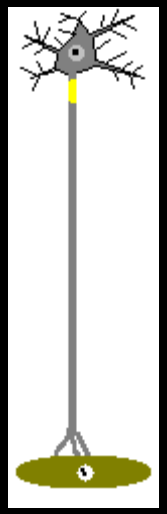
MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE
DISTANCE LEARNING CENTER

Lecture № 2

Excitable tissues. Resting membrane potential. Nerve action potentials. Propagation of the action potential



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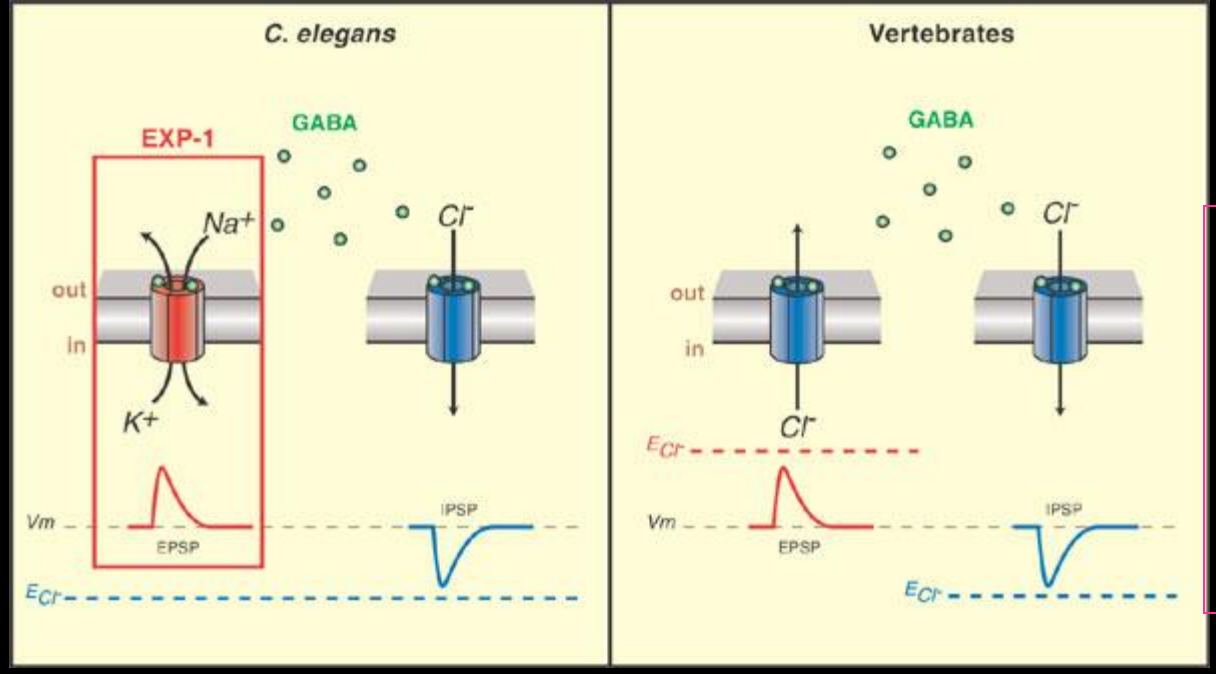
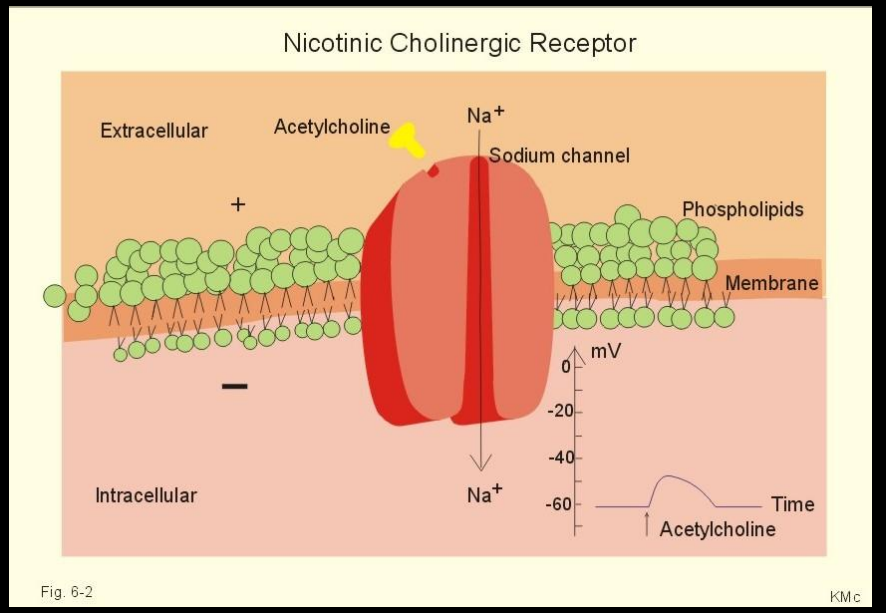
Excitable tissues

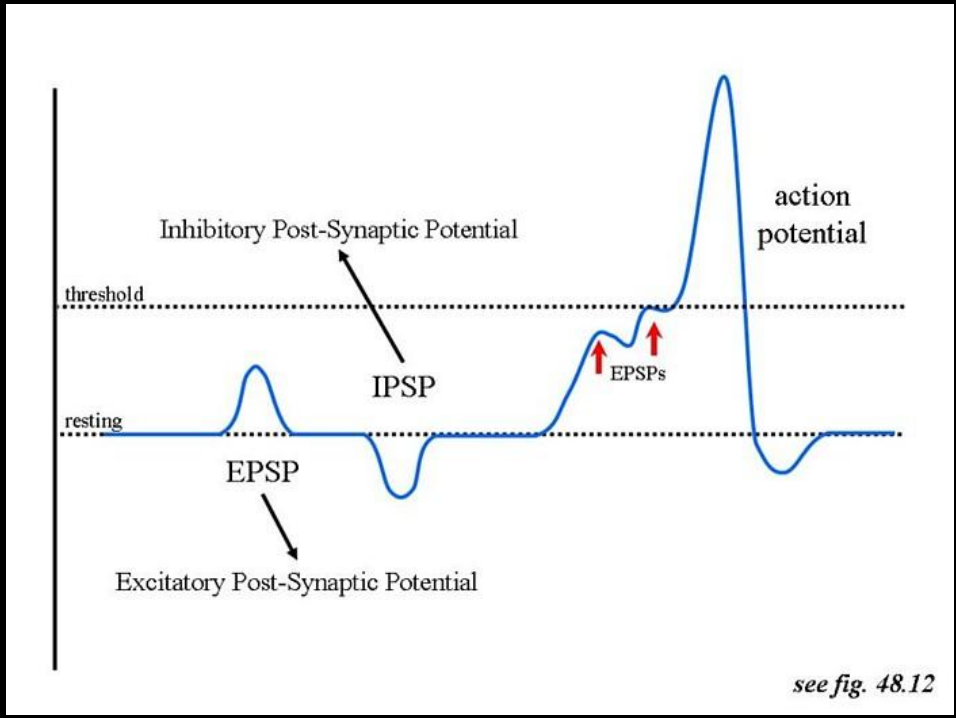
- Excitation is a process of changes in the cells under effect of applied stimulus.
- Irritability is the basic function of protoplasm however, the nerve cells and muscle fibers are specialized excitable cells of the body capable of conducting (transmitting) excitations along their membrane.
- There are two types of excitable membranes:

  1. electro excitable
  2. electro unexcitable (ligand excitable)

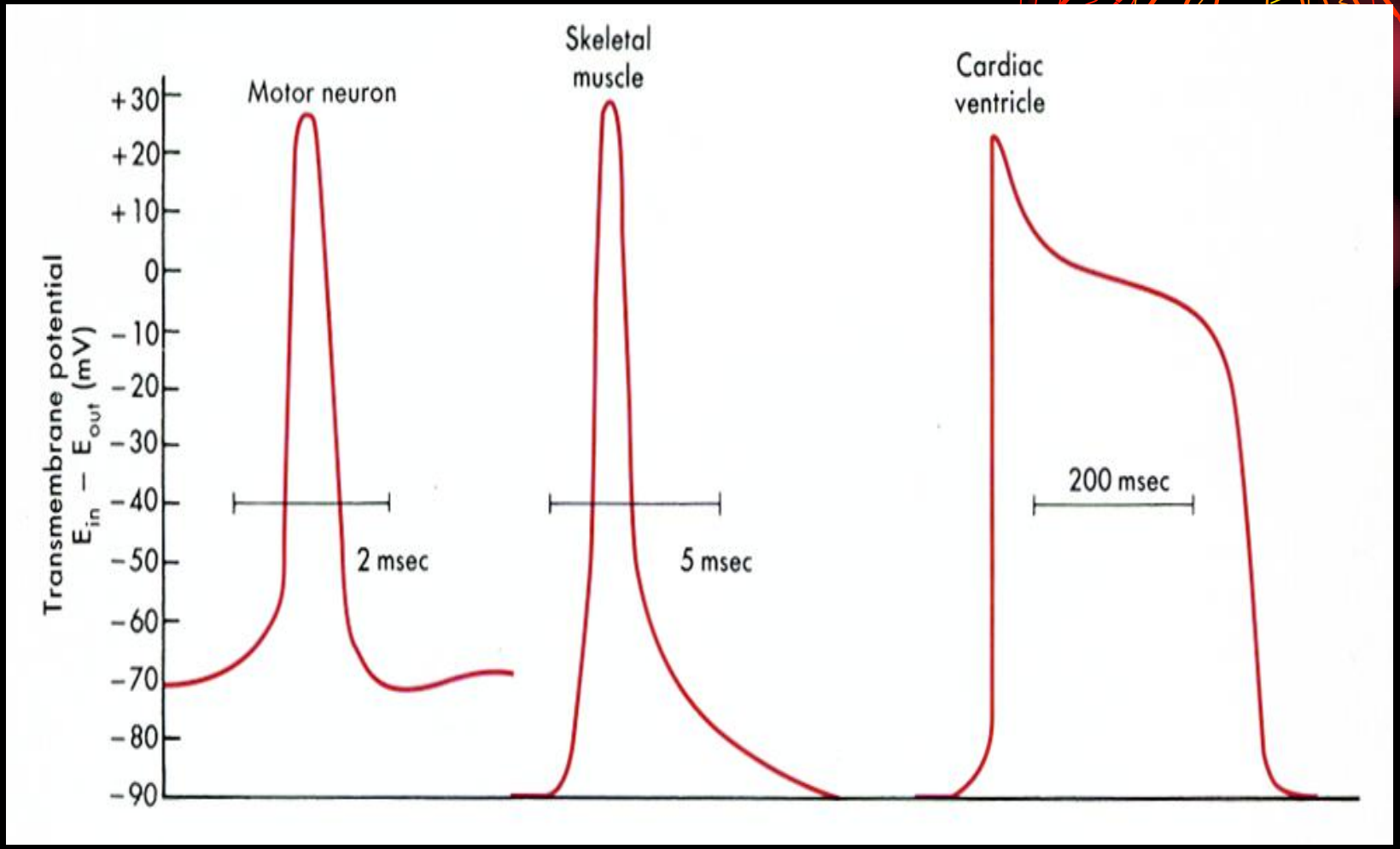


Electro unexcitable membranes (sensory receptors and postsynaptic membranes) generate Acute local potentials.





Action potentials of electro excitable membranes



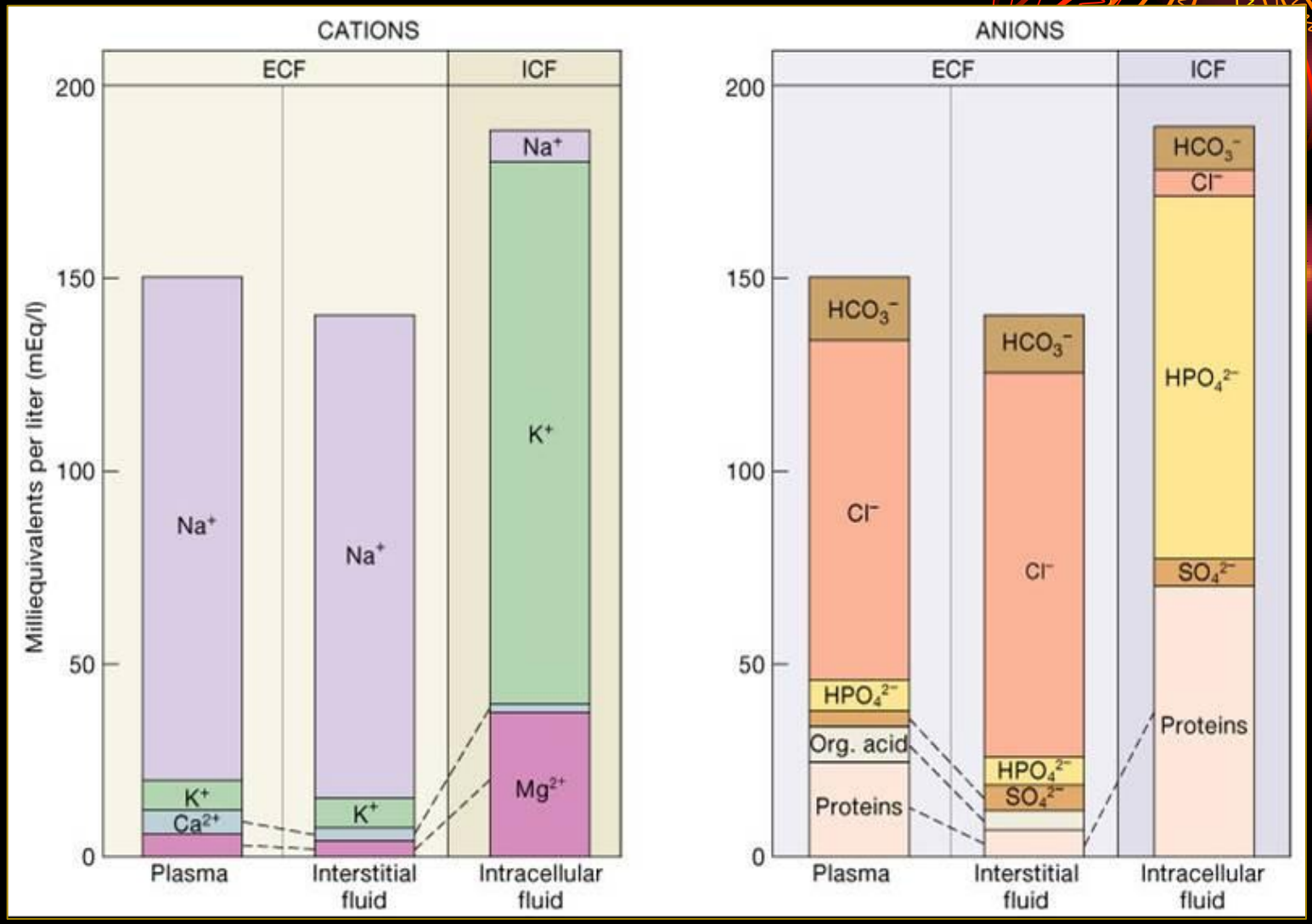
Membrane Potentials and Action Potentials

- Electrical potentials exist across the membranes of virtually all cells of the body.
- In addition, some cells, such as nerve and muscle cells, are capable of generating rapidly changing electrochemical impulses at their membranes, and these impulses are used to transmit signals along the nerve or muscle membranes.
- In still other types of cells, such as glandular cells, macrophages, and ciliated cells, local changes in membrane potentials also activate many of the cells' functions.
- The present discussion is concerned with membrane potentials generated both at rest and during action by nerve and muscle cells.

Table 54.1 The Ionic Composition of Cytoplasm and Extracellular Fluid (ECF)

Ion	Concentration in Cytoplasm (mM)	Concentration in ECF (mM)	Ratio	Equilibrium Potential (mV)
Na^+	15	150	10:1	+60
K^+	150	5	1:30	−90
Cl^-	7	110	15:1	−70

Ions composition of body fluids



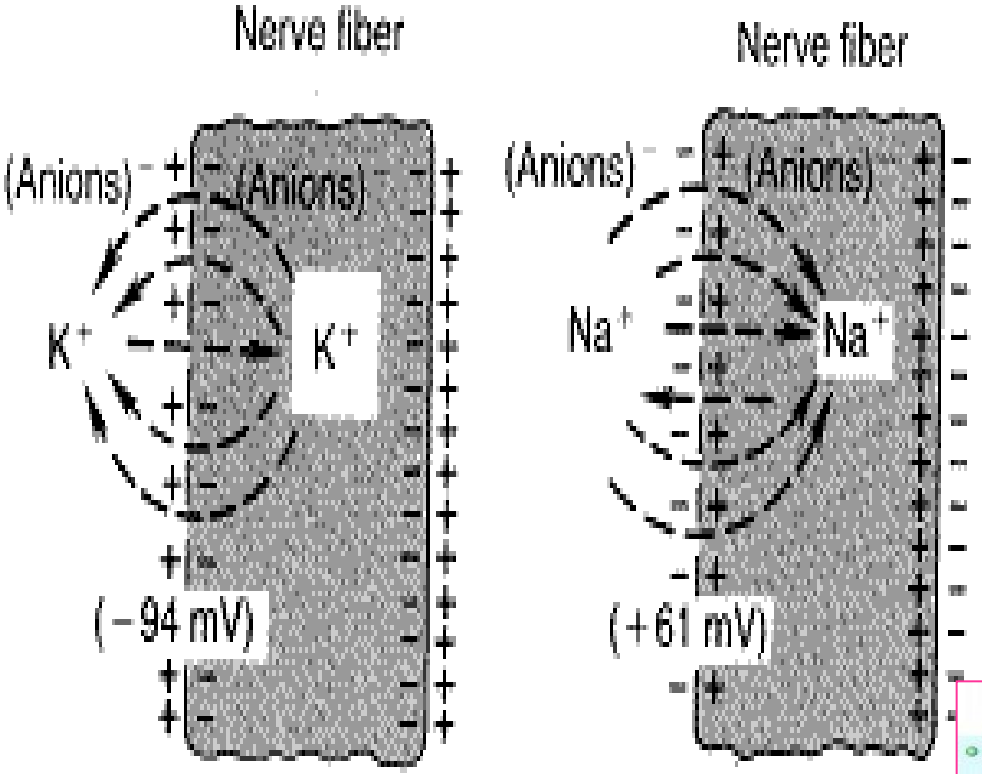
Basic Physics of Membrane Potentials

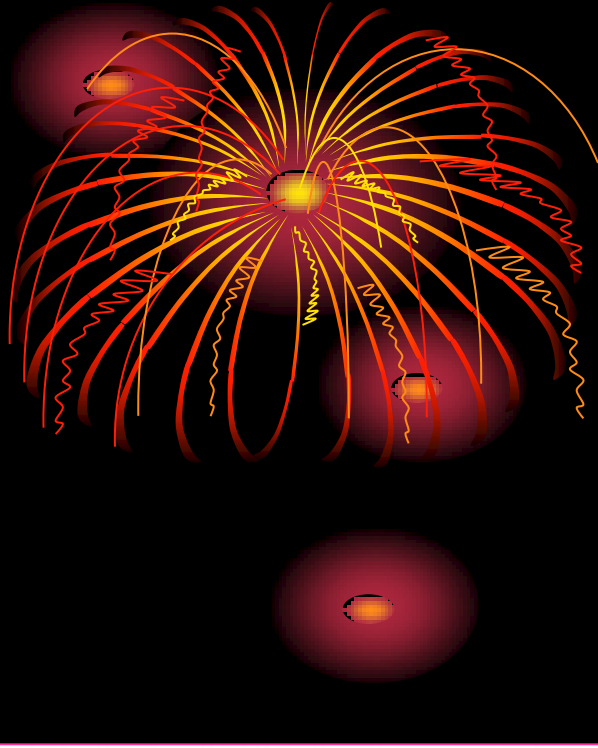
- The ECF contains a large amount of NaCl and bicarbonates along with nutrients O_2 and CO_2.
- The cell membrane (axolemma) is practically impermeable to complex proteins and other organic molecules of cytoplasm, but selectively permeable for simple organic and inorganic molecules.
- In resting condition it is moderately permeable to Na^+ but quite (50 to 100 times more) permeable to K^+ and Cl^- ions.
- ***Concentration of Na^+ and Cl^- ions in ECF is about 10 and 15 times more than in cytoplasm. Similarly, the concentration of K^+ ions in cytoplasm is about 30 times more than in ECF.***
- The result of above *concentration* difference is a continuous influx of Na^+ and Cl^- ions to the cytoplasm from ECF and a continuous out flux of K^+ ions from cytoplasm into the ECF.

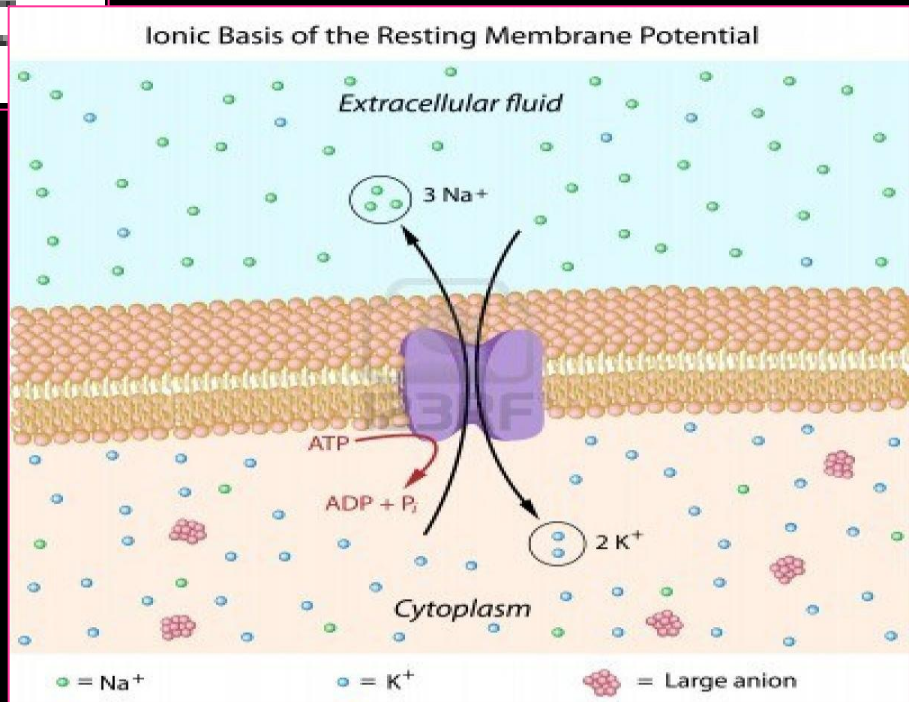
Membrane Potentials Caused by Diffusion

- Now let us assume that membrane for instance, is very permeable to K+ and not to any other ion. As the K^+ ions move outwards, they carry (+)ve charges to outside, thus creating a state of electro-positivity outside and electro-negativity on the inside of membrane because of (-)ve ions that remain behind.
- This new potential difference repels the (+)vely charged K^+ ions in a backward direction from outside to inside within a millisecond or the potential change becomes great enough to block further net diffusion of K^+ ions to the exterior despite the high K^+ ion Conc. gradient. In normal large human fiber the potential difference required is about - 94 mV.

- Again now let us assume that the membrane is highly permeable to Na^+ ions but impermeable to all other ions. Diffusion of Na^+ to inside now create a membrane potential with opposite polarity i.e., negativity outside and positivity inside.
- Again the membrane potential rises within milliseconds to block further net diffusion of (+)ve ions (Na^+) to inside, however this time for large human nerve fiber the potential is about +61mV.


Nerve fiber
(Anions)
(Anions)
K+
K+
(−94 mV)
Nerve fiber
(Anions)
(Anions)
Na+
Na+
(+61 mV)




Ionic Basis of the Resting Membrane Potential
Extracellular fluid
3 Na+
ATP
ADP + Pi
2 K+
Cytoplasm
= Na+
= K+
= Large anion

Membrane Potentials Caused by Diffusion

- **The potential level across the membrane that will exactly prevent net diffusion of an Ion in either direction through a membrane is called "*NERNST POTENTIAL*" of that particular ion. Its magnitude can be determined by the ratio of ion conc. on the two sides of the membrane. The following equation called *NERNST equation* is used to calculate the *Nernst potential* for any univalent ion at normal body temperature of 37^0C.**
- **EMF (mV) = ± 61 log (Conc. Inside : Conc. Outside)**

- **When using this formula, it is assumed that the potential outside membrane always remains exactly at zero & Nernst potential that calculated is the potential inside membrane.**

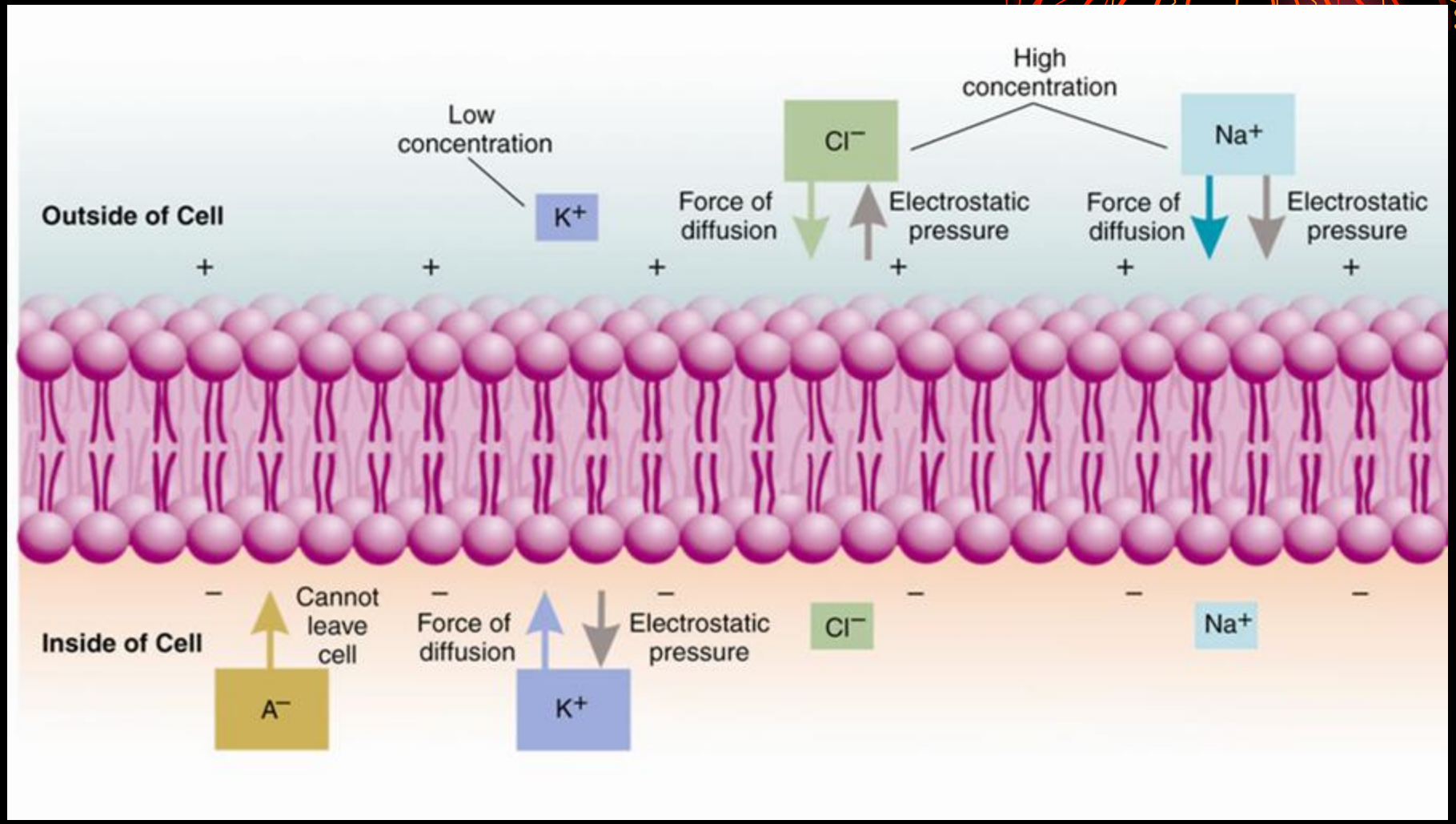
Diffusion potential when Membrane is permeable to Several different ions

- In this condition the diffusion potential that develops depends upon three factors:
  1. The polarity of electric charge of each ion
  2. The permeability of membrane (P) of each ion.
  3. The concentration (c) of respective ions on the inside (i) and outside (o) of the membrane.

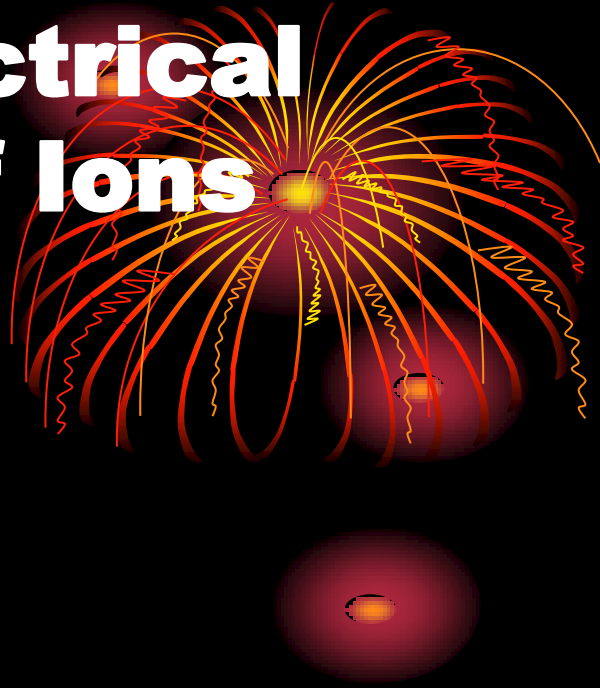
- Thus the following formula called the **GOLDMAN EQUATION or GOLDMAN-HODGKIN-KATZ EQUATION** gives the calculated membrane potentials when the Na^+, K^+, Cl^- ions are involved. The equation is:

$$EMF\ (mV) = -61 \log \frac{CNai.\ PNa + CKi.\ PKi + CClo.\ PClo}{CNao.\ PNa + CKo\ .PKo + CCli.\ PCli}$$

Diffusion potential when Membrane is permeable to Several different ions



Effect of Membrane Electrical Potential on Diffusion of Ions



- ***The "Nernst Potential."***

EMF (mV) = ±61 log Ci/Co

- ***The GOLDMAN EQUATION***

$$\text{EMF (mV)} = -61 \log \frac{CNai.\ PNai + CKi.\ PKi + CClo.\ PClo}{CNao.\ PNao + CKo.\ PKo + CCli.\ PCli}$$

The potentials calculated by above written formulas are:

- ***I. The Resting Membrane Potential of nerves***
  The membrane potential of large nerve fibres when they are not transmitting nerve signals is about -90 mV i.e., the potential inside the fiber is 90 mV more negative than the potential outside fiber is. The important factors in the establishment of such potential are as follows:

  1. Contribution of K^+ Diffusion potential - The contribution of K^+ ions to such potential due to their diffusion is of the order of -94 mV.

  2. Contribution of Na^+ Diffusion Potential - The contribution of Na^+ ions to such potential due to their diffusion is of the order of +61mV.

The potentials calculated by above written formulas are:

- The overall value of potential of membrane due to diffusion of Na^+ and K^+ ions [(by using Goldmann's equation) and as the permeability of membrane for K^+ is 100 times as great as to Na^+] comes out as - 86 mV inside the membrane. The rest -4 mV is contributed by Na^+-K^+pump.
- Thus, Resting membrane potential in large nerve or In large muscle = -90 mV.
- In small nerve fibers and small muscle fiber It is between - 40 mV to - 60 mV instead of -90 mV.

- ***II. The action potential of nerve***

- **Nerve signals are transmitted by action potentials which are rapid changes in the membrane potential. Each action potential begins with a sudden change from negative to positive membrane potential and then ends with an almost equally rapid change back again to the resting potential. To conduct the nerve signal the action potential moves along the nerve fibre until it comes to the fibre's end. The successive stages of action potential are as follows:**
- ***1. Resting stage (Polarised stage)*** **- The resting membrane Potential before the action potential occurs. The membrane is said to be "Polarised" during this stage because of the presence of such a (-) ve charge inside.**

II. The action potential of nerve

- ***2. Depolarisation stage*** **- The time when normal -90 mV polarized stage in lost, with potential rising rapidly in the pozitive direction. (DEPOLARIZATION).**
- **The phenomenon occurs due to a sudden change in the permeable nature of axolemma i.e., it becomes extremely permeable to Na^+, allowing trememdous inflow of Na^+ inside the axon through axolemma.**

II. The action potential of nerve

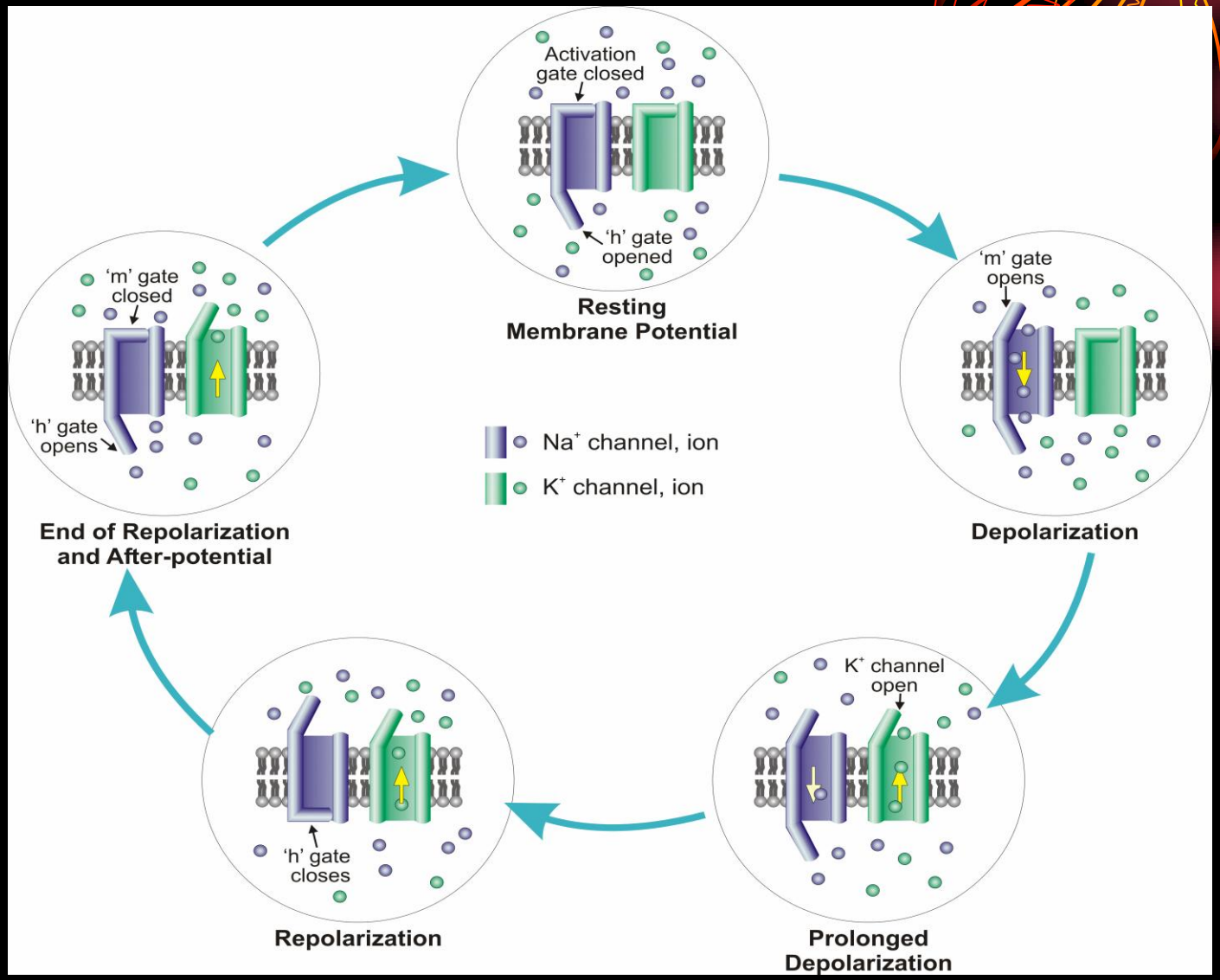
- ***3. Repolarisation stage*** - After depolarisation stage, a rapid diffusion of K^+ to exterior establishes the normal negative resting membrane potential. This is called repolarisation of membrane. The phenomenon occurs within a few 10,000ths of the second after depolarisation of membrane. The essential role in both depolarisation and repolarisation is played by voltage gated Na^+channels and also by voltage gated K^+channels. These two voltage gated channels are present in addition to Na^+- K^+pump and Na^+- K^+leak channels. The voltage gated Na^+channels has 2 gates - one near the outside of the channel called ACTIVATION GATE and another near the inside called INACTIVATION GATE.

- In the resting stage (-90 mV) the activation gate is closed which prevents any entry of Na^+interior of the fiber through these channels. However inactivation gate is open at this time.
- When membrane potential rises from - 90 mV towards zero and reaches a voltage about -15 - 20 mV more than -90 mV i.e., near about -70 mV, there occur all of a sudden a conformational change in the activation gate flipping it to the open position.
- This is called activated state during which Na^+ can literally pour inward through this channel (as both the gates are open now); thus increasing the permeability (for Na^+) of membrane 500 to 5000 fold.

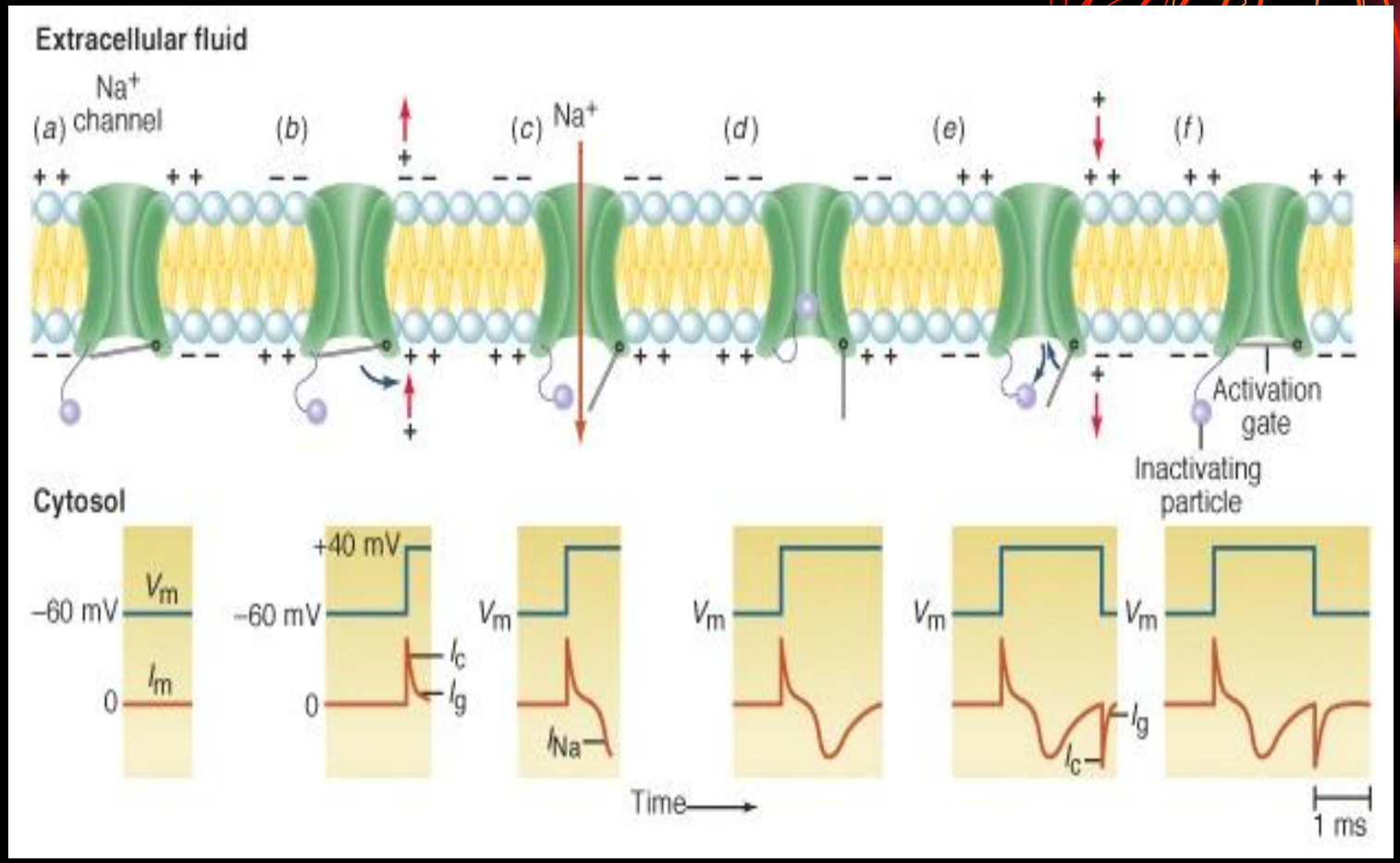
- The same increase in voltage (that opens the activation gate) also closes the inactivation gate. However, closure of inactivation gate occurs 10,000ths of a second after the activation gate opens i.e., the conformational change that flips the inactivation gate close is a slower process, whereas the conformational change that opens the activation gate is a very rapid process.
- Therefore we can say that the Na^+channel remained open for a few $10{,}000^{th}$ of a second and after that it closes so Na^+ can no longer pour to the inside of the membrane. At this point, the membrane potential begins to recover back towards the resting state (repolarization process)

- A very important characteristic of the Na^+ channel inactivation process is that the INACTIVATION GATE WILL NOT REOPEN AGAIN UNTIL THE MEMBRANE POTENTIAL RETURNS EITHER TO or NEARLY TO THE ORIGINAL RESTING MEMBRANE POTENTIAL LEVEL.
- Thus, it is not possible for Na channel to open again without the repolarization of nerve fiber.
- Thus movement of Na^+ ions back from inside to outside is not possible.
- To compensate such a huge entry of Na^+ the movement of K^+ occur from inside towards outside of cell through voltage gated K^+ channels.

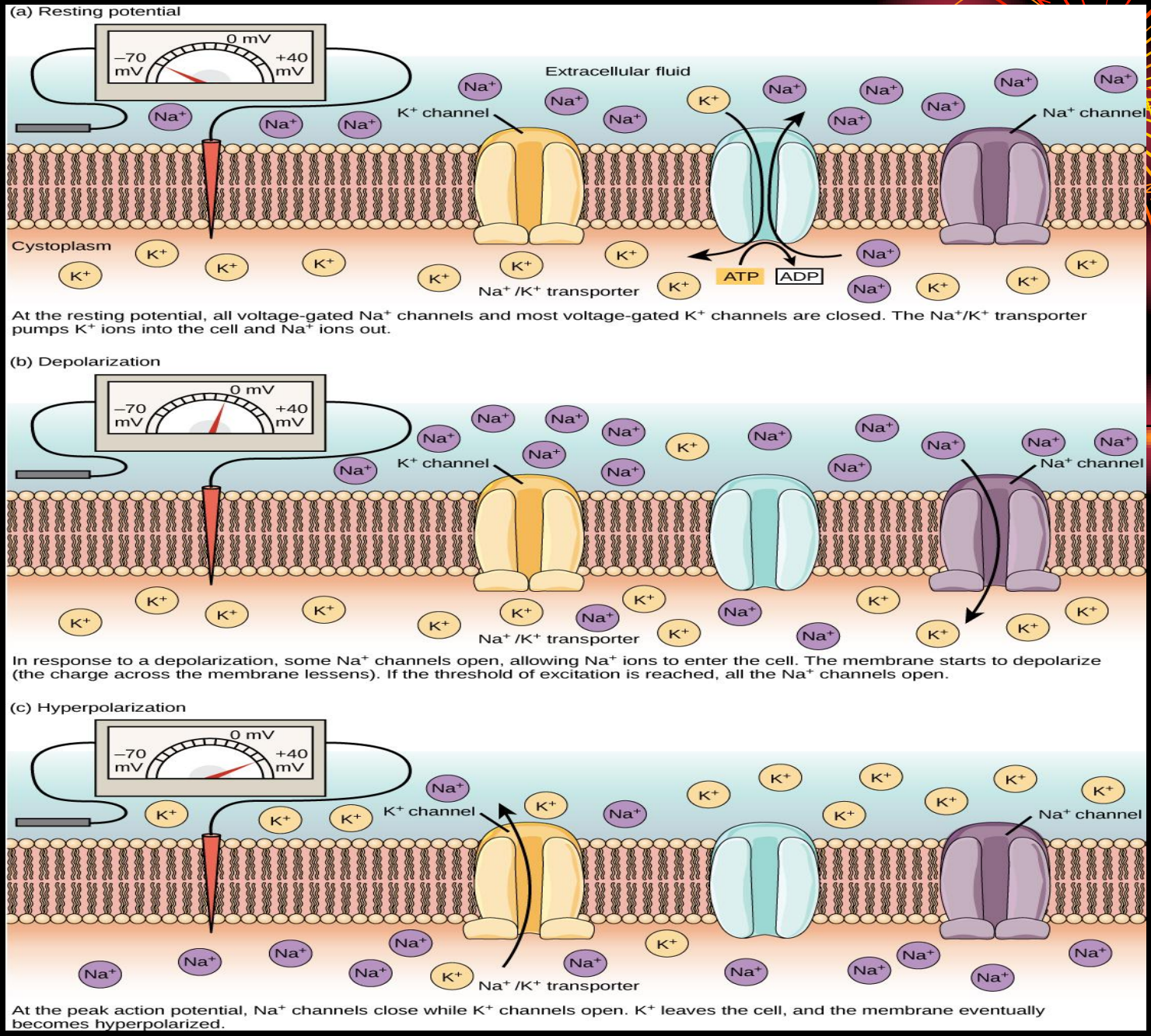
Potential gated sodium channels



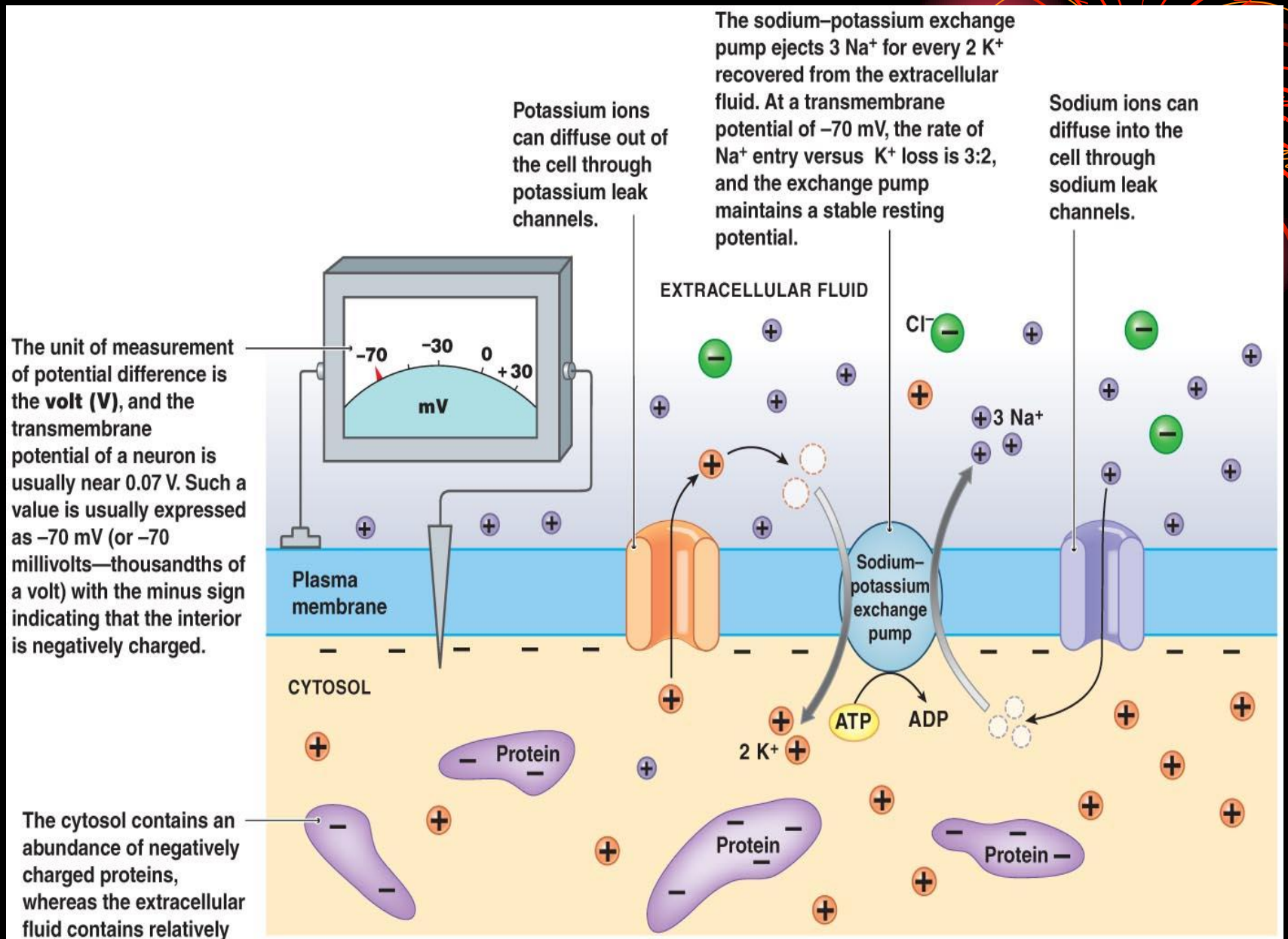
Na channels


Extracellular fluid
Na+ channel
(a)
(b)
(c)
Na+
(d)
(e)
(f)
Activation gate
Inactivating particle
Cytosol
–60 mV
Vm
Im
0
+40 mV
–60 mV
Ic
Ig
0
Vm
INa
Vm
Vm
Vm
Ig
Ic
Time
1 ms

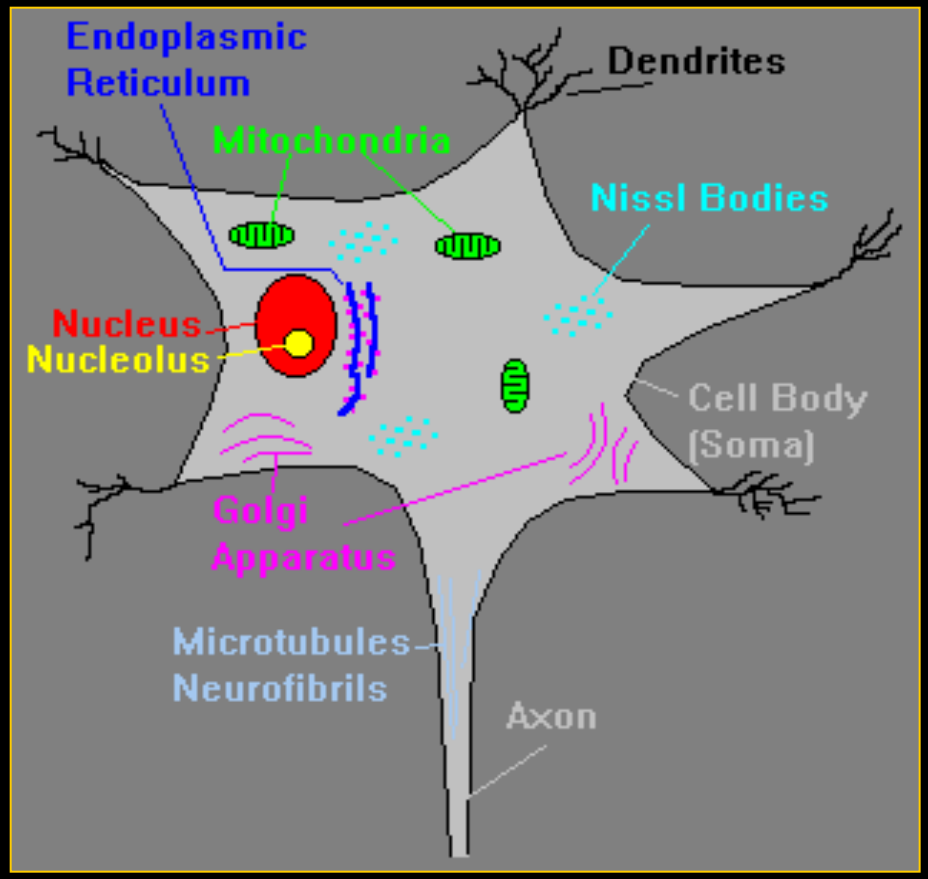
- The voltage gated K^+channel have only one gate near the inside of the channel.
- During resting stage the gate of K^+channel is closed, but when the potential rises from - 90mV towards zero the voltage change causes a slow conformational opening of the gate and allows increase K^+ diffusion outward through the channel.
- However, because of the slowness of opening of these channels, they mainly open just at the same time when the Na^+ channels are beginning to become inactivated and therefore are closing.
- Thus the decrease in Na^+ entry to the cell and simultaneously increase in the K^+ exit from the cell greatly speeds the repolarization process, leading within a few 10,000ths of a second to full recovery of the resting membrane potential.

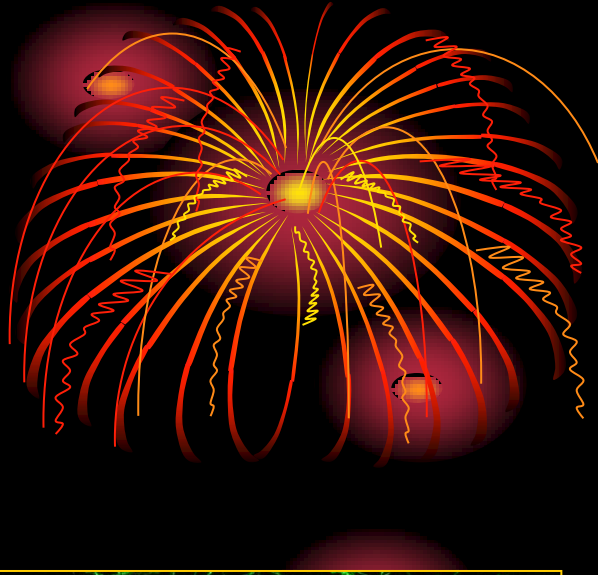

(a) Resting potential
0 mV
–70 mV
+40 mV
Extracellular fluid
K+ channel
Na+ channel
Cystoplasm
Na+ /K+ transporter
ATP
ADP
At the resting potential, all voltage-gated Na+ channels and most voltage-gated K+ channels are closed. The Na+/K+ transporter pumps K+ ions into the cell and Na+ ions out.
(b) Depolarization
0 mV
–70 mV
+40 mV
K+ channel
Na+ channel
Na+ /K+ transporter
In response to a depolarization, some Na+ channels open, allowing Na+ ions to enter the cell. The membrane starts to depolarize (the charge across the membrane lessens). If the threshold of excitation is reached, all the Na+ channels open.
(c) Hyperpolarization
0 mV
–70 mV
+40 mV
K+ channel
Na+ channel
Na+ /K+ transporter
At the peak action potential, Na+ channels close while K+ channels open. K+ leaves the cell, and the membrane eventually becomes hyperpolarized.

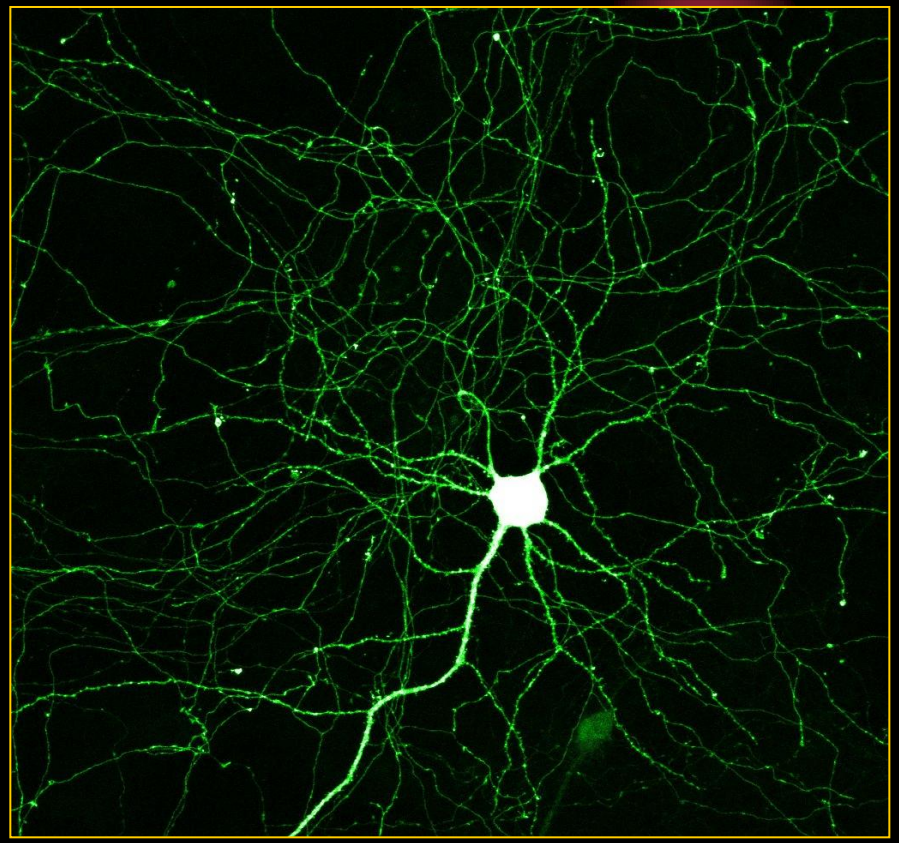
- To summaries the whole process we can say that during the resting state, the conductance of for K^+ions is shown to be 50 to 100 times as great as the conductance for Na^+ ions. This is caused by much greater leakage of K^+ than Na^+ through the leak channels. However at the onset of the action potential, the Na channels become instantaneously activated and allow an up to 5000 fold in Na^+ conductance.
- Then the inactivation gates closes the Na channels within another few fractions of a millisecond. The onset of action potential also causes opening of K channels (begin opening a fraction of a millisecond after the Na^+ channels open). At last the return of membrane potential to the negative state causes the K channels to close back to their original status but only after a short delay again.



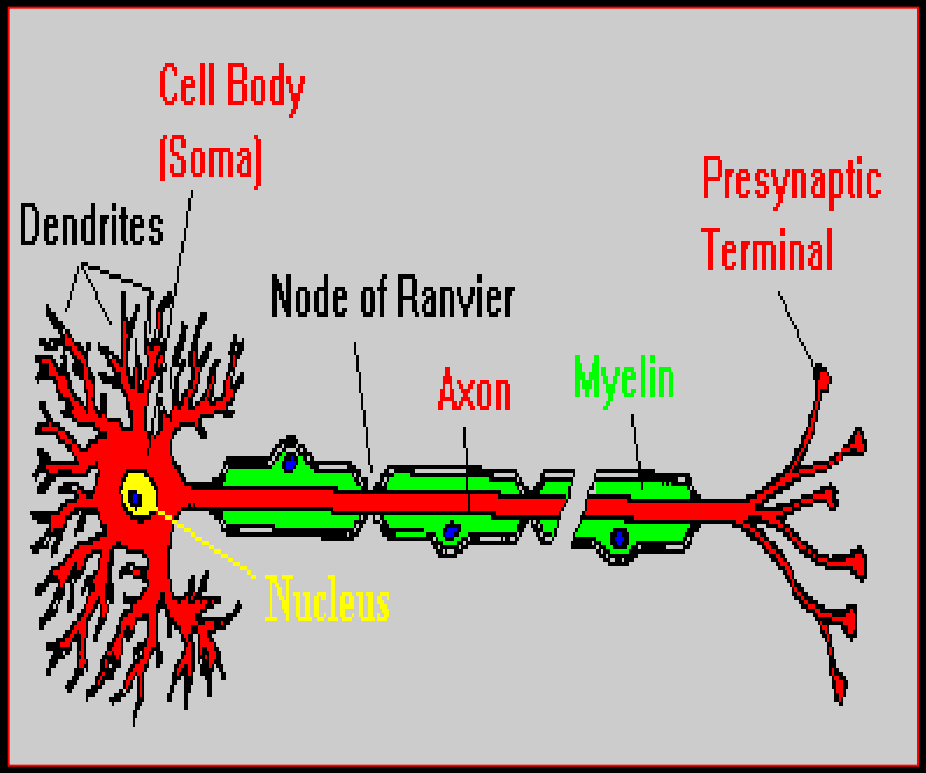
An overview of the events responsible for the normal resting potential of a neuron


Endoplasmic Reticulum
Dendrites
Mitochondria
Nissl Bodies
Nucleus
Nucleolus
Cell Body (Soma)
Golgi Apparatus
Microtubules
Neurofibrils
Axon

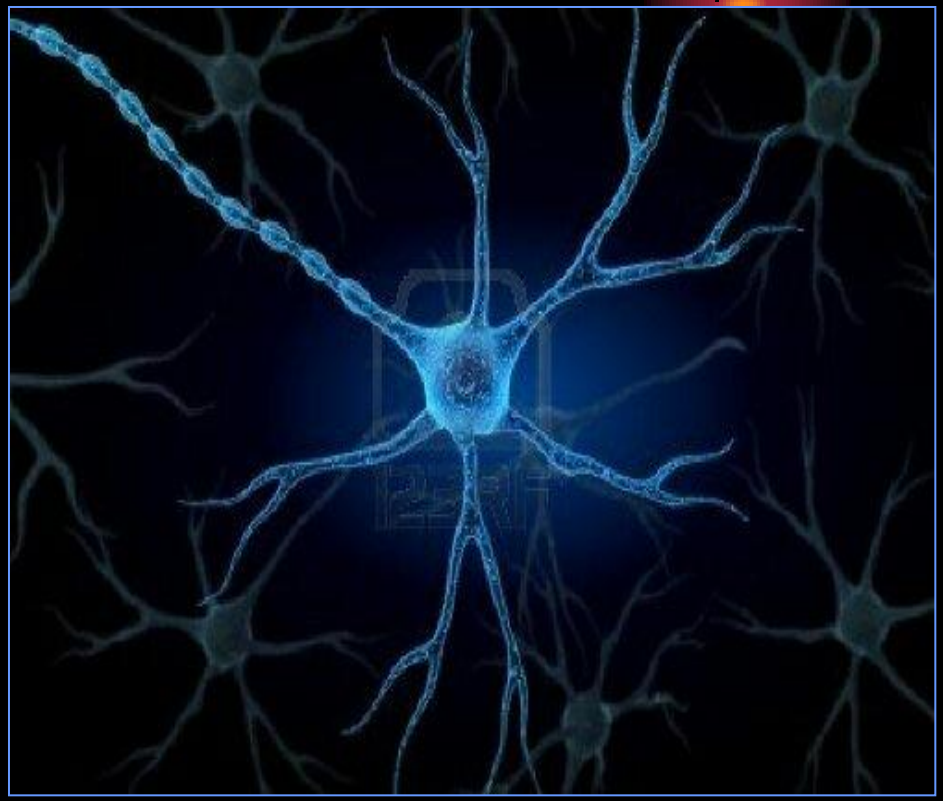


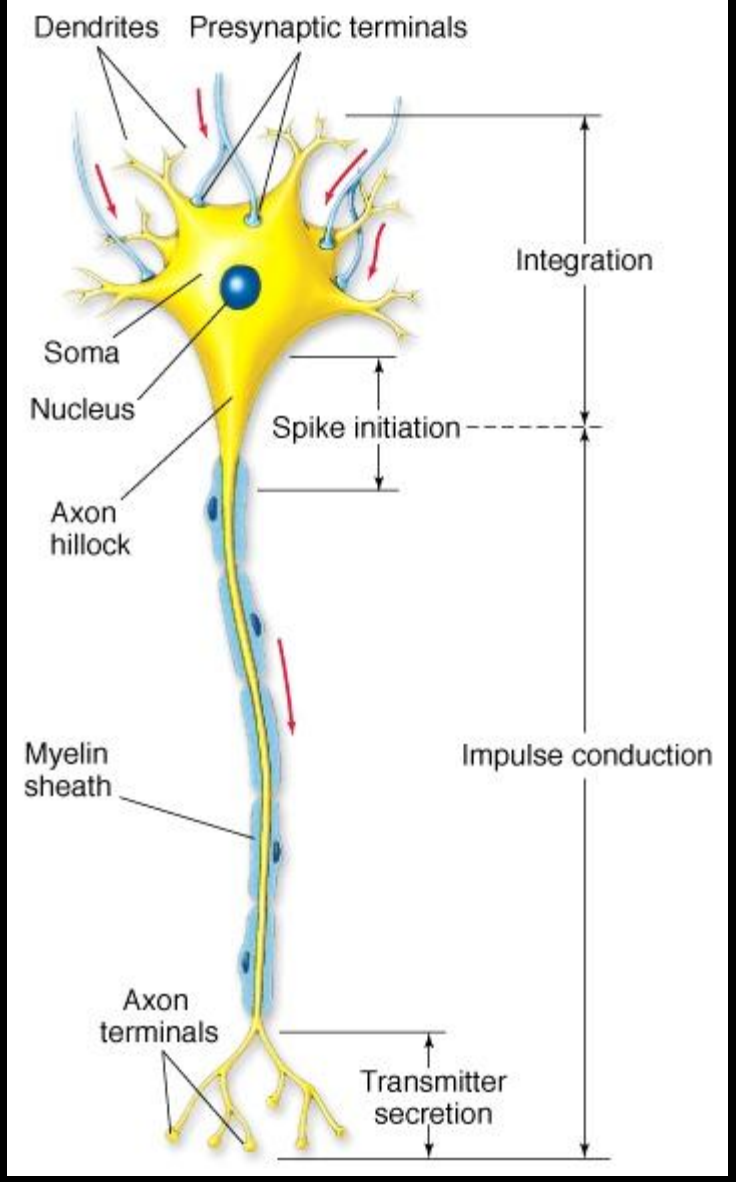


neuron

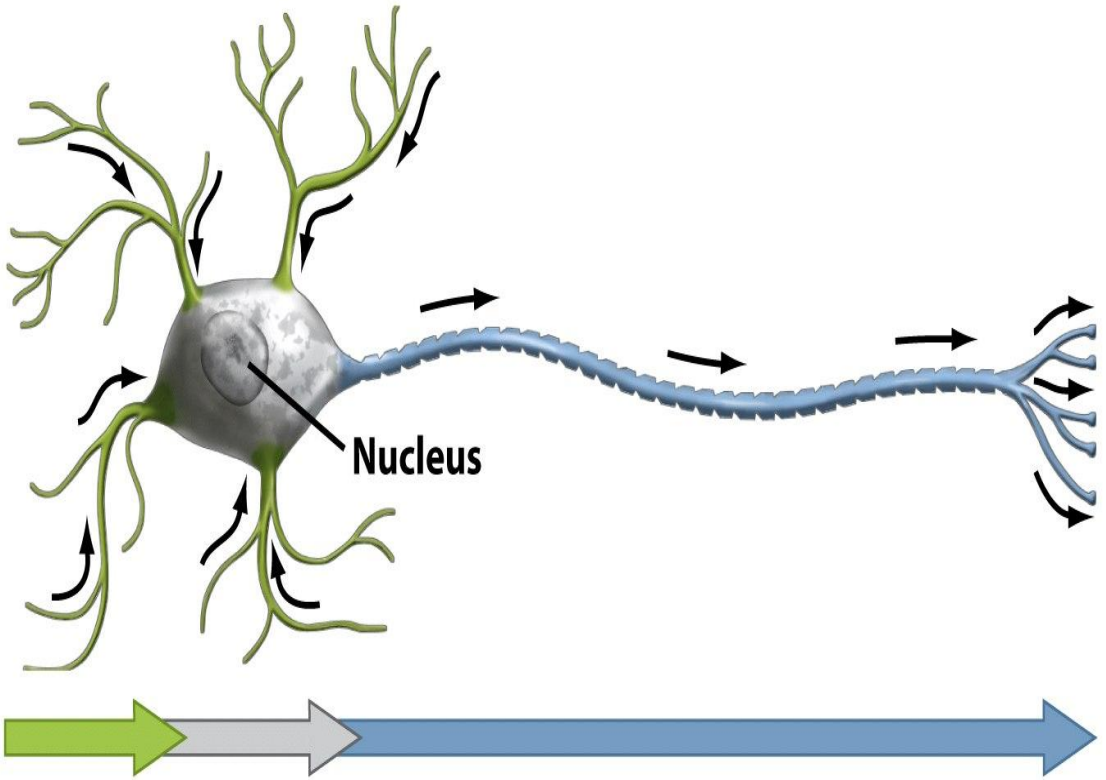

Cell Body
(Soma)
Dendrites
Presynaptic
Terminal
Node of Ranvier
Axon
Myelin
Nucleus

neuron





Information flow through neurons



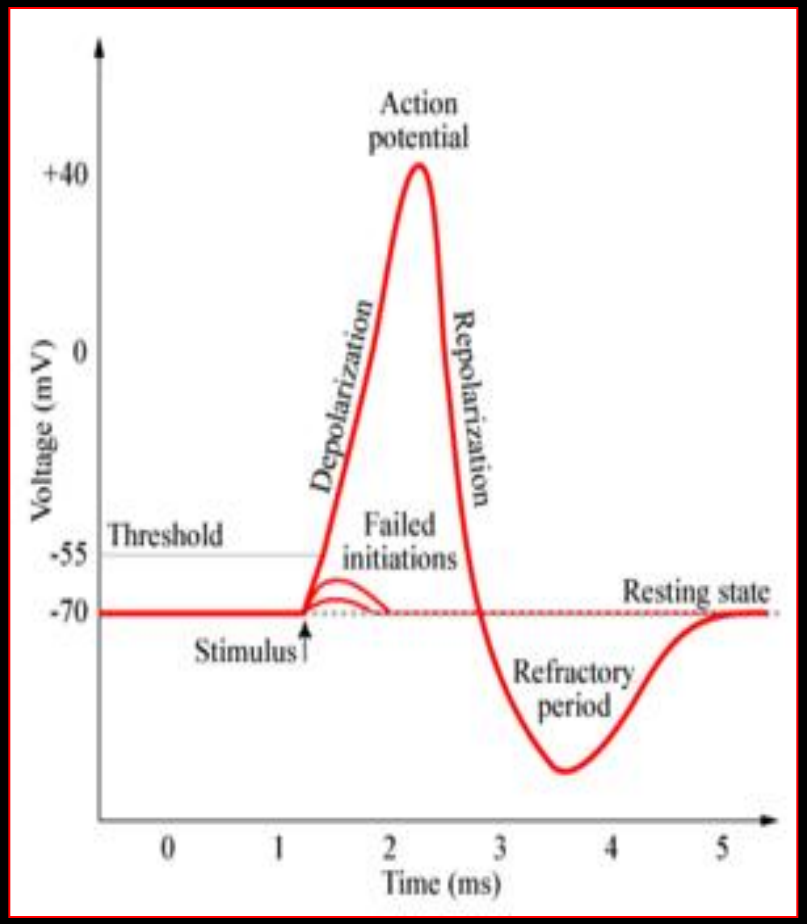
Dendrites
Collect electrical signals

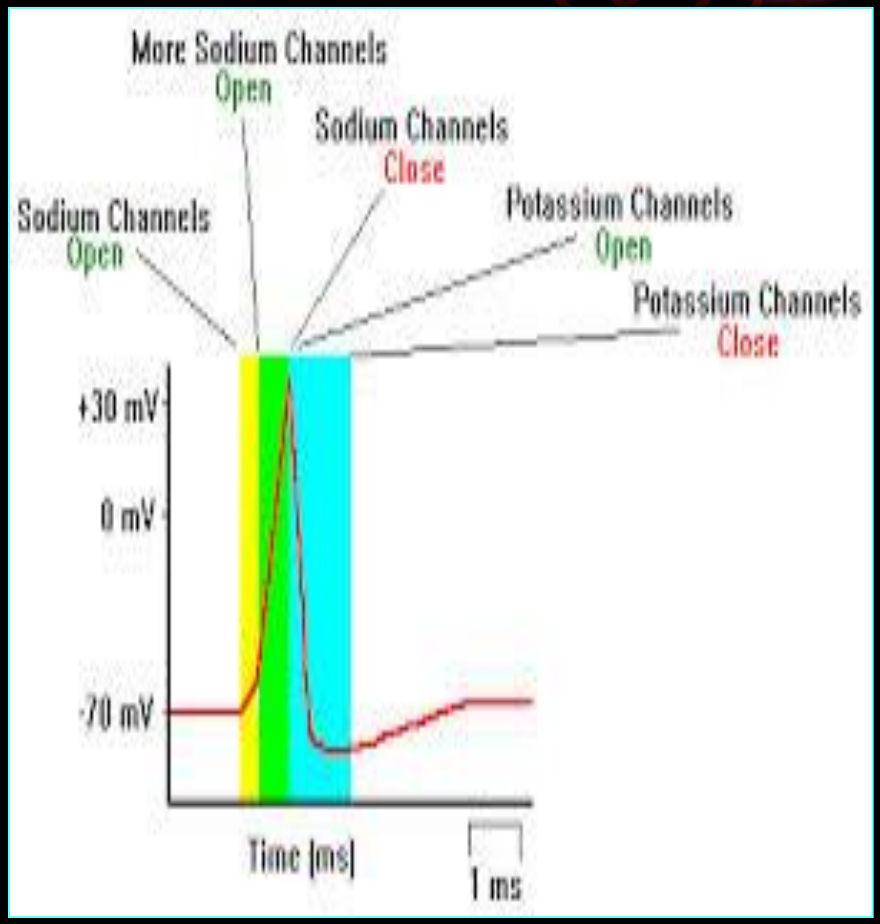
Cell body
Integrates incoming signals and generates outgoing signal to axon

Axon
Passes electrical signals to dendrites of another cell or to an effector cell

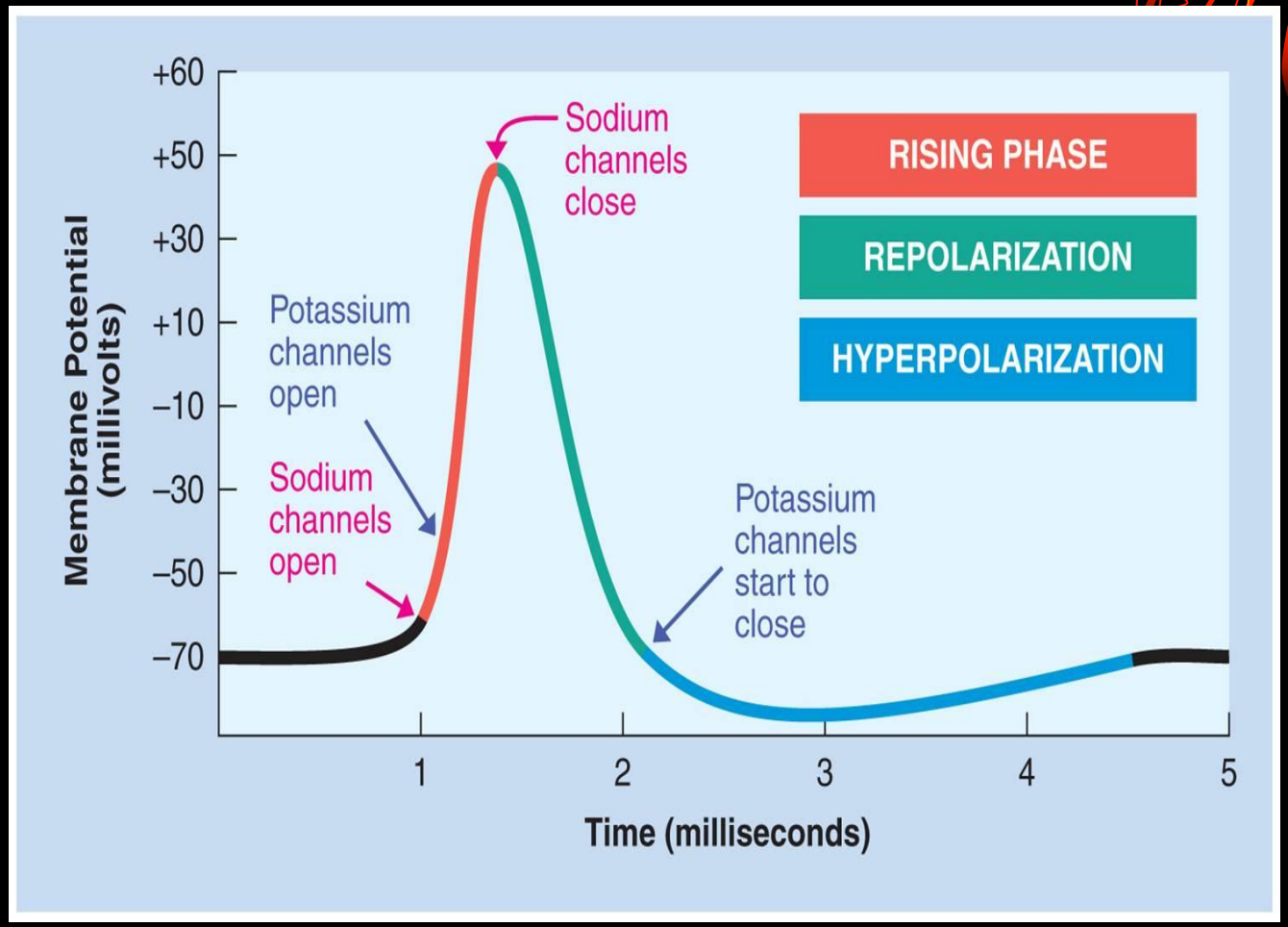
Figure 45-2b Biological Science, 2/e

To learn how neurons carry messages, we must understand the generation of the action potential.

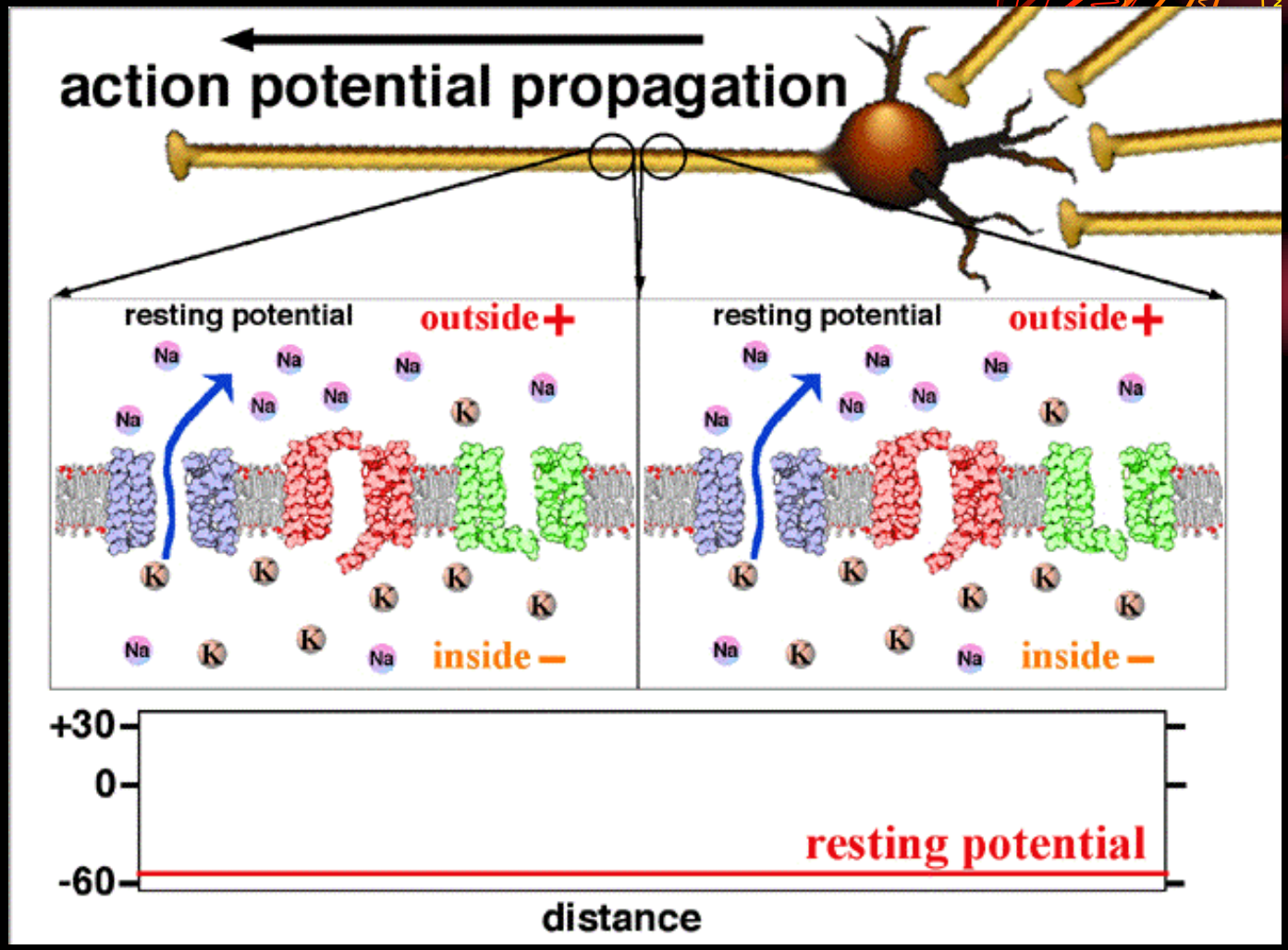




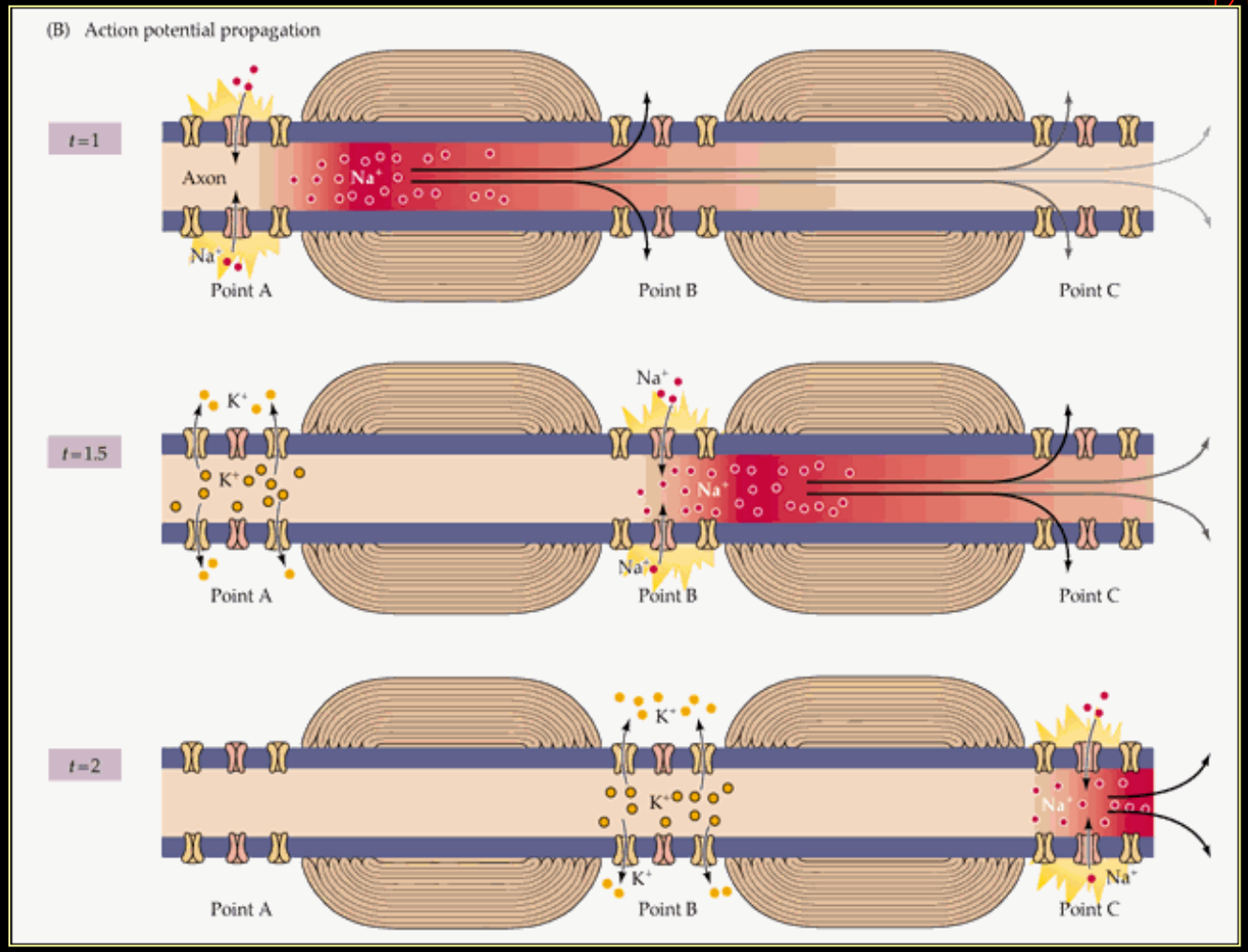
Action potential of the neuron



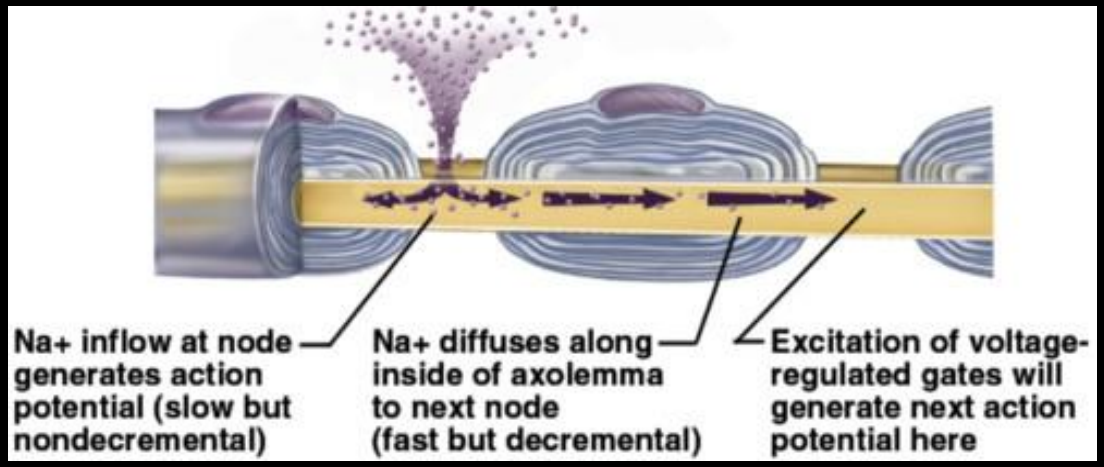
Neuronal action potential

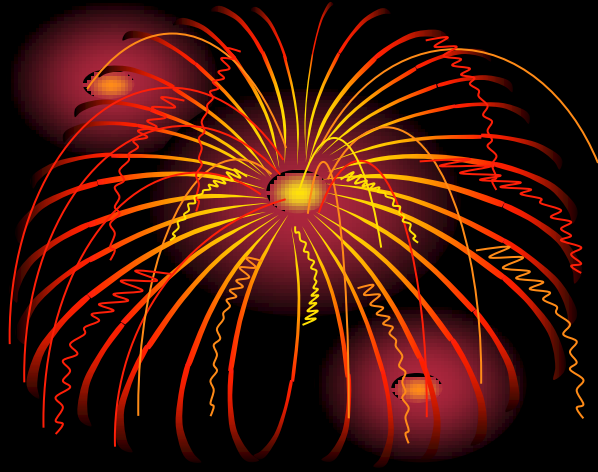


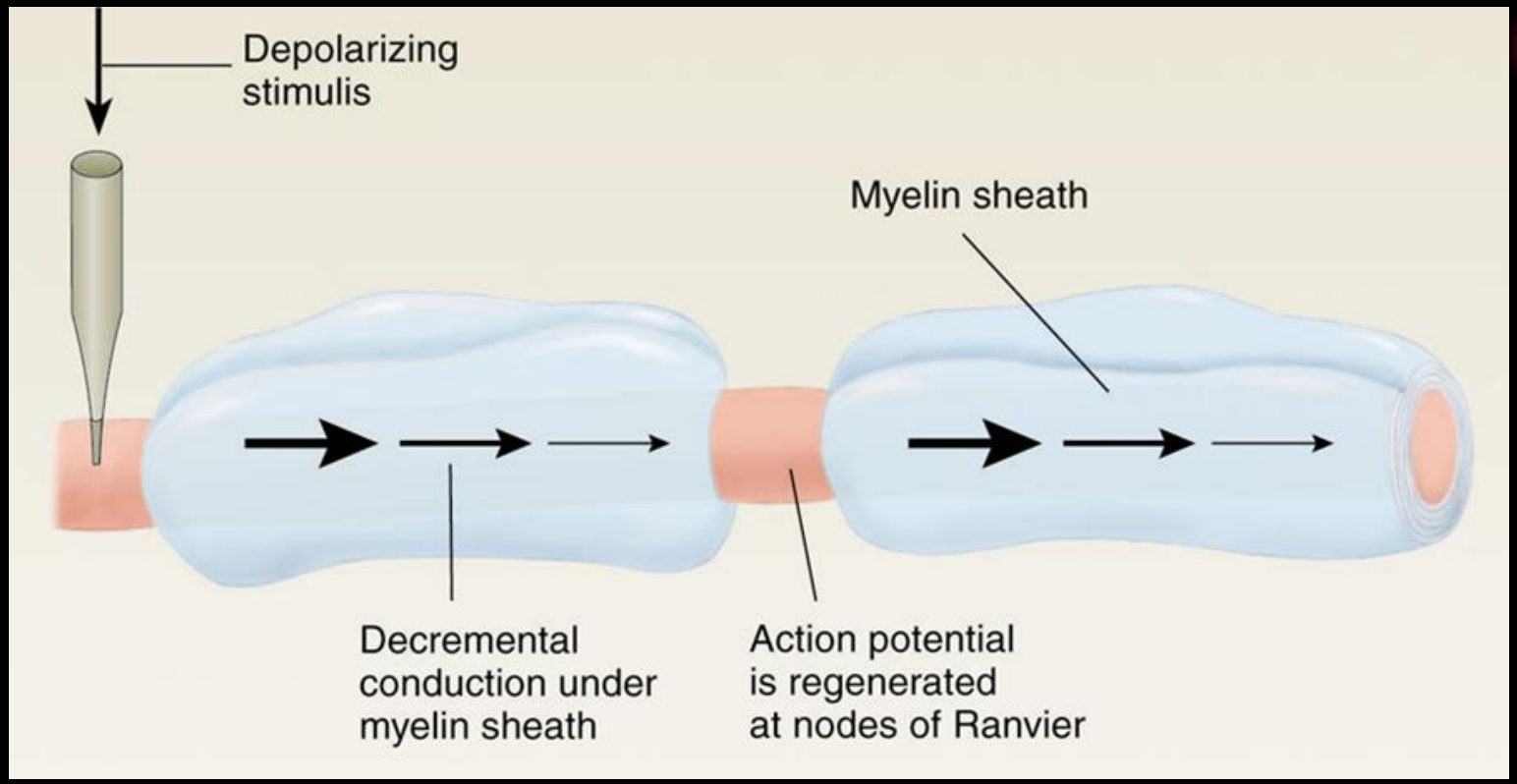
- **The depolarization process travels along the entire length of the fiber.**
- **This transmission of the depolarization process along a nerve or muscle fiber is called a *nerve* or *muscle impulse.***



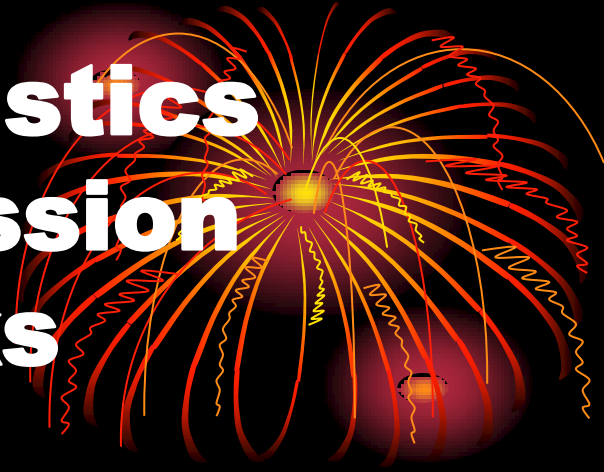
Action potential propagation


Na+ inflow at node generates action potential (slow but nondecremental)
Na+ diffuses along inside of axolemma to next node (fast but decremental)
Excitation of voltage-regulated gates will generate next action potential here




Depolarizing stimulis
Myelin sheath
Decremental conduction under myelin sheath
Action potential is regenerated at nodes of Ranvier

Special Characteristics of Signal Transmission in Nerve Trunks



- The large fibers are *myelinated*, and the small ones are *unmyelinated.*
- The average nerve trunk contains about twice as many unmyelinated fibers as myelinated fibers.
- "Saltatory" Conduction in Myelinated Fibers from Node to Node of Ranvier.
- The speed of transmission depends on diameter and myelination of the nerve fibers.

Lows of transmission of nerve signals

- 1. The neuron must be anatomically and functionally intact.
- 2. The nerve fibers conduct the action potential separately.
- 3. The nerve fibers has possibility to conduct action potential in two directions.

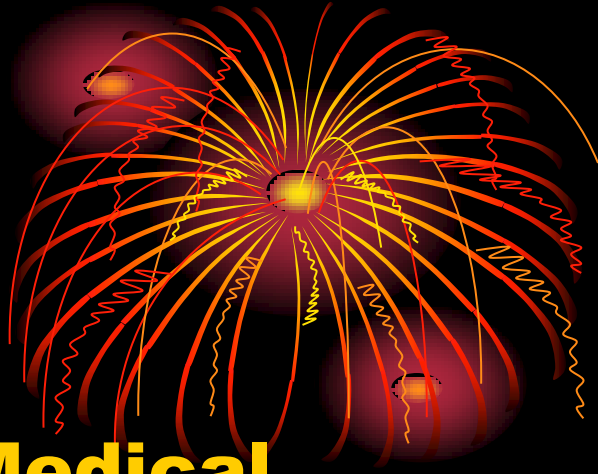
The type of nerve fibers

Table 2: Nerve Fiber Types and Nerve Blocking

Fiber Type	Function	Diameter (microns)	Mystification	Conduction Velocity (m/s)	Sensitivity to Nerve Block
Type A					
Alpha (α)	Proprioception, motor	12-20	Heavy	70-120	+
Beta (β)	Touch, pressure	5-12	Heavy	30-70	++
Gamma (γ)	Muscle spindles	3-6	Heavy	15-30	++
Delta (δ)	Pain, temperature	2-5	Heavy	12-30	+++
Type B	Preganglionic autonomic	<3	Light	3-15	++++
Type C					
Dorsal root	Pain	0.4-12	None	0.5-2.3	++++
Sympathetic	Postganglionic	0.3-1.3	None	0.7-2.3	++++

- Pain practitioners block the nerves transmitting pain impulses (Type A-δ, Type C)
- Lower concentrations of local anesthetic will only block the small unmyelinated and lightly myelinated (Type C and Type A-δ) fibers
- Middle-frequency currents (2,000-20,000 Hz) block smaller unmyelinated (Type C) and small myelinated (Type A-δ) fibers
- Larger fibers (Type A-α, β, γ) require high-amplitude currents and are usually spared in electrical, low-dose chemical (eg, labor epidural) blocks

Literature:



- Guyton & Hall, Textbook of Medical Physiology, 13th edition, SAUNDERS ELSEVIER Inc., Philadelphia, USA, 2016
- Linda S. Constanzo, Physiology, 5th edition, SAUNDERS ELSEVIER Inc., Philadelphia, USA, 2014
- Ganong's Review of Medical Physiology, 25th edition, International edition, Singapore, 2016

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