Part 3, Neural Signaling

3.1. Electrical signals of nerve cells

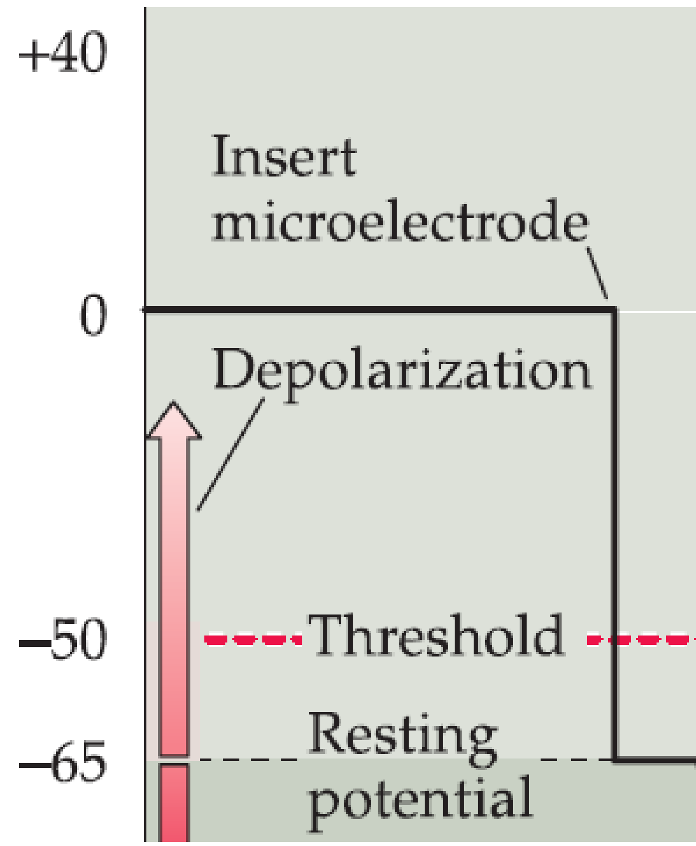
Electrical signals of nerve cells

- **Electrophysiological recording**: measuring the electrical activity of a nerve cell.
  - Microelectrode: a piece of glass tubing pulled to a very fine point (with an opening less than 1 μm in diameter) and filled with a good electrical conductor, such as a concentrated salt solution.
  - This conductive core can then be connected to a voltmeter, typically a computer, that records the transmembrane voltage of the nerve cell.
  - **Extracellular recording**: a microelectrode is placed near the nerve cell of interest to detect its activity.
    - particularly useful for detecting temporal patterns of action potential activity and relating those patterns to stimulation by other inputs, or to specific behavioral events.
  - **Intracellular recording**: the microelectrode is placed inside the cell of interest to measure the electrical potential across the neuronal plasma membrane.
    - detecting the smaller, graded changes in electrical potential that trigger action potentials, and thus allowing a more detailed analysis of communication between neurons within a circuit.
- Neurons employ several different types of electrical signals to encode and transfer information.

Resting membrane potential

- As soon as a microelectrode is inserted through the membrane of the neuron, the microelectrode reports a <u>negative potential</u>, indicating that neurons have a means of generating a constant voltage across their membranes when at rest.

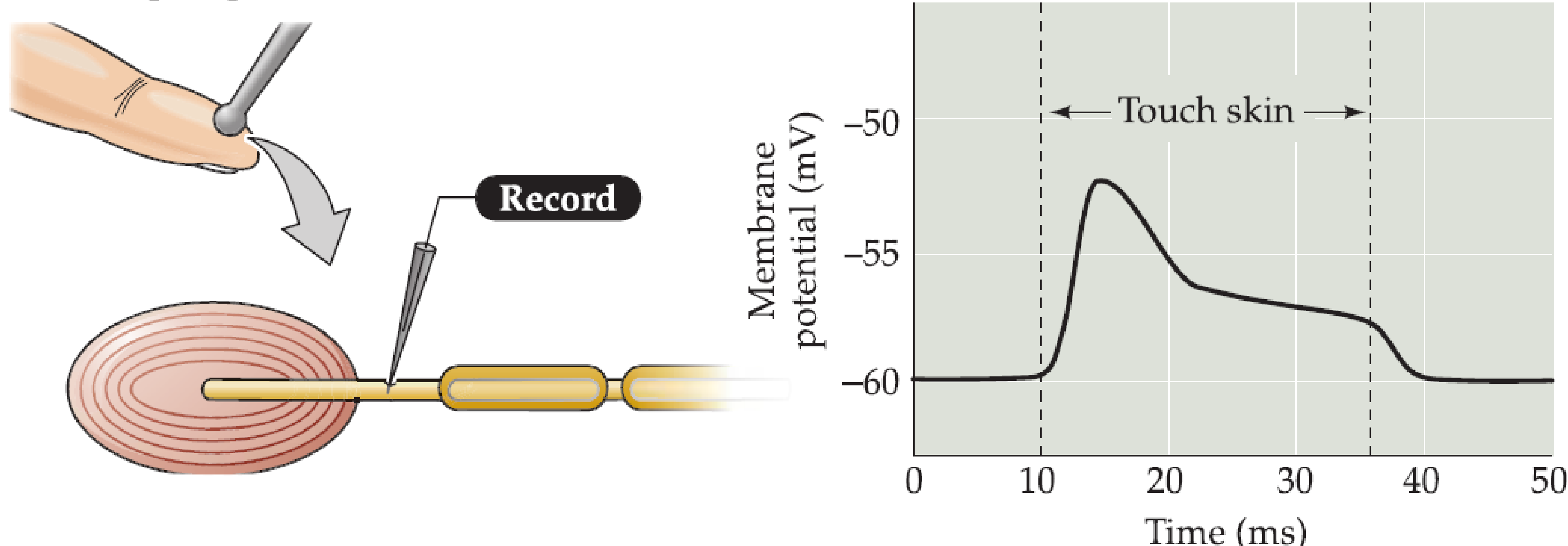
- **Resting membrane potential**: <u>-40 to -90 mV</u>, depending on the type of neuron being examined.



Receptor potential

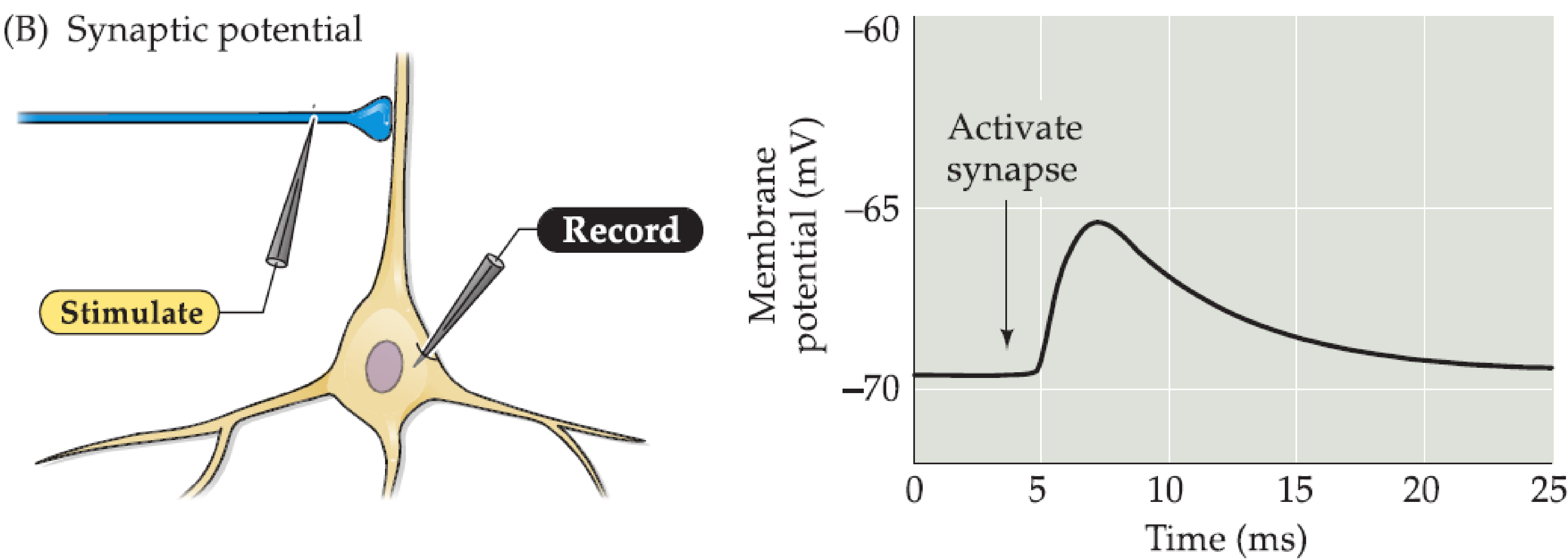
- **Receptor potentials** are due to the activation of sensory neurons by external stimuli, such as light, sound or heat.
  - Touching the skin activates Pacinian corpuscles, receptor neurons that sense mechanical disturbances of the skin.
  - These neurons respond to touch with a **receptor potential** that changes the resting potential.
  - These transient changes in potential are the first step in generating the sensation of vibrations (or "tickles") of the skin in the somatic sensory system.

(A) Receptor potential



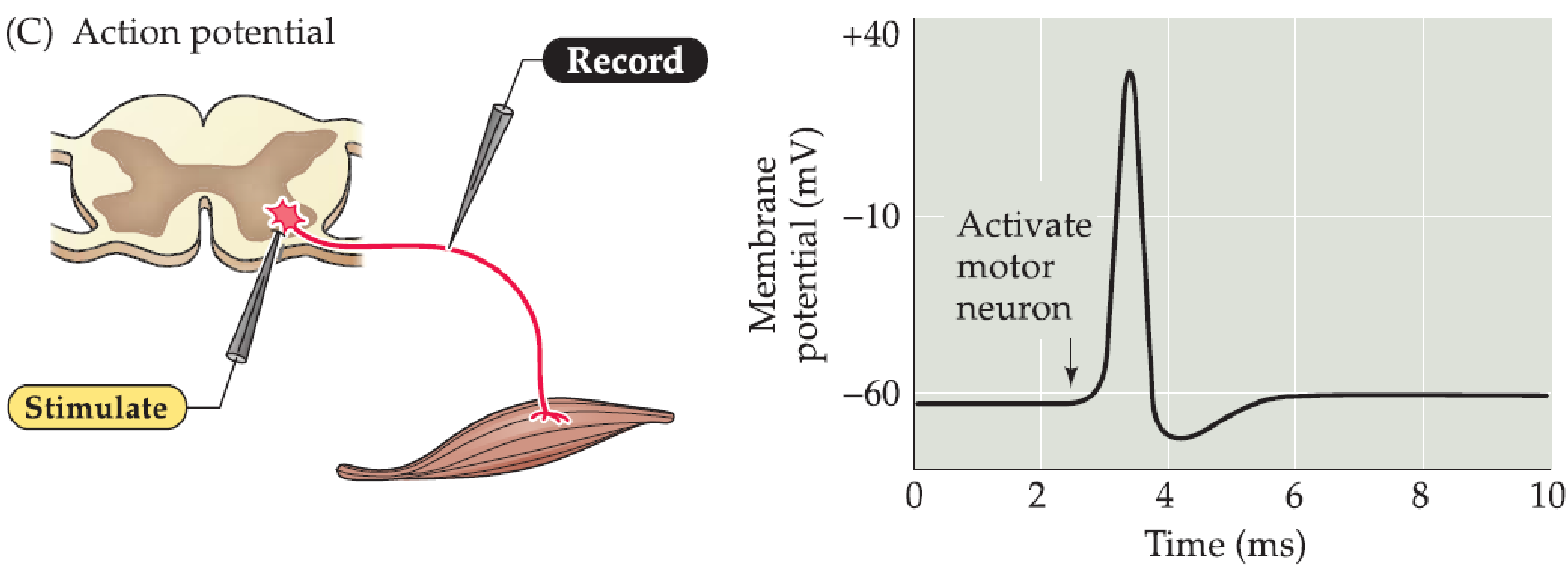
Synaptic potential

- Associated with communication between neurons at synaptic contacts.
- Activation of these synapses generates **synaptic potentials**, which allow transmission of information from one neuron to another.
  - Activation of a synaptic terminal innervating a hippocampal pyramidal neuron causes a very brief change in the resting membrane potential in the pyramidal neuron.
  - Synaptic potentials serve as the means of exchanging information in complex neural circuits in both the central and peripheral nervous systems.



Action potential

- Neurons generate a special type of electrical signal that travels along their long axons.
- **Action potentials**: “spikes" or "impulses”
- Action potentials are responsible for long-range transmission of information within the nervous system and allow the nervous system to transmit information to its target organs, such as muscle.

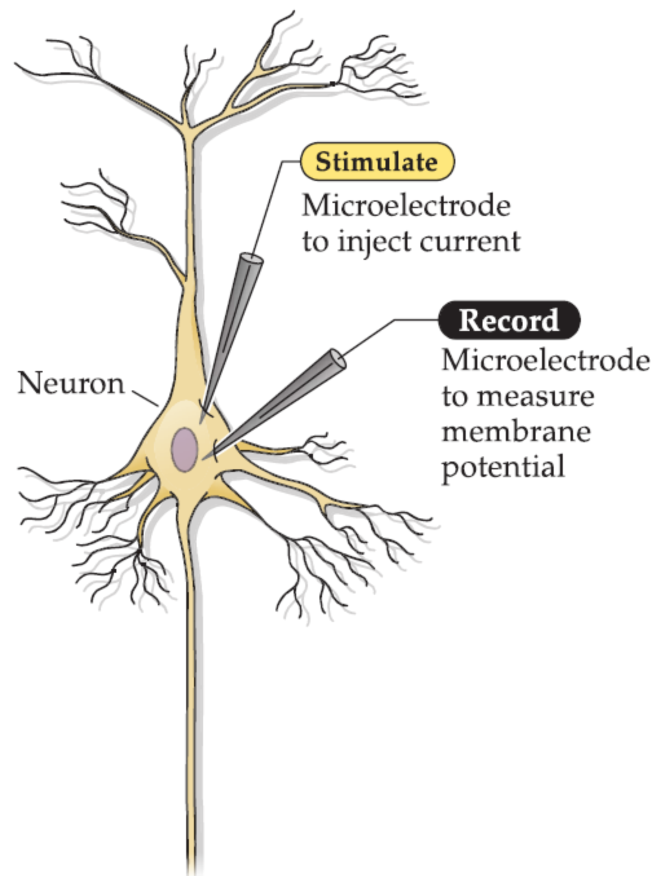


Action potential

- One way to elicit an action potential is to pass electrical current across the membrane of the neuron.

- In normal circumstances, this current would be generated by receptor potentials or by synaptic potentials.

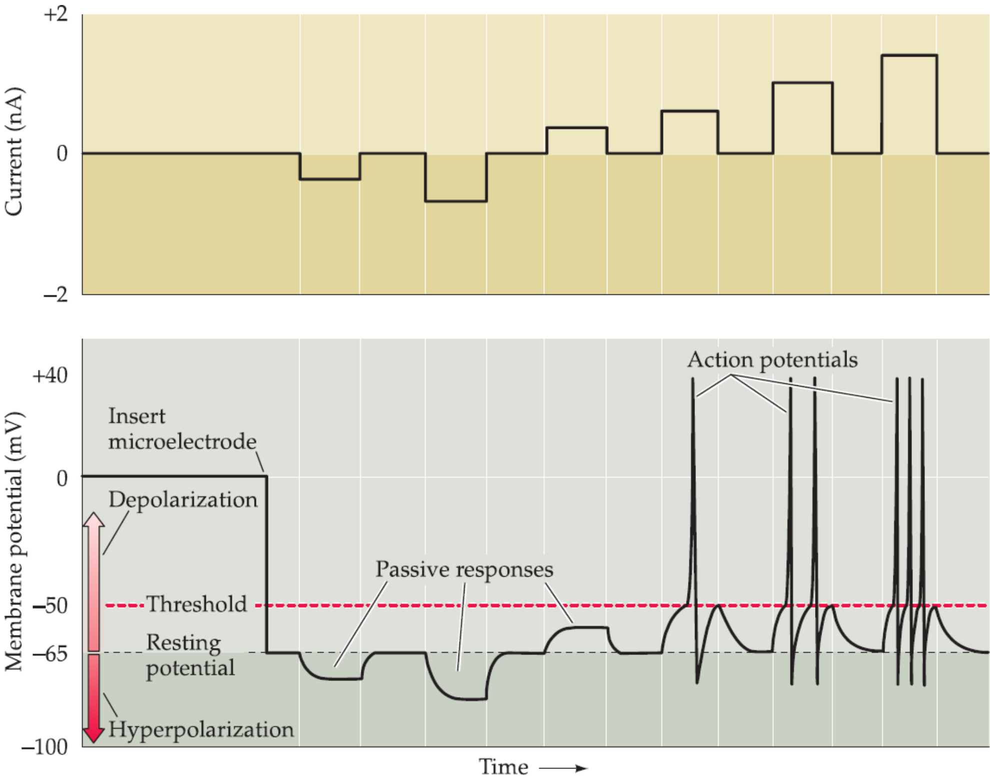
- In the laboratory, electrical current suitable for initiating an action potential can be readily produced by inserting a second microelectrode into the same neuron and then connecting the electrode to a battery.



Recording passive and active electrical signals

❖ **Hyperpolarization**: the current makes the membrane potential more negative.

- Nothing very dramatic happens.
- The membrane potential simply changes in proportion to the magnitude of the injected current.
- Such hyperpolarizing responses do not require any unique property of neurons and are therefore called **passive electrical responses**.



❖ **Depolarization**: current of the opposite polarity is delivered, so that the membrane potential of the nerve cell becomes more positive than the resting potential.

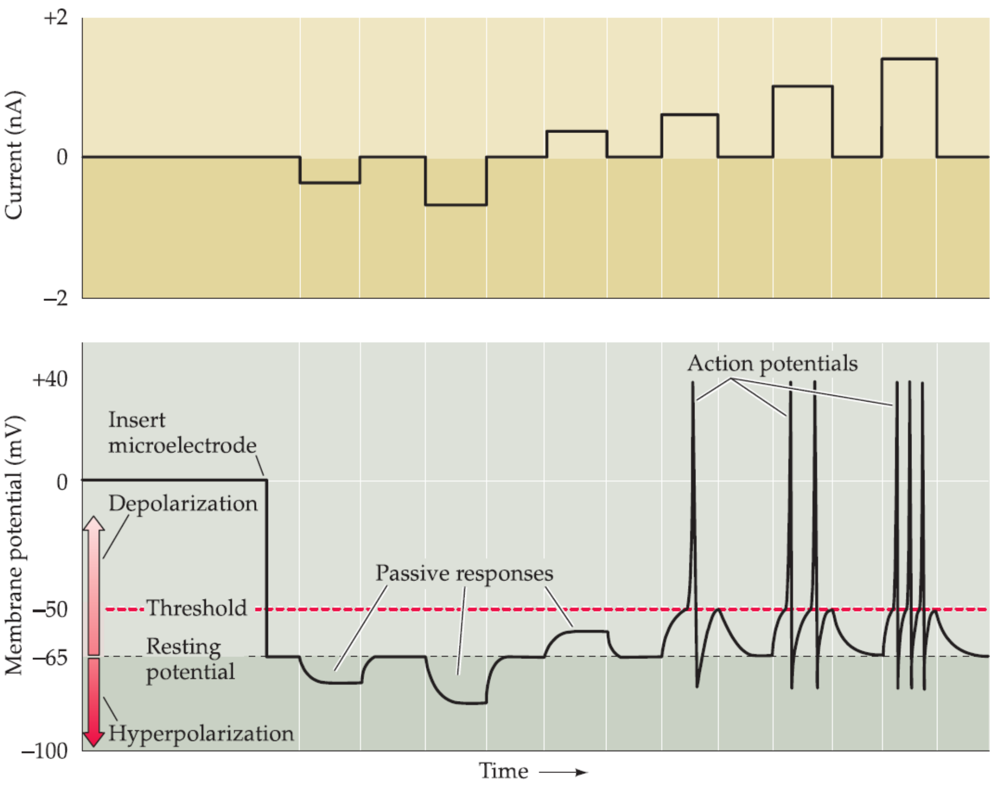
- At a certain level of membrane potential, called the **threshold potential**, action potentials occur.

Action potential

❖ **Action potential** is an active response generated by the neuron and typically is a brief (about 1 ms) change from negative to positive in the transmembrane potential.

❖ The <u>amplitude</u> of the action potential is <u>independent</u> of the magnitude of the current used to evoke it; that is, larger currents do not elicit larger action potentials.

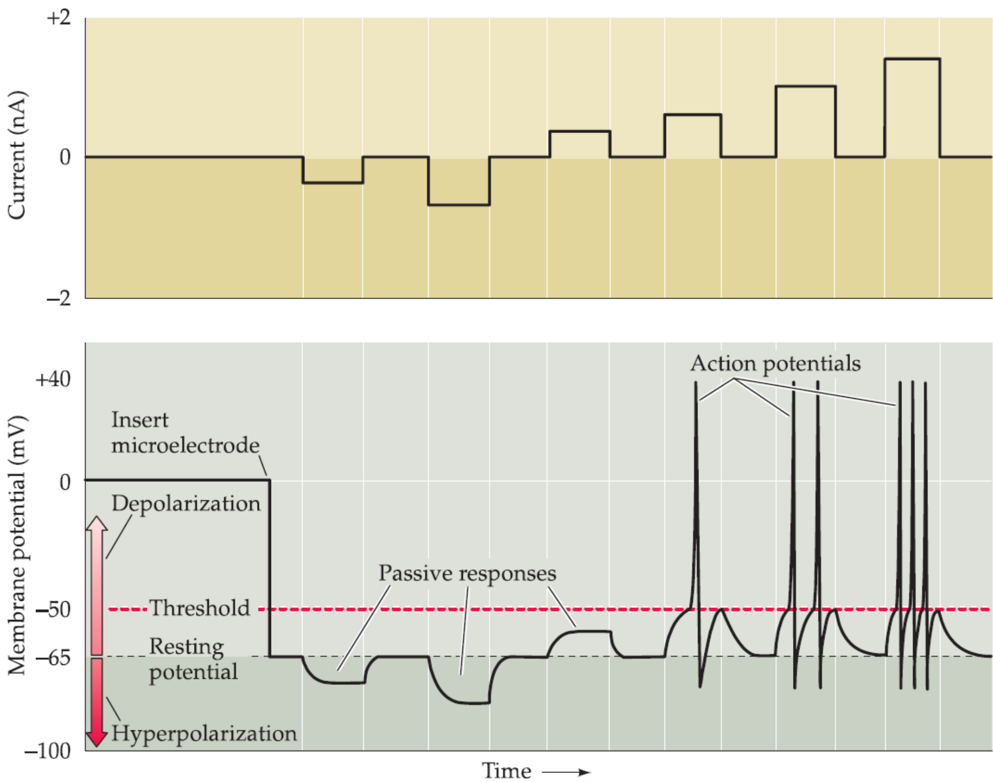
❖ The action potentials of a given neuron are therefore said to be *all-or-none*--that is, they occur fully or not at all.



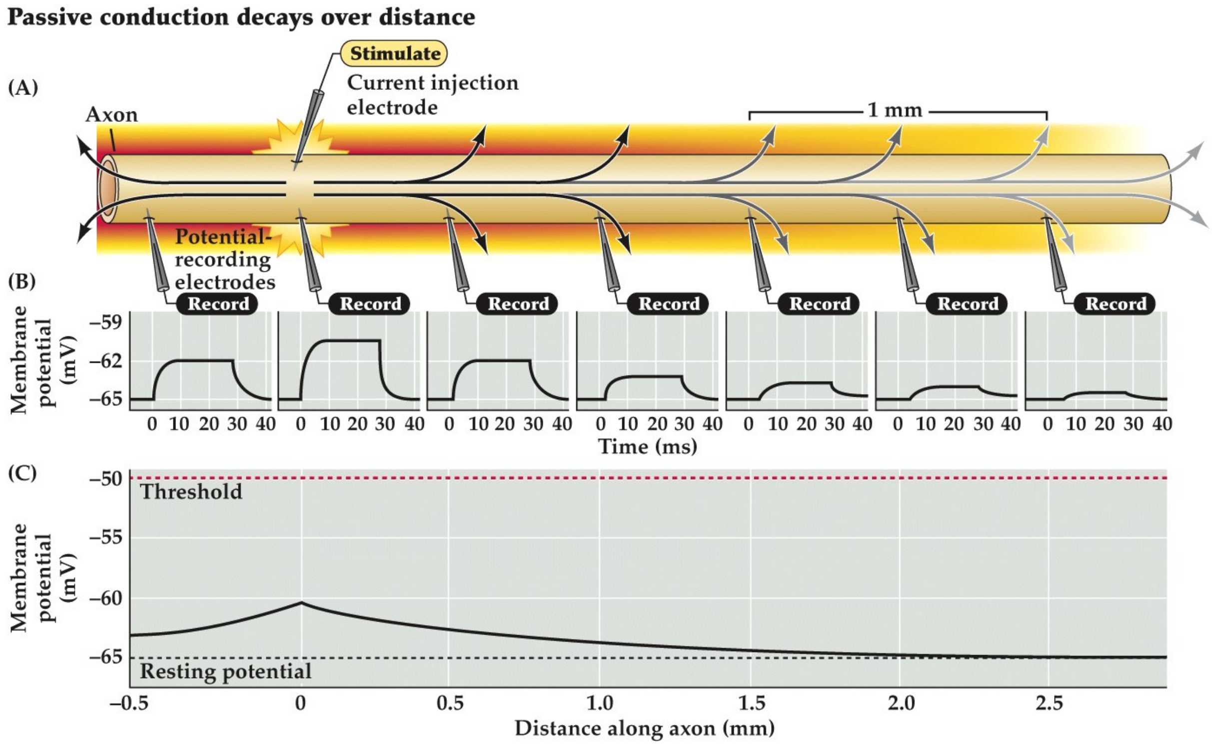
Action potential

- If the amplitude or duration of the stimulus current is increased sufficiently, multiple action potentials occur.

- The intensity of a stimulus is encoded in the frequency of action potentials rather than in their amplitude.
  - Receptor potentials: amplitudes are graded in proportion to the magnitude of the sensory stimulus.
  - Synaptic potentials: amplitudes vary according to the number of synapses activated, the strength of each synapse, and the previous amount of synaptic activity.



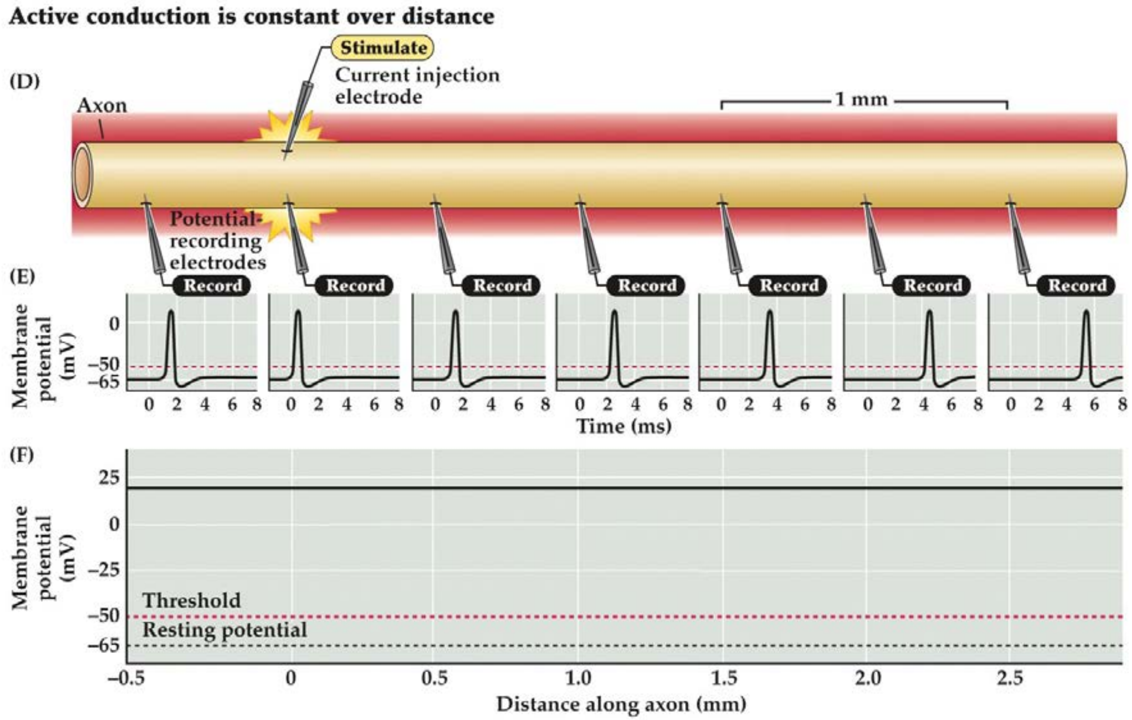
Passive and active current flow in axon



NEUROSCIENCE 5e, Figure 2.3 (Part 1)

- A current-passing electrode produces a current that yields a subthreshold change in membrane potential, which spreads passively along the axon.
- Potential responses are recorded at the positions indicated by microelectrodes.
- With increasing distance from the site of current injection, the amplitude of the potential change is attenuated as current leaks out of the axon.

Passive and active current flow in axon



NEUROSCIENCE 5e, Figure 2.3 (Part 2)

- If the experiment is repeated with a suprathreshold current, an active response, the action potential, is evoked.
- Action potentials are recorded at the positions indicated by microelectrodes.
- The amplitude of the action potential is constant along the length of the axon, although the time of appearance of the action potential is delayed with increasing distance.

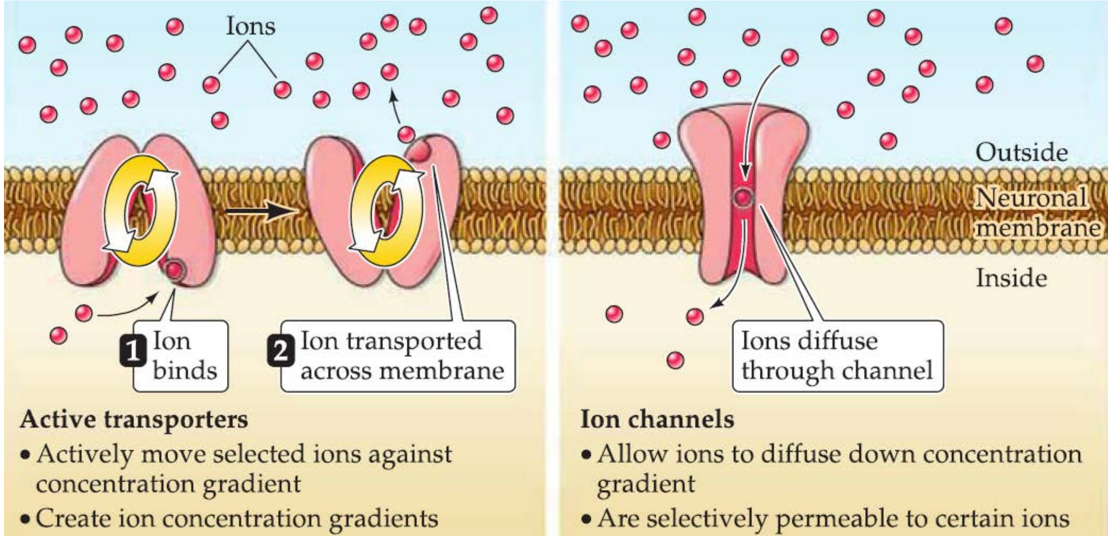
Passive and active current flow in axon

- The leakiness of the axonal membrane prevents effective passive conduction of electrical signals in all but the shortest axons (those 1 mm or less in length).

- To compensate for this deficiency, action potentials serve as a "booster system" that allows neurons to conduct electrical signals over great distances despite the poor passive electrical properties of axons.

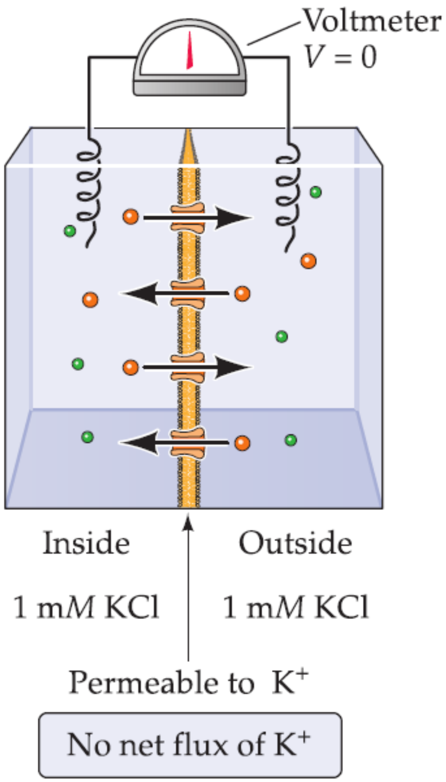
How neuronal electrical signals arise?

- Electrical potentials are generated across the membranes of neurons because:
  1) there are <u>differences in the concentrations of specific ions</u> across nerve cell membranes.
  2) the <u>membranes are selectively permeable</u> to some of these ions.



- These two facts depend in turn on two different kinds of proteins in the cell membrane:
  1) The ion concentration gradients are established by proteins known as **active transporters**.
  2) The selective permeability of membranes is due largely to **ion channels**.
  - Channels and transporters basically work against each other, and in so doing they generate the resting potential, action potential, and the synaptic potentials and receptor potentials that trigger action potentials.

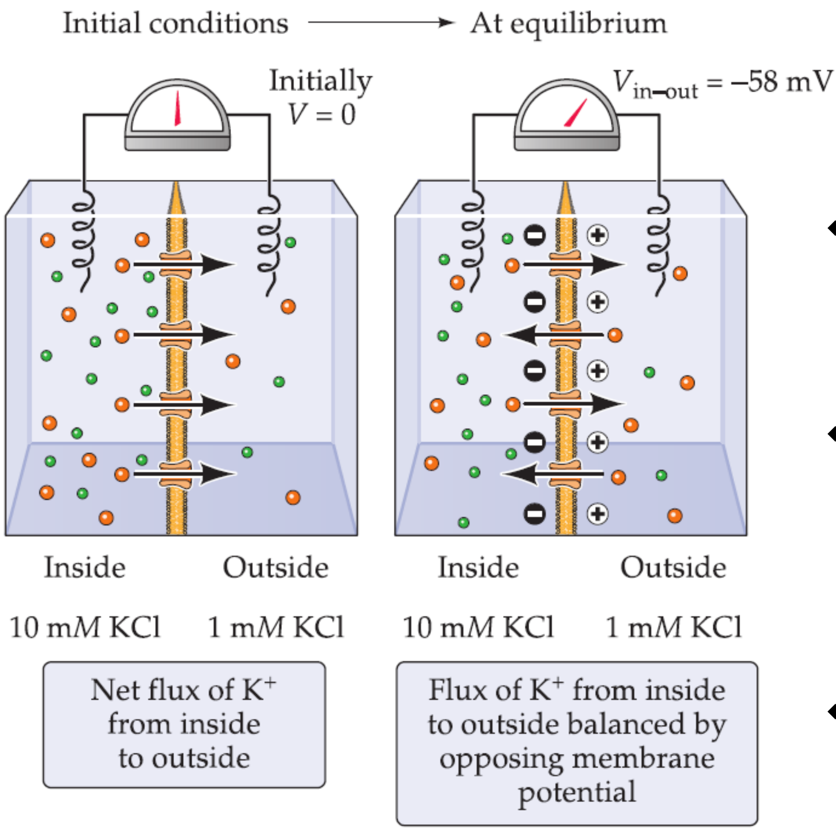
Electrochemical equilibrium



- A membrane permeable only to **K^+** separates the inside and outside compartments, which contain the indicated concentrations of KCl.

- If the concentration of **K^+** on each side of this membrane is equal, then no electrical potential will be measured across it.

Electrochemical equilibrium



- Initial conditions: increasing the KCl concentration of the inside compartment to 10 mM initially causes a small movement of K^+ into the outside compartment.
- As K^+ moves from the inside compartment to the outside, a potential is generated that tends to impede further flow of K^+.
- This impediment results from the fact that the potential gradient across the membrane tends to repel the positive K^+ ions that would otherwise move across the membrane.
- As the outside becomes positive relative to the inside, the increasing positivity makes the outside less attractive to the positively charged K^+.
- The net movement (or flux) of K^+ will stop at the point ("at equilibrium") where the potential change across the membrane (the relative positivity of the outside compartment) exactly offsets the concentration gradient (the tenfold excess of K^+ in the inside compartment).

Electrochemical equilibrium

- There is an exact balance between two opposing forces:
  1) the concentration gradient that causes **K^+** to move from inside to outside, taking along positive charge.
  2) an opposing electrical gradient that increasingly tends to stop **K^+** from moving across the membrane.

- The number of ions that needs to flow to generate this electrical potential is very small (approximately 10^{-12} moles of **K^+** per cm^2 of membrane, or 10^{12} **K^+** ions), which is significant in two ways:
  1) the concentrations of permeant ions on each side of the membrane remain essentially constant, even after the flow of ions has generated the potential.
  2) the tiny fluxes of ions required to establish the membrane potential do not disrupt chemical electroneutrality because each ion has an oppositely charged counter-ion (chloride ions for **K^+**) to maintain the neutrality of the solutions on each side of the membrane.

Electrochemical equilibrium

- **Equilibrium potential**: the electrical potential generated across the membrane at electrochemical equilibrium.
- It can be predicted by the **Nernst equation**:

$$E_X = \frac{RT}{zF} \ln \frac{[X]_{out}}{[X]_{in}}$$

Ex: the equilibrium potential for any ion X

R: the gas constant

T: the absolute temperature (Kelvin scale)

z: the valence (electrical charge) of the permeant ion

F: the Faraday constant

$[X]_{out}$, $[X]_{in}$: concentrations of ion X on each side of the membrane

- Performing calculations using base 10 logarithms and performing experiments at room temperature:

$$E_X = \frac{58}{z} \log \frac{[X]_{out}}{[X]_{in}}$$

- In case of **K^+** :

$$E_K = \frac{58}{z} \log \frac{[K^+]_{out}}{[K^+]_{in}} = \frac{58}{1} \log \frac{1}{10} = -58\text{mV}$$

Electrochemical equilibrium in an environment with more than one permeant ion

- **Nernst equation** considers only the simple case of a single permeant ion species.

- A more elaborate equation is needed, which takes into account both the <u>concentration gradients</u> of the permeant ions and the <u>relative permeability</u> of the membrane to each permeant species.

- **Goldman equation** (David Goldman, 1943):

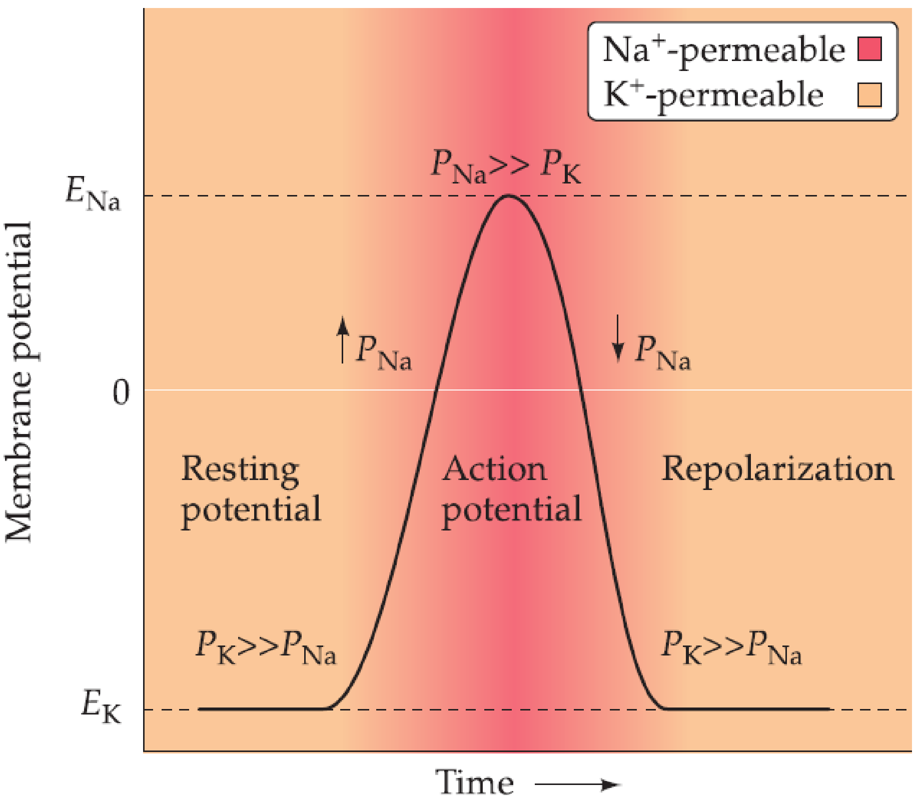
$$V == 58 \log \frac{P_{\mathrm{K}}\left[\mathrm{K}^{+}\right]_{\mathrm{out}} + P_{\mathrm{Na}}\left[\mathrm{Na}^{+}\right]_{\mathrm{out}} + P_{\mathrm{Cl}}\left[\mathrm{Cl}^{-}\right]_{\mathrm{in}}}{P_{\mathrm{K}}\left[\mathrm{K}^{+}\right]_{\mathrm{in}} + P_{\mathrm{Na}}\left[\mathrm{Na}^{+}\right]_{\mathrm{in}} + + P_{\mathrm{Cl}}\left[\mathrm{Cl}^{-}\right]_{\mathrm{out}}}$$

V: the voltage across the membrane

P: the permeability of the membrane to each ion of interest

Electrochemical equilibrium in an environment with more than one permeant ion

- The permeability for different ions changes during the generation of an action potential in a neuron.



- At rest, neuronal membranes are more permeable to K^+ than to Na^+; accordingly, the resting membrane potential is negative and approaches the equilibrium potential for K^+, E_K.
- During an action potential, the membrane becomes very permeable to Na^+; thus the membrane potential becomes positive and approaches the equilibrium potential for Na^+, E_{Na}.
- The rise in Na^+ permeability is transient, so that the membrane again becomes primarily permeable to K^+, causing the potential to return to its negative resting value.

Ionic basis of the resting membrane potential

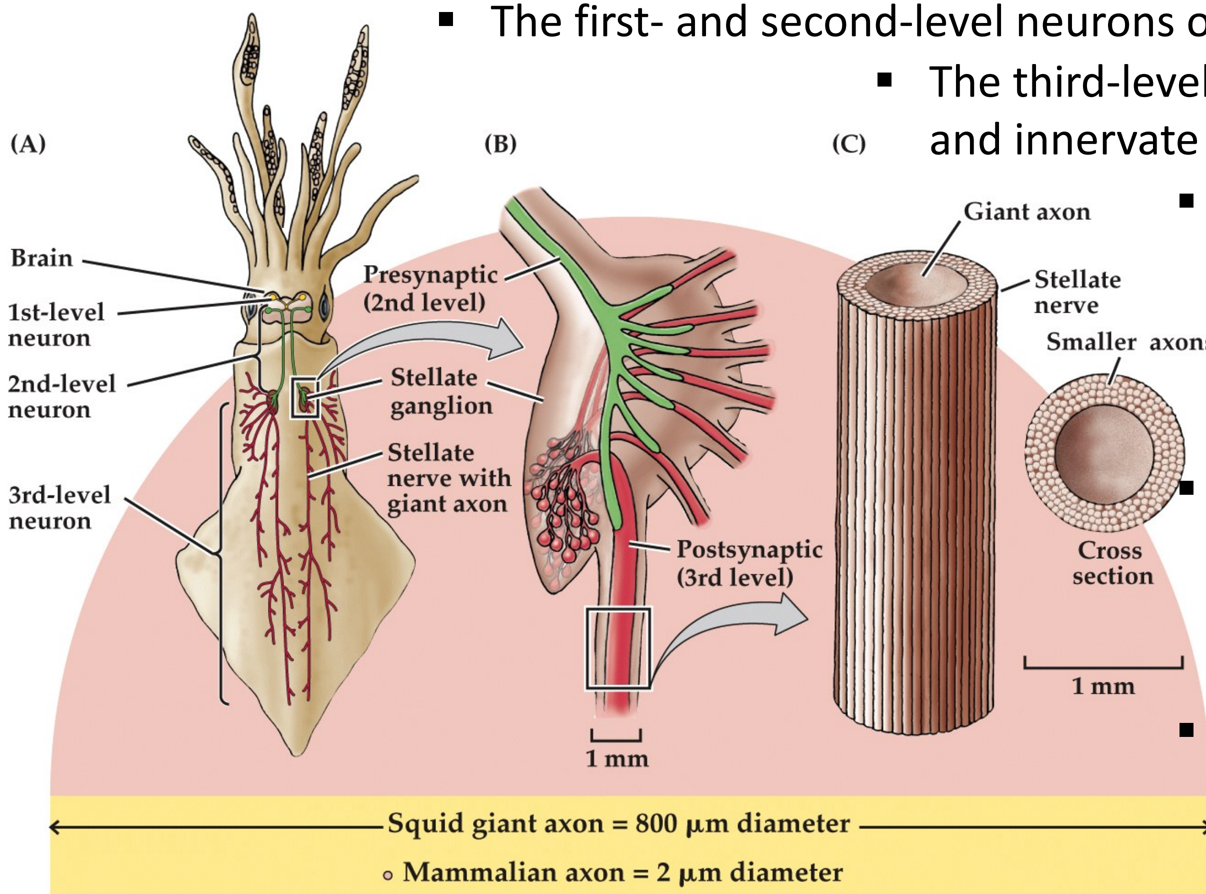
- The action of ion transporters creates substantial transmembrane gradients for most ions.
  - Such measurements are the basis for stating that there is much more K^+ inside the neuron than out, and much more Na^+ outside than inside.

TABLE 2.1 Extracellular and Intracellular Ion Concentrations

	CONCENTRATION (MM)	
ION	INTRACELLULAR	EXTRACELLULAR
Squid neuron		
Potassium (K^+)	400	20
Sodium (Na^+)	50	440
Chloride (Cl^-)	40–150	560
Calcium (Ca^{2+})	0.0001	10
Mammalian neuron		
Potassium (K^+)	140	5
Sodium (Na^+)	5–15	145
Chloride (Cl^-)	4–30	110
Calcium (Ca^{2+})	0.0001	1–2

The remarkable giant nerve cells of squid

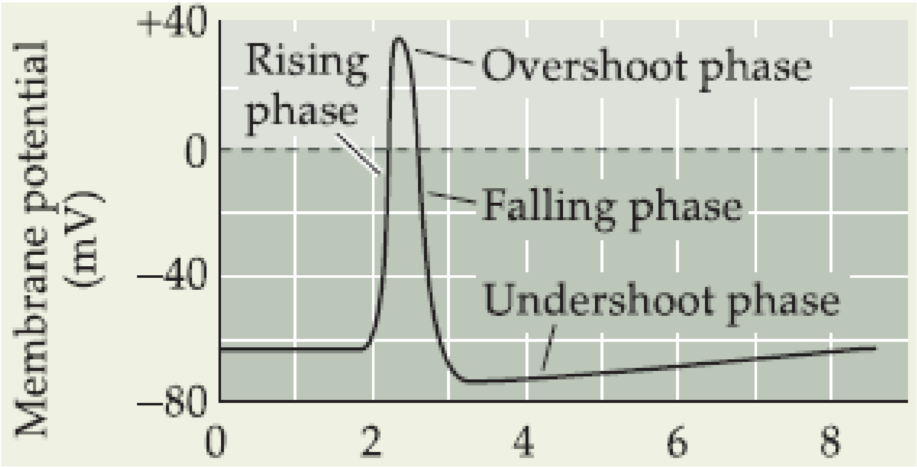
- Many of the initial insights into how ion concentration gradients and changes in membrane permeability produce electrical signals came from experiments performed on the extraordinarily large nerve cells of the **squid**.
  - The first- and second-level neurons originate in the brain.
  - The third-level neurons are in the <u>stellate ganglion</u> and innervate muscle cells of the mantle.
  - The second-level neuron forms a series of fingerlike processes, each of which makes an extraordinarily large synapse with a single third-level neuron.
  - The axons of these nerve cells can be up to 1 mm in diameter--100 to 1000 times larger than mammalian axons.
  - It is not difficult to insert simple wire electrodes inside these giant axons and make reliable electrical measurements.



NEUROSCIENCE 5e, Box 2B

- The relative ease of this approach yielded the <u>first</u> intracellular recordings of action potentials from nerve cells and the first experimental measurements of the ion currents that produce action potentials. -- John Z. Young at University College London, 1939

The phases of an action potential of the squid giant axon



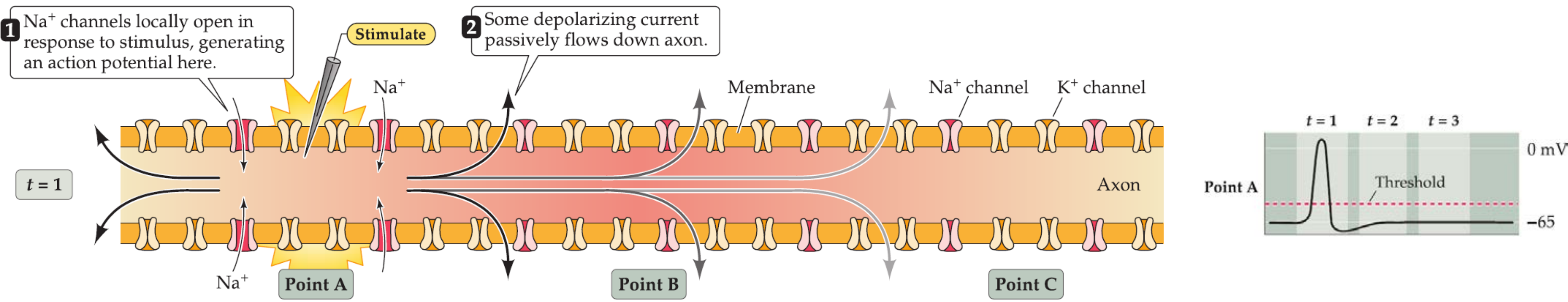
- While the **resting** neuronal membrane is only slightly permeable to Na^+, the membrane becomes extraordinarily permeable to Na^+ during the **rising phase** and the **overshoot phase** of an action potential.

- The length of time the membrane potential lingers near E_{Na} (about +58 mV) during the overshoot phase of an action potential is brief because the increased membrane permeability to Na^+ itself is short-lived.

- During the **undershoot**, the membrane potential is transiently hyperpolarized because K^+ permeability becomes even greater than it is at rest.

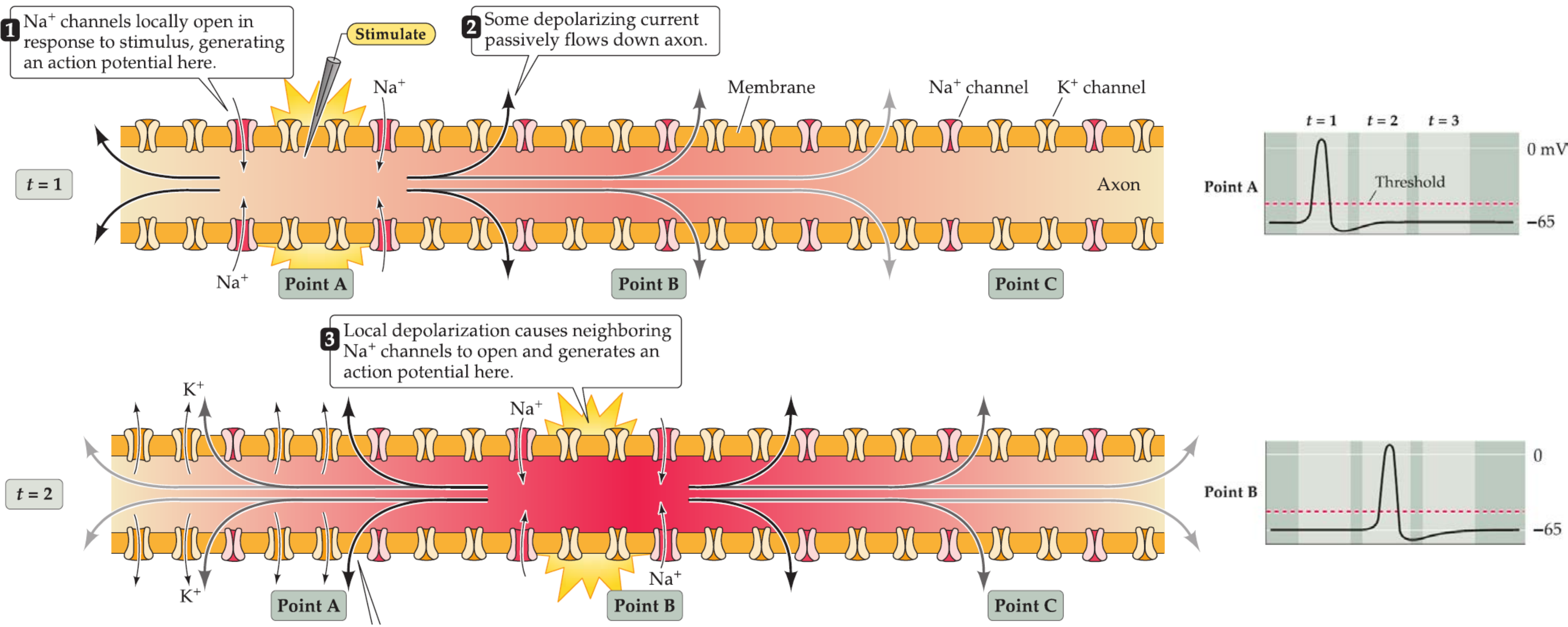
- The action potential ends when this phase of enhanced K^+ permeability subsides, and the membrane potential thus returns to its normal resting level.

Long-distance signaling by means of action potentials



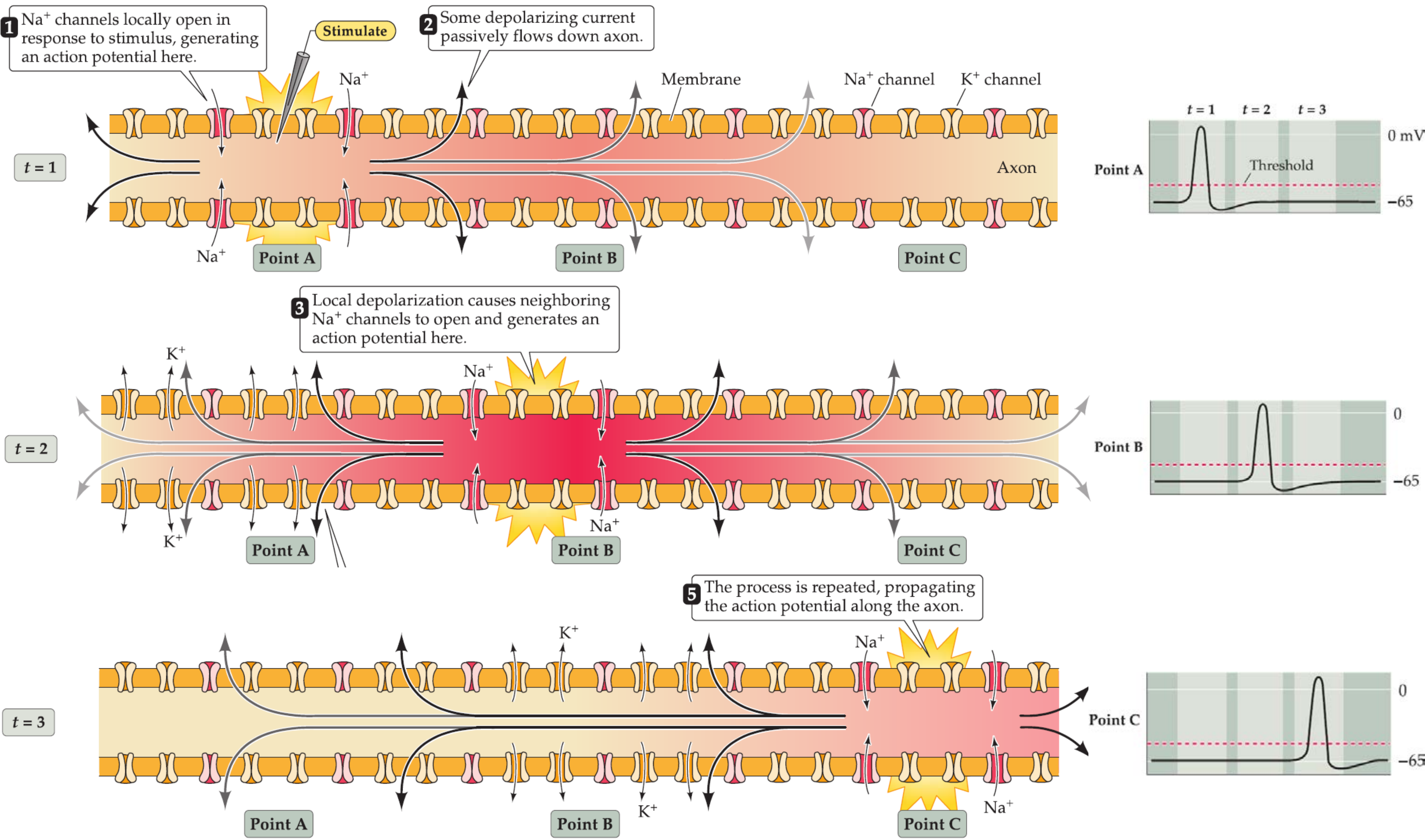
- A depolarizing stimulus--a synaptic potential or a receptor potential in an intact neuron, or an injected current pulse in an experiment--locally depolarizes the axon, thus opening the voltage-sensitive Na^+ channels in that region.
- The opening of Na^+ channels causes inward movement of Na^+, and the resultant depolarization of the membrane potential generates an action potential at that site.
- Some of the local current generated by the action potential will then flow passively down the axon.

Long-distance signaling by means of action potentials



- This <u>passive current flow</u> depolarizes the membrane potential in the <u>adjacent</u> region of the axon, thus opening the Na^+ channels in the neighboring membrane.
- The local depolarization triggers an <u>action potential</u> in this region.

Long-distance signaling by means of action potentials



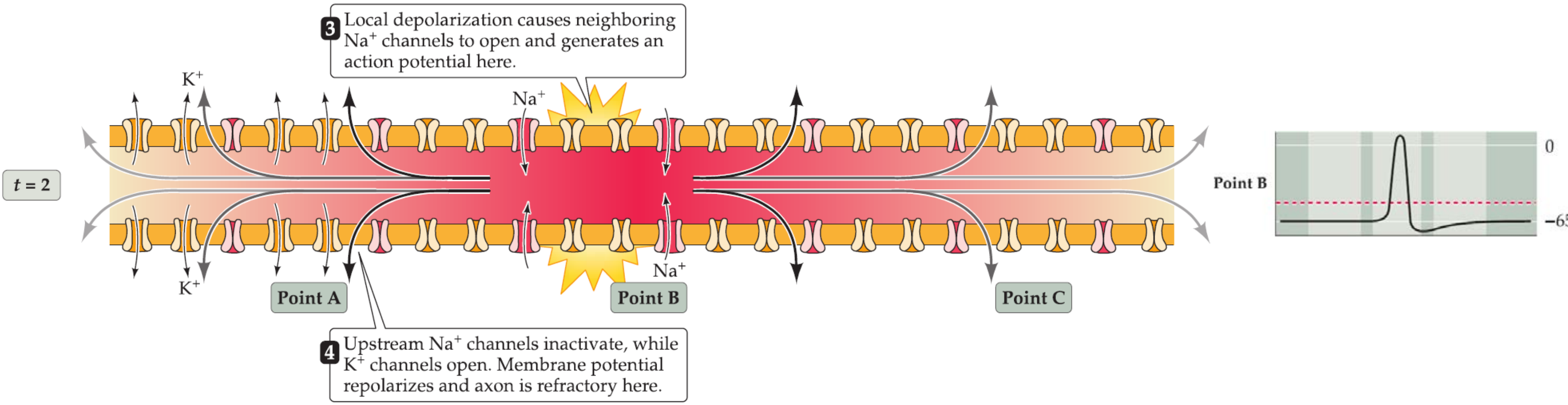
❖ Action potential then spreads again in a continuing cycle until the action potential reaches the end of the axon.

Long-distance signaling by means of action potentials

- Action potential propagation requires the coordinated action of two forms of current flow: <u>the passive flow of current</u> as well as <u>active currents</u> flowing through voltage-dependent ion channels.

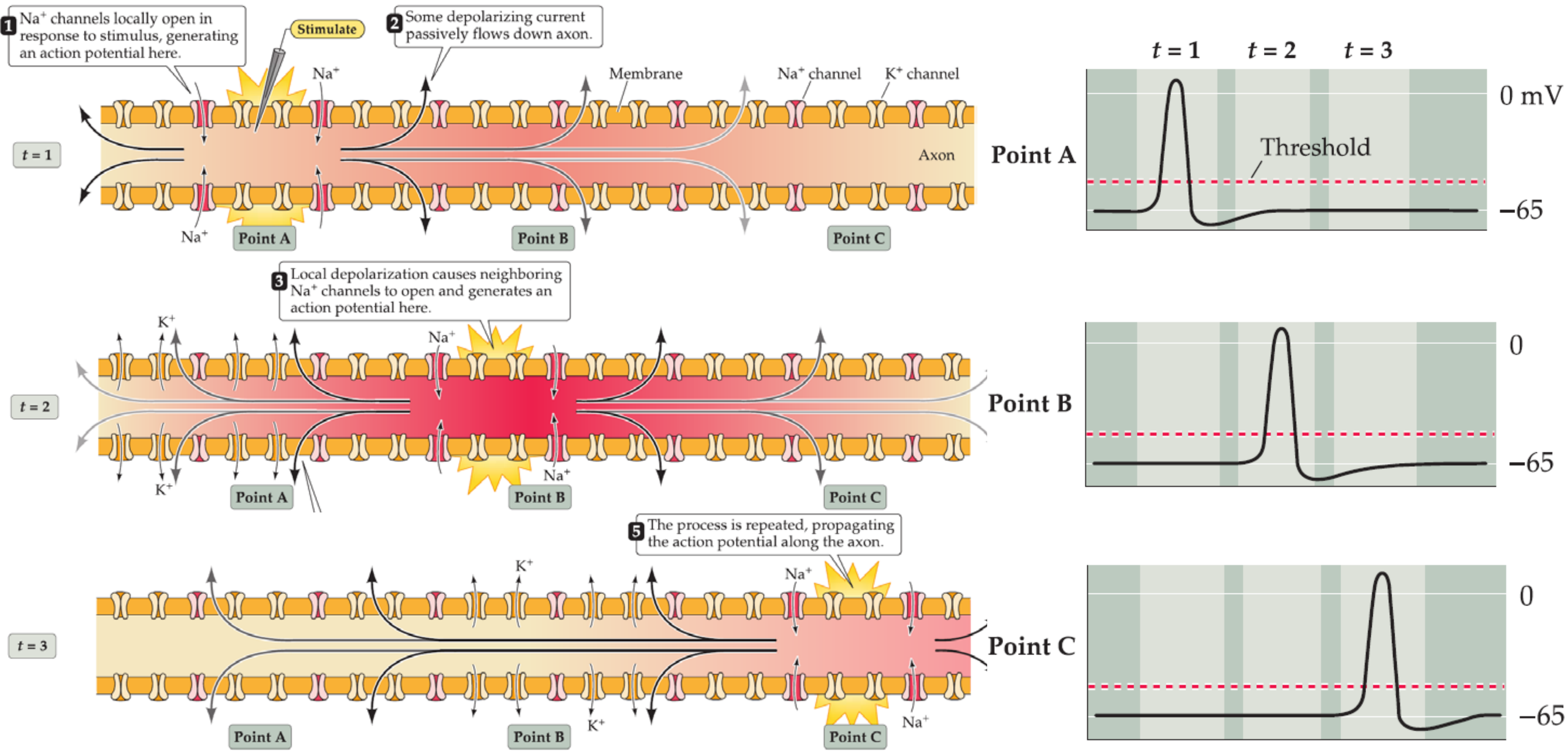
- The regenerative properties of Na^+ channel opening allow action potentials to propagate in an <u>all-or-none</u> fashion by acting as a <u>booster</u> at each point along the axon, thus ensuring the long-distance transmission of electrical signals.

Long-distance signaling by means of action potentials



- As the action potential spreads, the membrane potential repolarizes due to K^+ channel opening and Na^+ channel inactivation, leaving a "wake" of refractoriness behind the action potential that prevents its backward propagation.
- The refractory period arises because the depolarization that produces Na^+ channel opening also causes delayed activation of K^+ channels and Na^+ channel inactivation, which temporarily makes it more difficult for the axon to produce another action potential.
- This important feature prevents action potentials from propagating backward, toward their point of initiation, as they travel along an axon.
- Refractory behavior ensures polarized propagation of action potentials from their usual point of initiation near the neuronal cell body, toward the synaptic terminals at the distal end of the axon.

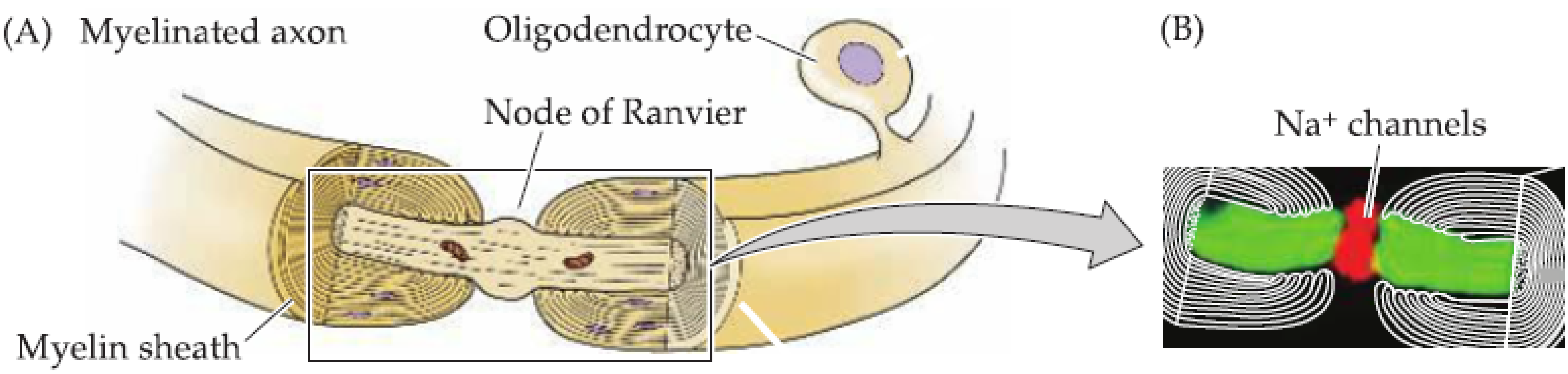
Conduction velocity



- As a consequence of their mechanism of propagation, action potentials occur <u>later and later</u> at greater distances along the axon.
- The action potential has a measurable rate of transmission, called the **conduction velocity**.
- Conduction velocity is an important parameter because it defines the time required for electrical information to travel from one end of a neuron to another.

Optimizing propagation of action potentials along axons

- Because action potential conduction requires passive and active flow of current, the rate of action potential propagation is determined by both of these phenomena.
- Strategies to improve the passive flow of electrical current:
  1. to increase the diameter of an axon, which effectively decreases the internal resistance to passive current flow.
  2. to insulate the axonal membrane, reducing the ability of current to leak out of the axon and thus increasing the distance along the axon that a given local current can flow passively.
- **Myelination of axons**: oligodendrocytes in the central nervous system (and Schwann cells in the peripheral nervous system) wrap the axon in myelin, which consists of multiple layers of closely opposed glial membranes.



Myelin increases action potential conduction speed

- By acting as an electrical insulator, myelin greatly <u>speeds up</u> action potential conduction.
- The major reason underlying this marked increase in speed is that the time-consuming process of action potential generation occurs only at specific points along the axon, called **nodes of Ranvier**, where there is a gap in the myelin wrapping.
- An action potential generated at one node of Ranvier elicits current that flows passively within the myelinated segment until the next node is reached.
- This type of propagation is called **saltatory**, meaning that the action potential <u>jumps</u> from node to node.