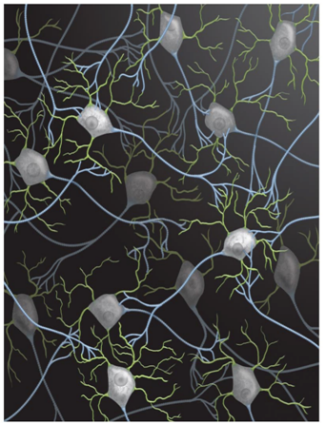
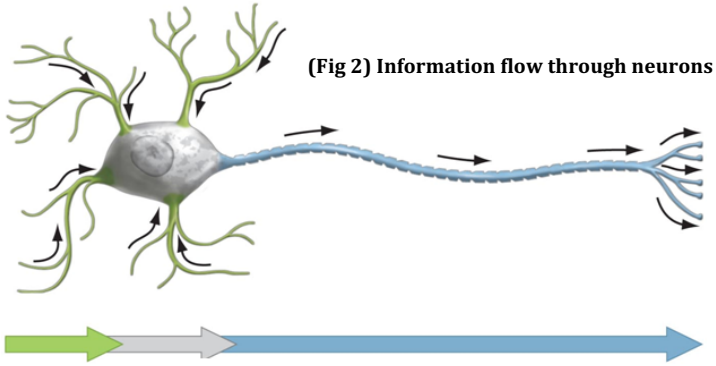
LAB 6: *Transmission* of Information

So far, we've only considered electro**statics**, where a **fixed** potential *landscape* is established across some region, encouraging charge to flow. We will soon discuss why *information* is typically encoded, physically (across a wide range of engineered systems) as voltage levels. In the case of (naturally occurring) nerve impulses, we associate transmission of information with a *change* in potential that travels out, much like a wave pulse propagating along a taut string. In a neuron, this *change* in potential travels along an axon as information to be transferred through a synapse to other neurons or muscle cells. For tonight's lab, it is important to note that **a *single* neuron can be a *meter or more* long** (*e.g.*, those connecting our toes to our spinal cord). We're interested in the "operational constraints" of such an *information transmission system*.



(Fig 1) Neurons form *networks* for *information* flow



(Fig 2) Information flow through neurons axon

Dendrites Collect electrical signals

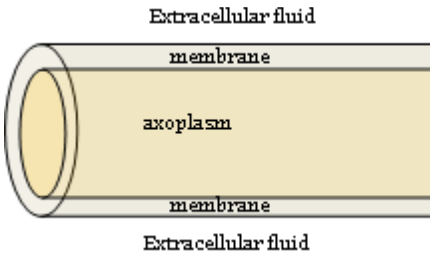
Cell body Integrates incoming signals and generates outgoing signal to axon

Axon Passes electrical signals to dendrites of another cell or to an effector cell axon

<u>*Structure and properties of a* ***transmission line:***</u>

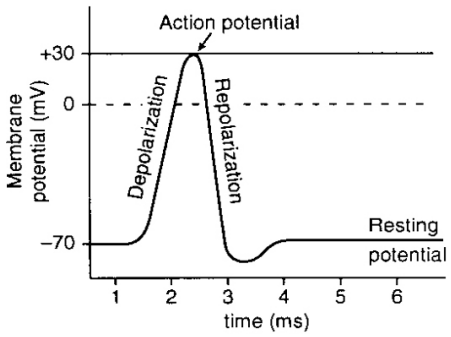
Nerve impulses are electrical signals. Whether you are seeing or hearing something, controlling a muscle, or just thinking, the *transmission process* along a nerve cell, or neuron, is the same: a sufficient stimulus received by the cell body initiates a ***change*** in **potential difference**, which physiologists (people who study the physics of living systems) call the ***action*** *potential*.

(Fig 3) Axon: cylinder MODEL



To understand the transmission of an action potential, we model the axon as a long, thin cylinder, like a pipe or <u>cable</u>. The axoplasm, or fluid inside the axon, contains ***mobile ions***, making it something of a conductor (not nearly as good as copper or anything like that – the resistivity of axoplasm is many orders of magnitude higher than that of any metal, but it clearly still *works*!). A very thin membrane encloses the axoplasm. The material outside the membrane, the extracellular medium, has roughly the same resistivity as the axoplasm does. It's sometimes said that the membrane is an insulator, but different kinds of very small channels within the membrane can allow specific ions to pass under particular conditions. (Sounds like pretty complicated hardware and, like many computing systems, it is! We'll only highlight a few key aspects.) The point is that although the resistivity of the membrane is higher than that of axoplasm, the membrane is far from a perfect insulator. When it's not carrying an action potential, the potential inside the axon, relative to outside, is about -70 mV, the *resting* potential difference. [In part, this arises because the sodium ion concentration is higher outside the axon than inside, but that's not a detail we'll need.]

(Fig 4) Membrane potential



Inner workings of the action potential:
The neuron's cell body integrates incoming electrical signals, sending the resulting signal to the axon. If that increases the potential drop across the membrane by more than about 20 mV (from -70 mV to a ***threshold*** of about -50 mV), then *voltage-gated* channels open and allow sodium ions to flow into the axon: this is the beginning of the action potential. Driven by both the concentration gradient and the potential gradient, Na^+ ions continue to pour in until the membrane potential difference changes from -70 mV to about +30 mV, a process referred to as depolarization. Because the local region into which Na^+ ions have flowed is now positive, positive ions will want to flow away from it, which forces them to move *along* the axon. Some of this electrical current traveling along the axon *leaks* through the membrane into the extracellular fluid and back to the negative region outside the axon at the site of the beginning of the action potential. [Fig 4] But, if we look downstream a bit, positive ions have moved along the axon, and so the membrane potential difference here has become less negative. Once the threshold potential difference is reached, voltage-gated Na^+ channels in this new section of the membrane will open, initiating a new depolarization, which regenerates the action potential. In this way, a change in membrane potential difference *travels along the axon*. In each local region, it only takes a millisecond or so, after the start of the depolarization, for the voltage-gated Na^+ channels to close, and the resting potential to be reestablished. In short, the figure above is **all you really need**: Fig 4 reiterates that we associate transmission of information with a *change* in potential that travels out, much like a wave pulse propagating along a taut string.

Prelab:
1. **Distinguish** between *resistance* and *resistivity*.

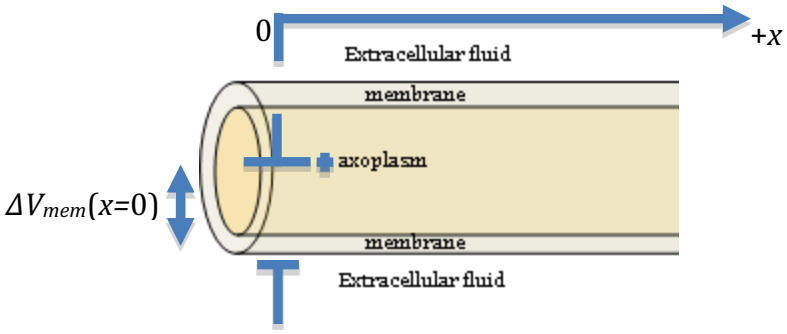
2. Describe an example of **exponential decay** that you're familiar with. Sketch and label a relevant graph. ***Why*** is it *exponential* decay, and not some ***other*** decreasing function?

INVESTIGATION 1: HOW *FAR* CAN A POTENTIAL DIFFERENCE *PASSIVELY* SPREAD ALONG AN AXON?

In this lab exercise, you will apply a change in potential difference across your (model of) a membrane at *one end* of a (model of an) axon, and then you'll examine ***how small*** the potential difference across the membrane, $\Delta V_{mem}(x)$, will become, at different distances x from the starting point. This *loss* in signal strength is a key issue.

Activity 1: Designing a model circuit.
We'll start with the very simplest model that we can imagine. If we find that our model is too simple to help us answer the questions that we've posed, we'll successively refine it until we find that it's useful in the context of these questions.

Let's say that the left end of the axon is depolarized – the inside of the axon switches from negative to positive – as in the start of an action potential. We can model this by drawing (in **blue**, below) a schematic **battery symbol** across the membrane. Since this is the membrane potential difference at one end of the axon (x = 0), we label it $\Delta V_{mem}(x=0)$.



1. If you were to complete a single loop, starting at the positive terminal of the battery and moving a bit along the axon before allowing for current to leak out to the extracellular fluid on the above diagram, **show** the path of conventional current inside and outside the axon (*i.e.*, go ahead and explicitly *make a drawing, of the current flowing from the positive of the battery to the negative of the battery*).

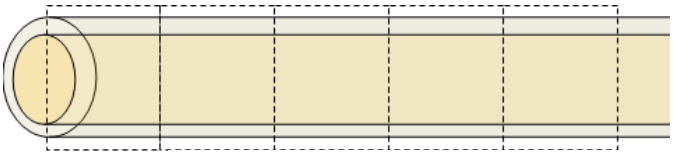
Now's let's think about that path: What *circuit element* should we use to model each part?

2. What circuit element should we use to model the ***inside*** of the axon – the axoplasm? Why? **Draw** this circuit element in the path of the current and give it an appropriate symbol.

3. What circuit element should we use to model the ***membrane***? Why? Draw this circuit element in the path of the current and give it an appropriate symbol.

4. Now consider the *outside* of the axon. Since the extracellular fluid is characterized by *resistivity*, we might model it as a **resistor**. But explain why the *resistance* outside of the axon must be small compared to the resistance inside the axon, and why it's therefore reasonable to *neglect it*. (Hint: Think about the cross-sectional area through which current can flow *outside* of the axon compared to *inside*…)

Hopefully, you've now created a very simple model of the flow of current in an axon in response to a change in the membrane potential difference applied at one end of the axon. Is it adequate for our purposes? Remember, we want to learn how the change in membrane potential difference varies along the axon. Our very simple model is a good description of the *first* short *segment* of axon, say 1 mm in length. Let's imagine a long axon as a *chain* of many short segments. (Fig 5) *Each segment* may be characterized by its individual R_{axon} and R_{mem}.



(Fig 5) Axon: chain of many segments

5. In the space below, extend your diagram in order to depict this more sophisticated model. **Show at least 3 segments**. Carefully **label** each circuit element. Remember to label the battery $\Delta V_{mem}(0)$. Also label the potential differences across each of the R_{mem}'s as $\Delta V_{mem}(1)$, $\Delta V_{mem}(2)$, *etc*.

6. A typical "unmyelinated axon" is **10 µm in diameter**, with a **10-nm thick membrane**. The resistivity of ***axoplasm*** is around **1.0 Ω•m** (Yes, those really are the correct units!). On the other hand, we'll take the ***membrane*** resistivity to be **1.0×10^8 Ω•m**. *Calculate* values for R_{axon} and R_{mem} for each segment. (Hint: To help you think about the resistance of the membrane, imagine unrolling the membrane flat. What is the "length" of this resistor? What is its "area"?)

7. ***Estimate*** appropriate values for R_{axon} and R_{mem} for each segment for your model circuit, and **justify** your choices. (Since the physical and geometric quantities we gave you for a typical unmyelinated axon are only approximate, it will not be necessary to try to exactly match your calculated values. In addition, you should consider whether you need to look for resistors *close* to your calculated values, or if only the *relative* values of R_{axon} and R_{mem} are important, or if perhaps even that constraint can be relaxed as we look, somewhat generically at the behavior of this *type* of model circuit.)

Activity 2: *Qualitative* reasoning with your model circuit.

Soon you'll *build* your model circuit and make measurements. But first, let's see if it can help us perform some qualitative reasoning, to enable us to ***predict*** how the membrane potential difference should vary with distance from the starting end of the axon.

1. Write Kirchhoff's **loop rule** for the first segment in your model. [Write it in terms of the potential difference across the membrane at the end of the axon $\Delta V_{mem}(0)$, the potential difference across the 1 mm-length of axoplasm ΔV_{axon} and the potential difference across the membrane 1 mm from the end $\Delta V_{mem}(1)$]. Use the equation you wrote to figure out how $\Delta V_{mem}(1)$ compares with $\Delta V_{mem}(0)$.

2. Now write Kirchhoff's **loop rule** for the second segment in your model, in a similar way. How does $\Delta V_{mem}(2)$ compare with $\Delta V_{mem}(1)$?

3. Now write Kirchhoff's **loop rule** for the third segment in your model. How does $\Delta V_{mem}(3)$ compare with $\Delta V_{mem}(2)$?

4. What is the general ***trend*** in $\Delta V_{mem}(x)$ as x increases?

From your above analysis, it should be clear that ΔV_{mem} decreases as you go further and further from the left end of the axon. But can we be more specific? If we create a mathematical model for $\Delta V_{mem}(x)$ as a function of distance from the left end of the axon, what ***functional form*** would we expect? As a reminder, common possibilities include:

(1) <u>linear</u> with a negative slope (rate of change of the graph would be constant),
(2) <u>inverse</u> (the *product* of the x- and y-axes of the graph would then be constant), or
(3) <u>exponential</u> decay (*percent change* would then constant).

5. It should help to consider the behavior of $\Delta V_{mem}(x)$ in the limiting cases. Examine the behavior of your model circuit: As x approaches 0, what happens to $\Delta V_{mem}(x)$? As x becomes very large, what happens to $\Delta V_{mem}(x)$? Compare with the behavior of each of the possible functional forms.

6. Make your **best guess** for the functional form. Explain any reasoning you may have. Sketch the corresponding graph of $\Delta V_{mem}(x)$ vs. x.

Activity 3: *Building* your model circuit and making measurements.

1. It's time to explore your model circuit with real components on a *circuit board*.

2. Use a voltage probe to measure $\Delta V_{mem}(x)$ for x = 0 to 10, and record your data in ***Igor Pro***. You'll only need ONE COLUMN, and you can **begin graphing your data as soon as you've entered two data points**. – Just let the x-axis be "calculated" (*i.e.*, the point #).

3. Try to create a mathematical model for your data, based on the functional form that you reasoned out above. Try one or more different possibilities if necessary. When you achieve a good fit, write your model equation below. Attach a printout of your graph.

We define the distance along the axon at which the potential difference has fallen to 1/e or 0.37 of the initial value the *length constant* of the axon, denoted by λ.

4. Using your model equation, determine the "*length constant*" of your model circuit.

5. Compare the *length constant* to the typical length of an axon. Can a change in the membrane potential difference applied at one *end* of a typical axon <u>*make it*</u> all the way to the other end? **Explain**.

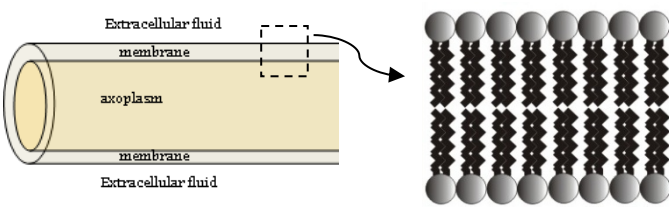
You've shown why *passive* transmission of a change in membrane potential difference isn't feasible: in order for an action potential to still be detectable after travelling the *full* length of an axon, it has to be *regenerated* at regular intervals as it travels along the axon. The point of this lab exercise was to show why that is so.

Everything that follows is just a set of possible INITIATIVES:

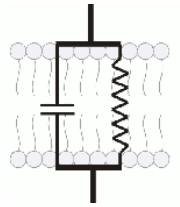
WHAT ADAPTATIONS ALLOW AN ACTION POTENTIAL TO TRAVEL FASTER?

How *fast* does an action potential travel along an axon? You're probably aware that it's finite – no one has truly instant reflexes. Yet, nothing in the model that you've devised has anything to say about how fast it travels. In fact, your model suggests that the process is nearly instantaneous, as it is for the usual resistive circuits that you've studied in here. We need to extend our model in order to understand *why* it takes time for an action potential to travel along an axon.

Let's take a closer look at the membrane of an axon. [Fig 7]. The channels are the paths through which ions flow (with some resistance). The equivalent resistance of all of these parallel channels in a single segment is R_{mem}. Now take away those channels and what do you have left? An insulating layer with conducting fluids on each side. That should remind you of a familiar device – a capacitor. The membrane is therefore properly viewed as a resistor and capacitor in parallel. [Fig 8] As current travels along the axon and enters each new segment, it takes time for charge to build up on the capacitor, and thus it takes time for the potential difference across the membrane to reach its final value. We refer to the time it takes the membrane potential difference to reach 63% of its final value as the time constant τ, equal to the product of the resistance and the capacitance of the membrane in a segment. It's only after several time constants that the membrane potential differences reach the approximate values that you obtained in Investigation 1.



(Fig 7) Membrane: magnifying view



(Fig 8) Membrane: RC circuit model

Speed depends on time constant and length constant

An action potential's speed (=distance/time) depends primarily on two things:

(1) It's *inversely proportional* to the time constant: The longer it takes the membrane potential difference to rise in each segment, the slower the action potential will travel. The time constant is given by $\tau = R_{mem}C$.

(2) It's *proportional* to the length constant. The greater the length constant, the further the depolarizing potential difference reaches down the axon, bringing successive segments to the threshold potential difference required to regenerate the action potential sooner. You measured the length constant of your model circuit in Investigation 1. In general, the length constant λ is proportional to $\sqrt{\frac{R_{mem}}{R_{axon}}}$. Makes sense: If the membrane resistance is really big

(or if the axon resistance is really small), current mostly flows *down* the axon, with just a little leaking across the membrane in each successive segment.

You can probably appreciate that faster propagation of nerve impulses confers an advantage to an organism. (Why? Think for a minute and discuss in your group.) In this investigation, we'll examine some possible adaptations leading to speedier action potentials.

Activity 1: A wider axon?

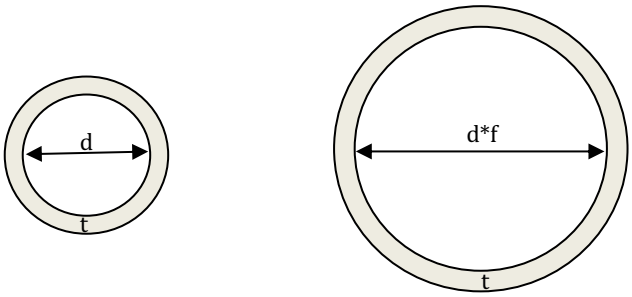
1. It should be apparent that increasing the diameter of the axon changes R_{axon}.

a. Does R_{axon} *increase or decrease*? Explain.

b. On that basis, would you expect the speed to *increase or decrease*? Explain.

So a wider axon might be one strategy for increasing the speed of an action potential. We need to be careful to account for changes in R_{mem} though. Let's carry out a scaling argument to discover exactly how the speed depends on the diameter of the axon.

2. Let's say the diameter of the axon is increased by a factor of *f*. [Fig 9]



(Fig 9) A wider axon

a. By what factor does R_{axon} change? (Note: The resistivity of axoplasm is constant, as is the 1 mm length of an axon segment.)

b. By what factor does R_{mem} change?

3. So, by what factor does the length constant λ change?

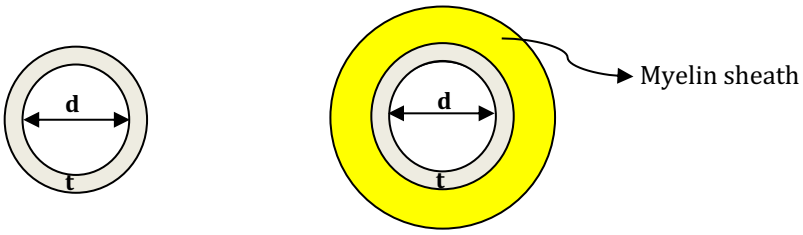
4. ***Assuming*** that the time constant doesn't change, by what factor does the speed therefore change?

5. By what factor would the diameter of the axon have to change to increase the speed by a factor of 10?

This strategy is found in the squid, whose "giant" axons make it a master of quick escapes.

Activity 2: A thicker membrane?

Wider axons work fine for a squid, but are highly impractical for organisms with lots of neurons like humans. (If each of your neurons were the size of a squid's, your head wouldn't fit through a doorway.) Let's explore another possible way of increasing the length constant and therefore the speed: To *increase* R_{mem}. This is the strategy commonly adopted by vertebrates like us. It's achieved by extra insulation (a myelin sheath) that's wrapped around the axon. [Fig 10]



(Fig 10) A myelinated axon

1. Let's say that myelination increases the membrane resistance by a factor of 1000. By what factor does the length constant increase? Why?

2. Assuming that the time constant doesn't change (you'll provide justification for this in homework), by what factor does the speed therefore change? Why?

3. One issue with myelination is that it obstructs the membrane's voltage-gated Na^+ channels which enable the action potential to be regenerated. Using your model results from Activity 1 and your response to (1) above, determine the length constant in a typical myelinated axon, and compare it with the typical length of an axon. Can a change in membrane potential difference applied at one end of a typical axon make it to the other end – in other words, is passive transmission of an action potential possible in myelinated axons? If so, explain. If not, describe the feature of myleninated axons which permit the regeneration of axon potentials.

Final Questions:

1. You showed in Investigation 2 Activity 1 that increasing axon diameter increases the length constant. Show that increasing the axon diameter has *no effect* on the time constant, justifying your conclusion that the increased length constant results in increased speed. Explain your assumptions and calculations.

2. In the next activity you showed that myelination increases the length constant. Show that myelination has *no effect* on the time constant, justifying your conclusion that the myelination results in increased speed. Explain your assumptions and calculations.

3. List three human functions possible due to neuronal communication.

4. MS, multiple sclerosis, is a demyelinating disease, which means the axons of neurons are intact, however the myelin sheaths are damaged. Why would loss or damage to the myelin sheath be a problem even if the axon was intact?