BIN 515 – Structural Bioinformatics
MIDTERM – Take-Home Exam

This take-home exam was released on **May 26, 2020 at 10:00**. The due date is **June 4, 2020, 23:59**. **Please submit a complete report and the program codes, input and output files and any other necessary files as the supplementary material to your report at ODTUclass. Discuss your results in your report.**
Copying, reviewing the report or analysis of another, joint development and sharing your design are not permitted.

1. **(20 pts.)** Short Questions

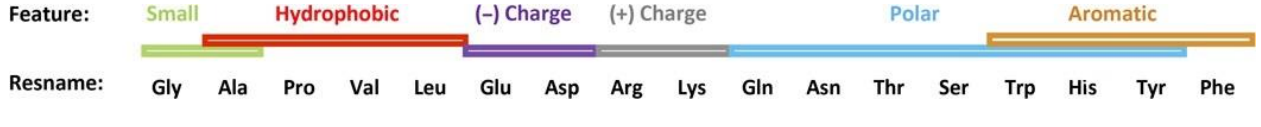
   a. Protein Data Bank entry 1H68 contains the structure of Sensory Rhodopsin II from Natronomonas pharaonis. Look at the distribution of hydrophobic and hydrophilic residues in this structure. Discuss your results.

   b. Protein Data Bank entry 1ZLL contains an ensemble of 20 NMR-derived structure of human phospholamban.
   Simmerman et al. (1996) identified residues whose mutation to Ala or Phe affected Phospholamban's ability to form a pentamer https://pubmed.ncbi.nlm.nih.gov/8621468/
   Locate these residues on the three-dimensional structure of phospholamban (e.g. colour these residues in VMD). Interpret this visualization by referring to the given publication.

2. **(30 pts.)** Proteins interact through their interfaces. Collect a set of interface residues by parsing at least 20 heterodimers deposited in PDB. Please use advanced search option in PDB to select the relevant PDB files. In your report, write the details of the selection criteria in PDB.
   a. Write a script to find interface residues (either by distance calculation or by ASA calculation. You can use your codes in your assignment as well). Explain each step of interface extraction in your report.

   b. Select one of the structures from your list and draw the heterodimer and the interface region in VMD to show that your calculation is correct in interface identification.

   c. Interface residues have different physicochemical properties when compared to the rest of the protein. Such as hydrophobicity, aminoacid propensity or conservation. Calculate the amino acid propensity and find if any specific aminoacid has tendency to be in the interface region. Additionally, divide the amino acids into groups based on physicochemical properties as shown in the figure below. Perform an analysis based on the residue types. Calculate the propensity of each residue type and write a commentary on your results.



3. **(50 pts)** In this question, the task is to screen ABL1, which is a tyrosine kinase, with four small molecules: imatinib, dasatinib, nilotinib, lesinurad. The receptor and the ligand molecules are given in the supplementary material.

    a. Write a general one paragraph introduction about the receptor and the given ligand molecules. Use Autodock to run docking for each protein-drug pair (grid box center: (15.7, 53.2, 17.5)).

    b. Analyze the Autodock output files and write a 250 words paragraph with supporting plots to present your results.

    c. The default docking parameters for AutoDock are set to provide 10 output docking poses. For each of the 4 compounds, how many of these 10 iterations correspond to reasonable docking poses for your docking runs?

    d. The experimental binding mode of compound imatinib in complex with ABL1 is available in PDB ID: 1eip. How does your best docking pose for imatinib compare to the experimentally determined binding mechanism?

    e. Find the interacting residues in receptor in the best docked pose for each drug molecule (You can use distance based calculation). Visualize best docked pose of each drug-protein pair in VMD. In your illustration, whole structure of the receptor, interacting surface and the drug molecule need to be easily distinguished. You can use different representations or colors for this purpose.

    f. Discuss the docking results in 500 words (maximum). Feel free to use as many figures as possible to support your discussion.

    g. Using the docking method outlined in the procedure, you used a rigid model of the receptor. However, proteins are continually changing conformation in solution. Can you think of a way to improve the docking method used in this exercise? (Just discuss some suggestions. No need for calculations.)