MOLECULAR MODELING & 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) Which of the following is NOT a force field model for water?
(a) T1P3P (b) TIP4P (c) SPC/E (d) AMBER.

(ii) Designing of peptidomimetics as putative drugs involve which of the following choices
(a) use a native peptide as the lead compound
(b) use a peptide obtained via recombinant means
(c) design of conformationally labile analogs of exogenous peptides
(d) none of the above.

(iii) The term $\sum_{\text{dihedrals}} 1/2V_n\,(1 + \cos n\varphi)$ in a energy expression for the conformation of a protein represents
(a) bond angle bend (b) Van der Waals interactions
(c) torsion angle energy contributions (d) electrostatic interactions

(iv) In QSAR calculations for CADD which of the following techniques are used for data analysis of modified structures?
(a) Partial least squares (b) Molecular Field Analysis
(c) Principal Component Analysis (d) All of the above.

(v) The Hammett electronic substituent constant, σ, is a measure of the
(a) electron-withdrawing/donating strength of a ring substituent in a ligand
(b) partition coefficient of the unionized form of the ligand
(c) binding capacity of the ligand to the receptor
(d) is a measure of the inductive effect of substituent on ligand.

(vi) 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.

(vii) Which of the following properties influence the ability of a potential drug to cross the blood-brain barrier?
(a) Molar Refractivity(MR) (b) Buried surface area
(c) Dielectric constant of p-dioxane (d) None of the above.

(viii) Ampicillin is eliminated by first-order kinetics. Which of the following statements best describes the process by which the plasma concentration of this drug declines?
(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.

(ix) 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 describe these results?
(a) Thiazide A is more efficious 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.

(x) The case of "Typhoid Mary" serves as an example of which of the following systems biology concepts
(a) an example of a directed graph
(b) an example of a "hub" in the disease transmission network
(b) an example of a tree on the disease transmission network
(c) an example of a labelled graph.

Group - B

2. (a) How are finite difference techniques used to generate molecular dynamics trajectories?

(b) Describe pharmacokinetics of a drug with all parameters and with labelled diagram?

(c) Describe the different techniques for target validation.

4 + 4 + 4 = 12

Group - E

8. (a) Enumerate four important general features of a molecular mechanics force field. Write out the mathematical expression for a molecular mechanics force field that represents the conformational energy for a protein.

(b) What is the full form for the AMBER force field? For what molecules is AMBER force field preferably used? What are the differences in AMBER force field compared to a generalized MM based one? In the Optimized potentials for Liquid Simulations (OPLS) force field, what are the combination rules applied for parameterisation of non-bonded and repulsion interactions? What is the special characteristic of the OPLS model with respect to hydrogen bonding?

(c) Calculate the energy of the VDW interaction between two hydrogen atoms using the following equation $V_{vdw} = D_{IJ}\{-2[\rho_{IJ}/\rho]^6+[\rho_{IJ}/\rho]^{12}\}$ where ($D_{ij} = 0.0152\ \text{kcal/mol and}\ \rho_{IJ} = 3.195\ A^0$).Assume the distance between the two hydrogen atoms is 2.0 A^0. What is the energy if the distance is 3.0A^0?

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

9. Hantsczh developed QSAR equations that were first used to rationalize biological activity by relating the latter to a molecule's electronic characteristics and hydrophobicity
(i) Define the parameters of the following QSAR equation and explain their significance with respect to the above statement:
$\log(1/C) = k_1 \log P - k_2 (\log P)^2 + k_3\sigma + k_4$
(ii) What properties of a potential drug does the hydrophobic component represent?
(iii) How can the above equation be re-parameterized with the term π? What are the physic-chemical implications of this newly parameterized equation?

6 + 2 + (2+ 2) =12

(b) Write out the steps of the Velocity Verlet algorithm. Explain precisely what are the differences between the velocity Verlet and the standard Verlet algorithms.

(c) How is molecular dynamics integrated into the process of experimental structure determination of a protein?

3 + 5 + 4 = 12

3. (a) Enumerate four specific differences between the molecular dynamics (MDS) and Monte Carlo simulation(MCS) methods. How can inter-ensemble sampling be achieved between the two simulation methods? Use the example of MDS of an intermolecular complex between DHFR (dihydrofolate reductase) and a triazine inhibitor to show the variation in torsion angles. Use a figure to illustrate your answer.

(b) Stepwise explain how the Gibbs Ensemble Monte Carlo (GEMC) algorithm can be used to investigate phase equilibria in biomolecular systems. What is this method's advantages over existing algorithms that simulated phase equilibria changes in biomolecular systems? How can MCS and MD be combined to perform long simulations of DNA molecules?

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

Group - C

4. (a) (i) Explain the difference between EC_{50} and ED_{50} through a concentration response curve of a neurotransmitter on muscle contraction.

(ii) Use a diagram to explain the formation and role of hydrophobic interactions in stabilization of a drug-receptor complex. Give an example of a drug where such hydrophobic interactions predominate.

(b) Draw a simple reaction scheme to represent the equilibrium between a drug, a receptor and a drug-receptor complex. Enumerate the important interactions (forces) that are involved in drug receptor interactions. *Your answer should include both covalent and non-covalent interactions* and highlight relevant *physico-chemical parameters*, *chemical structure* and *examples* of such *interactions in the pharmaceutical world*.

(2.5 × 2) + (1+ 6) = 12

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

(b) What are principle 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

Group - D

6. (a) Provide a detailed itemization of the criterion for target selection (*typically a protein*) linked to the disease against which a new drug has to be developed. You can assume that the new drug may be a small organic molecule pharmaceutical or a large molecule protein-based biopharmaceutical.

(b) For a drug to exert its desired effect, it must be delivered to the site of action. Compare the two most common modes of drug administration: oral and parenteral in view of their absorption and distribution characteristics. What physical properties of a drug make them *amenable for four other modes of administration*. Explain, in detail, the rationale behind your answer.

(c) Define an agonist drug. What are the three distinct regions of a dose response curve for membrane receptors against an agonist drug? Draw appropriate dose response curves for a single agonist and 4 full agonist drugs of differing potencies.

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

7. (a) Explain the mechanism of drug absorption through gastrointestinal tract.