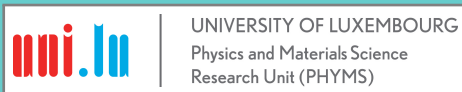


Scienteens Workshop:
Drug Design Computational Experiment

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Part I: Molecular Mechanics With WebMO

Intro to WebMO

Classical Mechanics on Ethanol

Quantum Mechanics on Ethanol


Classical versus Quantum Binding Energies

How to Open WebMO

- ▶ Open the WebMO server: `http://largemem.uni.lux/cgi-bin/webmo/login.cgi`
- ▶ Login with the codename for your assigned group and the password “sciteens”.
- ▶ You can have multiple sessions in multiple tabs.

Build Some Ethanol

WebMO isn't very fancy, but you can use it to build simple molecules.

- ▶ Click **New Job → Create New Job**
- ▶ Click **File → New**
- ▶ Click **Build → C** to start placing carbon atoms
- ▶ Put down two Carbons next to each other, then an Oxygen. Click and drag to link them with single bonds, in a line.
- ▶ Click **Cleanup → add Hydrogens**
- ▶ Great! You made an ethanol molecule ($\text{CH}_3\text{CH}_2\text{OH}$)
- ▶ Click the little curly arrow on the left () to go into view mode.

Hint: you can use **ctrl-Z** to undo if you make a mistake.

Try turning your molecule around with the mouse so you can have a look at it. What symmetry does it have?

Look At Your Ethanol

We can do some (basic) classical Molecular Mechanics directly in the browser.

To relax the structure until the net force on each atom is (close to) zero:

- ▶ Click Cleanup → Mechanics Optimize

To find the classical energy estimate for the optimised structure:

- ▶ Click Calculate → Strain Energy , make a note of the total.

Look at the output from the MM calculation. Some terms are (suspiciously) zero, because WebMO doesn't know and won't guess where the electrons are.

Finalise the Setup: Fix Symmetry

The next step will be more efficient if our ethanol is **exactly** symmetrical: the mechanics optimise isn't exact, so the molecule may still be somewhat bent.

- ▶ Fix the symmetry of the molecule:

Calculate → Symmetry → Symmetrize → OK




- ▶ View the symmetry:

Calculate → Symmetry → Display Symmetry Elements

- ▶ If it worked, you should see a single plane showing the reflection symmetry of the molecule.

Use Quantum Mechanics To Get An Accurate Energy

Seeing as ethanol is only a tiny molecule, we can try using quantum mechanics to get a better estimate of the formation energy.

- ▶ Click the little blue arrow on the right ()
- ▶ Choose Mopac as the calculation engine (to run on the server) .
- ▶ Choose a **Geometry Optimisation** as the calculation type, and .
- ▶ Wait a second... the job manager should show when the calculation is complete.

View QM output

- ▶ Hit the Magnifying Glass to view output.
- ▶ Hit “Raw output” (on the left): you should see a large amount of confusing text.
- ▶ Check and write down the “FINAL HEAT OF FORMATION”: is this the same as the classical estimate for total energy?
- ▶ Check the “NET ATOMIC CHARGES”: this is information which could go into making the classical calculation (for this or similar molecules) better.
- ▶ From the atomic charges, can you imagine how two ethanols would interact with each other? With water? **Note down your answers.**

Classical versus Quantum Binding Energies

- ▶ Click right again.
- ▶ Make a second ethanol molecule roughly where you think it will stick to the first.
- ▶ You can use the “Adjust” menu to move individual atoms or molecules around.
- ▶ Do a classical geometry optimisation,
Cleanup → Mechanics Optimize .
- ▶ Symmetrize
- ▶ Find and note down the classical and quantum energies for two molecules together.

Estimate ‘binding energy’ ΔG for two ethanols as the difference of the total energy for two and twice the energy for one:

$\Delta G = G_2 - 2G_1$. Did all groups get the same answers? Do the classical and quantum values agree?

Extra Time

If you finished everything and are waiting for breaktime:

- ▶ Use the symmetry tool in WebMO to view the symmetry operations for ethanol.
- ▶ Build a molecule with rotational symmetry, does WebMO's symmetry tool pick this up?
- ▶ Write your name in the molecule builder such that it will keep its shape when you add hydrogens and optimize.

Part II: Test an HIV Drug Using Classical Mechanics

Binding Energies: Reminder

Candidate Drug Molecules

Look at Your Molecule

Binding Energies: Reminder

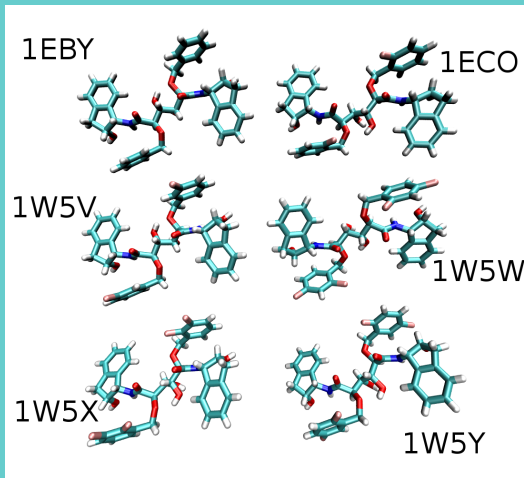
- ▶ To find a binding energy ΔG :
- ▶ Load the drug molecule (*'ligand'*):
 - ▶ Calculate the Energy, G_{ligand}
- ▶ Load the bare *'apo'* protein:
 - ▶ Calculate the Energy, G_{apo}
- ▶ Load the bound molecule+protein *'holo'*:
 - ▶ Calculate the Energy, G_{holo}

The affinity is determined by:

$$\Delta G = G_{holo} - (G_{apo} + G_{ligand})$$

Large negative ΔG indicates strong affinity.

Choose A Molecule



- ▶ Six variants on a known HIV drug: **each group picks the molecule matching their group code**
- ▶ Change is extra or missing Fluorine atoms (pink)
- ▶ Fluorocarbons: weak LJ **and** Coulomb forces: *hydrophobic* and **also** *lipophobic* ('non-stick').

Look at Your Molecule

I have prepared a collection of files to go with each of the six different drug candidates (*ligands*).

Download the file bundle for your choice from:

<http://berrymanscience.com/downloads.html> and unzip it.

- ▶ Click **New Job → Create New Job**
- ▶ Click **File → Import Molecule**
- ▶ Set the file format to **Tinker** and load the ligand (e.g. **1EC0_ligand.txyz**).
- ▶ Click the little curly arrow on the left (↶) to go into view mode.
- ▶ Try opening preferences (⚙) and setting the atom size to 100%.

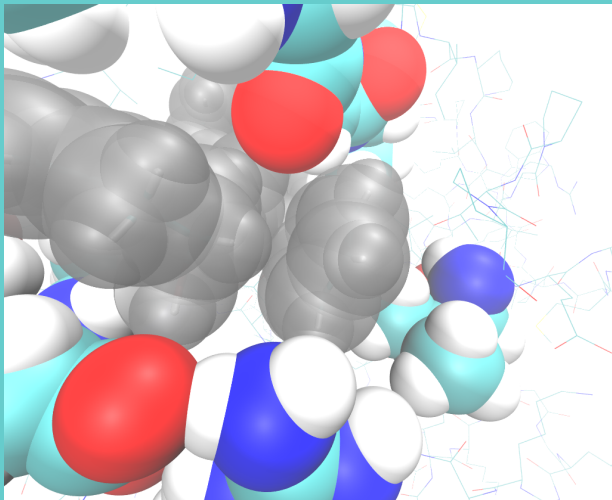
Bound Structure

For easy viewing I have prepared some molecular structures with only the active site cleft of the protease included. These won't work for molecular mechanics but they are less confusing to look at than the whole thing.

- ▶ Click `New Job → Create New Job`
- ▶ Click `File → Import Molecule`
- ▶ Set the file format to `tinker` and load the molecule (e.g. `1EC0_cleft_holo.txyz`).

Look at your molecule in the active-site cleft and try to estimate if it is a good fit. Set the atom size to 100% in order to estimate if it fits neatly, and try to guess where the lone pairs and polar hydrogens are.

Ligand In Site



Another look at the bound (*'holo'*) structure: blobs (made with a different program).

Full System Molecular Mechanics

The protein+ligand is far too big for a quantum calculation, and webMO's built-in classical mechanics engine is also not good enough.

We have no option except to load the coordinates and parameters from a text file and pass it straight to TINKER (a separate mechanics engine, to run on the server):

- ▶ In the job manager, hit: **New Job**→ **Execute Input File**
- ▶ Load the file "XX_webMoJob.txt" and look through to see what kind of information it has
- ▶ Set the 'engine' to tinker and run the job. Look at the raw output and note energies: **total**, **solvation** and **intermolecular** terms should be of interest.

Full System Optimize

The input systems were prepared just by cutting and pasting from crystal structures. To get better energies we should allow each system (*holo*, *apo* and *ligand*) to adjust to being in the solvent. This may take up to an hour for the *holo* and *apo* systems, so run them both at once. The server has 16 CPUs.

Load the control parameters as before, then change the file slightly:

- ▶ Replace “E” with “0.1” (this gives the required precision: smaller is slower).
- ▶ Replace “analyze” with “minimize”
- ▶ Set the engine to tinker and run the job. Look at the raw output and note energies: unfortunately, WebMO doesn’t have a way to scrape any more information than the total converged energy from the minimize calculation, but you can use this for the binding energy.

Which drug is best?

- ▶ Compare ΔG values across groups to see who picked the drug with the highest affinity.
- ▶ Which terms of the energy drive the binding process, and which ones are improved in the best drug relative to the others?

Extra time

- ▶ If everything seems to work out, then try downloading the output files, and pasting the time series of energy versus step number into excel or similar (whatever plotting program is on your notebooks).
- ▶ Does each system converge at the same rate?
- ▶ Does the ΔG converge faster than the individual G ?