

HPC Summer School 2024: Foundation in Computational Biomolecular and Biosystem Research.  
Research and Innovation Agency of the Republic of Indonesia (BRIN)  
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# Computational Chemistry in Drug Discovery, Molecular Docking, and Molecular Dynamics (MD)

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UNIVERSITAS GADJAH MADA, YOGYAKARTA



## Austria-Indonesia: Cultural Heritage Conservation

Symposium & Commemorative Event In Co-operation with the Austrian Embassy in Jakarta, the Indonesian Embassy in Vienna, the Austrian-Indonesian Society in Vienna  
Alumni and ASEA-Uninet, 29-30 September 2024, Krems, Austria

# Ethnochemistry in Keris Art Conservation: Understanding the Interaction between the art of making, maintaining and Culture in Traditional Art Heritage

Harno D Pranowo, Prof. Dr.

Novi Siti Kussuji Indrastuti

Prima Dona Hapsari

Bambang Pramono

Ajeng Kusumadewi Putri Jatmiko





# Ethnoscience

## Interdisciplinarity of ethnoscience



### Social Sciences

- History, Psychology, Political Science, Geography, Sociology, Philosophy, etc.



### Arts and Humanities

- Cultural Studies, Folklore, Cultural Heritage, Performing Arts, Digital Humanities, etc.



### Natural and Physical Sciences

- Biology (Zoology, Botany, Ornithology, etc.), Forestry, Mathematics, Physics, Astronomy, etc.

- Ethnoscience is a set of knowledge possessed by a society/ethnic group that is part of their tradition
- The emphasis in ethnoscience is the set of knowledge of a society, which is different from the knowledge of other societies.
- Ethnoscience will be able to predict the behavior of society in various activities related to the environment.
- Ethnochemistry is interdisciplinary, combining fields such as chemistry, anthropology, biology, and ecology.

## MEDICINAL HERBS



CALENDULA



LAVENDER



DOG-ROSE



CHAMOMILE



ST. JOHN'S WORT



CLOVER



VALERIAN

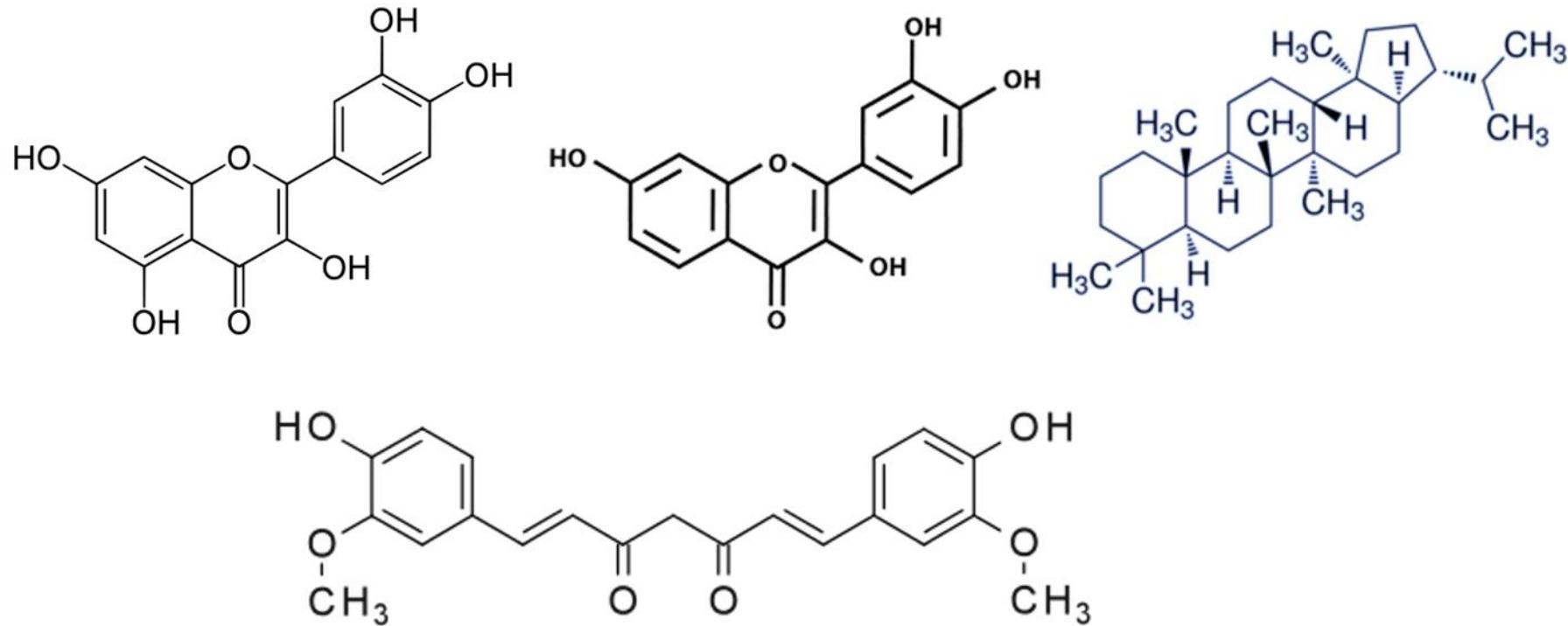


ECHINACEA

## LOGO OBAT ASLI INDONESIA



herbal      standardised  
herbal      Phytopharma-  
ceuticals



In Indonesia, herbs containing multiple components such as flavonoids, triterpenoids, quercetin, and curcumin are believed to be able to improve the immune system through the provision of antioxidant and anti-inflammatory factors.

(Ethnopharmacy)



In the Era of Society 5.0, ethnochemistry has great potential to help develop environmentally friendly and sustainable chemical solutions.



Indonesian batik was recognized as an intangible cultural heritage by UNESCO on October 2, 2009, which is then commemorated as National Batik Day. Indonesian batik is known to have a close relationship with depictions of customs and culture in various regions.

# Culinary in the relief of Borobudur Temple



Buddhist temple reliefs tell stories of life, including the abundance of food around the temple, and talk about culinary arts, the art of preparing, cooking and serving food.



More than 20 types of food ingredients depicted in the temple reliefs are processed into meals. Some are not native to the Borobudur and Indonesia. This implies that trade with other regions outside the archipelago has been going on for a long time considering that Borobudur was built in the 8th and 9th centuries AD.

Lingsir Wengi (Borobudur) by: Hanung Bramantyo  
<https://www.youtube.com/watch?v=7ZyIPRt2m6c>

# Keris in temple relief



Portrait of a sharp weapon with a form resembling a keris at Borobudur Temple (8<sup>th</sup> century)



Monkey troops attack Alengka troops with stabbing weapons similar to keris in the relief of Penataran Temple, Blitar, East Java (12<sup>th</sup> century)

# Keris, Tosan aji created by the Indonesian people

HarnoDepe Gallery



- In 2008, UNESCO recognized the keris as a world cultural heritage that must be preserved for the intangible category, Intangible Cultural Heritage
- Keris can be discussed from a cultural, aesthetic, and philosophical perspective.

## Ethnochemical side:

- Metallurgy techniques involving physics and chemistry.
- Materials of a keris: steel, iron, and pamor
- Coating or making a layer by colouring with a solution of arsenic-containing mining stones.
- Steel becomes greyish, greenish or bluish, iron becomes jet black, while *pamor* remains metallic white



caramenjamaskeris.blogspot.com



- Keris or heirloom cleaning can also be interpreted as a process of bathing or cleaning the heirlooms owned.
- In cleaning a keris, the most important process to do is the process of washing it properly so that the keris is well maintained.
- Cleaning rust and dirt on keris is done traditionally using husk ash and lime water solution. Acid that removes rust/metal oxidation products. Citric acid contained in lime has an acidity level (pH) <3.1.
- Keris is prepared to be washed with warangan. Warangan is a chemical liquid made from a mixture of lime and warangan stone powder and sometimes added with coconut water. The acid content in the liquid can dissolve dirt that sticks to the surface of the keris.
- After being dipped in warangan liquid, the keris will be lifted to be dipped in plain water again and cleaned with soap.
- Finally, the keris will be rinsed using water and dried with a towel. Then, the keris will be smeared with jasmine oil to make it shiny and fragrant.

# plant diversity

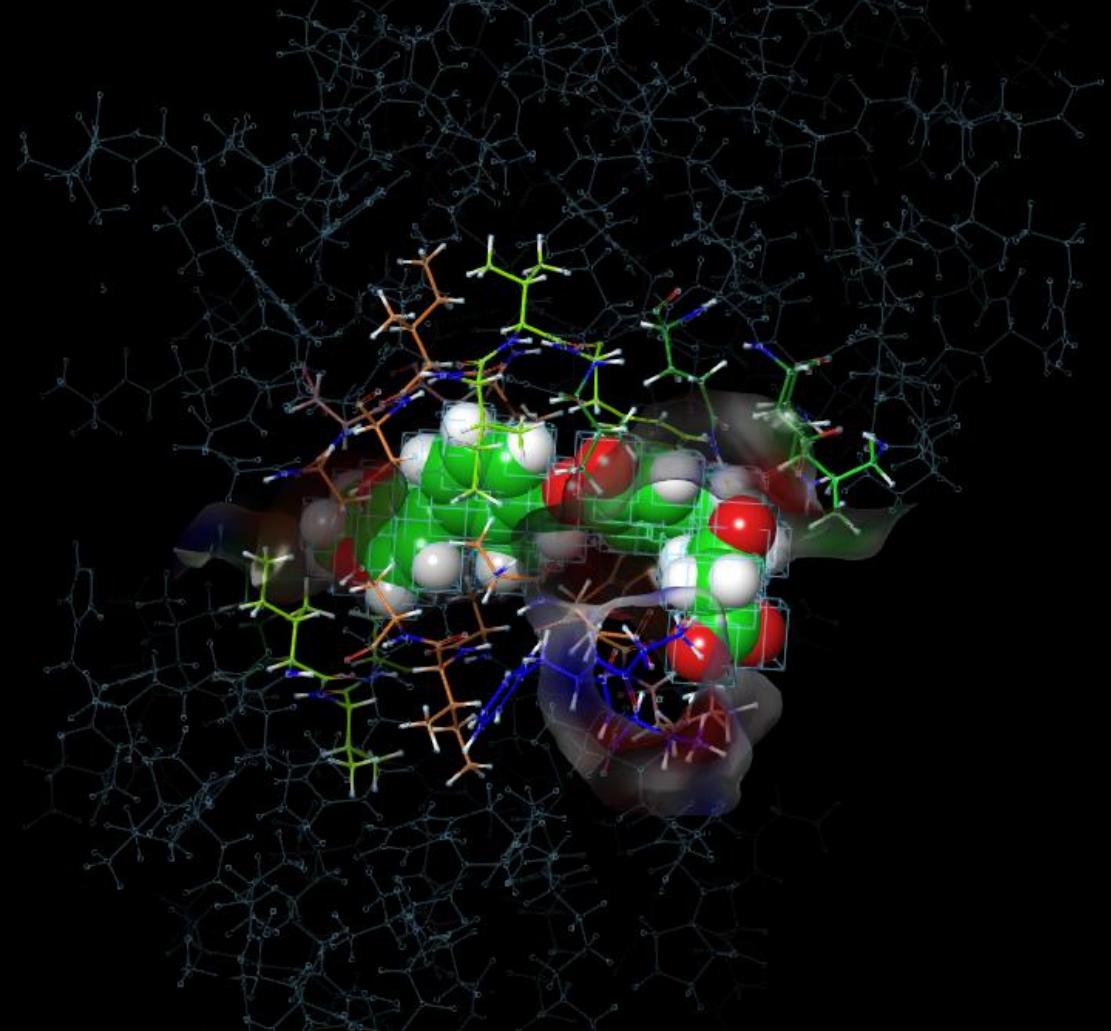
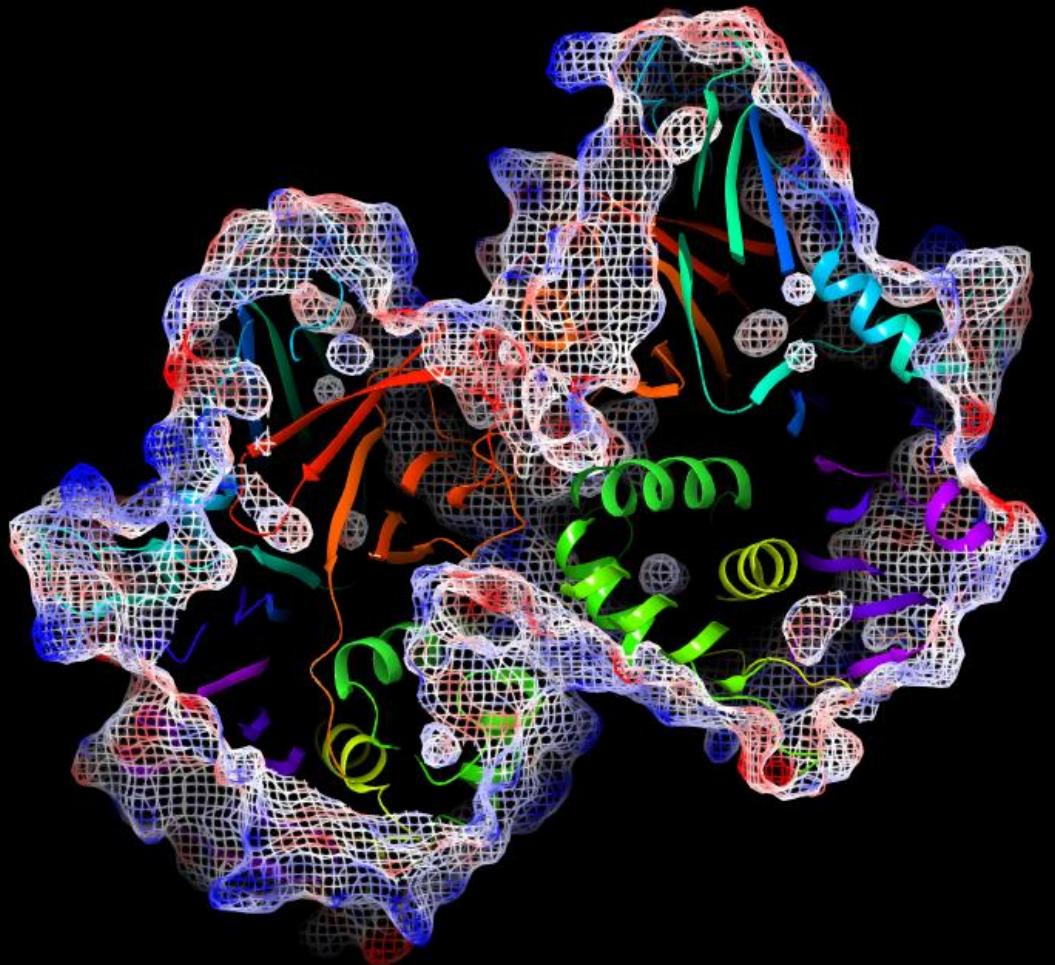


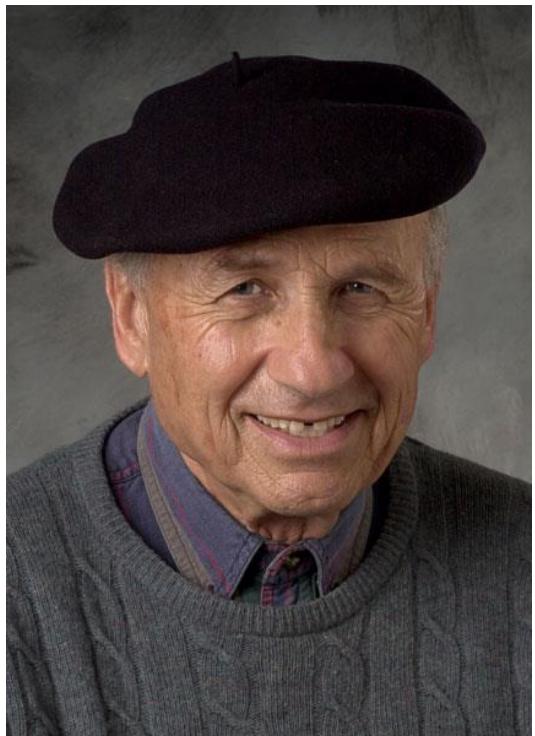
± 75% of plant species on earth are found in Indonesia

1/3 of plant species in Indonesia have medicinal properties

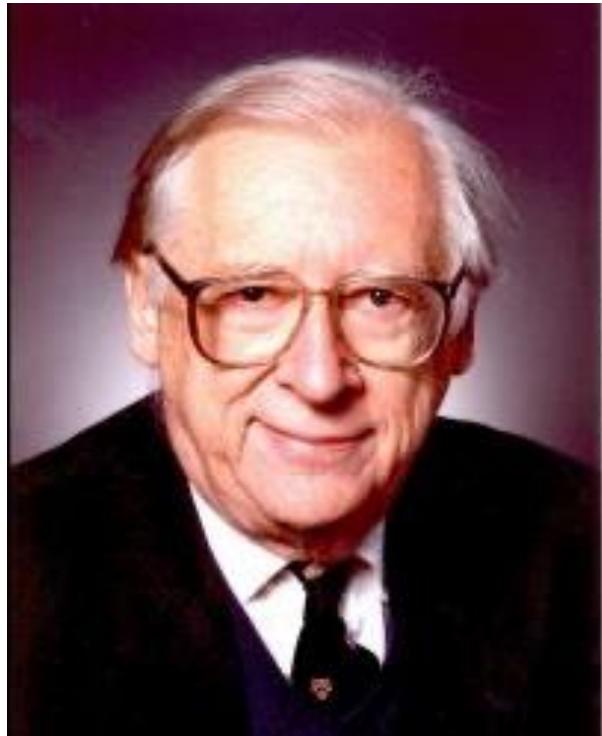
± 300 species have been used as traditional medicine ingredients by the traditional medicine industry.

# Introduction to Computational Chemistry in Drug Discovery:





*Walter Kohn*



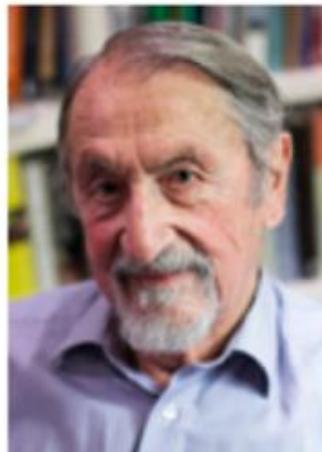
*John A. Pople*

"for his development of **computational methods** in quantum chemistry"  
(The Nobel Prize in Chemistry 1998)



The Nobel Prize in Chemistry 2013  
Martin Karplus, Michael Levitt, Arieh Warshel

# The Nobel Prize in Chemistry 2013



© Harvard University  
Martin Karplus



Photo: © S. Fisch  
Michael Levitt

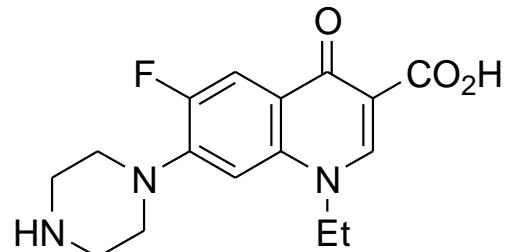


Photo: Wikimedia Commons  
Arieh Warshel

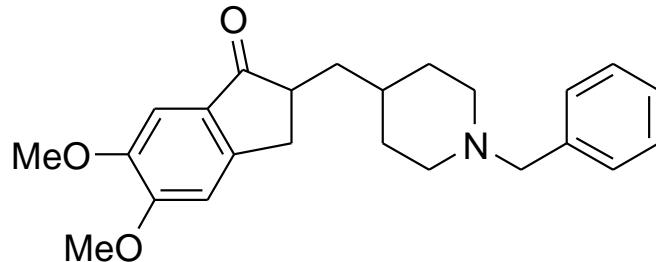
The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel "for the development of multiscale models for complex chemical systems".

# Drug Design Successes

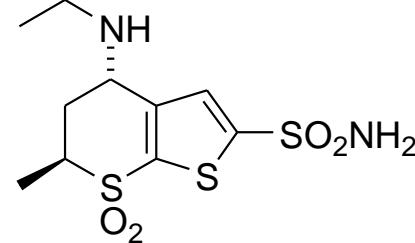
Many drugs have been developed with major contributions from computational methods



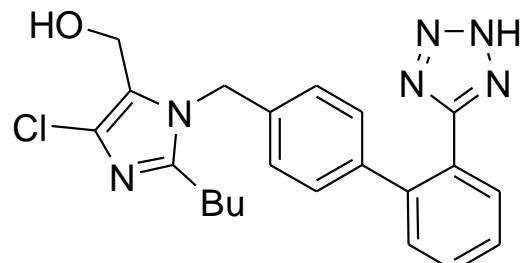
norfloxacin (1983)  
antibiotic  
first of the 6-fluoroquinolones  
QSAR studies



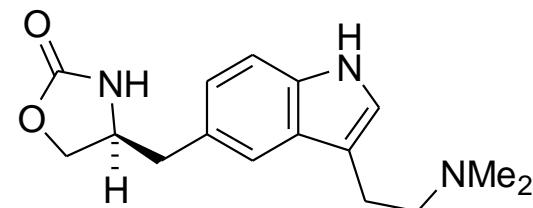
donepezil (1996)  
Alzheimer's treatment  
acetylcholinesterase inhibitor  
shape analysis and docking studies



dorzolamide [Trusopt] (1994)  
glaucoma treatment  
carbonic anhydrase inhibitor  
SBLD and *ab initio* calcs



losartan [Cozaar] (1995)  
angiotensin II antagonist  
anti-hypertensive  
Modeling Angiotensin II octapeptide



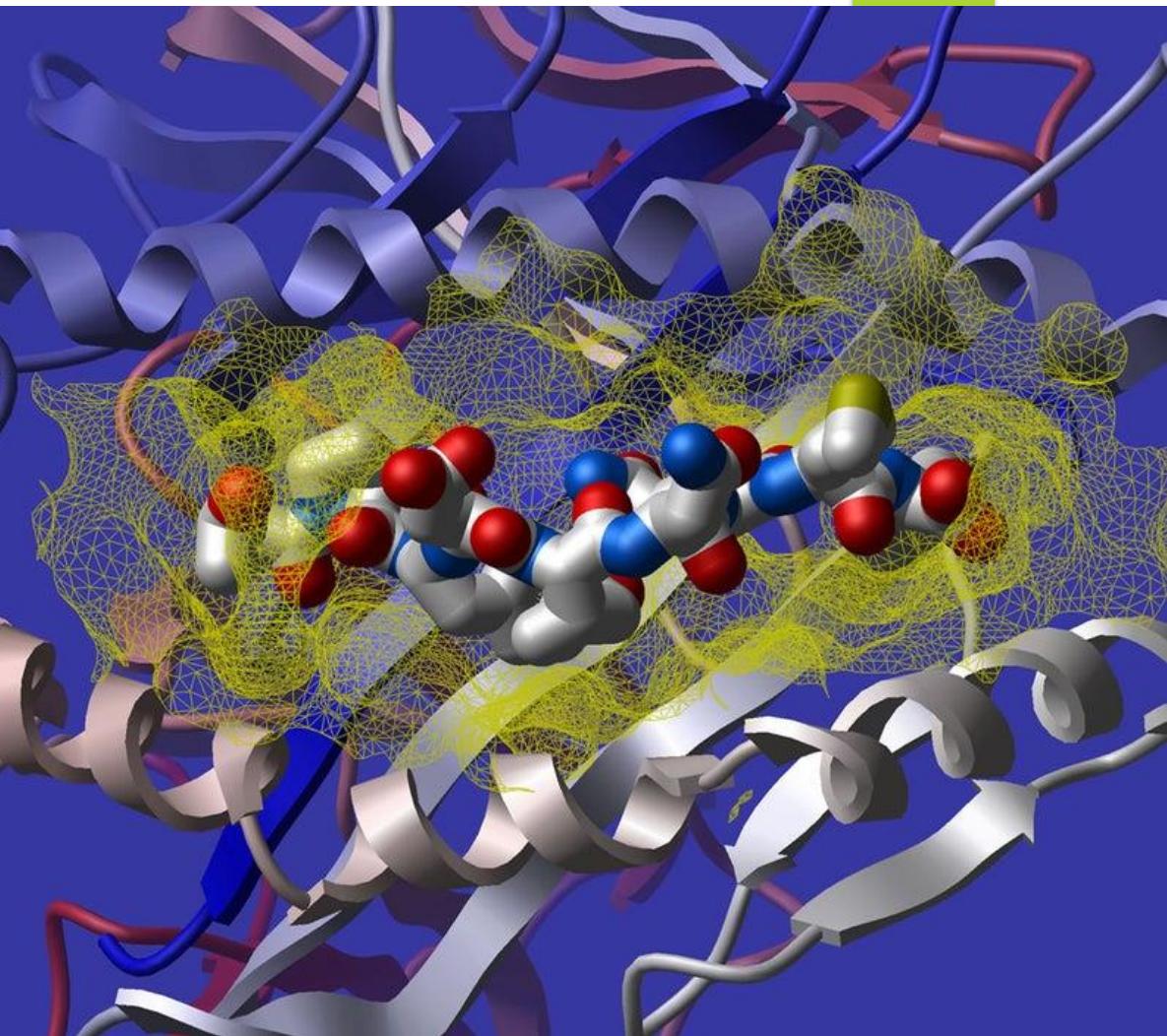
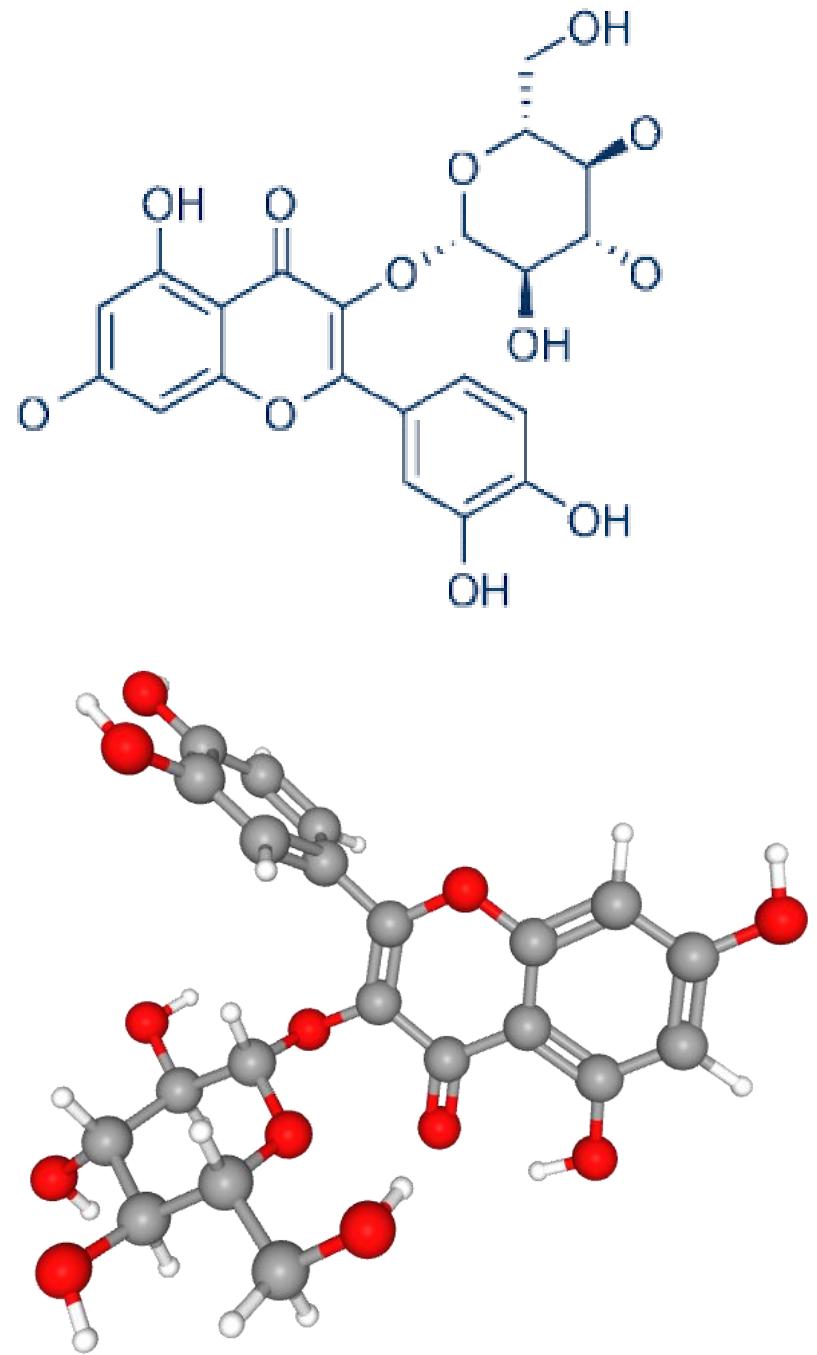
zolmatriptan [Zomig] 1995  
5-HT<sub>1D</sub> agonist  
migraine treatment  
Molecular modeling

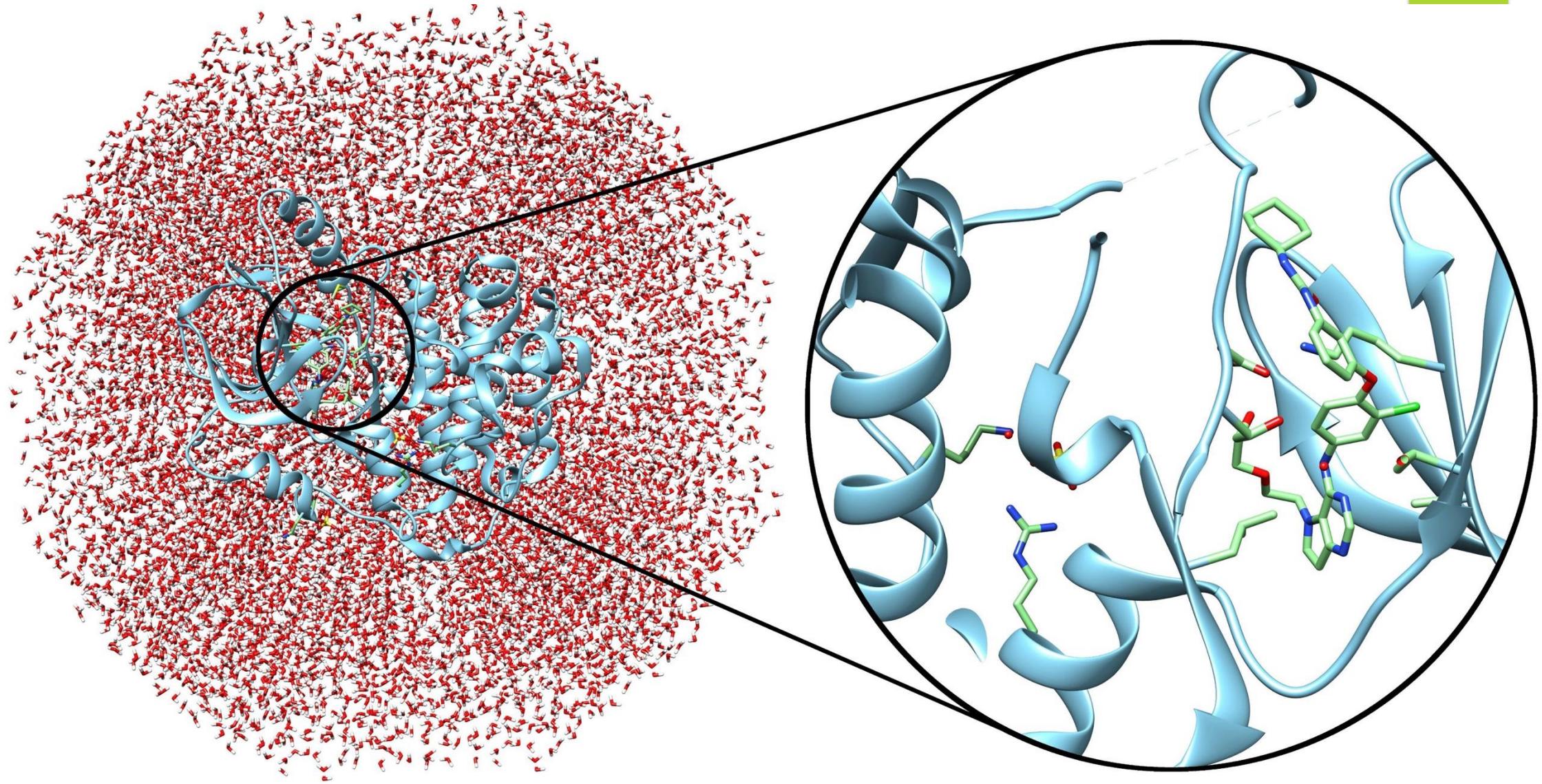


*“Computational chemistry simulates chemical structures and reactions numerically, based in full or in part on the fundamental laws of physics.”*

*Foresman and Frisch*

*In Exploring Chemistry with Electronic Structure Methods, 1996*







Heisenberg 1901-1976  
Nobel Prize Physics 1932

Schroedinger 1887-1961  
Nobel Prize Physics 1933

Slater 1908-1976

Hartree 1897 -1958 Fock 1898 -1974

Pople \* 1925  
Nobel Prize Chemistry 1998

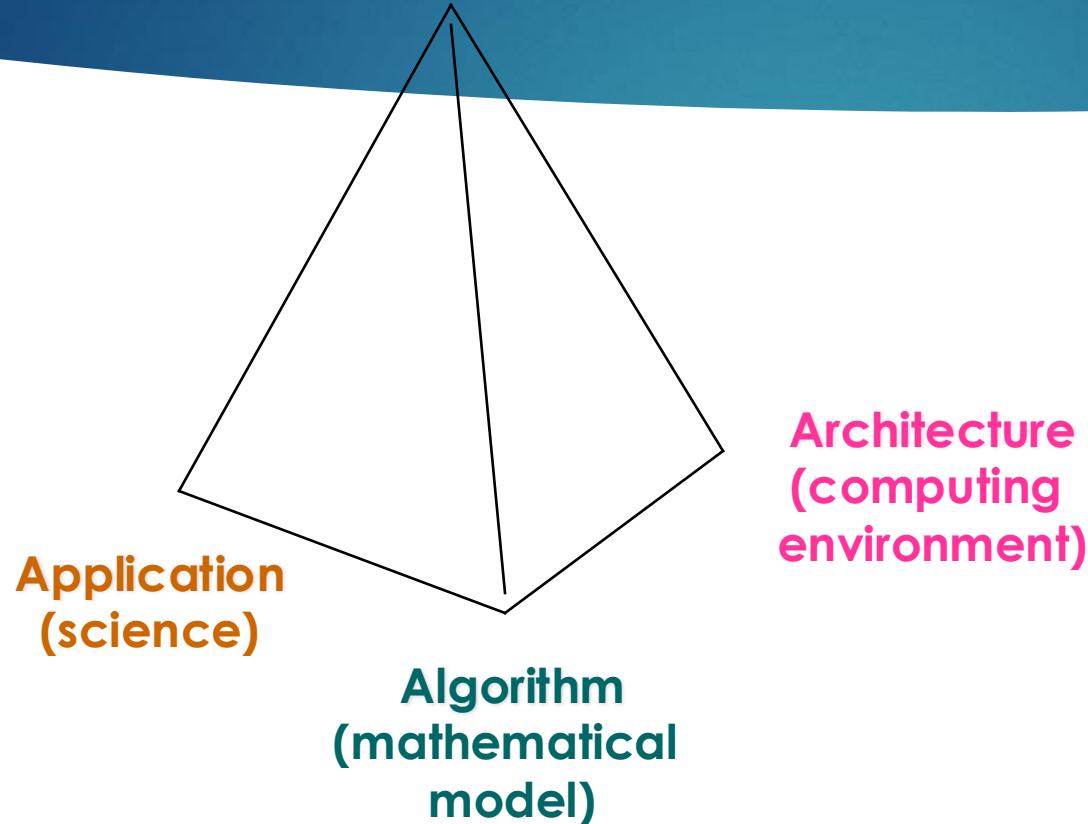
Kohn \*1923  
Nobel Prize Chemistry 1998

# 1927 Solvay Conference



Held in Belgium, the conference was attended by the world's most notable physicists to discuss the newly formulated quantum theory. Of the 12 individuals cited here in [History of Quantum Mechanics](#), only the three mathematicians were not in attendance: William Hamilton was dead, John von Neumann did not publish his book until 1932, and David Hilbert ("physics far too difficult for physicists") probably wasn't invited.

# Computational Sciences: a Tripartite Approach



- ▶ **Application :** understanding the science of the problem
- ▶ **Algorithm:**  
creating a mathematical representation of problem, the “mathematical model”
- ▶ **Architecture :** Choosing the right platform (hardware) to solve the problem

# Computational Chemistry: KIMIA KOMPUTASI

**Computational chemistry** is a branch of chemistry that **uses computer** simulation to assist in solving complex chemical problems. It exploits methods of theoretical **chemistry**, incorporated into efficient computer programs, to calculate **the structures, the interactions, and the properties of molecules**



# What is Computational Chemistry?

Chemistry in the computer instead of in the laboratory

Use computer calculations to predict the structures, reactivity and other properties of molecules

Computational chemistry has become widely used because of

- ▶ Dramatic increase in computer speed and the
- ▶ Design of efficient quantum chemical algorithms

The computer calculations enable us to

- ▶ explain and rationalize known chemistry
- ▶ explore new or unknown chemistry

# Why do Chemistry on a Computer?

- ▶ Calculations are **easy to perform** whereas experiments are difficult
- ▶ Calculations are **safe** whereas many experiments are dangerous
- ▶ Calculations are becoming **less costly** while experiments are becoming more expensive
- ▶ Calculations can be **performed on any chemical system**, whereas experiments are relatively limited
- ▶ Calculations give **direct information** whereas there is often uncertainty in interpreting experimental observation
- ▶ Calculations give **fundamental information** about isolated molecules without the complicating solvent effects

# What Properties can be Calculated?

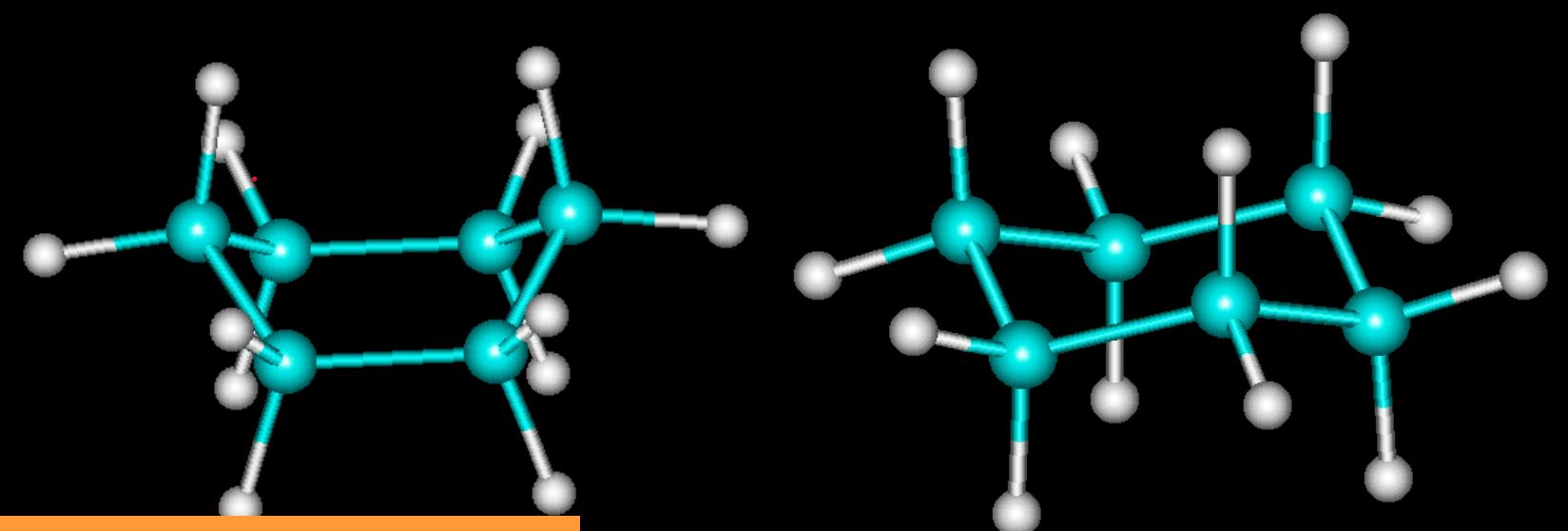
- ▶ Equilibrium structures
- ▶ Transition State structures
- ▶ Microwave, NMR spectra
- ▶ Reaction energies
- ▶ Reaction barriers
- ▶ Dissociation energies
- ▶ Charge distributions
- ▶ Reaction Rates
- ▶ Reaction Free Energies
- ▶ Circular Dichroism (optical, magnetic, vibrational)
- ▶ Spin-orbit couplings
- ▶ Full relativistic energies
- ▶ Excited States (vertical)
- ▶ Solvent Effects
- ▶ Density matrix methods/geminals
- ▶ Linear Scaling (ie of the methods with number of electrons/basis functions)
- ▶ Local correlation methods
- ▶ Accurate enzyme-substrate interactions
- ▶ Crystal structures (prediction)
- ▶ Melting points
- ▶ Protein folding
- ▶ Full reaction dynamics
- ▶ Molecular dynamics
- ▶ Solvent dynamics
- ▶ Systematic improvements of DFT
- ▶ Excited States (adiabatic)

# What Properties can be Calculated?

In order of difficulty:

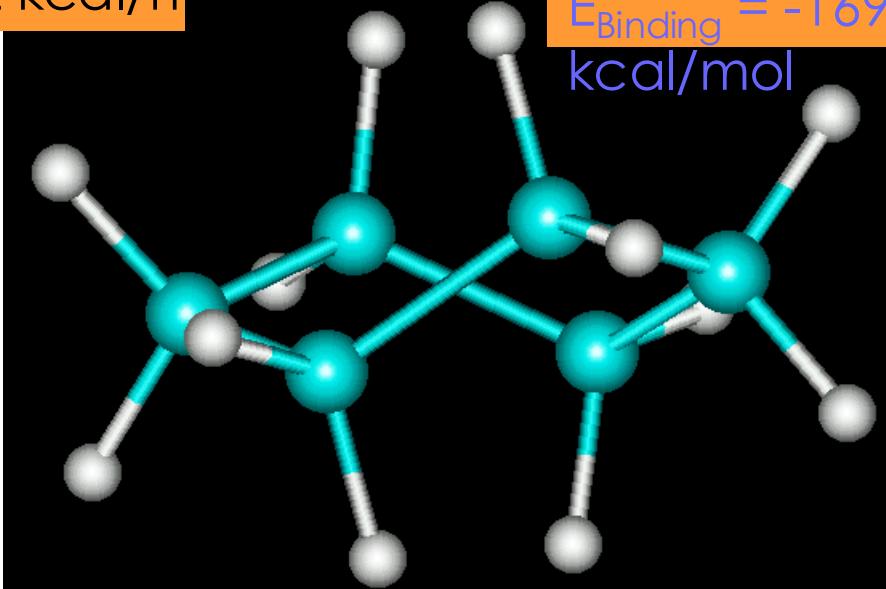
- ▶ Molecular Structures (+/- 1%)
- ▶ Reaction Enthalpies (+/- 2 kcal/mol)
- ▶ Vibrational Frequencies (+/- 10%)
- ▶ Reaction Free Energies (+/- 5 kcal/mol)
- ▶ Infrared Intensities (normally not too bad for fundamentals)
- ▶ Dipole Moments (depends...)
- ▶ Reaction Rates (errors vary enormously)

# Structure and energy



$$E_{\text{Binding}} = -1685,82 \text{ kcal/mol}$$

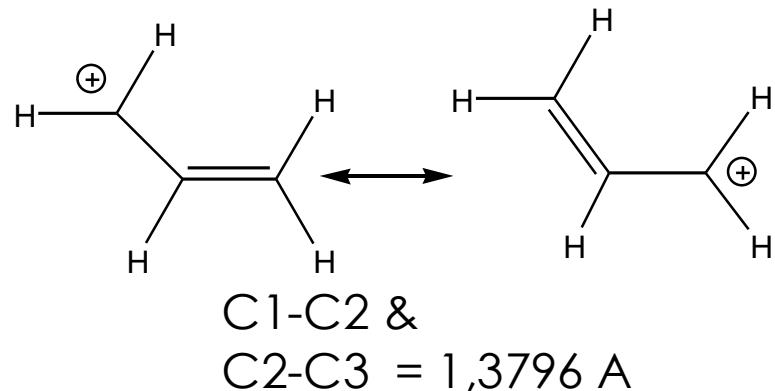
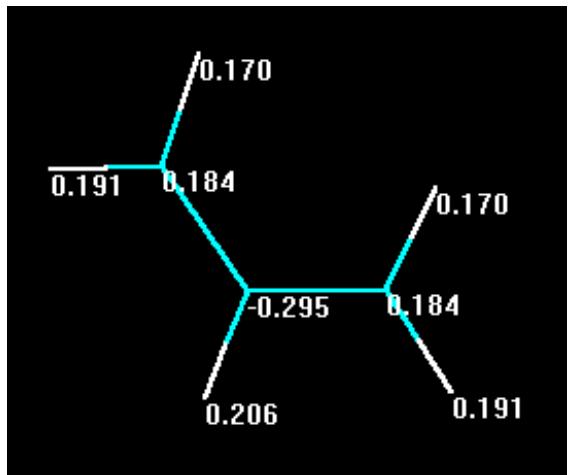
$$E_{\text{Binding}} = -1699,347 \text{ kcal/mol}$$



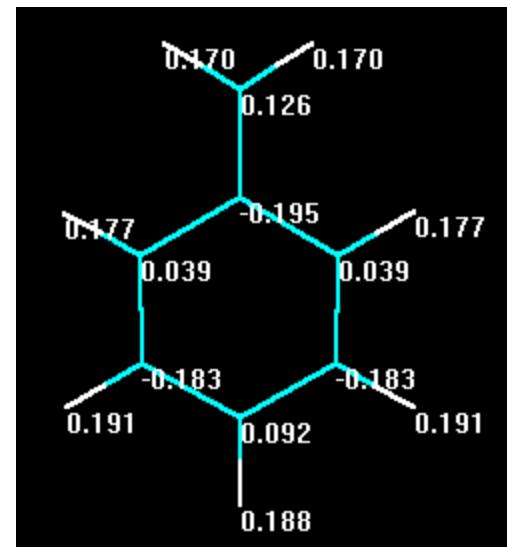
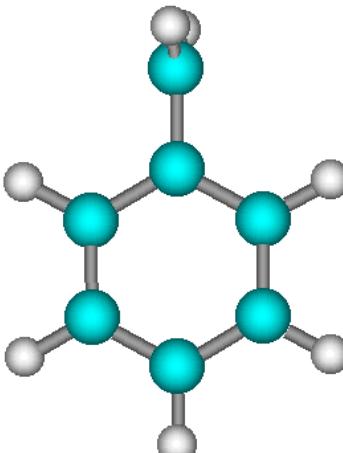
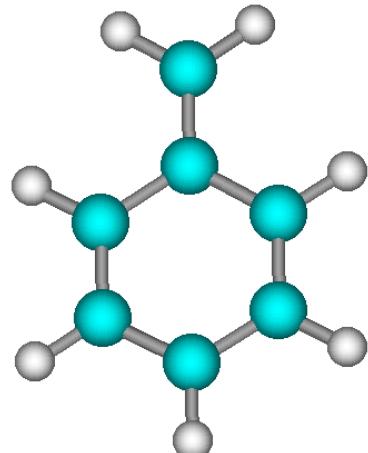
$$E_{\text{Binding}} = -1686,167 \text{ kcal/mol}$$

# Stability and Structure of Allilic and benzilic carbocation

## Allilic



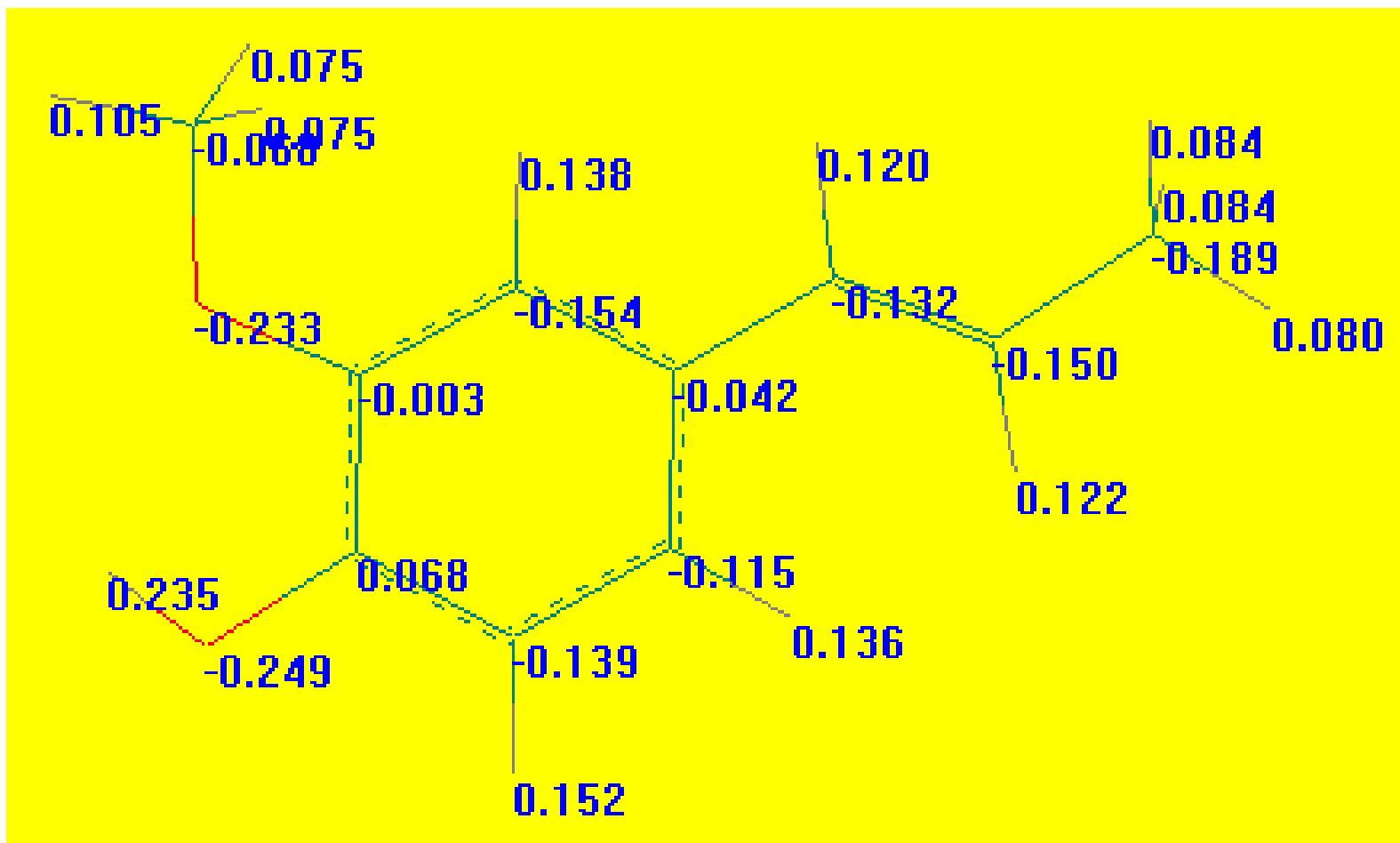
## Benzilic



$$\Delta H_f = 221,939 \text{ kkal/mol}$$
$$E_{\text{bin}} = -1339,005 \text{ kkal/mol}$$

$$\Delta H_f = 253,050 \text{ kkal/mol}$$
$$E_{\text{bin}} = -1307,894 \text{ kkal/mol}$$

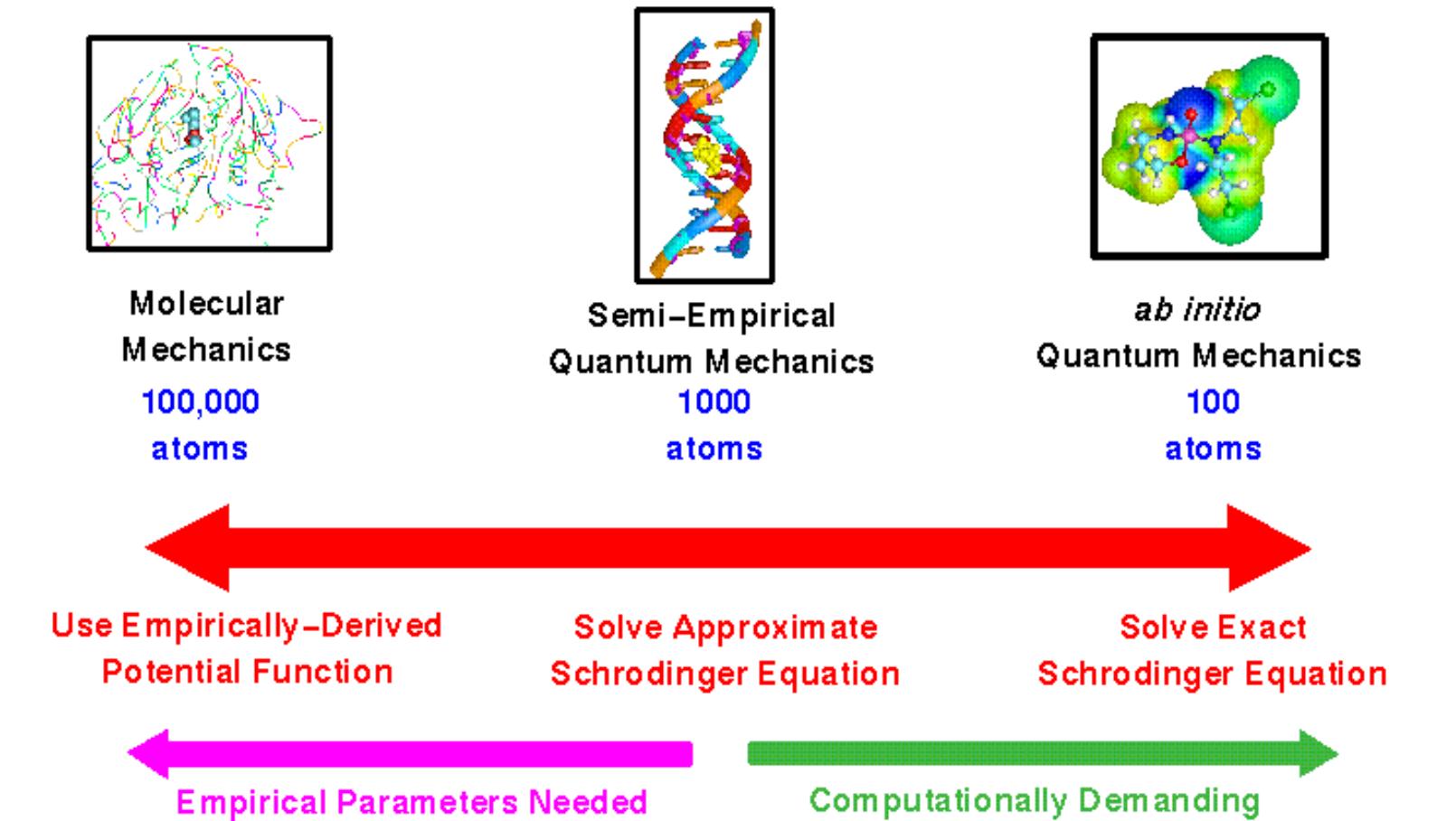
# Atomic Charge Neto



# Overview of Methods

- ▶ Molecular mechanics, force fields
  - ▶ easy to comprehend
  - ▶ quickly programmed
  - ▶ extremely fast
  - ▶ no electrons: limited interpretability
- ▶ Semiempirical methods
  - ▶ quantum method
  - ▶ valence electrons only
  - ▶ fast
  - ▶ limited accuracy
- ▶ *ab initio* methods
  - ▶ full quantum method
  - ▶ only experimental fundamental constants
  - ▶ in principle very high accuracy
  - ▶ complete (all interactions are included)
  - ▶ very time consuming ("expensive")
  - ▶ systematic improvement possible
- ▶ Density Functional Theory
  - ▶ quantum method
  - ▶ in principle "exact"
  - ▶ faster than traditional *ab initio*
  - ▶ variable accuracy
  - ▶ no systematic improvement

# COMPUTATIONAL CHEMISTRY METHODS



# Quantum Mechanics

## Shroedinger Equation

$$H\Psi = E\Psi$$



- Where are the electrons and nuclei of a molecule in space?  
*Configuration, conformation, size, shape, etc.*

- Under a given set of conditions, what are their energies?  
*Heat of formation, conformational stability, chemical reactivity, spectral properties, etc.*

# The Schrodinger Equation for a Molecule

$T_{\text{electron}}$

$V_{\text{electron-nucleus}}$

$$H = [(-h^2/8\pi^2m_e) \sum_{i=1,k} \nabla^2 - \sum_{j=1,N} \sum_{i=1,k} Z_j/r_{ji}]$$

$$+ \sum_{i=1,k-1} \sum_{l=1+1,k} 1/r_{il} + \sum_{j=1,N-1} \sum_{m=j+1,N} Z_j Z_m/R_{jm}$$

$V_{\text{electron-electron}}$

$V_{\text{nucleus-nucleus}}$

# Software computational chemistry

## Gaussian 09

### Major New Features:

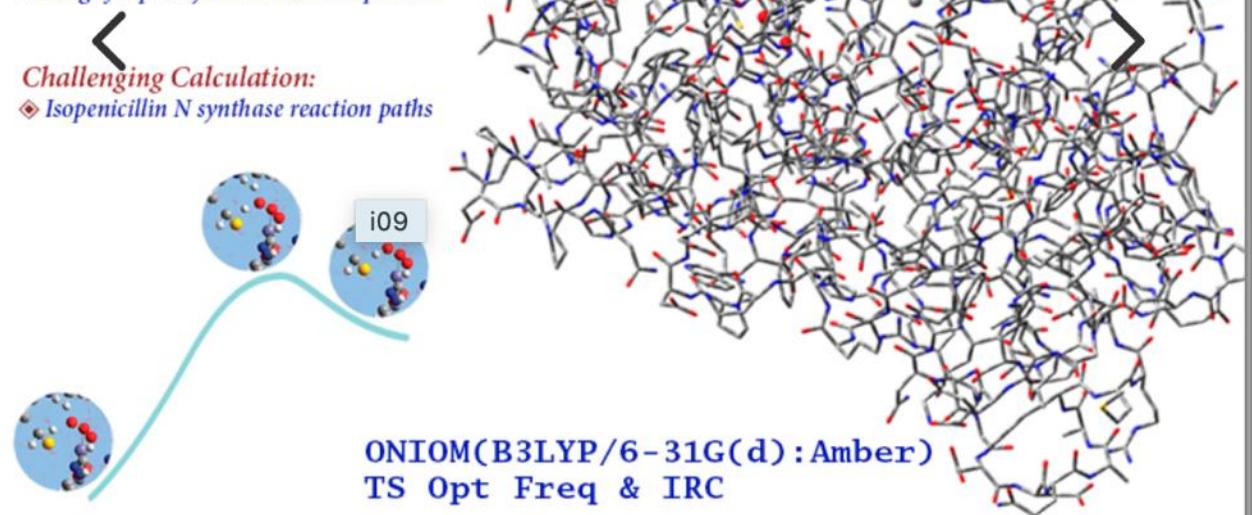
- ◆ ONIOM IRC & frequencies
- ◆ TD-DFT optimizations, EOMCC energies
- ◆ IEFPCM solvation for all properties
- ◆ Anharmonic frequencies, FCHT analysis

### Performance Enhancements:

- ◆ Optimizations for large molecules
- ◆ New IRC algorithm
- ◆ Large frequency calculations in parallel

### Challenging Calculation:

- ◆ Isopenicillin N synthase reaction paths



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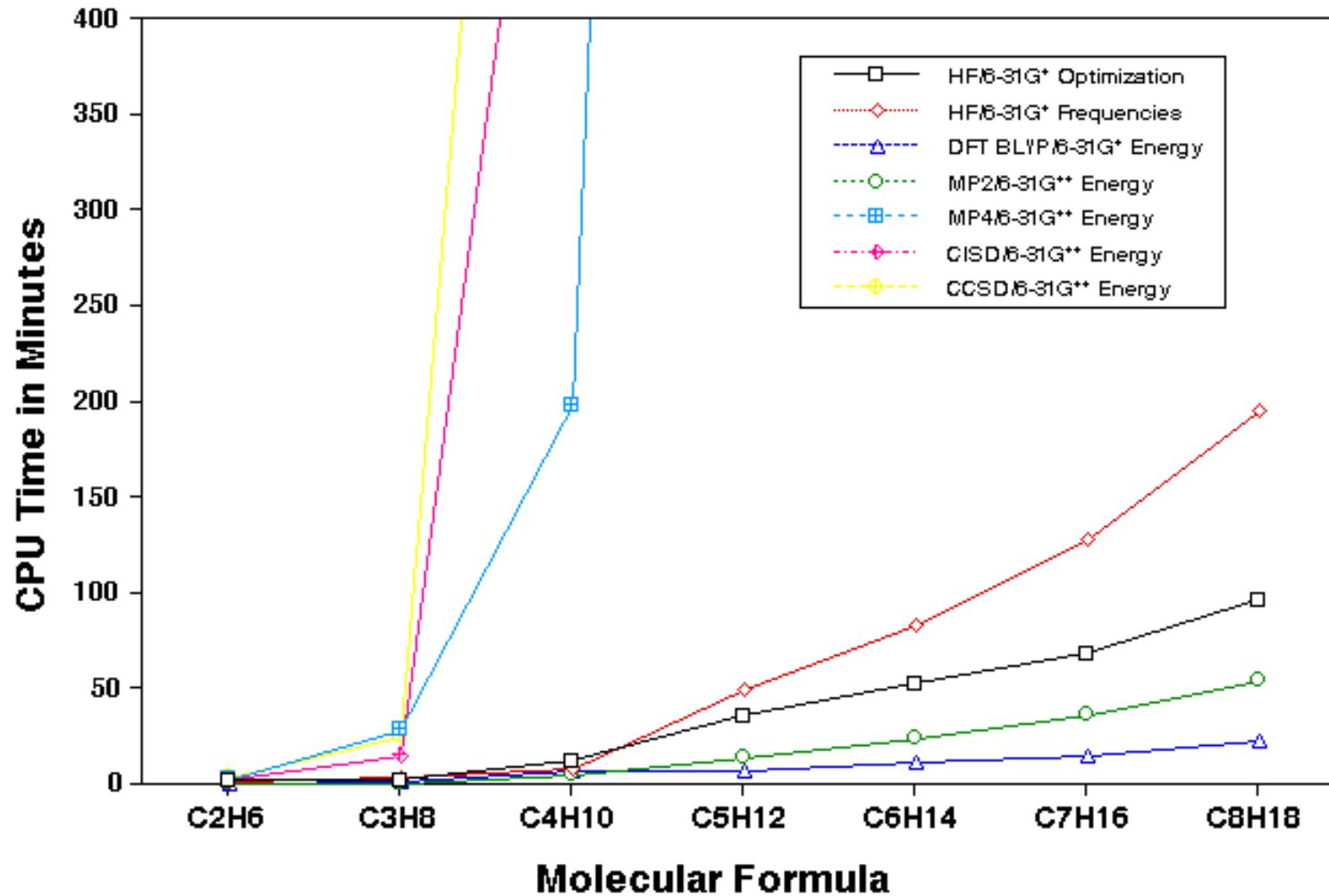
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## AutoDock Vina

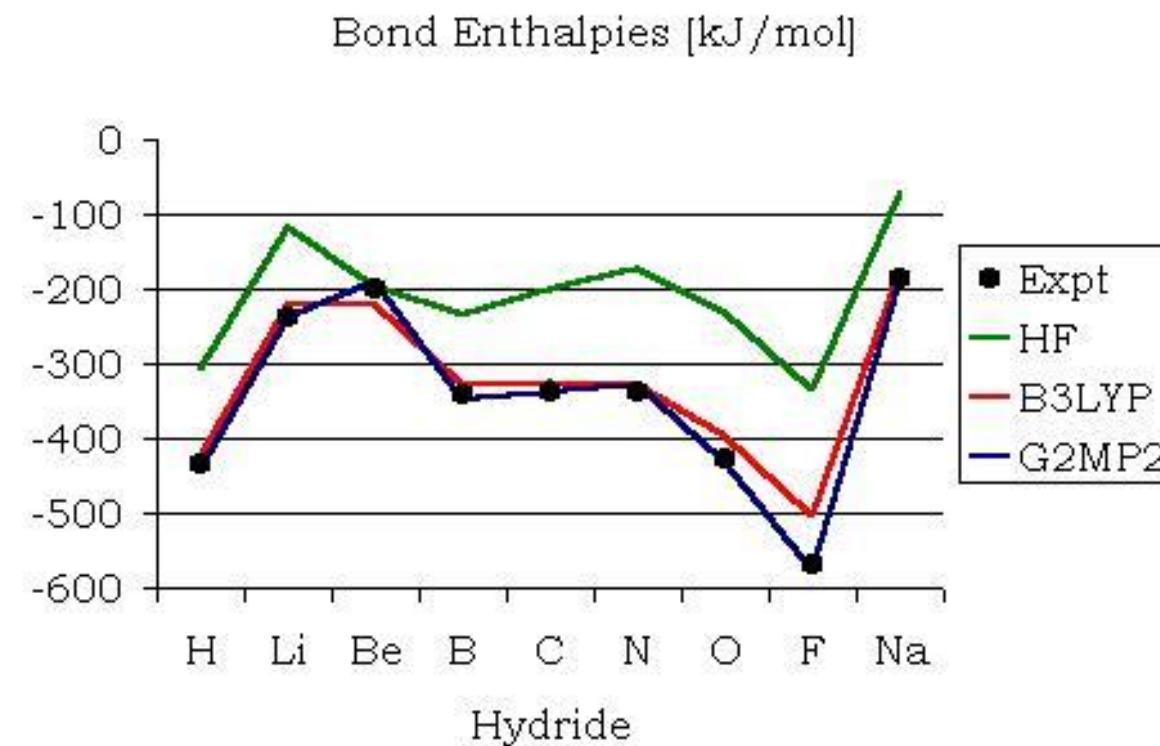
AutoDock Vina is an open-source program for doing molecular docking. It was designed and implemented by Dr. Oleg Trott in the Molecular Graphics Lab at The Scripps Research Institute.

The image on the left illustrates the results of flexible docking (green) superimposed on the crystal structures of (a) indinavir, (b) atorvastatin, (c) imatinib, and (d) oseltamivir bound to their respective targets.

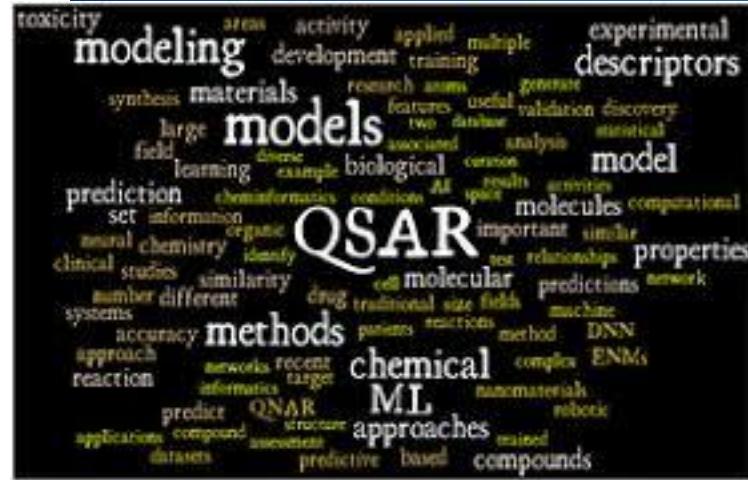
# CPU time vs method



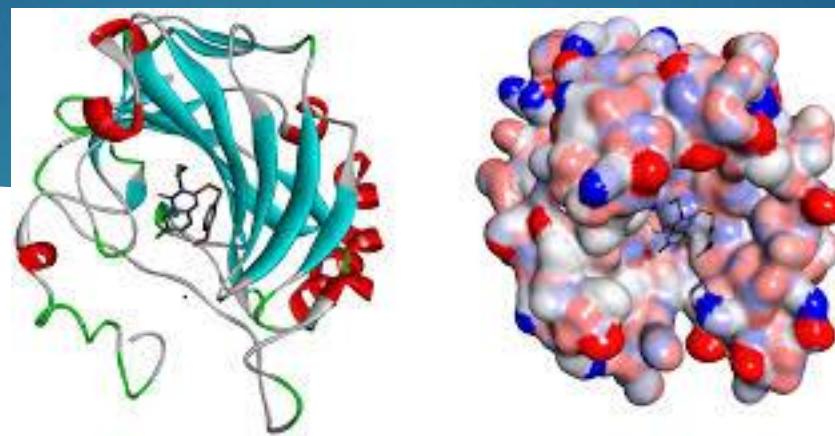
# Experimental vs theoretical



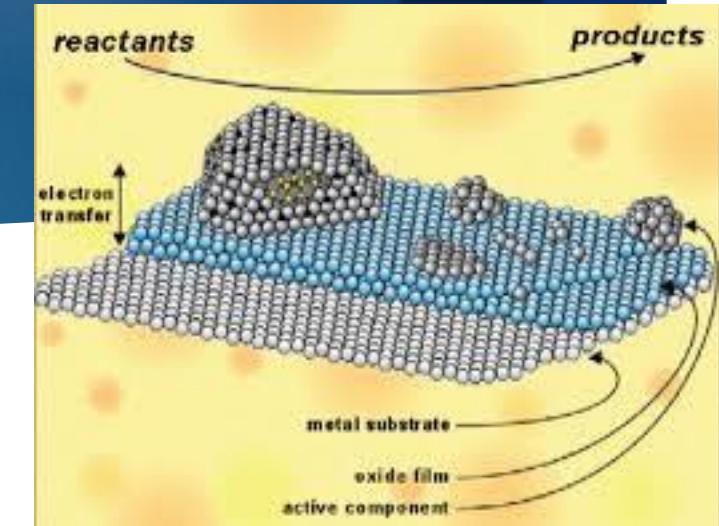
# INTERDISCIPLINARY APPROACH



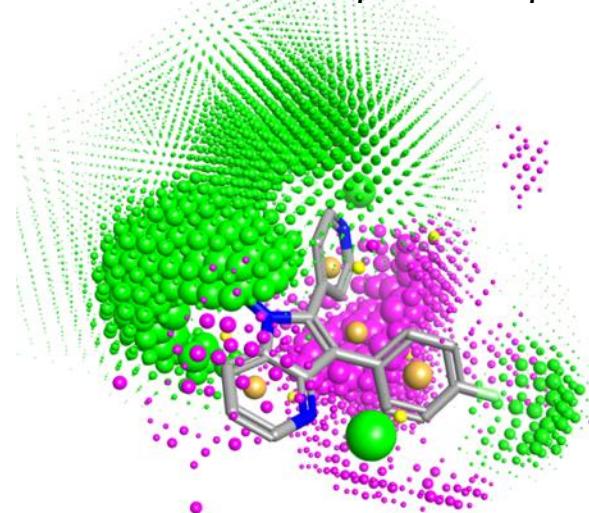
QSAR dan penerapannya



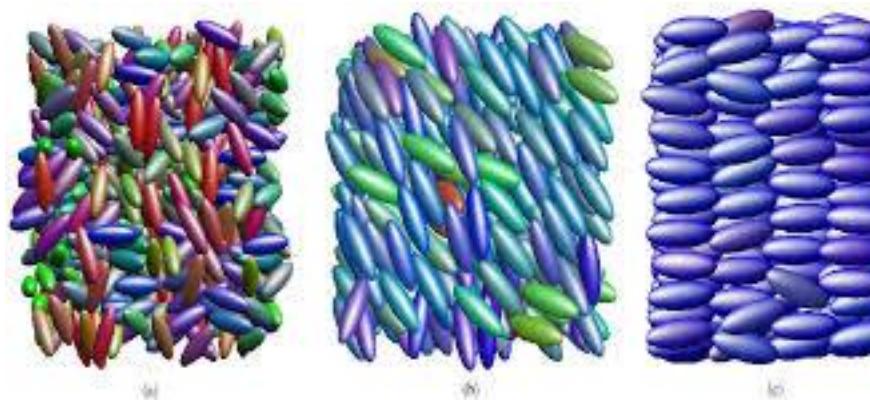
Molecular Docking



Catalytic Model



3D QSAR

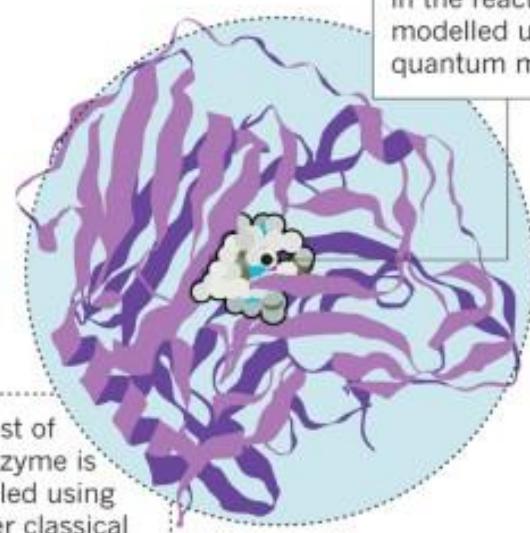


Modelling of Liquid Crystals

# INTERDISCIPLINARY APPROACH

Karplus, Levitt and Warshel married classical and quantum methods to model complex chemical processes computationally<sup>1,2</sup>.

An enzymatic reaction

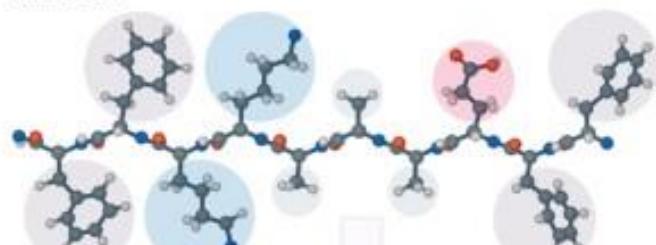


Only the atoms directly involved in the reaction are modelled using quantum methods.

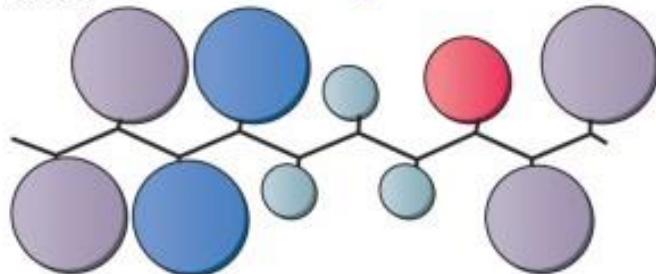
The rest of the enzyme is modelled using simpler classical methods.

Warshel and Levitt also showed that groups of atoms can be treated as rigid units to speed up modelling of large systems.

Molecule



Model



Modelling of an enzymatic reactions  
(Nobel price of Chemistry 2013)

