

BE 25 Winter 2025

Homework #5

Due at 9 AM PST, February 18, 2025

Problem 5.1 (A concave entropy, 10 pts).

Prove that the entropy

$$S = -k_B \sum_i p_i \ln p_i \quad (5.1)$$

is a concave function of the probabilities $\mathbf{p} = \{p_1, p_2, \dots\}$. What implications does this concavity have on the probability distribution(s) that maximize(s) entropy?

Problem 5.2 (Boltzmann's grave, 10 pts).

Consider a system where each microstate has the same energy. Show that the partition function Ω of such a system is equal to the number of microstates. Show further, starting with the Gibbs entropy, that $S = k_B \ln \Omega$. This equation is on Boltzmann's grave, except written as $S = k \log W$.

Problem 5.3 (Gibbs's inequality and entropy under constraints, 25 pts).

In this problem we will prove two key results, the Gibbs inequality and that any additional knowledge decreases the entropy.

a) Let p_i and q_i be discrete probabilities of states indexed with i , naturally with

$$\sum_{i=1}^N p_i = \sum_{i=1}^N q_i = 1. \quad (5.2)$$

The quantity

$$D_{\text{KL}}(p||q) = \sum_{i=1}^N p_i \ln \left(\frac{p_i}{q_i} \right) \quad (5.3)$$

is referred to as the **Kullback-Leibler divergence**. The fact that $D_{\text{KL}}(p||q) \geq 0$, with equality only when $q_i = p_i$ for all i is called **Gibbs's inequality**. Prove Gibbs's inequality. You may take Jensen's inequality as given in your proof.

b) Imagine we know a quantity x_i about each state i and we have a well-defined expectation

$$\langle x \rangle = \sum_{i=1}^N p_i x_i. \quad (5.4)$$

Prove that knowing about x_i necessarily increases the entropy, provided not all of the x_i are equal.

Problem 5.4 (Disulfide linkages in ribonucleases, 30 pts).

This problem is heavily based on a problem written by Doug Rees.

Christian Anfinsen won the Nobel Prize in Chemistry in 1972 for his work on ribonuclease. He learned that disulfide bonds in the enzyme were crucial for its function. His clever insight for his experiment was that the native state of ribonuclease could be recovered after unfolding the protein by reducing the disulfides, and then re-folding the protein under oxidizing conditions to yield nearly 100% active protein with the proper disulfide bonds.

In his 1972 Nobel Prize address, he said (emphasis added):

“Many others, including Anson and Mirsky in the '30s and Lumry and Eyring in the '50s, had observed and discussed the reversibility of denaturation of proteins. However, the true elegance of this consequence of natural selection was dramatized by the ribonuclease work, since the refolding of this molecule, after full denaturation by reductive cleavage of its four disulfide bonds, required that *only one* of the 105 possible pairings of eight sulfhydryl groups to form four disulfide linkages take place.”

Stanford Moore and William Stein (who shared the Nobel Prize with Anfinsen), figured out specifically which disulfide bonds formed. Labeling cysteines residues as A: 26, B: 40, C: 58, D: 65, E: 72, F: 84, G: 96, and H: 110, they found that the disulfide bonds were A-F, B-G, C-H, and D-E. As Anfinsen said, to get refolding, *only* this configuration works.

- If each of the 105 configurations of disulfide bonds has the same energy, what is the probability that a given refolded protein has the Moore-Stein configuration of disulfide bonds?
- Assuming all 104 configurations that are *not* the Moore-Stein configuration have the same energy, what must the energy difference be between the Moore-Stein configuration and each of the other 104 configurations in order to have 99% of the folded ribonucleases in the Moore-Stein configuration? What do you think about the magnitude of this energy difference?
- How many possible disulfide configurations are there for an even number n cysteines and $n/2$ disulfide bonds? Repeat part (b), say, for $n = 16$, which is twice as many disulfide bonds as in ribonuclease.

Problem 5.5 (Patch clamp experiments, 25 pts).

In a patch clamp experiment, current flowing through a single ion channel in a cell membrane may be measured. Furthermore, a voltage may be applied across the

membrane to provide a driving force for ion current. Traces from patch clamp experiments look like those below, which were taken for a sodium channel.

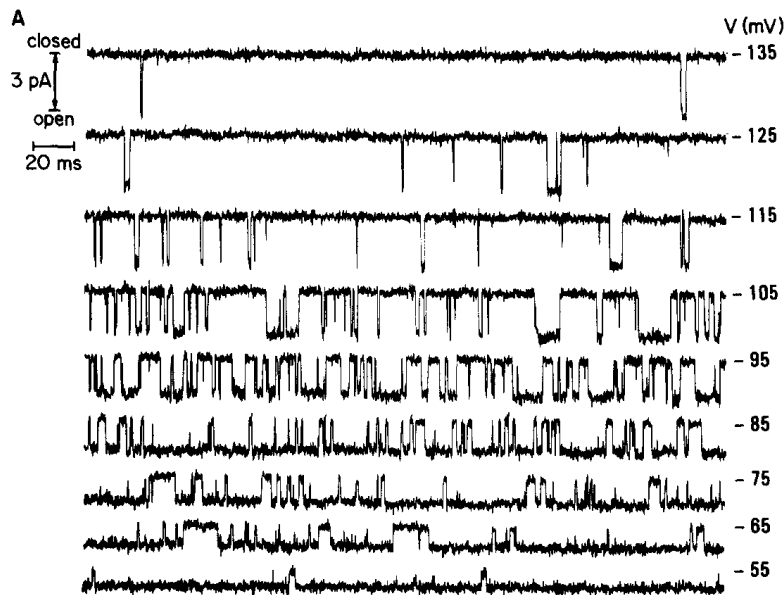


Figure 1: Current (vertical axis) versus time (horizontal axis) for patch clamp experiments for various applied voltages. Taken from Keller, et al., *J. Gen. Physiol.*, 88, 1–23, 1986.

From the traces, we clearly see two states, an open state where current flows through the channel, and a closed state where it does not. By analyzing the traces, one may calculate the probability that a channel is open as

$$p_{\text{open}} \approx \frac{\text{time open}}{\text{time closed}}. \quad (5.5)$$

In the above traces, for low-magnitude applied voltage ($V = -55$ mV), the probability of being open is high, and for high-magnitude applied voltage ($V = -135$ mV) the probability of being open is small. Let $\Delta E = E_{\text{open}} - E_{\text{closed}}$ be the energy difference between an open and a closed state. Assume that we can write ΔE as a linear function of applied voltage, V . Derive an expression for p_{open} as a function of voltage and sketch a plot of p_{open} versus V . Eyeballing the traces above, does the function to derived and sketch jibe with the experimental measurements. (You will not be able to compare quantitatively; just check to see if what you derived is roughly consistent.)