Two steps for virtual screening in the pocket of SARS-CoV-2 Mpro by MolAICal

Qifeng Bai
Email: molaical@yeah.net
Homepage: https://molaical.github.io
School of Basic Medical Sciences
Lanzhou University
Lanzhou, Gansu 730000, P. R. China

1. Introduction

In this tutorial, we introduce the fast way for drug virtual screening of SARS-CoV-2 Mpro based on the known database such as ZINC database. The premise for this tutorial is that you can deal with the receptor and ligand structures by MolAICal (see "Quick Start 1" in https://molaical.github.io). If users want to know more detailed molecular preparation process, you can learn from the tutorial: https://github.com/MolAICal/documents/tree/master/tutorials/002-AIVS. Here, MolAICal soft package is employed for this tutorial (https://doi.org/10.1093/bib/bbaa161).

2. Materials

2.1. Software requirement

1) MolAICal: https://molaical.github.io

2.2. Example files

1) All the necessary tutorial files are downloaded from:
https://github.com/MolAICal/tutorials/tree/master/003-VS
2) The file named "ligandSet.mol2" which contains 16 ligands obtained from ZINC database is chosen for demo. You can select your ligand database.
3) The protein file named "pro.pdbqt" that is PDBQT format structure of SARS-CoV-2 Mpro is used for molecular docking.

3. Procedure

Go to the tutorial directory:

```
#> cd 003-VS
```

1. Split ligands set into single molecule. If your drug database is built by single ligand with mol2 format, you can omit this step.

```
#> molaical.exe -tool mol2 -w split -n 1 -v true -m number -i ligandSet.mol2 -o splitdir
```

Note: when the second line content is valid, you can also use the second line string of mol2 file as the file name by using the below command:

```
#> molaical.exe -tool mol2 -w split -n 1 -v true -i ligandSet.mol2 -o splitdir
```

2. Running virtual screening. Before run below command, please make sure the previous docking results are removed.

```
#> molaical.exe -dock vs -i splitdir -nc 3
```

-nc: represents the number of used CPU cores.

4. Results

4.1 checking results

Users can use Pymol software (http://www.lfd.uci.edu/~gohlke/pythonlibs) to load ligands with PDBQT format directly. Here, UCSF Chimera is introduced to show docking results.

Open 003-VS\splitdir

1) Adding hydrogen (option)
#> molaical.exe -dock addh -i 1_out.pdbqt

2) Changing “pdbqt” to “pdb” format
#> molaical.exe -dock pdbqt2pdb -i 1_out.pdbqt

It will get a molecular file named “1_out.pdb”. And then use UCSF Chimera to load “1_out.pdb” and “protein.pdb”. The docking result is shown in Figure 1 that indicates MolAICal obtains the suitable ligand from the known molecular database.

Notice: I omit the surface show process in Figure 1. If users want to obtain the result like Figure 1, “Actions→Surface→show” should be selected in UCSF Chimera.

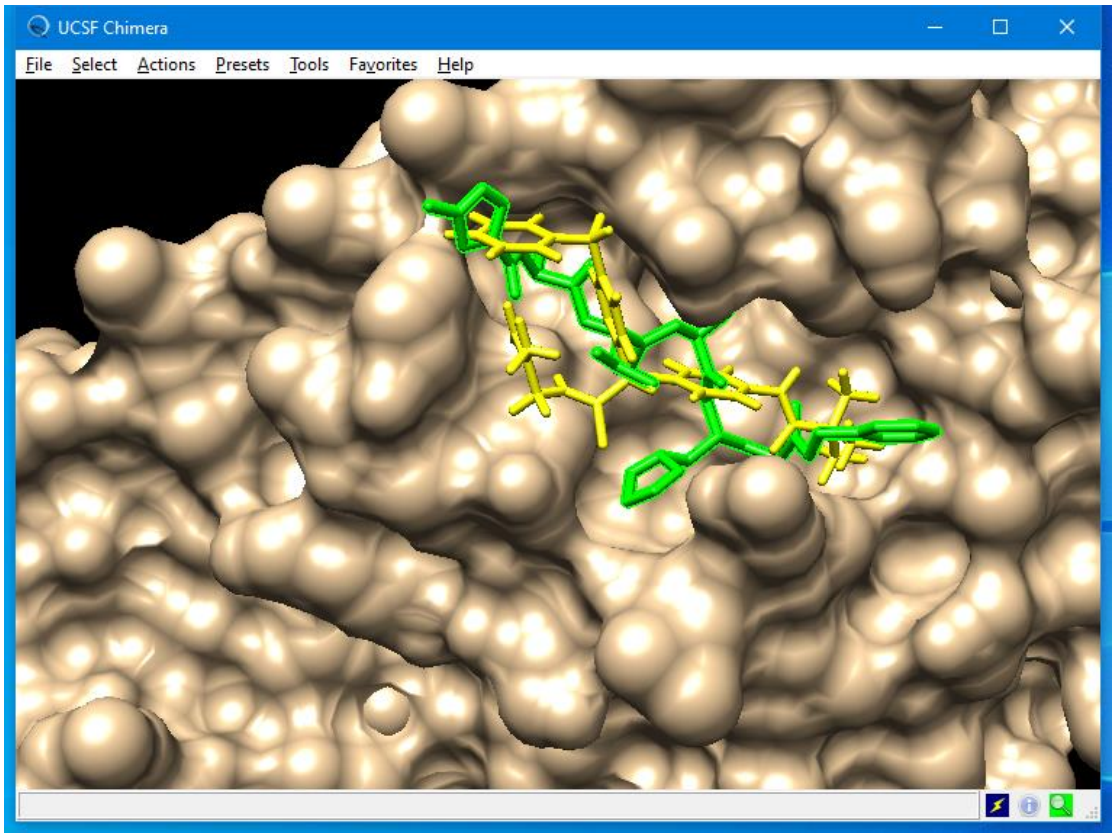


Figure 1. The ligand with green is the inhibitor N3 of SARS-CoV-2 Mpro. The ligand in yellow is obtained by virtual screening.

4.2 Ranking virtual screening results

Goto folder 003-VS, and run below command:

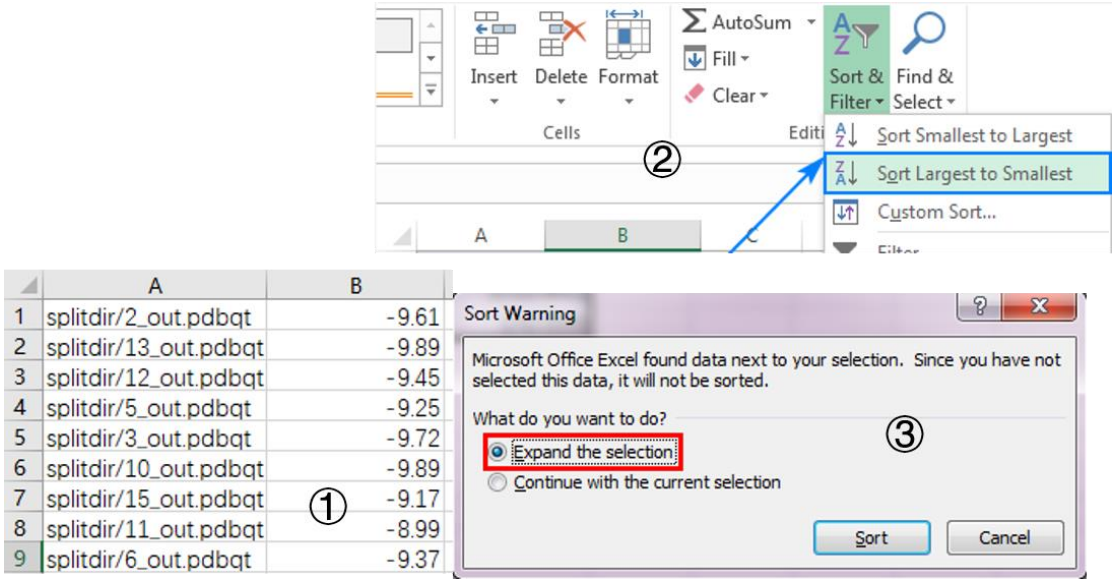
#> python /home/bai/MolAICal-xxx/scripts/printScore.py 'splitdir/*out.pdbqt'

It will show the ligand name and corresponding binding score. If users want to save results into a file, they can use below command:

#> python /home/bai/MolAICal-xxx/scripts/printScore.py 'splitdir/*out.pdbqt' > results.log

Note: "/home/bai/MolAICal-xxx" is your installed directory path of MolAICal. All the useful scripts are supplied into the folder "scripts" of MolAICal.

If you work in Window:
Open "results.log" by using Excel. In "Separator", tick the space. Or you can copy all the content of "results.log" into Excel, directly. Select all data in the second column and click "Sort Largest to Smallest" or "Sort Smallest to Largest" according to your needs (see Figure 2).



	A	B
1	splitdir/2_out.pdbqt	-9.61
2	splitdir/13_out.pdbqt	-9.89
3	splitdir/12_out.pdbqt	-9.45
4	splitdir/5_out.pdbqt	-9.25
5	splitdir/3_out.pdbqt	-9.72
6	splitdir/10_out.pdbqt	-9.89
7	splitdir/15_out.pdbqt	-9.17
8	splitdir/11_out.pdbqt	-8.99
9	splitdir/6_out.pdbqt	-9.37

Figure 2. Ranking results

If you work in Linux, users can do it as below:
#> sort -n -t ' ' -k 2r results.log > rank.dat

Note: parameter "2r" is "Sort Smallest to Largest", while "1r" is "Sort Largest to Smallest".

4.3 Extract top-ranked molecule into the new folder

If users want to move top-ranked molecules into new folder, for example, in this tutorial, if users want to move 2 top-ranked molecules into new folder named "results", they can use the command

as follows:

```
#> python /home/bai/MolAICal-xxx/scripts/molaicaldTopResults.py "splitdir/*out.pdbqt" 2 results
```

Two top-ranked molecules will be moved into folder “results”.