Biomolecular Structure 2005 Exam #1

This exam is to be worked on independently. You must not talk, or otherwise communicate, with *anyone* other than Professor Martin or Professor Hardy about *any* aspect of the exam. You may not communicate with your fellow students in the class, nor with any other colleagues, faculty or student. For some of the problems it is necessary to use PyMol. PyMol may be accessed from the Macintosh computers in the Chemistry Resourse Center, or may be downloaded onto your own computer for free at http://pymol.sourceforge.net/ . Please feel free to use additional pages if necessary to answer the questions.

Due in Craig Martin's office, October 31, 12:00pm

Honesty and integrity are absolute essentials for this class. In fairness to others, dishonest behavior will be dealt with to the full extent of University regulations.

1. Looks at the file Evolve.pse from the course website using PyMol. Based on the structures of the two proteins shown in this file, what can you surmise happened evolutionarily to get from one protein to the other. Comment on the relationship of the two proteins in structure and in sequence and the locations of any evolutionary events.

2. What forces drive a protein to fold into the native state? What assumptions do we make about the energetics of the native state? What are the possible outcomes for a protein that does not fold into the native state?

3. As part of the structural genomics initiative, Ivan recently solved the structure of a new protein, ABB1 that is 17 % homologous in amino acid sequence to the nearest neighbor. When he solved the structure he was surprised to find that it was a TIM barrel protein. What can he conclude about the function based on this finding?

4. Two pdb files from NMR structures 1HKS.pdb and 1CFD.pdb are available on the course website or from the Protein Data Bank. Based on the information in the pdb itself, which structure do you think is the better structure? Why?

5. On the course website you can download a file called ElectronDensity.pse. Please open this file in PyMol. For the electron density for one stretch of peptide from an intact protein is shown in this file. The backbone has been modeled in for you. This density is derived from a portion of the sequence:

YAWYQYERVDPRGVRYYWLYGRDLAPE

a. What stretch of the peptide shown above fits into this electron density?

b. What type of secondary structure is this stretch adopting? Please describe how you came to this conclusion.

c. Based on the amino acids present in this peptide, where do you surmise this peptide is found in the intact protein?

6. Jane recently isolated a new species of bacteria from a hydrothermal vent in the bottom of the ocean. Jane then isolated a gene (DMD1) that encodes a protein that is useful for converting methane to diamond. Explain in some detail each of the steps you would undertake for determining the crystal structure of the protein coded for by DMD1. Please note considerations and assumptions you made for this course of action. Your answer should be no more than one page single-spaced.

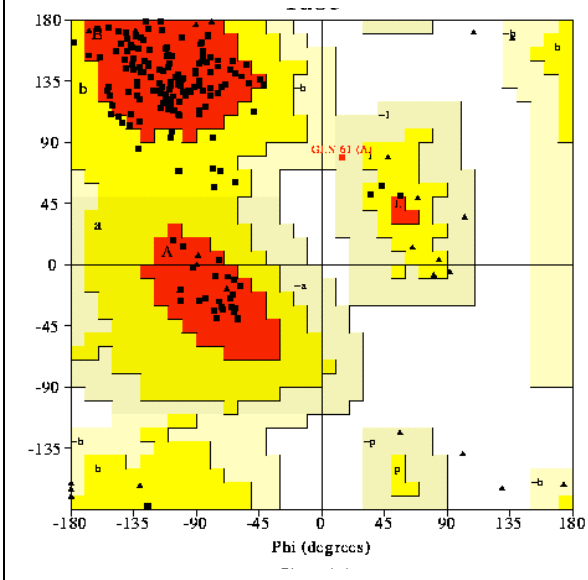
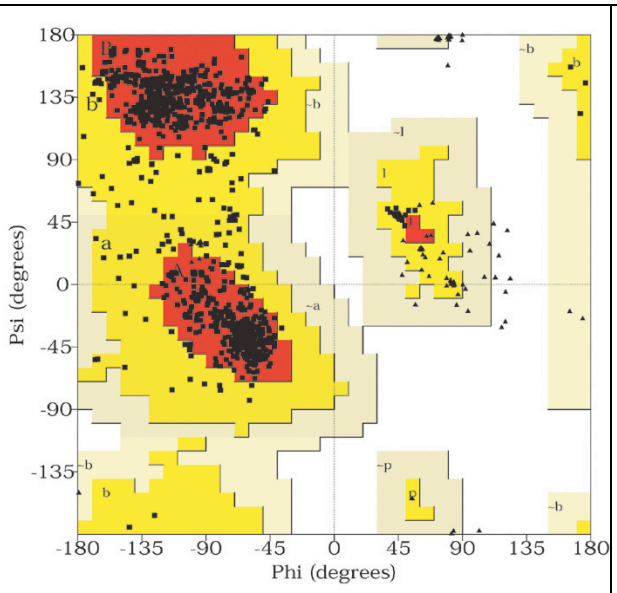
7. Two pdb files from x-ray crystal structures 1SHT.pdb and 1GQF.pdb are available on the course website or from the Protein Data Bank. Look at the text of these PDB files.

   a. What is your estimate of strength of these structures? Which is the better structure? What factors form the basis of your estimation?

   b. Which regions of these structures have the most imprecision in the coordinates? Why?

   c. Are there any regions of either PDB that you would completely ignore? Why?

8. Look at the two Ramachandran plots below. What can you conclude are the differences between proteins #1 and #2. What types of structures are the two proteins? Circle any residues below that you are concerned about and state why you are concerned.

Ramachandran Plot Protein #1	Ramachandran Plot Protein #2
	

9. John has developed an algorithm for repacking protein cores. He used his computational algorithm to redesign the core of ubiquitin. He then introduced those mutations into the core of ubiquitin protein. In his new variant the side chains are more optimally packed than in the wild-type protein.

   a. What effect do you predict optimal side-chain packing will have on the thermal stability of ubiquitin? Draw the thermal denaturation curves you expect for wild-type and mutant ubiquitin with the optimally repacked core.

   b. What effect will his mutations have on the ΔG of unfolding?

   c. What do you predict will be the effect on the function of the protein? Why?

   d. Why did ubiquitin not evolve to have the thermal stability that of John's designed variant?