Prerequisite:

- ➢ MOE 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.
- ➢ Ligand.
- ➢ Binding pockets of proteins.
- ➢ Binding affinities.
- ➢ Biological receptors.
- ➢ Molecular Docking.

Introduction:

Protein-protein docking is the method to predict the structure of a complex by giving the 3D structures of individual proteins as query. The main ideas behind the docking methodologies are the steric and physicochemical complementarity at the protein-protein interface. Since, MOE is a tool which integrates visualization, modeling and simulations, as well as methodology development for drug discovery, in one single package, we'll use the MOE

interface to design a vaccine using the a receptor protein to dock against a ligand-protein.

Steps:

- Open the MOE interface and go to ‘File’ and then click on ‘Open’ and then browse the file containing the ligand protein (the vaccine) and then in the “Symmetry” option, select ‘Biomolecule Assembly’ in the drop down list and then click OK.
  [This will load the ligand protein structure on the MOE interface.]
- Again go to ‘File’, then click on ‘Open’ and then browse the file containing the receptor protein, and then in the “Symmetry”, choose the ‘Biomolecule Assembly’ option from the drop down list and then click on ‘OK’ to load the receptor molecule on the MOE interface.
- From the right hand side tab, click on the ‘Center’ button to load the ligand and receptor structures at the center of the screen.
- Click on the ‘Ribbon’ button from the footer section, and remove all the bonds such as C-H bonds, H-X bonds, etc.
- To change the colors of the ligand and receptor proteins, click on ‘System’ from the tab present on the right hand side of the screen and then choose different colors for ligand and receptor proteins.
- Before moving on to dock the ligand protein against the receptor protein, you need to do the quick preparation and energy minimization first.

➢ **Quick Prep:**

- The quick preparation fixes the protonation and bond angles and other inaccuracies within the docking complex as well.
- To do so, click on the ‘QuickPrep’ option from the right hand side option list.
- A new pop-up window will appear on your screen where you can see multiple options and parameters that can be applied on the docking complex, leave all the parameters by default and then click on the ‘OK’ button and then ‘Yes’.

[It'll take some time for fixing the bond and angles and other inaccuracies.]

- Meanwhile, go to 'Compute' option and then click on 'Site Finder' to find the active site residues in the receptor protein.
    - From the drop down list present against the 'Atoms' option, select the 'Receptor_TLR' option and then click on the 'Apply' button.
    - A new pop-up window will appear where it'll show you the active site residues present in your receptor protein. Select all the residues and click on the checkbox of 'Select Residues in SE', to highlight the active site residues on the 3D structure of receptor protein and the click 'Close'.
    - Click on the "Seq" button from the header section to check the highlighted amino acid residues present at the active site of the receptor protein.

[To find the active site residues of your receptor protein, you can use different online servers as well such as COFACTOR server, CASTp server and other related servers.]

- After the fixation of inaccuracies in complex in the quick preparation step, go to 'Compute', then click on 'Dock' and then click on 'Protein-Protein' option.
    - In the drop down list of 'Receptor Atoms' click on 'Receptor_TLR'.
    - Then in the drop down list of "Site", select the 'Selected Residues' option, so that the ligand protein will be docked against the receptor protein at the active site only.
    - Then in the drop down list of "Ligand", select the file name having the ligand protein structure stored in it.
    - Then in the 'Output' enter the name of the docking file and then browse the location on your PC to store the file and click on OK.
    - Then click on the 'Run' button to start the docking process.

Note: Recrptor_TLR is the name of the file containing the receptor protein structure. So, you've to select the file containing the receptor protein.

- After the docking has been completed, go to ‘File’ and then ‘Open’ and then browse the file containing the docked complex.
- The results will be provided in a separate pop-up window in a tabular form.
- The best docking conformation can be evaluated from the ‘S’ score value. The higher the value of S-score in negative, the better the docking conformation would be.
- Select the docked models you want to save on your PC, then go to ‘File’, then ‘Save’ and then enter the name of the file and then browse the location on your PC, where you want to save the file.
- Then to load a specific docked complex on the interface of MOE, click on the ligand molecule from the resulting tabular file and then click on ‘Yes’.
- Then click on the respective receptor conformation and click ‘No’.
  [If you click ‘Yes’ after clicking on the receptor molecule, it will clear the ligand protein structure from the MOE interface.]
- Close the popped-up window showing the results in tabular form, and then click on ‘Center’ to place the docked complex at the center of the screen.
- Click on the ‘Ribbon’ button at the footer section to change the representation of the complex into ribbons, then click on the yellow colored arrow and remove the bonds from the complex.
- To check the properties of the receptor molecule, go to the ‘Protein’ option from the header section and then click on ‘Properties’.
- A new pop-up window will appear on the screen, where you’ve to select the option with the file name of your receptor protein (Receptor_TLR) and then click on ‘Calculate’.
- In another pop-up window, it’ll display the properties of the docked complex like ‘Protein Mass’, ‘Debye Screening Length’, etc.
- In the same way you can also check the properties of ligand protein.

Note: You cannot evaluate the docked complex based on the S-score only. So, in order to evaluate a good model to design an effective drug you need to watch the tutorials on PDBepisa Evaluation videos by BioCode.

Summary:

In this video tutorial of Molecular Docking, we got to know how to dock a ligand protein against a receptor protein (protein-protein docking) using the MOE software. We also came to know about different parameters and the values to be selected for those parameters as well as analyzed the results to select the best docking conformation for a particular drug candidate.