MOLECULAR MODELLING AND DRUG DESIGNING
(BIOT 3231)

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 assumptions is routinely made in molecular modelling calculations?
(a) Dreiding mechanical model
(b) Orthogonalization of Cartesian space
(c) CPK mechanical model
(d) Born-Oppenheimer approximation.

(ii) Which of the following statements best describes pharmacodynamics?
(a) The study of how drugs reach their target in the body and how the levels of a drug in the blood are affected by absorption, distribution, metabolism and excretion.
(b) The study of how drugs can be designed using molecular modelling based on a drug's pharmacophore.
(c) The study of how a drug interacts with its target binding site at the molecular level.
(d) The study of which functional groups are important in binding a drug to its target binding site and the identification of a pharmacophore.

(iii) The term $\sum_{\text{dihedrals}} 1/2V_n (1+\cos n\Phi)$ 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) Which of the following statements is not true about cytochrome P450 enzymes?
(a) They contain haem and magnesium.
(b) They belong to a general class of enzymes called monooxygenases.
(c) There are over 30 different cytochrome P450 enzymes.
(d) Variation in cytochrome P450 enzyme profile between individuals can explain individual variation in drug susceptibility.

(v) In order to accurately measure the similarity parameter S for comparison of target protein structures which of the following tests would be the most appropriate
(a) intermolecular comparison using RMSD
(b) intramolecular comparison using a DALI based algorithm
(c) global distance test
(d) a non-conserved residue structural test.

(vi) Which of the following is one of the rules in Lipinski's rule of five?
(a) A molecular weight equal to 500
(b) No more than five hydrogen bond acceptor groups
(c) No more than 10 hydrogen bond donor groups
(d) A calculated logP value less than +5.

(vii) The specificity of a ligand binding site on a protein is based on
(a) the absence of competing ligands
(b) the amino acid residues lining the binding sit
(c) the presence of hydrating water molecules
(d) the opposite chirality of the binding ligand.

(viii) Ampicillin is eliminated by first-order kinetics. Which one of thefollowing 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 oraladministration and has low bioavailability
(d) The rate of elimination is proportional to the rate ofadministration at all times.

(ix) Which of the following represents large scale motion in biological molecules?
(a) Sidechain motion (b) Domain motions (hinge bending)
(c) Helix motion (d) Helix coil transitions.

(x) Which of the following expressions is indicative of a Normal Mode Analysis?
(a) $\delta f/\delta x_i = 0$ (b) $\delta^2 f/\delta x_i^2 \approx 0$
(c) $U(T) = U_{trans}(T) + U_{rot}(T) + U_{vib}(T) + U_{vib}(0)$ (d) $\nu_i = \sqrt{\Delta_i}$.

Group- B

2. (a) Write out the steps of a Velocity Verlet algorithm. What are the differences in the measurables and output between the velocity Verlet and the standard Verlet algorithms? Why should the length of a molecular dynamics simulation (MDS) be long? [(CO1)(Understand-analyze/HOCQ)]
(b) How is molecular dynamics integrated into the process of experimental structure determination of a protein? [(CO1)(Remember-Understand/1OCQ)]
(c) "Many chemical and biological problems that are studied using molecular modelling involve non-covalent interactions between molecules. The study of such interactions is typically facilitated by examining three distinct surfaces of

the molecule." Elucidate this statement by naming these three surfaces and use a properly labelled diagram to represent them. [(CO2)(Analyze/IOCQ)]

5 + 3 + 4 = 12

3. (a) (i) Using a potential energy diagram and necessary mathematical details explain the unique step(s) of a Metropolis Monte Carlo algorithm for protein structure calculations. List 3 applications of Monte Carlo algorithms in the biomolecular domain.

(ii) Interpret the following equation $W_i=W_{i-1}1/k \sum \exp(-\nu_\tau(i)/k_BT]$ as a basis for performing Monte Carlo sampling efficiently.

[(CO1)(Understand-analyze/IOCQ)]

(b) What is the formal mathematical statement of the energy minimization problem? What are the two types of energy minimization algorithms? Use a diagram to represent a first order minimization method explaining the diagram in detail. [(CO1)(Remember-understand/LOCQ)]

(c) Draw a labelled Argand diagram to represent complex numbers. Where do complex numbers find use in molecular modelling? If you were to calculate the equilibrium thermodynamic parameters associated with a polyalanine polypeptide in an α-helical conformation, what sort of energy minimization application would that represent? Briefly explain your answer.

[(CO1)(Analyze/HOCQ)]

6 + 3 + 3 = 12

Group - C

4. (a) Define what a molecular descriptor means with respect to rational drug design. Develop the Structure Activity Relationship for penicillin defining the parameters in the SAR equation. [(CO2)(Remember/LOCQ)]

(b) For purposes of molecular modelling, a molecular mechanics (MM) based potential energy expression is required for the molecule of interest. Write out the terms in this potential energy expression and explain what the different terms mean. [(CO2)(Remember/IOCQ)]

(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 1.2 A^o.

(i) Sketch the potential as a function of A – B separation.

(ii) What is the energy if the bond is stretched by 65 A^o?

(iii) What is the energy if the bond is compressed by 0.5 A^o?

[(CO2)(Analyze/IOCQ)]

(2 + 3) + 4 + 3 = 12

5. (a) Explain the significance of the following physicochemical properties of drug (i) hydrophobicity, (ii) electronic effects. [(CO2)(Explain/IOCQ)]

(b) Explain is the difference between local energy and global energy minimum graphically? [(CO2)(Understand/LOCQ)]

(c) Explain the significance of "Lipinski's ruleof five". It contains four rule, then why is called rule of five? [(CO3)(Explain/HOCQ)]

(3 + 3) + 3 + 3 = 12

Group - D

6. (a) Define what is meant by the spare receptor of a drug. Use a graphical representation to explain its nature. [(CO4)(Remember-explain/LOCQ)]

(b) Define a prodrug. Using an example, explain its significance in two stages of the novel drug design process. [(CO4)(Remember-understand/IOCQ)]

(c) Explain the difference between EC_{50} and E_{max} by depicting the dose response and dose-binding graphs of a representative drug. [(CO4)(Analyse/IOCQ)]

(d) What is the mathematical expression for the apparent volume distribution V_d for a drug? Calculate this parameter for a particular drug X when the amount of the drug injected is 150 mg and the concentration of the drug in plasma at time t = 0 is 15 mg/L. [(CO4)(Analyse/HOCQ)]

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

7. (a) Explain the steps of Structure Based Drug Design (SBDD) using a flow chart. Provide one example of drug that is available for patients where SBDD was an integral part of its development. Your answer should highlight specific stages in the drug's development where SBDD was necessary. [(CO4)(Analyse/HOCQ)]

(b) Define bioavailability of a drug using an empirical expression. Itemize the factors on which the bioavailability parameter is dependent. How is bioavailability generally determined experimentally? If the bioavailability parameter for a drug was obtained computationally what would be the approach and assumptions? [(CO4)(Analyse/IOCQ)]

(c) The following information was obtained for a potential drug molecule undergoing Phase I clinical trials. Mechanistically this molecule is taken up by extravascular tissues so that the final amount in the extravascular compartment is 125 times the amount remaining in the blood plasma *at steady state*. What is the *probable* volume of distribution in a hypothetical individual with 8 L of blood and 4 L of plasma? [(CO4)(Analyse/HOCQ)]

5 + (1 + 2+ 2) + 2 = 12

Group - E

8. (a) "In a force field the potential terms are a sum of contributions due to covalently bonded interactions and non-bonded interactions". What are the two common non bonded interactions and why are they calculated pairwise? What is the parametric scale of such force fields? What are the typical parameters in a force field that are fitted to represent the behaviour of real molecules? What are the three major types of force fields and briefly itemize their difference(s). Cite two specific force fields and the family of different force fields that each belongs to. [(CO3)(Remember-understand/LOCQ)]

(b) The CHARMM force field is one of the prominent force fields used for studying biological systems. Use a figure to illustrate the variables involved in a basic all atom force field upon which CHARMM force field is also based. What are the additional terms incorporated in the CHARMM force field and what do they represent? State the nature of the energy functions used in CHARMM force fields and the classes of biomolecules for which CHARMM force field is applicable. In a simple table outline the difference in form and applicability between CHARMM22, CHARM27 and CGenFF force fields.

[(CO3)(Remember-understand /IOCQ)]

(c) Considerable effort has been expended to develop computer programs that can estimate logP values entirely on the basis of chemical structure. Why would such programs be useful? How have such computer applications been integrated into the drug discovery and development process?

[(CO2 & CO3)(Understand-apply/IOCQ)]

OR

(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}=0.0154 kcal/mol and ρ_{IJ} =3.2A^0. Assume that the distance between the two hydrogen atoms is 2.2 A^0. What is the energy if the distance is 3.3A^0? [(CO3)(Calculate/IOCQ)]

5 + 4 + 3 = 12

9. (a) Write out the mathematical expression for an all atom protein simulationforce field that uses simple terms for bonded and nonbonded interactionsto model the potential energy surface. Define and explain all the terms including the assumptions that are implicit for calculating non bonded interactions. Name two force fields that are commonly used in protein simulations,

[(CO5)(Remember-Understand/IOCQ)]

(b) What is the technical definition of molecular docking? How can its two measurables be used to computationally distinguish between a ligand-receptor binding reaction that occurs with conformational change and one that does not? Wherever feasible highlight your answer with quantitative arguments.

[(CO5)(Understand-Analyze/LOCQ)]

(c) The design of ACE (angiotensin-converting enzyme) inhibitors demonstrated how it is possible to rationally design drugs for a protein target even when the structure of the target is not well known. Use a labelled flowchart only to explain how this was specifically achieved methodologically through computer aided drug design. Name one ACE inhibitor drug that has been successfully used.

[(CO6)(Analyse-IOCQ)

5 + 3 + 4 = 12

Cognition Level	LOCQ	IOCQ	HOCQ
Percentage distribution	23.95	55.22	20.83

Course Outcome (CO):

After the completion of the course students will be able to

1. 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
2. Understand principles of classical molecular mechanics and physicochemical properties to understand the interactions between potential drugs (small molecule ligands) and their targets (proteins, nucleic acids)
3. Understand the physicochemical basis and criteria necessary for application of molecular modelling principles to computer aided drug design.
4. Application of pharmacokinetic and pharmacodynamic principles to the process for computer aided drug design.
5. Understand the concepts and steps and steps in molecular docking tools/algorithms and analyze the data obtained from them.
6. 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