1. In Figure 1 of Clackson, T. & Wells, J.A. (1995) ‘A Hot Spot of Binding Energy in a Hormone-Receptor Interface,’ *Science* 267, 383., the authors depict the change in buried surface area and the change in $\Delta\Delta G$ for alanine substitutions at different positions in the human growth hormone. The energetics of this association could be calculated from the desolvation free energy arising from the hydrophobic effect (for simple non-polar solutes), which is given by

$$\Delta G^o = \sigma \cdot A$$

where $A$ is the solute's (protein’s) accessible surface area in water and $\sigma$ is the solvation parameter, estimated to be about $-20$ to $-25$ cal mol$^{-1}$Å$^{-2}$ for water-to-hydrocarbon transfer.

(a) Calculate the $\Delta G$ for transfer of simple hydrophobic compounds and compare with the experimental measurements.

(b) What are the differences, if any?

c) If there are differences, describe which physical properties of protein associations may be contributing.


(a) What are the likely physical origins of this phenomenon?

(b) Given your understanding of protein and nucleic acid recognition, are the results likely to be identical with protein and RNA binding ligands?
3. Read the following articles:


(a) Describe the model described by Lancet et al. What are B, S, and L and what would you expect them to correspond to physically? How was the parameter α determined? Does α make physical sense as compared with the findings of Kuntz et al. (Problem 2)?

(b) Using the arguments presented in Lancet et al., describe the anticipated effect of increasing the library size in a selection. Is there some point beyond which changing the library size would be unimportant (use as an estimate a binding site containing 12 amino acids)?

(c) Ribosome display and mRNA display allow protein selection to be done entirely in vitro. Describe three potential advantages of these techniques relative to phage display.

(d) Suppose you wish to isolate all peptides that bind a monoclonal antibody combining site. The known epitope sequence is 10 amino acids long. Describe how an experiment to isolate these peptides could be performed using either phage display, ribosome display, or mRNA display. Will all the peptides be found? Explain. What if the epitope contained 6 amino acids?