

## 580.439/639 Solutions to Homework #4

### Problem 1

**Part a)** During the steady portions of a voltage clamp beginning at time 0, the HH parameter  $h$  satisfies the following equations:

$$\tau_H(V_2) \frac{dh}{dt} = h_\infty(V_2) - h \quad \text{and} \quad h(0) = h_\infty(V_1)$$

where  $V_1$  is the potential to which the cell was clamped prior to time 0 and  $V_2$  is the potential after time 0. As long as  $V_2$  is constant, this is a linear equation with solution

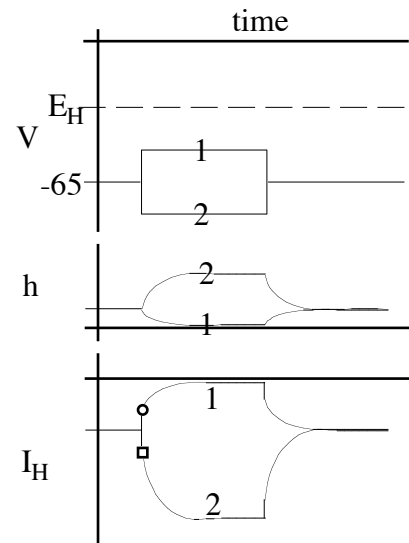
$$h(t) = h_\infty(V_2) + [h_\infty(V_1) - h_\infty(V_2)] e^{-t/\tau_H(V_2)}$$

so that  $h$  decays exponentially from  $h_\infty(V_1)$  to  $h_\infty(V_2)$ . The current is then:

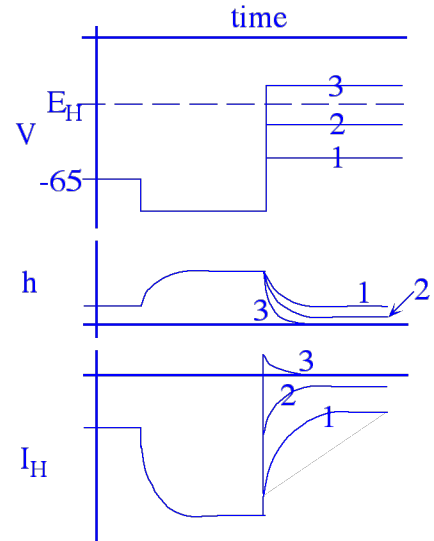
$$I_H(t) = \bar{g}_H [h_\infty(V_2) + [h_\infty(V_1) - h_\infty(V_2)] e^{-t/\tau_H(V_2)}] (V_2 - E_H) \quad (1)$$

The same equation works during the hold and tail-current periods, with different choices of time 0 and of  $V_1$  and  $V_2$ .

**Part b)** The sketch at right shows the membrane potential (top), values of  $h(t)$  during two voltage clamps (middle), and the resulting H currents (bottom). All the membrane potential values are negative to the equilibrium potential  $E_H$  of the channel, so the H-current values are all negative, inward currents. The current records in the figure can easily be understood from Eqn. 1, the values of membrane potential, and the values of  $h(t)$ . Notice the instantaneous steps of current (marked by the open circle and square) which occur at the onset (and the offset where they are not marked) of the voltage clamp. The current is always inward in this set of experiments and only appears to reverse polarity because the true zero of current is not marked on the data. The apparent reversal in polarity derives from the fact that  $h$  increases in one case (#2) but decreases in the other (#1).



**Part c)** The voltage clamp protocol at right will do the job. Note that the exponential tails now reverse polarity at  $E_H$  so that the reversal potential is clearly indicated. The first voltage clamp, to a hyperpolarizing potential, is necessary in this case because the real H current is almost inactivated at the resting potential, unlike the drawing at right, so it is necessary to hyperpolarize to activate enough current to allow the tails to be seen.



**Part d)** For the channel with a rectifying instantaneous current-voltage relationship, the tail current is given by:

$$I_H(t) = \bar{g}_H \left[ h_\infty(V_2) + [h_\infty(V_1) - h_\infty(V_2)] e^{-t/\tau_H(V_2)} \right] F(V_2, E_H)$$

Note that the non-linear current-voltage term  $F(V_2, E_H)$  is a constant in this equation, as long as  $V_2$ , the clamp potential during the tails, is constant. During the hold portion of the voltage clamp, by contrast, the non-linear term will vary, as the holding potential is varied, making it difficult to separate changes in  $h$  from non-linearities in  $F$ .

To determine  $h_\infty(V)$ , note that the current at time  $0^+$ , i.e. just after the change in clamp voltage from  $V_1$  to  $V_2$ , is

$$I_H(0^+) = \bar{g}_H h_\infty(V_1) F(V_2 - E_H)$$

Thus  $h_\infty$  can be determined by a plot of  $I_H(0^+)$  vs.  $V_1$ , the potential during the hold period. The constants  $\bar{g}_H F(V_2 - E_H)$  can be determined from the saturation value of the plot, since  $h_\infty$  must saturate at 1 for large hyperpolarizing values of  $V_1$ . The advantage of this method, as mentioned above, is that  $h_\infty$  is determined under fixed conditions, as opposed to the variable conditions (i.e. membrane potential) during the hold period.

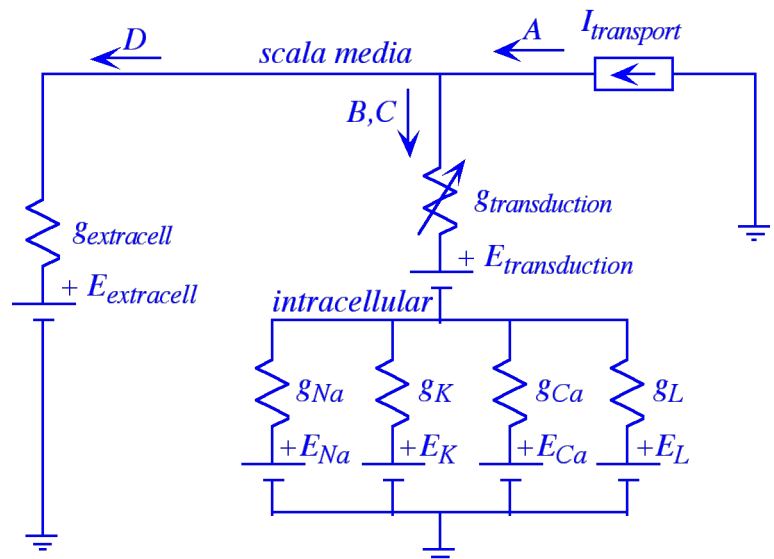
The time constant  $\tau_H(V)$  can be determined from either the hold or the tail period because the rise or fall of current during these times should be exponential with time constant  $\tau_H(V_2)$ . During the tail period

$$I_H(t) = k_1(V_2) + k_2(V_1, V_2) e^{-t/\tau_H(V_2)}$$

Although the constants  $k_1$  and  $k_2$  vary with both  $V_1$  and  $V_2$ , the time constant varies with only  $V_2$ , so can be determined as a function of the membrane potential during the tail current period.

**Problem 2**

**Part a)** The diagram at right shows a circuit which corresponds to the assumptions of the problem statement.



The values of the batteries are given below, as calculated from the concentrations given in the table in the problem statement.

$$E_{extracell} = ??$$

$$E_{transduction} \approx 0$$

$$E_{Na} = 110 \text{ mV}$$

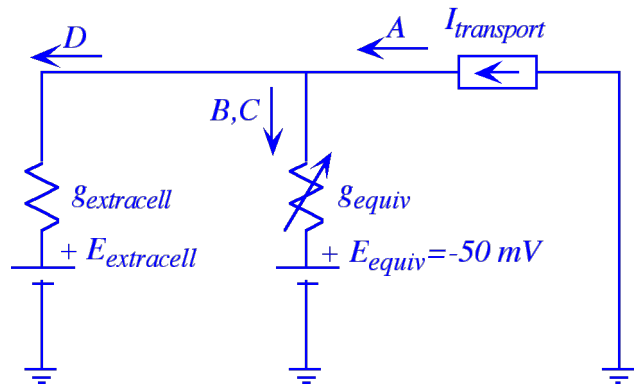
$$E_K = -102 \text{ mV}$$

$$E_{Ca} = 129 \text{ mV}$$

$$E_L = ??$$

The arrows show the directions of current flow, corresponding to the arrows in the diagram in the problem set.  $E_{extracell}$  and  $E_L$  are unknown because no information is given about their selectivity.  $E_{transduction} \approx 0$  because the channels are permeable to  $\text{Na}^+$  and  $\text{K}^+$ , whose equilibrium potentials are 0 between endolymph and intracellular fluids (no concentration gradients). The circuit can be simplified as at right below, by replacing the basal membrane of the hair cell with a Thévenin equivalent whose battery equals the resting potential; that is, the parallel combination of channels in the basal membrane must combine to produce a  $-50 \text{ mV}$  resting potential with the transduction channels closed ( $g_{transduction} = 0$ ), which is the definition of the Thévenin equivalent battery value. The Thévenin-equivalent and transduction conductances can then be combined as drawn. As stated in the problem set, the conductances  $g_{extracell}$  and  $g_{equiv}$  are approximately equal in the rest state.

**Part b)** If the current  $I_{transport} = 0$ , and if  $g_{extracell} \approx g_{equiv}$  then  $E_{extracell}$  must be  $\approx -100 \text{ mV}$  in order for the potential in scala media to be  $-75 \text{ mV}$ . This suggests that the leak pathway D must be selectively permeable for  $\text{K}^+$  ions, since that is the only ion known to have a large negative equilibrium potential between endolymph and perilymph. Because both batteries in the remaining circuit have negative potentials facing scala media, the normal positive potential in scala media must be produced by electrogenic transport in the stria vascularis, i.e.  $I_{transport}$  must be a positive current as drawn.



**Problem 3**

**Part a)** Substituting the small signal variables defined in Eqn. (2) in the problem statement into the differential equations for  $I_{ext}$  and  $n$  gives:

$$I_{ext}^r + i_{ext} = C \frac{d(V^r + v)}{dt} + \bar{g}_K (n^r + \eta)^4 (V^r + v - E_K) + \bar{g}_L (V^r + v - E_L) \quad (1)$$

$$\frac{d(n^r + \eta)}{dt} = (\alpha^r + k_\alpha v)(1 - n^r - \eta) - (\beta^r + k_\beta v)(n^r + \eta) \quad (2)$$

Note that the HH parameters  $\alpha(V)$  and  $B(V)$  have been replaced by the first two terms in a Taylor expansion around the equilibrium point, as discussed in the problem statement. The  $n^4$  term in Eqn. (1) can be approximated by the first two terms of the expansion as

$$(n^r + \eta)^4 \approx n^{r4} + 4n^{r3}\eta \quad \text{ignoring terms in } \eta^2, \eta^3, \text{ and } \eta^4 \quad (3)$$

At resting potential,  $dV/dt = dn/dt = 0$ , so the following equations relating the resting values of the variables must hold:

$$I_{ext}^r = \bar{g}_K n^{r4} (V^r - E_K) + \bar{g}_L (V^r - E_L) \quad (4)$$

$$0 = \alpha^r (1 - n^r) - \beta^r n^r \quad (5)$$

Now if Eqns. (1) and (2) are multiplied out, if second and higher order terms involving the small signal variables  $i_{ext}$ ,  $v$ , and  $\eta$  are ignored (such as  $\eta v$ ,  $\eta^2$ , etc.), if the equilibrium value Eqns. (4) and (5) are subtracted, and if it is noted that  $dV^r/dt = dn^r/dt = 0$ , then the result is the following equations for the small signal parameters:

$$i_{ext} \approx C \frac{dv}{dt} + \bar{g}_K n^{r4} v + 4\bar{g}_K n^{r3} \eta (V^r - E_K) + \bar{g}_L v \quad (6)$$

$$\frac{d\eta}{dt} \approx -\alpha^r \eta + k_\alpha (1 - n^r) v - \beta^r \eta - k_\beta n^r v \quad (7)$$

In terms of the matrix form suggested in the problem set:

$$\begin{bmatrix} \dot{v} \\ \dot{\eta} \end{bmatrix} = \begin{bmatrix} -(\bar{g}_K n^{r4} + \bar{g}_L)/C & -4\bar{g}_K n^{r3} (V^r - E_K)/C \\ k_\alpha (1 - n^r) - k_\beta n^r & -(\alpha^r + \beta^r) \end{bmatrix} \begin{bmatrix} v \\ \eta \end{bmatrix} + \begin{bmatrix} i_{ext}/C \\ 0 \end{bmatrix}$$

The matrix is the Jacobian of this system at resting potential (an equilibrium point), and could have been obtained with somewhat less algebra by differentiating Eqns. (1a) and (1b) in the problem set.

**Part b)** Laplace transforming Eqns. (6) and (7) with zero initial conditions gives the following (boldface indicates Laplace domain variables):

$$\begin{aligned} \mathbf{i}_{ext}(s) &= [Cs + \bar{g}_K n^{r4} + \bar{g}_L] \mathbf{v}(s) + 4\bar{g}_K n^{r3} (V^r - E_K) \mathbf{h}(s) \\ 0 &\approx [k_\alpha (1 - n^r) - k_\beta n^r] \mathbf{v}(s) - [s + \alpha^r + \beta^r] \mathbf{h}(s) \end{aligned} \quad (8)$$

Eliminating  $\eta(s)$  between the two parts of Eqn. (8) gives the following equation relating membrane current  $\mathbf{i}_{\text{ext}}(s)$  and membrane voltage  $\mathbf{v}(s)$ :

$$\mathbf{i}_{\text{ext}}(s) = \left\{ C s + \bar{g}_K n^{r^4} + \bar{g}_L + \frac{4\bar{g}_K n^{r^3} (V^r - E_K) [k_\alpha (1 - n^r) - k_\beta n^r]}{s + \alpha^r + \beta^r} \right\} \mathbf{v}(s) \quad (9)$$

**Part c)** The parallel electrical circuit in the problem set has the following current-voltage relationship (in terms of Laplace transforms with 0 initial conditions:)

$$I = I_C + I_{R_1} + I_{LR_0}$$

$$\mathbf{I} = sC \mathbf{V} + \frac{1}{R_1} \mathbf{V} + \frac{\mathbf{V}}{sL + R_0} \quad (10)$$

Eqns. 9 and 10 are identical as long as the capacitors are the same and

$$\frac{1}{R_1} = \bar{g}_K n^{r^4} + \bar{g}_L$$

$$L = \frac{1}{4\bar{g}_K n^{r^3} (V^r - E_K) [k_\alpha (1 - n^r) - k_\beta n^r]} \quad (11)$$

$$R_0 = (\alpha^r + \beta^r) L$$

Components of the electrical circuit correspond to the  $K^+$  channel if their values depend on the parameters of the original equations that were associated with the  $K^+$  channel. The inductor and the resistor  $R_0$  clearly derive wholly from the potassium channel. The other resistor  $R_1$  equals the leakage conductance of the membrane plus the resting conductance of the potassium channel. The capacitor is just the membrane's capacitance.

**Part d)** Consider first the partial derivative in the denominator:

$$\left. \frac{\partial g_K(t \rightarrow \infty)}{\partial V} \right|_{V=V^r} = \left. \frac{\partial \bar{g}_K n_\infty^4}{\partial V} \right|_{V=V^r} = 4 \bar{g}_K n_\infty^{r^3} \left. \frac{\partial n_\infty}{\partial V} \right|_{V=V^r}$$

where the superscript "r" means the value of the function at resting potential. In terms of the  $\alpha$  and  $\beta$  parameters,

$$\tau_n = \frac{1}{\alpha + \beta} \quad \text{and} \quad n_\infty = \frac{\alpha}{\alpha + \beta}$$

which can easily be verified by rearrangement of Eqn. 1b of the problem set. Using the small signal approximation of the  $\alpha(V)$  and  $\beta(V)$  functions given in the problem set,

$$\begin{aligned}\frac{\partial n_\infty}{\partial V} &= \frac{1}{\alpha + \beta} \frac{\partial \alpha}{\partial V} - \frac{\alpha}{(\alpha + \beta)^2} \frac{\partial(\alpha + \beta)}{\partial V} = \tau_n \frac{\partial \alpha}{\partial V} - \tau_n n_\infty \frac{\partial(\alpha + \beta)}{\partial V} \\ &\approx \tau_n k_\alpha - \tau_n n_\infty (k_\alpha + k_\beta)\end{aligned}\quad (13)$$

Then using Eqn. 12 and 13, the expression in the problem set becomes

$$\begin{aligned}L &= \frac{\tau_n(V^r)}{\left. \frac{\partial g_k(t \rightarrow \infty)}{\partial V} \right|_{V=V^r}} (V^r - E_K) = \frac{\tau_n(V^r)}{4 \bar{g}_k n_\infty^{r3} \left. \frac{\partial n_\infty}{\partial V} \right|_{V=V^r}} (V^r - E_K) \\ &\approx \frac{\tau_n(V^r)}{4 \bar{g}_k n_\infty^{r3} [\tau_n k_\alpha - \tau_n n_\infty^r (k_\alpha + k_\beta)] (V^r - E_K)} \\ &= \frac{1}{4 \bar{g}_k n_\infty^{r3} [k_\alpha (1 - n_\infty^r) - k_\beta n_\infty^r] (V^r - E_K)}\end{aligned}$$

which is the same as Eqn. 11.