Prerequisite:

- ➢ MOE installed on your PC.
- ➢ JavaScript or Java installed on your PC.

Prerequisite terminologies:

In order to have a thorough understanding of our main topic, you should have the basic concept of the following terminologies:

- ➢ Drug Designing.
- ➢ Protein-Ligand Docking using MOE.
- ➢ Binding free energy.

Introduction:

SwissDock is an online web server which is publicly available to predict the molecular interactions that may occur between a target protein and a small molecule. It proposes a suitable binding mode for a ligand, generates a complex to perform subsequent calculations, creates figures for your articles and designs inhibitors for the target of your choice. SwissDock is based on the docking software EADock DSS, whose algorithm consists of the following steps:

1. In the 1st step, many binding modes are generated either in a box (local docking) or in the vicinity of all target cavities (blind docking).
2. In the 2nd step, their CHARMM energies are estimated on a grid.
3. In the 3rd step, the binding modes with the most favorable energies are evaluated with FACTS, and clustered.
4. In the last step, the most favorable clusters can be visualized online and downloaded on your computer.

Steps:

- Click on the following link to visit the homepage of SwissDock server: http://www.swissdock.ch/
- On the homepage of SwissDock, it'll provide the detailed information about the SwissDock server in the following 6 sections:
    - What?
    - Why?
    - How?
    - Who?
    - Links?
    - Cite?
- Then in the 'Target Database' page, it provides the 264 entries of docked complexes which are publicly available to download for everyone who wants to analyze or study any of those complexes.
    - You can enter your receptor protein name in the search box to check if there is already a docked complex available on the 'Target Database'.
    - You can analyze the details about any complex by clicking on the 'view' hyperlink present against each entry or download the file by clicking on the respective hyperlink.
    - By default it'll show you only 10 entries in the table, but you can change it from 10 entries to 100 entries by clicking on the drop down button present against the 'Show' option.
- If you don't find your target protein-ligand complex in this table, click on 'Submit Docking'.

    - In the ‘Target Selection’ area, you can enter the PDB code, protein name, sequence, or URL or upload file (max 5MB).
    - In the ‘Ligand Selection’ area, you can enter the ZINC AC, ligand name or category (like scaffolds or sidechains), or URL or upload file (max 5MB).
    - Then in the ‘Description area’ provide your “Job name” and ‘Email address (optional)”.
- If you’re uploading the receptor and ligand files from your PC, you first need to perform the QuickPrep and energy minimization steps in MOE.
- To do so, open your MOE interface, then go to ‘File’ and then ‘Open’ and then browse the files of your receptor molecule.
    - Then click on the ‘SEQ’ button from the header and remove the extra ligands and water molecules attached to the receptor molecule.
    - Then click on the ‘Minimize’ button from the right hand side tab to perform the energy minimization on the receptor molecule.
    - Once the energy minimization is completed, click on the ‘QuickPrep’ button to fix the protonation and other problems.
    - After performing both the above steps, go to ‘File’ and then click on ‘Save’ and then browse the location to save the file on your PC, and enter the name of the file and select the .pdb format.
    - After saving the receptor molecule file, go to ‘File’ and then click on ‘Close’ to close the file.
    - Now open the ligand molecule file on the MOE interface.
    - Perform the energy minimization by clicking on ‘Minimize’ and then fix the protonation and other problems by clicking on the ‘QuickPrep’ button.
    - After performing both the steps on the ligand molecule, save the file on your PC in the .mol2 format.
    - Close the MOE interface and open the SwissDock server.
- Now upload the required files of receptor (.pdb format) and ligand (.mol2 format) on the SwissDock server.

- Then in the extra parameters, enter the values for x,y,z-coordinates for the position of active site residues (in the first row). And in the second row, enter the values x,y,z-coordinates for the size of the box.
    - In the “Flexibility” region, you’ve to provide the length of the side chain in Angstrom units or leave it by default.
- Then click on the ‘Start Docking’ button.
- Once your results are completed, you’ll receive the link via email or you can bookmark the webpage.

➢ **Results:**

- Open the results page, it’ll provide a list of the docked complexes in a tabular manner on the right hand side of the page and the 3D structure of the docked complex on the left hand side of the page (if you’ve installed the Java Runtime Environment on your PC).
- In the table, the first column namely ‘Show’ contains the radio buttons, by clicking on any one of those radio buttons, it’ll display the conformation for the complex against which it’ll present.
    - Then in the next two columns, it provides the number of conformations (in the ‘Elements’ column) against each cluster number (in the ‘Cluster’ column).
    - Then in the next column it provides the values for the ‘FullFitness’ and then in the next column, namely ‘Estimated ΔG’ it provides the estimated binding free energy of the complex.
- When you hover over the structure of a particular complex, it’ll provide the information about that region where your cursor will be hovering on.
- Using the SwissDock server, you should prefer the complexes that have lowest values of ‘Estimated ΔG’.
- You can also download the results or analyze the complexes in Chimera by clicking on the respective hyperlinks.

Note: You should not rely on the docking scores only to select the best docking conformation rather you should use other servers like PDBePISA or PDBsum for evaluating the docking complexes.

[Watch our tutorials on PDBePISA and PDBsum to have a better understanding of these servers and evaluation of the docking complexes.]

Summary:

In this video tutorial of Molecular Docking, we learned to use the SwissDock server for docking a ligand compound against a receptor molecule (Protein-Ligand Docking). We also came to know about different parameters that have to be selected for the docking purpose and learned to create ligand and receptor files in the required formats. We also got to analyze the docking results provided by the SwissDock server.