APh161: The Physics of Biological Structure and Function
Homework 4
Due Date: Tuesday, Feb. 20, 2007

"An ounce of application is worth a ton of abstraction." - Booker T. Washington

Reading: Read chap. 9 of PBOC and write a referee report in the usual way. Please remember as you are doing this that this is a huge help to us as we try to improve the book for its eventual publication. We appreciate it very much and it is a chance for you to construct a concrete written argument.

1. Nucleosome Formation and Assembly

The goal of this problem is for you to reexamine the ideas developed in class concerning the assembly and accessibility of the nucleosome and to rederive the expression for the DNA accessibility using a discrete model.

(a) Repeat the derivation given in class and arrive at an expression for the free energy of formation of nucleosomes. Make sure that you explain the qualitative features of the calculation and that you identify the numerical outcome of the analysis (please report your energies in units of k_BT). In particular, comment on the way in which you handle the elastic and interaction effects and rationalize the energy per length that you assign to each of these effects. Also, instead of pretending that the DNA wraps around the nucleosome fully two times, use the more precise description involving 147 base pairs of wrapped DNA leading to 1.75 wraps around the histones. A second refinement is to include the helical pitch of the DNA as it wraps around the nucleosome - here, just make an estimate to show that this refinement is not very important. (Hint: to do this you will need to remember that the bending energy is of the form

$$E_{bend} = \frac{\xi_p k_B T}{2} \int ds \kappa(s)^2, \tag{1}$$

where $\kappa(s)$ is the curvature.) In addition, take a look at papers describing the structure of the nucleosome (such as Nature, **389**, 251 (1997); Nature **423**, 145 (2003); J. Mol. Bio. **319**, 1097 (2002)) and make sure that you characterize the structural features of the nucleosome that you use in your model.

(b) In class, we examined the experiments of Polach and Widom (J. Mol. Biol., **254**, 130, (1995)) which examined the equilibrium accessibility of different sites within the nucleosome as a function of the distance within the nucleosome that the DNA binding site is buried. In this part of the problem, you will reexamine the derivation of the equilibrium accessibility and explicitly compare your results with those of Polach and Widom. As I did in class, derive expressions for the fractional coverage of different sites as a function of how deeply they are buried in the nucleosome and explain in detail the arguments leading to the result. Next, derive the equilibrium constant we call $K_{eq}^{conf}(x)$ and compare your results explicitly to those from Polach and Widom. Make sure you are careful in describing the logic of reconciling the microscopic model and the description in terms of equilibrium constants. As part of the procedure to compare to Polach and Widom, you will have to fit the adhesive energy γ that I used to characterize the histone-DNA interactions.

(c) Calculate the equilibrium accessibility assuming that there is a discrete number of contacts ($N = 14$). How does it compare to the continuum model? Obtain the corresponding value of γ_{discrete} and plot the equilibrium accessibility vs. burial depth for both models simultaneously.

(d) Look at some of the binding affinities of different DNA sequences to histones reported by Lowary and Widom (J. Mol. Biol. (1998) 276, 19). As we did in class and in the last two problems, assume that the electrostatic interaction between the histone and the different DNA molecules does not vary, that it is not sequence dependent. This is equivalent to saying that the difference between each sequence lies in its flexibility, in its bending energy. What would one expect the difference in their persistence lengths to be?