Protein-ligand docking with MOE: introduction

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This tutorial is designed to introduce docking calculations using MOE: preparation of ligand: minimization in gas phase and solution, analysis of the active site of a protein-ligand complex with known structure, docking of new ligand to the protein with Dock, and analysis of the docked complexes.

We start with a minimization of a potential model ligand (dicoumarol), investigate binding of duroquinone to an oxidoreductase in a crystallized complex, and dock dicoumarol to the oxidoreductase.

The system of interest is NAD(P)H/quinone acceptor oxidoreductase (QR1/NQ01). The apoenzyme structures of human (at 1.7-Å resolution) and mouse (2.8 Å) QR1 and the complex of the human enzyme with the substrate duroquinone-DQN (2.5 Å) (2,3,5,6- tetramethyl-p-benzoquinone) are available.
(Faig et al., PNAS 97, 3177-3182, 2000, PBD ID 1DXO)

Estimated time to complete this tutorial is 2.5 hrs.

Part I Initial preparation of dicoumarol

1. Software

VizLab: *MOE, ChemDraw, Avogardo*, text editor, graphing software of your choice.

2. Starting MOE on triton

Note: this tutorial can be completed on a local computer if MOE is installed.

Connect to the School cluster, triton:

>ssh –Y triton

Make new directory for current tutorial:

>mkdir moe-tutorial-dock-1

Go to the newly made directory:

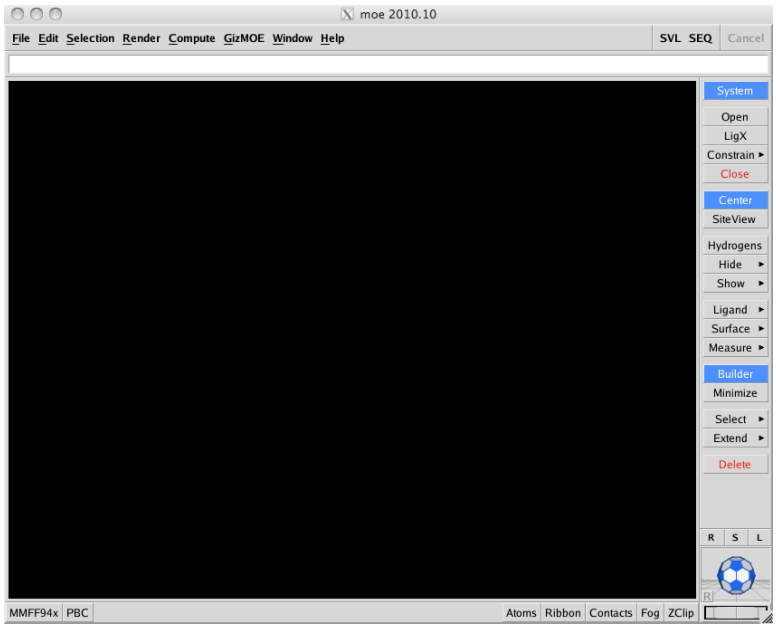
>cd moe-tutorial-dock-1

Start MOE:

>moe

(This command is alias for /mnt/linux/moe/moe2010/bin-lnux/moe)

The main window of MOE will appear:

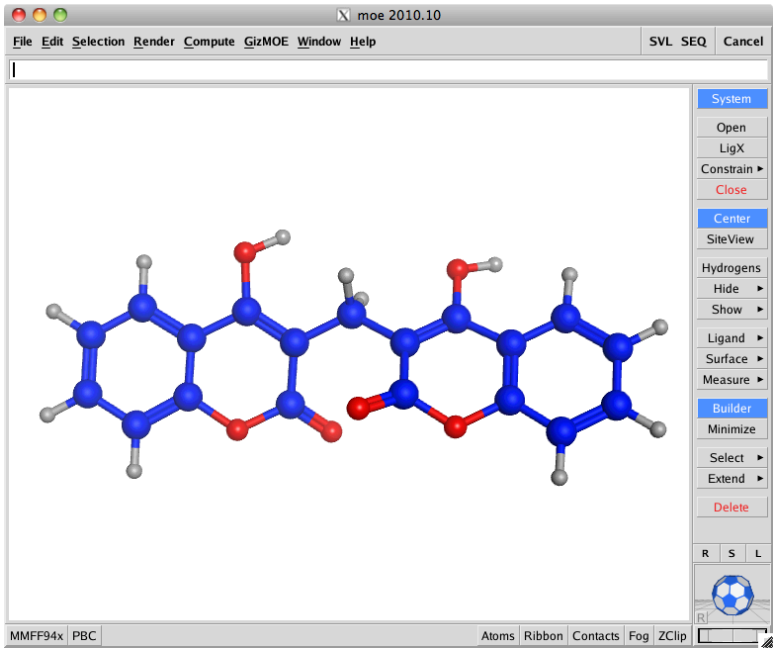


3. Load dicoumarol structure to MOE

Note: the pdb version of dicoumarol structure was created using *Avogardo*: read in the ChemDraw cdx file, let Avogadro create (planar) structure and save as pdb.

Note: you can build the structure in the MOE builder.

To chose representation you like: go Render-> Atoms-> select icon of your choice. To personalize the background color: Render -> Setup and for atoms color use the Atom tab in the lower right corner of the main window.



Inspect the newly loaded structure: is it planar? Are hydrogen atoms present and in the plane?

4. MOE minimization of dicoumarol in gas phase

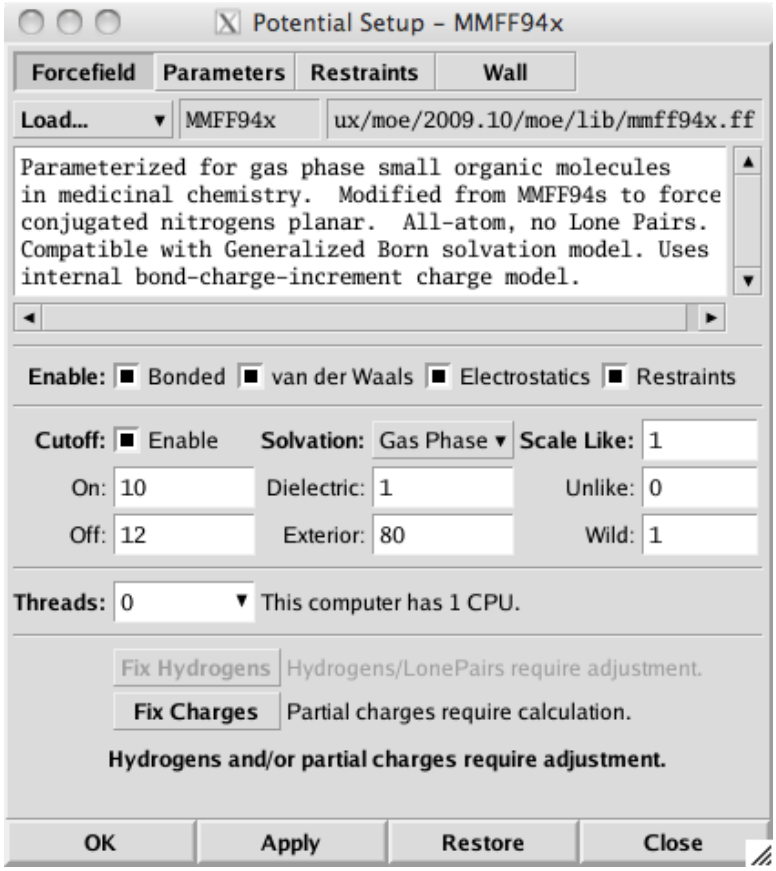
Note: the following list will be used almost every time when you need to set up a simulation

Step 1: Select the force field: Window->Potential Setup.

Select MMFF94x: ForceField->Load-> MMFF94x

Select gas phase simulation: Solvation->Gas Phase

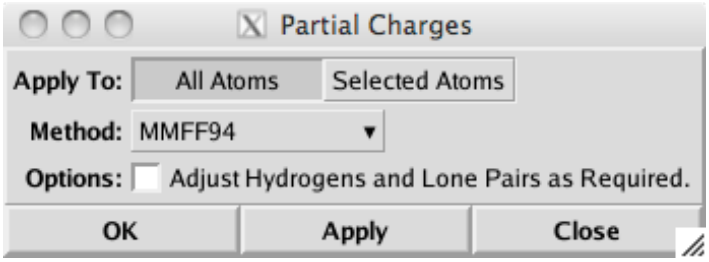
Increase cutoffs: from 8/10 Å to 10/12 Å. The resulting Potential Setup window:



Note: which force field components are enabled? What is the role of dielectric constant in the setup?

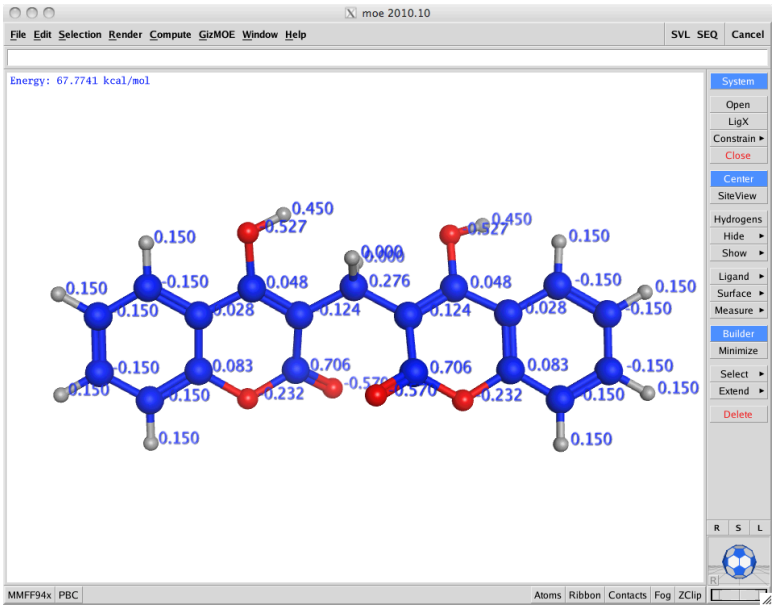
Note: partial charges need to be calculated. Click Apply if highlighted.

Step 2: calculate charges. Compute-> Partial Charges. Select MMFF94 force field:



Click OK. Display calculated charges: Render->Atoms->Charges or use the Atoms tab in the lower right corner.
Inspect the calculated charges.

Hint: by default charges will be displayed in white. Use the Effects & Text tab in the Visualization Setup (Render->Setup) to select the color of your choice (here is blue)

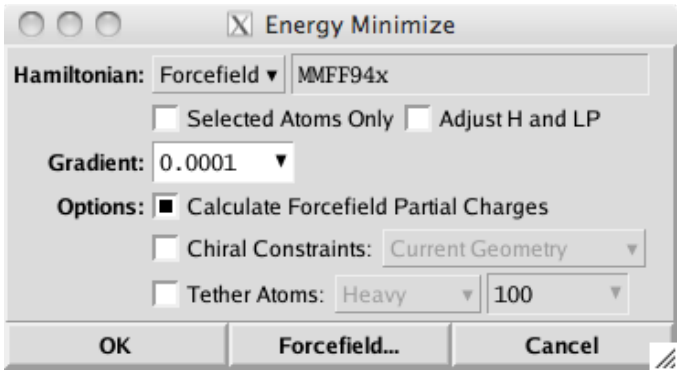


Save your results in the MOE format: dicoumarol-charges.moe

Step 3: Minimization.

First observe current energy: GizMOE->Energy.
Reflect on the value: is conformation stable? Why? Record the value. (see above Fig)

Set up minimization: Compute-> Energy Minimize. Select MMFF94x force field.
Change gradient to 0.0001:



Click OK.

Record the total energy and contributing terms: Compute-> Potential Energy.

Save your results in the MOE format: dicoumarol_min_gas.moe

Reflect: is the new conformation more stable with respect to the initial one?
How each term contributes to the stability? Is geometry planar? Why?

Repeat minimization few more times until energy value stop changing.

Review and summarize the steps we followed for minimization: we will need them often.

5. MOE minimization of dicoumarol in solution

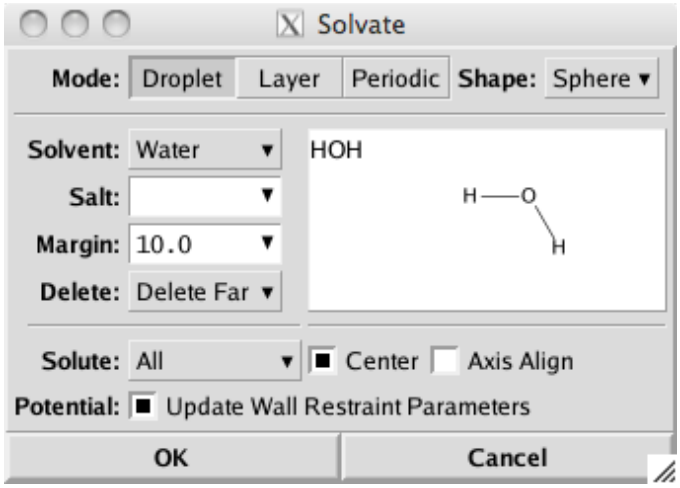
Now we will study how presence of explicit water molecules changes the minimized conformation.

Step 1: add solvent

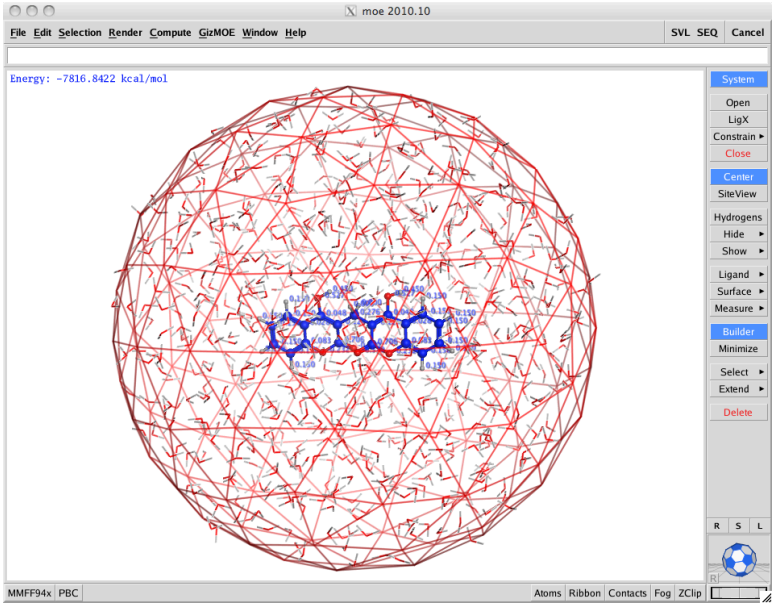
Close nay molecules you might have open in the main window.

Load the initial dicoumarol structure we made (dicoumarol-charges.moe - prior to minimization in gas phase).

Add water: Edit->Build->Water Soak. Soak Mode: Sphere. Increase solvent layer width to 10Å:



Click OK. Inspect the system.



Step 2: minimize the solvated system using the protocol above: calculate partial charges, select "Gas Phase" (since water is explicit), set cut off to 0.01.

Inspect resulting dicoumarol structure: is the structure planar? How it compares to the structure minimized in gas phase? Why are they different?
Hint: hide water molecules during minimization to simplify view: Hide->Solvent

Step 3: analysis

Record the total energy and contributing components (Compute->Potential Energy)

Step 4: save dicoumarol (only) in the MOE format (dicoumarol_only_min_wat.moe):

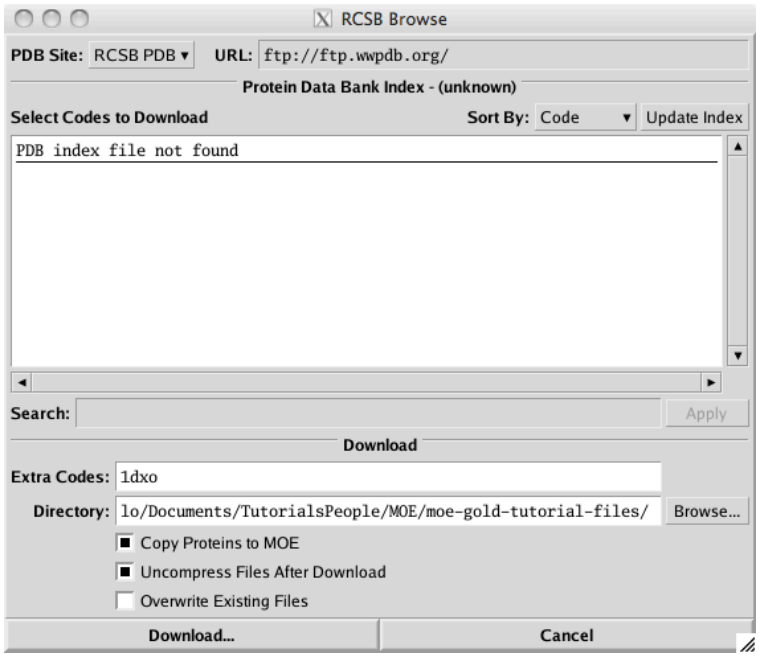
open Window-> Sequence Editor. Click on the button 1, LIG chain. File -> Save, highlight "Only Selected" and choose "Chain" from the menu.
Close structure: File -> Close

Part II Preparation and analysis of NQO1 complex structure

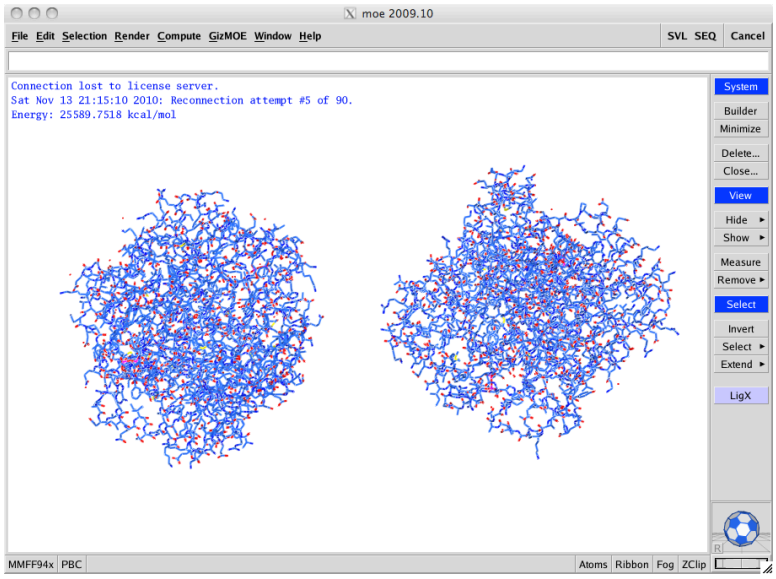
1. Prepare NQO1 structure

Step 1. Download NQO1 structure from PDB.org using MOE

File -> RCSB Download. Enter PDB ID (1dxo) and select buttons "Copy Protein in MOE" and "Uncompress Files after Download", see Figure.

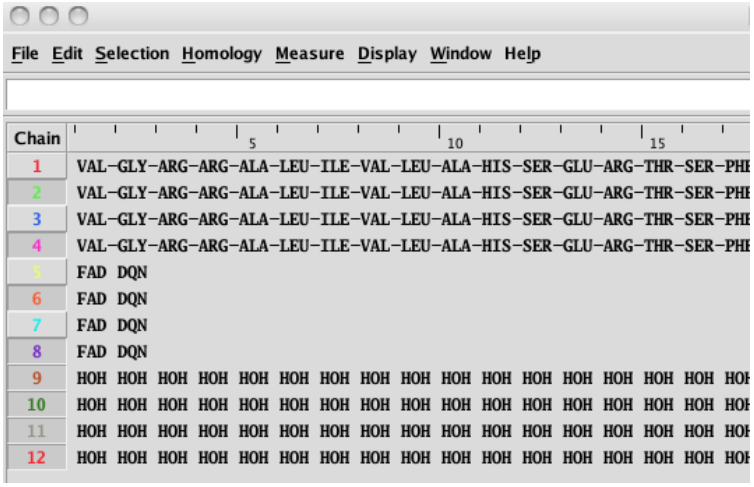


Protein-ligand complexes will be displayed:

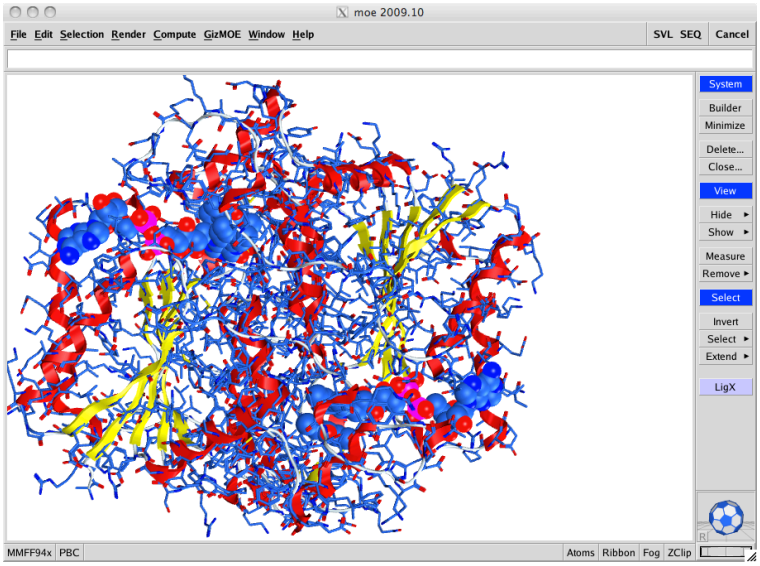


Step 2. Extract one homodimer and its ligands

Open Sequence Editor (click SEQ button in the upper right corner) and select chains to be deleted:



Right mouse click and select “Delete Selected Chains” or Edit -> Delete Selected Chains. Render in Ribbons: use Ribbon tab in the lower right corner.

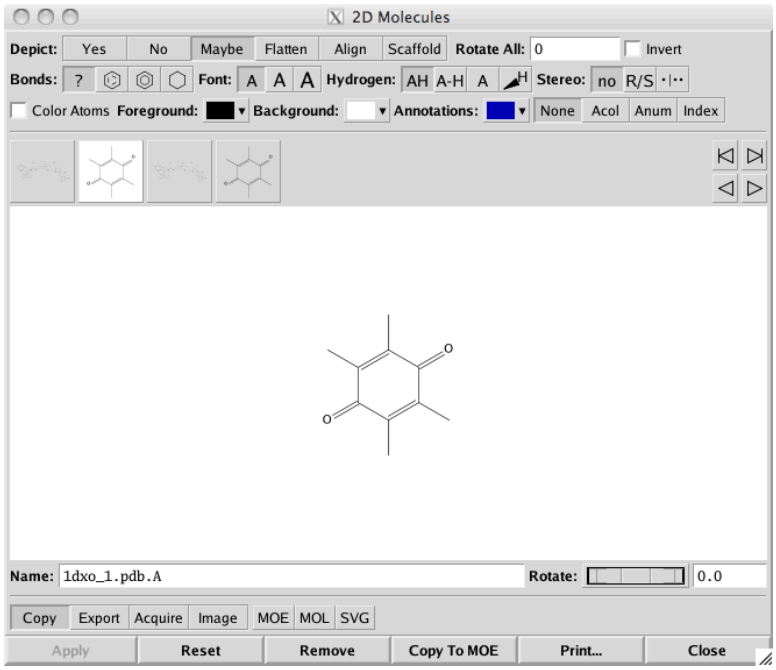


Save remaining homodimer and ligands as a pdb file, 1dxo_1.pdb.
Close Molecule: File -> Close

2. Analysis of ligand-protein interaction in 1DXO structure

Step 0: Load 1dxo_1.pdb

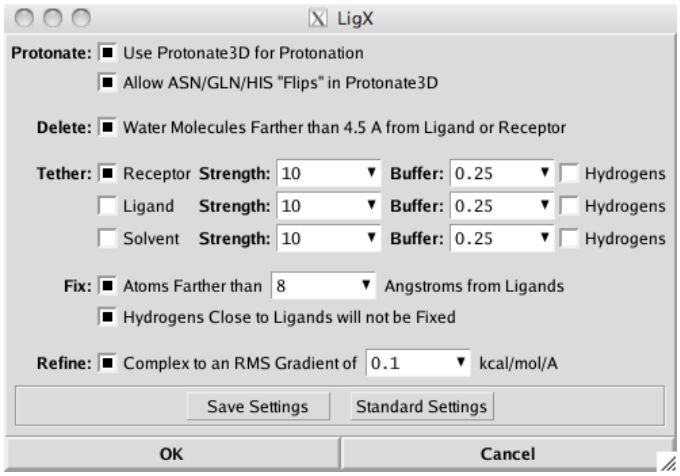
Step 1: Observe ligands with Ligand->2D molecules. Click through icon depicting detected planar molecules.



Step 2. Protonate the system.

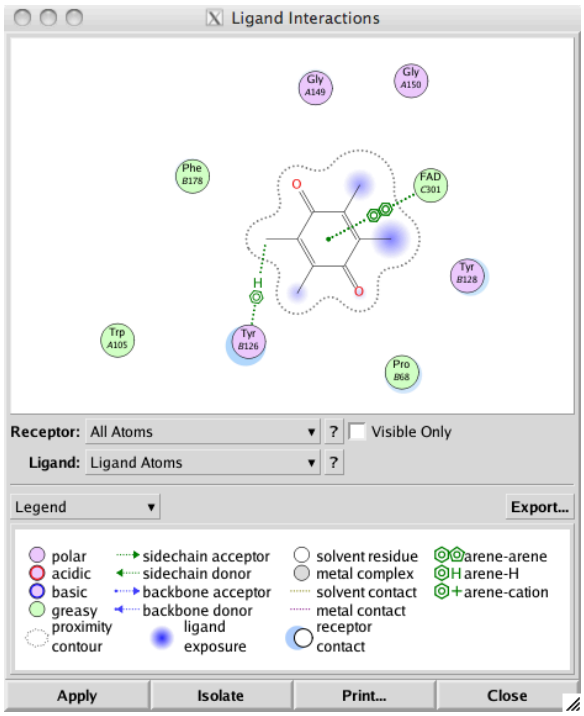
Note: Crystal structure of the complex does not have hydrogen atoms, which are needed for future analysis.
Launch LigX: click LigX button.

LigX -> OK. Hydrogen atoms and partial charges will be added to the complex. Minimization will be performed while side chains of the protein are kept rigid and ligand is flexible. This will take few minutes. Operation is complete when messages are removed from the main MOE window.

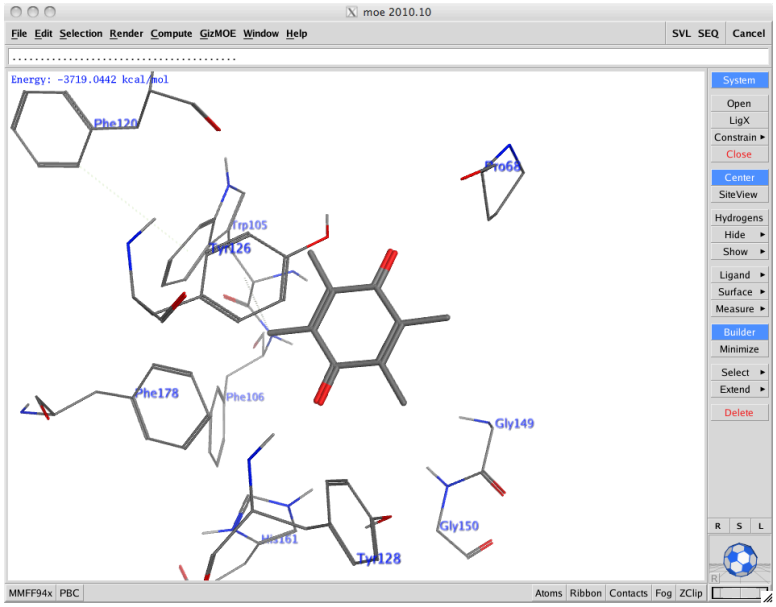


Step 3. 2D ligand interaction diagram.

Ligand-> Ligand Interactions. Observe the types of interactions detected.

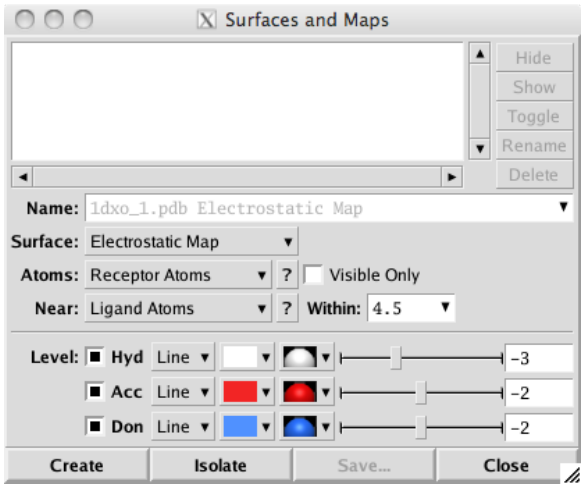


Click Isolate to show only atoms close to the ligand of interest.

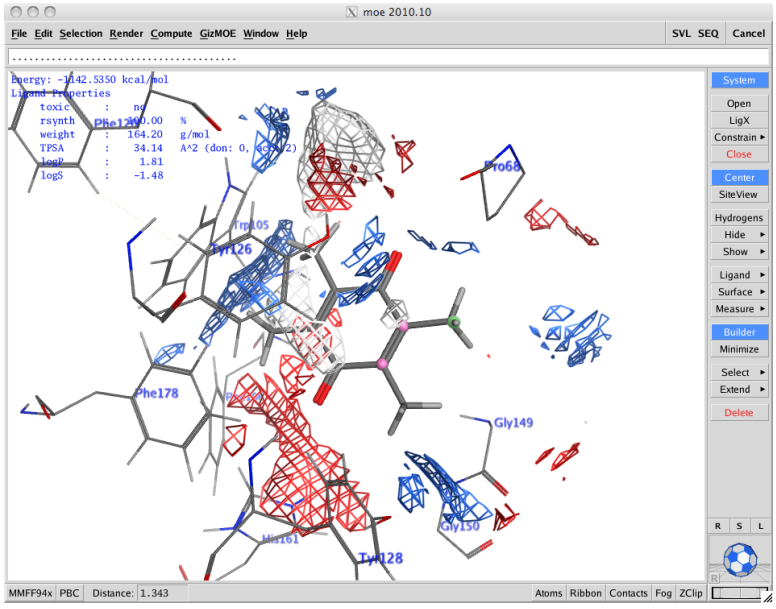


Step 4. Electrostatic Map of the active site

Surface -> Surfaces and Maps -> Electrostatic Map. Click Create.



The electrostatic map will be displayed in the MOE window.



Study the map and see what kind of modifications can be energetically favorable.

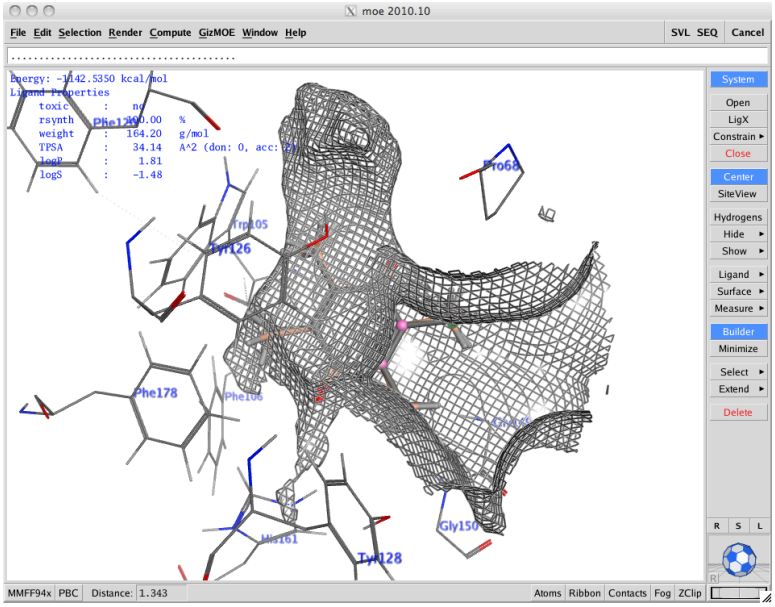
Notice the hydrophobic patches shown in white.

Surface and Maps -> Hide.

Step 5 Ligand properties, VdW map, hydrogen bonds, and binding free energy.

Show ligand properties: Ligand -> Ligand Properties.
Run minimization, Ligand -> Minimize and Energy will be displayed.

Surfaces and Maps -> Surface -> Interaction (VDW) will be shown. Observe steric clashes and voids for ligands expansion.



Save the system: LigX -> Save, 1dxo_ligand.moe

Step 7: Modification of the ligand. (independent)

Chose atom to modify. Open Builder. Select atom to modify and click needed group in the Builder window. When modification is complete perform minimization, LigX -> Minimize. Compare affinity and binding free energy of the modified ligand. Construct Interaction Map as above and compare as well.

Part III Docking of dicoumarol to NQO1 complex

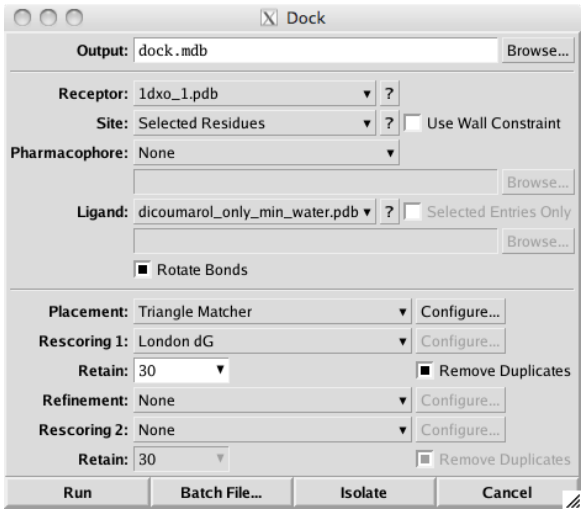
Idea: use NQO1 complex with DQ to dock solvated and minimized dicoumarol, using DQ location as docking site location.

Step 1: Load a single homodimer with two docked DQ. File -> Open -> 1dxo_1.pdb.

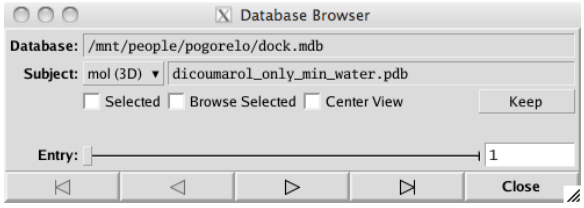
Step 2: Protonate the complex: Compute -> Protonate 3D

Step 3: Load minimized in water dicoumarol. File -> Open -> dicoumarol_only_min_wat.moe

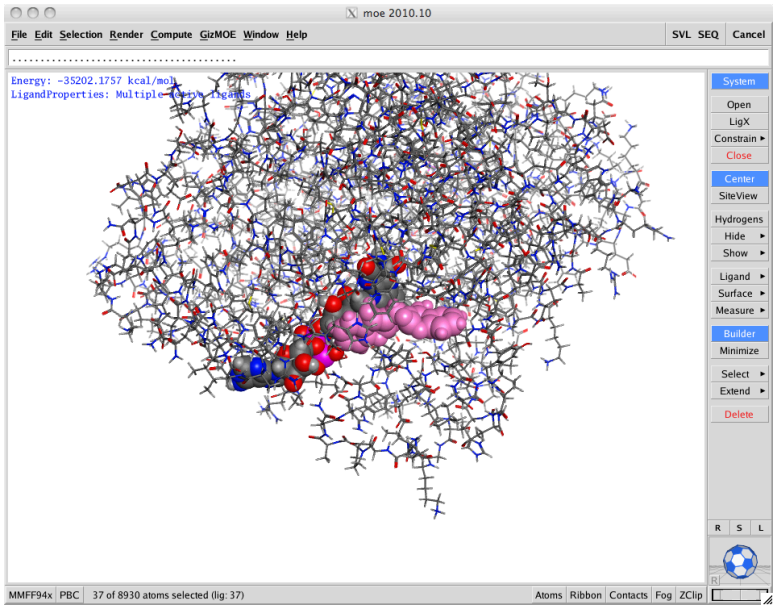
Step 4: Prepare Dock: Compute -> Simulations - > Dock. Open Sequence Editor and Click on DQN residue of Chain 4. Match the Dock menu to the Figure below. Selections of Receptor and Ligand are made to corresponding structures, where “Site” is assigned to “Selected Residue,” which correspond to the selected DQ. Click Run.



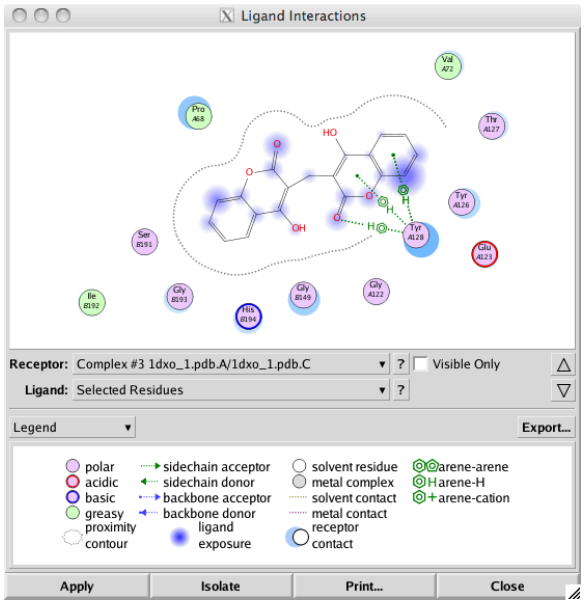
Step 5: Studying docking conformations. Once docking in complete Database Viewer will display results. To observe the conformations open Database Browser: Database Viewer -> File -> Browse. **Hint:** to have a better visibility of changes chose different Atom representations for dicoumarol and LIG after selecting them in Sequence Editor. Or select DQN in the chain 4 and Hide-> Unselected. Browse through results.



To improve the result, choose 1st predicted complex, remove DQN residue of Chain 4 and extra LIG of chain 5 (in Sequence Editor). Now minimize the new complex. Save the structure. Figure below shows the 1st complex after minimization, dicoumarol (in pick), FAD (in gray/blue) and energy value.



Study interactions between dicoumarol and the protein pocket: Ligand-> Ligand Interactions.



Step 6 (independent): Use the minimized complex to study active site as in Section II.2 now with dicoumarol docked. Start modifying decorations of dicoumarol and repeat.

Note: Quality of the docked complex can be improved by performing refinement using force filed selection in the Dock menu.

7. Summary

This tutorial introduced analysis of ligand-protein complexes, preparation of ligands for docking and docking using Dock in MOE environment.

8. Contact

If you found errors/typos or have suggestions or comments on material in this tutorial please contact us at the SCS Computer Center. We are looking forward to hearing from you.

9. Acknowledgment

We are very grateful to the Chemical Computing Group, especially Ms. Patricia Middleton, and for generous support in providing us with MOE teaching licenses. We also like to thank Ms. Elizabeth Parkinson (Hergenrother Lab) for suggesting the model system used in this tutorial.