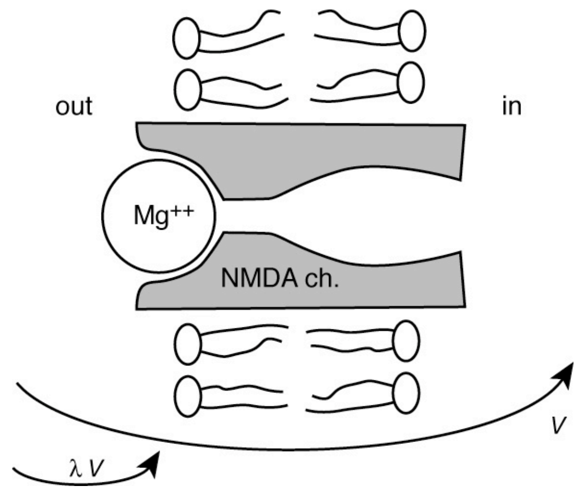
580.439/639 Midterm Exam, 2006

Closed book except for one piece of paper. 11 points for each part of each problem plus 1 point for your name. Turn in part of your answer on the attached sheet .

Problem 1:

This problem considers a model of blockade of NMDA receptor channels by Mg^{++} ions. As shown in the drawing, Mg^{++} ions can enter the NMDA receptor channel from the outside solution. They don't pass through the channel, however, and block it instead. Thus the channel is closed if either its gate is closed or there is a Mg^{++} in the channel. Gating of the channel is not a concern here.



Part a) Sketch a single-barrier model for the transition of the Mg^{++} ion into the channel as follows:

$$\text{Mg} + \text{Ch} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \text{Mg-Ch} \,,$$

where Mg-Ch means the concentration of Mg^{++} bound to the channel. Ignore the other ions (Na^+, K^+, and Ca^{++}) in the system, even though a full model would have to consider them. Assume that the Mg^{++} ion passes through a fraction λ of the transmembrane potential ΔV when it enters the channel. You will have to invent some parameters. Write equations for the rate constants k_1 and k_{-1}.

Part b) Write a differential equation for the binding of Mg^{++} to the channel, i.e. for d Mg-Ch $/dt$. It may be wise to make the assumption that independence does not hold in this case (there is a finite fixed amount of channel). In this case you should be able to write the differential equation in terms of Mg-Ch and Mg only, with no term for the concentration Ch.

Part c) Write an expression for the equilibrium fraction of **unbound channel**, that is the fraction of channels that are available to pass other ions, as a function of $[Mg^{++}]$. By equilibrium is meant dMg-Ch / $dt = 0$.

Part d) In a later problem, the following expression will be used for the current through an NMDA channel as a function of V and $[Mg^{++}]$, when its neurotransmitter gate is open. The current is a sum of Na^+, K^+, and Ca^{++} currents with a reversal potential E_{NMDA}.

$$I_{NMDA} = \frac{G_{NMDA}}{1 + [Mg^{++}]\, e^{-V/q} \big/ K_{Mg}} (V - E_{NMDA}) \ . \qquad (*)$$

Show that Eqn. (*) is consistent with your answer to Part c) above and write equations for the parameters of Eqn. (*) in terms of the parameters of your answer to Parts a)-c). Of course, the basic equation is $I_{NMDA} = G(V,[Mg^{++}])\,(V-E_{NMDA})$, so the problem is to explain why $G(V,[Mg^{++}])$ takes the form above.

Problem 2

Neurons in the forebrain that use dopamine as a neurotransmitter often have an unusual dendritic oscillation supported by current through NMDA channels and a Na transporter (active transport pump). This problem follows an analysis by Li, Bertram, and Rinzel (Neuroscience 71:397-410, 1996). When the dendrites are isolated from the cell body, there are three predominant currents: 1) current through NMDA channels, which is given by Eqn. (*); 2) current through a leakage channel, given by $G_L(V\text{-}E_L)$; 3) current carried by the active transporter which regulates the $[Na^+]$ in the cytoplasm;. The transporter current is as follows:

$$I_{pump}(Na) = R_{pump}\left[\phi(Na) - \phi(Na_{eq})\right] \,, \qquad (**)$$

where $Na = [Na^+]$ inside the cell and

$$\phi(Na) = \frac{Na^3}{Na^3 + K_P^3} \;.$$

N_{eq} is the equilibrium $[Na^+]$ toward which the pump strives. The pump is a Na-K ATPase, so it pumps 3 Na out for each 2 K pumped in. I_{pump} is the charge transport that results from the unequal rates of transport of Na and K.

Part a) Write the differential equations for this system. There should be one for membrane potential and one for *Na*, the concentration of Na^+ in the cytoplasm. For the latter, assume that the sodium current through the NMDA channels is

$$I_{Na,NMDA} = \frac{G_{Na,NMDA}}{1 + [Mg^{++}]\, e^{-V/q} \big/ K_{Mg}} (V - E_{Na})$$

That is, it has the same form as the total NMDA current (Eqn. (*)) with a different conductance and reversal potential.

It is sufficient to write the differential equations in terms of I_{NMDA}, $I_{Na,NMDA}$, I_{pump}, and I_{leak} and not necessary to substitute the complex expressions above.

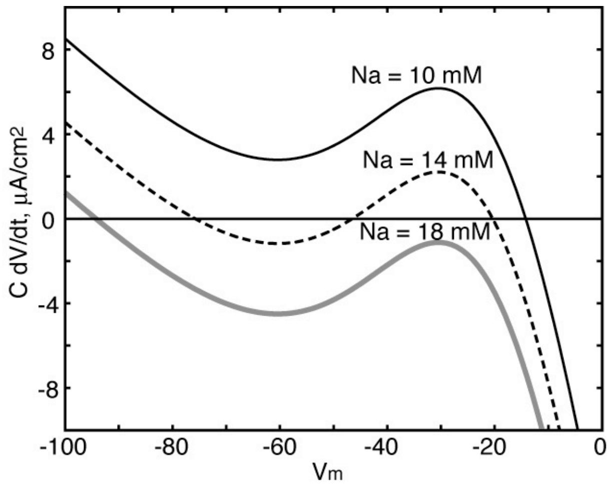
Assume that the currents above are specified as $\mu A/cm^2$, that V is in mV, and Na is in mM. It is sufficient to deal with current density. Assume the membrane has capacitance C_m $\mu Fd/cm^2$.

Your differential equation for *Na* should look like

$$\frac{dNa}{dt} = a\left[-I_{Na,NMDA} - b\, I_{pump}\right] \qquad (***)$$

To get credit for this part, you must tell what *a* and *b* are and justify the terms on the r.h.s. (hint: pay attention to units).

Part b) The figure at top-right on the next page shows a plot of dV/dt versus V calculated from the equation you should have derived in Part b). The calculation was done for three values of *Na*, defined in the legend. Although this is not a proper phase plane, in this case it can help to understand the behavior of the system qualitatively, because dNa/dt is much slower than dV/dt. That is, because V changes much faster than Na, the V component of the system behaves approximately like a 1-D system.



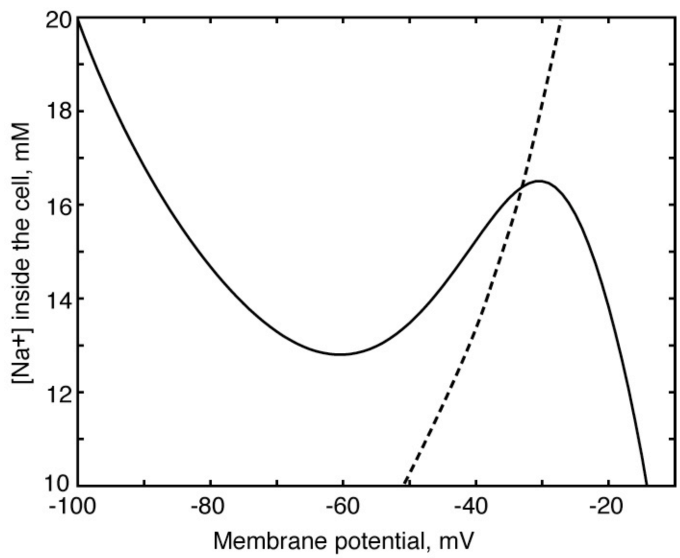
On the copy of this figure on the attached page, mark the equilibrium points for the 1D V system and tell whether each one is stable or unstable and why.

Suppose that when V is near –10 to -20 mV then $dNa/dt > 0$. Make a sketch to show how V and Na change with time until there is a bifurcation. Remember that $|dNa/dt| << |dV/dt|$. Continue the plot by assuming that when V is near –80 to –100 mV, $dNa/dt < 0$. Your plot should look like a limit cycle.

Part c) Write equations for the isoclines of this system. Again, do not write them out in their full glory, you won't be able to reduce them much; instead leave them in terms of I_{NMDA}, etc.

If $G_{NMDA} = G_{Na,NMDA} = 0$, which occurs in the absence of glutamate neurotransmitter, the equilibrium point is easy to compute. Do so. This equilibrium point is stable and a global attractor, so this case is not very interesting.

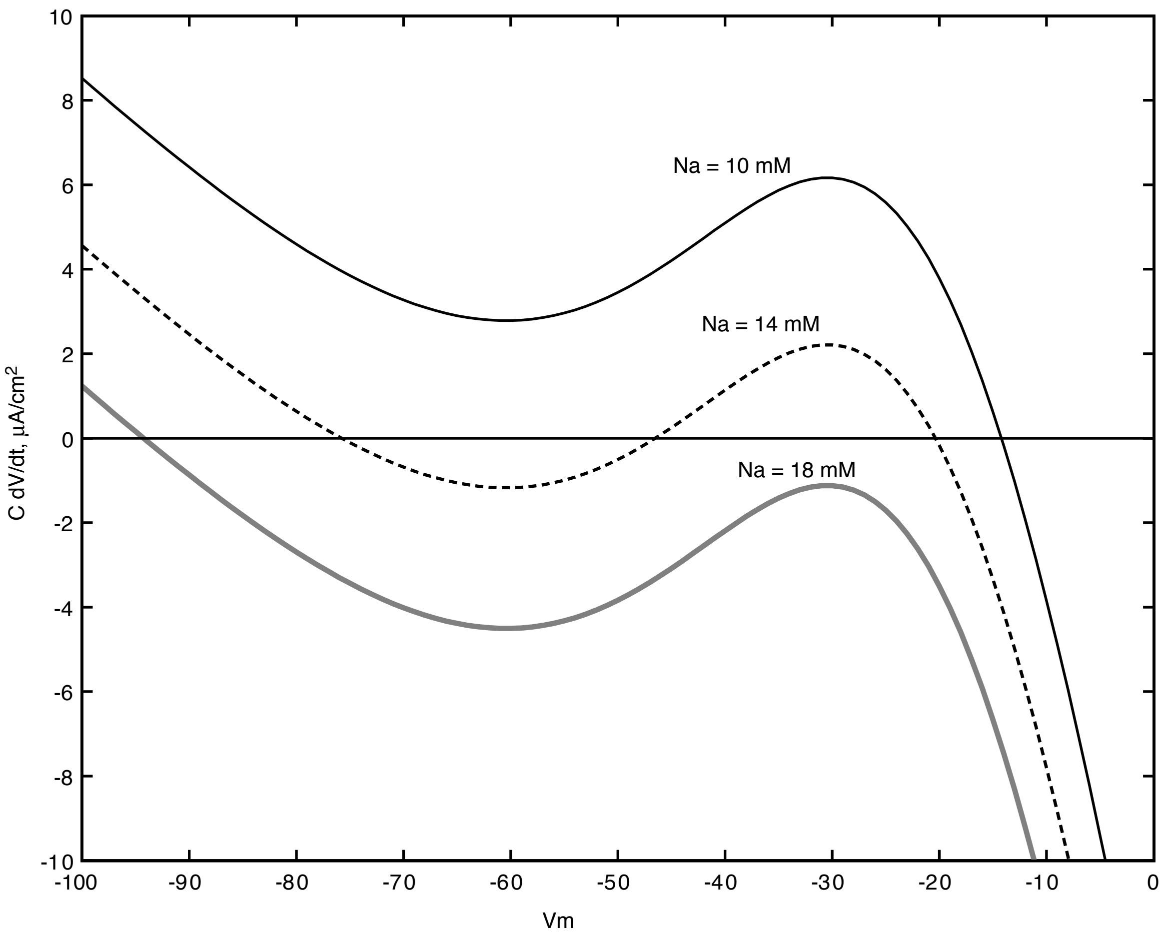
Part d) The figure at right and on the attached sheet shows the isoclines plotted in a proper 2D phase plane. Label this phase plane with the following features:



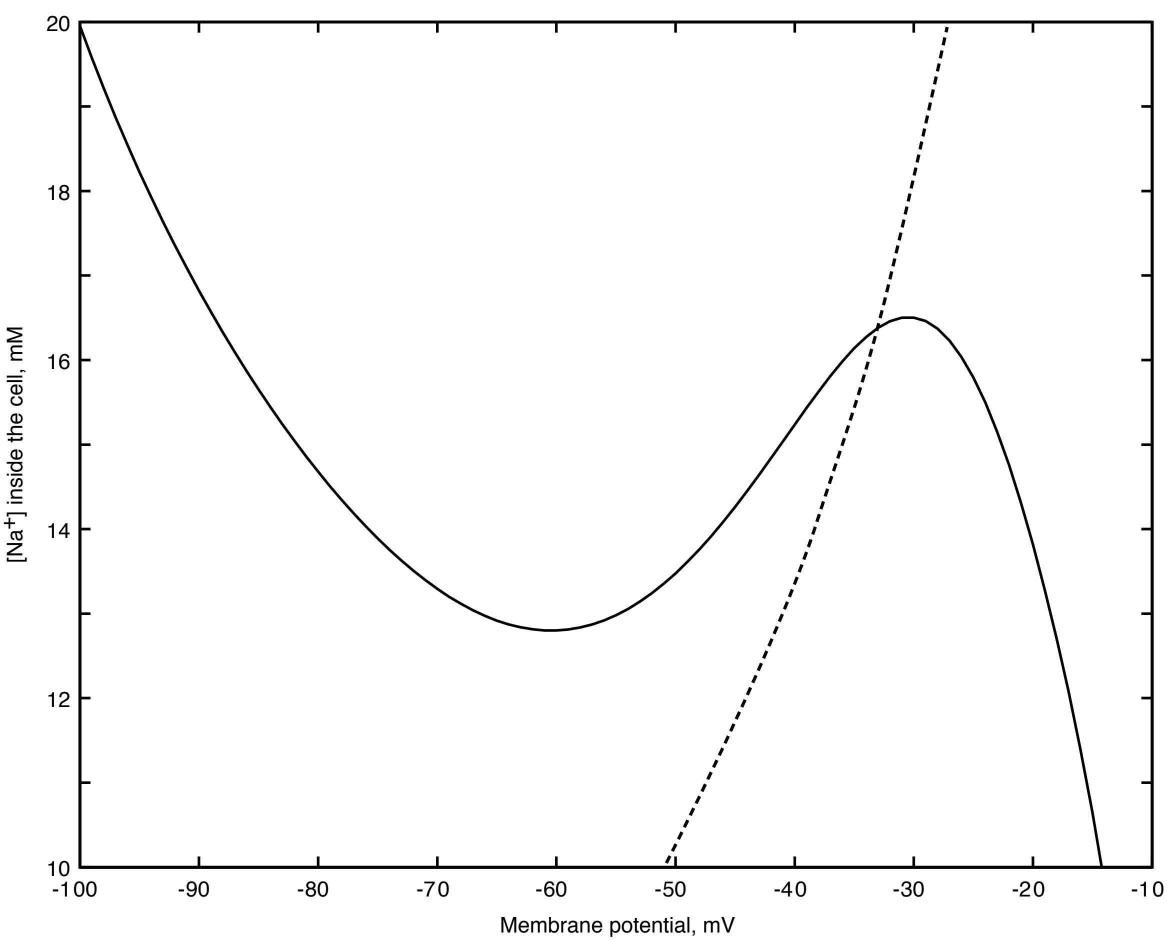
$$\frac{dV}{dt} = 0 \qquad \frac{dNa}{dt} = 0 \qquad \text{Eq. point} \qquad \text{Arrows}$$

where "Arrows" means arrows to show the directions of trajectories in the subregions of the plane. You will have to guess which isocline is which, but the graph in Part b) will help.

Part e) The equilibrium point in the phase plane of Part d) turns out to be stable. Can you show that the system does or does not have a limit cycle (without simulating it)? If so give the argument. It turns out there is one, as argued in Part b). Sketch it on the phase plane. Again, remember that $|dNa/dt| << |dV/dt|$.



Na = 10 mM
Na = 14 mM
Na = 18 mM
C dV/dt, μA/cm²
Vm



[Na+] inside the cell, mM
Membrane potential, mV