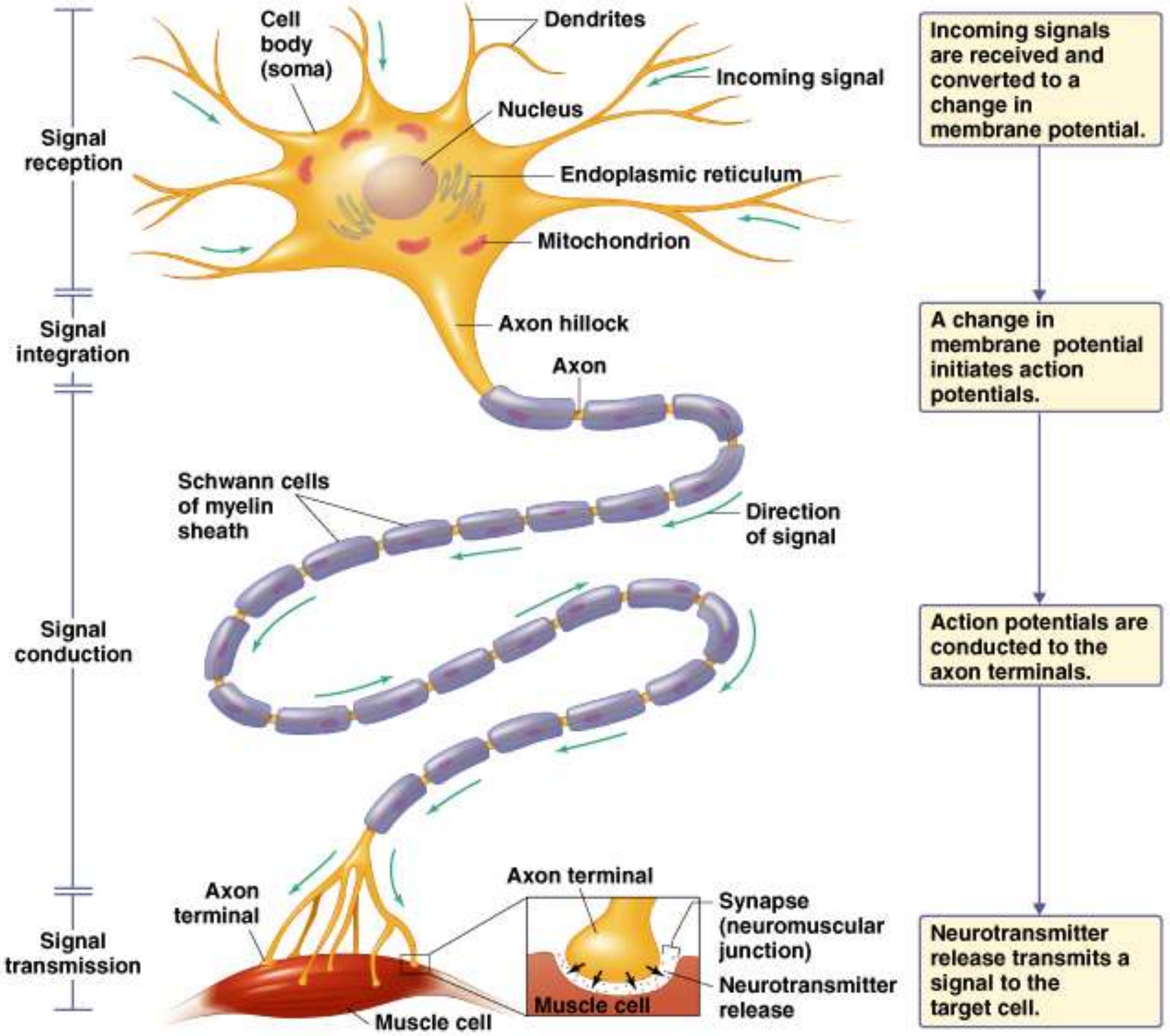
Excitable Tissue

- The nervous system coordinates the activities of many other organ systems. The nervous system
- activates muscles for movement,
- controls the secretion of hormones from glands,
- regulates the rate and depth of breathing, and
- is involved in modulating and regulating a multitude of other physiological processes.

- To perform these functions, it relies on neurons, which are designed for the rapid transmission of information from one cell to another by conducting electrical impulses and secreting chemical neurotransmitters.
- The electrical impulses travel along the length of nerve fiber processes to their terminals
- Here, they initiate a series of events that cause the release of chemical neurotransmitters.
- Release of neurotransmitters occurs at sites of synaptic contact between two nerve cells.

- Released neurotransmitters bind with their receptors on the postsynaptic cell membrane
- Activation of receptors either excites or inhibits the postsynaptic neuron.
- The propagation of action potentials,
- The release of neurotransmitters, and
- The activation of receptors constitute the means whereby nerve cells communicate and transmit information to one another and to non-neuronal tissues.

- Neurons communicate by a combination of electrical and chemical signaling.
- Generally, information is integrated and transmitted along the processes of a single neuron electrically and then transmitted to a target cell chemically.
- The chemical signal then initiates an electrical change in the target cell.
- Electrical signals that depend on the passive properties of the neuronal cell membrane spread electrotonically over short distances.
- These potentials are initiated by local current flow and decay with distance from their site of initiation.



Signal reception
Signal integration
Signal conduction
Signal transmission
Cell body (soma)
Dendrites
Incoming signal
Nucleus
Endoplasmic reticulum
Mitochondrion
Axon hillock
Axon
Schwann cells of myelin sheath
Direction of signal
Axon terminal
Axon terminal
Synapse (neuromuscular junction)
Neurotransmitter release
Muscle cell
Muscle cell
Incoming signals are received and converted to a change in membrane potential.
A change in membrane potential initiates action potentials.
Action potentials are conducted to the axon terminals.
Neurotransmitter release transmits a signal to the target cell.

- Alternatively, an action potential is an electrical signal that propagates over a long distance without a change in amplitude.
- Action potentials depend on a regenerative wave of channel openings and closings in the membrane

- The shape of a nerve cell is highly specialized for reception and transmission of information.
- One region of the neuron is designed to receive and process incoming information; another is designed to conduct and transmit information to other cells.
- The type of information that is processed and transmitted by a neuron depends on its location in the nervous system.
- For example:
- Nerve cells associated with visual pathways convey information about the external environment, such as light and dark, to the brain;

- Neurons associated with motor pathways convey information to control the contraction and relaxation of muscles for walking.

- Regardless of the type of information transmitted by neurons, they transduce and transmit this information via similar mechanisms.
- The mechanisms depend mostly on the specialized structures of the neuron and the electrical properties of their membranes.
- Emerging from the soma (cell body) of a neuron are processes called dendrites and axons

- Many neurons in the central nervous system (CNS) also have knob-like structures called dendritic spines that extend from the dendrites.
- The dendritic spines, dendrites, and soma receive information from other nerve cells.
- The axon conducts and transmits information and may also receive information.
- Some axons are coated with myelin, a lipid structure formed by glial cells (oligodendrocytes in the CNS or Schwann cells in the peripheral nervous system, the PNS).
- Regular intermittent gaps in the myelin sheath are called nodes of Ranvier.

- The speed with which an axon conducts information is directly proportional to the size of the axon and the thickness of the myelin sheath.
- The end of the axon, the axon terminal, contains small vesicles packed with neurotransmitter molecules.

- The site of contact between a neuron and its target cell is called a synapse.
- When a neuron is activated, an action potential is generated in the axon hillock (or initial segment) and conducted along the axon.
- The action potential causes the release of a neurotransmitter from the terminal.
- These neurotransmitter molecules bind to receptors located on target cells.

- The binding of a NT to its receptor typically causes a flow of ions across the membrane of the postsynaptic cell.
- This temporary redistribution of ionic charge can lead to the generation of an action potential, which itself is mediated by the flow of specific ions across the membrane.
- These electrical charges, critical for the transmission of information, are the result of ions moving through ion channels in the plasma membrane

Channels Allow Ions to Flow Through the Nerve Cell Membrane

- Ions can flow across the nerve cell membrane through three types of ion channels:
- nongated (leakage), ligand-gated, and voltage-gated
- Non-gated ion channels are always open.
- They are responsible for the influx of Na and efflux of K when the neuron is in its resting state.
- Ligand-gated ion channels are directly or indirectly activated by chemical neurotransmitters binding to membrane receptors.
- In this type of channel, the receptor itself forms part of the ion channel or may be coupled to the channel via a G protein and a 2^{nd} messenger.

- When chemical transmitters bind to their receptors, the associated ion channels can either open or close to permit or block the movement of specific ions across the cell membrane.
- Voltage-gated ion channels are sensitive to the voltage difference across the membrane.
- In their initial resting state, these channels are typically closed; they open when a critical voltage level is reached

- Each type of ion channel has a unique distribution on the nerve cell membrane.
- Non-gated ion channels, important for the establishment of the resting membrane potential, are found throughout the neuron.
- Ligand-gated channels, located at sites of synaptic contact, are found predominantly on dendritic spines, dendrites, and somata.
- Voltage-gated channels, required for the initiation and propagation of action potentials or for neurotransmitter release, are found predominantly on axons and axon terminals

- Next slide gives the approximate concentrations of important electrolytes and other substances in the *extracellular fluid* and *intracellular fluid*
- Note that ECF contains a lot of Na^+ small amount of K^+
- Opposite is true of the intracellular fluid lots of K^+ and less Na^+

Concentration of important ions

ECF

Cations:

Na$^+$ (142 mmol/L)

K$^+$ (4.2)

Mg^{2+} (0.8)

Anions:

Cl$^-$ (108)

HCO_3^- (24)

Nutrients:

O_2, glucose, fatty acids, & amino acids.

Wastes:

CO_2, Urea, uric acid, excess water, & ions.

ICF

Cations:

Na$^+$ (14)

K$^+$ (140)

Mg^{2+} (20)

Anions:

Cl$^-$ (4)

HCO_3^- (10)

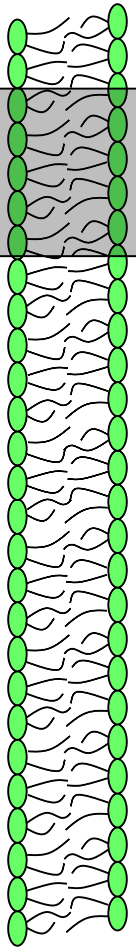
Phosphate ions

Nutrients:

High concentrations of proteins.

- ECF also has lots Cl^- ions whereas ICF has lots of Phosphates and proteins.
- Differences are extremely important to the life of the cell.

	inside (in mM)	*outside* (in mM)
Na^+	14	142
K^+	140	4
Mg^{2+}	0.5	1-2
Ca^{2+}	10^{-4}	1-2
H^+	(pH 7.2)	(pH 7.4)
HCO_3^-	10	28
Cl^-	5-15	108
SO_4^{2-}	2	1
PO_3^-	75	4
protein	40	5

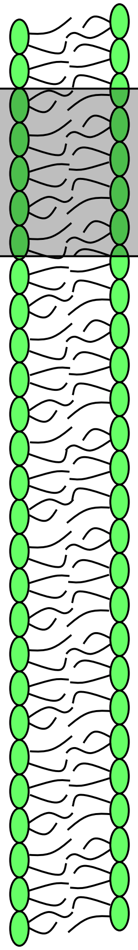


“Sidedness” of the membrane and some reasons why

Different permeability
Pumps
Protein channels

Remember to ask:
  Is there a gradient?
  Can it diffuse?
  If allowed to diffuse, which way would it go?

	inside (in mM)	*outside* (in mM)
Na^+	14	142
K^+	140	4
Mg^{2+}	0.5	1.2
Ca^{2+}	10^{-4}	1.2
H^+	(pH 7.2)	(pH 7.4)
HCO_3^-	10	28
Cl^-	5	108
SO_4^{2-}	2	1
PO_3^-	75	4
protein	40	5



Membrane potential caused by Diffusion

- K^+ conc'n is high inside a nerve fiber membrane and low outside
- Assume that membrane only permeable to K^+ only but no other ions
- Due to high conc'n gradient of K^+ from inside to outside, there is a strong tendency for extra no. of K^+ ions to diffuse outwards through the membrane
- As they do so, they carry +ve electrical charge to the outside , creating electropositivity to the outside and electronegativity to the inside because of the –ve anions that remain behind and do not diffuse with the K^+

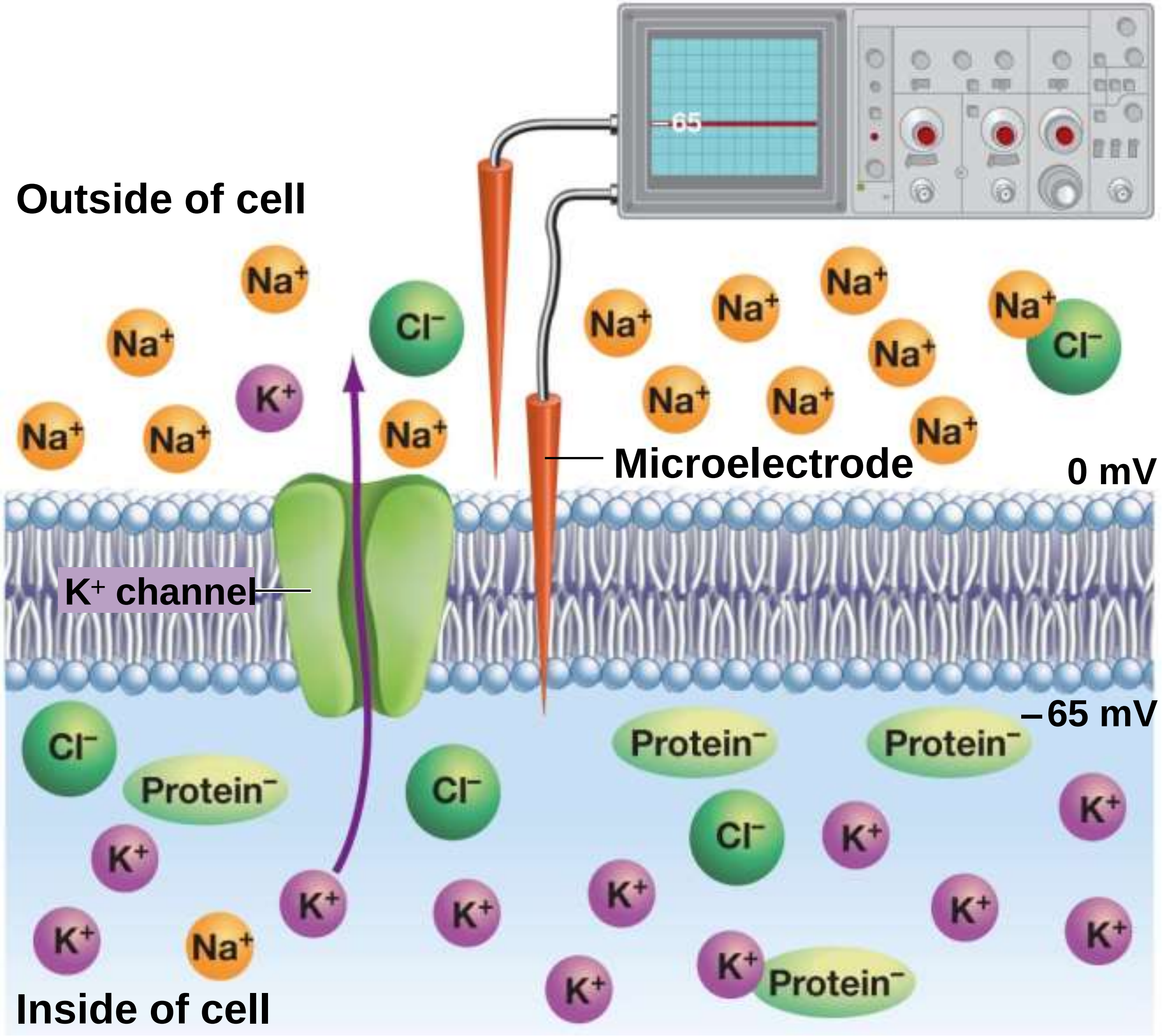
- As K leaves the cell, it takes a positive charge outside with it, so the inside is more negative.
- However, as the inside of the cell is becoming more negative, the outside of the cell is becoming more positive, the positive charges will want to flow back inside of the cell since they are attracted to the negative charges.
- Within a millisecond or so, the potential difference between the inside and outside, called the diffusion potential, becomes great enough to block further net potassium diffusion to the exterior, despite the high potassium ion concentration gradient.

- This is electrical potential that counters Net diffusion of K.
- In the normal mammalian nerve fiber, the potential difference required is about 94 millivolts, with negativity inside the fiber membrane.
- The electrical potential that counters net diffusion of K^+ is called the K^+ equilibrium potential (E_K).
- The equilibrium potential of K^+ is minus 94 mV
- So, if the membrane were permeable only to K+, Vm would be -94 mV (cell death from equilibrium)

Increasing [K+] outside the neuron

Equilibrium!

Increasingly negative charge inside the neuron

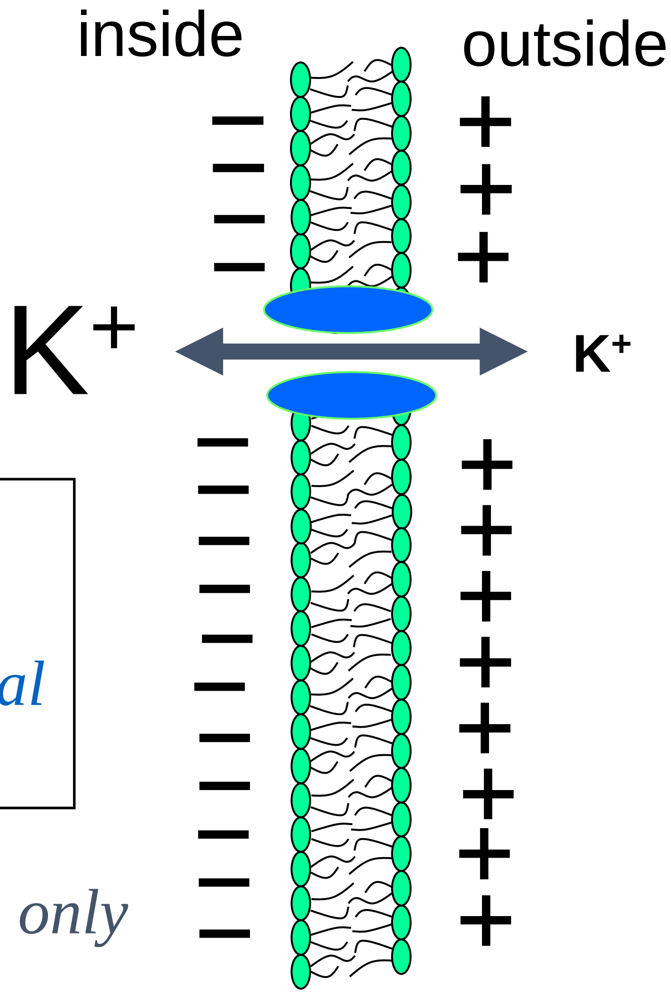


- The diffusion potential level across a membrane that exactly opposes the net diffusion of a particular ion through the membrane is called the Nernst potential for that ion.

$$\text{EMF (millivolts)} = \pm 61 \log \frac{\text{Concentration inside}}{\text{Concentration outside}}$$

Simplest Case Scenario:

If a membrane were permeable to only K^+ then…



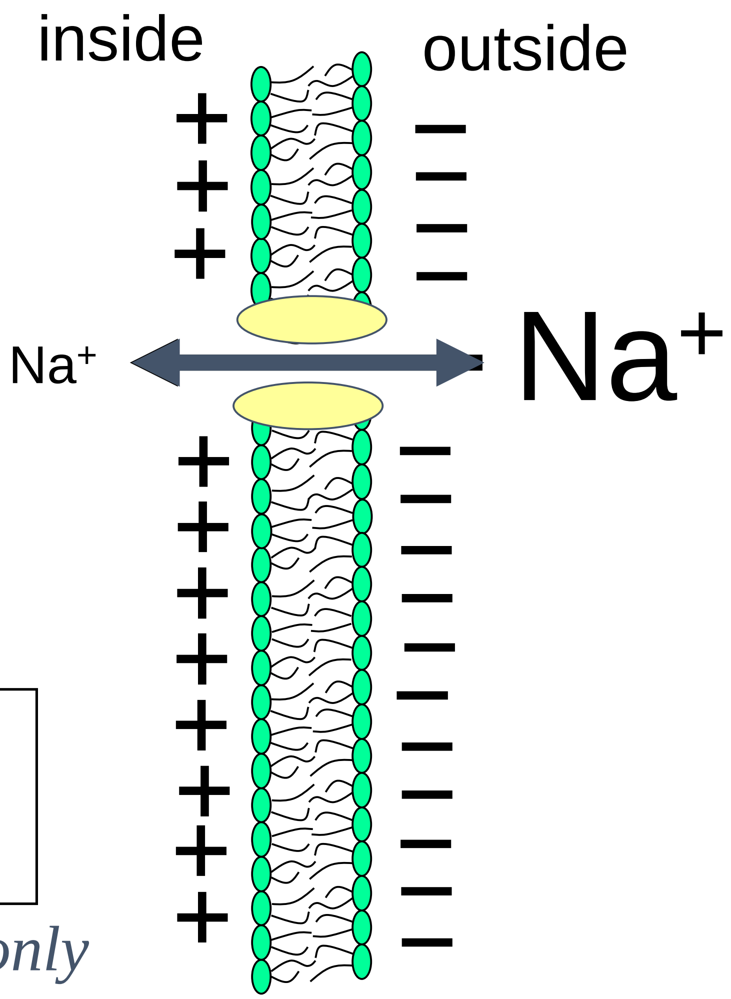
The electrical potential that counters net diffusion of K^+ is called the K^+ equilibrium potential (E_K).

So, if the membrane were permeable only to K+, Vm would be -94 mV

- In case membrane only permeable to Na^+, then the reverse would occur with the Na^+ moving to the inside due to conc'n gradient carrying +ve charges to the inside hence leaving the outside more electronegative and the inside more electropositive.
- Again the membrane potential rises high within milliseconds to block further diffusion of Na^+ ions to the interior.
- The potential is about 61 mv with positive inside fiber.

Simplest Case Scenario: 21st

If a membrane were permeable to only Na^+ then…



Na^+ would diffuse down its concentration gradient until potential across the membrane countered diffusion.

The electrical potential that counters net diffusion of Na^+ is called the Na^+ equilibrium potential (E_{Na}).

So, if the membrane were permeable only to Na^+, Vm would be +61 mV

- When a membrane is permeable to several different ions, the diffusion potential that develops depends on three factors:
- (1) the polarity of the electrical charge of each ion,
- (2) the permeability of the membrane (P) to each ion,
- (3) the concentrations (C) of the respective ions on the inside (i) and outside (o) of the membrane.
- Thus, the following formula, called the Goldman-Hodgkin-Katz equation, gives the calculated membrane potential on the inside of the membrane when two univalent positive ions, sodium (Na^+) and potassium (K^+), and one univalent negative ion, chloride ($Cl^–$), are involved.

$$\text{EMF (millivolts)} = -61 \cdot \log \frac{C_{\mathrm{Na^+}_i} P_{\mathrm{Na^+}} + C_{\mathrm{K^+}_i} P_{\mathrm{K^+}} + C_{\mathrm{Cl^-}_o} P_{\mathrm{Cl^-}}}{C_{\mathrm{Na^+}_o} P_{\mathrm{Na^+}} + C_{\mathrm{K^-}_o} P_{\mathrm{K^+}} + C_{\mathrm{Cl^-}_i} P_{\mathrm{Cl^-}}}$$

- Na^+, K^+ & Cl^- ions most important in development of membrane potential in nerves and muscle cells.
- Their conc’n gradient across the membrane helps determine the voltage of the membrane potential
- Degree of importance for each ion in determining voltage depends on permeability to it
- If zero permeability to K^+ & Cl^-, then membrane potential will be dependent of Na^+ only hence resulting potential will be equal to Nernst potential for Na^+
- Same holds for the other ions if membrane would be selectively permeable for either one of them alone

- +ve ion conc’n gradient to the outside causes electronegativity to the inside
- -ve ion gradient from the outside to the inside causes electronegativity to the inside since –vely charged Cl^- ions move to the inside leaving the non diffusible +ve ions to the outside
- The permeability of the K & Na channels undergoes rapid changes during transmission of an impulse whereas that to Cl^- does not change much.
- As such, rapid changes in Na and K permeability is primarily responsible for signal transmission in nerves as explained later

Resting Membrane Potential

- In the unstimulated state, nerve cells exhibit a resting membrane potential that is approximately -90 mV relative to the ECF
- The resting membrane potential reflects a steady state that can be described by the Goldman equation
- One should remember that the ECF conc’n of Na+ is much greater than for K+.
- Moreover, the permeability of the membrane to K+ (PK) is much greater than the permeability to Na (PNa) because there are many more leakage (non-gated) channels in the membrane for K+ than in the membrane for Na+
- As such, the RMP is much closer to the equilibrium potential for potassium (EK) than it is for sodium
- Because Na is far from its equilibrium potential, there is a large driving force on sodium, so Na+ ions move readily whenever a voltage-gated or ligand-gated Na+ channel opens in the membrane

The Resting Membrane Potential.

- Polarity. On the inner surface of the membrane resting potential is electronegative in respect of "zero" of the Earth.
- In other words, the outer surface of the membrane is charged positively, and internal - negatively.
- Sustainability of magnitude. Value of the RP for a particular structures (nerve fiber, muscle cells, neurons) are constant.
- Absolute value.
- RMP has the following meanings:
- Nerve fibers - -90 mV,
- Skeletal muscle fibers - -90 mV,
- Smooth muscle - -50-60 mV,
- Neurons of the central nervous system - -40-60 mV.

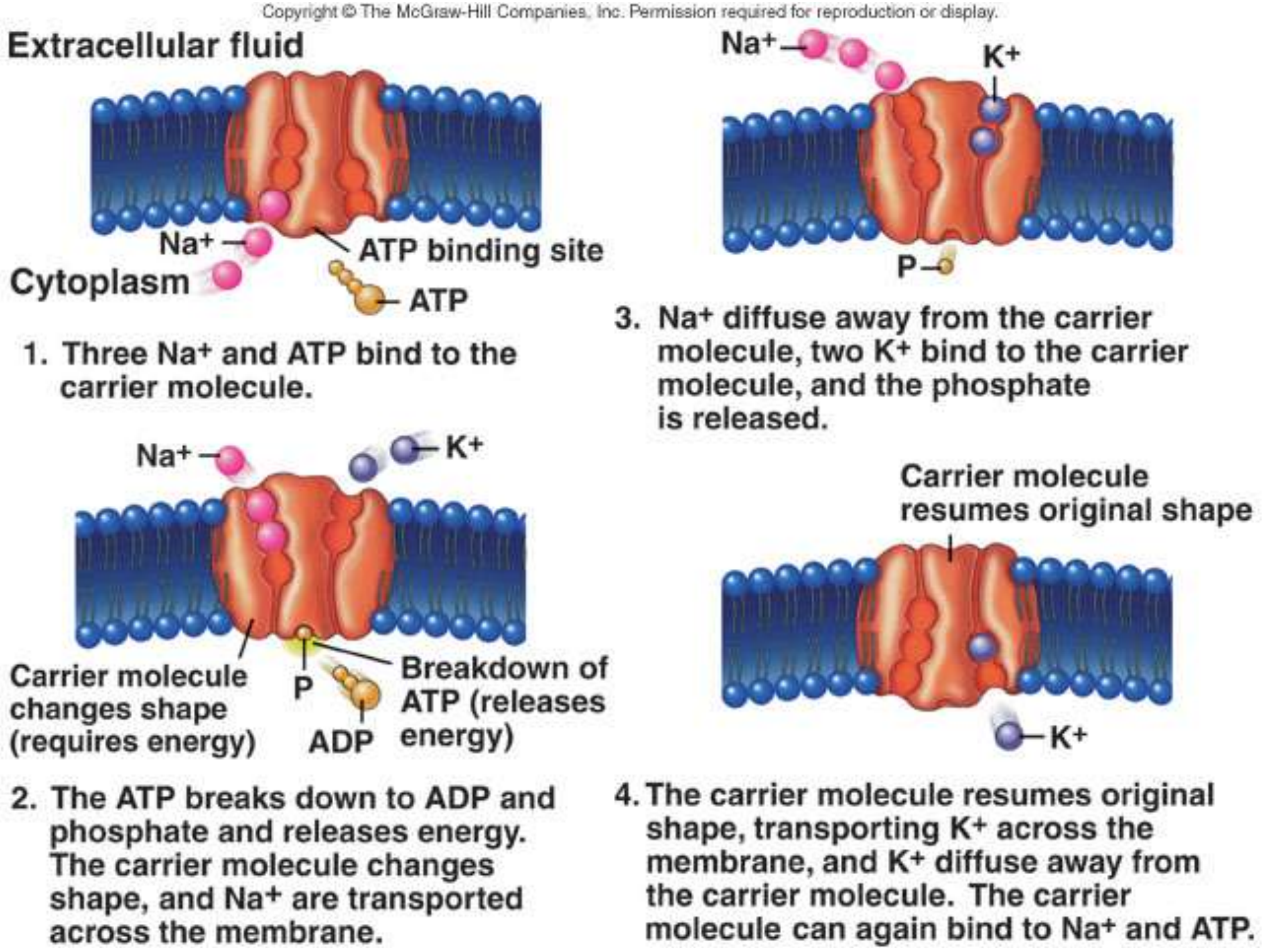
Resting Membrane Potential

- Normal RMP of large nerves at when not transmitting is -90mv
- Explained by the following

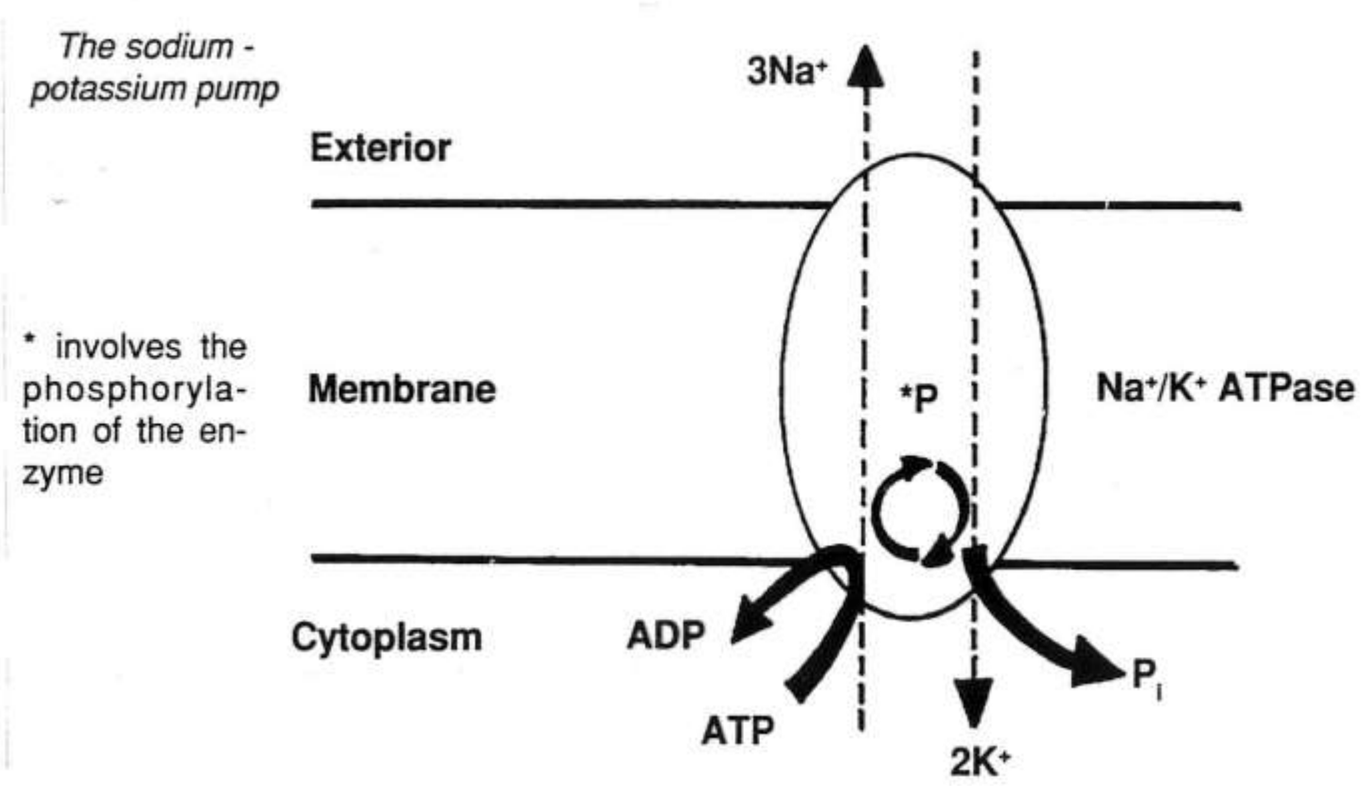
Transport properties of resting membrane

- Sodium Potassium (Na^+-K^+) Pump
- Continuously pumps Na^+ ions outside the cell and K^+ ions inside
- Is an electrogenic pump pumping 3 Na^+ ions outside for each 2 K^+ ions pumped inside
- Leaves net deficit of -ve ions on the inside causing –ve potential inside the cell membrane

Sodium-Potassium Exchange Pump



Na^+- K^+ pump



The sodium - potassium pump
* involves the phosphorylation of the enzyme
Exterior
Membrane
Cytoplasm
3Na+
*P
Na+/K+ ATPase
ADP
ATP
2K+
Pi

- This pump causes conc’n gradient for Na and k ions across the resting nervous membrane as below

	Inside	Outside
Sodium	14mEq/L	142mEq/L
Potassium	140mEq/L	4mEq/L

The ratios for the respective 2 ions from inside to outside are

Na^+ inside/Na^+outside = 0.1

K^+ inside/K^+outside = 35

Leak channels

- Leak channels are the passive channels, which maintain the resting membrane potential by allowing movement of positive ions (Na^+ and K^+) across the cell membrane.
- 3 important ions, sodium, chloride and potassium are unequally distributed across the cell membrane.
- Na^+ and $Cl^–$ are more outside and K^+ is more to the inside.
- $Cl^–$ channels are mostly closed in resting conditions $Cl^–$ are retained outside the cell.
- Na^+ is actively out of cell and K^+ is actively transported into the cell.
- Due to concentration gradient, Na^+ diffuses back into the cell through Na^+ leak channels and K^+ diffuses out via K^+ leak channels.

- In resting conditions, almost all the K+ leak channels are opened but most of the Na+ leak channels are closed.
- Due to this, K+, which are transported actively into the cell, can diffuse back out of the cell in an attempt to maintain the conc’n equilibrium.
- Among the Na+, which are transported actively out of the cell, only a small amount can diffuse back into the cell.
- That means, in resting conditions, the passive K+ efflux is much greater than the passive Na+ influx.
- It helps in establishing and maintaining the resting membrane potential.

- After establishment of RMP, (i.e. inside negativity and outside positivity), the efflux of K+ stops in spite of concentration gradient.
- This is due to:
- i. Positivity outside the cell repels positive K+ and prevents further efflux of these ions
- ii. Negativity inside the cell attracts positive K+ and prevents further leakage of these ions outside.

Factors determining RMP

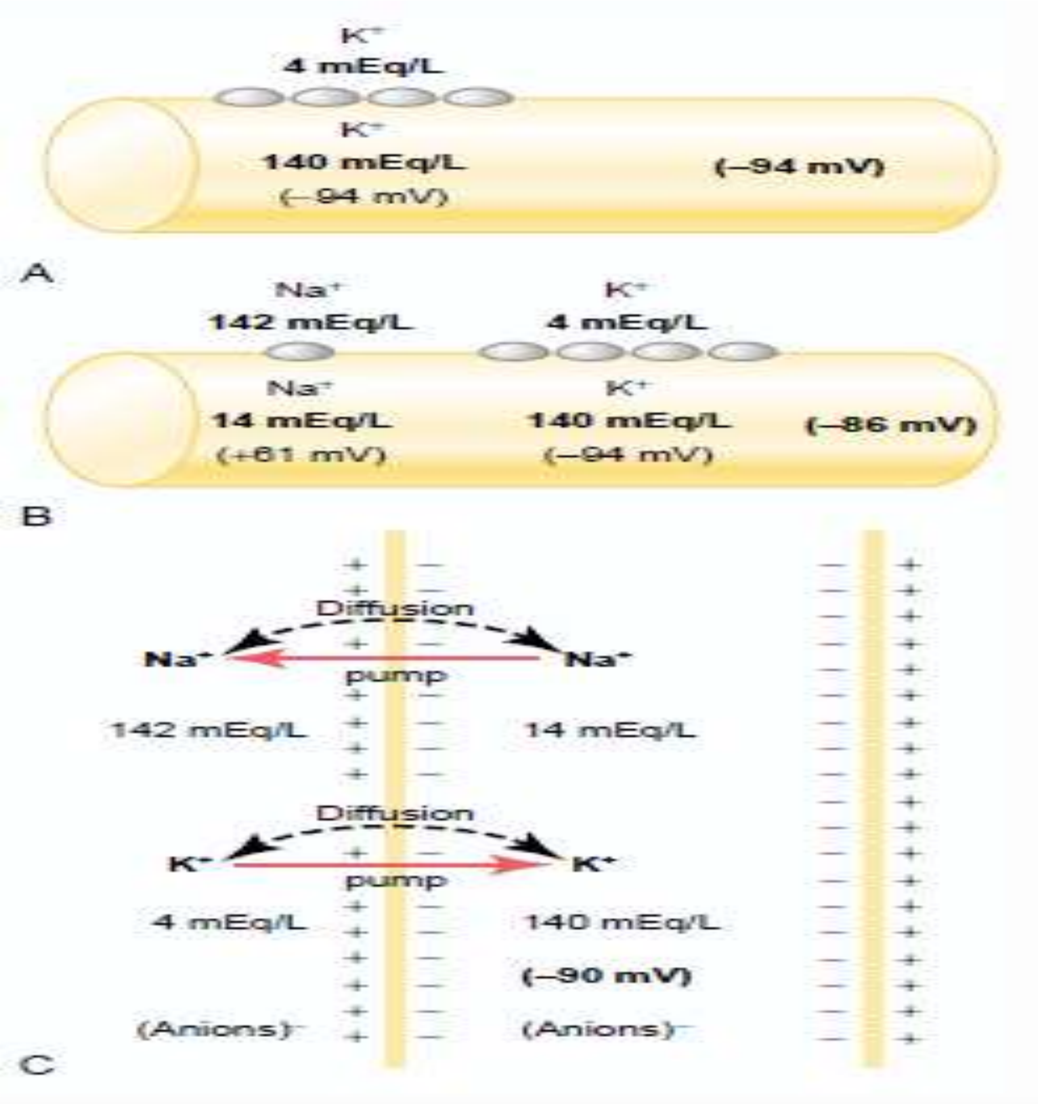
- Nernst potential for K^+, -94mv (-61*log 140/4)
- Nernst potential for Na^+, +61mv (-61log 14/140)

Net effect determined by Goldman equation as membrane much more permeable to K^+ through the leak channels. This net potential comes to -86mv

- The Na^+ -K^+ Pumps more Na^+ outside than K^+ hence more –ve inside membrane. This contributes additional -4 mv to membrane potential
- When all this factors operating at same time, then normal resting potential about -90mv

- K^+ and Na^+ diffusion alone causes a membrane potential of about -86 mv
- Na^+ - k^+ pump contributes about -4mv
- Total Membrane Resting Potential normally -90mv

Origin of the Normal Resting Membrane Potential



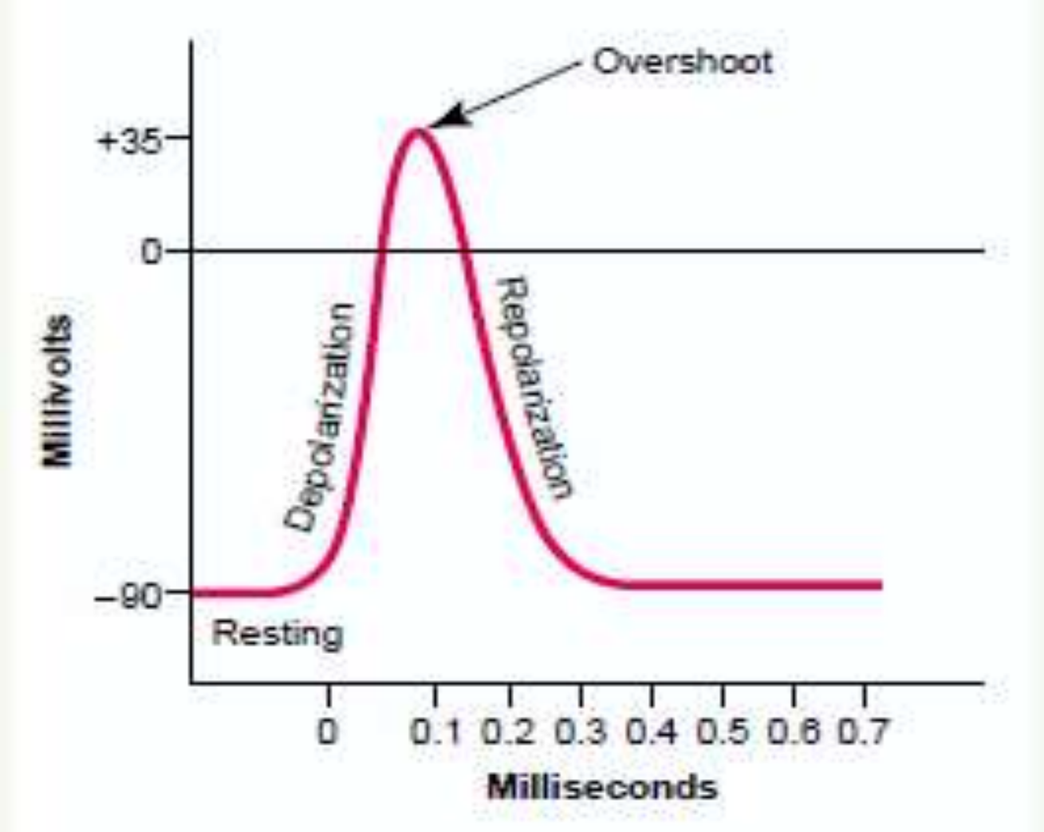
Contribution of the Na+-K+ Pump

- The Na+-K+ pump is shown to provide an additional contribution to the resting potential.
- There is continuous pumping of three sodium ions to the outside for each two potassium ions pumped to the inside of the membrane.
- The fact that more sodium ions are being pumped to the outside than potassium to the inside causes continual loss of positive charges from inside the membrane; this creates an additional degree of negativity (about –4 millivolts additional) on the inside beyond that which can be accounted for by diffusion alone.
- Therefore, the net membrane potential with all these factors operative at the same time is about –90 mV.

Action Potential

- Are rapid changes in membrane potential that spread rapidly along a nerve fibre
- Begins with rapid change in RMP to a positive potential ending with an almost rapid change to the negative potential.
- To conduct a nerve signal, the action potential moves along the nerve fiber until it comes to the nerves end

Action potentials are rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane.



- Shows changes occurring in membrane during AP
- Explosive onset of AP and equally rapid recovery to the –ve potential

Stages of AP

I. Resting stage
II. Depolarization
III. Repolarization stage

Resting Stage

This is the resting membrane potential before the action potential begins.

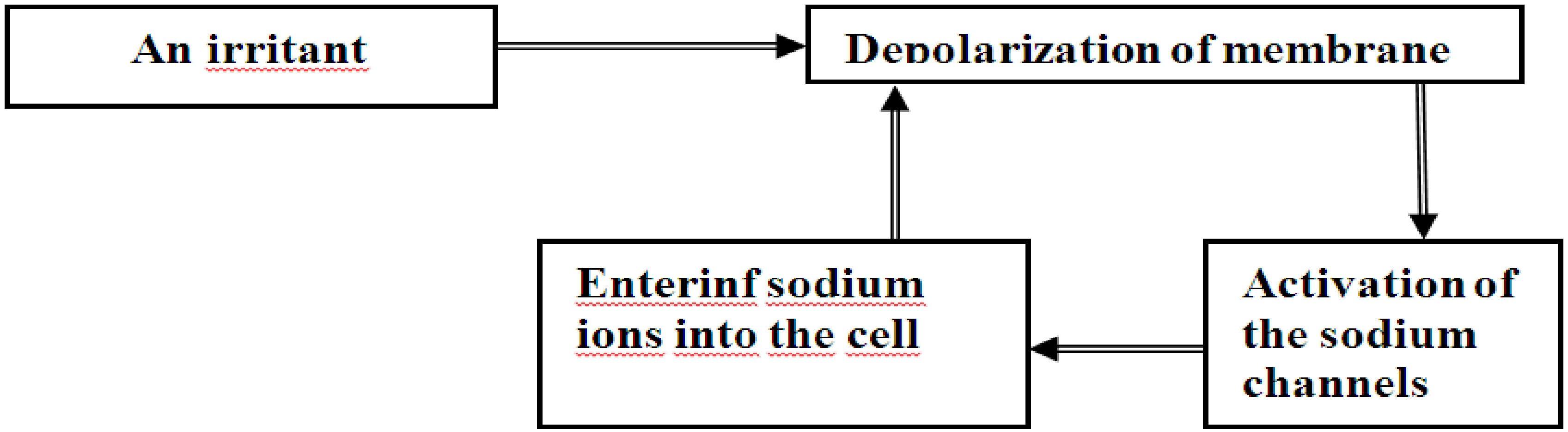
The membrane is said to be “polarized” during this stage because of the –90 millivolts negative membrane potential that is present.

Depolarization stage

At this time, the membrane suddenly becomes very permeable to Na+ ions, allowing tremendous numbers of positively charged Na ions to diffuse to the interior of the axon.

The normal "polarized" state of –90 millivolts is immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction.

This is called *depolarization.*


An irritant
Depolarization of membrane
Enterinf sodium ions into the cell
Activation of the sodium channels

Repolarization Stage

Within a few 10,000ths of a second after the membrane becomes highly permeable to Na ions, the Na channels begin to close and the K+ channels open more than normal.

Then, rapid diffusion of K+ ions to the exterior re-establishes the normal negative resting membrane potential.

This is called *repolarization* of the membrane.

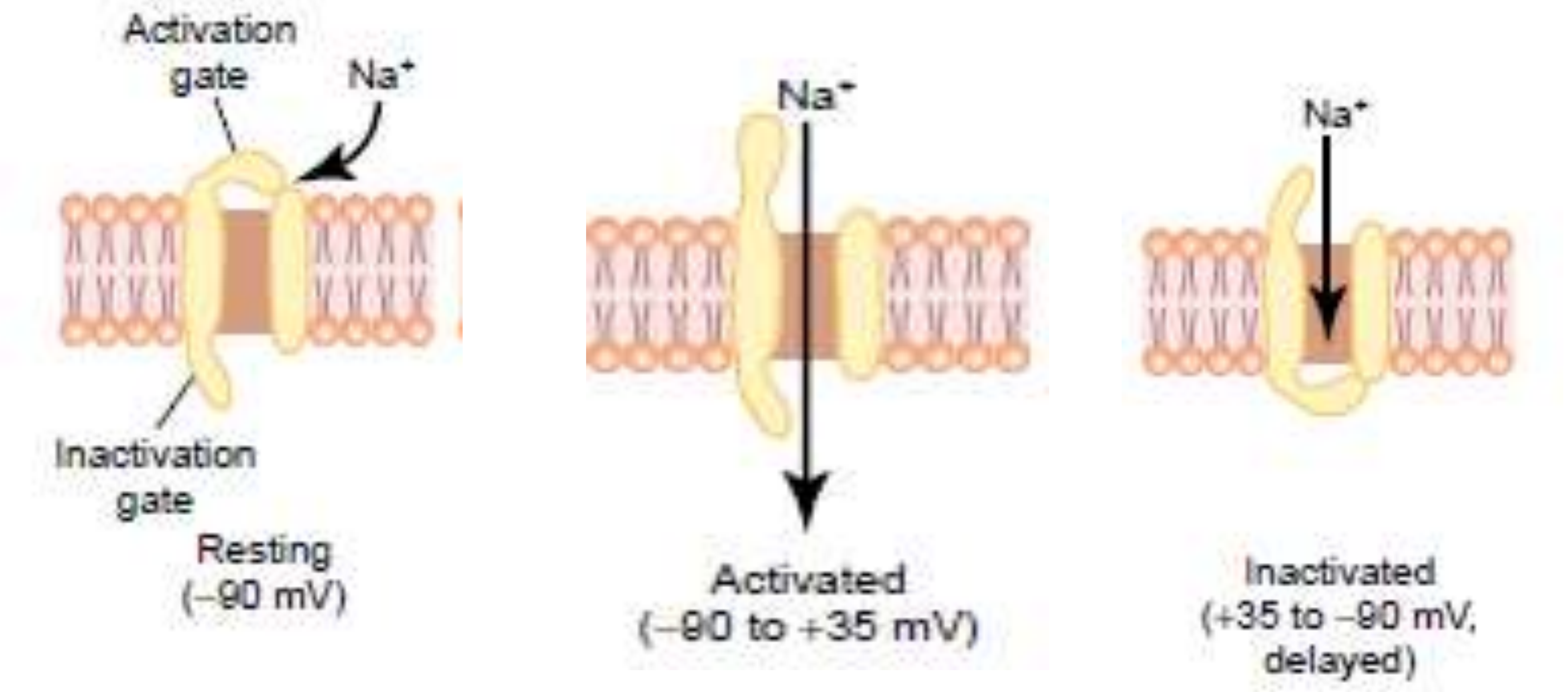
- In the absence of an action potential, a stimulus applied to the neuronal membrane results in a local potential change that decreases with distance away from the point of stimulation.
- The stimulus is the particular one which the nerve reacts to eg- if taste, then it is a chemical which stimulates that receptor and cause the local potential change. For salty taste, Na+ ions open specific Na channels which cause the change in potential which may lead to the AP
- The voltage change at any point is a function of current and resistance as defined by Ohm's law.
- If a ligand-gated channel opens briefly and allows +ve ions to enter the neuron, the electrical potential derived from that current will be greatest near the channels that opened, and the voltage change will steadily decline with increasing distance away from that point.

- The reason for the decline in voltage change with distance is that some of the ions backleak out of the membrane because it is not a perfect insulator, and less charge reaches more distant sites.
- Since membrane resistance is a stable property of the membrane, the diminished current with distance away from the source results in a diminished voltage change.
- An action potential depends on the presence of voltage-gated sodium and potassium channels that open when the neuronal membrane is depolarized.

Voltage gated sodium and potassium channels

- These channels play important part in depolarization and repolarization of the nerve membrane during AP
- Has 2 gates, a an activation gate near the outside and an inactivation gate near the inside
- At rest (-90mv) the inactivation gate is open with activation gate closed preventing entry of Na into the nerve

Voltage-Gated Sodium Channels



Activation

- When membrane becomes less –tive than during resting potential rising from -90 towards 0, it finally reaches a voltage (mostly between -70 to -50 mv depending on the nerve) that causes conformational changes in the activation gate causing it to open
- This is the activated state during which Na ions pour into the cell with membrane permeability to sodium increased to 500 -5000 fold

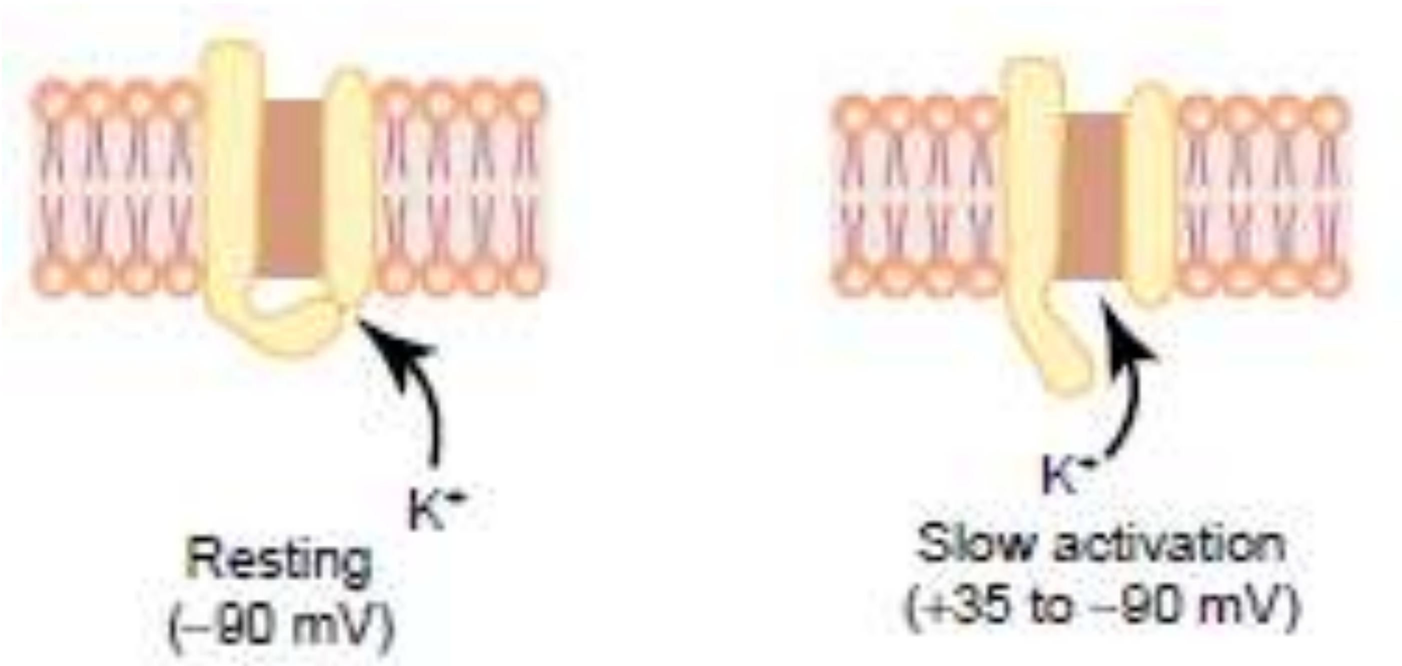
Inactivation

- Same voltage increase that opens activation gate also closes the inactivation gate
- However, this gate closes several 10,000ths of a second after the opening after activation gates
- The conformation change that closes the inactivation gate is a slower process than the conformational change that opens the activation gate
- No more Na can enter the cell
- The inactivation gate does not open again until the potential returns to near the RMP

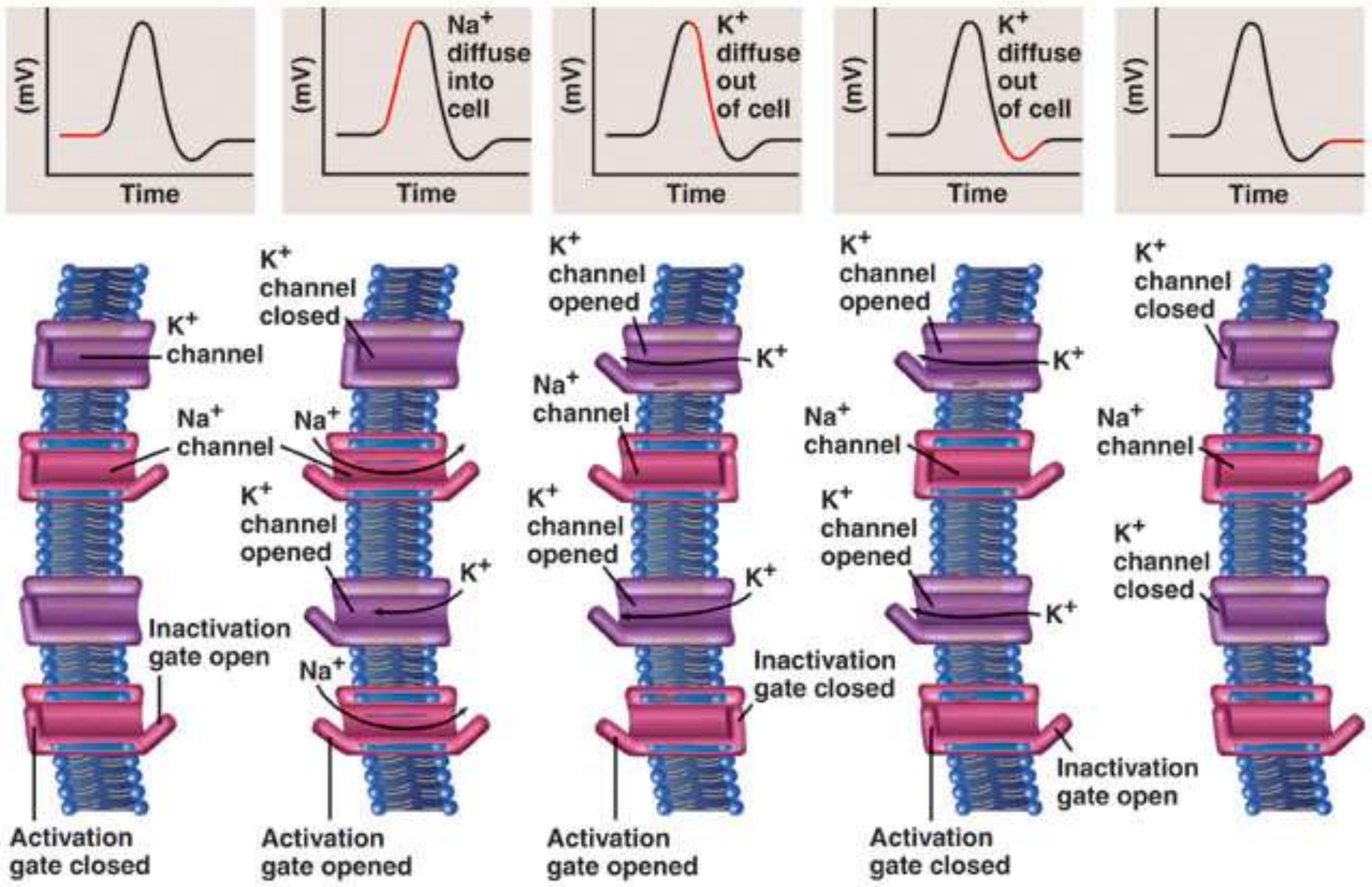
Voltage gated potassium channels

- At rest voltage gated potassium channels closed.
- When membrane potential rises from -90mv towards 0, a conformational change occurs allowing this channels to open with K^+ ions diffusing to the outside
- However, there is a delay in opening o f this channel with it opening just as the Na channels are beginning to close due to inactivation
- Thus, decrease in sodium entry to the cell and simultaneous increase in K^+ exit from the cell combine to speed the repolarization process leading to full recovery of membrane potential within another few 10,000th of a second

Voltage-Gated Potassium Channel



Action Potential



Initiation of the Action Potential: 28th Sept

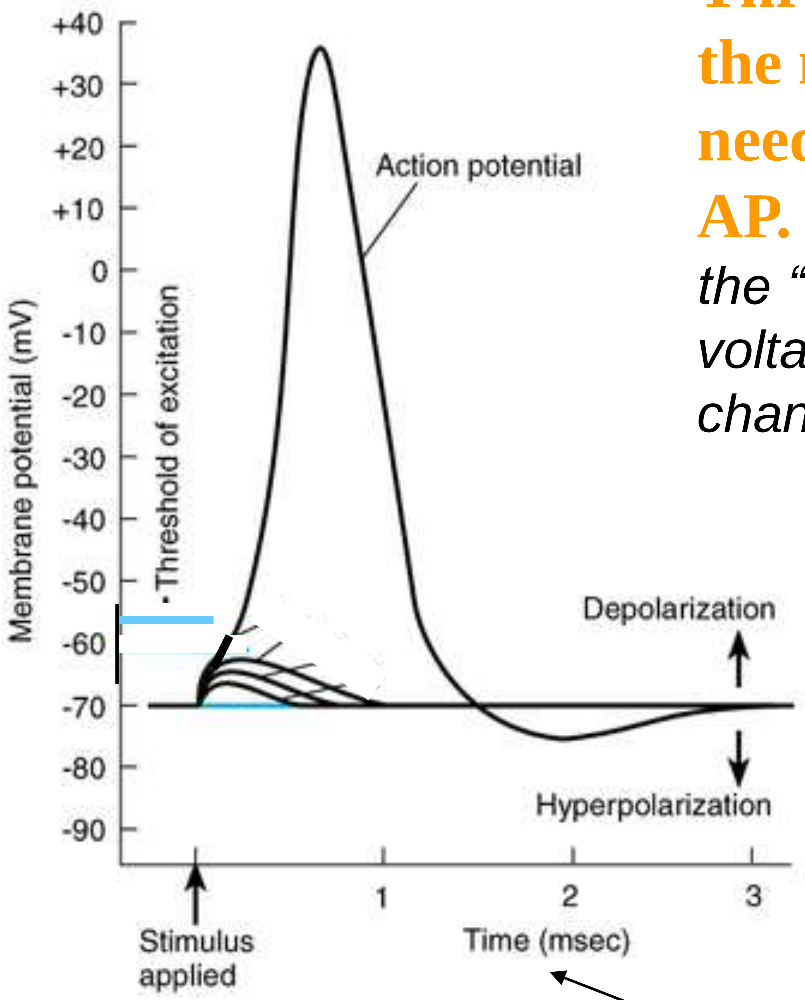
- As long as nerve fibers membrane remains undisturbed, no AP occurs
- If an event occurs to change potential from the -90mv towards 0, this rise cause many voltage gated Na channels to begin opening allowing rapid inflow of Na ions which causes further rise in membrane potential.
- This opens still more voltage gated Na channels and more ions streaming into the interior of fiber.

- This is a vicious +ve feedback cycle that, once the feedback is strong enough, continues till all voltage gated Na channels have become opened
- Then within another ms, the rising potential causes the na channels to close as well as opening the K channels and the action potential soon terminates

Threshold for Action potential

- An AP will not occur until the initial rise in potential is great enough to create the vicious cycle
- This occurs when the number of Na ions become higher than the number of K leaving the cell
- A sudden rise of about 15 – 30 mv often required
- Therefore a sudden increase in potential from -90 to about -65 mv usually causes the the explosive development of an action potential
- This level of -65 mv is said to be the threshold for stimulation

► Action Potential as Seen on an Oscilloscope Screen



Definition:

Threshold voltage is the minimum voltage needed to trigger an AP. *not a number, rather the "trigger" to open voltage operated channels*

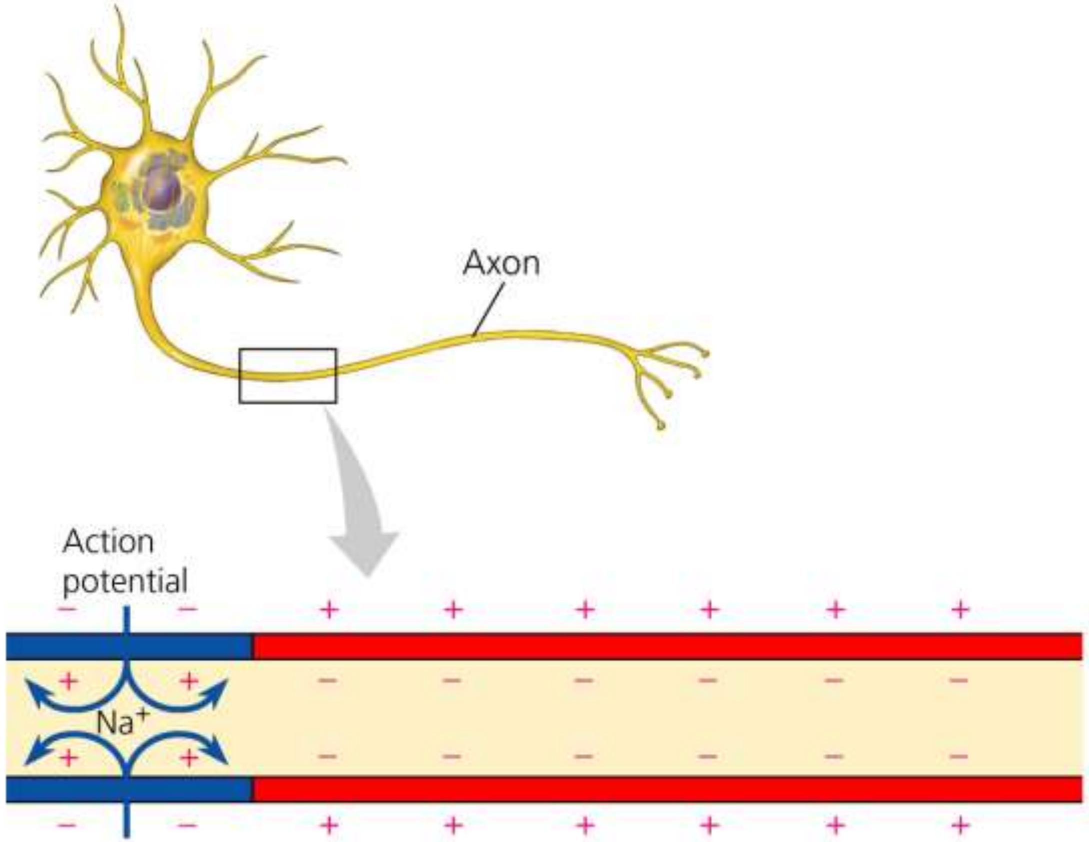
Note the timeframe for one AP

Propagation of the Action Potential

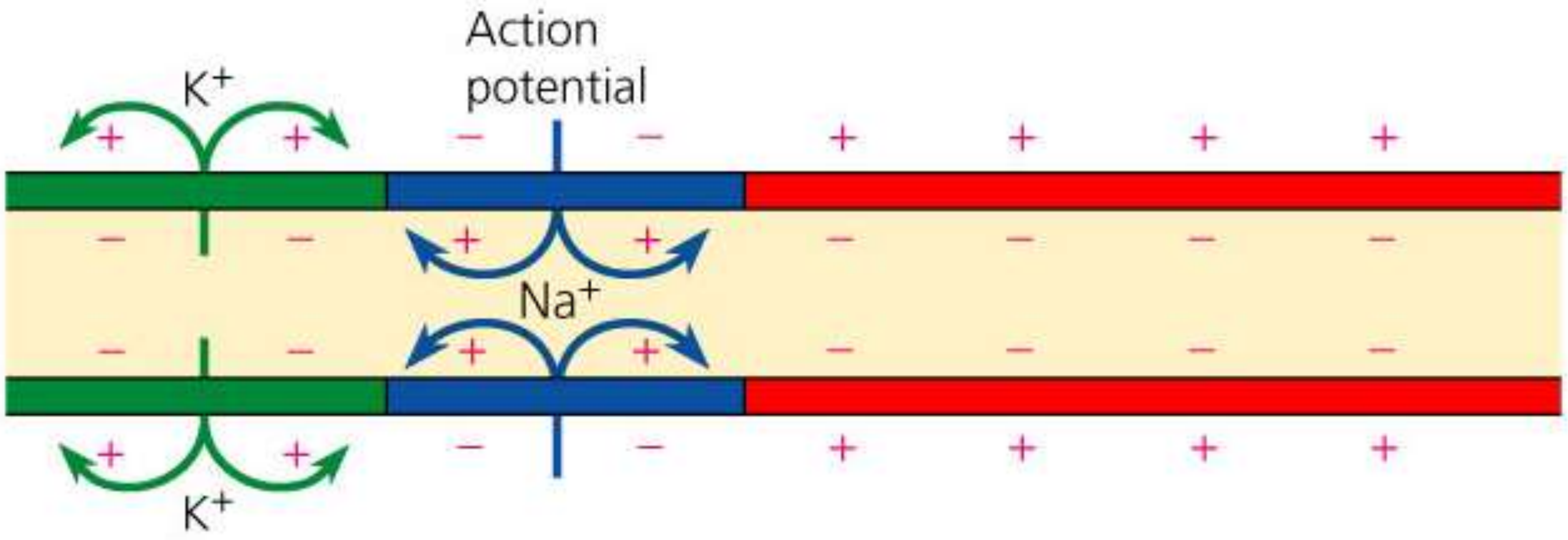
- An AP elicited at any one point of an excitable membrane usually excites adjacent parts of the membrane resulting in propagation of the AP along the membrane
- The +ve electrical charges are carried by the inward diffusing Na ions through the depolarizing membrane and then for several mm along the nerve fiber in both directions along the core of the axon.
- This +ve charges increase the voltage for a distance of 1-3mm inside the fiber to above threshold voltage for initiation of AP

- Therefore, Na channels in these new areas open and the explosive AP spreads
- These newly depolarized areas produce still more local circuits of current flow further along the membrane causing progressively more and more depolarization
- The depolarization process travels along the entire length of fiber
- This transmission of the depolarization process along a nerve or muscle fiber is called a nerve or muscle impulse

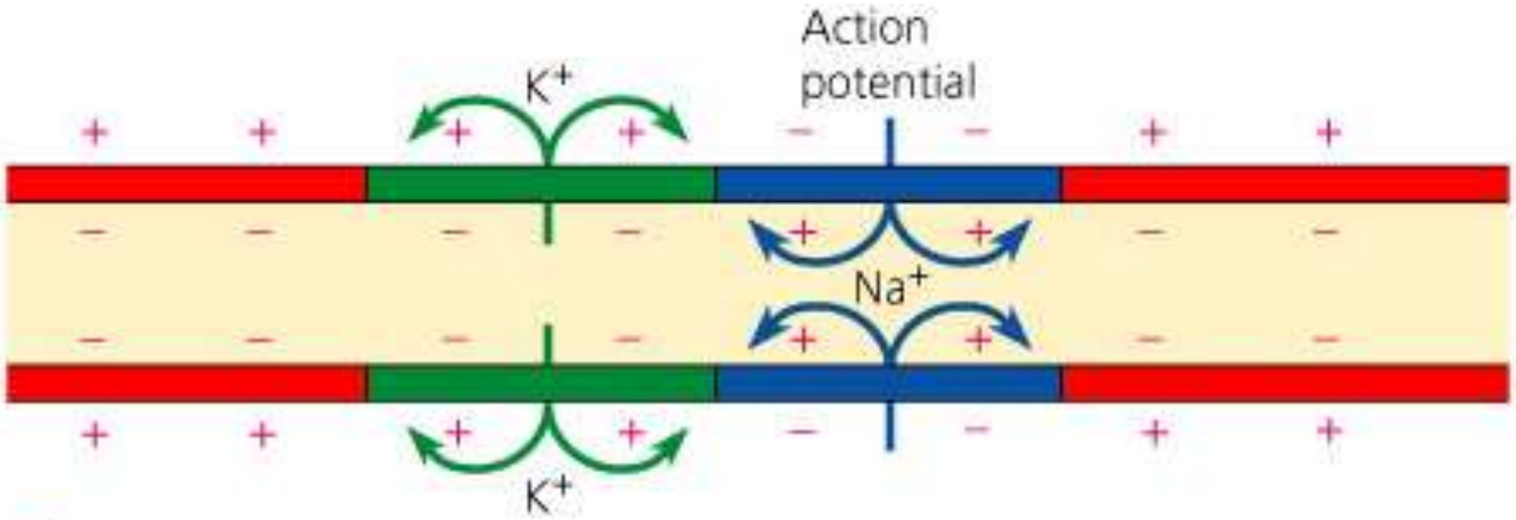
- Propagation and Speed of the Action Potential.
- After an AP is generated, it propagates along the axon toward the axon terminal; it is conducted along the axon with no decrement in amplitude.
- The mode in which AP’s propagate and the speed with which they are conducted along an axon depend on whether the axon is myelinated.
- The diameter of the axon also influences the speed of AP conduction: larger-diameter axons have faster AP potential conduction velocities than smaller-diameter axons.



1 An action potential is generated as Na^+ flows inward across the membrane at one location.



2 The depolarization of the action potential spreads to the neighboring region of the membrane, re-initiating the action potential there. To the left of this region, the membrane is repolarizing as K^+ flows outward.



3 The depolarization-repolarization process is repeated in the next region of the membrane. In this way, local currents of ions *across* the plasma membrane cause the action potential to be propagated *along* the length of the axon.

Step 1

- Adequate stimulus is applied to a neuron, then the **stimulus-gated Na+ channels** at the point of stimulus open, **Na+ diffuses rapidly into the cell** producing a **local depolarization**

Step 2

- If the magnitude of the depolarization surpasses a limit termed **THRESHOLD POTENTIAL (about -65 mV),** the **voltage-gated Na+ are stimulated to open**

Step 3

- As more Na+ rushes into the cell, the membrane **moves toward 0 mV, then continues to a peak of +30 mV** (the + indicates that there is an excess of +ions inside the membrane
  - If the local depolarization **fails to cross -65 mV the voltage-gated Na+ do not open** and the membrane simply recovers back to the resting potential of **-90 mV** **without producing an action potential**

Step 4

- **Voltage-gated Na+ stays open for only about 1 ms before automatically closing.** This means that once they are stimulated the Na+ always allow sodium to rush in. therefore the ***action potential is an all-or-nothing response***

Step 5

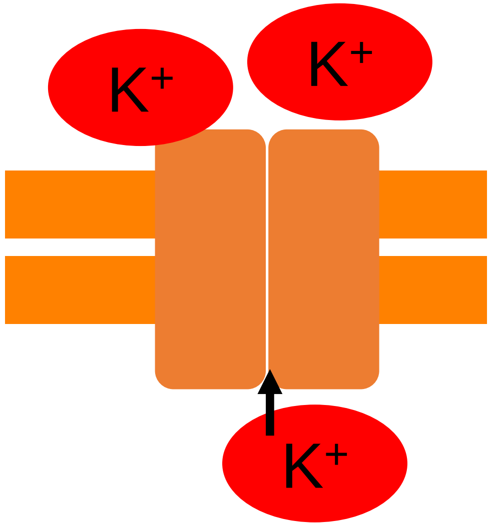
- Once the peak is reached the membrane potential begins to move back toward the resting potential termed REPOLARIZATION
- Surpassing the threshold not only triggers the opening of voltage-gated Na+ but also the voltage-gated K+ BUT these are slow to respond, however, and thus do not begin opening until the inward diffusion of Na+ has caused the membrane potential to reach +30 mV once the K+ are open it rapidly diffuses out of the cell.
- The outward rush of K+ restores the original excess of + ions on the outside of the membrane, thus repolarizing the membrane

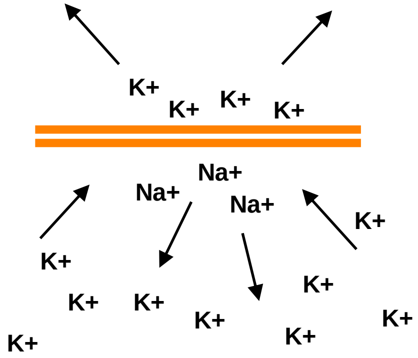
Step 6

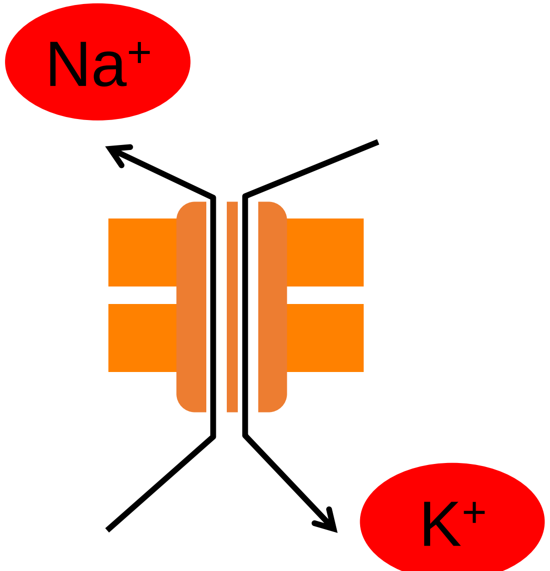
- Because the K+ channels remain open as the membrane reaches its resting potential, too many K+ may rush out of the cell.
- This causes a brief period of hyperpolarization before the resting potential is restored by the action of the Na+-K+ pump and the return of ion channels to their resting state

Action potentials: Resuming the Resting Potential

- Potassium channels close.
- Repolarization resets sodium ion channels.
- Ions diffuse away from the area.
- Sodium-potassium transporter maintains polarization.
- The membrane is now ready to “fire” again.







All-or Nothing Principle

- Once an AP has been elicited at any one point in the membrane, the depolarization process travels over the entire membrane if conditions are right or it will not travel at all
- This is the all or nothing principle
- At times, the AP reaches a point on the membrane where it does not generate sufficient voltage to stimulate the next area of the membrane.

- When this occurs, spread of depolarization stops
- For continued propagation of impulse, the ratio of AP to threshold fro excitation must be greater than 1
- This greater than 1 ratio is called the safety factor for propagation

ALL OR NONE RESPONSE

- The action potential doesn’t occur in a nerve if the stimulus is sub-threshold. If the stimulus is threshold and above, the action potential produced will be of same amplitude, regardless of intensity of stimulus.
- * The frequency of action potential increases with the increasing intensity of stimulus.

- Propagation of an action potential in an unmyelinated axon.
- The initiation of an action potential in one segment of the axon depolarizes the immediately adjacent section, bringing it to threshold and generating an action potential.
- The propagation of an action potential in a myelinated axon.
- The initiation of an action potential in one node of Ranvier depolarizes the next node.
- Jumping from one node to the next is called saltatory conduction.

Refractory Periods

- After the start of an action potential, there are periods when
- i. The initiation of additional action potentials requires a greater degree of depolarization and
- II. When action potentials cannot be initiated at all.
- These are called the relative and absolute refractory periods, respectively
- The inability of a neuronal membrane to generate an AP during absolute refractory period is due to the state of the voltage-gated Na channel.
- After the inactivation gate closes during the repolarization phase of an AP, it remains closed for some time; therefore, another action potential cannot be generated no matter how much the membrane is depolarized.

- The importance of the absolute refractory period is that it limits the rate of firing of AP’s
- The absolute refractory period also prevents AP’s from traveling in the wrong direction along the axon

- In the relative refractory period, the inactivation gate of a portion of the voltage-gated Na+ channels is open.
- Since these channels have returned to their initial resting state, they can now respond to depolarizations of the membrane.
- Consequently, when the membrane is depolarized, many of the channels open their activation gates and permit the influx of Na+ ions.
- However, since only a portion of the Na+ channels have returned to the resting state, depolarization of the membrane to the original threshold level activates an insufficient number of channels to initiate an AP

- With greater levels of depolarization, more channels are activated, until eventually an action potential is generated.
- The K+ channels are maintained in the open state during the relative refractory period, leading to membrane hyperpolarization.
- By these two mechanisms, the AP threshold is increased during the relative refractory period

GRADED POTENTIAL

- Graded potential is a mild local change in the membrane potential that develops in receptors, synapse or neuromuscular junction when stimulated.
- Also called graded membrane potential or local potential.
- It is non-propagative and characterized by mild depolarization or hyperpolarization.
- In most of cases, graded potential is responsible for the generation of AP
- In some cases it hyper-polarizes the membrane potential (more negativity than resting membrane potential) and inhibits the generation of AP

Action Potential vs Graded potential

Action Potential	Graded potential
Propagative	Non-Propagative
Long-distance signal	Short-distance signal
Both depolarization and repolarization	Only depolarization or hyperpolarization
Obeys all or none law	Does not obey all or none law
Summation is not possible	Summation is possible
Has refractory period	Has no refractory period