# Molecular Docking - An easy protocol

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## Abstract

To setup the docking, the Lamarckian genetic algorithm (LGA) was used, and docked conformations were compared and clustered based on the conformational similarities and root-mean-square positional deviation (rmsd). The numbers of runs were adjusted to 30 for all ligands. Rmsd was calculated based on rmsd conformational clustering tolerance of 2.0 Å. For genetic algorithms, parameters were setup as 150, 0.02, 0.8, 27000, and 2500000 for population size, mutation rate, crossover rate, maximum number of generation, and maximum number of energy evaluations, respectively. For LGA docking, the pseudo-Solis and Wets local search method was used with a maximum of 300 iterations per local search, and the probability of performing local search on an individual in the population was adjusted to 0.06, the size of local search space to sample, ρ, was 1.0, the maximum number of consecutive successes or failures before doubling or halving the ρ was four for both, and finally the lower bound on ρ was 0.01.

To have access to sample data and configuration files also check out: doi: 10.13140/RG.2.2.20407.42403

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## Guidelines

For each target, you need a separate folder in which you have folders of compounds (ligands). For each ligand, separate docking algorithm should be run.

## Before start

Install all required software:

MGL tools 4.2

UCSF Chimera

Accelrys Discovery Studio

Open babel

Cygwin

ChemSketch

SPDV Swiss PDBVIEWER

## Protocol

File conversion

**Step 1.**

Each compound should have pdb extension. So using Open babel you need to convert the files from mol, sdf, *etc* to pdb.

Protein optimization

**Step 2.**

Download your target from protein data bank.

For example: **4jkv**

Search pdb for 4jkv, and then download 4jkv.

Protein optimization

**Step 3.**

Open protein pdb file.

Protein optimization

**Step 4.**

Delet all HETATM lines we are refered to the previous dockied ligand.

The last line should be END. Edeit all HETAM till you have END after the last ATOM (Which refered the last atom of the last residue).

NOTES

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If water is important for your docking you can have HETATM related to HOH.

Energy minimization

**Step 5.**

Open SPDBV

Energy minimization

**Step 6.**

Open your protein.pdb (edited version).

Energy minimization

**Step 7.**

Using the top menu select All.

Energy minimization

**Step 8.**

Using Prefs at the top menu, click on Energy Minimization, and click OK.

Energy minimization

**Step 9.**

Save

Energy minimization

**Step 10.**

Open protein.pdb in notpad++

Energy minimization

**Step 11.**

Delet all coordinates related to SPDBV till END.

Energy minimization

**Step 12.**

Save

Enerfgy minimization

**Step 13.**

Copy the last protein pdb file into all folders of your compounds.

Docking setup

**Step 14.**

Open AutoDock 4.2

Docking setup

**Step 15.**

From the top menu (Read Molecule), go to the first folder and choose your protein to open it in AutoDock.

Add polar hydrogen

**Step 16.**

EDIT/HYDROGEN/ADD/PPLAR ONLY

Click OK.

Add Kollman Charges

**Step 17.**

EDIT/CHARGES/ADD KOLLMAN CHARGES

Setup

**Step 18.**

EDIT/ATOMS/ASSIGN AD4 TYPE

SAVE PDBQT FILE

**Step 19.**

SAVE/WRITE PDBQT

BROWSE and go to your first folder of which you already read the molecule.

Save the pdbqt file so that the file name is as the same as your pdb file.

Now select from **ATOM** to **END** and **ADD**

Check box for **SORT NODES**

Check box for **SAVE TRANSFORMING COODS**

**OK**

SAFETY INFORMATION

**Later on, carefully save your files in your previous folder (project). If you mistakenly save some files in other folders, you will definitely get error during your run.**

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If your pdb file is **4jkv.pdb**, your pdbqt file should be **4jkv.pdbqt.**

Ligand optimization

**Step 20.**

Using AutoDock and the LIGAND menu (INPUT), open the first LIGAND .

Open 1.pdb file.

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You can have numbers for your ligand folders.

1.pdb is located in your first folder.

Ligand optimization

**Step 21.**

LIGAND/TORSION TREE/DETECT ROOT

Ligand optimization

**Step 22.**

LIGAND/TORSION TREE/CHOOSE ROOT

SAVE LIGAND PDBQT

**Step 23.**

LIGAND/OUTPUT/SAVE PDBQT

Beside protein.pdbqt, now you have 1.pdbqt in the same folder.

SAFETY INFORMATION

**Again before saving, check the folder at which you are saving.**

GRID SETUP

**Step 24.**

GRID/MACROMOLECULES/CHOOSE

Select your protein (e.g. 4jkv).

SELECT MOLECULE

OK

Go to your folder and save it as your protein.pdbqt.

SAVE

YES (Replace the file)

GRID SETUP

**Step 25.**

GRID/SET MAP TYPES/CHOOSE LIGAND

Click on  1.

SELECT LIGAND

GRID SETUP

**Step 26.**

GRID/GRID BOX/CENTER/Picj=k an atom and Center Grid Box:

You must set the center of grid box on which the ligand is docked.

X=

Y=

Z=

NOTES

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You must already determine where you want to dock and identify the docking site or active site of your target.

For example:

For 4jkv, these are suggested:

X= -20.101

Y= 21.355

Z= 28.384

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If you want to perform blind docking to randomly dock, your grid box should be large enough to cover the whole protein.

GRID SETUP

**Step 27.**

CLOSE SAVING CURRENT

GRID SETUP

**Step 28.**

GRID/OUTPUT/SAVE GPF

Go to your folder (for example the folder number 1) and save **protein.gpf**.

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your grid parameter file (GPF) shoud be as the same as your protein (e.g. 4jkv.gpf).

## DOCKING SETUP

**Step 29.**

DOCKING/MACROMOLECULES/SET REGID FILE NAME

Go to your folder.

Click on protein.pdbqt.

OPEN

## DOCKING SETUP

**Step 30.**

DOCKING/LIGAND/CHOOSE

Click on 1 (your ligand)

SELECT LIGAND

ACCEPT the default parameters.

## DOCKING SETUP

**Step 31.**

DOCKING/SEARCH PARAMETERS/GENETIC ALGORITHM

ACCEPT the default parameters.

## DOCKING SETUP

**Step 32.**

DOCKING/OUTPUT/LAMARCKIAN GA

Go to your folder

SAVE **protein.dpf**

## CLOSE AUTODOCK

**Step 33.**

SETUP FOR THE FIRST COMPOUND AND TARGET IS FINISHED, YOU CAN CLOSE AUTODOCK OR REMOVE ALL OPENED MOLECULES TO START THE SECOND SETUP.

## RUNNING ALGORITHM

**Step 34.**

OPEN CYGWIN TERMINAL

## Go to your folder

**Step 35.**

You must go to your folder.

cmd COMMAND (Linux - Cygwin)

```
cd e:/
cd protein
cd 1
```

SAFETY INFORMATION

**you must already have two exe files in your folders. Copy autogrid4.exe and autodock4.exe to alll ligand folders. To have these files, go the the link located at the end of abstract of this protocol. A sample data contain one studied docking project in which you can find exe files as well.**

## AUTOGRID

**Step 36.**

cmd COMMAND (Linux - Cygwin)

```
$ ./autogrid4.exe –p target.gpf –l target.glg &
$ tail –f target.glg
```

## AUTODOCK

**Step 37.**

cmd COMMAND (Linux - Cygwin)

```
$ ./autodock4.exe –p target.dpf –l target.dlg &
$ tail –f target.dlg
```

## Editing the docked files

**Step 38.**

cmd COMMAND (Linux - Cygwin)

```
$ grep '^DOCKED' target.dlg | cut -c9->target_run.pdbqt
$ cut -c-66 target_run.pdbqt>target_run.pdb
```

## Reading DLG files

**Step 39.**

You can see the binding energy calculations and inhibition constants.

## Visualization/Interaction

**Step 40.**

Now you can open your docked files (target_run.pdb) by **UCSF Chimera** and **Accelrys DS**, and analyze the interaction between protein and ligand. You can also use **LigPlus**.

## Citation

**Step 41.**

**Please use and cite the following paper:**

Kaboli, P. J.; Bazrafkan, M.; Ismail, P.; Ling, K. H. Molecular Modelling of Berberine Derivatives as Inhibitors of Human Smoothened Receptor and Hedgehog Signalling Pathway Using a Newly Developed Algorithm on Anti-Cancer Drugs. *Recent Pat. Anticancer. Drug Discov.* **2017**, *12* (4), 384–400.