20.320 Problem Set #4

Due on October 21st, 2011 at 11:59am. No extensions will be granted.

General Instructions:

1. You are expected to state all of your assumptions, and provide step-by-step solutions to the numerical problems. Unless indicated otherwise, the computational problems may be solved using Python/MATLAB or hand-solved showing all calculations. The results of any calculations must be printed and attached to the solutions, and the corresponding code should be submitted on Course website.For ease of grading (and in order to receive partial credit), your code must be well organized and thoroughly commented with meaningful variable names.
2. You will need to submit the solutions to **each problem to a separate mail box**, so please prepare your answers appropriately. Staple the pages for each question separately and make sure **your name** appears on each set of pages. (The problems will be sent to different graders, which should allow us to get graded problem sets back to you more quickly).
3. Submit your completed problem set to the marked box mounted on the wall of the fourth floor hallway between buildings 8 and 16. Codes when relevant should be submitted on Course website.
4. The problem sets are due at noon on Friday the week after they were issued. There will be no extensions of deadlines for any problem sets in 20.320. **Late submissions will not be accepted.**
5. Please review the information about acceptable forms of collaboration, which is available on the course website and follow the guidelines carefully. Especially review the guidelines for collaboration on code. NO sharing of code is permitted.'

This assignment is meant to be an introduction to MATLAB coding. Please review the materials posted online, as an introduction to MATLAB. The basics of will additionally be covered in recitation, so if you do not have experience, please be sure to review the online information or attend recitation. To complete this assignment, you will need access to MATLAB (follow directions to download from http://web.mit.edu/student-matlab/)

Question 1 – Plotting with MATLAB

On homework one, you explored the secondary structure of P-glycoprotein using a ramachandran plot. For that question, you were asked to use pyRosetta to find the phi and psi angles of the protein and plot them. can also make similar plots. To learn how to import files to MATLAB and plot, you'll make the same plot, this time using MATLAB.

Download the excel file containing the phi and psi coordinates from the course website. To import an excel file into MATLAB, try familiarizing yourself with the function "xlsread". To plot a scatter plot, consider the tool "scatter."

If you're not sure how to use these commands, try "help xlsread" or "help scatter"

Please attach your MATLAB ramachandran plot, including axis labels and title generated with MATLAB. Be sure to upload the .m file you used to do this onto Course website!

To make your life easier with figures in MATLAB , "file publish" from your .m file window will save all the figures generated into your current directory, in the "html" folder.

a) Regenerate the ramachandran plot from homework 1, this time using MATLAB
b) Now, suppose you want to look at only the phi or psi angles, not both. Plot phi vs. residue number and psi vs. residue number, each as a subplot on the same plot (Note this plot is not meant to be very informative, but gives you practice at using subplots in MATLAB the function "subplot" will be helpful for you!).
c) Recall in the first homework, we estimated the amount of helical residues in the protein. Now, we'll do the same for helix and for beta sheet. Based on the angles below, what percentage of P-glyprotein is alpha helix? What percentage is beta sheet?
    a. Assume helices have phi from -90 to -10 and psi from -100 to -10
    b. Assume Beta sheets are –phi from -150 to -10 and psi from 60 to 180.

Question 2 – Curve Fitting with MATLAB

Assume a ligand interacts with a protein to form a complex in the basic manor:

Protein + Ligand <--> Complex

You performed an experiment where you were able to measure complex formation, after adding 100M ligand to your system, as a function of time, and want to see if you can determine the parameters k_{on} and k_{off}.

The data you found is as follows:

time(s)	Complex(M)
0	0.023
0.01	0.3887
0.02	0.5934
0.03	0.7252
0.04	0.807
0.05	0.8807
0.06	0.8774
0.07	0.9205
0.08	0.9908
0.09	0.9402
0.1	0.9142
0.11	0.9083

a) Plot this data using

b) You expect your curve to fit the following function:

$$C = \frac{L_0}{L_0 + \frac{k_{off}}{k_{on}}} * (1 - e^{-(k_{on} * L_0 + k_{off}) * t})$$

Using nonlinear fitting in , fit the curve to your data, and extract the parameters koff and kon. Be sure to include your units!

c) Include a new plot, with the data included as '+' signs, and overlay your best fit line. Be sure to label all axes, and include a legend with your figure. The command "hold on" will likely help you here.

Question 3 - Isothermal Titration Calorimetry

A high-throughput drug screen can identify small molecules with high affinity for a receptor or other target of interest. Small molecule compounds can then be modified to increase affinity or specificity for a target. Determining the thermodynamic properties of the drug-target interaction can guide attempts to increase affinity. For a compound of interest, SM10, the K_d for binding was estimated using the initial screen to be $2x10^{-7}$M at 25°C.

a) Design an ITC experiment to determine enthalpic vs. entropic contributions to the binding affinity (be sure to include protein and ligand concentrations, and relevant volumes)
b) Based on your experimental design from part a, calculate the heat absorbed or released after the fifth injection of ligand (from injection 4 to injection 5 only!) , given ΔH of binding = -11,000 cal/mol. Be sure to show all of your work!
c) Find the change in Entropy (ΔS) of binding given the information above and any necessary information from parts a and b
d) ITC does not work well for interactions that are extremely weak or extremely strong. Please explain this observation.

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