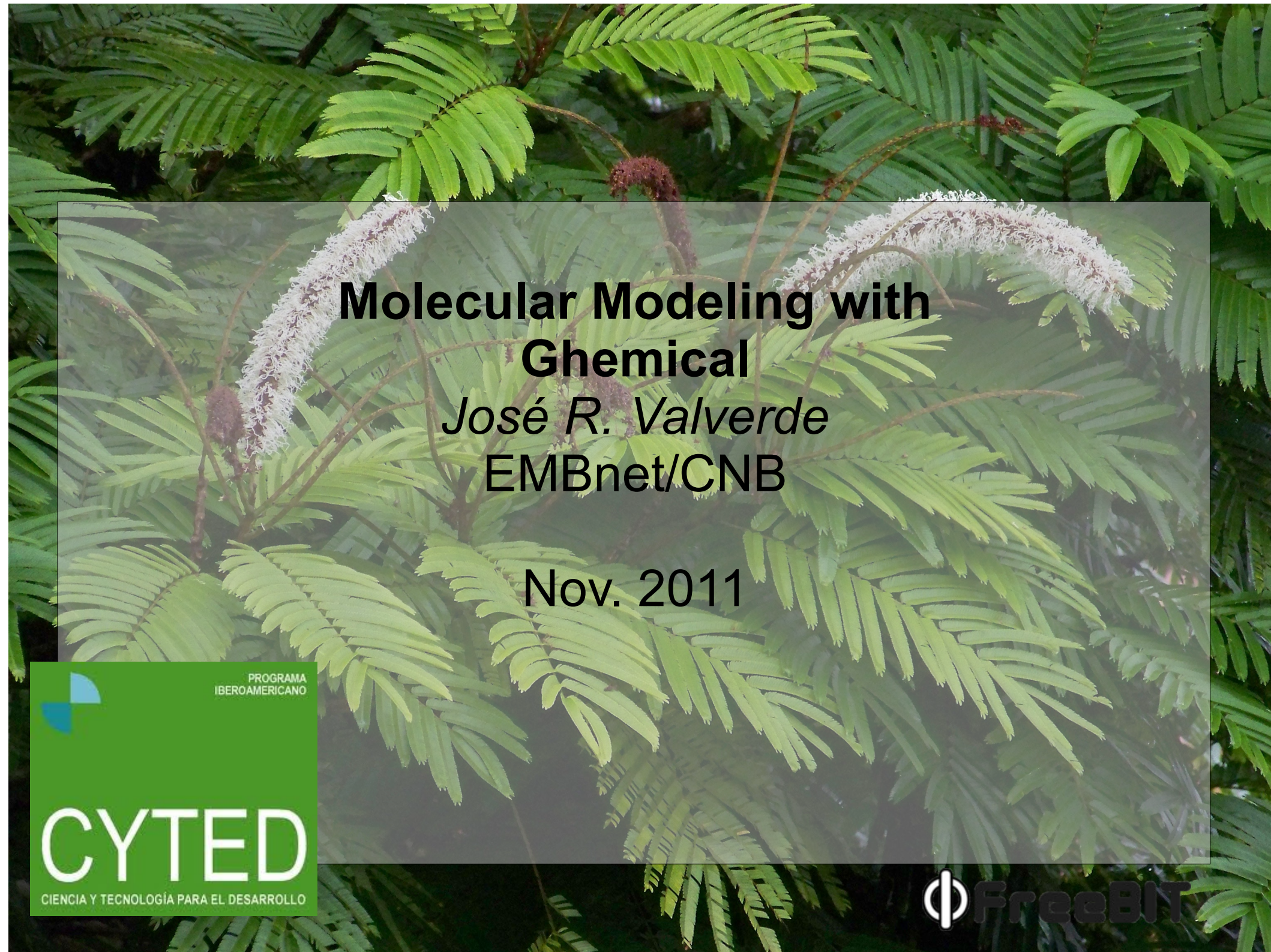

Molecular Modeling with Ghemical

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EMBnet/CNB

Nov. 2011

PROGRAMA IBEROAMERICANO
CYTED
CIENCIA Y TECNOLOGÍA PARA EL DESARROLLO

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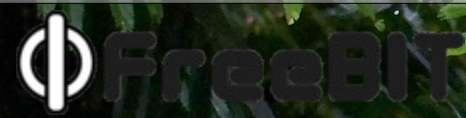
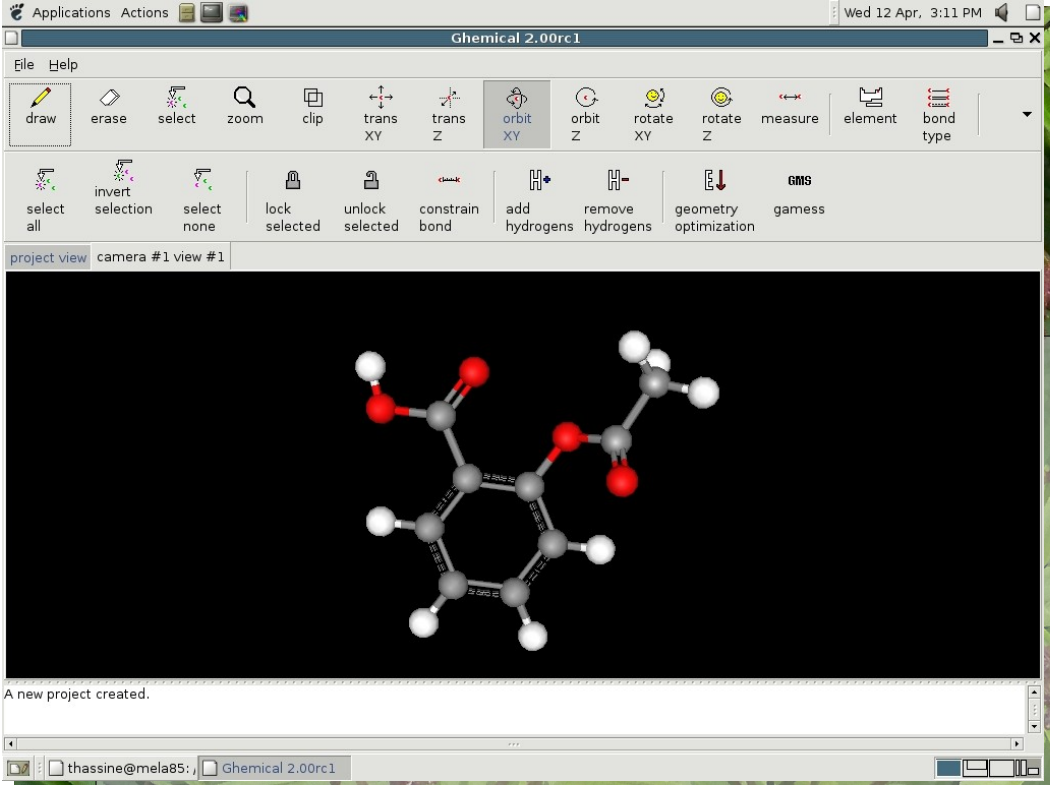
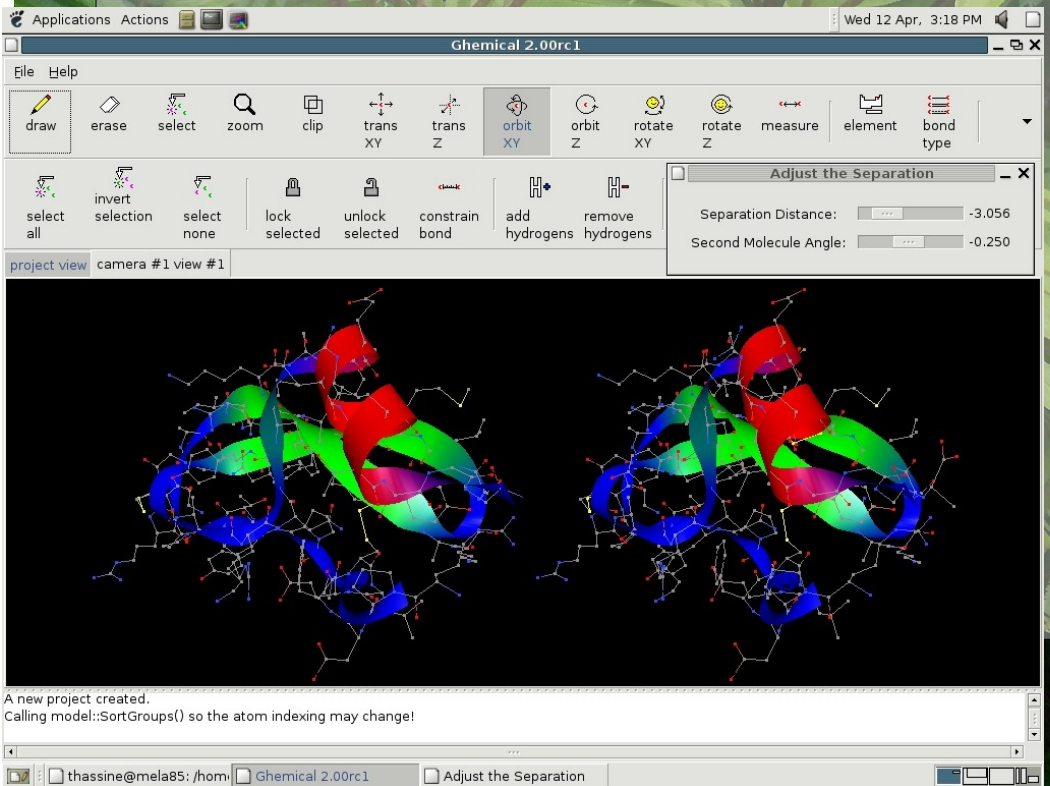
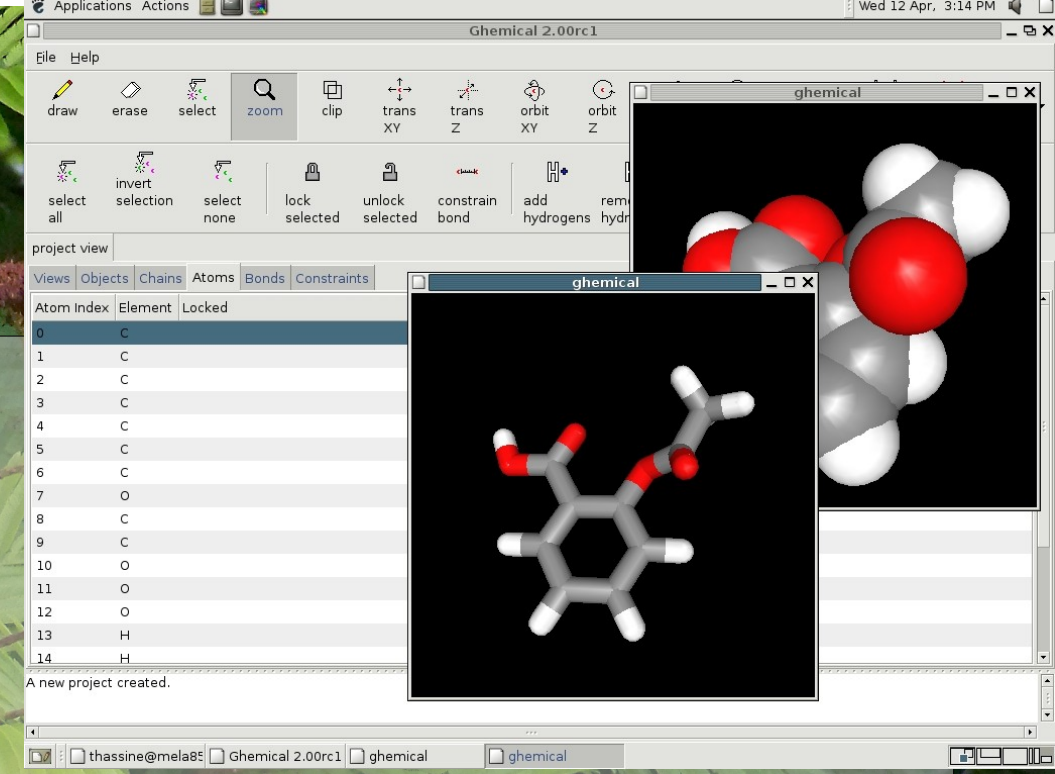
What is/are Ghemical?

- A molecular modeling tool with a GUI that allows Molecular Mechanics and Quantum Mechanics simulations
- http://bioinformatics.org/ghemical/
  - Molecular Mechanics/Dynamics (Tripos FF)
  - Semi-empirical QC (Mopac): mopac7.sf.net
  - *Ab initio* QC (MPQC) www.mpqc.org
- Windows version with GAMESS-US support
  - www.uiowa.edu/~ghemical/




Applications Actions
Wed 12 Apr, 3:11 PM
Ghemical 2.00rc1
File Help
draw erase select zoom clip trans XY trans Z orbit XY orbit Z rotate XY rotate Z measure element bond type
select all invert selection select none lock selected unlock selected constrain bond add hydrogens remove hydrogens geometry optimization gamess
project view camera #1 view #1
A new project created.
thassine@mela85: ... Ghemical 2.00rc1


Applications Actions
Wed 12 Apr, 3:18 PM
Ghemical 2.00rc1
File Help
draw erase select zoom clip trans XY trans Z orbit XY orbit Z rotate XY rotate Z measure element bond type
select all invert selection select none lock selected unlock selected constrain bond add hydrogens remove hydrogens
Adjust the Separation
Separation Distance: -3.056
Second Molecule Angle: -0.250
project view camera #1 view #1
A new project created.
Calling model::SortGroups() so the atom indexing may change!
thassine@mela85: /hom... Ghemical 2.00rc1 Adjust the Separation


Applications Actions
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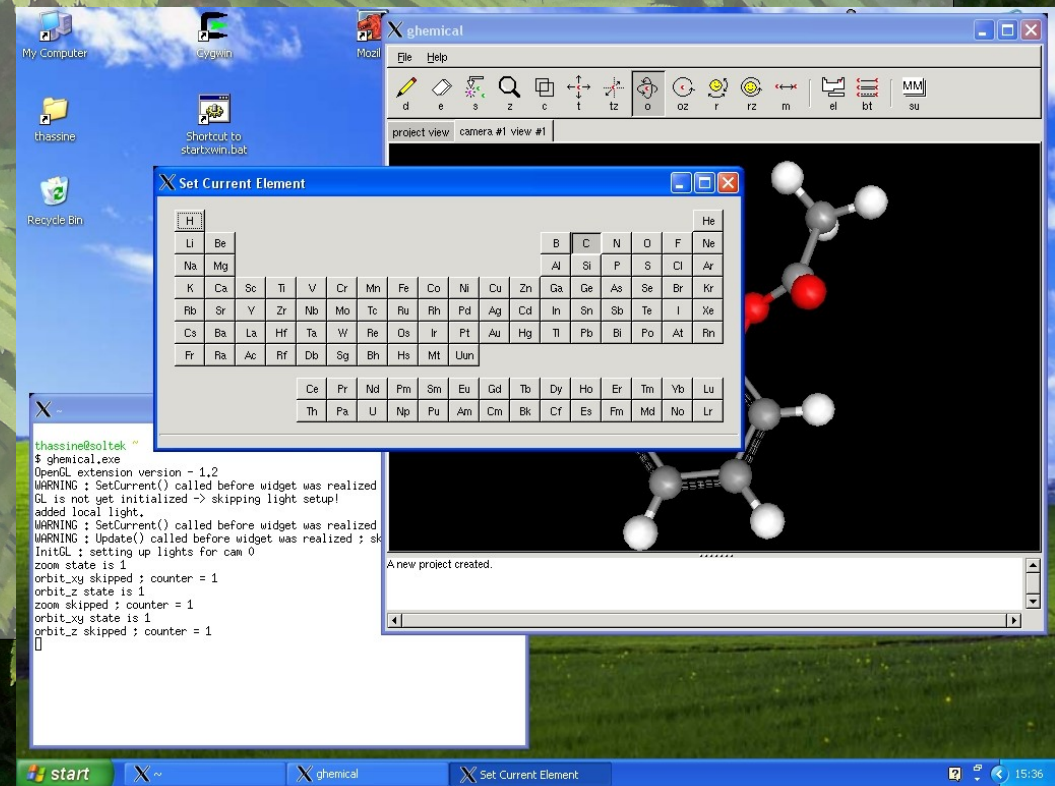
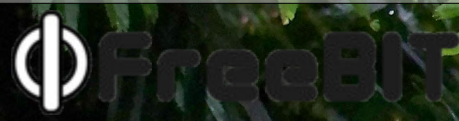
Ghemical 2.00rc1
File Help
draw erase select zoom clip trans XY trans Z orbit XY orbit Z
select all invert selection select none lock selected unlock selected constrain bond add hydrogens
project view
Views Objects Chains Atoms Bonds Constraints
Atom Index Element Locked
0 C
1 C
2 C
3 C
4 C
5 C
6 C
7 O
8 C
9 C
10 O
11 O
12 O
13 H
14 H
ghemical
ghemical
A new project created.
thassine@mela85 Ghemical 2.00rc1 ghemical ghemical


My Computer
Cygwin
thassine
Shortcut to startxwin.bat
Recycle Bin
ghemical
File Help
project view camera #1 view #1
Set Current Element
thassine@soltek ~
$ ghemical.exe
OpenGL extension version - 1.2
WARNING : SetCurrent() called before widget was realized
GL is not yet initialized -> skipping light setup!
added local light.
WARNING : SetCurrent() called before widget was realized
WARNING : Update() called before widget was realized ; sk
InitGL : setting up lights for cam 0
zoom state is 1
orbit_xy skipped ; counter = 1
orbit_z state is 1
zoom skipped ; counter = 1
orbit_xy state is 1
orbit_z skipped ; counter = 1
A new project created.
start
ghemical
Set Current Element
15:36

Avogadro

- Avogadro.openmolecules.net
- A derivative of Ghemical
  - Cross-platform
  - Fast
  - Extensible
  - Support for other QM packages as plugins



Overview

- Perform MD simulations using built-in engine
- Perform semi-empirical calculations
  - Dinucleotide
  - Tetraloop
  - Unfold alpha helix
- Perform *ab initio* calculations
  - aspirin
- Visualize results

Dinucleotide

- Launch Ghemical
- With right mouse button bring pop-up menu
  - File → **Import**
    - **Open is only for ghemical files!**
  - Open adenlyladenylate.pdb
- Run Molecular Dynamics simulation
  - Right mouse button → context menu → Compute → Molecular Dynamics

MD simulation

- Default simulation covers all standard steps:
  - Heating (5000 steps)
  - Equilibration (5000 steps)
  - Simulation (18000 steps)
  - Cooling (2000 steps)
- Default time step is 0.5 femtoseconds
- Default T is 300 K
- Default P is 1 bar
- Choice of Constant-T, P or both
- Only explicit solvent (Build → Solvate Box/Sphere)

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Tretaloop Hairpin

- Open gcaa.pdb
  - Right mouse button → Build → Zap all
  - Right mouse button → File → **Import**
- Run a molecular dynamics simulation
  - How long does it take?
- Cancel when you are tired of waiting
- For large simulations it is better to use specialized tools
  - GROMACS

Unfold alpha helix

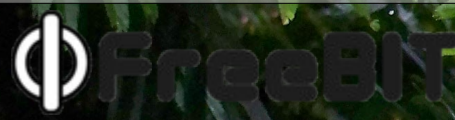
- Open polyala10helix.pdb
  - Right mouse button → Build → Zap all
  - Right mouse button → File → Import
- Run simulation at 1000 C
- Reload molecule and run simulation at 300 K
- Reload molecule and run simulation at 6000K
  - Did you see anything abnormal? No?
  - The default time step of 0.5fs is good enough for most simulations.

A saucerful of secrets

- Set the controls for the heart of the sun (Pink Floyd, 1968)
- Molecular dynamics does not handle bond-breaking or forming. I. e. it does not handle Chemistry.
- To deal with Chemistry we need a Quantum Mechanics approach
  - Analyze electronic structure
  - Analyze dynamical behaviour

Aspirin

- Load Wikipedia:aspirin in your browser
- Load aspirin.pdb
  - Right mouse button → Build → Zap all
  - Right mouse button → File → Import
- Set up computation method
  - Right mouse button → Compute → Setup...
  - All QM...
    - Mopac MP3

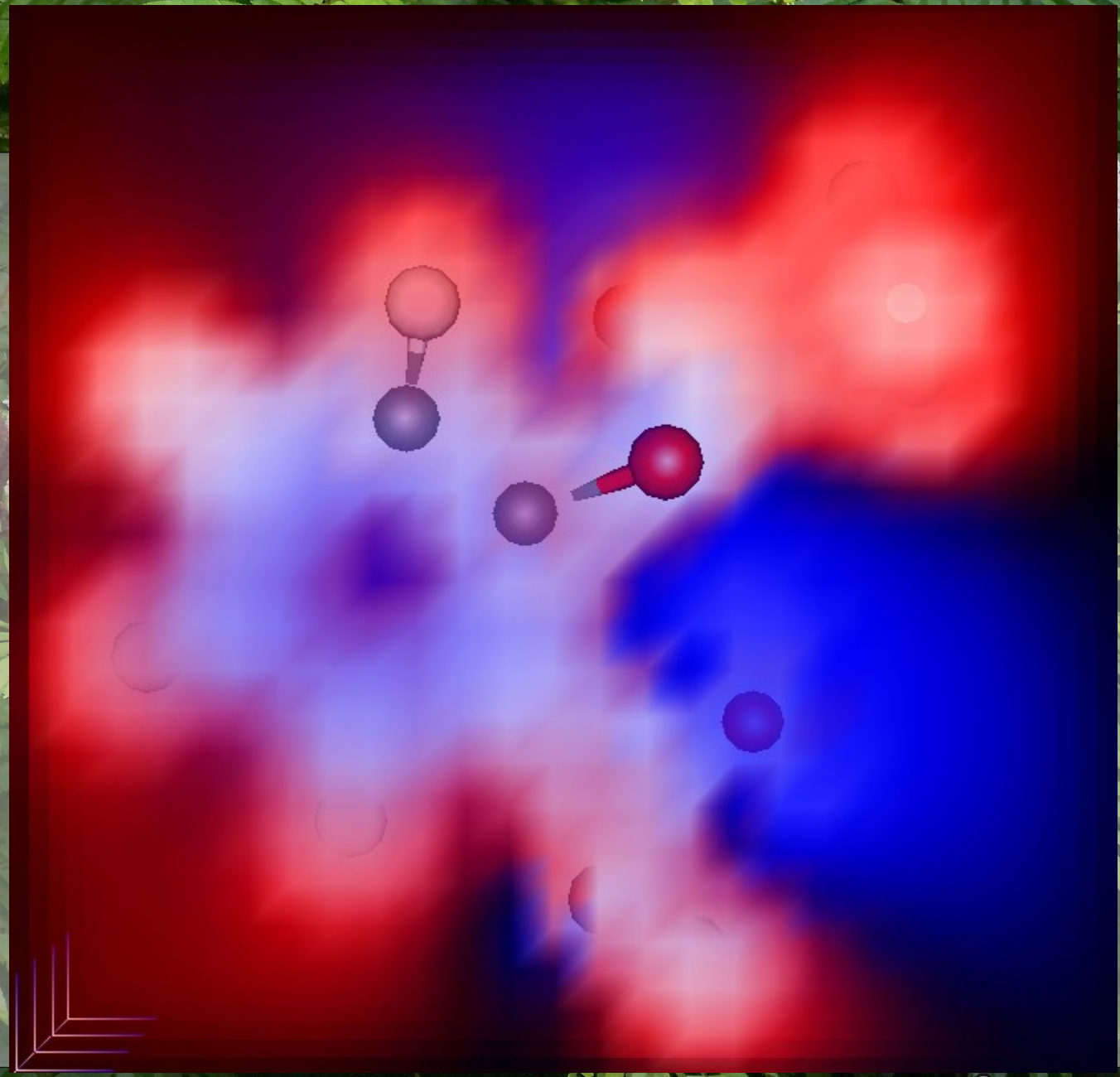


As a rule

CNDO < MNDO < AM1 < PM3 < PM6

Optimize Geometry

- Select Geometry Optimization
  - Right mouse button → Compute → Geometry Optimization...
- Watch as energy decreases and structure is refined
- Compute molecule energy
  - Right mouse button → Compute → Energy
- Display Electron Density
  - Right mouse button → Objects → Volume rendered ESP



Predicting reactivity

Electrostatic potential planes can be used predict the location of an electrophilic attack. An electrophile will typically attack in areas near an electrostatic potential minimum, which are colored blue.

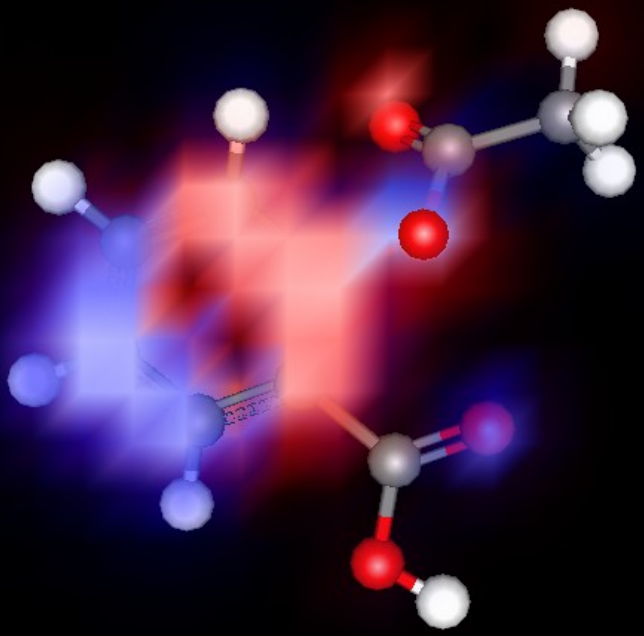
- Does it match what you'd expect?

HOMO/LUMO theory

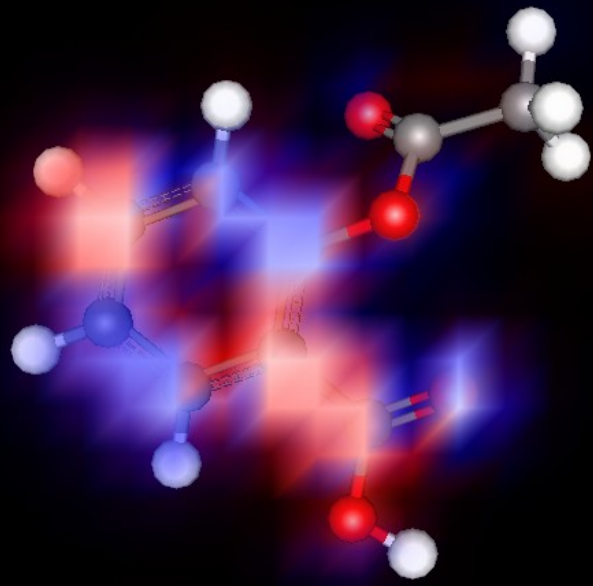
- HOMO can give electrons
- LUMO can take electrons

HOMO/LUMO

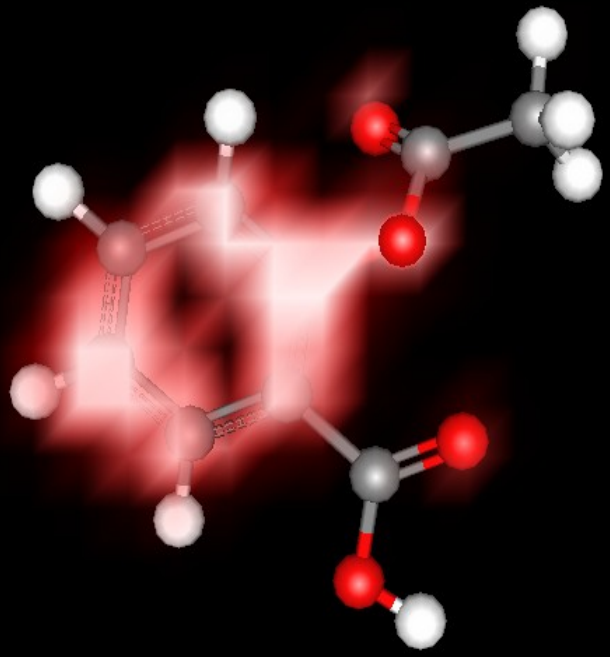
- Orbital count in Ghemical starts at zero
- HOMO is orbital 33
  - Right mouse button → Objects → Delete current object
  - Right mouse button → Set current orbital
    - Change X to 33
  - Right mouse button → Objects → Molecular orbital volume / MO density volume
- LUMO is orbital 34
  - Same as above but change X to 34

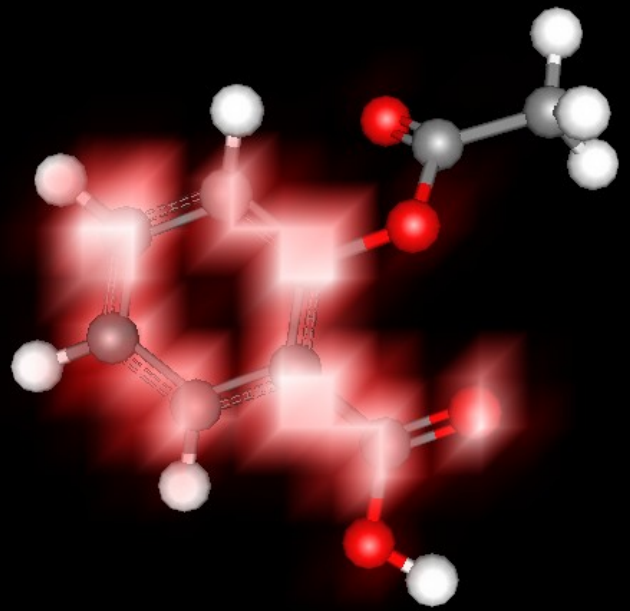


HOMO



LUMO





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Increasing precision

- Semi-empirical calculations often result in “approximate results”
- Semi-empirical calculations cannot work with non-parametrized atoms
- For increased accuracy use full *ab-initio* methods
  - STO-3G: minimal basis set
  - 6-311G**: standard basis set
  - Corrections for e-e interactions (MP2, CI, CC,...)

As a general rule

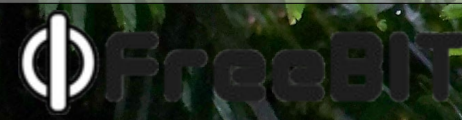
HF << MP2 < CISD < MP4(SDQ) ~ CCSD < MP4 < CCSD(T) < CCSDT

Comparing results

- Reference ground state
  - *Ab initio*: all electrons and nuclei separated by infinite distance
  - Semi-empirical: consider only valence shell electrons, separate atoms an infinite distance
    - Should yield heat of formation
    - Equivalent to semi-empirical minus a contant
- Differential results can be compared
- Direct results cannot be directly compared

Simulating reactions

- Find transition state
- Work out transition state, reactants and products
  - Intrinsic Reaction Coodinate (IRC)
    - Transition State Search
    - Follow IRC forward and backward
  - Dynamic Reaction Coordinate
    - Molecular Dynamics with energy conservation
- Build energy landscape
- Carr-Parrinello Molecular Dynamics



Method	Time
Molecular Mechanics	N^2
Molecular Dynamics	N^2
Hartree-Fock (HF)	N^2 - N^4 (depending on symmetry and cutoff use)
MP2	N^5
MP3, MP4	N^6
MP5	N^8
CC2	N^5
CCSD	N^6
CISD	N^6
CASSF	A! (depends on the number of orbitals)
CI complete	N!
Semiempirical methods	N^2 (for small systems)
Semiempirical methods	N^3 (for large systems)
DFT	N^3
DFT with linear scaling algorithms	N

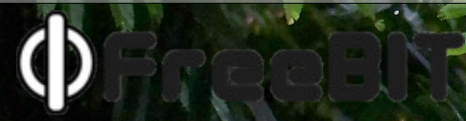
Note: adapted from *Computational Chemistry: A Practical Guide for applying Techniques to Real-World Problems*. David C. Young. Wiley & Sons. 2001.

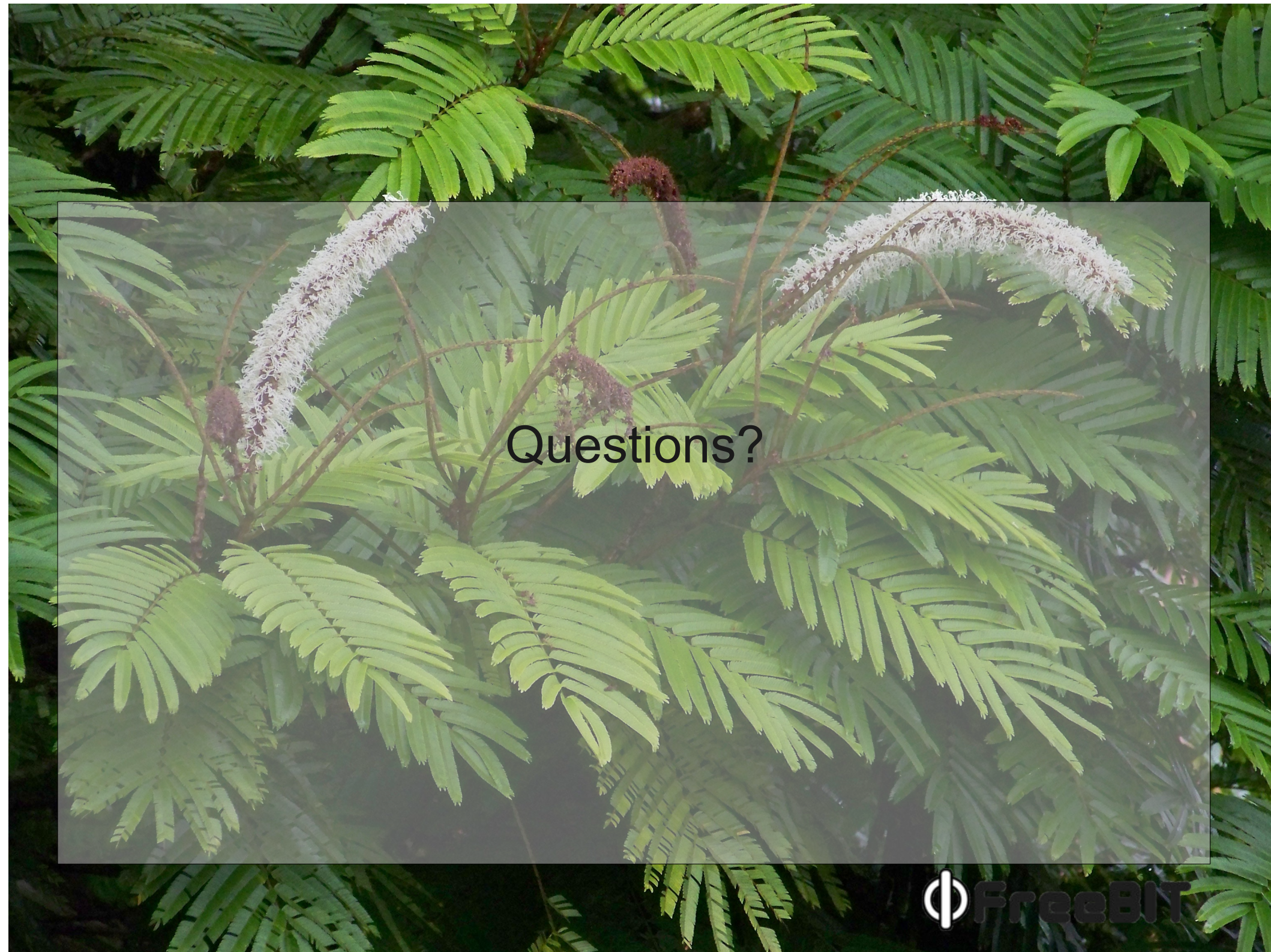
Increasing speed

- Use Semi-empirical methods
- Use DFT
- Use parallel programs on clusters
  - MPQC
  - NWchem
- Use modern methods
  - MOPAC/MOZYME
  - Siesta
- Combine QM/MM
  - NWchem, Gromacs, Ego VIII, etc...

The magic recipe

- Quantum Chemistry is computationally intensive
- Be careful when preparing data
- Pay attention to detail
- Document everything minutely
- Be patient
- Be patient
- Be patient




Questions?
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