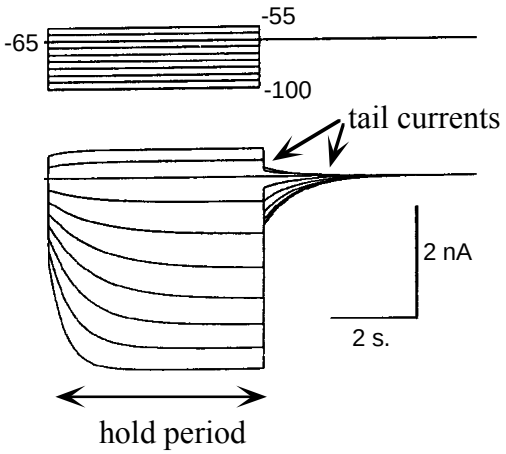
580.439/639 Homework #4

Due October 11, 2013

Problem 1



In developing a Hodgkin-Huxley type model for a channel current, the analysis is often based on tail currents, which are the currents which flow after the offset of a voltage clamp. An example is shown in the figure at right, taken from Huguenard and McCormick, *J. Neurophysiology*, 68, 1373, (1992). This example is the H-current (actually this figure shows the model currents, which are cleaner traces), whose HH model is

$$I_H = \bar{g}_H \, h(V,t)(V - E_H)$$

where h is described by the usual differential equation involving parameters $h_\infty(V)$ and $\tau_H(V)$. h is an inactivation gate, in the sense that h is large for potentials hyperpolarized from rest and rapidly goes to 0 as the cell is depolarized. Consider how the parameters of this model can be determined from data like that in the figure. The figures shows responses to the voltage clamp protocol at the top, with voltage steps spaced every 5 mV from –100 to –55 mV.

Part a) Write an equation for the current during the hold period and another for the tail-current period in terms of the parameters of the HH model and the parameters of the voltage clamp. Assume that the voltage clamp is held long enough that $h=h_\infty$ immediately prior to either voltage clamp transition.

Part b) For the H-current, the equilibrium potential E_H is about -43 mV. Explain why the voltage-clamp current appears to reverse polarity at -65 mV in the figure above (Hint: where is zero current in the figure?).

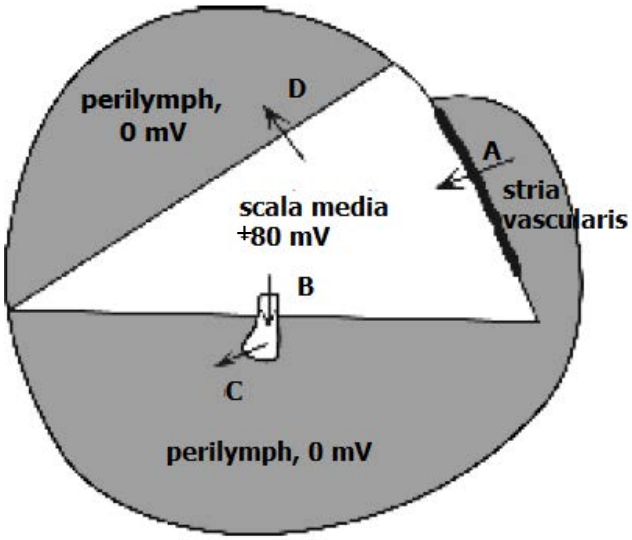
Part c) Describe how tail currents can be used to determine E_H experimentally.

Part d) Explain how tail currents can be used to determine $h_\infty(V)$ and $\tau_H(V)$. For a simple channel like the H-current, this may seem like overkill, in that the currents during the hold time should give the same information. However, suppose that the channel is not linear, as in the model used above, so that

$$I_H = \bar{g}_H \, h(V,t) \, F(V,E_H)$$

where $F(V,E_H)$ is a rectifying instantaneous current-voltage relationship, like the GHK equation. Argue that the tail currents are immune to distortions from such rectification whereas currents during the hold time are not.

Problem 2



The drawing at right below shows the scala media of the cochlea. This structure is filled with a high-K^+ extracellular fluid, called endolymph, which resembles normal intracellular solutions, in that it has a high K^+ concentration and a low Na^+ concentration. Endolymph is produced in a specialized epithelium, the stria vascularis, which actively transports K^+ into scala media and actively transports Na^+ out of scala media. There is a net positive potential of ≈+80 mV in scala media. Two other fluid-filled structures are adjacent to scala media; these are filled with perilymph, which is standard high-Na^+, low-K^+ extracellular fluid; the perilymphatic spaces are shaded and the endolymphatic space is unshaded at right. The major current pathways associated with scala media are shown in the drawing as arrows and are described below. Although the anatomy is more complex, assume that each of the current paths A-D behaves like flux across a single membrane.

A. Active transport between perilymph and endolymph; K^+ is transported into endolymph and Na^+ is transported out. There are no significant passive currents in A.

B. Passive flux of cations (approximately equal permeability for Na^+ and K^+, much less for Ca^{++}) through the transduction channel of hair cells, between endolymph and the intracellular solution of hair cells.

C. Passive flux of cations through ion channels in the hair cell basal membranes, between the intracellular solution of hair cells and perilymph. This membrane contains Ca^{++}, K^+, Na^+, and leak channels. The hair cell has a resting potential of about -50 mV with the transduction channels closed.

D. Passive flux through leak pathways between endolymph and perilymph; assume that this behaves like a single membrane barrier, directly between endolymph and perilymph. This pathway has approximately the same conductance as pathway B,C because of the extraordinary system of tight-junctions between the epithelial cells lining scala media. Its ionic selectivity is not yet known, but will be inferred below.

Assume the following ionic concentrations (these are made-up, but approximately correct):

ion	perilymph	endolymph	intracellular
K^+	3 mM	150 mM	150 mM
Na^+	140 mM	2 mM	2 mM
Cl^-	140 mM	150 mM	10 mM
Ca^{++}	2 mM	1 mM	10^{-7} M

Part a) Draw an electrical equivalent circuit for this system, showing the four current paths drawn above. Remember that a channel can be modeled by a resistor in series with a battery. Assume that all parts of perilymph are equipotential at ground. Estimate the values of the batteries, where possible. Leave out capacitors. Represent active transport A by a current source. Reduce

path B,C to a single Thévenin equivalent circuit, and argue that its battery value can be determined from the information given above.

Part b) When current A is set to 0, by blocking the active transporter with ouabain, the potential in scala media drops to -75 mV. What does this imply about the ionic selectivity of pathway D? How is the normal +80 mV potential in scala media produced?

Problem 3

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:

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

and

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

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.

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

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:

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

where the matrix elements *a, b, c,* and *d* are scalar constants (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.

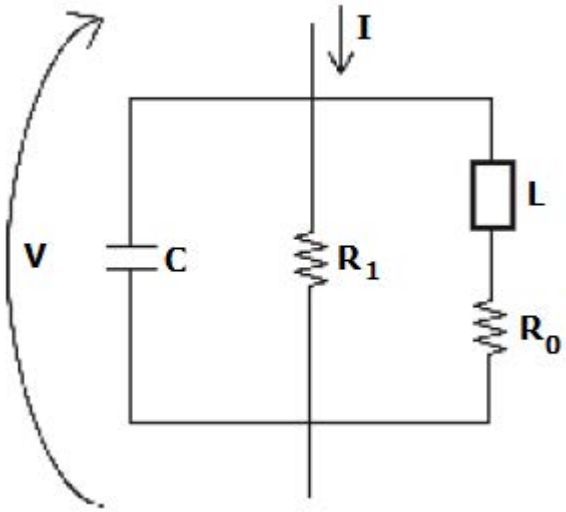
In carrying out this derivation, it will be necessary to assume that the Hodgkin-Huxley parameters $\alpha(V)$ and $\beta(V)$ are approximately linear for small voltage fluctuations, i.e. that

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

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

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

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