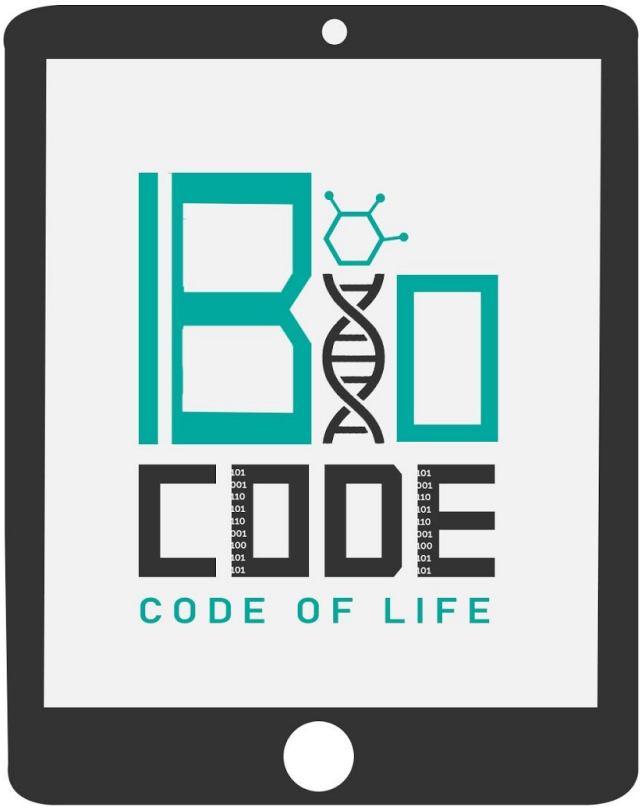

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Prerequisite:

➢ 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:

➢ Homology Modeling.

➢ Template protein.

➢ Target protein.

Introduction:

MOE stands for Molecular Operating Environment, is a platform for drug discovery. It is a multipurpose tool which integrates visualization, modeling and simulations, as well as methodology development for drug discovery, in one single package.

Homology Modeling or Comparative modeling of proteins is the construction of an 3D structure model of *target* protein from its amino acid sequence and an experimental 3D structure of a related homologous protein (*template* sequence). Homology modeling is done when we have a new amino acid sequence whose experimental protein structure is unknown, so we predict the 3D protein structure of our *target* sequence using different tools based on Homology Modelling Methods.

Steps:

- Prepare your query sequence (Target protein) in FASTA format.
- Run BLAST search against your query sequence to find out suitable homologs for template protein.
    - Go to NCBI and select BLASTp tool and paste your query sequence in FASTA format in the query box there.
    - Change the ‘Database’ to ‘Protein Data Bank pdb’ and then click on the ‘BLAST’ button at the bottom of the page.
    - On the results page of BLASTp, select the entry with both higher query coverage and percentage identity values and click on its accession number.
    - [It’ll open another web page containing the information about the particular entry.]
    - On the webpage of that particular entry, click on the ‘Download’ button present against the ‘PDB ID’ to save the template sequence and structure on your PC.
- Open the MOE interface and go to ‘File’, then ‘Open’ and then select the file containing the target protein sequence. OR

- Simply copy the target protein sequence in FASTA format, then click on the ‘Seq’ button present on the header of the MOE interface and paste the copied sequence there.
- To load the PDB structure of the template protein on the interface of MOE, go to ‘File’, then click on ‘Open’ and then locate the file containing the template protein structure on your PC.
- Click on the “Ball” button to rotate the 3D structure of the protein or click on the arrows below this button to rotate the 3D structure of your template protein.
- Click on the ‘Seq’ button on the header section of the MOE interface, to load the template protein sequence on the MOE. click on the extra ligands and water molecules to remove them from the template structure.
- To align both the template and target protein sequences, click on the ‘Alignment’ button, then click on ‘Align Sequences’ and then click on the ‘Align’ button.
- To check the conserved regions between template and target sequences, click on the ‘CCG’ button present in the ‘Sequence Editor’ area.
    - The aligned and conserved regions will be represented as asterisk (*) and the unmatched residues will be represented as alphabets for the corresponding residues.
    - To check the secondary structures within your template and target protein, click on the ‘ALA’ button with an arrow head on the button.

      [The arrows will represent the Beta-Sheets, the red lines represent the Alpha-helix while the blue lines will represent coiled regions present within your template and target proteins.]
    - To see the sequence in its corresponding 3-letter format along with the amino acid numbering, click on the ‘ALA’ button with ‘123’ written on the button.

- To create a 3D model of the target protein based on homology of the template protein, click on the ‘Protein’ button and then select ‘Homology Model’.
    - In the ‘Output Database’ enter the name of the output file and browse the location to save the file on your PC.
    - Click on the checkbox of ‘Load Final Model in MOE’.
    - Then in the ‘Model & Template’ area, it provides some parameters, which you can set manually or leave them by default.
    - After selecting the suitable parameters, click on OK.

  [The results will be provided in a separate pop-up window in a tabular form.]
- You can close the template protein structure by clicking on ‘File’ and then ‘Close’.
- Click on any homology model to load it on the MOE interface and analyze the structure.
- Click on the ‘Ribbon’ button present on the bottom right corner of the screen. And then click on the “Yellow arrow” to convert the homology model into its secondary structure.
    - Click on the “Red crosses” in the ‘Atoms’ section to remove the C-H bonds and other bonds as well.
- To align the target structure with the template structure, go to ‘File’, then ‘Open’ and then browse the file containing the 3D structure of your template protein.
    - Click on the ‘Center’ button from the list of different options provided at the right hand side of the screen.
    - Then click on the ‘Seq’ button and delete the water molecules and extra ligands attached to the template structure.
    - Then go to ‘Alignment’ and click on the ‘Align Sequences’ option and then click on the ‘Align’ button.
    - After aligning the sequences, click on the ‘Superimpose’ button to align the structures of both the template protein and target protein.

- To check the RMSD value, click on the ‘Seq’ button and then click on the ‘Plot RMSD’ option.
- To check the similarity between the sequences, click on the ‘CCG’ button and then select the ‘Similarity’ option.
    - The area of higher similarity will be shown in dark blue color on the graph while the area with lower similarity will be represented in light blue color.
- To check the RMSD plot, click on the ‘CCG’ button and then select the ‘Plot RMSD’ option.
    - It’ll plot the RMSD values and a graph where the areas in green color shows good RMSD values while the areas in red color represents not so good values for RMSD.

Summary:

In this tutorial video of predicting a homology model for a target protein whose structure is not known experimentally, we learned to generate a homology 3D model of a target protein based on the homology of a template protein using the MOE tool. We also got to analyze the results and how to align the two structures of the protein using the MOE tool.