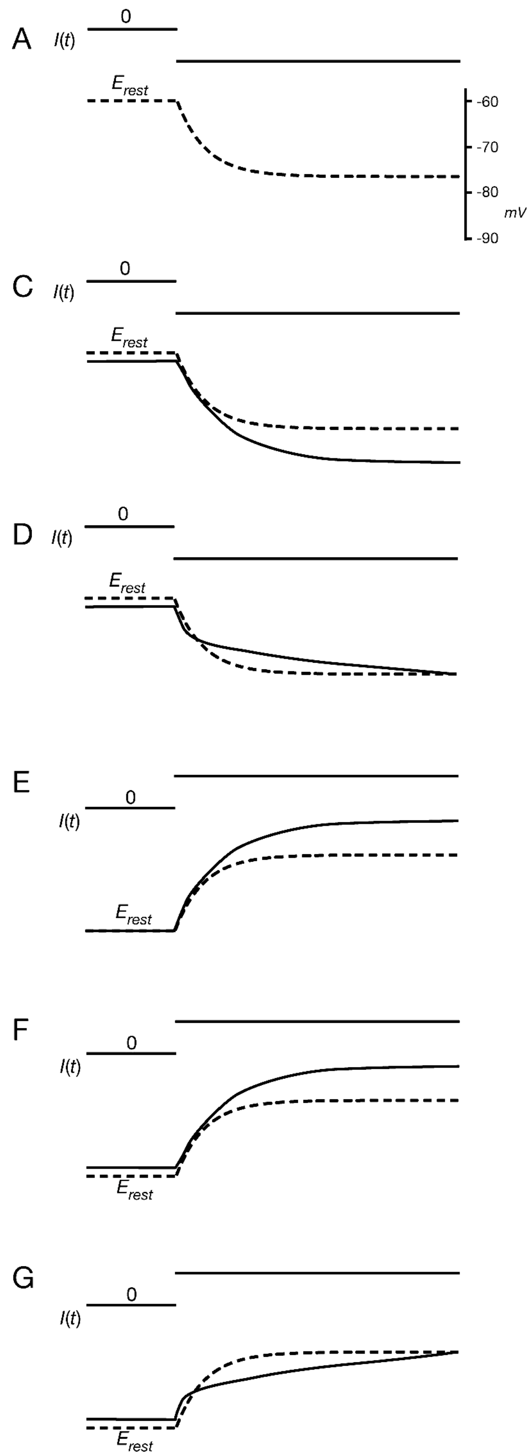
580.439/639 Final Exam

Do all problems. Closed book except for a two-page cheat sheet

Problem 1 (17 points/part)

In each example at right, a current is applied to a single node of membrane, consisting of a capacitor C in parallel with the combination of a leakage channel G_M in series with a battery E_{rest} (i.e. the standard membrane circuit, no cable properties). The resulting membrane voltage is shown along with the current. The dashed line in each case is the expected voltage with every voltage-dependent channel blocked, i.e. with only the leakage channel and the membrane capacitance. For each figure, provide a hypothesis for the channel gating that gives the membrane potential shown by the solid line. The hypothesis must consist of the ion (e.g. K^+ or Cl^-) and the Hodgkin-Huxley gating functions for the ion, e.g. $n_\infty(V)$ for the K^+ channel. Don't worry about the time constants, only the steady states. Assume the usual reversal potentials for the batteries. There may be more than one adequate answer for each part.



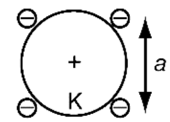
Part a) Write a differential equation for the circuit without any voltage-gated channels and derive the functional form of the dashed line for case A (this is easy, but you can't just write down the solution).

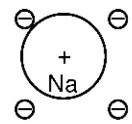
Part b) To help you work out the remaining cases, write an equation for the steady-state membrane potential with a D.C. current I applied, for the case of the leak channel plus one voltage-gated channel (the latter's conductance is assumed to be in steady state).

Parts c) – g) Tell what kind of channel could produce the solid line. This means the ion and the HH $n_\infty(V)$ gating function (sketch the latter).

Problem 2 (20 points/part)

The selectivity filter for the KCSA channel has a fourfold symmetry as sketched at right. When a K^+ ion is in the filter, it "just fits", meaning that it is symmetrically centered at the center of the four negative charges making up the corners of the filter. A fully-dehydrated Na^+ ion is smaller and so could be located somewhere other than in the center of the filter. The point of this problem is to consider the implications of the ion sizes for the free energy of the ion when located in the filter, using a (very) simplified electrostatic model. Consider only the component of the free energy of the ion due to the electrostatic attraction between the charge on the ion and the four negative charges making up the walls of the filter. This energy can be estimated as the negative of the work required to remove the ion from the filter.

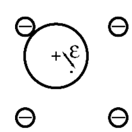




Part a) The Coulombic force between two point charges q^+ and q^- is given by $\alpha q^+q^-/r^2$ where α is a constant and r is the distance between the charges. Show that the work required to take one of the charges (say q^+) away to infinity from an initial location at distance r_0 from q^- is given by $\alpha q^+q^-/r_0$. This is the electrostatic part of the free energy of charge q^+ located at distance r_0 from fixed charge q^-.

Part b) Compute the electrostatic energy for the K^+ ion in the selectivity filter diagrammed above, assuming that the K^+ ion behaves like a point charge at its center. The length of a side of the filter is a and the K^+ ion just fits, so its center is at the center of the filter. (Hint: the energies induced by the four filter charges sum linearly).

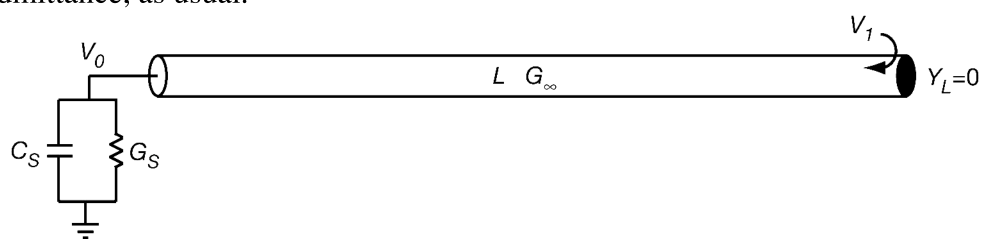
Part c) Compute the electrostatic energy for the Na^+ ion located in the same filter, with its center at a distance ε from the center of the selectivity filter, as sketched at right. It is easiest if the displacement ε is in the direction of one of the filter's charges as drawn. Again, assume that the Na^+ ion behaves like a point charge at its center. Based on the electrostatic energy of the ions, argue that K^+ is more stable in the selectivity filter than Na^+ based on this model. This problem can be made a lot easier by assuming that ε is small, so that $1/(1+\varepsilon) \approx (1-\varepsilon)$ and $\mathrm{sqrt}(1+\varepsilon)\approx 1+\varepsilon/2$, for example.



Part d) This model assumes that Na sits offset from the center of the selectivity filter as drawn in part c. Argue that this is not the minimum free-energy place for Na, based on the electrostatic energies (you already have all the calculations you need). Use the fact that Na^+ and K^+ have the same charge. What is the relevance of this final argument for the model developed in a-c above? Speculate on how the model that assumes that K^+ "just fits" the selectivity filter and Na^+ does not could be rescued.

Problem 3 (20 points/part)

Experiments over the last ten years have shown that action potentials initiated in the soma propagate into the dendrites. In fact, it is surprising that potentials propagate more strongly from soma to dendrite than the other way, even though that seems contrary to the normal direction of flow of disturbances in dendrites. To see what linear cable theory has to say about this problem, consider a neuron whose dendritic tree can be represented by an equivalent cylinder and whose soma can be represented by a conductance and capacitance, as in the picture below. The dendrites are terminated by a zero admittance, as usual.



Part a) Suppose the soma is voltage clamped to a potential V_0. Write an equation for potential V_1. Similarly, suppose the neuron is voltage clamped at the end of the dendrites to potential V_1, what is V_0? (of course, the latter situation is rather unlikely in practice, but we are trying to make a point here).

Part b) The two relationships derived in part a) are voltage gains A_{01} and A_{10}. Show that, at D.C., $A_{01} > A_{10}$, consistent with potentials propagating better from soma to dendrites.

Part c) The parameter G_∞/G_S is typically measured to be about 10 in neurons, meaning that the input conductance of neurons' dendritic trees is typically significantly larger than the somatic conductance. What does this say about the result in part b?

Would it help to consider transfer impedances instead, i.e. to compare the voltage at the soma produced by injecting a current at the end of the dendrite (K_{10}) with the opposite? If so, work it out. If not, explain why not. (Hint: this is easier than it looks.)

Problem 4 (20 points/part)

Consider the following pair of differential equations (Fitzhugh-Nagumo), which share some properties with the Morris-Lecar equations. V is the membrane potential and R is the potassium conductance variable. I is the external current injected into the model.

$$\frac{dV}{dt} = 10\left(V - \frac{V^3}{3} - R + I\right)$$
$$\frac{dR}{dt} = 0.8(-R + 1.25V + 1.5)$$

Part a) Sketch a phase plane for this system with I=0. Identify the equilibrium point(s) and compute stability.

Part b) Consider the same system with I=1.5. Prove that it has a limit cycle (Hint: Poincare-Bendixon).