How to Study Protein-Ligand Interaction through Molecular Docking

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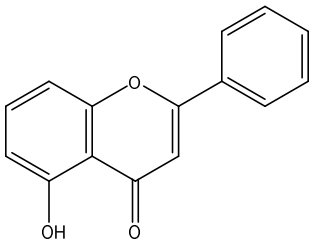
In general, Molecular docking refers to a computational algorithm that tries to find the best binding pose between two molecules. Many molecular docking programs have been developed (see https://www.click2drug.org/directory_StructureBasedScreening.html). Although these differ in the algorithms used, every docking program must be able to perform three (not necessarily distinct) basic operations:

1. Generate a reasonable candidate ligand conformations.
2. Place the ligand into the binding site
3. Assign a score or fitness value to the docked conformation.

Today's exercise: Molecular Docking of Serine Protease with its inhibitors

Ligand Preparation: Build and optimize ligand

1. Open **UCSF Chimera**
2. Open **pubChem in the browser (https://pubchem.ncbi.nlm.nih.gov/) and type 5-Hydroxyflavone**



5-hydroxyflavone

3. Get the SMILES string (Copy it) : **C1=CC=C(C=C1)C2=CC(=O)C3=C(O2)C=CC=C3O**
4. Go to UCSF Chimera ***Tools -> Structure Editing -> Build Structure -> SMILES string*** (Paste the SMILES string that we have copied from pubChem) -> **Residue name (type 5HF) -> Apply -> Close.**
5. Now we have our ligand molecule built.
6. Again ***Tools -> Structure Editing -> Minimize Structure*** *(here set steepest descent steps: 100 and Conjugate gradient steps:100)* ***-> Minimize***
   Now **Add hydrogens** will pop-up **click OK,** then **Assign Charges to minimize** select **Gasteiger** and enter **OK.** This will show the net charge of the molecule. Click **OK.**
7. Save ligand to the working directory: save as **5HF.mol2**

Protein Preparation: Download protein coordinates and prepare for docking

8. Open the PDB database (http://www.rcsb.org/pdb/home/home.do) and type ***1TNK -> Download files -> PDB format -> save as 1TNK.pdb*** (in the working directory)
9. Now go to UCSF Chimera again. Go to ***File -> Open -> 1TNK.pdb***
10. ***Tools -> Surface/Binding analysis –> DockPrep***

Now Remove solvent and fix non-standard residues, Add hydrogens (We can specify the protonation state for specific residues if needed) and charges (Protein charges are assigned using an AMBER force field).

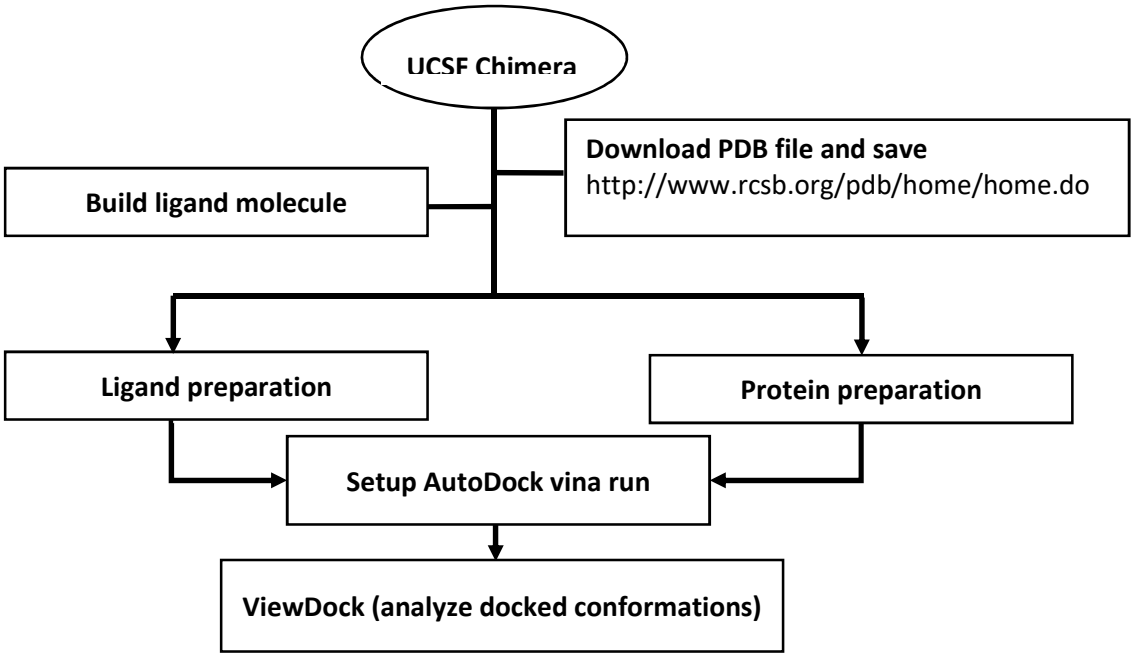
Save a mol2 file of the protein molecule as **1TNK.mol2** (For now we are retaining the ligand present in the protein molecule)

Docking Preparation and run: Setting up docking parameters and run.

11. In ***Tools -> Surface/ Binding Analysis -> AutoDock Vina***
12. *Set **Output file location*** (current working directory) **->1tnk_5HF**
13. *In the **receptor search volume options:*** set the listed values in the columns
    Center: x = 29.60, y = 15.39, z = 16.88
    Size: 15 X 15 X 15 *(after this step native ligand can be deleted from the molecule window)*
14. Set **Executable location** (current working directory)- locate **vina.exe** file
15. *Click **OK** (only once).*
16. *Now molecular docking has been started and once the run is completed **ViewDock interface** will open.*

Analysis of the docked poses

17. ***"ViewDock"*** interface will show the tabular list of poses
18. *Now click on **Hbonds -> Add count to entire receptor***
    *Choose **Intermodel Hbonds.***
    Relax constraints can be changed (optional)
    Now conformers can be sorted by Hydrogen bonds formed.



Flowchart for Docking using Chimera and AutoDock vina