Electrical signals in cells

Introduction:

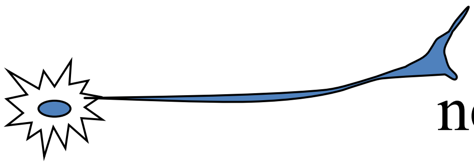
Nerves and muscles are called **excitable tissue** because they respond to:

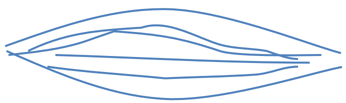
a) Chemical stimuli
b) Mechanical stimuli
c) Electrical stimuli

- Muscles demonstrate by **contraction,** while nerves by **integration and transmission**.

Excitable tissues

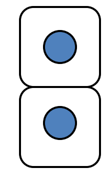
excitable


neuron


muscle

- Excitable tissues have more negative RMP
  (- 70 mV to - 90 mV)

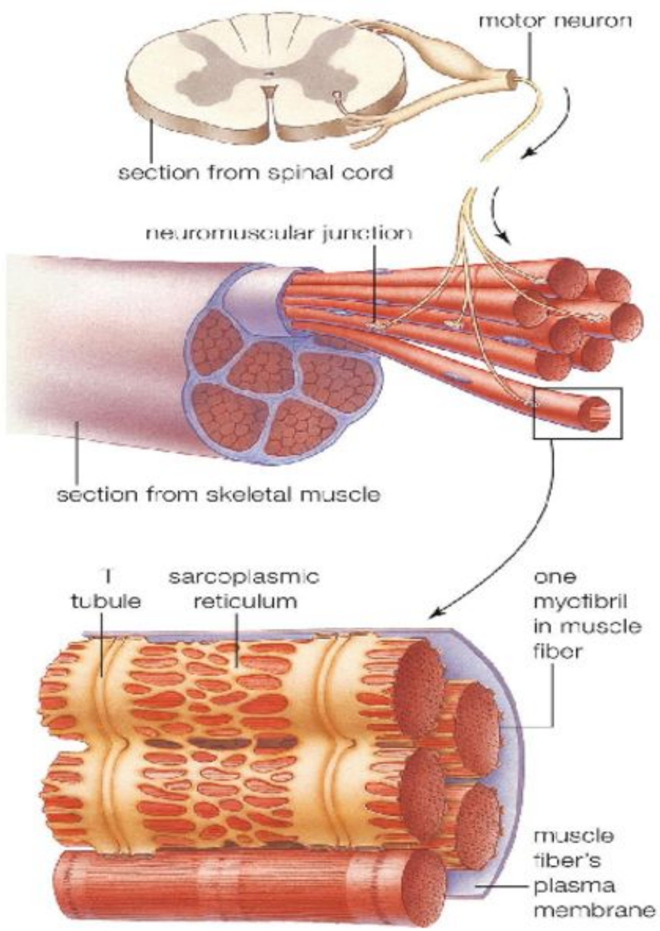
Non-excitable

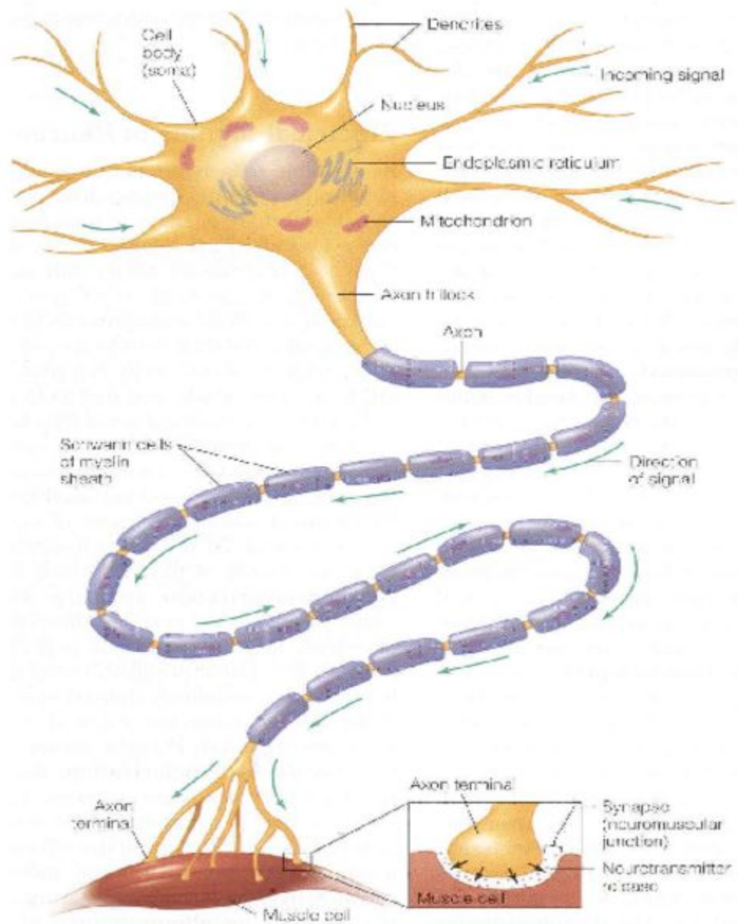

GIT

- Non-excitable tissues have less negative RMP

-53 mV epithelial cells
-8.4 mV RBC
-20 to -30 mV fibroblasts
-58 mV adipocytes

Excitable Cells





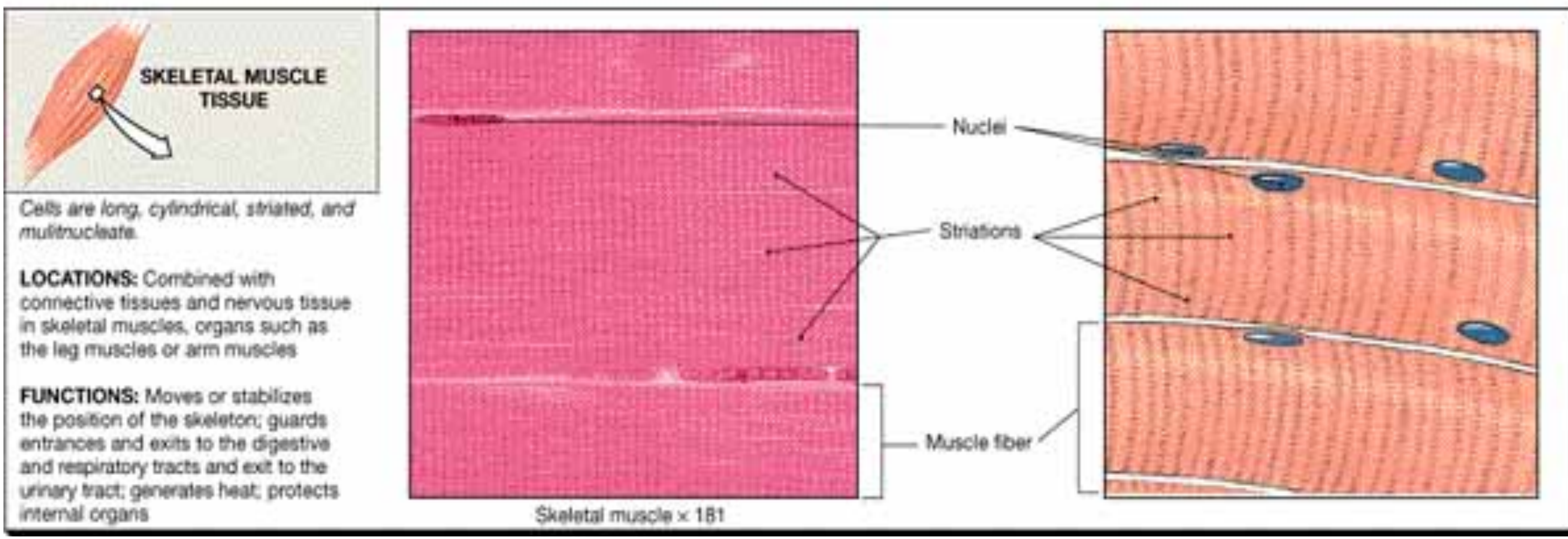
Types of Muscle

- **Skeletal**
  - Attached to bones
  - Makes up 40% of body weight
  - Responsible for locomotion, facial expressions, posture, respiratory movements, other types of body movement
  - ***Voluntary in action; controlled by motor neurons***
- **Smooth**
  - In the walls of hollow organs, blood vessels, eye, glands, skin
  - Some functions: propel urine, mix food in digestive tract, dilating/constricting pupils, regulating blood flow,
  - In some locations, autorhythmic
  - ***Controlled involuntarily by endocrine and autonomic nervous systems***
- **Cardiac**
  - Heart: major source of movement of blood
  - Autorhythmic
  - ***Controlled involuntarily by endocrine and autonomic nervous systems***

Types of muscle tissue:

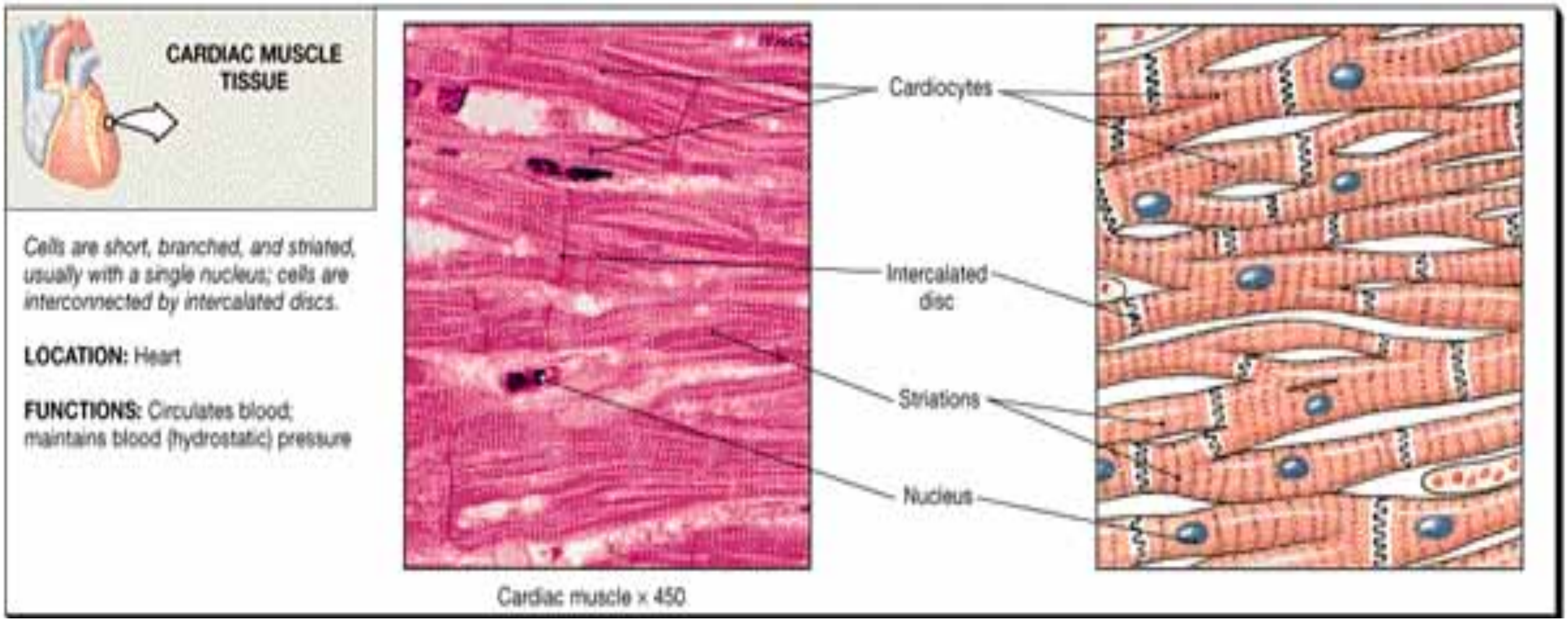
Skeletal muscle tissue

- Associated with & attached to the **skeleton**
- Under our conscious (***voluntary***) control
- Microscopically the tissue appears ***striated***
- Cells are **long**, **cylindrical** & **multinucleate**



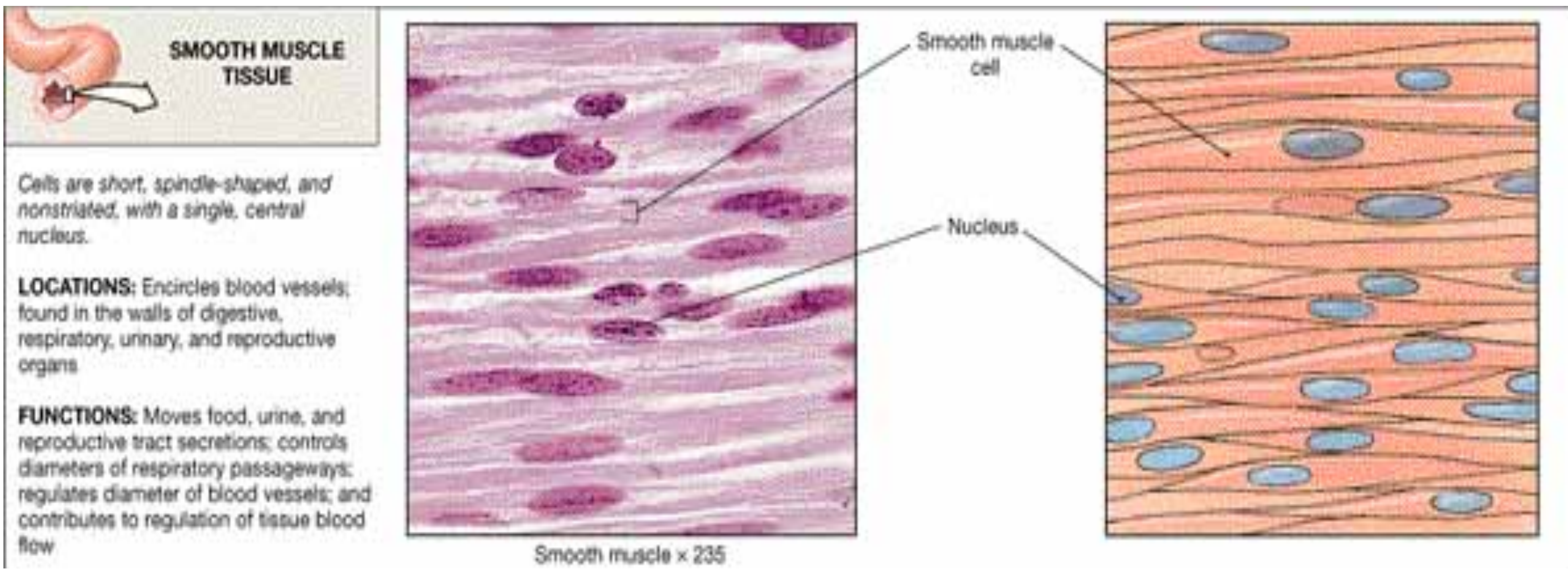
Cardiac muscle tissue

- Makes up **myocardium** of heart
- Unconsciously **(*involuntarily*)** controlled
- Microscopically appears ***striated***
- **Cells** are **short**, **branching** & have a **single nucleus**
- Cells connect to each other at ***intercalated discs***

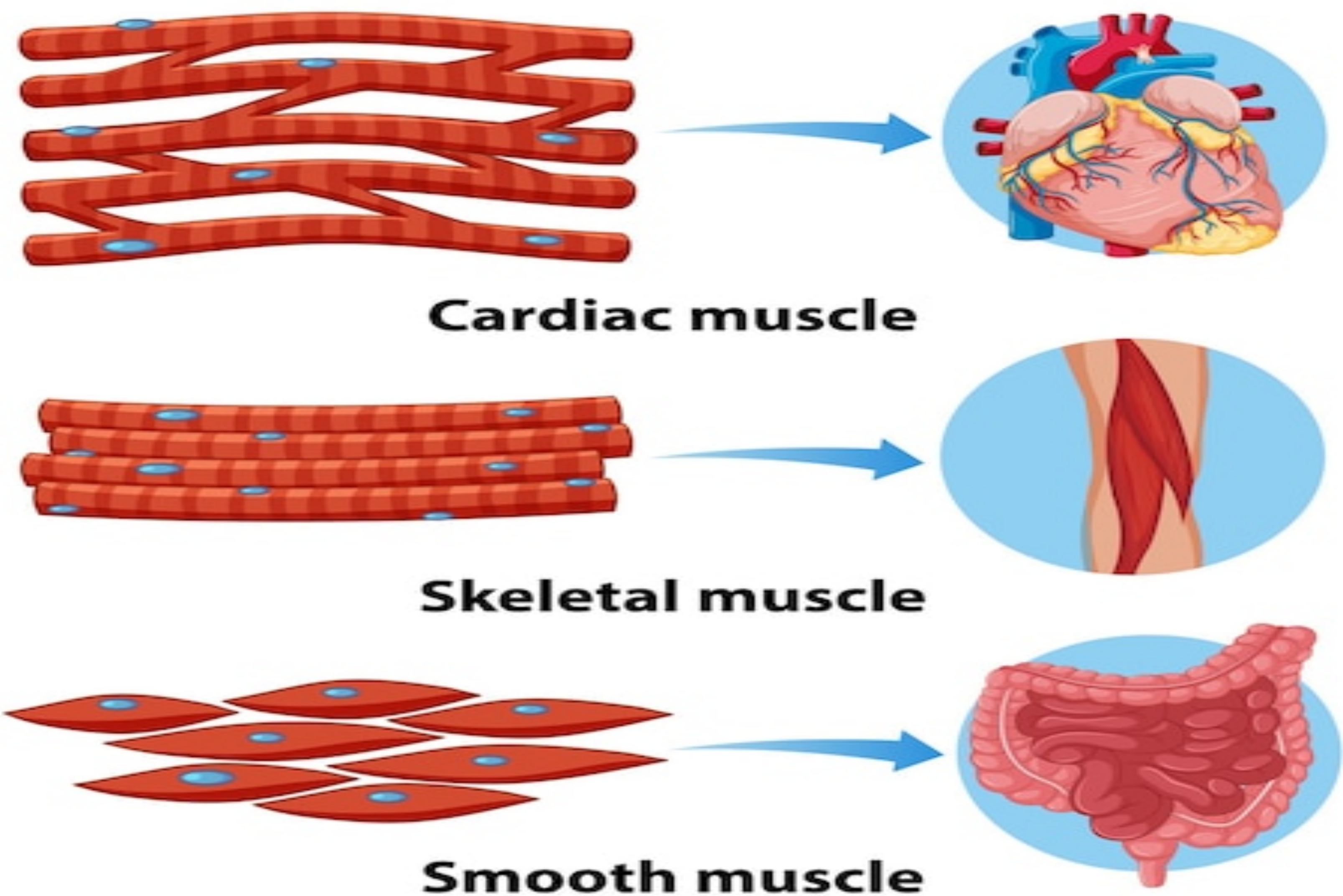


Smooth (visceral) muscle tissue

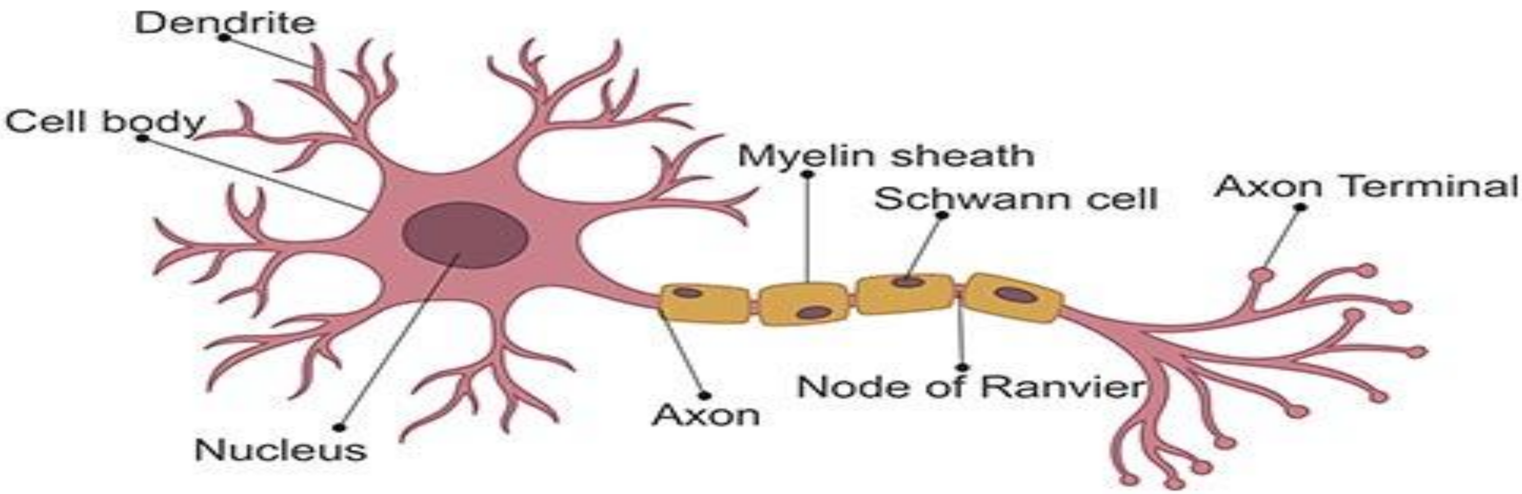
- Makes up walls of **organs** & **blood vessels**
- Tissue is ***non-striated*** & ***involuntary***
- Cells are **short, spindle-shaped** & have a **single nucleus**
- Tissue is **extremely extensible**, while still retaining ability to contract

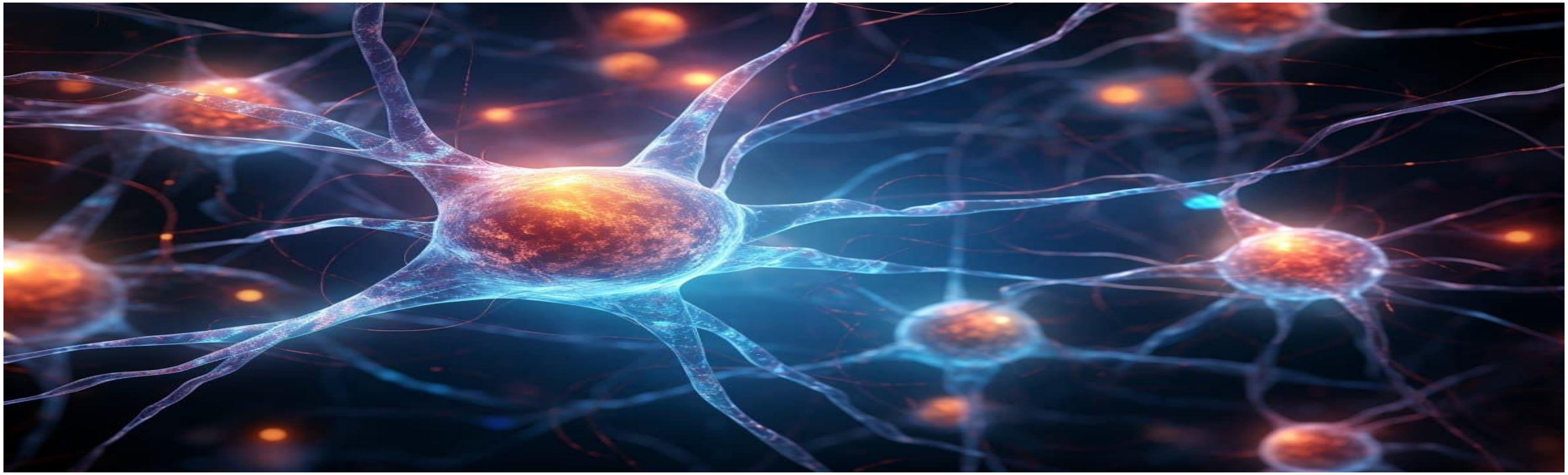


TYPE OF MUSCLE CELLS

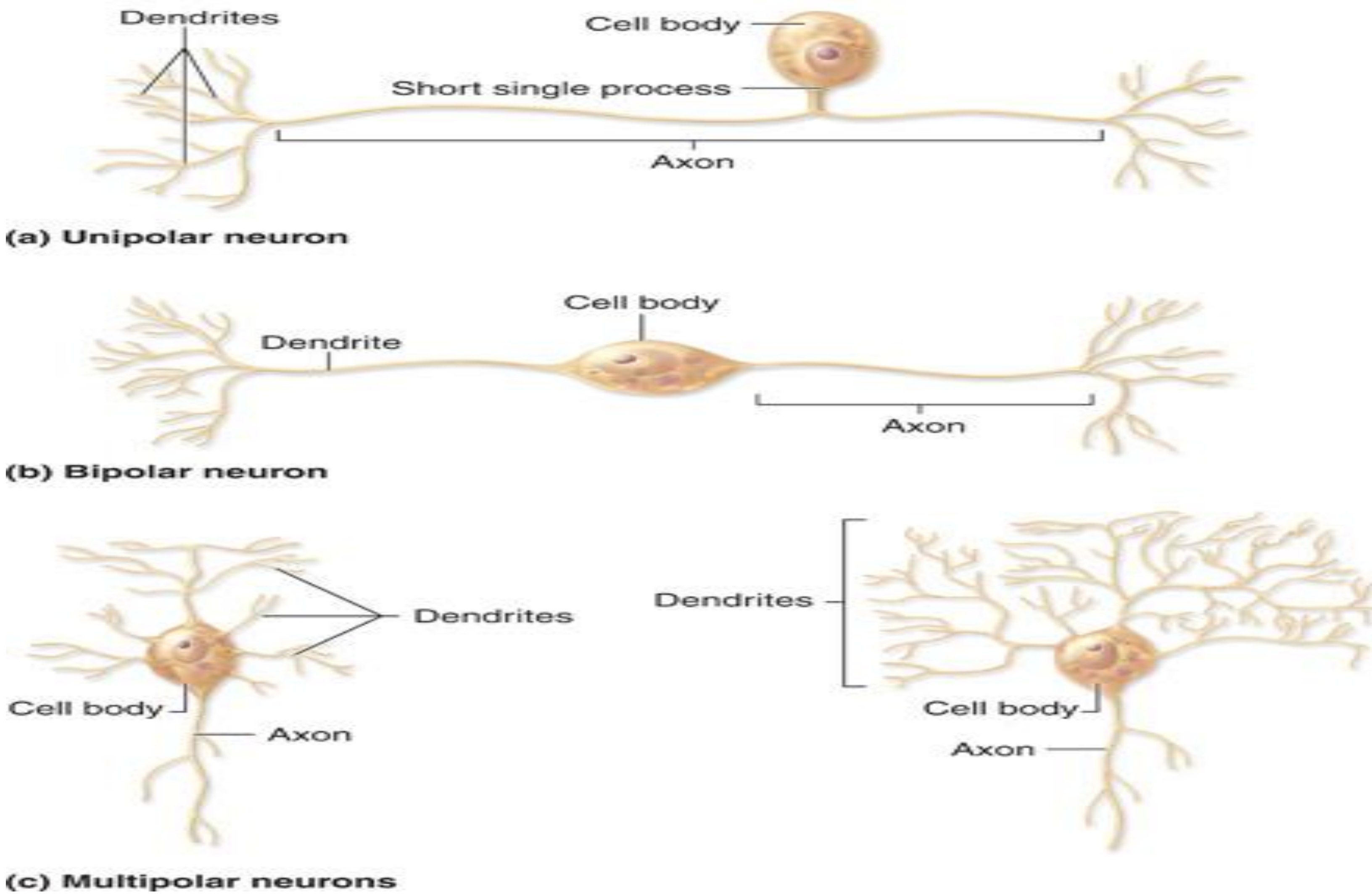


Neuron


Dendrite
Cell body
Myelin sheath
Schwann cell
Axon Terminal
Nucleus
Axon
Node of Ranvier



Types of Neurons



Electrical signals in neurons and muscle cells:

- Production of signals depend on two basic features of the plasma membrane of excitable cells:

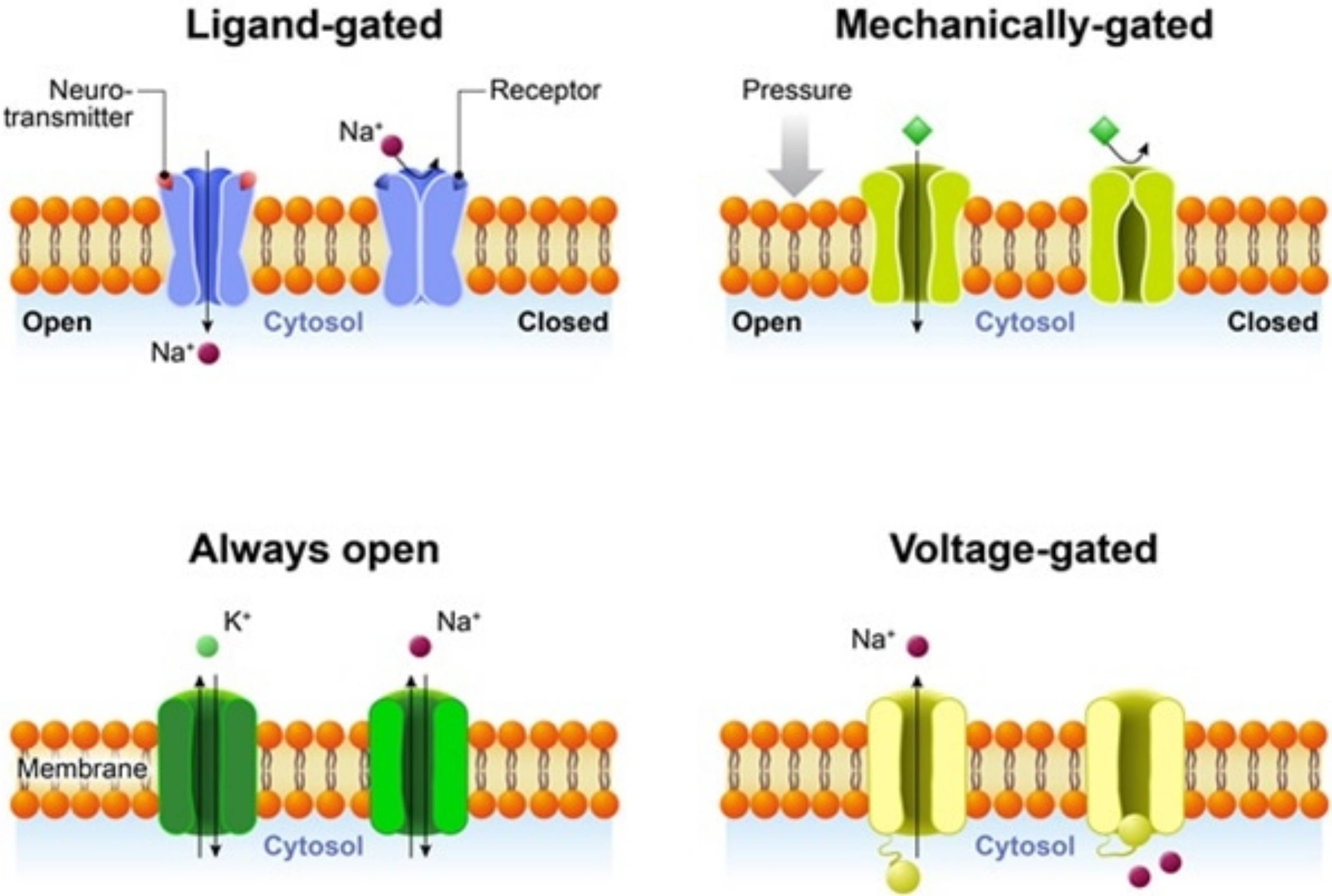
i) **Ion channels**

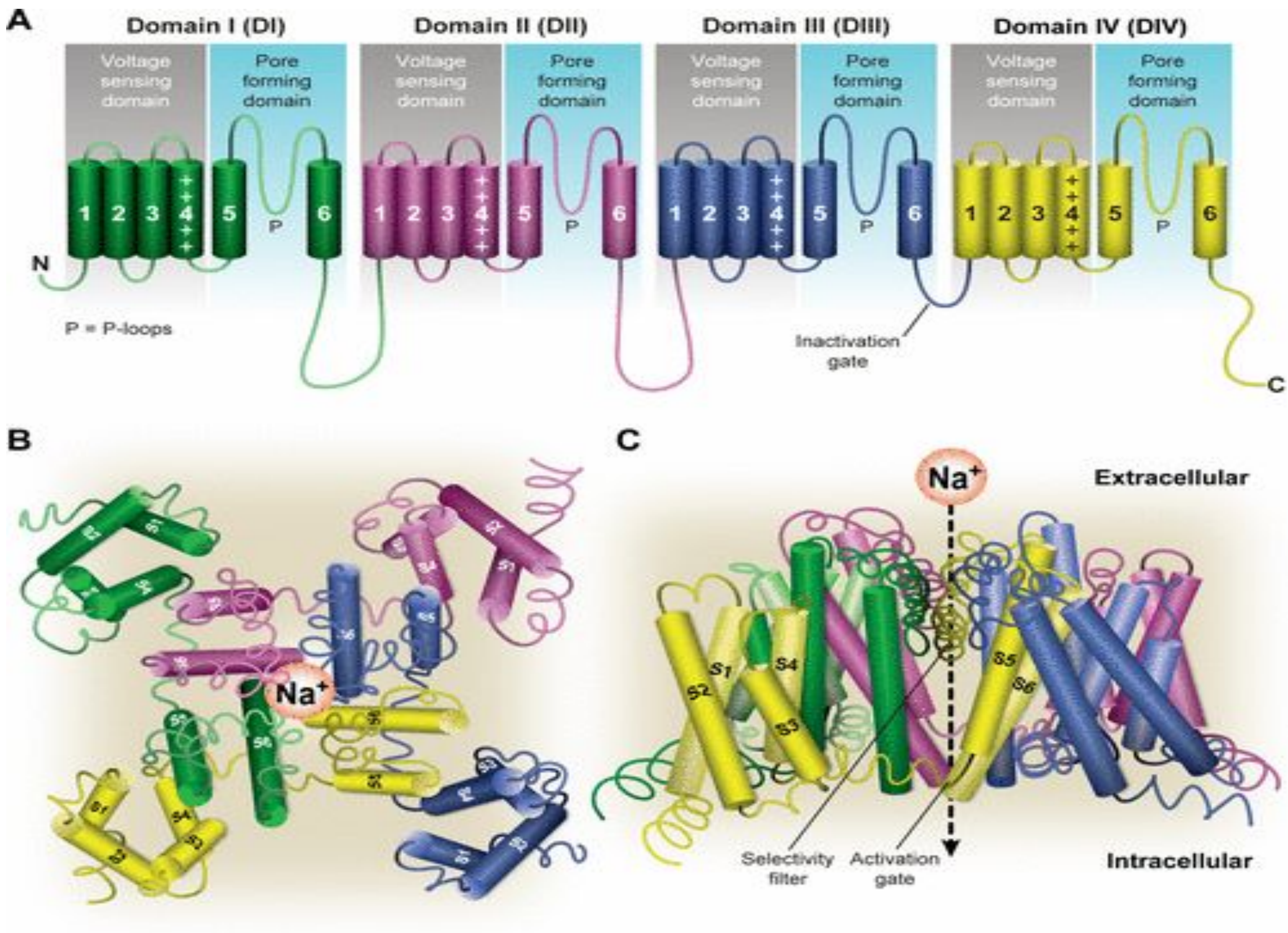
ii) **Resting membrane potential**

(i) Ion channels:

- Ion channels open and close due to **the presence of (gates).**
- ***Types***
  - **Leakage channels:** open and close randomly
  - **Voltage-gated channels:** opens to a change in Membrane Potential (voltage).
  - **Ligand-gated channels:** opens and close in response to chemical stimulus, such as Ach.
  - **Mechanical gated channels:** open or close in response to mechanical stimulation, such as touch or tissue stretching.

ION CHANNEL

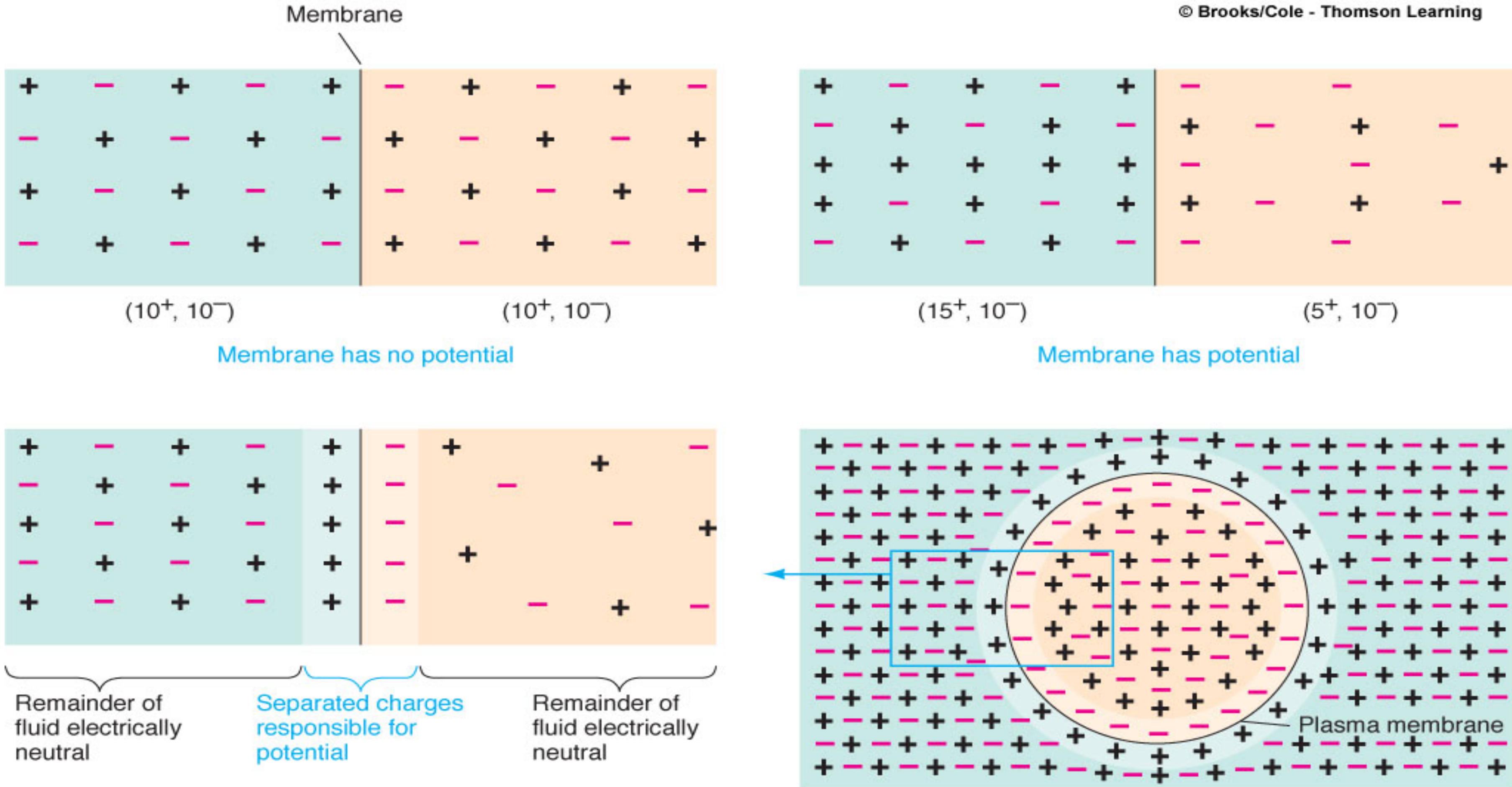

Ligand-gated
Neuro-
transmitter
Receptor
Na+
Open
Cytosol
Closed
Na+
Mechanically-gated
Pressure
Open
Cytosol
Closed
Always open
K+
Na+
Membrane
Cytosol
Voltage-gated
Na+
Cytosol

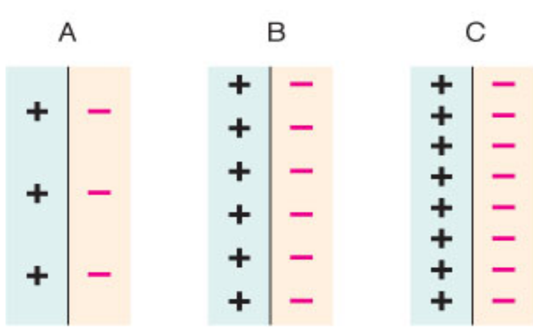

A
Domain I (DI)
Domain II (DII)
Domain III (DIII)
Domain IV (DIV)
Voltage sensing domain
Pore forming domain
1 2 3 4 5 P 6
N
C
P = P-loops
Inactivation gate
B
Na+
C
Na+
Extracellular
Intracellular
S1
S2
S3
S4
S5
S6
Selectivity filter
Activation gate

ii) Resting membrane potential(RMP):

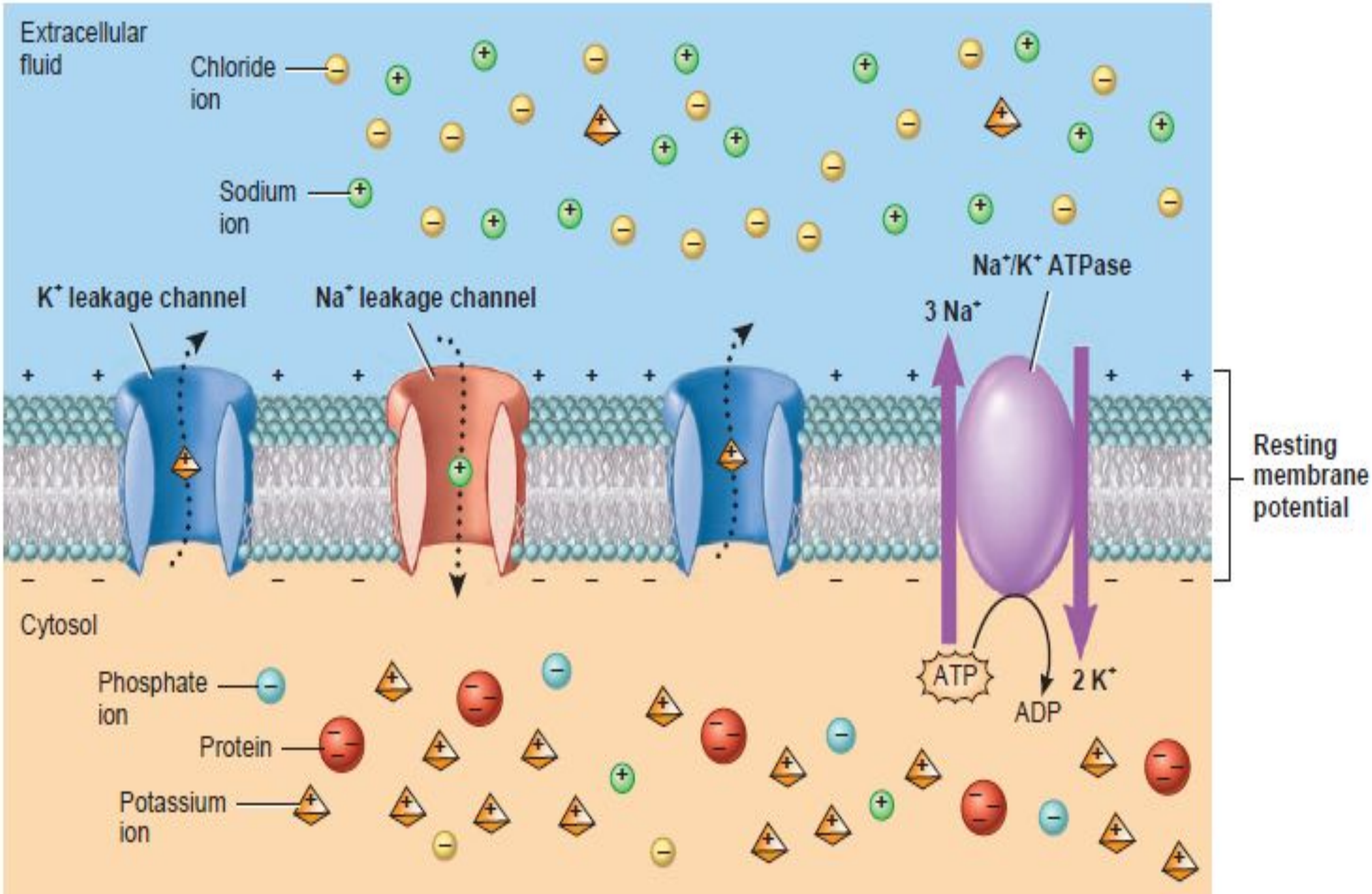
The difference in voltage across the cell membrane when a neuron or muscle cells is not producing an Action Potential.

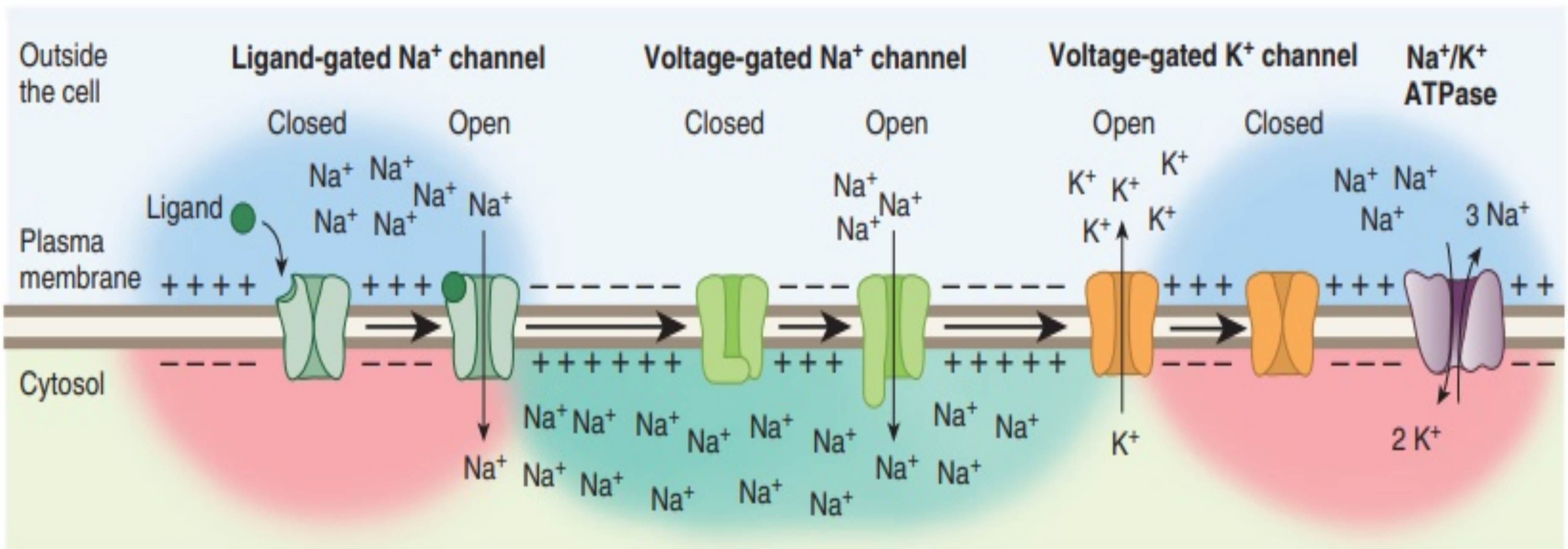
- A typical value is: **-70 mV(-50 to -90)**
- A cell that exhibits a membrane potential is said to be ***polarized.***





Which has the greatest membrane potential?


Extracellular fluid
Chloride ion
Sodium ion
K⁺ leakage channel
Na⁺ leakage channel
Na⁺/K⁺ ATPase
3 Na⁺
Resting membrane potential
Cytosol
Phosphate ion
Protein
Potassium ion
ATP
ADP
2 K⁺



Outside the cell
Ligand-gated Na+ channel
Voltage-gated Na+ channel
Voltage-gated K+ channel
Na+/K+ ATPase
Closed
Open
Closed
Open
Open
Closed
Ligand
Plasma membrane
Cytosol
3 Na+
2 K+

Genesis of Resting Membrane Potential

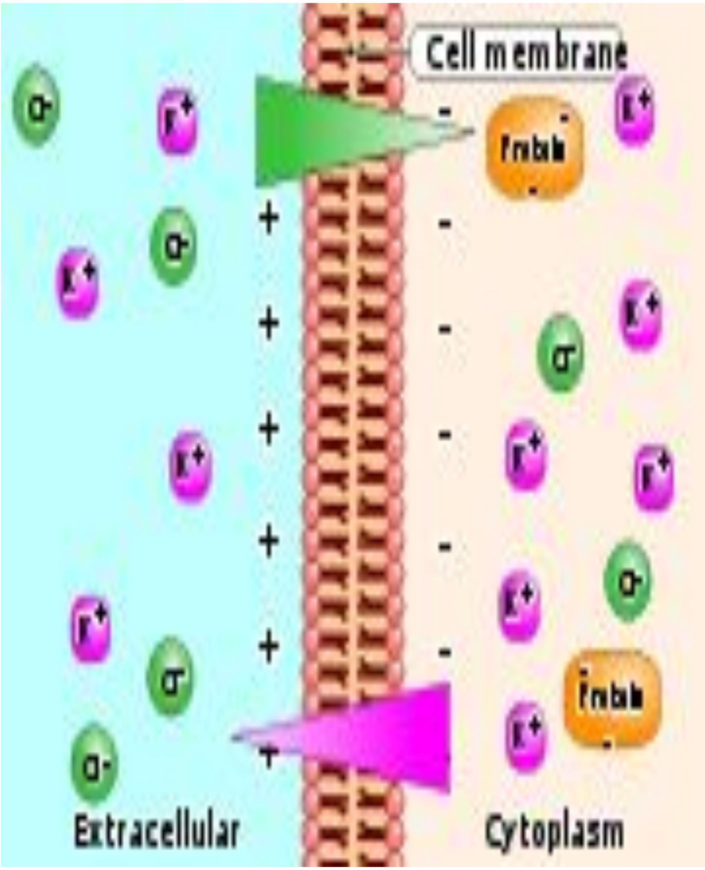
- Selective permeability of the cell membrane
- Gibbs'- Donnan equilibrium potential
- Nernst potential
- Goldman constant field equation
- Na^+ and K^+ pump

SELECTIVE PERMEABILITY OF CELL MEMBRANE

- The cell membrane is selectively permeable that is, it is freely permeable to K^+ and Cl^- , moderately to Na^+, and impermeable to proteins & organic phosphate which are negatively charged ions.
- Major intracellular cation is K^+ and major intracellular anions are proteins and organic phosphate. Major extracellular cation is Na^+ and anion is Cl^-.
- Presence of gated protein channels in the cell membrane is responsible for variable permeability of ions.

Gibbs Donnan Equilibrium

- When two solutions containing ions are separated by membrane that is permeable to some of the ions and not to others an electrochemical equilibrium is established.
- Electrical and chemical energies on either side of the membrane are equal and opposite to each other



- The forces acting on the ions across the cell membrane produces variations in the membrane potential. The magnitude of forces acting across the cell membrane on each ion can be analyzed by **Nernst equation**.

Concentration gradient :-

- The asymmetrical distribution of diffusible ions across the cell membrane in the form of excess diffusible cation inside due to Donnan effect results in concentration gradient.

Electrical gradient :-

- As a result of concentration gradient cation K^+, will try to diffuse back into ECF from ICF.

- But it is counter acted by electrical gradient which will be created due to presence of non diffusible anions inside the cell.
- The membrane potential at which the electrical force is equal in magnitude but opposite in direction to the concentration force is called equilibrium potential for that ion. The magnitude of equilibrium potential is determined by **Nernst equation**.

$$E = \frac{RT}{zF} \ln \frac{[\text{ion outside cell}]}{[\text{ion inside cell}]}.$$

Nernst potential (Equilibrium potential)

- The potential level across the membrane that will exactly prevent net diffusion of an ion

Ion	Intracellular	Extracellular	Nernst potential
Na^+	10	142	+60
K^+	140	4	-90
Cl^-	4	103	-89
Ca^{2+}	0	2.4	+129
HCO_3^-	10	28	-23

(mmol/l)

GOLDMANN-HODGKIN-KATZ (GHK) EQUATION

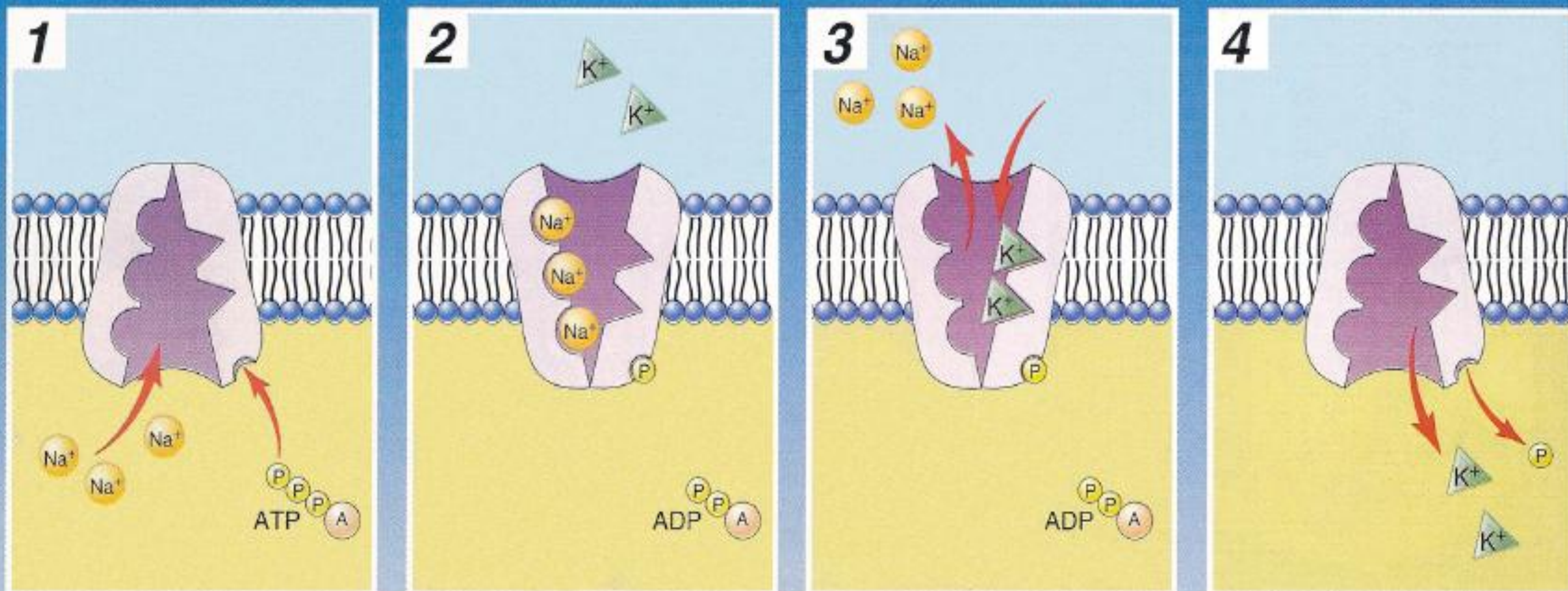
- The Nernst equation helps in calculating the equilibrium potential for each ion individually.
- However, the magnitude of membrane potential at any given time depends on distribution and permeability of Na^+, K^+ and Cl^- ions.
- The integrated role of different ions in the generation of membrane potential can be described accurately by the GHK equation.

$$V_m = \frac{RT}{F} \ln\left(\frac{p_K[K]_o + p_{Na}[Na]_o + p_{Cl}[Cl]_i}{p_K[K]_i + p_{Na}[Na]_i + p_{Cl}[Cl]_o} \right)$$

ROLE OF $Na^{\pm}$ - $K^{\pm}$ ATPASE PUMP

The role of Na^+-K^+ ATPase lies in building the concentration gradient. It pumps out three Na^+ ions and one Cl^- ion for every two K^+ ions it pumps in.

SODIUM-POTASSIUM PUMP



1. The sodium-potassium pump binds three sodium ions and a molecule of ATP.

2. The splitting of ATP provides energy to change the shape of the channel. The sodium ions are driven through the channel.

3. The sodium ions are released to the outside of the membrane, and the new shape of the channel allows two potassium ions to bind.

4. Release of the phosphate allows the channel to revert to its original form, releasing the potassium ions on the inside of the membrane.

Forces act on cell membrane at rest:

1- Diffusion: is the movement of molecules from a region of higher concentration to a region of lower concentration.

2- Electrical gradient: +ve ions move to the –ve area and –ve ions move to +ve area

3- Active transport: transport ions against their concentration gradient. Most important example is Na+_K+ pump(need energy); responsible transport of Na+ to the outside and K+ to the inside.

These forces are responsible for:

i- The maintenance of the RMP

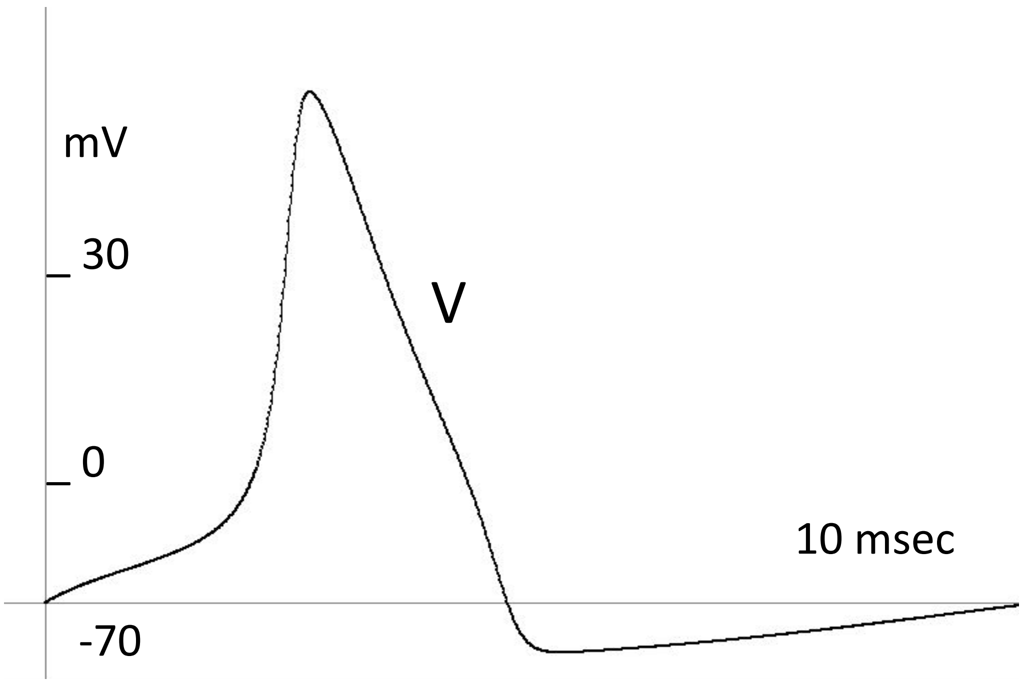
ii- The development of the AP

iii- Bringing the cell back to its resting state after the AP is over.

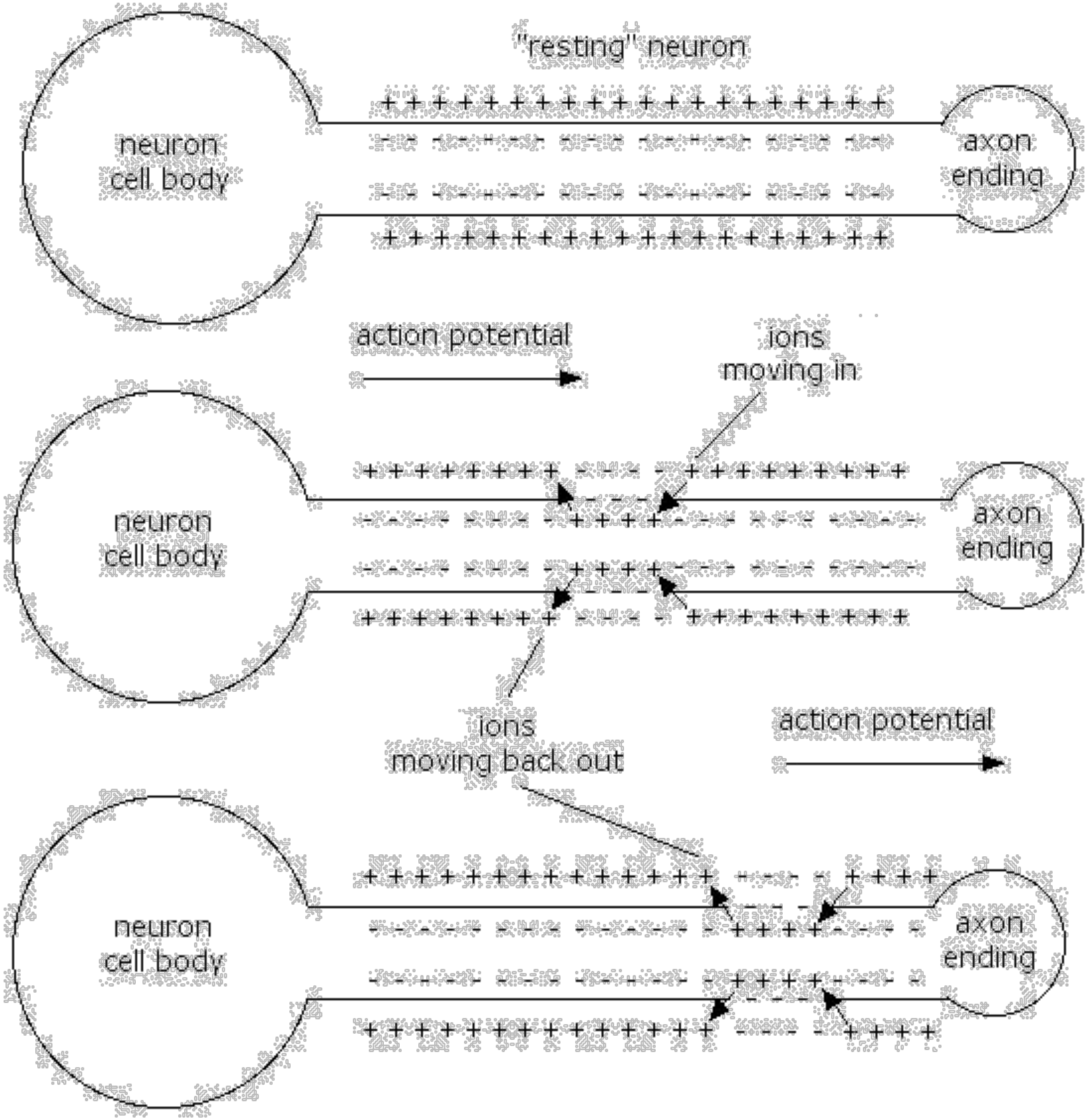
Hodgkin-Huxley Model

- Signals are propagated from nerve cell to nerve cell (*neuron*) via electro-chemical mechanisms
- ~100 billion neurons in a person
- Hodgkin and Huxley experimented on squids and discovered how the signal is produced within the neuron

Action Potential



- Axon membrane potential difference
  $\mathbf{V = V_i - V_e}$
- When the axon is excited, V spikes because sodium Na+ and potassium K+ ions flow through the membrane.

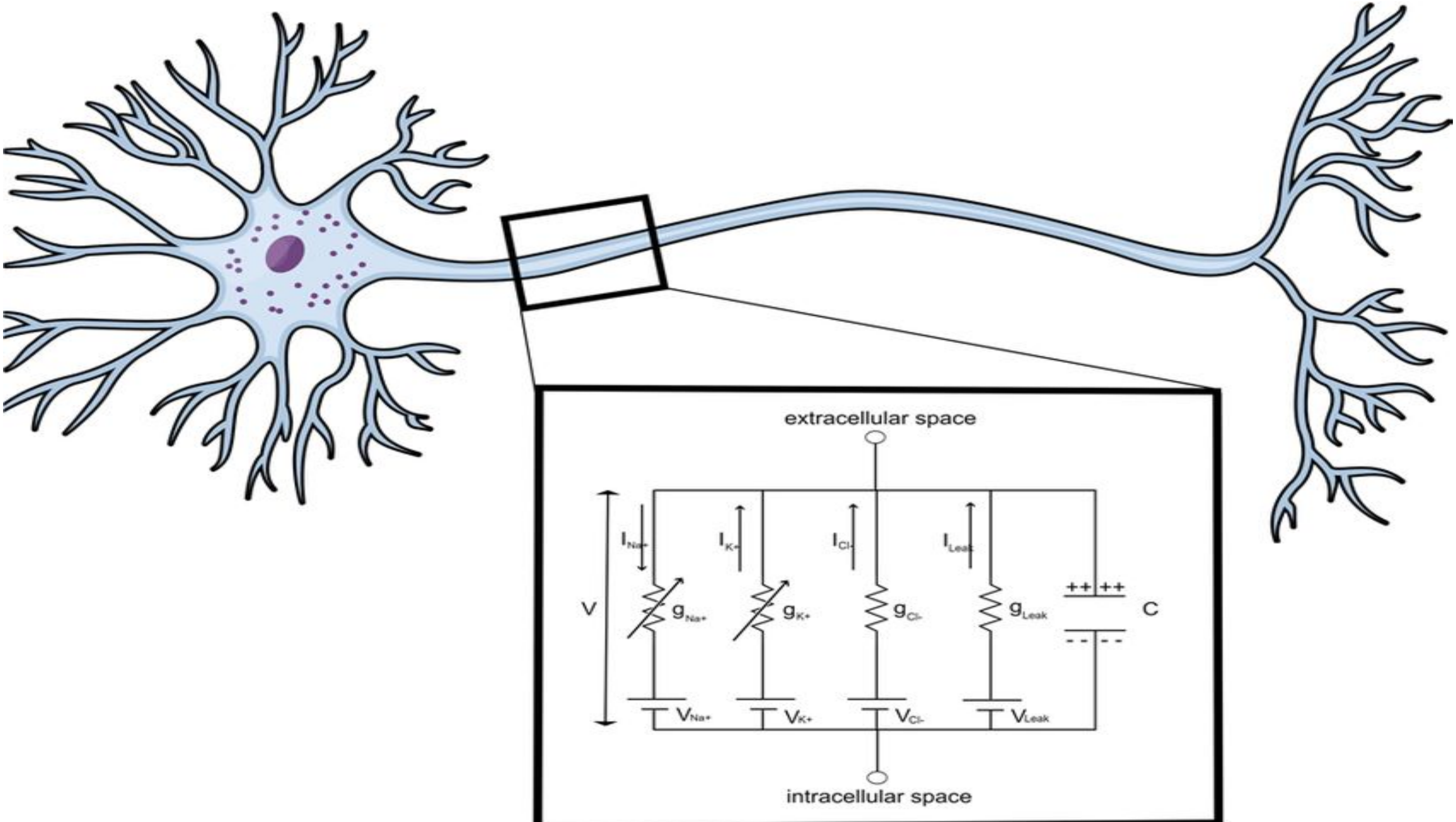


Nernst Potential

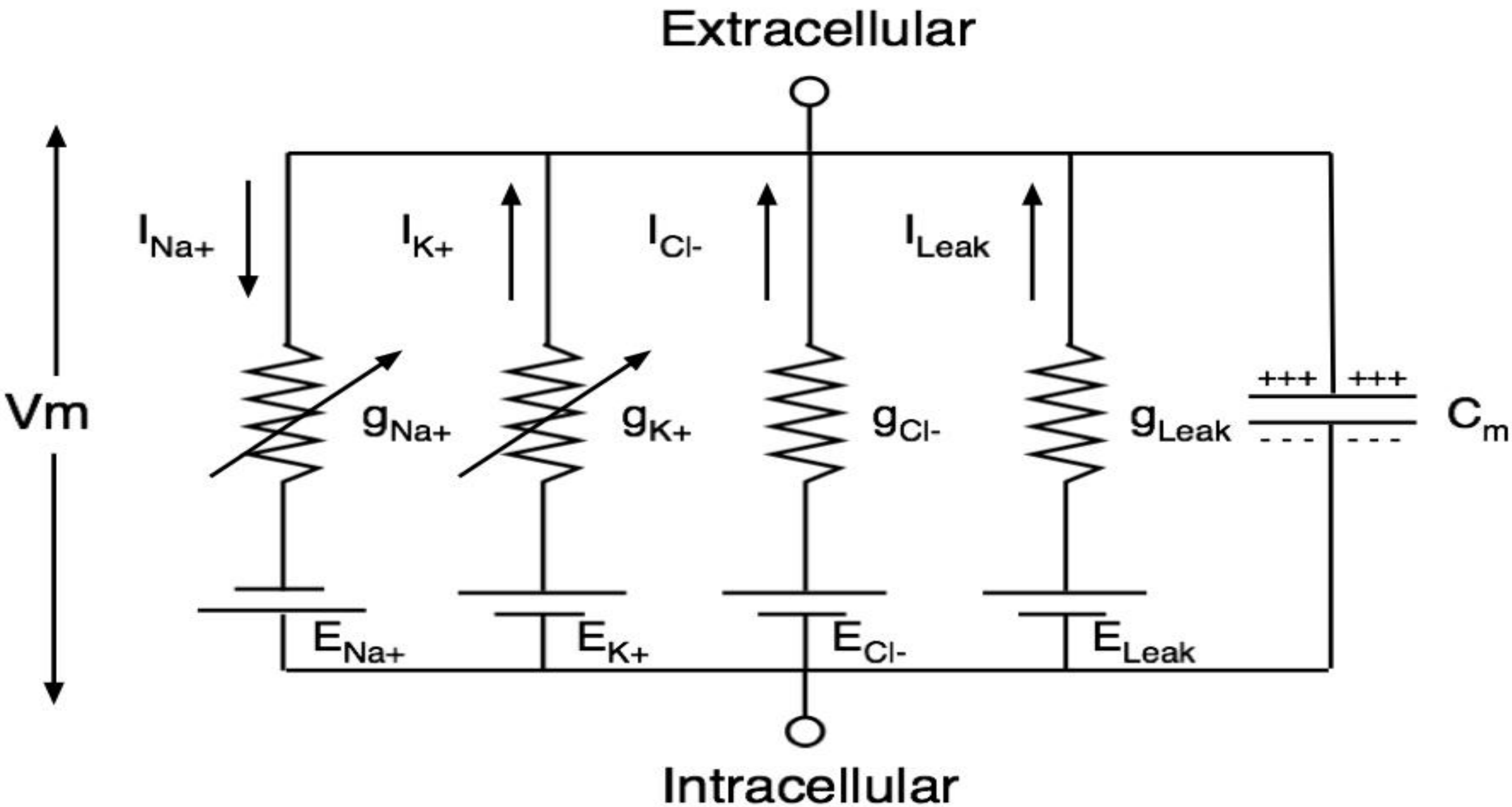
V_{Na} , V_K and V_r

Ion flow due to electrical signal

Traveling wave



extracellular space
I_{Na+}
I_{K+}
I_{Cl-}
I_{Leak}
V
g_{Na+}
g_{K+}
g_{Cl-}
g_{Leak}
C
V_{Na+}
V_{K+}
V_{Cl-}
V_{Leak}
intracellular space



Since the membrane separates charge, it is modeled as a capacitor with capacitance C. Ion channels are resistors.

$$1/R = g = \text{conductance}$$

Action potential (AP)

- **Definition:**

The AP **is a sudden reversal of membrane polarity by a stimulus.**

- **Importance:**

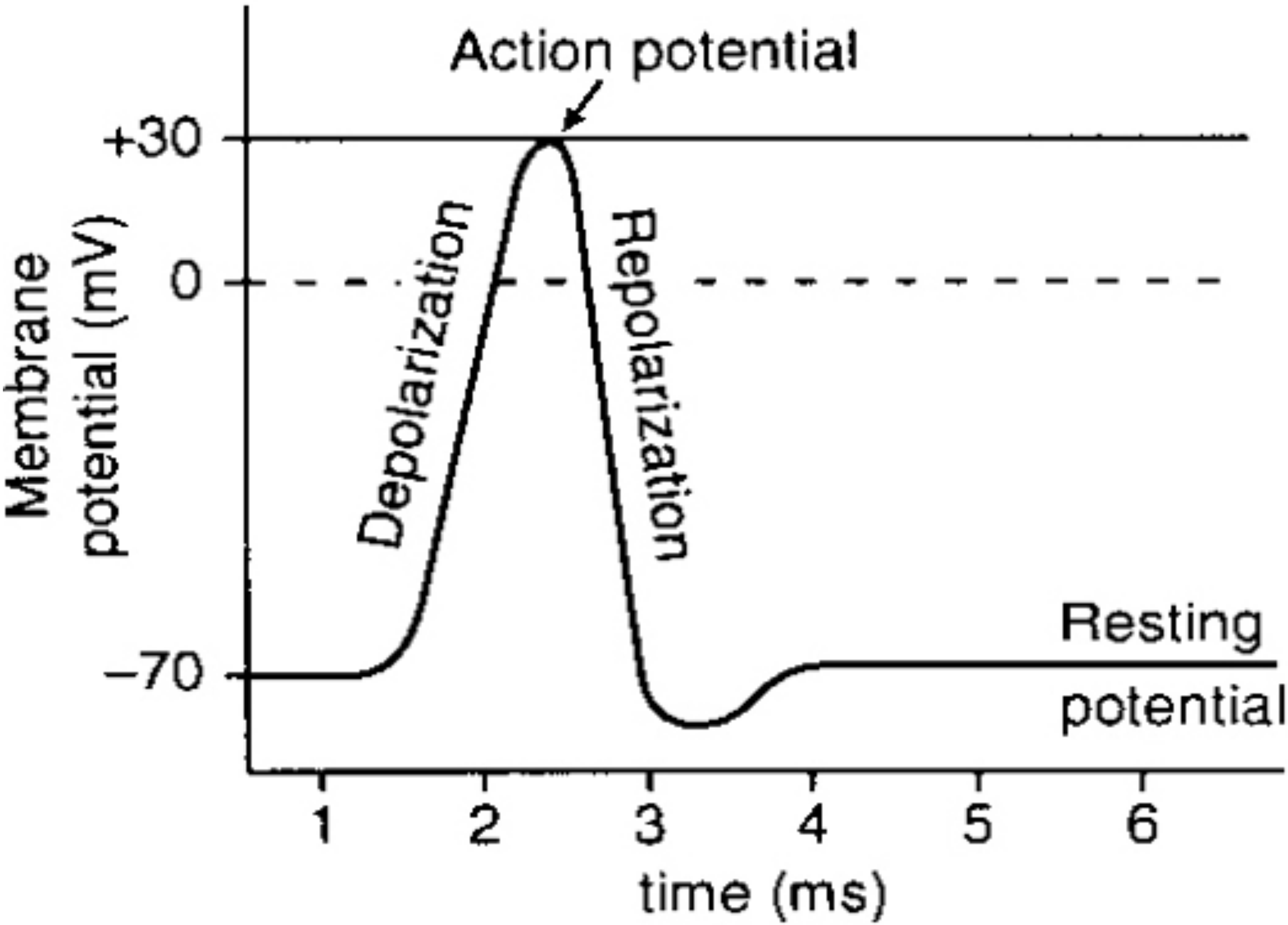
AP occurs in living organism to produce physiological effects such as:

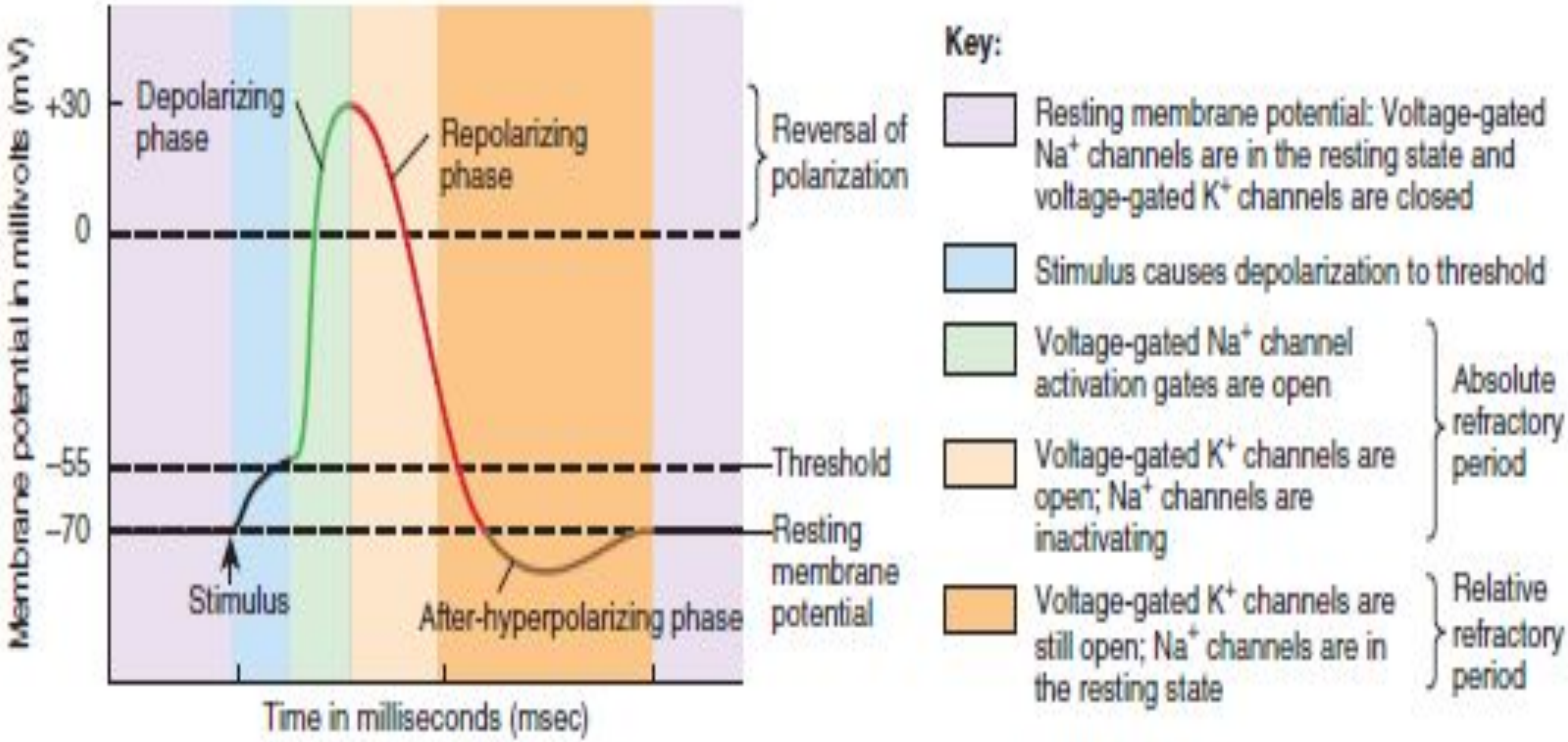
1. **Transmission of impulses along nerve fibers**
2. **Release of neurosecretions or chemical transmitters in synapses.**
3. **Contraction of muscle.**
4. **Activation or inhibition of glandular secretion.**

Development of the AP

- When a cell membrane is stimulated by a physical or a chemical stimulus, **the cell membrane permeability to Na+ is dramatically increased.**
- Sodium channels open and the sodium ions rush through the channels to the inside the cell **causing the inside the membrane to become positive** with respect to the outside. This is called ***depolarization***.
- The membrane potential becomes **reversed and reaches +35 mV.**

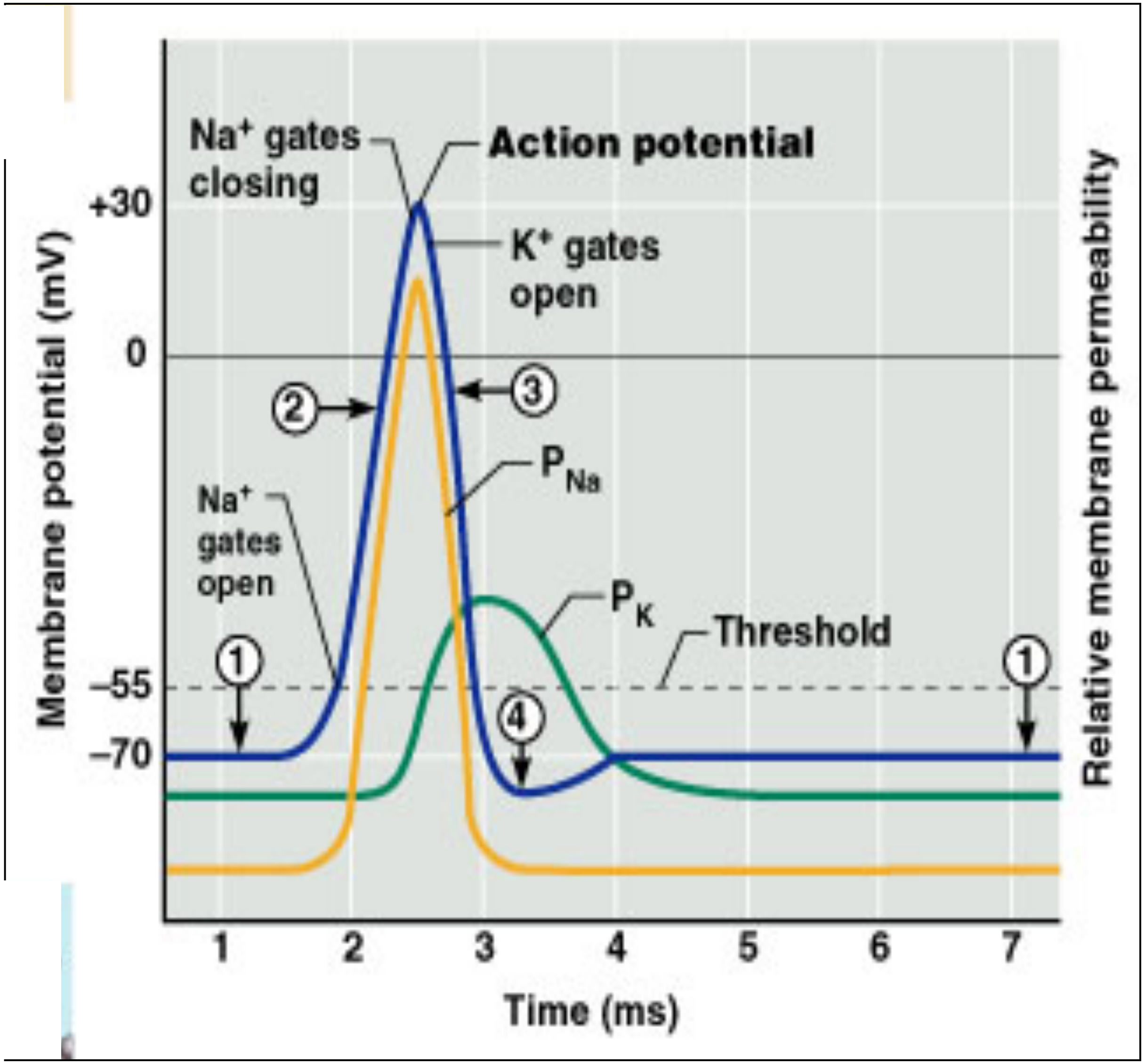
- Towards the end of depolarization, sodium permeability decreases and **potassium permeability increases.**
- K+ions leave the cell down their concentration gradient, **causing the inside the membrane to return quickly to its original potential.** This is called ***repolarization.***
- The membrane potential is brought back to **-70 mV**


Action potential
+30
0
-70
Membrane potential (mV)
Depolarization
Repolarization
Resting potential
1
2
3
4
5
6
time (ms)


Membrane potential in millivolts (mV)
+30
0
–55
–70
Depolarizing phase
Repolarizing phase
Reversal of polarization
Threshold
Resting membrane potential
Stimulus
After-hyperpolarizing phase
Time in milliseconds (msec)
Key:
Resting membrane potential: Voltage-gated Na+ channels are in the resting state and voltage-gated K+ channels are closed
Stimulus causes depolarization to threshold
Voltage-gated Na+ channel activation gates are open
Voltage-gated K+ channels are open; Na+ channels are inactivating
Absolute refractory period
Voltage-gated K+ channels are still open; Na+ channels are in the resting state
Relative refractory period

Phases of action potential

- Depolarization
- Repolarization
- Hyperpolarization



PROPAGATION OF THE ACTION POTENTIAL:

- An action potential elicited at any one point on an excitable membrane usually excites adjacent portions of the membrane, resulting in propagation of the action potential along the membrane.
- This transmission of the depolarization process along a nerve or muscle fiber is called a ***nerve or muscle impulse.***

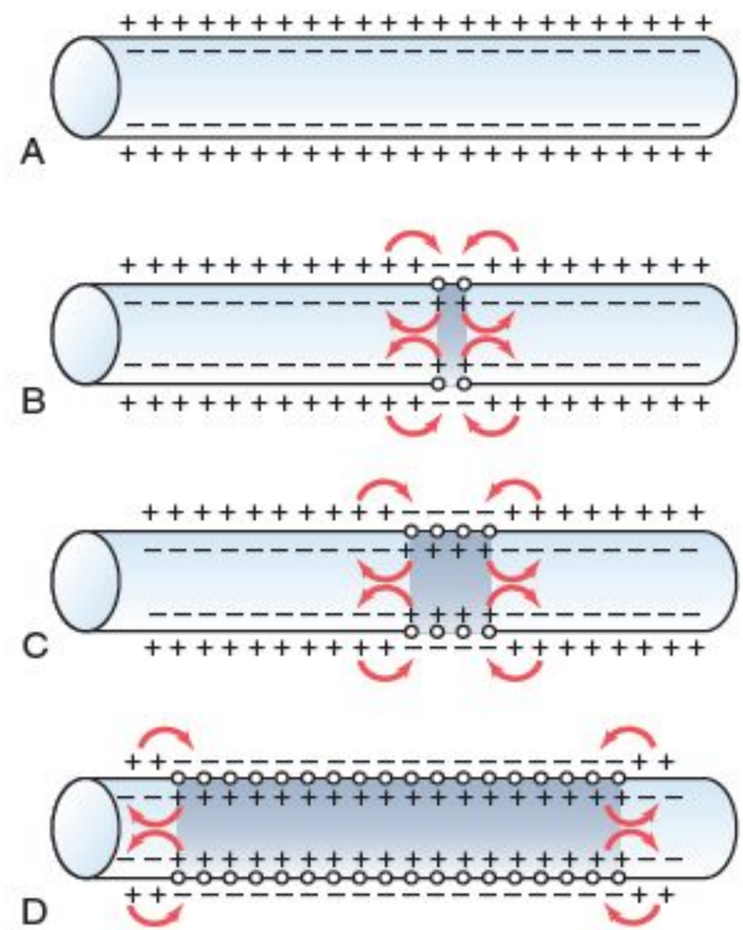


Figure 5-11. Propagation of action potentials in both directions along a conductive fiber.

Direction of Propagation:

- An excitable membrane **has no single direction of propagation,** but the action potential **travels in all directions away from the stimulus**—even along all branches of a nerve fiber—until the entire membrane has become depolarized.

Generation of action potential (AP):

The AP can be divided in five phases:

1. **The resting potential.**
2. **Threshold.**
3. **The rising phase.**
4. **The falling phase.**
5. **The recovery phase.**

1- Resting potential:

- When the neuron is at rest, **only a small of K+ channels are open**, permitting K+ ions to enter and exit the cell based on electrochemical forces.

2- Threshold:

- As a depolarizing stimulus arrives the membrane, a **few Na+ channels open permitting Na+ ions to enter the neuron.**
- The increase in positive ions inside the cell depolarizes the membrane (making it less negative).

3- Rising phase:

- If the depolarization reaches the threshold potential, **additional voltage-gated Na+ channels open.**
- As positive Na+ ions rush in to the cell the voltage across the membrane rapidly **reverses and reaches its most positive value.**

4- Falling phase:

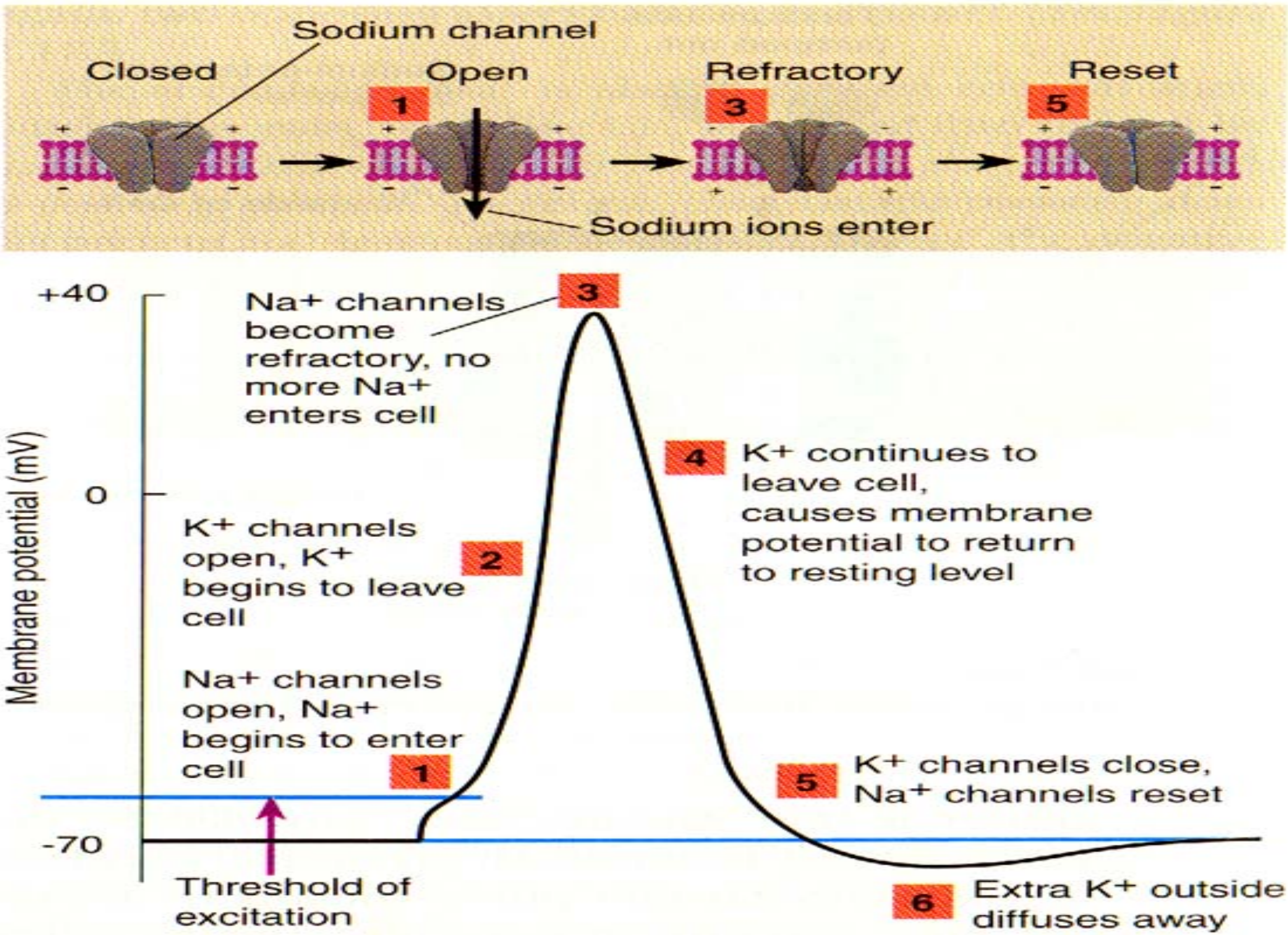
- At he peak of AP, two process occur simultaneously;

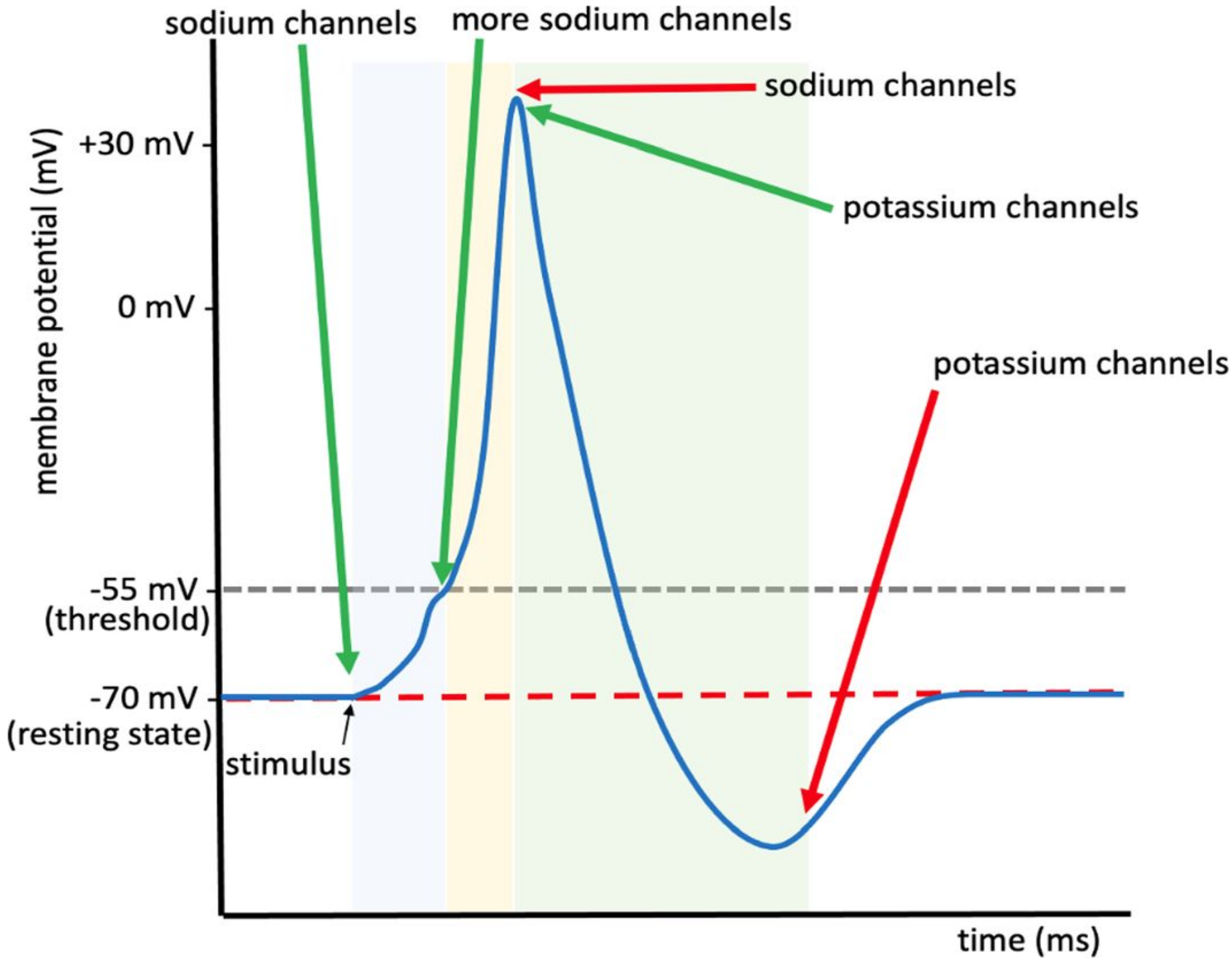
1. First: **many of the voltage-gated Na+ channels begin to close.**
2. Second: **many more k+ channel open, allowing positive charges to leave the cell**.

- This causes the Membrane Potential to begin to shift back toward the **Resting Membrane Potential.**
- As the Membrane Potential approaches the Resting Potential , **voltage-gated K+ channels are maximally activated and open.**

5- Recovery phase:

- This undershoot occurs because more K+ channels are open.
- The return to steady state continues as the additional K+ channels **that opened during the Action Potential now close.**
- The AP is now determined by the subset of the K+ channels that are normally open during the membrne’s resting state.


Sodium channel
Closed
Open
Refractory
Reset
1
3
5
Sodium ions enter
+40
0
-70
Membrane potential (mV)
3
Na+ channels become refractory, no more Na+ enters cell
4
K+ continues to leave cell, causes membrane potential to return to resting level
K+ channels open, K+ begins to leave cell
2
Na+ channels open, Na+ begins to enter cell
1
5
K+ channels close, Na+ channels reset
Threshold of excitation
6
Extra K+ outside diffuses away


sodium channels
more sodium channels
sodium channels
potassium channels
potassium channels
membrane potential (mV)
+30 mV
0 mV
-55 mV
(threshold)
-70 mV
(resting state)
stimulus
time (ms)

All-or-Nothing Principle:

- Also called **All or None Law.**
- Applies to all normal **excitable tissues.**
- The depolarization process travels over the entire membrane if conditions are right, but it does not travel at all if conditions are not right.
- A law stating that certain structures, such as a neuron or a muscle fiber, either **respond completely** (all) or **not at all** (none) to a stimulus.
- **There is no partial nerve impulse in a neuron, or partial contraction of a fiber muscle.**
- If the stimulus is any strength above threshold, the nerve or muscle fiber will either give a complete response or no response.

Refractory period:

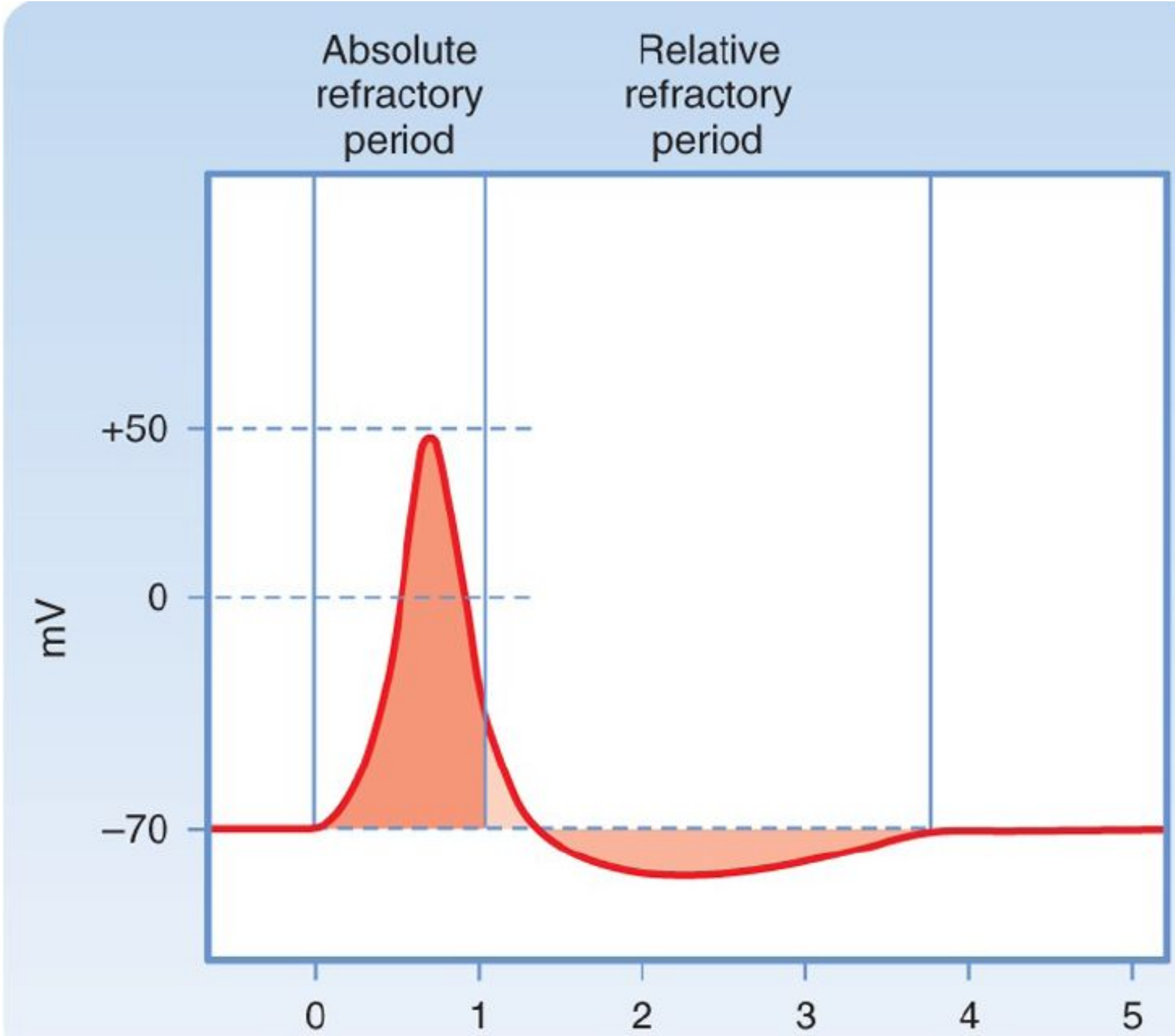
- It is the period which **an excitable cell cannot generate another AP in response to a *normal* threshold stimulus.**
- **<u>Types of refractory period</u>**:

1- Absolute refractory period: in which cannot initiate a second AP even a very strong stimulus.

- This period coincide with the period of voltage-gated Na+ channel activation gates are inactivating and cannot reopen; they first must return to the resting state.

2- Relative refractory period: during which a second action potential can be evoked, but only if the stimulus strength is increased.

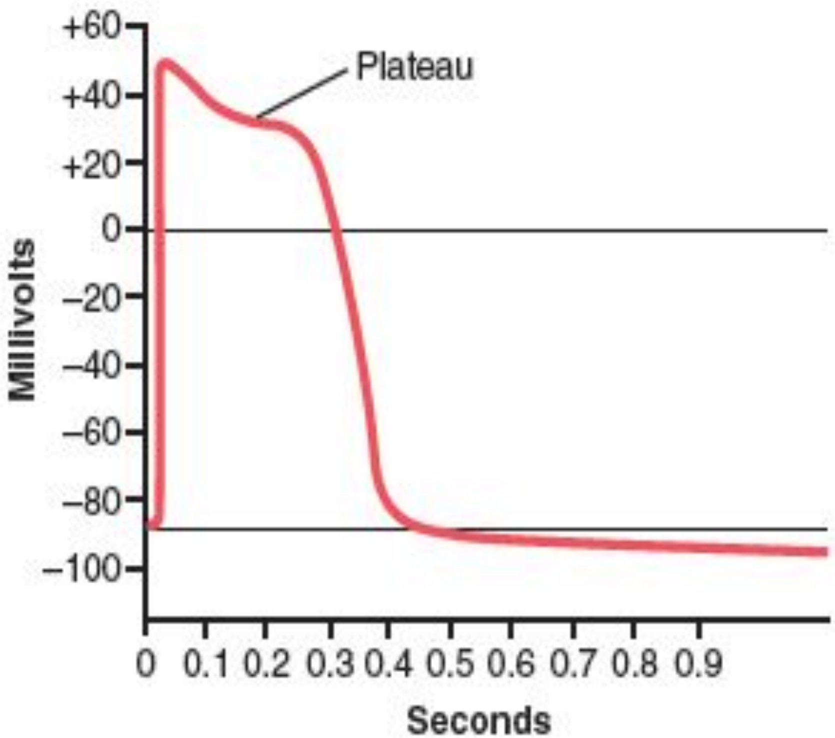
- It coincides with the period when the voltage-gated K+ channels are still open after inactivated Na+ channels have returned to their resting state.



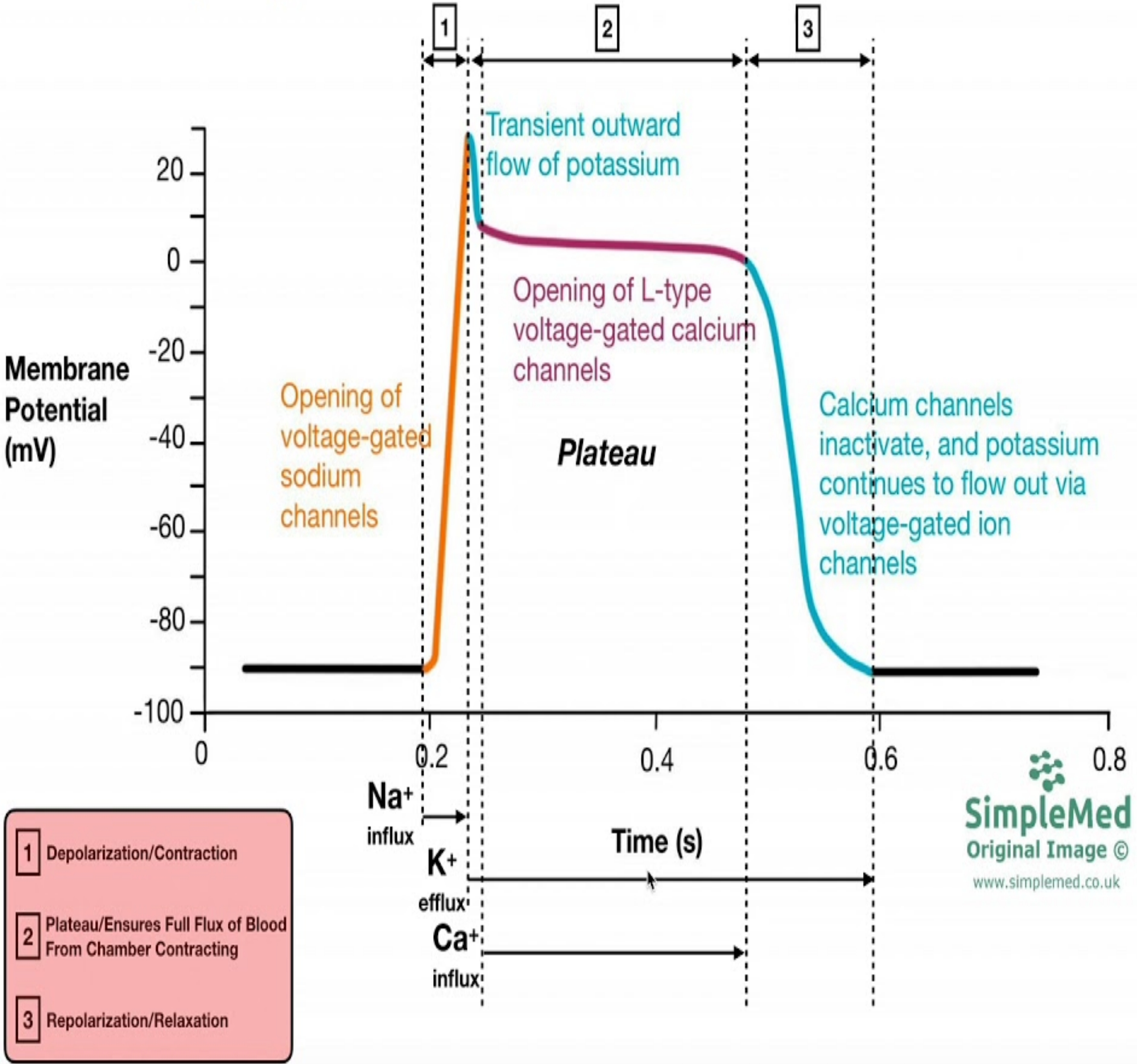
Absolute refractory period
Relative refractory period
mV
+50
0
–70
0
1
2
3
4
5

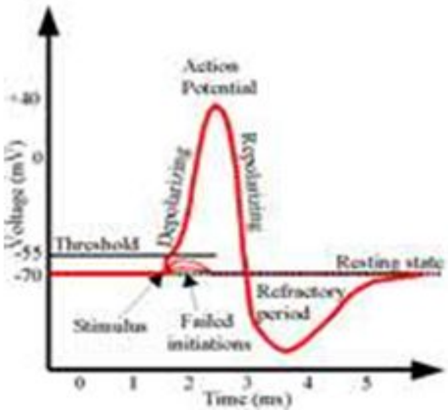
PLATEAU IN SOME ACTION POTENTIALS:

- In some instances, the excited membrane does not repolarize immediately after depolarization; instead, **the potential remains on a plateau** near the peak of the spike potential for many milliseconds.
- This type **of action potential occurs in heart muscle fibers.**
- The plateau ends when the **calcium - sodium channels close** and **permeability to potassium ions increases.**

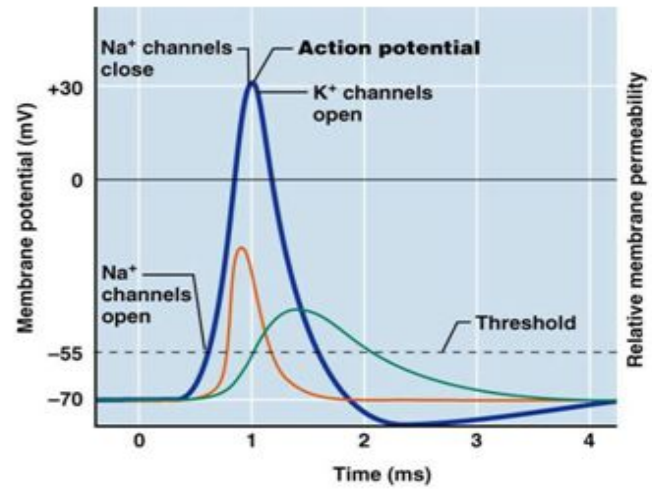


Cardiomyocyte Action Potential: One Individual Cell



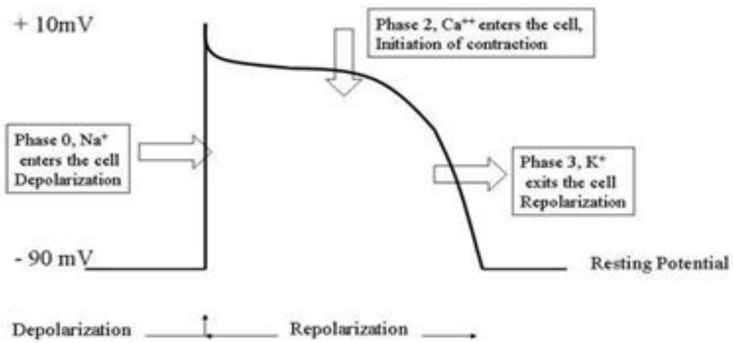


Neuron Action Potential



Skeletal Muscle Action Potential

Monophasic Action Potential (Cardiac Muscle Cell)



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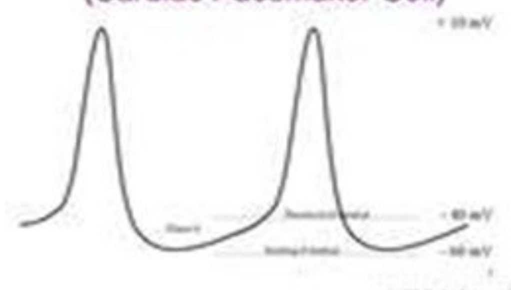
Monophasic Action Potential (Cardiac Pacemaker Cell)



RHYTHMICITY OF SOME EXCITABLE TISSUES—REPETITIVE DISCHARGE

- Repetitive self-induced discharges occur normally in the heart, in most smooth muscle, and in many of the neurons of the central nervous system.
- These rhythmical discharges cause:

(1) Rhythmical beat of the heart,

(2) Rhythmical peristalsis of the intestines.

(3) Neuronal events as the rhythmical control of breathing.

- All other excitable tissues can discharge repetitively if the threshold for stimulation of the tissue cells is reduced to a low-enough level.