MOLECULAR MODELLING AND DRUG DESIGNING
(BIOT 3231)

Time Allotted : 2½ hrs **Full Marks : 60**

Figures out of the right margin indicate full marks.

Candidates are required to answer Group A and any 4 (four) from Group B to E, taking one from each group.

Candidates are required to give answer in their own words as far as practicable.

Group – A

1. Answer any twelve: **12 × 1 = 12**

Choose the correct alternative for the following

(i) A hypothetical ligand binds to a receptor with an association constant (Ka) of 3 X $10^4 M^{-1}$ sec^{-1} and dissociation constant K_d of 6.90X 10^{-6} sec^{-1}. The equilibrium constant is given by
(a) 4.7 × 10^9 M^{-1} (b) 2.3 × 10^{-10} M^{-1}
(c) 2.3 X10^{10} M^{-1} (d) 3.3 × 10^{-6} M^{-1}

(ii) Botulinum toxin is a large protein molecule. Its action on cholinergic transmission depends on an intracellular action within nerve endings. Which one of the following processes is best suited for permeation of very large protein molecules into cells?
(a) Aqueous diffusion (b) Endocytosis
(c) First pass effect (d) Lipid diffusion.

(iii) The following potential energy expression, $V_{(r)}=4\epsilon\ [\ (\sigma/r)^{12}- (\sigma/r)^{6}]$ represents.
(a) an example of a potential where the r represents an infinite distance.
(b) a Beeman algorithm potential.
(c) an example of a periodic boundary condition (PBC).
(d) a Lennard-Jones potential.

(iv) Which of the following is the correct definition of bioavailability?
(a) Bioavailability is the length of time an administered drug is present in the body and thus is available to cause a physiological effect.
(b) Bioavailability is used to describe the fraction of the dose of drug administered that is present within the body and facilitates the desired physiological effects.
(c) Bioavailability describes the ability of the administered drug metabolites to cause undesirable physiological effects.
(d) Bioavailability describes the proportion of the drug administered that is metabolised very quickly and thus is not available to induce a physiological effect.

(v) Which of the following means IC_{50} of a drug?
(a) 50 µg of a drug that is required for 50 percent activation in an assay.
(b) 50 mg of a drug that is required for 50 percent inhibition in an assay.
(c) Concentration of a drug that is required for 50 percent activation in an assay.
(d) Cconcentration of a drug that is required for 50 percent inhibition in an assay.

(vi) A 55-year-old woman with hypertension is to be treated with a thiazide diuretic. Thiazide A in a dose of 5mg produces the same decrease in blood pressure as 500 mg of thiazide B. Which of the following statement best summarizes these results?
(a) Thiazide A is more efficacious than Thiazide B
(b) Thiazide A is about 100 times more potent than Thiazide B
(c) Thiazide A has longer half-life than Thiazide B
(d) Thiazide A has a wider therapeutic window than Thiazide B.

(vii) Structure-activity relationships (SAR)best describes by which of the following statement?
(a) The study of the structural features of a drug that are important to its chemical stability.
(b) The study of the structural features of a drug that are important to its biological activity.
(c) The study of the physicochemical properties that are important to the absorption of a drug into the blood supply.
(d) The study of which functional groups are important to the chemical reactivity of the drug.

(viii) The binding of an anti-bacterial drug (e.g. trimethoprim) to an enzyme (e.g. DHFR) has been studied computationally to exploit the structural differences between bacterial and vertebrate DHFR. Energy minimization is a necessary step in this computational binding process. Which of the following choices represents a correct conclusion from that and similar computational studies?
(a) the ligand-receptor interaction can lead to a conformation that is higher in energy than any of its energy structures.
(b) use of structures obtained from energy minimization calculations on isolated structures always leads to correct energy values.
(c) conformation of trimethoprim was the same in the free state and when bound to DHFR.
(d) None of the above.

(ix) Which of the following is one of the rules in Lipinski's rule of five?
(a) A molecular weight equal to 550
(b) No more than five hydrogen bond acceptor groups
(c) No more than 10 hydrogen bonds
(d) None of the above.

(x) Which of the following statements is true?
(a) A parallel combinatorial synthesis carried out in a specified number of vessels will produce less compounds than a mixed combinatorial synthesis.
(b) Mixed combinatorial synthesis involves the synthesis of a large number of compounds using a variety of different synthetic routes to produce a mixture of compounds in each reaction vessel.
(c) Parallel combinatorial synthesis involves the synthesis of a large number of compounds using different reaction sequences, where there is a different, single compound formed in each reaction vessel.
(d) Parallel combinatorial synthesis involves the synthesis of a large number of compounds using the same reaction sequence, where there is a mixture of compounds in each reaction vessel.

Fill in the blanks with the correct word

(xi) The computational equivalent of protein-ligand interaction is _____.

(xii) The term PK stands for _____.

(xiii) The Potential energy function of diatomic molecule is a sum of_____.

(xiv) The simulated Annealing is a consequence of_____.

(xv) An example of a MDS is _____.

Group - B

2. (a) Use simple diagrams and mathematical expressions to show the difference between two first order minimization methods . How can the differences be exploited in the simulation of a biological macromolecule? *[(CO1)(Understand-apply/IOCQ)]*
(b) With respect to a protein structure minimization problem, the following statement emerged out of an analysis "In this minimization problem, the higher the phenomenological temperature T the greater is the probability of an uphill energy move" What simulation is being referred to in this statement? What reasons make the idea in the statement particularly effective? How does the computation of simulated annealing in protein structures emerge out of the same statement-analysis? *[(CO3)(Analyse/HOCQ)]*
(c) Explain the following expression $p_{i=} \sum^{v}{}_{I} c_{i,i} x_j$ in the context of principal component analysis (PCA) defining the terms. What are the possible applications of PCA in the context of conformational analysis of ligands that may be useful for protein binding studies? Name one "wet" experimental technique where data analysis involves use of PCA? *[(CO2)(Apply/IOCQ)]*
4 + 4 + 4 = 12

3. (a) Write down the steps of Metropolis Monte Carlo simulation. What is its unique step? *[(CO1)(Analyse/IOCQ)]*
(b) Define the phenomenon of simulated annealing and explain how is it applied to protein structure optimization problems? *[(CO1)(Analyse/IOCQ)]*
(4 + 2) + (2 + 4) = 12

Group - C

4. (a) What are principle based on which molecular mechanics (MM) methods are developed? What are the applications of MM? *[(CO3)(Analyse/HOCQ)]*
(b) Write the mathematical equation for the calculation of total molecular mechanics potential energy of a molecule in the context of molecular modelling, explaining all the terms. *[(CO2)(Understand/LOCQ)]*
(c) The harmonic potential function of a bond stretching is expressed as

$$V_{bonds} = 0.8\ K_b\ (r_{AB} - r_{AB}^{o})^2$$

The stretching force constant for the bond A – B is 200 kcal/mol/A^2 and the equilibrium bond length r_{AB}^{o} is 1.5 A^{o}.
(i) Sketch the potential as a function of A – B separation.
(ii) What is the energy if the bond is stretched by 60 A^{o}?
(iii) What is the energy if the bond is compressed by 0.6 A^{o}? *[(CO2)(Analyse/HOCQ)]*
(1.5 + 1.5) + (1.5 + 1.5) + (2 + 2 + 2) = 12

5. (a) How you will determine the bioavailability of orally delivered drug experimentally? Bioavailability of a drug depends on which factors depends? *[(CO3)(Analyse/IOCQ)]*
(b) Morphine has an apparent volume distribution of 150 L, and half-life of elimination of 2 hours. In a 70 Kg man, what is its approximate rate of clearance? *[(CO4)(Apply/HOCQ)]*
(c) Describe molecular descriptor with an example? Give the Structure Activity Relationship of Penicillin. *[(CO3)(Describe/LOCQ)]*
(4 + 2) + 2 + (2 + 2) = 12

Group - D

6. (a) Explain the mechanism of drug absorption through gastrointestinal tract. *[(CO4)(Explain/IOCQ)]*
(b) Describe pharmacokinetics and pharmacodynamics with all parameters with labelled diagram. *[(CO4)(Understand/IOCQ)]*

(c) What is prodrug? Define apparent volume distribution of drug. Calculate apparent volume distribution of drug when amount of a drug injected is 100 mg and plasma drug concentration at t = 0 is 10 mg/L. *[(CO4)(Analyse/HOCQ)]*

4 + (2 + 2) + (1 + 1 + 2) = 12

7. (a) Based on two state receptor model explain the mechanism of action for an agonist and or an antagonist drug. *[(CO3)(Explain/IOCQ)]*

(b) Explain how you will determine the ED_{50} and LD_{50} of a new drug experimentally in mice? *[(CO4)(Understand/LOCQ)]*

(c) Mr Jones has zero kidney function and is undergoing hemodialysis 3 days per week while awaiting a kidney transplant. He takes metformin for type 2 diabetes mellitus and was previously stabilized (while his kidney function was adequate) at a dosage of 500 mg twice daily, given orally. The plasma concentration at this dosage with normal kidney function was found to be 1.4 mg/L. He has had 6 dialysis procedures and metformin toxicity is suspected. A blood sample now shows a metformin concentration of 4.2 mg/L. What was Mr Jones' clearance of metformin while his kidney function was normal? *[(CO6)(Analyse/HOCQ)]*

4 + (3 + 3) + 2 = 12

Group - E

8. (a) Write out the expression for a classical mechanical force field defining all the terms. *[(CO6)(Analyse/HOCQ)]*

(b) What are the two measurables for docking? What are the types of docking experiments and what physico-chemical interactions do they measure? *[(CO5)(Remember/LOCQ)]*

(c) Use a flowchart to represent the virtual screening tunnel for a representative computational experiment. *[(CO5)(Apply/IOCQ)]*

4 + 4 + 4 = 12

9. (a) Define a molecular descriptor in the context of computer aided drug design. What are the characteristics that that are generally incorporated in such a molecular descriptor? Briefly explain the significance of the following three molecular descriptors: Connectivity index ($^1\lambda$), Molar refractivity (MR) and Heat of formation (ΔH_f). *[(CO5)(Understand-explain/IOCQ)]*

(b) Write the mathematical expression for an empirical force field (Class I) for finding the potential energy function for a molecule. Explain the different terms. Why is transferability considered to be a key property of a force field? When are Class II and higher force fields needed? *[(CO5)(Understand-explain/IOCQ)]*

(c) Hydrogen bonds in protein-ligand (drug) interactions play an important role in the measurables of docking. How is this incorporated into a docking algorithm/methodology? What physicochemical parameters in the ligands and in the target, proteins are important? If the docking methodology/algorithm were to incorporate a DNA-ligand(drug) interaction what changes, if any, would have to be made? *[(CO5)(Understand-explain/IOCQ)]*

4 + 6 + 2 = 12

Cognition Level	LOCQ	IOCQ	HOCQ
Percentage distribution	17.71	56.25	26.04

Course Outcome (CO):

After the completion of the course students will be able to

CO1: Understand the principles of molecular simulation techniques of Monte Carlo, molecular dynamics and energy minimization methods and their applications to studying equilibrium and dynamic properties of biological macromolecules and their interactions

CO2: Understand principles of classical of classical molecular mechanics and physicochemical properties to understand the interactions between potential drugs (small molecule ligands) and their targets (proteins, nucleic acids)

CO3: Understand the physicochemical basis and criteria necessary for application of molecular modelling principles to computer aided drug design.

CO4: Application of pharmacokinetic and pharmacodynamic principles to the process of computer aided drug design

CO5: Understand the concepts and steps in molecular docking tools/algorithms and analyze the data obtained from them

CO6: Applications of principles and concepts of molecular modelling and computer-aided drug design to real life examples of drug discovery and development.

**LOCQ: Lower Order Cognitive Question; IOCQ: Intermediate Order Cognitive Question; HOCQ: Higher Order Cognitive Question.*