CH163: HW5

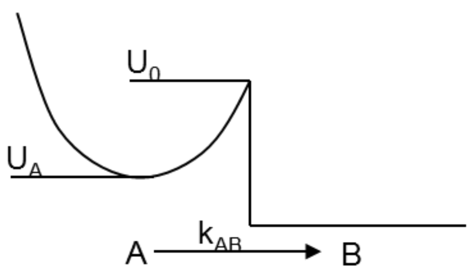
Due 10/28/2022 (5 pm)

1) Final Project

Write down one (or more) ideas for topics for the final project. For each idea, look up a few references on the subject. Email your ideas and list of references to Ryan and to Adam. If you unsure what to do, we are both happy to discuss possibilities with you.

Problem 2) Kramers theory for a kinked well

Consider the following potential:



This is a good approximation for a particle that is harmonically bound, but beyond a certain displacement can break free.

In class we derived a formula for the rate going from *A* to *B* in terms of the curvatures of the potential at *A* and at the transition state. In this example, the potential is kinked at the transition state so the curvature there is undefined. But the transition rate should still be finite. Derive an expression for k_{AB} for this potential. (hint: model your calculation on the derivation we did in class, but approximate the potential as decaying *linearly* at the transition state, rather than quadratically). Let α be the spring constant, and κ be the slope of the potential approaching the transition state.

Problem 3) Temperature-sensing ion channels

Humans have a remarkably good sense of heat: we can easily distinguish temperature changes as small as 0.1 °C. What choices would you make about ΔS^0 and ΔH^0 for the opening transition if you were designing a very temperature-sensitive ion channel? Here is an article for guidance:

Clapham, David E., and Christopher Miller. "A thermodynamic framework for understanding temperature sensing by transient receptor potential (TRP) channels." Proceedings of the National Academy of Sciences 108.49 (2011): 19492-19497.

Problem 4) Balance of electrical and chemical energies

The *E. coli* antiporter NhaA exchanges two H^+ ions for one Na^+ ion and is important for maintaining a low intracellular sodium concentration in this species.

Write an expression for the reversal potential of this transporter in terms of pH_{in}, pH_{out}, $[Na^+]_{in}$ and $[Na^+]_{out}$.

What is the relation of the reversal potential of the transporter, to the reversal potentials of H^+ and $[Na^+]$ individually?

E. coli typically have an intracellular pH of ~7.5, but they can live in the human gastrointestinal tract where the external pH is as low as 5. The sodium concentration in an *E. coli* is typically ~5 mM and the sodium concentration outside is ~100 mM. At what membrane potential will H^+ and Na^+ exchange be in equilibrium?

You can read more about electrogenic exchangers and pumps here:
Cohen, Adam E., and Veena Venkatachalam. "Bringing bioelectricity to light." Annual review of biophysics 43 (2014): 211-232.

Problem 5) Some simple parameters for electrophysiology

a) Estimate the capacitance per unit area of cell membrane. The formula is:

$$C = \frac{\epsilon \epsilon_0 A}{d}$$

where ε is the dielectric constant of lipid (~3), ε_0 is the permittivity of free space (8.85 x 10^{-12} F/m), A is the surface area, and d is the thickness. What is the capacitance of a typical Eukaryotic cell with diameter 10 μm?

b) Typical membrane voltages are of order ~100 mV. How big is the electric field in a cell membrane? Compare to the dielectric strength of air, i.e. the electric field required to initiate a spark, as in a lightning bolt (~3 x 10^6 V/m). Does this comparison surprise you?

c) In units of k_BT at room temperature, how much work would it take to move a Na^+ ion from the inside of a cell sitting at -80 mV to the outside of the cell? What about for a Ca^{2+} ion?

d) In class, I asserted that the amount of charge that crosses the membrane to induce a change in membrane voltage is small compared to the total quantity of charge contained in the ions in the cytoplasm. Here you will test this assertion. Consider a 10 μm diameter spherical cell. How many Coulombs of charge must cross the membrane to change the membrane voltage by 100 mV? How many moles of ions is this? If these ions were distributed homogeneously throughout the cell, what would their concentration be? Compare this number to the basal concentrations of some common intracellular ions: K^+ (~140 mM), Na^+ (~5 mM), Ca^{2+} (100 nM).

e) It turns out that bacteria produce electrical spikes too (a fact that my lab discovered!).[1] If we approximate a bacterium as a 1 μm diameter sphere, what change in concentration of intracellular ions results from a change in the membrane voltage of 100 mV?

f) When we do electrophysiology, we usually model the dynamics by calculating the average number of ion channels that are open. We then calculate the mean current through these channels. We ignore the statistical fluctuations in the number of open channels. Let's see if this approximation is justified. In a neuron, the conductance of a single voltage-gated sodium channel (a Na_V channel for aficionados) is of order 10 pS (10 picoSiemens). If the sodium reversal potential is +30 mV, and the channel opens at a potential of -40 mV, what is the current through the channel? How many ions per second is this?

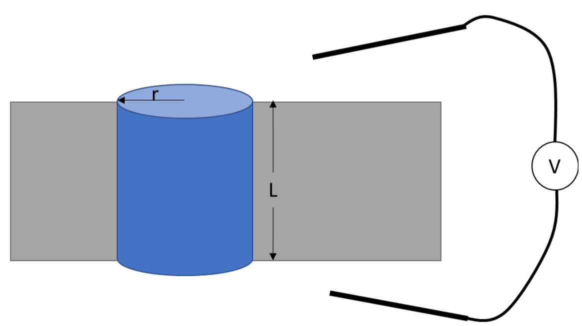
If the current through only one channel were responsible for charging our 10 μm diameter cell from -40 to +30 mV, approximately how long would this process take?

When a neuron fires an action potential, the upstroke typically lasts ~0.5 ms. Approximately how many Na_V channels must be acting in parallel to drive this upstroke? Are we justified in treating the activity of the Na_V channels in a mean-field limit, i.e. ignoring statistical fluctuations in their opening and closing?

Now consider an action potential in a bacterium (1 μm diameter sphere). Bacterial spikes have upstroke and downstroke that lasts ~1 s. How many channels must open to switch the bacterial membrane potential over this timescale? Are statistical fluctuations important?

Problem 6) Simple estimate of ion channel conductance

Here we will make a simple estimate of the conductance of a single ion channel. We will model the channel as a cylindrical pore in a membrane. Consider a cylindrical tube of radius *r* and length *L* filled with a solution containing 100 mM NaCl. A voltage *V* is applied across the faces of the tube. You can assume that the tube is long compared to its width, so the voltage at one face is *V* and the other is 0.



a) What is the electric field in the tube?

b) The diffusion coefficient of Na^+ ions in room-temperature water is approximately $D = 1.5 \times 10^{-5}$ cm^2/s. What is the relation between the voltage

[1] Kralj, Joel M., et al. "Electrical spiking in Escherichia coli probed with a fluorescent voltage-indicating protein." Science 333.6040 (2011): 345-348.

V and the mean velocity, v, of an ion in the tube? For an "ion channel" with L = 5 nm and V = 100 mV, what is v?

c) What is the formula for the total electric current, i, carried by Na^+ ions? How many ions per second, Γ, enter the cell? Estimate numerical values for i and Γ, assuming r = 0.5 nm.

d) What is the conductance of the channel?