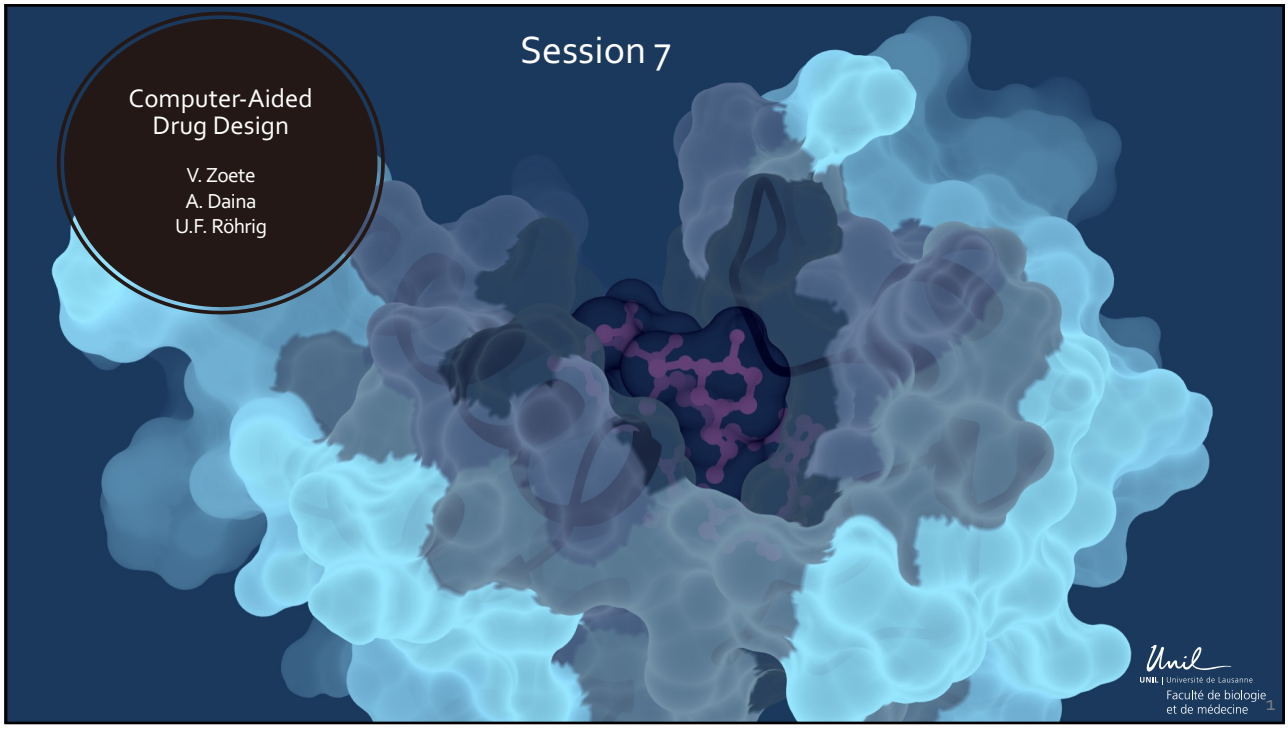


1

Lectures & Practices Agenda

Session	Lecture	Practice
1	Prologue: molecular representation	
	Introduction to (computer-aided) drug design	
	Origin of 3D structures	
	Molecular recognition	Use of UCSF ChimeraX to analyze protein-ligand complexes
2	Binding free energy estimation	
	Introduction to molecular docking	Ligand-protein docking with **SwissDock**
3	Introduction to molecular (virtual) screening	Ligand-based virtual screening with **SwissSimilarity**
4	Short introduction on target prediction of small molecules	Use of **SwissTargetPrediction** to perform reverse screening.
5	Introduction to ADME, pharmacokinetics, druglikeness	Estimate physicochemical, pharmacokinetic, druglike and related properties with **SwissADME**
6	Short introduction to bioisosterism	Use of **SwissBioisostere** to perform bioisosteric design
7	Introduction to quantum methods for drug design	Use of WebMO to perform quantum chemical calculations

UNIL | Université de Lausanne SIB
2

2

Introduction to Quantum Methods for Drug Design

- Introduction and Motivation
- A Very Brief Recall of Quantum Mechanics
  - Schrödinger Equation
  - Born-Oppenheimer Approximation
  - Atomic and Molecular Orbitals
  - Basis Sets
  - Hartree-Fock Theory
  - Beyond Hartree-Fock
- Use of QM in Docking
  - Hybrid QM/MM Approach
  - Attracting Cavities Docking Algorithm
- Covalent Inhibitors
  - Motivation and Mechanism
  - Classical and QM/MM Docking of Covalent Ligands with Attracting Cavities
- Practical Aspects
  - Convergence
  - Partial Atomic Charges
  - Molecular Frontier Orbitals

3

Resources

Books:

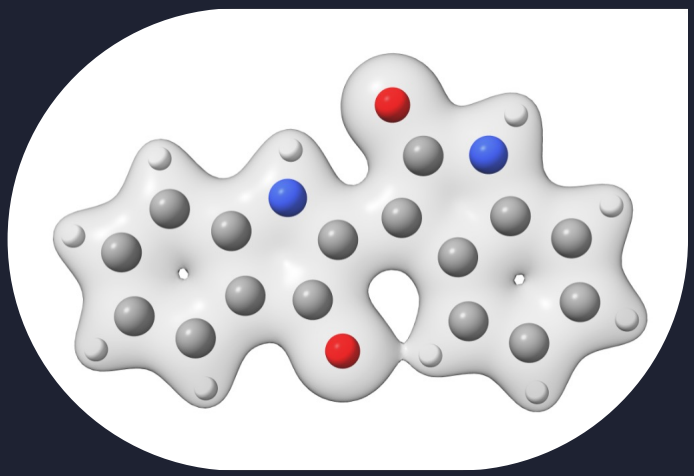
Andrew R. **Leach**, *Molecular Modelling: Principles and Applications*, Pearson Education, 2nd edition, 2001

Tamar **Schlick**, *Molecular Modeling and Simulation: An Interdisciplinary Guide*, Springer, 2nd edition, 2010

Online:

Notes from the group of David **Sherrill**, Georgia Institute of Technology (https://vergil.chemistry.gatech.edu/resources)

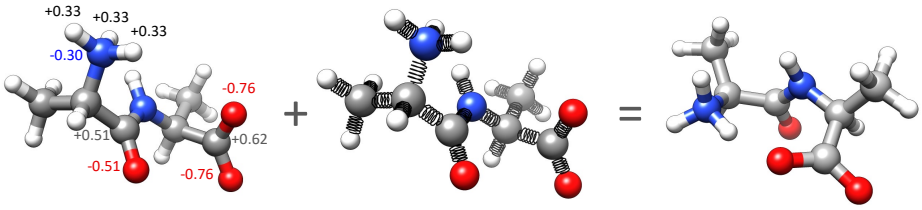
4



Introduction and Motivation

5

Classical Description of a Molecule



Atom:
- Radius
- Mass
- Partial Charge
- 3D Coordinates

Molecule:
- Topology (Bonds, Angles,…)

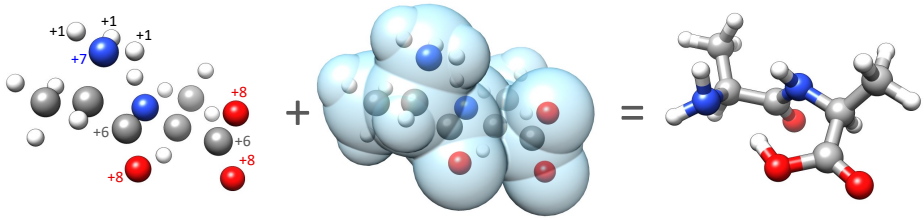
Results:
- New Coordinates
- Energy

- Force Field (empirical parameters)
- Classical/Newtonian Mechanics (MM, molecular mechanics)

6

6

Quantum Description of a Molecule



System:
- Atomic Nuclei
  - Mass
  - Integer positive charge (chemical element)
  - 3D Coordinates
- Electrons

Results:
- New Coordinates
- Energy
- **Topology**
- **Charge Distribution**

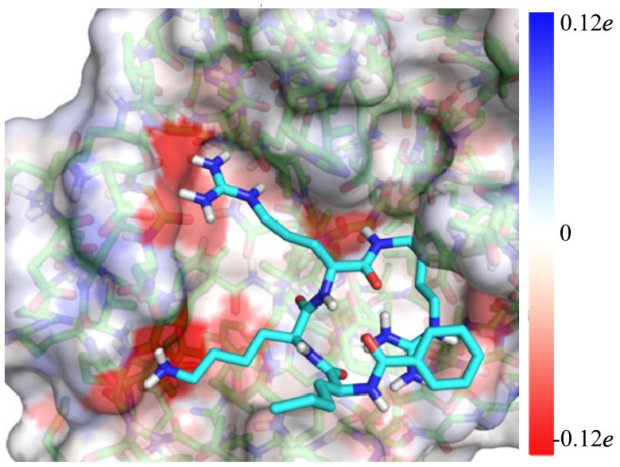
- Physical Description
- Quantum Mechanics (QM)

7

7

Quantum Mechanics in Drug Design: Polarization

Polarization of Protein Atoms Due to Inhibitor Binding



West Nile virus
NS3 serine protease

T. Zhou, D. Huang, A. Caflisch, *Curr. Top. Med. Chem.* **10**, 33 (2010)

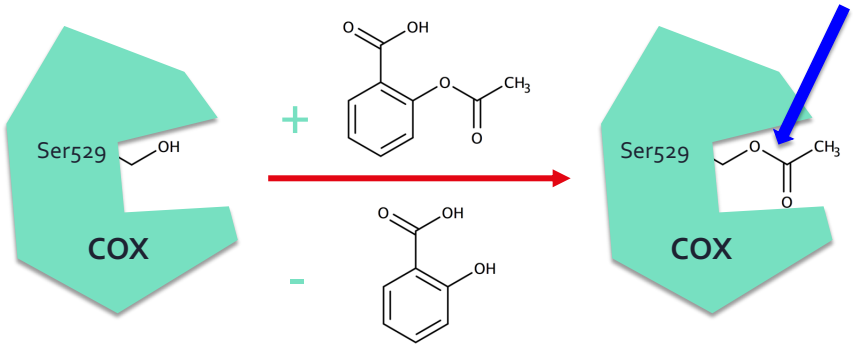
8

8

Quantum Mechanics in Drug Design: Chemical Reactivity

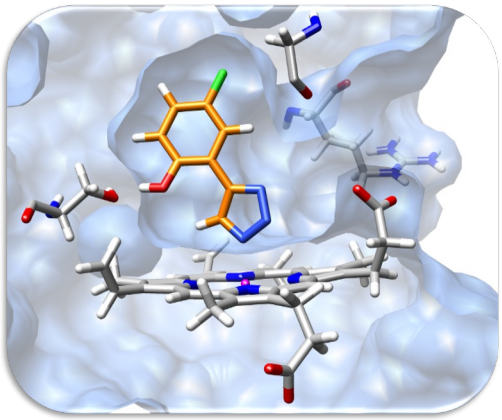
Covalent Inhibitor-Protein Complex

- Aspirin (acetyl-salicylic acid)
- Mode of action: acetyl group covalently attached to serine in the active site of COX1 and COX2



Quantum Mechanics in Drug Design: Transition-Metal Interactions

Ligand Binding to Heme Cofactor



Drug Design for Immuno-Oncology

- Indoleamine 2,3-Dioxygenase
- Optimal ligand-iron interaction
- pK_a lowered by substituents
- IC_{50} value 60 nM
- Selective, non-toxic

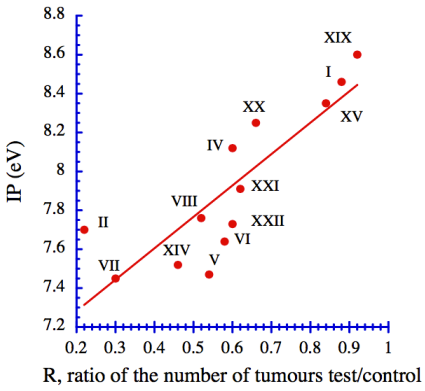
U.F. Röhrig, S. Reddy Majjigapu, A. Grosdidier, S. Bron, V. Stroobant, L. Pilotte, D. Colau
P. Vogel, B. J. Van den Eynde, V. Zoete, O. Michielin, *J. Med. Chem.* **55**, 5270 (2012)

Quantum Mechanics in Drug Design: QSAR

Quantitative Structure — Activity Relationships

Ionization Potential (IP):
energy required to detach an electron from a molecule

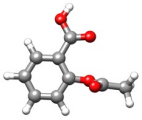
$$M \rightleftharpoons M^{\bullet+} + e^-$$

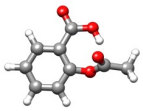


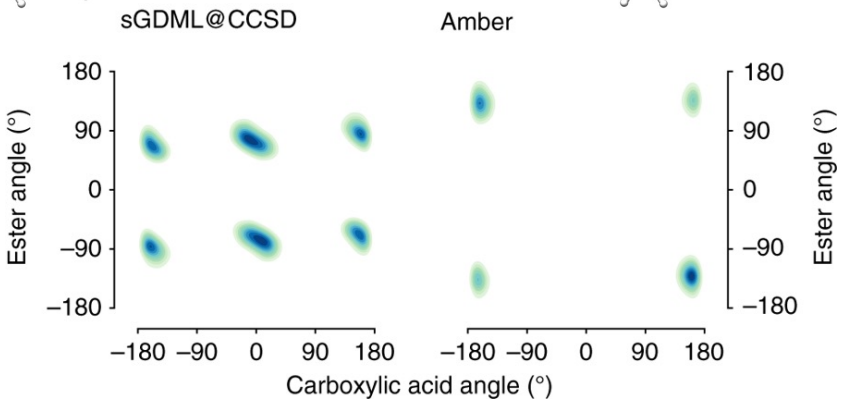
Bensasson et al., *Int. Reviews Phys. Chem.* **32**, 393 (2013)

Quantum Mechanics in Drug Design: Force Field Development

Aspirin probability distribution of dihedral angles







S. Chmiela *et al. Nature Comm.* **9**, 3887 (2018)

Quantum vs. Classical Methods

Quantum	Classical
More accurate (typically)	Less accurate (typically)
Equations more complicated	Equations less complicated
Computationally more expensive	Computationally less expensive
Can describe motions of electrons: necessary for UV/Vis spectra, electron transfer reactions, etc.	Cannot describe motions of electrons
Involves no empirical parameters ("ab initio" method) or only a few ("semi-empirical" method)	Involves many empirical parameters

Quantum mechanical calculations + machine learning used to develop and improve classical force fields

13

Disambiguation

- Electronic Structure Theory
- Quantum Mechanics
- Quantum Chemistry
- Theoretical Chemistry
- Computational Chemistry
- Molecular Modeling

Physics (solid state, soft matter)

Chemistry (soft matter, small molecules)

Biology (large molecules)

14

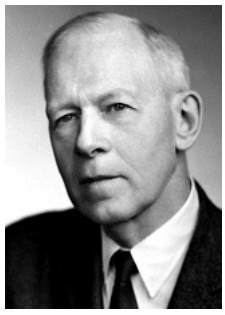
Nobel Prizes for the Development of Quantum Mechanics

- 1918: Max Planck
- 1921: Albert Einstein
- 1922: Niels Bohr
- 1929: Louis de Broglie
- 1932: Werner Heisenberg
- 1933: Erwin Schrödinger, Paul Dirac
- 1945: Wolfgang Pauli
- 1954: Max Born

15

Nobel Prize for Computational Chemistry (1966)

"for his fundamental work concerning chemical bonds and the electronic structure of molecules by the molecular orbital method"

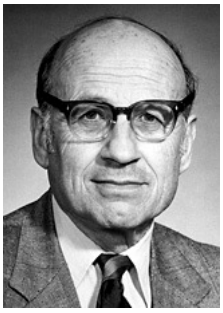


Robert S. Mulliken

Photo: © The Nobel Foundation

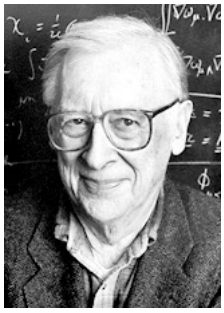
16

Nobel Prize for Computational Chemistry (1998)



Walter Kohn

"for his development of the density-functional theory"



John A. Pople

"for his development of computational methods in quantum chemistry"

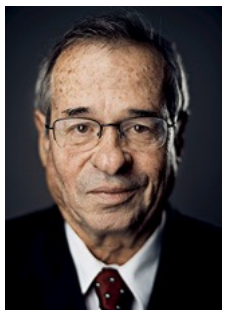
Photos: © The Nobel Foundation

17

Nobel Prize for Computational Chemistry (2013)

Martin Karplus

Michael Levitt

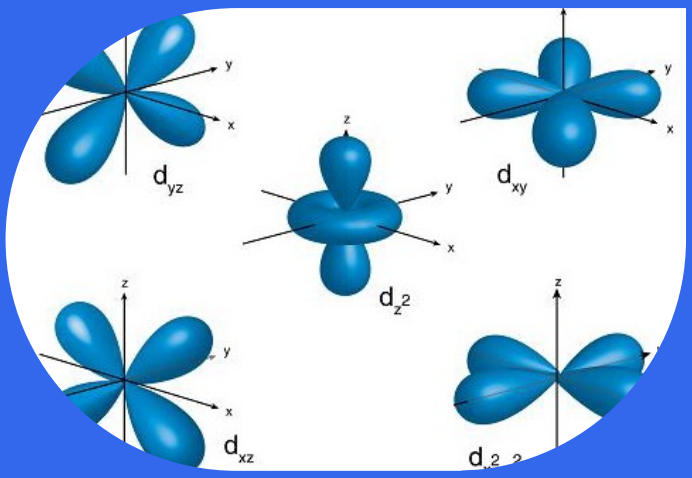


Arieh Warshel

"for the development of multiscale models for complex chemical systems"
= biological

Photos: © The Nobel Foundation

18



A Very Brief Recall of Quantum Mechanics

19

A Short Quiz...

1 Go to wooclap.com

2 Enter the event code in the top banner

Event code
CLBEXP

20

20

Why Quantum Mechanics?

- QM explains observations which cannot be reconciled with classical physics
- QM describes the nature of matter at the atomic scale
- Differences to classical physics:
  - Quantities may be restricted to discrete values (quantization)
  - Objects have characteristics of both particles and waves (wave-particle duality)
  - Limits to the precision in which pairs of physical quantities can be known (uncertainty principle)
- Elementary particles and atomic nuclei carry an intrinsic form of angular momentum called spin

Schrödinger Equation

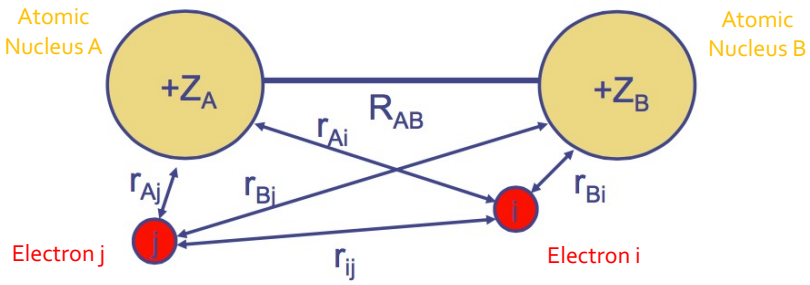
$$\hat{H}\Psi = E\Psi$$

$$\Psi = \Psi(x_1, y_1, z_1, \omega_1, x_2, y_2, z_2, \omega_2, \cdots)$$

- The fundamental equation of quantum chemistry
- Time-independent form for stationary states
- Wavefunction Ψ describes a stationary state of the system
- Hamiltonian Ĥ:
  - operator corresponding to the total energy of the system
  - sum of the kinetic energies of all the particles, plus the potential energy of the system

Any observable (=quantity which can be measured in a physical experiment) is associated with an operator

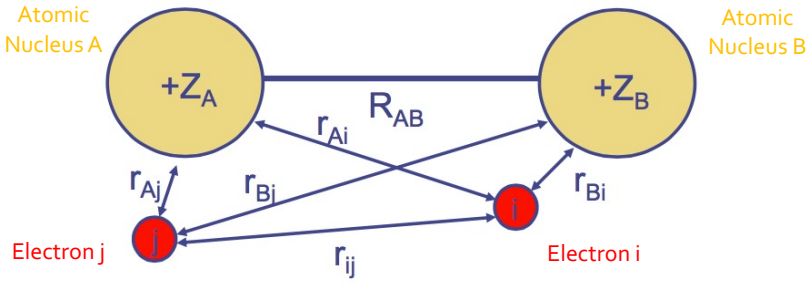
The Molecular Hamiltonian



$$\hat{H} = \hat{T}_N(\mathbf{R}) + \hat{T}_e(\mathbf{r}) + V_{eN}(\mathbf{r},\mathbf{R}) + V_{NN}(\mathbf{R}) + V_{ee}(\mathbf{r})$$

Nuclear kinetic E | Electronic kinetic E | Electron/nuc attraction | Nuc/nuc repulsion | Elec/elec repulsion

The Molecular Hamiltonian

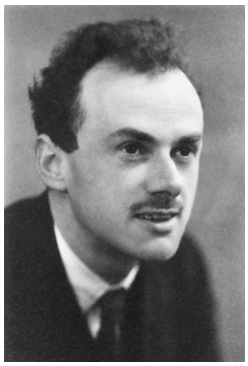


$$\hat{H} = -\sum_{A}^{\text{nuc}} \frac{\hbar^2}{2M_A}\nabla_A^2 - \frac{\hbar^2}{2m}\sum_{i}^{\text{elec}}\nabla_i^2 - \sum_{A}^{\text{nuc}}\sum_{i}^{\text{elec}} \frac{Z_A e^2}{4\pi\epsilon_0 r_{Ai}} + \sum_{A>B}^{\text{nuc}} \frac{Z_A Z_B e^2}{4\pi\epsilon_0 R_{AB}} + \sum_{i>j}^{\text{elec}} \frac{e^2}{4\pi\epsilon_0 r_{ij}}$$

Nuclear kinetic E | Electronic kinetic E | Electron/nuc attraction | Nuc/nuc repulsion | Elec/elec repulsion

Quantum Mechanics of Many-Electron Systems

"The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble."



Paul Dirac

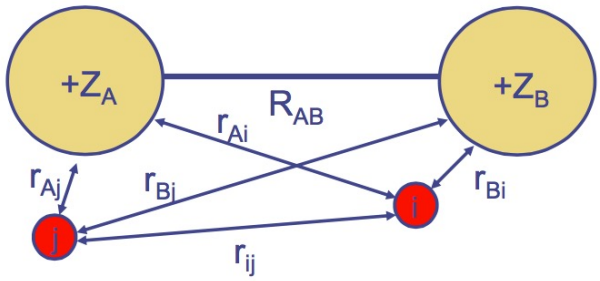
Paul A.M. Dirac, *Proc. R. Soc. Lond. A* **123** 714-733;
DOI: 10.1098/rspa.1929.0094 (1929)

Photo: © The Nobel Foundation

25

25

The Molecular Hamiltonian



$$\hat{H} = \hat{T}_N(\mathbf{R}) + \hat{T}_e(\mathbf{r}) + V_{eN}(\mathbf{r},\mathbf{R}) + V_{NN}(\mathbf{R}) + V_{ee}(\mathbf{r})$$

Nuclear kinetic E | Electronic kinetic E | Electron/nuc attraction | Nuc/nuc repulsion | Elec/elec repulsion

© Sherrill

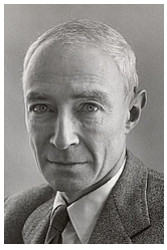
26

26

The Born-Oppenheimer Approximation

- Developed by Max Born and J. Robert Oppenheimer (~1927)
- Separation of nuclear and electronic parts of the Schrödinger equation, despite V_{eN} term
- Nuclei are much heavier than electrons (>2000 times)
- Nuclear motions are much slower than electronic motions
- Approximation: electrons move "instantly" compared to nuclei
- Equivalently: nuclei frozen compared to electrons

Max Born



J. Robert Oppenheimer

BO-Approximation: the Nuclear Schrödinger Equation

Split wavefunction into nuclear and electronic parts:

$$\Psi(\boldsymbol{r}, \boldsymbol{R}) = \Psi_e(\boldsymbol{r}; \boldsymbol{R})\Psi_N(\boldsymbol{R})$$

Neglect of small terms leads to:

$$\{\hat{T}_N(\boldsymbol{R}) + E_{el}(\boldsymbol{R})\}\Psi_N(\boldsymbol{R}) = E_{tot}\Psi_N(\boldsymbol{R})$$

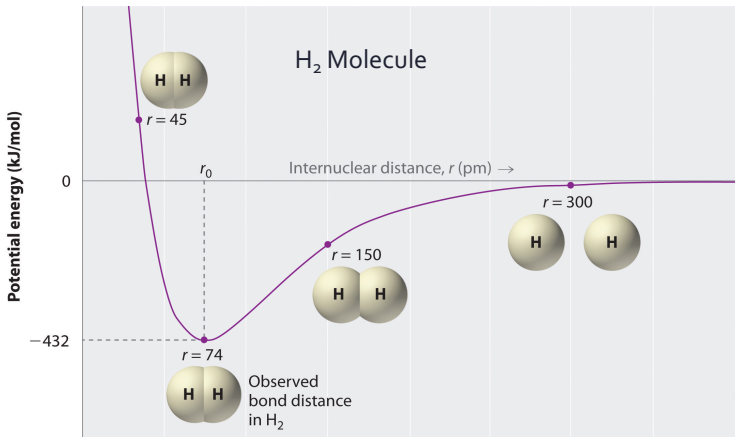
Kinetic Energy

Potential Energy

The nuclei move in the potential E_{el} created by the electrons ("potential energy surface")

Potential Energy Surfaces (PES)

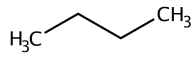
- The (electronic) energy E_{pot} is the potential that the nuclei feel. It depends on **R** and is called the potential energy surface (PES)
- The electronic energy for an individual molecule does not change due to translation or rotation, it only depends on the internal degrees of freedom



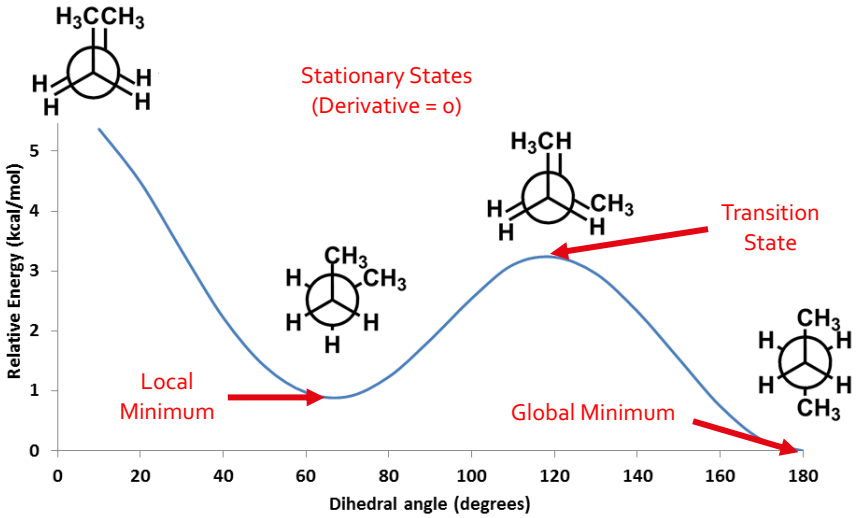
https://chem.libretexts.org/

29

PES: One-dimensional Projection



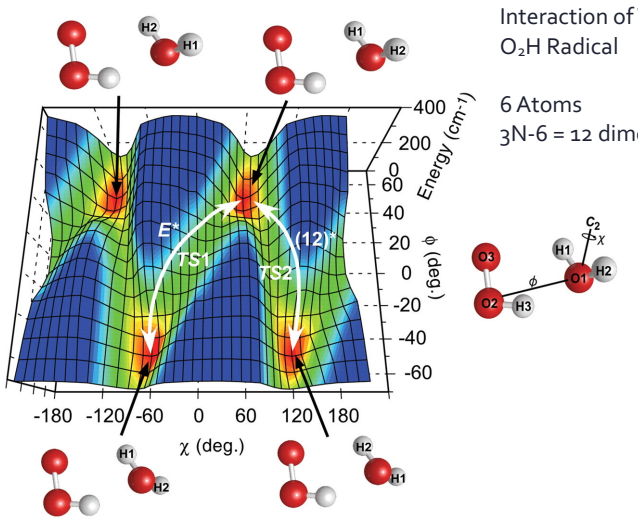
Butane (C_4H_{10})
14 atoms
3N-6 = 36 dimensions



Coordinate scan done at B3LYP/6-311+G(2d,p) using WebMO
http://www.chem.wisc.edu/content/conformations-alkanes

30

PES: Two-Dimensional Projection



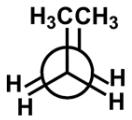
Interaction of Water with O_2H Radical

6 Atoms
$3N-6 = 12$ dimensions

K. Suma et al. *Science* **311**, 1278 (2006)

Geometry Optimization using Quantum Mechanics

Butane Molecule

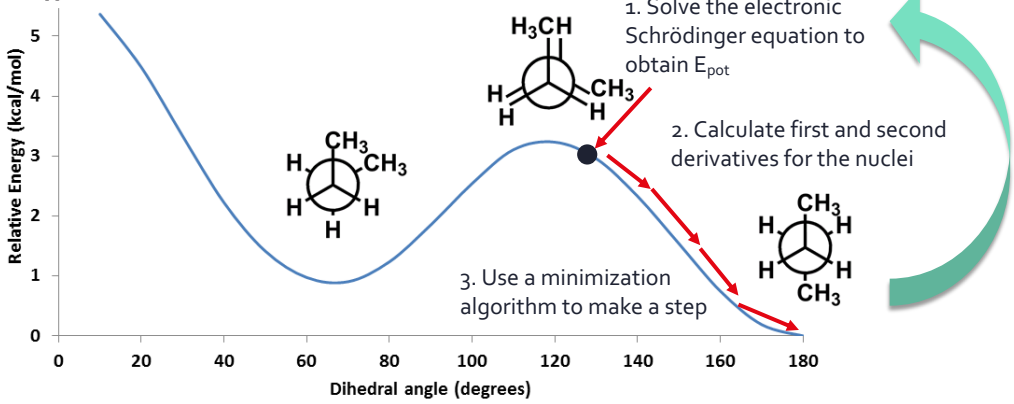


0. Invoke the BO Approximation

1. Solve the electronic Schrödinger equation to obtain E_{pot}

2. Calculate first and second derivatives for the nuclei

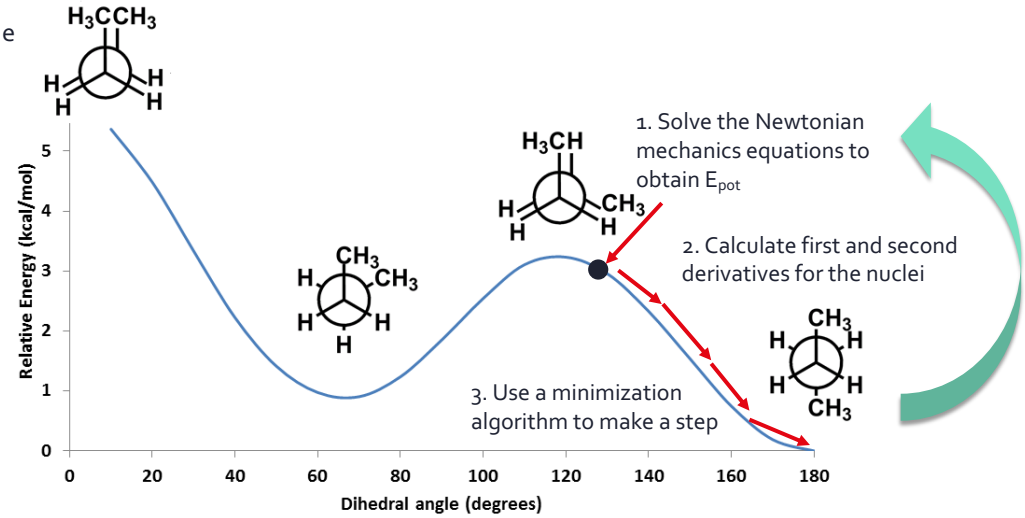
3. Use a minimization algorithm to make a step



https://chem.libretexts.org/

Geometry Optimization using Classical Mechanics

Butane Molecule



https://chem.libretexts.org/

33

33

Solving the Electronic Schrödinger Equation: Orbitals

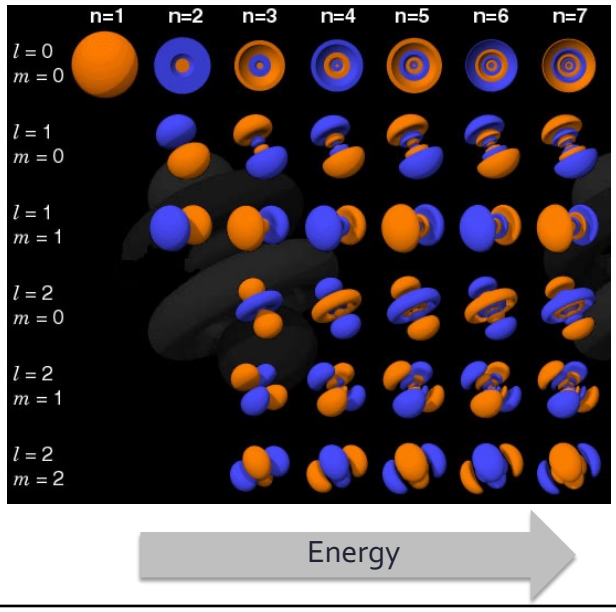
- Orbital: a mathematical function that describes the wave-like behavior of an electron and that can be used to calculate the **probability of finding an electron in any specific region**
- Orbital: **one-electron function**
- Electron: **spatial** coordinates (x,y,z) and **spin** coordinate ω (spin orbital)
- Electrons are **fermions**, spin of +½ or -½
- One orbital can contain a **maximum of two electrons**; the two electrons must have opposing spins (Pauli exclusion principle)
- Orbitals can be calculated analytically for atoms with **one single electron only** (H, He^{+}, Li^{2+},…)

34

34

Atomic Orbitals of the Hydrogen Atom

- The principal quantum number ***n*** determines the radius of an orbital and the number of *nodal surfaces* (**n-1**)
- A *nodal surface* is a region of space in which the **probability of finding an electron is zero**
- ***n, l, m***: principal, angular, magnetic quantum numbers
- **s**: spin quantum number
- **4 quantum numbers** (n,l,m,s) describe properties of an electron in an atom



35

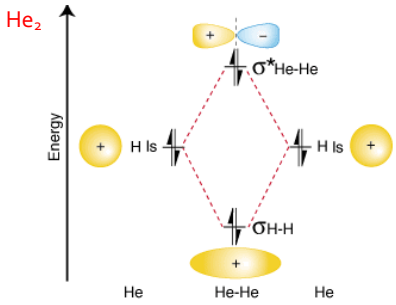
Atomic Orbitals of Multi-Electron Atoms

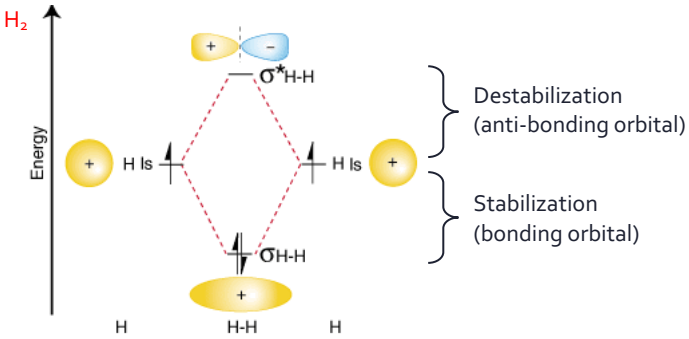
- Schrödinger equation **cannot be solved exactly** for systems with more than one electron
- **Electron correlation**: movement of each electron is influenced by the presence of all other electrons.
  1. **Fermi correlation** (exchange correlation): correlation preventing two parallel-spin electrons from being found at the same point in space
  2. **Coulomb correlation**: correlation between the spatial position of electrons due to their Coulomb repulsion
- Despite electron correlation, orbitals of multi-electron atoms **resemble the hydrogen atom** orbitals
- **Core** orbitals: low energy, filled with two electrons, chemically unreactive
- **Valence** orbitals: higher energy, outer shell orbitals, sometimes filled by an unpaired electron, participate in chemical bonding

36

Molecular Orbitals: Linear Combination of Atomic Orbitals

Combination of s-type orbitals (angular quantum number zero, spherical shape)





σ orbitals: symmetrical about the internuclear axis

The H_2 molecule is stable

The He_2 molecule is not stable

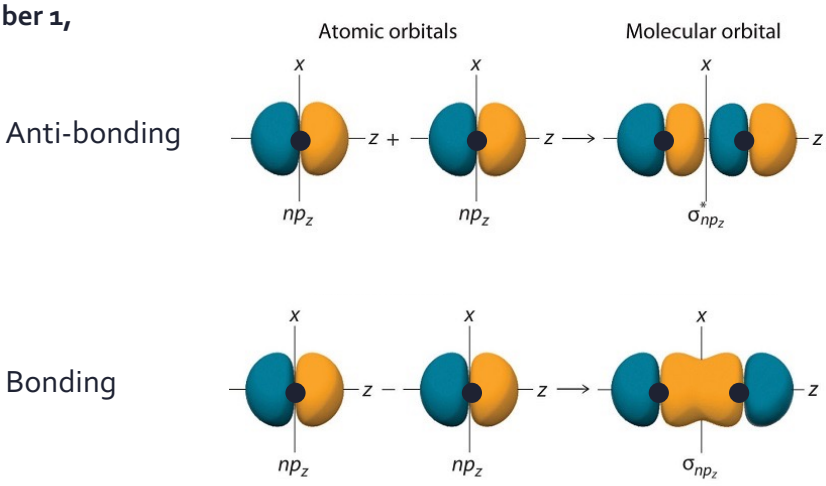
https://chem.libretexts.org/

37

37

Molecular Orbitals: Linear Combination of Atomic Orbitals

Combination of p-type orbitals (1st possibility) (angular quantum number 1, dumbbell shape)



σ-orbitals: symmetrical about the internuclear axis

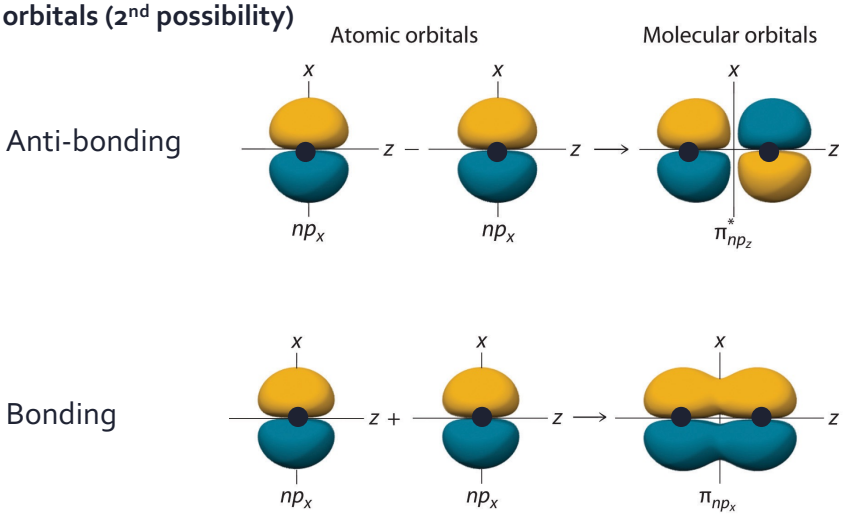
https://chem.libretexts.org/

38

38

Molecular Orbitals: Linear Combination of Atomic Orbitals

Combination of p-type orbitals (2nd possibility)



π-orbitals: nodal plane along the internuclear axis

https://chem.libretexts.org/

39

39

Orbitals on a Computer: Introduction of a Basis Set

- Quantum chemical equations are easier to solve if each (atomic) orbital is written as a linear combination of fixed basis functions

$$\chi_i = \sum_{\mu=1}^{K} C_{\mu i} \tilde{\chi}_\mu$$

orbital — basis function

- The basis functions are usually atom-centered Gaussian functions (or plane waves in physics)

© Sherrill

40

40

Basis Sets

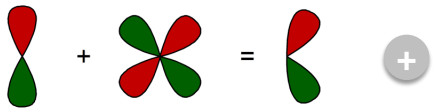
- Gaussian type orbitals (GTO): $\phi_{abc}^{GTO}(x,y,z) = Nx^a y^b z^c e^{-\zeta r^2}$
- a, b, c: control angular momentum
- Convenient for calculations

- Each basis function can in turn be composed of a fixed linear combination of primitive Gaussian functions with the **same exponent** (zeta)
- **Minimal basis set**: one basis function for each atomic orbital (AO)
- **Double-zeta**: two basis functions for each AO
- **Triple-zeta**: three basis functions for each AO
- **Split-valence basis**: one basis function for each core AO, more basis functions for each valence AO

41

Basis Sets

- Polarization functions:

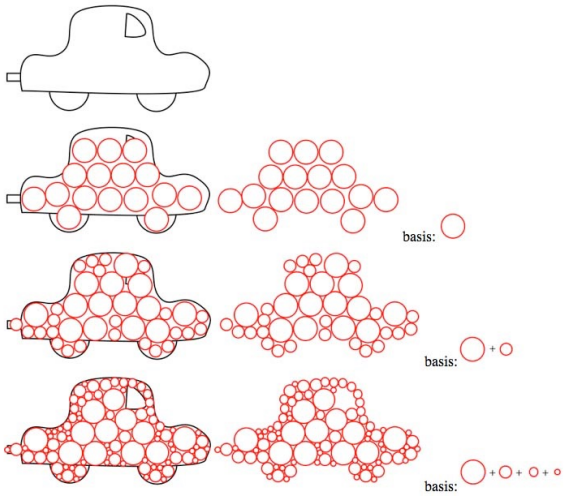


- Diffuse functions: extended Gaussian basis functions with a small exponent
  - Necessary, e.g., for anions or electronegative atoms (fluorine) with a lot of electron density
  - Necessary for accurate binding energies of van der Waals complexes (bound by dispersion)

42

Examples of Pople Basis Sets

- **6-31G**: split-valence, double-zeta for valence orbitals, 6 gaussians for core AO, 3+1 gaussians for valence AO
- **6-31G*** or **6-31G(d)**: same as above, but with polarization functions on non-hydrogen atoms
- **6-311+G*** or **6-311+G(d)** : split-valence, triple-zeta for valence orbitals, with polarization and diffuse functions
- The bigger the basis set, the better (= lower) the energy but the higher the computational time



Hartree-Fock Molecular Orbital Theory

Foundation of quantum chemistry ('ab initio' methods)

1. Invoke the Born-Oppenheimer approximation
2. Express the electronic wavefunction as a Slater determinant of (trial) spin orbitals
3. Solve iteratively for those orbitals (basis set coefficients) which minimize the electronic energy
   (variational method: all approximate solutions have a higher energy than the true energy)

Mathematically equivalent to assuming each electron interacts only with the average charge cloud of the other electrons (Coulomb correlation missing)

Performance of Hartree-Fock Molecular Orbital Theory

Property	Accuracy
Bond Lengths	± 0.02 Å
Bond Angles	± 2°
Vibrational Frequencies	± 11%
Dipole Moments	± 0.3 D
Dissociation Energies	± 25-40 kcal/mol

Hartree-Fock struggles with bond-breaking, diradicals, transition metals, excited states

Beyond Hartree-Fock: Electron Correlation

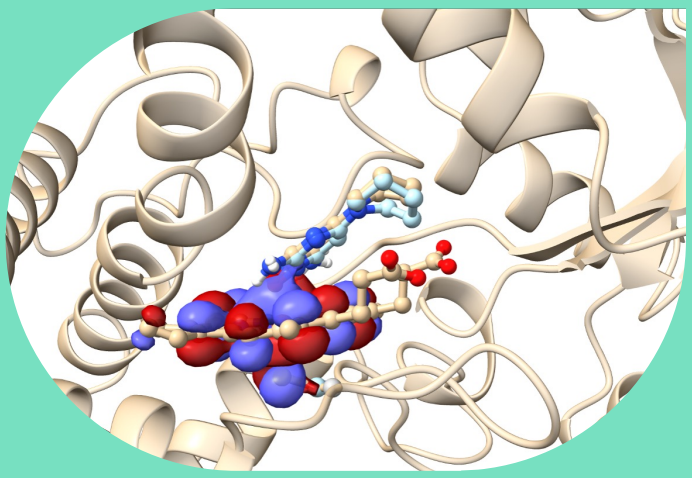
- **Semi-Empirical Methods:** fit some parameters to experimental values
- **Wavefunction-Based Electron Correlation Methods**: Express the wavefunction as a linear combination of several Slater determinants
  - Configuration interaction (e.g. CISD)
  - Many-body perturbation theory (e.g. MP2)
  - Coupled-cluster theory (e.g. CCSD(T))
- **Density Functional Theory (DFT)**: Use the electron density as the fundamental quantity instead of the wavefunction
- **Quantum Monte Carlo Methods (QMC)**

Computational Costs

Method	Accuracy	Max. Nr. Atoms
Semi-empirical	Low/Medium	~10000
Hartree-Fock	Low	~1000
DFT	**Medium/High**	**~1000**
MP2	High	~500
CISD	High	~50
CCSD(T)	Very High	~50
Quantum Monte Carlo	Very High	~50
Multireference CI,CC	Ultra High	~20

Density Functional Theory

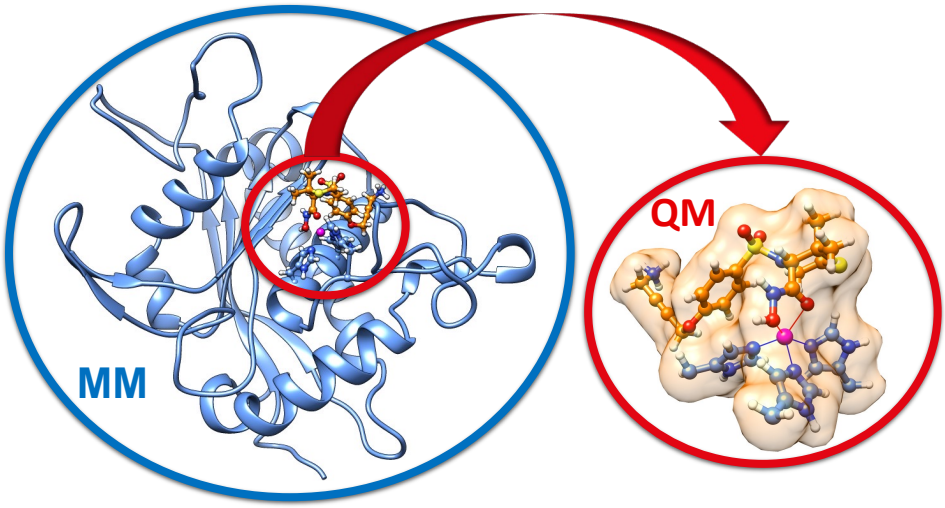
- DFT improves upon Hartree-Fock by including an approximate treatment of the correlated motions of electrons
- Treatment of electron correlation is computationally much cheaper than in correlated wavefunction methods
- The electron density ρ is the measure of the probability of an electron being present at a point in space
- Kohn-Sham DFT: all terms can be exactly computed, except for the exchange-correlation functional $E_{xc}[\rho]$
- No systematic "best functional", but a hierarchy exists
- Popular functionals: BLYP, B3LYP
- DFT struggles to describe dispersion interactions, but corrections have been developed



Use of QM in Docking

49

Hybrid Quantum/Classical (QM/MM) Description



Molecular Mechanics

Quantum Mechanics

50

50

Nobel Prize for Computational Chemistry (2013)

Martin Karplus

Michael Levitt

Arieh Warshel

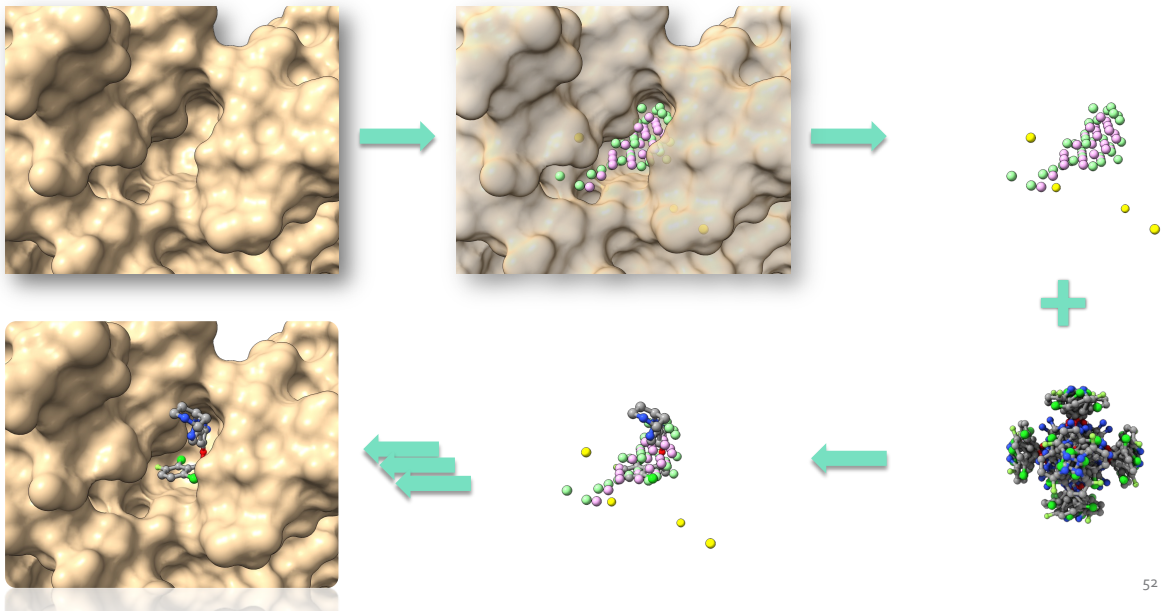
"for the development of multiscale models for complex chemical systems"

Photos: © The Nobel Foundation

51

51

Attracting Cavities: Sampling Algorithm



52

52

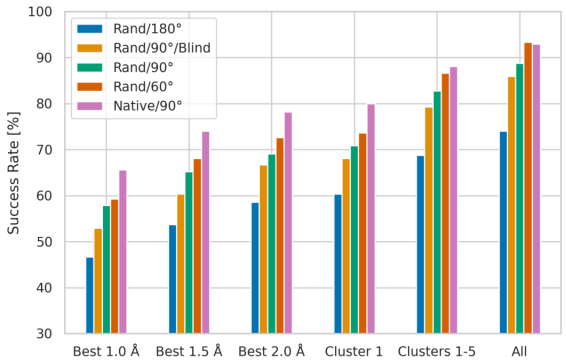
Attracting Cavities: Scoring and Features

- Scoring:
  - CHARMM force-field for the target
  - Merck Molecular Force Field (MMFF) for the ligand
  - Fast analytical continuum treatment of solvation (FACTS) for implicit solvation
- Python code running CHARMM molecular modeling program
- Parallelization for shared-memory nodes
- Sampling tunable by many parameters: high-confidence to fast docking
- Target flexibility
- Covalent docking
- Free access through SwissDock webserver (www.swissdock.ch)

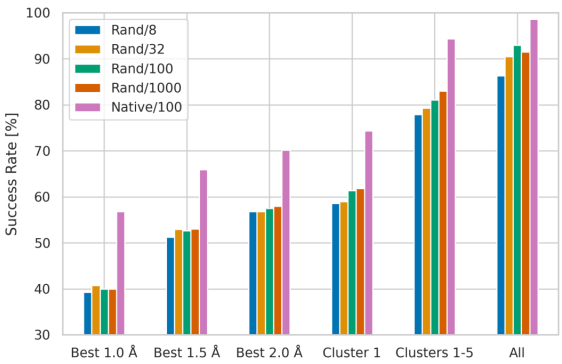
U.F. Röhrig, A. Grosdidier, V. Zoete, O. Michielin, *J. Comput. Chem.* **2009**, *30*, 2305
V. Zoete, M. A. Cuendet, A. Grosdidier, O. Michielin, *J. Comput. Chem* **2011**, 32, 2359
M. Goullieux, V. Zoete, and U.F. Röhrig, *J. Chem. Inf. Model.* **2023**, *63*, 7847

Redocking Success Rates

Attracting Cavities (AC)



AutoDock Vina



AC:
- Higher success rates (both better sampling + scoring)
- Success rate increases systematically with better sampling
- Global (blind) docking yields similar success rates

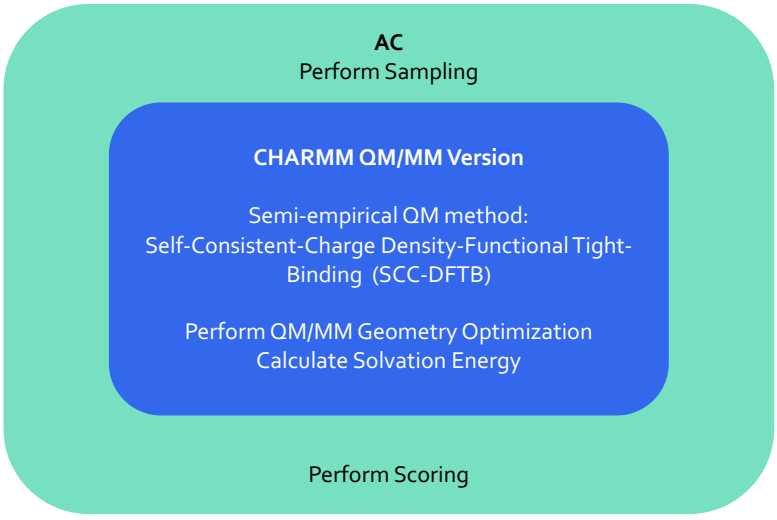
Rand: randomized ligand conformation
Native: bioactive ligand conformation taken from complex structure

Redocking Success Rates and CPU Timings

	Success Rate [%]	CPU Time [min]
AC		
Rand, 180°, 4 RIC	58.6	9.2
Rand, 90°, 4 RIC	69.1	51
Rand, 90°, 4 RIC, global	67.0	270
Native, 90°, 4 RIC	78.2	50
AutoDock Vina		
Rand, Exh. 8	56.8	0.9
Rand, Exh. 16	58.2	2.0
Rand, Exh. 100	57.9	11
Native, Exh. 100	70.2	11

Rand: randomized ligand conformation
Native: bioactive ligand conformation taken from complex structure

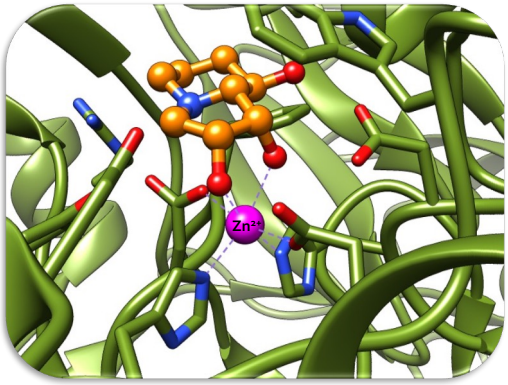
Hybrid QM/MM Docking in AC 1.0



P. Chaskar, V. Zoete, U.F. Röhrig, *J. Chem. Inf. Model* **54**, 3137 (2014)
P. Chaskar, V. Zoete, U.F. Röhrig, *J. Chem. Inf. Model* **57**, 73 (2017)
Cui, Q.; Elstner, M.; Kaxiras, E.; Frauenheim, T.; Karplus, M. A. *J. Phys. Chem. B* **105**, 569 (2001)

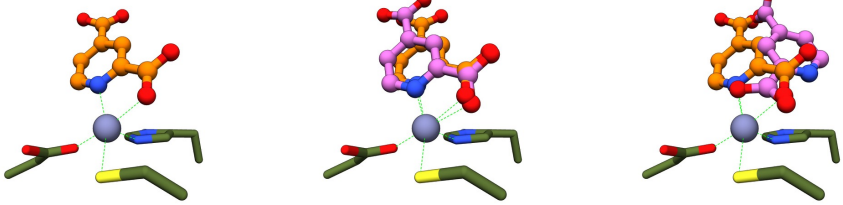
QM/MM Docking Application: Zinc Metalloproteins

- Strong polarization by zinc ion (2+)
- Many high-quality ligand-bound X-ray structures available
- Diversity: members of all major enzyme classes
- Include many drug targets
  - Carbonic Anhydrases
  - TNF-α converting enzyme (TACE, ADAM17)
  - Matrix metalloproteinases (MMPs)
- Benchmark set:
  - High-quality, curated X-ray structures
  - 226 Zinc-bound complexes
  - QM system: ligand + Zn + coordinating side chains



QM/MM Docking Success Rate for Zinc Metalloproteins

Docking Success: root-mean-square deviation (RMSD) < 2 Å



X-ray Structure Reference | RMSD 1.0 Å Success | RMSD 2.7 Å Failure

Method	Success Rate
Classical AC 1.0	58%
AutoDock	30%
AutoDock Vina	38%
QM/MM AC 1.0	**72%**

Higher success rate due to better description of polarization and charge distribution

QM/MM Docking Success Rates for Different Targets

Method	Non-covalent Drugs	Zinc-binding Ligands	Heme-binding Ligands	CPU Time
AutoDock	47%	30%	34%	~ 7 h
AutoDock Vina	60%	38%	59%	~ 0.6 h
GOLD	66%	54%	**84%**	**~ 0.006 h**
Classical AC 1.0	**79%**	58%	38%	~ 3 h
QM/MM AC 1.0	**75%**	**72%**	**75%**	~ 8 h

➔ On-the-fly QM/MM Docking performs well for all types of cases (balanced, covalently bound, polarized)

P. Chaskar, V. Zoete, U.F. Röhrig, *J. Chem. Inf. Model* **54**, 3137 (2014)
P. Chaskar, V. Zoete, U.F. Röhrig, *J. Chem. Inf. Model* **57**, 73 (2017)

61

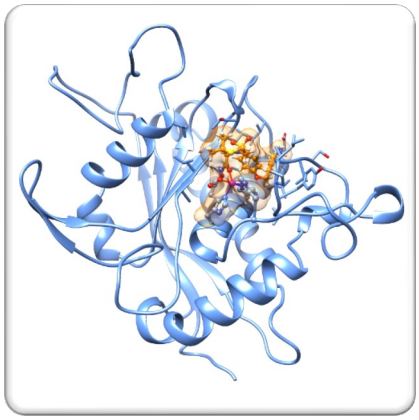
TNF-α Converting Enzyme (TACE)

Zinc-dependent protease (also called ADAM17)

Potential target in cancer, heart disease, diabetes, rheumatoid arthritis, kidney fibrosis, Alzheimer

Ligand binding influences pK_a of active site Glu

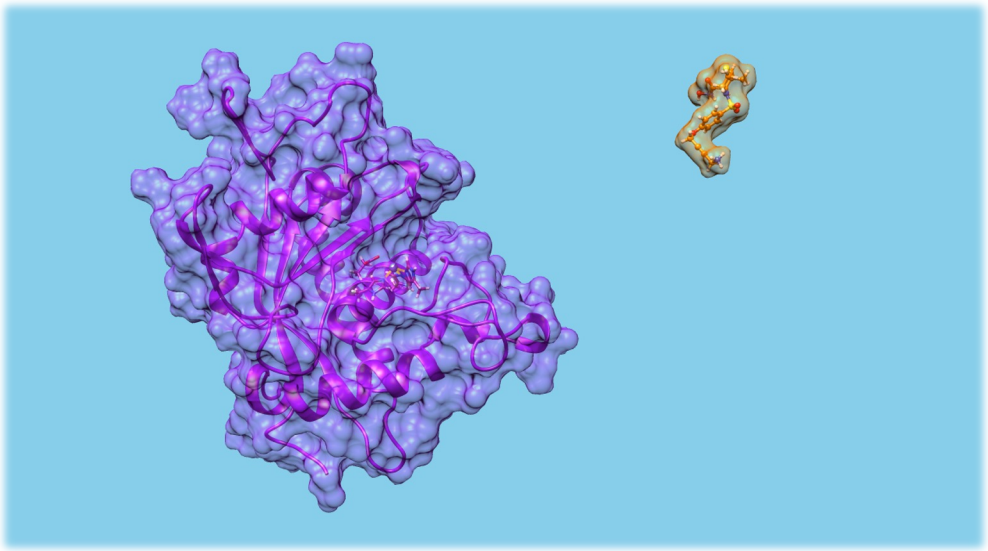
15 complexes in benchmark set



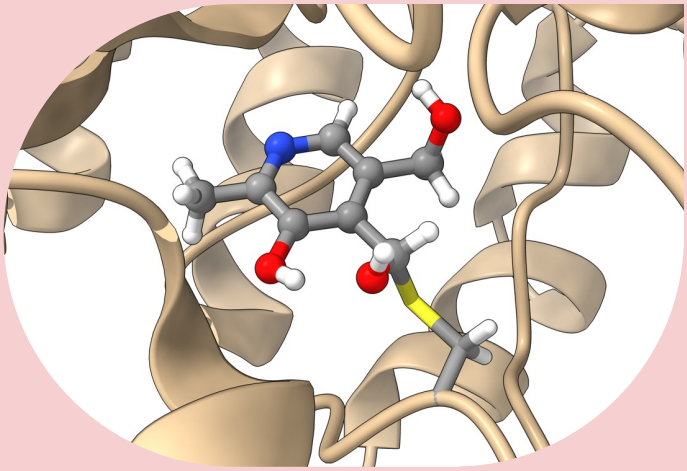
Method	Docking Success Rate
Classical AC 1.0	0%
QM/MM AC 1.0	**93%**

62

Proton Transfer in TACE



63



Covalent Inhibitors

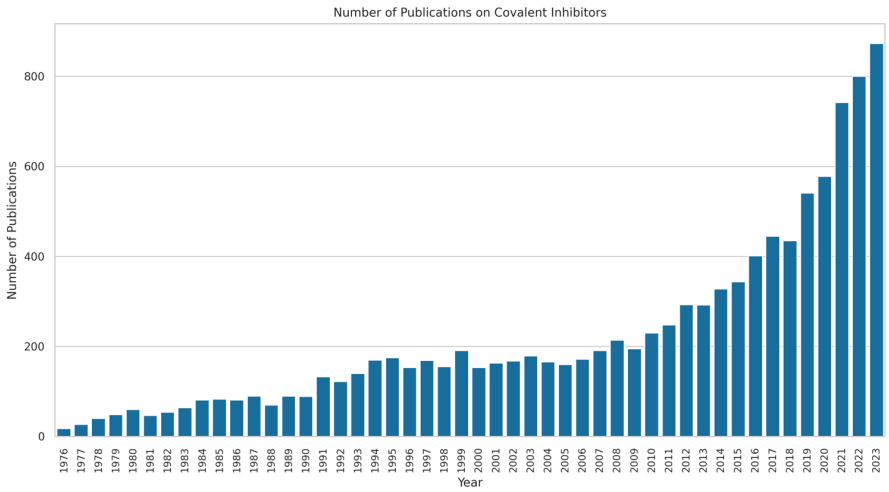
64

Covalent Inhibitors

- Prominent examples:
  - β-lactam antibiotics
  - proton pump inhibitors
- Safety concerns hampered development
- Advantages:
  - extended duration of action
  - prevention of drug resistance
  - applicability to targets with shallow binding sites not amenable to conventional approaches

65

Comeback of Covalent Inhibitors



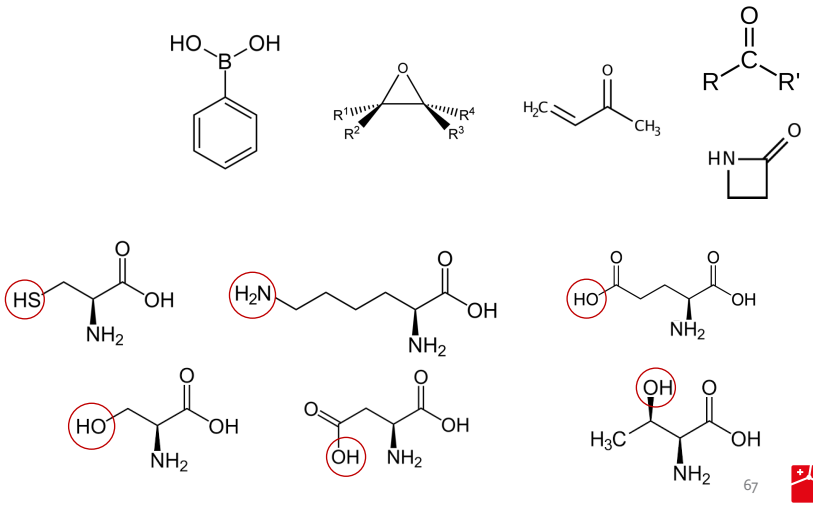
Recent FDA Approvals:
- Oncology
- Anti-bacterials
- Hepatitis C

Also important for inhibitors of the main protease of SARS-CoV-2

66

Covalent Inhibition Mechanism

- Electrophilic ligand "warheads" react with nucleophilic amino acid sidechains (Lewis acid-base reaction)
- Examples of electrophiles:
  - Boronic acids
  - Epoxides
  - Michael acceptors
  - Carbonyls
- Nucleophilic sidechains:
  - Cysteine
  - Serine
  - Lysine
  - Aspartate
  - Glutamate
  - Threonine

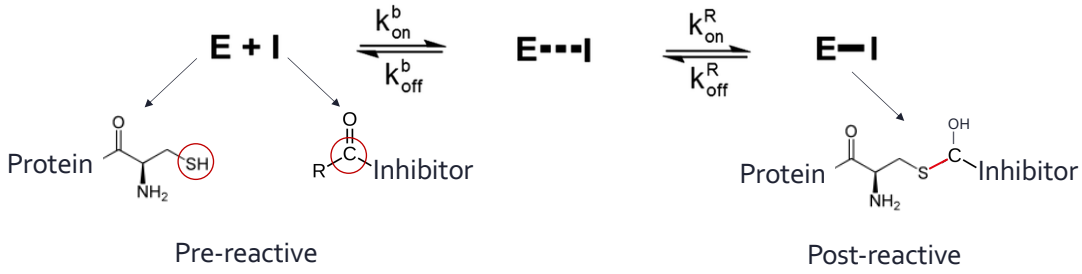


67

Covalent Inhibition Mechanism

Two-step mechanism

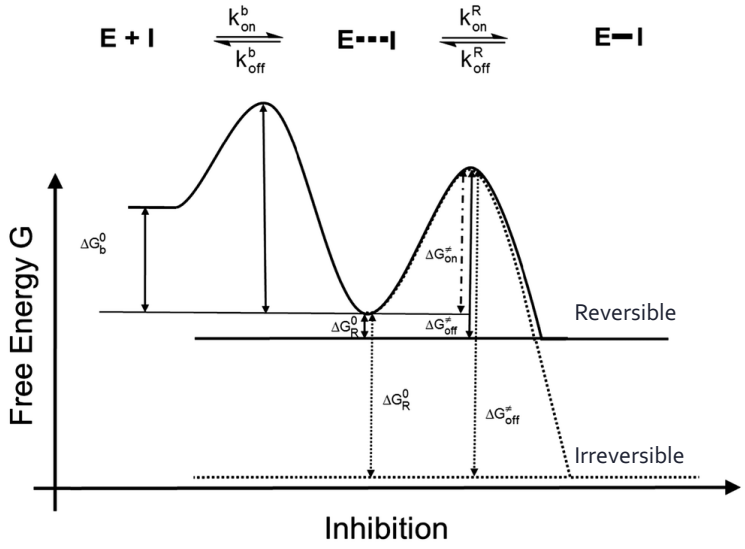
1. Non-covalent complex (vdW and electrostatic interactions)
2. Covalent complex (formation of covalent bond)



Can be reversible or irreversible

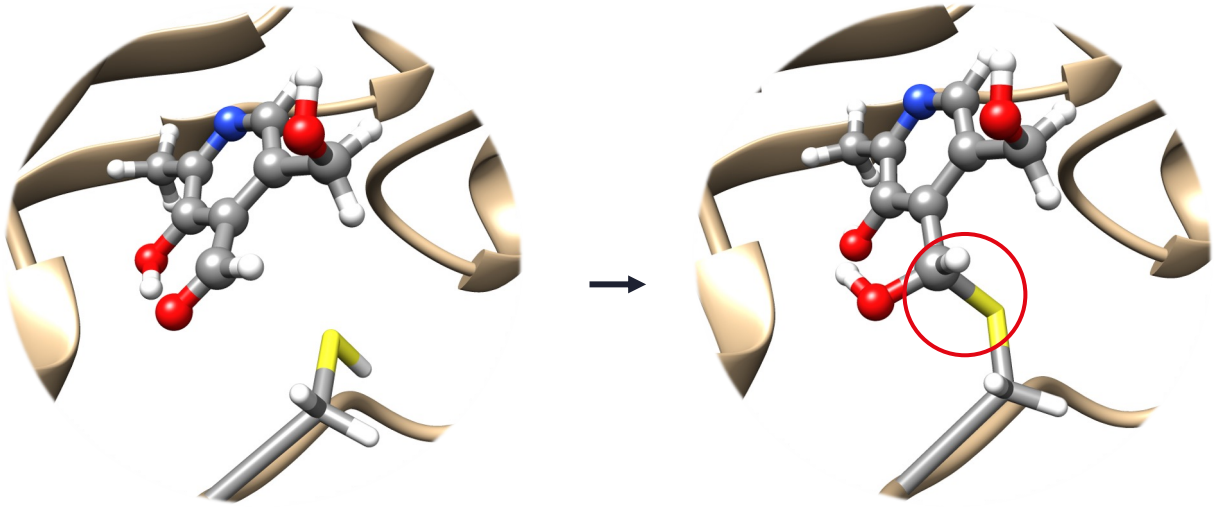
68

Covalent Inhibition Mechanism



Schneider *et al.*, *New J. Chem.* **39**, 5841 (2015)

From non-covalent to covalent

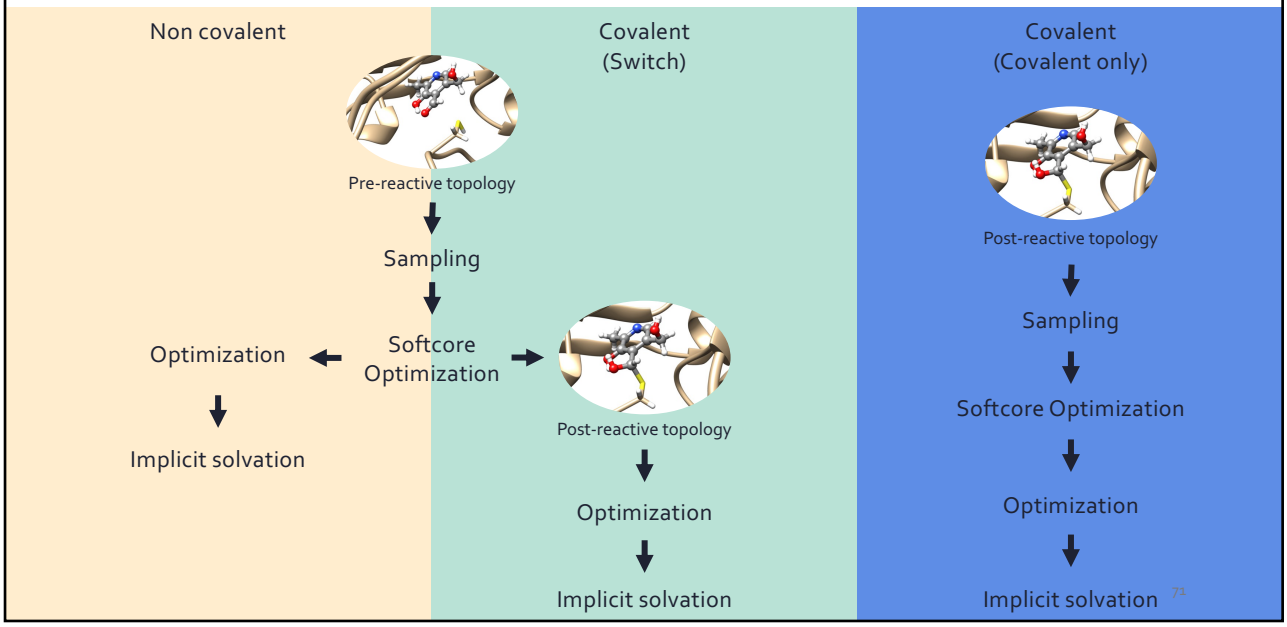


Non-covalent complex
(pre-reactive topology)

Covalent complex
(post-reactive topology)

Structure of 1td2 (Pyridoxal kinase), Martin K. Safo et al., *J. Bacteriol.* **186**, 8074-8082 (2004)

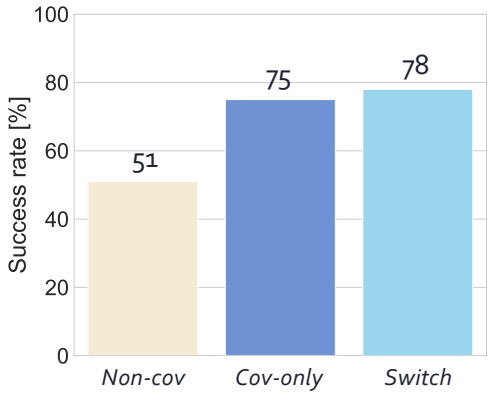
Classical Covalent Docking with AC 2.0



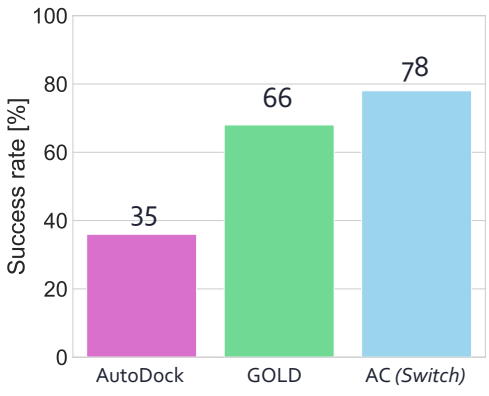
71

Classical Covalent Docking with AC 2.0

Comparison of different methods in AC



Comparison of AC with AutoDock and GOLD



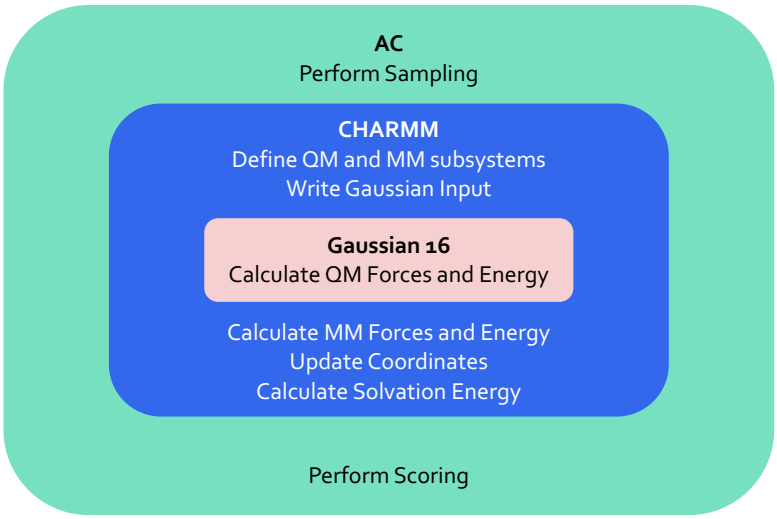
Test set of 304 experimentally resolved covalent complexes

M. Goullieux, V. Zoete, U. F. Röhrig, **Two-Step Covalent Docking with Attracting Cavities**, *J. Chem. Inf. Model.* **63**, 7847–7859 (2023)

72

72

Hybrid QM/MM Docking with AC 2.0

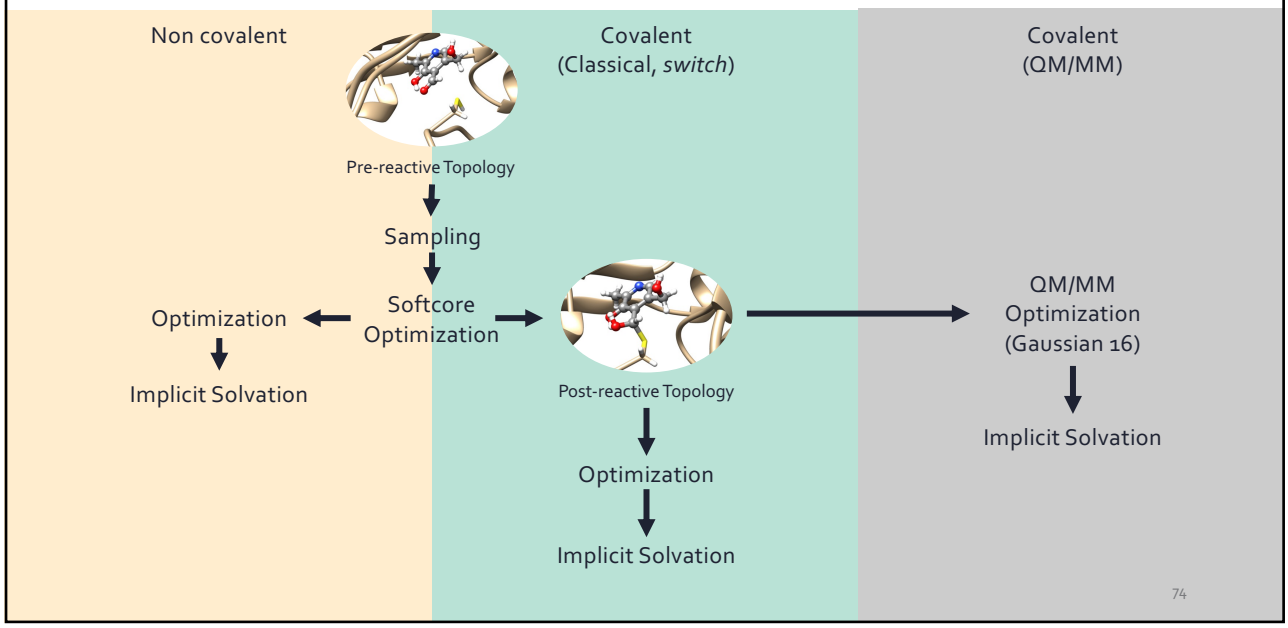


M. Goullieux, V. Zoete, U.F. Röhrig, **Hybrid Quantum/Classical Docking with AC: Covalent and Non-Covalent Ligands**, under review

73

73

Hybrid QM/MM Covalent Docking with AC 2.0



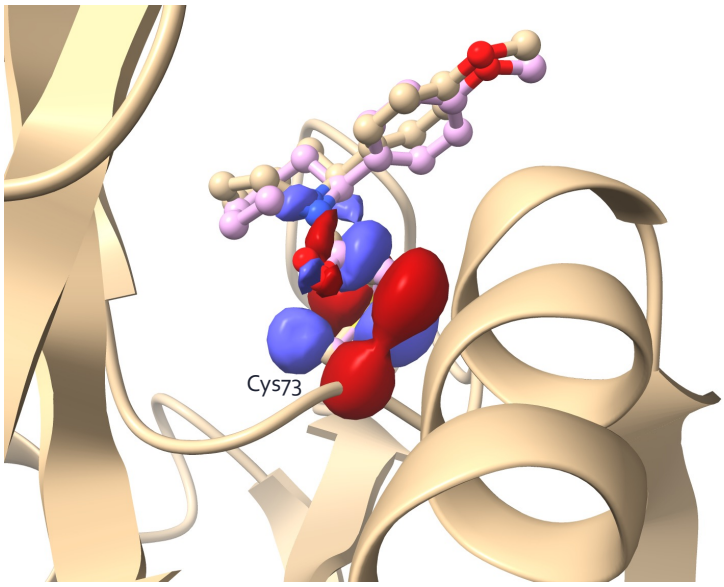
74

QM/MM Docking Results

	Success rate [%]	CPU time [min]
Covalent complexes		
Classical	**71**	30
QM/MM, PM7	70	120
Heme complexes		
Classical	16	25
QM/MM, PM7	**86**	280

- Covalent docking: QM/MM performs as well as force-field method, but not better (very sensitive to structural details and quality of experimental data; solvation not optimal)
- Hemoprotein docking: large improvement due to electronic structure description
- Calculation times on one standard CPU, calculations can be parallelized

Example of Covalent QM/MM Docking

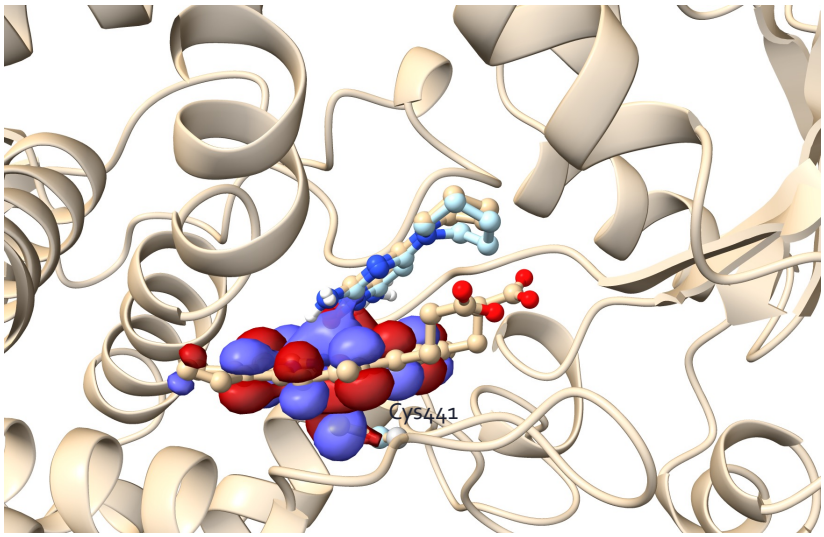


NUDT7 Hydrolase

Experimental structure
Best classical pose
Best QM/MM pose
HOMO Orbital

PDB ID 5qh8

Example of QM/MM Docking of Heme Ligand



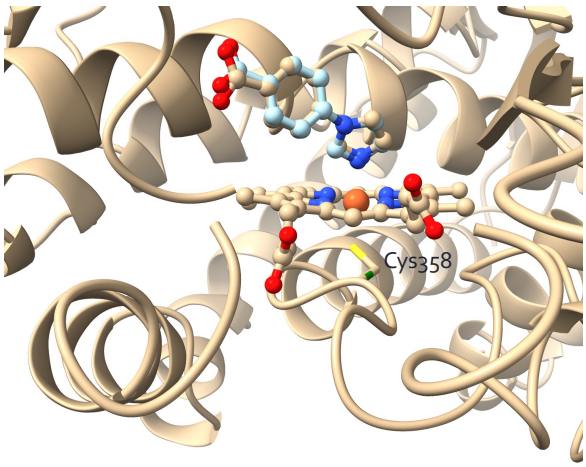
Human Prostacyclin Synthase
with Minoxidil

Experimental structure
Best classical pose
Best QM/MM pose
HOMO Orbital

PDB ID 3b6h

77

Example of QM/MM Docking of Heme Ligand



Cytochrome P450

Experimental structure with ferric heme
Best QM/MM pose with ferrous heme
Best QM/MM pose with ferric heme

"Upon reduction of the heme, the imidazole-based inhibitor Fe–N ligation was not retained."

PDB ID 6u31

M.N. Podgorski et al., *Inorg. Chem.* **2022** *61*, 236-245 DOI: 10.1021/acs.inorgchem.1c02786

78

Summary QM/MM Docking

Advantages:

- QM/MM description can describe electronic structure of ligand/protein complex
- Potentially important for correctly describing ligand/protein interactions
- Application for example for metalloproteins, covalent binders, strongly polarized systems

Disadvantages:

- Very sensitive to quality of structural data
- Computationally more demanding than classical docking

79

Mathilde Goullieux

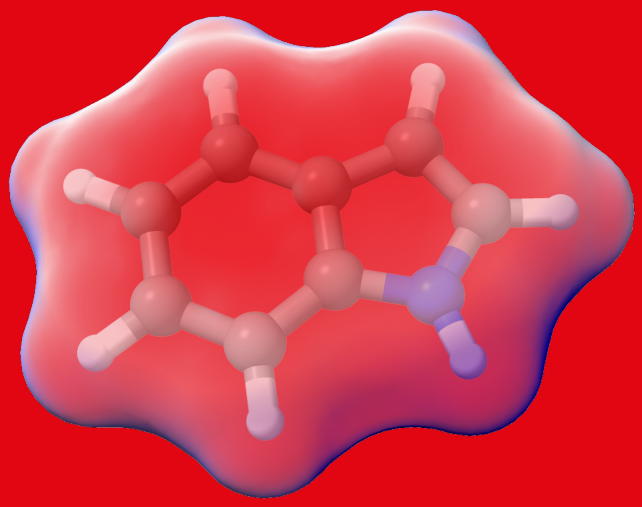
Vincent Zoete

Marine Bugnon

Thank you!

sib.swiss

80



Practical Aspects

82

Before Starting a Quantum Mechanical Calculation

a) What do I want to know about a molecular system?
b) How accurately do I need to know it?
c) How long am I willing to wait for the answer to be computed?
d) What software/hardware can I use to accomplish the task?

At UNIL: curnagl cluster, Gaussian16 license

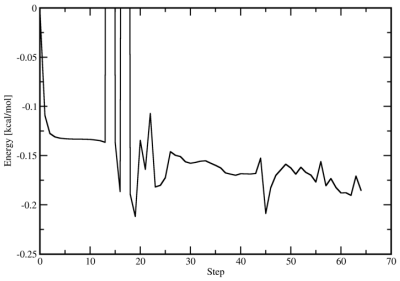
S. C. Sendlinger and C. R. Metz, Journal Of Computational Science Education (2010)

83

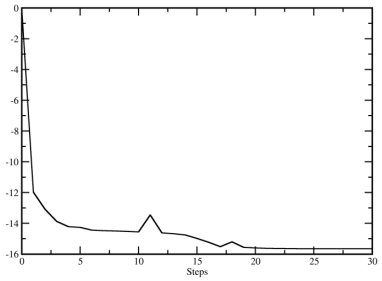
83

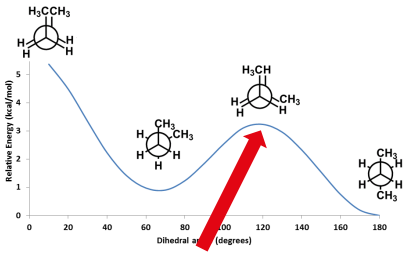
Convergence of Geometry Optimizations

Not Converged



Converged



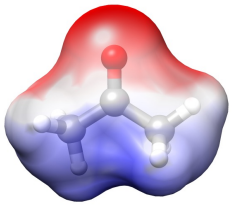


- Convergence criteria for energy and gradients
- Check convergence at the end of a calculation!
- Check vibrational frequencies to detect if a minimum or a saddle point was found (imaginary frequency ⟶ saddle point)

84

Derivation of Partial Atomic Charges

- Not a physical observable, but useful in different contexts
  - Fitting of classical force fields
  - Comparison of chemical properties
- Different possible derivations:
  - Population analysis of wavefunctions (e.g. Mulliken charges)
  - Partitioning of electron density distributions (e.g. Bader or Hirshfeld charges)
  - Electrostatic potential analysis (e.g. RESP charges)



85

Mulliken Charges

- Most widely used quantum-mechanically derived atomic point charges
- Calculate gross orbital populations for each of the contributing atomic basis functions
- Off-diagonal elements distributed equally among contributing atomic centers
- Known problems:
  1. large changes in charges with small changes in basis sets
  2. overestimation of the covalent character of a bond (charges too small)
- In the exercise: valid approximation, because we use the **same basis set** and only consider relative trends in charges of **similar molecules**

Molecular Frontier Orbitals

- Two important molecular orbitals:
  - highest occupied molecular orbital (HOMO)
  - lowest unoccupied molecular orbital (LUMO)
- Important because most likely to be involved in chemical reactions
- **HOMO**: can donate electrons to another molecule, determines a molecule's ability to act as an **electron donor** or **reducing agent**
- **LUMO**: can accept electrons from another molecule, determining a molecule's ability to act as an **electron acceptor** or **oxidizing agent**
- In Lewis acid-base reactions, the HOMO of the base donates electrons into the LUMO of the acid
- Often used for QSAR studies

Exercises with WebMO

- https://www.swiss-webmo.ch/
- Login: your UNIL e-mail address, all in **lower-case** letters
- Password: CADD-qm-2025
- Links available from pdf file