PhD Entrance Examination
Physics and Chemistry of Biological Systems
March 2022

IMPORTANT GUIDELINES

- Solve **three** of the following problems.
- No extra credit is given for attempts to solve more than three problems.
- Do not write your name on the problem sheet nor use any mark that can identify you, as this would invalidate your exam.
- Write out solutions clearly and concisely. State each approximation used. Diagrams welcome.
- Number page, problem, and question clearly.
- All essays/solutions should be written in English.

Exercise 1

Consider one circular particle of radius R in *two dimensions* surrounded by $N \gg 1$ circular particles of radius $r < R$. The large particle is *impenetrable* to the smaller ones, while the interactions between the small particles are negligible. The particles are placed inside a container of total area $= A \gg R^2 > r^2$, and the total temperature of the system is $= T$.

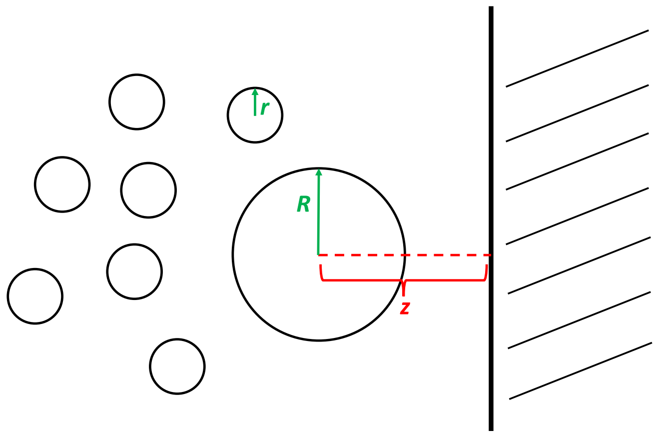


Figure 1:

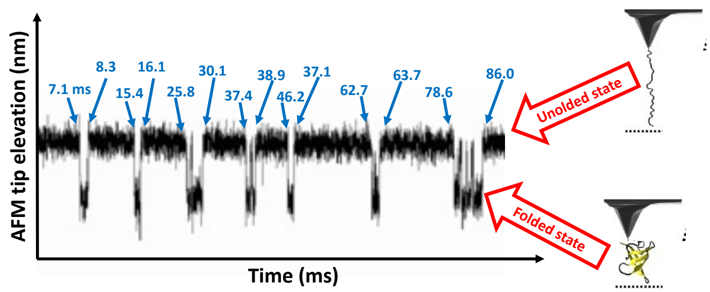
1. Derive the expression for the *configurational* free energy $\mathcal{F} = \mathcal{F}(z)$ of the system as a function of the distance z of the center of the large particle from one wall of the container (Fig. 1). Sketch a plot of $\mathcal{F}(z)$.

2. Explain why the large particle is effectively attracted towards the wall, and find the expression of the corresponding force.

3. Discuss (qualitatively) how the force at point (2) changes if the large and small particles interact via a soft potential, instead of the hard core one.

Exercise 2

The trace in Figure has been recorded in an Atomic Force Microscopy (AFM) experiment, in which one terminus of a protein is linked to a substrate (dashed line in the cartoons), and the other is linked to the AFM tip. The AFM records the distance of the tip from the substrate as a function of time. In the time of the experiment the protein undergoes 7 transitions between the unfolded state (large distance) and the unfolded state (small distance).



1. Using the time of the transitions between the folded and the unfolded states, labeled in blue in Figure, estimate the probability of observing the system in the folded state.

2. Estimate the unfolding time, and compute the statistical confidence of this estimate.

3. The experiment has been performed at a temperature $T = 370$ K. The trace can be used to estimate approximately the *folding temperature* T_f of the protein, namely the temperature at which the folded and the unfolded states are observed with equal probability. Choose one of these three options and justify your choice: (a) $T_f \simeq 390$ K ; (b) $T_f \simeq 330$ K; (c) $T_f. \simeq 370$ K.

Exercise 3

A protein is diluted in an aqueous buffer.

At 298 K the enthalpy of the system with the protein folded (with reference to an arbitrary but defined state) is computed by molecular dynamics simulation at constant standard pressure and is found to be $H^f_{298} = -109$ kcal/mol and its constant pressure heat capacity is $c^f_p = 6.9$ cal/(mol K).

At the same temperature and pressure the enthalpy of the system with the protein unfolded is $H^u_{298} = -54$ kcal/mol and its constant pressure heat capacity is $c^u_p = 8.4$ cal/(mol K).

Assume both heat capacities approximately constant in the range of temperature considered.

The temperature of melting could not be determined but is assumed to be between T=350 and T=370 K.

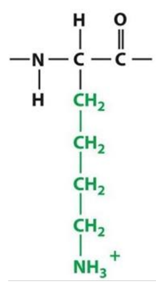
1. Estimate the range of the entropy of melting at 298 K.

2. Assume the temperature of melting is 355 K. Express the free energy of melting as a function of the temperature. For the parameters found describe the thermodynamics of melting (enthalpy, entropy and other features).

(Hints: i) Due to the limited range of temperature it is possible to use approximations. ii) It is useful to refer all quantities to the given melting temperature).

Exercise 4

The following question considers the molecular interactions associated with the thermodynamics of the amino acid Lysine in biological settings. Lysine consists of a side chain that has both a hydrophobic tail made up of hydrocarbons as well as a positively charged group at pH=7 illustrated below:



Answer the following questions showing as much of your work/thinking:

1. What types of molecular interactions occur between the CH2 groups and the surrounding water? Compare the strength of these interactions to thermal energy $k_B T$.

2. What types of molecular interactions occur between the positively charged NH_3 group and surrounding water? Compare the strength of these interactions to thermal energy $k_B T$.

3. The Born free energy difference associated with moving a charge q with radius r from a medium with dielectric constant ϵ_1 to ϵ_2 is given by: $\Delta G = \frac{333}{2r} q^2 (\frac{1}{\epsilon_2} - \frac{1}{\epsilon_1})$. Use this fact to explain whether you expect to find Lysine on the surface of the protein (exposed to the solvent) or in the center of the protein in the hydrophobic core. If it helps, consider a positive charge ($q = 1$) with radius 2Å, and with $\epsilon_1 = 80$ for water and $\epsilon_2 = 10$ for the center of a protein.

Exercise 5

A protein can be found in three states: folded (F), unfolded (U) and intermediate (I). The free energy of the F, U, and I states are 0 kJ/mol, 1.7 kJ/mol, and 4.5 kJ/mol, respectively. Assume the Boltzmann constant to be 8.31 $\times 10^{-3}$ kJ/(mol K) and the temperature to be $T = 300$ K. The gyration radius of the F and I states are identical and equal to $R_{g,FI}$=15 Å.

1. Compute the population at equilibrium for the three states F, U, and I.
2. Using SAXS experiments you find out that the root mean square value of the gyration radius is $R_g = 17 \pm 1$ Å. Compute the gyration radius of the U state $R_{g,U}$ along with its uncertainty, assuming that the free energies of the three states and the gyration radius of the F and I states are known exactly.
3. Now assume that also the gyration radius of F and I states are provided with an uncertainty, $R_{g,FI} = 15 \pm 1$ Å, though they are known to be exactly identical. Compute the resulting uncertainty on the gyration radius of the U state $R_{g,U}$.

Exercise 6

A one-dimensional system of harmonic oscillators.
Consider a one-dimensional system of three harmonically-coupled particles described by the potential:

$$U = \frac{k}{2}\left[(\delta x_1 - \delta x_2)^2 + (\delta x_2 - \delta x_3)^2 + (\delta x_1 - \delta x_3)^2\right]$$

where δx_i is the displacement of the ith particle from its reference position and k is the harmonic spring constant.
Assume that the middle particle is constrained in its reference position, $\delta x_2 = 0$, and that the system is in canonical equilibrium at temperature T.

1. Compute the canonical expectation value of the potential energy, $\langle U \rangle$.
2. Compute the mean squared value of the displacement of particle 1, $\langle \delta^2 x_1 \rangle$.
3. Repeat the calculation of $\langle U \rangle$ when the constraint $\delta x_2 = 0$ is removed and, instead, the center of mass of the system is kept fixed in space.