580.439/639 Final Exam, 2001

Three hours, answer all questions. Closed book, but two 8.5"x11" sheets of notes are allowed. Each part of each question is worth 20 points for a total of 300 points.

Problem 1

Part a) Glutamate activates two families of ionotropic receptors, called AMPA and NMDA receptors. What are the functional differences between NMDA and other glutamate receptors (at least three), other than that they are different gene products?

Part b) Other glutamate receptors are metabotropic. How do they differ from the ionotropic ones?

Part c) Why might a burst of spikes in the presynaptic terminal produce current through postsynaptic NMDA receptors when a single spike would not? You may need to assume that both AMPA and NMDA receptors are present in the postsynaptic terminal to make this work.

Problem 2

In class, a hypothesis about the role of voltage-gated potassium channels in regulating the dynamic range of synaptic inputs was discussed (Bernander et al. *J. Neurophysiol.* 72:2743-2753, 1994). The idea is that potassium channels broaden the range of synaptic conductance changes to which a cell can respond. This problem considers how that hypothesis could be investigated using a model.

Part a) Draw a circuit model for a single compartment containing a membrane capacitance, a leakage channel, a voltage-gated potassium channel, and an excitatory synaptic channel. Give reasonable values for the battery voltages. Write the equations needed to model this system, assuming the potassium channel is a delayed-rectifier (Hodgkin-Huxley) type. Use a simple "alpha-wave" model for the synaptic conductance.

Part b) Show that the steady-state change in membrane potential produced by a synaptic conductance increase g_S (also steady) is a saturating function of g_S. For this part, assume the potassium channel has a fixed conductance g_{K0} at its resting value. ("Steady" above means that the synaptic conductance is set to g_S and held steady till the membrane potential comes to a steady value; this is done to simplify the calculations.)

Part c) Explain qualitatively how the voltage-gating of the potassium channel will broaden the dynamic range for conductance increase. One approach is to derive an expression for g_{Shalf}, the synaptic conductance at which the membrane potential is halfway between rest and saturation and show the effect of increases in g_K on g_{Shalf}. (Again, use steady conductances.)

Part d) Consider the expressions used above for the steady-state membrane potential at a fixed value of g_S,. Show how to solve for the equilibrium point of the equations derived in part a, for a fixed value of g_S. The problem is to solve simultaneously for the steady values of V and n. (hint:

this could be done graphically on a plot of membrane potential V versus potassium conductance or potassium activation n).

Problem 3

Recently it was claimed in a paper that neurons that release synaptically the neurotransmitter dopamine are inhibited following a period of spiking activity by a novel mechanism in which current is carried through the membrane by a dopamine transporter (Falkenburger et al., *Science* 293:2465, 2001). The dopamine transport involves a co-transport of sodium (Na^+) ions, by a mechanism something like the following (simplified):

$$Na_i^+ + D_i \underset{k_{-2}}{\overset{k_2}{\leftrightarrow}} (NaD)_i^+ \underset{k_{-1}}{\overset{k_1}{\leftrightarrow}} (NaD)_o^+ \underset{k_2}{\overset{k_{-2}}{\leftrightarrow}} Na_o^+ + D_o$$

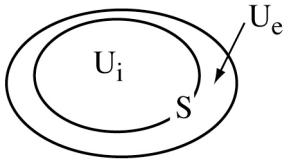
where Na_i and D_i are sodium and dopamine concentrations inside the cell, $(NaD)_i$ is the concentration of transporter on the cell inside to which both sodium and dopamine are bound, and the remaining symbols are the concentrations outside the cell.

Ordinarily this reaction is driven strongly to the left (uptake of dopamine from the extracellular space, which terminates synaptic transmission by dopamine) by the free energy stored in the sodium transmembrane gradient (higher concentration of sodium outside the cell, negative resting membrane potential). When the cell is excited to fire action potentials, the sodium concentration inside the cell increases and the net free energy difference for the reaction can reverse, resulting in outward transport of sodium and dopamine, and therefore an outward current.

To model this system, assume the following:

1. The reactions in which sodium and dopamine bind to the receptor (with rate constants k_2 and k_{-2} are fast and are at equilibrium. Transmembrane transport, with rate constants k_1 and k_{-1}, is the rate-limiting step.

2. Dopamine distributes between spaces with the volumes and surface areas shown in the figure at right. U_i and U_e are the intra- and extracellular volumes in which dopamine accumulates and S is the surface area across which dopamine flows between these volumes. The dopamine transporters are in the surface S.



3. Sodium concentration in the extracellular space (U_e) is constant in time, because of other mechanisms which regulate sodium. The sodium concentration inside the cell is primarily controlled by sodium currents through the membrane and sodium transporters (e.g. Na-K ATPase), so that the sodium concentration Na_i can be considered to be an input to the model, represented as a fixed function of time $Na_i(t)$. The sodium-dopamine co-transport rate is small compared to these other mechanisms and does not affect the sodium concentration.

4. There is an excess of the dopamine transporter, so that saturation of the transporter does not have to be considered in the model (i.e. assume independent transport).

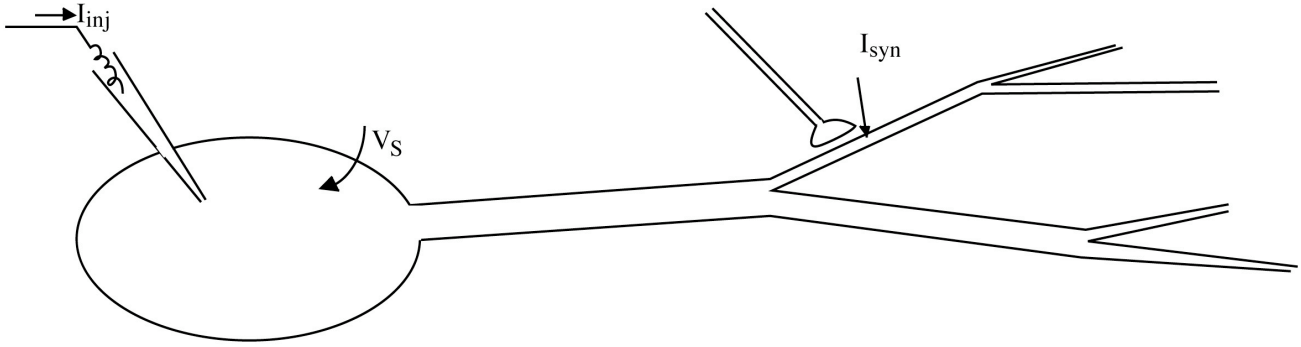
Part a) Write an equation for the net flux J_{ND} of *Na-D* complex through the membrane in terms of the concentrations of sodium and dopamine in the intracellular and extracellular volume. It is convenient below to make the units of this equation Moles/m^2·s.

Part b) Write the condition for equilibrium of this transporter, i.e. zero net flux. Your answer should include membrane potential, which has not been considered so far and will have to be added to the model. Argue from thermodynamic considerations that if the sodium concentration inside the cell increases, the direction of transport will be outward.

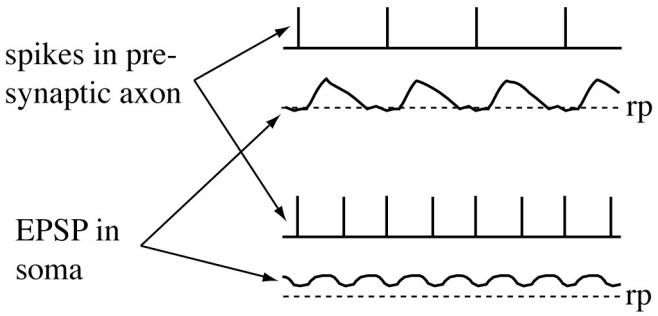
Part c) Write a set of differential equations that would allow you to solve for the dopamine concentrations inside and outside the cell, given a sodium transient $Na_i(t)$ and fixed Na_o and transmembrane potential. Remember, as in 3 above, that the sodium concentrations are assumed to be determined by other larger fluxes, so that the sodium-dopamine co-transport does not affect either Na_i or Na_o. <u>You should be able to express this model in terms of only one state variable</u>, even though the dopamine concentrations in both intracellular and extracellular spaces will change with time.

Problem 4

Consider the transfer function between synaptic inputs on the dendritic tree and membrane potential in the soma for the neuron sketched below. Current I_{syn} is injected into the dendrites by a synapse. The potential V_S is measured in the soma. The AC steady-state is approximated by electrically stimulating the synaptic input (i.e. causing action potentials to fire in the synaptic input) at frequency *f*. Ignore the current (I_{inj}) injected into the soma until later.

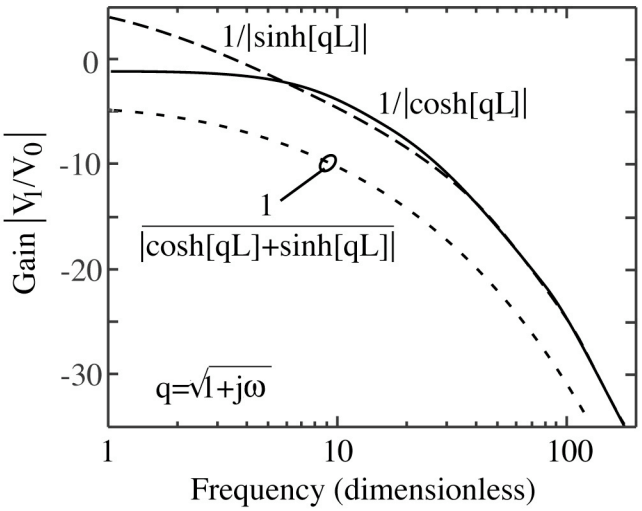


The AC potential in the soma V_S decreases with frequency of stimulation as sketched at right for two frequencies (the dashed line marked *rp* is the resting potential). We want to account for the fact that the EPSPs are smaller at the higher frequency of stimulation. To simplify the problem, ignore the fact that the input is applied as a conductance change to the dendrites and assume that the synapse applies a <u>current</u> I_{syn} as diagrammed above. Also assume that the whole system is in an AC steady state, meaning that transients associated with the beginning of stimulation have decayed, so that currents and voltages in the system are periodic with frequency *f*, the



frequency of the input. Recall that in this case the transform variable in the cable theory is $q=(1+j\omega)^{1/2}$, in terms of dimensionless frequency ω. Also assume that the dendritic tree is passive, i.e. that linear cable theory applies.

Part a) Argue from the basic structure of a linear cable that the transfer function of the dendritic cable in the AC steady state should be low-pass, i.e. should have gains that decrease with frequency. As a specific example, write the voltage transfer function A_{0l} for a cable of length L voltage-clamped at end 0 with voltage V_0, and terminated at end 1 with a closed-end (zero-current) boundary condition. That is, write an equation for V_l/V_0, in Fourier transformed form where $q=(1+j\omega)^{1/2}$.



For reference the plot at right shows some examples of the magnitude of the AC steady state transfer functions for a cable of length L=0.5. The gain is plotted in dB, i.e. as $20*\log_{10}$[gain]. One of them should be a plot of your answer to Part a), the others are not. All are low-pass.

Note that the low-pass filtering of the dendritic cable provides a way to explain the reduction in EPSP size, assuming that all other effects (like the strength of the synaptic input) do not change as stimulus frequency f increases.

To model the situation described in the drawing at the start of this problem, use the Rall motorneuron model. Assume that the cell's dendritic tree can be reduced to a single equivalent cylinder of length L, terminated with a closed end, and that the synaptic current is injected at a distance L_1 from the soma ($0<L_1<L$). Model the soma as passive, consisting of a capacitance C_S in parallel with a conductance G_S.

Part b) Write an equation for the transfer function in the AC steady state, $q=(1+j\omega)^{1/2}$ between the current injected in the dendrite and the voltage in the soma for the situation described above. The result may be quite hairy. Write your final answer in terms of real frequency f in Hertz (i.e. not dimensionless frequency and not radian frequency).

Your answer above should contain two time constants, called τ_m and $\tau_S=C_S/G_S$ in class. Explain what these are (i.e. of what they are the time constants) and explain how they are related to q, the transform variable in the cable theory .

Part c) Show, from your answer to part b), that the DC gain (ratio of DC voltage in the soma to the DC current injected at the synapse) decreases as L_1 increases. Does it decrease exponentially, as it would in an infinite cable?

Part d) Why is there a DC component in the synaptic signal? (this has nothing to do with cable theory!). That is, why is there a DC offset from the resting potential in the EPSP sketch above?

In a recent seminar, the speaker showed data like the EPSP plot above and claimed that only part of the reduction in EPSP magnitude with frequency is due to the lowpass filtering of the dendritic tree. His argument was that when he injected sinusoidal current into the soma, he obtained a low-pass behavior, in that the voltage produced in the soma was smaller at higher frequencies of current injection, for equal amplitudes of current. However, the attenuation of the voltage with frequency was less for current injection into the soma than for activation of the synapse. That is, he argued that the transfer function from current injected into the soma to voltage in the soma could be used to predict the transfer function from current injected at the synapse site to the voltage in the soma. Perhaps this argument is not correct.

Part e) To see why, write an expression for the voltage produced in the soma of the cell model considered in part b) when a sinusoidal current is injected into the soma (i.e. the transfer impedance from soma to soma). Is this expression the same as your result in part b?

The plot at right shows an example for a dendrite tree of length L=1 with current injected either at the soma (L_1=0) or in the middle of the dendritic tree (L_1=0.5), assuming that G_∞/G_S=10 and $\tau_m=\tau_S$. Note that the slope of the lowpass function is steeper if the current is injected in the dendritic tree and the gain is less.