580.439/639 Final Exam Solutions, 2001

Problem 1

Part a) AMPA channels have a linear current-voltage relationship when activated, as opposed to NMDA channels which rectify strongly because of Mg^{++} block at negative potentials.

NMDA channels admit Ca^{++} along with other cations, whereas AMPA channels may or may not admit Ca^{++}.

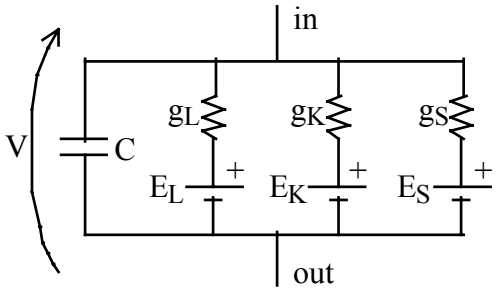
The receptors of the two families are blocked by different molecules, hence the names.

Part b) Ionotropic receptors include an ion channel as an integral part of the receptor. Metabotropic receptors do not and instead lead to activation of a G-protein and hence to a second-messenger cascade.

Part c) A single spike may not produce current in NMDA receptors because of Mg^{++} block at the resting potential of the cell. A burst of spikes may depolarize the cell sufficiently through the AMPA receptors to release the Mg^{++} block.

Problem 2

Part a) The usual membrane patch circuit is drawn at right. The battery voltages should be something like $E_L \approx$-60 mV, $E_K \approx$-90 mV, and $E_S \approx 0$ mV.



Equations to model this system are as follows:

$$C\frac{dV}{dt} = I_{ext} - g_L(V - E_L) - \bar{g}_K n^4 (V - E_K) - g_S(t)(V - E_S)$$

$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)}$$

$$g_S(t) = \bar{g}_S(t - t_0)e^{-(t-t_0)/\tau_S}$$

The state variables are V and n. The usual Hodgkin-Huxley formalism has been used for the potassium channel and the synaptic conductance is a function of time.

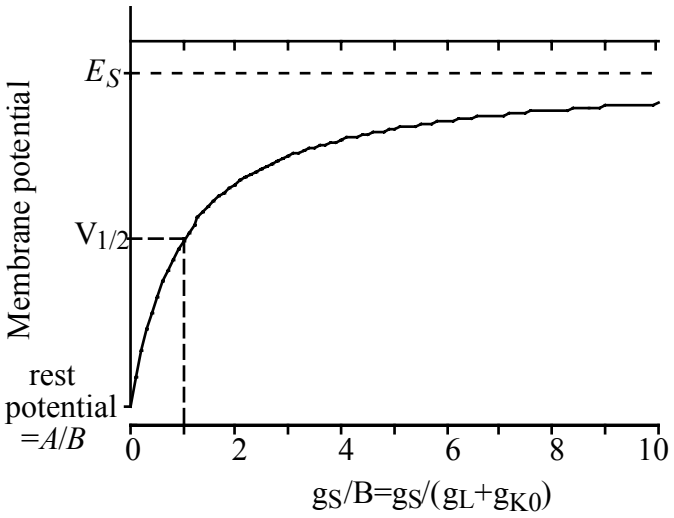
Part b) If a synaptic conductance is applied in a steady (as opposed to transient in the equations above) way, the steady state value of membrane potential is

$$V = \frac{g_L E_L + g_{K0} E_K + g_S E_S}{g_L + g_{K0} + g_S}$$

This equation is the solution for V obtained by setting dV/dt=0 in the system model above. To see how this varies with g_S, note that ($g_L E_L + g_{K0} E_K$) and ($g_L + g_{K0}$) are constants, A and B respectively, under the assumptions of this part, so the membrane potential becomes

$$V = \frac{A/E_S + g_S}{B + g_S} E_S$$

Clearly this is a saturating function of g_S, plotted at right. The dynamic range of the system can be considered to be the range of conductances over which the membrane potential changes rapidly. A measure of the width of the dynamic range is the conductance at which the membrane potential is halfway between resting potential and saturation potential E_S, called $V_{1/2}$ in the figure.



Part c) Qualitatively, increasing g_K decreases the abscissa variable in the plot above, moving the operating point to the left and avoiding saturation. When synaptic inputs are applied, the resulting depolarization activates the potassium conductance, increasing g_K, which opposes the depolarization, broadening the dynamic range as described above.

More quantitatively, the half saturation conductance g_{Shalf} is the solution to:

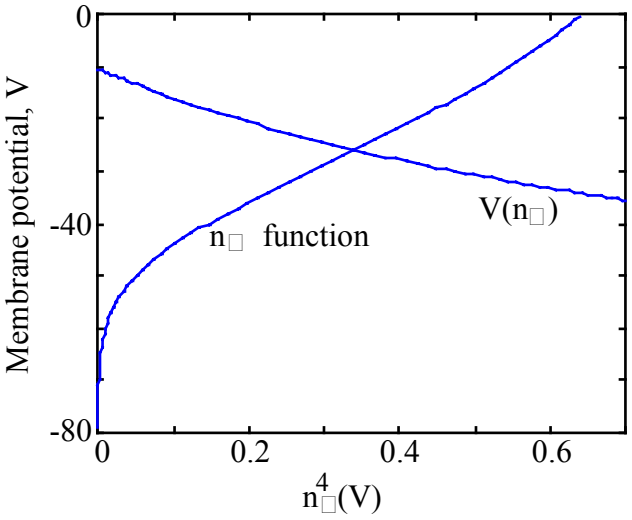
$$V_{1/2} = \frac{A/E_S + g_{Shalf}}{B + g_{Shalf}} E_S = \frac{1}{2}\left(\frac{A}{B} + E_S\right)$$

With some algebra, the solution is $g_{Shalf}=B=g_L+g_{K0}$. Clearly when g_K increases, g_{Shalf} increases, broadening the dynamic range.

Part d) The desired solution for V is the equation plotted in the figure above. Writing it out in terms of all variables

$$V = \frac{A/E_S + g_S}{B + g_S} E_S = \frac{g_L E_L + \bar{g}_K n_\infty^4(V) E_K + g_S E_S}{g_L + \bar{g}_K n_\infty^4(V) + g_S}$$

This equation must be solved simultaneously with $n = n_\infty(V)$ (sorry, this aspect of the problem was not clear in the original problem statement). One way to find an explicit solution is to make a plot of the function above on axes of V versus $n_\infty^4(V)$ and then plot $n_\infty^4(V)$ versus V on the same axes. The solution(s) are at intersection(s) of the two curves. An example is shown at right for $g_S = g_L + \bar{g}_K$ and the other parameters as in the HH model. The steady-state synaptic potential in this case is the intersection of the curves. Note



that these curves are essentially the isoclines of the nonlinear system.

Problem 3

Part a) The usual transport equation applies

$$J_{ND} = k_{-1}(NaD)_o - k_1(NaD)_i$$

where J_{ND} is the flux (Mo/m^{2}s) into the intracellular compartment. Assuming that the reactions between free sodium and dopamine and the transporter are at equilibrium gives

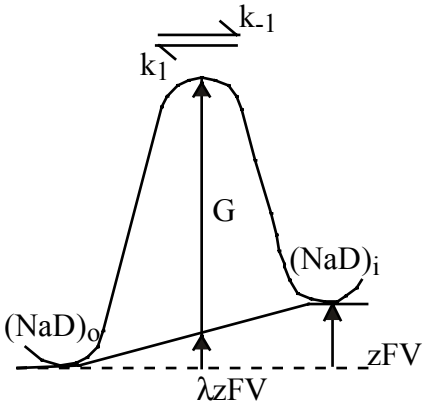
$$\frac{(NaD)_o}{Na_o D_o} = \frac{k_2}{k_{-2}} = K_2 \quad \text{and} \quad \frac{(NaD)_i}{Na_i D_i} = \frac{k_2}{k_{-2}} = K_2 \qquad (*)$$

$$\text{so} \quad J_{ND} = k_{-1} K_2 Na_o D_o - k_1 K_2 Na_i D_i$$

Part b) At equilibrium, J_{ND}=0 so

$$J_{ND} = k_{-1} K_2 Na_o D_o - k_1 K_2 Na_i D_i = 0$$

$$\Rightarrow \quad \frac{Na_o D_o}{Na_i D_i} = \frac{k_1}{k_{-1}}$$



As stated in the problem, the fact that sodium (and the sodium-dopamine complex) is charged requires that membrane potential be involved. In fact, membrane potential enters the equation above because the rate constants are voltage dependent. Using the standard barrier model for translocation of the sodium-dopamine complex through the membrane, as in the drawing at right, gives the following for the rate constants:

$$\frac{k_1}{k_{-1}} = \frac{\alpha e^{-(G+\lambda zFV - zFV)/RT}}{\alpha e^{-(G+\lambda zFV - 0)/RT}} = e^{zFV/RT}$$

Thus

$$\frac{Na_o D_o}{Na_i D_i} = \frac{k_1}{k_{-1}} = e^{zFV/RT} \quad \text{so} \quad \mathrm{V} = \frac{\mathrm{RT}}{\mathrm{zF}} \ln \frac{Na_o D_o}{Na_i D_i}$$

The same result could be derived by writing the molar free energy of the constituents on the two sides of the membrane.

If the sodium concentration inside the cell increases, that will increase the molar free energy of internal sodium, so that sodium will flow out of the cells.

Part c) The first step is to identify the state variables. The sodium concentrations and membrane potential are fixed by assumptions, so are not candidates. The only remaining variables

are the dopamine concentrations inside and out and the sodium-dopamine complexes. Because the latter are assumed to be at equilibrium with the sodium and dopamine in solution, either dopamine or sodium-dopamine complexes can be state variables, not both. Another way to say this is that Eqn. (*) above fixes the concentration of complex, given the concentration of dopamine and sodium (or vice versa), so only one of the two (dopamine or dopamine-sodium complex) can be a state variable. It seems reasonable to choose the dopamine concentrations D_i and D_o as state variables. The following equations can be written for these concentrations:

$$\frac{dU_e D_o}{dt} = -SJ_{ND} = -S\left[k_{-1}K_2\,Na_o\,D_o - k_1K_2\,Na_i\,D_i\right]$$

$$\frac{dU_i D_i}{dt} = SJ_{ND} = S\left[k_{-1}K_2\,Na_o\,D_o - k_1K_2\,Na_i\,D_i\right]$$

where U_eD_o and U_iD_i are the total dopamine content of the extra- and intracellular spaces; their change with time is equal to the surface area S across which transport takes place times the flux J_{ND}. Notice that these two equations are identical, except for a sign. Therefore there is really only one state variable in this system, which is the total cumulative flux of dopamine through the membrane into the cell. That is, define a state variable T as below

$$T(t) = \text{cumulative dopamine flux} = \int_0^t SJ_{ND}\,dt$$

then the dopamine concentrations can be defined as follows

$$U_e\,D_o(t) = U_e\,D_o(0) - T \quad \text{and} \quad U_i\,D_i(t) = U_i\,D_i(0) + T$$

and the following single differential equation is sufficient to characterize the system:

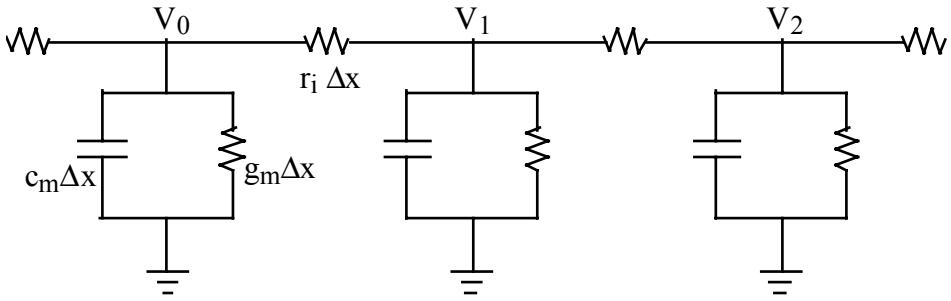
$$\frac{dT}{dt} = \frac{dU_iD_i}{dt} = -\frac{dU_eD_o}{dt} = SJ_{ND} = S\left[k_{-1}K_2Na_oD_o - k_1K_2Na_i(t)\,D_i\right]$$

$$= S\left[k_{-1}K_2Na_o\left(D_o(0) - \frac{T}{U_e}\right) - k_1K_2Na_i(t)\left(D_i(0) + \frac{T}{U_i}\right)\right]$$

where Na_o is a constant and $Na_i(t)$ is a given input function, consistent with the assumptions in the problem statement.

Problem 4

Part a) The usual circuit for a passive cable is drawn below. The circuit has the structure of a sequence of low-pass filters, so that V_1 is a low-passed version of V_0 with the low pass filter consisting of the series resistance $r_i\Delta x$ and the parallel capacitance $c_m\Delta x$; in fact, the situation is more complex because the capacitor is in parallel with a conductance ($g_m\Delta x$) and the rest of the cable. It is simpler to work out the actual transmission characteristics using the cable equation.

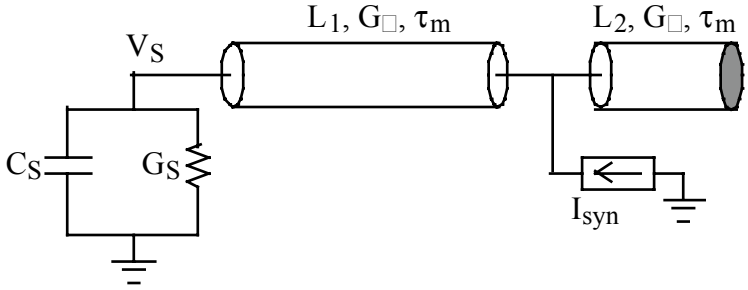


For a cable of length L voltage clamped at its left end and terminated at its right end by an admittance Y_L, the voltage transfer function was shown in class to be:

$$\frac{V(L)}{V(0)} = \frac{1}{\cosh(qL) + \frac{Y_L}{qG_\infty}\sinh(qL)}$$

where q is the appropriate transform variable. For the case considered in this problem, Y_L=0, so $V(L)/V(0)$=1/cosh(qL) = $1\Big/\cosh\left(\sqrt{1+j\omega}\,L\right)$. The magnitude of this function is shown in the problem.

Part b) The situation is sketched below. The soma is represented by the parallel capacitance and conductance at left. The dendritic tree is represented by an equivalent cylinder which is broken



into two, one of length L_1 and the second of length L_2, where L_2=L-L_1. The synaptic current is injected at the break between the two cylinders. The desired transfer function is the transfer impedance from I_{syn} to V_S. The load admittances are the parallel combination of the soma capacitance and conductance at the left end and the input admittance of the L_2 cylinder at the right end. The L_2 cylinder is terminated with a closed end boundary condition, so that its load admittance is 0. In lecture, the transfer impedance was written as follows:

$$\frac{V_S}{I_{syn}} = K_{IS} = \frac{1}{(Y_{soma} + Y_{L_2})\cosh(qL_1) + \left(\frac{Y_{soma} + Y_{L_2}}{qG_\infty} + qG_\infty\right)\sinh(qL_1)}$$

where

$$Y_{soma} = G_S + j\Omega C_S = G_S\left(1 + j\frac{\omega}{\tau_m}\tau_s\right) \quad \text{and} \quad Y_{L_2} = qG_\infty\tanh(qL_2)$$

where $q = \sqrt{1 + j\omega}$ is the transform variable appropriate to the AC steady state, ω is dimensionless frequency, and Ω is real frequency in radians/s. The two are related by $\omega=\Omega\tau_m$. where τ_m is the membrane time constant of the dendritic membrane, equal to c_m/g_m. τ_s is the time constant of the somatic membrane, equal to C_S/G_S.

The equations above are quite messy, but can be reduced a little using some algebra and the equations for cosh(x+y) and sinh(x+y) (this simplification was not necessary for the exam).

$$\frac{V_S}{I_{syn}} = \frac{1}{G_S} \frac{\cosh(qL_2)}{(1 + j\omega\tau_s/\tau_m)\cosh(qL) + \sqrt{1 + j\omega}\,\rho_\infty \sinh(qL)}$$

where $\rho_\infty=G_\infty/G_S$ is the dendritic dominance, or ratio of the characteristic conductance of the dendrites to the conductance of the soma.

The magnitude of this complex transfer function is plotted versus dimensionless frequency in the last figure in the problem set, for a typical set of neuron parameters (L=1, τ_S/τ_μ=1, ρ_∞=10, L_1=0 or 0.5, and L_2=L-L+1).

Part c) The DC transfer function can be obtained from either of the previous equations by setting ω=0 or q=1.

$$\frac{V_S(0)}{I_{syn}(0)} = \frac{1}{G_S} \frac{\cosh(L - L_1)}{\cosh(L) + \rho_\infty \sinh(L)}$$

As L_1 increases form 0 to L, the cosh in the numerator decreases, whereas the denominator is constant. The decrease is not exponential, because the gain is proportional to $\cosh(L_2)=\exp(L_2)+\exp(-L_2)$.

Part d) The current injected by the synapse consists of only an inward current (if it is a strictly excitatory synapse), so it has a DC component and therefore produces both a DC and an AC potential at the site of the synapse.

Part e) The response to current injection at the soma can be obtained from the transfer impedances above by setting L_1=0, giving

$$\frac{V_S}{I_{syn}} = \frac{1}{G_S} \frac{\cosh(qL)}{(1 + j\omega\tau_s/\tau_m)\cosh(qL) + \sqrt{1 + j\omega}\,\rho_\infty \sinh(qL)}$$

$$= \frac{1}{G_S} \frac{1}{(1 + j\omega\tau_s/\tau_m) + \sqrt{1 + j\omega}\,\rho_\infty \tanh(qL)} = \frac{1}{Y_{soma} + Y_{in\ equiv\ cylinder}}$$

where $Y_{in\ equiv\ cylinder}$ is the input admittance of the whole equivalent cylinder. Clearly this is different than the functions above for an arbitrary injection site L_1. The difference is plotted in the last figure in the problem set. The dendritic tree is much more low-pass for synaptic sites out in the tree, versus at the soma.