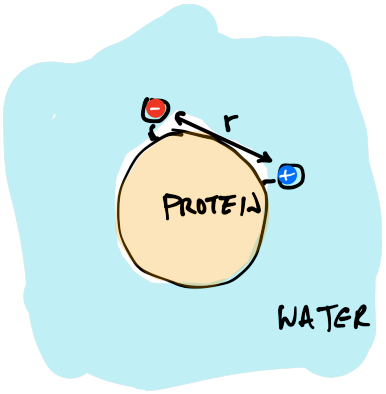
Instructions:

- Turn in your results in some kind of clear form (handwritten, typed, pdf).
- Feel free to work in groups.
- I have tried to be consistent in my language in my prompts if I want something specific.
  - *Sketch:* Hand draw a plot. Axes should be labeled conceptually, with key features indicated and explained.
  - *Generate a plot:* Plot using software. Label axes, use appropriate significant figures, etc.
  - *Calculate:* Actually calculate numbers using math. Report units and uncertainty, as appropriate.
  - *Describe/Argue:* Use any combination of writing, sketching, plotting, and calculation to argue for an interpretation.
  - Finally, I will sometimes specify the sort of explanation I want.
    - *Molecular*: Describe what the atoms and molecules are doing in space and time. Depending on the context of the question, this might also involve explaining the result in terms of atomic properties like hydrophobicity.
    - *Energetic*: Describe in energetic terms (entropy, free energy, statistics).
    - *Mathematical*: Answer in terms of how the functions behave. For example, if I asked "mathematically, why does $Kx/(1+Kx)$ saturate with increasing x" the answer would be: "because as $x \to \infty$, $Kx \gg 1$ and the function tends to 1."
- Some of the questions may require you to play with math and/or ideas we did not explicitly discuss in class. This is intentional. Many times in science you will be faced with a paper that uses an approach you are not familiar with. Learning how to gather enough information to critically evaluate their findings, as well as understand any mathematical models employed, is important.
- Some questions are listed as **GRAD STUDENT** questions. Undergrads are free to do those questions, but it is not required.

4 Structure-based calculations

1. Estimate the strength of the Coulomb interaction between the charged amino acids shown in the diagram below. In a crystal structure of the protein, you find $r = 7$ Å. Please justify any assumptions you make when doing this calculation.



2. You are studying the movement of ions through a bilayer at $pH = 7.0, T = 298\ K$. You are investigating ammonium ions, which have the following characteristics:

$$NH_4^+ \rightleftarrows NH_3 + H^+$$

$$pK_a = 9.4$$

$$r_{ion} = 1.43\ \text{Å}$$

   (a) Estimate the energy required to transfer a positively charged charged amino group from water to the center of a bilayer. You may assume $\varepsilon_{bilayer} = 2$ and $\varepsilon_{water} = 80$.

   (b) You measure the transfer energy and find that it takes 24 $kJ \cdot mol^{-1}$. Come up with two possible explanations for any difference between what you estimated in (a) and the measured value.

   (c) You repeat the transfer experiment at different pH values and find the following:

pH	$\Delta G_{H2O \rightarrow bilayer}$
8.0	18.3 $kJ \cdot mol^{-1}$
7.0	24.0 $kJ \cdot mol^{-1}$
6.0	29.7 $kJ \cdot mol^{-1}$
5.0	35.4 $kJ \cdot mol^{-1}$

   Can you explain these results mechanistically?

   (d) Predict $\Delta G_{H2O \rightarrow bilayer}$ at pH 3 and pH 11.

3. Both $\Delta G_{coulomb}$ and ΔG_{born} use dielectric constants.

   (a) What does a dielectric constant measure?

   (b) Why, molecularly, is the dielectric constant of oil ($\varepsilon_{oil} \approx 2$) lower than water ($\varepsilon_{water} = 78.5$)?

   (c) If you lyophilize a water-soluble protein (e.g. dry it out almost completely), it has a dielectric constant of $\varepsilon_p \approx 4$. What does this tell you about the chemical features of protein molecules?

   (d) Why might it be difficult to map this "bulk" dielectric constant back to individual protein molecules?

4. Proteins often bury ion pairs in active sites. We are going to explore whether this is favorable or not.

(a) Derive an equation that expresses the electrostatic component of the energy to transfer an ion pair from water to the protein interior ($\Delta G^{\circ}_{transfer}$). This will be a function of the system dielectric constants (ε_{water} and $\varepsilon_{protein}$), the charge on each ion (q_i and q_j), the radius of each ion (r_i and r_j) and the distance between the centers of mass for each ion (r_{ij}). You may ignore the effects of salt in this analysis.

(b) Create three plots, all as a function of the protein dielectric constant ε_p: ΔG°_{born}, $\Delta G^{\circ}_{coulomb}$, and $\Delta G^{\circ}_{transfer}$. You may assume that $\varepsilon_{water} = 78.5$, $q_i = 1$, $q_j = -1$, $r_i = r_j = 2$ Å, and that $r_{ij} = 3$ Å.

(c) Does the Coulomb interaction *ever* fully offset the desolvation penalty? Whatever your answer: can you justify this result molecularly?

5. Estimate the strength of the homodimer interface for the protein $\beta B1$ crystallin (PDB ID: 1OKI).