Molecular docking by MolAICal

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1. Introduction

SARS-CoV-2 caused the rapid spread of coronavirus disease 2019 (COVID-19) throughout the world. In this tutorial, the SARS-CoV-2 main protease (Mpro) which plays an important role in the replication of coronavirus is selected as the example target. The crystal structures of SARS-CoV-2 Mpro have been reported (PDB ID: 6LU7, 6Y2F, etc) [1, 2]. In this tutorial, the molecular docking between protein and ligand is introduced based on MolAICal (https://doi.org/10.1093/bib/bbaa161). Autodock Vina has the Pearson and Spearman correlation coefficients (rp/rs) are 0.5259 and 0.5421 based on the experimental binding affinity of the 3130 complexes if the ligand with lowest RMSD has the lowest binding affinity value among the 20 docked ligands. For MolAICal, rp/rs are 0.5335 and 0.5489 at the same assay conditions of Autodock Vina. It indicates that MolAICal has better 'docking' and 'ranking' power than Autodock Vina.

2. Materials

2.1. Software requirement

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

2) UCSF Chimera: https://www.cgl.ucsf.edu/chimera

2.2. Example files

1) All the necessary tutorial files are downloaded from:
https://github.com/MolAICal/tutorials/tree/master/0000-docking

3. Procedure

3.1. Dealing with receptor and ligand

1. Open the file of SARS-CoV-2 main protease in complex with ligand (PDB ID: 6Y2F): File→Open (see Figure 1).

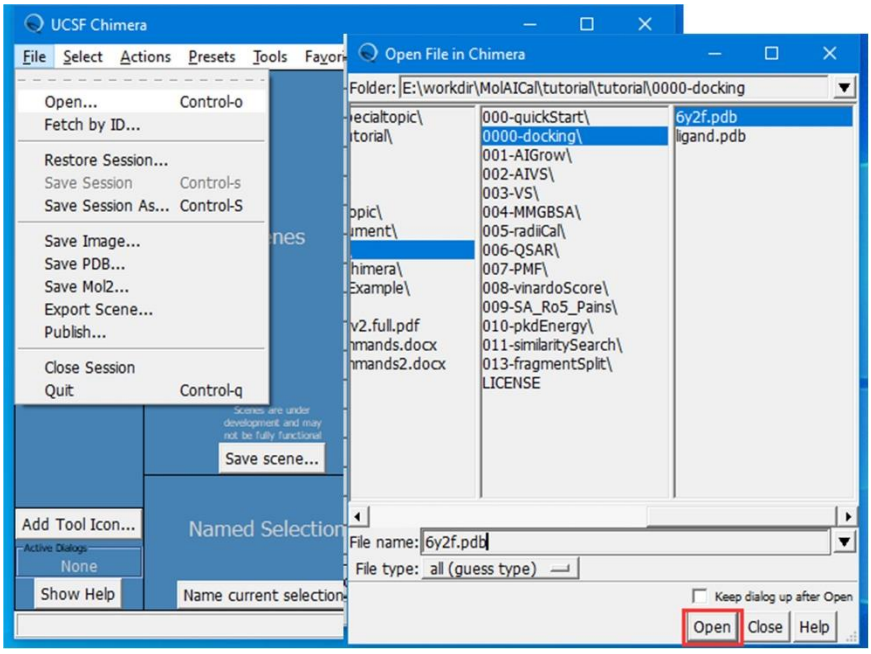

Figure 1

2. Prepare the Mpro receptor and save Mpro receptor named “protein.pdb”. The detail procedure is shown in the Figure 2.

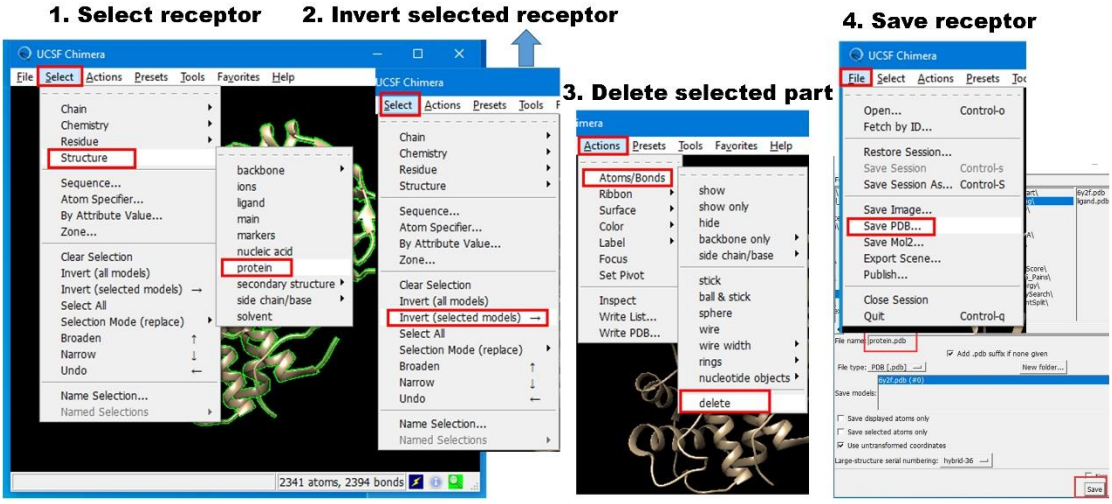

Figure 2

3. Prepare ligand and save ligand named “ligand.pdb”.

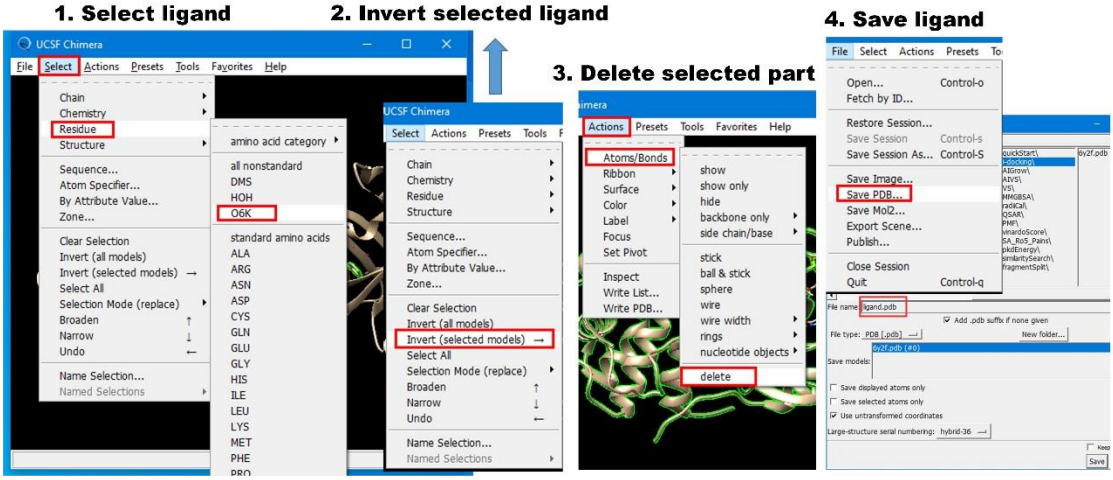

Figure 3

3.2. Convert receptor and ligand into PQBQT format

1. Get PDBQT format of receptor by using below command:

#> MolAICal-xxx\molaical.exe -dock receptor -i protein.pdb

Note: MolAICal-xxx is your downloaded version of MolAICal.

It will generate the file named “protein.pdbqt” which has the same prefix name of “protein.pdb”.

2. Get PDBQT format of ligand by using below command:

#> MolAICal-xxx\molaical.exe -dock ligand -i ligand.pdb

It will generate the file named “ligand.pdbqt” which has the same prefix name of “ligand.pdb”.

Notice: Each molecular file should contain full structure. If molecular file is **lack of hydrogen**, it will not generate molecular file in PDBQT format. Users should firstly employ UCSF Chimera to add hydrogen on the molecule which is lack of hydrogen, or use MolAICal to convert molecule in PDBQT format by the following command (users should replace 1.mol2 into their own filename):
#> molaical.exe -tool format -i E:/1.mol2 -o E:/1.pdbqt

3.3. Obtaining the center and length of docking box

1. Open protein.pdb and ligand.pdb in order. And then open “Command Line” of Chimera: Favorites→Command Line (see Figure 4).

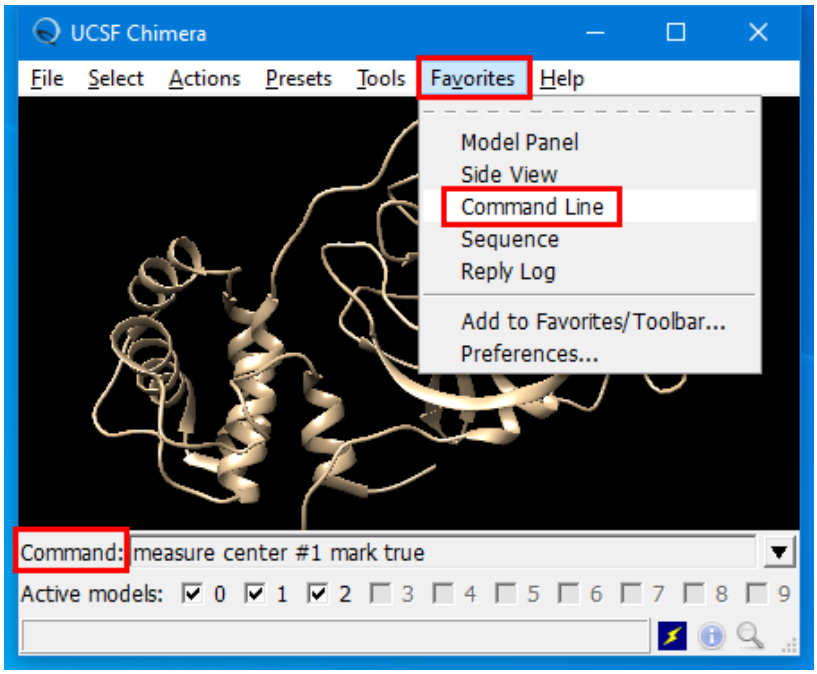

Figure 4

2. Make sure the open sequence of ligand. If protein is open firstly, it will correspond to “Active models 0”. Second open corresponds to “Active models 1”, and so on (see Figure 5). Here, ligand is secondly open (“Active models 1”). Put the below command in to command line (see Figure 5):
define centroid mass false #1
And click **“Enter” key. And then, click following the sequences in Figure 5.** It will show geometric center coordinates (x, y, z) of ligand is (10.879, -0.251, 20.754).

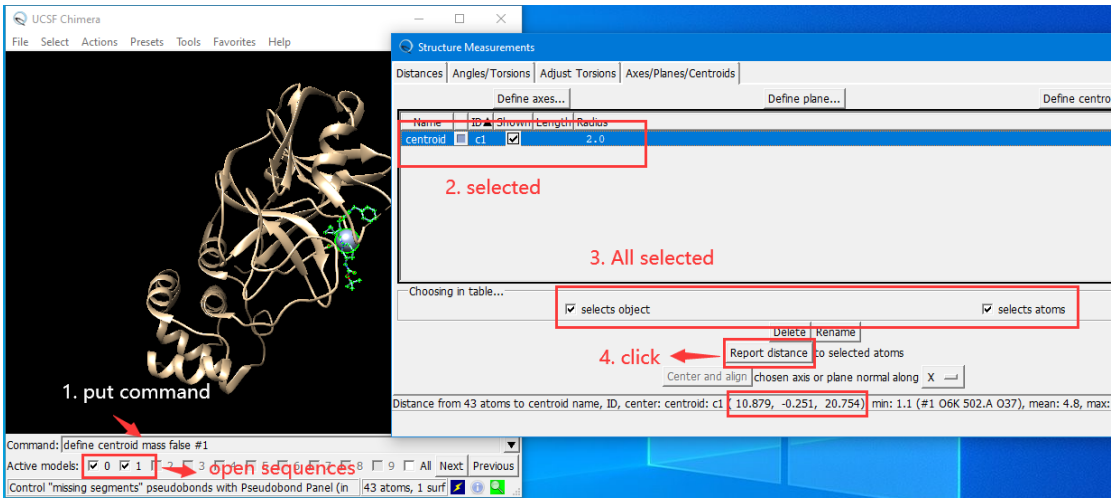

Figure 5

3. Determine the box size and center by UCSF chimera.

Open box tool: Tools→Surface/Binding Analysis→Autodock Vina

Check box: Select the right receptor (here, it is named "protein.pdb") and ligand (here, it is named "ligand.pdb") (see Figure 6). Put the above center coordinates "10.879, -0.251, 20.754" into center box (see Figure 6), the size can be tried by users until the box has a suitable size.

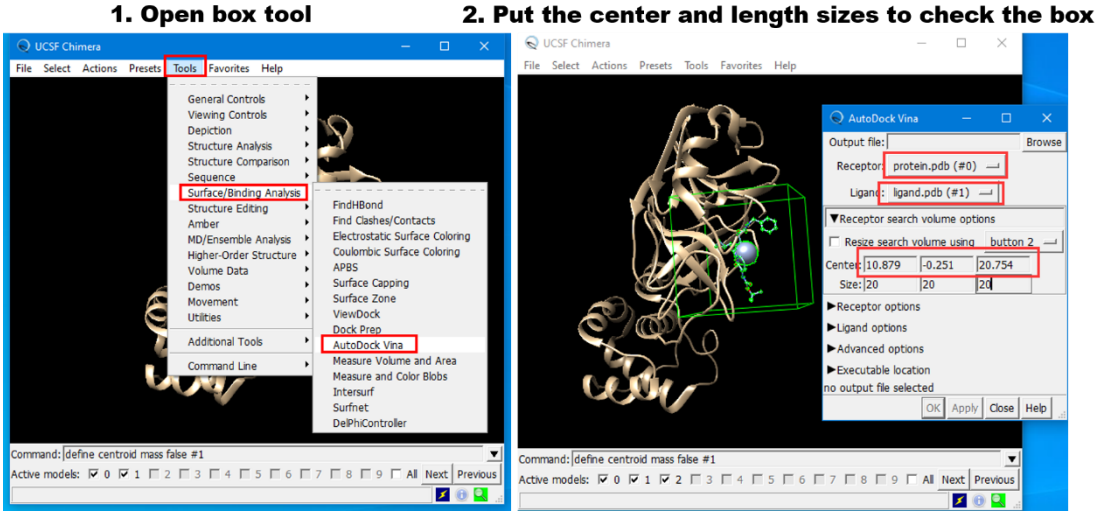

Figure 6

Note: the users can tick "Resize search volume using button 1, 2 or 3". Button 1, 2 or 3 represents left, middle or right click of mouse. If the users select this function, they adjust the box size via mouse. If you are interested in it, you can try this function.

4. Assuming the configure file is named "conf.txt", the final configure file can be written as follows:

```
out = all.pdbqt
cpu = 4
receptor = protein.pdbqt
center_x = 10.879
center_y = -0.251
```

center_z = 20.754
size_x = 20
size_y = 20
size_z = 20
num_modes = 3

Where “Out” is output file name. “cpu” is number of using CPU. “receptor” represents receptor name. “num_modes” is number of generated docking conformations. If “num_modes” is 3, it will generate 3 docking structures of ligand.

3.4. Molecule docking by MolAICal

1. Now, MolAICalD which is in the MolAICal soft package is used for molecular docking between receptor and ligand:
#> MolAICal-xxx\molaicald --config conf.txt --ligand ligand.pdbqt

Note: MolAICal-xxx is your downloaded version of MolAICal.
Sometimes, **the ligand such as this ligand in this tutorial** has many rotatable bonds, under these circumstances, the molecular docking should be run many times to compare with the original crystal ligand. And then, users can screen the suitable random seed to repeat the good results, and use this random seed for further molecular docking and virtual screening (see Figure 7).

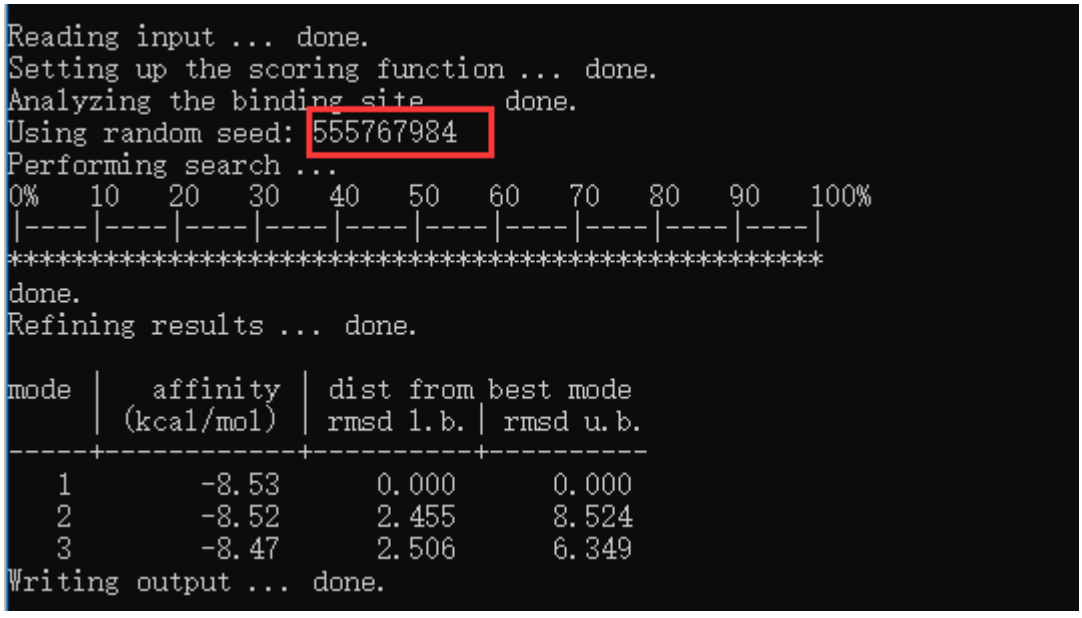

Figure 7

For example, I screen random seed 555767984 for better docking results. Users can repeat the better results like me by using random seed 555767984. Please input the below command:

#> MolAICal-xxx\molaicald --config conf.txt --ligand ligand.pdbqt --seed 555767984

2. Splitting results into single molecule

#> MolAICal-xxx\molaical.exe -tool pdbqt -i all.pdbqt -o ./

The single molecule is named 1.pdbqt, 2.pdbqt or 3.pdbqt, *etc*. "1.pdbqt" contains the docking conformation with the best binding affinity and the like.
Users can check the 1.pdbqt, 2.pdbqt or 3.pdbqt by Pymol software directly. Here, UCSF Chimera is used to check results. It needs to change "pdbqt" to "pdb" format firstly by MolAICal with the below commands:

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

2) Changing "pdbqt" to "pdb" format
#> MolAICal-xxx\molaical.exe -dock pdbqt2pdb -i 1.pdbqt

Users can use the same way for 2.pdbqt and 3.pdbqt in this tutorial. Now, open UCSF Chimera and load protein.pdb, 1.pdb, 2.pdb and 3.pdb:

3) Users can choose to show or hide molecules when all molecules are loaded via Favorites→Model Panel (see Figure 8)

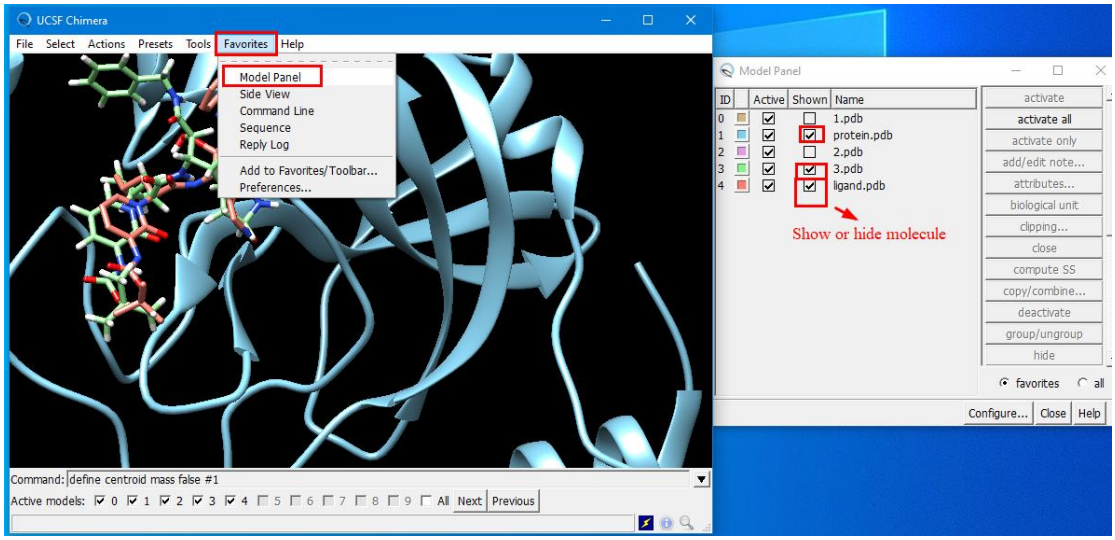

Figure 8

Note: Users can choose to add hydrogen on protein.pdb if they want to analyze interaction between protein and the docked ligands.

The results show "1.pdb" has some part overlap with the original crystal ligand, while "3.pdb" has some similar pose to the original ligand. I had performed molecular dynamics (MD) simulations on this system (**see: MM/GBSA tutorial in https://molaical.github.io/tutorial.html**). The MM/GBSA results based on MD simulations show Andricioaei entropy of original crystal ligand N3 is -84.70646297459386 (kcal/mol). It indicates the crystal ligand N3 is not stable in the pocket of SARS-CoV-2 main protease.

References

1. Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, et al. Structure of Mpro from COVID-19 virus and discovery of its inhibitors. bioRxiv. 2020.
2. Zhang L, Lin D, Sun X, Curth U, Drosten C, Sauerhering L, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved alpha-ketoamide inhibitors. Science. 2020. doi: 10.1126/science.abb3405. PubMed PMID: 32198291.