C2006/F2402 -- 2015--Outline of Lecture #19 – Electrical Communication
(c) Stuart Firestein & Deborah Mowshowitz, Columbia University, New York, NY. *Last update 3/29/2012.*
Original Notes on electrical communication by Chris Kelly 2005

Handouts Needed
18C -- Lactation (in CW Handouts for registered students)
19A -- Recording & Nodes of Ranvier (in CW Handouts for registered students) -- ***See Sadava fig. 45.12 or see Becker fig. 13-14 for Nodes.***
19B -- Action Potentials
19C -- sample neuron (Same as 18D of last year)

Paper copies of all handouts are in the cubbies on the 7th floor of Mudd.

I. Lactation

A. Important features

1. An Example of how hormones and nerves co-operate to run a circuit.

2. An example of positive feedback.

B. Details of Circuit (See handout 18-C -- may only be accessible online by registered students)

1. Overall Loop: Suckling by baby → milk ejection ("letdown) → more suckling → more milk ejection etc. Loop continues until baby stops nursing.

2. Signaling Pathway: Suckling by baby stimulates nerve endings in nipple → nerve signal to HT → release of oxytocin and prolactin as follows:

a. Oxytocin: HT → release of oxytocin from neuron endings post. pit. → contraction of myoepithelial cells (similar to smooth muscle) surrounding alveolus (milk producing section of mammary gland) → milk ejection from lumen of alveolus → more suckling → etc.

b. Prolactin: HT → PIH (= DA) down and PRH (?) up in portal vessel → AP releases prolactin (PL) → stimulates inner layer of cells surrounding lumen of alveolus → promotes milk production and secretion of milk into lumen of gland.

3. Receptors. Oxytocin uses a GPCR; PL & GH (the pseudo tropic hormones) use tyrosine kinase receptors (TK receptors or RTKs).

Question to think about: what does the circuit look like here? What's the IC? The effector? Etc.

Try problems 7-15 & 7-19.

Oxytocin is not just for contractions! An article from NPR: When the 'Trust Hormone' is out of balance.
http://www.npr.org/templates/story/story.php?storyId=126141922

Note: No specific figures are referenced in the neuro part of this lecture, but the material is covered extensively in chapter 45 of Sadava and chapter 13 of Becker.

II. Neurons: structure and function (Handout 19C)

- **The main function: information transfer and signaling**
  - The basic circuit: the body encounters a stimulus, peripheral nerves produce an afferent (incoming) signal that comes into the brain (or spinal cord) for processing. The result is an efferent (outgoing) signal, carried through nerves, to some target, resulting in a behavioral response.
    - You step on a thumbtack, a pain signal goes to the spinal cord, contacts a motor neuron, signal goes

out to the leg muscle, leg retracts.
- Baby suckles, signal goes to HT, sends signal to PP (via nerves) and AP (via hormones): AP and PP send signal to breast (via hormones).

- **4 Big Steps in Information Transfer**

1. Input to first cell -- step on tack, baby suckles
2. Message/signal is carried down the axon of the first cell -- propagation
3. Signal crosses gap between cells (synapse) & signals next cell

(Steps 2 & 3 are repeated through a chain of afferent and then efferent cells)

4. Signal causes effector (muscle, gland, etc.) to respond -- leg retracts, breast secretes more milk.

- **Two major divisions**: central nervous system (CNS) and peripheral nervous system (PNS). *
  - CNS: brain and spinal cord.
  - PNS: everything else (motor neurons, sensory neurons).
    - There are a few exceptions: the retina, for example, is in the back of the eye but is considered part of the CNS.

* There is also the ENS = enteric nervous system; controls GI tract. It is largely autonomous (with its own sensory neurons), but gets some input from the CNS via the PNS. In this course we will stick to the CNS & PNS.

- **The functional unit in both PNS & CNS is a neuron (See handout 19C).**
  - There are 10^{11} neurons in the adult human brain.
  - There are about 1000 connections per brain cell. Therefore about 10^{14} synapses in brain!
  - Neurons were not always recognized as distinct cells: until Ramon y Cajal proved otherwise, people believed there was one big interconnected "nerve net."
  - Neurons can be extremely large (up to 40 meters long in a whale) or extremely small.
  - There are two main consequences of Ramon y Cajal's discovery that neurons are distinct units:
    - 1) The law of dynamic polarization: information only moves in one direction down a neuron (most of the time).
    - 2) Specific connectivity: the specificity of the connections in the nervous system is critical. Think of the wires behind your computer or TV.

- **Major parts of the neuron**, common to nearly all neuron types
  - **Soma / cell body**: site of protein synthesis, metabolism, etc.

  - **Dendrites** (Gr: *tree*): protoplasmic extensions continuous with the cytosol.
    These branch and divide, thereby sending projections all over a tissue, and thin as they extend.
    Composition of membrane is the same as that of the soma.

  - **Axon**: A long cable that extends from the soma but is functionally distinct from it.

    The plasma membrane of an axon contains lipids (& proteins) different from those in the soma's membrane.
    The axon may branch out, but it remains isodiametric in all of its projections.
    If a neuron is particularly large, as in the whale, it is because its axon is long.

  - **Synaptic terminal**: sometimes referred to as the "bouton." It is the end of the axon that contacts a dendrite, muscle, etc.

- **We can now revisit the dynamic polarization principal of Cajal.**
  - Information enters the dendrites, travels through the tree to the soma, then (if it meets the threshold) enters

the axon, and travels its length until the synaptic terminal, which then passes the signal to the next cell.

III – Membrane Potential

- **We keep referring to a "signal" — what is it?**
  - A signal is encoded as changes in membrane potential.
- **Membrane potentials**
  - Refers to voltage created when the cell separates charges on opposite sides of the membrane. It puts work into separating opposite charges, thereby creating potential energy as voltage.
  - Voltage always refers to two points: i.e. here with respect to there. "There" is usually ground; in physiology, ground is the outside of the cell. So, voltage refers to the inside of the cell with respect to the (neutral) outside.
    - If the cell's potential is –50 mV, then the cell is negative with respect to the surrounding IF.
- **How can you measure potential?**
  - Use an electrode. (See handout 19A)
    - An electrode is an extremely thin glass capillary with an open tip that is about one micron in diameter. You fill the electrode with a conducting salt solution and insert a wire connected to a voltmeter. You then poke the electrode through the cell membrane and measure the intracellular potential against that at ground.
    - This method reveals that neurons usually have negative resting membrane potentials, between –50 and –90 mV.
    - This potential is often referred to as V_m = Resting membrane potential = RMP.
- **What constitutes and creates this resting membrane potential?**
  - In electronics, potentials and current come from the position and movement of electrons. In cells, we are not concerned with electrons, but with ions.
  - Common ions involved in establishing V_m:
    - Sodium (Na^+)
    - Potassium (K^+)
    - Calcium (Ca^{++}) = Ca^{2+}
    - Chloride (Cl^-)

- **How does the potential arise?**
  - The cell maintains an asymmetric distribution of ions across the membrane and makes the membrane selectively permeable. Both of these merit further discussion.

  - **<u>Asymmetric distribution</u>**:
    - Plasma membrane contains a lipid bilayer, so charged particles cannot pass through unless it's through a pump (like the Na/K ATPase) or channel.
    - Na+/K+ pump (= Na/K ATPase) sets up gradients of Na^+ and K^+.

    - A typical distribution is in table below. The relative differences are more important than the exact numbers, which vary from organism to organism.

	Inside	Outside
[Na^+]	10 mM	130 mM
[K^+]	140 mM	5 mM

    - Other ions involved
      - Inside: negatively-charged macromolecules (nucleic acids & proteins), chloride
      - Outside: chloride, calcium

  - **<u>Selective Permeability:</u>**

Just having an asymmetric distribution is not enough, however: we still haven't created any potential. Potential only arises when SOME of the ions can get through the membrane. This is achieved through having **selectively permeable channels** in the membrane.

- Let's say we poked some holes in the membrane that only permeated potassium … NOT sodium.
  - The first response will be for potassium to flow down its concentration gradient, out of the cell.
  - This outward flow leaves behind unpaired anions within the cell, though. Eventually, the negative charge inside the cell will become so great that the diffusive force on the potassium ions, directed outward, will be outweighed by the electrical force on the potassium ions, directed inward to the negatively charged cytosol. An equilibrium condition is then created where the number of ions leaving the cell equals the number of ions entering the cell.
  - We can then say that potassium has reached an equilibrium condition, which has an associated electronic potential, measured as E_K= -91 mV.
  - We can make a similar calculation for sodium, if we make the cell selectively permeable to sodium ONLY: E_{Na}= +65mV.
    - *Think about where the diffusive force will drive sodium, and where the electrical force will drive it. Refer to the concentrations above.*
- If we measure the resting membrane potential of a neuron, we see it is around –75 mV. This is between the equilibrium potentials for potassium and sodium, but closer to that of potassium. So, we see that the cell is mostly permeable to potassium, but also slightly permeable to sodium.
- Equilibrium vs the steady state:
  - The equilibrium potential for a single ion, once reached, will remain the same indefinitely without further energy input.
  - The steady state RMP generated by selective permeability to two ions will NOT remain the same, but will run down, unless energy is supplied to maintain it. Neither ion is at equilibrium, and each will move if permeability is increased.

- This is the Qualitative description of how this happens. We can gain a deeper appreciation if we also derive a Quantitative description. This description was first developed to understand electrochemical forces in batteries by the Biophysicist Walter Nernst in 1888. It works, remarkably, for neurons as well, because each neuron is an electrochemical device.

IV. Derivation of the Nernst Equation

This derivation is included FYI. It is useful to know the Nernst equation and how to use it, but the details of the derivation are FYI. The basic idea is to calculate the work needed to push the ion across a membrane (by electrical forces or chemical forces). Then you can set up an equation because the two types of work are equal at equilibrium. The Nernst equation is what you get if you rearrange the equation to relate differences in concentration on the two sides of the membrane to potential (voltage) across the membrane. What good is this equation? If you know the concentrations on the two sides you can calculate the potential; alternatively if you know the potential, you can calculate the relative concentrations on the two sides.

Here's the derivation:

1. KA dissociates into K^+ and A^- ions

2. K^+ are able to move down their concentration gradient and flux from side 1 to side 2. This is simple movement by diffusion and the work that is done to concentrate ions on one side or the other can be described by the relation:

$W_c = RT \ln (c2/c1)$

R = gas constant (related to energy of the ionic solution)
T= absolute temperature (higher temp = more movement)
ln c2/c1 because this is same as (ln c2 - ln c1). (We use ln – natural log -- because diffusion is an exponential process) c2 = concentration on side 2, and so on.

3. But as K^+ ions diffuse down their concentration gradient they are leaving behind an excess of negative charges on side 1 and at the same time an excess of positive charges is building up on side 2. This creates a **potential (electrical) difference** between the two sides.

4. What effect will this have on the K^+ ions trying to move down their concentration gradient???

It will oppose this movement by performing electrical work in the opposite direction. K^+ ions will find it harder to get to the more positive side because like charges repel. Also A^- charges will be holding them back.

This electrical work can be described by:

$W_e = zFE$

z = valence
F = faraday (analogous term to R for electrical particles)
E = potential difference (like concentration difference)

5. At some point the chemical work in direction 1 to 2 will be exactly opposed by the electrical work in direction 2 to 1. So at equilibrium:

$W_c = W_e$

$zFE = RT \ln (c2/c1)$

rearranging: **$E_k = RT/zF \ln (c2/c1)$**

This is the **NERNST EQUATION**. (1888 Walter Nernst)

6. The Nernst Equation describes equilibrium:

Keep in mind that there are still **2** processes at work here.
Note that this describes an **EQUILIBRIUM CONDITION for *one* ion.**
No energy input is required (but see * below).
If the membrane is selectively permeable to K^+ (only), this situation (equilibrium for K^+) will occur naturally.
*An energy input is required to set up the original K^+ gradient, but not thereafter.

7. Let's simplify the equation a little more:

for K^+ ion at room temp (25^oC) , RT/zF= 25 mV
change from ln to log -- multiply by 2.303 -- then

$E = 58 \log (c2/c1)$

CONVENTIONS

measure voltage as side 1 with respect to side 2.
in cells measure as inside with respect to outside

8. Lets look at a "real" cell using the K^+ ion & Na^+ ion concentrations given in the table. A real cell is in a steady state, not at equilibrium.

E_K= -91 mV.

E_{Na} = +65 mV

Actual RMP = around -75 mV. This shows neither ion is at equilibrium, because cell is permeable to both ions, and that cell is much more permeable to K^+ than to Na^+ (since the RMP is closer to the K^+ equil. pot. than to the Na^+equil. pot.)

- Using the Nernst Equation and/or similar reasoning: What would the RMP (resting membrane potential) be if the situation were reversed, if the cell were more permeable to sodium than to potassium?

- The RMP of a cell, then, is found by individually weighting the equilibrium potentials of the various ions involved, based on the membrane's permeability to each one. Then you just add. This is quantified by the GHK (constant field) equation; see book for details if you're interested.

V. Ion Channels.

- **So far, we have referred to selective permeability without discussing how it arises. The cell creates it with ion channels.**
  - Ion channels are sophisticated transmembrane proteins that form a selective aqueous pore in the membrane. The channels have some important properties:

    - 1) They are highly selective.
      - Channels become selective by varying their shape/size and flanking certain regions of the pore with positive or negative charges. The degree of selectivity can vary: some only let cations through; others only let potassium through. See books or web for details.

    - 2) They have a specific degree of conductance -- ability to let ions through.
      - Some are fairly big and allow large numbers of ions through per unit time; others are smaller.

    - 3) They are usually gated.
      - **A**ll cells have leak channels (ungated); neurons also have ligand-ated and voltage-gated channels.
      - In order to control the membrane potential, the neuron must be able to control the open/closed status of its various gated channels. For now, we will only consider voltage-gated channels (i.e. channels that only open when faced with a certain voltage range); in synaptic signaling (signaling from one neuron to the next), we will see the importance of ligand-gated channels.

- **How do you detect these ion channels? They are too small to be seen. Instead, scientists use a method known as patch clamping.** (Handout 19A)

  - One applies a glass electrode, as described above, to the membrane of a cell. Applying a little bit of suction causes a piece of the membrane to become attached to the electrode; one can then record through the small patch or pull off the electrode and take the membrane section with it (detached patch). Because the seal between the electrode and the membrane piece is very tight, one can then treat the inside of the electrode and the bath in which you place a detached patch as different sides of the cell.

Once you have isolated one or two channels in your membrane fraction, you can measure the current that flows through them, given certain conditions. This current is on the order of picoamps. (For reference, electronics typically use 10-20 A — thirteen orders of magnitude greater.)

- The trace you see after measuring the current reveals that individual channels open and close very quickly and apparently randomly. By varying the voltage to which the channels are subjected, however, one can vary the length of time those channels will remain open (or closed).

Neher & Sakmann received the Nobel Prize in Physiology & Medicine in 1991 for inventing patch clamping. See http://nobelprize.org/nobel_prizes/medicine/laureates/1991/ or Sadava text.
For an animation and more info on nerve signaling, see http://nobelprize.org/educational/medicine/nerve_signaling/

To keep everything straight -- Summary of the different types of Potential

- **Equilibrium potential: applies to specific ions**
- **Resting membrane potential: describes the overall potential of the membrane, based on the contributions of each ion's weighted equilibrium potential.**
- **Action potential: rapid and invariant change in membrane potential, to be described next.**

VI. Action Potentials

- **So far we have talked about static situations — *resting* membrane potentials. How do you change this potential to create an electrical signal?**
  - The cell uses action potentials, which are rapid, transient, and invariant changes in V_m. The whole process takes 2-3 msec.
  - What does invariant refer to?
    - The shape, size, and duration of an action potential is always the same, for reasons to be explained below . The only variable aspect is the frequency at which they occur.
  - If action potentials are always the same, how can you encode anything?
    - Frequency: Freq. is proportional to the magnitude of the stiumulus. Different frequencies indicate different stimulus intensities, *quantities*. A typical firing frequency is between 4-40 Hz, though neurons can fire at 100 Hz or faster.
    - Pathway: connections are specific, so an action potential down a certain neuronal tract is assumed to code for a certain stimulus *quality*. That is, an electrical signal in the optic nerve must, by definition, code for a visual stimulus. (Or, by occurring in the optic nerve, an action potential is assumed to be coding for visual stimulus.)
    - Population frequency: Sometimes, stimulus intensity is also coded for by the number of relevant neurons firing action potentials at the same time. A stronger stimulus causes more neurons to fire.
- **General terms to describe changes in membrane potential:**
  - *Hyperpolarization*; change in voltage in the negative direction. A cell that goes from –40 mV to –70 mV has hyperpolarized.
  - *Depolarization*: change in voltage in the positive direction. A cell that goes from –40 mV to –20 mV has depolarized. So has a cell that goes from +20 to +40 mV or -20mV to +10mV.
- **Action potential was discovered by recording from the squid giant axon. Several distinct phases:** (See

handout 19B)

- 1) Slight, steady depolarization (usually due to input from senses or previous neuron)
- *(threshold crossed -- trigger 'big bang')*
- 2) Rapid depolarization – the "spike" in the picture. This is called the *rising phase*.
- 3) Rapid hyperpolarization, the downward part of the spike. This is called the *falling phase*.
- 4) Undershoot: the cell hyperpolarizes beyond its resting membrane potential. While it is extra hyperpolarized, it is in the refractory period and cannot fire another action potential until it starts to move back toward normal RMP.

- **How do these various phases arise?**
  - As expected, through changes in relative permeabilities, resulting in ion flow.
    - The ions that move (a few 1000) are a very small fraction of the number available. Therefore, large changes in permeability and consequently voltage occur, but have no significant effect on the ion concentrations inside and outside. (See below at *.)
    - During depolarization, (voltage-gated) sodium channels open. The sodium equilibrium potential of +50 (or more) is thus weighted more heavily, and the cell's voltage moves toward it.
    - The cell enters the rising phase because *lots* of sodium channels suddenly open. So the +50 value is weighted even more heavily.
    - All of a sudden, lots of potassium channels then open. The potassium equilibrium potential is now the more heavily weighted, so the cell races back down toward –75 mV … this is the falling phase and undershoot.
    - The cell then equilibrates the Na^+ and K^+ permeabilities to normal and reaches standard RMP.
    - Notice that there is little room for variety in this process, which is why action potentials are *(1) invariant*, and *(2) all-or-nothing*. You cannot have half of an action potential.

  What changes during the various phases?

- *IMPORTANT: at no point have you changed the concentrations significantly on either side of the membrane! Ions are indeed moving, but these changes are negligible as far as concentrations are concerned.
- *The drug oubain inhibits the Na^+/K^+ pump. Were you to poison the Na^+/K^+ pump with oubain, eliminating the cell's ability to restore those ions to the correct side of the membrane, the neuron could still fire another 150,000 action potentials before the concentrations started to become insufficient.
- All that has thus really changed (at any point) is the RELATIVE permeabilities to the various ions, and thus which ones contribute more strongly to the cell's membrane potential (at that point).
- Firing an action potential, then, simply involves changing the number of open channels permeating a particular ion.

To review the action potential, try problem 8-2, A-C, & 8-3 to 8-4.

VII. Recap of Action Potential -- How the channels open and shut. See handout 19B, bottom.

- **Phases**
  - Depolarization (initial)
    - Stimulus usually causes the ligand-gated cation channels to open, causing a passive spread of depolarization inside the cell.
  - Rising phase of 'spike' -- actual action potential
    - If that depolarization is sufficient (10 to 15 mV more positive), voltage-gated sodium channels at the axon hillock suddenly open, causing an enormous influx of sodium and the rapid depolarization spike.
    - This is essentially a positive-feedback cycle: sodium entering the cell causes it to depolarize. These depolarized conditions cause more sodium to enter the cell (because voltage-gated channels open). This depolarizes the cell even more, making more sodium channels open, and so on.
  - Falling Phase of 'spike'
    - Two factors contribute to the cell then racing back down toward negative potential:
      - 1) Voltage-gated sodium channels inactivate after being open for a certain time. So, those channels that opened, permitting the depolarization, slam shut.
      - 2) Voltage-gated potassium channels, which were tripped during the depolarization (around –20 mV), begin to open. Why did they not open as soon as the voltage hit –20 mV? They are slow to undergo the proper conformational changes.
      - Note: inactivated channels cannot be opened again until the cell has “reset” itself back to RMP. This prevents the signal from going backwards.
    - The net effect is that the permeability to potassium once again far outweighs that to sodium, so the cell approaches E_K.
  - Undershoot
    - The potassium permeability is so high, in fact, that the cell goes closer to E_K than during RMP – it hyperpolarizes. (Remember there are many anions in the cell, so if cations move out, the negative charge is 'uncovered.') This brief hyperpolarization can be divided into two phases.
      - Absolute refractory period (negative slope)
        - Voltage-gated sodium channels are still inactivated, and thus cannot be opened by anything. Since action potentials depend on these channels, no action potential is possible. Also, even if such an Na influx were possible, the K+ current is too high to be overcome.
        - Voltage-gated sodium channels have two closed states -- closed, but able to open, and locked or inactivated. Those channels that opened, permitting the depolarization, slam shut and are locked or inactivated -- they cannot be opened again until the cell has “reset” itself back to RMP.
        - The absolute refractory period = time when voltage gated Na+ channels are locked.
      - Relative refractory period (positive slope)
        - Voltage-gated sodium channels are released from inactivation, making action potential possible again. However, more stimulus than usual is required since the cell is farther from

threshold than usual.

- **Note on refractory periods:** There is some disagreement between authorities on the timing of the refractory periods. According to Dr. Firestein, Becker, and most texts, the absolute refractory period comes right after the spike of the action potential. According to some, the absolute refractory period coincides more or less with the spike, and the relative refractory period follows after the spike. All agree about the underlying mechanism. The absolute refractory period corresponds to the time when the Na+ channels are inactivated (so depolarization is not possible). The relative refractory period corresponds to the time when the Na+ channels can be activated, but the voltage gated K+ channels are still open (so depolarization to threshold requires a larger stimulus).

VIII. Propagation

- **So what is the use of all this? An action potential is worthless if it does not travel somewhere.**
  - Action potentials are designed for long-distance signaling, unlike graded changes in potential (i.e. depolarizations that do not reach threshold and ***do vary in amplitude***, unlike action potentials).
  - The action potential is propagated along the axon.
    - Think of the axon like a fuse: when you light a fuse, the end heats up the next segment, which flares up and heats up the following segment, which then flares up. Unlike a piece of string, a fuse carries the flame all the way down to the other end.
- **Where does the action potential begin?**
  - At the beginning of the axon, where it first leaves the soma, there is a high concentration of voltage-gated sodium channels. This area is called the initial segment, or axon hillock. The propagation down the axon begins with these channels opening.
  - When these channels open, positive charge enters the cell and spreads passively down the axon. This positive charge trips the next voltage-gated sodium channels on the axon, causing a sodium influx there, which then causes the next channels to open, and so on.
- **Why doesn't the signal go backward?**
  - Remember the absolute refractory period. The positive charge will, in fact, passively spread in both directions in the axon. When it reaches the segment that just fired, however, those voltage-gated sodium channels will still be inactivated, and thus unable to fire an AP.
  - Another way to put it: Voltage gated Na+ channels have two gates -- one of them closes the channel; the other 'locks' the channel briefly, so it will not open again until it is 'unlocked.' During the absolute refractory period, the locking gate is closed.
- **How can one ensure that the propagation will make it?**
  - Axons can be leaky, and concentration of voltage-gated sodium channels can vary. A situation could arise in which the positive charge that enters the axon is not able to trip the next channel in the series. In that case the signal would die out. This is prenented in two ways.
    - In invertebrates, the axons are wider, and thus the conductance is greater. (Have a larger hose, so to speak.) So charge is more easily able to spread, and propagation is ensured.
    - In vertebrates, many axons are *myelinated*. (Hose is insulated.) Myelin is a fatty substance produced by glial cells that can wrap itself around the axon membrane. This produces an insulating effect, allowing charge to travel more easily in the axon.

        - In the first case, you have reduced the cable resistance. In the second case, you have increased the membrane resistance (and thus reduced "leakiness"). Both result in more conductance down the axon.

    - **The myelin "sheath" is useless, however, unless it has gaps**.

        - Ions clearly cannot pass through myelin. So having a myelin sheath around the axon would *prevent* signaling unless there are gaps in the myelin dotted along the axon. These gaps are known as the nodes of Ranvier. (See handout 19A.)

        - The signal (potential or charge difference) is transmitted passively from one node to the next node. The myelin acts as an insulator, but if the distance were too long, the signal would die out. However, it is regenerated at each node.

        - At each node, there is a high concentration of voltage-gated sodium and potassium channels. So when the positive charge reaches the node, the series of electrical events described by the action potential will occur there. The signal is regenerated. This kind of signaling is called saltatory conduction, since it appears the action potential is "jumping" from one node to the next.

        - Since action potentials take some time, having the myelin sheath accelerates the signaling process by reducing the number of action potential events along the axon. So signaling in myelinated axons is faster than in unmyelinated axons.

            - Conduction velocity can be up to 20 m/s.

        - There are several demyelinating diseases in the nervous system. Multiple sclerosis (MS) is a famous one, in which an inappropriate autoimmune response results in the destruction of myelin, thereby interrupting signaling in nerves. One can see these diseases in images of the nervous system because the characteristic white color of the myelin is missing in certain places.

        - Note on terminology: even though the cell is firing action potentials all along its axon, we say that it has fired a single action potential and simply propagated it.

To review propagation, try problem 8-2 D-E & 8-6.

IX. Synapses (Probably next time)

- **So the action potential travels down the axon — what then?**
- **How does a signal cross a synapse and get passed on to the next cell?**
- **What is the nature of the synapse?**
    - The big question is whether the link is an electrical or chemical one.
    - Otto Loewi showed that these links are primarily chemical by placing two frog hearts in bath solution, innervating (stimulating through a nerve) only one of them, and then observing that both hearts are affected. In that particular case, the chemical was acetylcholine, and it was causing the hearts to slow down their beating. There was no electrical connection between the hearts, just a chemical one (the solution in which they were placed).
    - There *are* some electrical synapses in the body; they are created by gap junctions. The myocytes in the heart, for example, are connected by electrical synapses so that they can depolarize as a unit, giving a unified heartbeat.
- **What is the structure of the synapse? How does chemical transmission work?** Stay tuned!!

So far: Have explained how nerve signal is generated (within a cell) and transmitted down an axon. Next, how is it passed on to the next nerve? Then, how does signal get started? How does it have an effect? These Qs will be addressed in the next lecture.