1. (WC) (1) To account for the experimentally observed protein-protein interactions and also to predict new types of protein-protein interactions, a new computational methodology called “interface modeling” has been developed. Briefly describe (i) the basic assumptions, (ii) the procedure, and (iii) drawbacks of this method (15 points).

   (2) Protein-protein interactions can be modulated both kinetically and thermodynamically. For binding of a particular protein to multiple interaction partners, briefly describe how multiple interactions can be differentiated (10 points).

2. (LF) (1) For homology interface modeling, what is the 30 % rule? (10 points)

   (2) How is homology modeling done? (10 points)

   (3) Why are SH3 domains often used to test homology modeling methods? (5 points)

3. (RJK) Figure 7 describes the results of modeling the interaction of ubiquitin-like domains in complex with Ras and the Ras-like protein Rap1. Thresholds for binding and nonbinding were based on experimental binding energies for some of the interactions.

   A) The figure suggests that homology modeling with loops (7. a) is more discriminating than homology modeling of the interaction without loops (7. b).
   (1) What differences between a) and b) form the basis for this observation?
   (2) Explain why sequence differences in loop regions are more likely to affect complex formation than sequence differences in α helix or β sheet regions.

   B) The experimental binding energies (ΔH) for some of the interacting domains are indicated above the calculated free energy values. In most cases the binding energies are much smaller than the calculated energies. Provide an explanation for the difference between these values.

4. (LM) (1) Structure-based methods can predict whether two proteins interact, and in some cases, the thermodynamic or kinetic properties of the interaction. Assume that a predicted interaction between two proteins is validated by in vitro experiments. Do the proteins necessarily interact in vivo? Why or why not? (10 points).

   (2) Describe two (2) NON-structure-based methods used to predict whether proteins and/or domains interact in vivo. (15 points).