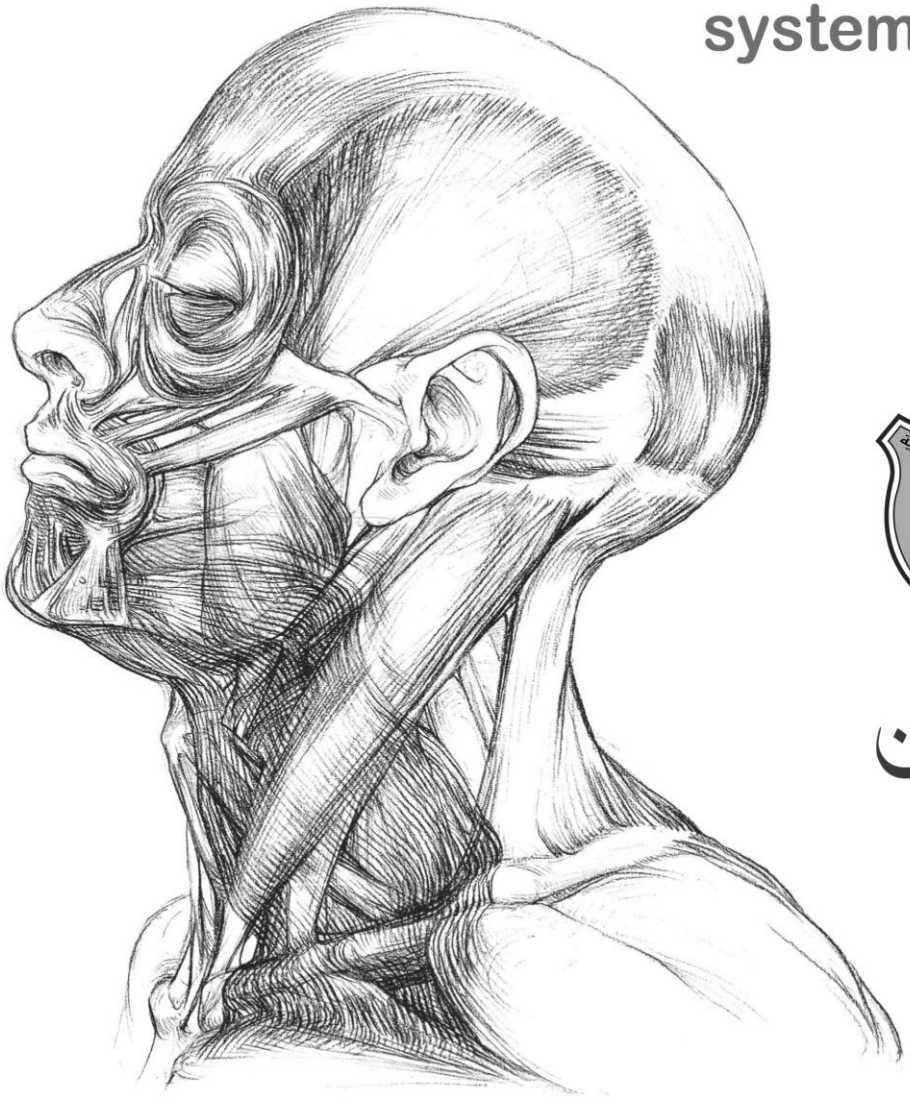
The skin & Muscloskeletal system



PHYSIOLOGY

SLIDES ☐
SHEET ■
LECTURE # 1

DOCTOR: Mohammad Khatatbeh
DONE BY: Abed Alshraideh
CORRECTION: Abdel-Mu'ez Siyam

Membrane and Action potentials:

***NOTE**: At the end of the sheet, there are some details NOT mentioned in the handout. Please have a look…*

*This is going to be a review for what we took last year; hence this should be somewhat easy.

-Cell membranes are separating two compartments (extra and intracellular compartments) and we have different compositions in those two compartments.

-Excitable membranes establish what we call a resting membrane potential.

-Resting membrane potential is established by the HIGH permeability for the potassium ion (K+) and some permeability for the sodium ion (Na+), in addition to the Na/K pump. And by that we're establishing a resting membrane potential which is very close to the equilibrium potential for the potassium ion.

- How can we calculate the equilibrium potential for a specific ion?

Using the Nernest equation

$$E_{ion} = \frac{61}{z} \log \frac{[ion]_{out}}{[ion]_{in}}$$

- Let's take the K+ and Na+ ions for example:

For (k+):

$$E = 61.5 \log \frac{[K^+]_{outside}}{[K^+]_{inside}}$$

$E_{(k+)}$ = -94mV

For (Na+):

$$V_{Na} = \frac{RT}{(+1)F} \ln \frac{[Na^+]_o}{[Na^+]_i}$$

$E_{(Na+)}$= +61mV

So if the equilibrium potential for K+ is -94mV, and

the equilibrium potential for Na+ is +61mV , while the membrane equilibrium potential (Resting membrane potential) is -90mV. What does this mean?

It basically means that the K+ permeability is way much more than the Na+ permeability (Around a Hundred times more!)

-According to what was mentioned above we can deduce that any changes in the K+ permeability or the Na+ permeability will lead to changes in membrane potentials.

Changes in K+ and/or Na+ permeability (mainly Na+)

Changes in membrane potential

Action Potentials:

Action potential and the role of Na+ channels:

Action potentials are generated by a stimulus causing the influx of Na+ ions creating what we call "Depolarization" (The negativity of the resting membrane potential decreases.... it becomes less negative)

How do these ions enter the cell?

By Na+ gated channels which are two types:

1- Chemical gated Na+ channels

2- Voltage gated Na+ channels

Na+ ions first influx is through the **chemical** gated channels until a certain point is reached where the membrane potential reaches a specific potential *(Less than -90mV for sure because we're in the depolarization stage...the membrane's potential becomes less negative)* called the "**Threshold**".

Note: Na influx could also occur due to ionic currents like in the propagation of the action potential along the membrane, and this helps in reaching the threshold.

After reaching the threshold the voltage gated channels are activated causing even more depolarization but this time it's much faster (This stage is called **the firing stage**).

Action potential and K+ channels:

After depolarization (firing), the membrane reaches a potential of around +30 then the Na+ voltage gated channels close resulting in the end of the firing stage and the beginning of a new stage called the "**Repolarization stage**" also known as the falling stage.

In this stage the K+ channels are opened causing the membrane's potential to become more negative heading back to the resting membrane potential. However, it goes further

than the resting membrane potential by a little bit (more negative than the resting membrane potential) due to the excess in K+ efflux outside of the cell. This is known as **positive afterpotential (after hyperpolarization).**

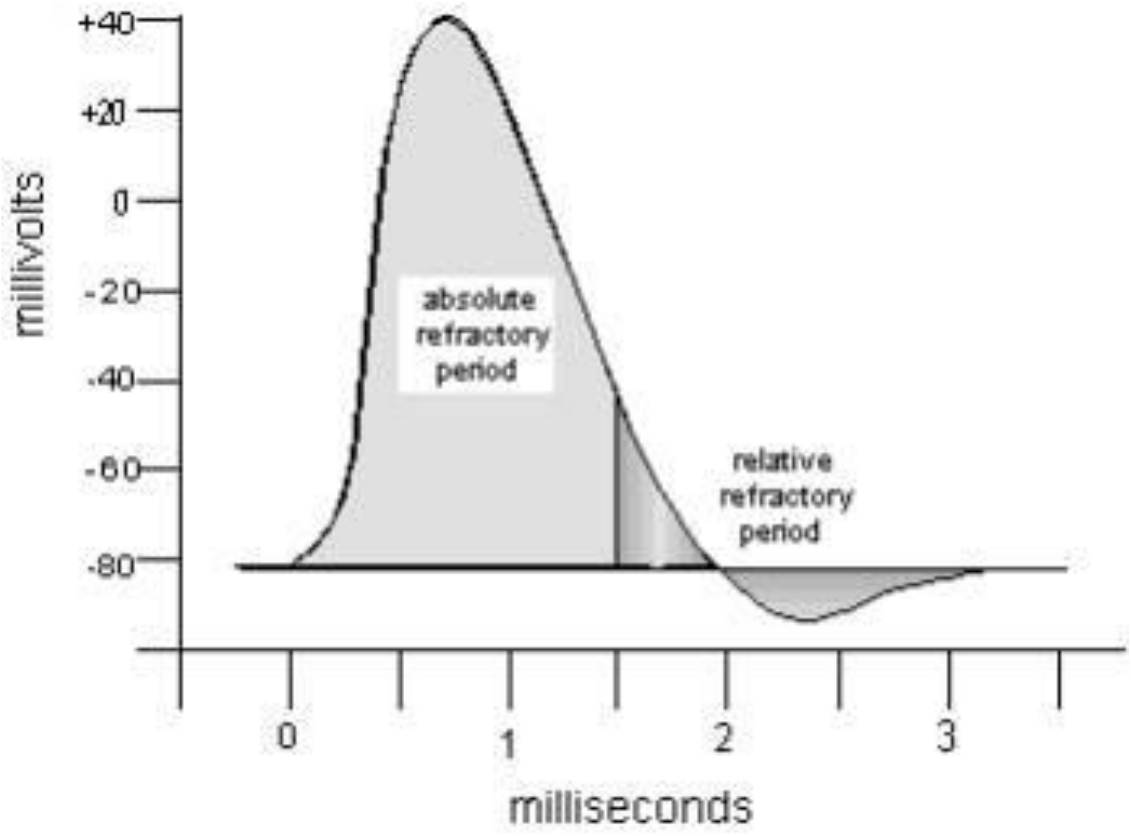
Refractory periods of an action potential:

A period of time during which the membrane is not responding to any stimulus affecting it.

There are two types of refractory periods:

1- Absolute refractory period: There is no response even if a stronger stimulus is applied *(From the firing stage to the first third of the repolarization stage)*

2- Relative refractory period: Applying a stronger stimulus would cause another action potential to occur *(from the second third of repolarization to the end of the action potential)*



The periods depend on the activity of Na+ channels. These channels pass through three states during action potential. During resting potential, Na+ channels are **closed but capable for opening** when stimulated. During the raising phase (firing), almost all Na+ channels are **opened** and any other stimulus (even stronger one) will not cause activation of more Na+ channels and so this is called the Absolute refractory period.

In the third state, when voltage dependent Na+ channels become closed after the membrane potential has reached positive values. At this state Na+ channels are not capable for

opening. During all the falling phase of an action potential, these channels remain **closed and not capable for opening**. They can pass to the first state (closed and capable for opening) when the membrane potential returns to its normal level or to a more negative potential than resting potential. During this period, the membrane is in relative refractory period. This means that a stronger (suprathreshold) stimulus may activate the closed channels that are not capable for opening by normal stimulation. In addition to the role of voltage gated Na+ channels in establishing the relative refractory period, the presence of widely opened K+ channels during falling phase, which cause excess flow of positive charges to the outside, may also play a role by opposing stimulating signals.

Why are the refractory periods so important?

-The presence of refractory periods during action potential is very important in the conduction of impulse. The refractory periods ensures the **one-way (unidirectional)** propagation of action potential. Once an area has developed an action potential, the previous region is still under refractory period (unresponsive area). This area will not develop another action potential ,but the following area that is at resting potential is capable of initiating an action potential.

Na+ -K+ pump and action potential:

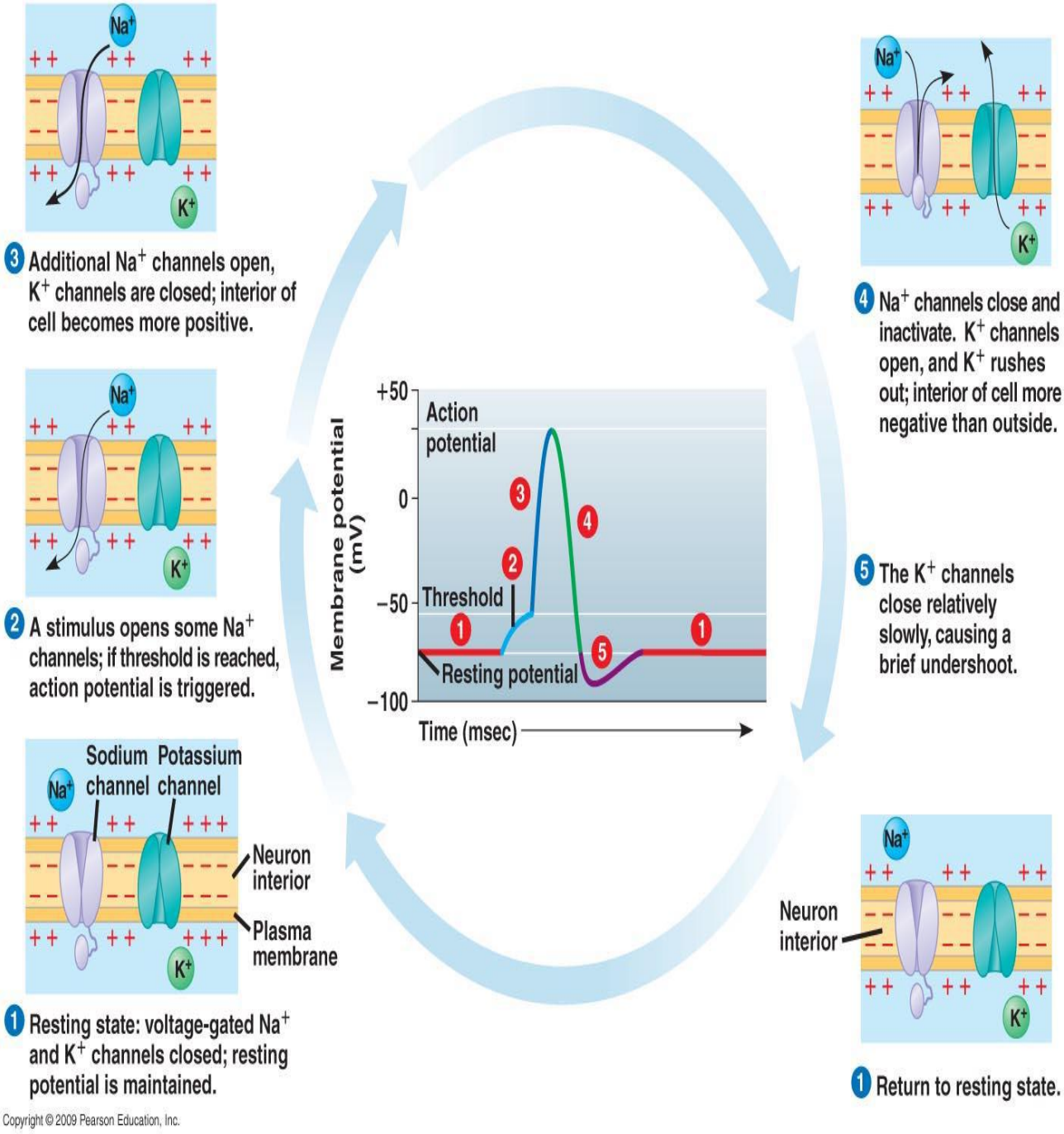
This pump has **no** role in the electrical activity that is taking place during action potential. But it plays an important role in

restoring ionic composition that has been altered during action potential. This role is important in maintaining the ionic composition of the intra-and the extra-cellular fluids.

Action potential and Ca++:

As we discussed before, the raising phase of an action potential results by fast activation of Na+ channels. These are called *fast channels*. In some excitable cells, like in the cardiac muscle and uterine muscle, cells are equipped with another type of channels known as *slow* Na+ – Ca++ *channels*. These channels are activated at slower rate than Na+ channels. The slow and prolonged opening of slow channels will cause mainly Ca++ to enter the cell and prevents the rapid fall induced by activation of K+ channels, and the membrane potential is maintained for a while then the potential falls to its resting level. This is known as **plateau** in action potential. The presence of plateau in this type of cells is important in prolonging the time of an action potential, giving more time for the cell to be able to respond to another stimulus, because the cell remains for a longer time in the **refractory period**.

A quick summary to what we went through so far:

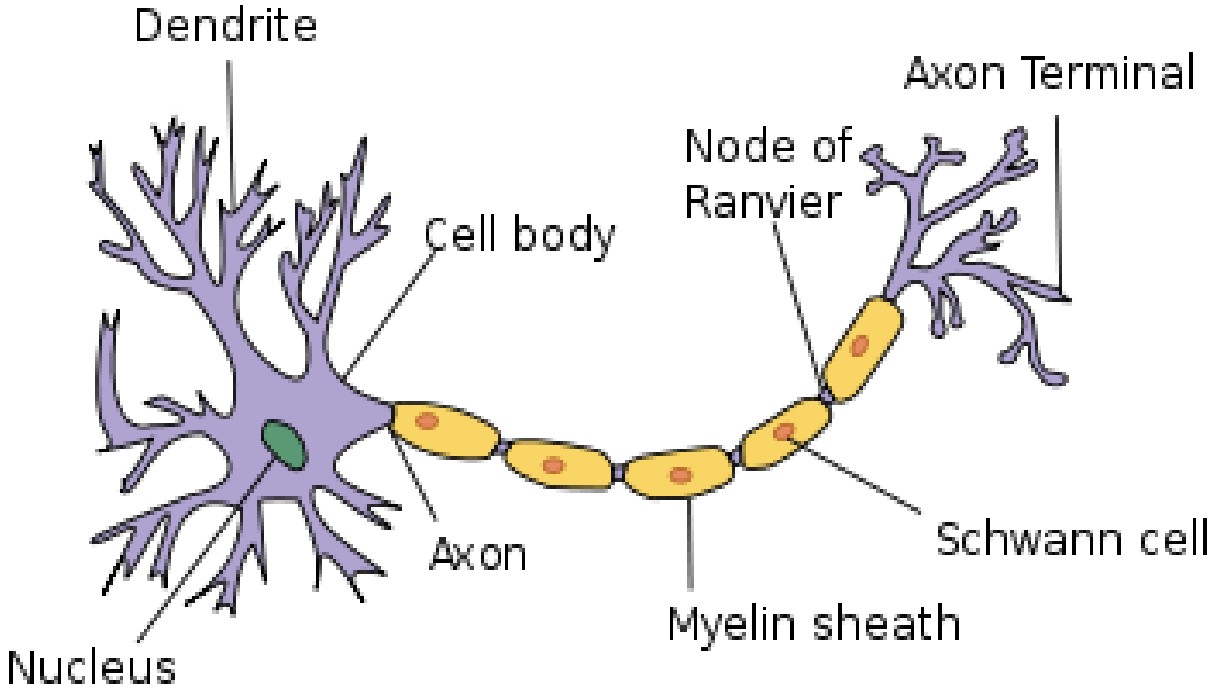


Nerve Cells (Neurons)

The nervous system is formed of neurons and supportive cells. A neuron, typically consists of 3 basics parts: **cell body, dendrites, and axon** (or nerve fibre). Dendrites are short projections from the cell body, which receive inputs from neighbouring neurons. Axon is a long tubular like structure which projects from a cone-shaped elevation in the cell body

known as **axon hillock** (means small hill). The impulse begins at the junction between axon hillock and the initial segment of the axon. Axon ends into fine processes called axon terminals. Some of these terminals end with a bulb-shape structure called **synaptic end bulb (synaptic knob)**, where neurotransmitters are stored in vesicles and are ready to be released.

Neurons can be classified according to several criteria for example their shape, function, neurotransmitter they release, myelination, location…etc.



Supportive cells and function (NEUROGLIA):

Many types of supportive cells around neurons have been described (at least 6). Microglia, Astrtocytes, oligodendrogliocytes have been shown around neurons from the CNS. And glial cells which are similar to astrocytes from the CNS have been described in the neural network of the GI tract.
These cells perform the following functions:
*Maintenance of neural environment.
-uptake of K+ and neurotransmitters from the interstitial fluid around the neurons.
*Synthesize and release neurotrophic factors maintain the survival and protection of neurons
* Other specialized supportive cells are responsible for myelination of axons.
In the CNS these cells are called oligodendrogliocytes.
In the peripheral nervous system, these cells are known as **Schwan cells**. These cells wrap around axon segments and secrete myelin sheath (a protein lipid complex that insulates the nerve fiber). There are gaps in myelin sheaths known as **Nodes of Ranvier**, which appear at intervals along axon. These gaps are used for the transmission of impulse along myelinated nerve fiber.

TRANSMISSION OF ACTION POTENTIAL ALONG NERVE FIBERS:

Motor neurons that innervate muscles have:

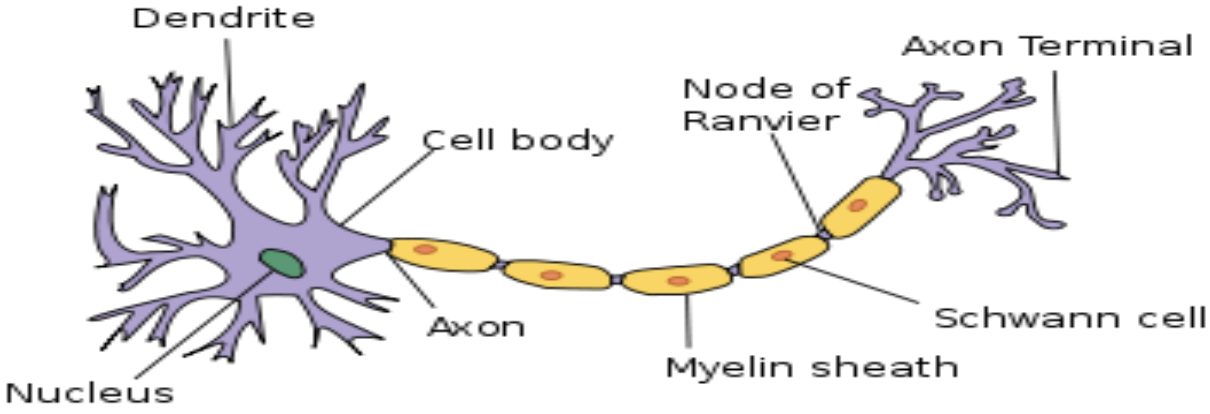
1-Cell bodies located in the spinal cord

2- Long axons that project outside the spinal cord to directly or indirectly control effector organs, mainly **muscles** and **glands.**

Those neurons could be **myelinated** or **unmyelinated** meaning they have myelin sheaths or lack them respectively.

Myelinated Neurons have myelin sheaths but also have some places in the axon in which they aren't myelinated and exposed to the extracellular fluid called Nodes of Ranvier.

Look at this picture to make things easier for you:



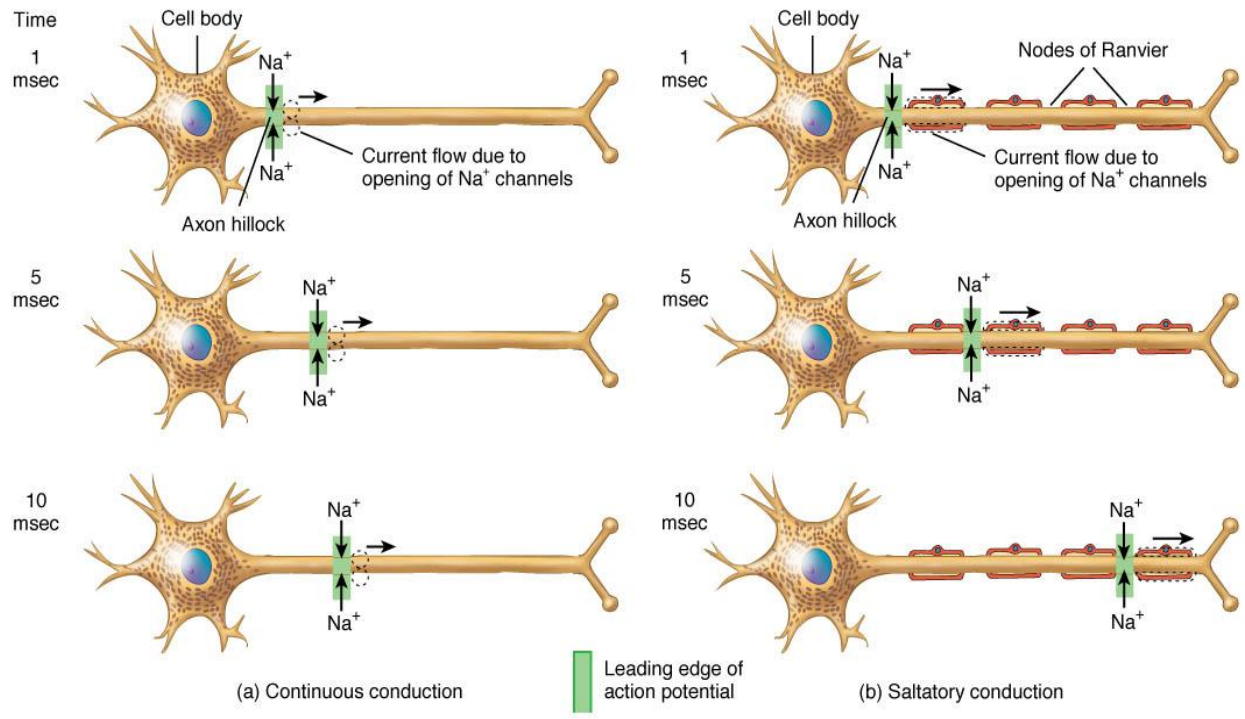
In **Myelinated Neurons** the action potential travels from one Node of Ranvier to the next jumping over the myelin sheaths *(This way of transduction is fast....50 times faster than unmyelinated neurons because it's skipping myelin sheaths)*

This type of transduction is called "**Saltatory conduction**".

In **Unmyelinated Neurons** the action potential travels continuously through the long axon that doesn't have myelin sheaths.

This type of transduction is called "**Continuous conduction**"

Here's a picture to demonstrate how fast those two ways are:



SYNAPSES AND INTEGRATION OF RESPONSES:

Synapses:

Neurons may terminate at one of three structures: a neuron, a muscle, or a gland. The junction between 2 neurons is known as a synapse. The first neuron ends with end bulb (**synaptic**

knob), where neurotransmitters are stored in vesicles and ready for their release. The membrane of the synaptic knob is known as a **presynaptic membrane**. When secretory vesicles fuse with the presynaptic membrane, they release their content into a small space between two membranes known as the **synaptic cleft**. The released transmitters act on the second neurons by binding to their receptors at the second membrane, which is called the **postsynaptic membrane** (**subsynaptic membrane**).

Synapses operate in one direction. Transmitting signals from one neuron to the adjacent neuron. When the impulse from the presynaptic neuron reaches the synaptic knob, this will cause activation of voltage dependent Ca++ channels. This will result in Ca++ diffusion into the synaptic knob. The increase in Ca++ concentration inside axon terminal will trigger the release of neurotransmitter from vesicles into the synaptic cleft by a process of exocytosis. Inactivation of the synaptic knob by inhibitory inputs that may synapse with the membrane at the nerve terminal may induce inhibition of the release of transmitter. This inhibition that appears at this site reduces the effectiveness of transmission in the synapse. This type of inhibition is known as presynaptic inhibition.

Once released, neurotransmitters bind to their receptor at the postsynaptic membrane. According to the transmitter – receptor combination, this will induce either a decrease in membrane potential (depolarization) or an increase in membrane potential (hyperpolarization). When there is a decrease in membrane potential, the developed postsynaptic

potential is called **EPSPs** (**E**xcitatory **P**ost **S**ynaptic **P**otentials), while the increase in membrane potential is called **IPSPs** (**I**nhibitory **P**ost **S**ynaptic **P**otentials).
After inducing the appropriate response at the postsynaptic membrane, the transmitter is inactivated or removed, leaving the postsynaptic membrane ready to receive additional messages from the same presynaptic membrane. The inactivation of the transmitters takes place by postsynaptic membrane bound enzymes. An example of these enzymes is *acetylcholine esterase*, which destroys acetylcholine (Ach) into acetyl and choline molecules, which then are transported back to the synaptic knob, where they combine again to form new Ach molecules. Some types of transmitters are transported back, without inactivation, into synaptic knob. Conditions that alter the activity of destroying enzymes, uptake of transmitters by nerve terminal, or induce release of high concentration of transmitters (presynaptic facilitation) alter the activity of the synapse by prolonging the activation of receptors at the postsynaptic (subsynaptic) membrane. In addition to that, some drugs may combine with receptors and prevent binding of a transmitter to its receptor. These drugs are known as **blockers**. An example of these is hexamethonium, which can bind to acetylcholine (Ach) receptor at postsynaptic membrane and prevents Ach from binding. This will inhibit transmission induced by Ach neurons.

The EPSPs are not action potentials. They are small depolarization (subthreshold potential) that can be induced by activation of few Na+ channels.

The IPSPs are usually induced by the activation of K+ channels. Which results in the efflux of K+ and change in the membrane potential to a more negative potential. Some transmitters activates Cl- channels, the activation of these channels will not induce hyperpolarization (during rest, neural cell is near the Ecl, and the opening of Cl- channels will not induce inward diffusion of Cl-). But this activation is inhibitory on neural activity. This inhibition is achieved by holding the membrane at its resting potential and preventing depolarization.

The time it takes for a signal from the first neuron to induce changes in the membrane potential of the second neuron is known as **synaptic delay**.

Integration of responses at postsynaptic membrane:

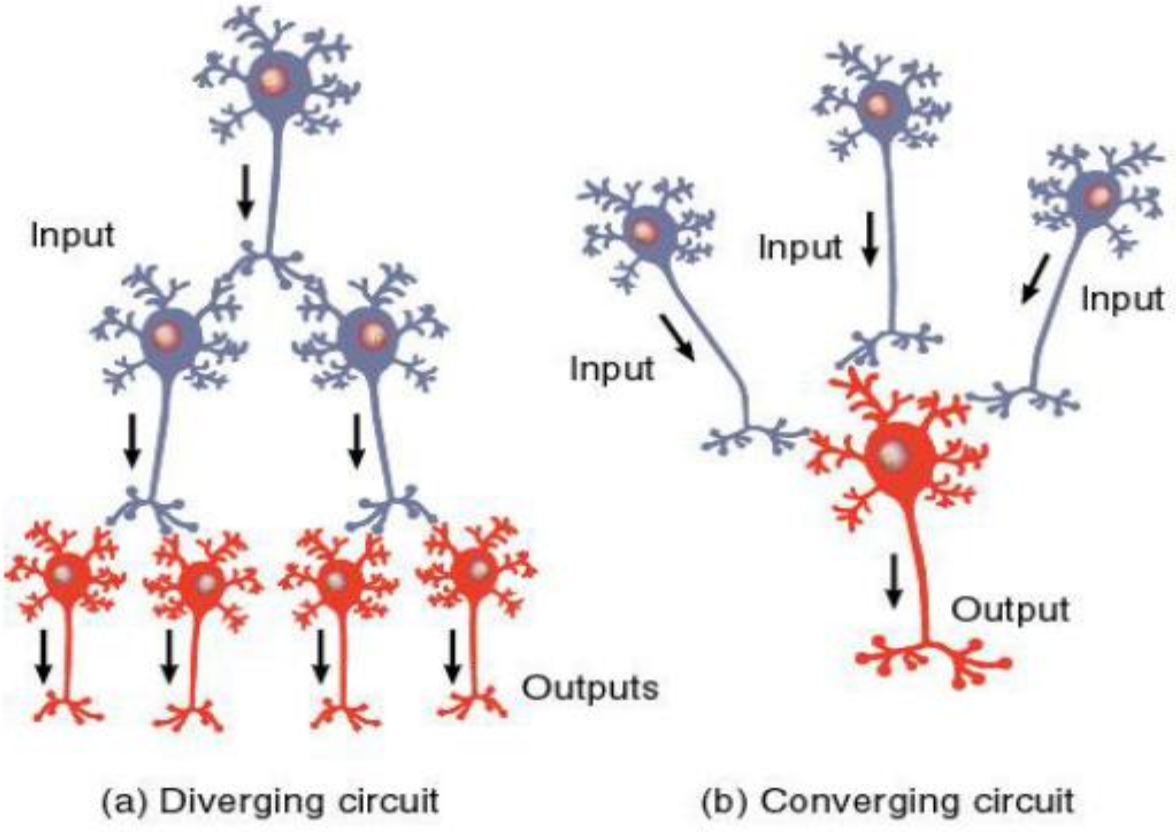
Usually, the complexity of neural network connections permit synapsing of many axonal terminals from different neurons to one neural cell body (called **convergence**), and branching of one nerve fiber to many terminals that synapse to different neurons (**divergence**). This complexity results in converting the signal from one neuron to many postsynaptic neurons in the case of divergence, and many inputs from presynaptic neurons can be received by single postsynaptic neuron in the case of convergence.

As mentioned before, one stimulus may induce depolarization or hyperpolarization at the postsynaptic membrane. The induced depolarization is not an action potential, but it is a subthreshold potential. The action potential will develop only when the threshold is achieved. In neural network, to have

subthreshold potentials eliciting an action potential, **summation** (two depolarizations can sum to elicit a higher depolarization) must take place between responses at the postsynaptic membrane.

Two types of summation are known at the postsynaptic membrane. **Spatial Summation** appears when 2 or more responses from 2 or more different neurons have appeared simultaneously (at the same time) at the same site of postsynaptic membrane, which result in summing of these responses into a final response. This summation can take place between 2 or more IPSPs to elicit more hyperpolarization, two or more EPSPs to elicit more depolarization in the membrane, or between excitatory and inhibitory potentials which results in cancellation of potentials and induction of postsynaptic inhibition.

The second type of summation is called **Temporal Summation** which appears when 2 or more postsynaptic potentials, which were elicited by **one** presynaptic neuron at different times, sum to induce more depolarization in the membrane potential. In this case, the repetitive excitation of postsynaptic membrane from a single input induces a higher depolarization that may elicit an action potential at the postsynaptic membrane.



Recordings of action potential:

Recording of **Monophasic action potential** is by placing one electrode inside the cell and the other electrode outside the cell. While a different configuration of an action potential can be obtained by placing the two electrodes outside the cell membrane. The later recording is known as **biphasic action potential**. Two waves are obtained in the recording of biphasic action potential, the first represents depolarization, and the second is in the reverse direction of the first and represents repolarization.

Note: At the level of the **spinal cord**, we have many terminals synapsing with motor neurons (which innervate skeletal muscles). Normally, most of the input is inhibitory to the motor neuron –we have some excitatory input but mainly its inhibitory. Think about it this way: Neurons are synapsing with the motor neuron so their membranes are the presynaptic membranes, and they release inhibitory neurotransmitters (mainly) to bind to surface receptors found on the postsynaptic membrane (motor neuron membrane). This inhibition makes the neuron membrane less excitable and prevents involuntary contractions in skeletal muscles. If a patient has **hypocalcemia**→since the release of the inhibitory neurotransmitters is calcium-dependent, it will be severely compromised. This will cause the motor neuron membrane to have less inhibition and thus, it becomes more excitable. These patients present with unpleasant **muscle contractions**.