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# Quantitative Physiology: Cells and Tissues

**Homework Assignment #9** Issued: November 30, 2006
Due: December 7, 2006

**Exercise 1.** The membrane current through a myelinated fiber at the internode differs from that at the node of Ranvier while the membrane potential is quite similar at the two locations. For both the internode and the node of Ranvier, determine whether the relation between membrane current and membrane potential given in Figure 5.23 of volume 2 of the text is qualitatively consistent with the cable model or not. Briefly discuss the significance of your finding for the mode of conduction of action potentials in myelinated fibers.

**Exercise 2.** Explain why the membrane current through the internode of a myelinated nerve fiber contains two peaks of outward current as an action potential propagates down the fiber (Figure 5.17 in volume 2 of the text).

**Exercise 3.** State whether each of the following are true or false and give a reason for your answer.

a) Myelinated fibers conduct action potentials more rapidly than do unmyelinated fibers.

b) The action potential of a myelinated nerve fiber hops from node to node.

c) The action current of a myelinated nerve fiber hops from node to node.

d) Saltatory conduction results because the internodes are covered by the insulating myelin while the nodes are not.

**Exercise 4.** Define the *safety factor*.

**Problem 1.** A squid giant axon (which is an unmyelinated axon) has a diameter of 500 $\mu$m. The ionic currents during the passage of one action potential are shown in Figure 1. The normal internal concentration of sodium is 40 mmol/L. In contrast, consider a frog myelinated fiber for which the axon diameter (not including the myelin) is 10 $\mu\mathrm{m}$, the fiber diameter (including the myelin) is 14 $\mu\mathrm{m}$, the internodal length is 2 mm, the nodal length is 0.7 $\mu\mathrm{m}$, and the nodal area is 22 $\mu\mathrm{m}^2$. We shall assume that action potentials occur only at the nodes. The ionic currents at the node of Ranvier during the passage of an action potential are also shown in Figure 1. You may assume that the sodium current is negligible in the internodes. The normal internal concentration of sodium is 10 mmol/L in the frog fiber.

Both the squid unmyelinated fiber and the frog myelinated fiber conduct action potentials with about the same conduction velocity. This problem concerns the energetic efficiency of these two fibers.

a) Compute the number of moles of sodium entering each fiber per action potential per unit length of fiber.

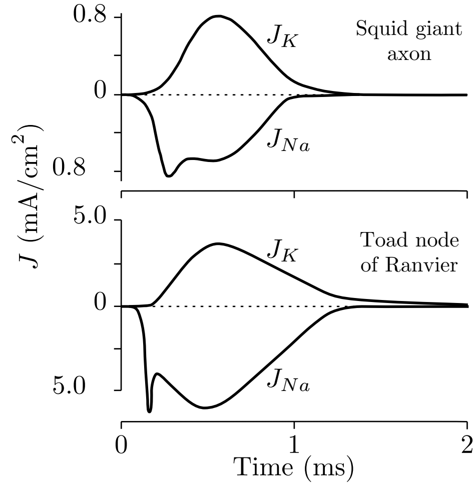



Figure 1: Comparison of ionic currents during an action potential for an unmyelinated squid giant axon and a myelinated toad node of Ranvier. These ionic currents are based on calculations of models of the squid giant axon (adapted from Cooley and Dodge, 1965, Figure 2.4) and toad node of Ranvier (adapted from Frankenhaeuser and Huxley, 1964, Figure 6).

b) Assume that the energy expended to pump the accumulated sodium out of the cell can be measured in terms of the number of ATP molecules hydrolyzed to ADP and assume that 3 moles of $\mathrm{Na}^+$ are transported out of the axon for every mole of ATP hydrolyzed to ADP inside the axon by the ($\mathrm{Na}^+$-$\mathrm{K}^+$)ATPase pump. Find the ratio of energy expended per unit length per action potential in order to pump out the accumulated sodium for the squid unmyelinated fiber to that for the frog myelinated fiber.

c) Describe the advantages of the frog myelinated fiber over the squid unmyelinated fiber.

**Problem 2.** Figure 2 shows a detail of a propagating action potential calculated using a model of a myelinated nerve fiber (Figure 5.31 in volume 2 of the text).

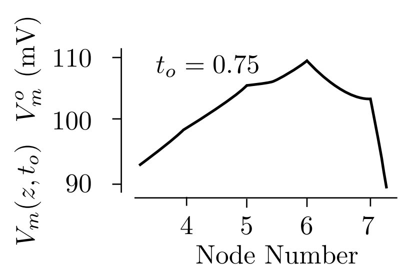
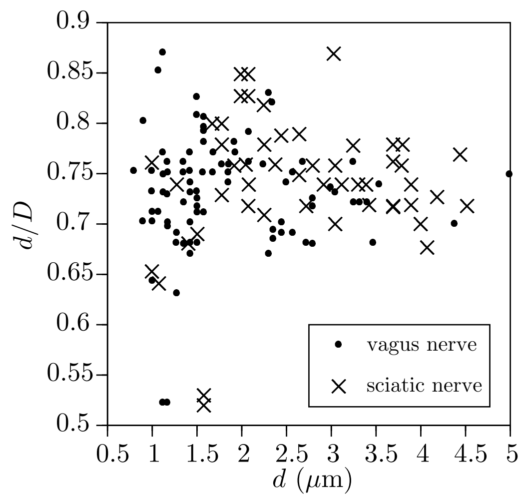



Figure 2: Membrane potential along a myelinated fiber computed from a model of electrical characteristics of the node and internode (Figure 5.31 in volume 2 of the text). The membrane potential is plotted as a function of distance along the fiber (expressed in units of internodal length where $L = 1.38$ mm).

a) Describe a method by which the data in Figure 2 could be analyzed to estimate the current $I_m$ flowing out of a node. Apply your method to calculate the current flowing out of node 6 at $t_0 = 0.75$ ms. Assume that $r_i = 140$ MΩ/cm$>> r_o$.

b) Describe a method by which the data in Figure 2 could be analyzed to estimate the current density $K_m$ flowing out of an internode. Apply your method to determine whether current is flowing into or out of the internode between nodes 5 and 6 at $t_0 = 0.75$ ms.

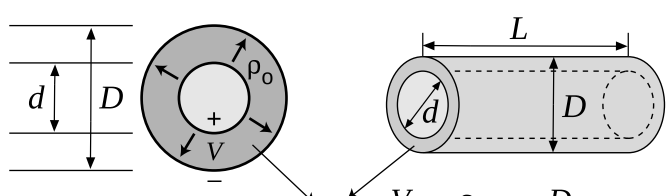
**Problem 3.** Although there is considerable scatter, the ratio of the inner diameter $d$ to outer diameter $D$ of the layer of myelin that encircles a myelinated fiber tends to be about 0.74, as shown in the following figure, where every symbol represents measurements of $d/D$ and $d$ for a different fiber.





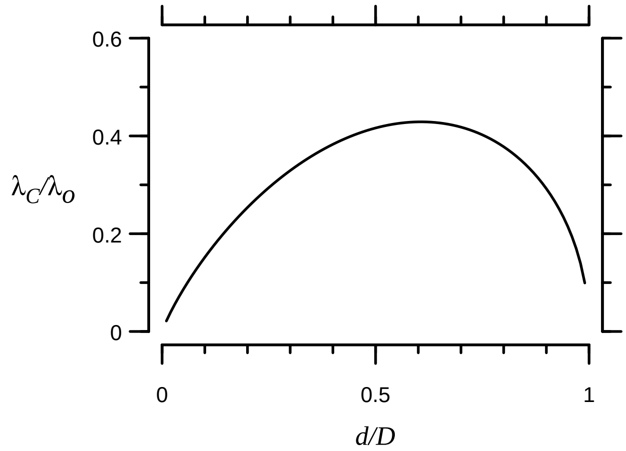
The point of this problem is to investigate the hypothesis that this relation between $d$ and $D$ results from an evolutionary optimization of the cable model.

**Part a.** Assume that the myelinated part (the internode) of a myelinated fiber can be represented by the cable model. Assume the myelin can be represented by a homogeneous electrical material with resistivity $\rho_m$ and permittivity $\epsilon_m$. Assume the intracellular conductor is a homogeneous conductor with resistivity $\rho_w$. Assume that the extracellular conductor has negligible resistance. Determine an expression for the space constant $\lambda_C$ of this model in terms of the inner diameter $d$ and the outer diameter $D$ of the layer of myelin. Hint: The radial resistance of a cylindrical shell is given below.




$$R = \frac{V}{I} = \frac{\rho_o}{2\pi L} \ln \frac{D}{d}$$

**Part b.** The expression derived in part a is plotted below



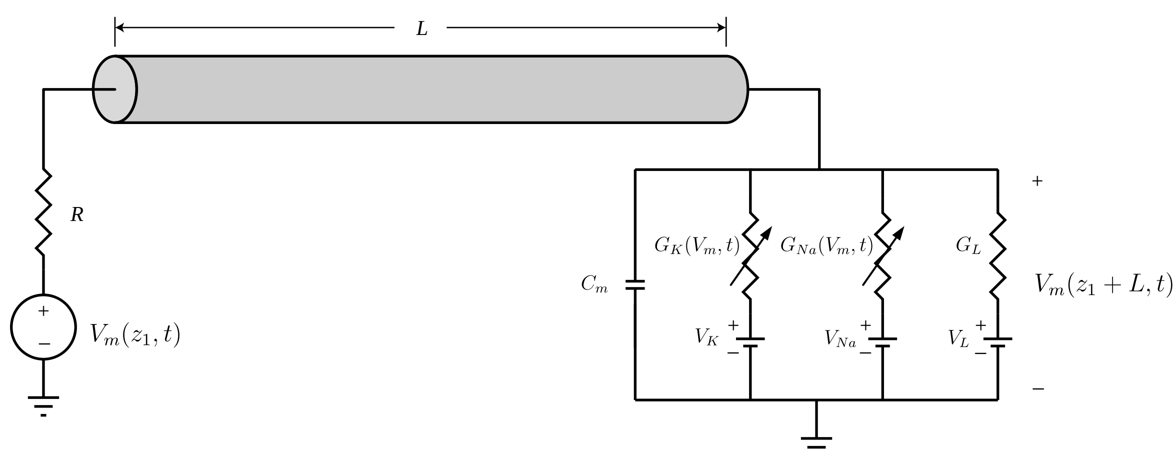

where $\lambda_o = D\sqrt{\rho_m/8\rho_w}$. Thus, if $D$ is fixed (i.e., if the axon is constrained to fit into a constant volume), then $\lambda_o$ is a constant, and $\lambda_C$ is maximum when $d \approx 0.6D$.

**b1)** Explain in physical terms why the space constant gets smaller as the value of $d$ decreases below $0.6D$.

**b2)** Explain in physical terms why the space constant gets smaller as the value of $d$ increases above $0.6D$.

**Part c.** The value of $d/D$ that maximizes the space constant of the cable model is remarkably close to the ratio of 0.74 seen experimentally. Nevertheless, it is smaller. One possible reason why it is smaller is that we ignored the resistance of the outer conductor $r_o$. How would the space constant's dependence on $d/D$ change if the resistance of a thin layer of saline (thickness = $0.1D$) were included in the calculation. Make a plot that contains both the old relation (shown in the previous plot) and the new relation. Briefly describe how the addition of the outer resistance changes the predicted space constant.

**Problem 4.** This problem involves the analysis of a simple model of the dependence of the conduction velocity $\nu$ of a *myelinated* fiber on the length of the internodes, $L$, with all other parameters of the myelinated fiber held fixed. Consider the simple model shown below, in which the time it takes to generate an action potential at a node is assumed to result from the time it takes for one node to charge the membrane capacitance of a contiguous node until some threshold potential is reached.



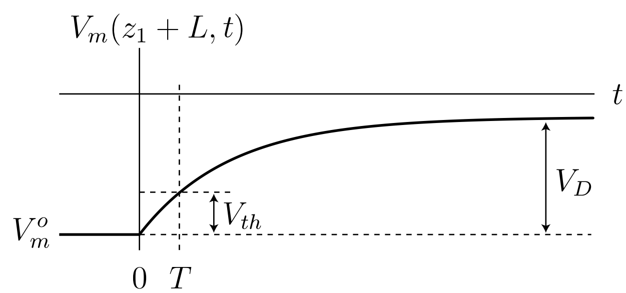

To simplify the analysis, assume the following:

- The myelin is a perfect insulator, i.e., no current flows through the membrane in the internode.
- While the right node is being charged, the capacitive current is larger than any of the ionic currents. Therefore, the right model can be approximated by ignoring the sodium, potassium, and leakage branches.
- The time constants of the Hodgkin-Huxley model are fast compared to the time it takes to charge the node through the internode. Therefore, the action potential at the left node can be approximated as a step change in membrane potential, from $V_m(z_1, t) = V_m^o$ for $t < 0$ to $V_m(z_1, t) = V_m^o + V_P$ for $t > 0$.
- The right node will produce an action potential when its membrane potential $V_m(z_1 + L, t)$ reaches a threshold voltage of $V_m^o + V_T$.
- The internal longitudinal resistance per unit length of axoplasm in the internode is $r_i$ Ω/cm. The external longitudinal resistance is so small that it can be taken to be zero.
- The diameters of the inner and outer surfaces of the myelin are $d$ and $D$, respectively The surface area of the node is $A$.

**Part a.** Draw an equivalent electric network that represents the active and stimulated nodes as well as the intervening internode. Label all part values as well as the input $V_m(z_1, t)$ and output $V_m(z_1 + L, t)$ of the network.

**Part b.** Determine a differential equation that relates the input $V_m(z_1, t)$ and output $V_m(z_1 + L, t)$ of the network in Part a.

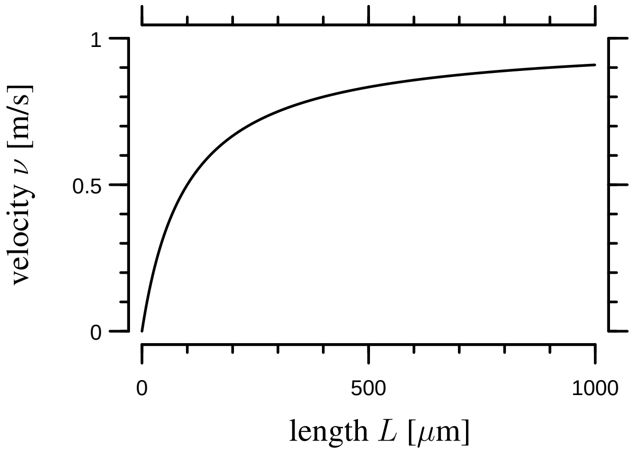
**Part c.** The step response of the network in Part a is shown in the following figure.




Determine an expression for the time constant $\tau$ and the voltage $V_D$, which represents the difference between the steady-state value of $V_m$ and the resting potential.

**Part d.** Determine an expression for the time $T$ that it takes for the membrane potential to reach threshold at the right node. Also, determine the corresponding expression for the velocity of propagation, $\nu$.

**Part e.** The expression for velocity from Part d is plotted below for $R = 10$ MΩ, $r_i = 10$ kΩ/m, $AC_m = 1$ pF, and $V_T/V_P = 0.1$.




**Part e1.** Explain why the velocity is roughly proportional to $L$ for small $L$.

**Part e2.** Explain why the velocity approaches a constant for large values of $L$.

**Part e3.** This model suggests that increasing the length of an internode always increases the velocity of propagation. This result does not fit with measurements of propagation velocity in myelinated fibers. Suggest a deficiency of this model that might account this discrepancy. Explain how correcting the deficiency would worsen performance for large values of $L$.