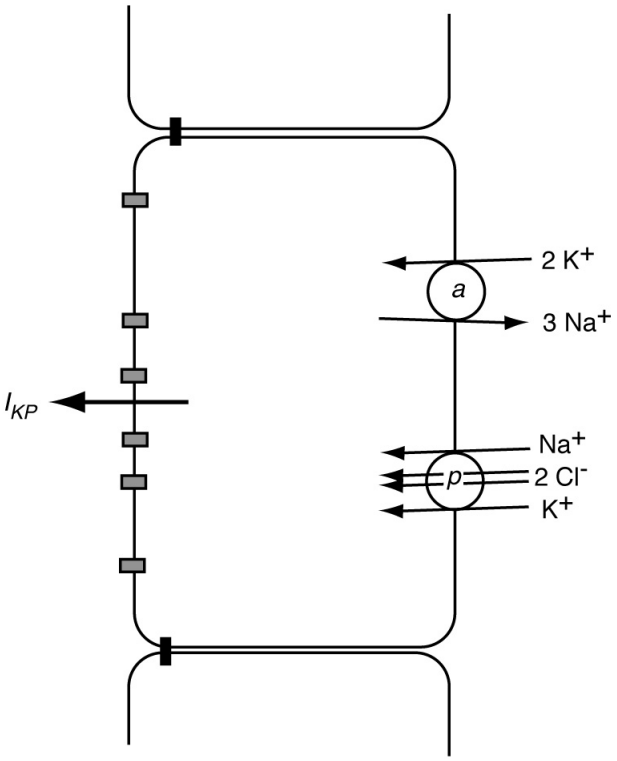
580.439/639 Final Exam, 2011

3 hours, closed book except 2 sheets of paper
Do all problems.

Problem 1

Short answer questions:

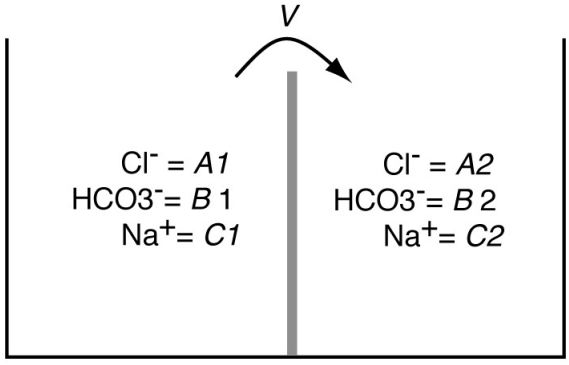
Part a) Consider the cell drawn at right, which is a component of a transport epithelium in the inner ear. In the right-hand membrane there are two transporters, a Na-K-ATPase (*a*), which consumes ATP to transport potassium and sodium, and a Na-K-Cl cotransporter (*p*) which uses the energy stored in the electrochemical potential of sodium to transport potassium and chloride as shown. *a* and *p* are the rates of transport in moles/(cell s), i.e. *a* is 1/3 the flux of sodium and *p* equals the 1/2 the flux of chloride. In the left-hand membrane there are only passive potassium channels through which a potassium current I_{KP} passes.



Assuming that the other transporters for sodium (channels or any other transporters) carry negligible fluxes, and ignoring the chloride transport, write an equation for the passive flux I_{KP} in the steady state. You should be able to write I_{KP} in terms of the rate of active transport *a*. Define suitable units for *a* and *p* and give I_{KP} in units of current.

Part b) The CFTR (cystic fibrosis transmembrane regulator) is an ion channel permeable to Cl^- and HCO_3^-, but no other physiological ion. Suppose that the ion path in the channel pore is lined with weak charges. Are they likely to be negative or positive? Explain why.

Part c) Suppose a membrane containing only CFTR channels separates two solutions with the constituents shown in the figure at right. The membrane potential *V* is measured. Write an expression for the relative permeability of HCO_3^- and Cl^- based on the concentrations given and the measured *V*. For this problem, use the GHK equation and the constant-field equation and assume the gates of the CFTR channels are open.



Part d) A recent paper contains a methods description similar to the following: "We made in-vivo whole-cell recordings. Stimuli were used to activate synapses on the cell. The sensitivity to

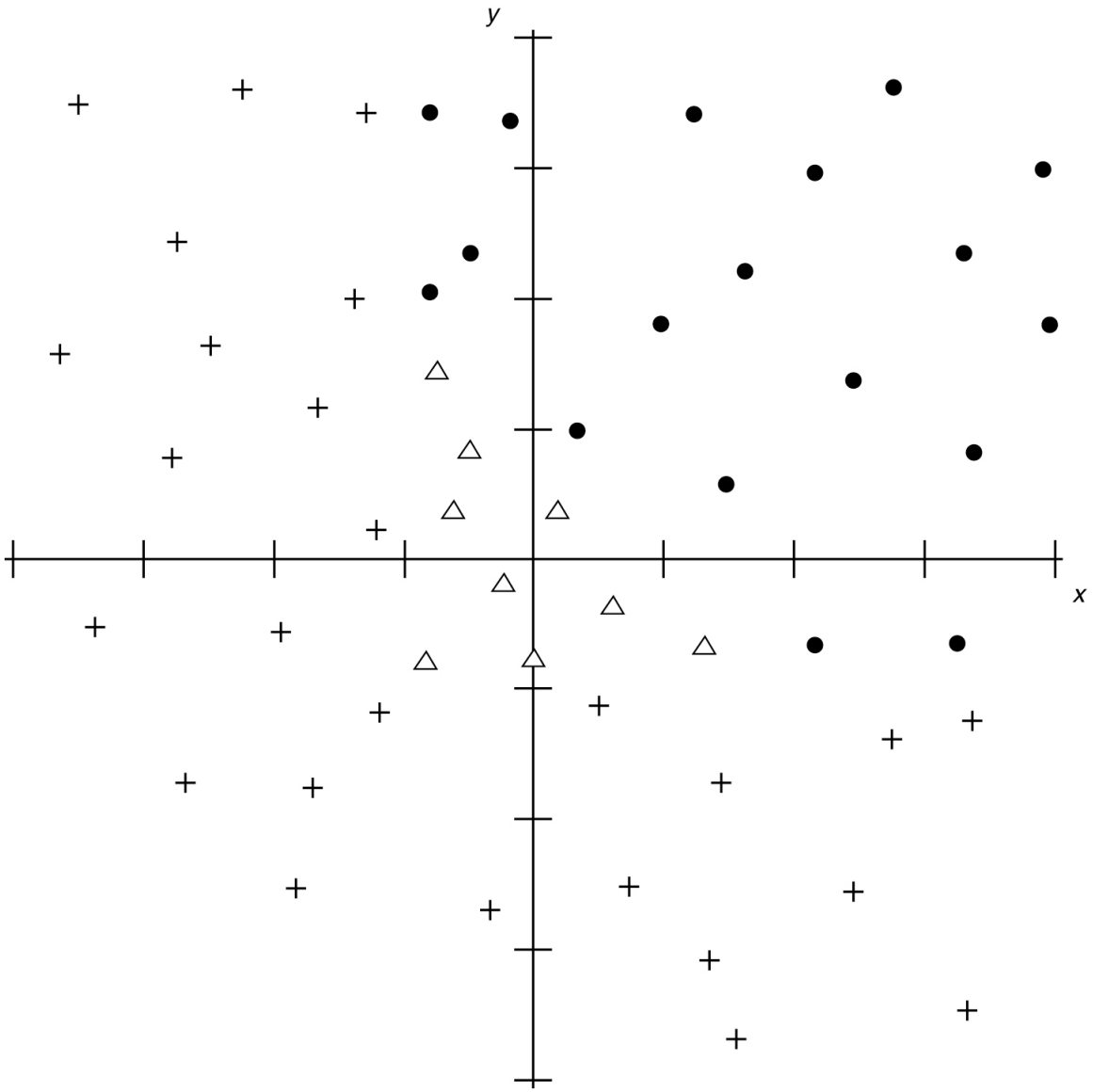
different stimuli was assessed in voltage-clamp by holding the cell at hyperpolarized (≈–70 mV) and depolarized (≈–20 mV) membrane potentials to reveal excitatory and inhibitory postsynaptic currents (EPSCs and IPSCs), respectively." Draw a circuit for a single-compartment cell containing only membrane capacitance, a resting channel, an excitatory synaptic channel, and an inhibitory synaptic channel. Use the diagram to explain how these voltage clamps allow EPSCs and IPSCs to be measured separately, even though the stimuli activate them both simultaneously. In this experiment, voltage-gated channels were eliminated by a cocktail of channel antagonists (TTX, TEA, Cd^{++}, etc.).

Part e) Consider the two-dimensional separation problem shown in the plot on the next page. The data points are vectors in the [*x*,*y*] plane which must be classified into three groups (circles, pluses, and triangles). Sketch a multi-layer perceptron network that will do this classification. There is more than one answer. The input layer should consist of two neurons taking on the values *x* and *y*. You will need a hidden layer with some number of neurons (you pick) and an output later with three neurons, one of which lights up (+1) for each of the three classes. Use neurons with a sgn(*x*) squashing function as below for the hidden and output layers. If it is convenient, you can use the next page to write out your answer.

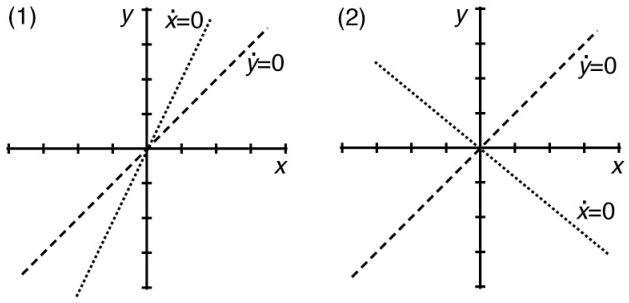
$$\tau \frac{dV}{dt} = -V + S\left(\vec{w} \cdot \vec{u} - \gamma\right) \qquad \text{where} \qquad S(x) = \text{sgn}(x)$$

As usual, V is the output of the neuron, $\vec{u}$ is the input vector, and $\vec{w}$ is the weight vector.

Part f) Linear cable theory implies that synapses that are further from the soma should produce smaller post-synaptic potentials and currents in the soma. Yet it is often observed in cortical neurons that EPSPs or EPSCs have about the same amplitude in the soma regardless of the location of the synapse on the dendrites. Explain how this comes about.


y
x

Problem 2



In the vicinity of an equilibrium point, the nullclines can be approximated as two intersecting straight lines as in the figures at right. These plots are drawn centered on the equilibrium point, which is at the origin. In the examples discussed in class, cases like (1) were saddles (*V* nullcline steeper than the *w* nullcline), whereas cases like (2) were stable. This problem considers whether these statements are always true. Suppose the linearized differential equations near the equilibrium point are as follows.

$$\frac{dx}{dt} = ax - by$$
$$\frac{dy}{dt} = x - y \qquad (*)$$

For this problem, assume that $b>0$ and a can be either positive or negative. For the nullclines drawn above, the $\dot{y}$ nullcline has slope 1 and the $\dot{x}$ nullcline has slope a/b. It turns out that differential equations like the MLE or similar 2nd-order neural models can be rearranged to the form of Eqn. (*) (see part d below; note that this is not generally true for 2nd order systems!).

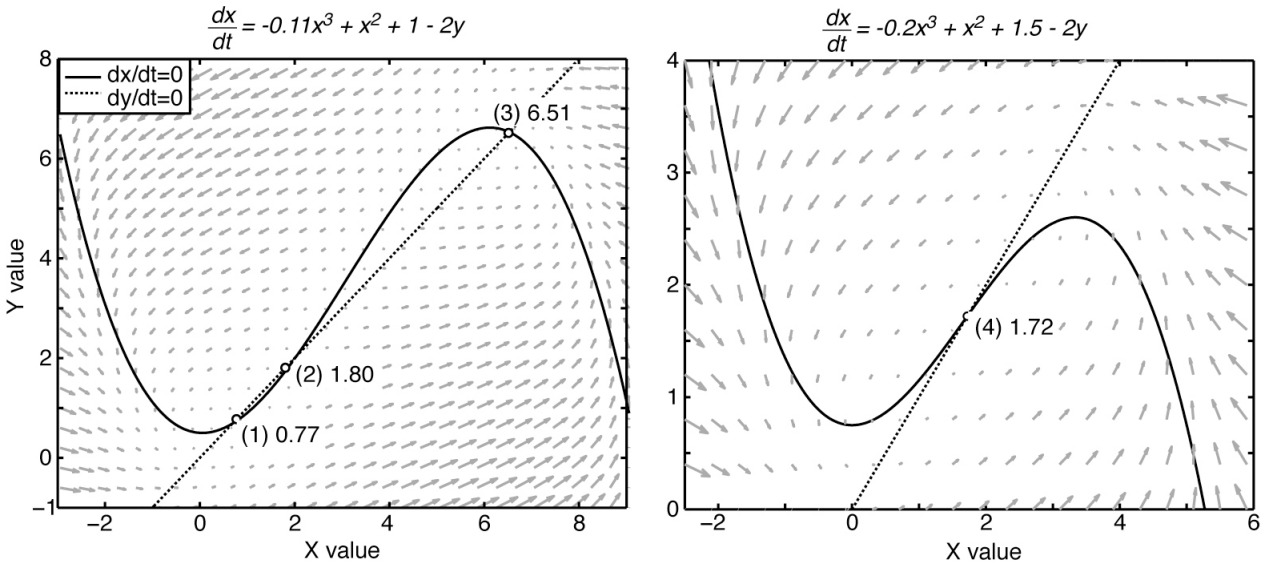
Part a) Write the Jacobian for Eqn. (*) at the equilibrium point [0,0] and compute its eigenvalues. Show in a plot of the *a*-versus-*b* plane the regions where the equilibrium point has various properties (stable, unstable, real, complex, saddle).

Part b) For the two sketches (1) and (2) shown in the drawing above, what are the possibilities for the classifications of the equilibrium points? This should be clear from your answer to part a).

Part c) Consider the differential equations

$$\frac{dx}{dt} = px^3 + x^2 + q - 2y$$
$$\frac{dy}{dt} = x - y$$

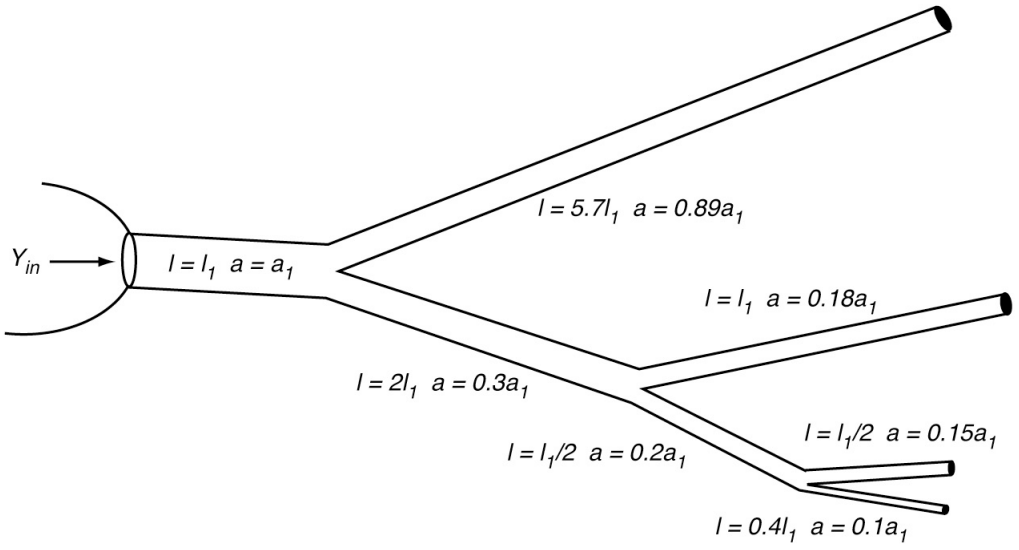
Below are shown two phase planes for various values of *p* and *q*. The *dx/dt* equation is shown at the top of each phase plane. The equilibrium points are numbered and their *x* and *y* values (which are equal) are given. Classify each of them. For some of them, you should be able to classify by inspection using your answer to part a). For others, you will have to compute one value from the differential equation (it is OK to compute the Jacobian and do the whole analysis, but that will take extra time).



Part d) EXTRA CREDIT. This is hairy. Do it last. Start with the Morris-Lecar equations and show that they can be linearized at an equilibrium point to Eqn. (*). To reduce this to a two-parameter problem, it will be necessary to scale both V and w, replacing them with $V' = V/l$ and $w' = w/k$ as well as scaling the time axis as $t' = t/m$, where l, k, and m are scalars. This is analogous to replacing x and t in the cable equation with χ and T.

Problem 3

Consider the dendritic tree sketched below. The radii and lengths of branches are given. Assume as usual that the radii of branches are constant between branch points, but change at the branch points.

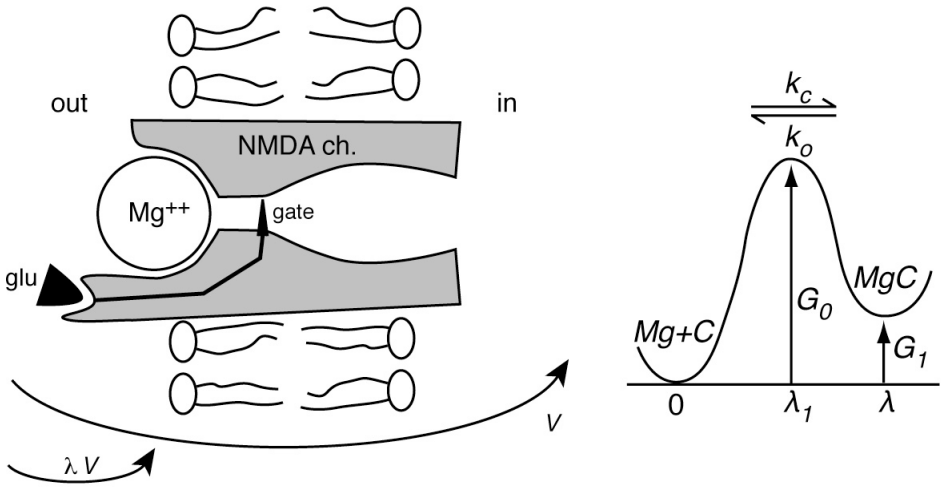


Part a) Write an expression for the input admittance Y_{in} of the tree, assuming that the tree is passive with open circuits ($Y_L = 0$) at the ends of the terminal branches. There's an easy way and a hard way. Consider the equivalent cylinder.

Part b) Show that if $|qL|<<1$, then $Y_{in} = (const)\ Area$, where *Area* is the total area of the dentritic membrane in the tree. Show that this result equals the input conductance of a single compartment (C_D in parallel with G_D) with the parameters of the equivalent cylinder, ignoring cable effects. (HINT: $q = \sqrt{1+s}$ but be careful about units; the series expansion for $\tanh(z) = z - z^3/3 + 2z^5/15 - \ldots$).

Problem 4

In class, amplification of post-synaptic potentials by NMDA channels was discussed. This problem considers the voltage-dependent gating of NMDA receptors. The figure below shows a conceptual diagram of an NMDA channel. The gate is opened by glutamate molecules binding at sites on the channel (two are required, only one is shown), but an open pore also requires removing the Mg^{++} ion from the channel pore.



Part a) Suppose the Mg^{++} block can be described by a first-order reaction, as shown in the barrier diagram at right; the diagram is shown for transmembrane potential V=0. The channel (C) is not Mg^{++} blocked when in the state marked "0" or "*Mg + C*" but is blocked in the state λ or *MgC*. The Mg^{++} ion moves through a fraction λ of the membrane potential in binding to the channel. Show that the steady-state fraction of unblocked channels is given by

$$\frac{C}{T} = \frac{1}{1 + ae^{-bV}} \quad ,$$

where T is the total concentration of channels. Give expressions for a and b.

Part b) The analysis above is for static conductances in a steady state of block or synaptic activation. In fact, NMDA channels gate slowly and it may be desirable to model the dynamics of G_{NMDA}. Write differential equations to model the Mg^{++} block and the glutamate activation of the NMDA channels. These should look like HH equations. For the Mg^{++} block, use the dynamics

implied by the barrier diagram given in part a). For the glutamate binding, assume the following (simplified) reaction sequence. The channel is open in the ON_2 state.

$$C + 2N \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ON_2 \quad ,$$

where C is the channel and N is the neurotransmitter glutamate.

Treat the Mg^{++} block and the glutamate binding as independent and assume that both must be open for the channel to be open.