General Physiology
Second Semester , 2024
Lecture 13 and 14
Part 1: Action potential of neurons
Ionic basis and properties of action potential
Part II Cardiac action potentials

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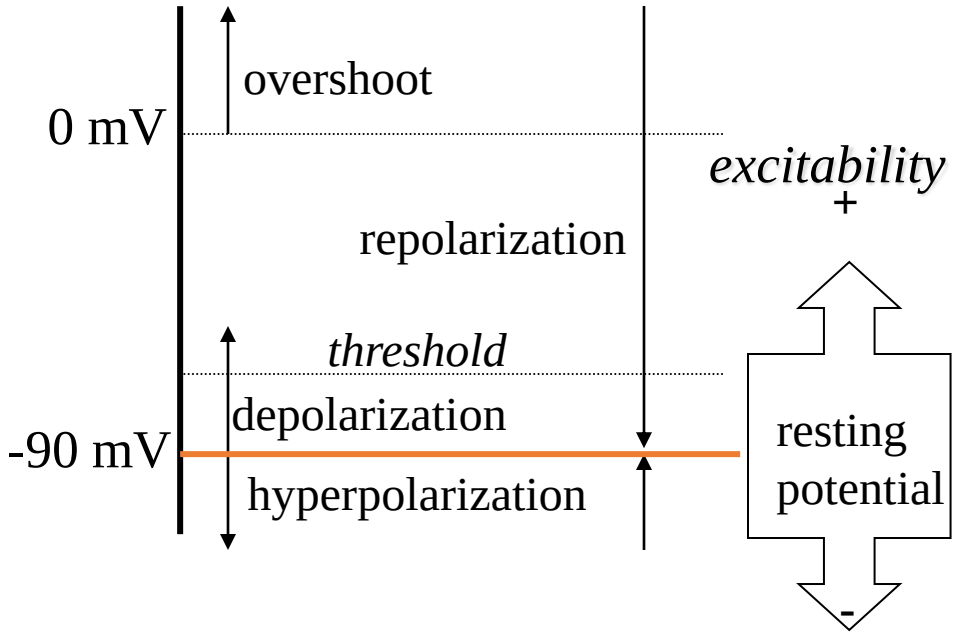
Lectures Objectives

- Define the nerve action potential and properties
- Describe the activation of action potentials and describe the ionic basis of action potential .
- Describe the membrane currents underlying action potentials.
- Describe the activity of channels producing action potentials.
- Define threshold of for initiation of action potential threshold and different phases of action potential , depolarization, overshoot , repolarization and refractory period.
- Explain the propagation of nerve impulse along axons membranes in myelinated and non myelinated nerve fibers
- Explain the consequences of myeline loss on nerve function and give example of demyelinated diseases
- Describe and explain actions of calcium, local anesthetics, and neurotoxins on action potentials.
- Define pacemaker potentials and identify phases of SA node action potential
- Identify phasis of action potential of cardiac muscles and compare neuronal action potential Skeletal muscles and cardiac muscle action potential

Action potentials : Terminology

- ***There are some terms that need to be understood & remembered:***
  - **Depolarization**
  - **Hyperpolarization**
  - **Overshoot**
    - means positive to 0 mV
  - **Repolarization**
    - towards resting potential
  - **Excitability**
  - **Threshold** *(for action potential generation)*



Action Potential : Terminology

- Depolarization is the process of making the membrane potential less negative
- Hyperpolarization is the process of making the membrane potential more negative
- Inward current is the flow of positive charge into the cell. Thus, inward currents depolarize the membrane potential. An example of an inward current is the flow of Na+ into the cell during the upstroke of the action potential
- Outward current is the flow of positive charge out of the cell. Outward currents hyperpolarize the membrane potential. An example of an outward current is the flow of K+ out of the cell during the repolarization phase of the action potential.

What is an action potential

- The action potential is a phenomenon of excitable cells such as nerve and muscle and consists of a rapid depolarization (upstroke) followed by repolarization of the membrane potential.
- Action potentials are the basic mechanism for transmission of information in the nervous system and in all types of muscle
- Triggered by by application of an appropriate stimulus
- For example: application of an electrical current to the nerve cells axons

Intracellular recording of action in the axon of a nerve cell via microelectrodes

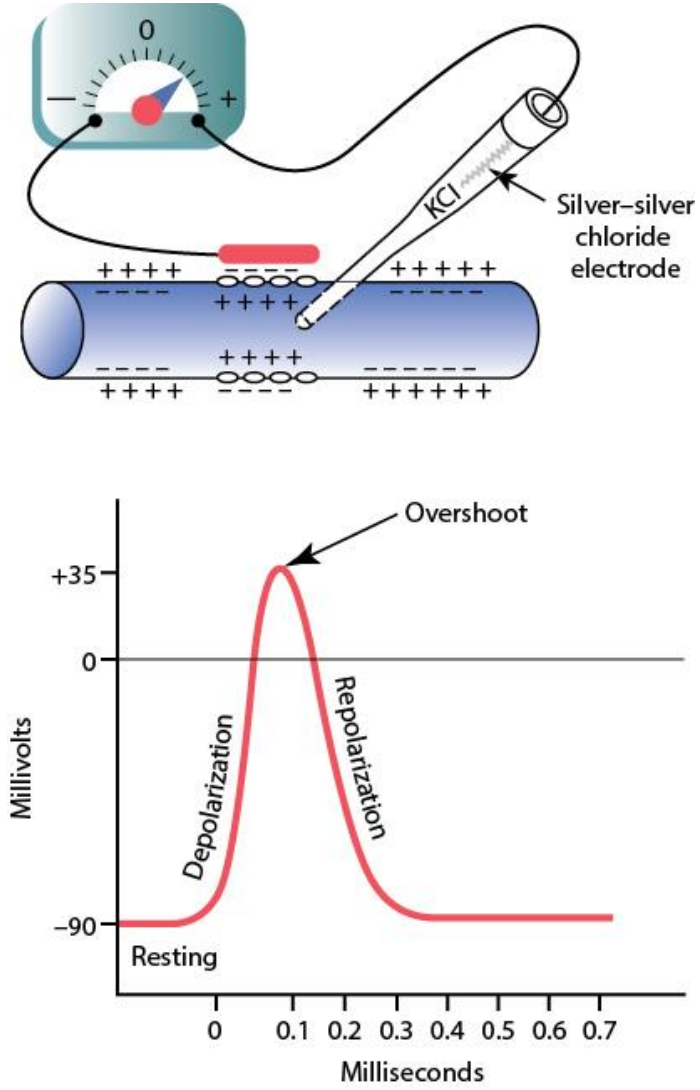


Figure 5-6

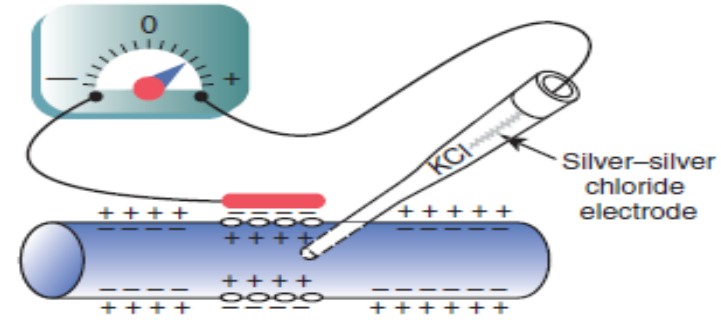
Schematic Diagram of action potential and membrane potential changes during the successive stages of action potential

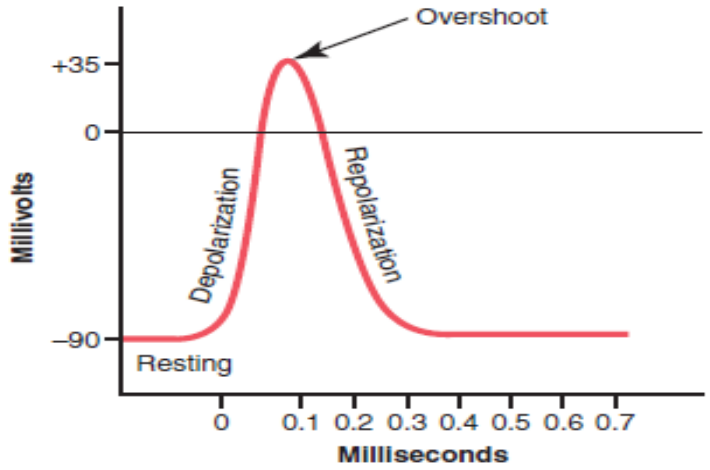
Stages of action potential

Resting Stage::
Membrane is polarized

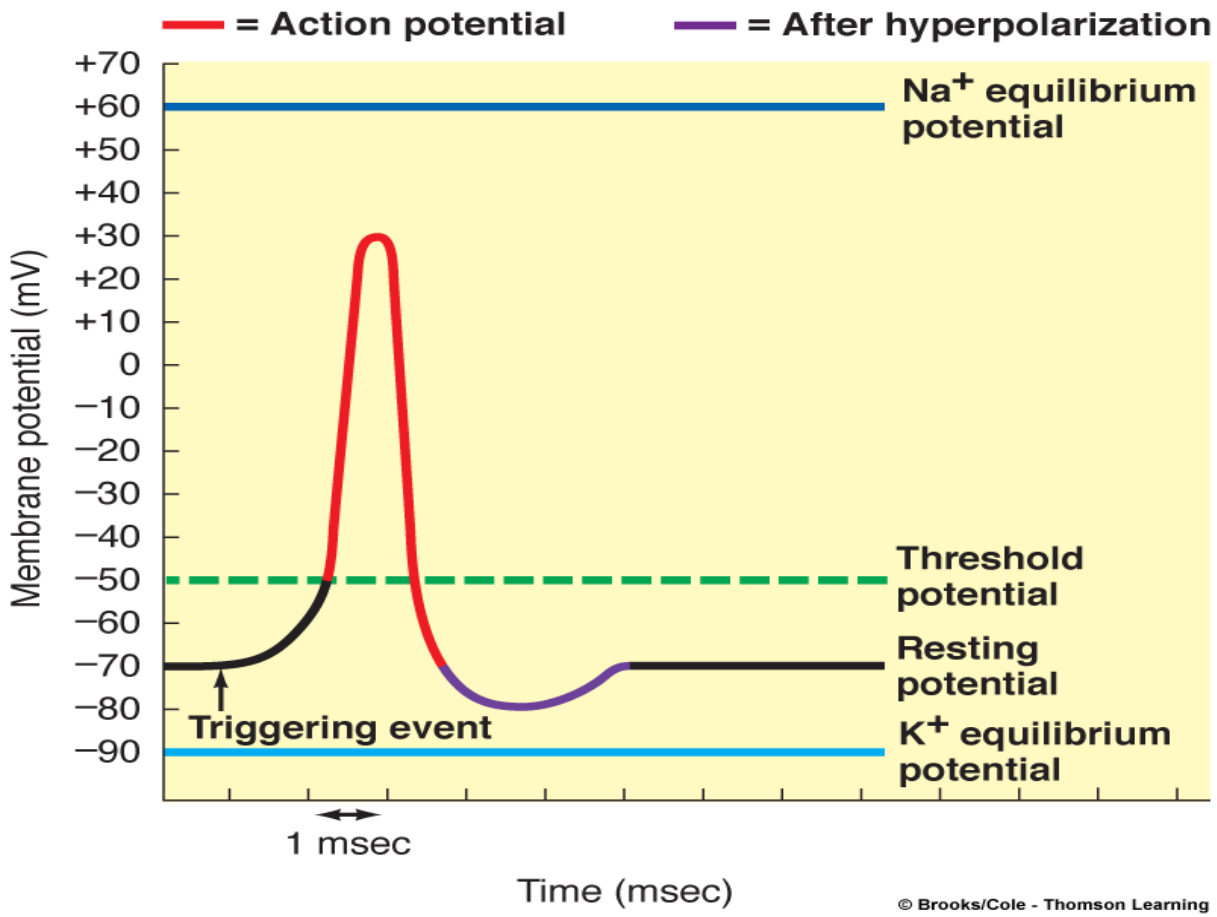
Depolarization Stage

Repolarization Stage





Initiation of Action Potential



NEURON ACTION POTENTIAL
Successive stages of the action potential

- **Resting Stage.** The resting stage is the resting membrane potential before the action potential begins. The membrane is said to be “polarized” during this stage because of the -70 millivolts negative membrane potential that is present.
- **Depolarization Stage**. The normal polarized state of −70 millivolts is immediately neutralized by the inflowing, positively charged sodium ions, with the potential rising rapidly in the positive direction—a process called *depolarization.* In large nerve fibers, the great excess of positive sodium ions moving to the inside causes the membrane potential to actually overshoot beyond the zero level and to become somewhat positive. In some smaller fibers, as well as in many central nervous system neurons, the potential merely approaches the zero level and does not overshoot to the positive state.
- At this time, the membrane suddenly becomes permeable to sodium ions, allowing positively charged sodium ions to diffuse to the interior of the axon. The normal “polarized” state of −90 millivolts is immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction in some nerve cells
- **Repolarization Stage**. Within a few msec after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close and the potassium channels open to a greater degree than normal. Then, rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential,

Changes in sodium and potassium conductance during the course of the action potential. Sodium conductance increases several thousand–fold during the early stages of the action potential, whereas potassium conductance increases only about 30-fold during the latter stages of the action potential and for a short period there after.

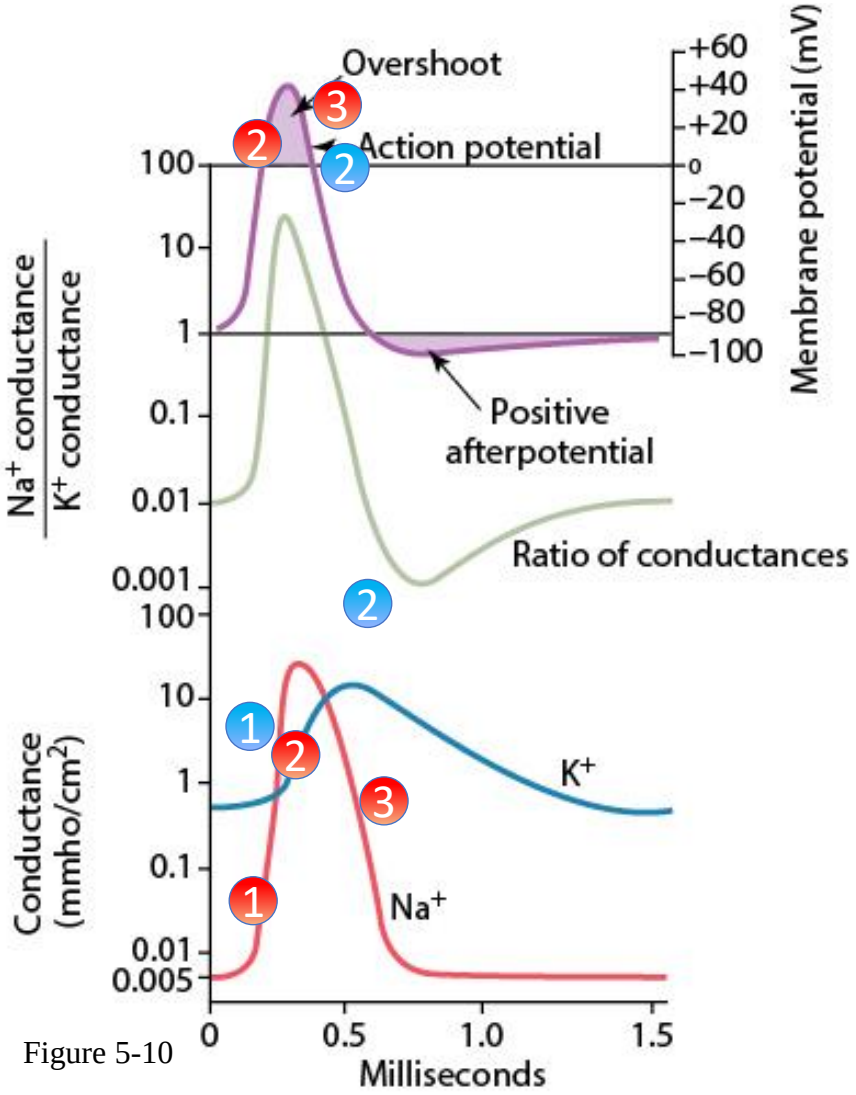


Figure 5-10

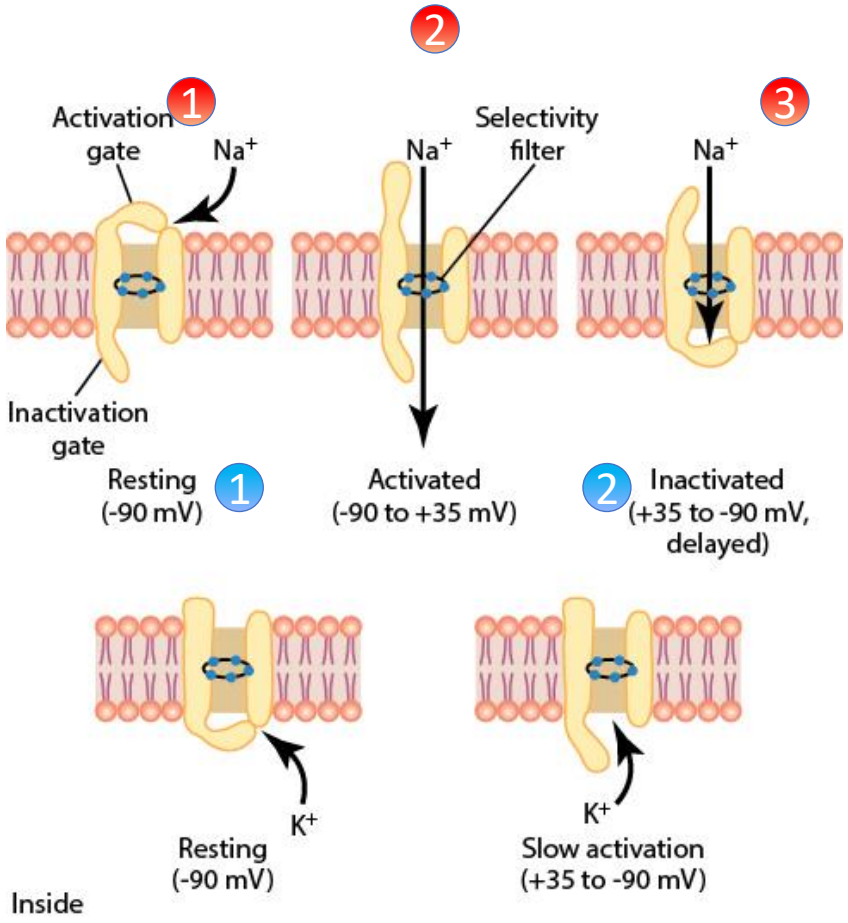
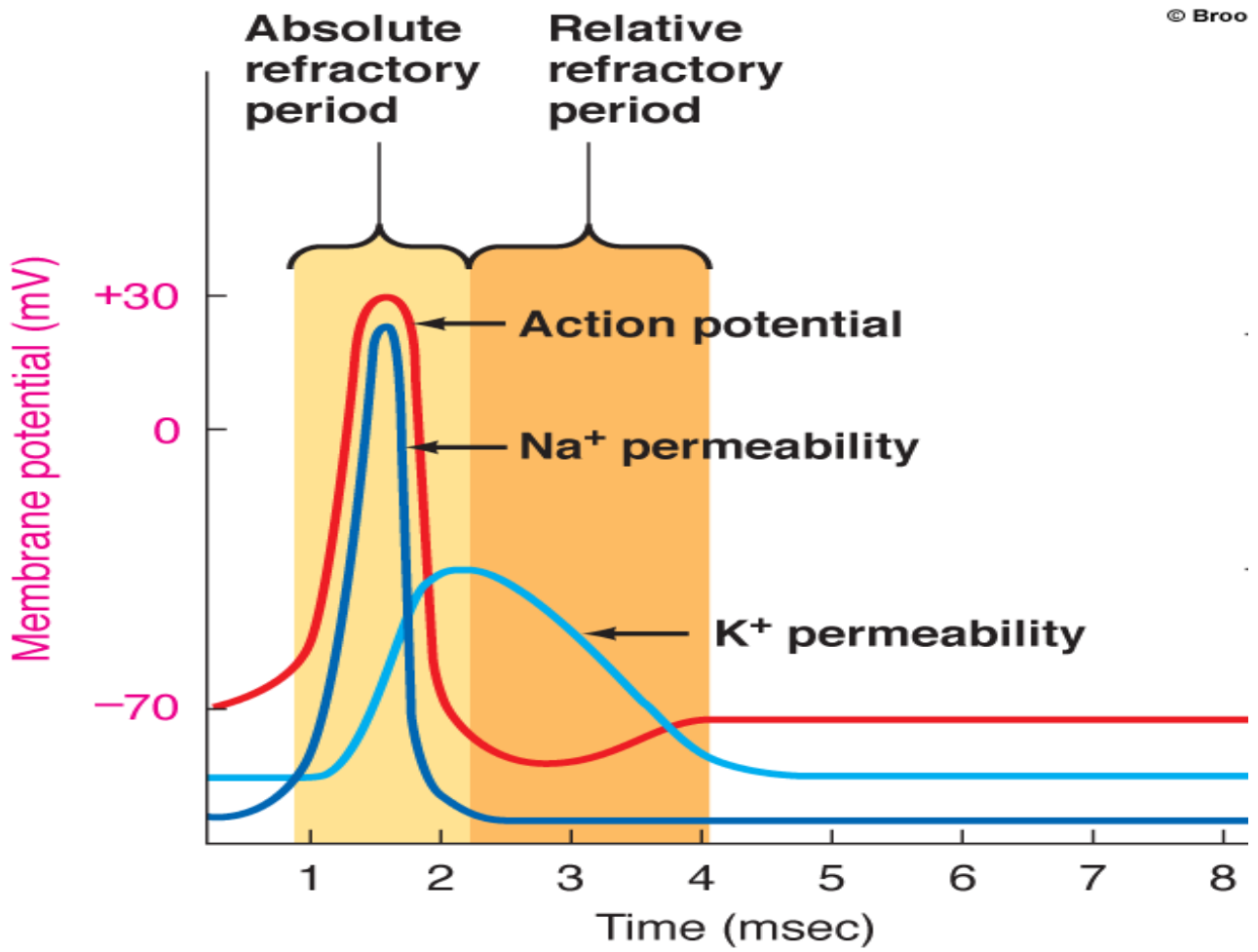


Figure 5-7

The absolute and relative refractory periods during an action potential

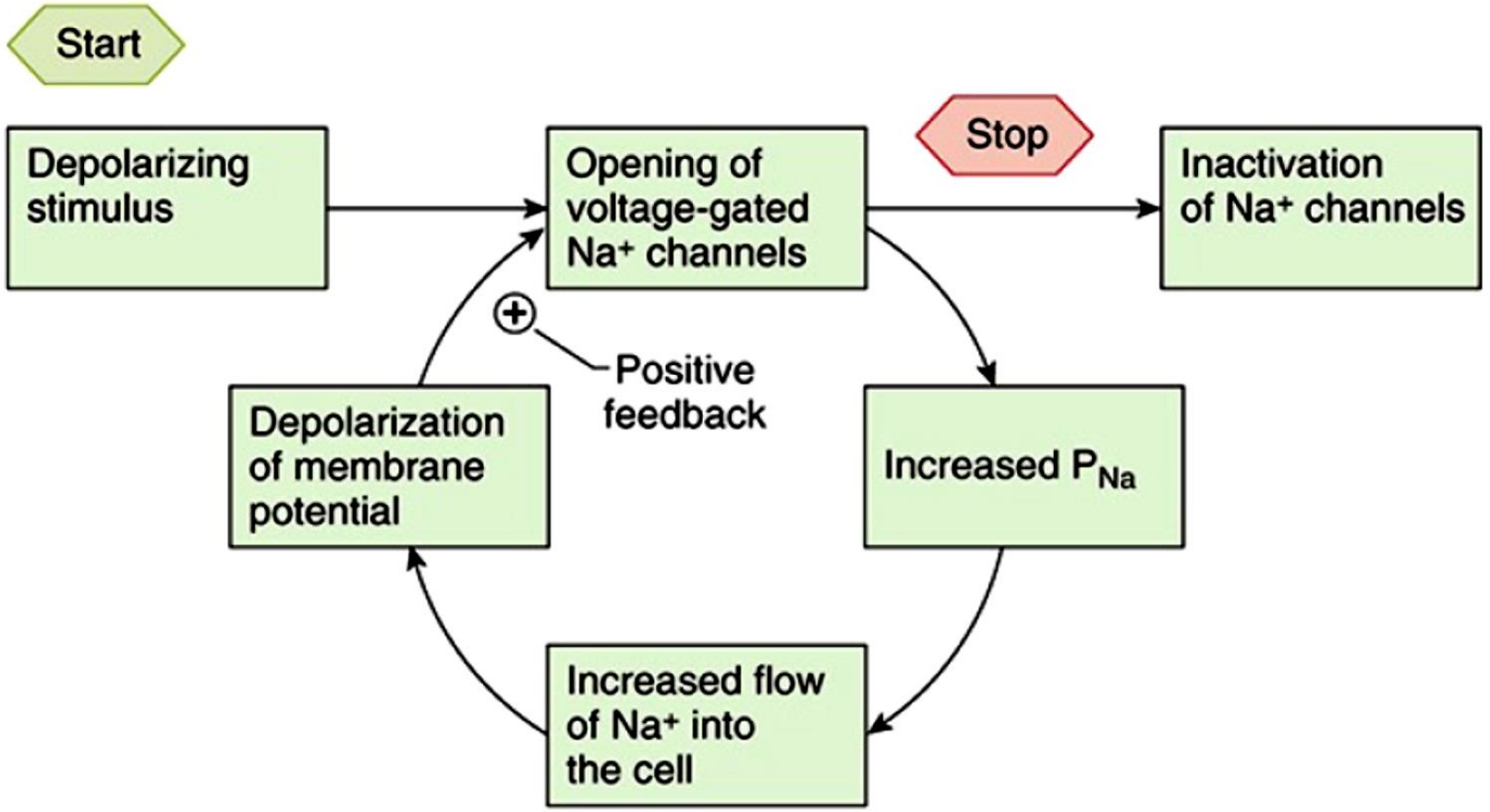
During the absolute refractory period no stimulus, however large, can elicit a second action potential.

During the relative refractory period a second action potential can be elicited but it requires a larger stimulus than that in the resting state

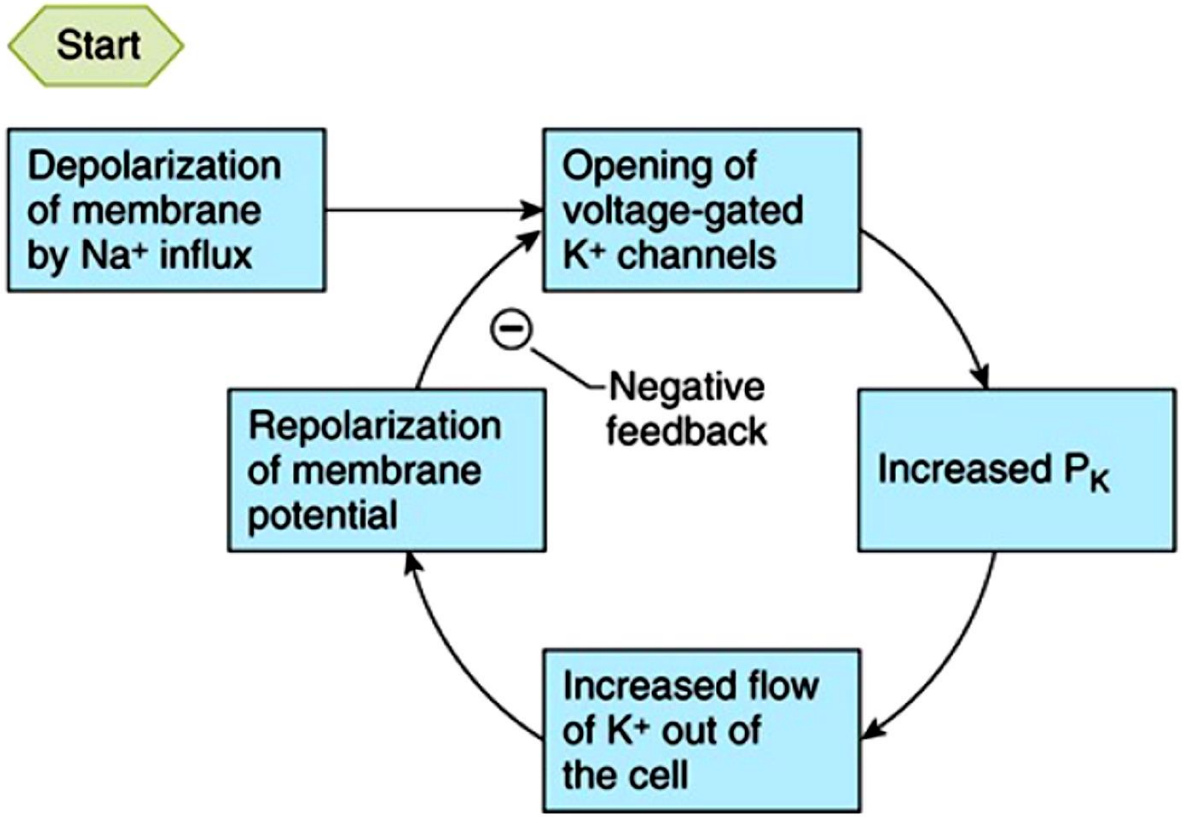


INITIATION OF THE ACTION POTENTIAL

Positive-Feedback Cycle Opens the Sodium Channels.

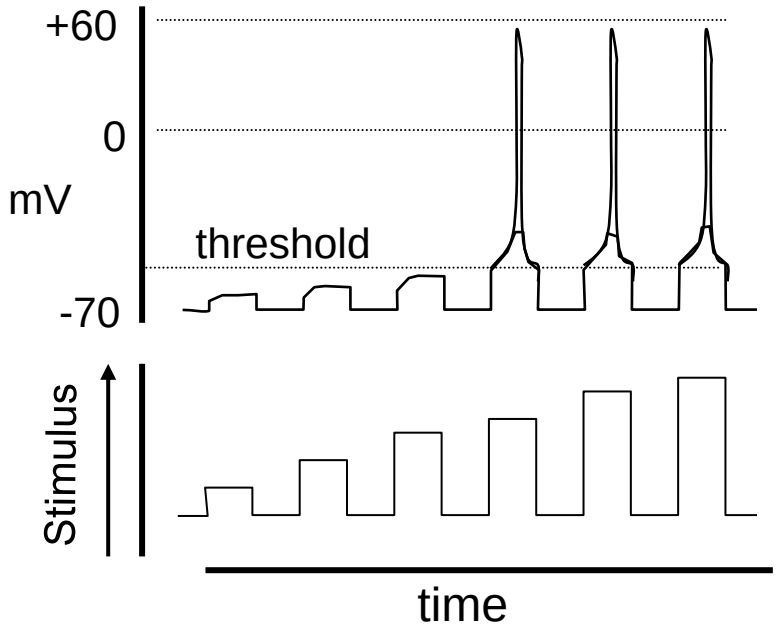


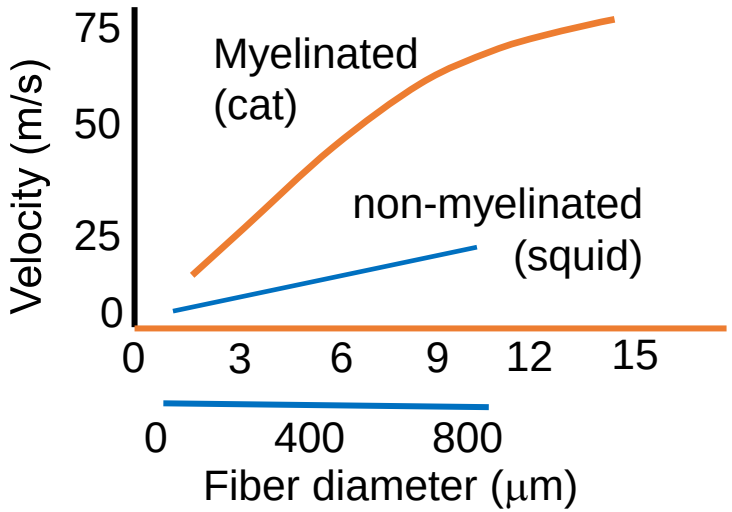
K channels exert negative feed back and cause repolarization



Properties of action potentials

- **Action potentials**:
  - **are all-or-none events**
    - threshold voltage (usually 15 mV positive to resting potential)
  - **Self-propagation**
  - **are initiated by depolarization**
    - action potentials can be induced in nerve and muscle by extrinsic (percutaneous) stimulation
  - **have constant amplitude**
    - APs do not summate - information is coded by frequency not amplitude.
  - **have constant conduction velocity**
    - True for given fiber.
    - Fibers with large diameter conduct faster than small fibers. As a general rule:
      - ***myelinated*** fiber diameter (in mm) x 4.5 = velocity in m/s.
      - Square root of ***unmyelinated*** fiber diameter = velocity in m/s





Threshold for Initiation of the Action Potential.

- An action potential will not occur until the initial rise in membrane potential is great enough to create the positive feedback described in the preceding paragraph.
- This occurs when the number of sodium ions entering the fiber (inward Na+ current) becomes greater than the number of potassium ions (K outward current) leaving the fiber.
- A sudden rise in membrane potential of 15 to 30 millivolts is usually required.
- For example , a sudden increase in the membrane potential in a large nerve fiber from −90 millivolts up to about −65 millivolts usually causes the explosive development of an action potential. This level of −65 millivolts is said to be the *threshold* for stimulation.
- If net inward current is less than net outward current, the membrane will not be depolarized to threshold and no action potential will occur (All-or-none response)

Threshold for Excitation and “Acute Local Potentials.”

- A weak negative electrical stimulus may not be able to excite a fiber. However, when the voltage of the stimulus is increased, there comes a point at which excitation does take place.. A weak stimulus at point A causes the membrane potential to change from −90 to −85 millivolts, but this change is not sufficient for the automatic regenerative processes of the action potential to develop. At point B, the stimulus is greater, but the intensity is still not enough. The stimulus does, however, disturb the membrane potential locally for as long as 1 millisecond or more after both of these weak stimuli. These local potential changes are called *acute local potentials,* and when they fail to elicit an action potential, they are called *acute subthreshold potentials.*

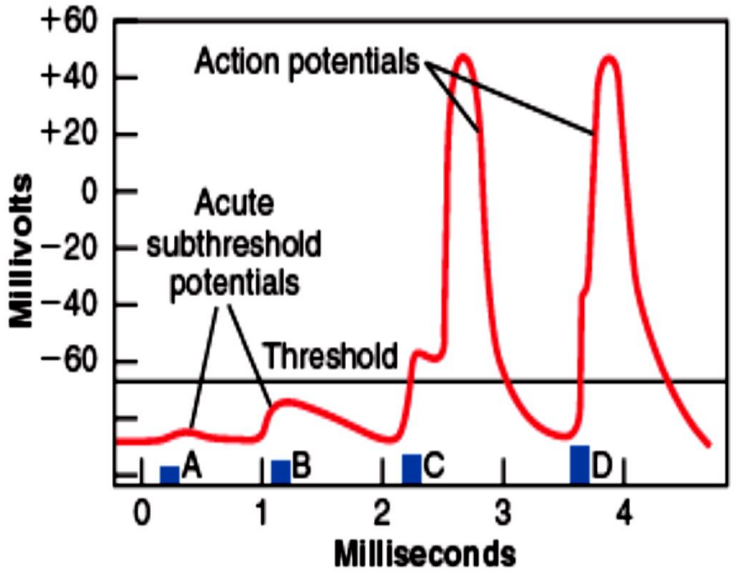


Figure 5-18. Effect of stimuli of increasing voltages to elicit an action potential. Note development of acute subthreshold potentials when the stimuli are below the threshold value required for eliciting an action potential.

All or none principle of action potential

- Once an action potential has been elicited at any point on the membrane of a normal fiber, the depolarization process travels over the entire membrane if conditions are right, but it does not travel at all if conditions are not right. This principle is called the *all-or- nothing principle,* and it applies to all normal excitable tissues. Occasionally, the action potential reaches a point on the membrane at which it does not generate sufficient voltage to stimulate the next area of the membrane. When this situation occurs, the spread of depolarization stops.

Re-establishing sodium and potassium ionic gradients after action potentials are completed—importance of energy metabolism

- Very small amount of Na enters the cells and very small amount of K leaves the cell during an action potential
- Indeed, 100,000 to 50 million impulses can be transmitted by large nerve fibers before the concentration differences reach the point that action potential conduction ceases.
- Even so, with time, it becomes necessary to re-establish the sodium and potassium membrane concentration differences, which is achieved by action of the Na+-K+ pump in the same way as described previously for the original establishment of the resting potential

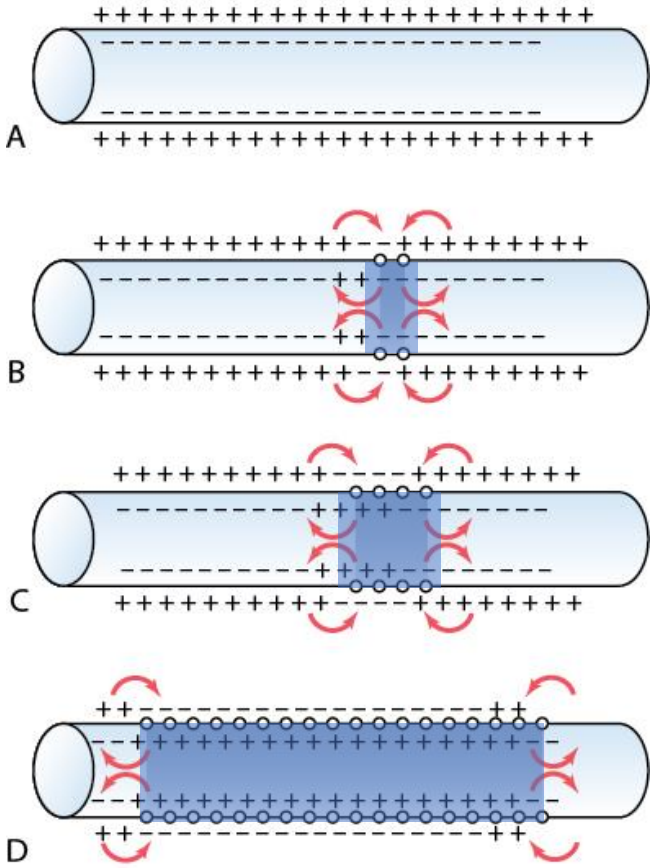
Propagation of Action Potential

Opening of Na^+ channels generates local current that depolarizes adjacent membrane, opening more Na^+ channels…

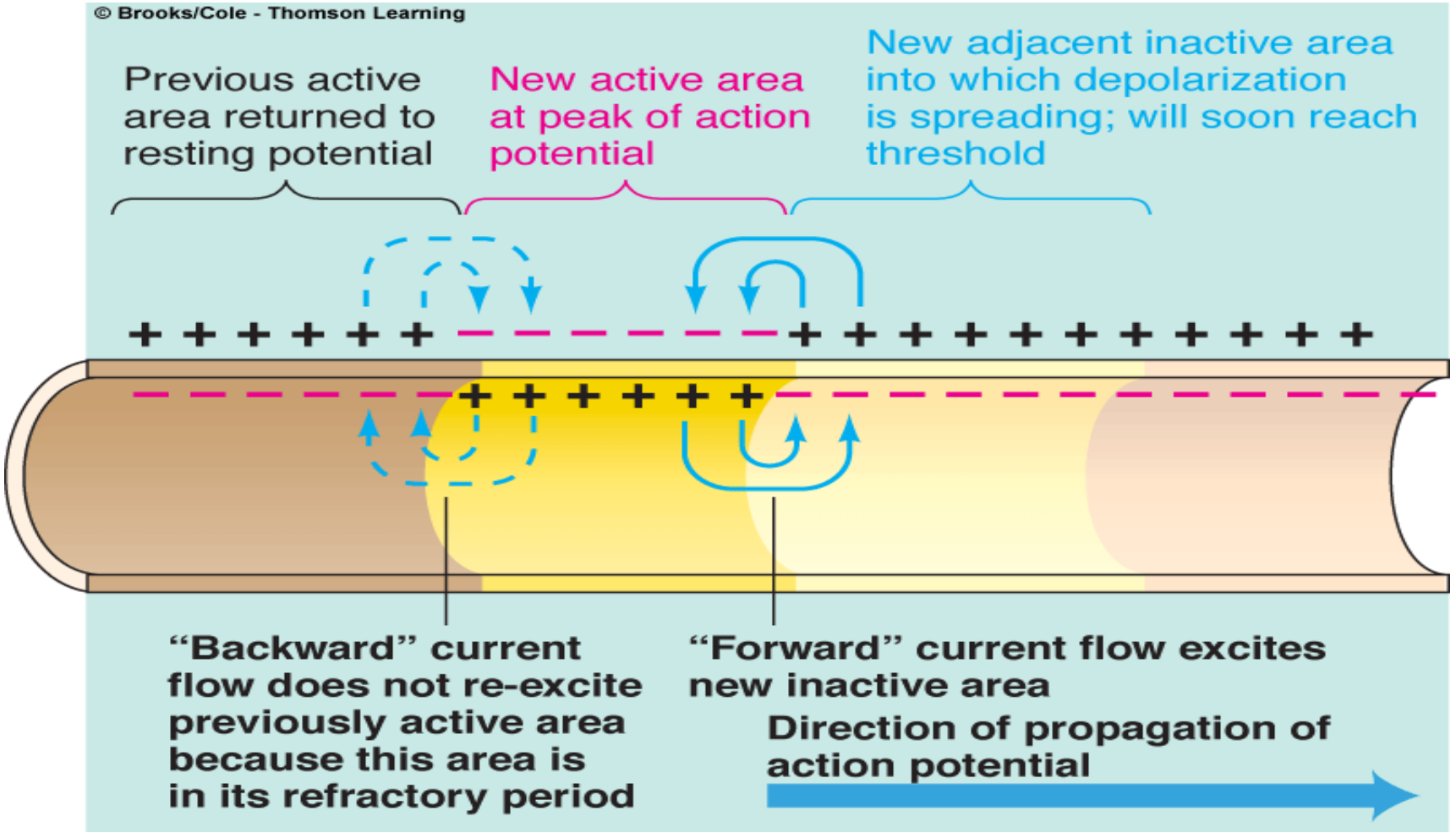
Rest

Stimulated
(local depolarization)

Propagation
(current spread)



Action potential propagation in none myelinated nerves



Signal Transmission

Myelination

- **Schwann cells** surround the nerve axon forming a myelin sheath

- Sphingomyelin decreases membrane capacitance and ion flow 5,000-fold

- Sheath is interrupted every 1-3 mm by a **node of Ranvier**

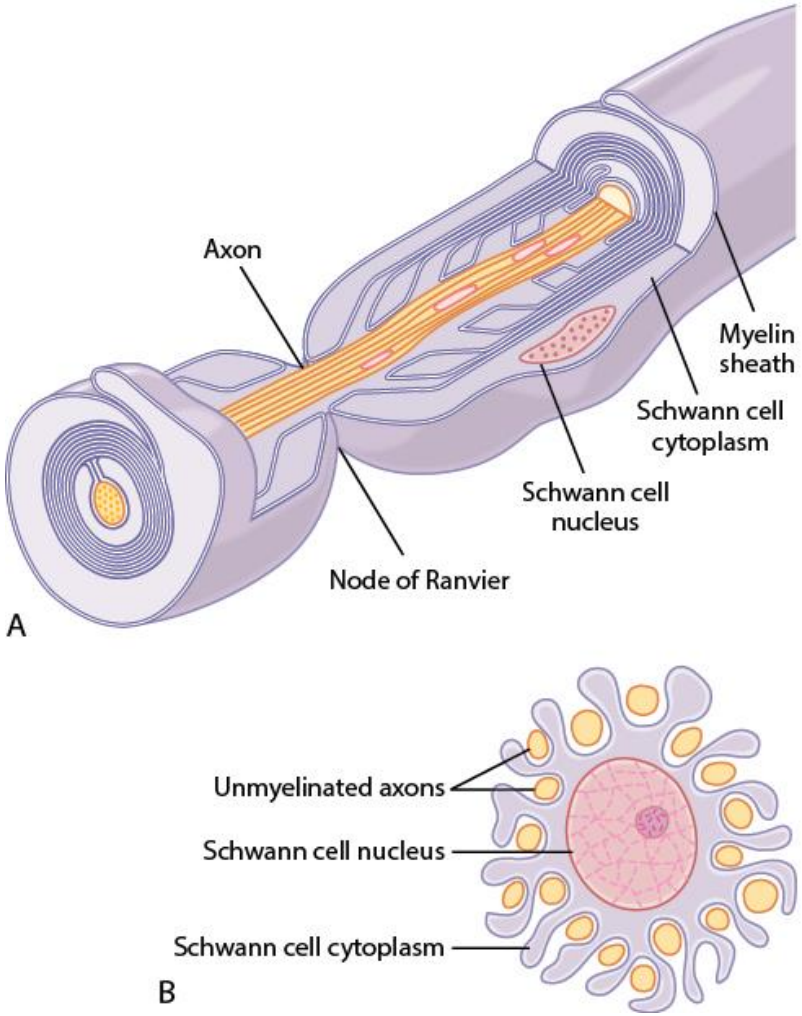


Figure 5-16

Saltatory Conduction

- AP's only occur at the node (*Na channels are concentrated here!*)
- Increased velocity
- Energy conservation

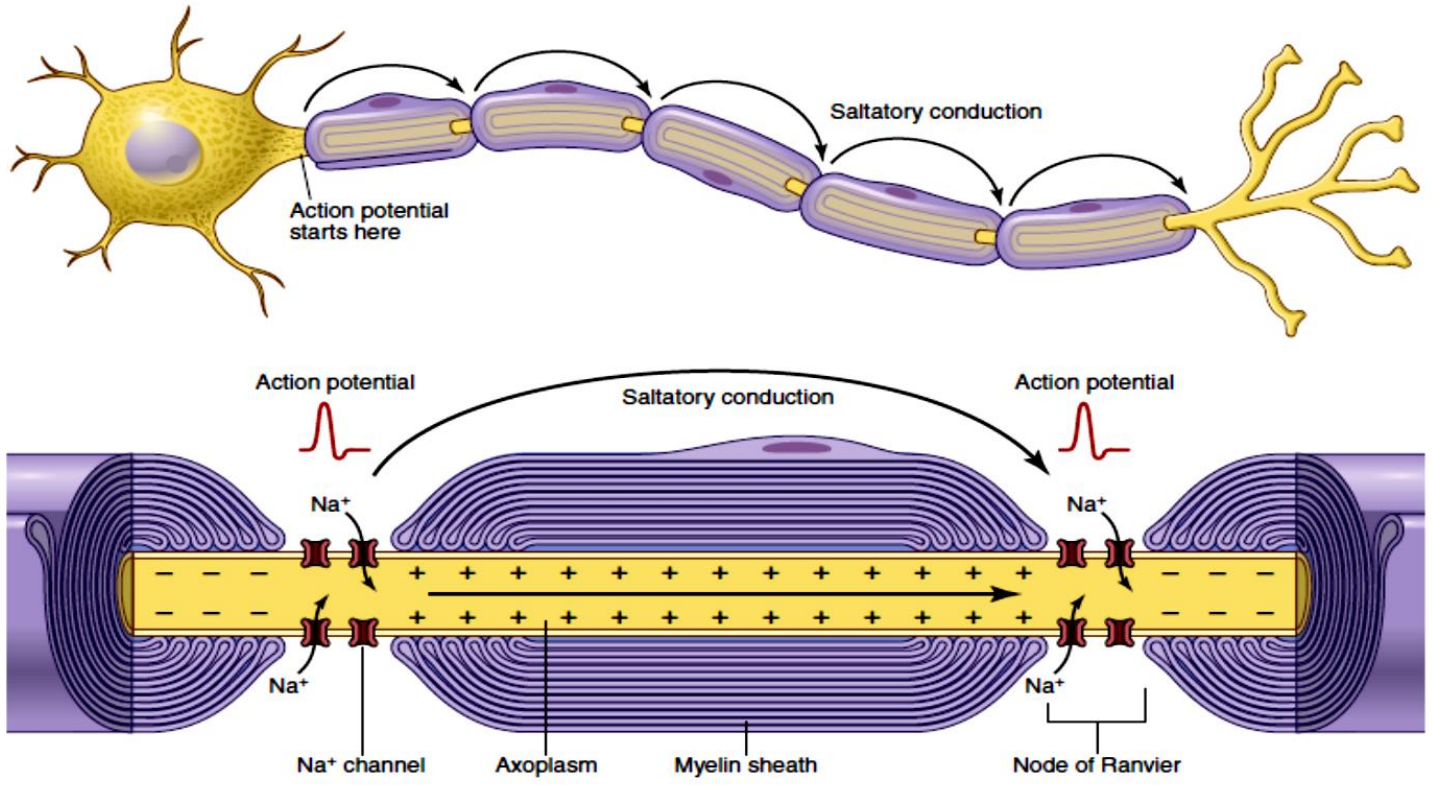
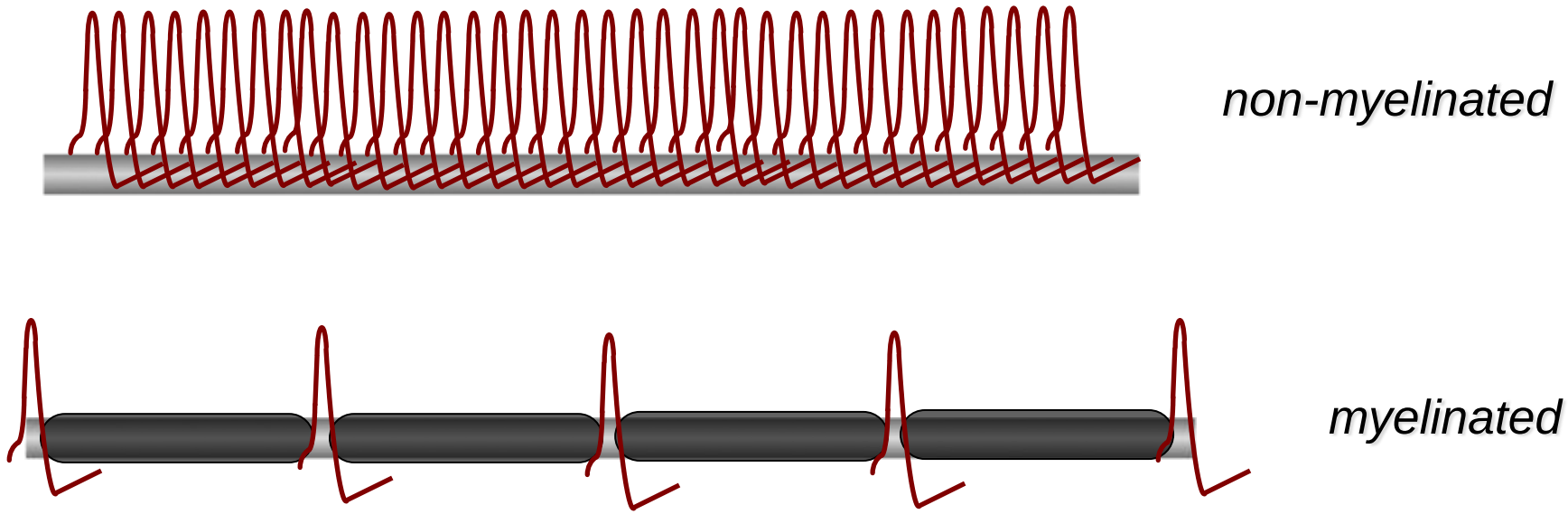


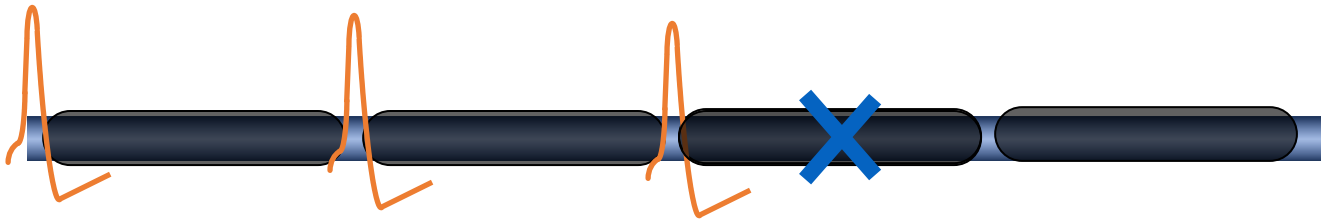
Figure 5-17 Saltatory conduction along a myelinated axon. The flow of electrical current from node to node is illustrated by the *arrows*.

Conduction velocity

- non-myelinated vs myelinated -



Multiple Sclerosis



- *MS is an immune-mediated inflammatory* ***demyelinating*** *disease of the CNS -*

- *About 1 person per 1000 in US is thought to have the disease - The female-to-male ratio is 2:1 - whites of northern European descent have the highest incidence*

Patients have a difficult time describing their symptoms. Patients may present with paresthesias of a hand that resolves, followed in a couple of months by weakness in a leg or visual disturbances. Patients frequently do not bring these complaints to their doctors because they resolve. Eventually, the resolution of the neurologic deficits is incomplete or their occurrence is too frequent, and the diagnostic dilemma begins.

 http://www.emedicine.com/pmr/topic82.htm

Effects of Drugs and Toxin on Action Potential

- **Tetrodotoxin** (TTX), a poison found in the internal organs of puffer fish, selectively blocks nerve Na channels at nanomolar concentrations.
- **Local anesthetics such as *lidocaine*** or ***benzocaine*** also block NaV channels.
- **Tetraethyl ammonium (TEA) ions** and 4-aminopyridine are among the KV channel blockers.
- There are also compounds that activate NaV channels, such as veratridine, pyrethroid insecticides.

Functions of action potentials

- **Deliver sensory information to CNS**
  - APs in sensory nerves are blocked by local anesthetics. This usually produces analgesia without paralysis. **WHY?** LAs are more effective against small diameter neurons with a large surface area to volume ratio. **Hence**, small C-fibers that conduct pain sensations are affected more than a-motorneurons.
- **Information encoding**
  - The frequency of APs encodes information (amplitude of AP is constant).
- **Rapid transmission over distance (nerve cell APs)**
  - The speed of transmission depends on fiber size and whether it is myelinated. Information of lesser importance is carried by slowly conducting unmyelinated fibers.
- **In non-nervous tissues, APs initiate various cellular responses**
  - muscle contraction
  - secretion (eg. Epinephrine from chromaffin cells of medulla)

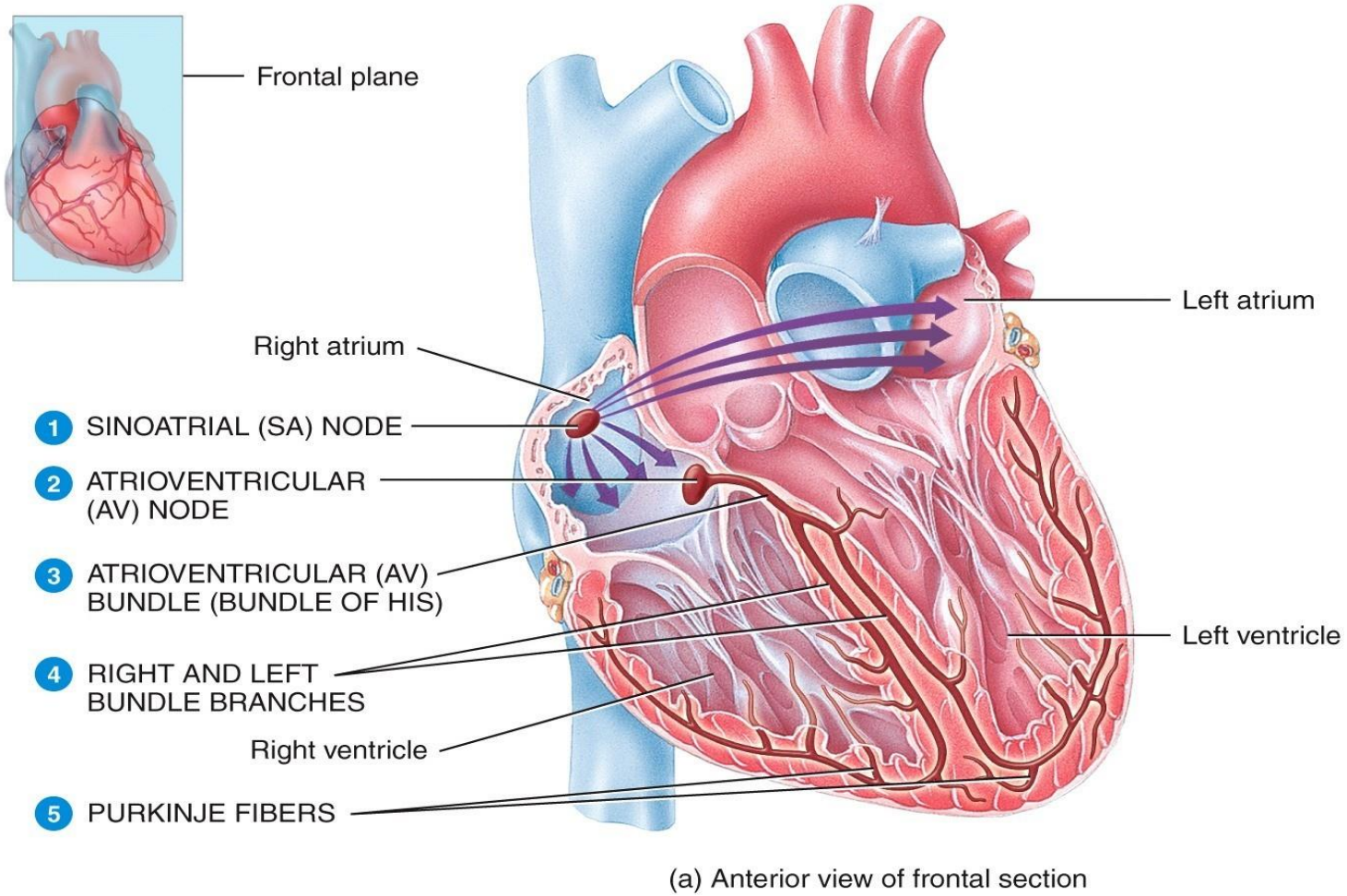
Electrical Properties of Cardiac Cells and Cardiac Cell Action Potential

- Cardiac action potentials differ sharply from those of skeletal muscle or nerve in three important ways that promote synchronous rhythmic excitation of the heart
- They can be self-generating
- They can be conducted directly from cell to cell via gap junctions
- They have long durations.
- Slower conduction velocity

Types of Cardiac Muscle Cell

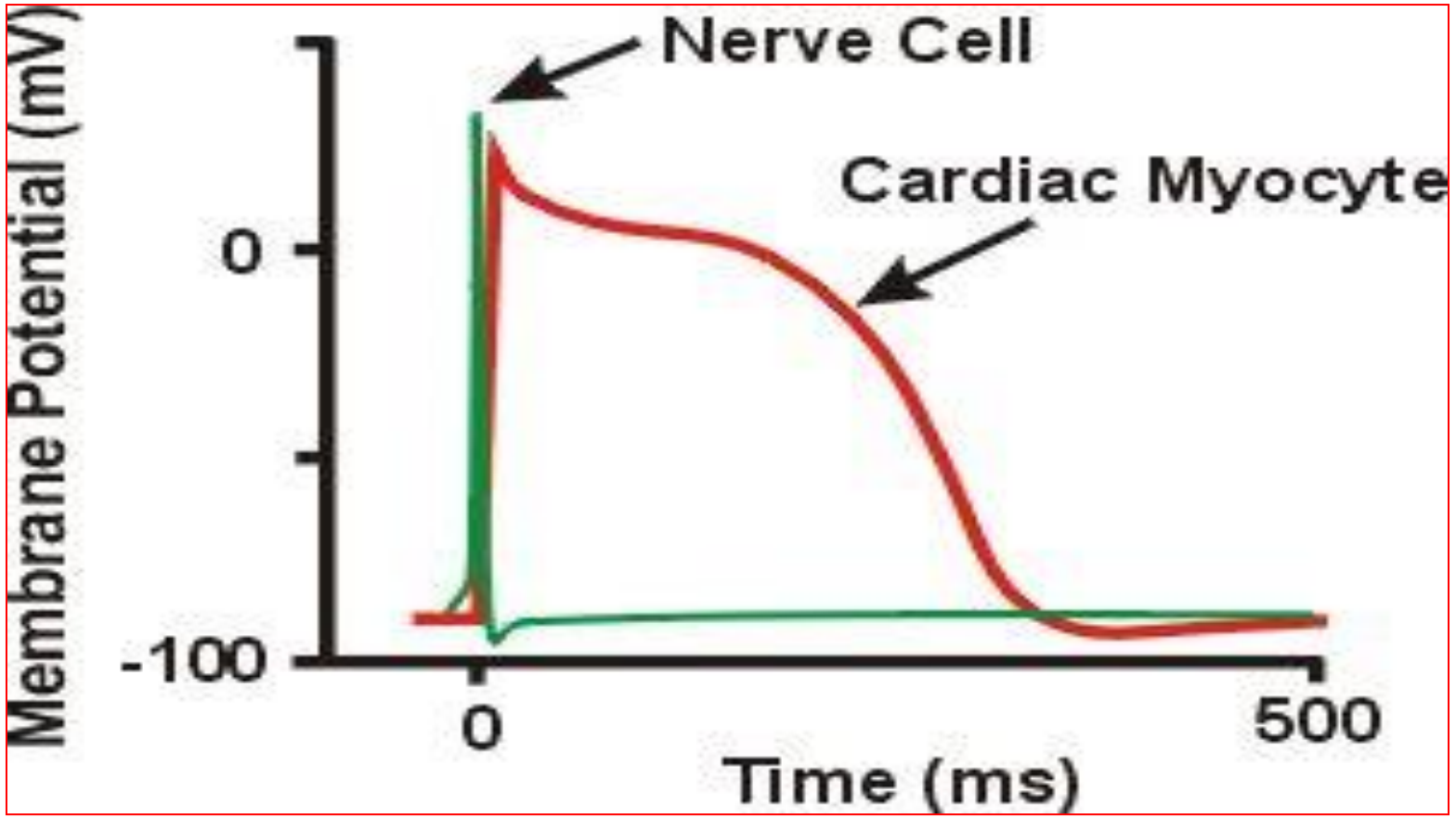
1. Contractile cells (Atrial and Ventricular)
   - 99% of cardiac muscle cells
   - Contract during the cardiac cycle and pump blood
2. Autorhythmic cells: Pacemaker cells
   - Exhibits spontaneous depolarization
   - Do not contract. Known as (conductive system of the heart).
   - Specialized for initiating and conducting action potentials responsible for contraction of atria and ventricle

Conduction system of the heart and spread of electrical activity



(a) Anterior view of frontal section

Action potential in nerve cells and cardiac cells

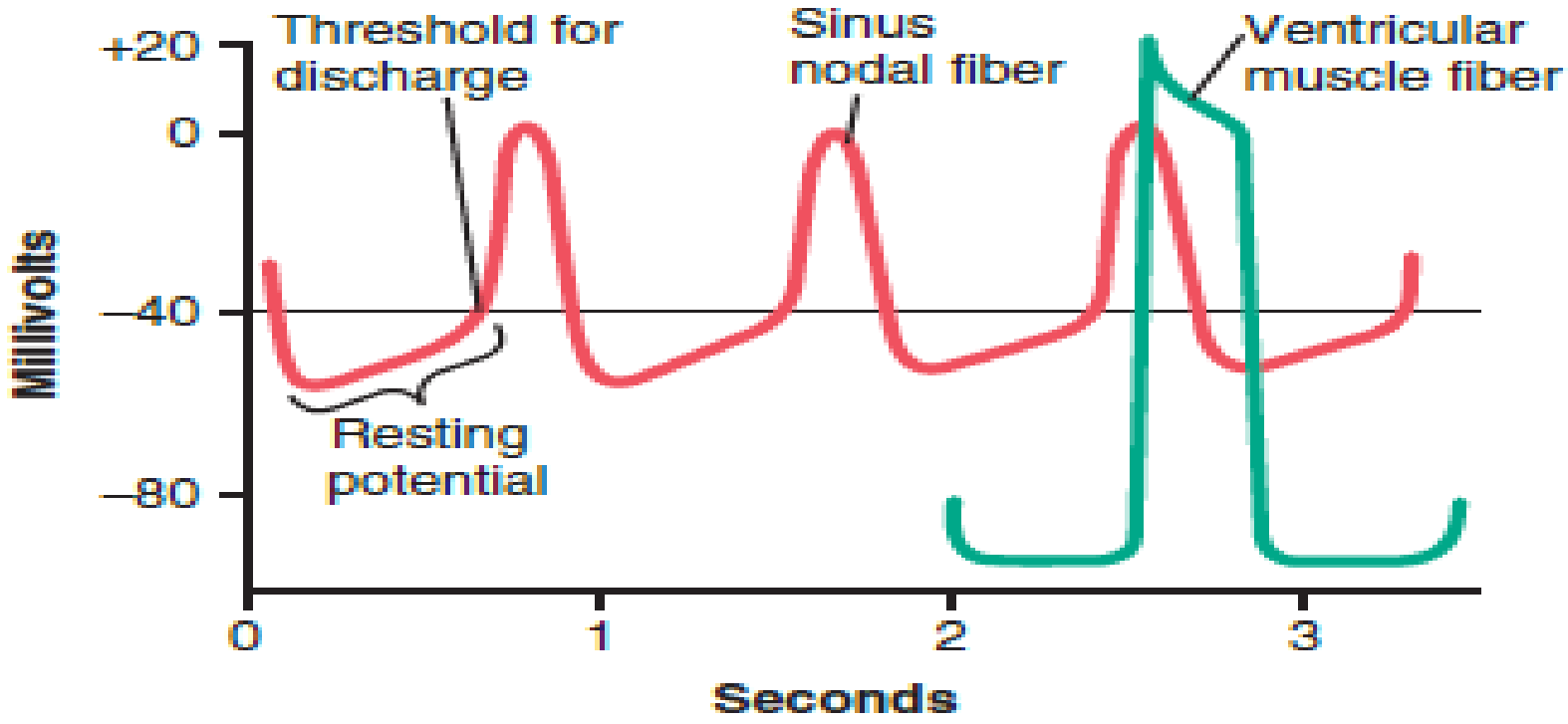


Cardiac Muscles AP

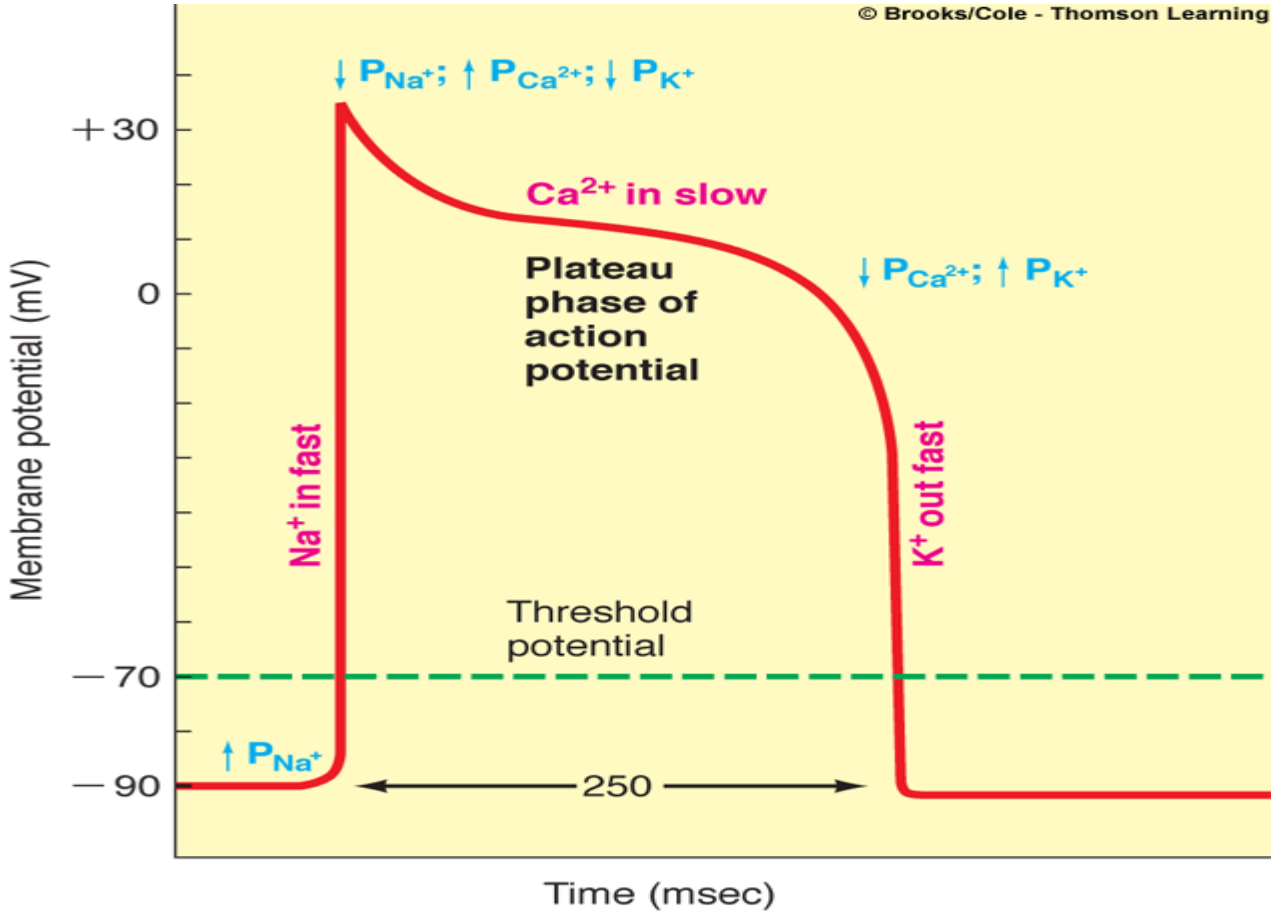
There are two cardiac action potentials produced by myocytes,

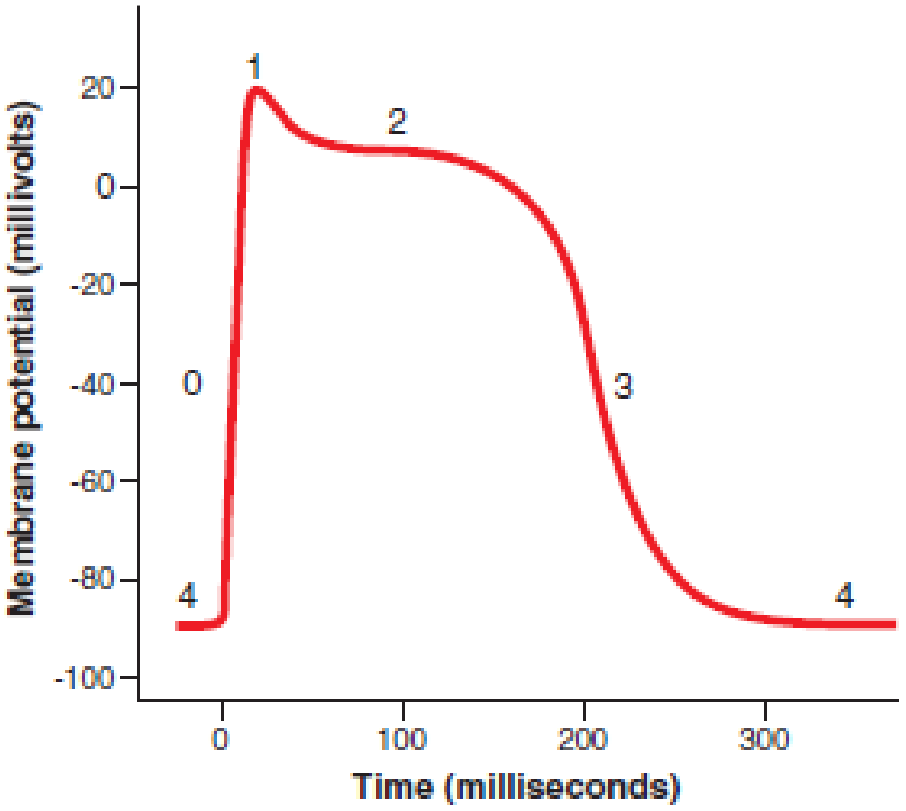
1- Fast AP: is characterized by containing a plateau phase. Usually seen in the normal contractile cardiomyocytes.

2- The Slow AP: As seen in the conductive system (for example SA node and Av node cells



Cardiac action potentials Ventricular and Purkinje system (Intracellular recording)
Phases of action potentials and its ionic basis of action potential





Cardiac Action Potentials of Ventricular Cells

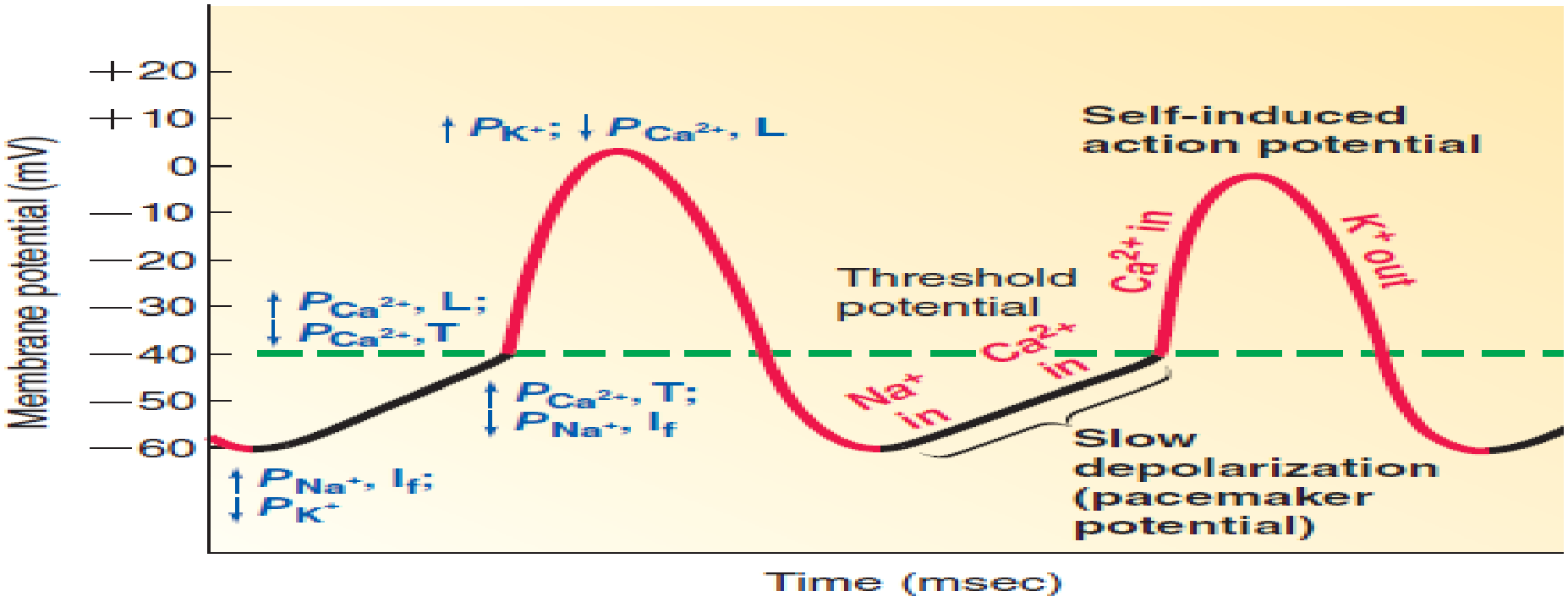
- *Phase 0 (depolarization)*

When the cardiac cell is stimulated and depolarizes, the membrane potential becomes more positive. Voltage gated sodium channels (fast sodium channels) open and permit sodium to rapidly flow into the cell and depolarize it. The membrane potential reaches about +20 millivolts before the sodium channels close

- *Phase 1 (initial repolarization)fast sodium channels close*.
  - The fast sodium channels close, the cell begins to repolarize, and potassium ions leave the cell through the activation fast potassium channels.
- *Phase 2 (plateau)*

  Due to the opening or activation of *L-type calcium channels (slow calcium channels),* which are also called *calcium-sodium channels open and fast potassium channels close*.
- *Phase 3 (rapid repolarization)*
  - *calcium channels close and slow potassium channels open*. The closure of calcium ion channels and increased potassium ion permeability, permitting potassium ions to rapidly exit the cell, ends the plateau and returns the cell membrane potential to its resting level.
- *Phase 4 : (resting membrane potential) averages about −90 millivolts*.

Pacemaker Activity Of Cardiac Autorhythmic Cells
pacemaker potential (prepotential) and action potential of SA node cells



KEY

I_f = Funny channels
T = Transient-type Ca^{2+} channels
L = Long-lasting Ca^{2+} channels

Pacemaker Electrical Activity of Sinoatrial Node (pacemaker potential and action potential)

- **Pacemaker potential**
- The first half of the pacemaker potential is the result of simultaneous opening of unique funny channels, which permits inward Na current, and closure of K channels, which reduces outward K current.
- The second half of the pacemaker potential is the result of opening of T-type Ca ions channels.
- **Action potential**
- Once threshold is reached, the rising phase of the action potential is the result of opening of L-type Ca ions channels, whereas the falling phase is the result of opening voltage gated of K channels

Pacemaker Potential and Action Potential of SA Node Cells Summary

- After hyperpolarization of SA node cells that is caused by activation of K channels , a different channel open that can pass both K and Na is activated
- Because this channel is activated following hyperpolarization, it is referred to as an “h” channel; however, because of its unusual (funny) activation, it has been of this has also been given a nick name (funny channel , f channel)
- As the depolarizing current moves through the h channels increases, the membrane begins to depolarize, forming the first part of the prepotential. Then Transit Ca channels (T Channels are activated
- and completes the prepotential, and the cell reaches the threshold
- At this point L type Ca channels are opened and cause the second depolarization phase of action potential
- Finally, the L type Ca channels close and Voltage gated K channels are activated causing repolarization and slight hyperpolarization

Action Potential in SA and AV node

- The action potentials in the SA and AV nodes are largely due to Ca 2+ , with no contribution by Na + influx. Consequently, there is no sharp, rapid depolarizing spike before the plateau, as there is in other parts of the conduction system and the atrial and ventricular fibers.
- In addition, prepotentials are normally prominent only in the SA and AV nodes.
- However, “latent pacemakers” are present in other portions of the conduction system that can take over when the SA and AV nodes are depressed or conduction from them is blocked.
- Atrial and ventricular muscle fibers do not have prepotentials, and they discharge spontaneously only when injured or abnormal

Thank you for your attention

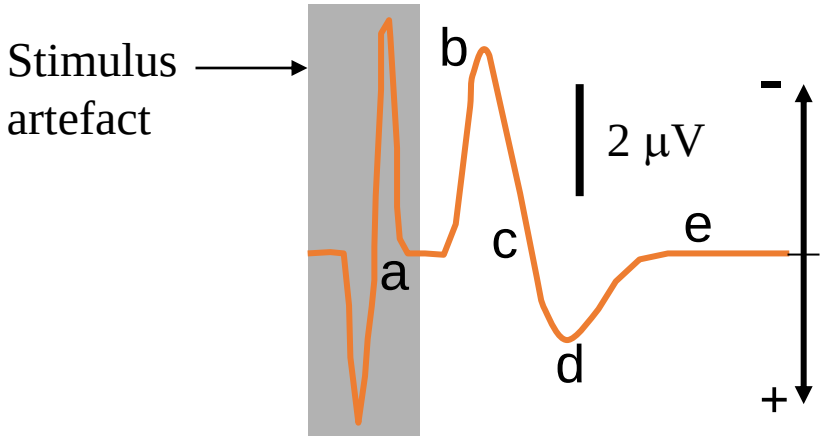
Extra reading for action potential in a nerve truck : Optional reading

- The following two slides are related to recording of electrical activity of nerve truck It gives useful information on conduction velocity of action potentials and more

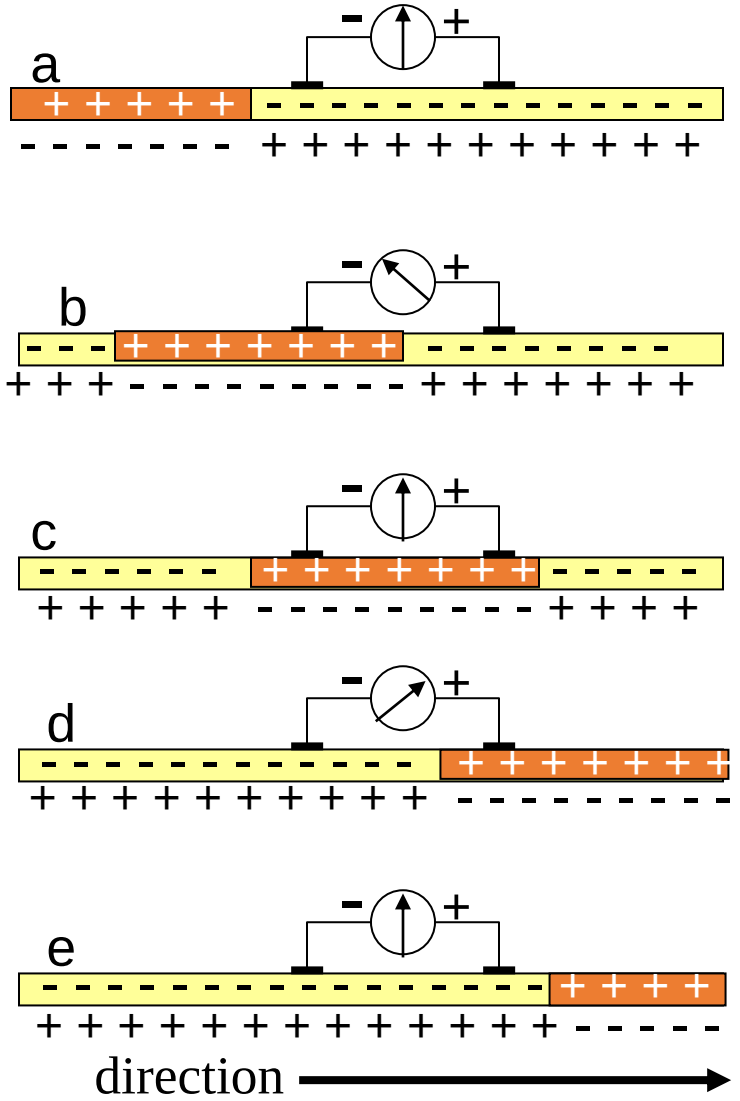
That is the method used in neurology to assess the conduction of sensory and motor fibers

Extracellularly recorded APs

- Most text books show intracellularly recorded action potentials
  - Such recordings are usually not made in clinical practice. Extracellular recordings are made in clinical practice.
  - A so-called '***bi-polar***' action potential is shown

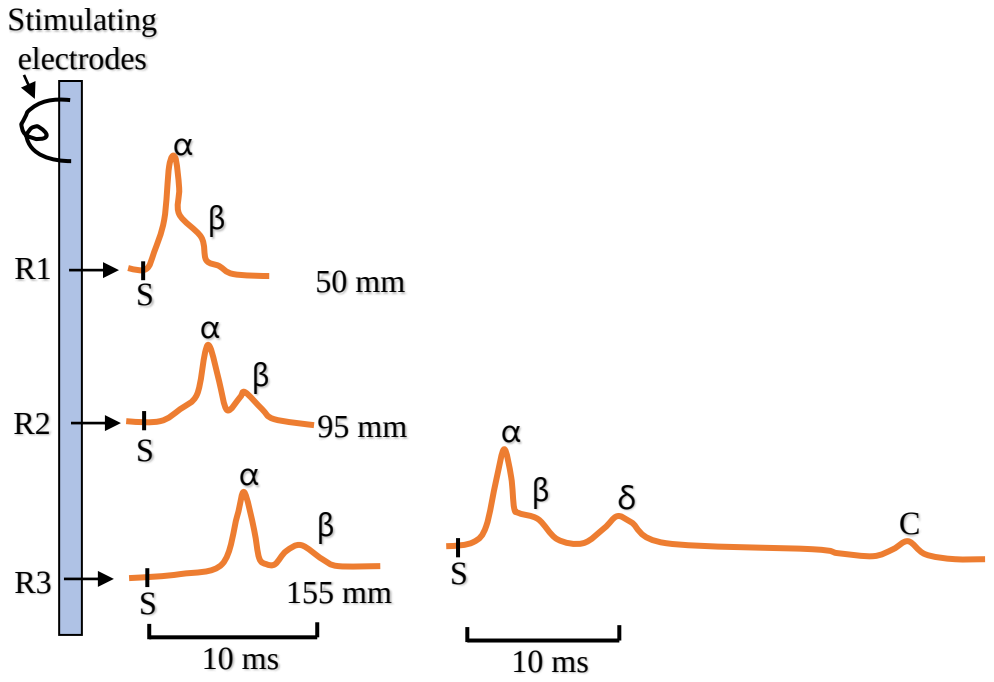


- ***Why does the bi-polar action potential look like this?***



Conduction velocity of AP

- Compound action potentials are recorded from ***nerve trunks***
  - measured percutaneously from nerves that are close to surface (e.g., ulnar nerve)
  - passage of action potentials in all axons of nerves is seen as a small (mV) voltage signal on body surface
  - as recordings are made further from the site of stimulation the waveform develops into several discrete peaks



  - ***The first signal to arrive at a distant recording site has travelled the fastest!***
    - Thus, each peak represents a set of axons with similar conduction velocity
      - velocity is calculated from the distance between R1 and R3 and the time taken to traverse that distance - distance/time = velocity (ranges from 0.5 to ~100 m/s)