AutoDock Tutorial

1. Prepare target protein for docking

AutoDock expects that the input protein has polar hydrogens and that all the water molecules have been removed. You will get errors if this is not the case.

1.1 Open hsg1.pdb in pyMol and remove all water molecules.

1.2 Open file hsg1.pdb in ADT.
File->Read Molecule
You can rotate the structure with the middle mouse button. Zoom with the middle mouse button while holding down the shift key.

1.3 Add polar hydrogens to target structure
Edit->Hydrogens->Add
Make sure that you select Polar only

1.4 Save the structure
File->Save->Write PDB
Make sure that it points to the correct file path. The write dialog allows you to set which record types should be saved. Do not make any changes here.

2. Initialize ligand for docking

Before initializing a ligand you should make sure that it has all its hydrogens attached. For this tutorial the ligand ind.pdb already has its hydrogens attached.

2.1 Hide the protein in view.
Display->Show/Hide Molecule

2.2 Load the ligand file. The default file type in the file open dialog is .pdbq. Change it to pdb.
Ligand->Input->**Open...(AD3)**
Note that we used the "Open...(AD3)" option and not the "Open..." at the top. This is because we are going to run AutoDock3 and Not Autodock4, in which case we would have used the "Open..." option.
ADT initializes the ligand file and adds gasteiger charges. If the ligand was a peptide it would have added Kollman charges.

2.3 Detect the root of the ligand.
Ligand->Torsion Tree->Detect Root...

2.4 View rotatable bond
Ligand->Torsion Tree->Choose Torsions...
This opens a dialog that allows you to set which bond AutoDock is allowed to rotate. Note that amide bonds are set to non-rotatable. Click Done without changing anything.

2.5 Set rotatable bond (**Active torsions**) to **6** while allowing the **fewest atoms** to move.
Ligand->Torsion Tree->Set Number of Torsions

2.6 Save the Ligand
Ligand->Output->**Save as PDBQ...(AD3**)
In the file save dialog, explicitly type the file name "Ligand.pdbq".

3. Prepare Grid map

Grid is placed on the target active site and should contain all atoms that could possibly interact with the ligand. It should be large enough to allow the ligand to fully rotate.

3.1 Set target protein in which the ligand will dock.

Grid->Macromolecule->**Choose...(AD3)**
Select the protein target prepared in step 1. Immediately after the file opens ADT opens the file save dialog to save the initialized target protein. Save this structure is the directory in which you will run AutoDock. Explicitly type “Protein.pdbq”.

3.2 Set the Map types that will be used for the grid.
Grid->Set Map Types->**Choose Ligand...(AD3)**

3.3 Set the Grid Box position and size.
Grid Box...
For this exercise: Set each of the dimensions of the grid box to 60 points.
Use the (2.5, 6.5, -7.5) x,y,z coordinates for the center of the box.

3.4 Save the current grid positioning
File->Close Saving Current

3.5 Save Grid file
Grid->Output->**Save GPF...(AD3)**
In the file save dialog explicitly type “Grid.gpf”.

4. Setup docking parameter file

4.1 Set the protein target to be docked
Docking->Macromolecule->**Set filename...(AD3)**
Select the Protein.pdbqs file.

4.2 Select the ligand to be docked
Docking->Ligand->**Choose...(AD3)**
A ligand parameters window opens. Leave all parameters at the default values.

4.3 Set search parameters
Docking->Search Parameters->Genetic Algorithm...
Make the following changes to the parameters:
Number of runs -> 50
Population size -> 50
Maximum number of energy evaluations -> 1500000
Leave the rest of the parameters at the default values

4.5 Set Docking parameters
Docking Parameters...
Make the following changes to the parameters:
Translation -> 0.2
Quaternion -> 5.0
Torsion -> 5.0
RMS Cluster Tolerance -> 1.5
Leave the rest of the parameters at the default values

4.6 Set the Docking output parameter file
Docking->Output->**Lamarckian GA...(AD3)**
In the file save dialog explicitly type “Dock.dpf”.

5. Running AutoGrid and AutoDock

AutoDock and AutoGrid have to be run in the same directory as Ligand.pdbq, Protein.pdbqs, Grid.gpf and Dock.dpf.

5.1 Run AutoGrid3 in the command line

autogrid3 –p Grid.gpf –l Grid.glg &

5.2 Run AutoDock3 in the command line
autodock3 –p Dock.dpf –l Dock.dlg &

6. View Docking Results

6.1 When AutoDock completed its run, you can view the results in ADT.
Analyze->Dockings->Open...
Open the Dock.dlg file

6.2 Load macromolecule into view
Analyze->Macromolecule-.Choose

6.3 Select the macromolecule
Select->Direct Select->Molecule List ...
Make sure that only the macromolecule is selected.

6.4 Color the atoms of the macromolecule
Color->by Atom Type

6.5 Compute the molecular surface of the macromolecule
Compute->Molecular Surface->Compute Molecular Surface

6.6 View the conformations
Analyze->Conformations->Play ...
Use the player to look at the conformations

6.7 View conformational clusters
Analyze->Clustering->Show ...
Select a cluster to view

6.8 Set play options
Press **&** on the player dialog
Select Show Info and Build Hydrogen Bonds

Suggested reading

- Using AutoDock with AutoDockTools: A Tutorial.
- Users Guide: AutoDock.
- Morris G.M., Goodsell D.S., Halliday R.S., Huey R., Hart W.E., Belew R.K. Olson A.J. (1998). Automated Docking Using a Lararckian Genetic Algorithm and an Empirical Binding Free Energy Function. Journal of Computation Chemistry **19:** 1539-1662.
- http://autodock.scripps.edu/