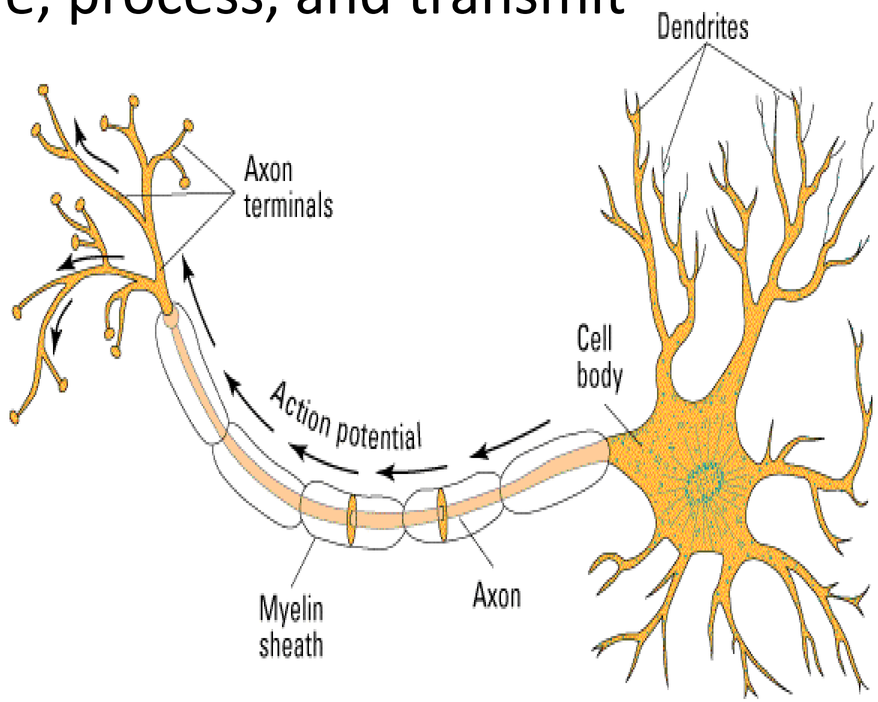
GRADED POTENTIALS AND ACTION POTENTIALS

Near East University
Faculty of Medicine
Department of Biophysics
Dr. Aslı AYKAÇ

Nervous System

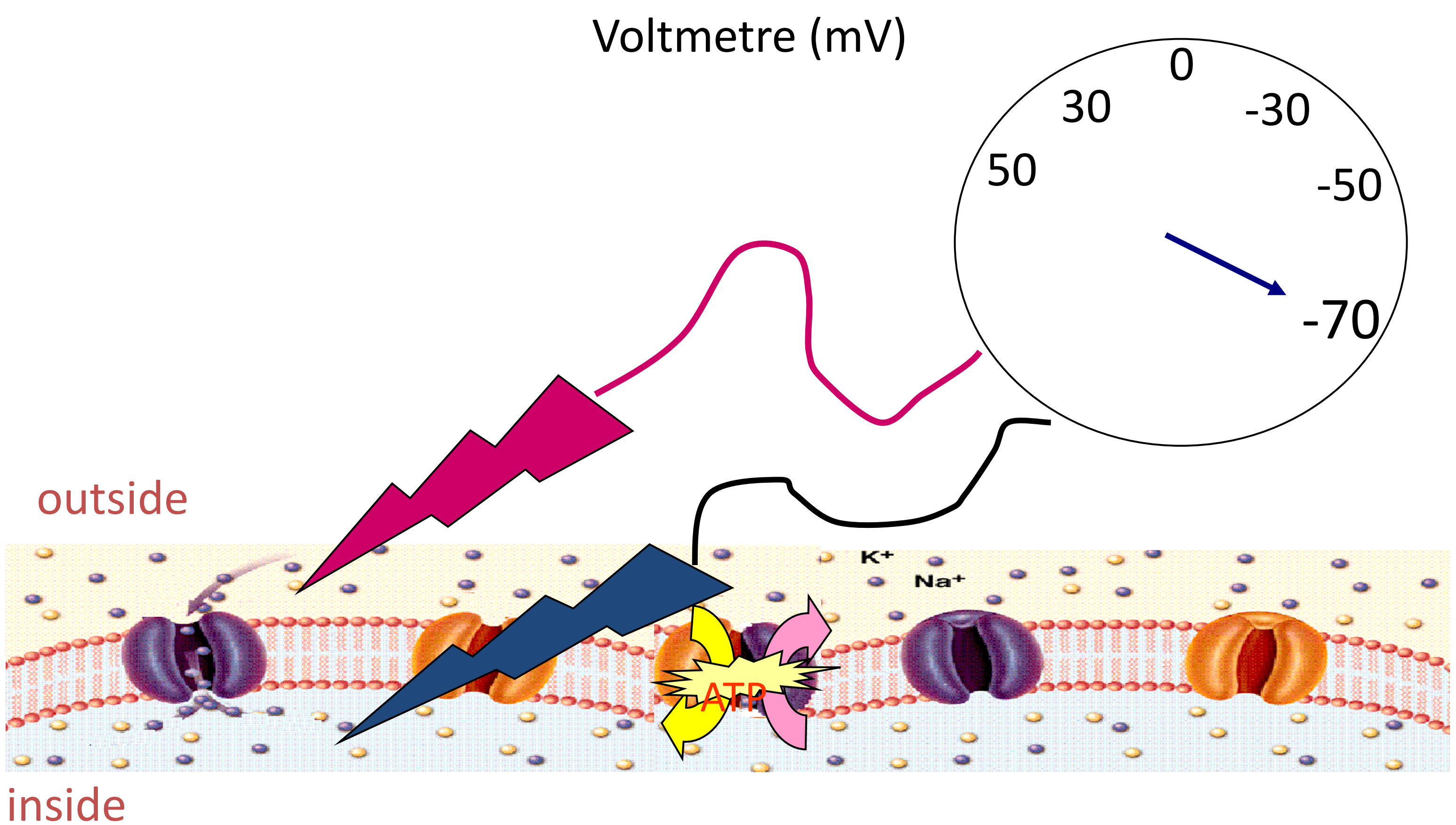
Nervous system cells are comprised of glia and neurons.

Neurons are responsible for receive, process, and transmit information in nervous system.



- Glia
  - Not specialized for information transfer
  - Support neurons
- Neurons (Nerve Cells)
  - Receive, process, and transmit information

Information travels in one direction
Dendrite → soma → axon



- All cells have electrical potential difference between inside and outside of the cell.

- Transient changes in the membrane potential of its resting level produce electrical signals.
  - Such changes are the most important way that nerve cells process and transmit information.

These signals occur in two forms:

1. graded potentials
2. action potentials

Graded potentials are important in ***short distances***.

Action potentials are the ***long distance*** signals of nerve and muscle membranes.

- Nerve and muscle cells as well as some endocrine, immune, and reproductive cells have plasma membranes capable of producing action potentials.

- These membranes
  - are called **excitable membranes.**
  - Their ability to generate action potentials is known as **excitability.**

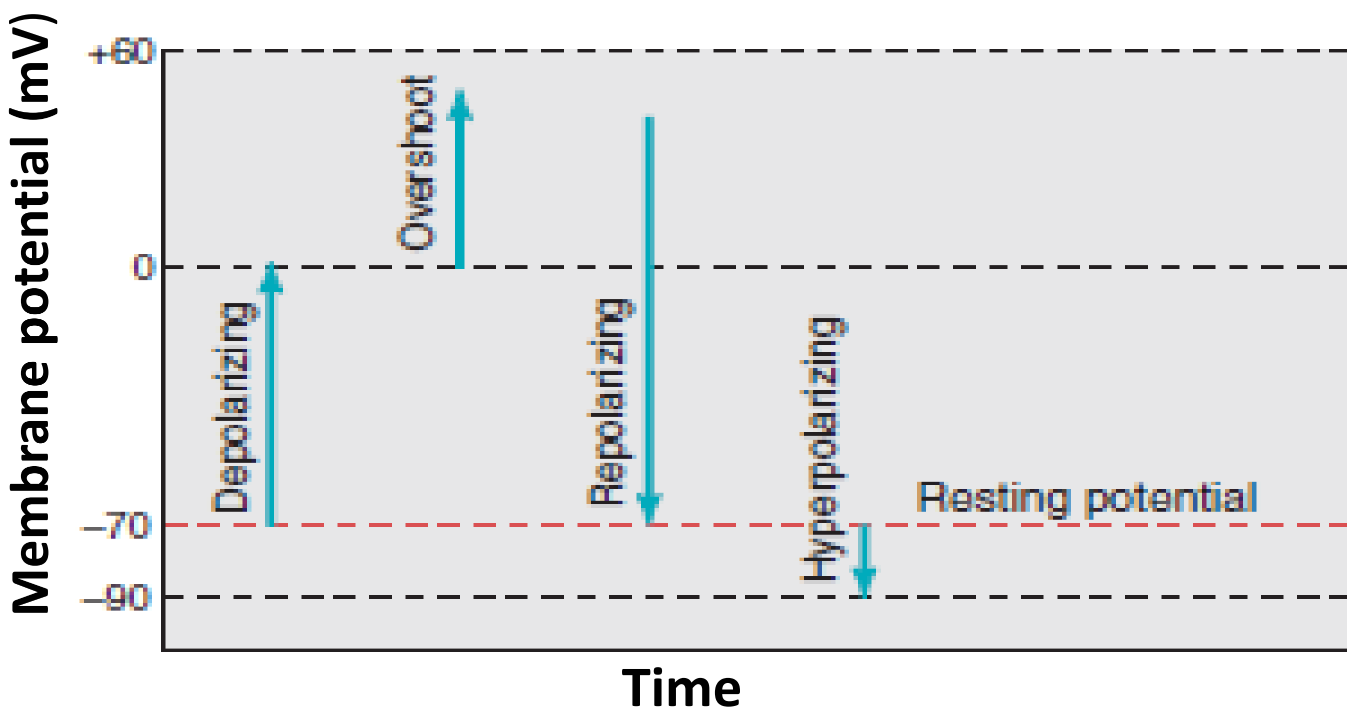
- **All cells** are capable of *conducting* ***graded potentials***, but **excitable membranes** can conduct ***action potentials***.

Changes in Membrane Potential

The terms

- depolarize
- repolarize
- hyperpolarize

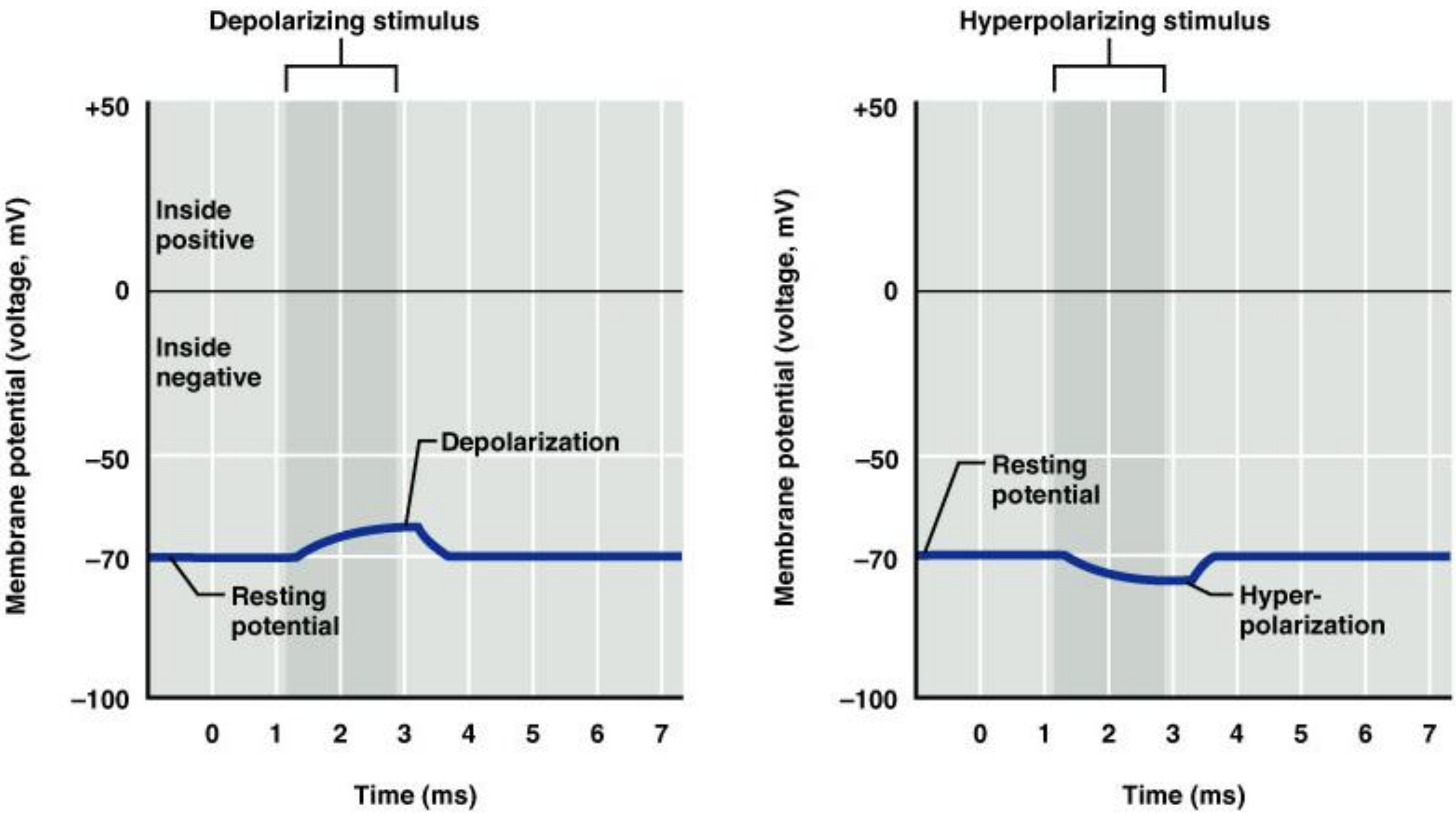
are used to describe the direction of changes in the membrane potential relative to the resting potential.

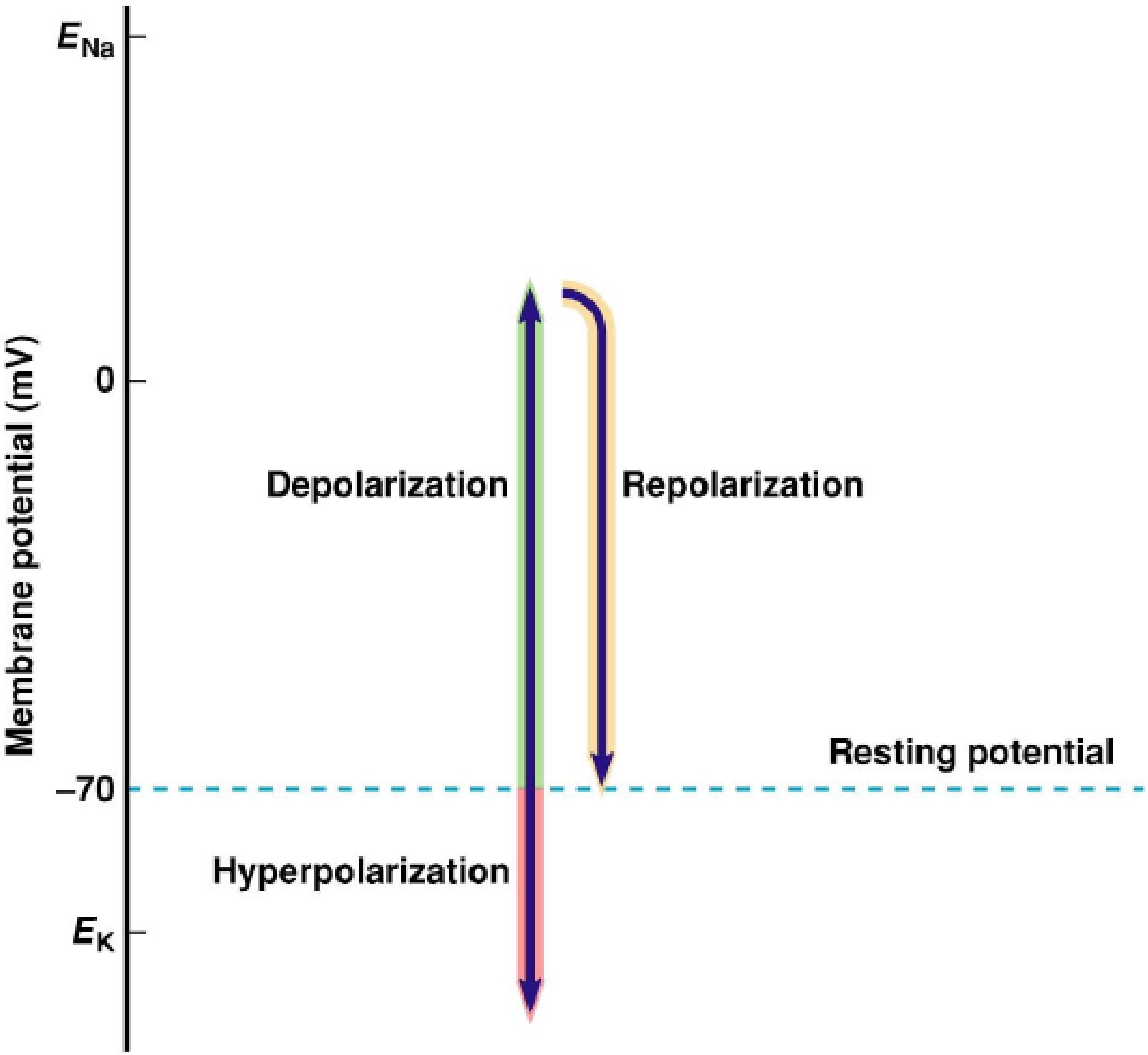


The resting membrane potential (at -70 mV) is polarized. "Polarized" means that the outside and inside of a cell have a different net charge.

- The membrane is said to be ***depolarized*** when its potential is ***less negative*** than the resting level.
- The membrane is ***repolarized*** when the potential ***returns toward*** the resting value.
- The membrane is ***hyperpolarized*** when the potential is ***more negative*** than the resting level.

Changes in Membrane Potential




E_{Na}
0
–70
E_K
Membrane potential (mV)
Depolarization
Repolarization
Resting potential
Hyperpolarization

Graded Potentials

- Short-lived, local changes in membrane potential
- Decrease in intensity with distance
- Their magnitude varies directly with the strength of the stimulus
- Sufficiently strong graded potentials can initiate action potentials

Graded Potentials

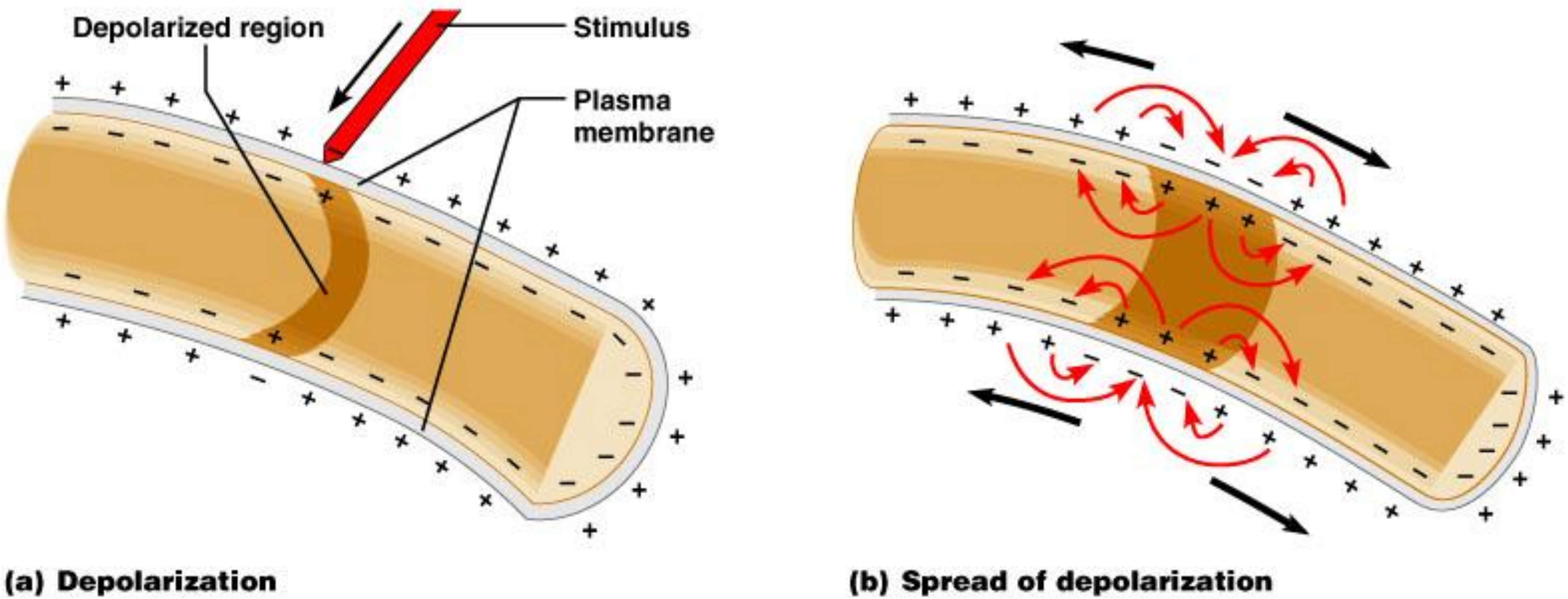


Figure 11.10

Graded Potentials

- Can only travel short distances
- Voltage changes in graded potentials are gradual
- Current quickly spreads and disappears due to the leaky plasma membrane

Terms Describing the Membrane Potential

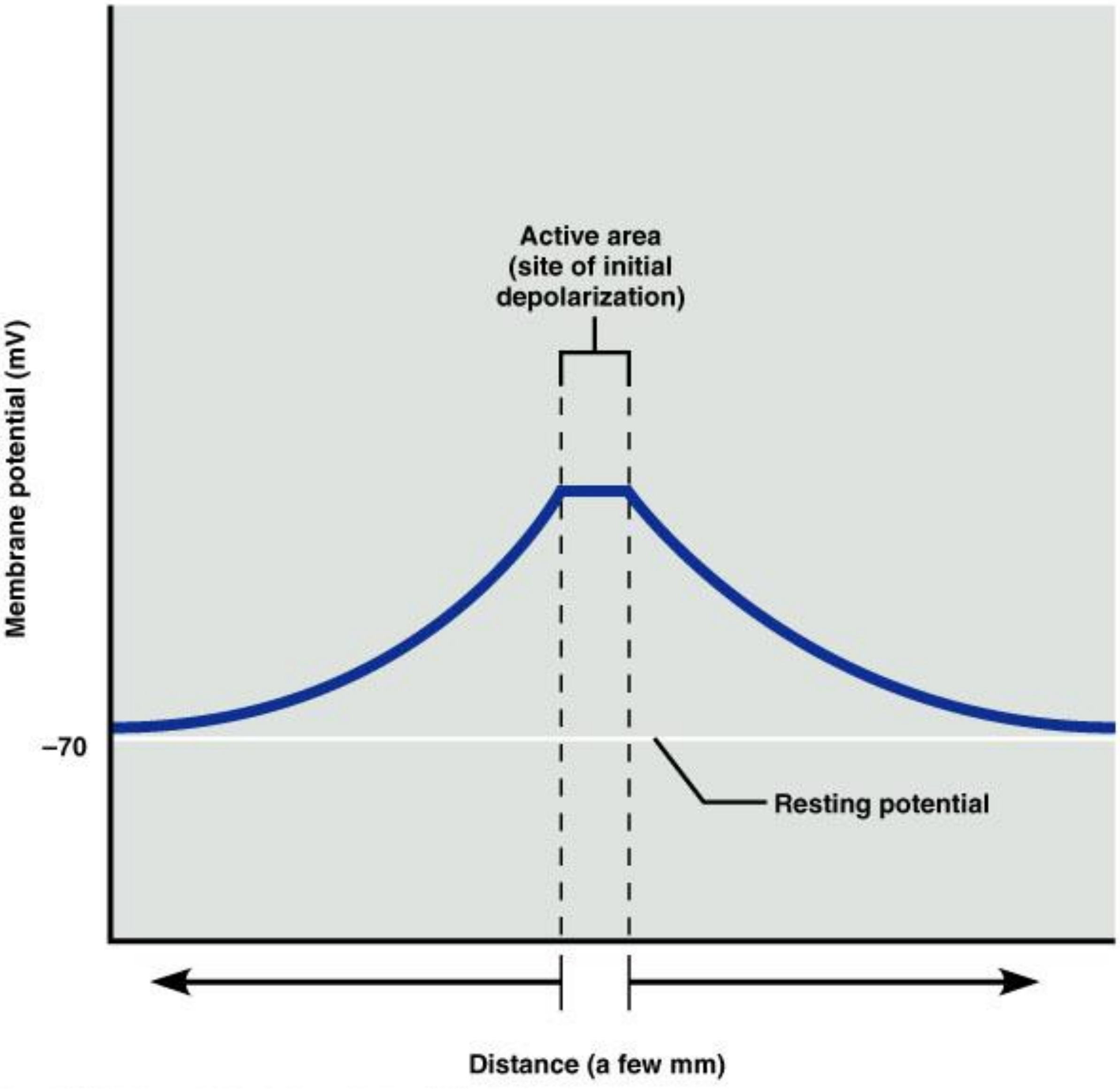
Potential = potential difference	The voltage difference between two points.
Membrane potential =transmembrane potential	The voltage difference between the inside and outside of a cell.
Equilibrium potential	The voltage difference across a membrane that produces a flux of a given ion species that is equal but opposite to the flux due to the concentration gradient of that same ion species.

Terms Describing the Membrane Potential

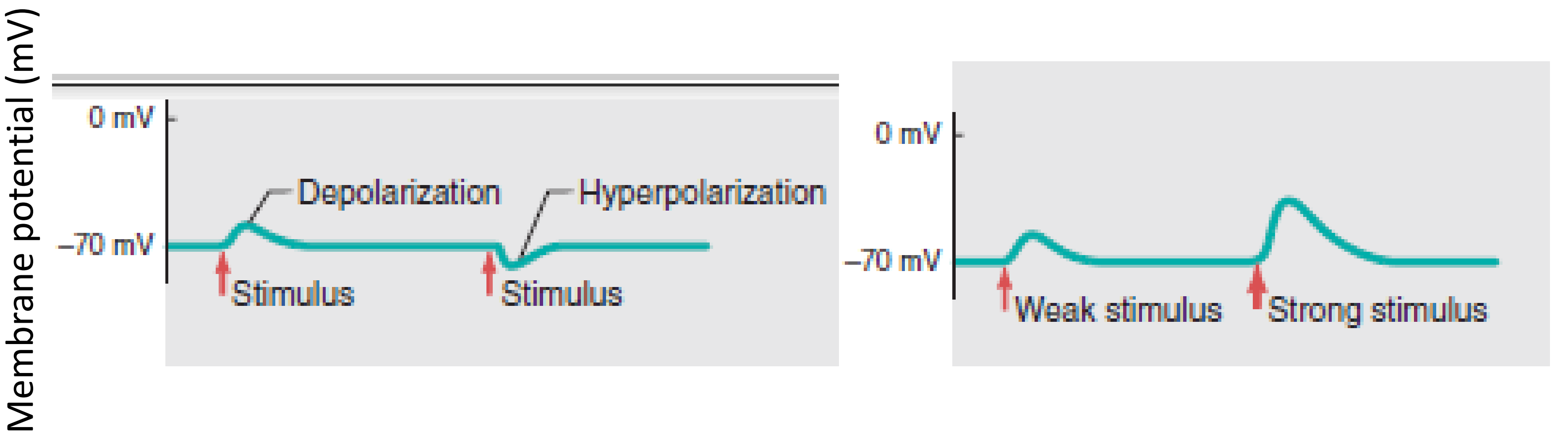
Resting membrane potential = resting potential	The steady transmembrane potential of a cell that is not producing an electric signal.
Action potential	A brief all-or-none depolarization of the membrane, reversing polarity in neurons; it has a threshold and refractory period and is conducted without decrement.
Threshold potential	The membrane potential at which an action potential is initiated.

- A small region of a membrane has been depolarized by a stimulus,
  - Opens membrane channels
  - produces a potential less negative than adjacent areas.
  - inside the cell, positive charge will flow through the intracellular fluid away from the depolarized region and toward the more negative, resting regions of the membrane.
  - outside the cell, positive charge will flow from the more positive region of the resting membrane toward the less positive regions just created by the depolarization.

- Thus, it produces a decrease in the amount of charge separation (i.e., depolarization) in the membrane sites *adjacent to the originally depolarized region, and* the signal is moved along the membrane.

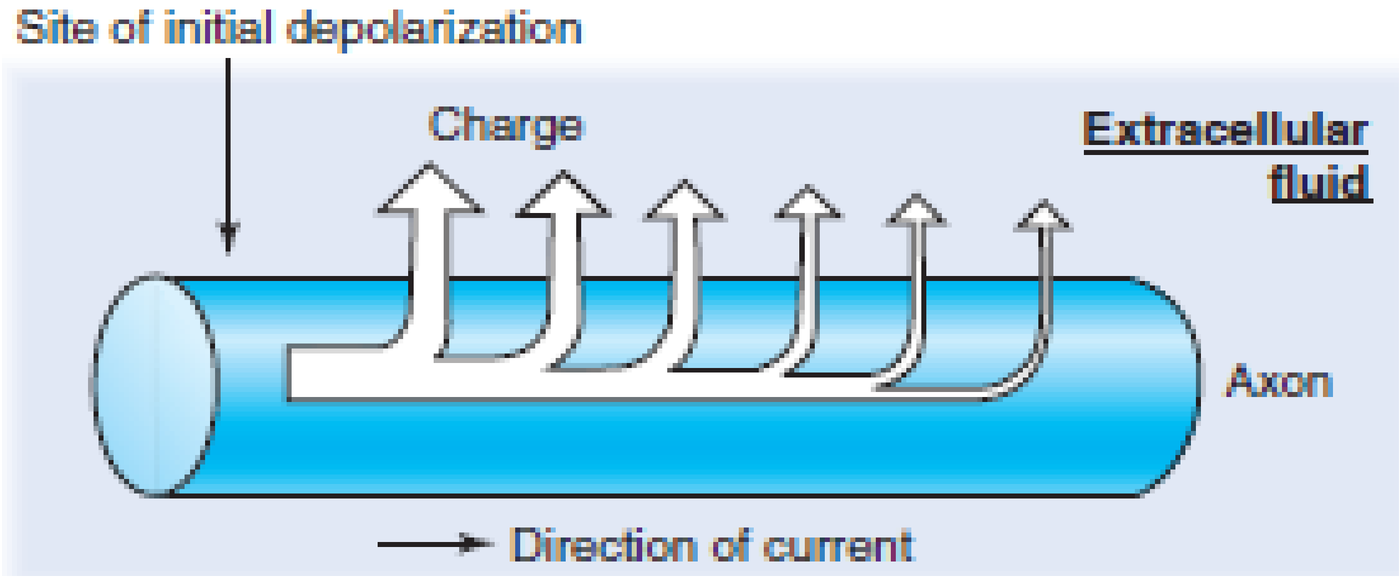

Active area
(site of initial
depolarization)
Membrane potential (mV)
–70
Resting potential
Distance (a few mm)

- Depending upon the initiating event, graded potentials can occur in either a depolarizing or a hyperpolarizing direction.



Such experiments show that graded potentials
(a) can be depolarizing or hyperpolarizing,
(b) can vary in size.
* The resting membrane potential is -70 mV.

- Charge is lost across the membrane because the membrane is permeable to ions through open membrane channels.
- As a result, the membrane potential changes decreases by the distance from the initial site.



- Because the electrical signal decreases with distance, graded potentials can function as signals only over very short distances.
- If additional stimuli occur before the graded potential has died away, these can be added to the depolarization from the first stimulus. This process is termed **summation.**
- Graded potentials are the only means of communication used by some neurons.
- They play very important roles in the initiation and integration of long-distance signals by neurons and some other cells.

- The mechanisms by which a neuron sorts out its various graded potentials and decides whether to generate an action potential is called integration.
- There are many factors which affect integration, including strength of the signal, time course, type of transmission, spike frequency adaptation, accommodation, and threshold;the two main types are temporal and spatial integration.

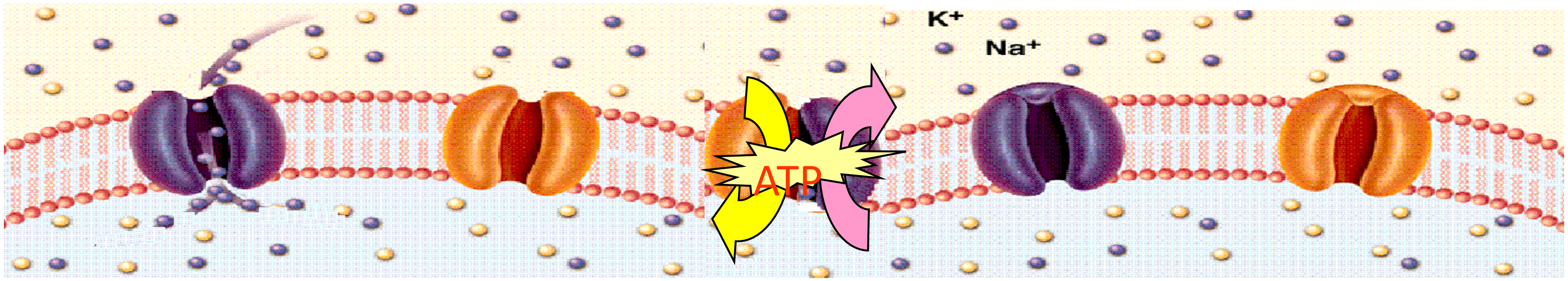
- Temporal integration takes into account the relative times at which the various graded potentials were generated.
- The standard measure is the time constant, τ (the Greek letter tau), which is given by the time which must elapse from the generation of a graded potential until V_m reaches 63% of its final value; this ranges from one to twenty milliseconds in most neurons.
- If a second graded potential begins before τ has elapsed, the two graded potentials will be added, producing a larger, integrated potential. If, however, the second graded potential is generated after τ has elapsed, the first signal will not affect the strength of the second one.

- Spatial summation considers the distance between two simultaneously occurring stimuli. It is measured by the Greek letter lambda (λ), which is defined as the distance from the original location of stimulation to where the signal (Vm) has decayed to 37% of its original value. The usual value for l is between 0.1 and 5 millimeters. λ is given by the square root or the ratio of r_m to r_a. Just as with τ, a second input will be summed with the first if it is generated within λ from the first input. If the two inputs are farther apart than λ, they will not be summated.

Action Potential

- Neurons communicate over long distances by generating and sending an electrical signal called a nerve impulse, or action potential.

outside



inside

- When a stimulus applied to the membrane in a resting potential, what happens???

Disturbed by the stimulus

Action Potentials (APs)

- A brief reversal of membrane potential with a total amplitude of 100 mV
- Action potentials are only generated by muscle cells and neurons
- They do not decrease in strength over distance
- They are the principal means of neuronal conduction
- An action potential in the axon of a neuron is a nerve impulse

- is very rapid
- all-or-none
- may occur at a rate of 1000 per second
- some cells have plasma membranes capable of producing action potentials.
- Voltage-dependent ion channels in the membrane are the basis for APs.
- The propagation of action potentials is the mechanism used by the nervous system to communicate over long distances.

Resting State

- Na^+ and K^+ channels are closed
- Leakage accounts for small movements of Na^+ and K^+
- Each Na^+ channel has two voltage-regulated gates
  - Activation gates – closed in the resting state
  - Inactivation gates – open in the resting state

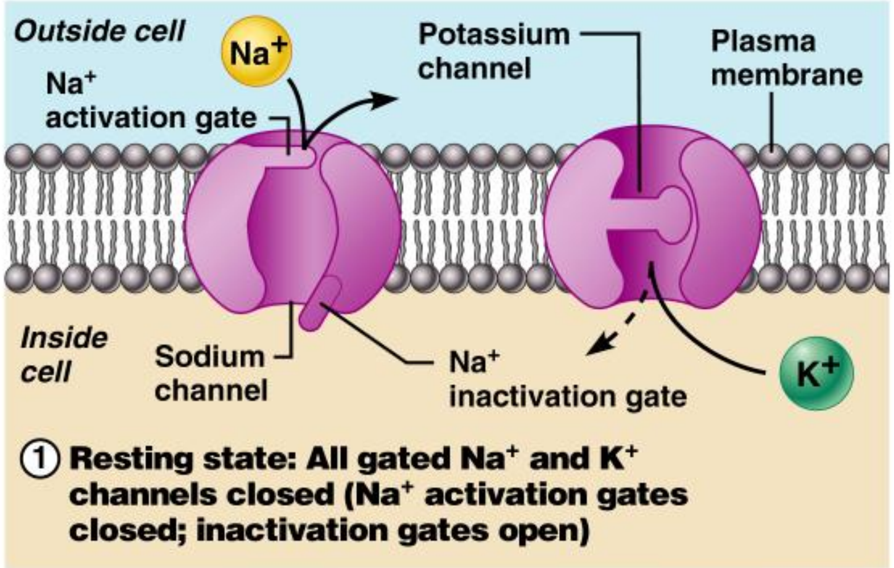
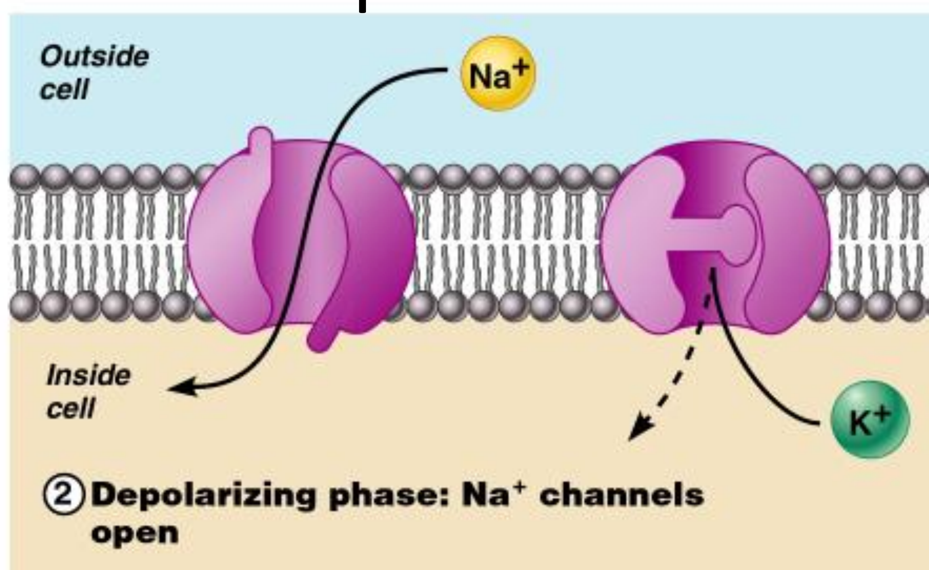


Figure 11.12.1

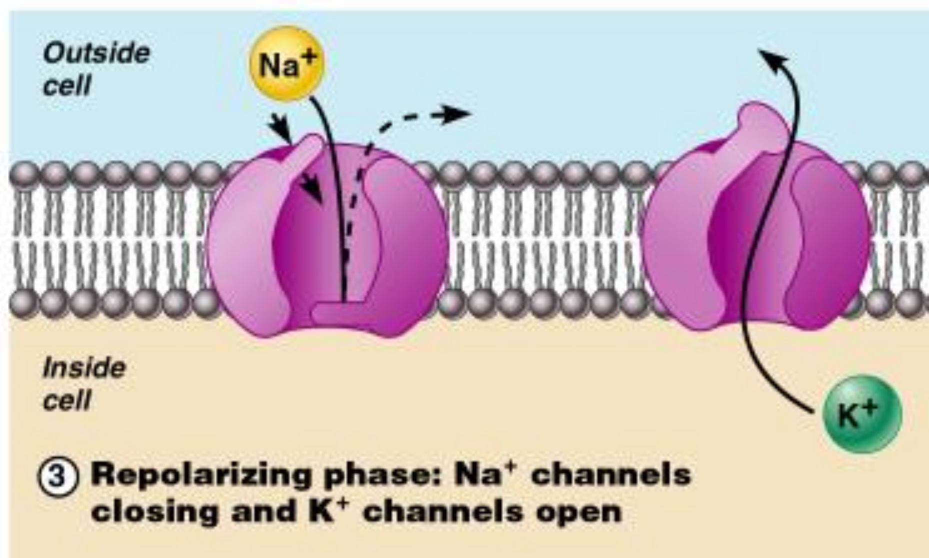
Depolarization Phase

- Na^+ permeability increases; membrane potential reverses
- Voltage gated Na^+ channels are opened, but K^+ are closed
- Threshold – a critical level of depolarization (-55 to -50 mV)
- At threshold, depolarization becomes self-generating



Repolarization Phase

- Sodium inactivation gates close
- Membrane permeability to Na^+ declines to resting levels
- As sodium gates close, voltage-sensitive K^+ gates open
- K^+ exits the cell and internal negativity of the resting neuron is restored



Hyperpolarization

- Potassium gates remain open, causing an excessive efflux of K^+
- This efflux causes hyperpolarization of the membrane (undershoot)
- The neuron is insensitive to stimulus and depolarization during this time

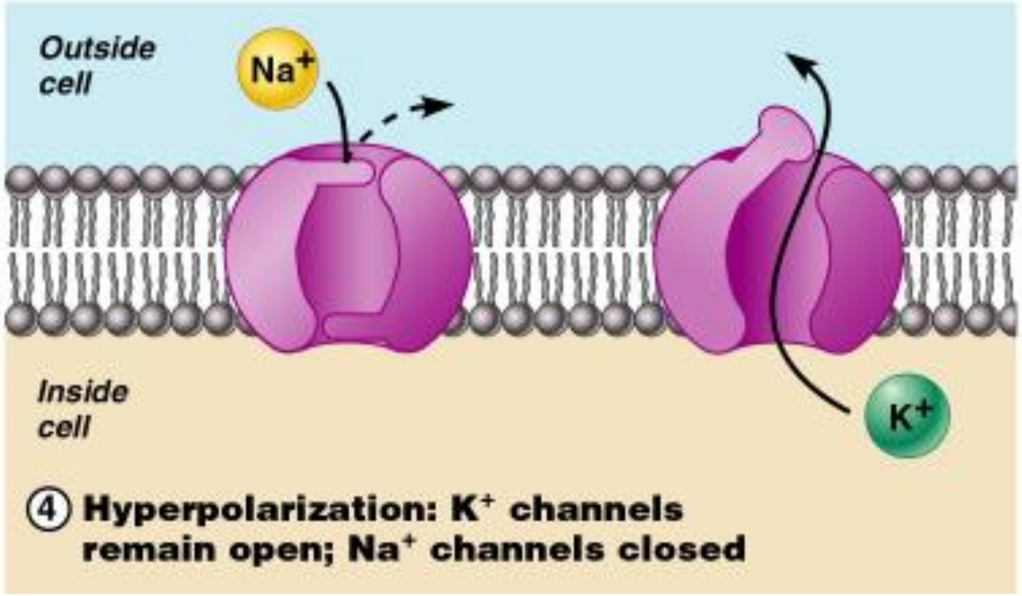


Figure 11.12.4

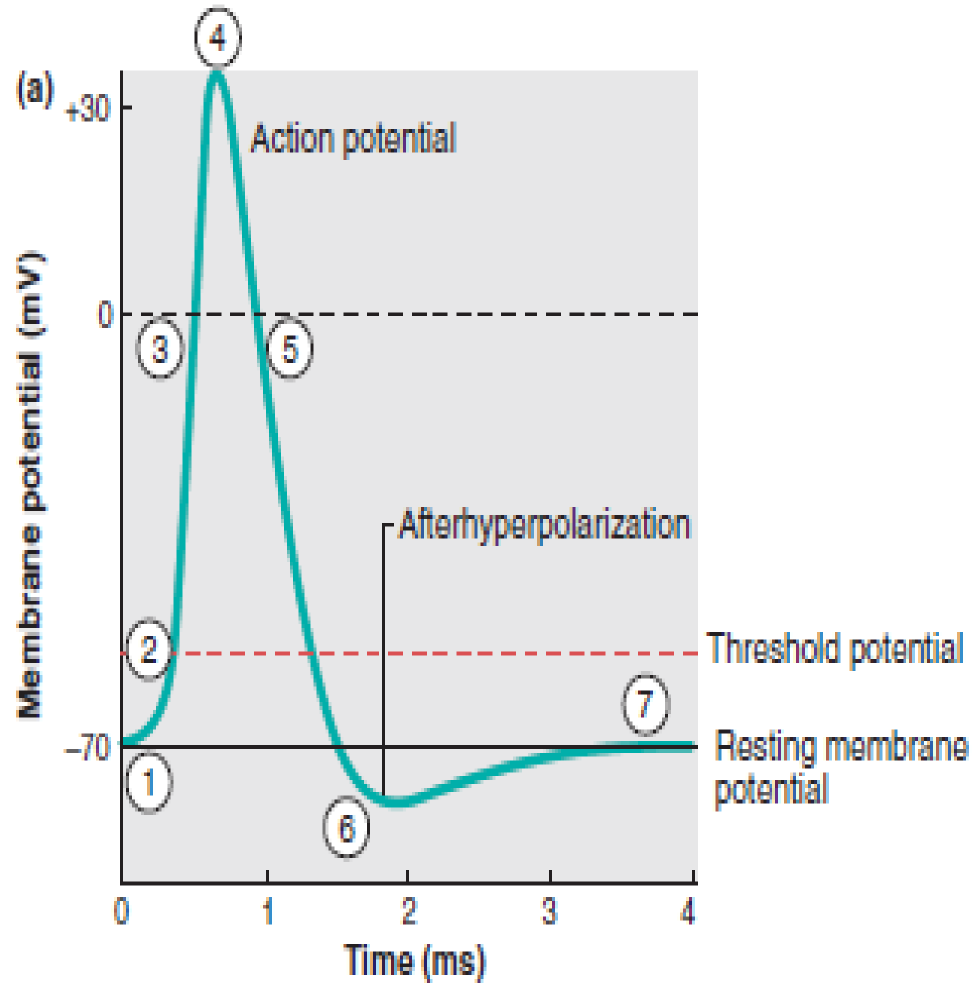
Action Potential: Role of the Na-K Pump

- Repolarization
  - Restores the resting electrical conditions of the neuron
  - Does not restore the resting ionic conditions
- Ionic redistribution back to resting conditions is restored by the sodium-potassium pump

The Action Potential: An Overview

- The action potential is a large change in membrane potential from a resting value of about -70 mV to a peak of about +30 mV, and back to -70 mV again.
- The action potential results from a rapid change in the permeability of the neuronal membrane to Na^+ and K^+. The permeability changes as voltage-gated ion channels open and close.

Action potentials are rapid, large alterations in the membrane potential during which time the membrane potential may change 100 mV, from -70 to 30 mV, and then repolarize to its resting membrane potential .



What is responsible for the change in membrane permeability during the action potential?

- Although called "action"potential, it is **NOT an active (energy-consuming) event** for the cell.
- It is purely a **passive event**. It is due to diffusion of ions!
- It is dependent on
  - ionic **electrochemical gradients** (Na^+, K^+) **and**
  - the membrane's **permeability**.

Excitable cells have "fickle(unstable)" cell membranes…they keep changing their permeabilities.

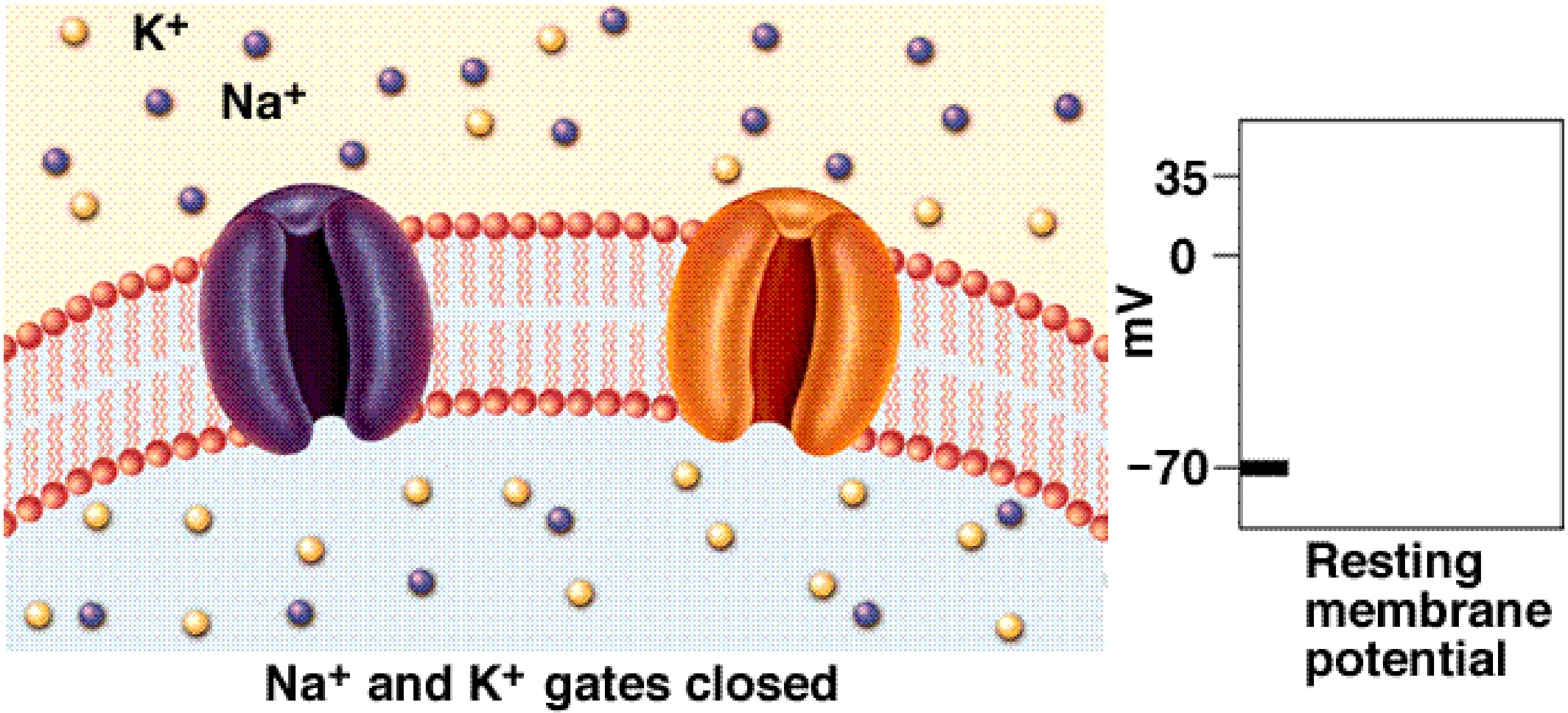
What determines the membrane's permeability at any moment?

Answer: GATED ion channels—These allow SIMPLE DIFFUSION of ions down their electrochemical gradients

Ionic Basis of the Action Potential

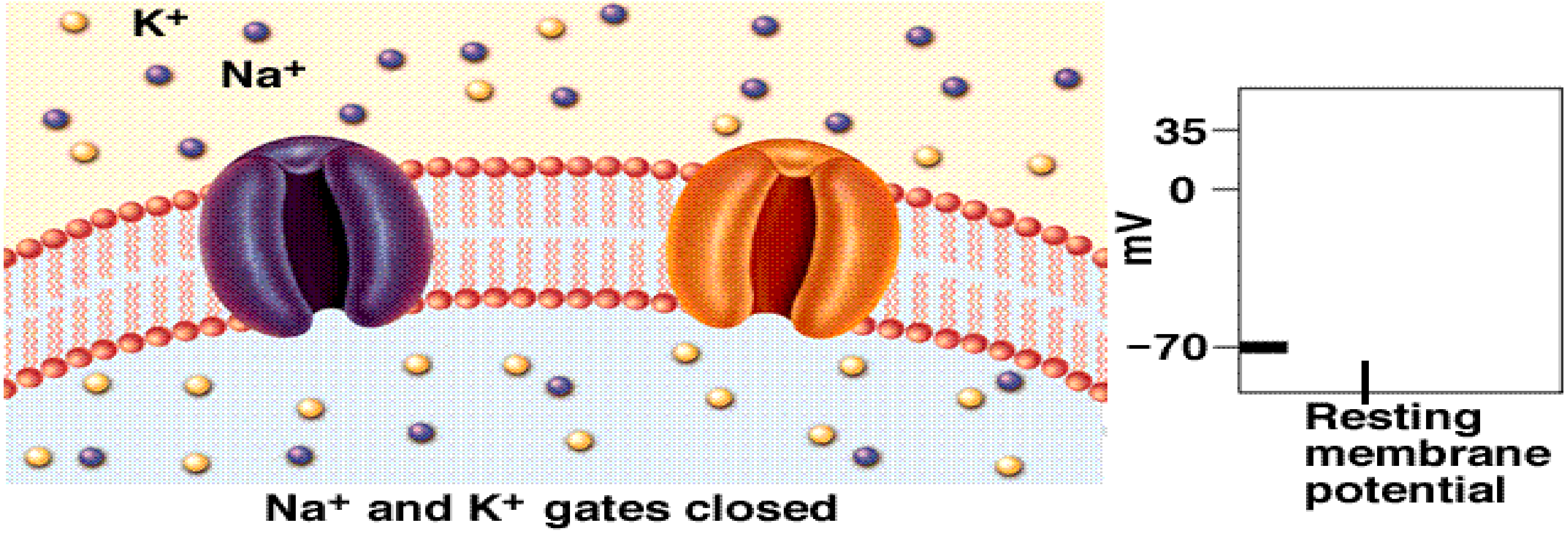
- The action potential is initiated by a transient change in membrane ion permeability, which allows Na^+ and K^+ ions to move down their concentration gradients.

Ionic Basis of the Action Potential



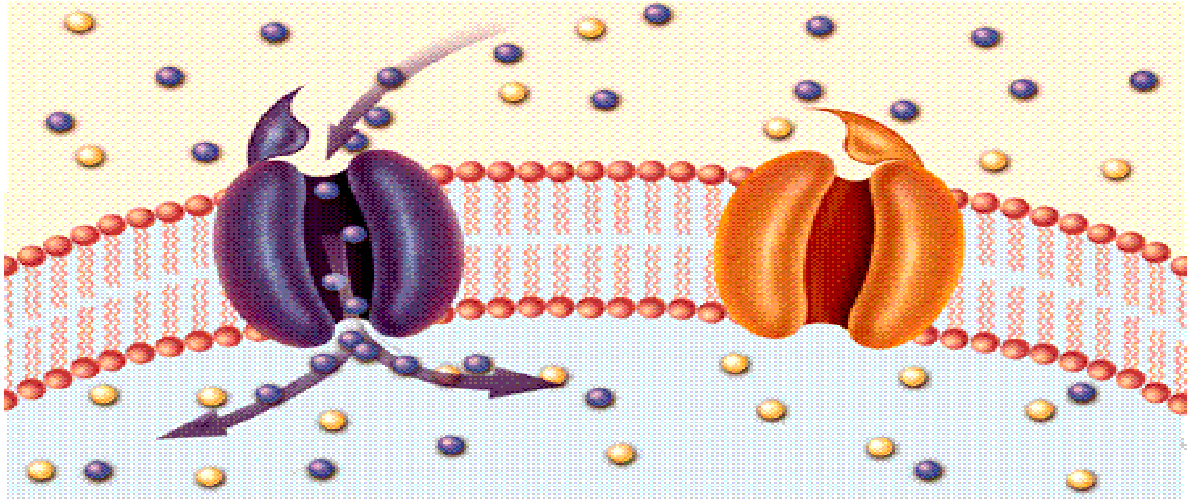
Ionic Basis of the Action Potential

When a stimulus applied in the membrane of the cell

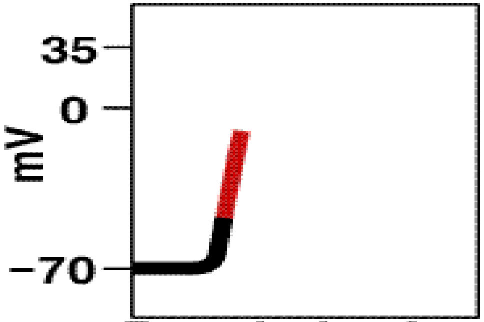


Ionic Basis of the Action Potential

Voltage gated Na^+ channels are open immediately, and K^+ channels open slowly



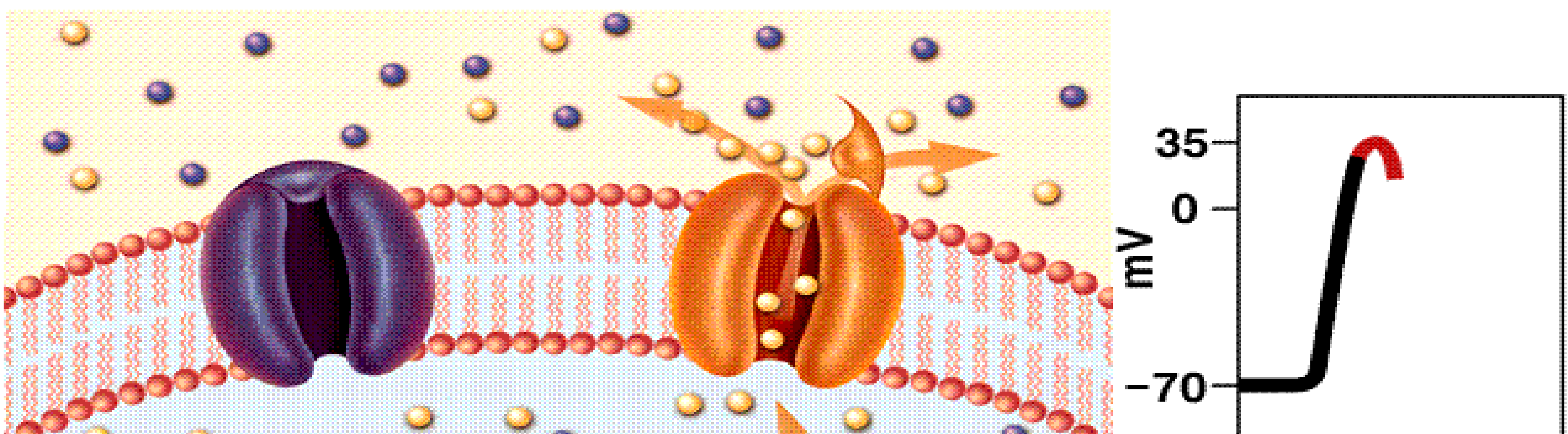
Na^+ gate open, Na^+ enters cell, K^+ gate beginning to open



Depolarization begins

Ionic Basis of the Action Potential

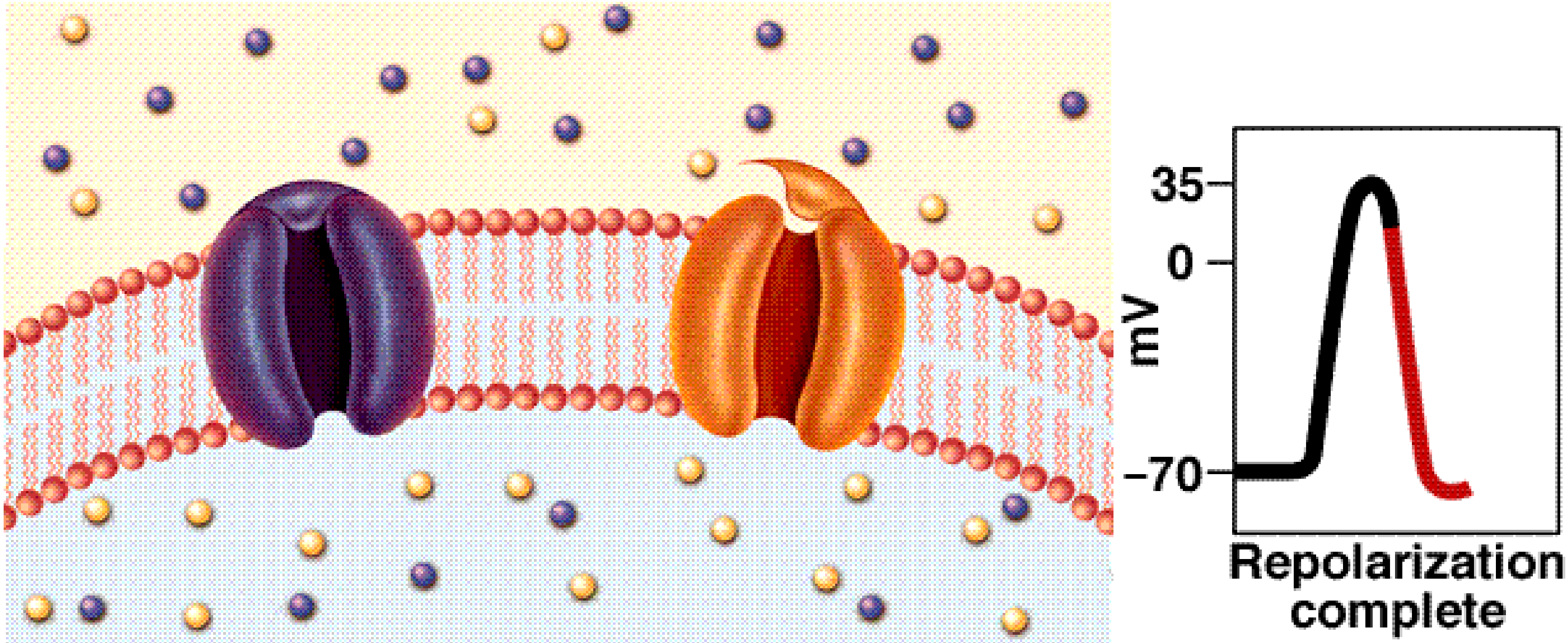
Voltage gated Na^{+} channels close



Na^{+} gate closed, K^{+} gate fully open, K^{+} leaves cell

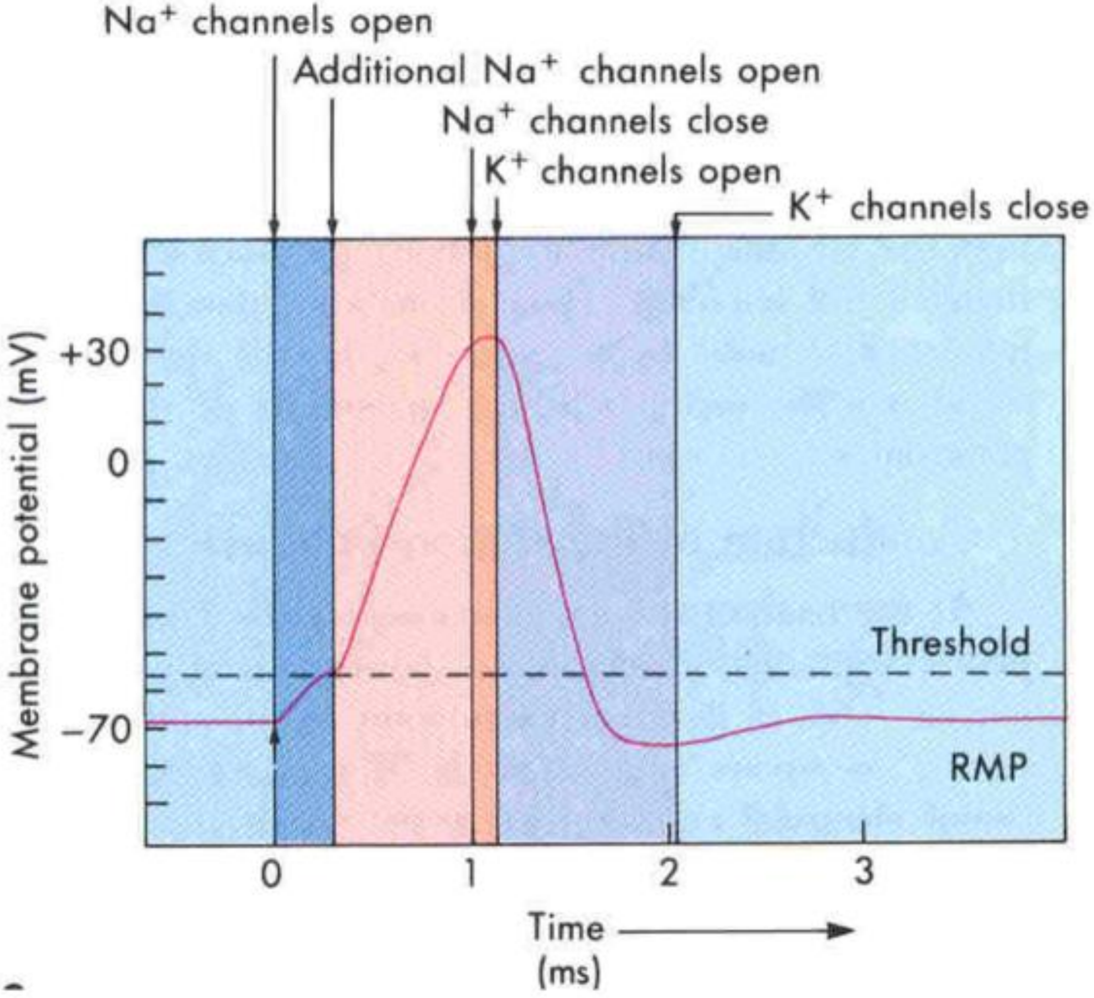
Depolarization ends, repolarization begins

Ionic Basis of the Action Potential



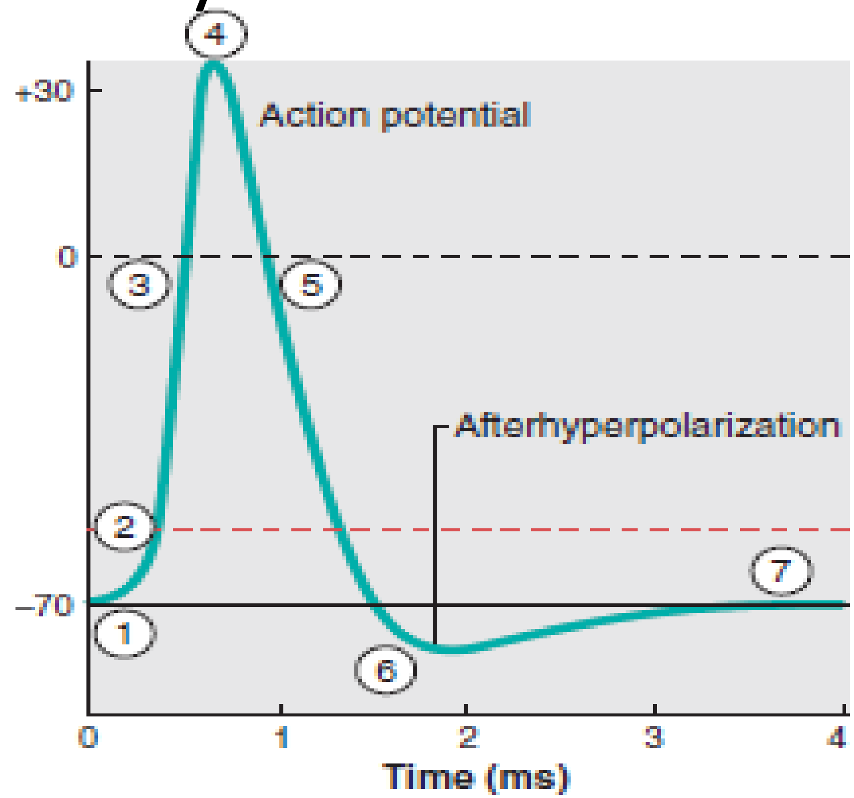
Na+ gate closed, K+ gate closing

Channels of APs

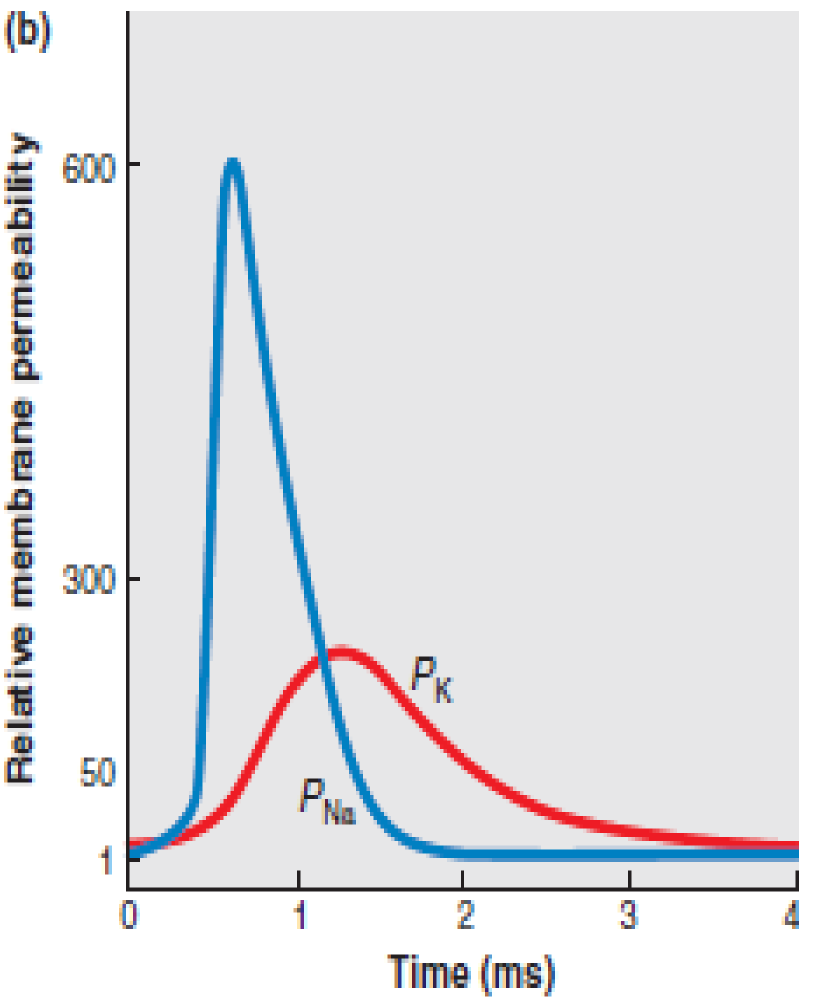


❖ 1. PHASE: In the resting state,

- The leak channels in the plasma membrane are predominantly those that are *permeable to K^+ions.*
- Very few Na^+ ion channels are open.
- **The resting potential is close to the K^+ equilibrium potential.**

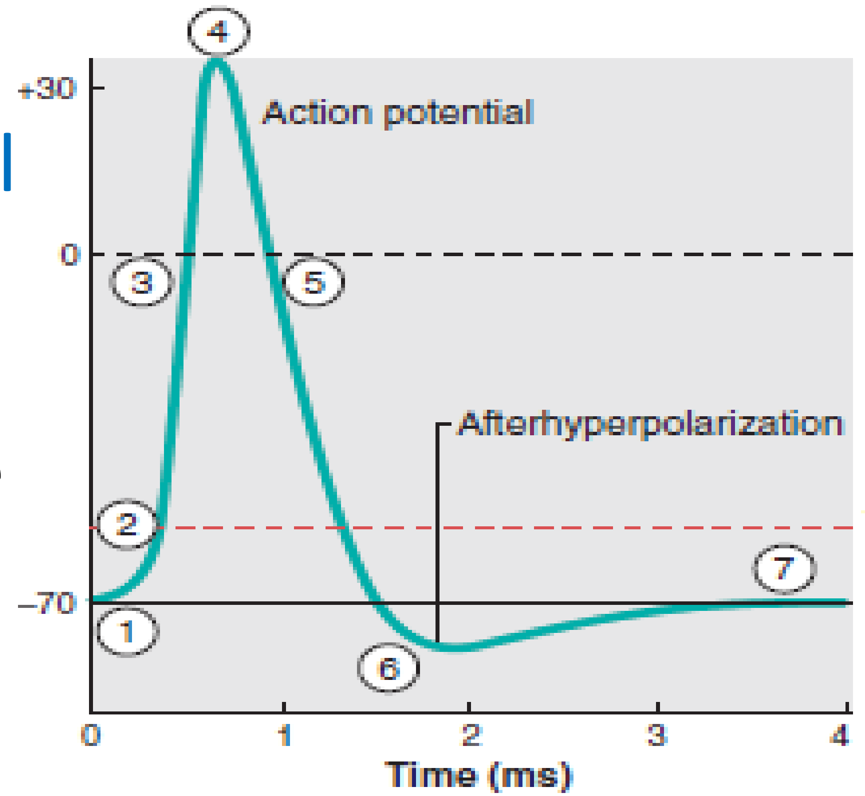


- The action potential begins with depolarization of the membrane in response to a stimulus.
- This initial depolarization opens sodium channels, which increases the membrane permeability to sodium ions



❖ Phase 2

- More sodium ions move into the cell.
- The cell becomes more and more depolarized until a threshold (2) is reached to trigger the action potential. This is called the ***threshold potential***.

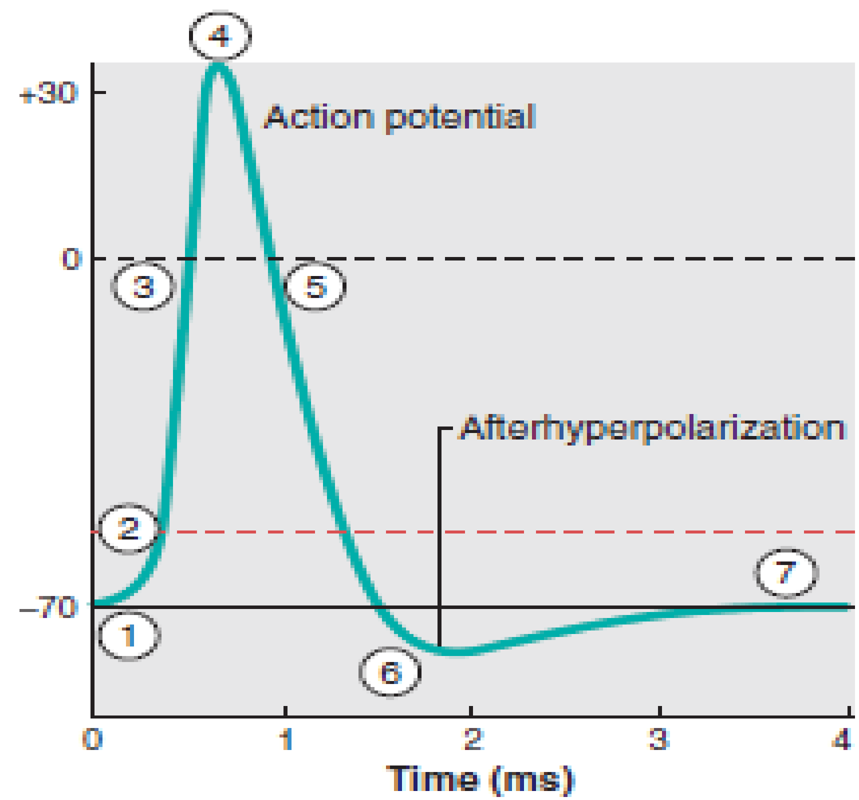


Threshold and Action Potentials

- Threshold – membrane is depolarized by 15 to 20 mV
- Established by the total amount of current flowing through the membrane
- Weak (subthreshold) stimuli are not relayed into action potentials
- Strong (threshold) stimuli are relayed into action potentials
- All-or-none phenomenon – action potentials either happen completely, or not at all

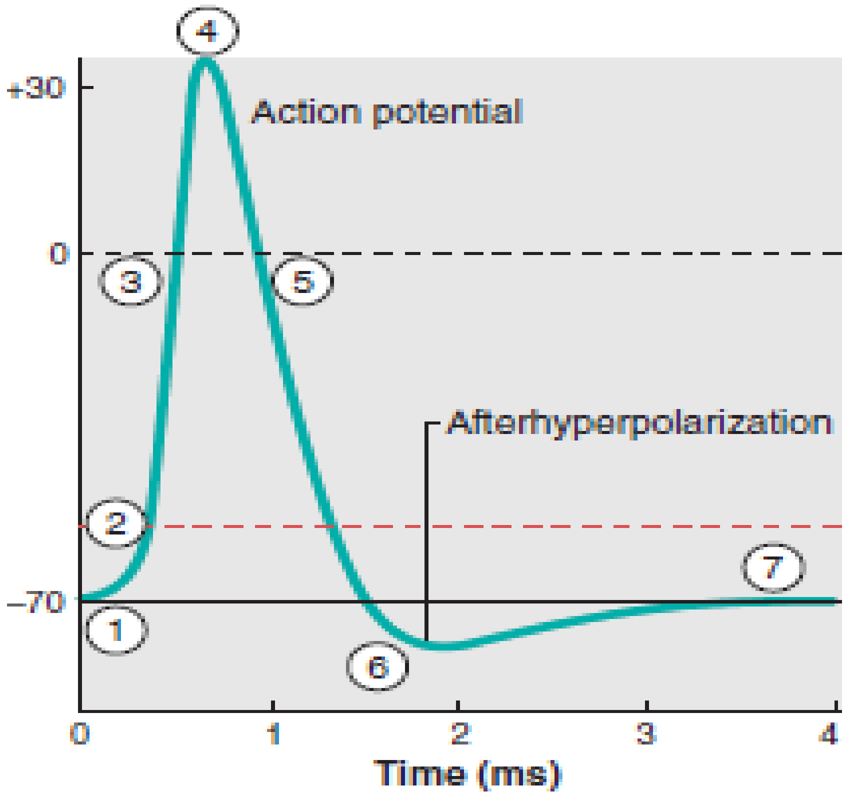
❖ Phase 3

- After the threshold potential is reached, voltage-gated sodium channels open (3).
- The membrane potential overshoots, becoming positive on the inside and negative on the outside of the membrane.
- In this phase, the membrane potential approaches but does not quite reach the sodium equilibrium potential (E_{Na}=60 mV).



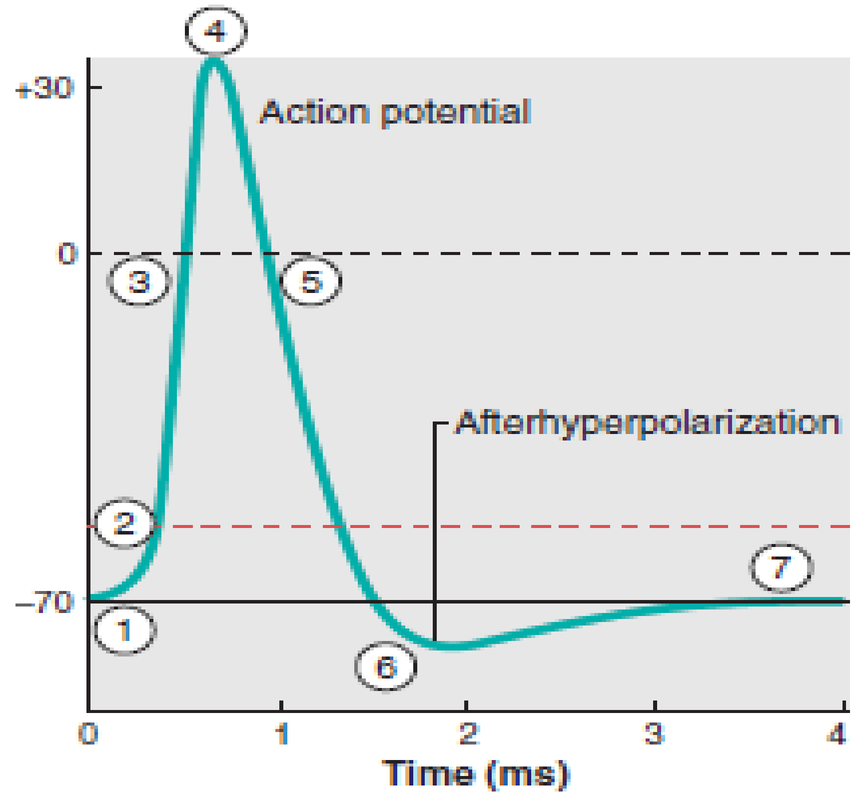
❖ Phase 4

- At the peak of the action potential (4), Na^+ permeability abruptly decreases and voltage-gated potassium channels open.



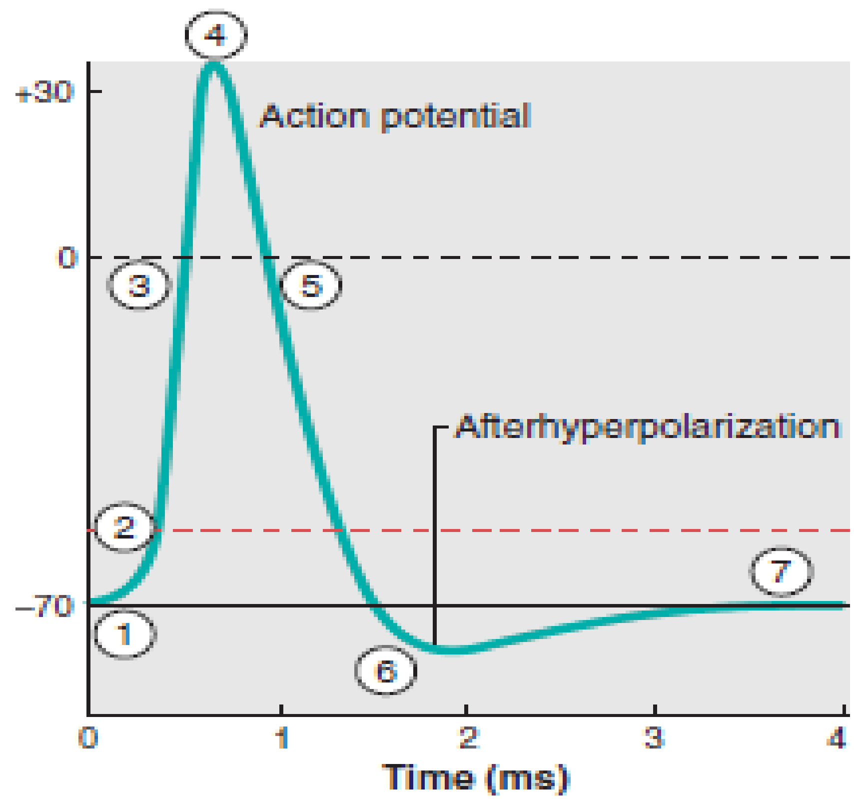
❖ Phase 5

- The membrane potential begins to rapidly repolarize (5) to its resting level.



❖ Phase 6

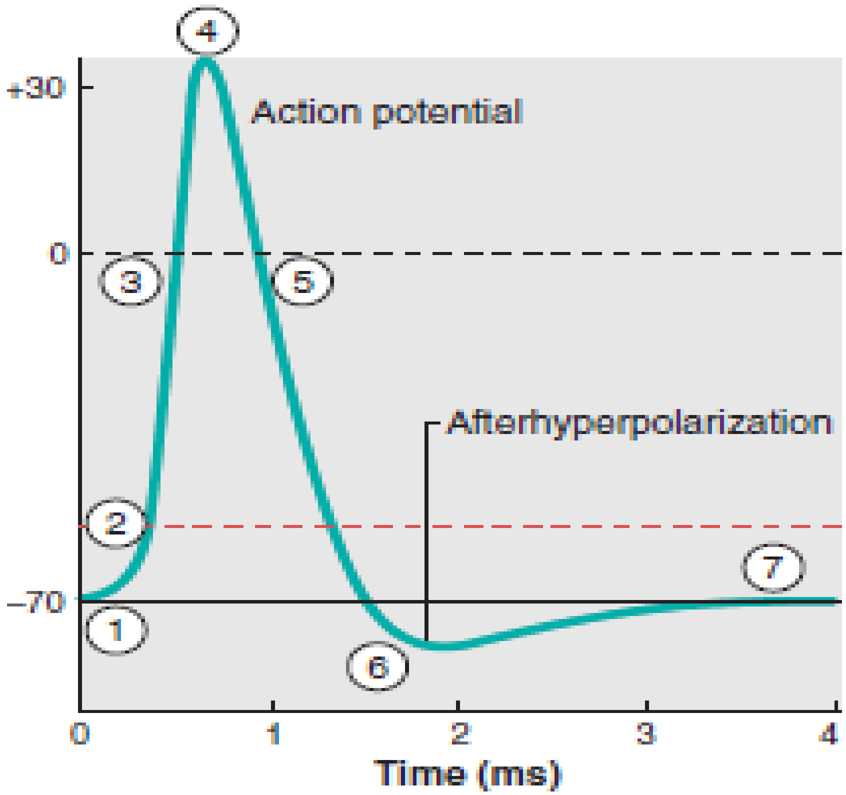
- After the sodium channels have closed, some of the voltage-gated potassium channels are still open, and in nerve cells there is generally a small hyperpolarization (6) of the membrane potential beyond the resting level called the **after hyperpolarization**.



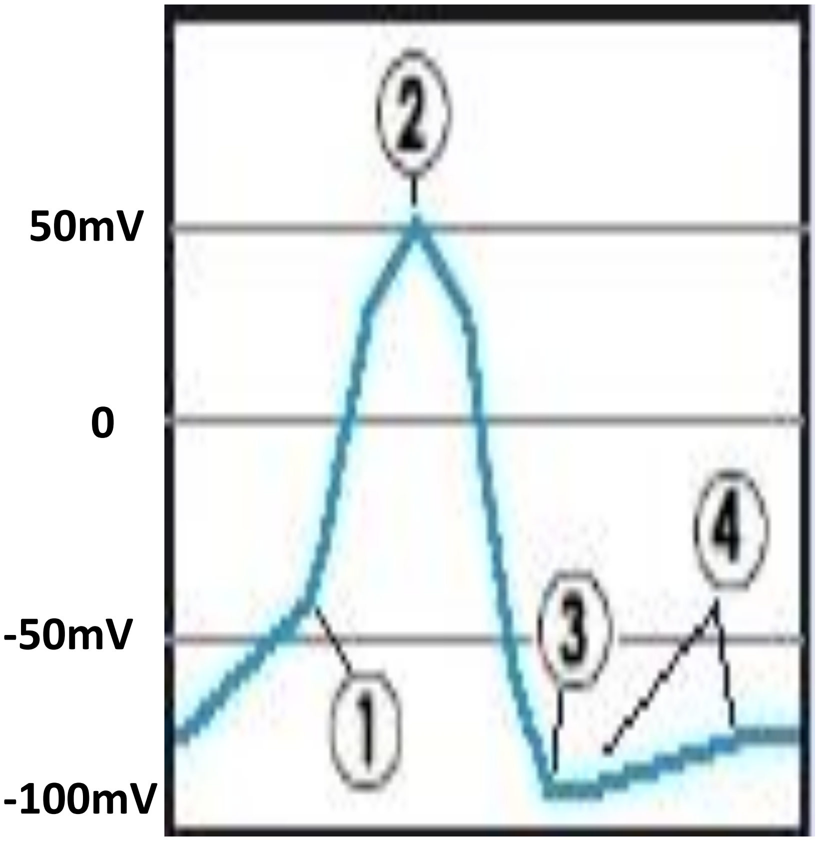
❖ Phase 7

- Once the voltage-gated potassium channels close, the resting membrane potential is restored (7).
- Na^+/ K^+ pump restore potential to -70mV in 1-2 msec.

- ***Chloride permeability*** does not change during the action potential.



- **0: Between -70 to -40 mV** Na^+ channels open & Na^+ ions flood inside.
- **1: At -40mV**, Voltage-gated Na^+ channels open & Na^+ ions flood inside.
- **2: At +50mV**, Na^+ channels close & K^+ channels open so that K^+ ions flood outside.
- **3:** Voltage decreases to **-90 mV** & K^+ channels close
- **4:** Na^+/K^+ pump restores potential to **-70mV** in 1-2msec.



Resting membrane Potential

Na^+ concentrated on outside.

K^+ concentrated on inside

Depolarization Begins

Na^+ gates open and Na^+ begins to flow rapidly into the axon

Depolarization Continues

Na^+ continues to flow rapidly into the axon

K^+ gates open and K^+ begins to flow slowly out of the axon

Depolarization Peaks

Na^+ channels close and Na^+ stops flowing into the axon

K^+ has only just started to leave the axon

Na^+ and K^+ are now both briefly concentrated on the inside of the axon resulting in the inside being positive relative the outside of the axon

Hyperpolarization Begins

The Na^+ channels close, the Na^+ pump forces the Na^+ out of the axon, back to where it started.

K^+ channels start to close. Because positive ions are both concentrated on the outside of the axon, the outside is now more positive than when the axon is at rest. In other words, the inside is more negative than resting.

Axon Returns to The Resting State

Na^+ has been pumped back outside

K^+ has been pump back inside

- Many cells that have graded potentials cannot form action potentials because they have no voltage-gated sodium channels.

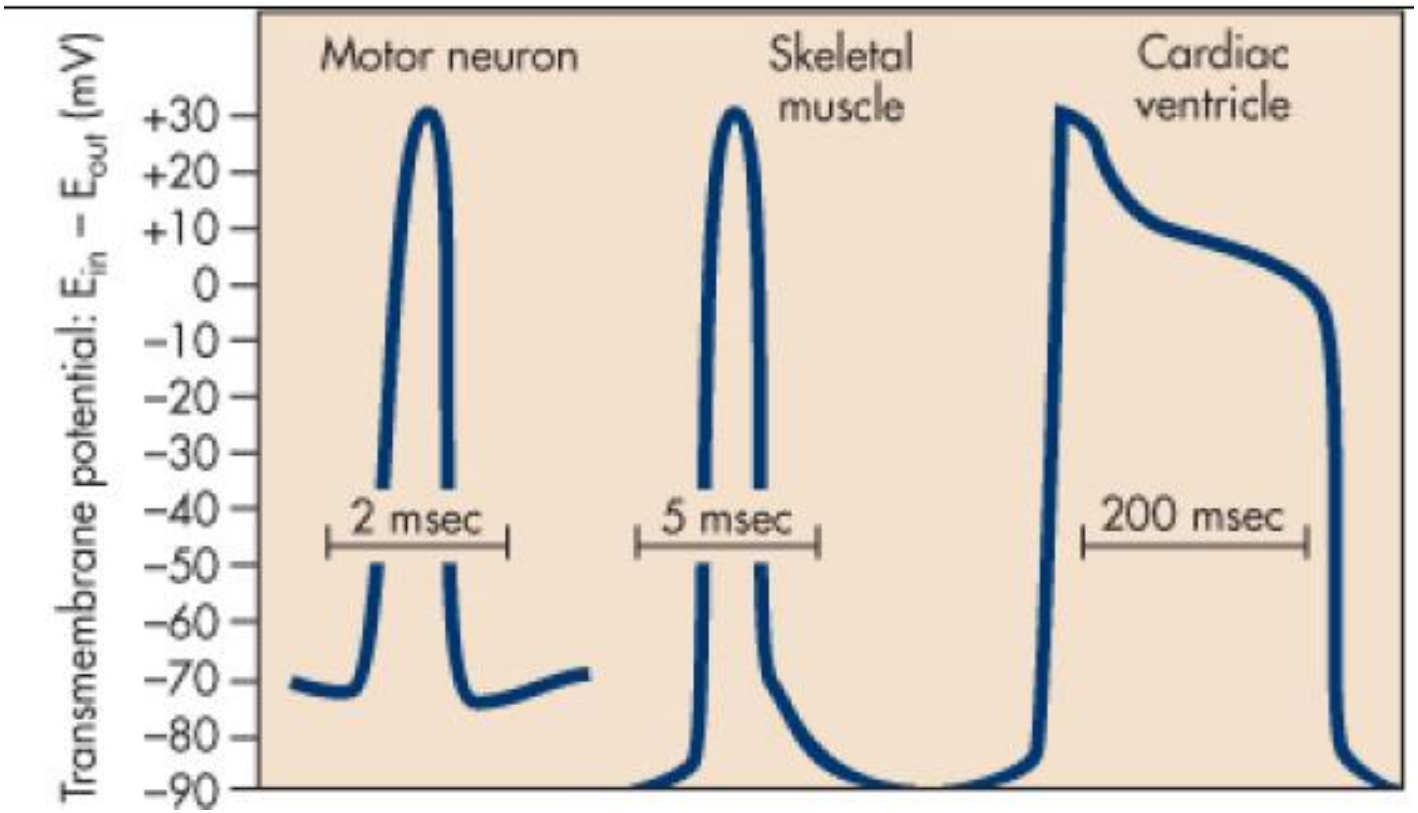
What is achieved by letting Na^+ move into the neuron and then pumping it back out?

- Na^+ movement down its electrochemical gradient into the cell generates the electrical signal necessary for communication between the parts of the cell.
- Pumping Na^+ back out maintains the concentration gradient so that, in response to a new stimulus, Na^+ will again enter the cell and create another signal.

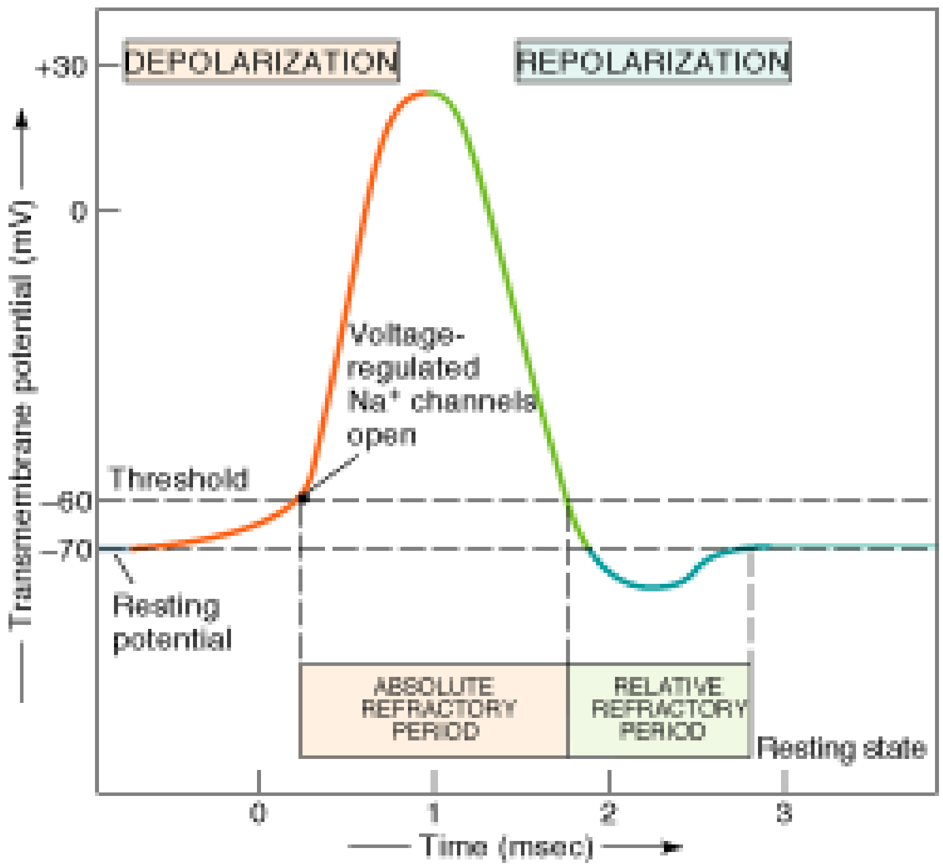
Characteristics of Action Potential

- 1- It propagates along the axon with the same size (amount of depolarization) and shape (change of potential with time)
- 2- It is an all or none response. It starts only if a threshold point is passed. The ion channels are either open or closed; there is no half-way position. And this means that the action potential always reaches +40mV as it moves along an axon, and it is never reduced by long axons.
- 3- Size and shape differ from one type of cell to another.

Different types of action potential



Refractory period



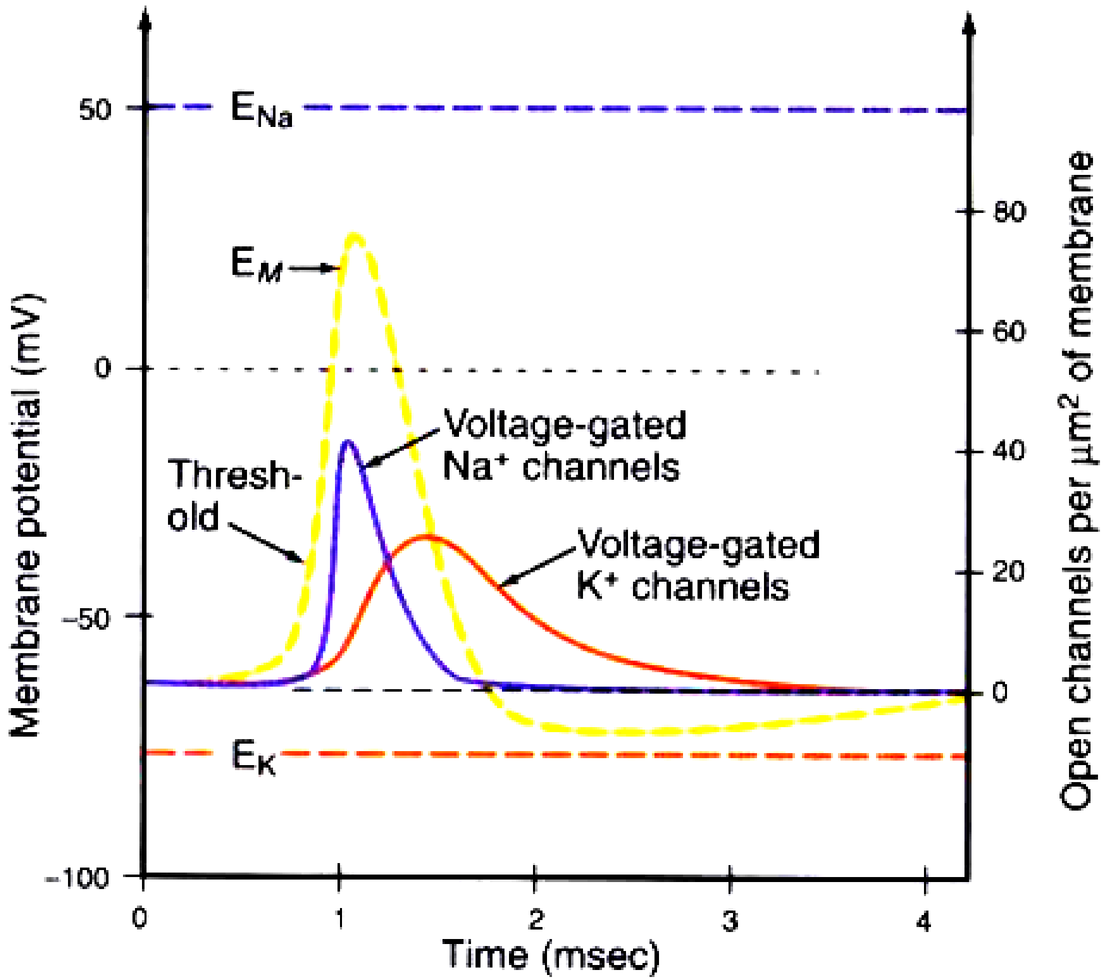
- Ionic equilibrium returns back to resting potential.
- At this stage the cell close to new stimuli.
- In the relative period stimuli that reach over threshold level can initiate action potential.

Absolute Refractory Period

- Time from the opening of the Na^+ activation gates until the closing of inactivation gates
- The absolute refractory period:
  - Prevents the neuron from generating an action potential
  - Ensures that each action potential is separate
  - Enforces one-way transmission of nerve impulses

Relative Refractory Period

- The interval following the absolute refractory period when:
  - Sodium gates are closed
  - Potassium gates are open
  - Repolarization is occurring
- The threshold level is elevated, allowing strong stimuli to increase the frequency of action potential events

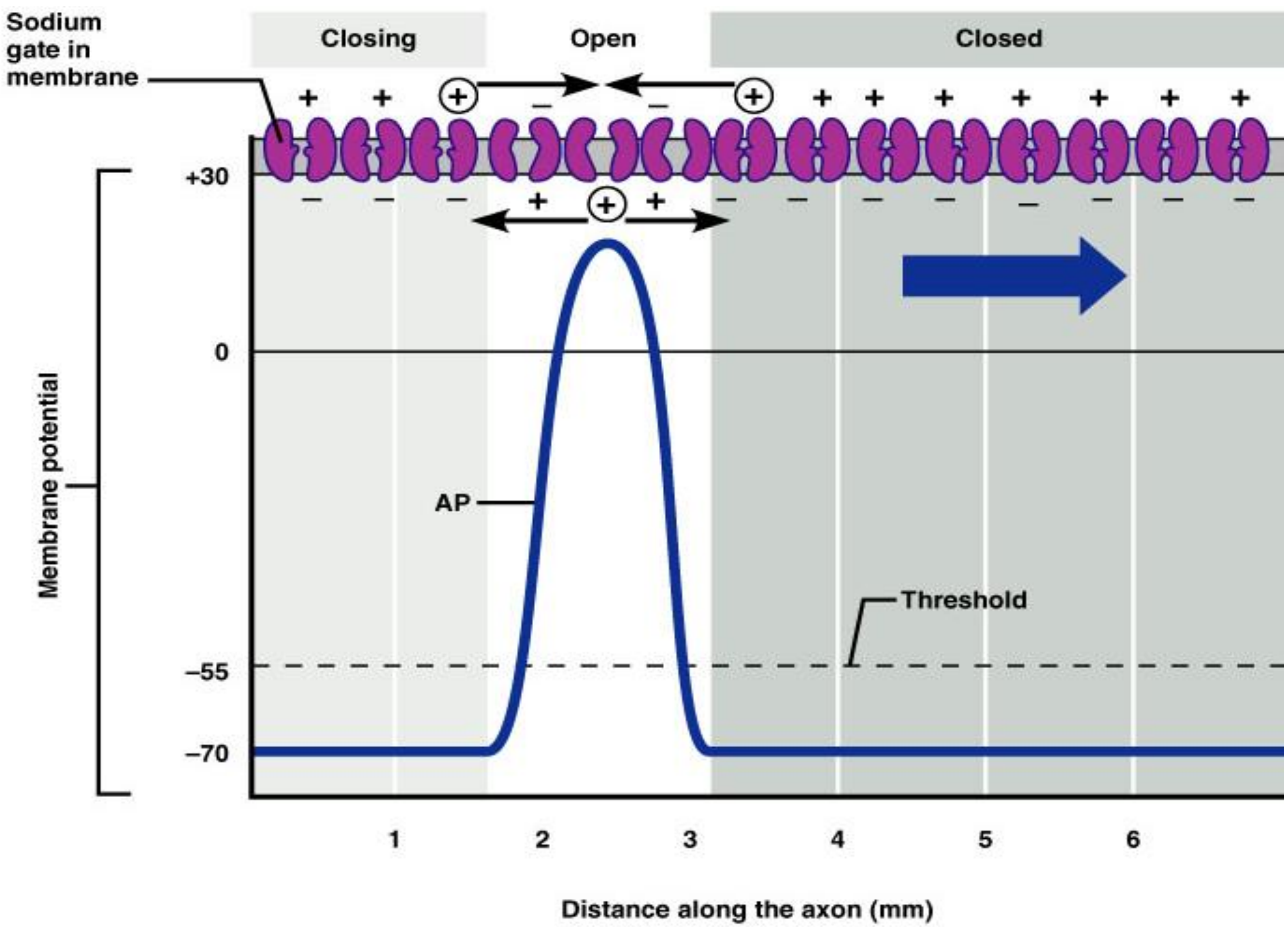


50
0
−50
−100
Membrane potential (mV)
E_Na
E_M
Thresh-
old
Voltage-gated
Na⁺ channels
Voltage-gated
K⁺ channels
E_K
80
60
40
20
0
Open channels per μm² of membrane
0
1
2
3
4
Time (msec)

Propagation of an Action Potential (Time = 0ms)

- Na^+ influx causes a patch of the axonal membrane to depolarize
- Positive ions in the axoplasm move toward the polarized (negative) portion of the membrane
- Sodium gates are shown as closing, open, or closed

Propagation of an Action Potential (Time = 0ms)

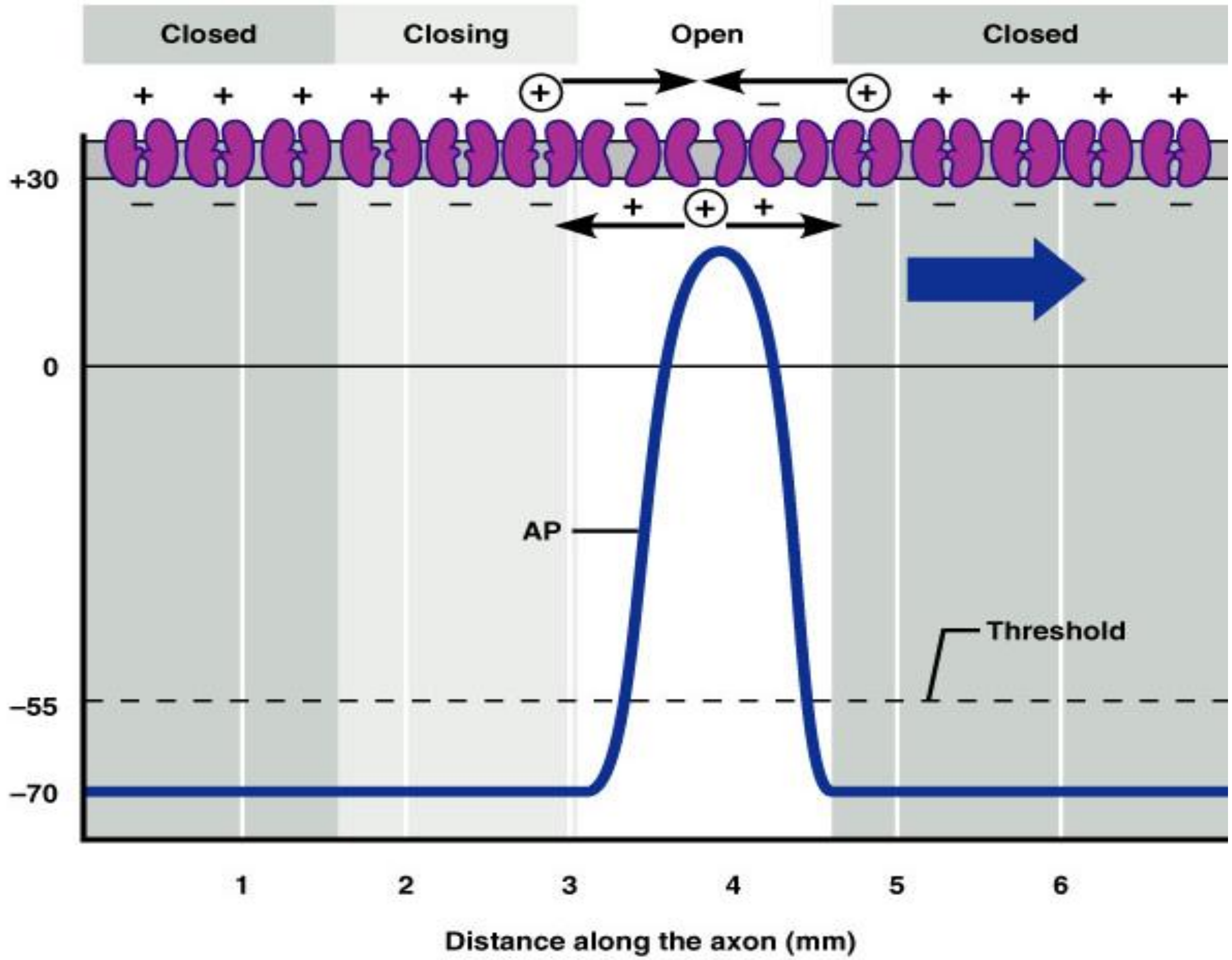


(a) Time = 0 ms

Propagation of an Action Potential (Time = 1ms)

- Ions of the extracellular fluid move toward the area of greatest negative charge
- A current is created that depolarizes the adjacent membrane in a forward direction
- The impulse propagates away from its point of origin

Propagation of an Action Potential (Time = 1ms)

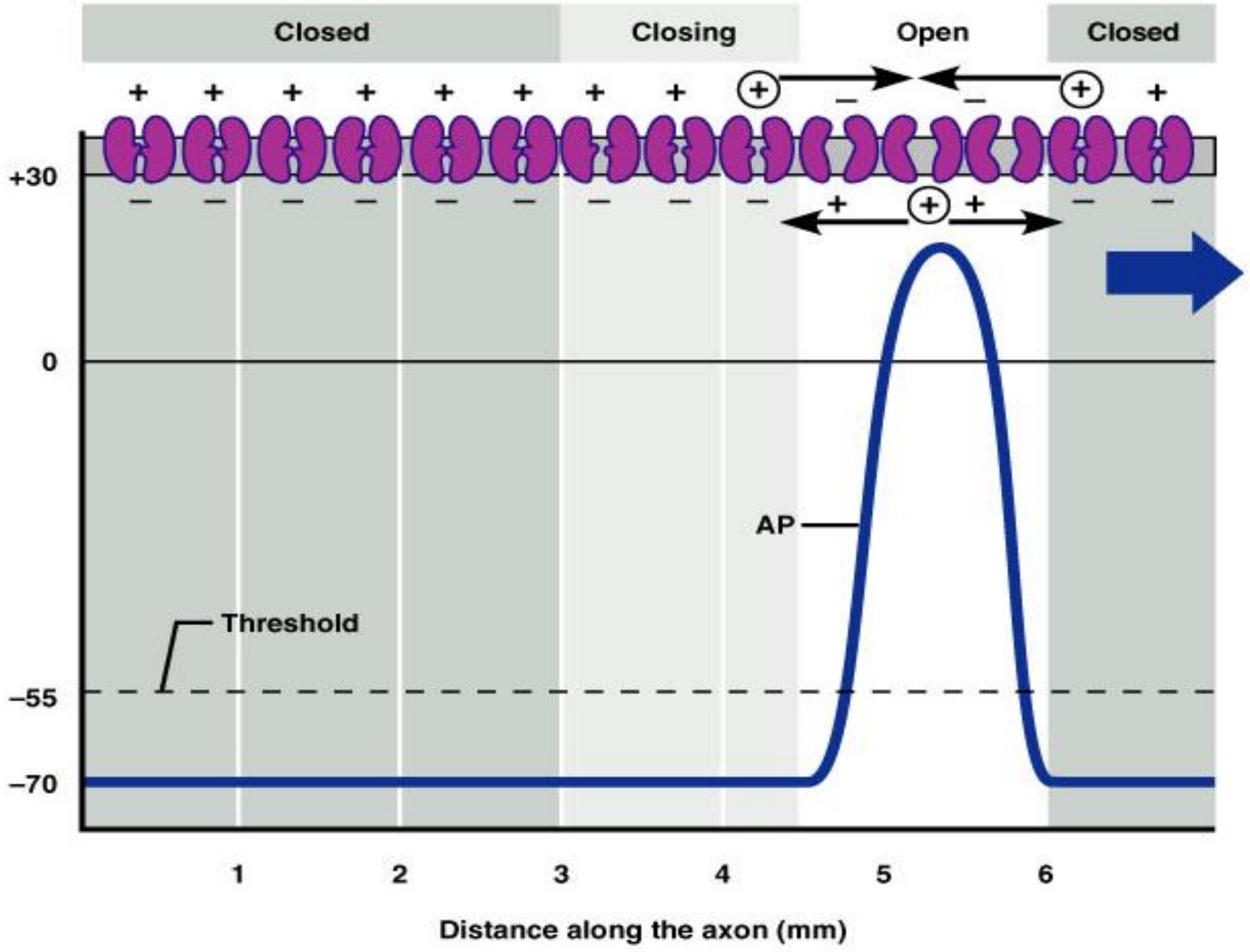


(b) Time = 1 ms

Propagation of an Action Potential (Time = 2ms)

- The action potential moves away from the stimulus
- Where sodium gates are closing, potassium gates are open and create a current flow

Propagation of an Action Potential (Time = 2ms)



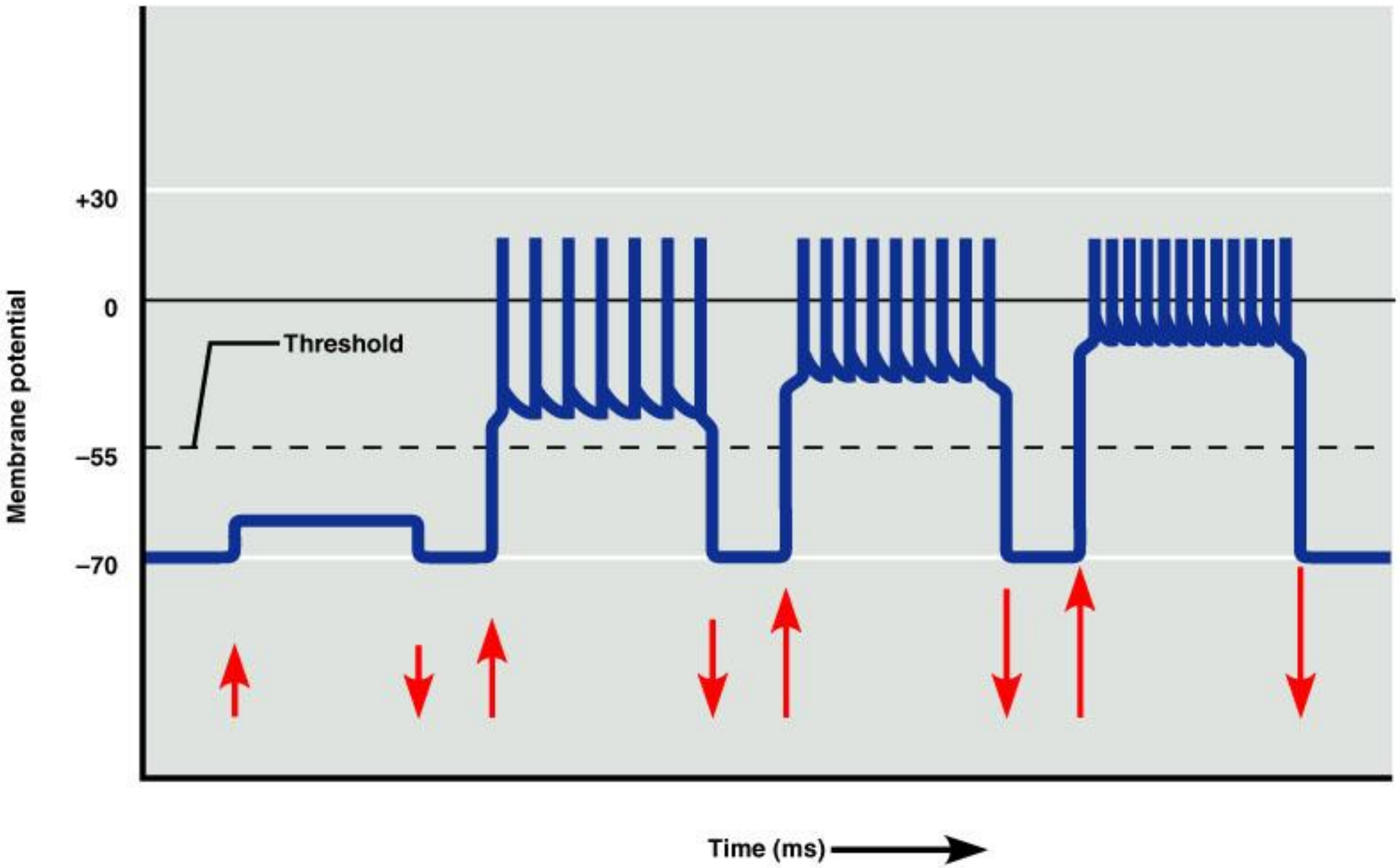
(c) Time = 2 ms

Coding for Stimulus Intensity

- All action potentials are alike and are independent of stimulus intensity
- Strong stimuli can generate an action potential more often than weaker stimuli
- The CNS determines stimulus intensity by the frequency of impulse transmission

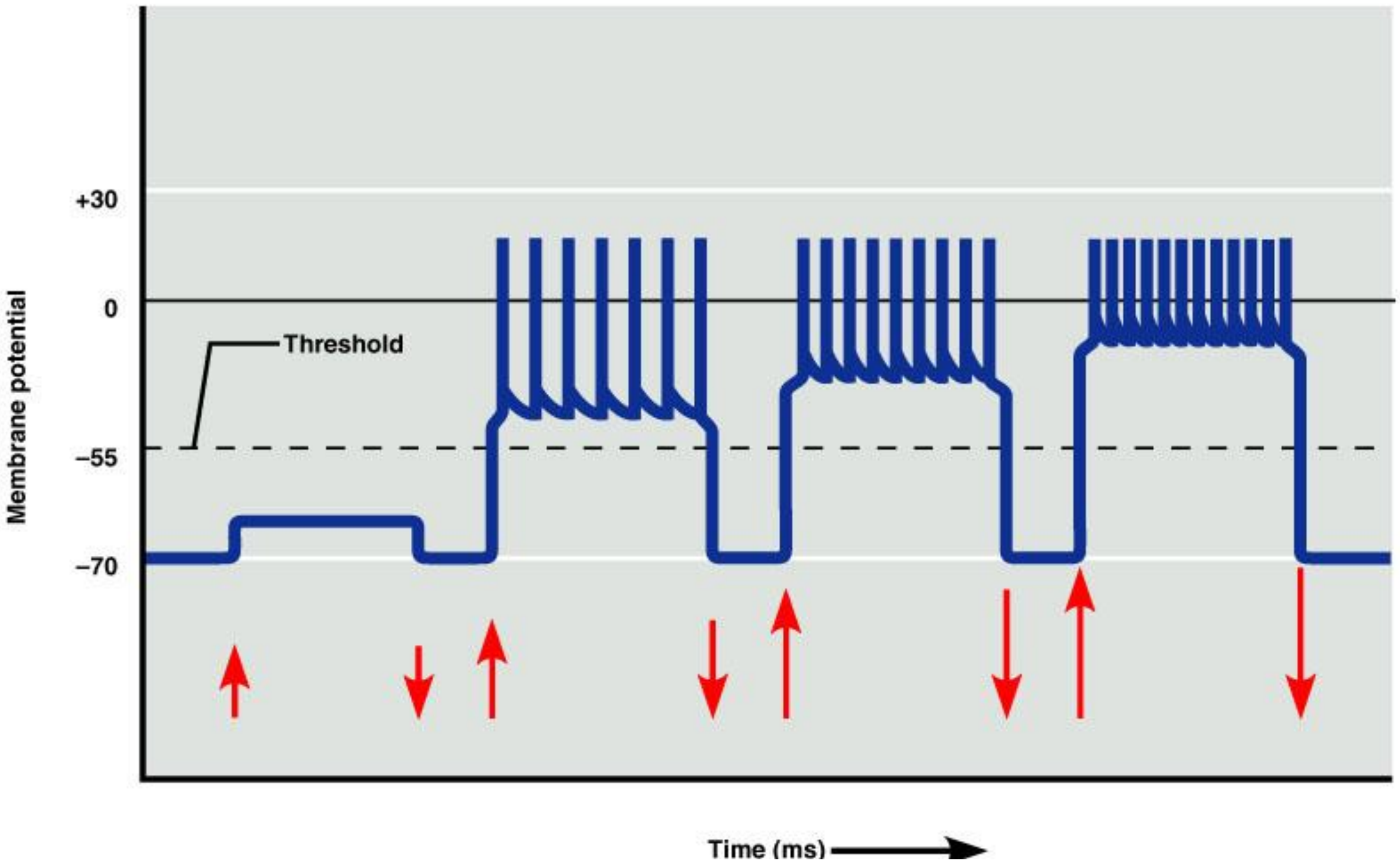
Coding for Stimulus Intensity

- Upward arrows – stimulus applied
- Downward arrows – stimulus stopped



Coding for Stimulus Intensity

- Length of arrows – strength of stimulus
- Action potentials – vertical lines



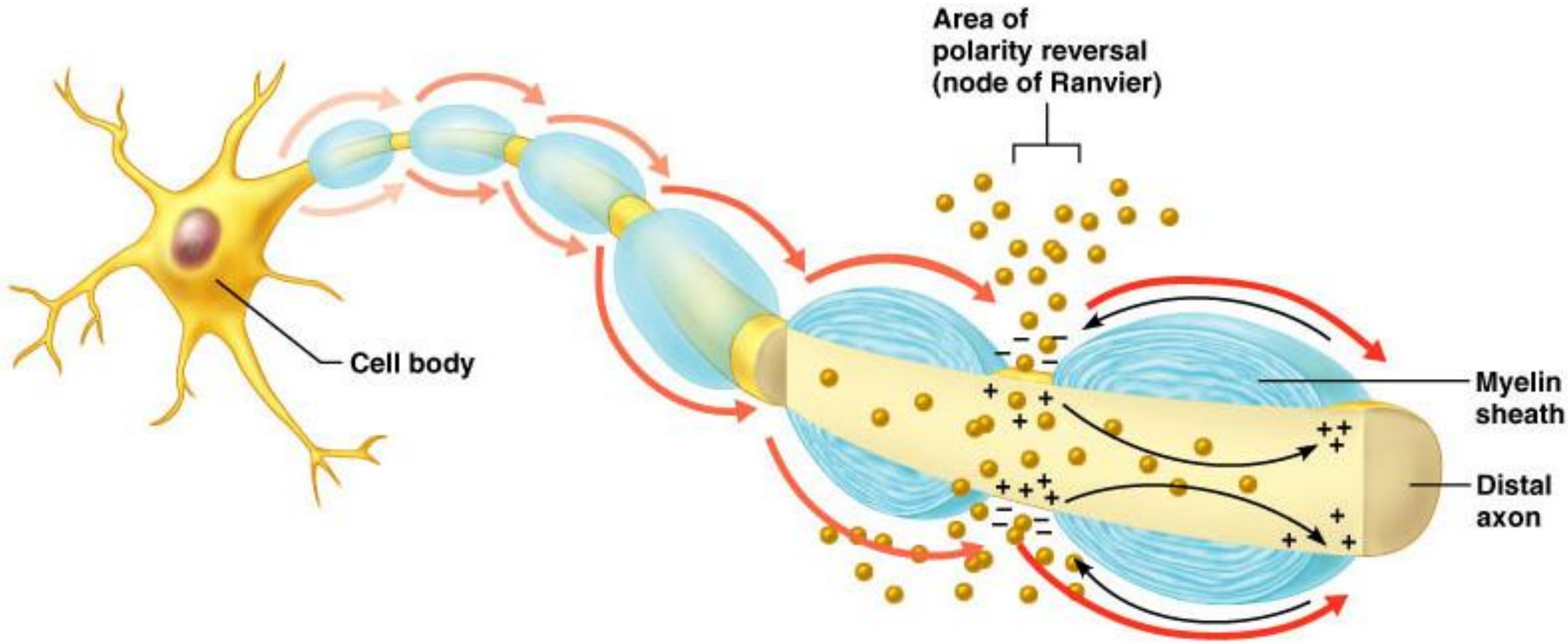
Conduction Velocities of Axons

- Conduction velocities vary widely among neurons
- Rate of impulse propagation is determined by:
  - Axon diameter – the larger the diameter, the faster the impulse
  - Presence of a myelin sheath – myelination dramatically increases impulse speed

Saltatory Conduction

- Current passes through a myelinated axon only at the nodes of Ranvier
- Voltage-gated Na^+ channels are concentrated at these nodes
- Action potentials are triggered only at the nodes and jump from one node to the next
- Much faster than conduction along unmyelinated axons

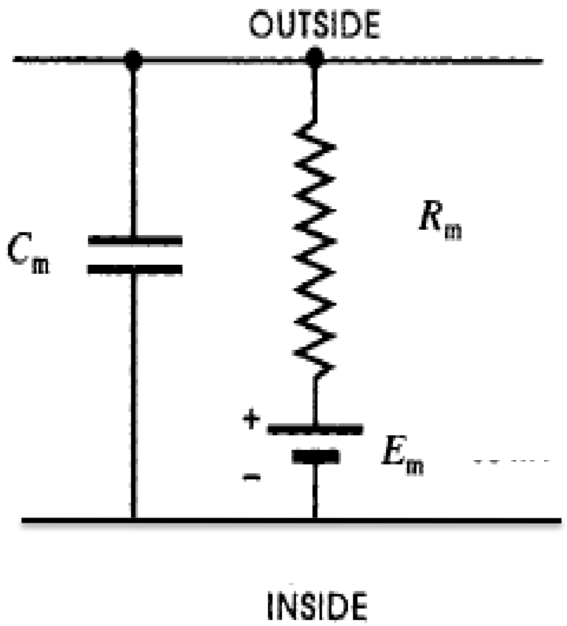
Saltatory Conduction



EQUILIBRIUM POTENTIALS

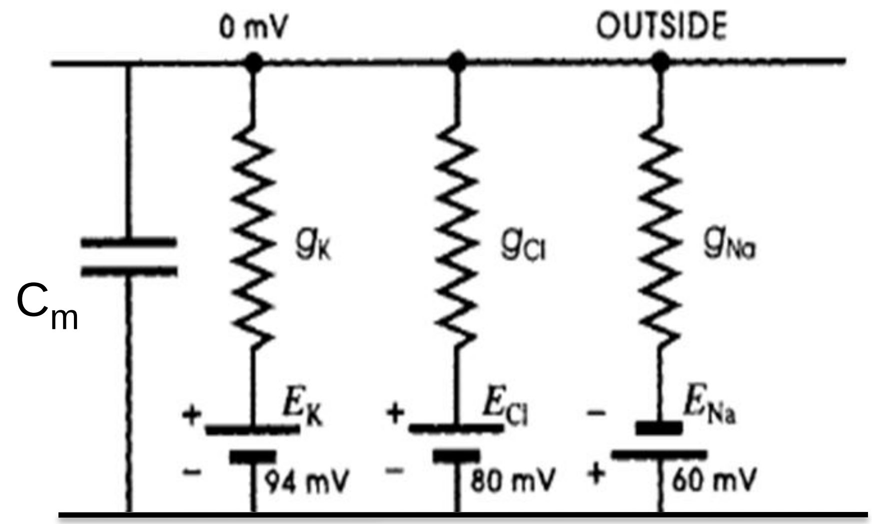
- Equivalent Electrical Circuit
- Nernst Equation

Equivalent Electrical Circuit



- The electrical equivalent circuit of the cell membrane at rest is represented.
- The membrane is indicated as a parallel resistance (R_M) and capacitance (C_M).

- The equivalent circuit for the resting membrane is composed of 3 major components. These are K^+, Cl^- and Na^+.
- Each of these ions provide conductance of the membrane.
- The respective permeability are g_K, g_{Cl}, and g_{Na}



- **The polarity of each battery is as shown: namely the pole facing inwards is negative for K^+ and Cl^- and positive for Na^+.**
- **These polarities are based on the directions of the concentration gradients and charge on the ions.**

Nernst Equation

- For each ionic species distributed unequally across the cell membrane, an equilibrium potential *(E_i) or battery can be* calculated for that ion from the Nernst equation.

$$E_i = -\frac{RT}{zF} ln \frac{C_i}{C_0}$$

- C_i *is the intemal concentration of the ion,*
- C_O *is the extracellular* concentration,
- R is the gas constant (8.3 J/mol.K),
- T is the absolute temperature in kelvins (K =273+^{O}C)
- $\mathcal{F}$ is the Faraday constant (96 500 C/eq),
- z is the valence (with sign).
- Taking the *RT/* $\mathcal{F}$ *constants* and the factor of 2.303 for conversion of natural log (In) to log to the base of 10 (log10) gives:

$$E_i = -\frac{RT}{zF} ln \frac{C_i}{C_0}$$

$$E_i = -\frac{2.303RT}{zF} log \frac{C_i}{C_0} = -\frac{61mV}{z} log \frac{C_i}{C_0}$$

- The Nernst equation gives the **potential difference (electrical force) that would exactly oppose the concentration gradient (diffusion force).**

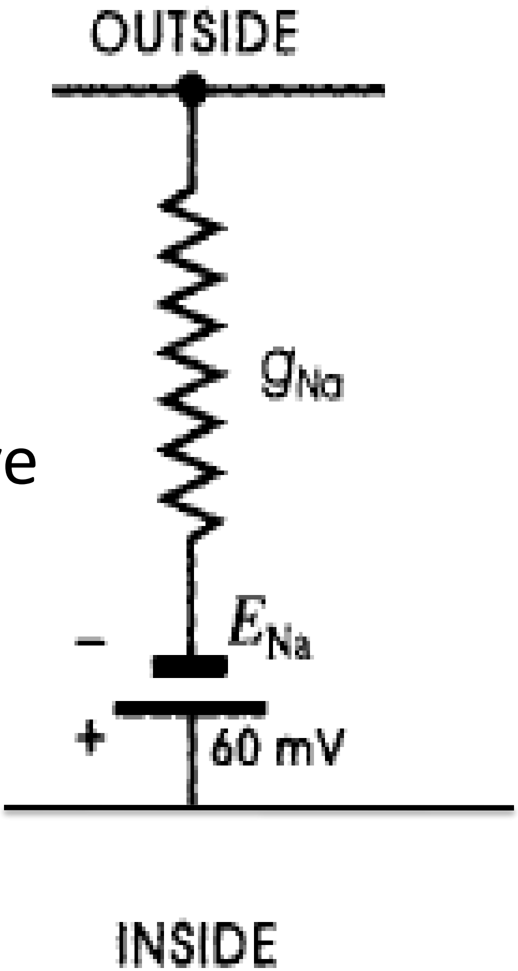
- Only very small charge separation (Q, in coulombs) is required to build a very large potential difference.

$$E_M = Q / C_M$$

- C_M *is the membrane capacitance.*

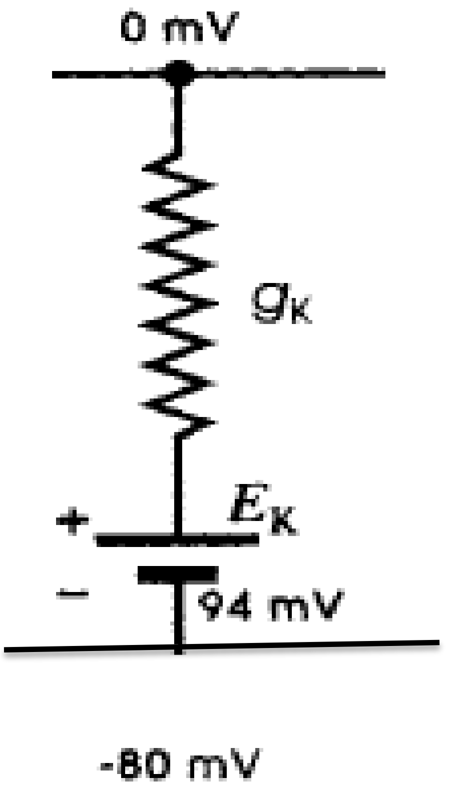
E_{Na} = +60 mV

- Because Na^+ is higher outside (145 mM) than inside (15 mM), the positive pole of the Na^+ battery (E_{Na}) is inside the cell.



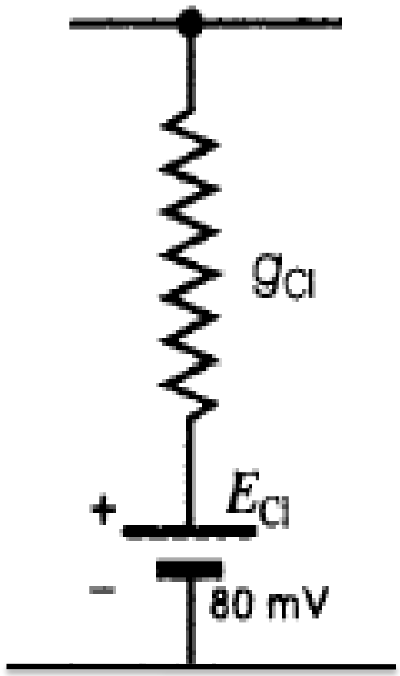
$E_K = -94$ mV

- K^+ is higher inside (150 mM) than outside (4.5 mM), and so the negative pole is inside.



E_{Cl}= -80 mV

- Because Cl^- is higher outside (100 mM) than inside (5 mM), the negative pole is inside.



Electrochemical Driving Forces

and

Membrane Ionic Currents

Electrochemical Driving Forces

- The electrochemical driving force for each type of ion is difference between its equilibrium potential E_i *and the membrane potential* E_M.
- *The total driving* force is the sum of two forces:
  - **an electrical force**
    - the negative potential in a cell at rest tends to pull in positively charged ions
  - **and a diffusion force**
    - based on the concentration gradient

Driving force = $E_m - E_i$

- Thus, in a resting cell, the driving force for Na^+ is

$$(E_m - E_{Na}) = -80mV - (+60mV)$$

$$(E_m - E_{Na}) = 140mV$$

- The negative sign means that the driving force is directed to inside for Na^+.

- The driving force for K^+ is

$$(E_m - E_K) = -80\ mV - (-94\ mV)$$
$$(E_m - E_K) = +14\ mV$$

The driving force for K^+ is small and directed to outside.

- The driving force for Cl^- is nearly zero for a cell at rest in which Cl^- is passively distributed.

$$(E_m - E_{Cl}) = -80\ mV - (-80\ mV)$$

$$(E_m - E_{Cl}) = 0$$

Membrane Ionic Currents

- The net current for each ionic species *(I_i) is equal to its driving* force times its conductance *(g_i)* through the membrane.
- This is essentially Ohm's law,

$$I=V/R$$

$$I=V/(1/g)$$

$$I= g.V$$

$$I_i = g_i\,(E_M - E_i)$$

- For the 3 ions, the net current can be expressed as

$$I_{Na} = g_{Na}\,(E_M - E_{Na})$$

$$I_K = g_K\,(E_M - E_K)$$

$$I_{Cl} = g_{Cl}\,(E_M - E_{Cl})$$

- In steady state condition, net charge carried by passive flow must be zero.
- Therefore at rest

$$\sum I_i = 0 \quad \text{or} \quad \sum I_K + I_{Na} + I_{Cl} = 0$$

- In a resting cell, Cl^- can be neglected, and the Na^+ current (inward) must be equal and opposite to the K^+ current (outward) to maintain a steady resting potential:

$$I_K = - I_{Na}$$

$$g_K (E_M - E_K) = g_{Na} (E_M - E_{Na})$$

In the resting membrane the driving force for Na^+ ion is much greater than that for K^+, g_K is much larger than g_{Na}, so the currents are equal.

$$I_K = g_K(E_m - E_K)$$

$$I_{Na} = g_{Na}(E_m - E_{Na})$$

$$I_{Cl} = g_{Cl}(E_m - E_{Cl})$$

$$\sum I_K + I_{Na} + I_{Cl} = 0$$

$$g_{Na}(E_m - E_{Na}) + g_K(E_m - E_K) + g_{Cl}(E_m - E_{Cl}) = 0$$

When I_{Cl}=0

$$g_{Na}(E_m - E_{Na}) + g_K(E_m - E_K) = 0$$

$$g_{Na}(E_m - E_{Na}) = -g_K(E_m - E_K)$$

$$E_m = \frac{E_K + E_{Na}\left(\frac{g_{Na}}{g_K}\right)}{1 + \frac{g_{Na}}{g_K}}$$

- There is a continuous leakage of Na^+ inward and K^+ outward, even in a resting cell, and the system would run down if active pumping were blocked.
- Because the ratio of the Na^+ to K^+ driving forces (-140 mV/-14 mV) is 10, the ratio of conductances *(g_{Na}/g_K) will be about 1:10.*
- ***The fact that g_K is much greater* than g_{Na} accounts for the resting potential being close to E_K and far from E_{Na}**

- In the resting condition, every ion willl try to move with an electromotive force which is equal to its Nernst resting potential (E_{Na}, E_K, E_{cl}).
- Membrane shows resistance to each ion (R_{Na} , R_K, R_{Cl})
- Charge stored in membrane is constant since potential is constant (C_m , E_m). If E_m is constant, we can take capacitive current as zero.
- Chloride ions are in equilibrium, so chloride ion current is zero.
- Passive passage of Na ions is equal and opposite to active current – so does the K
- Total current due to ions should be :$I_{Na}+I_K+I_{Cl}=0$

Goldman-Hodgkin-Katz Equation

- A Modification of the Nernst Equation is the Goldman-Hodgkin Equation can be used to predict E_m when the membrane is permeable to multiple ions.

$$E_m = -\frac{RT}{zF} ln \frac{P_K[K]_{out} + P_K[Na]_{out} + P_K[Cl]_{in}}{P_K[K]_{in} + P_K[Na]_{in} + P_K[Cl]_{out}}$$

$$E_m = -\frac{RT}{zF} \ln \frac{P_K[K]_{out} + P_K[Na]_{out} + P_K[Cl]_{in}}{P_K[K]_{in} + P_K[Na]_{in} + P_K[Cl]_{out}}$$

***E_m*:** *Membrane potential*
R *: Gas constant [8314.9 J/(kg mol K)]*
T : *Absolute temperature (temperature* measured on the Kelvin scale: degrees
centigrade 273)
F : *Faraday (the quantity of electricity* contained in 1 mol of electrons: 96.500 C/mol of charge)
ln : Logarithm taken to the base *e*
***P_K, P_{Na}, and P_{Cl}*:** *Membrane permeabilities for* K, Na, and Cl,respectively
K_o, Na_o, and Cl_o: Extracellular concentrations of K, Na, and Cl respectively
K_i, Na_i, and Cl_i: Intracellular concentrations of K, Na, and Cl respectively

- When Na/K pump working and chloride is in ($I_{Cl}=0$ or $P_{Cl}=0$)

$$E_m = \frac{RT}{zF} \ln \frac{P_K [K]_{out} + {}^{PNa}/_{PK} [Na]_{dış}}{P_K [K]_{in} + {}^{PNa}/_{PK} [Na]_{iç}}$$

Example

$[K]_{in}$= 155 mM $[Na]_{in}$= 12 mM   T= 25 ºC

$[K]_{out}$= 4 mM $[Na]_{out}$= 145 mM   RT/F= 26.7mV

$P_K:P_{Na}$= 100:1 P_{Na}/P_K= 1/100

$$E_m = 26.7 \times 2.3 \log \frac{4 + 1/100\ (145)}{155 + 1/100\ (12)}$$

E_m= -89 mV

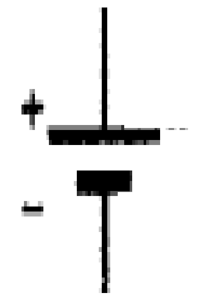
Difference between permeability and conductivity

- Permeability is an intrinsic property of membrane: depends on the types and numbber of ion channels present
- Conductance: ability of membrane to carry a current: depends not only on the properties of membrane, but also on the concentrations of ions in solution.
- A membrane can have high permeability to potassium, but is no ions exist in the solution, there will be no current.

K^+ permeability (P_K or g_K)

- K^+ ions will move through the membrane because of the concentration difference, and this movement will be an interaction between the ions and the membrane.
- The interaction is indicated by a resistance, it is just similar to the electron flow. The flow can be shown by a battery and the direction will be obtained from the Nernst equation.

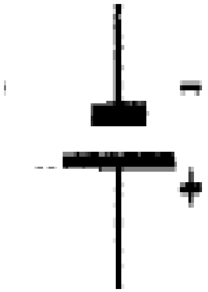
The negative pole of battery will be toward inside and the positive pole will be toward outside. When the membrane potential is equal to battery potential then the net flow will be equal to zero. This is the potential difference between inside and outside, 1/R (R:resistance) is called conductivity.



$$I_K = g_K(E_m - E_K)$$

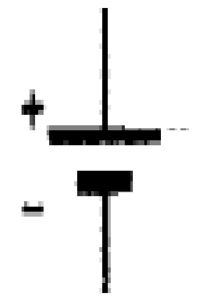
Na^+ permeability (g_{Na})

For Na^+ the equilibrium potential is positive therefore it will be represented by a battery which its + pole is toward inside and – pole toward outside. The flow across the battery depends on the potential differences in the membrane and the battery potential.



$$I_{Na} = g_{Na}(E_m - E_{Na})$$

Cl^- permeability (g_{Cl})



- Its equilibrium potential is negative so the battery + pole will be toward outside and the negative pole toward inside.

$$I_{Cl} = g_{Cl}(E_m - E_{Cl})$$

In general

$$I_i = g_i(E_m - E_i\ )$$

Where

I_i, is the ionic current for specific ion

g_i, is the conductance for that the type of ion

E_i , is the equilibruim potential for the ion

E_m ,is the membrane potential.

$$E_K = -81.4\ mV$$
$$E_{Na} = +60\ mV$$
$$E_{Cl} = -72.6\ mV$$

g_{Na}= 1.2x10^{-6} Siemens/cm^2
g_K= 12x10^{-6} Siemens/cm^2

- General equation for passive current

$$I_i = g_i(E_m - E_i\ )$$

E_m= -72.6mV

Passive K^+ current:

$$I_K = g_K(E_m - E_K)$$

E_m= -72.6 mV=-72.6x10^{-3} V

$$I_K = 12 \times \frac{10^{-6}S}{cm^2} \times [-72.6 \times 10^{-3}V - (-81.4 \times 10^{-3}V)]$$

$$I_K = 105.6 \times \frac{10^{-9}A}{cm^2} = 105.6 \times \frac{10^{-9}C}{s.cm^2}$$

$$1\ mole = 96500\ C$$

(Siemens/cm^2) × Volt = (Amper/cm^2) =Coulomb/(s × cm^2)

$$I_K = 105.6 \times \frac{\frac{10^{-9}A}{cm^2}}{\frac{96500C}{mole}} = 1.06 \times 10^{-12}\frac{mole}{s.cm^2}$$

At the resting membrane potential, the passive K^+ current will be positive (directed out of the cell)

Passive Na^+ current:

$$I_{Na} = g_{Na}(E_m - E_{Na})$$

E_m= -72.6 mV=-72.6x10^{-3} V

$$I_{Na} = 1.2 \times \frac{10^{-6}S}{cm^2} \times [-72.6 \times 10^{-3}V - (+60 \times 10^{-3}V)]$$

$$I_{Na} = -159 \times \frac{10^{-9}A}{cm^2} = -159 \times \frac{10^{-9}C}{s.cm^2}$$

$$1\ mole = 96500\ C$$

(Siemens/cm^2) × Volt = (Amper/cm^2) =Coulomb/(s × cm^2)

$$I_{Na} = -159 \times \frac{\frac{10^{-9}A}{cm^2}}{\frac{96500C}{mole}} =$$ -1.59x10^{-12} moles/s.cm^2

At the resting membrane potential,the passive Na^+ current will be negative (directed into the cell)

Passive Cl^- current:

$$I_{Cl} = g_{Cl}(E_m - E_{Cl})$$

E_m= -72.6 mV = E_{Cl}

$$I_{Cl} = g_{Cl}(72.6 - 72.6)$$

$$I_{Cl} = 0$$

Since Cl^- is in equilibrium with the resting membrane potential, the net passive current for Cl^- equals to zero.

Since the membrane potential does not balance the force of the chemical energy (concentration difference) of Na^+ or K^+ ions, Na^+ and K^+ are not at equilibrium.

- However due to these passive currents, after a while, the concentration of Na^+ and K^+ inside the cell will change. In order to maintain a constant concentrations, the pump carries the same amount of Na^+ and K^+ currents across the cell membrane but in opposite direction.
- $g_{Na}/g_K = 1/10$
- $I_{Na} = 1.59\times10^{-12}$ moles/s.cm^2
- $I_K = -1.06\times10^{-12}$ moles/s.cm^2
- $I_{Na} = -(3/2)\ I_K$

- The conductance for K^+ is 10 times larger than the conductance for Na^+ and the reason is that the passage of K^+ is much more easier than Na^+
- The driving force for Na^+ ions is 132.6mV while it is 8.8 mV for K + ions So, we need a larger force to push Na^+ ions.

- The potential difference is called driving force.

Passive Electrical Properties

- Membrane composition
- Membrane capacitance
- Membrane resistivity

A)Membrane Composition

- The membrane is made of lipid. But ions can not dissolve in the lipid structure. Therefore ions can penetrate the membrane only through water filled channels.
- The lipid bilayer thickness is about 50-70 A^o.

* $1A^o = 10^{-10}$ m

B) Membrane Capacitance

- Lipid bilayer
  - acts like an insulator separating two conducting media:
    1. The external medium of the cell
    2. The internal medium of the cell
  - have a specific membrane capacitance (C_M).
  - C_M is about 0.4-1.0 μF/cm^2

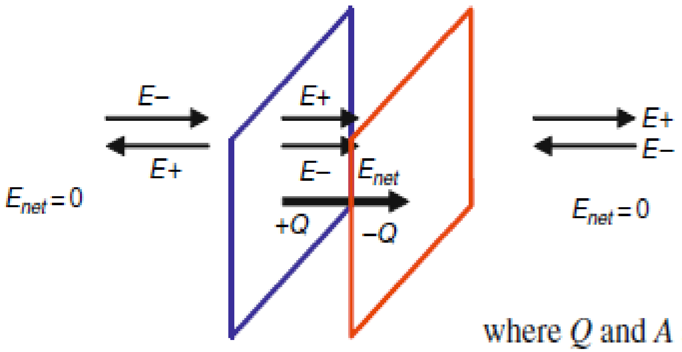


FIGURE 15.20 *A charged parallel plate capacitor, showing the cancellation of electric fields outside and net E field within the capacitor. The electric field from each plate is constant and points either away from the positive or toward the negative plate. Superposition of these electric fields leads to confinement of the electric field between the capacitor plates.*

cancel in the space outside the plates as shown. The electric field between the plates (away from the edges where boundary effects occur) is therefore constant and given by

$$E = \frac{Q}{\varepsilon_o A}, \tag{15.17}$$

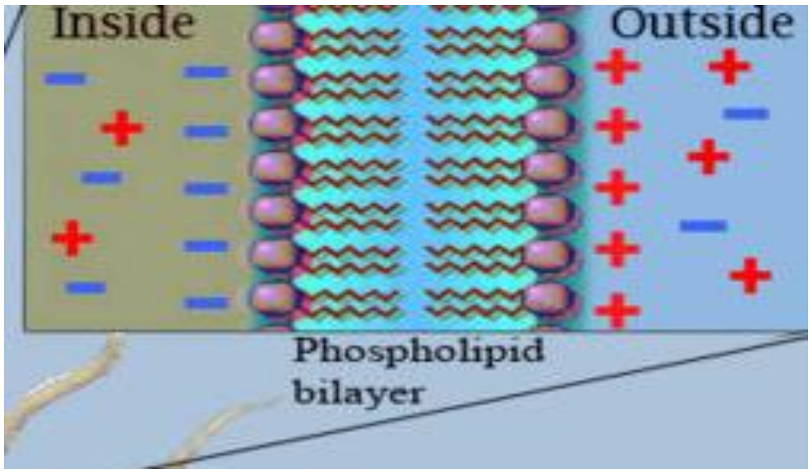
where Q and A are the charge on an area of one of the plates. Because E is a constant, the potential difference between the plates is given by Equation (15.6) as

$$V = Ed = \frac{Qd}{\varepsilon_o A}, \tag{15.18}$$

where d is the plate separation. From Equations (15.16) and (15.18), we find that the capacitance of the parallel-plate capacitor is given by purely geometric factors as

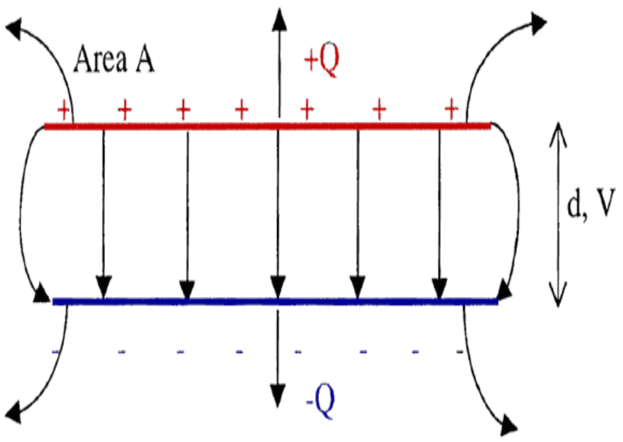
$$C = \frac{\varepsilon_o A}{d}. \quad \text{(parallel−plate C)}. \tag{15.19}$$

The fact that the capacitance depends entirely on geometry is a general result, regardless of the capacitor's shape. Units for capacitance are given by those of Q/V or 1 C/V = 1 farad (F). A farad is an enormous value for capacitance and units of pF to µF are common.



Membrane as a capacitor

– Ions can not pass through the membrane so the negative charges are stored on the inside of the membrane and positive ions on the outside of the membrane, and the membrane will act as a capacitor.



Membrane capacitance

– Because of this property, phospholipids allows charge separation across the membrane and provide the capacitive property of the membrane (C_m).

– Each plate is a conductor, at constant potential. Potential difference between the plates is **V.**

- ***A voltage difference is established across a cell membrane as a result of separating charge across the membrane.***
- The cell membrane is very thin, it behaves like a capacitor. The relation between the voltage across the plate of a capacitor and the charge stored on the plates is:

$$Q = C_m \times E_m$$

Capacitive properties of the membrane

- C_m=1μF/cm^2 (1μF=1 $\times 10^{-6}$ F)
- E_m=-72mV
- $Q = C_m \times E_m$
- $Q = 1\times10^{-6} F/cm^2 \times 72\times10^{-3} V$

  $Q = 72\times10^{-9}$ Coulomb/cm^2

- The only way to change the transmembrane voltage is to change the charge separated across the membrane.
- When the charge stored on the membrane changes with time (dQ/dt), the membrane potential will also change with time (dE_m/dt).
- The change in charge with time is defined as capacitive current (I_C)
- That is

$$Q = C_m \times E_m$$

$$I_c = dQ/dt = C_m(dE/dt)$$

C) Membrane Resistivity

- The presence of proteins that span across the thickness of the cell membrane must account for the relatively low resistance of the cell membrane.

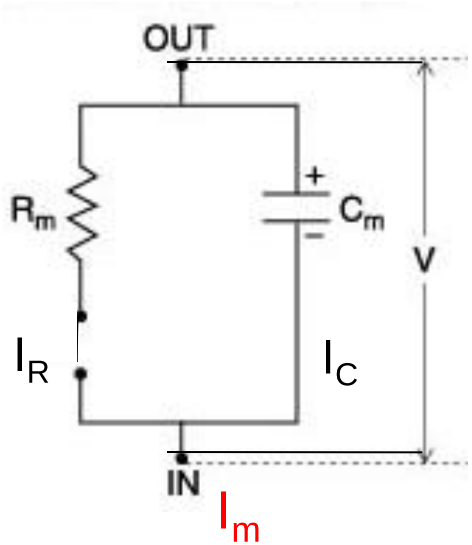
- The artificial lipid bilayer membrane
  - has a specific resistance (R_M)
  - about 10^6-10^9 Ω cm^2

- **The capacitance is due to the lipid bilayer matrix.**

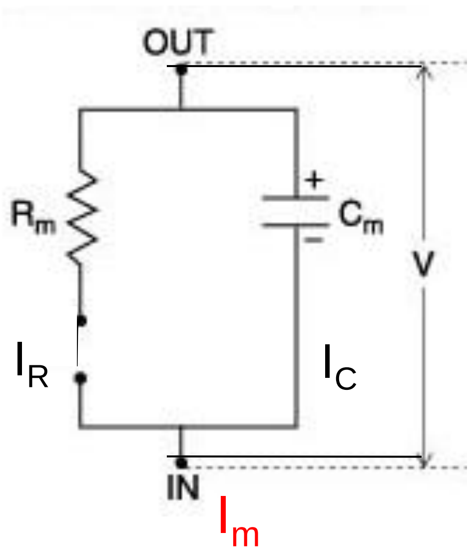
- **The conductance is due to proteins inserted in the lipid bilayer.**

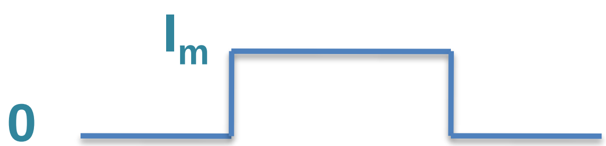
- There are two types of current:
  - The initial current is capacitive current
  - This will cause a change in the membrane potential, this change will cause a flow through the pores, this flow is called resistive current.

p.s: capacitive current, which flows only at the step onset and offset
resistive current (through leak channels), also given by Ohm's law (I = V/R)



- Current crossing the membrane can flow either through ion channels (resistance) or through capacitor.
- Capacitor current will change the charge stored on the membrane.
- R_m is the total resistance of the membrane to Na^+, K^+ and Cl^- ions.





$$I_m = I_R + I_C$$

$$I_R = E_m / R_m \qquad I_C = C_m \frac{dE_m}{dt}$$

$$\frac{C_m \, dE_m}{dt} = (I_m - E_m/R_m)$$

$$\frac{dE_m}{(I_m - E_m/R_m)} = \frac{dt}{C_m}$$

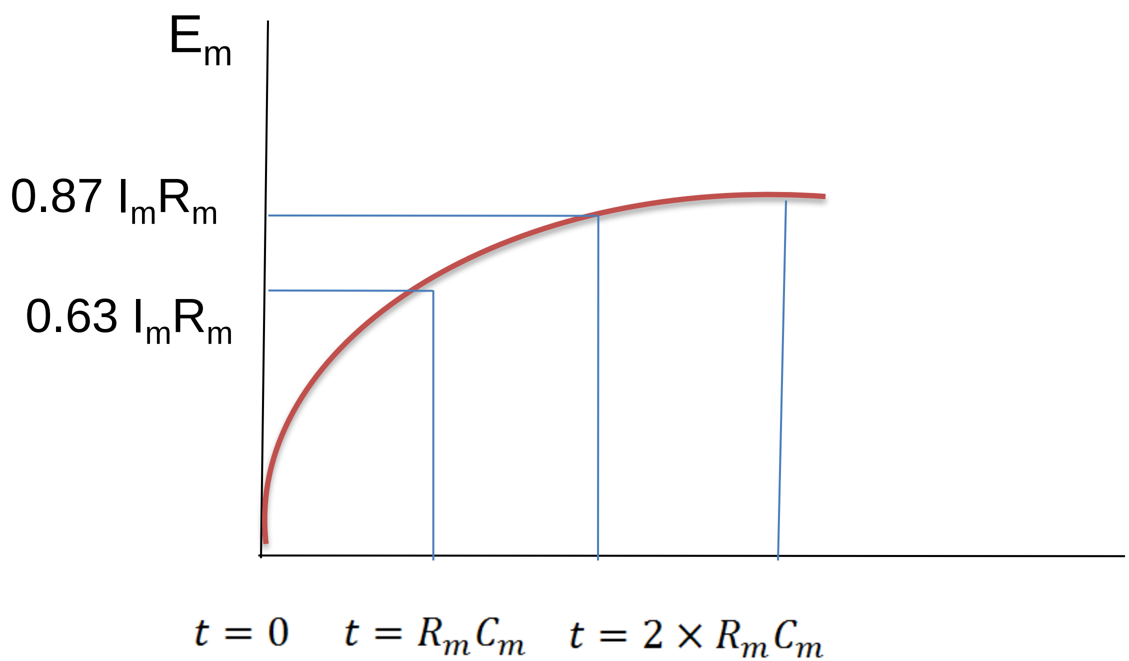
$$E_m = I_m R_m \left(1 - e^{-t/R_m C_m}\right)$$

$$E_m = I_m R_m \left(1 - e^{-t/R_m C_m}\right)$$

$t = 0 \qquad E_m = 0$

$t = R_m C_m \qquad E_m = I_m R_m (1 - e^{-1}) = 0.63\, I_m R_m$

$t = 2 \times R_m C_m \qquad E_m = I_m R_m (1 - e^{-2}) = 0.87\, I_m R_m$

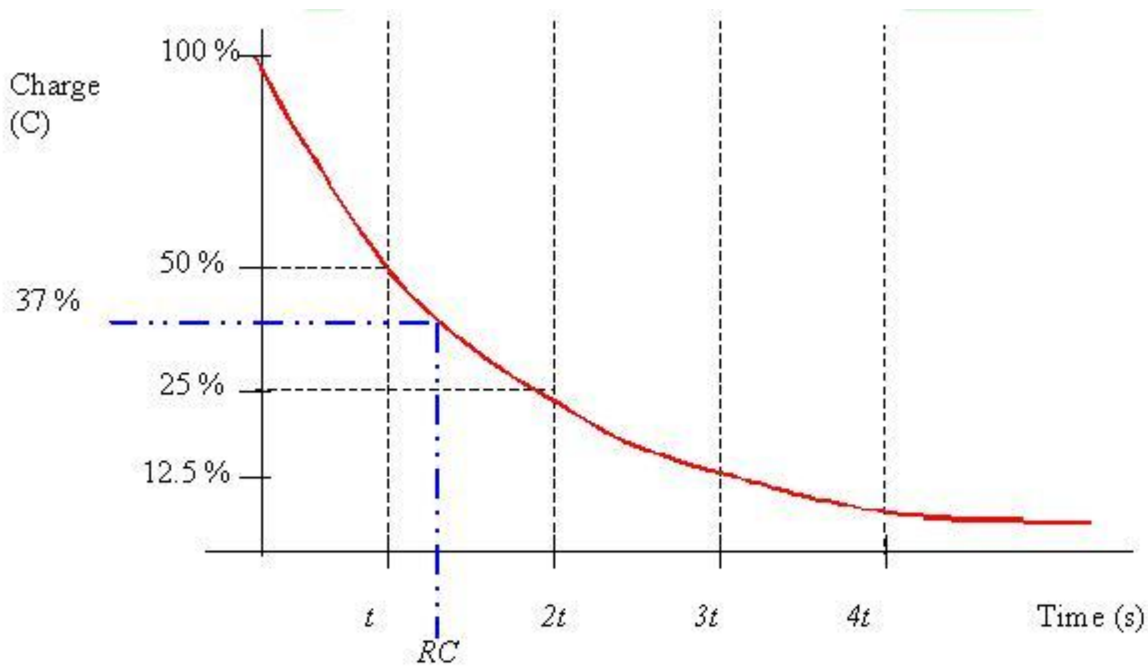


- When the current pulse is stopped, the membrane potential decreases exponentially as the capacitance discharges through the resistor:

- $E_m = I_0 R_m \, e^{-t/R_m C_m}$

- Time constant, **τ**, is defined as the time it takes the potential to rise to (1-1/e) of its final value and it is determined by both the resistance and capacitance of the circuit:
- $\tau = R_m \times C_m$

$$V = V_0\, e^{-t/RC} \quad ; \quad I = I_0\, e^{-t/RC}$$



Active currents

In living cells, the total current carried by each ion must be equal zero for the concentration gradients across the membrane to remain constant.

We need to have this pump in order to get a constant membrane potential.

At the steady state, the sum of passive and active current must be zero.

$$I_i = I_{i(passive)} + I_{i(active)} = 0$$

$$I_{Na} = I_{Na(passive)} + I_{Na(active)} = 0$$

$$I_{Na(passive)} = -I_{Na(active)}$$

The active Na^+ current is equal in magnitude but opposite in direction to the passive Na^+ current.

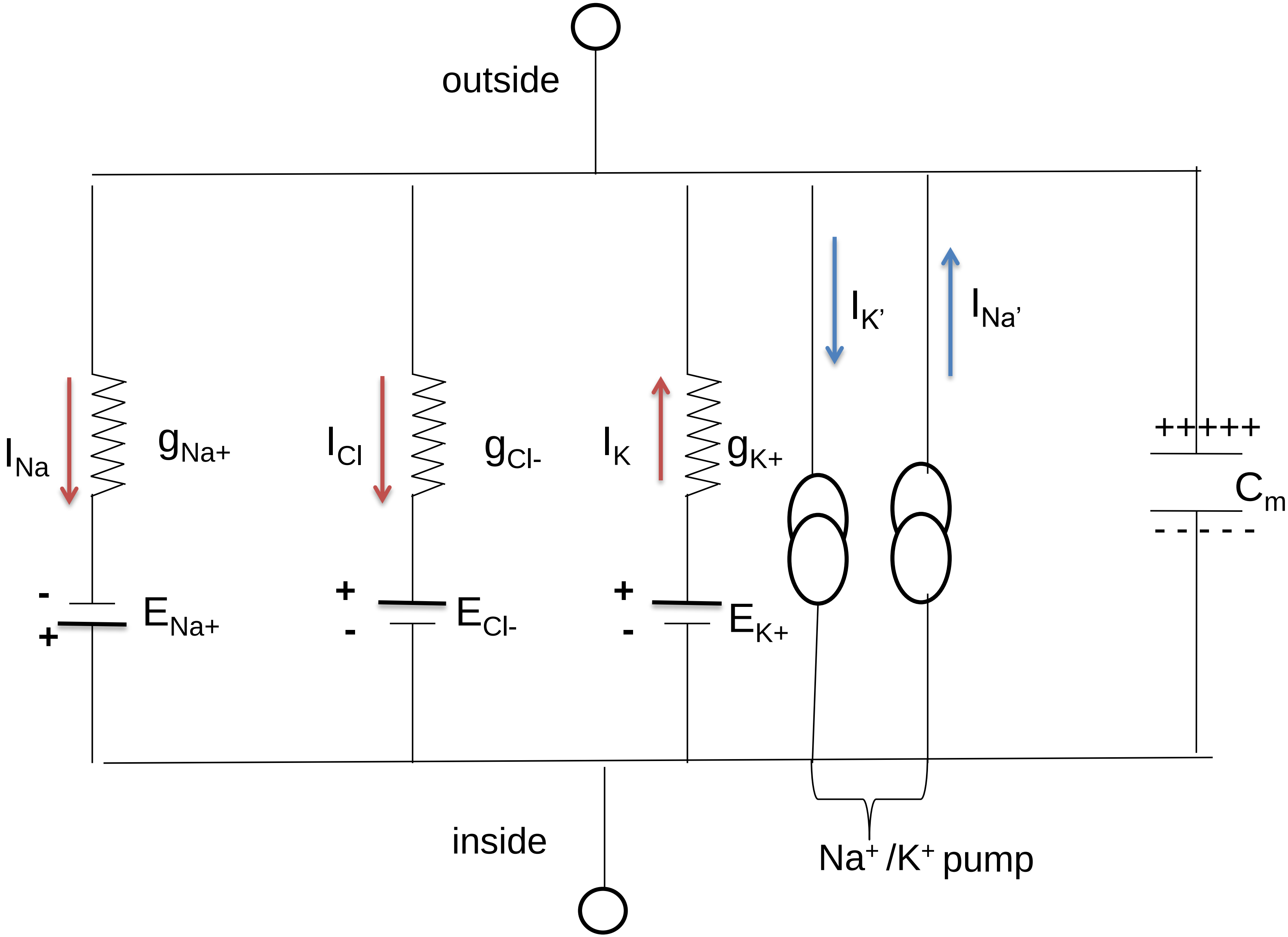
$$I_K = I_{K(passive)} + I_{K(active)} = 0$$

$$I_{K(passive)} = -I_{K(active)}$$

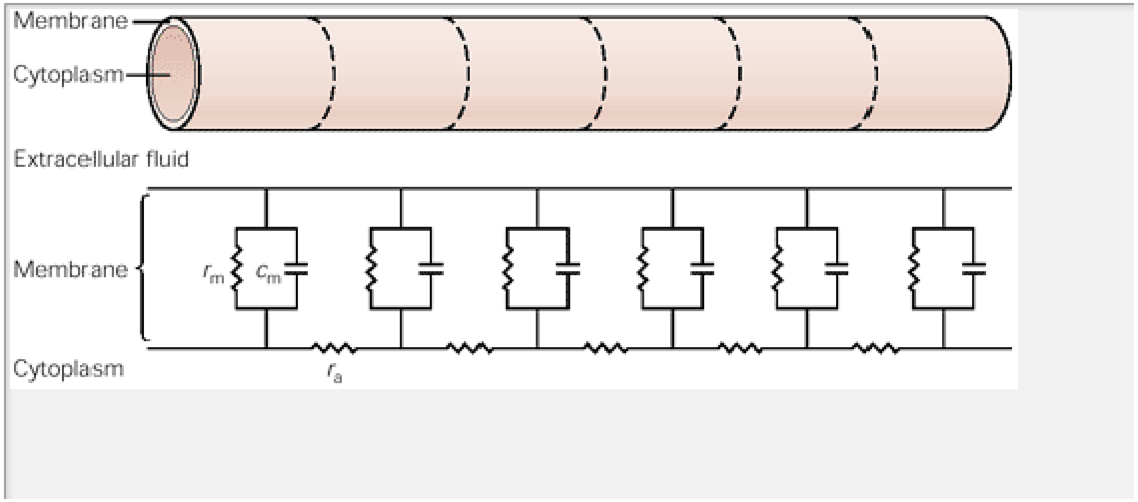
Sum up

- The structural and chemical composition of the cell membrane defines the resistive and capacitive properties of the membrane.
- The net ionic movement can be inward or outward across the membrane, depending on the direction of the electrochemical gradient and Na^+/ K^+ coupled pump.

- Cl^- is usually **passively distributed according to the membrane** potential, that is, not actively transported.
- The contribution of the Na^+-K^+ pump to the resting E_m *depends* on
  - the coupling ratio of Na^+ pumped out to K^+ pumped in,
  - the turnover rate of the pump,
  - the number of pumps,
  - the magnitude of the membrane resistance.



outside
I_{Na}
g_{Na+}
I_{Cl}
g_{Cl-}
I_K
g_{K+}
$I_{K'}$
$I_{Na'}$
+++++
C_m
- - - - -
-
+
E_{Na+}
+
-
E_{Cl-}
+
-
E_{K+}
inside
Na^+/K^+ pump



Synaptic potentials in dendrites are conducted toward cell body and trigger zone.
The cytoplasmic core shows resistance (small cross-sectional area)
Greater the length, greater the resistance
Larger the diameter, lower the resistance (number of charge carriers)
If we divide dendrite into units and inject a current from a point....

If $t \gg \tau$, a step current long enough to make membrane potential max and I_c is zero.
Then potential will change with distance solely depending on resistance

Injected current will flow through the succesive membrane cylinders, where there will be two resistance: axial resistance, r_a . X, and membrane resistance, r_m

Potential will decrease as we go far from injection site : $V = V_0 . e^{-x/\lambda}$, λ is the membrane length constant, V_0 is the potential change at the site of current injection

- The length constant is defined as the distance along the dendrite where potential has decayed to 1/e, or 37% of its initial value
- And it is defined as $\lambda = \sqrt{(r_m / r_a)}.$

The better the insulation of membrane, better the conducting properties of the inner core, greater the length constant

The larger the diameter, longer the length constant (since r_m/r_a is directly proportional to diameter)

- Sum up
- Time constant, τ, defined the rate of transmission, maximum frequency and synaptic transmission
- If τ is small, neurons can easily be depolarized and transmit fast

- Length constant, λ, defined the spread of voltage over distance.
- The better the insulation greater the length constant
- The larger the diameter, longer the length constant

- References
- Medival physiology- Guyton
- Human physiology- Wander