# 580.439/639 Final Exam

3 hours, closed book with two pages of cheat sheet. Do all problems, 300 points total.

Problem 1

Recently a way of making the gating of a potassium channel light-sensitive was described (Banghart et al. Nature Neurosci. 7:1381, 2004). As shown in the figure at right, an organic linker molecule (MAL-AZO-QA) whose *length* is light sensitive (as in part a at right) is attached to a point on the S6-P linker on the extracellular face of potassium channels, as shown in part b. The attached molecule has a TEA-like (quaternary ammonium) group on the end (the ball marked +) that sticks in the pore to block the channel, shown at left in b. In the presence of UV light (380 nm), the linker shortens so the blocker cannot reach the channel pore, at right in b. This produces a gate that is open in the presence of UV light. For this problem, assume the channel is a standard HH (Hodgkin-Huxley) delayed rectifier without an inactivation gate.
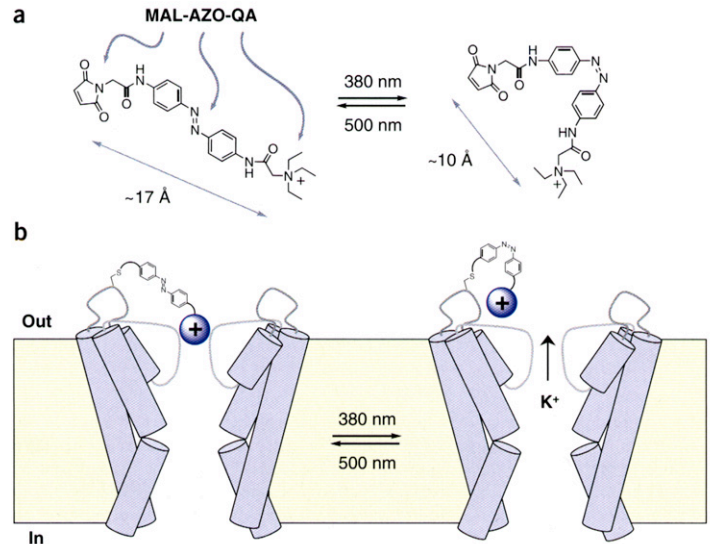

Part a) (10) Speculate on why a positive charge on the blocking moiety (the ball) is necessary.

Part b) (10) If this system is studied in a detached patch configuration with 0 mV across the membrane, current flows through the channel in the presence of UV and not in its absence. However, if the system is studied in an <u>intact neuron at its resting potential</u> (whole cell recording), no current flows through the channel with or without UV. Explain why (hint: the answer is not that the MAL-AZO-QA gate is not working).

Part c) (15) A mutation in the S4 segment of the channel fixes the problem of part b; that is, current through the channel appears in the presence of UV light. Explain how a mutation in this part of the molecule could have this effect.

Problem 2

A typical neuron for a neural network model is sketched at right. The model is described by the differential equation below, which assumes that the output of the summing node is a current proportional to the weighted sum of the inputs. The variable V is the membrane potential *V*.
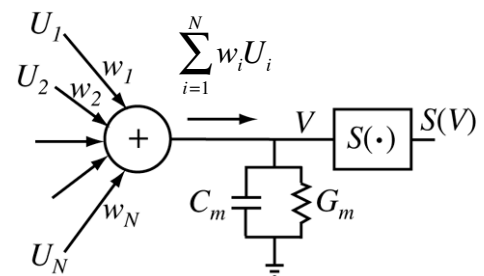
$$C_m \frac{dV}{dt} = -G_m V + \sum_{i=1}^{N} w_i U_i$$

Part a) (10) Explain why there is no battery in series with the membrane conductance G_m. That is, why does leaving out the battery not change the behavior of the model?

Part b) (10) List some differences between the summation of inputs in the model above relative to the summation of inputs in a real dendritic tree.

Part c) (10) Suppose you wanted to study the effects of a certain type of potassium channel on this model. How would you add such a channel to the model? The answer will include a modified circuit and a differential equation, and an equation for the HH parameters of the channel.

Problem 3

Inactivation gating is probably not voltage-dependent in Na channels, in the sense of having an associated gating charge that moves in the membrane when the gate opens or closes. Nevertheless, HH models contain an explicitly voltage-dependent inactivation. Consider the simplest possible inactivating channel model, whose kinetics are as follows:
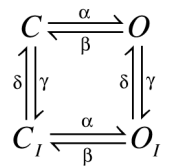
$$C \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} I \tag{*}$$

This is the model for the whole channel, not one subunit. Assume that k_1 and k_{-1} are voltage-dependent whereas k_2 and k_{-2} are not. By this definition, inactivation is not itself voltage-dependent in this model.

Part a) (20) Write differential equations for variables O and I, the fraction of channels in the open and inactivated states, respectively. Part of this is arguing that a third differential equation for C is not needed. NOTE: write these equations in the form $dO/dt = $ (something), not in the form of flux equations. A barrier diagram is not relevant to this problem.

Part b) (15) Solve for the fraction of channels in the inactivated state I in the steady state. This is analogous to $h_\infty(V)$ in HH theory. Argue that the steady-state value of I is voltage-dependent. DON'T bother to work out the actual voltage dependence, as from a barrier model, just express your answer in terms of rate constants and argue from there.

Part c) (20) Consider an HH type model that might be developed for this system, sketched at right. The states of the channel are closed C, open O, closed/inactivated C_I, and open/inactivated O_I. Activation gating opens from left to right, with rate constants α and β, and inactivation gating opens from bottom to top, with rate constants γ and δ. Again assume that there is only one subunit per channel so that the channel is open for the fraction of channels in the O state. Write differential equations for this system in the same form as in part a), i.e. for the fraction of channels in the O, O_I, and C_I states. Again, argue that an equation for C is not necessary.

$$C \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} O$$
$$\delta \Big\Uparrow \gamma \qquad \delta \Big\Uparrow \gamma$$
$$C_I \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} O_I$$

Part d) (20) Solve for the steady-state fraction of channels in the two inactivated states $C_I + O_I$. (Hint: using the differential equations from part c, find the condition for $d(O_I + C_I)/dt = 0$.)

Part e) (15) Suppose we wanted to try to make the steady-state inactivation behavior of the HH model of part d the same as that of the actual system in Eqn. (*). Argue that at least one of γ and δ in the HH model must be voltage dependent in order to do so. Write equations for γ and δ in terms of the rate constants k_i of the model of parts a) and b) to illustrate your claim (NOTE: this last part of the answer is not unique).

Problem 4

A gain factor for dendritic trees that was not considered in class is the current transfer ratio $\bar{B}_{is}$, which is the ratio of the current flowing into the soma to the current injected at point i in the dendritic tree. NOTE: for this problem, the notation $\bar{X}$ means the Laplace transformed value of $X(t)$, i.e. for $q = \sqrt{1+s}$.

Part a) (20) Derive an equation for $\bar{B}_{is}$ in terms of the transfer across a cylinder as in the drawing at right, for which $\bar{B}_{is} = \bar{I}_s / \bar{I}_i$. There's an easy way to do this and a hard way. Either is satisfactory.
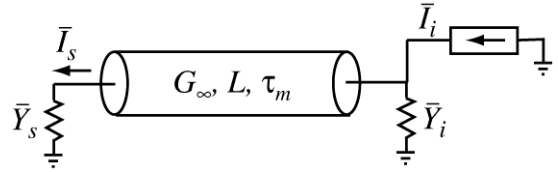
Part b) (10) Using the idea of a transfer impedance, argue that the result obtained in Part a) is generally true, regardless of branching and multiple cylinders between point i and the soma. In other words, if you have not already done so, write $\bar{B}_{is}$ in terms of transfer impedances and $\bar{Y}_s$.

The current gain can be used to derive a useful measure of synaptic efficiency, the *charge gain*. The charge gain C_{is} is defined as the fraction of charge injected at point i that reaches the soma. The nice thing about the charge gain is that it is a simple real number and can be computed from the D.C. properties of the dendritic tree, regardless of the waveform of the injected current.

Part c) (15) Define the total charge injected by current $I_i(t)$ at point i as $Q_{\infty i}$ and the total charge reaching the soma through current $I_s(t)$ as $Q_{\infty s}$. Show that these are equal to $\bar{I}_i(s=0)$ and $\bar{I}_s(s=0)$, respectively. That is, equal to the D.C. values of the Laplace transforms of the currents. Assume that the currents are zero for $t<0$, but can have any waveform after that, except that both charges are finite.

Part d) (20) Argue that $C_{is} = \bar{B}_{is}(s=0)$, i.e. the D.C. value of the current gain. The final value theorem can be used for this, but it doesn't have to.

Problem 5

Consider a network of N neurons $\{x_1, x_2, \ldots x_N\}$ that are fully interconnected with excitatory and inhibitory connections, the latter in a divisive gain control. The neurons have the following differential equations:

$$\tau \frac{dx_i}{dt} = -x_i + \frac{\left(a + \sum_{j=1}^{N} w_{ij} x_j\right)^2}{1 + b\sum_{j=1}^{N} x_j^2} \quad \text{for } i = 1, 2, 3, \cdots N$$

The excitatory interconnections with weights w_{ij} are represented by the sum in the numerator and the divisive gain control (inhibition) by the sum in the denominator. The term a is spontaneous or background activity, which turns out to be important in this model. The constant b is the magnitude of the gain control effect. NOTE that the excitatory input and the divisive normalization involve squared functions of the network values. Also, the system only makes sense if $a \geq 0$, $w_{ij} \geq 0$ $\forall i, j$, and $b \geq 0$.

Part a) (20) To simplify things, we would like to consider the special case where all the neurons take the same value. That is, we can represent the entire network by the following single differential equation:

$$\tau \frac{dX}{dt} = -X + \frac{(a + cX)^2}{1 + dX^2} \qquad \text{where } X = x_1 = x_2 = \cdots = x_N$$

for a, c, and d constants, all ≥ 0. Write equations for c and d and give a necessary condition (on the weights) to allow this reduction.

Part b) (20) Consider the steady-state values of this network in the special case with $d=0$, i.e. no divisive gain control. Show that equilibrium points exist only for a range of values of a, the spontaneous activity. This can be done analytically, but it may be more enlightening to do it graphically, especially considering parts c) and d) below. By graphically is meant plotting the left and right sides of the equation for the equilibrium point against X and looking for intersections.

Part c) (20) Show with an example that adding divisive gain normalization, i.e. $d>0$, produces an equilibrium point, regardless of the value of $a>0$. In this case the equation for the equilibrium point is cubic and you will have to solve the problem graphically. To make it easier, consider the special case $a=1$, $c=1$, and $d=0.1$. HINT: consider what happens in the vicinity of the origin ($|X|<2$) and for $X \rightarrow \infty$ and argue that there has to be an equilibrium point in between. NOTE: it will not be sufficient to just note that a cubic equation has up to 3 roots, so there must be another equilibrium point.

Part d) (20) Is the system with divisive gain ($d>0$) stable at its equilibrium points? Don't try to solve the problem explicitly by computing eigenvalues. Instead, take advantage of the fact that it's a first-order system. (This is hard and messy and only a partial answer is possible without some computing. Do it last).