Docking Molecules to a Protein: Estimating Affinity

The problem is set up using AutoDock Tools. Then, the problem is solved using Vina.

Start AutoDock Tools (on the “Start” menu under “MGL Tools”). Click “Dismiss” to close the AutoDock selection dialog box, if it appears.

The dashboard is used to select what is displayed and how it is displayed.

On the menu go to **File/Read Molecule**, then navigate to My Documents\Biochemistry Lab\vina\_tutorial\, and open “protein.pdb” from there (the protein structures that Vina can read end with .pdb, indicating they are from the protein database). The protein should appear in the program’s window.

 Note: the protein can be moved on the screen using the following:

The right mouse button “rotates”,

The scroll wheel changes the zoom level.

The left mouse button “translates” the protein

Shift right mouse button draws a box and selects atoms in that box. (To unselect, click the  icon.)

Most PDB structures don’t have hydrogen atoms. The hydrogen atoms need to be added by placing them in calculated positions. **Edit/Hydrogens/Add**, then select **polar only**, and **OK**. (The polar hydroges are required by the pdbqt format used later.)

The dashboard can be used to display a molecular surface, to color atoms according to type, etc.

The space within and around the molecule has to contain a grid. To set this up, in the brownish bar below the icons, click “**Grid**”, and select “**Macromolecules**”, then “**Choose**”. Click on the item needing a grid (the protein, in this case), then click **Select Molecule**. The warning “initializing protein.pdb” appears. Click **OK**, which brings up a “file save as” dialog. Save the file as “protein.pdbqt” in the same directory as before (My Documents\Biochemistry Lab\vina\_tutorial\). (If asked to replace it because it already exists, do so.)

To speed up the process of finding the ligand-receptor binding site with the lowest energy, only the area around the receptor’s active site will be searched. This search space is set by setting some grid options. Go to **Grid/Gridbox…**, which then shows the Grid Options dialog box.

Click View at the top of the dialog box, and put a check next to “Show box”.

Specify the center of the search space in the boxes below Center Grid Box:. (Sometimes Enter has to be pressed to get the view to update.) Enter values of 11, 90.5, and 57.5 for x, y, and z center were used in the tutorial.)

Enter the size of the search box using the sliders.

Make the spacing between grid units be 1 Ångstrom by setting “Spacing” to 1.000 (moving the sliders is a bit tricky at first).

Select values of 22, 24, and 28 for x, y, and z-dimensions.

The search space box changes size as the values are changed.

The values of the center of the search space should be written down, because they are needed later.

Close the box: “File/Close saving current”.

Go to Ligand, Input, Open, select file type “.pdb” (from the drop-down menu), and go to the usual directory (My Documents\Biochemistry Lab\vina\_tutorial\) to open ligand.pdb.

The ligand file is analyzed and the number of rotatable bonds is reported.

Use the dashboard to hide the protein, so the ligand can be seen.

It is recommended that ligand structures already have the correct hydrogens on them. When such a structure is opened, the nonpolar hydrogens are removed (merged), leaving just the polar hydrogens.

The ligand may be treated as flexible by indicating which bonds are rotatable. Go to **Ligand/Torsion tree/Choose torsions…**. Just click on a bond to make it rotatable (green). Click done. (Nothing needs to be changed, initially.)

Save ligand structure as a pdbqt file: Go to **Ligand/Output/Save as PDBQT…**. Put it in the usual directory (My Documents\Biochemistry Lab\vina\_tutorial\).

Close the AutoDock Tooks, since it is not needed.

Before Vina can be run, a configuration file, conf.txt, must be present in the Vina\_Tutorial directory. Go to that directory and double-click on conf.txt; it should then open in notepad. Ensure that the following are in that document.

receptor = protein.pdbqt

ligand = ligand.pdbqt

log = log.txt

center\_x = 11

center\_y = 90.5

center\_z = 57.5

size\_x = 22

size\_y = 24

size\_z = 28

exhaustiveness = 8

The “exhaustiveness” option specifies how carefully to look for the best fit (8 is the default). The “log” option specifies a name for the log file.

Run Vina by double-clicking on Vina.bat (in the Vina\_Tutorial directory). (Other Vina options can be seen by double-clicking on VinaHelp.bat.) Running the program takes around ten minutes.

The output file, log.txt, shows the best “modes” of binding that the program found, based on the affinity, which is the estimated binding energy of the ligand to the protein. The more negative the affinity, the more tightly the ligand is bound to the receptor. The structures of the various modes of binding are stored in the file, ligand\_out.pdbqt. To see these, open that file with the Python Molecule Viewer, PMV, using **File/Read Molecule**. An option menu appears; select “conformations” and “yes” for using the right and left arrow keys to see the different conformations. Click in the molecule display window to use the arrow keys. Likewise, open protein.pdbqt, so you can see how the structures fit into the receptor site. Use the dashboard to make the ligands appear as space-filling models (the “C” option).

Left-click on “Protein”, and select “Hide molecule”, so that only the ligand is shown. Load the file “ligand\_experiment.pdb”. Display both ligands as “Lines”. Have the instructor go over the structure with you.

# Setup

Download MGLTools from <http://mgltools.scripps.edu/>.

Install MGL Tools. The setup program will first download and install Python. You may want to change the directory to C:\Program Files\Python25\.

Download Vina from <http://vina.scripps.edu/>. You may want to change the installation directory to C:\Program Files\vina\. (Vina will not appear when run until the configuration file is changed.)

Download OpenBabelGUI from <http://openbabel.org/wiki/Main_Page>. (Only needed for converting from one file type to another.)

Create a directory structure something like this:

My Documents

 Biochemistry Lab

 Vina\_Tutorial

The Vina\_Tutorial directory will eventually have the following files:

conf.txt The Vina configuration file

Docking Molecules to a Protein.docx This document

Endocrine disruptor info A directory with other info in it; not necessary for this lab

ligand.pdb The starting ligand file

ligand.pdbqt The final ligand input file, created by students

ligand\_experiment.pdb Experimental result for how the ligand binds

ligand\_out.pdbqt Program output

log.txt Program output

protein.pdb The starting receptor file.

protein.pdbqt The final receptor file, created by the students

Vina.bat Runs the Vina program, using the configuration file

VinaHelp.bat Runs the Vina program, but just shows the Vina help file

Create the following two files using Notepad.

Vina.bat contents:

cmd /k "C:\Program Files\Vina\vina.exe" --config conf.txt

VinaHelp.bat contents:

cmd /k "C:\Program Files\Vina\vina.exe" –help