Chemistry 478 — Molecular Modeling

Laboratory #10 — Docking Indinavir to HIV Protease Using AutoDock

In this lab you will perform a docking of the HIV protease inhibitor indinavir into the active site of the protease. Using the AutoDock software, full flexibility of the inhibitor and partial flexibility of protein residues will be incorporated. The best docking "poses" will be determined and compared with the known crystal structure of the protein complexed with the drug molecule.

Protocol

(1) Download the **`autodock-4.2.5.1.tar`** and **`mgltools-1.5.7.dmg`** files from the web site for this lab. Move both files to your home directory. Unpack the **`.tar`** file via the command **`tar xvf autodock-4.2.5.1.tar`**. This will put the **`autogrid`** and **`autodock`** executables into an /autodock directory.

(2) Next, double click on the **`.dmg`** file. This will bring up a window with the MGLTools package installer. Double click on the installer, and proceed with the installation (you may need administrator access to do the install. If so, ask me to enter the appropriate password.) This will create an MGLTools icon in the usual Applications folder, and under this icon you will have access to the ADT (AutoDockTools) and PMV (Python Molecular Viewer) programs needed for the lab.

(3) Get the "AutoDock Tutorial" which is available as a PDF file on the lab web. Also download the PDB files containing the HIV protease (**`hsg1.pdb`**) and the indinavir molecule (**`ind.pdb`**). Start with Exercise 5 on page 21 of the tutorial (Editing a PDB File). To begin Exercise 5, launch the ADT program, and then open the protease PDB file in ADT.

(4) Continue following the tutorial through Exercise 12 (Starting AutoDock 4). This will lead you through the complete docking protocol, starting from the original PDB files.

Questions

(1) Two key papers describing the search algorithm and the scoring function from AutoDock 4 are provided in the "Reading" section of the course web site. Briefly describe the procedure followed by the search method (use a flow chart to illustrate the steps). Give a short description of the components of the scoring function (include explicit formula for the individual terms).

(2) How well does the best inhibitor pose generated by AutoDock agree with the authentic crystal structure? What is the RMSD of your best AutoDock-generated inhibitor pose *vs.* the inhibitor as found in the crystal structure of the complex?