

580.439/639 Final Solutions

Problem 1

The answer to this problem should include a standard Hodgkin-Huxley type cable with active conductances in the membrane compartments, a model for potassium accumulation in the extracellular space, and a model for the effect of potassium on the membrane equations. The potassium effect can be modeled either by changing E_K or by using a GHK formulation for potassium current. The equations below vary E_K , the simplest approach.

Equations for the spread of electrical potential in the j^{th} compartment:

$$\begin{aligned} \frac{(V_{j-1}^i - V_j^i)}{r_{ij}} - \frac{(V_j^i - V_{j+1}^i)}{r_{ij}} &= C_j \frac{d(V_j^i - V_j^e)}{dt} + g_{Na_j}(V_j^i - V_j^e - E_{Na}) + g_{K_j}(V_j^i - V_j^e - E_{K_j}) + \\ & \qquad \qquad \qquad g_L(V_j^i - V_j^e - E_L) \\ \frac{(V_{j-1}^e - V_j^e)}{r_{ij}} - \frac{(V_j^e - V_{j+1}^e)}{r_{ij}} &= -C_j \frac{d(V_j^i - V_j^e)}{dt} - g_{Na_j}(V_j^i - V_j^e - E_{Na}) - g_{K_j}(V_j^i - V_j^e - E_{K_j}) - \\ & \qquad \qquad \qquad g_L(V_j^i - V_j^e - E_L) \end{aligned}$$

where V_j^i is the intracellular potential in the j^{th} compartment and V_j^e is the extracellular potential in the same compartment. These equations follow from Kirchoff's current law at the intracellular and extracellular nodes. Note that the potassium equilibrium potential E_{K_j} also varies from compartment to compartment (see below). The membrane conductances g_{Na_j} and g_{K_j} in the j^{th} compartment are given by the usual HH equations:

$$\begin{aligned} g_{Na_j} = \bar{g}_{Na} m_j^3 h_j \quad \text{where} \quad \frac{dm_j}{dt} &= \frac{m_\infty(V_j^i - V_j^e) - m_j}{\tau_m(V_j^i - V_j^e)} \quad \text{and} \quad \frac{dh_j}{dt} = \frac{h_\infty(V_j^i - V_j^e) - h_j}{\tau_h(V_j^i - V_j^e)} \\ g_{K_j} = \bar{g}_K n_j^4 \quad \text{where} \quad \frac{dn_j}{dt} &= \frac{n_\infty(V_j^i - V_j^e) - n_j}{\tau_n(V_j^i - V_j^e)} \end{aligned}$$

and there is a separate set of equations of this type for each compartment. Note that the m_∞ , τ_m , etc. functions are functions of $V^i - V^e$, the transmembrane potential.

Potassium accumulation is handled by assuming an extracellular volume v_j corresponding to the j^{th} electrical compartment. Then the simplest model is

$$v_j \frac{dK_{out j}}{dt} = \left. \begin{array}{l} \text{time rate of} \\ \text{change of extracell.} \\ \text{potassium in the} \\ \text{j}^{\text{th}} \text{ compartment} \end{array} \right\} = \bar{g}_K n_j^4 (V_j^i - V_j^e - E_{Kj}) / F - P K_{out j} + \\ D(K_{out j-1} - K_{out j}) - D(K_{out j} - K_{out j+1})$$

where the net flux of potassium into the extracellular compartment is the difference between the potassium transmembrane current (first term on the r.h.s.), the rate of pumping of potassium back into the cell (second term) and the diffusion of potassium along the axons (third and fourth terms). F in the first r.h.s. term is the Faraday, to convert current to moles.

Finally, the potassium equilibrium potential varies from compartment to compartment:

$$E_{Kj} = \frac{RT}{F} \ln \frac{K_{out j}}{K_{in}}$$

The model can be made more complex by adding additional effects. It can also be made more accurate by using the GHK equation for membrane currents, in which case the effect of $K_{out j}$ on the membrane is built into the Kirchoff's current law equations.

Problem 2

There are two parts to the problem: 1) show that the current of interest is a chloride current and 2) show that it is calcium dependent. To show that the current is chloride, one can manipulate the chloride equilibrium potential and show a reversal in the mystery current at the point predicted by E_{Cl} , replace Cl^- ions in the intracellular or extracellular space with various anions and show that the current goes away, or eliminate the alternatives by blocking other possible currents in the system. How the latter is done depends on the nature of the mystery current. If it is an outward current, then potassium is the most likely alternative and the experiments should focus on manipulating potassium currents.

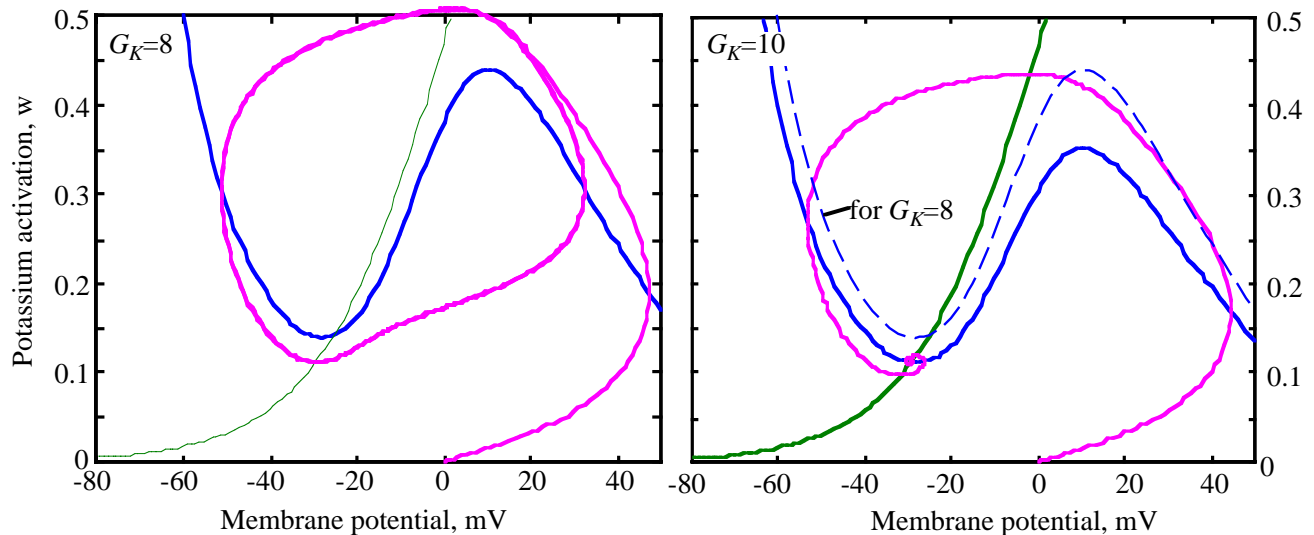
To show that the current is calcium dependent, three common approaches are 1) eliminate extracellular calcium and show that the mystery current disappears; 2) fill the cell with a calcium chelator like BAPTA and show that the current disappears; and 3) show that the amplitude of the mystery current increases or decreases as the amount of calcium entering the cell changes. The latter can be done by voltage clamping the cell at various potentials and showing that the strength of the mystery current is proportional to the calcium current.

Problem 3

Part a) Of course, increasing G_K increases the potassium current, stabilizing the membrane and blocking the current-driven regular spiking. In terms of nonlinear dynamics, increasing G_K moves the equilibrium point and changes the stability of the linearized system at the equilibrium point from unstable to stable. The phase planes below apply to the system with G_K at the two values used in the problem (8 and 10 mS/cm²). The dV/dt isocline is given by

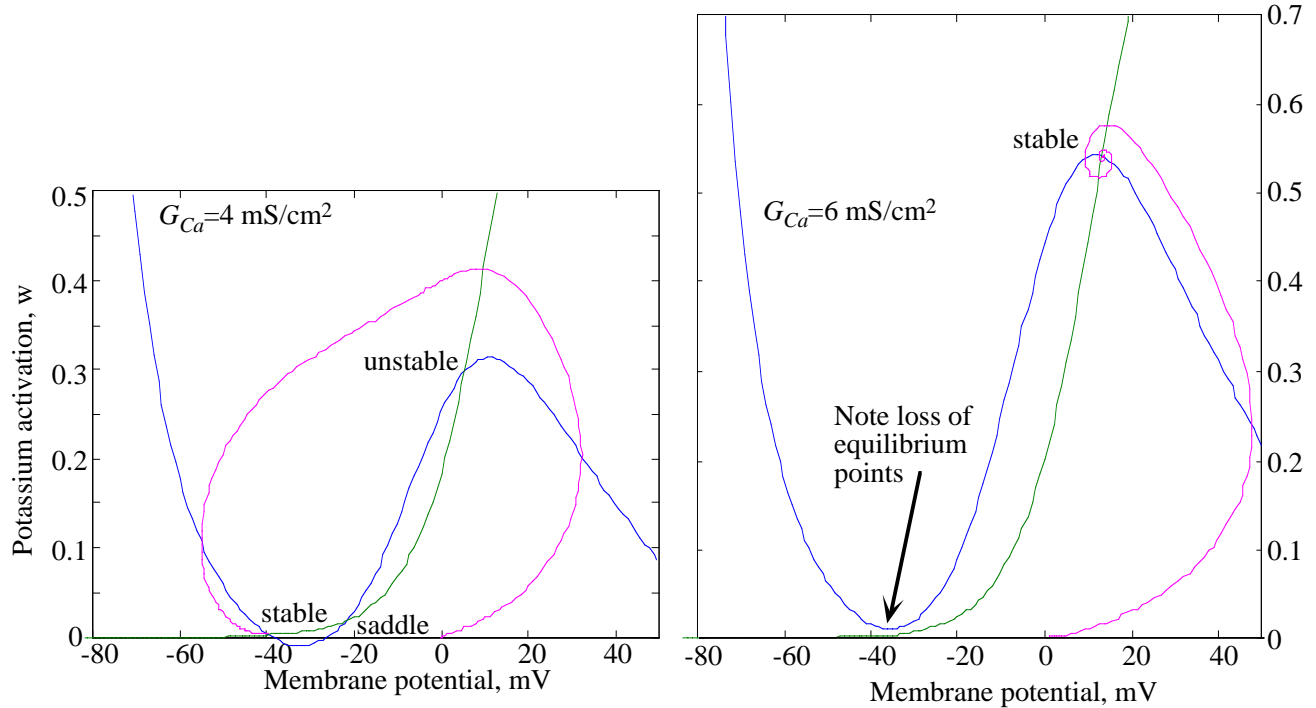
$$w_{\dot{v}\text{isocline}} = \frac{I_{\text{ext}} - G_{Ca} m_{\infty}(V)(V - E_{Ca}) - G_L(V - E_L)}{G_K(V - E_K)}$$

When G_K is increased, this isocline (blue) moves downward, moving the equilibrium point, as drawn at right.

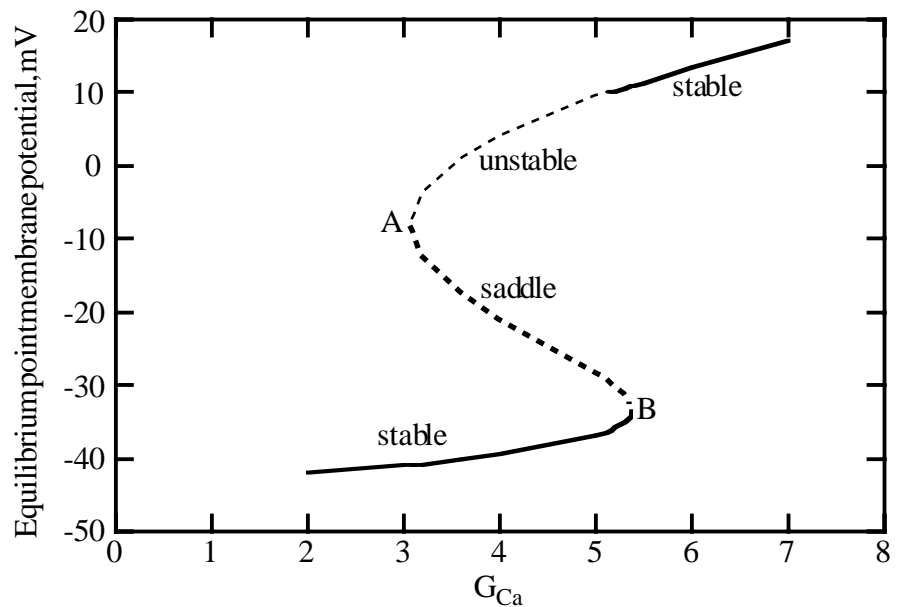


Trajectories from an initial condition of (0,0) are shown. With $G_K=8$ (left), the trajectory is a limit cycle. In this case, the equilibrium point is unstable, as determined from its eigenvalues ($0.003 \pm j0.08$). The limit cycle is the only stable state of the system. The Poincaré-Bendixson theorem can be used to argue that a limit cycle must exist. With $G_K=10$, the equilibrium point is stable, with eigenvalues $-0.003 \pm j0.09$. In this case index theory shows that no limit cycle is possible. Indeed, the system settles to the equilibrium point from any initial condition. The example at right above is from initial value (0,0).

Part b) Increasing G_{Ca} moves the isocline in the upward direction in the phase plane, as can be inferred from the equation above (recall that $V < G_{Ca}$). The phase planes below show the situation with G_{Ca} at the two values used in this problem. At left, there are three equilibrium points, one stable, one saddle, and one unstable, as marked. As was discussed in class, the system has no limit cycles because of the manifolds associated with the saddle node. A trajectory is shown from (0,0), giving a single action potential after which the system settles at its stable equilibrium point. At right, the phase plane with $G_{Ca}=6$ mS/cm² is shown. The dV/dt isocline has moved vertically, eliminating the two equilibrium points at negative potentials. This is a form of saddle node bifurcation. The only remaining equilibrium point is now at +13 mV and it is stable, with eigenvalues $-0.07 \pm j0.27$. Thus the system has a new resting potential at positive voltages.



A bifurcation diagram plotting equilibrium-point membrane potentials (y axis) versus G_{Ca} is shown at right. There are three equilibrium points over the range $G_{Ca}=[3.09,5.36]$. As G_{Ca} increases, the lower two (stable and saddle) move together and annihilate at B , leaving only the one stable point at positive potentials (≈ 10 mV). This is the bifurcation that produces the behavior discussed above. Two other events occur. At A , the upper two equilibrium points



merge at another saddle bifurcation, leaving only the lower stable point at lower values of G_{Ca} . Finally, at about $G_{Ca}=5.165$, the upper equilibrium point goes from unstable to stable. Ordinarily, this would produce a limit cycle for $G_{Ca}<5.165$, but that is blocked in this case by the manifolds associated with the saddle node.

Problem 4

Part a) This problem is exactly the same as a homework problem where the method was applied to the delayed-rectifier potassium channel. A fuller development of the linearization can be found in Mauro et al., *J. Gen. Physiol.* 55:497 (1970). Essentially the problem is to linearize the following equations around the resting potential V_R , assumed to be an equilibrium point:

$$\begin{aligned}\frac{dV}{dt} &= \frac{1}{C} [I_{ext} - g_L(V - E_L) - \bar{g}_{Na} m^3 h (V - E_{Na})] \\ \frac{dm}{dt} &= \alpha_m (1 - m) - \beta_m m \\ \frac{dh}{dt} &= \alpha_h (1 - h) - \beta_h h\end{aligned}\quad (4.1)$$

To simplify the problem, it is assumed that changes in h are slow, so that the approximation $h = h_\infty(V_R)$ is made, i.e. h is fixed at its steady-state value at the resting potential. This assumption eliminates the third differential equation in Eqn. 4.1. Linearization can proceed by replacing each variable by a constant plus a small-signal deviation (as in the homework problem solutions) or by computing the Jacobian of the r.h.s. in the first two parts of Eqn. 4.1. In either case, the result is below, in terms of linearization variables v , i_{ext} , and μ . i_{ext} is not a state variable and is usually not included in linearizations. However it can be treated in the same way as a state variable and is needed here in order to connect the membrane model to the rest of the cell.

$$\begin{aligned}\frac{dv}{dt} &\approx \frac{1}{C} \left\{ i_{ext} - [\bar{g}_L + \bar{g}_{Na} m_\infty^3(V_R) h_\infty(V_R)] v - 3\bar{g}_{Na} m_\infty^2(V_R) h_\infty(V_R) (V_R - E_{Na}) \mu \right\} \\ \frac{d\mu}{dt} &\approx [k_{cm}(1 - m_\infty(V_R)) - k_{\beta m} m_\infty(V_R)] v - [\alpha_m(V_R) + \beta_m(V_R)] \mu\end{aligned}\quad (4.2)$$

where k_{cm} and $k_{\beta m}$ are the slopes $d\alpha_m/dV$ and $d\beta_m/dV$ evaluated at V_R .

Part b) Laplace transforming Eqn. 4.2 from 0 initial conditions and rearranging gives:

$$\begin{aligned}\mathbf{i}_{ext}(s) &= [sC + \bar{g}_L + \bar{g}_{Na} m_\infty^3(V_R) h_\infty(V_R)] \mathbf{v}(s) + 3\bar{g}_{Na} m_\infty^2(V_R) h_\infty(V_R) (V_R - E_{Na}) \boldsymbol{\mu}(s) \\ 0 &= [k_{cm}(1 - m_\infty(V_R)) - k_{\beta m} m_\infty(V_R)] \mathbf{v}(s) - [s + \alpha_m(V_R) + \beta_m(V_R)] \boldsymbol{\mu}(s)\end{aligned}\quad (4.3)$$

where the boldface indicates Laplace transformed variables. Eliminating $\boldsymbol{\mu}(s)$ between equations gives

$$\mathbf{i}_{ext}(s) = \left\{ \begin{aligned} &sC + \bar{g}_L + \bar{g}_{Na} m_\infty^3(V_R) h_\infty(V_R) + \\ &\frac{3\bar{g}_{Na} m_\infty^2(V_R) h_\infty(V_R) (V_R - E_{Na}) [k_{cm}(1 - m_\infty(V_R)) - k_{\beta m} m_\infty(V_R)]}{s + \alpha_m(V_R) + \beta_m(V_R)} \end{aligned} \right\} \mathbf{v}(s) \quad (4.4)$$

The current-voltage relationship of the circuit in Fig. 1 of the problem can be written as:

$$I = I_C + I_{R_1} + I_{L R_0}$$

$$\mathbf{I}(s) = \left\{ sC + \frac{1}{R_1} + \frac{1}{sL + R_0} \right\} \mathbf{V}(s) \quad (4.5)$$

Matching terms in Eqns. 4.4 and 4.5 gives the result that the capacitor is C in either case and the resistors and inductors are related as follows:

$$\frac{1}{R_1} = \bar{g}_L + \bar{g}_{Na} m_\infty^3(V_R) h_\infty(V_R)$$

$$L = \frac{1}{3\bar{g}_{Na} m_\infty^2(V_R) h_\infty(V_R) (V_R - E_{Na}) [k_{cm} (1 - m_\infty(V_R)) - k_{\beta m} m_\infty(V_R)]} \quad (4.6)$$

$$R_0 = (\alpha_m(V_R) + \beta_m(V_R)) L$$

Part c) The original Hodgkin- Huxley equations are expressed in terms of conductance per square cm of membrane. In these terms, the parameters of Eqn. 4.6 have the following values:

$$R_1 = 3.28 \text{ K}\Omega \cdot \text{cm}^2 \quad L = -1.1 \text{ Hy} \cdot \text{cm}^2 \quad R_0 = -4.63 \text{ K}\Omega \cdot \text{cm}^2 \quad (4.7)$$

using the parameter values in the Appendix of the problem (NOTE that \bar{g}_{Na} is $60 \text{ mS}/\text{cm}^2$, instead of the usual value of 120. The resting potential was assumed to be -60 mV and the temperature 6.3° , so that no correction for the Q_{10} of the rate constants is necessary. The only parameters in Eqn. 4.6 that are not straightforward are k_{cm} and $k_{\beta m}$ which can be computed as follows:

$$k_{cm} \approx [\alpha_m(-59.9 \text{ mV}) - \alpha_m(-60.1 \text{ mV})] / 0.2 \text{ mV}$$

$$\text{and } k_{\beta m} \approx [\beta_m(-59.9 \text{ mV}) - \beta_m(-60.1 \text{ mV})] / 0.2 \text{ mV}$$

Both α_m and β_m are approximately linear in the vicinity of -60 mV , so the approximations above are quite good. The quality of the approximation can be checked by using smaller or larger delta values.

Note that the units used above are consistent with the general Hodgkin- Huxley system, in which Ohm's law can be written as follows:

$$V = IR \quad \text{with} \quad \text{mV} = \mu\text{A} / \text{cm}^2 \times \text{K}\Omega \cdot \text{cm}^2$$

$$C \frac{dV}{dt} = I \quad \text{with} \quad \mu\text{Fd} / \text{cm}^2 \times \frac{\text{mV}}{\text{ms}} = \mu\text{A} / \text{cm}^2 \quad (4.8)$$

$$V = L \frac{dI}{dt} \quad \text{with} \quad \text{mV} = \text{Hy} \cdot \text{cm}^2 \times \frac{\mu\text{A} / \text{cm}^2}{\text{ms}}$$

The most important point about these calculations is that both R_0 and L are negative. This occurs because $V_R < E_{Na}$. The fact that these components are negative is consistent with the function of the sodium channel which is to depolarize the membrane in a regenerative way. Such a non-linear role is analogous to a negative resistance which produces power instead of consuming it.

Part d) You have also seen this problem before, in a homework on cable theory. The general form of the cable equation is

$$\frac{1}{r_i + r_e} \frac{\partial^2 V}{\partial x^2} = I_m(x, t, V) = \text{membrane current / unit length of cylinder} \quad (4.9)$$

For this problem, we assume that the membrane current I_m is flowing through the circuit provided by the linearized membrane conductance derived above. In Fourier transformed form:

$$\mathbf{I}_m = \mathbf{V} \mathbf{Y}_m = \mathbf{V} \left[j\omega C + \frac{1}{R_1} + \frac{1}{j\omega L + R_0} \right] 2\pi a \quad (4.10)$$

where boldface again indicates transformed variables. The factor of $2\pi a$ is necessary to convert the membrane conductances from conductance per unit area of membrane (S/cm^2 , etc.) to conductance per unit length of membrane cylinder (S/cm , etc.). The conductances were derived above in area units, but conductance/length of cylinder is appropriate for the cable equation.

Fourier transforming Eqn. 4.9, ignoring r_e and using Eqn. 4.10 gives the linear cable equation for this situation (now an ordinary differential equation):

$$\frac{d^2 \mathbf{V}}{dx^2} = \mathbf{I}_m(x, t, V) = 2\pi a r_i \left[j\omega C + \frac{1}{R_1} + \frac{1}{j\omega L + R_0} \right] \mathbf{V} = \boldsymbol{\gamma}^2(j\omega) \mathbf{V} \quad (4.11)$$

where $\boldsymbol{\gamma}(j\omega)$ is a generalized length constant, written as a function of $j\omega$ to emphasize that it is a complex function of frequency.

Part e) Assuming a semi-infinite cylinder with a current injected at the closed end gives the following boundary conditions:

$$-\frac{1}{r_i} \frac{d\mathbf{V}}{dx} \Big|_{x=0} = \mathbf{F}[I_0 e^{j\omega_0 t}] = 2\pi I_0 \delta(\omega - \omega_0) \quad \text{and} \quad V(x, t) < \infty \text{ as } x \rightarrow \infty \quad (4.12)$$

where $\mathbf{F}[\cdot]$ means the Fourier transform of the function in the brackets. As usual, one boundary condition is a regularity condition. The solution to the differential equation 4.11 is

$$\mathbf{V}(x, j\omega) = \mathbf{A}(j\omega) e^{\boldsymbol{\gamma} x} + \mathbf{B}(j\omega) e^{-\boldsymbol{\gamma} x} \quad (4.13)$$

$\boldsymbol{\gamma}^2$ is complex, so there are two possible values of $\boldsymbol{\gamma}$, one with a positive real part and a second with a negative real part. Chose the positive-real root; choosing the other root gives the same ultimate

answer. The regularity condition in Eqn. 4.12 then implies that $\mathbf{A}(j\omega)=0$. Applying the boundary condition in Eqn. 4.12 allows the solution to be written:

$$-\frac{1}{r_i} \frac{dV}{dx} \Big|_{x=0} = \frac{\boldsymbol{\gamma}}{r_i} \mathbf{B}(j\omega) = 2\pi I_0 \delta(\omega - \omega_0) \quad \text{so that} \quad V(x, j\omega) = \frac{2\pi I_0 r_i}{\boldsymbol{\gamma}} \delta(\omega - \omega_0) e^{-\boldsymbol{\gamma}x} \quad (4.14)$$

Equation 4.14 is the Fourier transform of the membrane potential in the cylinder. Because of the delta function, this transform is easy to invert:

$$\begin{aligned} V(x, t) &= \frac{1}{2\pi} \int_{-\infty}^{\infty} \frac{2\pi I_0 r_i}{\boldsymbol{\gamma}} \delta(\omega - \omega_0) e^{-\boldsymbol{\gamma}x} e^{j\omega t} d\omega \\ &= \frac{I_0 r_i}{\boldsymbol{\gamma}} e^{-\boldsymbol{\gamma}x} e^{j\omega_0 t} \\ &= \left| \frac{I_0 r_i}{\boldsymbol{\gamma}} \right| e^{-\text{Re}[\boldsymbol{\gamma}]x} e^{j\omega_0 t + \theta} \quad \text{where} \quad \theta = \angle \left[\frac{1}{\boldsymbol{\gamma}} \right] - \text{Im}[\boldsymbol{\gamma}]x \end{aligned} \quad (4.15)$$

where $\angle[1/\boldsymbol{\gamma}]$ is the negative of the phase of $\boldsymbol{\gamma}$.

Part f) The membrane potential in the cylinder is given by the bottom part of Eqn. 4.15, so the magnitude of the membrane potential is:

$$|V(x, t)| = \frac{I_0 r_i e^{-\text{Re}[\boldsymbol{\gamma}]x}}{|\boldsymbol{\gamma}|} \quad (4.16)$$

The value at D.C. can be found by setting $\omega=0$ in Eqn. 4.16:

$$\boldsymbol{\gamma}(\omega = 0) = \sqrt{2\pi a r_i \left[j\omega C + \frac{1}{R_1} + \frac{1}{j\omega L + R_0} \right]} \Big|_{\omega=0} = \sqrt{2\pi a r_i \left[\frac{1}{R_1} + \frac{1}{R_0} \right]} \quad (4.17)$$

The D.C. length constant λ of standard linear cable theory is

$$\lambda = \sqrt{\frac{r_m}{r_i}} = \sqrt{\frac{R_m}{2\pi a r_i}} \quad (4.18)$$

where R_m is the resistance of a unit area of membrane. For the membrane considered here, R_m is just the parallel combination of R_1 and R_0 , i.e. the equivalent D.C. resistance in the membrane compartment. Setting $1/R_m = 1/R_1 + 1/R_0$ and combining 4.17 and 4.18 gives

$$\boldsymbol{\gamma}(\omega = 0) = 1 / \lambda \quad (4.19)$$

so that Eqn. 4.16 becomes

$$|V(x, t \rightarrow \infty)| = I_0 r_i \lambda e^{-x/\lambda} = \frac{I_0}{G_\infty} e^{-x/\lambda} \quad (4.20)$$

which is the same as the result obtained in class by applying a steady D.C. current.

The effect of the sodium channel is to increase R_m , making λ longer, thus making the cylinder electrotonically shorter and allowing D.C. potentials to propagate further. The sodium channel increases R_m because R_o is negative so that $1/R_m = 1/R_i + 1/R_o < 1/R_i$. For the values computed here, R_m is $3.3 \text{ K}\Omega\text{cm}^2$ in the absence of the sodium channel and $11.3 \text{ K}\Omega/\text{cm}^2$ with the sodium channel. Thus the D.C. length constant is increased by a factor of 1.8 by the presence of the sodium channel.