Quiz-1 Rubric

Computer-Aided Drug Design (CADD) BIO563

Total Marks: 20
Total Time: 1 Hour

Section A

MCQ (Choose the most appropriate answer for each question.)

(1*10=10 marks)

Question 1: Which of the following is most common for flexible docking?

A) Protein is rigid, and ligand is flexible
B) Both are rigid
C) Both are flexible
D) Ligand is rigid, and protein is flexible

Question 2: Which of the following is not the key step in the lead optimization process?

A) Chemical synthesis
B) Biological evaluation
C) Data analysis
D) clinical trials

Question 3: Choose the correct sequence for drug discovery:

A) Hunch → Anecdotal findings → Literature precedent → Cell model → Animal model → Pharmacology in animal model → Pharmacology in human disease B) Hunch → Literature precedent → Anecdotal findings → Cell model → Pharmacology in animal model → Animal model → Pharmacology in human disease
C) Anecdotal findings → Hunch → Literature precedent → Animal model → Cell model → Pharmacology in human disease → Pharmacology in animal model
D) Literature precedent → Hunch → Anecdotal findings → Cell model → Animal model → Pharmacology in human disease → Pharmacology in animal model

Question 4: Which of the following is the primary focus of Phase I clinical trials?

A) Efficacy in patients
B) Large-scale testing for regulatory approval
C) Safety and dosage testing in healthy individuals
D) Post-market surveillance

Question 5 : Which neurotransmitter system is primarily targeted in the treatment of depression?

A) Dopaminergic system
B) Biogenic amine system
C) Cholinergic system
D) GABAergic system

Question 6: Which of the following is **NOT** a part of ADME properties?

A) Absorption
B) Digestion
C) Metabolism
D) Excretion

Question 7: Which of the following approaches are involved in target validation? A) Collecting all available information in the public domain that supports the hypothesis B) Developing in vitro and in vivo systems to support the hypothesis
C) Entering into agreements with external experts for hypothesis verification
D) All of the above

Question 8: In an aqueous environment, how do proteins fold?
A) Polar side chains move to the core of the protein
B) Nonpolar side chains form a hydrophobic core
C) Nonpolar side chains are exposed to water
D) Hydrogen bond is formed inside the core of the protein

Question 9:In drug discovery, the DOOR paradigm primarily focuses on:
A) Efficacy of drug candidates
B) Toxicity prediction
C) Accessibility
D) Computational modeling of drug interactions

Question 10: Which of the following is **NOT** generally associated with lead identification and optimization?
A) Selectivity
B) Drug-like properties
C) Potency
D) Scale-up potential

Section B (Short Answer Questions)

(2*5=10 marks)

Question 11: Why is the identification and optimization of leads, and targets crucial in drug discovery, and how does the sequence of these steps impact the efficiency and success of developing a viable therapeutic?

Answer:

Importance of identification and optimization of leads, and targets (1 Mark) ● Target Identification: Determines the specific biological molecule (usually a protein) that a drug or therapeutic compound will interact with to produce a desired effect. This target is usually involved in a disease pathway, and modifying its function can lead to a therapeutic benefit. **(0.5 Mark)**

● Lead Identification & Optimization: identification ensures compounds have desirable selectivity, physicochemical, Drug-like and metabolic properties, and have favorable ADME (Absorption, Distribution, Metabolism, Excretion) characteristics.

Optimization enhances potency, selectivity, and drug-like properties for effective therapeutic development. **(0.5 Mark)**

Impact of Sequence on Drug Discovery Success (1 Mark)

- Identifying a valid target first prevents wasted resources on ineffective compounds. **(0.5 Mark)**
- Optimizing leads before clinical testing reduces failure risks, increasing the likelihood of developing a viable therapeutic. **(0.5 Mark)**

Question 12: While it is possible to model a protein using a single template, in what scenarios would using multiple templates be necessary, and how does this approach improve the accuracy and reliability of the predicted protein structure?

Answer (Note: Any one point from each section will account for full marks.)

Scenarios Where Multiple Templates Are used (1 Mark)

- **Low Sequence Identity to a Single Template :** If the target protein has low sequence identity (<30%) to any single template, using multiple templates can help compensate for missing or uncertain regions.
- **Structural Variability and Improvements :** Some proteins undergo conformational changes or have flexible regions. Using multiple templates representing different conformations helps capture structural diversity.

How Multiple Templates Improve Accuracy (1 Mark)

- **Enhanced Structural Coverage** : Different templates contribute complementary structural information, improving the completeness of the model.
- **Better Loop and Secondary Structure Prediction :** By aligning multiple structures, the best-fitting conformations for flexible regions (like loops) can be selected, reducing errors introduced by a single inaccurate template.

Question 13: What do you understand by black box and mechanistic approach to drug discovery?

Answer:

Black Box Approach : (1 Mark)

In this approach, drugs are discovered and developed based on observed effects rather than a complete understanding of their molecular mechanisms.

Mechanistic Approach: (1 Mark)

This method is based on a deep understanding of disease pathology, molecular interactions, and biological pathways.

Question 14. What is the significance of Phase 4 clinical trials, and why are they often conducted over many years?

Answer: (any 2 points will account for full marks, i.e 1 mark for each point) ● Large-Scale Participation and Long-Term Safety and Benefits: Involves thousands of patients and can last for many years allowing researchers to detect rare side effects. ● Usage

Optimization: Provides insights into how drug use can be modified.
- Drug repurposing: May reveal additional therapeutic applications for the medicine.

Question 15: If a ligand binds to a protein and interacts with eight residues that are closely positioned in its quaternary structure, does this imply that these residues are also close in the protein's primary sequence? Justify your answer with structural reasoning. Anwer:

No, the residues interacting with the ligand in the protein's quaternary structure are not necessarily close in the primary sequence. **(0.5 marks)**

Protein Folding and Tertiary Structure: In a protein's primary sequence, residues can be far apart in terms of sequence numbering. However, during folding, these residues can come close in the three-dimensional (tertiary/Quaternary) structure due to the formation of secondary structures. **(1 marks)**

Ligand interaction : the residues that interact with the ligand could come from different positions or even subunits. These residues might be distant in their respective primary sequences but are brought together in the functional three-dimensional structure. **(0.5 marks)**