580.439/639 Homework #4

Due October 12, 2009

Problem 1

Under certain conditions, nerve membrane behaves like a resonant electrical circuit. For example, small (subthreshold) steps of current injected into squid giant axon may produce potential changes which undergo underdamped oscillations (try this with the HH model you build in project 1). The resonant behavior derives from the active properties of channels, which can be shown to be equivalent to a linear RLC circuit under small signal conditions (e.g. Mauro et al., J. Gen. Physiol. 55:497, 1970). In this problem, we work out the small signal behavior of the delayed rectifier K$^+$ channel of squid giant axon membrane. The development below is equivalent to linearizing the system around an equilibrium point.

Assume that the membrane consists of K$^+$ and leakage channels only, so that the following differential equations describe the membrane:

$$I_{ext} = C\frac{dV}{dt} + \bar{g}_K n^4 (V - E_K) + \bar{g}_L (V - E_L) \tag{1a}$$

and

$$\frac{dn}{dt} = \alpha(V)(1-n) - \beta(V)n \tag{1b}$$

I_{ext} is total membrane current (externally applied current), n is the Hodgkin-Huxley activation parameter for the potassium channels, and $\alpha(V)$ and $\beta(V)$are functions of membrane potential only. In order to make a small signal analysis, we express I_{ext}, V, and n as deviations from their values in the rest state, i.e.

$$I_{ext} = I_{ext}^r + i_{ext} \quad \text{and} \quad V = V^r + v \quad \text{and} \quad n = n^r + \eta \tag{2}$$

I_{ext}^r, V^r, and n^r are constants equal to the values of the three variables at resting potential V^r, which is an equilibrium point for the system. i_{ext}, v, and η are small deviations in the values of the three variables from their rest values.

a) By substituting the variables in (2) into the differential equations (1) and taking advantage of the fact that the resting potential is an equilibrium point, derive a pair of ordinary, linear differential equations relating i_{ext}, v, and η. For this derivation, ignore second and higher order terms like v^2 or η^4. This is justified by the small signal assumption, i.e. that $v << V^r$, $\eta << n^r$, and $i_{ext} << I_{ext}^r$,. The resulting equations should be expressible in matrix form as:

$$\begin{bmatrix} \dot{v} \\ \dot{\eta} \end{bmatrix} = \begin{bmatrix} a & b \\ c & d \end{bmatrix} \begin{bmatrix} v \\ \eta \end{bmatrix} + \begin{bmatrix} i_{ext}/C \\ 0 \end{bmatrix} \tag{3}$$

where the matrix elements *a, b, c,* and *d* are scalar <u>constants</u> (i.e. not functions of *t, V,* or *n*). Give expressions for *a, b, c,* and *d*. Note that the matrix in Eqn. (3) is the Jacobian of the system.

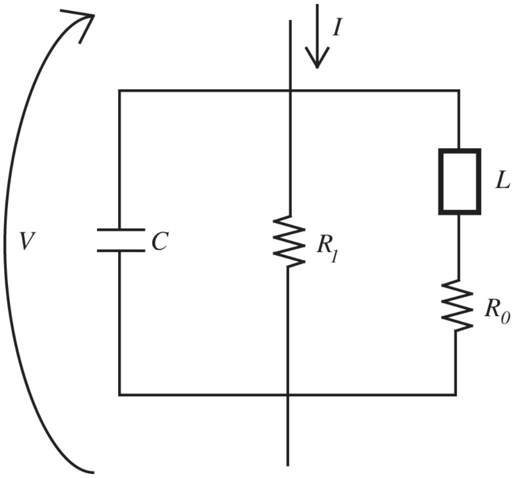
In carrying out this derivation, it will be necessary to assume that the Hodgkin-Huxley parameters α(*V*) and β(*V*) are approximately linear for small voltage fluctuations, i.e. that

$$\alpha\left(V^r + v\right) \approx \alpha^r + k_\alpha v \quad \text{and} \quad \beta\left(V^r + v\right) \approx \beta^r + k_\beta v$$

where α^r and β^r are the values of α and β at rest potential.

b) Derive a small-signal relationship between i_{ext} and *v* by eliminating η between the equations derived in a). By far the easiest way to do this problem is to use the Laplace transformed (from 0 initial conditions) version of Eqn. (3).

c) Show that the relationship between i_{ext} and *v* derived in b) is equivalent to the I-V relationship of the electrical circuit drawn at right (*L* is an inductor). Give values for R_0, *L*, R_1, and *C* in terms of the parameters of the channel model. Which components of the electrical circuit correspond to the potassium channel in the original membrane model?



d) Show that

$$L = \frac{\tau_n(V^r)}{\left.\dfrac{\partial g_k\left(t \to \infty\right)}{\partial V}\right|_{V=V^r}\left(V^r - E_K\right)}$$

where $g_K\left(t \to \infty\right)$ is taken to mean the steady-state value of g_K at the resting potential.

Problem 2

Consider the following pair of differential equations:

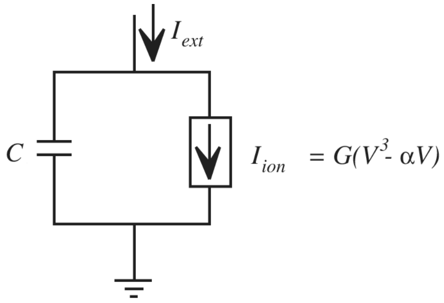
$$\frac{dx}{dt} = -\frac{1}{\varepsilon}\left(x^3 - 3x + y\right) \quad \text{and} \quad \frac{dy}{dt} = g(x,y)$$

If ε is small, then the first equation is fast compared to the second, i.e. *dx*/*dt* >> *dy*/*dt*, and the trajectories in phase space (i.e. space defined by *x* vs *y*) can be approximated by a sequence of fast legs where *y* is approximately constant and *x* moves towards its nullcline, and slow legs, where the system follows the *dx*/*dt*=0 nullcline in a direction controlled by the *dy*/*dt* equation. For the two functions *g*(*x,y*) listed below, draw the (*x,y*) phase space, including the nullclines, and equilibrium points. Tell whether the equilibrium points are stable. Draw approximate trajectories in phase space for the system starting at the initial values listed; in drawing these, make use of the assumption that $\varepsilon \ll 1$ discussed above. Do you think that the system has a stable limit cycles in these cases?

a)	$g(x,y) = -(y - 3x - 4.5)$	initial values = (-1, -0.5) and (0, -1)
b)	$g(x,y) = -(y - 5x)$	initial values = (-1, -0.5) and (0, -1)

Problem 3

Consider the membrane model diagrammed at right. The box contains a combination of channels whose instantaneous *I*-*V* relationship is given by the cubic equation shown. Assume that these channels have no gating, so there is no difference between the instantaneous and steady-state *I*-*V* relationships. Because there is no gating, this system has only one state variable.



a) Write the differential equation(s) needed to model this system. It will simplify the algebra in the rest of the problem to change the time variable in the equation(s) to $s = tG/C$.

b) With $I_{ext} = 0$, what are the equilibrium points of this system? Classify them as stable or unstable and explain why. Since the system has only one state variable, the usual phase plane cannot be used. Instead, plot dV/ds (or dV/dt) versus V and show the equilibrium points on this sketch. Note that analysis of one-dimensional systems is simpler than for two-dimensional systems.

c) As I_{ext} increases, a bifurcation occurs. Sketch the plot of dV/ds (or dV/dt) versus V at the bifurcation. What is the value of I_{ext} at the bifurcation? What kind of bifurcation in 2-state-variable systems does this one resemble? What happens to membrane potential when I_{ext} is driven above the bifurcation value?