BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE, PILANI (RAJ.)

FIRST SEMESTER 2009-2010

BIO C417, BIOMOLECULAR MODELING

COMPREHENSIVE EXAMINATION

TOTAL WEITAGE 30% Date: 07.12.2009 DURATION: 3Hrs. (Part A & Part B)

Total Marks (70+30) =100

- **Answer Part A and Part B in separate answer sheets.**
- **Irrelevant answer may attract penalty.**

PART – A (CLOSED BOOK) (Max. duration: 2 Hrs., Max. Marks 70)

1. a) Draw and explain the preferred orientation of phi (ϕ) and phi (ψ) torsion angles in polypeptide (other than glycines and prolines) on the basis of steric interaction only. Why do you think in nature, those torsion angles (phi and psi) in proteins can take up many other values which are sterically disallowed. **[4+2]**

b) It is observed that in general, chi-1 ($\chi 1$) torsion angle of a particular residue is very well correlated with corresponding phi (ϕ) and phi (ψ) torsion angles, where as subsequent torsion angles like $\chi 2$, $\chi 3$, … are not directly related to ϕ and ψ angles of backbone. Explain the above fact with proper diagram. **[4]**

c) Account for the difference in frequency of α-helix (~97%), 3_{10} helix (~3%) and π-helix (extremely rare) in nature. **[3]**

d) Comment on the relative abundance of β-turns and γ-turns. **[2]**

2. a) The following table shows the average torsion angles (in °) for nucleic acid helices**.**

α	β	γ	δ	ε	ζ	χ
-50	**172**	**41**	**79**	**-146**	**-78**	**-154**

Explain (with "Newman projection diagram" in each torsion angle) the rationale of nucleic acid helix to adopt this conformation. Which type of DNA helix generally adopts this conformation? Justify your answer. **[8+2]**

b) What are the structural parameters which are distinctly different in A, B and Z form of DNA? Those parameters signify which structural features of three forms of DNA? **[5]**

3. a) What are the usefulness of having so many different graphical representation of biomolecules? What are the features of biomolecules that are well described by (i) CPK model (ii) SMILE representation (iii) TOPS representation (iv) RIBBON diagram (iv) Connectivity matrix. **[2+5]**

b) Comment on the statement "In an ideal world, we would be able to accurately predict protein structure from the sequence only" **[3]**

c) If you are asked to improve the Chou-Fasman algorithm of secondary structure prediction, what will be your line of action? Justify your plan of action. **[5]**

4. a) Why does homology modeling become "most successful approach for predicting 3D structure of protein"? **[3]**

b) What are the underlying principles of selecting a template in homology modeling? **[3]**

c) What are the measures one should adopt to improve quality of homology modeled structure? **[3]**

d) What are the principles behind the developing of threading scoring function? **[3]**

e) Why is it mentioned that Threading is in between homology modeling and *ab initio* technique of structure prediction? **[3]**

5. a) Draw typical van der Waal's potential and electrostatic interaction plot with respect to atomic separation and explain each part of the plot. **[4]**

b) Compare conjugate gradient method and steepest descent method of energy minimization technique. **[2]**

c) Draw a flow chart depicting the steps of molecular dynamic simulation. Mention the important parameter setting during a typical explicit water simulation. **[4]**

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PART – B (OPEN BOOK) (Max. duration: 1 Hr., Max. Marks 30)

1.a) Our growing understanding of how proteins fold allows researchers to make predictions about protein structure based on primary amino acid sequence data. Consider the following amino acid sequence.

Ile-Ala-His-Thr-Tyr-Gly-Pro-Phe-Glu-Ala-Ala-Met-Cys-Lys-Trp-Glu-Ala-Gln-Pro-Asp-

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Gly-Met-Glu-Cys-Ala-Phe-His-Arg

21 22 23 24 25 26 27 28

i) Where might bends or β turns occur?

ii) Where might intrachain disulfide cross-linkages be formed?

iii) Assuming that this sequence is part of a larger globular protein, indicate the probable location (the external surface or interior of the protein) of the following amino acid residues: Asp, Ile, Thr, Ala, Gln, Lys. Explain your reasoning. **[1+1+3]**

b) A majority of promoter region comprised of AT rich sequence. From your knowledge of sequence dependent DNA structure, discuss the advantage and disadvantage of AT rich sequence at promoter region. **[5]**

2. a) A "famous" experiment demonstrates that deletion of small part at C-terminus end of protein sequence leads to complete loss of protein structure as well as function. Explain this on the basis of your understanding of protein folding. **[5]**

b) Discuss different forces and their contribution on protein folding which leads to functional form of protein. **[5]**

3. Critically discuss the following methodology used in molecular dynamic simulation and mention the key features of the methodology. **[10]**

Methodology:

The uniform quadruplex helical structure, with all four chains in parallel orientation, as proposed from fiber diffraction studies was chosen as the starting structure. The 7-mer quadruplexes were surrounded by 24 Na+ counterions to neutralize the negative charges on the phosphate groups. The counterions were placed 6 Å from each of the phosphorus atoms, along the bisector of the two pendant oxygens, using the EDIT module of AMBER. DNA and counterions were then placed in a pre-equilibrated box of TIP3P water molecules. The periodic box of water was extended to a distance of 5 Å from DNA and counterions, thus effectively covering a distance of ~10 Å from the phosphate cylinder (1103 water molecules solvate the system). Molecular dynamics was performed under NPT condition with SANDER module of AMBER 4.1 program using the PARM 94 all atom force field and particle mesh Ewald method (PME) was used for the calculation of electrostatic interactions. Periodic boundary conditions were imposed in all directions. The long range electrostatic interactions have been calculated without any truncation, while a 9 Å cutoff was applied to Lennard-Jones interactions. The nonbonded pair list was updated every 20 steps and the SHAKE algorithm was applied to constrain the covalent bonds. A time step of 2 fs was used and the structures were saved after every 100 steps, i.e., at every 0.2 ps interval, for the entire duration of the MD run.

Initial systems were energy minimized to a root-mean-square (rms) gradient of 0.1 kcal/molÅ. To equilibrate the solvent molecules, all the waters and surrounding counterions were subjected to 20 ps dynamics at 100 K, keeping DNA fixed, followed by an energy minimization of the entire system. The quenched system was then heated slowly, from 0 to 300 K, by coupling to a heat bath whose temperature was raised at the rate of 50 K for every 2 ps of MD run. The system was equilibrated for another 88 ps and the dynamics run continued for a further 3 ns during which the structures were coupled to a heat bath at 300 K with a coupling constant of 0.1 ps. To test the quadruplex stability at higher temperature and facilitate the movement of counterions, the system temperature is raised to 400 K and the MD simulation is continued up to 4.6 ns. Then the system is quenched to 300 K, and the simulation is continued for another 1.5 ns. Thus, the total duration of the entire simulation is 6.1 ns.

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