

Notes on the Evolution of Behavioral Systems Basic Neuron and Neural Network Function

Eth. & Behav. Ecol.
Biology 287
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I. AN OVERVIEW AND REVIEW OF THE OPERATION OF NEURONS

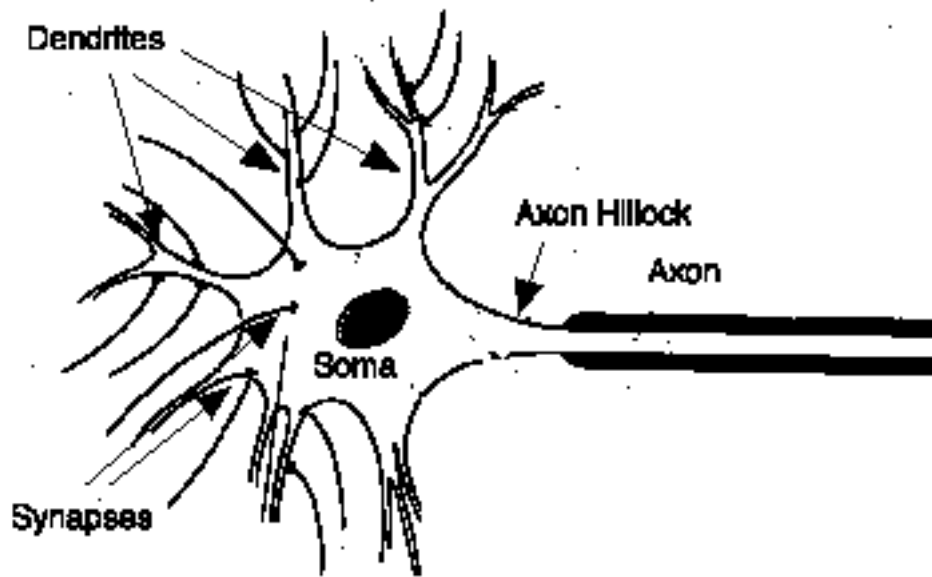
A. Review

1. Computation: In the last section we read about how proteins could be used to register certain events -- certain informational states by undergoing allosteric changes. At a fundamental level, computation in cells occurs at the protein level. However, in fact (as we also saw), proteins act as populations to register events. Moreover, those populations of proteins are found in individual cells or even parts of cells. And, each type of protein often accomplishes somewhat different tasks in these computations.

2. Communication: In the last section, we also saw that at the fundamental level, cell communication goes from one protein molecule to another. We considered how this would happen when chemical signals were involved. Communication between proteins can also be accomplished via an electric field. Proteins are well suited for this sort of thing because they can contain sufficient numbers of electrically charged groups that they can be made to be sensitive to voltage changes. Moreover, they can be made to undergo allosteric changes in response to voltage changes. However, in communication as in computation, we also need to understand the process both in terms of protein to protein and also in terms of what is happening at larger scales -- how the summed action of many protein molecules effects other proteins; how entire cells function.

3. So, we will shift our focus to take into account the function of whole excitable cells. We will explain their action based on the action of proteins. You should constantly be thinking not only about mechanism, but also about how all this system could change and how natural selection could have produced differences in neurons (because there are differences).

4. First a quick review of neuronal structure:



(note that only part of the axon is shown)

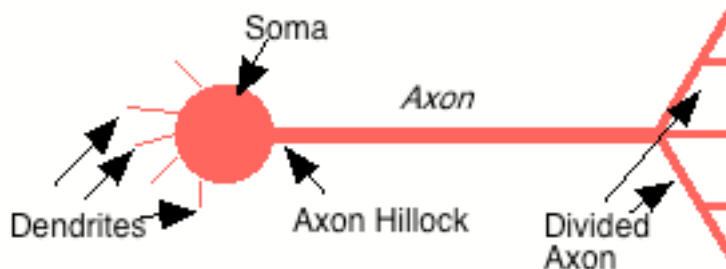
5. Parts of a Neuron:

(a) The **soma** (body) is the "main" and the part of the neuron that most resembles other cells. It contains the nucleus, is the site of protein synthesis etc. Attached to the soma are a number of projections.

(b) Typically there are numerous short (typically shorter than the diameter of the soma) projections called **dendrites** and

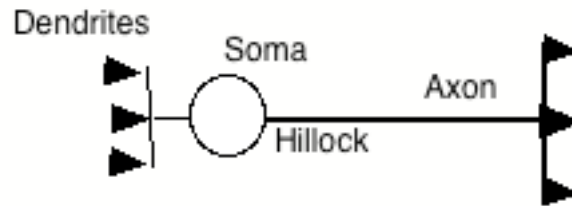
(c) one or more long projections called **axons**. The axons typically have a constant diameter and may extend for a considerable distance (in some cases several meters but more commonly less than a cm¹. Axons commonly divide into many branches distal from the soma (see below).

(d) The point where axons leave the soma is very important (it is a major decision making center) and is called the **axon hillock**. One final point. In most cases, axons divide at their distal ends (the ends away from the soma) into many, many small "processes" (fine cylinders -- not shown in the previous diagram). We can schematize an axon as below:



¹ But this is still very long compared to the length of a cell.

Or we can make the diagram simpler yet:



6. **Connections with other cells:** Like many cells neurons can communicate with other cells. Generally (and this is an important feature of nervous systems, the communication is very specifically directed at and taken from certain cells. An area of close contact between a neuron and another neuron or effector cell (example -- muscle cell) is called a **synapse**. There are two general types of synapse:

(a) **Electrical synapses:** These occur in regions called **gap junctions** where two cells are essentially tied to each other. Thus, the cells are continuous with each other at the gap junction. Electrical synapses are found between smooth muscle cells, between cardiac muscle cells and are also common within the central nervous system (brain and spinal cord) and related structures such as the retina of the eye. Although quite common and vital for many examples of cell-to-cell communication, electrical synapses lack the ability to be involved in decision-making. We will say little more about this type of synapse.

(b) **Chemical synapses** are the more common and interesting synapse. They are found between neurons and neurons and target tissues such as glands and muscles. With chemical synapses, there is **no direct contact between the cells**. Nevertheless, these are areas where cells can communicate with each other via chemicals called **neurotransmitters**. We will learn in some detail how these work and how they are involved in neural decision-making.

6. Movement of information: We will see that **information generally moves through the nervous system from dendrite and soma to axon and then to the next cell** first via the dendrite or soma and then eventually to the axon. We will see that one of the features of chemical synapses is that they are what force information to move in one direction. So, a bit of terminology that centers around the synapse². With respect to the flow of information:

(a) the cell that first possesses information is termed the **presynaptic neuron**

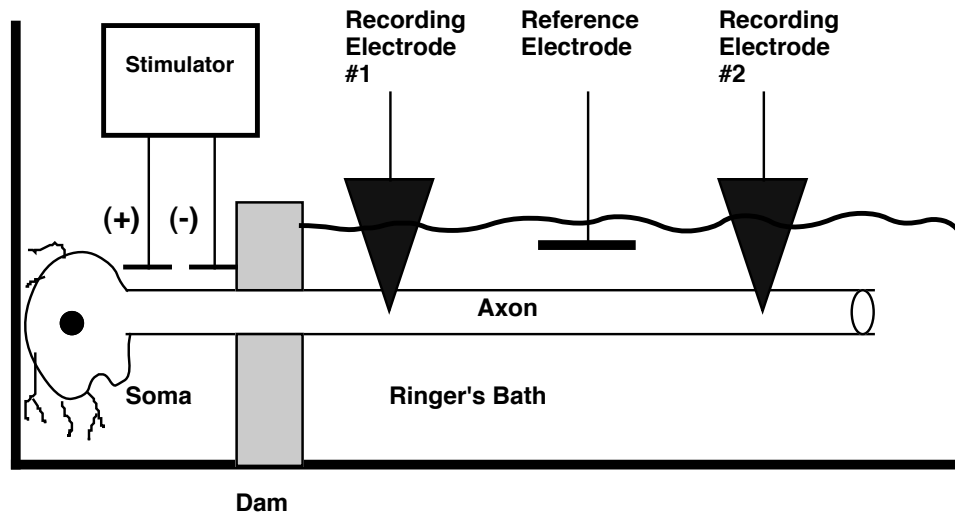
(b) the receiver of this information is the **postsynaptic neuron**.

² which could be called the informational connection between two cells.

Typically the post-synaptic portion of the synapse is on neural dendrites or the soma. In the case of a connection with a muscle, the postsynaptic part is a specialized region of the muscle called the neuromuscular endplate (don't learn this)

7. **Review of Bioelectric Potentials:** With this anatomy out of the way, let's look at communication within neurons. In most cells, signals move around inside cells as various chemicals. This is a slow process. Neurons transmit information having only use within themselves by this means. But, as you almost certainly know, neurons are famous for their ability to transmit signals rapidly from one end to the other via electrical currents. These signals, generally called **bioelectrical potentials** only carry information that the neuron will pass on to another cell. In fact neurons are specialized for this activity. Moreover, it is closely related to their ability to make "decisions".

There are two general types of bioelectrical potentials. What is a potential? All cells exhibit a slight voltage difference when their inside is compared to the outside. We need not understand where this comes from but we will need to understand its consequences. In excitable cells (neurons and muscles) this potential is called the **resting potential**. It is measured by placing electrodes inside and outside of the cell and then hooking them up to some form of a volt meter (usually something called an oscilloscope):

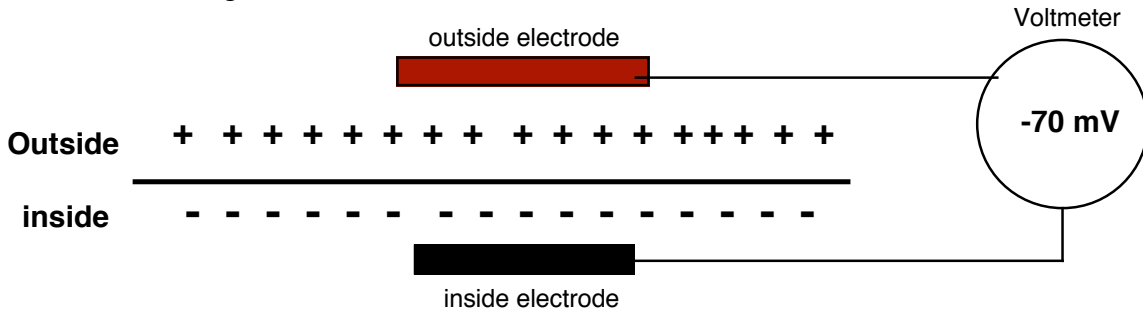


knp

Typically, in an excitable cell, the voltage on the inside will be somewhere between - 60 and -90 millivolts when compared to the outside³ (depending on conditions and the type of cell). Thus, the inside has a slight negative charge compared to the outside (about 20X less than an AAA , C or D battery).

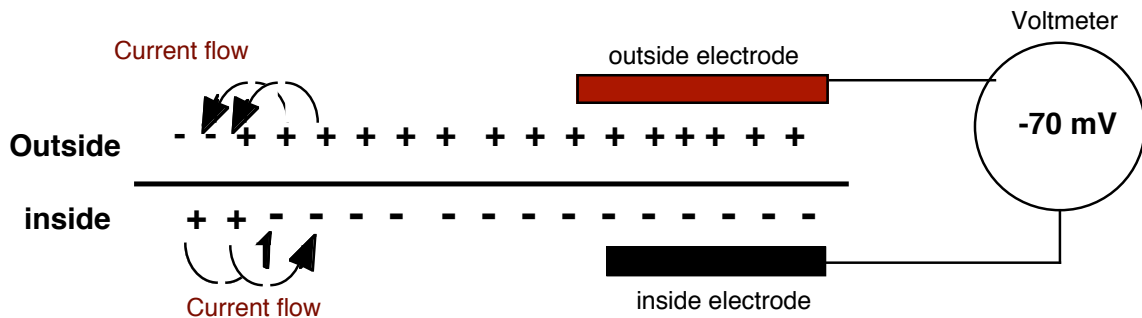
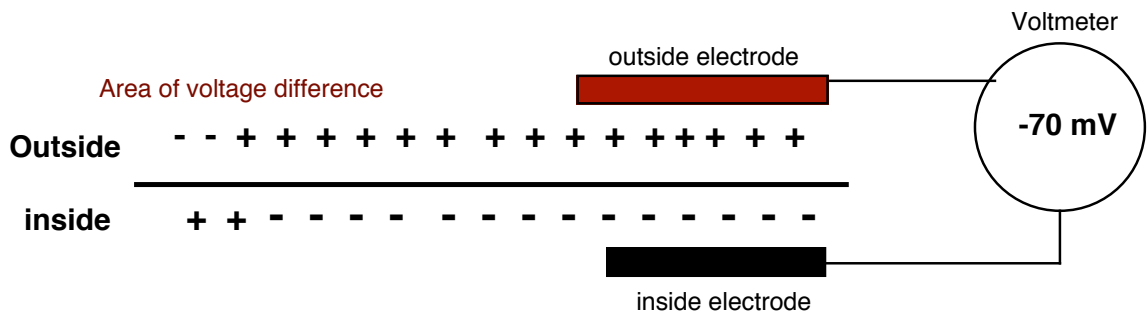
³ We could just as well say that the outside is +60 to +90 mV relative to the inside. It means the same thing.

Normally in a resting cell the same voltage is found everywhere along the cell. The outside is all at one constant positive voltage and the inside is all at one constant negative voltage (exactly equal and opposite to the outside). We can think of a resting cell like this:



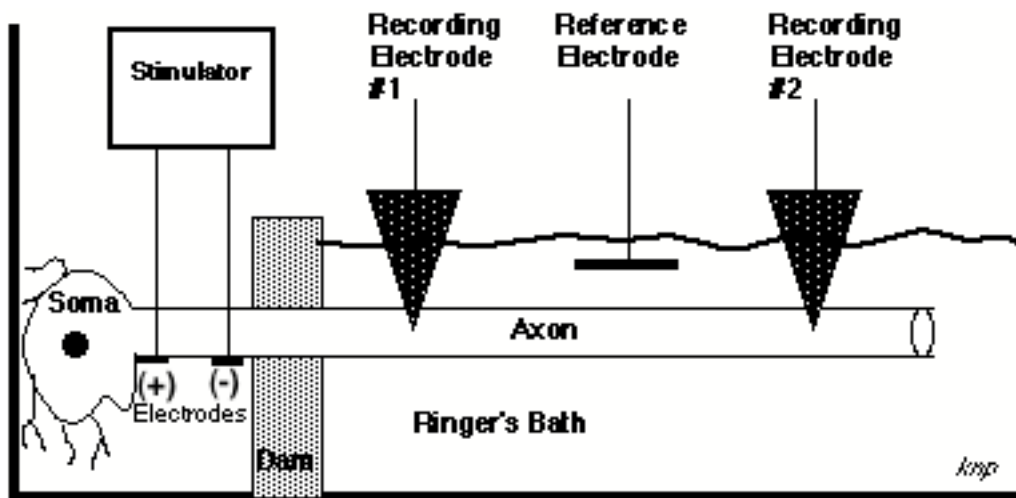
Notice that on the outside there is nowhere where the number of charges is any different from anywhere else and the same is true on the inside. Charges only move in response to differences in attraction and repulsion (called electrical potentials) and since there are no such differences, no electricity flows.

Now, what happens if something causes the density of charge to change in some place? (Let's not worry about what did this, just assume that it does). This means there is a difference in electrical potential energy between points along the cell. As a result, charged particles will begin to flow (called a current) and the change in electrical potential will begin to move from the center of the original disturbance:



B. Large Scale (Cellular) Responses: Graded (Electrotonic) and Action Potentials.

1. Experimental setup: assume we have a device (the stimulator) that can change the potential at the membrane by a known amount. It is on the left of the picture below and happens to be in the area of the axon hillock (not that it matters in this case). At some distance along the axon are two recording electrodes that are stuck into the cell and each referenced against another electrode outside of the cell. Any signal started by the stimulator will obviously pass by electrode #1 and then #2:

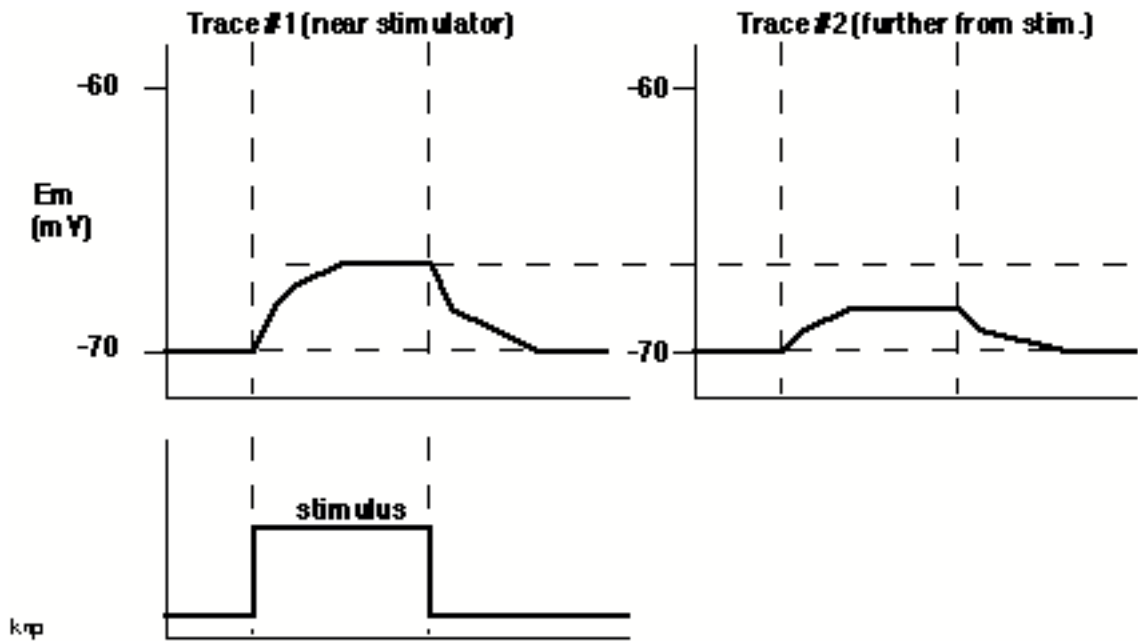


Please imagine the electrodes to be in direct contact with the neuron.

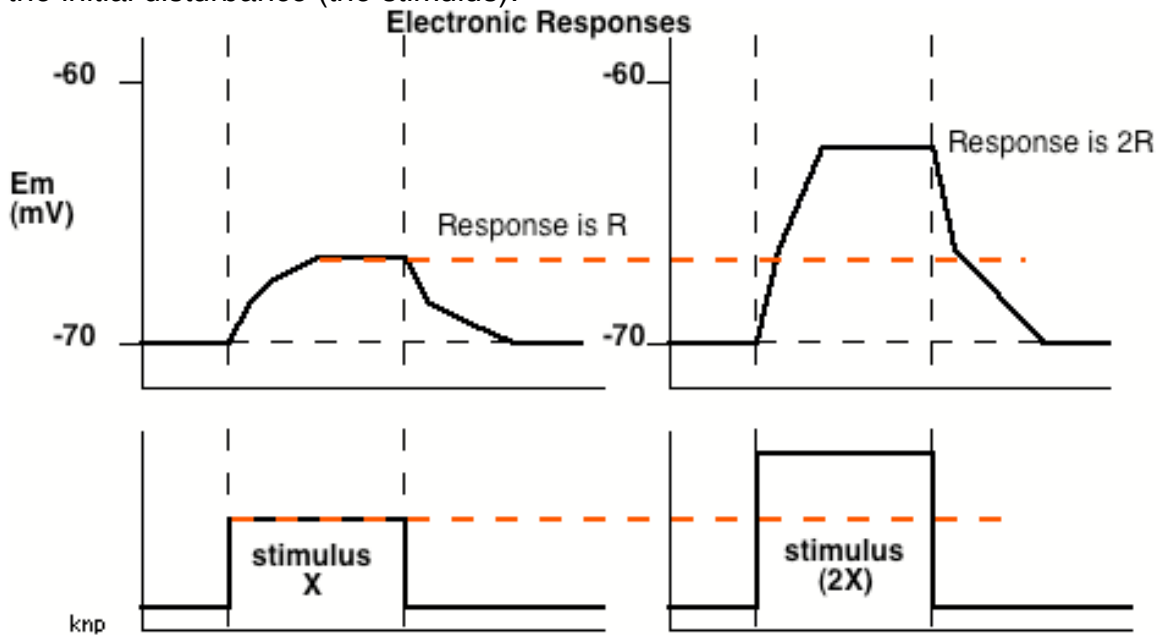
As we indicated in the last set of notes, we record what happens using an instrument called an oscilloscope (actually we usually use a computer set up to act like an oscilloscope) to record the output of the two recording electrodes. The oscilloscope essentially **creates a graph where the X-axis is time and the Y-axis is voltage.**

2. Responses to different degrees of stimulation: The figures below gives the stimulus and then the "response" -- the electrical potential at the two electrodes shown in the last figure.

Case #1 shows what happens if the stimulus (the lower part of the diagram) is very small and causes only a tiny (several millivolt) change in the cell's membrane potential:



This response pattern is called an **electrotonic** or **graded response**. Let's continue the experiment and see what happens if we increase the size of the initial disturbance (the stimulus):



Notice that when a small stimulus (left) is made twice as strong⁴ (right), the size of electrotonic response at any distance is larger (in fact twice as big at a common position as the electrotonic response from the smaller stimulus).

⁴ But it is still a weak stimulus.

Don't worry about the fact that the response has a different shape than the stimulus -- it need not concern us in this course.

Let's summarize what these diagrams show us about electrotonic responses:

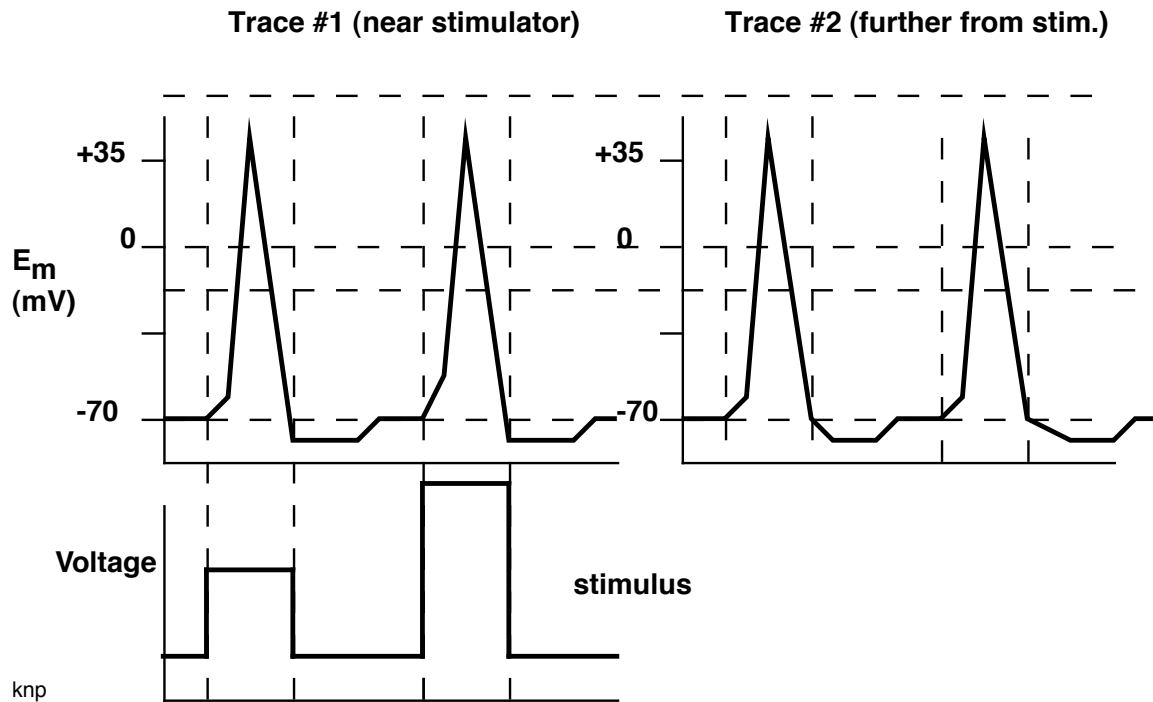
- Their sizes (**amplitudes**) at any place relative to the stimulus are **always proportional to the stimulus** -- the bigger the stimulus, the larger the electrotonic response
- They **decrease in amplitude over distance**. The further you go from where it was generated, the weaker the electrotonic response.

The two properties just listed are the reason that we say that electrotonic responses are **graded** -- their size changes according to how far they travel or the strength of stimuli. This will clearly contrast with the type of potential we will look at next.

- **Electrotonic responses can be created anywhere on a cell**. They extend away from the site where they originate like waves on a pond.
- Under normal conditions, electrotonic responses are **always weak waves**, even at their origin, and therefore are **not capable of traveling any appreciable distance**. The maximum distance before they have died out so much as to be un-noticeable is a bit more than the length of the soma.
- They move very rapidly and are truly like an electrical signal moving through a cable (but not a wire – ask me if you want to know the difference).

If we continue to increase the size of the stimulus, the response continues to increase in strength but still is not very large and dies out with distance. However, eventually a stimulus level is reached where the response suddenly becomes very large. Moreover, it does not die out over distance. Furthermore, if we continue to increase the stimulus, this response remains the same

size:

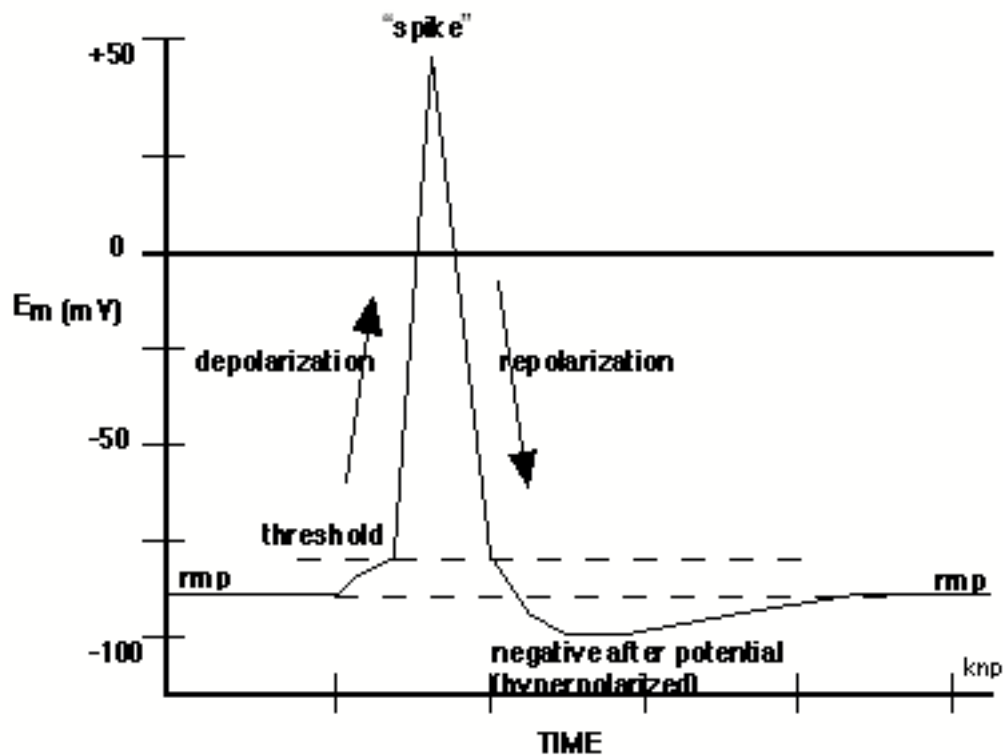


These responses are called **action potentials**. They are very different from the electrotonic responses that we first considered. Let's list some of the most important differences:

- **Threshold:** there exists a minimum stimulus required for the cell to produce an action potential. There is no minimum potential required to produce an electrotonic response. We will see that the threshold is key to understanding neural decision making. We will also see that threshold itself is a property that can be explained reductionistically -- by going to the properties of proteins found in the cell.
- **All-or-None:** related to the idea of threshold; simply states that either you get the full blown, typical action potential in response to a signal or you get nothing at all.
- regenerated
- **Conducted Without Decrement:** unlike graded responses, action potentials continue to have the same amplitude at distance from where they started. They do not decrease with distance. Neurobiologists discovered around 1950 that the reason that an action potential (AP) was conducted in this manner was that it was **CONSTANTLY REGENERATED** as it moved along. The regeneration largely had to do with the actions of proteins in the cell -- proteins that were essentially signalling each other. More about this below.

- **APs are restricted entirely to axons.** Therefore, APs first appear at the hillock and so the hillock must be seen as the central decision-making area of the cell.
- **APs travel very slowly compared to electrotonic responses.** The fastest only move about 1000 m/s and many go less than 1 m/s. Electrotonic responses move orders of magnitude more rapidly; their velocity being largely determined by something called the time constant of the membrane (it has to do with electrical (resistance and capacitance) properties of the membrane and surrounding medium). Thus, **APs are not primarily electrical signals;** we will see that they are **chemical events involving changes in proteins** -- we can view a traveling action potential as a ring of allosteric changes that move down the axon.

A few more details about action potentials (that are important):



Notice the following:

- The monitored area starts at its resting potential (a negative voltage usually between -60 and -100 mV; 0.06 and 0.1 V)
- **Depolarization** refers to the potential moving in a positive direction away from the resting membrane potential (rmp).
- **Repolarization** refers to the potential moving **back towards the rmp immediately after a depolarization.**

- **Hyperpolarization** refers to a membrane potential that is more negative than normal; there is a hyperpolarization period after every AP spike and this period is very important to our story.
- The **threshold** is very close to the normal resting potential.
- **Refractory Periods:** There are two important properties related to the ability of a cell to fire an AP at any moment in time. Both are together referred to as "**refractory periods**" -- times when it is more difficult if not impossible for to get an axon to produce an action potential. There are two types of refractory period.
 - **Absolute Refractory Period (ARP):** a period of time when no second stimulus no matter how strong, can cause an AP. It is due to the fact that when Na^+ gated channels close, they must remain closed for a certain period of time. They cannot open and therefore Na^+ cannot enter the cell which cannot depolarize and cannot produce an AP.

The ARP puts a maximum response rate on the cell. Explain why this is.

- **The Relative Refractory Period:** This is a period of time that comes after the ARP when a second stimulus that is greater than the minimum threshold stimulus can elicit another AP. Thus, it comes after the Na^+ gated channels have completed their mandatory "rest" after an AP. The value of the stimulus required to get an AP varies during the RRP; more about this later. The RRP has to do with hyperpolarization. Here's how:
 1. Assume that for a given cell the threshold tends to usually remain at a constant membrane potential.
 2. Thus, there is a certain voltage difference between the cell's normal resting potential and the threshold. In fact this is often termed the threshold although a better term for it is "threshold stimulus". For example, if a cell rests at -75 mV and the threshold is at -55 then the threshold stimulus is +20 mV.
 3. Now, when the cell is hyperpolarized after an AP, it is by definition more negative than normal. Thus, the threshold stimulus required to reach the threshold from the present membrane potential is greater than at rest. So, a larger than normal stimulus is required.

To make a cell more easily excitable, what should happen to the threshold? How about the resting potential?

We will see that changes in excitability change the computational features of a given neuron.

B. A Closer Look at Action Potentials:

1. We have seen above that action potentials have a number of properties very different from electrotonic responses:

a. They do not decrease as they travel some distance -- thus they are "**conducted without decrement**". Since all purely electrical signals tend to decrease in voltage over distance due to resistance to current flow, this implies that an AP is not really like a purely electrical current. In fact, this evidence shows that the AP is a signal that is **regenerated** as it travels -- thus, it never gets weaker.

b. They exhibit a property called **threshold** (minimum condition to elicit an action potential). Associated with the threshold is the idea of "**all or none**" -- either the stimulus exceeds threshold and causes an AP or it doesn't and we get no action potential. There is no in-between potential -- either a regular AP is produced or none at all. Thus, action potentials represent a kind of "yes" vs. "no" or binary response to events. At the most fundamental level

2. Now, what causes these important properties? They are largely the result of two general types of things:

a. **An uneven distribution of ions, especially potassium ions (K^+) and sodium ions (Na^+).** This distribution has a lot to do with setting up the electrical potential that we learned exists across a cell membrane - whether it is resting or conducting an action potential or electrotonic response. We need not worry how this works; it is well understood by neurobiologists but all we have to do is accept the ideas that:

1. there is more K^+ inside than out

2. there is more Na^+ outside than in

3. due to this distribution and especially to the fact that K^+ and certain other ions can always move whereas normally Na^+ cannot, there is a resting potential -- a voltage difference across the membrane.

4. when Na^+ is given the opportunity to move, it will enter the cell and cause the membrane potential to change in positive direction.

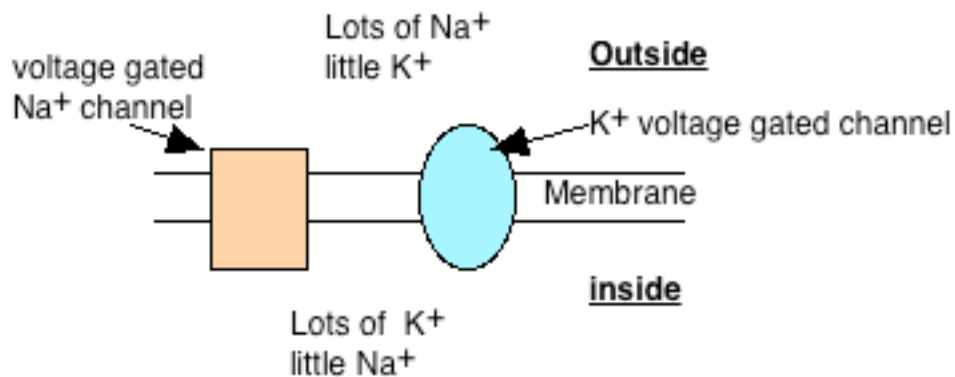
b. Proteins exist, called **channels** and **gated channels** that allow specific ions to pass through the membrane.

1. **channels** are proteins that are always opened to a particular type of ion. The fact that K^+ can always move whichever way forces dictate is due to the fact that all cells have K^+ channels that are always open. These have a lot to do with the resting membrane potential

2. **gated channels** are proteins that have specific ion channels that are only open (like a gate) under specific conditions. Gates can be opened (gated) by

3. changes in voltage (**voltage gated channels**) -- example Na^+ or K^+ gated channels (see next section).

4. binding to certain chemicals such as neurotransmitter (**chemically gated channels**) -- example -- neurotransmitter receptor.



c. All parts of a neuron have channels, especially K⁺ channels. This, is feature is associated with the resting membrane potential, which is the same everywhere on the cell. However, **only the axon has voltage gated channels** and it is the properties of these channels that cause the action potential. So, let's look quickly at these proteins:

d. **Na⁺-gated channels**. When these open, Na⁺ which normally cannot easily more, can travel through the membrane. Because neurons keep more Na⁺ outside than inside and because the inside of a resting cell is negatively charged, Na⁺ will come in via these gated channels if it can. Since Na⁺ is , well, positive, then the more of it that enters the cell, the more positive (less negative) the membrane potential becomes. Recall this is called depolarization and it is exactly what we know happens during an action potential.

Na⁺ gated channels are proteins that are sensitive to changes in charge. They sit in the membrane running from the inside to the outside. If the electrical charge on the membrane changes a specific amount (this amount is very close to the **THRESHOLD** for the cell) the protein senses this change and rapidly undergoes an extreme shape change which you know is called an **ALLOSTERIC CHANGE**. The result is that a sufficient depolarization (change in electrical charge) in the membrane around a Na⁺ gated channel will cause the allosteric change followed by a movement of Na⁺ into the cell via the channel. The cell becomes more depolarized. This movement causes the positive "upswing" of the action potential.

This upswing in voltage brings all the nearby Na⁺ gates to their thresholds and they also open. The result is that more Na⁺ enters the cell, the membrane is depolarized and the entire disturbance moves down the membrane as more and more Na⁺ gates open and create the conditions to open the gates near them.

Notice that we observed earlier that APs move slowly -- much more slowly -- than electricity. It should now be evident why -- what is really moving is the change in the shape of Na⁺ gates. This allosteric change must happen to generate the voltage change at each place along the membrane. The AP can

not move any faster than the Na^+ gates open, depolarize the area, and then cause more distant gates to open! It is like each Na^+ gate is communicating with its neighbors via changes in an electrical field -- in fact, that is exactly what is happening.

e. Now, notice that **we have a problem**. If the **gates remain open, the cell will remain depolarized** and be locked at a new higher electrical potential. We will not be able to send any more information. **So there must be a way to repolarize the cell -- to move it back from a "1" to a "0" if we think of this as a binary signalling system**. Repolarization is handled by doing two things:

1. Not allowing anymore Na^+ to enter. The Na^+ gates close after a short period of opening, regardless of whether or not the membrane potential is above threshold. In fact, when the Na^+ gates close the membrane potential is always above threshold as this event occurs near the peak of the AP. Not only do they close but the gates won't even open again for a short period of time. During this period of time the cell cannot produce a new action potential. This period is called the **ABSOLUTE REFRACTORY PERIOD (ARP)**. The ARP is totally a property of the Na^+ gates and it sets a limit on the maximum number of APs that a cell can produce per second (**it limits the cell's FIRING RATE**).

OK -- so no more Na^+ enters the cell. We still haven't gotten back to resting potential. How does that happen?

2. This is accomplished via the action of the **voltage-gated K^+ channels**. These start to open in response to the positive voltage that occurs during the depolarization of the AP. They remain open for a longer time than do the Na^+ gates.

Notice that their kinetics are different from the Na^+ gates. They open more slowly and under different conditions and they remain open longer. Could you imagine changes, picked out by selection, that could affect the kinetics? Would such changes affect the characteristics of neuronal function?

Now, what happens when these K^+ gates open? Earlier I said that K^+ is more concentrated inside the cell than outside. Combine this with the fact that during the AP the inside of the cell is positive, the result is that K^+ leaves the cell when these gates open. And since K^+ is positive, when it leaves, it removes positive charges and makes the cell more negative again -- its leaving **repolarizes the cell**. Its movement has the effect of removing all the + charges that entered when the Na^+ entered the cell early in the AP and the cell is restored to the resting potential.

Notice that the properties of the Na⁺ and K⁺ gates in large part determine the properties of the AP. For instance, the threshold of the Na⁺ gates determines the threshold of the cell. Since both are proteins, we will learn soon that the way they function depends on a mix of information from genes and from the environment. Anything that changes the structure of these -- or any other protein -- will result in some change of function

II. Encoding Information in the Firing Rate of Single Neurons:

A. Neurons respond to something that they "consider" important by firing an AP. Put another way, production of an AP is how neurons register an event that is significant. So, in one way, neurons are binary signalling devices. All of the input they receive is in one sense reduced entirely to a NO (below threshold, unimportant) or YES (above threshold, worth taking note of).

B. However, **imagine a case where a stimulus gradually exceeds threshold by greater and greater amounts.** The **resulting action potentials are no bigger**. They are always the same size -- any stimulus that is greater than threshold always results in the same size AP for a given neuron.

C. If that was all there was to coding information by neurons they wouldn't be very good at deciding how strong a stimulus was beyond weak vs. strong enough. However, neurons do have a way of reporting stimulus strength. Their **firing rate is proportional to the strength of the stimulus**.

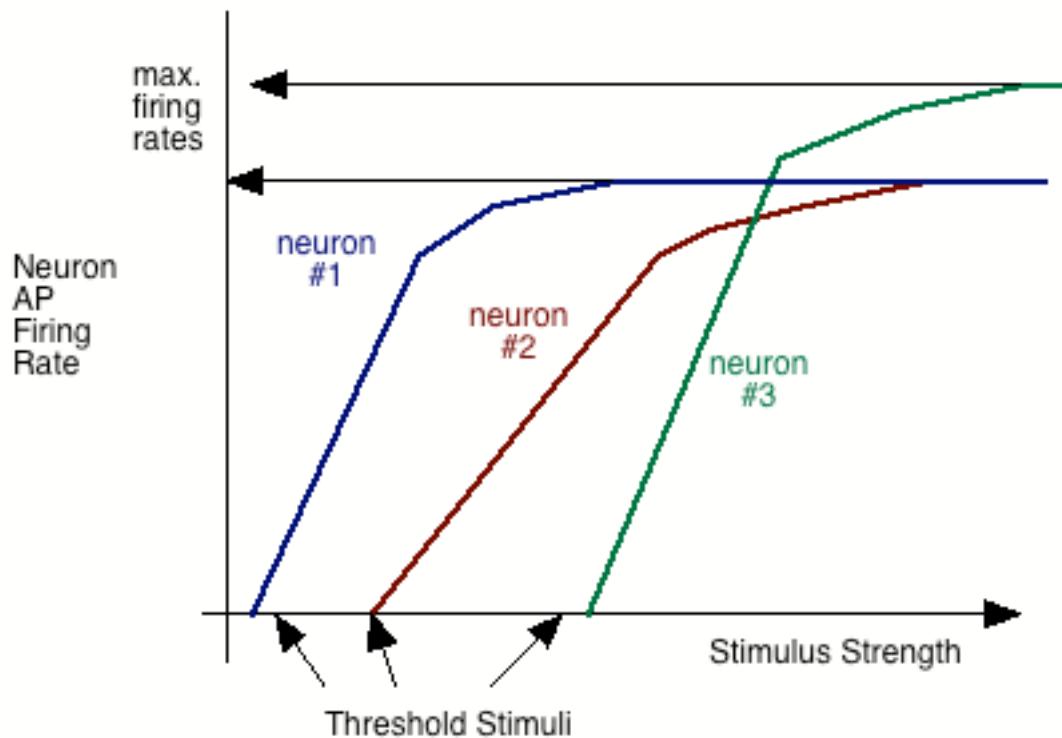
1. As a persistent stimulus applied to a neuron becomes stronger and stronger (imagine a heavier and then heavier yet weight on your foot) the firing rate increases.

2. This continues as the strength increases further until we finally get to a point where there is no further increase in firing rate. This happens when the neuron reaches its maximum firing rate which is determined by its absolute refractory period (since the neuron cannot fire during this period)⁵.

Between the threshold (weakest stimulus which produced an AP response) and the highest firing rate, the overall picture looks like this:

(please see next page)

⁵ Here's how the ARP sets the maximum firing rate. Imagine that after a gate opens for 0.5 milliseconds it must close for 1.5 milliseconds. Thus, the earliest a second AP could be produced was 0.5 + 1.5 milliseconds after the last one (the time of the first AP plus the ARP). So, the maximum rate the neuron could fire would be 1000 milliseconds per sec / 2 milliseconds per firing = 500 times per second. Generally the maximum rate of typical neurons is quite a bit lower than this!



Notice in the picture above that each neuron has its own characteristic threshold, rate of response to the stimulus (note the different slopes which tell how much the firing rate changes with a given stimulus change) and maximum firing rate. So, they all "code" stimulus information in a somewhat different manner which is very useful. For instance, neuron #1 is very sensitive to both low levels of stimulus and to change in strength while neuron #2 is less sensitive to low levels but can deal with a wider range of strengths, etc.

The threshold, response rate, and maximum firing rate are all properties of either single proteins found in neurons or are the result of the properties of a rather small number of neurons. Once again, the shapes of the proteins determine their properties and the shapes are determined by genetic and environmental information.

One other point about the graph on the last page -- Notice that the response lines are linear for a while and then curve before reaching their maximum firing rate. The curved area is due to the **relative refractory period (RRP)**. Recall that the RRP is caused by the fact that after an AP there is a brief period of time when the cell is hyperpolarized. Thus, it takes a bigger stimulus than normal to fire the cell. It can fire, but it is harder to get it to do so. The result is a curved line with a lower slope than previously -- a bigger stimulus is required to get the cell to fire, so a

larger change in stimulus is required to get to increase the firing rate a certain amount!

III. Cell to Cell Communication and Neural Computation: For the moment, let's assume that APs mysteriously move down axons -- we need not really worry how at the moment. We learned previously that at the end of an axon there will be connections with other cells called synapses. Here is the first decision point between the two cells.

A. **If the synapse is electrical**, we can just imagine that the AP continues to move along just as it did on the axon. No decision making (not strictly true, but we'll assume it is for our purposes, end of story). Thus, electrical synapses represent a great way to move but not to process information.

B. **About Chemical Synapses**; Recall that axons divide near their ends. When there are chemical synapses, they do not touch the next cell; instead there is a fluid-filled **synaptic gap** between them. Communication is the result of the release of a chemical. Most signalling involves chemicals being released from storage areas (called **synaptic vesicles**) located at the end of the axon.

In any case, once again, a number of proteins are involved. The released chemical, called a **neurotransmitter (NT)** is typically released for the period of time when the action potential is present (it dies out at this point). Generally, they are rather **small, simple compounds**. Examples of some of the most common include the following:

acetylcholine (very common in the CNS and PNS -- the only one we will discuss in any detail)

norepinephrine -- released by neurons that control muscles in places such as your intestine, blood vessels, etc. Important in physiology.

dopamine: important in parts of the brain

glutamate: important in retina

glutamine: in the CNS

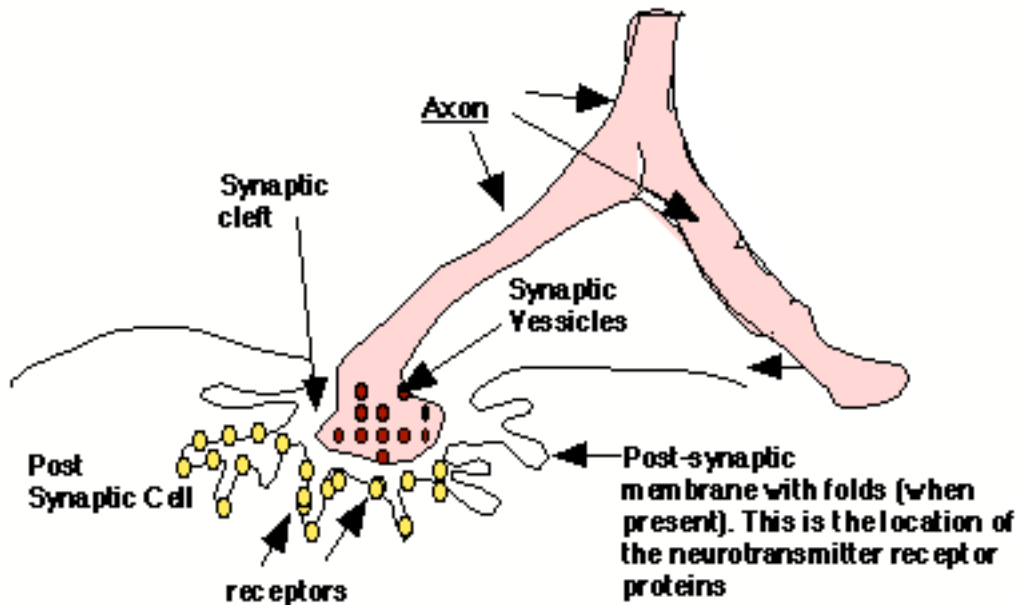
endorphin: a CNS NT and hormone, release results in a muted sense of euphoria (ex: runner's high)

Neurotransmitters travel the short distance to the post-synaptic cell (usually dendrites or soma (sometimes they will contact other axons and in many cases the next cell is an effector such as a muscle). There communication will only occur if the NT binds to a protein that is specific for it -- called **neurotransmitter receptor**. Furthermore, we will see that a large number of receptors must actually bind the NT for there to be any chance of getting the next neuron to fire an AP.. More about this shortly. Finally, it is very important the NT be broken down or removed.

Why must the NT be removed. What do you suppose would happen if NT is not removed? Could information continue to pass from cell to cell? Would changes in the rate of NT removal affect how the entire nervous system operated?

What we just described is called **antegrade transmission**. Sometimes we will see that the post-synaptic cell releases chemicals that communicate with the presynaptic axon (**postgrade transmission**) but the type of information that moves in this case is often very different. Notice that in antegrade transmission information moves in only one direction (pre synaptic to post synaptic) because the NT is only released from the axon and the receptors are only present on the dendrites or soma.

Here is a diagram of a chemical synapse:

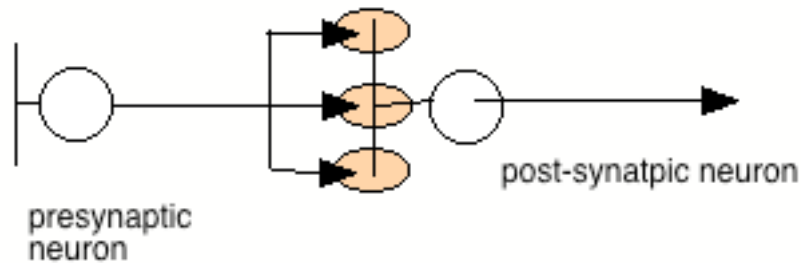


When you look at the picture above, think about the relationship between the number of receptors, cell surface area, and the signal generated on the post-synaptic cell.

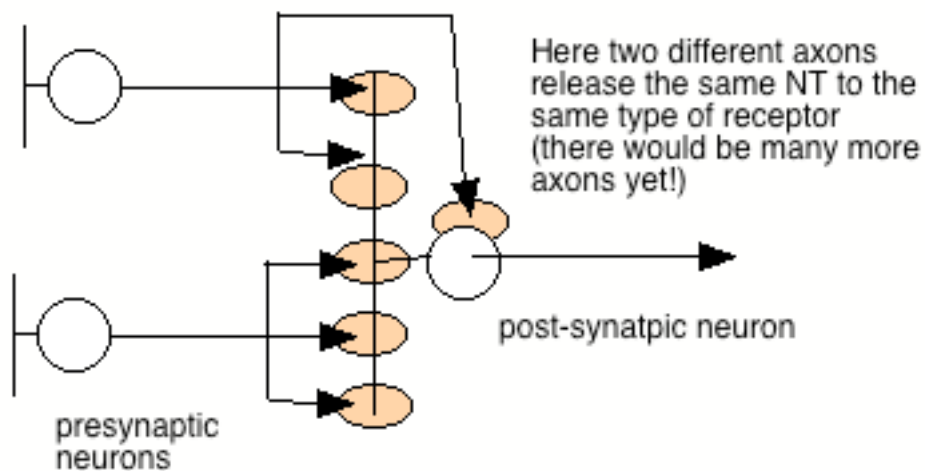
For our purposes, **a given synapse will have only one type of NT receptor on the post-synaptic side of the synaptic cleft.**⁶ So each synapse involves the release of only one type of NT on the presynaptic side and it has only one type of NT receptor, specific for the NT released nearby and no others, on the post-synaptic side.

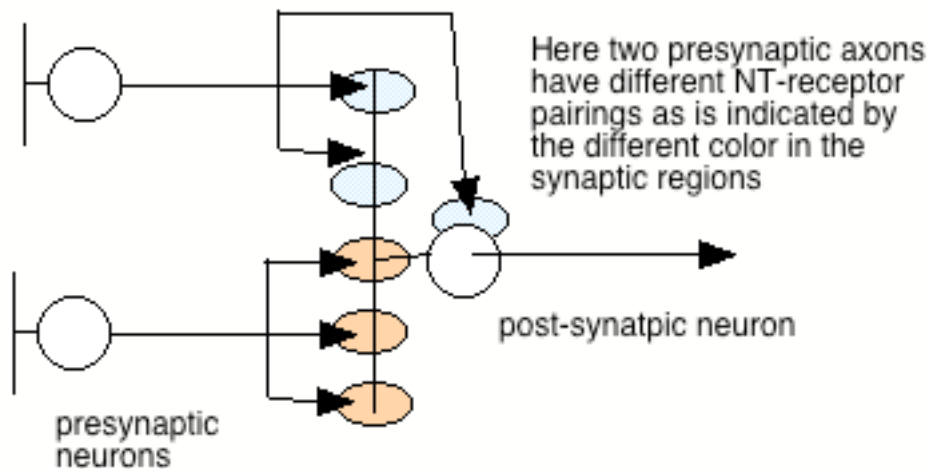
⁶ This is actually not true -- it used to be thought to be true, but now we know otherwise. Nevertheless, for our purposes act like a given neuron will only release one kind of NT.

synapses: color indicates area near each synapse and the same NT- receptor pair type
 Here all are the same because only one neuron synapses with the post-synaptic cell



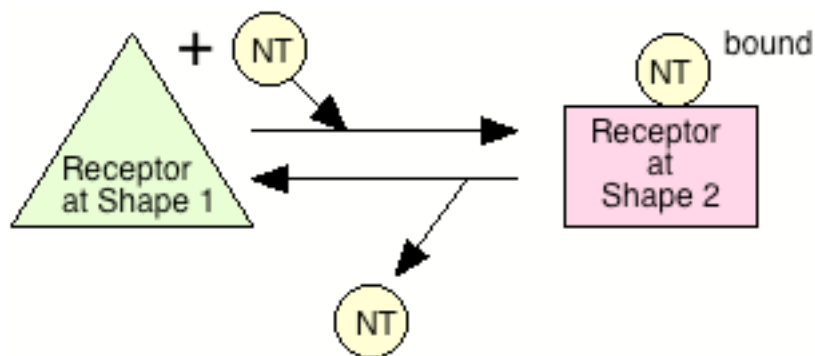
However, a given cell has many synapses, usually thousands. **Many of these synapses may well have different NT-receptor pairings.** So, to restate -- one synapse has only one type of NT-receptor pair and if one post synaptic cell has a number synapses with the same presynaptic cell, all will have the same NT - receptor pairing and all will be activated at about the same time. On the other hand, synapses with other cells could well involve the same or different NT-receptor pairs (see next page):





Receptors, Post-Synaptic Potentials, and Neural Computation:

1. **What do the NT receptors do?** They induce graded potentials (the **electrotonic responses** we learned about earlier) on the post synaptic cell. A given kind of receptor can either produce a depolarization or a hyper polarization. For the period of time when the NT binds to the receptor, the receptor undergoes an **allosteric change**. As usual, imagine the NT receptor has two possible shapes (a binary type response) -- one shape when the NT is attached and one when it is bound:



Now, these shape changes are what lead to a change in the electrical charge around the receptor molecule (the changes open or close paths for certain ions to move through the membrane --we need not worry about the details, all we need to know is that the shape change causes the charge on the membrane and therefore the membrane potential to change.

The effect of NT binding to its specific receptor is to open one or more ionic channels and create a small electrotonic response. The more NT receptors that are activated at a given moment, the larger the response. Thus, this will have something to do with:

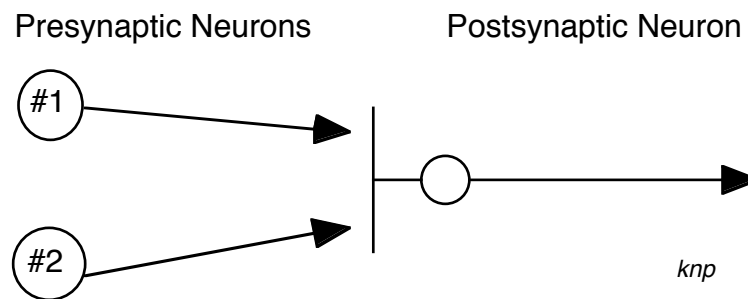
- the number of NT molecules released

- the number of NT receptors available
- the NT receptor types (not all proteins are the same) and the resulting potential. Post-synaptic electrotonic potentials come in two types:
 1. those that represent depolarizations and which move the cell towards threshold called **EXCITATORY POST SYNAPTIC POTENTIALS (EPSPs)** and
 2. those which hyperpolarize the cell and therefore move the potential further from threshold and make it less likely to fire an AP -- they are called **INHIBITORY POST-SYNAPTIC POTENTIALS (IPSPs)**

Let's look at what happens in some detail:

Neurons decide whether or not fire in response to stimuli based on a number of factors but the crucial factor is always whether or not they are depolarized to threshold. Let's consider a simple model for studying neuron computation:

Neural Computation -- the Basic Model



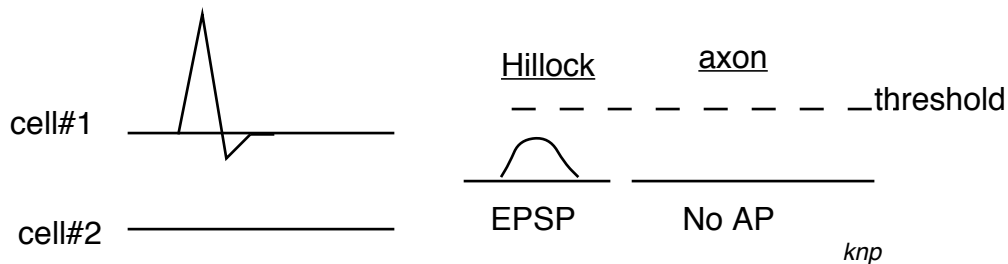
Notice that the post-synaptic cell can receive input from cell 1, cell 2 or both. The original potential on the post synaptic cell are all graded responses. The binding of a neurotransmitter causes the membrane to depolarize (or hyperpolarize) locally, this disturbance will spread electrotonically. The only way to go is towards the soma and axon. **Think of the moving graded potential as being like a wave on a pond that spreads outward from where a rock hit. Keep one problem with this analogy in mind -- these "waves" will only be above the mean water level (i.e., let's say depolarized from normal E_M) or below the normal level (like an IPSP) in the other -- no continuous up and down movement as in "real" waves.** As these waves spread from the source, they gradually decay to a value that is closer and closer to the mean water level (resting potential) -- just like graded responses always do. If the wave is an EPSP depolarization, it, by itself, is unlikely to ever be large enough to reach the first point where an AP can be produced⁷ at a sufficiently large depolarization to

⁷ Recall that on a neuron this is called the **axon hillock** the place where the axon emerges from the soma

cause an AP. Usually a process called **summation** is necessary. Before looking at summation let's familiarize ourselves with a simple system we will use to illustrate summation:

First let's consider again what happens if there is no summation. In the example on the next page, the EPSP that results from cell #1's release of NT is sub-threshold -- there is no AP:

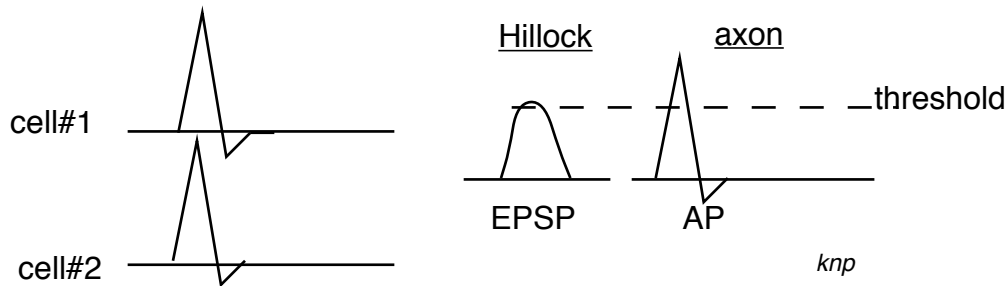
I. No Summation



b. **SUMMATION**: a process whereby one or more electrotonic responses are added together. The addition is made possible by the capacitive properties of the membrane. There are two general types of summation:

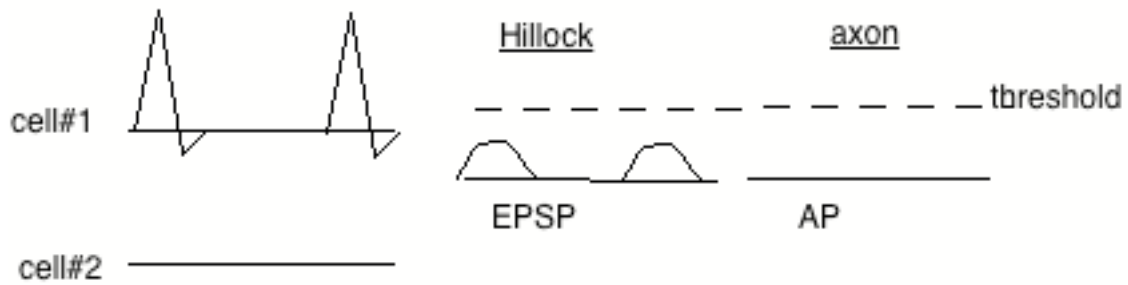
1. **SPATIAL SUMMATION**: where potentials that originated in different parts of the post synaptic potential come together at the same time on the hillock. If the voltages add enough to exceed threshold, an AP is triggered (see figure):

II. Spatial Summation

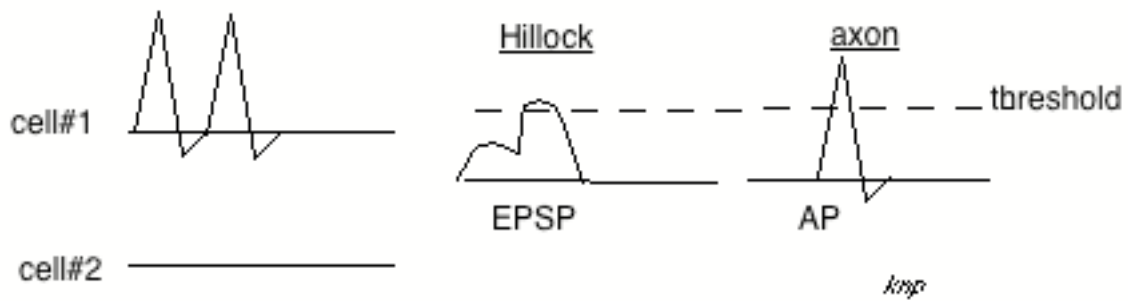


2. **TEMPORAL SUMMATION**: occurs where two or more potentials that originated at slightly different times come together and sum at the hillock. The figure on the next page shows such a process where cell #1 fires. In the top diagram, the APs are far enough apart that the graded potentials do not add and neither can reach threshold and fire the neuron. In the second example, the APs come so close together that the EPSPs merge into a stronger potential that triggers an AP. This is temporal summation.

IIIa. Temporal Summation Fails

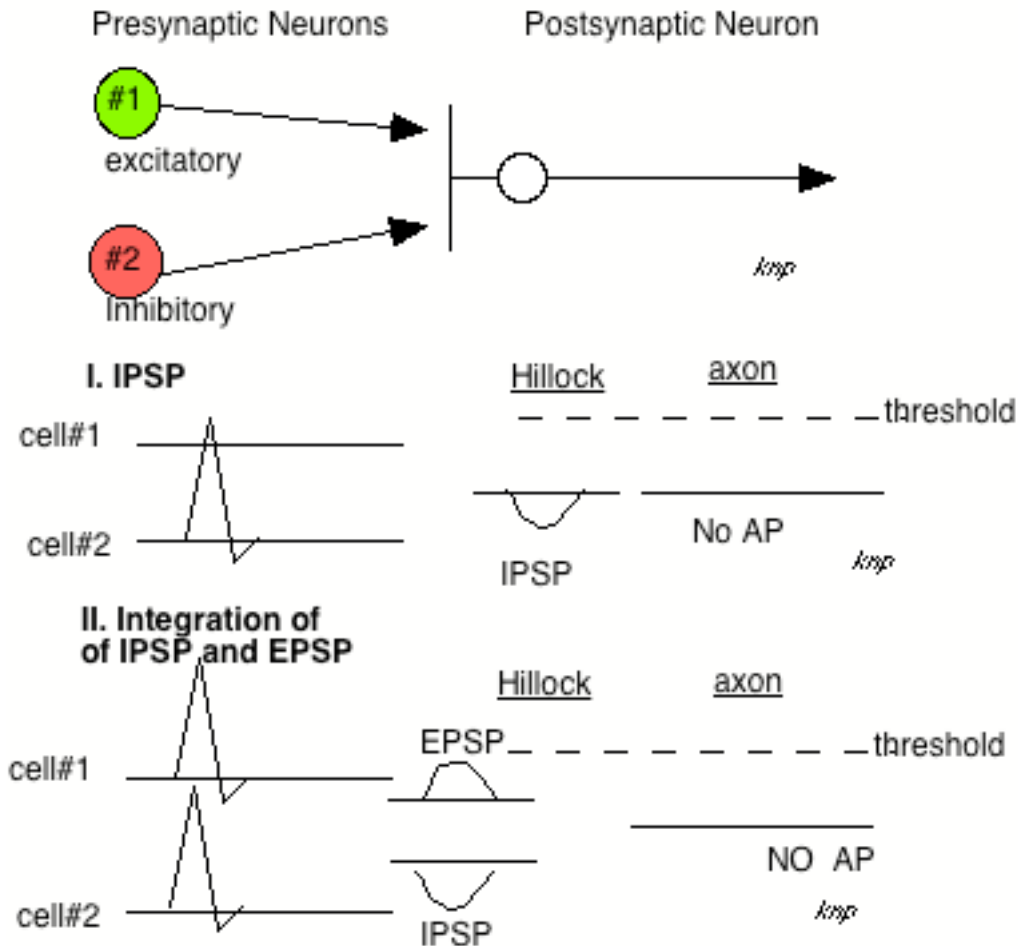


IIIb. Temporal Summation



3. In many cells it is possible that both IPSPs and EPSPs will come together and sum. Thus, inhibitory neurons can make it difficult for an axon to fire since the EPSPs and IPSPs add algebraically (next page):

Neural Computation #2



Most summations involve many neural inputs and both temporal and spatial summation often from both excitatory and inhibitory inputs.

4. Here are some additional, more specialized, terms:

a. **FACILITATION**: the tendency to produce bigger EPSPs when a cell is fired many times in rapid succession. It may involve extra release of transmitters.

b. **SYNAPTIC FATIGUE** -- as mentioned earlier, this is the decrease of release of transmitter as supplies are fatigued.

c. **PRE-SYNAPTIC INHIBITION**: three neurons are involved, the pre and postsynaptic neurons and an inhibitory neuron that ends near the terminus of the pre-synaptic neuron.

1. the presynaptic neuron has receptors for the inhibitory neuron transmitter

2. the inhibitory neuron depolarizes the pre-synaptic neuron, this causes it to release less transmitter each time it transmits an AP.

3. One similar mechanism involves the presence of receptors on the presynaptic neuron for its own transmitter, the presence of which also causes the presynaptic neuron to depolarize.

Removal of the signal. This is a very important point. As the NT was bound to the receptor, the receptor would cause an alteration in the electrical potential near it -- *i.e.*, it would cause a change in the resting potential in the vicinity of the receptor. So, if the events in the presynaptic and post-synaptic cell are to mimic each other, there must be a way to remove the NT quickly from the receptor. It should not persist much longer than an AP would normally last.. If not, one could imagine the post-synaptic cell getting "behind" and not producing its own signal each time the presynaptic cell signaled.

Removal of the NT essentially resets the receptor (see last diagram -- go from the diagram's right to its left). This is essentially the same thing that closing fast Na⁺ and opening slow K⁺ channels do to the membrane potential on an axon. In both cases the result is that the membrane potential around the receptors and synapse goes back to its normal resting membrane potential (we need not worry about how). The shape of the NT receptors and the membrane potential can be seen changing back and forth kind of like a Morse code signal (but there is more to it than Morse code). We say that the membrane potential and the shape of proteins (NT receptors and gates) **toggle** back and forth, like a light switch.

Typically but not always, the NT is removed from the receptor by being broken down chemically. Usually this is accomplished by a specific protein catalyst. This protein, an example of a group called enzymes, makes the breakdown happen much faster than it would without the enzyme being present. There is typically one kind of enzyme that specializes in removing each type of NT from its receptor⁸ so there are many different types of these enzymes. The one example you should know is called **cholinesterase** (more properly, **acetylcholinesterase**) -- it breaks down the NT acetylcholine (into acetic acid and choline) and thereby rapidly removes it from the receptor so that they can respond to the next release of NT.

This is a very crucial task. Some of the most deadly compounds known are inhibitors of cholinesterase. Some of these are the infamous nerve gases such as serin. By preventing acetylcholinesterase from working, acetylcholine from normal neural activity rapidly builds up and saturates receptors. The result is that muscles contract with full force and lock in contraction. Muscles tear, bones may even break and the person cannot breathe because their diaphragm is locked in contraction. A terrible death will probably result; these weapons are truly awful.

⁸ Note in some cases the NT is not broken down but is instead simply removed into the cell where it is recycled or otherwise used.

Is the electrotonic signal that inputs to the axon hillock essentially analog (continuous) or discrete?
Is the response of an axon analog or discrete?
In what sense is an axon making a decision? What decision is being made?
What does this decision have to do with information flow?
Start thinking about how you can get more complex decisions from a system built from neurons.
Start thinking about the roles of proteins in all of this. We will consider them in more detail soon.