Date: Thursday, November 9

Instructions: You may utilize notes and problem set solutions (both your solutions and the posted solutions). You may not, however, discuss the problems with others.

Problem 1:	/	12
Problem 2:	/	15
Problem 3:	/	16
Problem 4:	/	30
Problem 5:	/	27
Total:	/	100

Equations you may find useful:

$$1 = \int_{-\infty}^{\infty} dx\, \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$$

$$\mu = \int_{-\infty}^{\infty} dx\, \frac{x}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$$

$$\sigma^2 = \int_{-\infty}^{\infty} dx\, \frac{(x-\mu)^2}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$$

$$P(\nu) = \frac{e^{-\beta E(\nu)}}{Q(\beta)} \quad \text{[Canonical]}$$

$$S = k_{\mathrm{B}} \ln \Omega$$

$$-\beta A = \ln Q \quad \text{[Canonical]}$$

$$\beta = \frac{1}{k_{\mathrm{B}} T} = \frac{1}{k_{\mathrm{B}}} \left(\frac{\partial S}{\partial E}\right)_{N,V}$$

$$C_V = \left(\frac{\partial \langle E \rangle}{\partial T}\right)_{N,V}$$

$$Q(\beta) = \sum_{\nu} e^{-\beta E(\nu)} \quad \text{[Canonical]}$$

$$\ln n! \approx n \ln n - n$$

$${}_M C_N = \frac{M!}{N!(M-N)!}$$

1. **System size scaling. [12 pts.]** For each of the following, identify the dependence on N. Answers should be in the form of a proportionality. For example, you might answer that the object is proportional to N, proportional to $\ln N$, proportional to 1, or proportional to some other function of N. (Saying something is proportional to 1 is another way of saying there is no N dependence.) For full credit, also provide a brief rationale for each answer.

   (i) The number of classical microstates for N particles to be arranged in a box of size V with energy E: $\Omega(N, V, E)$. **[2 pts.]**

   [Hint: You may want to subdivide the system into M independent cells, each with volume v, density $\rho = N/V$, and energy density $\epsilon = E/N$. Let the number of microstates of one such cell be $\tilde{\omega}$. Your answer will involve $\omega = \tilde{\omega}^{1/\rho v}$.]

   (ii) The entropy of a material with N particles in a volume V with energy E: $S(N, V, E)$. **[2 pts.]**

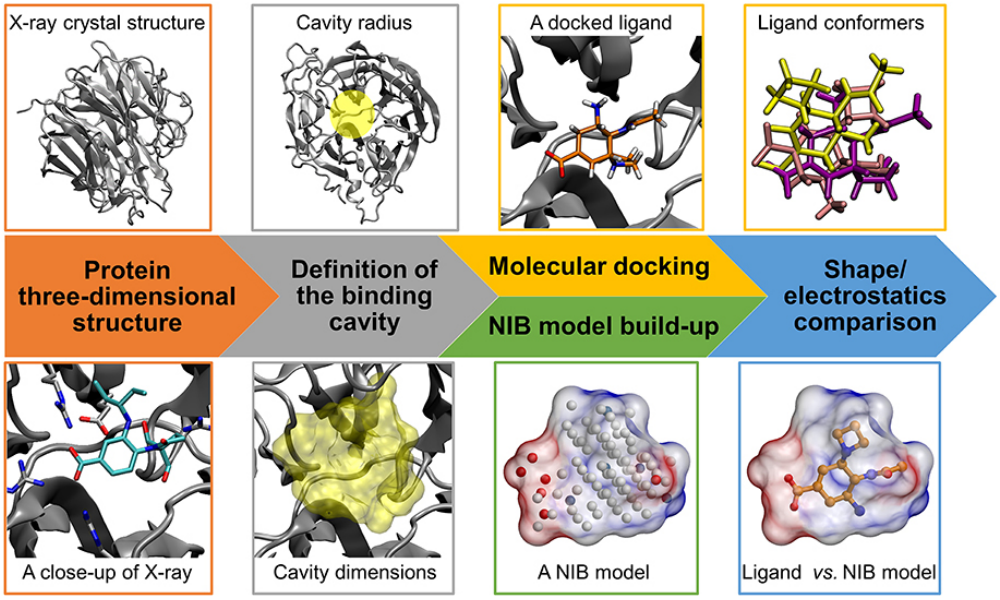
   (iii) The Gibbs free energy of a material with N particles kept at pressure p and temperature T: $G(N, p, T)$. **[2 pts.]**

   (iv) The inverse temperature of a N-particle bath of volume V: $\beta = \frac{1}{k_B}\left(\frac{\partial S}{\partial E}\right)_{N,V}$. **[2 pts.]**

   (v) The mean squared length between endpoints of a **one**-dimensional lattice polymer: $\langle R^2 \rangle$. As you hopefully recall from homework, each bond of the lattice polymer is equally likely in all directions, irrespective of the other bonds. For a one dimensional polymer that means steps left and right, each occur with probability $1/2$. **[2 pts.]**

   (vi) The mean squared length between endpoints of a **three**-dimensional lattice polymer: $\langle R^2 \rangle$. Each bond is still independent of the others and each of the six directions is still equally likely. **[2 pts.]**

2. **Protein-ligand binding. [15 pts.]** The pharmaceutical industry routinely wrestles with the challenge of identifying small molecules which can act as drugs by binding to disease-related proteins. For decades they have used computers to help screen through candidates of potential drugs. A common approach to such screens, known as docking, is summarized in the following picture:



Briefly, the idea is to take the structure of a frozen protein from a crystal, understand the shape and charge distribution around some binding pocket (cavity), then computationally try to fit different ligands into that pocket. The picture refers to that last step as "shape/electrostatics comparison".

You can perhaps imagine that powerful quantum chemistry techniques like density functional theory could be used to compute the energy for the protein configuration in the presence of the ligand, and you could seek ligands which minimize that energy. That approach makes me a little uncomfortable because it has "integrated out" all of the solvent degrees of freedom. My stat mech upbringing makes me worried that ignoring the solvent could cause problems.

To make me feel more comfortable, Roel proposes that he could offer me a computer big enough to explicitly include the solvent. He says that if I can provide him with a microstate (a configuration of the protein, ligand, and surrounding solvent molecules), he could compute for me the energy of that microstate. He suggests I could identify ligands that bind tightly to the protein by looking for ligands with a low microstate energy.

Explain why computing those microstate energies does not fully indicate whether a drug will be likely to bind to the cavity. A good answer will *discuss* the issue(s) in a paragraph or two. You may even be able to indicate how Roel's capabilities could be useful as a piece of a more complete approach. Feel free to use analogies, plots, drawings, or any other tools that help you make your point(s) more clearly.

[The next page is blank to provide room to answer, but I do not expect you to need the whole page.]

3. **Fluctuating energy and particles. [16 pts., 2 pt. each]** Imagine a system surrounded by a rigid, permeable wall. This system can exchange both energy and particles with a much larger reservoir which has an inverse temperature β and a chemical potential μ. Fill in the following blanks in the description of this ensemble.

   The equilibrium probability for microstate ν is

$$P(\nu) = \begin{cases} \dfrac{\exp\left(-\beta E(\nu) + \boxed{}\right)}{\Xi\left(\boxed{}\right)}, & \text{if } \boxed{} \\ 0, & \text{otherwise,} \end{cases}$$

   where

$$\Xi = \sum_{\nu \text{ with } V(\nu)=V} \exp\left(\boxed{}\right).$$

   Various Legendre transforms of the internal energy yield thermodynamic potentials. A list of such transformations includes: $E, A = E - TS, G = E - TS + pV, H = E + pV, \mathcal{F} = E - \mu N, \Phi = E - TS - \mu N, W = E + pV - \mu N$. The partition function Ξ can be connected to one of these thermodynamic potentials as

$$-k_{\mathrm{B}}T \ln \Xi = \boxed{}.$$

   Let us call that thermodynamic potential ☹ (so as not to give away the previous answer). A small change in ☹ could be related to small changes in the three natural variables as

$$d☹ = \boxed{\_d\_ \quad \_d\_ \quad \_d\_}$$

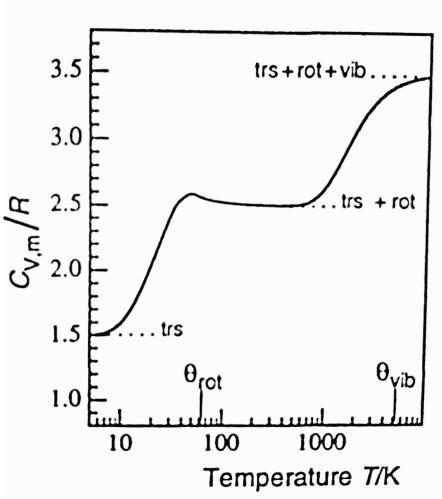
   The partition function can furthermore be used as a generating function. The first two derivatives yield

$$\left(\frac{\partial \ln \Xi}{\partial(\beta\mu)}\right)_{T,V} = \boxed{}$$

   and

$$\left(\frac{\partial^2 \ln \Xi}{\partial(\beta\mu)^2}\right)_{T,V} = \boxed{}.$$

4. **Heat capacity. [32 pts.]** The heat capacity per mole of a diatomic gas, HD, is plotted below in terms of the gas constant $R = N_{\mathrm{A}} k_{\mathrm{B}}$, with N_{A} being Avogadro's number.



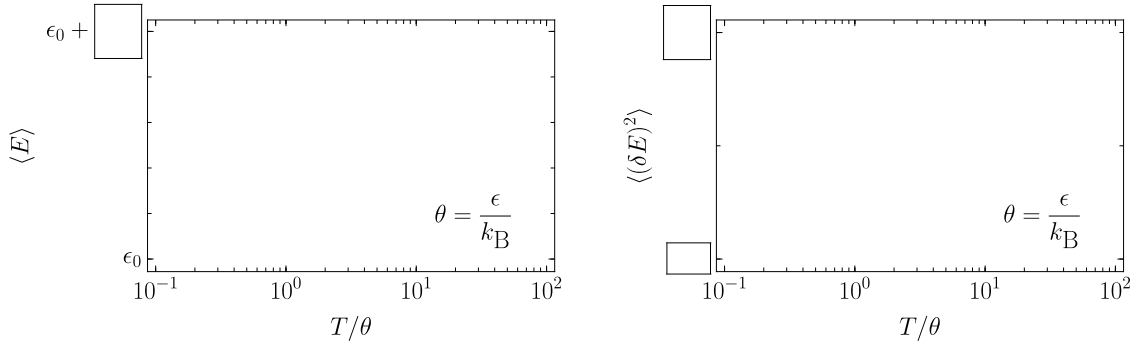
Based on the labels and your chemical intuition, you see that as you move to higher temperatures you "unlock" higher energy states. At low temperatures the molecules have translational motion but are stuck in the ground rotational and vibrational states. At a high enough energy, the rotational excitations start to become relevant, and at a still higher temperature the vibrations also influence the heat capacity.

Todd tries to claim that the HD heat capacity should be simple to understand—the heat capacity should go up the more microstates you unlock. You point out to him that the behavior around $T = \theta_{\mathrm{rot}}$ seems to contradict his simplistic explanation.

The population of the excited states will monotonically increase as temperature increases, but the heat capacity has a peak! This problem will help you convince Todd that a non-monotonic heat capacity is not a concern (and indeed could have been anticipated quite simply).

(i) The two-state model you studied in Problem Set 6 is a good starting point. Remember, that model has only two possible energy levels that differ in energy by ϵ. Demonstrate that the probability of the excited state in the two-state model increases monotonically with temperature. **[5 pts.]**

(ii) *Roughly sketch* plots of average energy $\langle E \rangle$ and of fluctuations in energy $\left\langle \delta E^2 \right\rangle$ for the two-state model. Fill in the boxes to label the axes with the correct limiting behavior. In case it is not obvious, when I ask for a rough sketch, I'm paying attention to a few distinguishing features like: does it go up, does it go down, what are the low-temperature limits, what are the high-temperature limits, how many peaks does it have, where are the peaks, etc. **[8 pts.]**



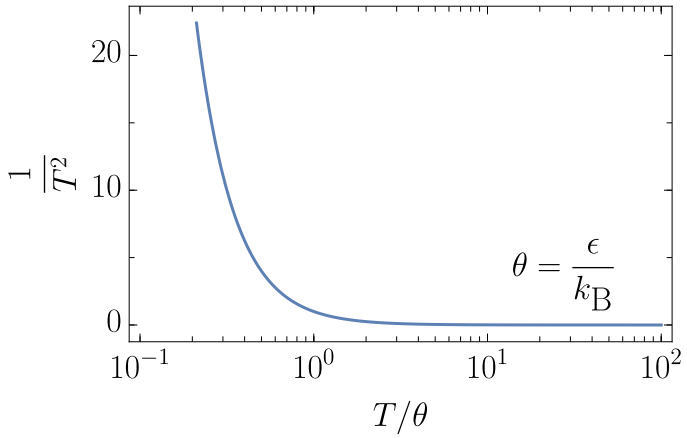
(iii) Derive the two-state model's heat capacity:

$$C_V = \frac{\epsilon^2 e^{-\epsilon/(k_\mathrm{B}T)}}{k_\mathrm{B}T^2 \left(1 + e^{-\epsilon/(k_\mathrm{B}T)}\right)^2}.$$

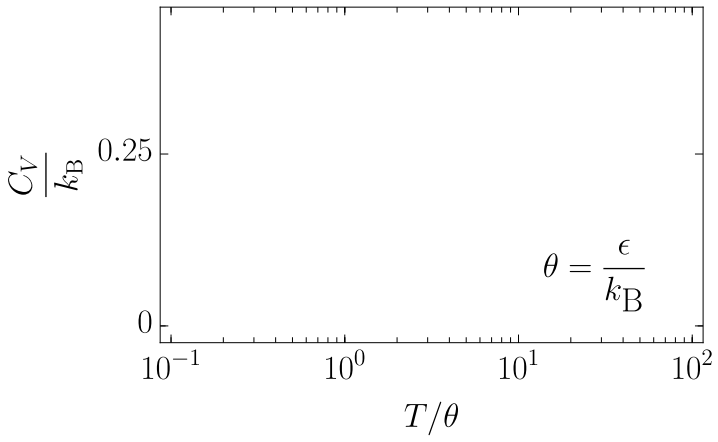
Don't be shy about including some sentences that explain what you are doing in each step. **[5 pts.]**

(iv) Combine results from parts (ii) and (iii) to express C_V in terms of k_B, T, and one or more cumulants of energy. **[3 pts.]**

(v) Use your answers to (ii) and (iv) to *roughly sketch* C_V. In making your sketch, you will probably find it useful to also think about the plot of $1/T^2$:



Do not worry about matching up the height of the y axis. Take it as given that I have put it on a reasonable scale so that your plot should fill up the space. **[4 pts.]**



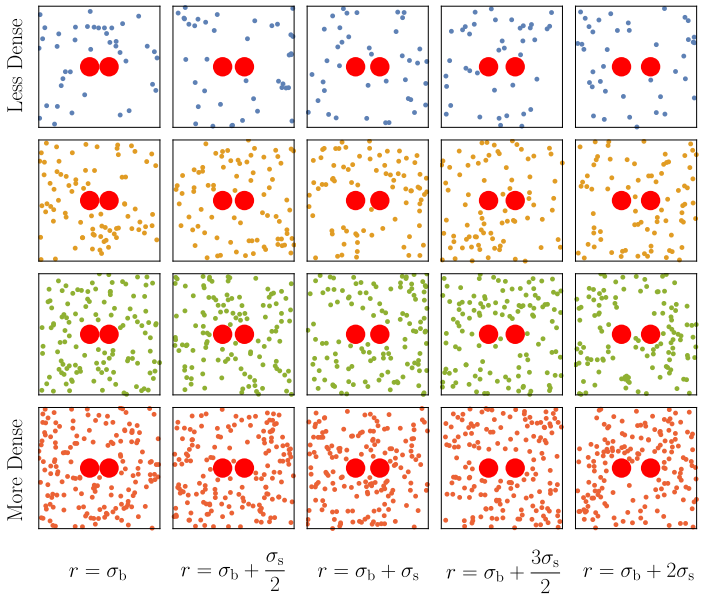
(vi) Hopefully by now your work has convinced me that the heat capacity can have non-monotonic features. But your work with the two-state model does not look exactly like the HD heat capacity. One difference is that the HD heat capacity jumps up multiple times; we can easily understand that difference as having to do with new classes of motion (rotations and vibrations) which are unlocked at higher temperatures. The bigger difference is that the high temperature limits do not seem compatible. The HD heat capacity per mole plateaus at 3.5 k_{B} while your two-state model heat capacity has a different limit. Explain the origin of the difference. **[5 pts.]**

5. **Hard Spheres. [27 pts.]** This year's Nobel Prize in Chemistry was awarded for quantum size effects, including in colloidal nanoparticles. While much of the interest in those colloidal nanoparticles has focused on their optical properties, it is also been interesting to consider how multiple colloids interact with each other. As roughly spherical crystals, you might reasonably approximate a nanoparticle as if it is just a "hard sphere". Like billiard balls, such a model would express (a) that is is impossible for two nanoparticles to overlap each other and (b) that two nanoparticles separated by a gap do not exert forces on each other. Mathematically, one would express these facts with the pair potential:

$$V(r) = \begin{cases} \infty, & r < \sigma \\ 0, & r > \sigma, \end{cases}$$

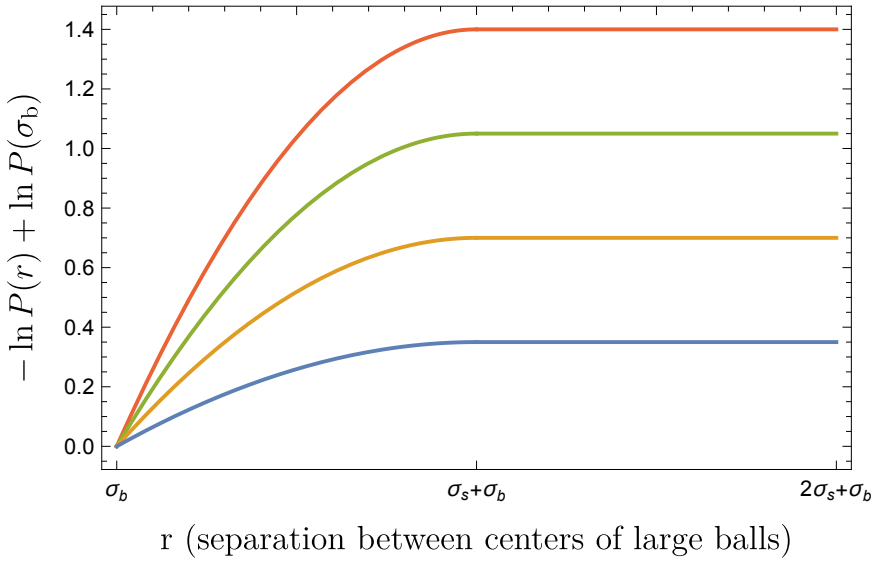
where r is the distance separating the center of the two spheres and σ is the diameter of the spheres. Models of hard spheres are most natural in two dimensions (hard disks) or three dimensions (hard spheres), though sometimes they're even considered in higher dimensions. In this problem, we will discuss an important statistical mechanical consideration for how two nanoparticles can interact in two-dimensional space.

We already said that when the two nanoparticles are separated by $r > \sigma$, they are not touching, so they don't really exert forces on each other. Suppose, however, that I put the hard disks in a solution of other smaller disks. To keep track of the difference, I will now call my comparatively big "nanoparticle" disk diameter σ_b and my comparatively small "solvent" disk diameter σ_s. The following picture gives you a sense of what configurations of the red nanoparticles look like in the solution of small solvent disks (colored by solvent density). Along the x axis I am adjusting the separation between the nanoparticles and along the y axis I am adjusting the density of the solvent particles.



Recall that we learned that it is much easier to work with models that have non-interacting particles, so let us treat the solvent as if each solvent disk is non-interacting with each other. In other words, multiple solvent disks can overlap each other (they are essentially an ideal gas). *However*, the solvent disks are assumed to still be hard with respect to the nanoparticles–small disks and large disks cannot overlap. The beauty of this simplification is that the impact of the solvent on the nanoparticles can be considered *one solvent disk at a time* without worrying about interactions between solvent disks.

(i) It is possible to exactly compute an NVE probability of each microscopic configuration, and to marginalize that distribution to get the probability $P(r)$ of finding the center of two nanoparticle disks separated by a distance r:



The four different lines on the plot are color coded to match the solvent densities of the configurations on the first page. According to the plot, does the solvent density affect the probability that the nanoparticles would be touching? Why or why not? **[5 pts.]**

(ii) Suppose the nanoparticles were initially separated by a distance $\sigma_\mathrm{b} + \sigma_\mathrm{s}$. How much reversible work would I need to apply to separate them further? Does your answer depend on the solvent density? Justify both answers. **[5 pts.]**

(iii) Suppose the nanoparticles were initially touching each other and you wanted to pull them apart. Describe how one would use the plot to determine the equilibrium mean force you would need to apply to pull them apart. Without solvent, the force would have been zero. The nonzero force in the presence of solvent is an example of a "fluctuation-induced effective force" that emerges. The two nanoparticles do not *directly* exert force on each other, but due to interactions with the solvent they *effectively* do exert force. **[5 pts.]**

(iv) Give an entropic argument to explain why the density of the solvent impacts the amount of reversible work it would take to separate the initially touching particles. [Hint: I am not merely asking you to use the plotted $P(r)$ here; I am asking of a physical argument you could have given even without seeing those explicit plots. The pictures of microscopic configurations may help some.] **[7 pts.]**

(v) Suppose a new Mirkin group member asks you how to make their nanoparticles stick together without altering the nanoparticles. Now that you've worked through this problem, you suggest introducing some polystyrene beads that are even smaller than the nanoparticle. Does this hard sphere model provide insight you can share with them about the temperature-dependence of the effective force between nanoparticles? If so, what is the insight? If not, why not? **[5 pts.]**