

Practical 3 - protein-ligand docking with Autodock

 gent.uab.cat/jdidier/content/practical-3-protein-ligand-docking-autodock

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Autodock is a flexible ligand-protein docking program which basically runs as a two steps procedure: the calculation of the map of interactions of the binding site with some general atom types (performed with autogrid) and the posing of the ligand respecting this map of interaction (performed with autodock).

Some of the algorithms detailed during the theoretical courses are available in Autodock. The actual version of the program (the version we will use here) is the version 4.0 which provides with important new features for docking prospect like protein residue flexibility and high quality scoring functions.

In this tutorial, you will be introduced the docking approaches by undertaking undertaking on your own some docking experiments on the androgen binding receptor seen in the tutorial I. The different steps for the initial study as well as the possible extension of the work are summarize below.

1. Ligand and Protein Set up

Autodock scoring function is applied using an adapted AMBER force field therefore the atoms of the protein and the ligand have to be set up in accordance with this ff. To prepare our files, we will use the visual interface available for Autodock that allow to prepare, study and analysis dockings.

Probably less visually attractive than pymol, the autodock interface (called ADT) offers pretty much the same standard functionalities with the advantage of an optimized environment to preparing autodock inputs.

Go to the Kuubuntu menu and search for the MGLtools. Then click on the AutoDockTools 1.5.0 icon to start the interface.

We will continue working on the 2amb structure we used at the end of the pymol tutorial. You should separate the ligand and the protein file of this pdb file.

- Adding hydrogens to molecules

Previous to docking, we need to add the hydrogen to the ligand and the protein.
ligand:

Go to File --> Read Molecule and open ligandfile.pdb

Then Edit --> hydrogen--> add

Be sure that **all hydrogens** will be added (posterior procedures will remove non polar hydrogens), that **Method** is set to {noBondOrder} (that will not read info from the pdb file) and then {OK.} Save this file for future work in pdb format

{receptor:}

For clarity, remove the ligand from the screen. click in the dashboard with the right button on the ligand name then choose delete

Do the same procedure than for the ligand and save the file in the pdb format

- Preparation of the ligand and macromolecule for docking

ligand:

In the Autodock menu, Choose your ligand file: {ligand} --> {input} --> {open} then select the file of the ligand you added the hydrogens to.

Once opened the file, adt searches for the non polar hydrogens and merge them, then set the atoms types and the charges of the atoms. You will have a message popping up.

Your next step is to define the atom that will be use as criteria for translation-rotations (root) {ligand} --> {torsion tree} --> {detect root}

A green sphere is put on root atoms.

Finally, for consistence with the force field, rename the aromatic carbons to A ({ligand} --> {aromatic carbon} --> {rename C >}A). Then save your file.

receptor:

Choose your receptor file: {Grid} --> {macromolecule} --> {open} adt performs the same steps as for the ligand and ask you to save the pdbqt file. No renaming is needed in this step. At this stage you have both ligand and protein set up for initiating the docking procedure.

2. Mapping of the binding site

Autodock computes the possible interaction points in the binding site of the protein prior to exploring the conformations. Our next step is therefore to set up the grid.

In the docking menu, go to {Grid} --> {macromolecule} --> {open} and choose the macromolecule you want

Determine which kind of interaction you want to precompute in the binding site

{Grid} --> {set map types} --> here you select the ligand you have in the binding site for this tutorial so click on {choose ligand}, and choose your ligand

Now you need to define the quality of the grid you want the interaction to be precomputed:

{Grid} --> {Grid Box}

In the menu of the dialog box, click on {Center} then on select {center on ligand}.

Move the scrolls on the number of points to the maximum allowed and then reduce the spacing to something like 1.5 Å.

Save the box: {File} --> {close saving current}

Define the name of the grid parameter file: {Grid} --> {output} --> {save gpf}

Finally, run the computation of the grid:

{Run} --> {Run autogrid} (check that the path and the filename of the gpf is correct)

With the condition of the docking we asked for, this run will need a bit of time. In the meanwhile, go swimming over literature on the protein you work on.

3. Docking

Once the grids have been calculated, we can perform the docking on its own.

First we select our receptor:

{Docking} --> {macromolecules} --> {set Rigid Filename}

Then we choose the ligand:

{Docking} --> {Ligand} --> {choose} --> (click on your selected ligand - check the answers) --> {accept}

Select the kind of search algorithm you want (think on the main differences that exist between them)

{Docking} --> {Search parameters} --> Choose{ genetic algorithms} or {simulated annealing} (check the values) --> {accept}

{Docking} --> {Output} --> select your search approach --> give a name to the output

Finally edit the parameter files to check for possible errors (maps names for examples).

Then run the docking: {Run} --> {Run Autodock}

Check the pathname and the name of the files.

4. Analysis

Once the calculation has finished we can analysis the conformations obtained and their energy. We will do this directly in the adt tool. Go to {Analysis} and search around, also look at the output file to see if you could follow the process performed by Autodock.

5. Further considerations

Some considerations you may want to explore:

- 1. take the ligand and use Gaussian to perform an AM1 minimization in gas phase or in different solvent conditions. What is the form of the resulting structures with the one observed in the binding site of the protein? Try to dock the minimized structures into the 2amb cavity. What could you tell about this experiment?
- 2. Look in the pdb at the structure of some mutant resistant in prostate cancer treatment. Look at the binding site form of the structure. What could you conclude? What about docking in this structure?
- 3. Make your own experiments!