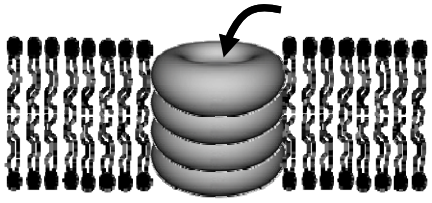
Introduction to Bioinformatics
Problem Set: Protein Structure



1. Some antibiotics form rings that stack and create a pore through the membrane. Consider a cyclic polypeptide antibiotic in which each ring is composed of four amino acids, serine, glycine, threonine, and alanine, connected by peptide bonds. If each atom of the backbone of the amino acids is about 2 angstroms in diameter, estimate the circumference of the pore (presume it to be a circle) and the diameter of a molecule that could fit through it. Approximate the circumference ($\pi \cdot$diameter) to be 3·diameter. (Show work)

2. Before you cook an egg, the egg "white" is not at all white: it's clear. After you cook the egg, the "white" ***is*** white, because the large amount of globular protein has denatured (i.e., unfolded), and as a consequence, the protein has precipitated. Why should unfolding globular protein that are normally soluble in water cause them to stick to each other (which is what "precipitate" means)?

3. Lactate dehydrogenase (the last enzyme in human anaerobic glycolysis) is a soluble, multimeric protein. If you were to try to fold a single linear polypeptide chain of lactate dehydrogenase, you would find it impossible to do so without leaving a large number of hydrophobic amino acids exposed to water. Explain.

4. Make a set of 20 different graphical symbols representing the 20 amino acids. You may use colors, shapes, fill style, etc, but no letters or numbers. The symbols should be organized so that important characteristics shared by more than one amino acid are reflected in the symbols.

5. A child presents to you, her pediatrician, with all the classical symptoms of diabetes. Upon testing, you find that antibody against insulin detects only very low levels of insulin in her blood, but she responds normally to administered insulin. You are surprised to find, however, that the same antibody detects levels of insulin in the pancreas that are grossly higher than normal. What mutation might account for these findings?

6. An enzyme has a molecular weight of 60,000 daltons. When it is exposed to detergent, the protein breaks up to identical inactive components with molecular weights of 20,000 daltons. If the detergent is removed by dialysis, the 60,000-dalton protein reforms and regains enzymatic activity. You have isolated two mutant proteins. Mutant 1 shows no enzymatic activity and has a molecular weight of 20,000 daltons whether or not detergent is present. Mutant 2 has a molecular weight of 60,000 without detergent and 20,000 with detergent but shows no enzymatic activity in either case.

    a. Suggest defects to explain the behavior of each of the mutant enzymes.

    b. A person is heterozygous for Mutant 2 (i.e., has 50% Mutant 2 enzyme and 50% normal enzyme). How would you explain an observation that the person has 87.5% of the enzymatic activity of a normal person? How would you explain an observation of 12.5% activity?

    c. Ascribe the terms "dominant" or "recessive" to the mutation leading to Mutant 2, according to the two situations presented in **b**.

7. Many proteins that form channels through membranes pass through the membrane multiple times. For example, rhodopsin, the light receptor protein in the rod cells of the retina, passes through the membrane seven times as alpha-helical chains. Below is a cartoon showing the side view of part of a hypothetical channel-forming protein -- call it rhodopsin. The circles are amino acid residues, the number of each corresponding to the amino acid's position in the chain. The roman numerals refer to membrane-spanning alpha-helical segments of the protein (only the first two are shown here). The top view shows how the seven α-helices participate in the formation of a pore through the membrane. The pore serves as the means by which protons can pass the membrane in response to light.

   Congenital retinitis pigmentosa is a genetic disease leading to night-blindness. The disease exhibits a variety of symptoms of different severities, which, in many cases, have been linked to specific mutations in rhodopsin. For each given molecular outcome, choose one or more plausible amino acid mutations that could account for it. In each case, explain, briefly, why your choice(s) would lead to the outcome.

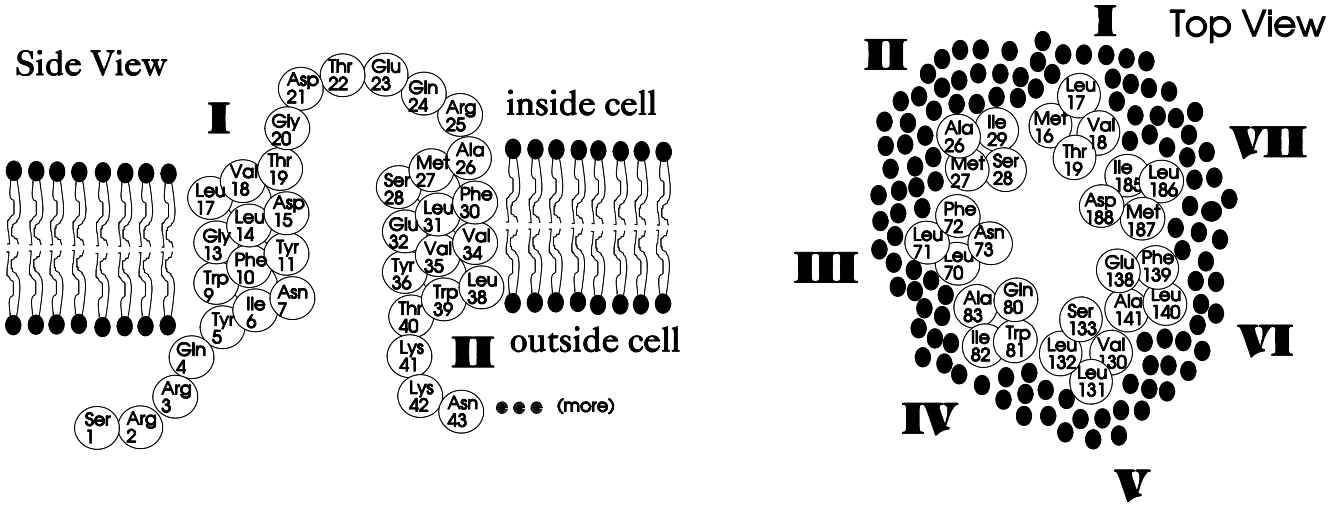
   a. Rhodopsin found in cytoplasm, fails to insert in membrane.

   b. Radical change in structure of rhodopsin. Channel doesn't form properly.

   c. Overall structure of rhodopsin normal, but channel does not conduct protons.

   d. Structure and function of rhodopsin normal.

   A. Insertion of three glutamates between Thr_{22} and Glu_{23}.
   B. Insertion of three glutamates between Phe_{30} and Leu_{31}.
   C. Glu_{138} mutated to arginine.
   D. Asp_{188} mutated to leucine.
   E. Mutation in amino acid not found in mature rhodopsin.



Abbreviations: **Ala**=alanine, **Arg**=arginine, **Asn**=asparagine, **Asp**=aspartic acid, **Cys**=cystine, **Gln**=glutamine, **Glu**=glutamic acid, **Gly**=glycine, **His**=histidine, **Ile**=isoleucine, **Leu**=leucine, **Lys**=lysine, **Met**=methionine, **Phe**=phenylalanine, **Pro**=proline, **Ser**=serine, **Thr**=threonine, **Trp**=tryptophan, **Tyr**=tyrosine, **Val**=valine