

## ACTION POTENTIAL TRANSMISSION\*

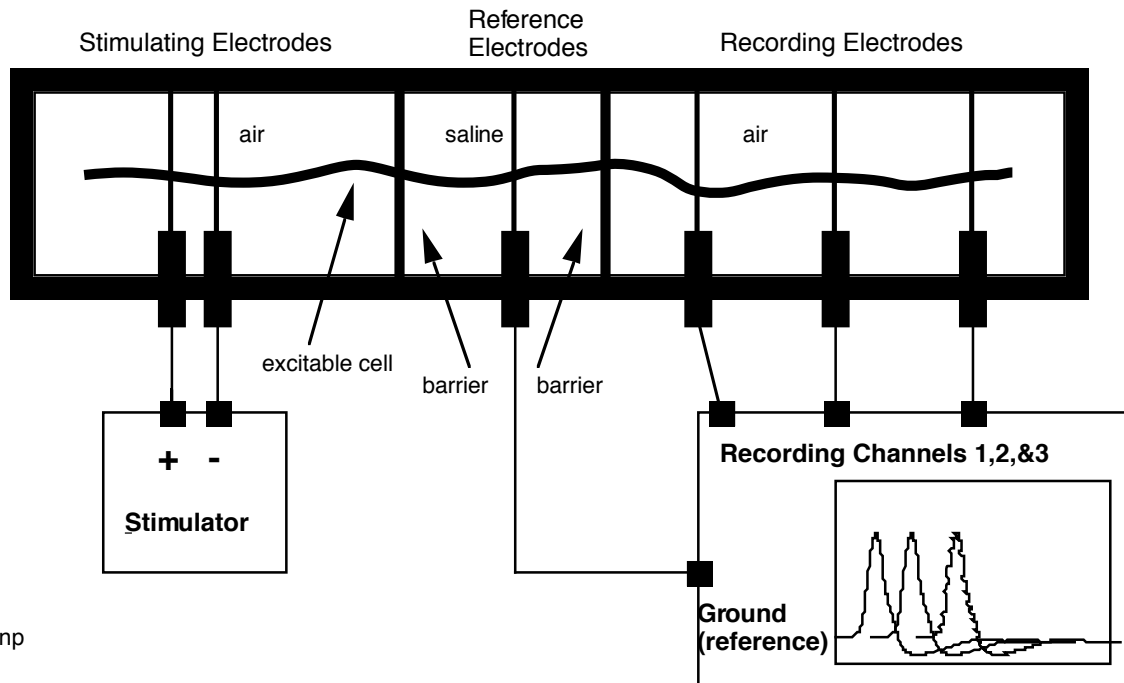
**Summary:** In this section we consider the factors that determine the means of action potential propagation along a single cell. We will review the electrotonic response and cable properties; examine how an electrotonic response travels and how membrane characteristics determine the propagation of these signals. The concepts of space constant and time constant are introduced. After this, we will see the relationships between an AP and the electrotonic response that it generates and examine how this electrotonic response sets off more areas of AP generation. Finally, we will consider the factors that determine rate of AP transmission especially in light of the time and space constants.

### I. Background

A. So far we have only considered membrane potential changes at one place on the membrane.

B. If these voltage changes are to have any value in communication, there must be movement of them from one part of a cell to another and also from one cell to another.

C. Here is the apparatus that is used for studying the transmission of active and electrotonic responses:



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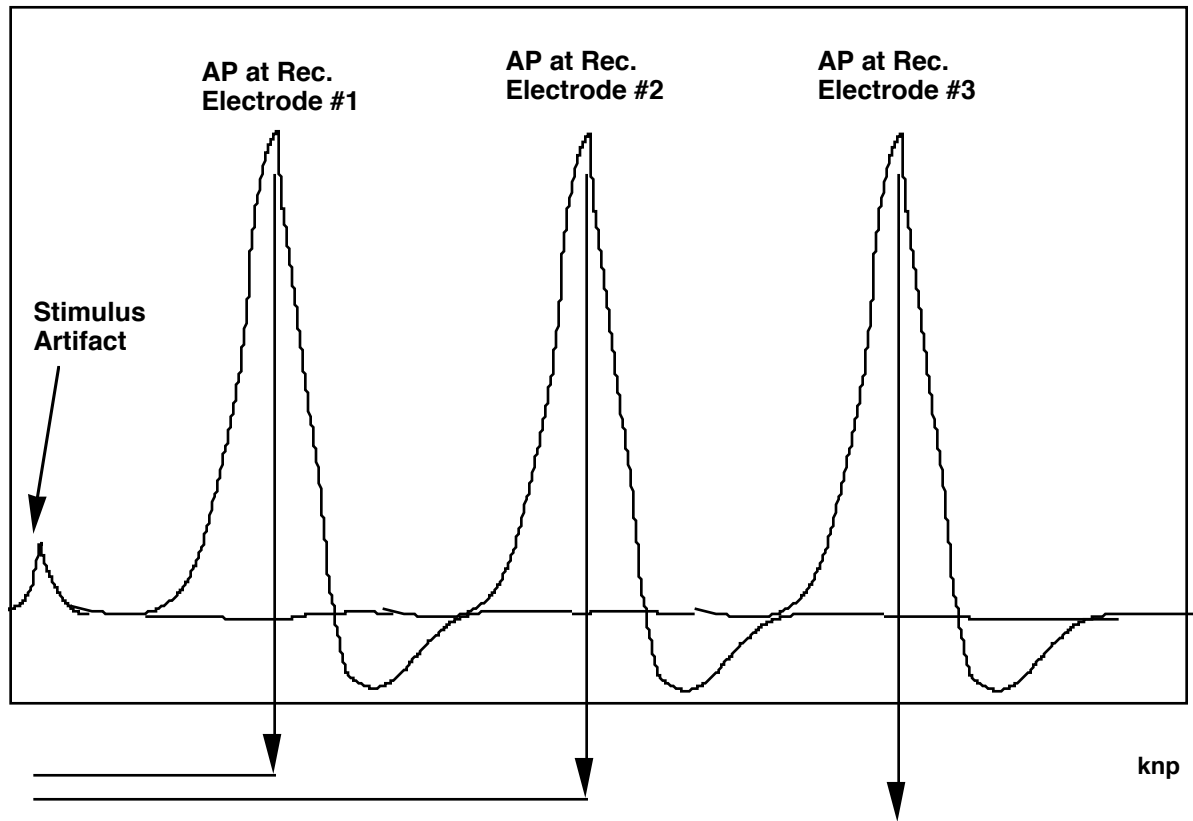
Note that when the axon is stimulated sufficiently to produce an action potential, the response moves towards the right (the left-moving signal is blocked by the hyper-polarized area under the anode -- ask me about it in class).

Note also that since the distance is known between the 3 recording electrodes and since the time needed to travel that distance can be monitored from the oscilloscope (see below); the velocity can be easily found.

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C. An illustration of the types of recordings taken from this apparatus after a super-threshold stimulus are shown on top of the next page:



**Times since stimulus artifact to the peak of the AP**

1. Note that a **STIMULUS ARTIFACT** precedes the AP. This is the passively conducted remnant of the stimulus; it is an example of what is called an **electrotonic response**. The one shown above is probably that recorded by electrode #1 -- by the time it gets to later electrodes it is probably too weak to be noticed.

2. Recall that in this type of recording that the X-axis is time. Thus, the "three" APs seen in the record really correspond to the AP as it passes by electrode #1 (Left); then a bit later by electrode #2 and so on. Since the distance between successive electrodes is known and since the time required to pass this distance can be measured from the record given above, the velocity of the AP can be found.

In this case, assume that recording electrodes 1 and 2 are 1 cm apart and that the peak of the "second" AP above is found to follow the "first" by 5 msec. What is the velocity of the AP between these two points?

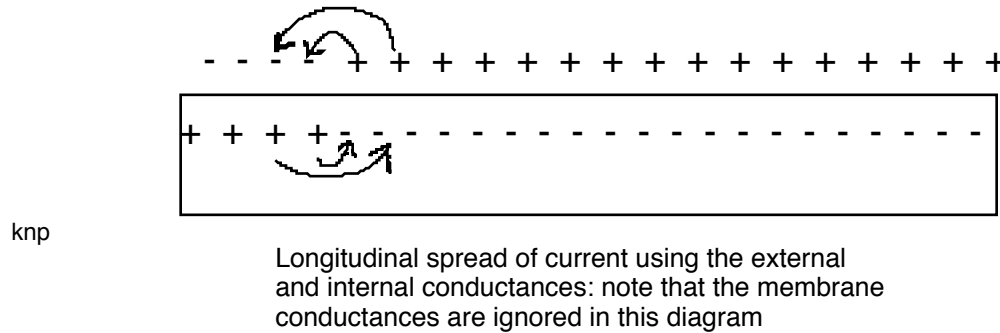
ANS:  $0.01\text{m} / 0.005\text{ s} = 2\text{ m / s}$ .

3. We will see that **electrotonic responses move at rates of tens of thousands of meters per second while active responses move at less (usually much less) than 500 m/s -- commonly just a few cm/s to around 100 m/s.**

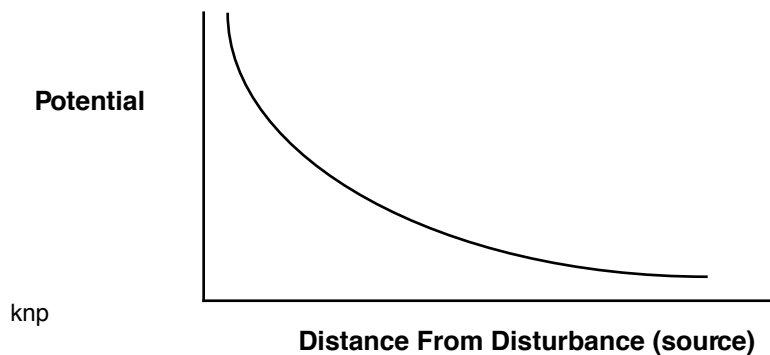
D. So, where is this going here? **Here is an overview of the process:**

1. The production of a spike potential at any particular place along an **axon sets up a difference in voltage between the area where the AP is occurring and adjacent areas that may be at resting potential. What happens in this regard is no different than what happens with any depolarization/hyperpolarization – with any area where different potentials are connected by conductor.**

2. This disturbance (here by an AP but again, by anything) leads to current flow and depolarization of the areas near to the present "location" of the action potential<sup>1</sup>.



3. This depolarization disturbance extends over some distance but gradually decreases in amplitude (we will see that it is measured by something called the **space constant**).



4. At any given place on the membrane, the **rate at which the membrane's potential can change** is determined by **resistance to current flow and membrane capacitance** (these being measured by something called a **time constant**).

5. The **speed at which the depolarization can move** is therefore determined by how far down the axon the disturbance extends (**space constant** related) and more importantly by how quickly the electric potential surrounding distant  $\text{Na}^+$  gated channels<sup>2</sup> can be brought to threshold (as measured by the **RC time constant**). Note that although this change in potential "moves" along the axon very rapidly, it does not do so at the speed of light as would be true of an electrical field or an electrical current in a copper wire.

6. We say that the electrotonic response is conducted passively because it will tend to decrease with distance.

<sup>1</sup> We will see that the AP is not really in one place at a time but to make this easy, for the moment imagine that it is!

<sup>2</sup> or other channels depending on the cell

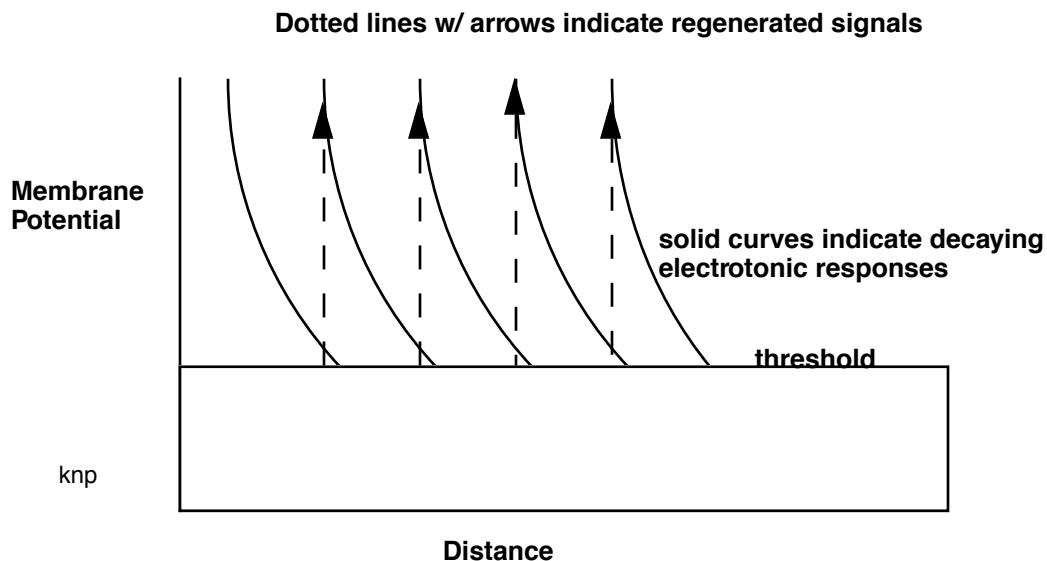
Note that passive, electrotonic responses are the only types of potentials found on the soma and dendrites of neurons. That is because these parts of the cell have no voltage gated sodium channels to produce active responses (APs). By contrast, axons conduct both types of potentials.

7. **Any time an active response (last set of notes) is produced, in one place, a passive electrotonic response spreads quickly from that area.** If the electrotonic response causes sufficient depolarization around voltage-gated channels, they will open and produce an active response. Since this opening of the gated channel involves an allosteric change and it also takes time. But notice that **the result is that the action potential now generated in a place adjacent to where it was previously. IT IS PROPAGATING OR "MOVING".**

8. The propagation is dependent on an electrotonic response but it is very different and much slower.

9. Notice that **an excellent way to think about all of this is to image that fast Na<sup>+</sup> channels are communicating with each other via a changing electrical field** (instead of via a chemical substance).

- (a) The electrical field is produced when one gate opens.
- (b) It propagates away electrotonically.
- (c) If it causes other fast Na<sup>+</sup> gates to open, they have essentially registered or completed the communication (review information notes).
- (d) The process is then repeated.



Note that the **shape of the stimulus artifact** is as expected -- even though a square wave stimulus was administered, the **capacitive properties of the membrane** have transformed it into a different shape (review notes on RC circuits).

## II. The Electrotonic Response and the Cable Properties of an excitable cell membrane.

A. The scheme just outlined makes the electrotonic, passive response out to be very important on every part of a neuron. It is the only means that signals are conducted on the dendrites and the soma and it is central to the propagation of the AP down the axon (although it

is not an AP). This section will examine in detail the determinants of the most important features of electrotonic responses.

B. **CABLE PROPERTIES OF THE CELL:** are the properties that control the propagation of electrical signals down a cell independently of any active response (i.e., independent of any opening and closing of gated channels). Thus, when we discuss cable properties, we are simply talking about the propagation of **ELECTROTONIC RESPONSES**. Cable properties include the aforementioned:

1. Space constant
2. Time Constant

### C. The Space Constant:

1. The figures on the previous page showed that passive responses die out with distance. Notice that the decrease fits a negative exponential function. Therefore we can describe the voltage at any position  $x$  away from the source of the disturbance<sup>3</sup> as:

$$1. \quad E_x = E_0 * e^{-\frac{x}{\lambda}}$$

where  $E_x$  is the voltage at some distance  $x$  from the reference point (i.e., from the source of the disturbance),  $E_0$  is the voltage at the source of the disturbance,  $e$  is the base of the natural logs,  $x$  is the distance and  $\lambda$  is a decay constant called the **SPACE CONSTANT** which is also a (see below)

2. If we wish to find the voltage at a point where  $x$  is equal to the decay constant, that is **where**:

$$2. \quad x = \lambda$$

then equation 1 becomes:

$$3. \quad E_x = E_0 * e^{-1} = 0.37E_0$$

3. Put another way, **the SPACE CONSTANT  $\lambda$  is the distance ( $x$ ) at which the voltage has decayed to a value that is 37% of its original value.**

4. The decay of voltage with distance is due to various resistances. This should make sense -- the effect of resistance is always to reduce voltage -- voltage drops across resistance. Let's see how this works:

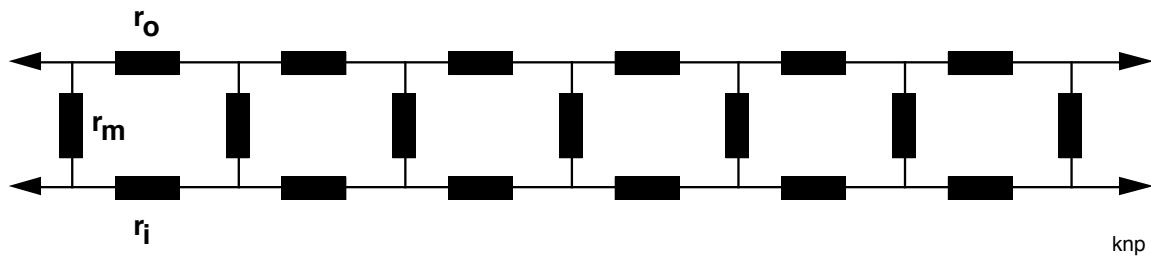
(a) Consider the paths for current flow on the inside and outside of the cell. They have resistances  $R_i$  and  $R_o$  respectively. They will tend to increase with distance. Moreover, they will tend to add because a complete circuit requires that ions move on both the outside and inside of the cell. Thus, the total resistance for traveling some distance  $x$  away from the disturbance is the sum of the resistances for the inside and outside paths for that distance --  $R_i + R_o$ . Let's relate this to the space constant. The greater the resistance, the less distance a signal will travel and so the lower the space constant. They are inverses and so:

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<sup>3</sup> Here "source of disturbance" means the place where the change in membrane potential ( $E_M$ ) from the normal resting value is the largest. Therefore, this could be from a point of stimulation or from the place where the peak of an AP is present.

4. 
$$\lambda \propto \frac{1}{(R_i + R_o)}$$

(b) current can also divide and flow through the membrane instead of just along the outside and inside. Thus, current can also flow through a membrane resistance,  $R_m$ . A good model of a membrane with respect to resistances looks like the next figure:



Assume that all of the membrane resistances are of equal value to each other -- the idea is that any large area of membrane (large when compared to the size of channels) will have about the same number of each type of channel).

Further assume that for a given diameter cell, internal resistance (the lower, horizontally oriented resistors) is a constant for each unit length, as it is in any conductor of a constant composition and diameter. Assume the same to be true for the outside (extracellular) resistance; but DO NOT ASSUME THAT  $R_i$ ,  $R_o$  and/or  $R_m$  are equal to each other per unit length.

Suppose we want to know the effect of a disturbance at the left of the diagram on the potential on the extreme right. A current flows outward along the outer and inner membrane. Since both are resistances, it decreases with distance. Moreover, everywhere there is an ion channel, some current can also flow back into the cell through  $R_m$ , the membrane resistance, and follow a shorter path. The effect of these short circuits is to further decrease the membrane potential with distance.

Now, notice that as  $R_m$  becomes larger, there is less short-circuiting and therefore the signal remains more intense than it would if  $R_m$  was lower. Thus:

5. 
$$\lambda \propto R_m$$

If we combine all of these resistances (let's not worry about the math of what is being done here) we get:

6. 
$$\lambda \propto \sqrt{\frac{R_m}{(R_i + R_o)}}$$

? Construct a graph of  $E_m$  vs. distance ( $x$ ) that shows the effects of different space constants. Make a similar graph that has qualitative plots to show the effects of two different values of internal (or external) resistance and two values of membrane resistance. You will not need to solve the equations above but you should certainly be able to explain or use the ideas in eqs. 1-3 and 6.

5. The space constant in many unmyelinated vertebrate neurons is approximately 2-3 mm and is roughly similar to this in most other cells of the same general size.

? What is the significance of the actual value of the space constant (just given) to the evolution of signaling systems? You should be able to discuss this with regard to (i) need for regeneration in relationship to (ii) signal to noise ratio and (iii) speculations about limits of protein sensitivity to voltage changes.

#### D. The Time Constant

1. in the "Electricity Review" handout, there was a discussion of **time constants in RC circuits** -- the time required in a given RC to circuit for the potential across its capacitor to change. Let's review RC circuits and then look more closely at time constants.

2. Remember that capacitors are charge storage devices where the amount of stored charge is directly proportional to the voltage across the capacitor:

7. 
$$E = \frac{Q}{C}$$

where  $Q$  is the charge in coulombs and  $C$  is the capacitance in farads (coulombs/volt). Note that capacitance is determined by things such as how close the capacitors conductors are from each other, the size of the conductors, and the insulation between them. For our purposes, we will always consider capacitance per unit cell membrane area (thus removing conductor size as a variable) and we will consider all lipid bilayers to have the same width and insulation properties (thus removing these two properties (but wait -- I will play with the insulation part eventually).

Thus, the **typical value for membrane capacitance is  $\frac{1 \mu F}{cm^2}$ .**

Now, recall that we can also talk about current flowing into or out of a capacitor (charging and discharging the capacitor) by taking the time derivative of eq. 7:

The same expression, except for current:

9. 
$$\frac{dE}{dt} = \frac{1}{C} \cdot \frac{dQ}{dt} = \frac{i}{C}$$

where  $i$  is current and  $t$  is time.

Recall that the other part of RC circuits is the resistive part that has the role of limiting the rate at which current can flow in or out of a capacitor.

Thus the rate at which current can flow in or out is determined by resistance and therefore the time it takes for a certain amount of charge to leave or enter is also being partially determined by resistance. Likewise, the "bigger" the capacitance, the more charge that can be stored for a given voltage and the more that needs to leave before a certain change in voltage can occur.

Therefore, the time constant,  $\tau$ , is:

10. 
$$\tau = RC$$

3. How does one find the value of resistance to use? We need not go into the derivation but we use a measure called the effective resistance,  $R_{eff}$  that is the geometric mean of the membrane and length (in and out) resistances:

$$11. \quad R_{effective} = \sqrt{R_m R_i}$$

4. If we substitute eq. 11 into 10 we get:

$$12. \quad \tau = C\sqrt{R_m R_i}$$

4. Now, let's describe the process of change. Charging and discharging a capacitor (the membrane) is another type of exponential decay or increase. This time, since we are interested in seeing how much voltage changes across the membrane capacitor in a certain time, we write:

$$13. \quad \Delta E_t = \Delta E - (\Delta E e^{-\frac{t}{RC}})$$

where  $\Delta E_t$  is the change in voltage across the capacitor at time  $t$ ,  $\Delta E$  is the total voltage change of the capacitor in going from one value to another,  $e$  is the base of natural logs,  $R$  is resistance in ohms and  $C$  is capacitance in farads.

As with any such equation, if we solve for  $\tau = RC$  then:

$$14. \quad \Delta E_t = \Delta E - (0.37\Delta E) = 0.63\Delta E$$

We call this particular **value of  $t$**  associated with this condition the **time constant**. That is, **the time constant is the amount of time needed to change the potential (and therefore the charge) by 63%**.

4. the **biological significance of the time constant** is that **the smaller it is, the faster the membrane can depolarize** by a given amount **and the greater the rate of electrotonic and perhaps AP transmission**.

### III. Real Examples: What can you do to make an excitable cell conduct APs really fast (or for that matter, really slowly!)?

**A. Make them fat!** In excitable cells unlike just about anything else, being more "robust" means being faster. The increase in speed is due to a decrease in the time constant and an increase in the space constant. Let's see how it works.

1. Membrane Capacitance and the amount of current that must flow:

Assume that the cell is cylindrical such as in an axon or a muscle fiber. With such geometry, the cell's **membrane surface area** ( $A_s$ ) increases with radius according to the following equation:



15.  $A_s = 2\pi rL$

and the **cross sectional area** ( $A_{x-s}$ ) of this cell:

16.  $A_{x-s} = \pi r^2$

Now:

- TOTAL  $C_m$  increases directly with the membrane SA but
- $R_m$  decreases; it is proportional to the inverse of the area and
- $R_i$  is proportional to the inverse of the square of the radius (inversely proportional to the x-sectional area)
- 

? Explain each of these changes in terms of what you know about capacitors and series and parallel resistances. You need not be quantitative; just give approximate explanations.

Let's **assume that radius doubles**. If that happens then, **according to eqs. #15 and #16:**

- (i) membrane **surface area will double** but
- (ii) internal **cross sectional area will increase by 4X**.

Now, since  $R_m \propto \frac{1}{A_s}$  then **if the radius doubles,  $R_m$  is halved**.

Similarly, since  $C_m \propto A_s$ , **if the radius doubles,  $C_m$  doubles**.

**Lastly,  $R_i \propto 1/A_{x-s}$ ; thus if the radius doubles,  $R_i$  decreases by 4 fold.**

Putting all of this together: if the radius of the cell doubles and we substitute the changes above for  $R_m$ ,  $C_m$ , and  $R_i$  into eq. #12:

$$\tau = C\sqrt{R_m R_i} = 2\sqrt{0.5 * 0.25}$$

Since the time constant ( $\tau$ ) is a measure of how fast the membrane depolarizes and therefore is proportional to how fast the membrane will depolarize to threshold, then the factorial change in the time needed to reach threshold when the radius is doubled is:

17. 
$$\frac{\tau_{\text{double radius}}}{\tau} = \frac{2\sqrt{0.5 * 0.25}}{1\sqrt{1 * 1}} = 2\sqrt{0.125} = 0.707$$

thus, **doubling the radius** cuts the time constant to about 71% of its previous value and all else being equal, **increases the velocity of AP transmission by 1.414X (1 / 0.707) by increasing the rate of electrotonic transmission by that same factor!**

2. Effects of increase in size on the space constant. Recall that

6. 
$$\lambda \propto \sqrt{\frac{R_m}{(R_i + R_o)}}$$

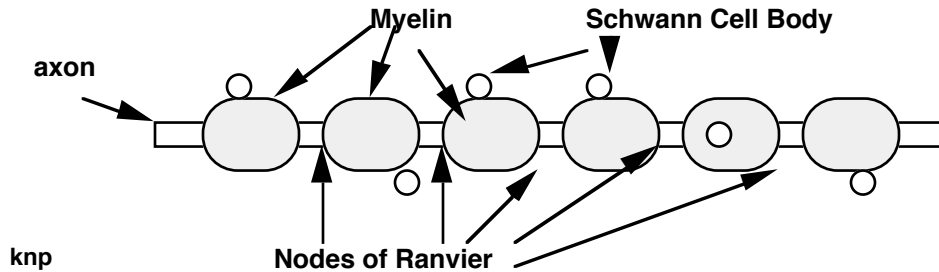
From above, doubling the radius will cut  $R_m$  in half and cut  $R_i$  to 0.25 of the value for the smaller cell. It has no effect on  $R_o$ . The **trend for the result is:**

6b. 
$$\lambda \propto (0.5 / 0.25)^{0.5} \propto 1.4$$

So the space constant increases and a greater proportion of the membrane will depolarize as a result of a given disturbance.

**B. Solution #2: Myelination:**

1. Myelination is the wrapping of a type of glial cell, called a Schwann cell, around an axon:

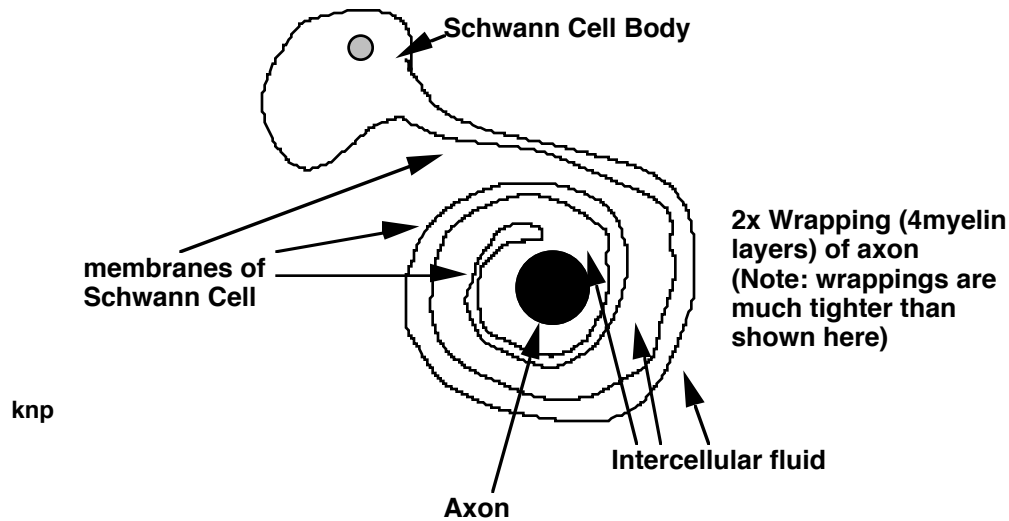


It is a successful solution to the speed problem that evolved only in chordates (in addition to changes in diameter).

Myelin increases speed by (surprise):

- (a) **affecting the time constant** and
- (b) **increases the space constant**

2. More **About myelin:** Schwann cells are a particular type of oligodendrite (Glial) cell. During development, they grow around an axon in a spiral manner and enclose the axon in a series of continuous concentric rings separated by intercellular fluid. The amount of cytoplasm in the portion of the Schwann cell that wraps the cell is rather small. A given Schwann cell my wrap an axon anywhere from just a few times to more than 100! Each winding of the cell adds two thicknesses of membranes around the axon:



Now, each double membrane acts as a capacitor in the intercellular fluid (note that these are different from the membrane capacitors). However, these and the membrane capacitors are all in series with each other!

The formula for total capacitance from a number of capacitors in series is:

18. 
$$\frac{1}{C_t} = \frac{1}{C_1} + \frac{1}{C_2} + \frac{1}{C_3} + \dots + \frac{1}{C_n}$$

Thus, placing capacitors in series reduces total capacitance. The reason for this is that when capacitors are hooked in series the conductor of one polarity is directly connected to one of the opposite polarity. Therefore less charge can be stored on a given capacitor conductor at a given voltage which is essentially the same as reducing the area of the conductor. Another way to look at it is that when capacitors are in series, the voltage is divided across all of the capacitors. This means less stored charge per capacitor (remember that  $C = Q/E$ ).

! Draw this out and satisfy yourself that it is correct -- compare this with a parallel arrangement where capacitances add.

**The effects of myelination on capacitance and resistance:**

**1. Capacitance:** Let's assume that a particular axon has **50 layers of myelin** around it. When compared to an unmyelinated cell, 50 additional capacitors have been added in series to the axonal  $C_m$ . According to eq. #18, the **total are-specific capacitance of the myelinated area of the membrane has been reduced to 1/50<sup>th</sup> of what it was**

**2. Resistance:** On the other hand, myelin has **no effect on either  $R_o$  or  $R_i$**  since in one case it is totally irrelevant (myelin is external) and it has no effect on external resistance because it does not impede the flow of current along the long axis of the cell external to the myelin. However, it does greatly **increase  $R_m$**  since it reduces the ability of current to flow through the membrane -- each layer of membrane acts as a series resistance and therefore adds to the total. Once again, per unit area we can assume that each area has roughly the same resistance and **therefore  $R_m$  increases by about 50X if there are 50 layers of myelin.**

**3. A calculation of the time constant in myelinated regions:** If we now use a simplified version of eq. 18 (dispensing with the ratio where 1 is the denominator – see two pages ago in these notes we have the factorial change in the time for  $E_m$  to change in the myelinated region (not the Nodes of Ranvier) as:

$$19. \quad \Delta t_{\text{threshold}} = C\sqrt{R_m R_i}$$

and solving using the numbers just discussed for resistance and capacitance:

$$\Delta t_{\text{threshold}} = \frac{1}{50}\sqrt{50 * 1} = \frac{1}{50}\sqrt{50} = 0.141$$

which is about 7.1X faster ( $1 / 0.141$ ) than the time constant in unmyelinated areas of axon of the same diameter. Thus, in these regions, the electrotonic response that is responsible for causing membrane depolarization at some distance and initiating an action potential in these areas moves 7X faster and therefore the velocity of transmission must increase by at least this much.

However, there is even more!

**4. Calculation of the space constant in myelinated areas:** Notice that within each myelinated region,  $R_m$  is high while  $R_i$  and  $R_o$  are about the same as usual. Since the space constant  $\lambda$  can be estimated from eqs # 6 and 7::

$$E_x = E_0 * e^{-\frac{x}{\lambda}} \quad \text{and} \quad \lambda \propto \sqrt{\frac{R_m}{(R_i + R_o)}}$$

then increasing  $R_m$  by 50X while leaving  $R_i$  and  $R_o$  the same will:

$$\Delta \lambda \propto \sqrt{\frac{50}{1}} = 7.07$$

that is, for a given decrement in  $E_m$  the electrotonic signal will travel roughly 7X further!

#### **IV. Other useful ideas related to understanding AP transmission:**

A. **FUSE ANALOGY:** the action potential, like a burning fuse is self-regenerating. Both produce the environment necessary for their continued propagation. The fire on the fuse heats the area next to it causing it to also burn and as a result the burning (= AP) moves along the fuse (= axon). A fast burning fuse is simply one that is capable of causing an area further from the present site of burning to also start burning. Likewise, faster conducting axons are those that are capable of exciting areas further from the present site of the AP.

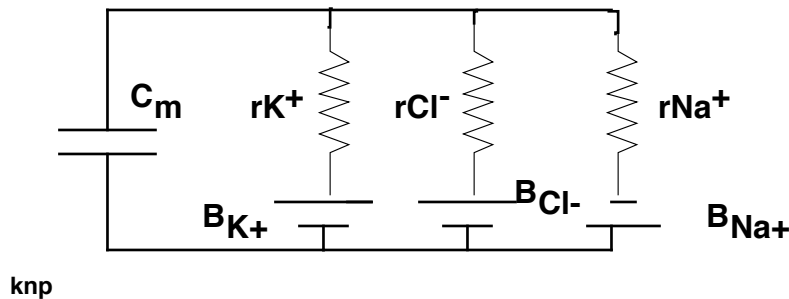
2. **SAFETY FACTOR:** You may ask the question of why the AP is so large? After all a smaller depolarization would be sufficient to depolarize the adjacent areas of a membrane and allow propagation. This could be managed by letting in less  $\text{Na}^+$ . As a result, the  $\text{Na}^+/\text{K}^+$  pump would not have to work as hard. So why is the AP so large? Realize that selection can act on the amplitude of an action potential; APs are the way they are for reasons.

Other questions:

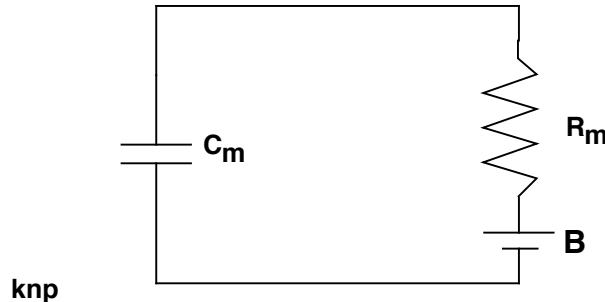
? If areas at different distances from a disturbance are all above threshold, will they all necessarily fire together? Explain.  
 ? Is the action potential limited to one very thin ring (section) of the axon at one moment in time? Or is it "smeared out" along the axon? How about the electrotonic response? Explain and make some drawings. What is the relationship between different  $E_m$  at different places and electrotonic response?

**V. Final Review of the Electrical Model of Excitable Cell Membranes:**

A. . Let's review our earlier "complete" model a small section of the membrane:



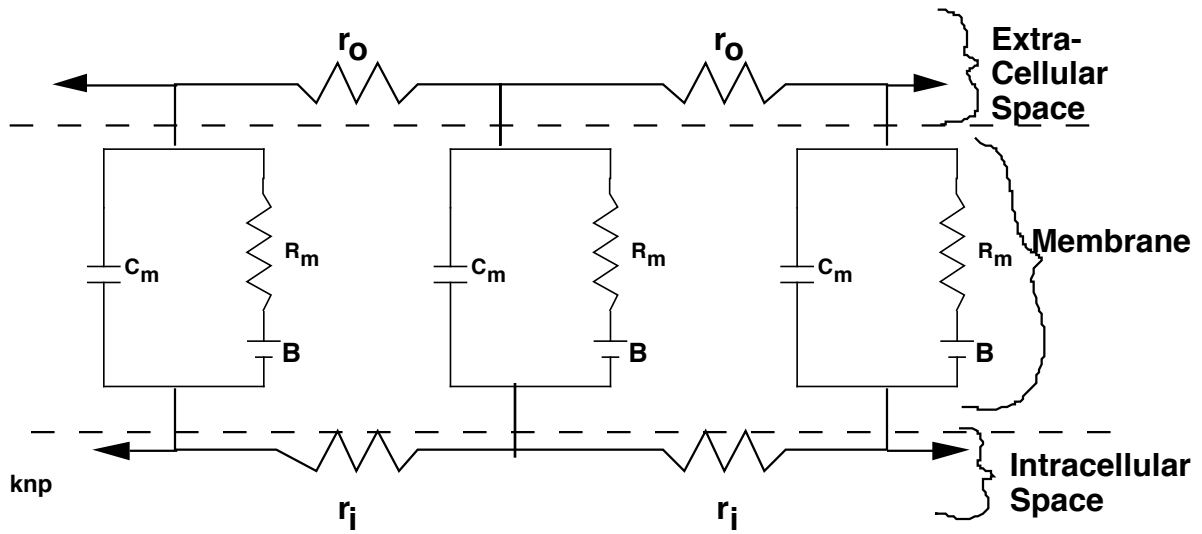
let's simplify this model and lump all membrane conductances together into  $R_m$ :



2. For our discussion of cable properties, we need to upgrade this model to its "final" incarnation (for this class anyway!).

a. Since we are now concerned with the movement of an electrical event along the cell (instead of simply the movement of ions across the membrane at just one spot) we must consider that **the INTRA and EXTRA CELLULAR FLUIDS are also resistances; they must be included along with the membrane-bound resistances (the ion channels).**

b. Thus, our model for one small membrane section becomes:



Notice that the model above is for only one small section of the cell and its surrounding environment -- that is in part indicated by the arrows that imply that the units depicted above will continue to repeat. You should also realize that the membrane is cylinder-like and therefore the structure also continues in three dimensions surrounding the core intracellular space.

**! IMPORTANT:** Note that the membrane capacitance and resistances and also the intra- and extra-cellular resistances are **constant properties** for any length of membrane. That is why they are shown repeating over and over.