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?
(a) Dreiding mechanical model (b) CPK mechanical model
(c) Orthogonalization of Cartesian space (d) Born-Oppenheimer approximation.

(ii) Which of the following enzymes is a microsomal enzyme?
(a) Cytochrome P_{450} (b) Trypsin
(c) Lipase (d) none of the above.

(iii) In a Monte Carlo simulation, the minimum conformational energy is given by $\varepsilon(x)$, where the variable x could be
(a) Set of atomic coordinates (b) Mainchain torsion angles
(c) sidechain torsion angles (d) all of the above

(iv) Potential energy function of a diatomic molecule is a sum of
(a) energy of all atoms
(b) expression of forces acting on electron
(c) the bonded and non-bonded force fields
(d) total energy of the system.

(v) The CHARMM program whose physico-chemical concepts are general, are applied to which one of the following simulations?
(a) energy maximization
(b) molecular dynamics simulations (MDS)
(c) simulations that apply only to solvation
(d) energy optimization techniques that apply to lipids only.

(vi) In calculating the bond order, B_{AB}, between two atoms using an empirical formalism (e.g. Mayer's formalism), which of the following parameter combinations are needed?
(a) P(spinless density matrix), P^{α}, $PS_{\mu\nu}$ (b) Z_A,φ, r-R_A
(c) E_{tot}, E_{elec}, ZDO(zero differential overlap) (d) none of the above.

(vii) 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 eliminatio
(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.

(viii) 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

(ix) Factors that affects rate of drug distribution in our body is
(a) blood perfusion (b) membrane permeability
(c) both (a) and (b) (d) pH.

(x) Which of the following choices represent an optimal one for conformational searching in medium to large biological macromolecules for ligand binding applications?
(a) "smart" grid searching (b) distance driven searching
(c) random search (d) all of the above.

Group – B

2. (a) Using a potential energy diagram, list the mathematical steps of the Metropolis Monte Carlo algorithm. Explain the specific uniqueness of this algorithm. Cite two examples of the use of the Metropolis Monte Carlo algorithm in structure simulations of biological macromolecules.

(b) Define the concept of *importance sampling* in molecular simulations. How is the Metropolis Monte Carlo method considered an example of *importance sampling*?

(c) Tabulate the differences between a Monte Carlo simulation(MCS) and molecular dynamics simulation(MDS). Use an example of a molecular simulation of a biological macromolecule to highlight how MCS and MDS algorithms are combined together. Briefly state the theoretical basis for combining these two types of simulations.

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

3. (a) "Molecular Dynamics simulations (MDS) can provide detailed information on fluctuations and conformational changes of proteins and nucleic acids". Explain this statement by giving examples of (i) specific motions in biological molecules and their timescales and (ii) complex dynamic processes that occur in biological systems.

(b) In MDS, the classical mechanical numerical solution of the integration algorithms assume that the positions, velocities and accelerations can be approximated by a Taylor series expansion. Write the corresponding algebraic expressions for $r(t+\Delta t)$,$v(t+\Delta t)$,$a(t+\Delta t)$ in such a generalized integration algorithm. What is the mathematical expression for the Verlet algorithm? What are its unique characteristics? Tabulate its advantages and disadvantages.

(c) Name three derivative minimization methods. Outline the essential mathematical characteristics of *any ONE* of them. Enumerate the general and specific applications of energy minimization. How can an energy minimization technique and associated analysis be used to study the binding of an anti-bacterial drug to an enzyme?

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

Group – C

4. (a) Itemize in detail the principles and assumptions on which molecular mechanics (MM) methods are based. Cite the applications of MM paying special emphasis on computations involving biological macromolecules.

(b) Write out the functional mathematical form of a force field that represents the total potential energy of a molecule. Define all the covalent and non-covalent terms in the equation. What sort of molecular systems are modelled by such a force field?

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

5. (a) (i) Define a molecular descriptor in the context of molecular modelling and drug design. Give one example of such a molecular descriptor and its specific use(s).

(ii) Molecular descriptors in molecular modelling operate on the basis of structural similarity between a query molecule and molecules in a database. What parameter is used to represent this similarity? Explain your answer.

(b) Define drug metabolism and its specificity characteristics. Describe the mechanism of drug metabolism in our body with reference to sites of metabolism and modes of administration of a drug.

(3 + 2) + (2 + 5) = 12

Group – D

6. (a) What are the principles behind drug target selection? Itemize and briefly discuss the different techniques that are available for validation of selected drug targets.

(b) Use a labelled flowchart to represent the different steps and parameters necessary to evaluate the pharmacokinetic profile of a potential drug. Briefly describe the function of the different parameters and steps with examples wherever appropriate.

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

7. (a) Use a flow chart to represent the essential steps of Ligand based drug design (LBDD). Cite one example each of a drug that was commercially produced using LBDD in its developmental steps and one that used structure based drug design (SBDD).

   (b) Define characteristics of the dose response curve of drug concentration with time after administration of single dose. Morphine has an apparent volume distribution of 220 L, and half life ($t_{1/2}$) of elimination of 3 hours. In a 70 Kg man, what is its approximate rate of clearance?

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

Group – E

8. (a) (i) Give a general definition of a biological force field. Comment on the parameterization that is commonly employed in such force fields. Cite two specific applications of such force fields with respect to proteins and nucleic acids.

   (ii) What are the differences in the specialized force fields CHARMM and AMBER? Your answer should include specific differences in non-covalent energy contributions between these specialized force fields.

   (b) Explain the methodological differences between rigid and flexible docking. What are the differing assumptions involved? What intrinsic property exhibited by a protein binding to a ligand makes flexible docking more accurate computationally? Use an example to highlight your answer.

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

9. (a) Use the steps of ANY docking algorithm to explain the concept of shape and size complementarity in molecular docking. Name the other parameters that contribute to docking affinity. Stepwise explain how SBDD can be used to eliminate "off target interactions" in a potential lead modification/optimization step in computational drug design. Use two examples to highlight your answer.

   (b) How have genetic algorithms been incorporated into molecular docking procedures? Your answer should include the specific steps in molecular docking that have been influenced by genetic algorithms.

   (c) In a virtual screening experiment, scoring functions are used to approximate the binding free energy for the ligand binding to a receptor. An expression for scoring function determination is as follows:

$$\Delta G_{bind} = \Delta G_{solvent} + \Delta G_{conf} + \Delta G_{int} + \Delta G_{rot} + \Delta G_{1/r} + \Delta G_{vib}.$$

   Define all the contributions explaining *which ones can be ignored and why*. Name a docking tool that utilizes such a function.

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

Department & Section	Submission Link
BT	https://classroom.google.com/w/MjQ4NzE4MDU3NzM3/tc/MzY1MjQ0NjY4NTU3