MOLECULAR MODELLING AND DRUG DESIGNING
(BIOT 3241)

Time Allotted : 3 hrs **Full Marks : 70**

Figures out of the right margin indicate full marks.

Candidates are required to answer Group A and any 5 (five) from Group B to E, taking at least one from each group.

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

Group – A
(Multiple Choice Type Questions)

1. Choose the correct alternative for the following: **10 × 1 = 10**

(i) 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.

(ii) A hypothical ligand binds with receptor with an association constant (K_a) of 3.0×10^4 M^{-1} Sec^{-1} and dissociation constant (K_d) of 6.90×10^{-6} Sec^{-1} What is the equilibrium dissociation constant?
(a) 4.7×10^9 M^{-1} (b) 2.3×10^{-10} M^{-1}
(c) 2.3×10^{10} M^{-1} (d) 3.3×10^{-6} M^{-1}.

(iii) 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.

(iv) Which of the following is general form of a QSAR equation?
(a) $\nu = f(p)$
(b) $\Phi(r) = \varphi_p(r) + \varphi_\sigma(r)$
(c) $\Delta G_{ass} = \Delta G_{sol}(LR) - \Delta G_{sol}(L) - \Delta G_{sol}(R)$
(d) $A = k_B \iint dp^N dr^N \exp(+H(p^N, r^N)) \rho(p^N, r^N)$.

(v) The term $\sum_{bonds} K_r (r - r_o)^2$ in an energy expression is indicative of
(a) torsion angle interaction (b) van dar Waals interactions
(c) hydrogen bonds (d) bond stretching.

(vi) Which of the following parameters *approximate* molecular docking scoring functions?
(a) Binding free energy for the ligand binding to the receptor
(b) Binding enthalpy for the ligand binding to the receptor
(c) Non-linear regression analysis of the protein ligand binding
(d) Interactions of the solvent with the ligand and the receptor.

(vii) Which of the following macromolecular system(s) have been modeled by molecular dynamics simulation methods?
(a) Complex formation between the enzyme dihydrofolate reductase and a triazine inhibitor
(b) Motion of lipid bilayers
(c) Motion of chain amphipiles
(d) All of the above.

(viii) Which of the following enzymes is a microsomal enzyme?
(a) Cytochrome P_{450} (b) Trypsine
(c) Lipase (d) None of the above.

(ix) Factor that effects rates of drug distribution in our body is
(a) blood perfusion (b) membrane permeability
(c) both (a) and (b) (d) pH.

(x) Ampicillin is eliminated by first-order kinetics. Which one of the following statements best describes this pharmacokinetic process?
(a) There is only 1 metabolic path for drug elimination.
(b) The half-life is the same regardless of the plasma concentration
(c) The drug is largely metabolized in the liver after oral administration and has low bioavailability.
(d) The rate of elimination is proportional to the rate of administration at all times.

Group – B

2. (a) Mathematically explain the difference between the time and ensemble average of a molecular system. What is the mathematical expression for probability density of the same molecular ensemble under conditions of constant number of particles, volume and temperature?

(b) Explain the basic steps of the Metropolis-Monte Carlo algorithm in physico-chemical terms. Enumerate the methodological differences between Molecular dynamics and Monte Carlo simulation methods.

(c) Define and explain the use of phase space in computer simulations. Use a schematic illustration ONLY of an energy surface to explain how MC and MD methods can be used to explore the conformational space of biological molecules.

(2 + 2) + (2 + 3) + (1.5 × 2) = 12

3. (a) Explain the statement "As the time step increases, the RMS energy fluctuation also increases" in the context of molecular dynamics integration algorithms for molecular modelling.

(b) $r(t + \Delta t) = r(t) + \delta t v(t + \delta t)$ and $v(t + 1/2\delta t) = v(t-1/2\ \delta t) + \delta t\ a(t)$. What do these two equations represent? What are the special characteristics of this physico-chemical relationship? How is it implemented in practice? What are the advantages of this method over the standard variation? Cite one distinct disadvantage.

(c) What are the features that characterize a "quality" molecular dynamics integration method?

(d) Explain why the Verlet algorithm is referred to as a "fourth order" integration method?

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

Group – C

4. (a) Describe the role of following physicochemical parameters in drug design: (i) Ionization constants, (ii) chelation, (iii) solubility, (iv) partition Co-efficient.

(b) What are principles, based on which, molecular mechanics (MM) methods are developed? What are the applications of MM?

(c) 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.

(d) 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?

4 + (1 + 1) + 3 + 3 = 12

5. Define the following with examples:
(i) Prodrug, (ii) Pharmacokinetics, (iii) ED_{50}, (iv) Pharmacodynamics.
In considering the binding of a ligand to a receptor as a prototype for computer aided drug design, explain the role that the solubility of the ligand, its distribution in aqueous and nonaqueous layers and state of ionization plays in its choice as an ideal drug candidate.

(2 × 3) + (2 × 3) = 12

Group – D

6. (a) Write the names of different roots of drug delivery. What you understand by pharmacodynamics of a drug? Describe graphical nature dose-response and dose-binding graphs of a drug showing EC_{50}, Emax.

(d) What is spare receptors for a drug? Describe it's nature with graph.

(c) What is prodrug? Describe its significance with example.

(d) 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.

(1 + 1 + 3) + (1 + 2) + 2 + 2 = 12

7. (a) Explain steps of LBDD using a flow chart and give example of successful drug developed by LBDD.

(b) What is bioavailability of a drug. On which factors does it depend? Describe how bioavailability is determined experimentally.

(c) Describe the mechanism of drug interaction with different types of receptor present in a human cell with a diagram.

(d) A new drug is under study in phase 1 trials. It is found that this molecule is avidly taken up by extravascular tissues so that the final total amount in the extravascular compartment at steady state is 100 times the amount remaining in the blood plasma. What is the probable volume of distribution in a hypothetical person with 8 L of blood and 4 L of plasma?

4 + (1 + 1 + 3) + 2 + 2 = 12

Group – E

8. (a) Define the word pharmacophore as it applies to drug design. Draw the diagram of an antihistamine 3D pharmacophore. What is pharmacophore mapping? Outline 2 typical problems that are encountered in the calculation of 3D pharmacophores.

(b) Explain the use of (i) genetic algorithms and (ii) distance geometry to perform molecular docking.

(c) Illustrate the use *of an indicator variable* for an extended QSAR equation. Give an example of such a variable being used in the CADD of a small molecule pharmaceutical.

(3 × 1 + 2) + (2 × 2) + 3 = 12

9. (a) Write a mathematical expression for a molecular docking scoring function. Define all the terms explaining where the contributions originated from.

(b) What type of scoring functions were used in computer aided drug design of HIV protease inhibitors? Explain the limitations in this approach that were later rectified in developing antagonist drugs against e.g. muscarinic M_3 receptor.

(c) In developing quantitative structure activity relationships (QSAR) for organic molecule ligand-protein drug target interactions, how has the molar refractivity (MR) parameter been used? Answer this question by emphasizing how MR values are calculated for organic molecules as ligands.

(2 + 2) + (2 + 3) + 3 = 12