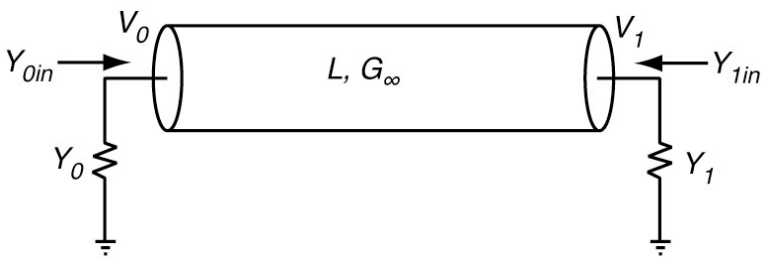
580.439/639 Final Exam 2013

3 hours, closed book with a two-page cheat sheet. Do all problems.

Problem 1



An important property of neurons is the asymmetry of voltage gains in dendrites, meaning that electrotonic spread of potentials is larger (higher gain) in the outward direction, i.e. spread of potentials away from the soma, as opposed to toward the soma. To understand this property, consider the symmetry of voltage gains across a single dendritic branch, as sketched above. Assume a linear model of the dendritic tree for this problem.

Part a) (20 pts) Show that the voltage gains are proportional to the input admittances, meaning that

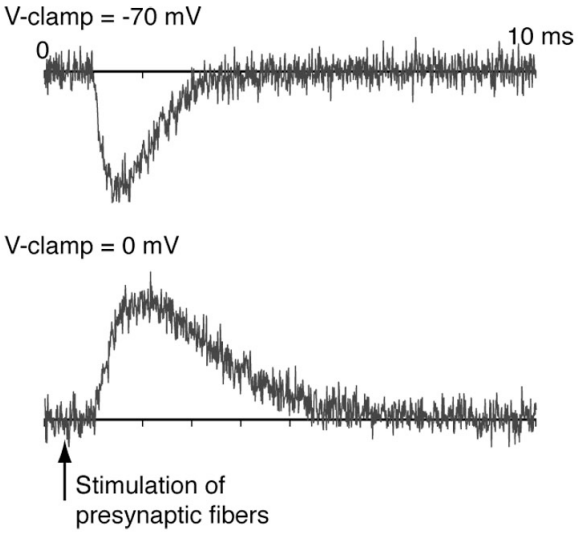
$$\frac{A_{01}}{A_{10}} = \frac{Y_{00}}{Y_{11}} \ .$$

Recall that the voltage gain $A_{ij} = V_j / V_i$, where V_j is the potential produced at point j when a voltage V_i is applied at point i. $Y_{00} = 1/K_{00}$ is the input admittance of the dendrite at point 0, the parallel combination of the load Y_0 and the input admittance Y_{0in} of the dendritic branch. Y_{00} is the admittance that an electrode inserted at point 0 in the tree would see. (Hint: This is easier than it looks. Think about injecting a current at 0 to produce a potential there that spreads to 1 and use the transfer impedance.)

Part b) (15 pts) The development above refers to a single dendritic branch. Does the symmetry property also hold between any two points on the dendritic tree, regardless of branching? Explain your answer.

Problem 2

In experimental studies in which intracellular recording is done with the goal of studying synaptic inputs, the membrane potential is often voltage-clamped to 0 mV or to –70 mV while synaptic inputs are activated. Synaptic effects are then measured as the current required to maintain the voltage clamp. Examples of (simulated) currents in response to activating synaptic inputs (at the arrow) are shown at right for the two voltage clamps. In each case, the steady-state current required to maintain the voltage clamp is shown by the horizontal line. The synaptic currents are the large deviations from the horizontal lines. Ignore the (simulated) noise on the records.



Part a) (20 pts) Explain why this approach gives the current mainly through either inhibitory or excitatory synaptic channels, depending on the clamp voltage. That is, it allows the separation of excitatory and inhibitory channel effects. Tell which is which in the figure above and explain why. It may help in thinking about this problem to draw the standard circuit for a patch of membrane, including synaptic channels. Do not concern yourself with cable effects, i.e. assume the synapses are on the soma.

Part b) (15 pts) Why don't voltage-gated channels interfere with the measurement by gating? Will there be currents through voltage gated channels in this protocol? For both holding potentials, name a voltage-gated channel that might conduct significant current and tell whether its current should be positive or negative. (Hint: the voltage clamp is applied for a long time before the presynaptic fibers are stimulated).

Part c) (15 pts) This approach works for most synaptic channels, but often does not work for NMDA channels, for which no currents are seen at either clamp voltage. Explain why.

Part d) (20 pts) In this experiment, both excitatory and inhibitory synapses are activated by the stimulus, as shown in the figure above. Suppose the voltage clamp is turned off, so the membrane potential returns to rest at -60 mV, and then the same fiber tract is activated while measuring the cell's membrane potential. What will happen (depolarization or hyperpolarization, i.e. EPSP or IPSP) to the membrane potential? Explain your answer. Sketch the approximate voltage waveform. Again, ignore cable effects and also ignore voltage-gated channels. Your circuit of part a) should be helpful. (Hint: from the currents above, what is the relative conductance of the excitatory and inhibitory channels?)

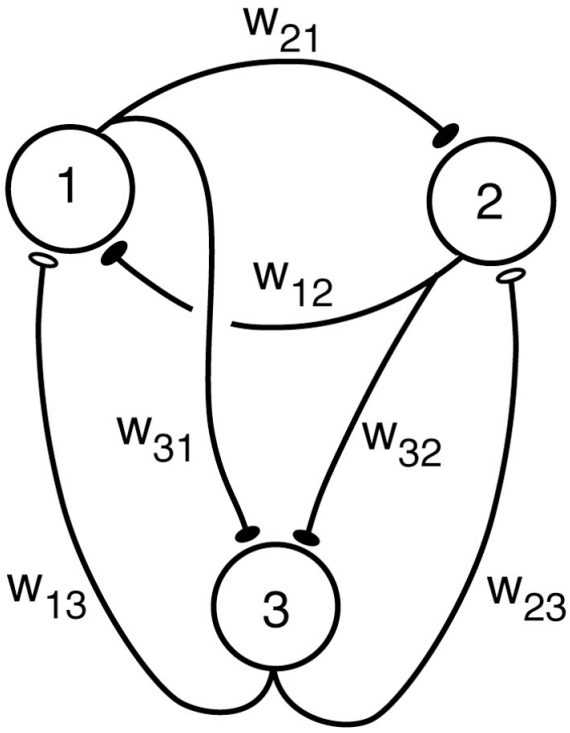
Problem 3

Consider the neural network sketched at right. There are two excitatory neurons (#1 and #2) and one inhibitory neuron (#3). The weights connecting the neurons are given by the w_{jk}. These will be positive or negative values, depending on whether their source is excitatory or inhibitory. Each neuron is described by a differential equation like the following:

$$\frac{dx_j}{dt} = -x_j + \sum_k w_{jk} x_k \quad .$$

Notice that the neurons are linear, i.e. no squashing function. Finally, to simplify, assume that the weights are related as follows:

$$w_{12} = w_{21} > 0 \quad w_{31} = w_{32} > 0 \quad w_{13} = w_{23} < 0$$



Part a) (15 pts) This network is described by a system of three differential equations, and can be written in the form $d\vec{x}/dt = \mathbf{W}\vec{x}$, where $\vec{x}$ is the state vector of the neuron activations x_j and **W** is a matrix of weights. Write the matrix **W** for this system.

Part b) (15 pts) Because of the symmetries in the weights, the two excitatory neurons have the same differential equation. Assuming that the initial conditions are the same, their responses will be identical to each other. Thus the two excitatory neurons can be combined into one equivalent, making the overall system 2-dimensional. Assuming that this is so, let $x_a = (x_1+x_2)/2$ be the equivalent neuron and rewrite the differential equations in terms of x_a and x_3. That is, what is **W** for this system?

Part c) (15 pts) What is the Jacobian of the system of part b)? Does the Jacobian depend on the equilibrium point at which it is analyzed? Write an equation for its eigenvalues.

Part d) (20 pts) Based on the eigenvalues, what can you say about stability of this system? What effect does increasing the strength of the inhibitory effect (making w_{13}=w_{23} more negative)? DO THIS LAST.

Part e) (20 pts) Suppose the model of part b) is made nonlinear by adding a squashing function $S(x)$, for example $1/(1+e^{-x})$, so that the differential equations are

$$\frac{dx_j}{dt} = -x_j + S\left(\sum_k w_{jk}x_k\right)$$

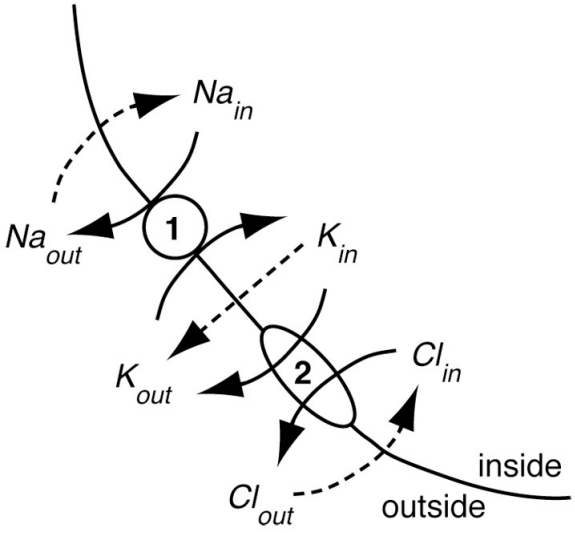
How will this change affect the Jacobian derived in part c)?

Problem 4

The cellular steady state requires that the concentrations of ions and the membrane potential (along with everything else) be constant in time. Consider a cell with only Na, K, and Cl in the internal and external solutions.

Part a) (15 pts) State explicitly the conditions for a steady state in this cell. Specify these in terms of fluxes through the membrane or time derivatives of the important variables.

Part b) (25 pts) In the figure at right, the cell has passive transport through ion channels (dashed lines) and active transporters (solid lines). The Na-K ATPase transporter (marked "1") moves 3 Na ions out of the cell for each 2 K moved in, using the energy from the hydrolysis of an ATP molecule to ADP. The KCL transporter ("2") moves equal numbers of K and Cl ions out of the cell, driven by the electrochemical gradient of the ions (i.e. no energy sources). Write equations for the relationships among the ionic fluxes (J_i in Moles/(cm^{2}s)) in steady state for this cell. Use the convention that J_i is positive for net flux of the ion i into the cell. Your equations should have both passive (e.g. J_K^p) and active (J_K^{a1} and J_K^{a2}) transport terms. Do you need a separate equation for steady state of charge? (Note, this problem doesn't ask you to solve for the fluxes explicitly.)



Part c) (15 pts) Using the equations from part b), show that the sum of the passive ion currents, i.e. the currents through ion channels $(I_K^p + I_{Na}^p + I_{Cl}^p)$, is not zero. Use the convention that I_i is positive when charge flows out of the cell. Remember that $I_i = -z_i J_i$, as defined in class.

Part d) (15 pts) To derive a membrane potential equation like the GHK equation, the usual approach is to begin with a current-sum relationship like $I_K^p + I_{Na}^p + I_{Cl}^p = 0$ into which the constant-field current equations can be substituted to yield the equation for membrane potential in the steady state. For example, for the usual GHK equation:

$$I_x = const\ u_x\ V\ \frac{X_{inside} e^{z_x FV/RT} - X_{outside}}{e^{z_x FV/RT} - 1} \quad \text{giving} \quad V = \frac{RT}{F} \ln \frac{u_K K_{outside} + u_{Na} Na_{outside} + u_{Cl} Cl_{inside}}{u_K K_{inside} + u_{Na} Na_{inside} + u_{Cl} Cl_{ouftside}} \ .$$

The currents I_x are substituted into the current-sum equation in the previous paragraph to derive the voltage equation. From your results in part c), work out a suitable current-sum equation, of the form $aI_K^p + bI_{Na}^p + cI_{Cl}^p = 0$, where *a, b,* and *c* are constants. Write the GHK voltage equation that results from using your current-sum equation.

Part e) (20 pts) Ouabain is a poison that works by blocking NaK ATPase. Suppose that ouabain is given to eliminate pump 1 in this cell. What will be the concentrations of ions inside the cell in this case, in the long-term steady state? Assume that the concentrations outside the cell are maintained by mechanisms external to the cell and that the total concentration of cations equals the concentration of anions, $K_{out}+Na_{out}=Cl_{out}$, say 145 mM Na, 5 mM K, and 150 mM Cl, close to physiological values. (Hint: think about this without equations first.)

Part f) (20 pts) The previous question (part e)) refers to the long term true steady state. However immediately after the ouabain is applied, the ion concentrations will stay at their values in the steady state analyzed in parts a) – d). This is not a true steady state, because the ion concentrations are changing with time. However, they change slowly and an immediate steady condition will occur in which the net charge flow through the membrane is very close to zero. This is so because net charge flow through the membrane produces a very large membrane potential which rapidly adjusts the ionic currents to a state of near-zero membrane current. Assuming that such an adjustment occurs, work out the membrane potential for this near steady-state. (Hint: To do this, you will have to argue that you can ignore the currents through the KCl transporter, #2).