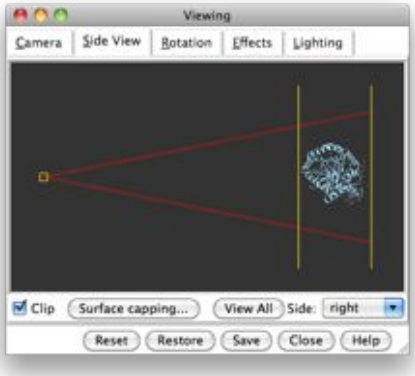
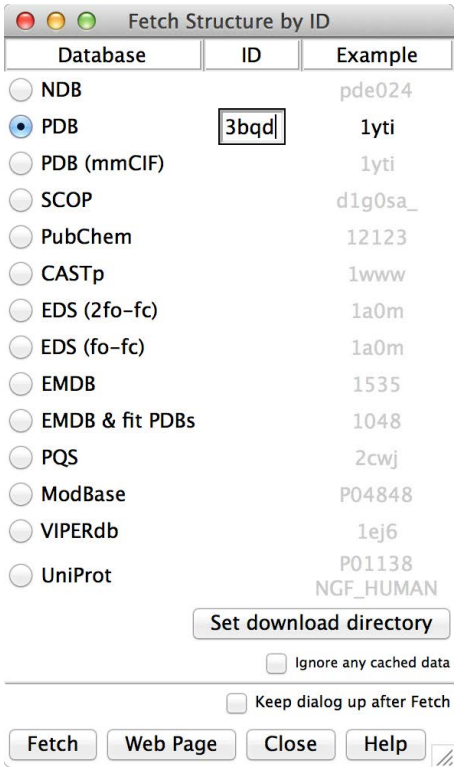
Advanced Computational Drug Design

Exercise 0: Mousing and manipulating the view

0a: Mouse Left drag = rotate Middle (or Alt/Option) drag = move Right (or two-finger) drag = zoom Scroll wheel or two-finger swipe = zoom quickly Ctrl-Left Click = select/deselect Shift-Ctrl-Left Click = add to selection Slab: "Favorites > Side View"	
0b: Center of view and rotation Zoom to the selection: "Actions > Focus" Rotate about the selection: "Actions > Set Pivot" or Ctrl-Left Double Click and select "Set Pivot".	*TIP: If nothing is selected, "Focus" and "Set Pivot" revert to the whole.*

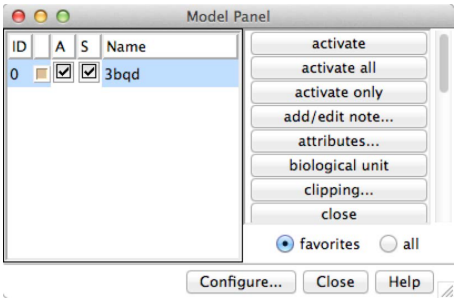
Exercise 1: Docking with AutoDock Vina

1a. Opening Chimera and load the receptor 1. Click on the Chimera icon. This will open a single window. 2. Use the File menu to open the "Fetch by ID…" dialog box. 3. Choose PDB and type "3bqd" into the ID box. Then click "Fetch". A crystal structure of the Glucocorticoid Receptor will appear in the black 3D structure area.	

1b. Model Panel

1. "Favorites > Model Panel". Use the Model Panel to hide and show molecules, surfaces, and specialty representations.

   The Model Panel can be used to color objects and bring up various dialogs.



1c. Find the Ligand centroid

1. Tools>>Utilities>>Reply log

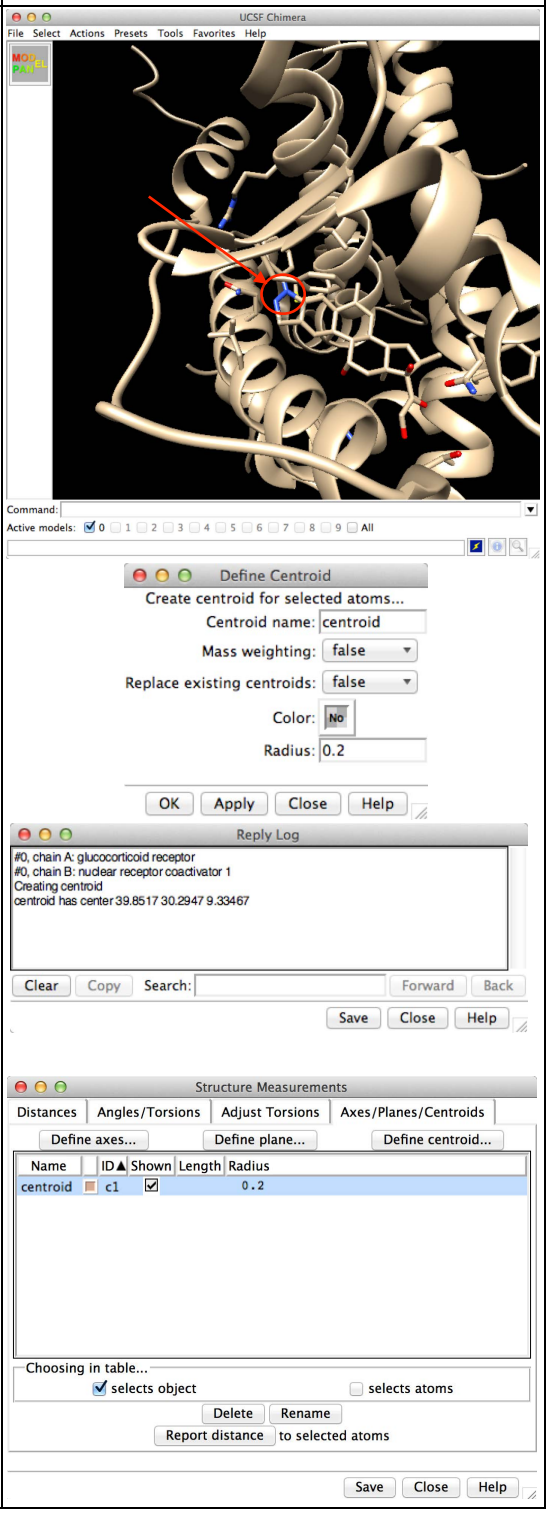
2. Control-click one of the two adjacent N atoms (only seen on the ligand), then up arrow to select whole ligand, which will be outlined in green.

2. Tools>>Structure Analysis>>Axes/Planes/Centroids
3. Click Define Centroids

5. Click OK in the Define Centroid dialog box

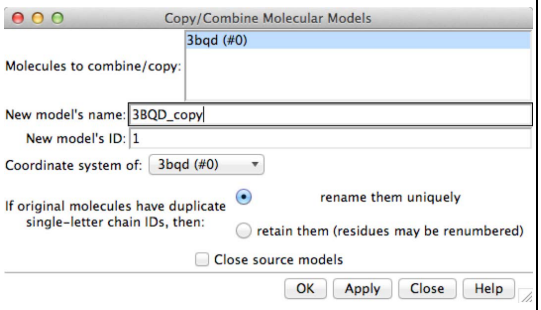
6. Note coordinates of centroid in Reply Log

7. Select the centroid c1 in the dialog box and click delete, then close the dialog box

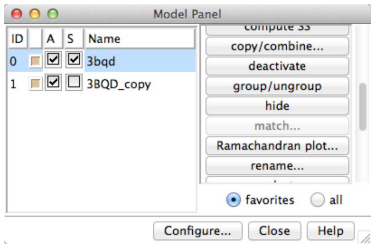


1d. Separate ligand from protein

1. In Model Panel, scroll menu and choose “copy/combine…”

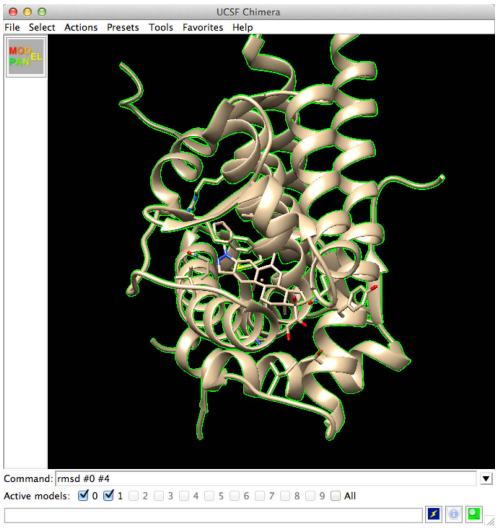


2. Select #0, in the field “New model’s name" enter “3BQD_copy”, then click OK

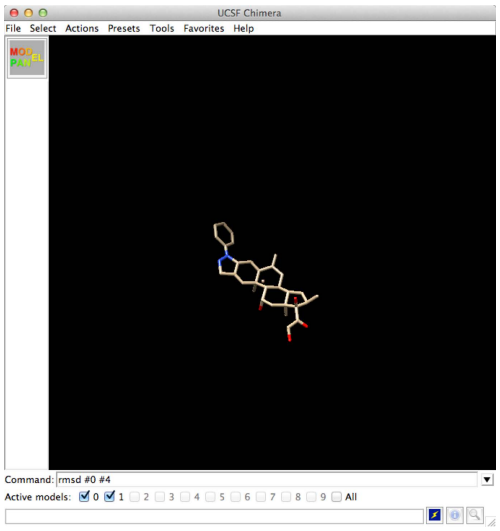


3. In Model Panel, uncheck 3BQD_copy in “S” column

4. Verify that the ligand is still selected, then choose Select>>Invert (selected models)->. The protein should now be selected



5. Choose the menu item Actions>>Atoms/Bonds>>delete. Only the ligand should remain visible.

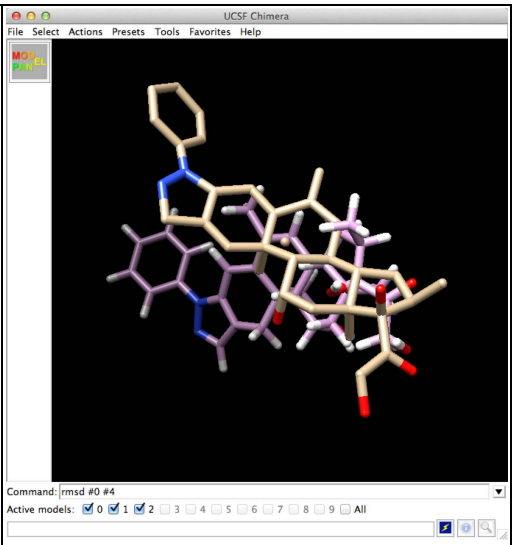


6. In Model Panel, select the model with ID #0 (3BQD.pdb), and scroll to choose “rename…” in the Model Panel menu. In the dialog box, enter “3BQD_ligand” for the new name and click OK.

1e. Load a version of the ligand with arbitrary pose, that will be docked into the receptor+

1. File>>Open and choose the file:

   dac_3d_renum_vina.mol2



1f. Submit the AutoDock Vina docking calculation

1. Tools>>Surface/Binding Analysis>>AutoDock Vina

2. Click "Browse", navigate to current directory, enter an output filename and “Set Output Location”
3. Specify Receptor: 3BQD_copy (#1)
4. Specify Ligand: 3032474 (#2)

5. Enter Receptor search volume options
   i. Center: centroid coords from step 1c-6 in Reply Log (2 decimal places)
   ii. Size: 15 for x, y, z (graphics box will appear)

6. Enter Recepter options

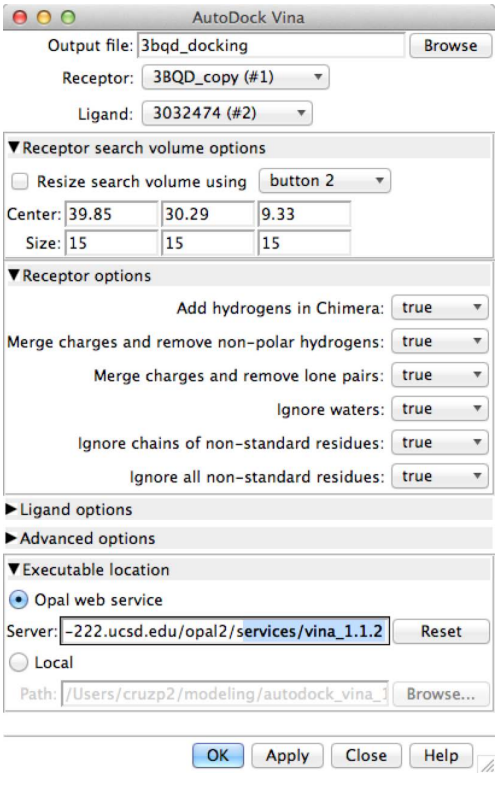
   Ignore all non-standard residues: true

7. Executable location

   Click “Opal web service”

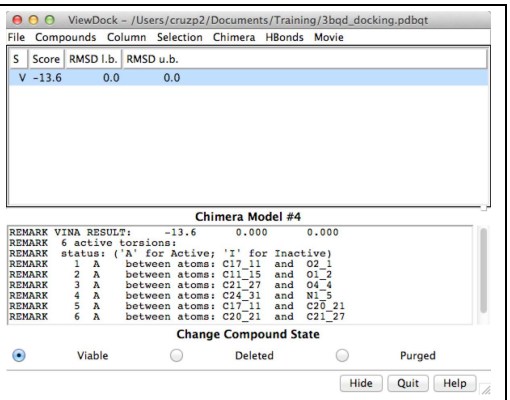
   Verify url: http://nbcr-222.ucsd.edu/opal2/services/vina_1.1.2

5. Click OK to start job



1g. Examine results

1. When job concludes, a new model, Docked 3032474, will appear in the graphics window with ID 4 in the Model Panel. The ViewDock dialog which shows the docking score will also appear. Make sure only the new model #4 and #0 are selected in the "S" column of the Model Panel, to visually examine how well the program did.



1h. Do an RMSD calculation to quantify how well the program did

1. Delete hydrogen atoms on the docked molecule (ID 4)
   a. Note that there are 3 H atoms, colored white, attached to oxygen atoms.
   b. Control-click one of them to select
   c. Actions>>Atoms/Bonds/delete
   d. Repeat steps b. and c. for the other 2 H atoms

2. At the Command prompt type:

   rmsd #0 #4

3. The RMSD will appear in the Reply Log and in message window at the bottom of the main graphics window