

SYNAPTIC TRANSMISSION¹

I. OVERVIEW

A. In order to pass and process information and mediate responses cells communicate with other cells. These notes examine the two means whereby excitable cells can rapidly communicate with each other. In both of these cases the communication will be manifest when electrical activity of one cell affects the electrical activity of another cell.

1. **PRE-SYNAPTIC CELL:** the cell that usually will be the one that most directly influences the behavior of the next cell, called the **POST-SYNAPTIC CELL**. Thus, our scheme involves information moving from pre- to post-synaptic cell.

2. **SYNAPSE:** an area where communication occurs between two cells

a. **CHEMICAL SYNAPSE:** the cells do not touch each other. The pre-synaptic cell releases chemicals that diffuse across a short gap between the cells (the SYNAPTIC CLEFT). These chemicals, called **neurotransmitters**, either bind to the membrane or the post-synaptic cell takes them up. In either case, the result is a graded, electrotonic potential.

1. Chemical synapses always a **SYNAPTIC DELAY**, a short time (usually less than 1 ms) needed for the chemical transmitter to diffuse and cause an effect.

2. chemical synapses are usually **UNIDIRECTIONAL CONDUCTORS**; they usually will only conduct information from the pre- to post-synaptic cell. They are the analog of a RECTIFIER (such as a diode²) or one-way valve (fluid flow).

b. **ELECTRICAL SYNAPSE:** where there is actual physical contact between two cells at one or more **GAP JUNCTIONS**. Thus, the cytosol of the two cells is continuous. However, keep in mind that these gap junctions are relatively small and few in number when compared to the great area of the two plasma membranes.

? Compared to the cell as a whole, do electrical synapses represent a high or low resistance area? Why?

1. Electrical synapses usually show no synaptic delay.

2. Electrical synapses are usually **BI-DIRECTIONAL**, that is, they do not act as rectifiers. However, many do seem to have a preferred direction of conduction (for reasons that are not understood). As a result, an AP moving in the preferred direction is attenuated less than one moving in the other direction, this is described with a **COUPLING RATIO**.

3. Chemical and Electrical synapses are spread throughout the nervous and muscular systems. Chemical synapses are definitely more common, especially in the nervous system, but even there, electrical synapses are also found. **We will focus most of our attention on chemical synapses since the features of their operation are unique (electrical synapses function mostly by mechanisms that we have already discussed). Furthermore, the understanding of chemical synapses is especially vital in medicine since it is possible to influence the action of synapses pharmacologically and thereby exert profound effects on the body as a whole.**

B. Nomenclature regarding synapses. Synapses are distinguished by

1. **LOCATION:** e.g., neuromuscular, spinal etc.

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² Diodes only allow current to flow in one direction.

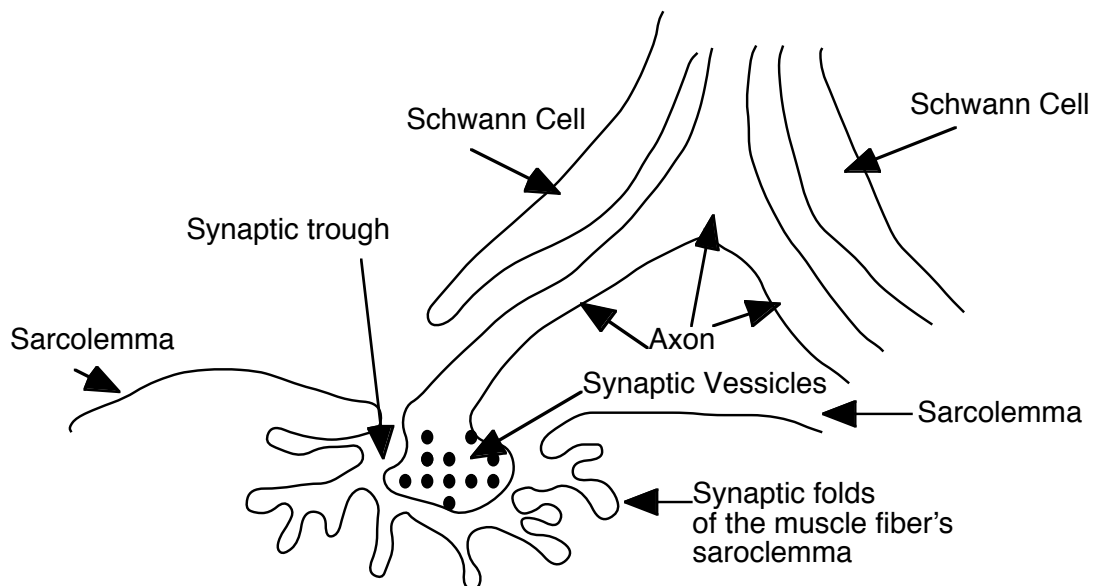
2. **TRANSMITTER:** type of transmitter released by the presynaptic cell. Ex: acetylcholine (ACH)
3. **RECEPTOR:** specific type of receptor on the post-synaptic cell. What does it do when it attaches to the transmitter?
 - a. receptors often define much of the synaptic activity because they are specific for a certain transmitter and also they exhibit a certain effect. Actually, **it is the receptor that determines the effect of the transmitter.**
 - b. Example: there exist at least two types of acetylcholine receptors and they have very different effects:
 - (i) **Nicotinic Acetylcholine Receptor: excite the post-synaptic cell.** Properly, we should consider two types, one that is at neuron-neuron junctions (true nicotinic receptor) and another that should be called a **NEUROMUSCULAR ACH RECEPTOR**. We will dwell mainly on the latter one.
 - (ii) **Muscarinic Acetylcholine Receptor: inhibit the post-synaptic cell.**

-- We will begin with a consideration of an excitatory chemical synapse, the nicotinic neuromuscular junction. We will consider other receptor types in later classes.

II. Excitatory Chemical Synapses

A. NICOTINIC NEUROMUSCULAR JUNCTION: these are the synapses that exist between neurons of the **SOMATIC NERVOUS SYSTEM** and **SKELETAL** (also called **VOLUNTARY** or **STRIATED**) muscles. They are excitatory in nature, that is, an AP in the somatic ns can cause an AP on the muscle.

1. Basic Anatomy of the junction:



DEFINITIONS OF TERMS IN THE FIGURE ABOVE

SYNAPTIC TROUGH (CLEFT): the gap between neuron and muscle

MOTOR ENDPLATE: the portion of the muscle cell that is associated with the synapse. The actual plasma membrane of the muscle cell that is in the motor endplate is called the **POSTJUNCTIONAL PLASMA MEMBRANE.**

SYNAPTIC FOLDS: in-foldings of the end plate that increase surface area, these are loaded with receptors.

SYNAPTIC VESICLES: vesicles contained in the pre-synaptic cell adjacent to the synapse. They are filled with transmitter substance. (WHAT IS THE TRANSMITTER IN THIS CASE?). Note that the transmitter is synthesized in the terminal region of the axon. The fact that this is an energy-intensive process is indicated by the large number of mitochondria found there.

2. Function:

a. An AP arrives at the end of the axon

1. Note that **the AP divides at the neuromuscular junction and follows many small axonal processes.**

Why do axons divide near their ends?

In neurons that innervate muscles, this allows one axon to control many muscle fibers (cells).

In neurons that innervate other neurons, this allows for:

- multiple inputs to each post-synaptic neuron. Such multiple inputs are at the heart of neural processing and decision-making and are associated with a process called summation (see below).
- signals to become **diffuse and follow many parallel paths** where the information is processed separately.

2. When the AP reaches the terminal area:

a. A series of voltage-gated Ca^{++} channels open on the pre-synaptic membrane

b. The influx of Ca^{++} appears (there's still some debate) to trigger the fusion of a certain number of vesicles with the presynaptic membrane.

c. exocytosis of the ACH follows fusion.

d. The ACH diffuses across the synaptic cleft.

3. **the Neuromuscular ACH Receptor:**

a. contains a **binding site for ACH**

b. this site **operates a Na^+ and K^+ channel**

c. adjacent to the receptor is a large amount of **ACETYLCHOLINESTERASE** (or, simply **CHOLINESTERASE**), an enzyme that degrades ACH to choline and acetate (-) ion. These can no longer bind to the receptor and are released. About half of these hydrolysis products are taken up by the presynaptic cell and recycled into ACH.

Acetylcholinesterase and Information Transfer

The acetylcholinesterase performs a vital function that we first considered when we discussed proteins and information processing. In order to continue to transmit information along a particular pathway, there must be a way to toggle each element between various states. In the case of the **acetylcholine receptor-gate**, the states involve being **opened** so that Na^+ and K^+ can pass **or closed**. The gate is opened by Ach. If there was no way to close it, no further information could pass. So, shortly after it arrives, Ach is broken down by cholinesterase.

4. Experiments that determined some of the main features of receptors. Let's take the neuromuscular Ach receptor as an example of a technique that was used to find out which ions move in response to a neurotransmitter. As usual there will be both a theoretical and experimental component.

a. The **experimental component**.

(i) a neuron connected to a single muscle cell ("muscle fiber") is used in this experiment.

(ii) the neuron is stimulated electrically to produce action potentials and thereby release neurotransmitter that then binds to the receptors.

(iii) The potential of the postsynaptic membrane is adjusted using another electrode that "injects" current. Notice that in this area the no AP is produced since there are no fast Na^+ channels.

(iv) a recording electrode is placed in the muscle cell and the changes in muscle cell E_m that follow each AP on the neuron firing are measured. These are called end-plate potentials.

b. The theoretical component -- the **CHORD CONDUCTIVE EQUATION**.

Follow this derivation (but don't learn the derivation or any of these equations) and try to understand the application of the equation in generating testable hypotheses:

Recall that the current for any ion (i_{ion}) is given as:

$$1. i_{ion} = G_{ion} * (E_m - E_{ion})$$

At equilibrium, there is no NET current and so we know that the sum of all the ionic currents must equal 0:

$$2. I_{K^+} + I_{Cl^-} + I_{Na^+} = 0$$

or,

$$3. G_{K^+}(E_m - E_{K^+}) + G_{Cl^-}(E_m - E_{Cl^-}) + G_{Na^+}(E_m - E_{Na^+}) = 0$$

Now, let's assume that Cl^- distributes itself passively (which it does in most situations) according to whatever the E_m currently (a joke, get it) is.

Put another way, let's say that we have reason to believe that the conductance of K^+ and Na^+ will for a time be very high compared to that of Cl^- and therefore are the only players that matter. So, we can drop the Cl^- term so the eq. becomes:

$$4. G_{K^+}(E_m - E_{K^+}) + G_{Na^+}(E_m - E_{Na^+}) = 0$$

(note that it is not always true that $E_{Cl^-} = E_m$)

If we now solve for E_m :

$$5. \quad E_M = \frac{G_{K^+}}{(G_{K^+} + G_{Na^+})} E_{K^+} + \frac{G_{Na^+}}{(G_{K^+} + G_{Na^+})} E_{Na^+}$$

as with the Goldman, it can be seen that the chord equation will predict the E_m as a weighed average that depends on the conductance of each ion.

2. We can use this equation to generate hypotheses as to the operation of the receptor. We will use it to predict the E_m for situations where the Ach receptors have become activated. Since we don't yet know what ions that the Ach receptor allows to enter, we will solve the equation for a series of different conductances and predict what the value of E_m should be.

(a) For instance, if we assume that this receptor does nothing to change K^+ conductance (*i.e.*, its conductance to Na^+ is 0) the entire equation reduces to E_{Na} .

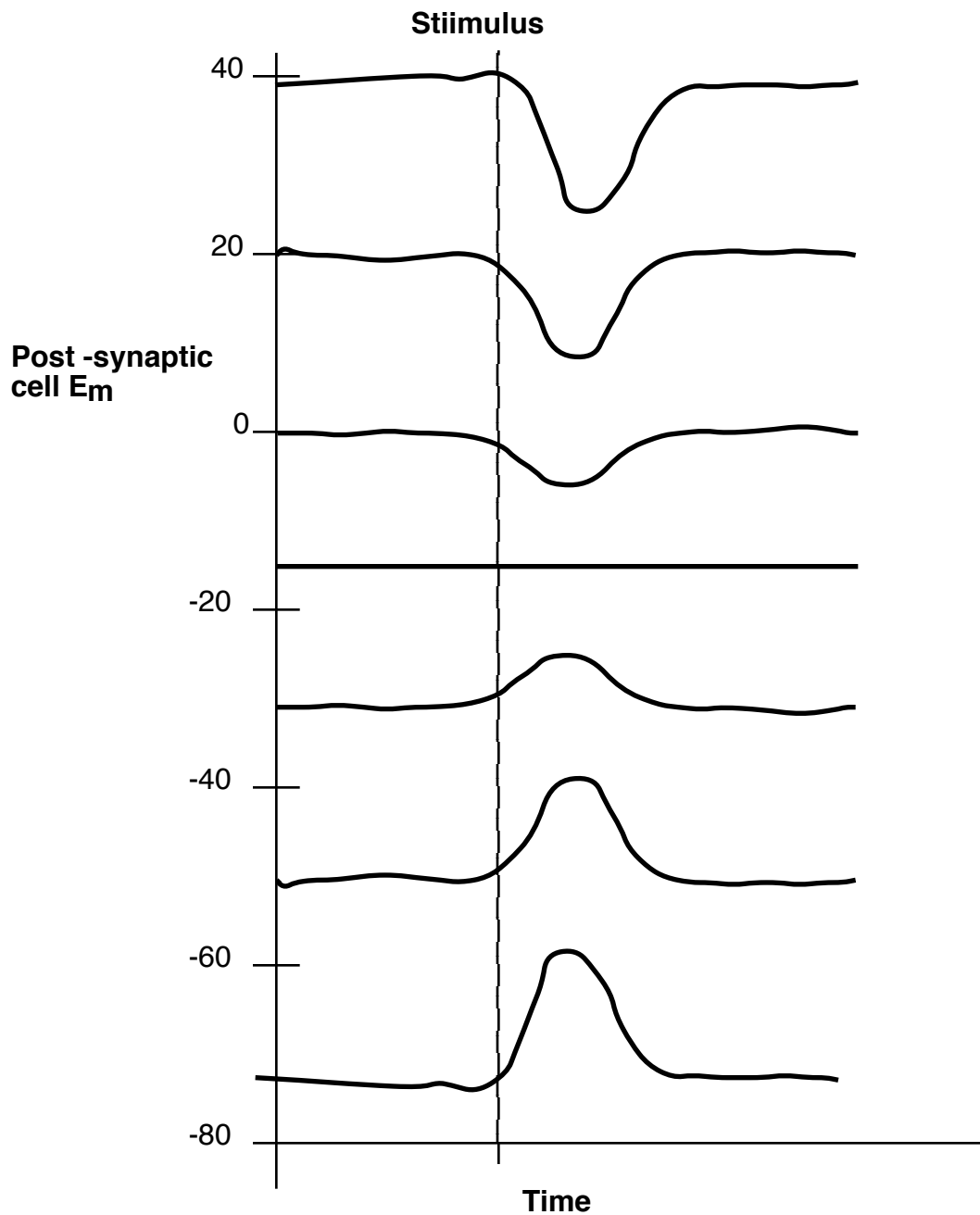
(b) likewise, if it only allowed K^+ to pass, the equation would reduce to E_K .

Both of these results should make good sense to you based on all you have learned about bioelectricity.

(c) On the other hand, suppose that the nicotinic receptor appears to conduct both Na^+ and K^+ equally well. As a result, since $G_{Na^+} = G_{K^+}$ then eq. 5 becomes:

$$6. \quad E_M = \frac{1}{2} E_{K^+} + \frac{1}{2} E_{Na^+}$$

When the receptor membrane was "clamped" at different values and then Ach was released, the results clearly were not consistent with either or the one ion channel models. In fact, the membrane potential near the receptors **briefly** changed to a value that was about midway between E_K and E_{Na} as predicted if the conductances of the two ions became equal. The fact that the response was brief argued that the receptors opened channels for a short period of time and then closed. This time period was later shown to correspond to the time after Ach bound but before it was broken down by cholinesterase. (This was shown by adding cholinesterase inhibitors -- in this case an extended change in E_m resulted). The results are on the next page:



Note that at -15 mV there was no further effect on the E_m due to ACH release. This voltage represents the E_m given by the ionic distributions of Na^+ and K^+ if the membrane is equally permeable to both (see eq. 6).

? Is there any ionic flow at -15 mV? What flows are occurring above and below this E_m ? What would happen if G_{K^+} and G_{Na^+} were not equal?

b. This flow of ions thus depolarizes a small section of the membrane near the receptor. This action persists for a short period of time until the ACH is destroyed and the channel(s) close.

c. Normally, a presynaptic AP causes the release of a large amount of ACH (many vesicles) and therefore many receptors are activated.

1. In this case the result is an **END PLATE POTENTIAL (EPP)**.

2. The **size of the EPP is graded by the amount of ACH released** (usually constant for an AP -- often referred to as a (shudder) quantum of NT). In conditions of repeated, rapid release ACH can either build up or be depleted). Moreover, repeated stimulation sometimes induces changes in and the number of functional receptors (so called **up** and **down** regulation).

MYASTHENIA GRAVIS: a neuro-muscular junction disease characterized by an autoimmune attack on the neuromuscular ACH receptors thereby reducing their total number. Muscle weakness results.

? WHY?

3. If the EPP is large enough and affects a big enough area, an AP is produced on the muscle.

4. Pharmacological Agents and the Neuromuscular Junction:

i. **ANTICHOLINESTERASES:** drugs that prevent cholinesterase from destroying ACH. What would be their predicted effects?

Examples: **Nerve Gases (DPIF), organophosphate insecticides**

ii. **AGONISTS:** compounds that attach to the receptor and mimic the action of ACH, but are often more persistent. Ex: **CARBACHOL**, and, at certain doses **Nicotine**.

iii. **ANTAGONISTS:** Compounds that attach to the receptor but block ACH from binding and thereby prevent its effect. Example: **CURARE** (also called tubocurane), **ATROPINE** (although this one is more specific for another type of ACH receptor).

? What pharm. agents would be best to treat myasthenia gravis? Why?

Note: It was formerly believed, based on work with goldfish endplates that NTs were released in distinct "quanta" – one vesicle per AP and each vesicle was about the same size and contained about the same number of NT molecules and therefore produced a more or less discrete size PSP. This has been disputed recently (see *Nature* **449**, 124-125 (13 September 2007) and I am going to drop it from this section until there is better evidence that this phenomenon, if it occurs, does so in more than just a few unusual cases.

6. Visualizing the Neuromuscular ACH Receptor:
 - a. the receptor will bind irreversibly with a type of snake toxin called **a-Bungarotoxin**.
 - b. This toxin can be labeled with radioactive elements or fluorescent compounds to allow visualization of the receptor.
 - c. the density of these receptors may be as high as 50,000 per mm^2 .

B. Neuron-Neuron ACH synapse:

1. Excitation and Inhibition

a. Morphology and Simple physiology:

1. the presynaptic axon ends as a broadened area called a **TERMINAL BOUTON**.
2. these are positioned over either the dendrites or the soma of the post-synaptic cell.
3. the dendrites and soma can only conduct electrotonic responses.
4. the post-synaptic cell area at the synapse is specialized for "chemical sensitivity"
5. the axon hillock is specialized for electrical sensitivity and has a lower threshold for AP generation than any other part of the cell. It is also the first place that can develop an AP.

b. **EXCITATORY POST SYNAPTIC POTENTIALS (EPSP)**: these are potentials that tend to depolarize the cell, the amount of depolarization is proportional to the number of transmitter molecules that bind to the receptor.

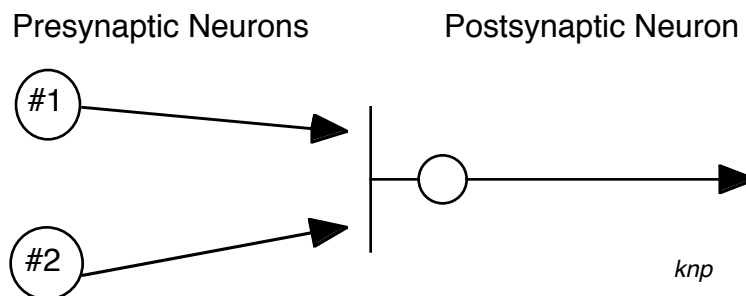
c. **INHIBITORY POST SYNAPTIC POTENTIAL (IPSP)**: these are potentials that tend to **HYPERPOLARIZE** the cell.

These have been shown to principally involve increases in Cl^- conductive (so I have lied to you all along -- Cl^- is also a little out of whack with respect to E_m). In other types of receptors, increases in K^+ conductance are the cause of the hyperpolarization and inhibition.

2. Integration and Neural Computation:

a. 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:

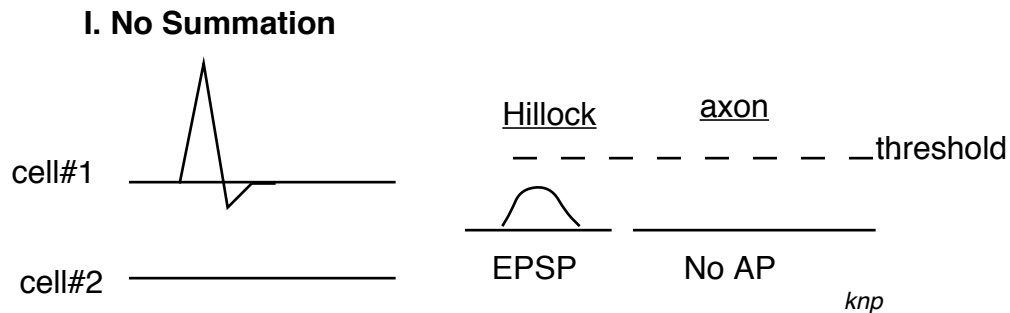
Neural Computation -- the Basic Model



Notice that the post-synaptic cell can receive input from either cell 1, cell 2 or both. The original potential on the postsynaptic cell are all graded responses. The binding of a neurotransmitter causes the membrane to depolarize (or hyperpolarize) locally, this disturbance will spread

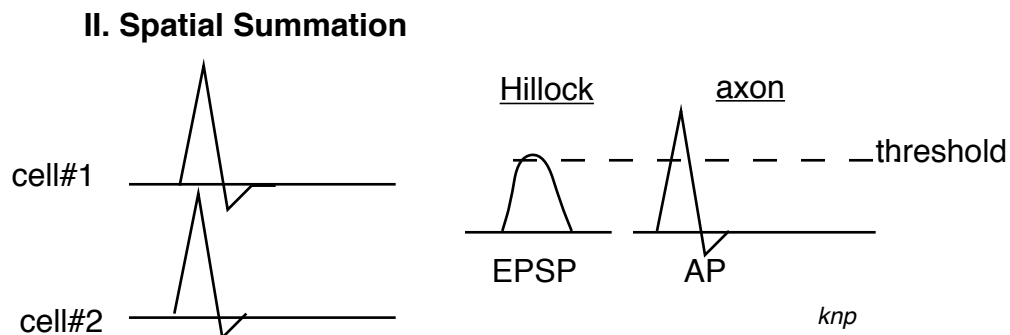
electrotonically. The only way to go is towards the soma and axon. **Think of the moving graded potential as being like a wave on a pond that spreads outward from where a rock hit. Keep one problem with this analogy in mind -- these "waves" will only be above the mean water level (i.e., let's say depolarized 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 produced³ at a sufficiently large depolarization to 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 below, the EPSP that results from cell #1's release of NT is sub-threshold -- there is no AP:



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 postsynaptic potential come together at the same time on the hillock. If the voltages add enough to exceed threshold, an AP is triggered (see figure):

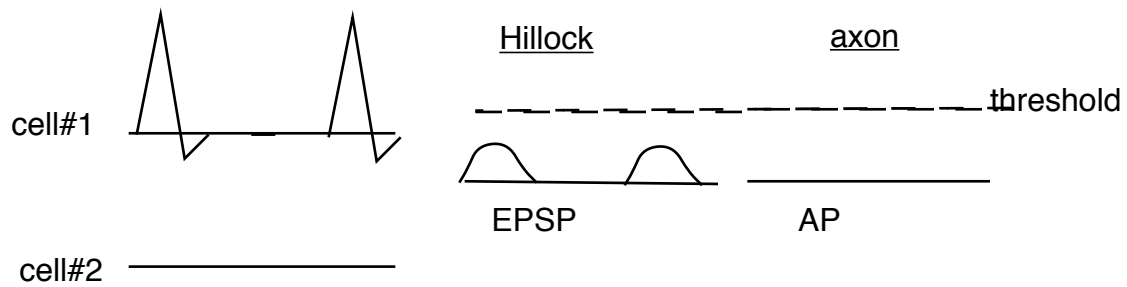


2. **TEMPORAL SUMMATION**: occurs where two or more potentials that originated at slightly different times come together and sum at the hillock. The figure on the next page shows such a process where cell #1 fires. In the top diagram, the APs are far enough apart that the graded potentials do not add and neither can reach threshold and fire the neuron. In the second

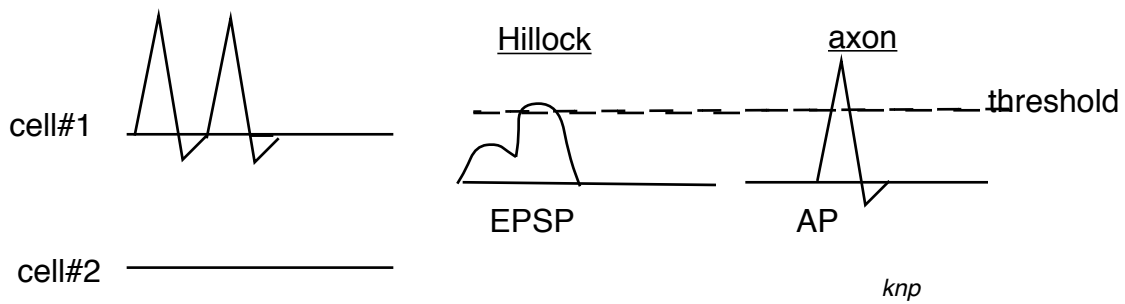
³ On a nerve called the **axon hillock** the place where the axon emerges from the soma

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

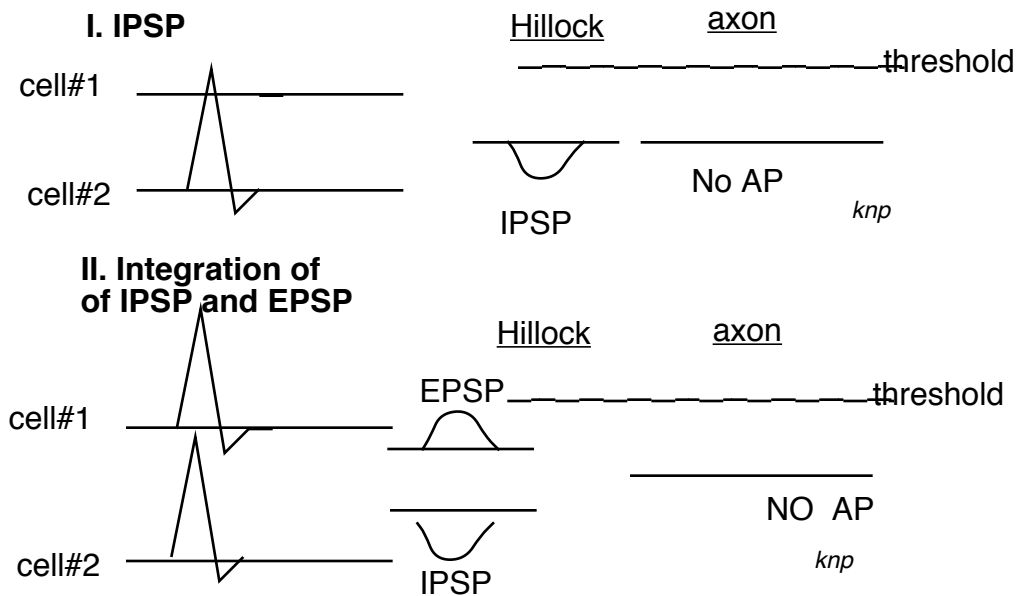
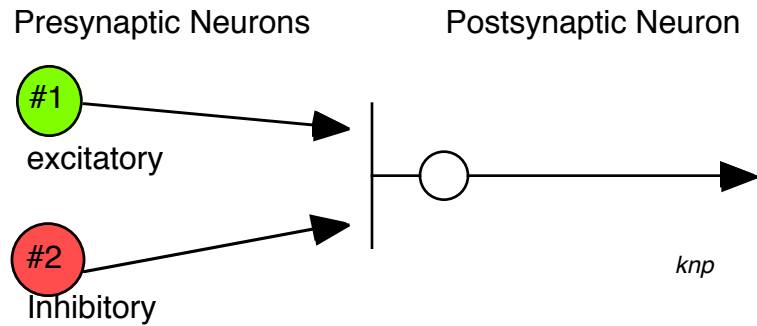


IIIb. Temporal Summation



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.

C. Norepinephrine (NE) and Neurotransmission: As a contrast in how neurotransmitters work, the autonomic NS transmitter (next set of notes) Norepinephrine acts by stimulating the production of cyclic AMP instead of directly operating some ion channel as in ACh. The cyclic AMP can have diverse effects depending on the target cell, one of the effects can be increased entry of ions into the cell, especially Ca^{++} . Also the transmitter is not degraded at the receptor but is instead actively taken into either the pre or postsynaptic cell and then either recycled or degraded.