CHEM 498Q / CHEM 630Q: Molecular Modelling of Proteins
TUTORIAL #5: Molecular docking

INTRODUCTION

In this tutorial, we will learn the basic procedure for "docking" a flexible ligand into the binding site of a receptor. We will use AutoDockTools (http://mgltools.scripps.edu) to prepare PDBQT files of the receptor and the ligand. The PDBQT format is an extension of the PDB format that contains partial charges ("Q") and atom types ("T"). We will perform the docking calculation using AutoDock Vina (http://vina.scripps.edu), one of the simplest and most efficient docking software currently available.

The docking poses will be visualized using PyMOL and will be compared to those found in the crystal structures of similar proteins.

REQUIRED PRE-LAB READING

AutoDock Vina article:

http://dx.doi.org/10.1002/jcc.21334

PRE-LAB REPORT

✦ List a few of the amino acids of your enzyme known to interact with the substrate or to participate directly in the catalysis. Refer to them using the residue numbers from the PDB file "`step3_pbc-setup.pdb`" from Tutorial #4.

READING

Chapter 12 of Leach ("The Use of Molecular Modelling…"): Sections 12.1, 12.6, and 12.7.

REFERENCE MATERIAL

AutoDock Vina video tutorial:
http://vina.scripps.edu/tutorial.html

AutoDock Vina Manual:
http://vina.scripps.edu/manual.html

PROCEDURE

STEP 1: Save one frame of the trajectory into a PDB file

Load the PSF and DCD files from Tutorial #4 into VMD:

```
$ vmd ./step3_pbcsetup.xplor.ext.psf step5_production.dcd
```

Using menu "File > Save Coordinates…" save the frame of the trajectory you have picked at Step 14 of Tutorial #4 (example, 999) as a PDB file. Keep only the protein and its cofactors (including the metal cofactors), using the following options:

• Selected atoms: "not water and not resname POT CLA"

• Frames: First = 999, Last = 999, Stride = 0

Save the file in a directory "`tutorial5`", under the name "`nosolvent.pdb`".

Note:
This tutorial makes the assumption that the best structure to dock the ligand into is that of the "naked" protein. In general, it might be useful to keep some water molecules at the active site, especially if they are thought to bridge protein and ligand.

STEP 2: Prepare the PDBQT file for the receptor

Start AutoDockTools:

```
$ adt
```

Load file "`nosolvent.pdb`" ("File > Read Molecule" menu) and remove non-polar hydrogen atoms ("Edit > Hydrogens > Merge Non-Polar" menu).

To create the PDBQT file of the receptor, use menu "Grid > Macromolecule > Choose" and select the only molecule available: "nosolvent". Save the united-atom structure under the name "`nosolvent.pdbqt`".

STEP 3: Define the search space

Use menu "Select > Select From String" to highlight the residues identified in the PRE-LAB. For each residue, type its residue number and click on the button "Add". (You should see yellow crosses on all atoms of the highlighted residues.)

Use the "Grid > Grid Box…" menu and adjust the spacing of the grid points to 1.000 Å (instead of the default 0.375 Å). Use 20 grid points in all three directions — so that your search space will be a cubic volume of 20 Å of side.

Adjust the three "offset" dials such that all highlighted residues are inside the search space. Write down the values of "x center", "y center", and "z center". (They will be used in STEP 5.)

STEP 4: Prepare the PDBQT file for the ligand

Go to the "Ligand Expo" webpage (http://ligand-expo.rcsb.org/ld-search.html) and search for the component identifier (3-letter code) appropriate for your enzyme:

- Glutamate racemase: 003 ("zero, zero, three")
- Matrix metalloproteinase: RS2
- Carbonic anhydrase II: BZU
- Dihydrofolate reductase: FOL
- NS3 protease: NDL
- Beta-lactamase: TBE

Click "Go" and download the ideal coordinates of the atom in PDB format. This file should be named "`???_ideal.pdb`". Write down the chemical details of that component: name, structural formula, formal charge, and InChiKey descriptor.

Load the ligand PDB file in your AutoDockTools session using the "Ligand > Input > Open…" menu.

Identify the rotatable bonds using the "Ligand > Torsion Tree > Choose Torsions…" menu. (The rotatable bonds are colored in green.) You could in principle make any "non-rotatable" bond "rotatable" by clicking on it.

Click "Done" and save the ligand in PDBQT format using the "Ligand > Output > Save as PDBQT…" menu.

STEP 5: Run AutoDock Vina

Create a file "`conf.txt`" containing the following text, with the question marks ("???") replaced by the values you chose in STEP 3 and STEP 4.

`conf.txt`

```
receptor = nosolvent.pdbqt
ligand = ???_ideal.pdbqt

out = all.pdbqt
log = all.log

size_x = 20
size_y = 20
size_z = 20
center_x = ???
center_y = ???
center_z = ???

exhaustiveness = 12
```

Run AutoDock Vina:

```
$ vina --config conf.txt
```

This calculation should take less than 5 minutes.

✦ Report the affinity values of all binding modes.

STEP 6: Load the docking results in PyMOL

Start PyMOL and open the following files:

- `nosolvent.pdb`
- `all.pdbqt`

✦ Produce a figure showing the best pose of the ligand and its interaction with the active site residues. Represent the ligand and the interacting side chains using sticks, and highlight any polar contact.

INSTRUCTIONS FOR THE LAB REPORT

The procedure is fairly straightforward, so keep the report short.

Motivate your choice of the active site using the scientific literature.

Discuss the best docking pose(s) in reference to the scientific literature. In particular, try to find published protein structures that contain the ligand you used for the docking study and see how the poses obtained from AutoDock Vina compare to the poses found in those crystal structures. Compare the poses in terms of polar contacts and hydrophobic contacts formed between the ligand and the receptor.

Discuss the non-optimal poses (that have lower affinities) the same way—in terms of the polar and hydrophobic contacts *missing*.