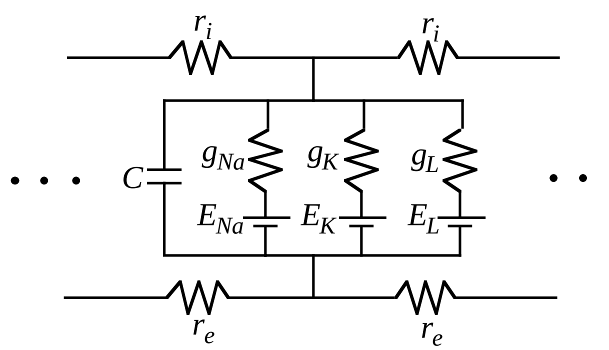
580.439/639 Final Examination

Take home. All sources may be consulted except that the exam may not be discussed with another person. Computers may (should) be used. The exam must be returned within 24 hours of the time it is picked up (to either 144 NEB or 505 Traylor). Do all problems.

Problem 1



40 pts Consider the problem of the effects of potassium accumulation in the extracellular space on propagation of the action potential in an unmyelinated axon. Each time there is an action potential at a point on the axon, some potassium is released from the axon into the extracellular space. Because the volume of extracellular space in real neural tissue is small and the extracellular potassium concentration is low, this potassium can have a significant effect on the axon's electrical properties. Write the equations necessary to model this situation. Consider the axon to be a series of compartments as in the standard model at right. Each membrane compartment contains a Hodgkin-Huxley sodium, potassium, and leakage channel, along with a membrane capacitance. Notice that the resistance of extracellular space is included in the model. Write equations to model the propagation of electrical activity in this model. Include the accumulation of potassium in the extracellular space and the effects of that accumulation on the electrical membrane model. You will have to define many terms to do this. Draw a sketch to show how you are handling the potassium accumulation, which should be done in compartments that correspond to the electrical compartments.

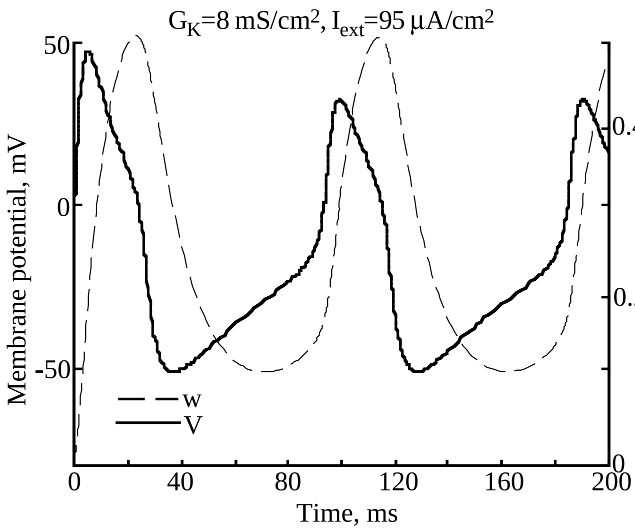
Problem 2

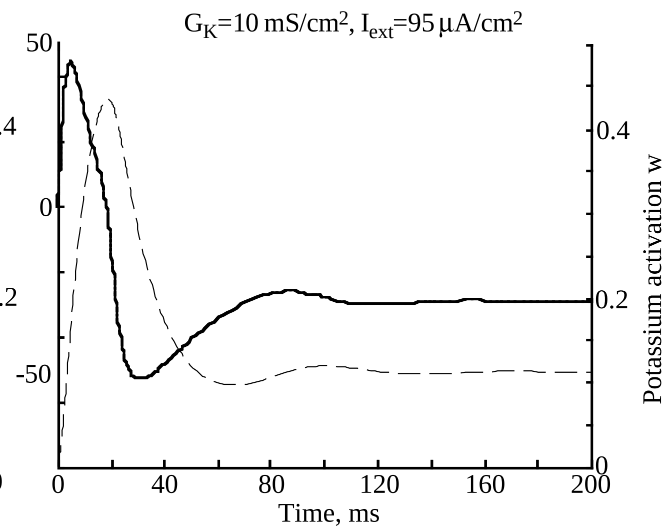
40 pts Suppose that someone told you that a certain cell has a calcium-activated chloride conductance in its membrane. Describe the experiments that you would do to test this idea. You have to provide plausible evidence that the membrane has a calcium-activated chloride channel, while eliminating the obvious alternatives. You have available patch and whole cell recording from the cell, the usual variety of pharmaceuticals for sodium, potassium, and calcium channels but none for chloride channels. You also have calcium chelators.

Problem 3

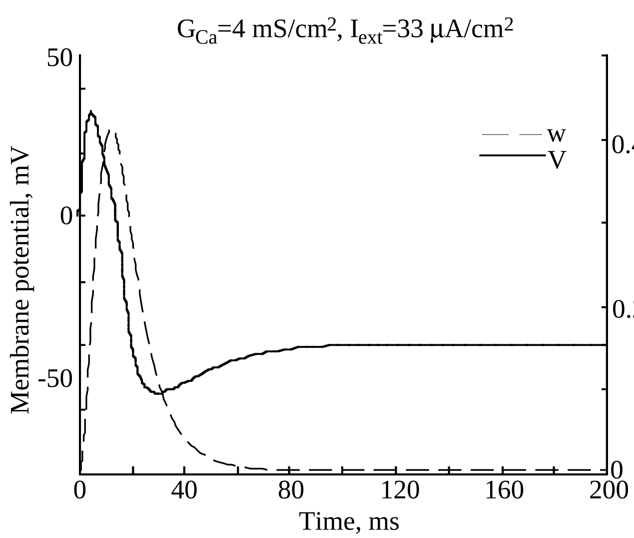
30 pts **Part a)** The Morris-Lecar equations produce a train of action potentials (a limit cycle) regardless of initial conditions, when used with the parameters of Fig. 7.1 of Rinzel and Ermentrout and an external applied current of 95 μA/cm^2. The first two cycles of this response, beginning from zero initial conditions, are shown at left below. However, if the value of G_K is changed from 8 to 10 mS/cm^2, the limit cycle disappears and a much larger current is required in order to see it again. The response from the same initial conditions is shown at right below. Explain why G_K has this effect,

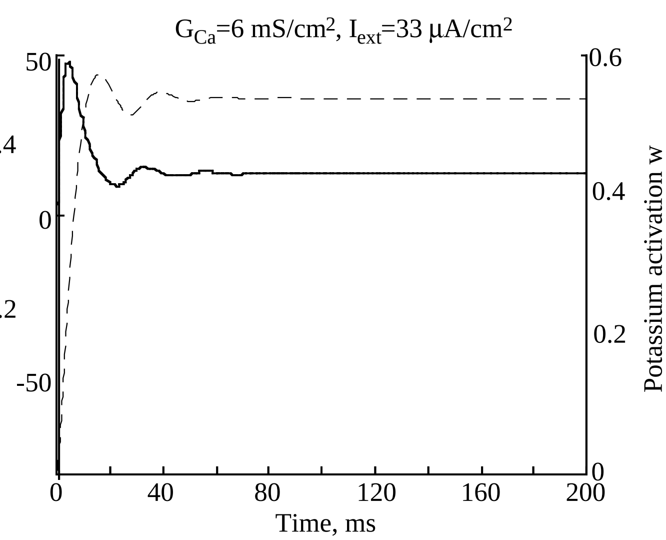
using phase plane concepts. Your answer should include the effects of the change of G_K on the features of the phase plane and an analysis of the conditions for the existence of a limit cycle.





Part b) With the parameters of Fig. 7.4 of Rinzel and Ermentrout the Morris-Lecar model produces a single action potential and then settles to its resting potential, as shown at left below. However if G_{Ca} is increased to 6 mS/cm^2 the system settles to a new resting potential near +13 mV,
30 as shown at right below. Explain this behavior, again using phase plane concepts. A form of
pts bifurcation occurs as G_{Ca} is varied from 4 to 6. Describe the bifurcation and sketch a diagram showing the equilibrium points and limit cycles in this system as a function of G_{Ca} over this range.





Problem 4

Consider a dendritic membrane which consists of a membrane capacitance, a linear (i.e. constant-conductance) leakage channel, and a Hodgkin-Huxley style voltage-gated sodium channel. This problem considers the effect of the sodium channel on the cable properties of the dendrite.

Part a) Compute a linearized approximation of the system around the resting potential V_R
20 (don't worry about what V_R is, just assume that there is one). To make this algebraically tractable,
pts assume that the inactivation variable h can be ignored, so that the sodium conductance is given by $g_{Na} = \bar{g}_{Na} m^3 h_\infty(V_R)$, with the inactivation gate held fixed at the h_∞ value at the resting potential. To make it easier, express the linearized model in terms of Laplace transformed variables (from 0 initial conditions).

Hint: you have seen this problem before; the linear approximation should take the form $d\vec{x}/dt = \mathbf{J}\vec{x} + \vec{i}$, where $\mathbf{J}$ is the Jacobian of the system at the resting potential and $\vec{i}$ is a vector containing external current excitation.

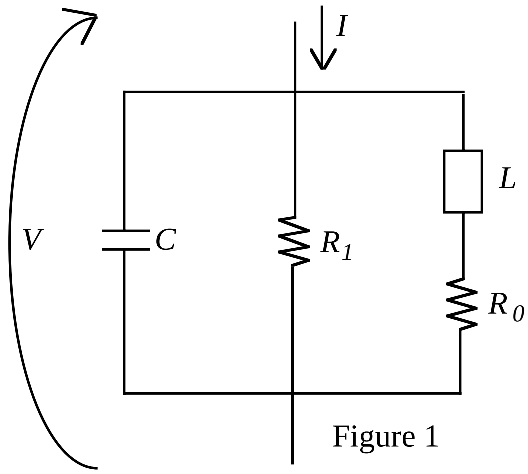


Figure 1

Part b) Show that the linearized model is
20 equivalent to the circuit at right. Write expressions for C,
pts R_0, R_1, and L in terms of the parameters of the original Hodgkin-Huxley model.

Part c) Compute the values of the circuit elements in Figure 1 for the Hodgkin Huxley model at a resting potential of –60 mV and a temperature of 6.3°. For reference, the Hodgkin-Huxley equations are attached as an appendix (you should already have Matlab code
30 written for these equations from Project 1). Use the
pts parameters of the standard Hodgkin-Huxley model except change $\bar{g}_{Na}$ to 60 mS/cm^2. EXPRESS YOUR RESULTS IN A CONSISTENT SET OF UNITS, I.E. SO THAT THE IMPEDANCE EQUATION $V = IZ$ HAS THE SAME V AND I UNITS FOR RESISTANCE, CAPACTIANCE, AND INDUCTANCE. Argue that some of the elements of this circuit have positive values and some have negative values. This will require considering carefully the signs of the various parameters in the model. Some signs will depend on the membrane potential. Assume that the membrane potential is near the resting potential.

Part d) Write the cable equation for a membrane cylinder with the membrane conductance
30 in Figure 1. That is, the usual linear cable with the addition of inductance L and resistance R_0 to its
pts transmembrane impedance. Express this in Fourier transformed form, i.e. consider the system in sinusoidal steady state.

Part e) Write the boundary conditions for this cable model for a semi-infinite cylinder with a
30 current $I_0\exp(j\omega_0 t)$ applied at x=0. That is, the cylinder runs from $x=0$ to positive infinity. Solve the
pts cable equation for potential in the cylinder $V(x,t)$ with this boundary condition and the usual regularity condition that V is finite as x goes to ∞. (Hint: use the Fourier transform pair $\exp(j\omega_0\tau) \leftrightarrow 2\pi\,\delta(\omega-\omega_0)$).

The complex exponential is used to make the problem easier. Usually one is interested in the results of applying a sinusoidal current $I_0\cos(\omega t)$, which can be done by applying a sum of complex exponentials.

30 pts **Part f)** Write an expression for the magnitude $|V(x,j\omega)|$ of the membrane potential as a function of distance down the cylinder and frequency. This will be a bit hairy. Show that at DC, the answer is the same as was obtained in class; as part of this, state the relationship between the parameters of this problem and the DC electrotonic length λ. What is the effect of the sodium channel on the propagation of potential at DC?

APPENDIX: Hodgkin Huxley equations for a resting potential of -60 mV.

Note: in all cases below, the units of the rate constants (α_n, β_n etc.) are /ms.

For the delayed-rectifier potassium channel:

$\overline{G}_K = 36$ mS/cm^2 $E_K = -72$ mV $\alpha_n = \dfrac{-0.01\ \phi\ (V+50)}{\exp[-(V+50)/10] - 1}$ $\beta_n = 0.125\ \phi \exp[-(V+60)/80]$

For the sodium channel:

$\overline{G}_{Na} = 120$ mS/cm^2 $E_{Na} = 55$ mV $\alpha_m = \dfrac{-0.1\ \phi\ (V+35)}{\exp[-(V+35)/10] - 1}$ $\beta_m = 4\ \phi \exp[-(V+60)/18]$

(but use 60 mS/cm^2)

$\alpha_h = 0.07\ \phi \exp[-(V+60)/20]$ $\beta_h = \dfrac{\phi}{\exp[-(V+30)/10] + 1}$

For the leakage channel:

$\overline{G}_L = 0.3$ mS/cm^2 $E_L = -43$ mV

Temperature coefficient:

$\phi = Q^{(T-6.3)/10}$ $Q = 3$

Membrane capacitance:

$C = 1\ \mu$Fd/cm^2