END-SEM (2025)

Computer-Aided-Drug-Designing(CADD) **Total Marks:30**

Time: 2 hours

Section-A (MCQ) (15 Marks)

1. Match the algorithm or tool to its main application:

A.chou-Fasman	1. Sequence alignment
B. Smith-Watermann	2. Secondary structure prediction
C. Modeller	3. Hidden Markov model for transmembrane proteins
D.TMHMM	4. Stereochemical constraints

A. A-2, B-1,C-4, D-3
B. A-1, B-3, C-4,D-2
C. A-4, B-1, C-2, D-3
D. A-2, B-1, C-3, D-4

2. During the ligand-protein docking, which best describes the Potential energy (PE) curve?

A. It peaks when a ligand binds to the active site.
B. The ligand approaches a stable and energetically favorable bound state
C. The ligand is moving away from its most favourable conformation
D. PE increases gradually as the ligand settles in the final pose

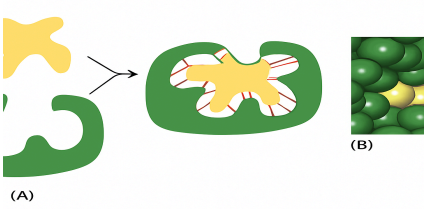
3. What is the correct sequence in a typical docking strategy pipeline?

A. Matching → Surface Representation → Scoring → PDB input
B. Scoring → Patch Detection → Candidate Complexes → Matching
C. Patch Detection → Surface Representation → Scoring → Filtering
D. PDB input → Surface Representation → Patch Detection → Matching → Scoring

4. Which of the following correctly represents the hierarchical order in the CATH classification system?

A. Fold → Architecture → Class → Topology → H-level
B. Class → Topology → Architecture → Fold → H-level
C. Class → Architecture → Topology → Fold families → H-level
D. Architecture → Class → Fold → H-level → Topology

5. Based on the lock-and-key representation in diagram (A), what conclusion can be drawn about ligand specificity?



A. Ligands can bind randomly to any protein surface
B. Binding requires covalent modification of the protein
C. Ligand binding depends on complementary shape and noncovalent compatibility
D. Binding occurs only in the nucleus

6. Match the docking tools with their correct category:

Tools	**Category**

A.ZDOCK 1. P-L docking
B.FlexX 2. Active site prediction
C. Surfnet 3. P-P docking
D.Glide 4. Ligand docking

A. A–3, B–1, C–2, D–4
B. B. A–1, B–2, C–3, D–4
C. C. A–3, B–4, C–2, D–1
D. D. A–4, B–1, C–2, D–3

7 . Which groups only contain amino acids with nonpolar side chains?

A. Valine, Glycine, Isoleucine
B. Tyrosine, Glutamine, Serine
C. Arginine, Aspartic acid, Histidine
D. Asparagine, Methionine, Glutamic acid

8. A researcher runs the command `gmx pdb2gmx` and obtains a `.gro` file and `.top` file. What is the most likely input he started with?

A. .gro coordinate file
B. .pdb structure file
C. A force field directory
D. A MD trajectory

9.A force field calculates molecular potential energy by including terms like bond stretching, angle bending, dihedrals, and _____ interactions.

A. Non-bonded
B. Ionic
C. Covalent
D. Hydrogen

10. To exclude non-bonded interactions between atoms three bonds apart in a protein. Which `topol.top` field is directly responsible for this?

A. resnr
B. cgnr
C. nr
D. nrexcl

11. Which of the following sections must be present in a complete bonded topology for a protein simulation?

A. Atoms, bonds, angles
B. Atoms, dihedrals, bonds, angles, restraints
C. Atoms, bonds, angles, dihedrals
D. Ions, Atoms, bonds, angles, dihedrals

12. Which phase of clinical trials primarily involves healthy volunteers and focuses on safety and tolerability rather than efficacy?

A. Phase 1
B. Phase 2
C. Phase 3

D. Phase 4

13. Which MD simulation analysis commands is correct for its function:

A. **gmx Rmsf**: per-residue flexibility, **gmx gyrate**: backbone deviation vs time

B. **gmx Rmsf**: per-residue flexibility, **gmx rms**: backbone deviation vs time

C. **gmx gyrate**:folding status, **gmx rmsf**: backbone deviation vs time

D. Gmx mdrun:for running simulation, gmx gyrate:per residue flexibility

14. In classical rigid-body protein-protein docking, how many degrees of freedom are typically considered for the relative movement of the two proteins, and what do they correspond to?

A. 2 degrees of freedom – rotation only

B. 3 degrees of freedom – translation only

C. **6 degrees of freedom – 3 rotational and 3 translational**

D. 6 degrees of freedom – 2 translation and 4 rotation

15. **After ligand binding, the entropy decreases due to loss of _____ freedom and conformational restriction.**

A. Internal

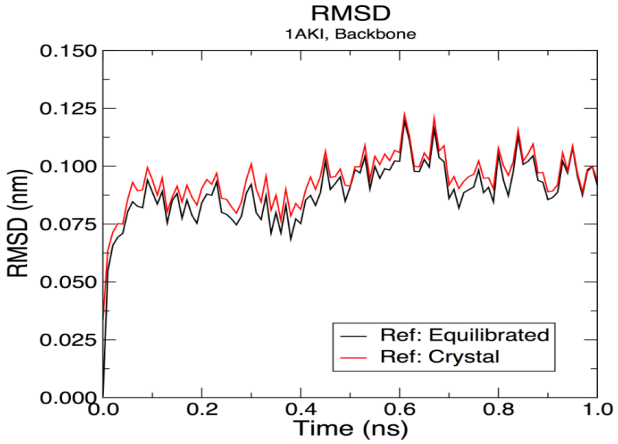
B. translational/rotational

C. Covalent

D. Bond angle

Section-B(short answer questions) (2 marks)

1. What is the purpose of RMSD and what do you interpret from it?(1.5) What does the plateau in the RMSD graph indicate about the behaviour of the protein during MD simulation?(0.5)



1. It evaluates the structure stability during simulation of the protein structure.(0.5)
   Interpretation:(1)
   Lower RMSD means more stable structure
   High RMSD means significant structural changes
   A plateau in the RMSD graph indicates that the system has reached structural equilibrium and is now stable over time.(0.5)

2. **a.) What is the expected behavior of the temperature profile during NVT equilibration in MD simulations, and why is this important?(1)**

b.) what if temperature fluctuates continuously, suggest two correct actions one should consider.(1)

a.The temperature must rise to 300k then form a stable plateau, which indicates that system has reached equilibrium(0.5).it is important because it is essential for reliable and reproducible results of simulations(0.5)

b. Two correct actions are:

Increase the equilibrium time in nvt.mdp file (0.5)

Check for bad atomics contacts or unstable ions.(0.5)

3. **Mention the two approaches used in the comparative modeling and the tools used in each.(2)**

Manual model building - Modeller (1 mark)

Automatic modeling servers- Swissmodel, iTasser (any one) (1 mark)

4. **Based on the Ramachandran plot, explain which amino acid exhibits more flexibility than other amino acids and why it make plot so much populated. How does the conformational structure of proline influence Ramachandran plot distribution? (2)**

Glycine exhibits more flexibility. (0.5) it has no side chains and has only H-atoms that make it sterically less hindered to adopt a broader range of φ (phi) and ψ (psi) angles, that is why the Ramachandran plot is more populated with glycin (0.5)

Proline has a cyclic side chain that restricts the φ angle due to its rigid ring structure. This limits its conformational flexibility, leading to a much smaller allowable region in the plot.(1)

5 . Write the difference between for following:

Protein-Protein docking and Protein-Ligand docking(1)

Orthologs and Paralogs(1)

a.In P-P docking molecules are usually considered rigid, and in P-L docking, the Ligand is flexible, the receptor is rigid. In P-P, search space is small and in P-L, search space is large due to ligand flexibility. In P-P tool used is Autodock, in P-L tool used is ZDOCK.

b.In orthologs, Genes in different species that evolved from a common ancestral gene via speciation, whereas in Paralogs, Genes within the same species that arose by duplication.

Section-C (Long answer questions) (5 marks) Attempt any one

1. **You are given a target protein sequence for performing advanced homology modeling. During template selection, it was observed that the best templates query coverage is only 70% of target sequence and 30 % identity.**

a.Illustrate the process of advance modeling steps in diagramatic flowchart from Template identification to model validation.(3)

models	molpdf	DOPE score	GA341 score
1XYZ.B99990001.pdb	1185.43982	-31210.45871	1.00000
1XYZ.B99990002.pdb	1101.32812	-31389.98212	1.00000
1XYZ.B99990003.pdb	1079.27711	-31455.78214	1.00000
1XYZ.B99990004.pdb	1052.94351	-31290.14389	1.00000
1XYZ.B99990005.pdb	1132.56111	-31567.00984	1.00000

B. 5 models were generated for the target protein. Based on the data provided, which model would you select as the best predicted structure, and why? Justify your answer using both molpdf and DOPE score.(2)

C. You notice unusual geometry in a loop region of your structure. What might be the cause, and how would you attempt to correct it? (1)

a.

b.Best model: 1XYZ.B99990005.pdb (0.5)

Although model 4th has the lowest molpdf, model 5th has the lowest (most negative) DOPE score, a stronger indicator of model quality. Hence, model 1XYZ.B99990005.pdb is the best model, combining a reasonably low molpdf with the best DOPE score.(1.5)

c.The cause could be poor alignment or lack of template coverage in flexible regions.(0.5) It can be corrected using targeted loop remodeling or local energy minimization.(0.5)

OR

2. **You have a ligand–protein complex with no known binding data for other molecules at this target. You want to compare the binding affinities of 10 candidate ligands at the same site. How would you select these 10 molecules, and what steps would you follow to compare their binding affinities with the known ligand? Given the binding pocket is flexible and ligand binding may induce conformational changes, explain why molecular modeling and MD simulations would be important in this case, and how they would improve prediction reliability.**

- Download the Protein–Ligand Complex
- Prepare the Protein
  - Remove the existing ligand.
  - Remove water molecules
  - Add polar hydrogens and assign charges.
  - Save the protein in `.pdbqt` format
- Define the Binding Site
  - Use the coordinates of the original ligand to define the docking grid. (0.5 marks)
  - Draw a grid box that covers the binding pocket properly.
  - Create a configuration file

- Select 10 Potential Ligand Molecules
    - use Ligand Similarity Screening or Pharmacophore-Based Screening to select best 10 Molecules (1 mark)
- Ligand Preparation
    - Download the 3D structures (SDF/MOL2/PDB) of the selected 10 molecules.
    - Convert each ligand to `.pdbqt` format
- Molecular Docking
    - Dock all 10 ligands and the original ligand into the prepared protein. (0.5 marks)
    - Use the same grid box settings for all ligands to ensure fair comparison.
- Analyze Docking Results

There is no need for molecular modeling (1 marks)

Molecular modeling and MD simulations are essential when the binding pocket is flexible, as they capture protein and ligand movements that static docking misses. MD allows observation of induced fit, stabilizes docked poses, and reveals key interactions over time. This improves binding affinity predictions, especially when experimental data is unavailable, by providing a more realistic and dynamic view of ligand binding.(1.5 marks)