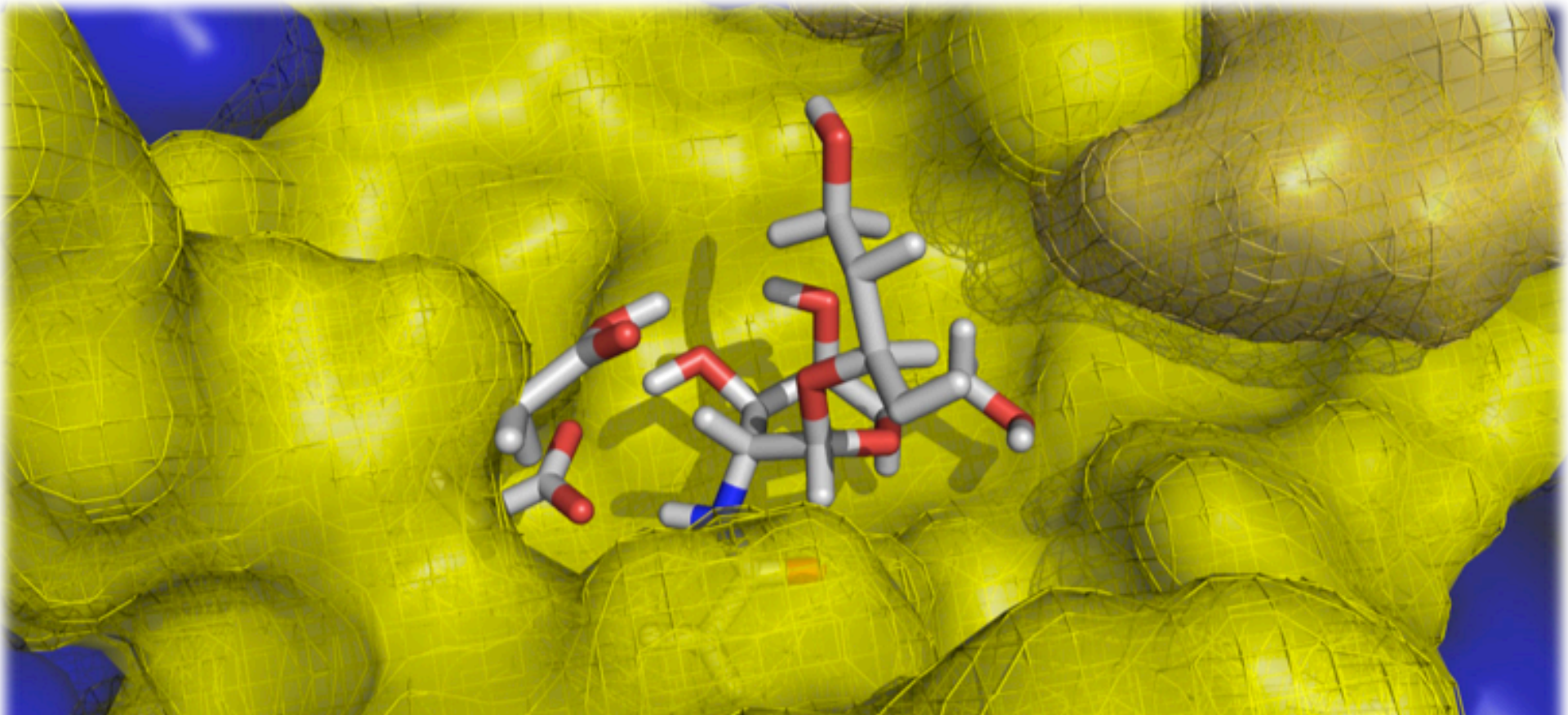
Challenges for the Simulation of Biomolecules

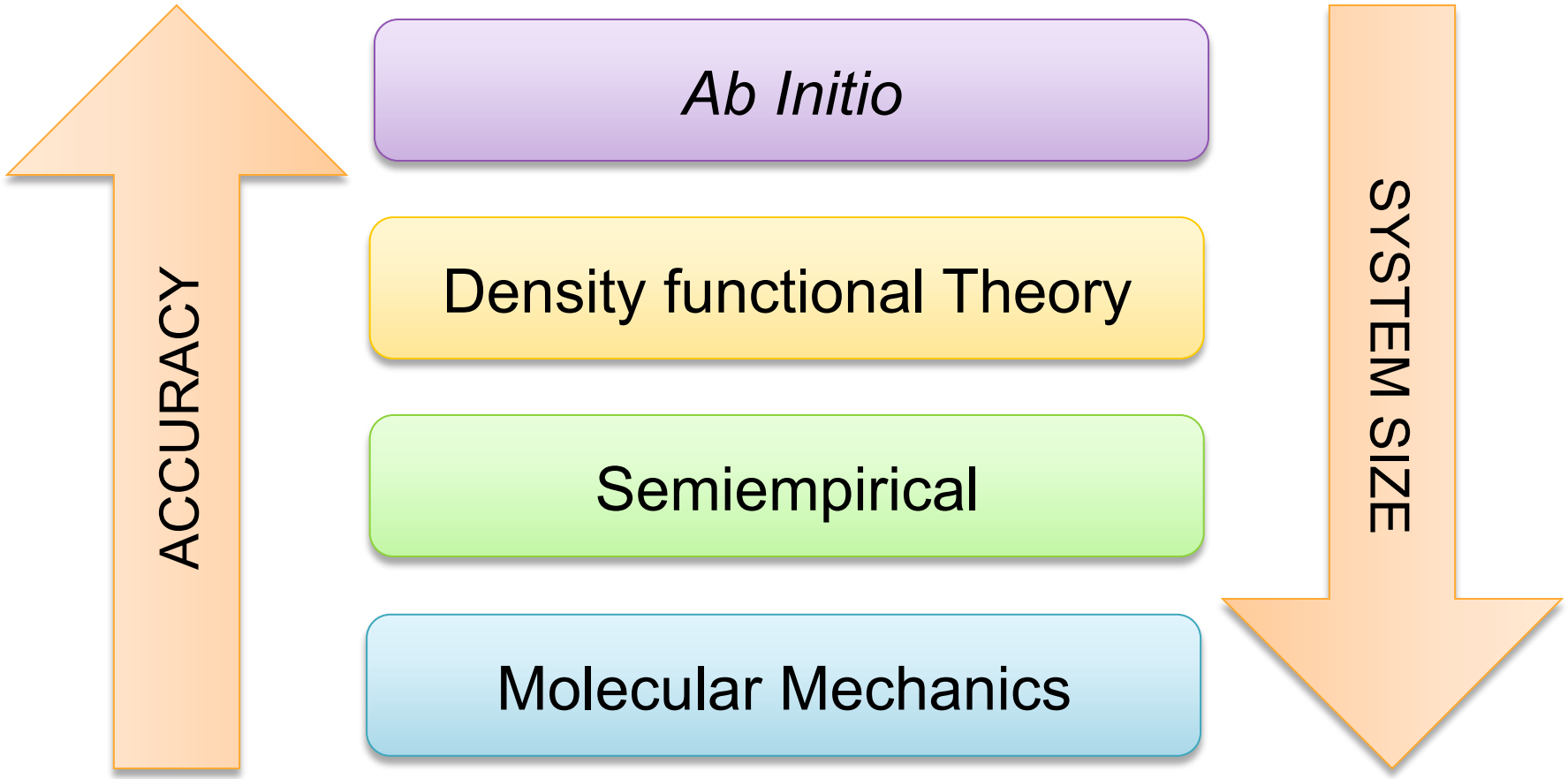
Pedro Alexandrino Fernandes,

Dep. Chemistry & Biochemistry, University of Porto, Portugal

pedro.fernandes@fc.up.pt



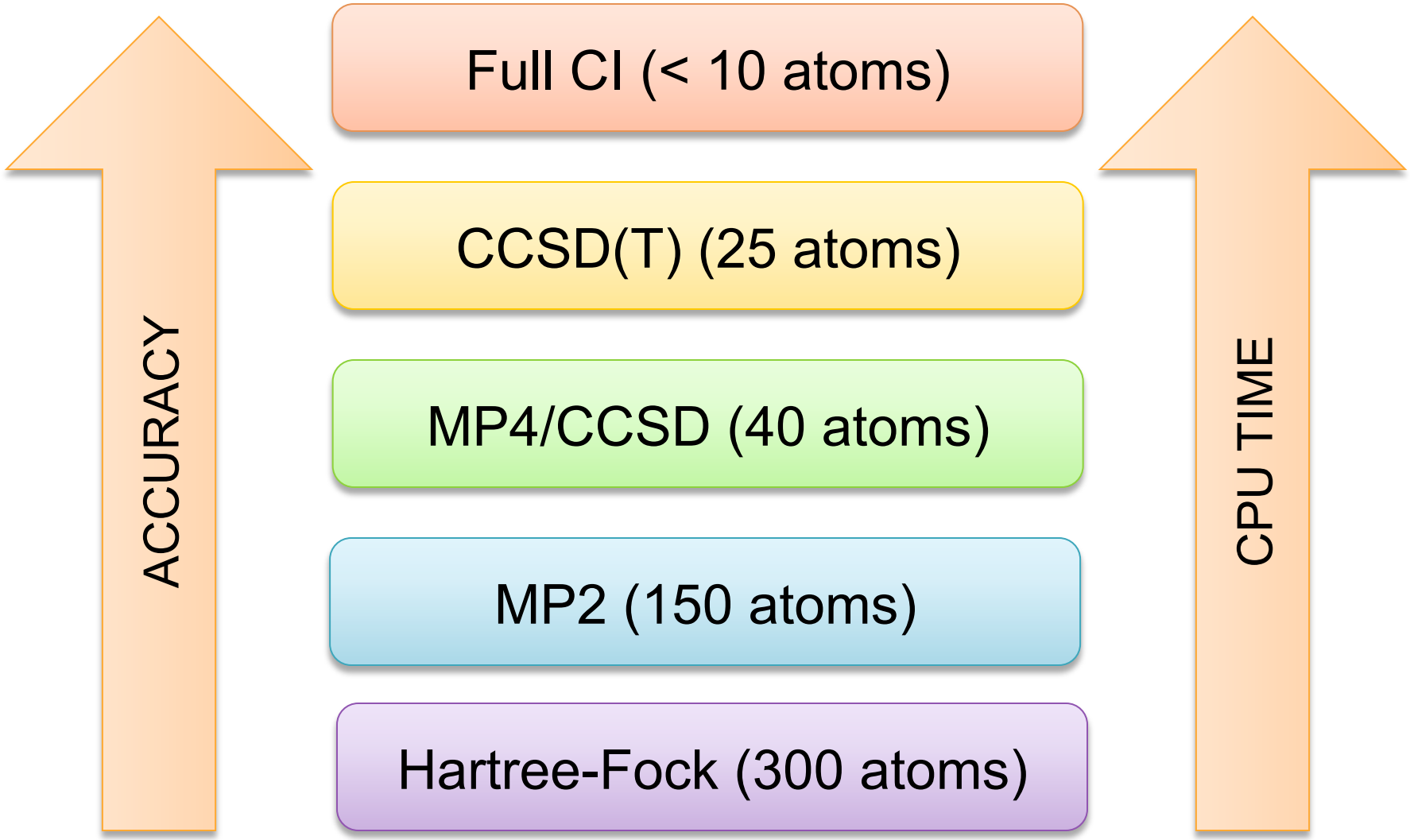
Theoretical Methods



Theoretical Methods – *Ab Initio*

Method	*Ab Initio*
Description	• Based on the wave function. • No empirical parameters. • Rigorous mathematics.
Advantages	•Can be used in every system. • Do not need any experimental data. • Allow to calculate transition states and excited states.
Disadvantages	•Very much CPU demanding.
System Size	• 25-300 atoms.

Theoretical Methods – *Ab Initio*



Theoretical Methods – Density Functional Theory

Method	Density Functional Theory
Description	• Based on the ground state electronic density. • May be *ab initio* or include parameters. DFT itself is *ab initio.*
Advantages	•Include electron correlation. •Faster than *ab initio* methods of similar quality. •Allows to calculate transition states and excited states (TDDFT).
Disadvantages	•Less accurate than **the best** *ab initio* methods. •Not possible to systematically improve the accuracy. •Less accurate for dispersive interactions.
System Size	•Up to a few hundred atoms.

Theoretical Methods – Semiempirical

Method	Semi-empirical
Description	•Based on the wave function. •Mathematical approximations. •Uses experimental parameters to simplify equations.
•Advantages	•Less CPU demanding than *ab initio* methods. •Allows to calculate transition states and excited states.
Disadvantages	•Requires experimental or *ab initio* parameters. •Less accurate than *ab initio* or DFT methods. •Results not reliable outside the parameterization range.
System Size	•Up to one thousand atoms.

Theoretical Methods – Molecular Mechanics

Method	Description
Description	•Based on classical physics. • Hamiltonian partly based on empirical equations and parameters.
Advantages	•Very fast. •Appropriate for very large systems. •Accuracy depends on the quality of the parameters.
Disadvantages	•Does not describe explicitly electronic properties. •Needs experimental or QM data to derive parameters. •Can only be used in systems for which the parameters are available.
System Size	•Up to one million atoms.

Biomolecular systems

Ab Initio

Density functional Theory

Semi empirical

Molecular Mechanics

Biomolecular systems

Ab Initio

Need "*ab initio* accuracy"

Density functional Theory

Semi empirical

Molecular Mechanics

Biomolecular systems

Ab Initio

Density functional Theory

Semi empirical

Molecular Mechanics

Need "*ab initio* accuracy"

Have "molecular mechanics" size

Biomolecular Timescale

Phenomenon	Timescales
Solvation Bond vibration Angle vibration Side chain oscillation Membrane capillary waves	fs-ps

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Enzyme Catalysis Protein Folding Protein Oligomerization Lipid Flip Flop	ms-h

System size

Biochemical systems classified by size within a computational perspective

1. **Small systems:**

   Less than 300 atoms

   Described with QM

2. **Intermediate systems:**

   300-1000 atoms

   Described with semiempirical methods or hybrid QM/QM methods

3. **Large systems:**

   Over 1000 átomos

   Described with hybrid QM/MM or with classical MM methods

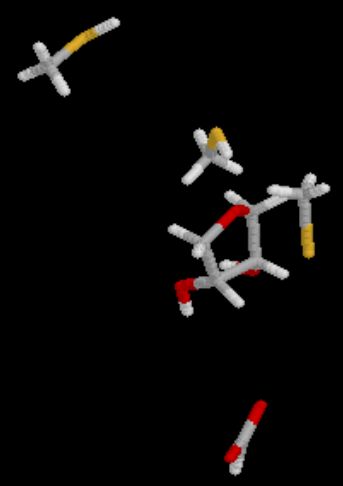
•B3LYP/6-311++G(3df3pd)
•Only active site
•Solvent: C-PCM

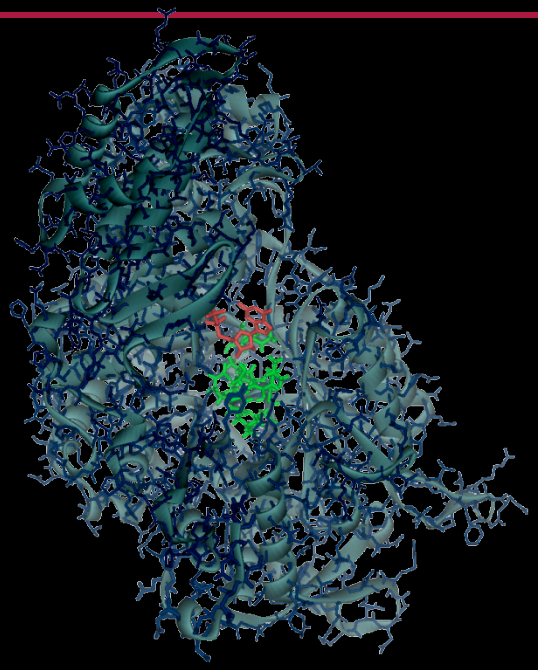
•B3LYP/6-3
•Shell of 8
•Solvent: C

•B3LYP/CHARMm
•Complete enzyme
•Explicit solvent or implicit dielectric solvent

n around
zen borders

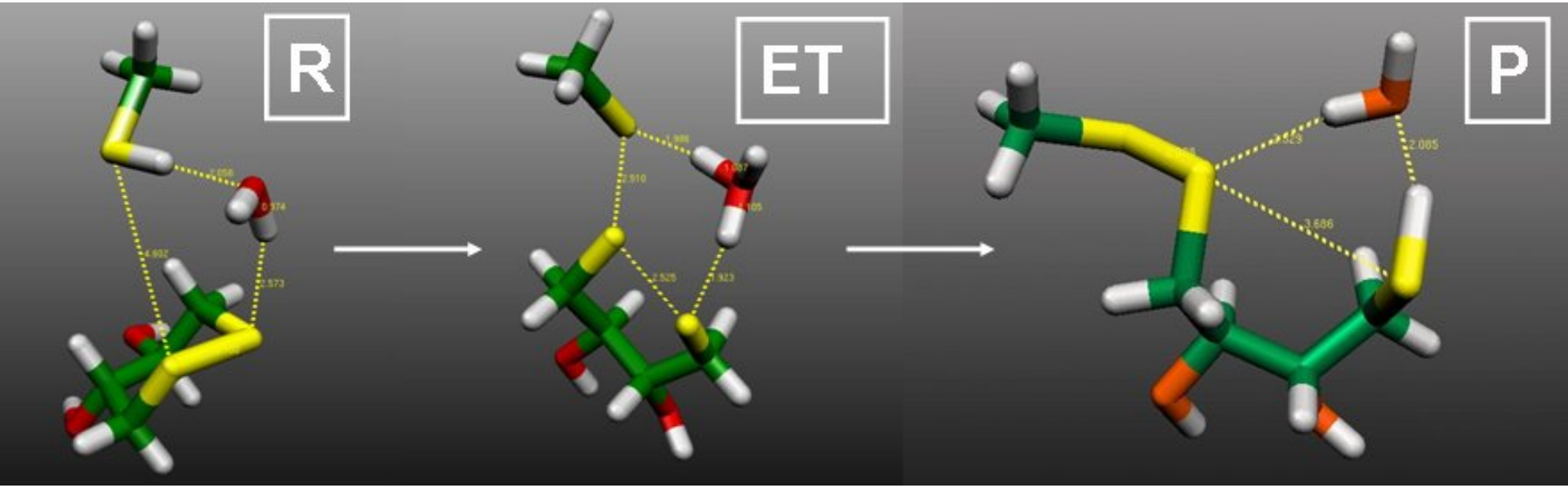
30 atoms **160 atoms** **1640 atoms** **11600 atoms**





Small systems

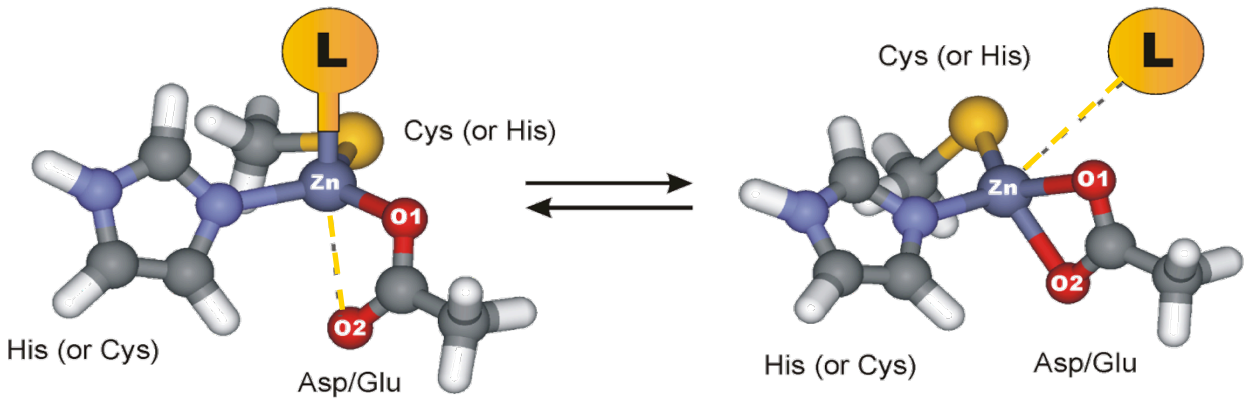
Small molecules, simulated in vacuum or in implicit solvent

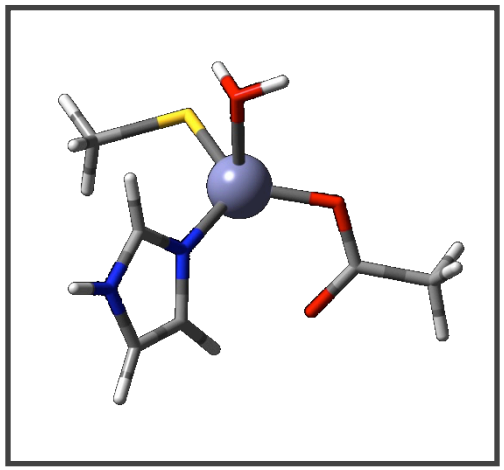


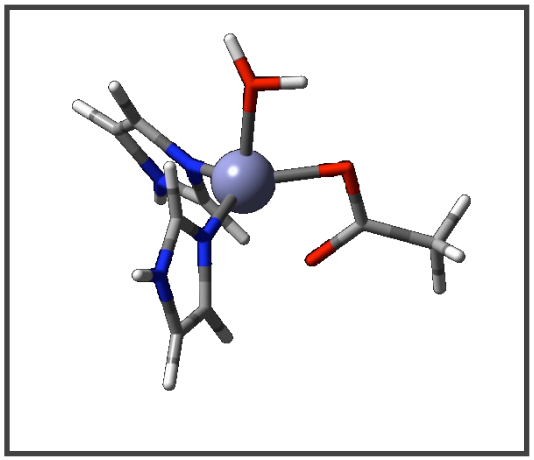
Chem. Eur. J., 10, 257, 2004

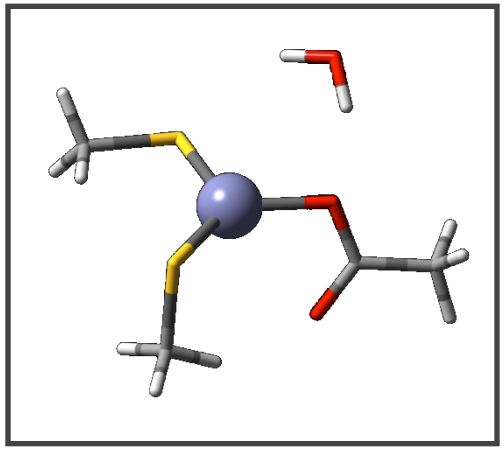
Small systems

Transition metal complexes





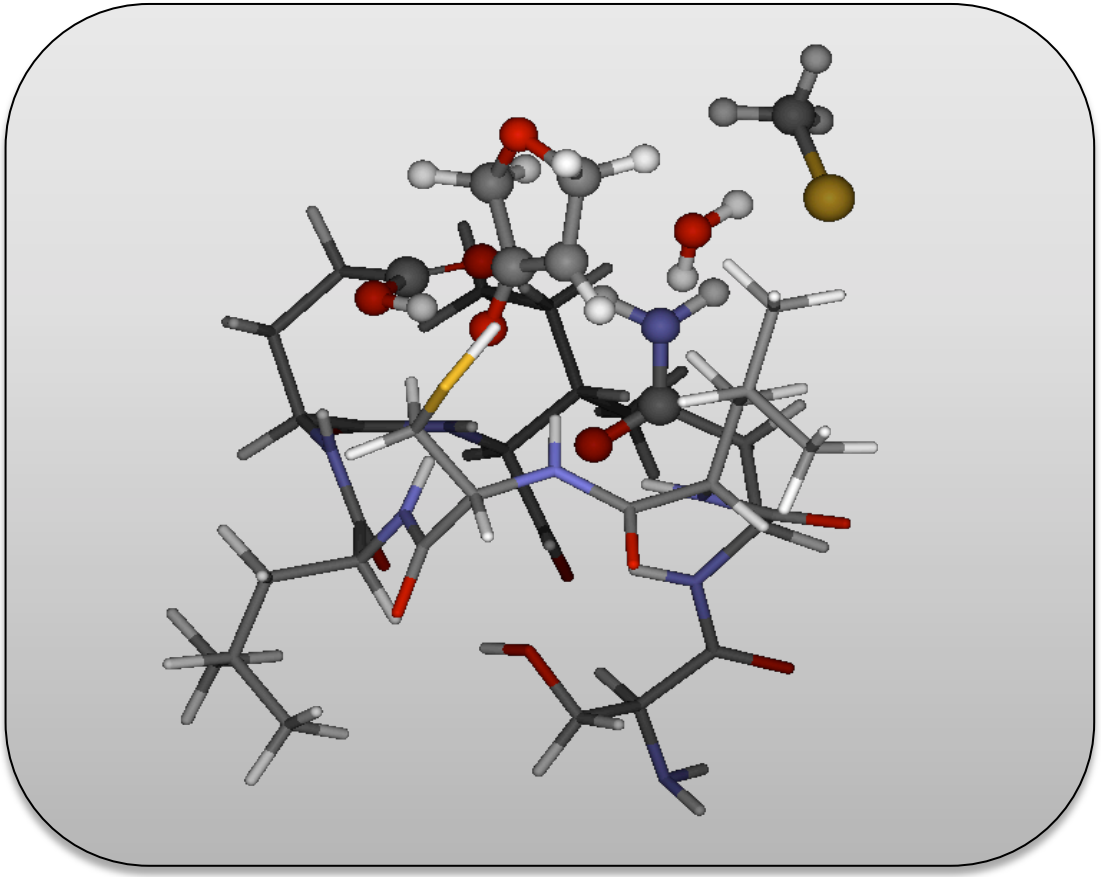




JACS 129, 1378, 2007

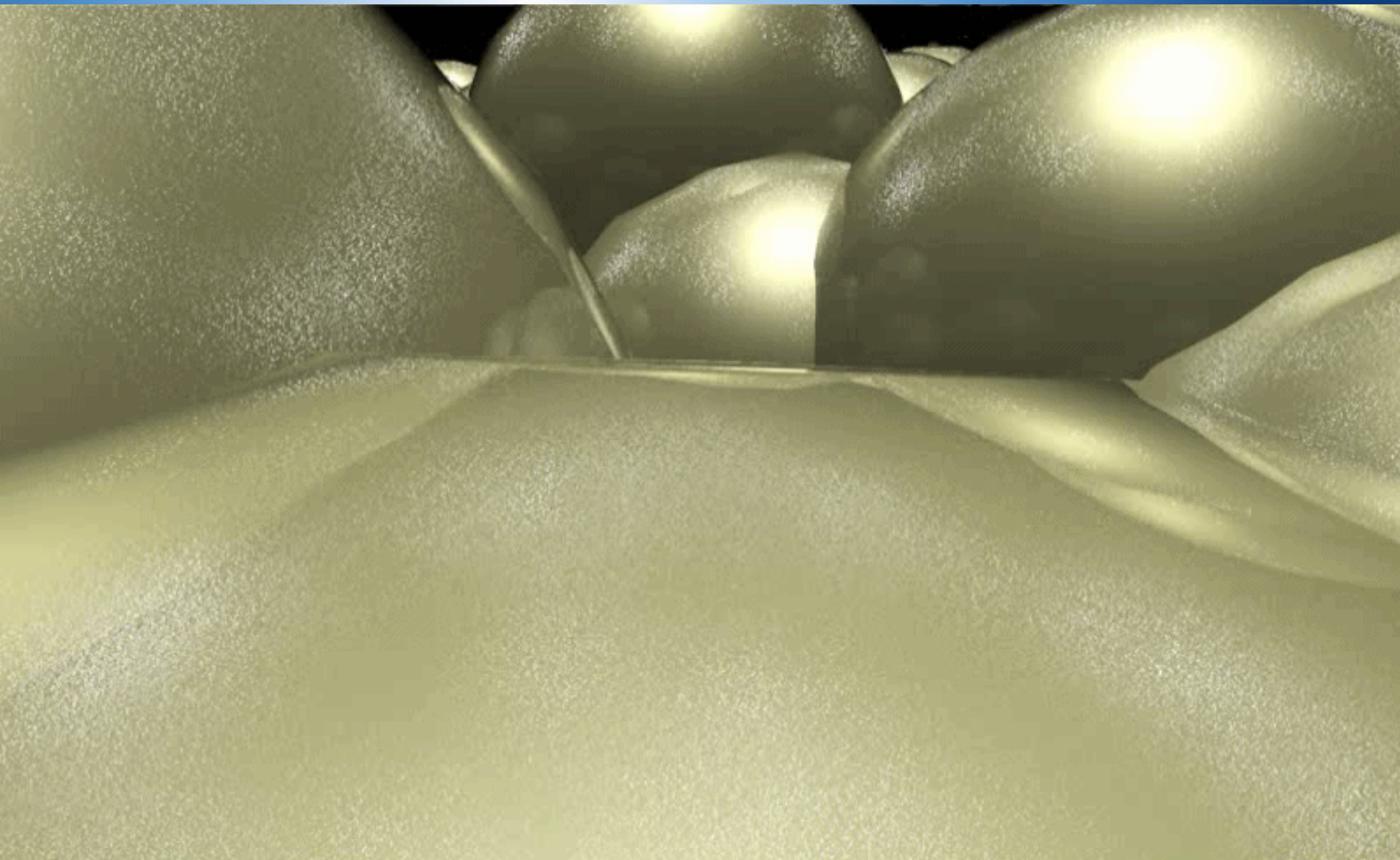
Small systems

Active sites of enzymes – Cluster models



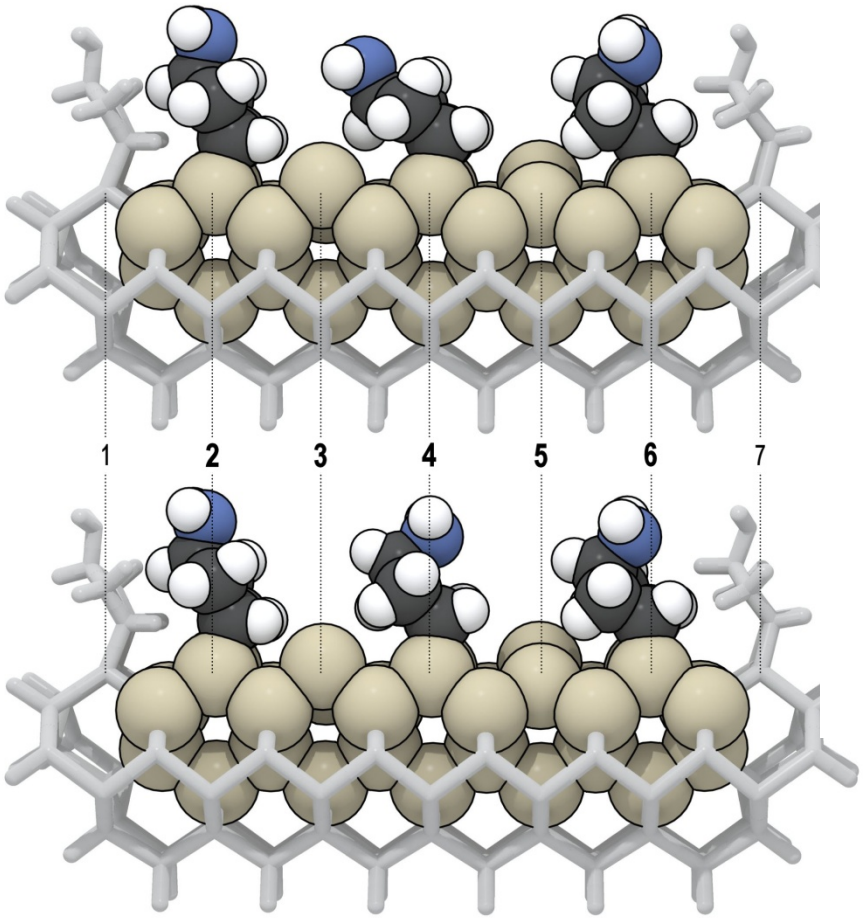
Chem. Eur. J., 13, 8507, 2007

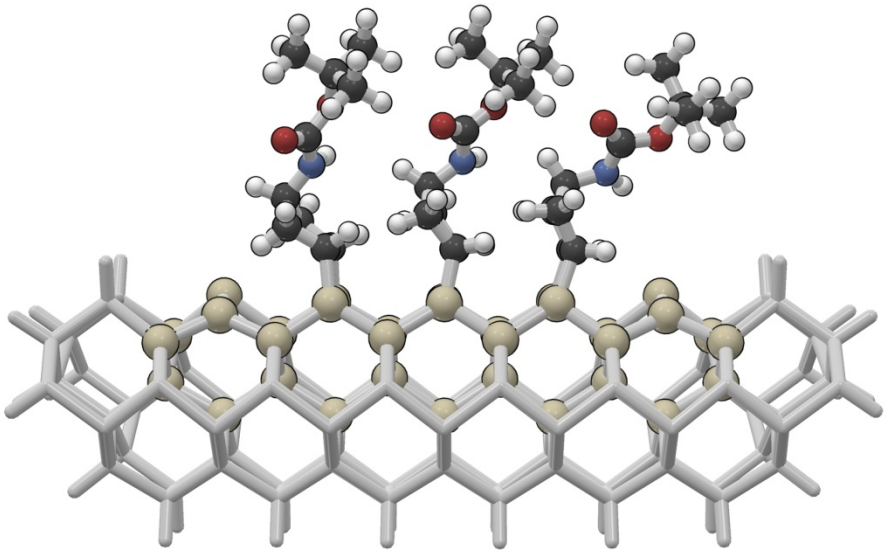
Medium Systems – Adsortion on Si surface



Medium Systems – Adsortion on Si surface

Funcionalization of Si for DNA adsortion

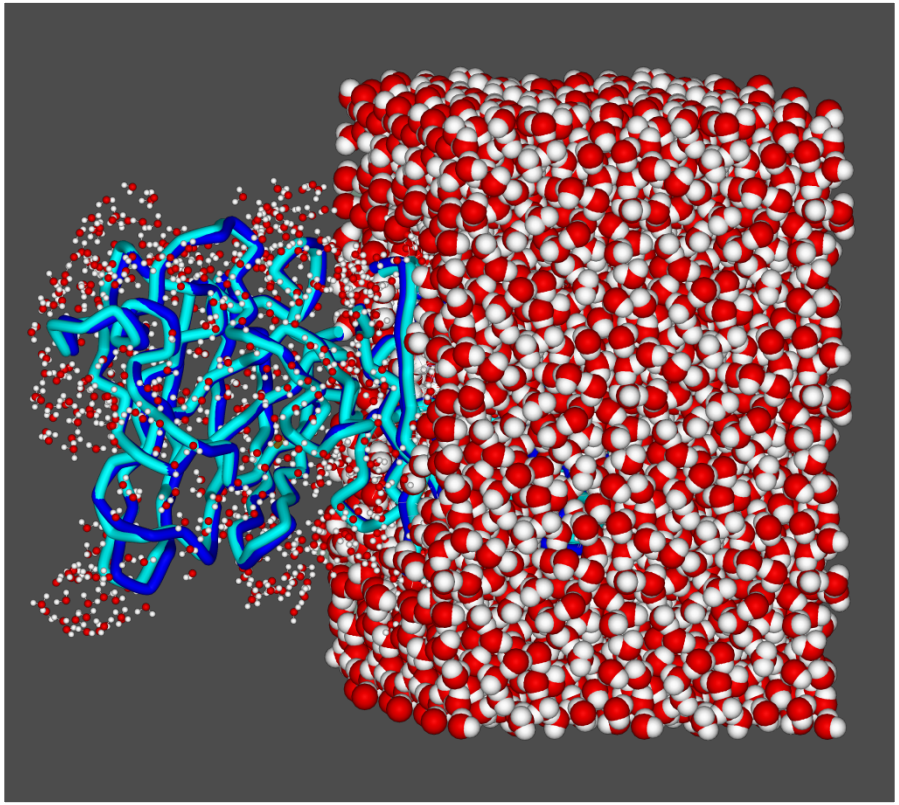


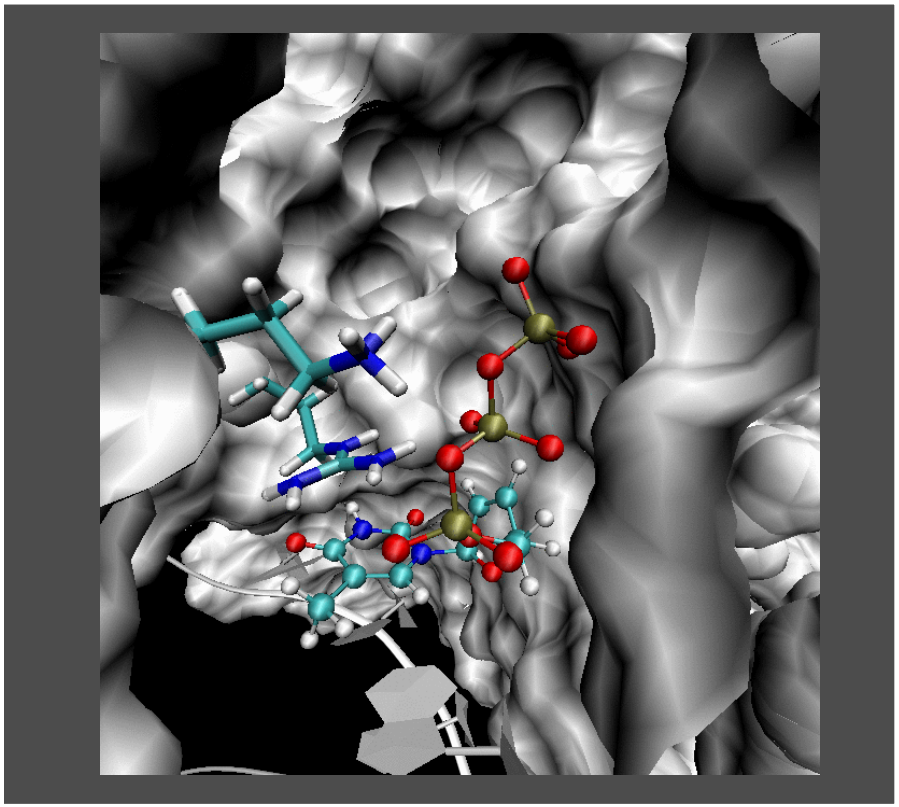


B3LYP/SHC* : AM1

Large Systems

Structural and dynamic properties of enzymes

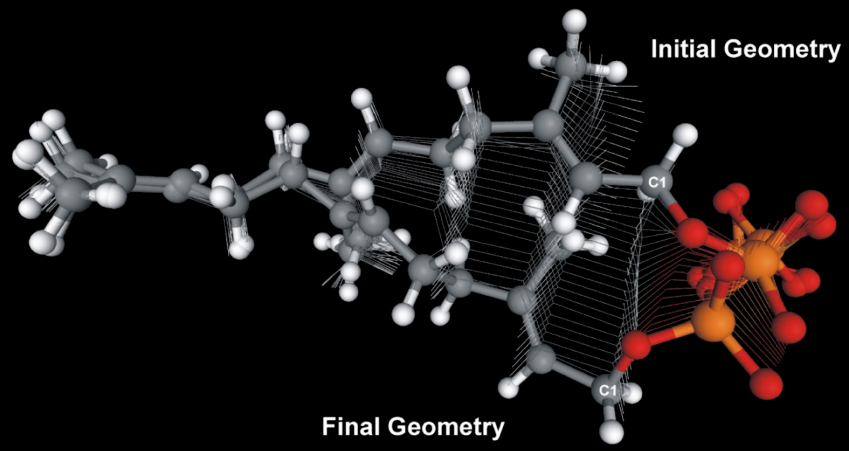


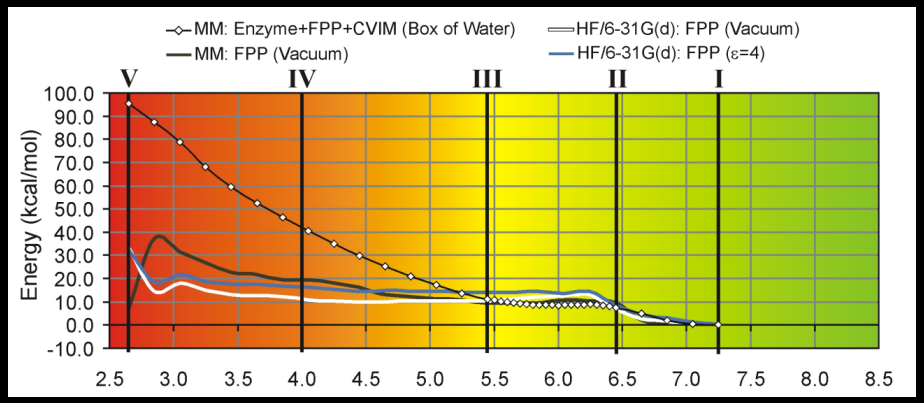


Need complete enzymes and solvent

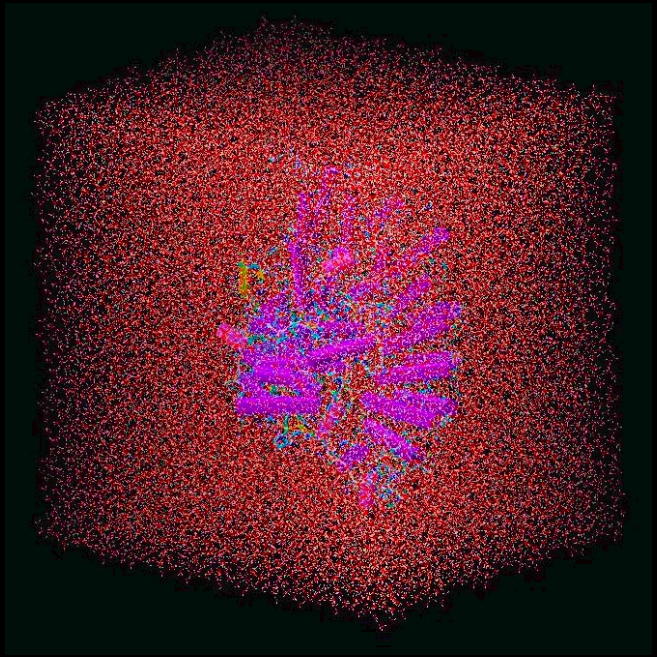
Large Systems

Conformational transitions in macromolecules





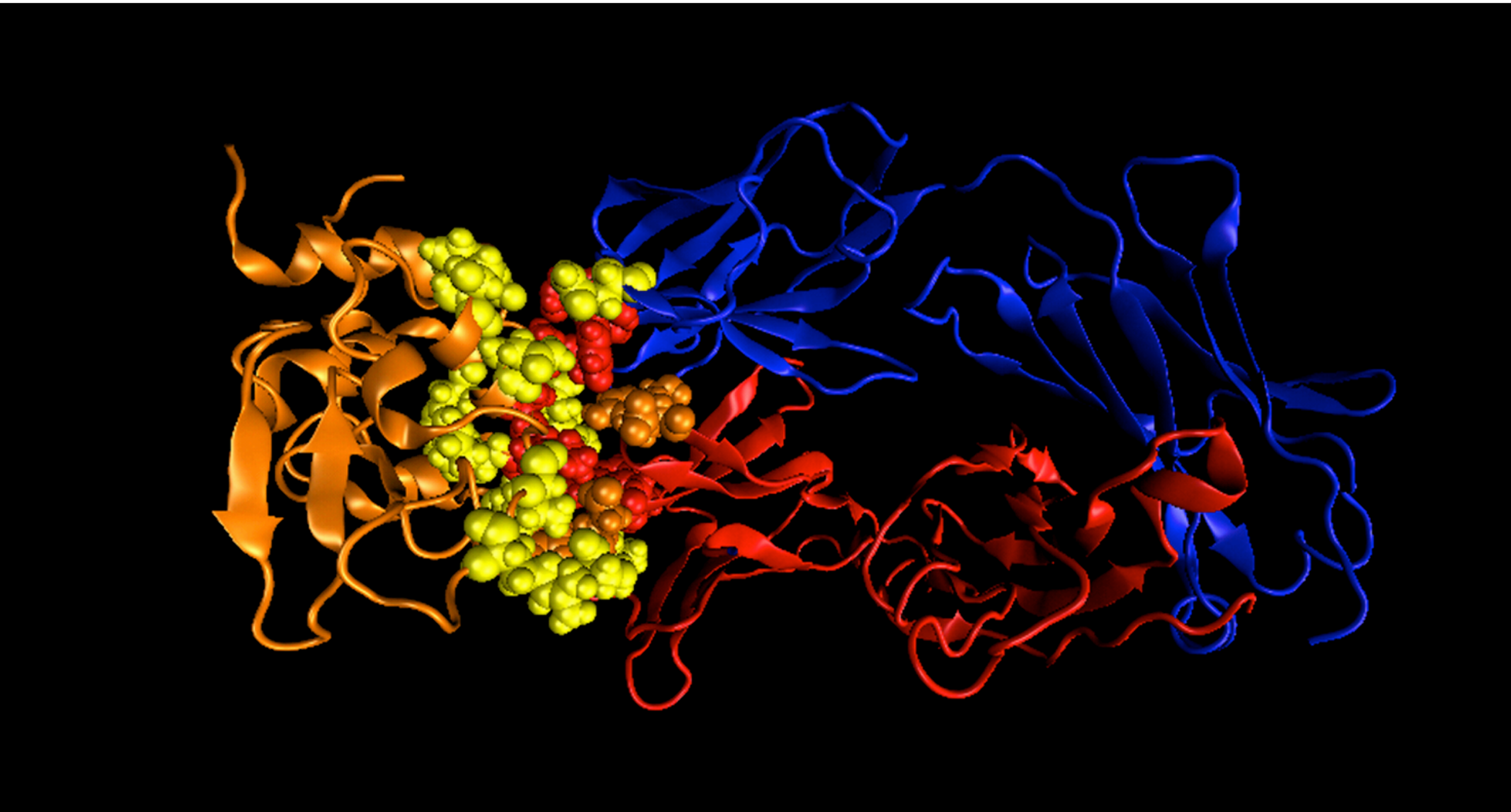
Even small conformational transitions need full models to be accurately modeled



PROTEINS, 66, 205, 2007

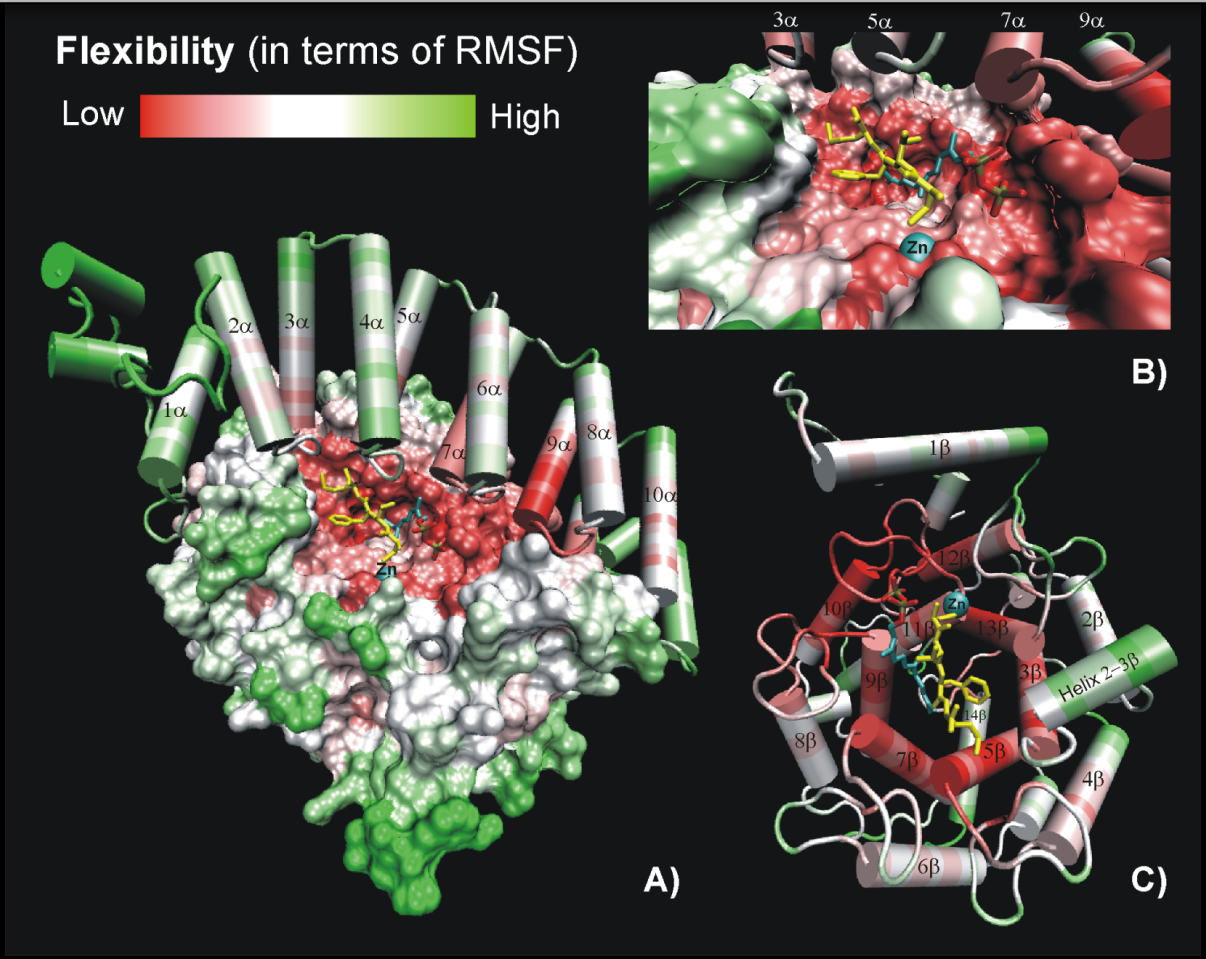
Large Systems

Non-covalent macromolecular interactions



Large Systems

Flexibility in macromolecules



J. Phys. Chem. B, 112, 8681, 2008.

Conclusion

Advantage of MM = disadvantages of QM

1. Conceptual simplicity
2. Very fast calculations
3. Treat systems with a very large number of atoms
4. Calculate with acceptable accuracy the thermodynamic and dynamic properties of a system

Conclusion

Disadvantages of MM = advantages of QM

1. Need to parameterize all intervening molecules
2. Inability to study electronic properties, including bond breaking and bond formation
3. Results depend on the used parameters
4. Accuracy is inferior to QM methods

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