580.439/639 Final 2014

3 hours, closed book except for cheat sheet. Do all problems.

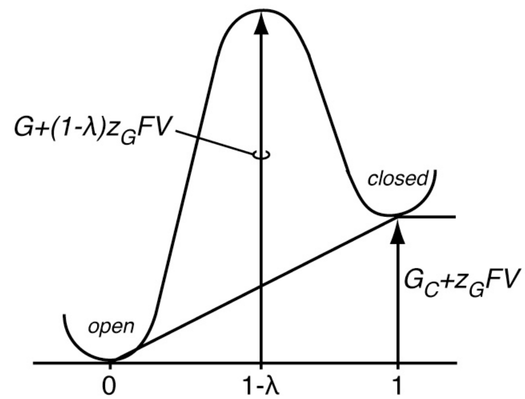
Question 1

Part a) (5 points) A transport mechanism moves an H^+ ion and an uncharged molecule X through the membrane in a coupled fashion, i.e. H^+-X moves through the membrane as a complex. Given that the cell's membrane potential is -60 mV and the pH is 7 everywhere (inside and outside the cell), what is the equilibrium concentration of X inside the cell if the concentration outside is 1 μM?

Part b) (5 points) Same question, except X has a charge of –1, i.e. H^+-X^- moves through the membrane as a complex?

Question 2

Consider the Boltzmann model of the potassium channel n-gate that was studied in a homework problem. The model works out expressions for $n_\infty(V)$ and $\tau_n(V)$ based on a single barrier model, at right. Remember that n is the fraction of channels in the open state. The results are as follows:



$$n_\infty(v) = \frac{1}{1+e^{-z_G(v+v_h)}} \qquad \tau_n(v) = \frac{1}{\alpha\, e^{\lambda z_G v}\left[1+e^{-z_G(v+v_h)}\right]}$$

where $$v_h = \frac{G_C}{z_G RT} \qquad \alpha = k e^{-(G-G_C)/RT} \qquad v = \frac{FV}{RT}$$

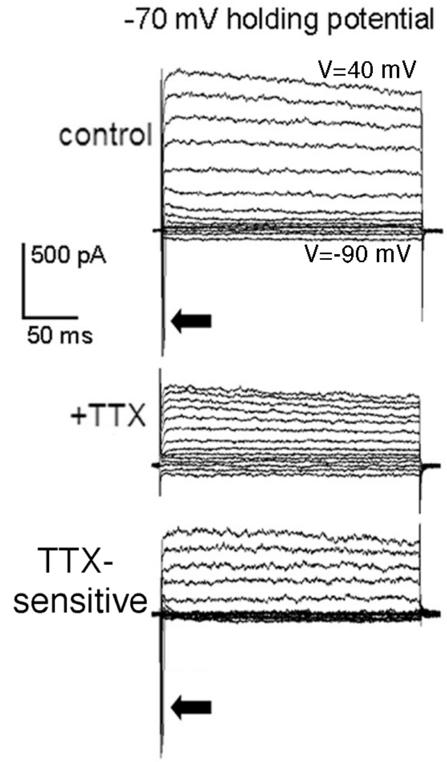
and z_G is the charge on the gate.

Part a) (10 points) Show starting with the energy diagram that, at equilibrium, $n = n_\infty(V)$. That is show that the equation for n_∞ derived from the differential equation for n is the same as the equilibrium distribution of channel in the open state.

Part b) (10 points) Starting with the HH differential equation for dn/dt, what is the condition for a steady state of n? How does steady state differ from equilibrium here? If they do not differ, explain why.

Part c) (15 points) If the single-barrier above were used to model flux through an ion channel <u>in the independence regime</u> (instead of gating of a channel), the model would be drawn in the same way, with "open" and "closed" replaced by S_1 and S_2 the concentrations of ion on the two sides of the membrane. Write the conditions for equilibrium and steady state in this case, assuming the ion has charge z_G. Be careful, don't just write the Nernst equation, we are assuming that some solute interaction raises the free energy of S_2 by G_C, not usually the case. Can the conditions at equilibrium differ from those at steady state in this case? If so, explain why this case is different from the n-gate model (i.e. how the assumptions differ).

Question 3 (from Hage and Salkoff *J. Neurosci*. 32:2714, 2014)



The figure at right shows voltage-clamp currents in a cell containing only sodium and potassium channels. The membrane was clamped to potentials from -90 to +40 mV in 10 mV steps and the figure shows the membrane currents evoked by those clamps. The important data for this question are the easily-seen currents at the highest clamp voltages (the most positive currents). The top plot shows large outward currents that get larger as the clamp voltage increases. The middle plot shows the currents that remain after TTX (tetrodotoxin, which blocks all sodium channels) is applied to the preparation. The currents are still outward, but smaller. The bottom plots shows the "TTX sensitive" current, which is the difference between the top and middle plots. These data are offered as evidence for sodium-dependent potassium channels (K_{Na}), i.e. potassium channels whose gates are opened by a rise in intracellular sodium concentration. Explain how that conclusion is drawn, by answering the following.

Part a) (15 points) The top plot contains both potassium and sodium currents, the second plot contains only potassium currents, because TTX is a very reliable blocker of all sodium channels and doesn't directly affect potassium channels. Explain why these two plots are evidence for a K_{Na} channel. For example, why can't the difference between the top and middle plots be explained by the loss of sodium currents alone?

Part b) (10 points) What is the large negative deflection at the start of the voltage clamp in the bottom and top plots (pointed to by the arrow) and why is it missing in the middle plot?

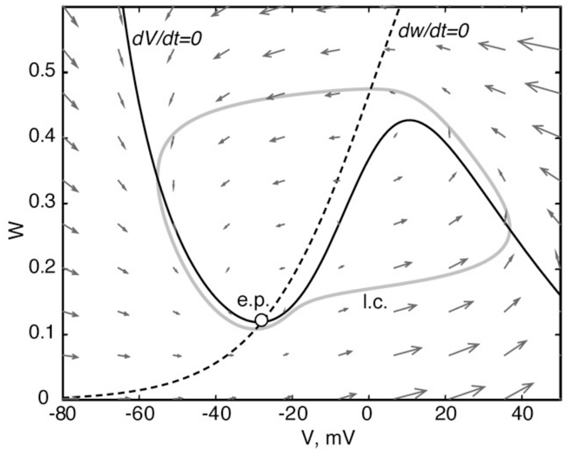
Part c) (15 points) What ion carries the outward (positive) currents in the bottom plot? Also, what ion carries the outward currents in the middle plot? How are these two outward currents different, do they flow through the same channels?

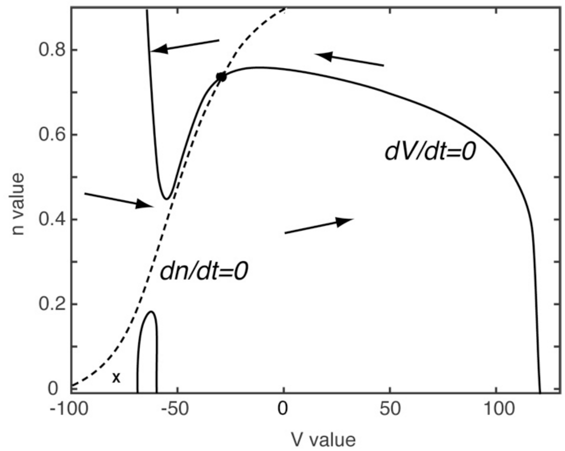
Part d) (10 points) There are two kinds of sodium channels, those with inactivation and those without (called "persistent"). Which kind of sodium channels are likely to be coupled to the *K* channels, given the figure above (Hint: the duration of the currents)? Do these data conclusively eliminate one type of channel and argue for the involvement of the other?

Part e) (10 points) How could the uncertainty that remained in your mind in part d) be eliminated by veratridine, which enhances currents in persistent sodium channels but not in sodium channels with an inactivation gate?

Question 4

Part a) (15 points) The phase plane drawn at left below is one that was discussed extensively in class and project 1. It shows the MLE with an applied current very near the Hopf bifurcation produced by applied external current. At this current, the system is bistable, it has a stable equilibrium point (e.p.) and a stable limit cycle (l.c.). At first the Poincaré-Bendixson theorem does not seem to apply to this system, because it is not clear that there is a region *R* in which the system has no equilibrium point but from which the system cannot escape. Argue that there is such a region, so the theorem actually does predict the existence of the limit cycle. (Hint: not everything is drawn in this phase plane.)





Part b) (20 points) The phase plane drawn at right above is from a modification of the reduced HH model with two state variables (*V* and *n)* studied in the last three parts of project 1. The nullclines of *V* and *n* are shown by solid and dashed lines. The modification is not important, but it produces the small inverted-U shaped piece of *V* nullcline in the lower left part of the phase plane. This connects to the rest of the *V* nullcline outside the reachable portion of the phase plane. There is one <u>unstable</u> equilibrium point (solid dot). Argue that there is a limit cycle in this system and sketch its likely trajectory, using the "low-temperature" assumption, that $|dV/dt| >> |dn/dt|$, which is true except at the *V* nullclines.

Then, sketch a likely trajectory beginning at the **X** in the lower left corner of the phase plane. Use the attached page for the sketches. (from Doiron et al. 2014).

Question 5

Part a) (15 points) The cable equation with <u>applied current</u> inputs is linear. Describe two (or more) ways in which dendritic trees are non-linear, i.e. ways in which summation of inputs in dendrites departs from the predictions of linear cable theory with inputs applied by current injection.

Part b) (15 points) Real neurons have thousands of synaptic inputs, all of which are active at some moderate rate in vivo. What should be the effect of the activation of postsynaptic channels in this way on the electrotonic parameters of a cable (e.g. λ, τ_m, G_∞). What are the effects on transfer functions from dendrite to soma, say the voltage gain A_{synS} at D.C. (0 frequency). Remember that A_{synS} is equal to the ratio of the potential V_S produced in the soma and the potential V_{syn} produced at the synaptic site by the synapse. This question assumes ongoing random inputs, so that the effect of the synaptic activity can be approximated as a steady moderate synaptic input. Use equations where necessary.

Part c) (15 points) If the reversal potential of an inhibitory synapse is equal to the resting potential, so there is no IPSP, the synapse can still have an inhibitory effect. Explain how and tell whether there are any constraints on the relative placement of excitatory and inhibitory synapses to make this work.

Part d) (15 points) Explain from linear cable theory why action potentials should backpropagate (from soma into the dendrites) more strongly than to forward-propagate (from dendrites to soma). It will help to mention the MET.

Question 6

The voltage gain A_{01} was defined in class as the ratio of the potential V_1 at site 1 in a dendritic tree to the potential V_0 at site 0; the assumption is that the potential V_0 produces the potential V_1. For example a voltage clamp to V_0 at site 0 produces spreads throughout the tree, and has value V_1 at site 1.

Part a) (15 points) Derive a formula for A_{01} in terms of K_{01}, the transfer impedance from current injected at 0 to voltage produced at 1.

Part b) (20 points) One might expect that there is some symmetry in voltage gains, for example that A_{01}=1/A_{10} or that A_{01}=A_{10}. Show by counterexample that neither of these is true. (Or work out the correct relationship of A_{01} and A_{10}.)

Question 7

Consider a neural network containing two neurons, whose activations are E_1 and E_2. The differential equations defining the neurons are given below.

$$\frac{dE_1}{dt} = -E_1 + F(E_2 + K)$$
$$\frac{dE_2}{dt} = -E_2 + F(E_1 + K)$$
$$\text{where} \quad F(x) = \frac{1}{1 + e^{-10(x-0.5)}}$$

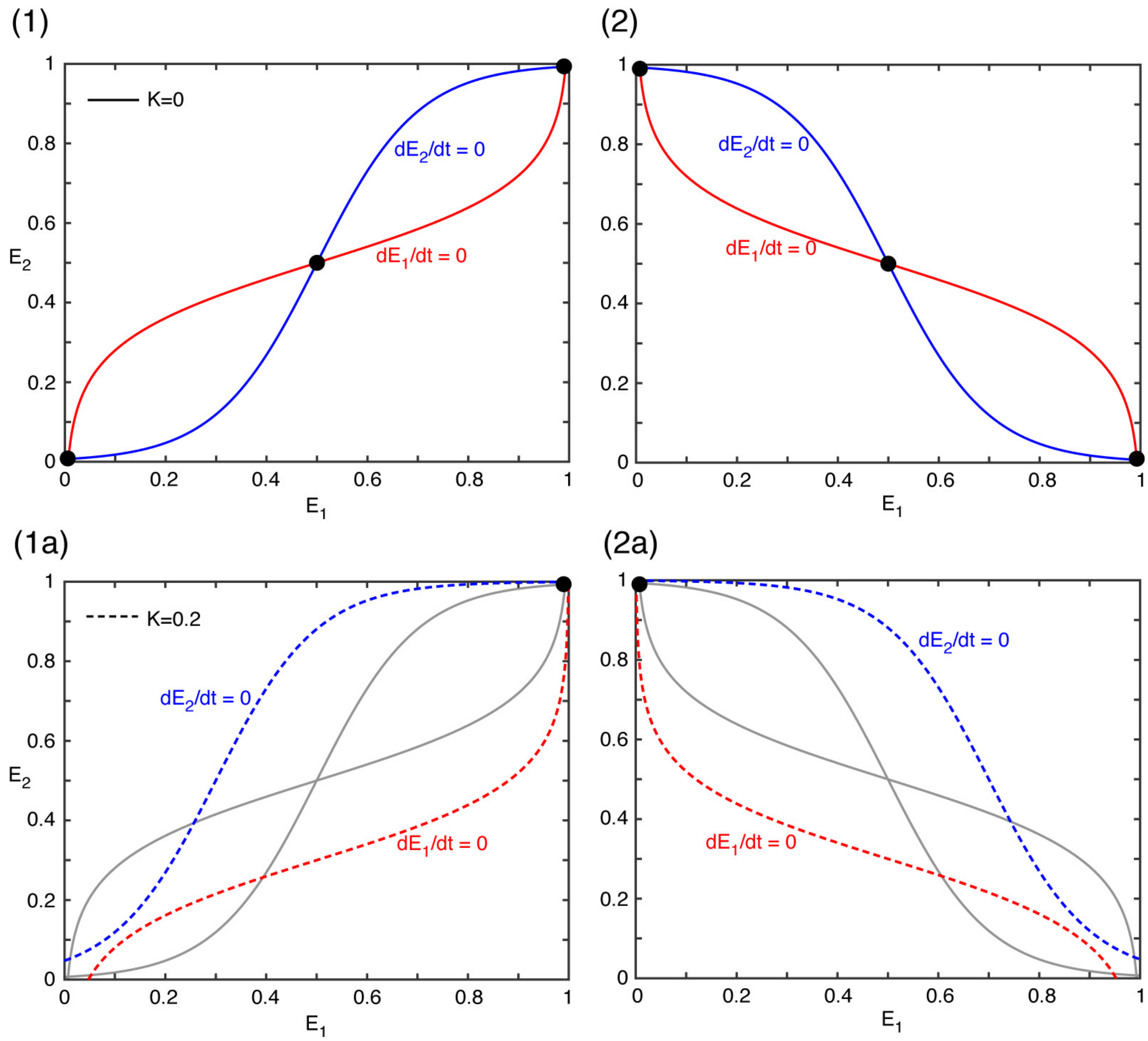
The neurons provide mutual recurrent excitation and receive a common input K (a constant). The squashing function is the function $F(x)$ given at right. This problem concerns the stability properties of this 2nd order system of model neurons, which is a simple memory circuit.

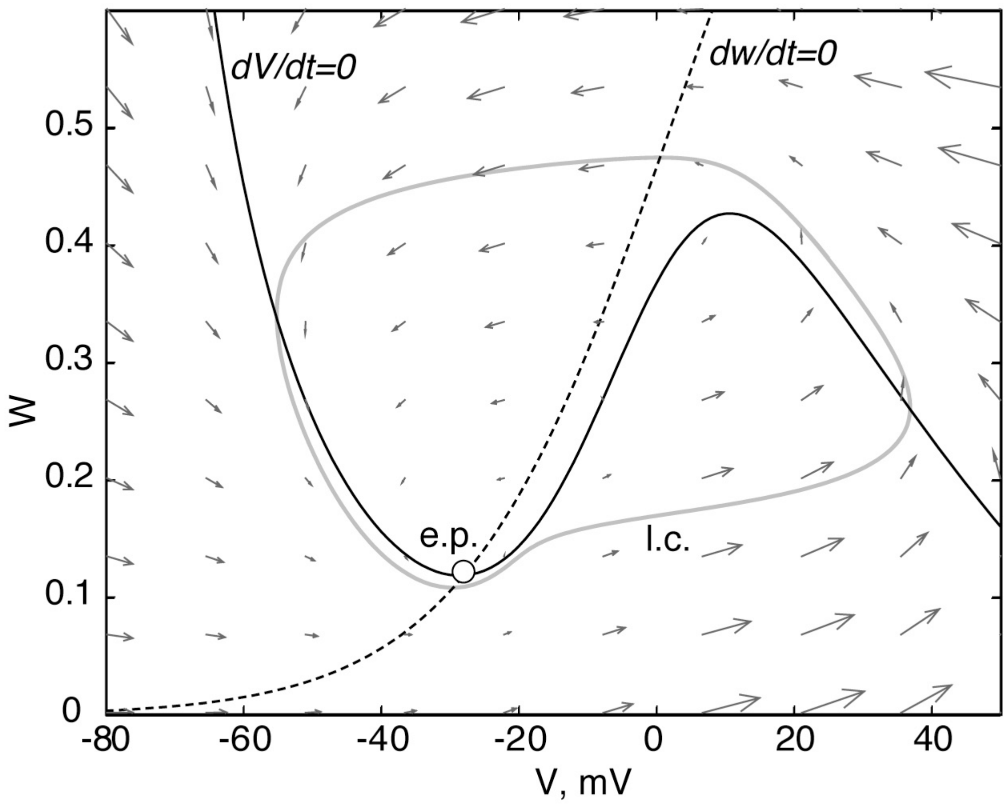
Part a) (15 points) The figure below shows two phase planes labeled (1) and (2). Which is the appropriate phase plane for the model above (for K=0)? Draw arrows on the phase plane to show the direction of trajectories in various places.

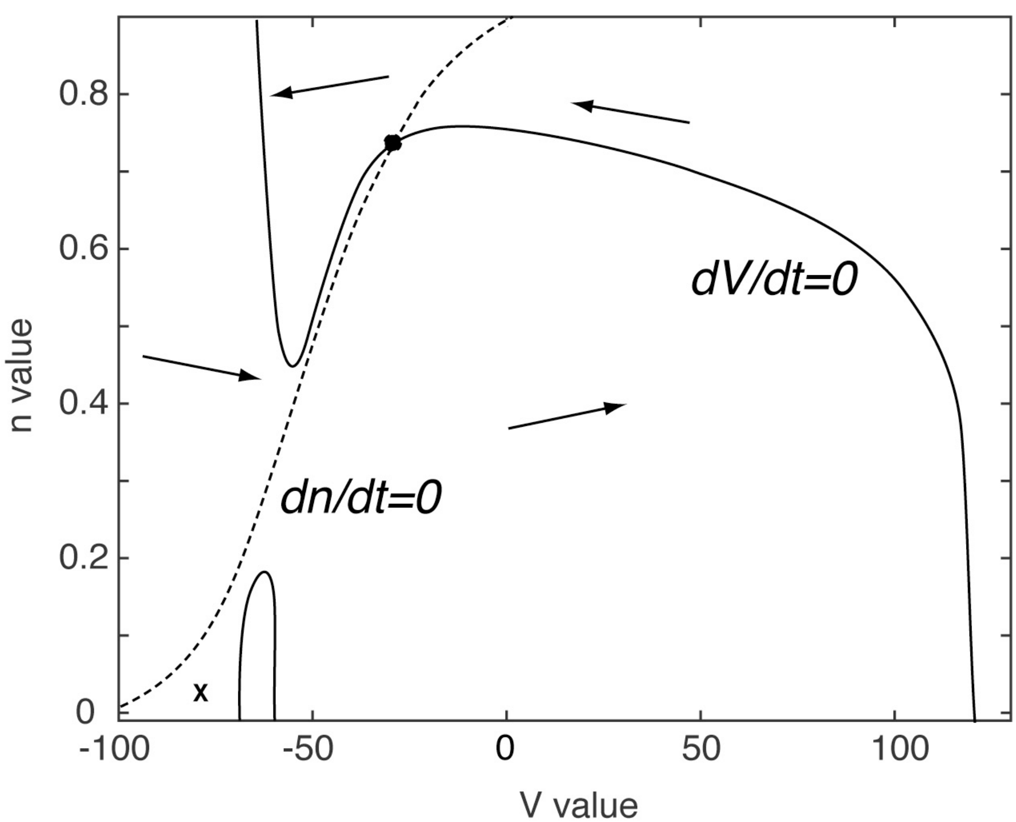
Part b) (15 points) The system has three equilibrium points, shown by the black circles. To compute their characteristics, write an expression for the Jacobian of the system. Compute the eigenvalues at the equilibrium points, assuming that they are located at 0, 0.5, or 1 (not quite correct, but close enough).

Part c) (15 points) The phase plane for the system with an input K = 0.2 is shown in (1a) or (2a). Tell what the steady state of the system will be with this input. What will happen if the input is K=-0.2?

Part d) (20 points) Sketch the bifurcation diagram for this system over a range of K from about -0.5 to 0.5. From the bifurcation diagram show how this system could be used as a memory.




dV/dt=0
dw/dt=0
e.p.
l.c.
W
V, mV
0.5
0.4
0.3
0.2
0.1
0
-80
-60
-40
-20
0
20
40


dV/dt=0
dn/dt=0
x
n value
V value
0.8
0.6
0.4
0.2
0
-100
-50
0
50
100