# Biology 5357

# Chemistry & Physics of Biomolecules

# Examination #1

Proteins Module

September 28, 2018

**Name:** _____

**Question 1 (10 points)**

**(A)** What is the 1-letter code for the amino acid Tyrosine. Draw the structure of the naturally occurring L-Tyrosine in its zwitterionic form, as it would exist in solution at pH = 7. Show the chirality at the α-carbon atom on your drawing. What is the approximate $pK_a$ of the side chain of Tyrosine?

**(B)** For most of the 20 natural amino acids as found in PDB structures of proteins, the $X_1$ side chain torsional angle is close to one of three minimum energy conformers, +60°, 180° or -60°. The +60° conformation is usually the least common of the three. Make a clear 3-D drawing to show the $X_1$ = +60° structure for L-Tyrosine, for example by giving a Newman projection along the bond defining the $X_1$ rotation. Why is the +60° structure uncommon?

**Question 2 (10 points)** Consider the *cis-trans* isomerization of a peptide bond. For a bond between two amino acids other than proline, the equilibrium constant is usually about $K_{eq} = 1000$ in favor of *trans*. If proline is the residue following the peptide bond, then $K_{eq} = 4$ is typical.

**(A)** Why is the equilibrium constant different for peptide bonds followed by proline?

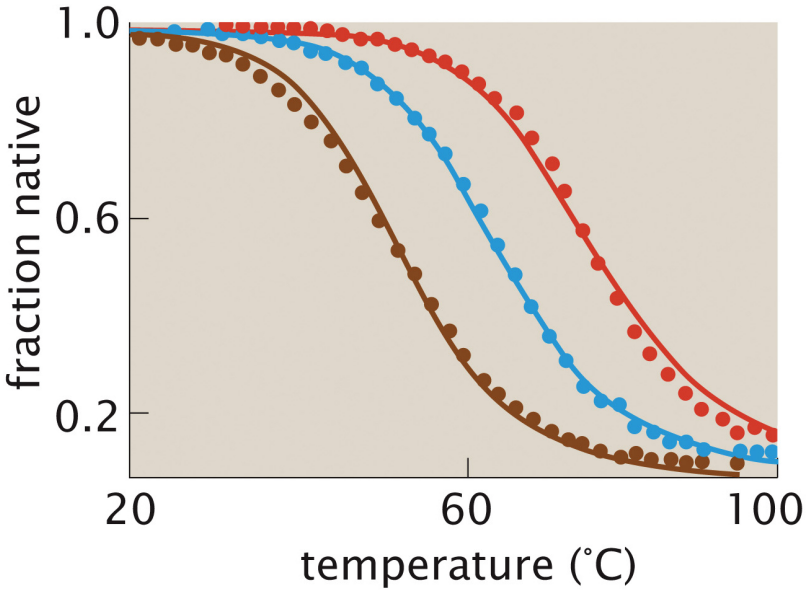
**(B)** What is the $\Delta G°$ between the two isomers in the two cases above, at room temperature?

**Question 3 (10 points)** Close to its melting temperature, lysozyme undergoes reversible thermal unfolding at pH = 7 with $\Delta H° = 130$ kcal/mol and $\Delta S° = 373$ cal/K/mol. At room temperature of 25°C, the corresponding values are $\Delta H° = 60$ kcal/mol and $\Delta S° = 155$ cal/K/mol.

**(A)** What is the melting temperature of lysozyme in °C?

**(B)** What percentage of lysozyme molecules are unfolded, on average, at 25°C?

**Question 4 (20 points)** The plot below shows denaturation of the three-helix bundle protein alpha 3C at three concentrations of urea, 2.0 M, 1.5 M and 1.0 M.



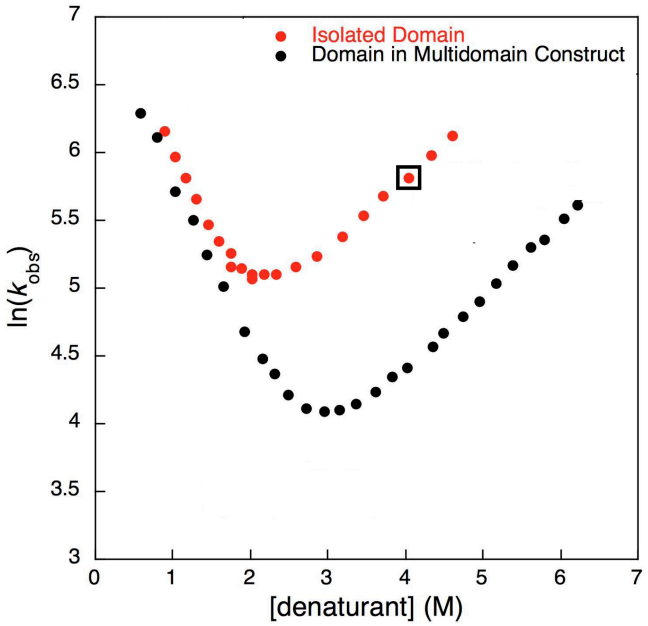

**(A)** Which of the curves corresponds to 1.0 M urea denaturation? Explain briefly.

**(B)** What is the difference in stability between the folded and unfolded forms of alpha 3C for the date shown in the blue curve above?

**(C)** Estimate the stability of the alpha 3C protein at room temperature in the absence of urea.

**(D)** Describe the helix-helix packing expected for a three-helix bundle.

**Question 5 (15 points)** Shown below are chevron plots for an isolated protein domain (red points), and for the same domain when part of a full multidomain protein construct (black points).



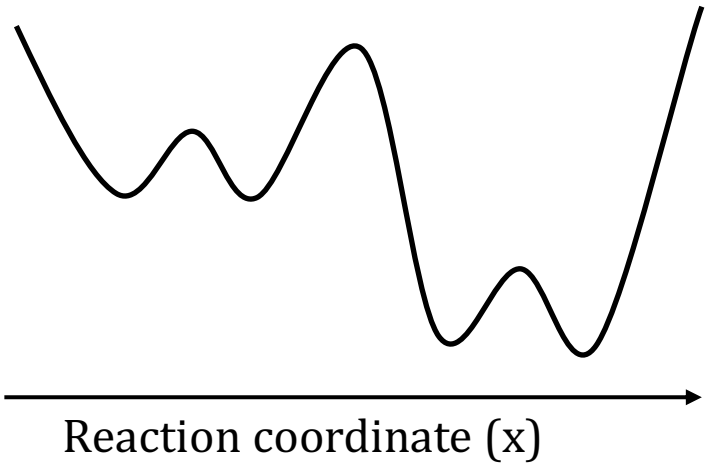

**(A)** Briefly describe the kind of experiment and data analysis that might be performed to obtain the red data point inside the black.

**(B)** Estimate the free energy difference in stability of the folded *vs.* unfolded forms of the isolated domain and domain as part of the multidomain protein.

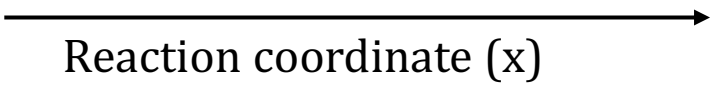
**(C)** Suggest a structural explanation for the difference between the isolated and multidomain curves shown.

**Question 6 (10 points)**

Suppose you and your collaborators determine the free energy function shown below, with a single reaction coordinate labelled x, is a good model for some single molecule data you collected.

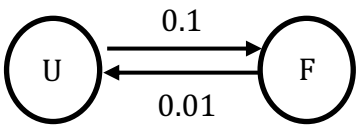



Draw a Markov state model (MSM) for this landscape. Connect the pair of states that will interconvert most slowly with two lines, and pairs of states that will interconvert more quickly with a single line. You can assume that the dynamics is continuous, so the system cannot jump from the far left to the far right without passing through all the conformations in between.

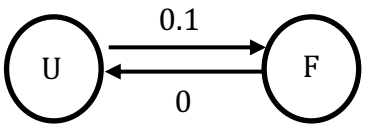


**Question 7 (10 points)**

**(A)** The simple model below has a folded state (F) and an unfolded state (U). The probability of folding in a fixed time interval is 0.1 and the probability of unfolding is 0.01. What is the free energy difference between the folded and unfolded states?




**(B)** What is the probability that a protein will adopt the folded state (F) at equilibrium (*i.e.*, as time goes to infinity) for the model shown below.




**Question 8 (5 points)**

Name one method for improving the efficiency of molecular dynamics simulations. Describe one advantage and one disadvantage of the method you suggest.

**Question 9 (10 points)**

In class, we discussed the temperature replica exchange algorithm. In this approach, simulations are run at multiple temperatures and, at regular intervals, a Monte Carlo move is used to determine whether configurations at neighboring temperatures will be swapped. In a related approach, called Hamiltonian replica exchange, simulations are run with multiple potential energy functions and, at regular intervals, a Monte Carlo move is used to determine whether configurations with neighboring potentials will be swapped. Use the detailed balance condition to derive the probability that configuration $X_i$ with potential energy function $U_1$ will be swapped with configuration $X_j$ with potential energy function $U_2$. You can assume that both simulations are running at the same temperature.