INTRODUCTION TO NEUROSCIENCE

UNIT NATS 6001

Lecture 3a- Action potentials initiation and propagation in the nervous system

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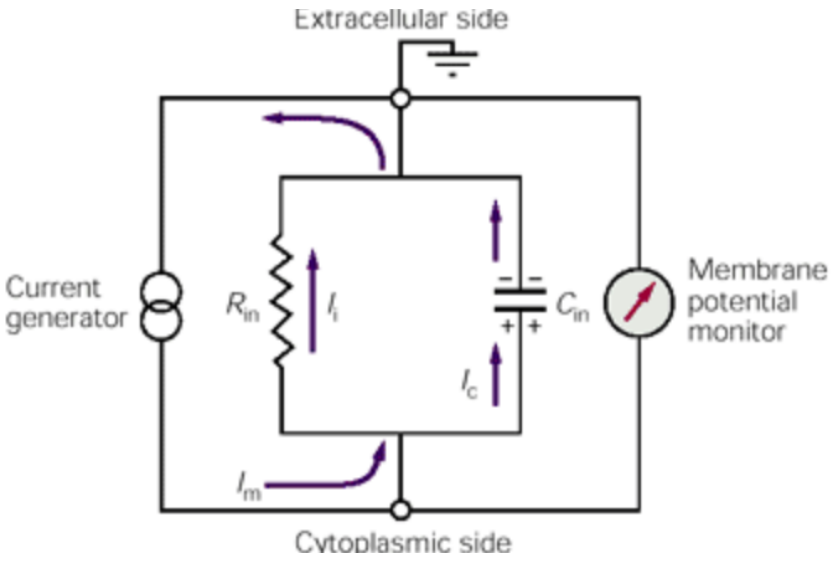
In the previous lecture….

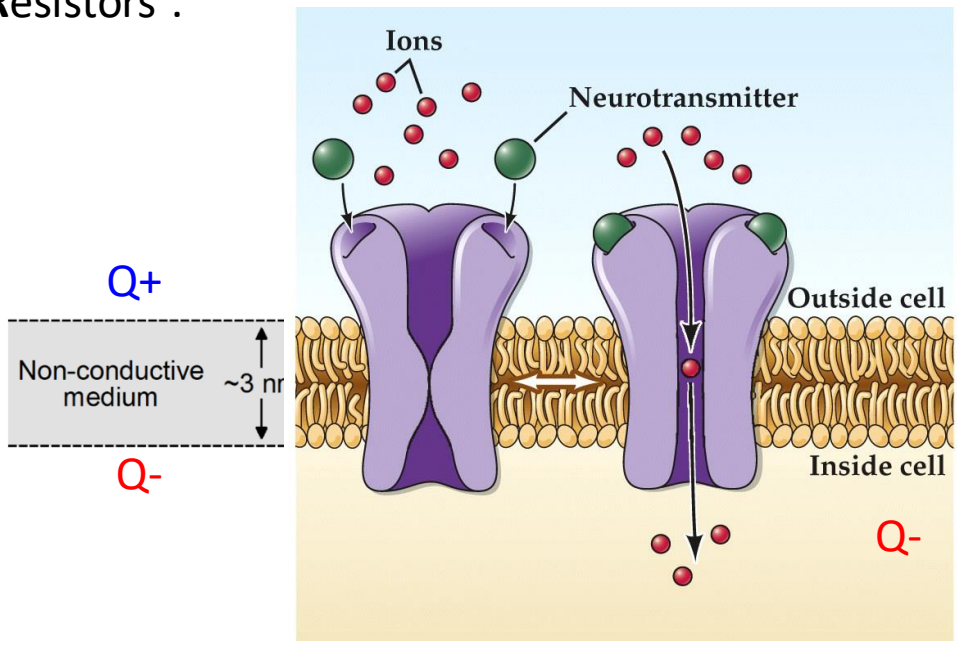
We saw that one way of looking on membranes is as an electrical circuit

Passive membrane properties Equivalent electrical circuit

One way of looking on membranes is as an electrical circuit

The neuronal membrane act as an RC circuit, in which the phospholipid bilayer is the "**C**apacitor" and the ion channels are the "**R**esistors".





An **electric current** is a flow of electric charge. In neurons the electric charge is carried by ions through ion channels, hence resistors

The forces that creates the membrane potential

In neurons, ions move according to their Equilibrium (Nernst) potential.

Electrical force Chemical force

$$E_{ion} = \frac{RT}{zF} \ln \frac{[ion]_{out}}{[ion]_{in}}$$

Walther H. Nernst
1920 – Nobel prize

Equilibrium potential (E_i) - the transmembrane voltage at which the ***electrical gradient (E)*** is equal and opposite to the ***concentration gradient*** for a particular ion (no net ionic flow across the membrane) **.** It is the ion "battery", and the ions will always move towards their ($\mathbf{E_i}$).

where **R** is the gas constant, **T** is the temperature in degrees Kelvin, **z** is the valence of the ionic species, and **F** is the Faraday constant.

Passive membrane properties Equivalent electrical circuit

From Ohm's law $V = IR$ or $I = gV$

A current (I_{ion}) is flowing according to its ***driving force*** and ***conductance*** through the membrane

The ***driving force*** for a certain ion is the difference between the membrane potential (V_m) to its equilibrium potential (E_i), we can write the equation as

Ion conductance

Ion driving force

$$I_{ion} = g_{ion}(V_m - E_{ion})$$

Resting membrane potential (The potential that the ion experience)

Nernst equilibrium potential (Where the ion wants to go)

Passive membrane properties Equivalent electrical circuit

From Kirchhof law, at ***resting membrane potential*** I_m = 0

$$I_K + I_{Na} + I_{cl} = I_m = 0$$

Therefore

$$g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K) + g_{Cl}(V_m - E_{Cl}) = \mathrm{I_m} = 0$$

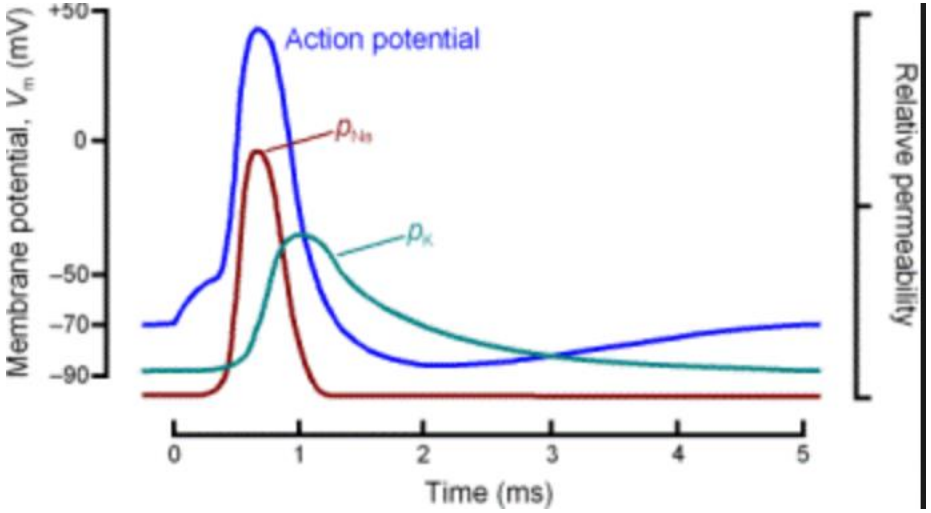
During ***resting state***, the membrane potential is the equilibrium potential of Na, K and Cl multiplied by their relative conductances

$$V_m = \frac{g_{Na} * E_{Na} + g_K * E_K + g_{Cl} * E_{Cl}}{g_{Na} + g_K + g_{Cl}}$$

Resting membrane potential

What would happen if the membrane permeability to Na^+ will increase?

$$V = 58 \log \frac{P_K[K]_2 + P_{Na}[Na]_2 + P_{Cl}[Cl]_1}{P_K[K]_1 + P_{Na}[Na]_1 + P_{Cl}[Cl]_2}$$

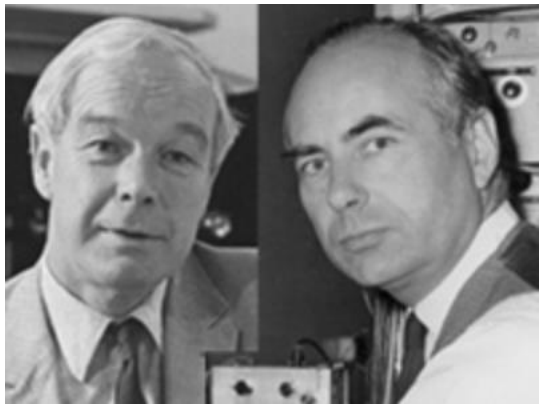


Active membrane properties

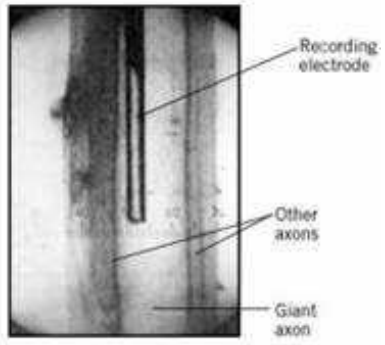
Learning objectives

- Action potentials initiation (H&H) and propagation (the cable theory)
- Electrical and Chemical transmission
- Synaptic transmission

Resting membrane potential



"it's the squid that really ought to be given the Nobel Prize" Hodgkin, A.L., 1973

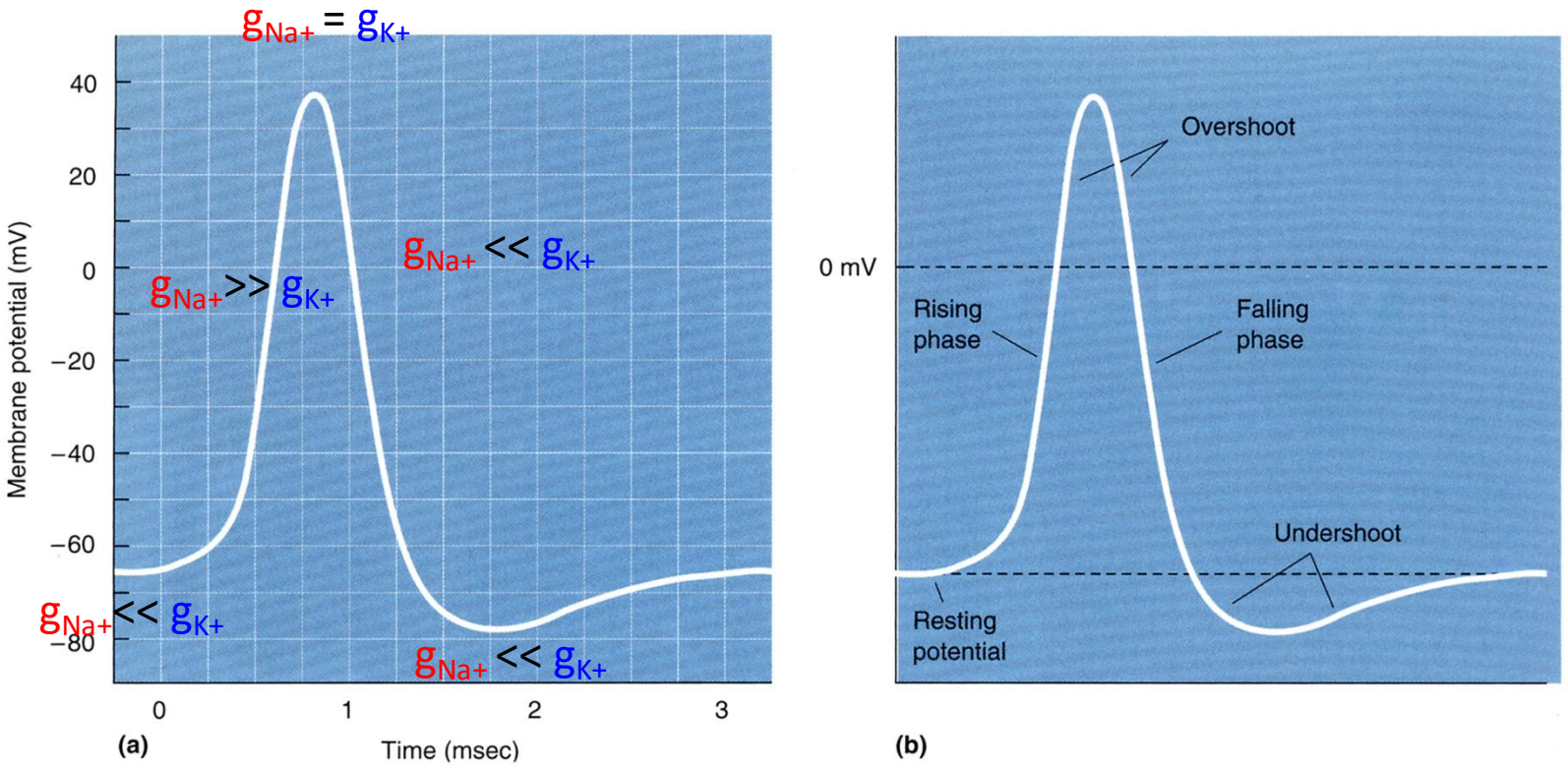


- Alan L. Hodgkin and Andrew F. Huxley first to record **resting membrane potential and action potential** from living neuron using an amplifier at 1939
- Used squid giant axon (0.5 mm in diameter)

Active membrane properties

What is an action potential

An **action potential** is a short-lasting event in which the electrical membrane potential of a cell rapidly rises and falls, following a consistent trajectory. There are 4 phases during action potential, and in each one of them the relative conductance of Na^+ and K^+ is changing

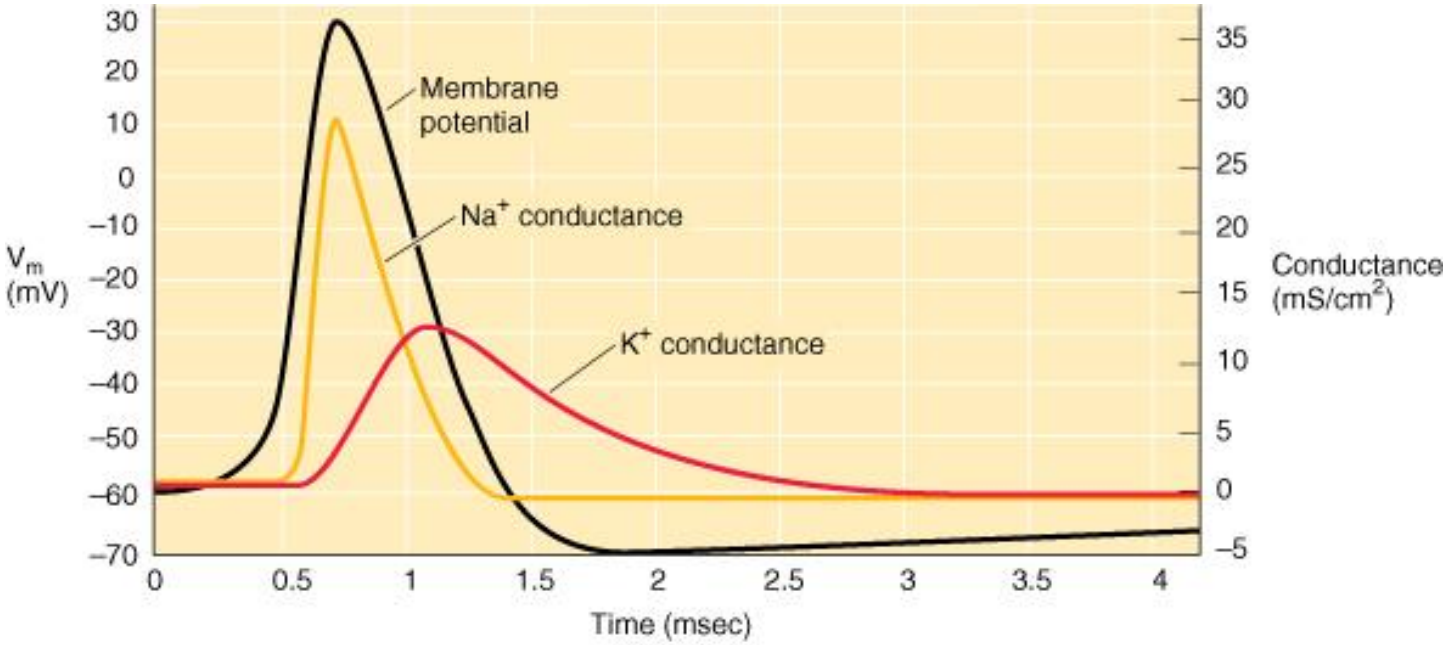


Active membrane properties action potential

Generation of action potential according to H&H

Depolarization through receptor potentials activates fast voltage-gated Na^+ channels, causing Na^+ influx into the cell, which is driven by the electrochemical gradient. The ***rapid increase in Na^+ conductance*** is followed by a ***slower K^+ conductance*** that repolarize the membrane potential to resting values.

Much of the change in membrane potential during an action potential can be explained by the Na^+ current



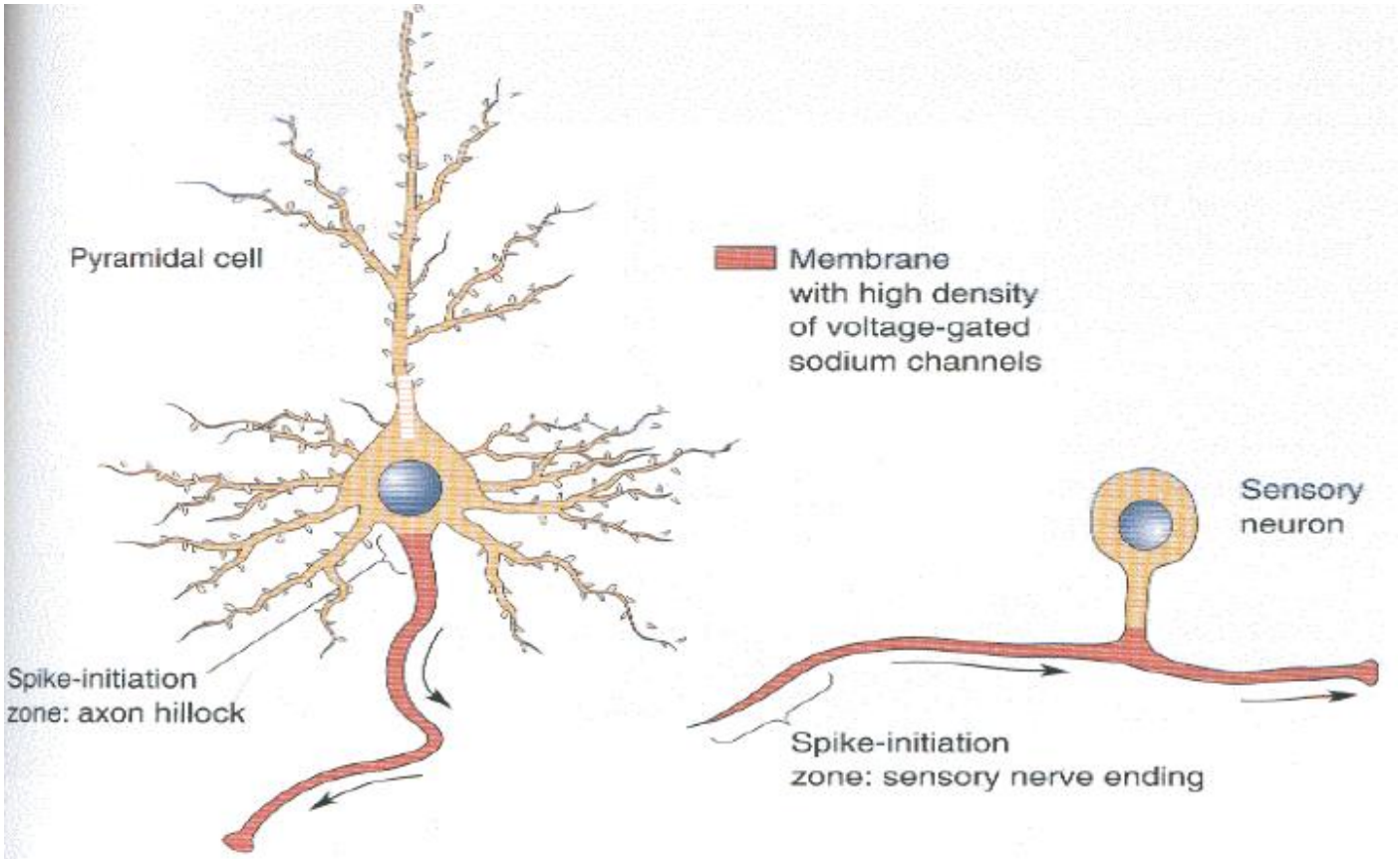
Active membrane properties action potential

Questions about action potentials-

Where is the action potential initiating and why?
What is the functional significance of the action potential?
Can it be regulated?

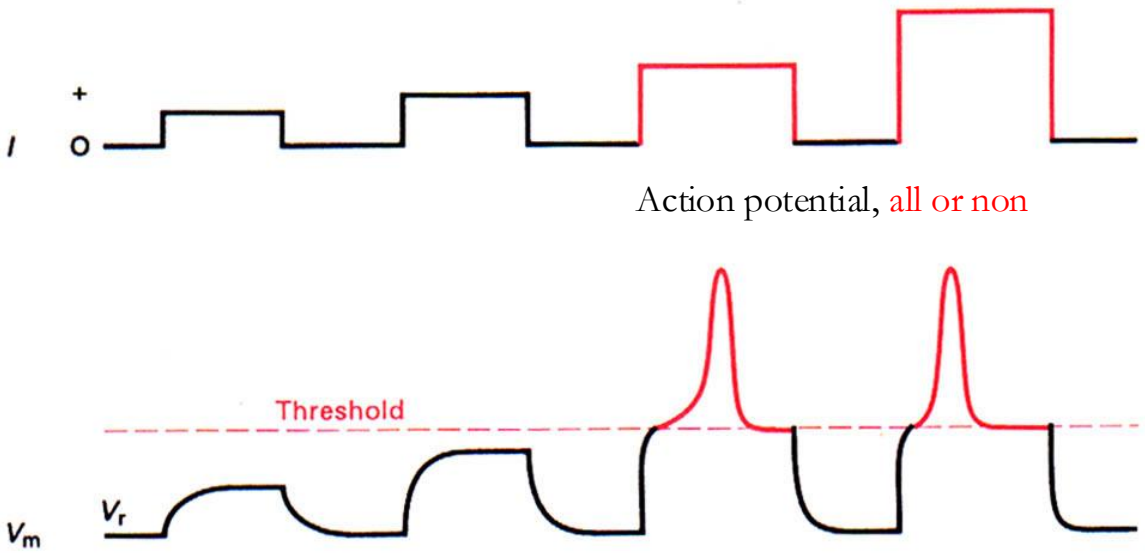
Active membrane properties action potential

Action potentials usually start at the ***Axon Hillock*** (or Axon Initial Segment) ***AIS*** where the ***voltage gated Na^+ channels*** density is much higher relative to other cell compartments



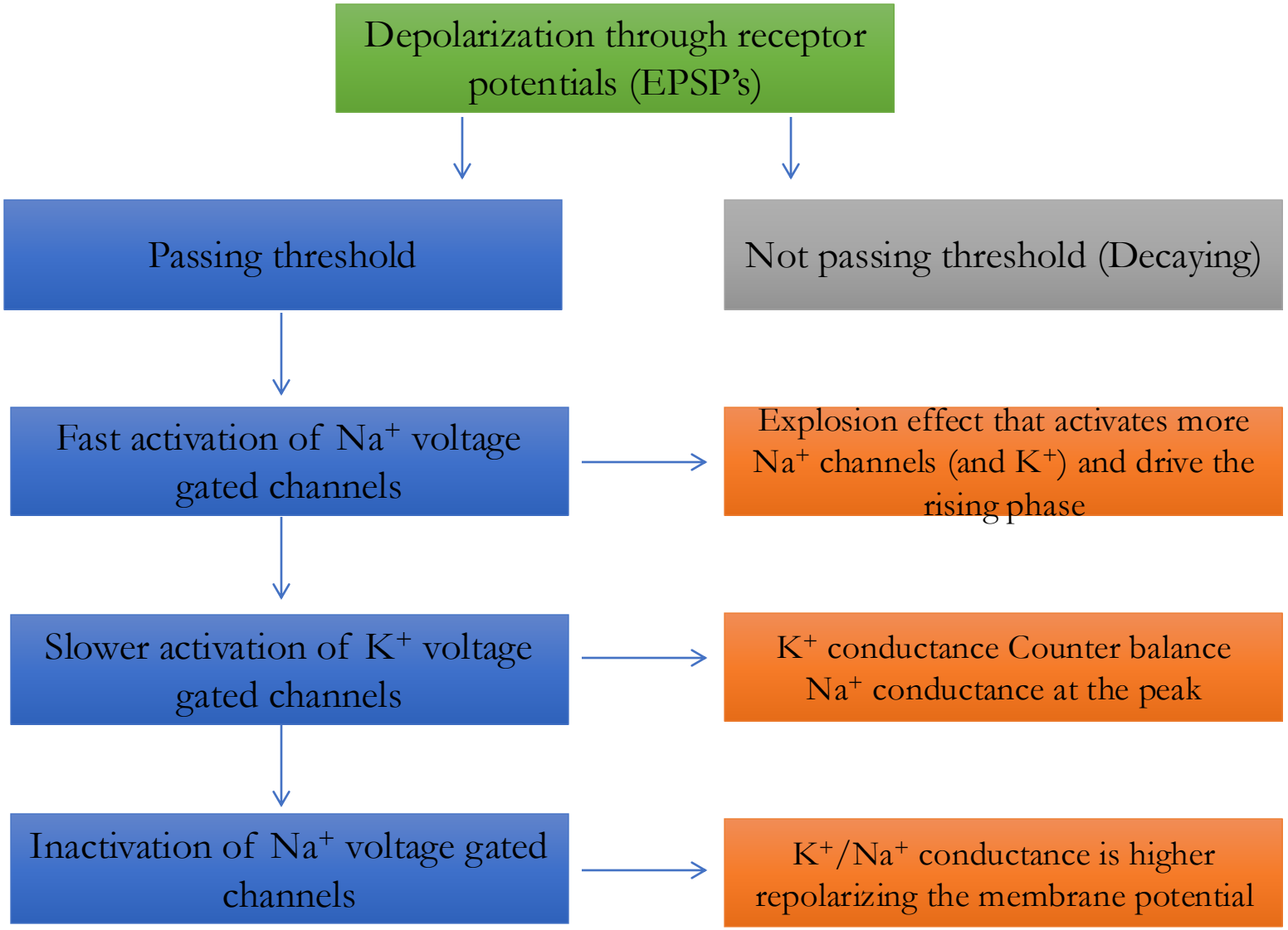
Active membrane properties action potential

- Action potentials are said to be ***all-or-none*** signals, since either they occur fully or they do not occur at all.
- The amplitude of an action potential is independent of the amount of current that produced it.
- larger currents do not create larger action potentials.
- Once generated, action potentials typically propagate along the entire length of a nerve fiber without attenuation



Action potential, all or non

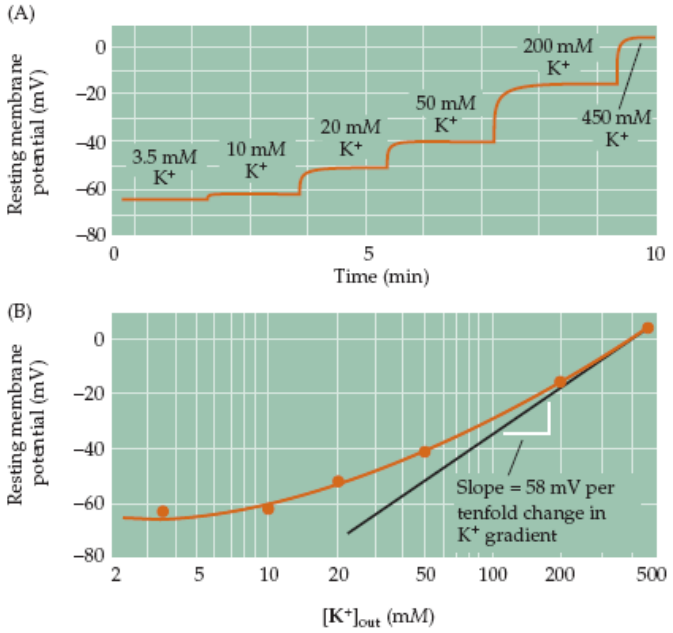
Active membrane properties action potential



Active membrane properties action potential

Experimental evidence

Although the ***resting potential*** depends mostly on potassium concentration



Active membrane properties action potential

The ***action potential*** depends mostly on sodium conductance

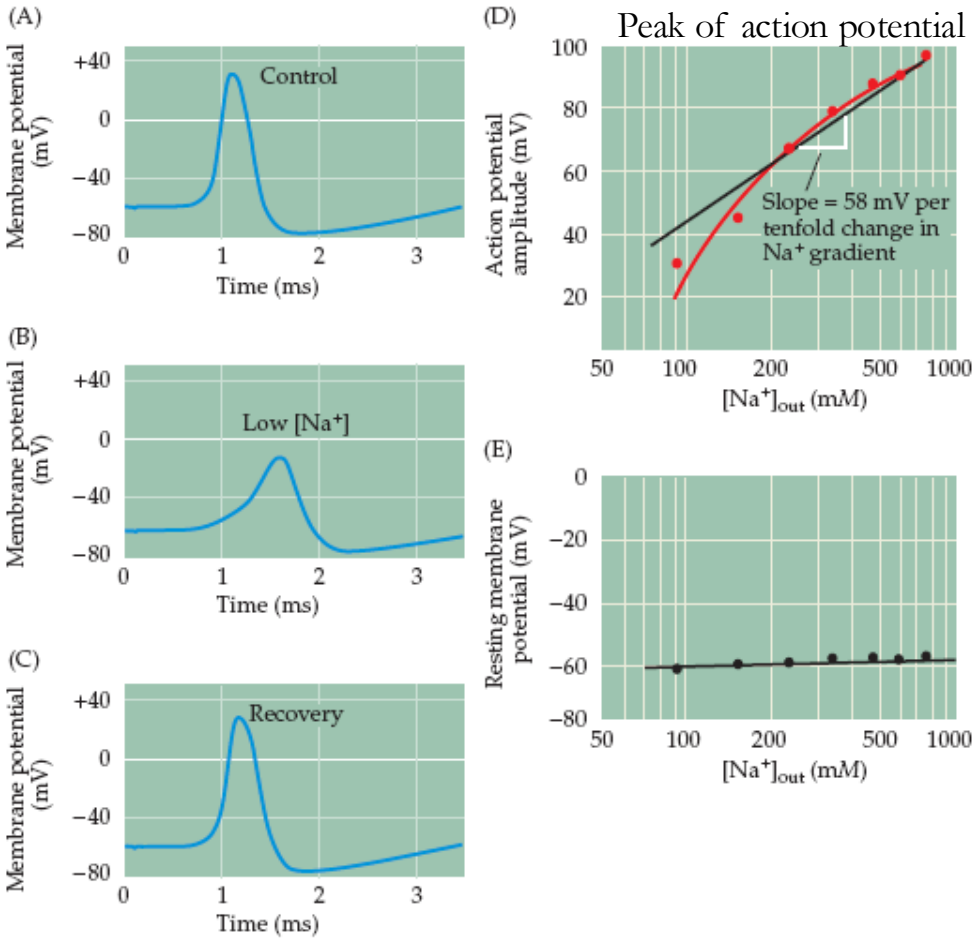
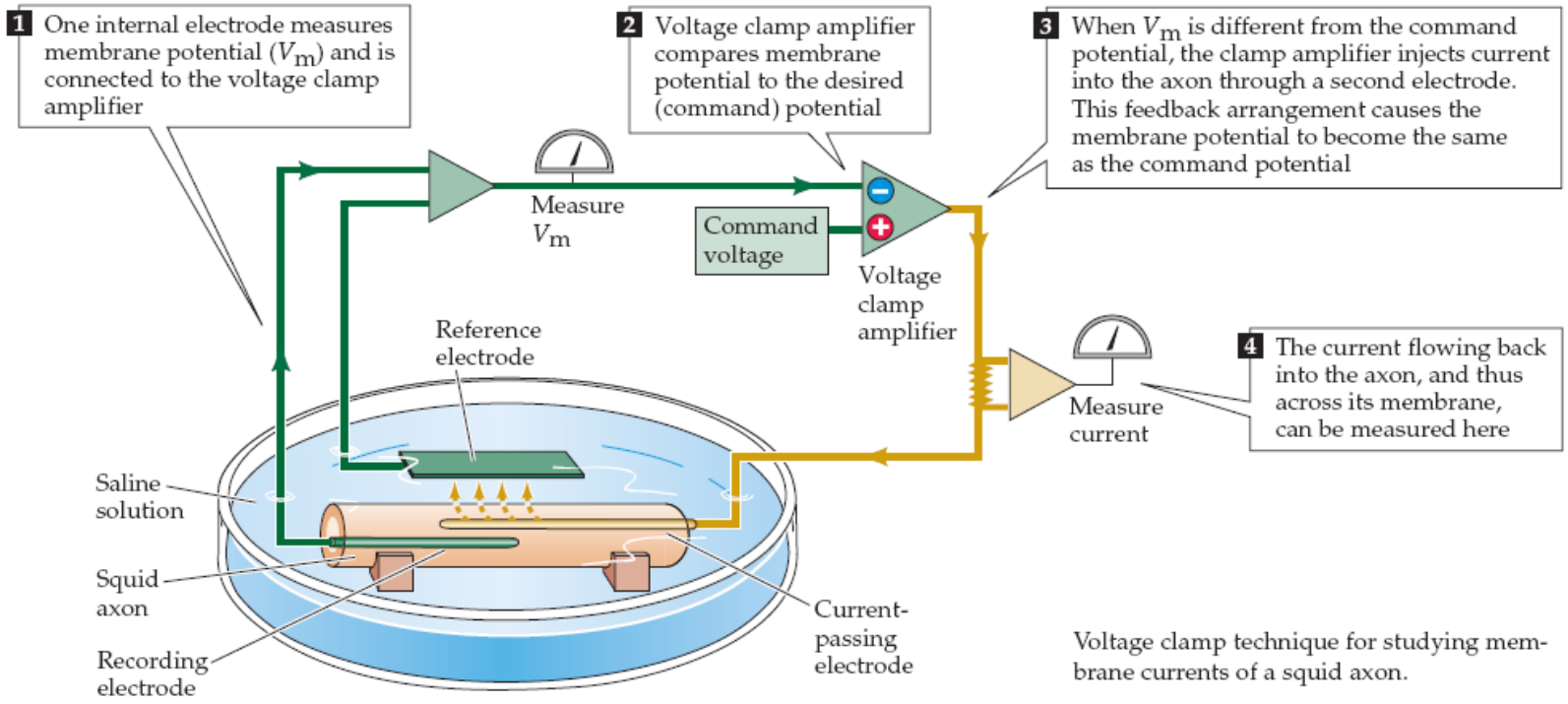


Figure 2.8 The role of sodium in the generation of an action potential in a squid giant axon. (A) An action potential evoked with the normal ion concentrations inside and outside the cell. (B) The amplitude and rate of rise of the action potential diminish when external sodium concentration is reduced to one-third of normal, but (C) recover when the Na^+ is replaced. (D) While the amplitude of the action potential is quite sensitive to the external concentration of Na^+, the resting membrane potential (E) is little affected by changing the concentration of this ion. (After Hodgkin and Katz, 1949.)

Active membrane properties action potential

The preparation and recording method of Two electrode voltage clamp



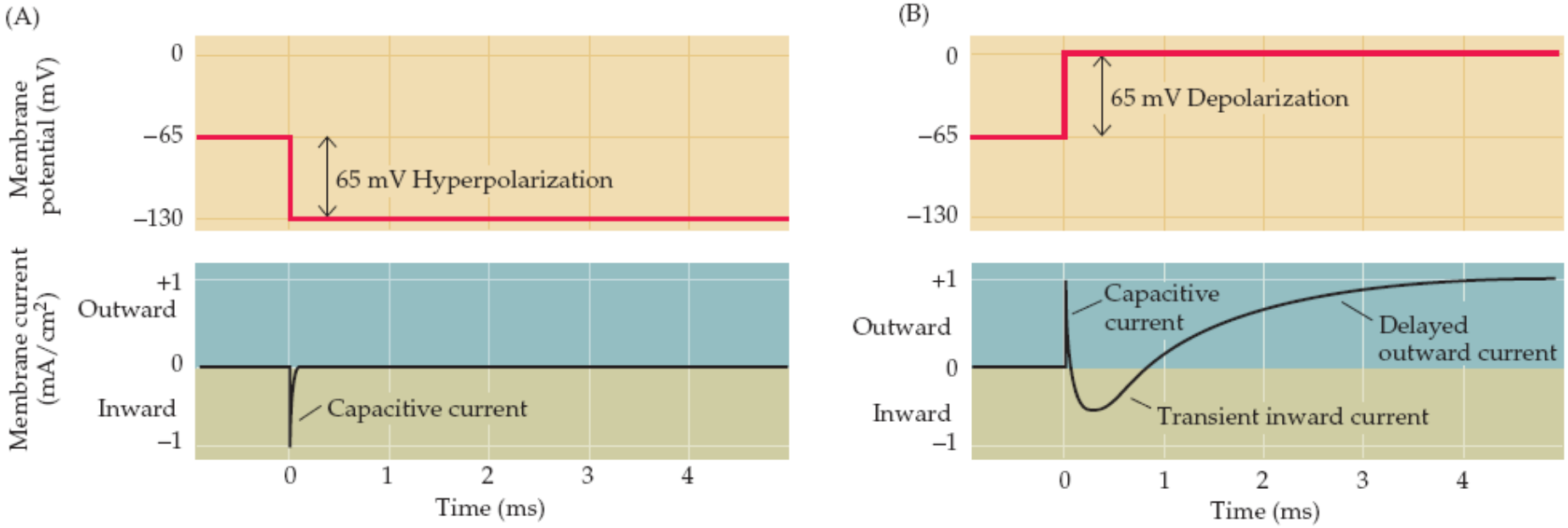
Voltage clamp technique for studying membrane currents of a squid axon.

Voltage clamp was invented by Kenneth Cole and George Marmount in the 1940's

Active membrane properties action potential

H&H reports that:

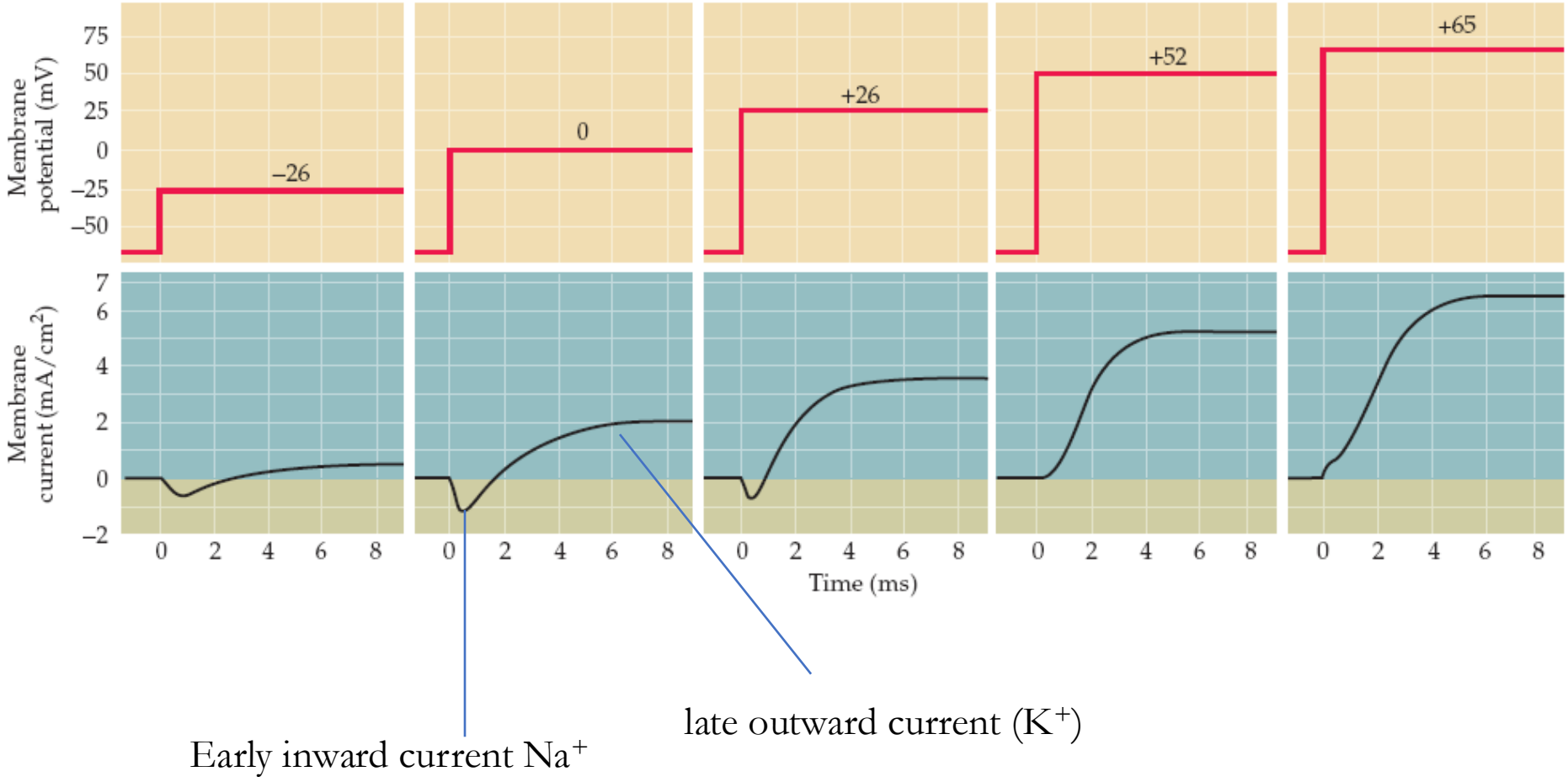
Depolarization (under voltage clamp) results with ***early inward current*** followed by ***delayed (late) outward current***.



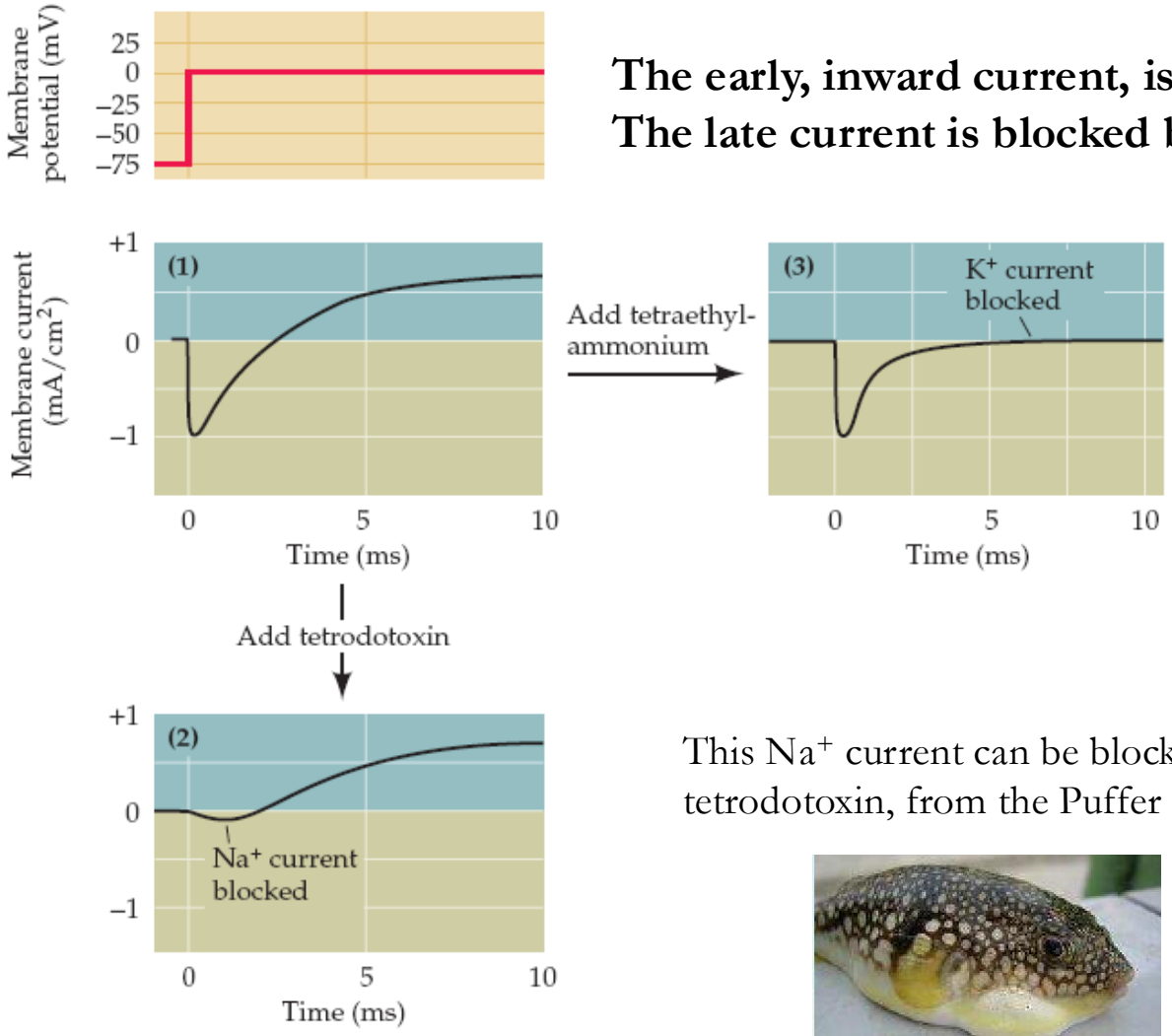
Active membrane properties action potential

Inward and outward currents are voltage dependent:

The inward current reversed at +55 mV, which is exactly as expected from the Nernst potential of Sodium for the squid giant axon (out: 440 mM) and (in 40 mM)



Active membrane properties action potential



The early, inward current, is blocked by tetrodotoxin (TTX)
The late current is blocked by tetramethylammonium (TEA)

This Na^+ current can be blocked by the poison tetrodotoxin, from the Puffer fish (*fugu*)

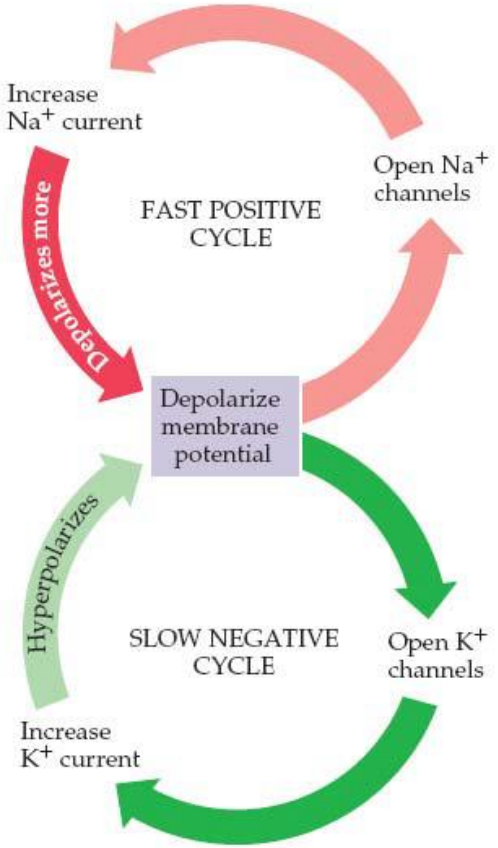
Active membrane properties action potential

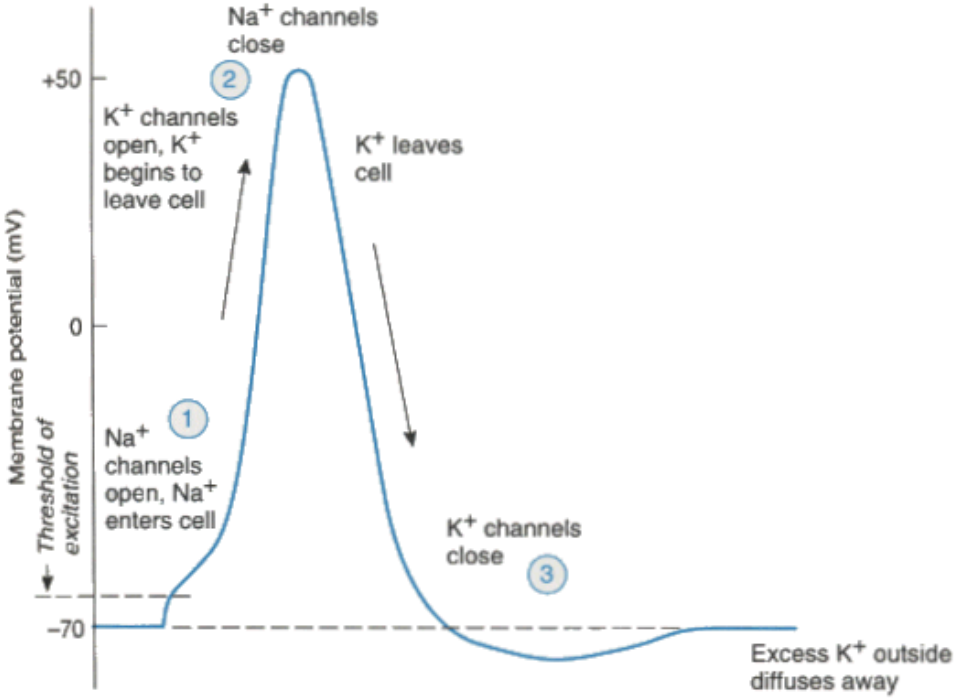
H&H experiments showed that the currents involved in the generation of the action potential are Inward Na+ current and outward K^+ current.

They have measured the activation and inactivation of Na^+ and K^+ channels to test the impact of there kinetic on the action potential and came with the Hodgkin-Huxley model.

Active membrane properties action potential

Hodgkin – Huxley model consist of fast positive Na^+ cycle and slow negative K^+ cycle

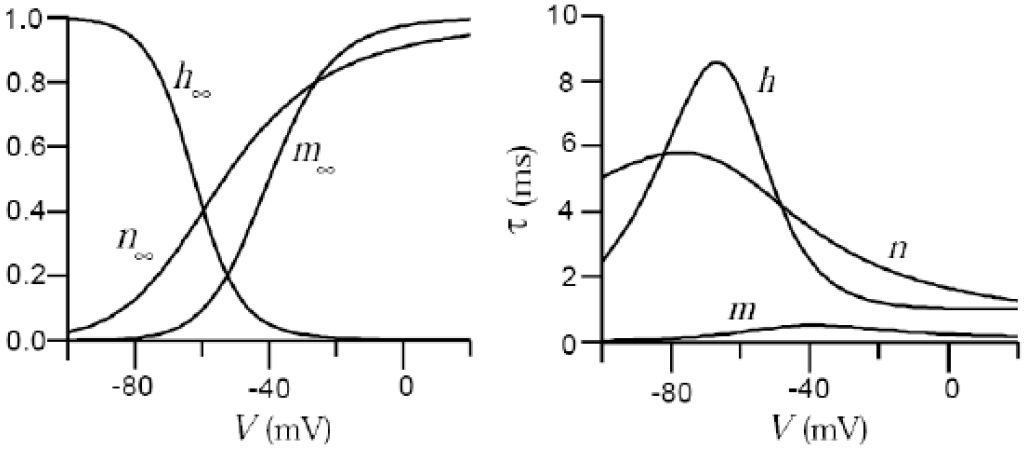




Active membrane properties action potential

The full Hodgkin Huxley model – spike generation

Current flows in, raises V
→ m increases (h slower to react or closed) → g_{Na} increases
→ more Na current flows in → ...more depolarization..
→ V rises rapidly toward reversal potential of V_{Na}
Then h starts to decrease → g_{Na} shrinks
→ V falls, aided by n opening for K current
Overshoot, recovery

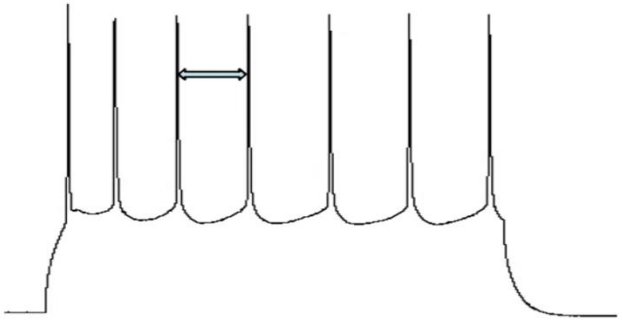


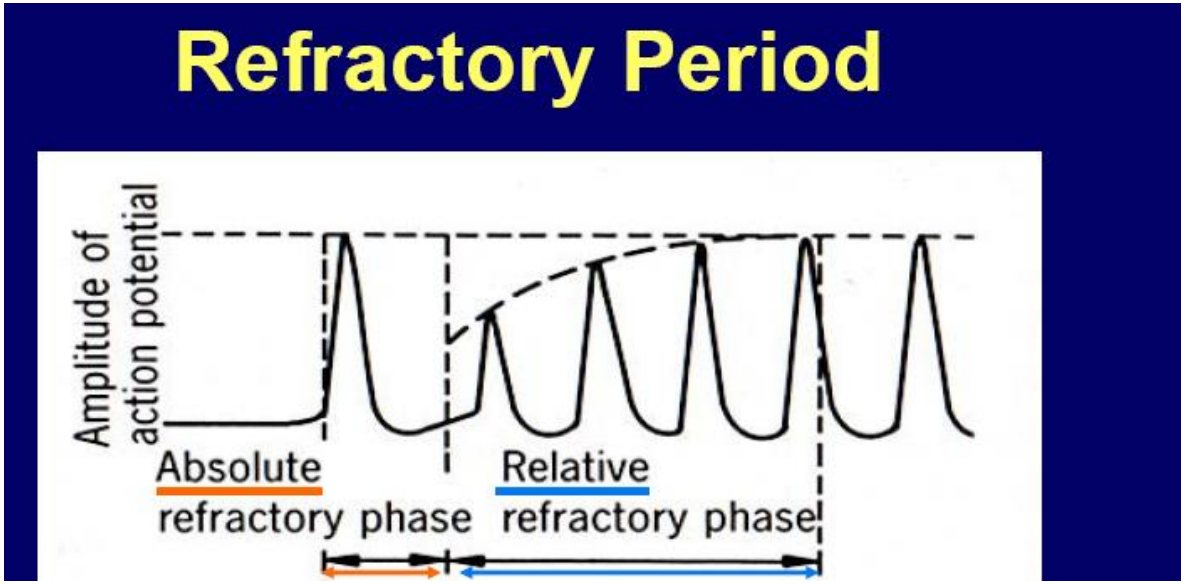
Active membrane properties action potential

What happens after a spike?

What will happen if we will give a long-lasting stimulus?

Active membrane properties action potential





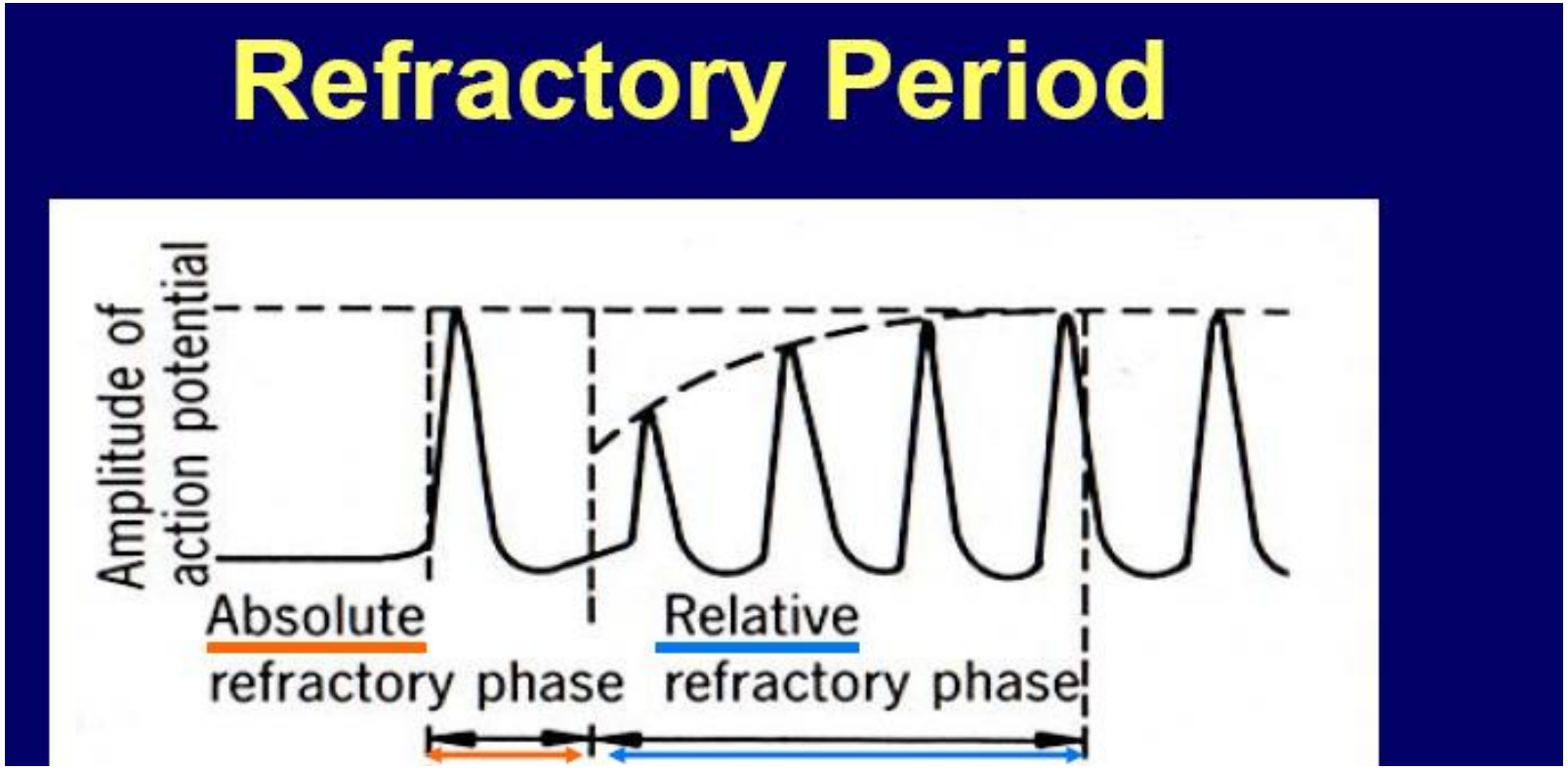
Active membrane properties action potential

Action potential "Refractory period"

For a short period after the passage of a spike, the **threshold** for stimulation is raised, such that if a neuron is stimulated twice in quick succession, it **may not respond** to the second stimulus.

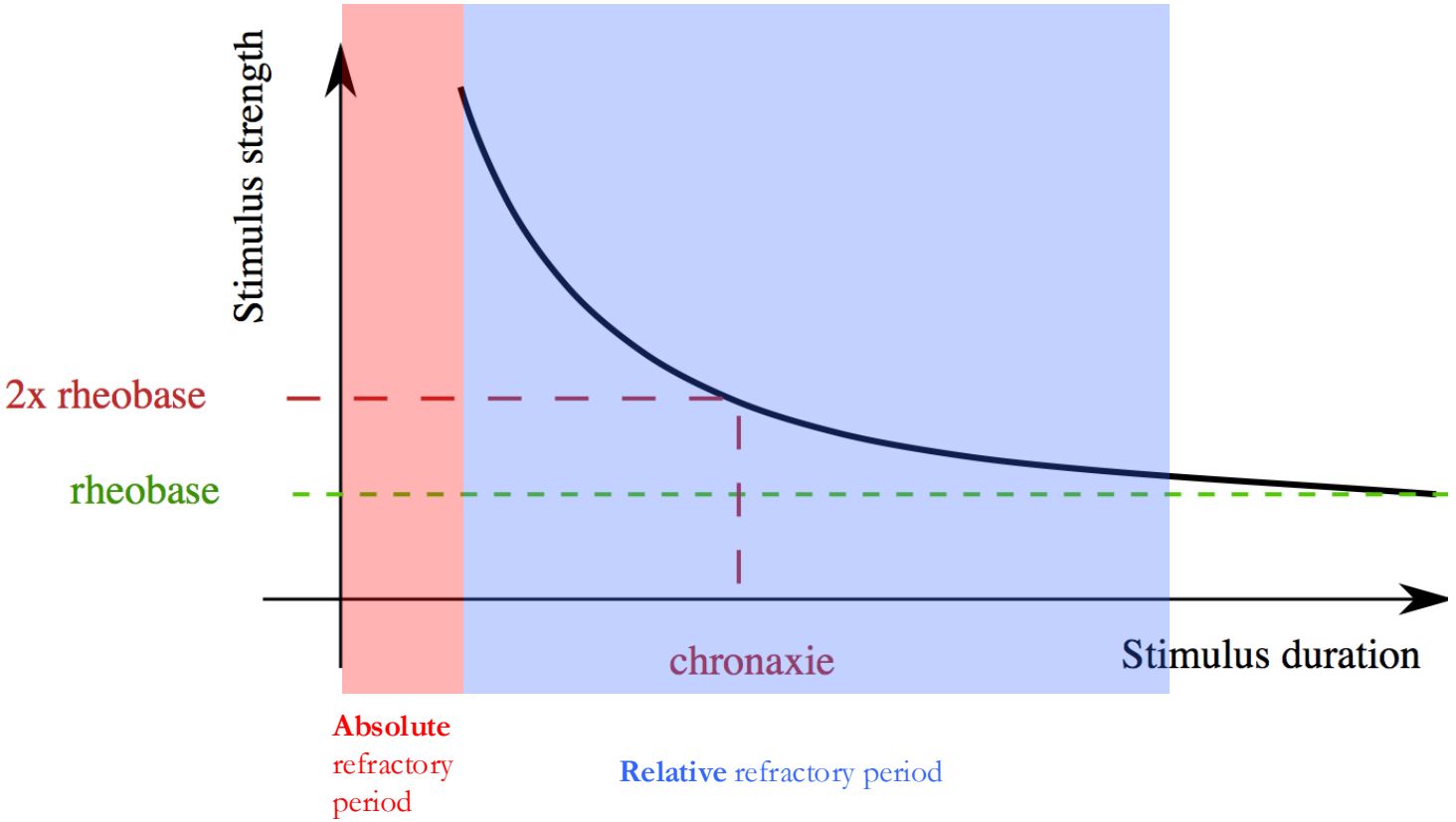
The **inactivation of Na^+ channels** and the delayed increase in K^+ conductance are the underlying ionic conductance changes which can explain the refractory period.

Active membrane properties action potential

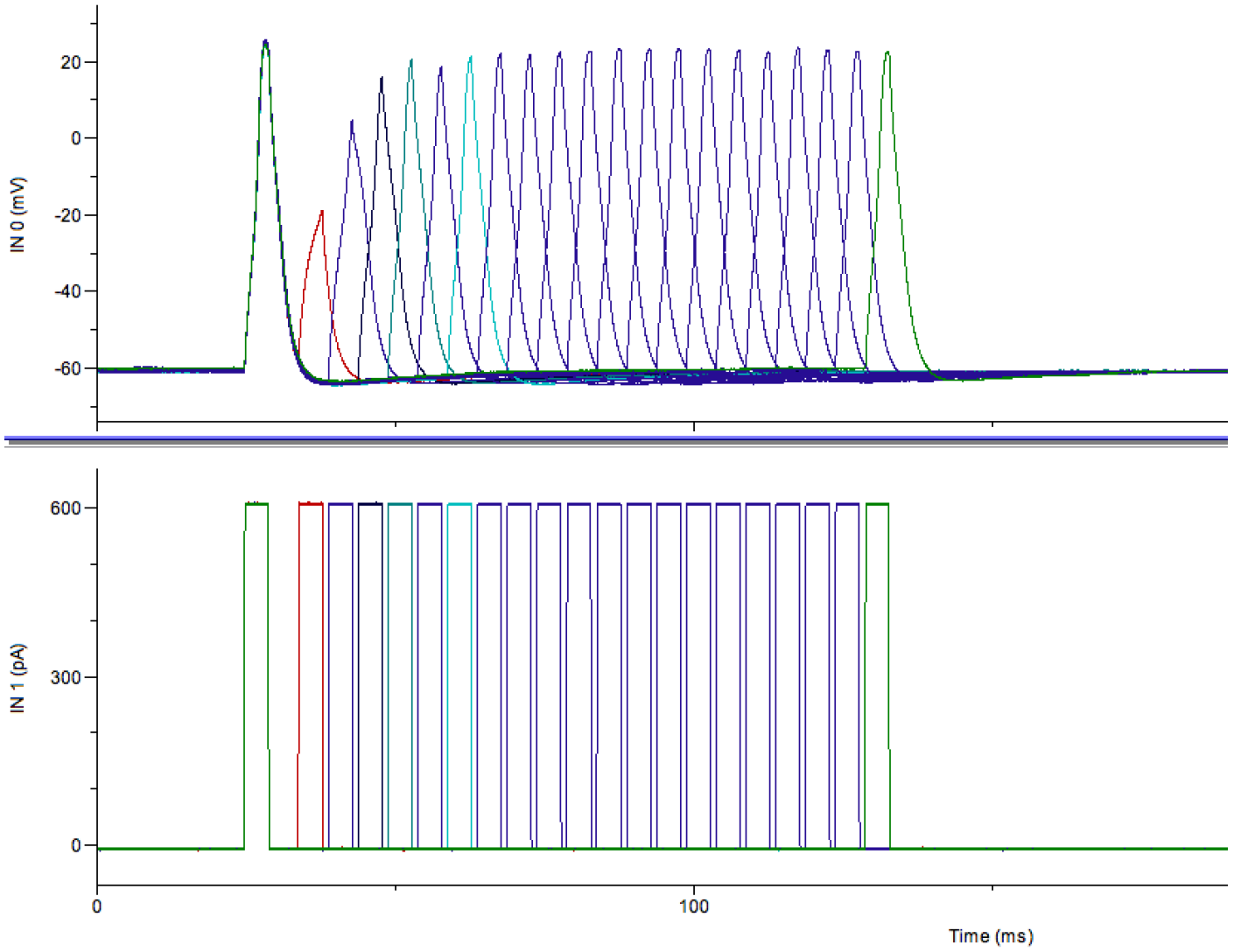


Active membrane properties action potential

Strength-duration curve for stimulus of an excitable tissue



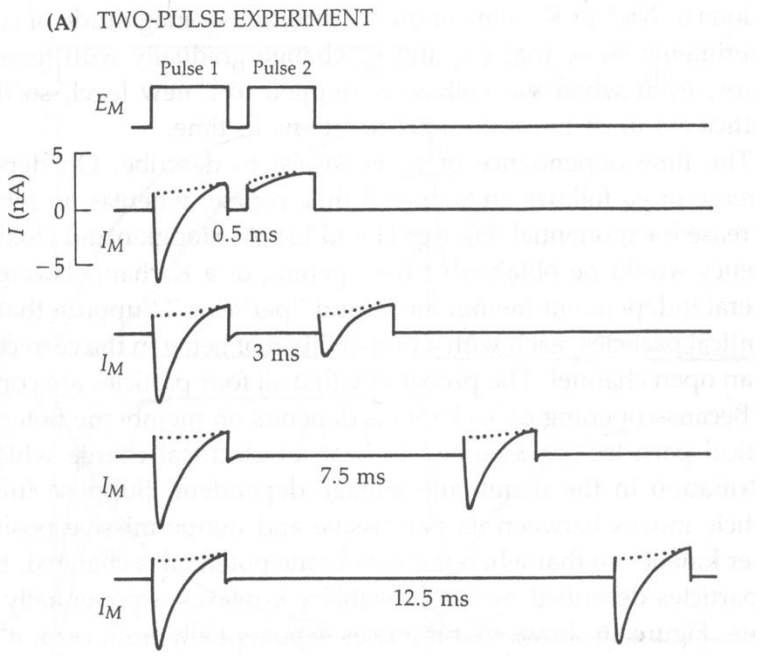
Action potentials refractory period



Action potentials refractory period

The main effectors on the refractory period are:

1) **inactivation of Na^+ channels**
2) **Delayed increase in K^+ conductance**



Action potentials refractory period

Summary – Refractory period

For a short period after the passage of a spike, the threshold for stimulation is raised, such that if a neuron is stimulated twice in quick succession, it may not respond to the second stimulus.

The inactivation of Na^+ channels and the delayed increase in K^+ conductance are the underlying ionic conductance's which can explain the refractory period.

The absolute refractory period is the brief interval after a successful stimulus when no second stimulus, however maximal, can elicit another response.

The absolute refractory period is followed by the relative refractory period, during which a second response can be obtained if a strong enough stimulus is applied.

Action potentials refractory period

The refractoriness of a nerve after conducting an impulse sets an upper limit to spike frequency.

The maximal frequency at which an axon can conduct impulses is limited by the **absolute refractory period** of the axon (~1 ms), within which the axon is inexcitable

The absolute refractory period for myelinated axons is ~1 ms, for unmyelinated axons it is ~2 ms

Active membrane properties

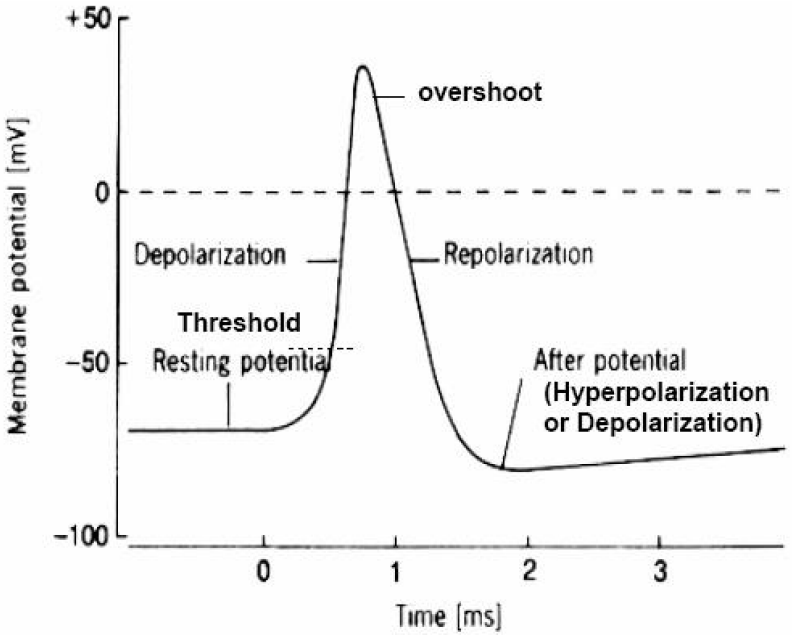
Neurons are excitable cells:

Their resting membrane potential can be modified by **excitatory** or **inhibitory** drive from other neurons.

In general:

Excitation moves the resting membrane potential towards spike threshold (depolarization)

Inhibition makes the resting membrane potential more negative *(hyperpolarization)* and further from spike threshold

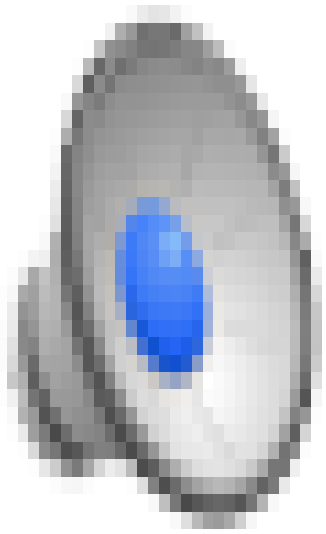


Excitability is defined as ***1/threshold current***, hence the more current one needs to excite a membrane, the less excitable it is**.**

Accommodation defined as a change in the membrane excitability.

The cable theory

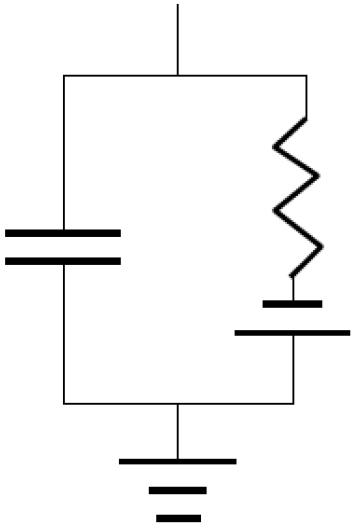
How action potentials propagate along the axon?



The cable theory

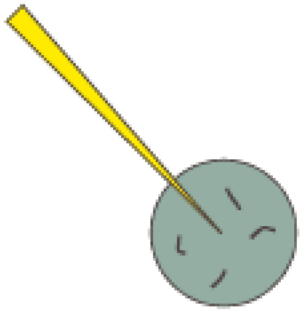
Till now we considered neurons as

Spherical, isopotential and ***single compartment*** point neurons



$G_m = 1/R_m$

E_m ("resting potential")

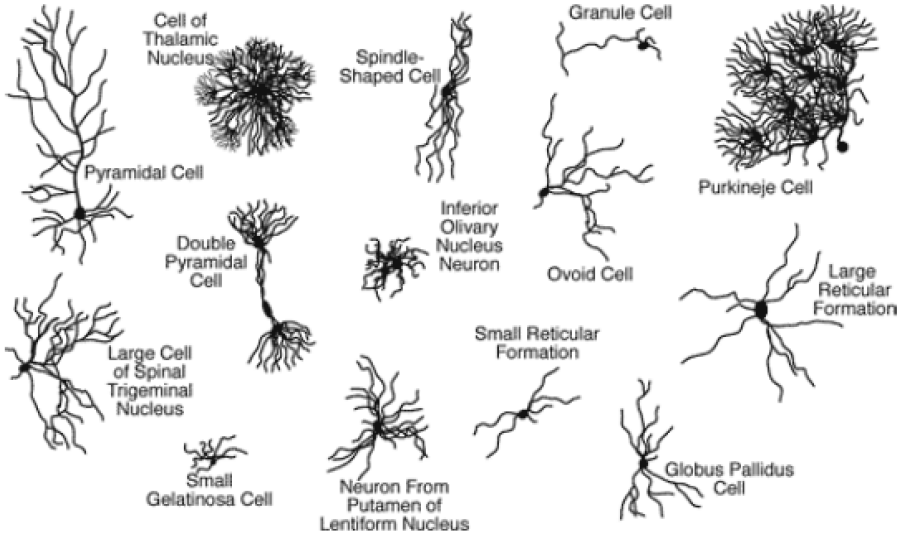


But this is not a realistic picture of a neuron…even when considering the passive properties.

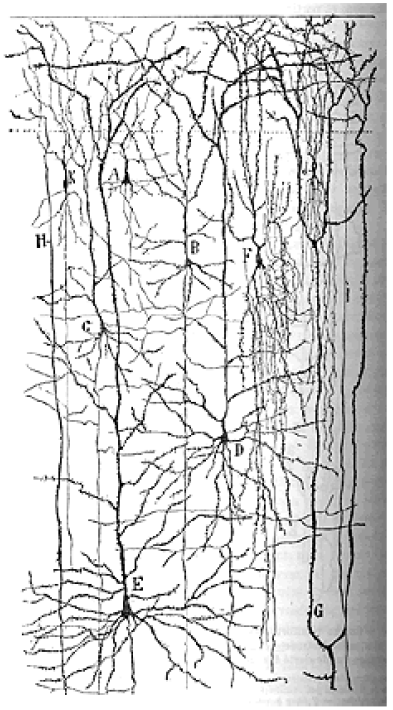
The cable theory

Real neurons have long dendritic processes with multiple divisions and in the shape of cylinder

Dendrites

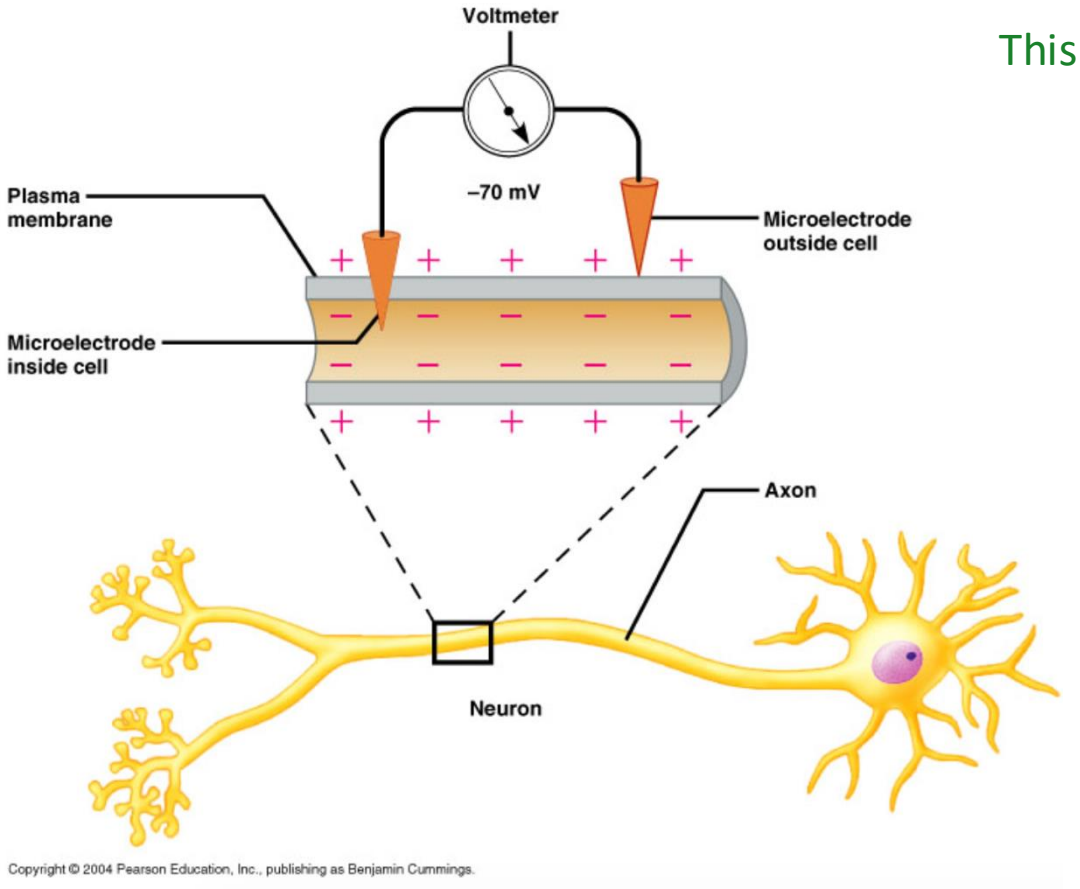


Based on drawings made by Cajal

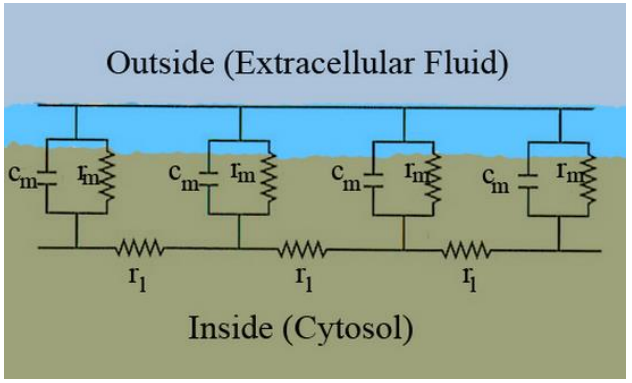


The cable theory

How the shape of neurons impact the propagation of the electrochemical signals?
How the signals will look after passing through long dendrites? Say from distal synapse to soma?



This is the origin of the cable theory

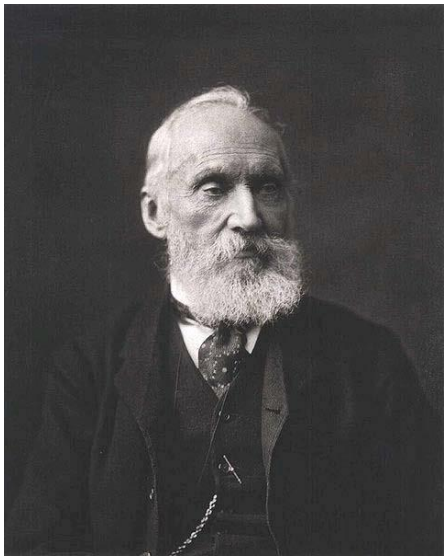


Multiple RC circuits connected

The cable theory history

*'In order to understand how signals are transmitted from one place to another in the nervous system it is essential to know how they are **generated** in individual neurons and how they **spread** from one region of the cell to the next.'*

- In the 1850s it was developed by William Thomson (Baron Kelvin), for deep water telegraph lines.
- Was further developed and applied for neurons by Hermann an Kremmer during early 20th century
- Was experimentally tested by Kenneth Stewart Cole, Sir Alan Lloyd Hodgkin, and Rushton during the 20^{s} and 30^{s}.
- Perfected by willfrid Rall during early 60's



William Thomson

The cable theory

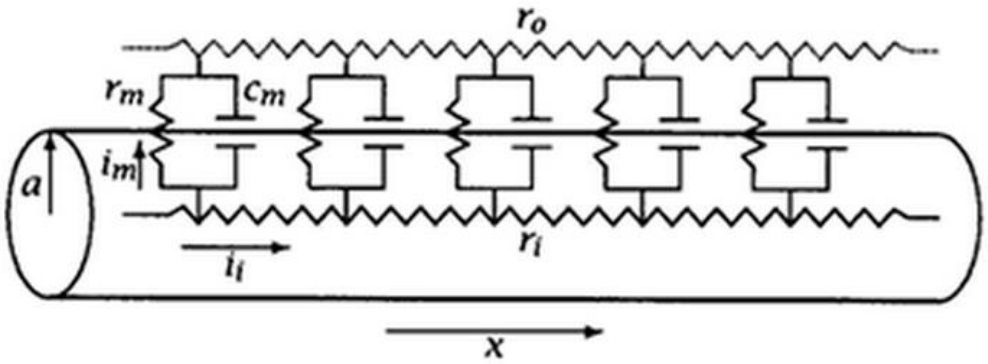
What is the cable theory

- The cable theory uses mathematical models to calculate the electric current (and accompanying voltage) along passive dendrites that receive synaptic inputs at different sites and times.

- Estimates are made by modeling dendrites and axons as cylinders composed of segments with capacitances c_m and resistances r_m combined in parallel.

- The resistance in series along the fiber r_{in} is due to the axoplasm's significant resistance to movement of electric charge.

r_o - resistance of the extracellular fluid



The cable theory

The cable theory take into account that signals propagate along cylinder shape fibers, thus using specific units of electrical properties of the cell membrane (normalized to surface area).

Specific units (for any shape)

- R_m – Ωcm^2 — Membrane resistance per unit area
- R_i – $\Omega * cm$ — Internal resistance (of cytoplasm) per unit area)
- C_m – F/cm^2 — Membrane capacitance per unit area

Specific electrical properties of cylinder segment – related to 1 cm of fiber

$$r_m = \frac{R_m}{2\pi a}$$

a-axonal radius

*Adding parallel resistors according to kirchhoff law

$$r_i = \frac{R_i}{\pi a^2}$$

The volume of a unit length of fiber with radius a

$$c_m = C_m \, 2\pi a$$

The surface area of a unit length of fiber with radius a

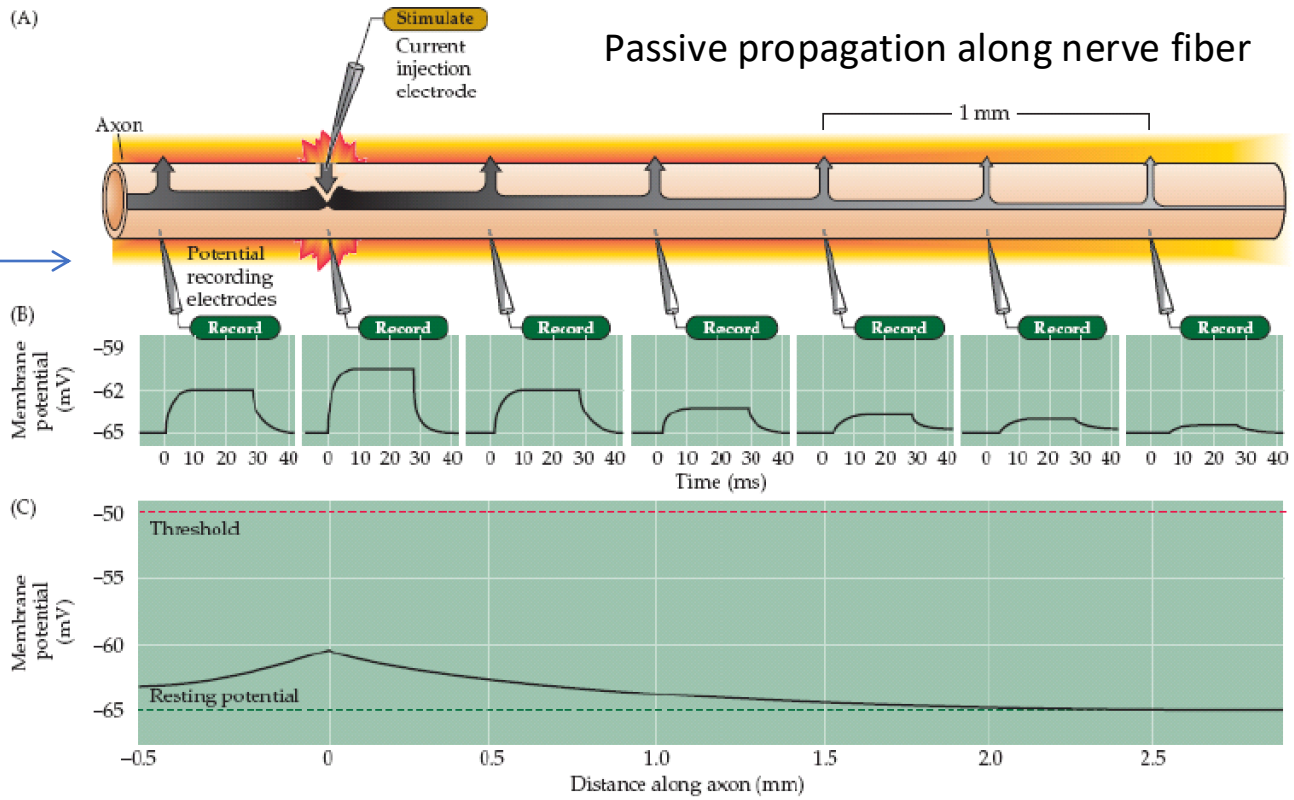
*Adding parallel capacitors according to kirchhoff law

The cable theory

The basic question that the cable theory test is-

How the potential/current will spread after local injection, as happens in synaptic transmission?

Experiment where one injecting current at one point along a fiber and measure the voltage decay at multiple points along the fiber

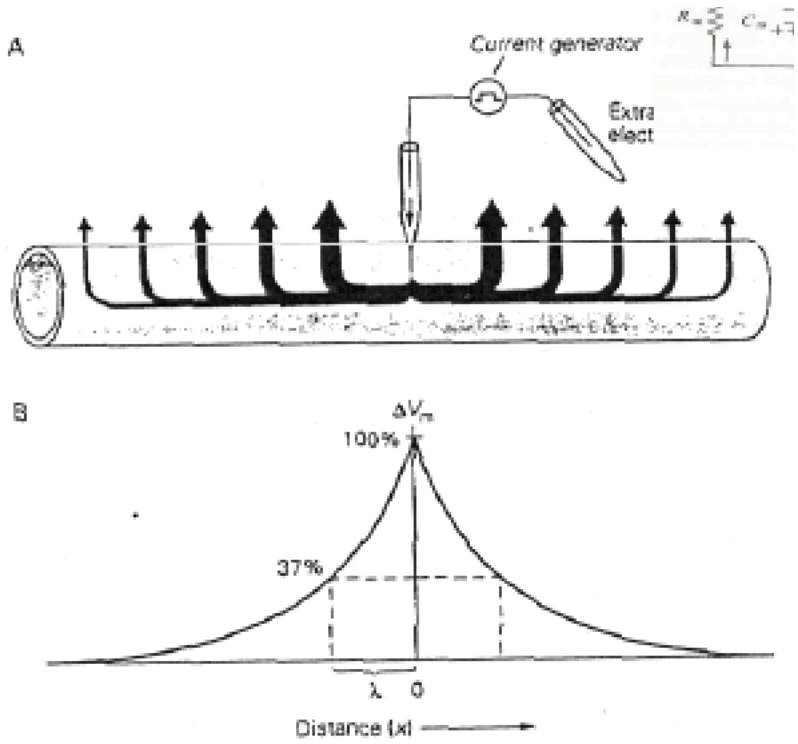


Empiric equation $V_x = V_0 e^{-x/\lambda}$

The spread of membrane potential decaying as exponential function that depends on the length constant

The cable theory

The potential along a passive fiber fall exponentially with distance (***electronic potential***)



Distance from the current source

Length constant

$$V_x = V_0 e^{-x/\lambda}$$

When x=λ

$$V_x = V_0 e^{-1} = 37\%\ V_0$$

And it is the distance at which the voltage drops to 37% of the max voltage amplitude

The length constant is defined as

$$\lambda = \sqrt{\frac{r_m}{r_i + r_0}}$$

Extracellular fluid resistance, usually neglected as very small

The cable theory

From the length constant equation, we can see that

$$\lambda = \sqrt{\frac{r_m}{r_i}} = \sqrt{\frac{l * R_m}{R_a / l}} = \sqrt{\frac{\frac{l * R_M}{\pi * d * l}}{\frac{4 * l * R_A}{l * \pi * d^2}}} = \sqrt{\frac{d}{4}\frac{R_M}{R_A}}$$

Space constant increased with Diameter: Voltage in thick axons decays less

As the time constant is independent of shape

$$\tau_m = r_m c_m = R_M C_M = R_m C_m$$

Time constant is independent on the shape, length or the width of the fiber

Which explains why the propagation velocity in thicker fibers is faster than thin fibers

The cable theory

Intuitive approach…

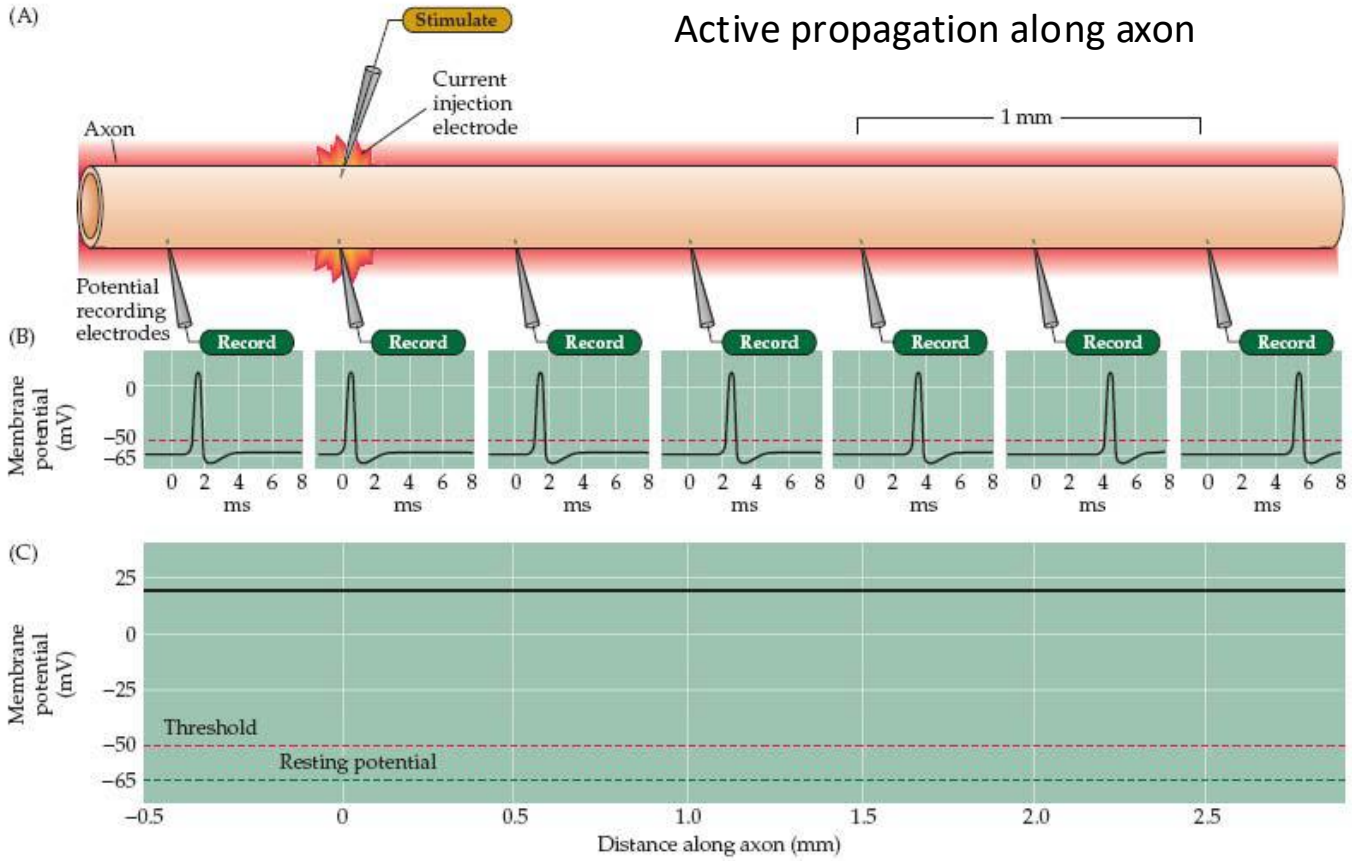
Refer to a cable as a leaking hose

The stronger the source current, the further it will go.

More holes (lower membrane resistance) will reduce the distance the current will flow.

The cable theory

How it looks during action potential (unmyelinated)

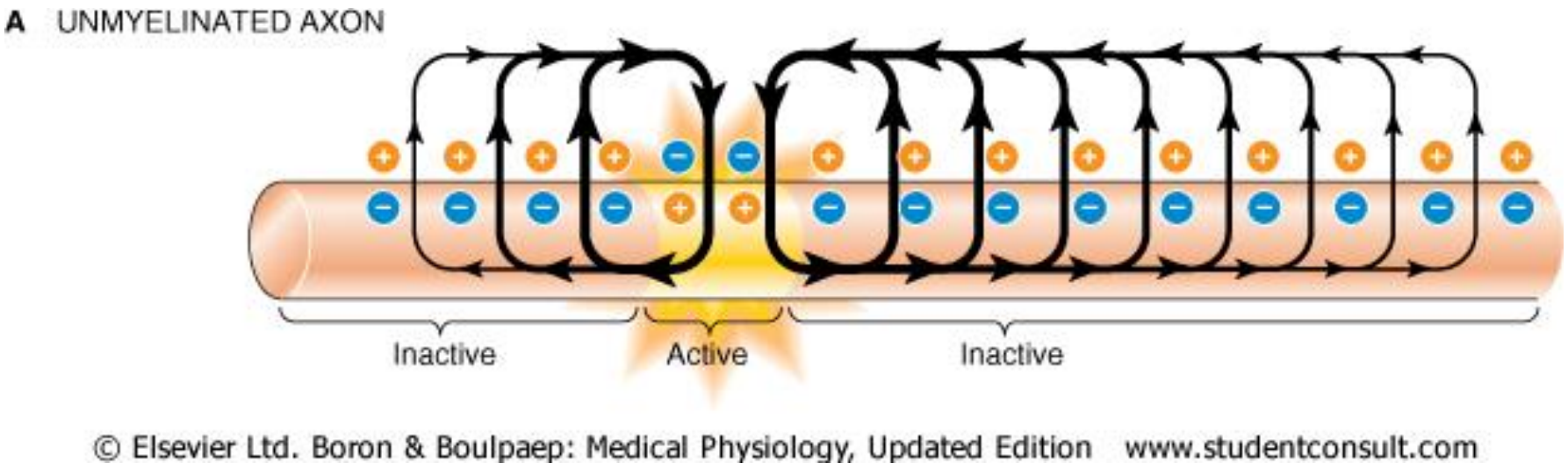


Active propagation along axon

No attenuation of the membrane potential, how come?

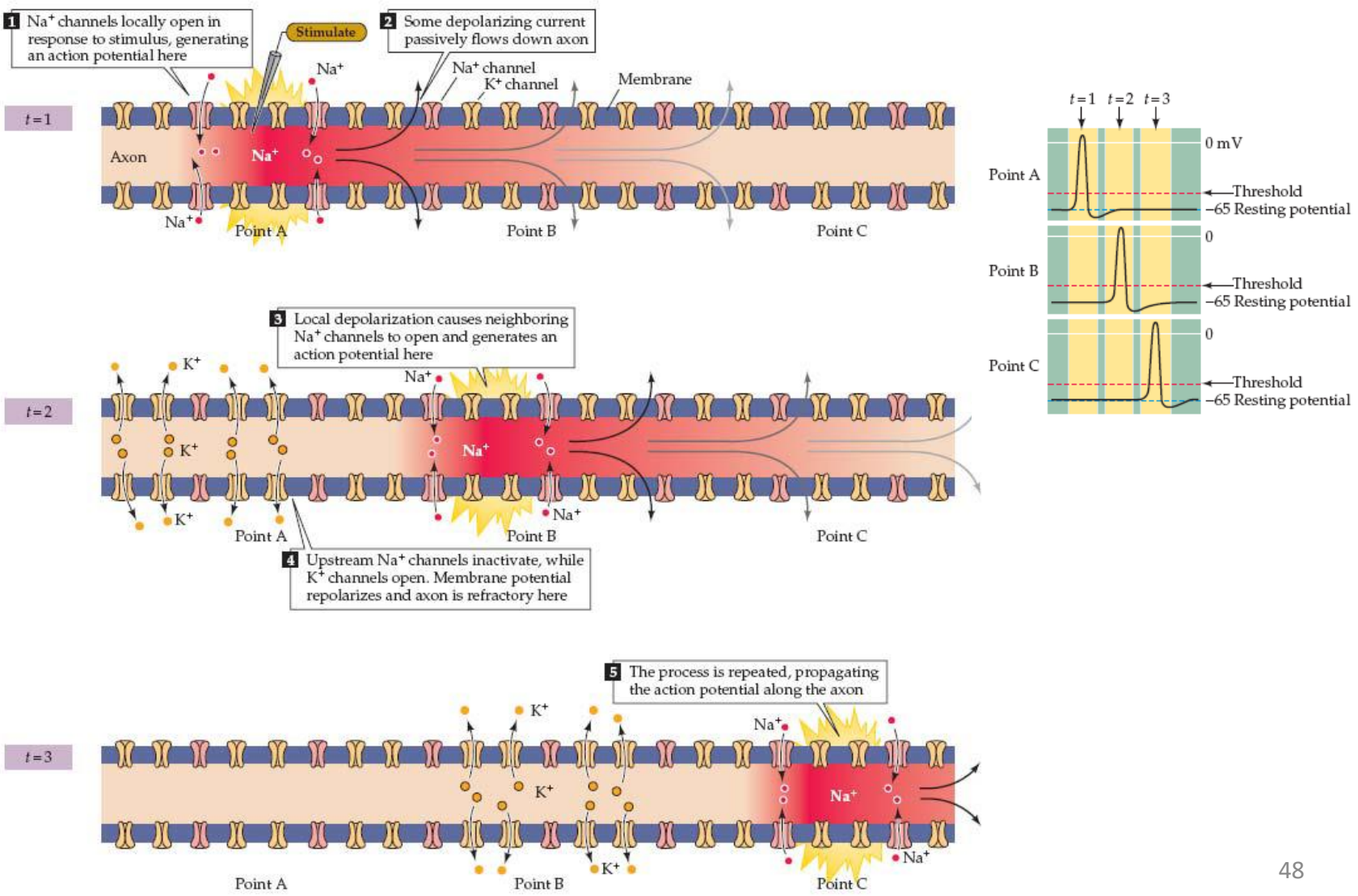
The cable theory

Action potential propagation as a regenerative current along the axon



Action potentials that propagate along unmyelinated axons conduct slowly (~1 m/s)

The cable theory



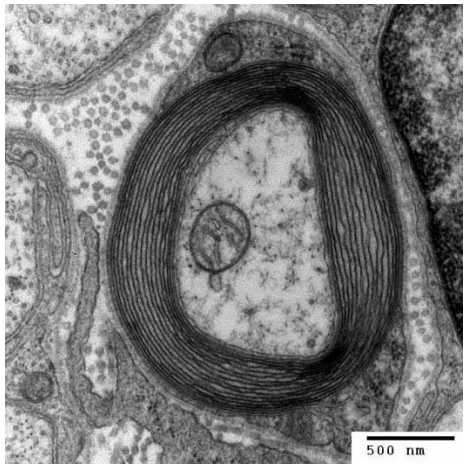
The cable theory

How can one increase the propagation velocity along the axon?

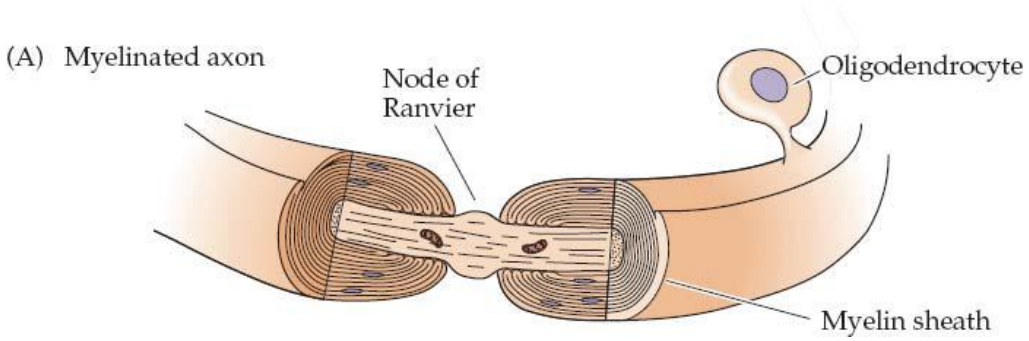
$$\lambda = \sqrt{\frac{r_m}{r_i}}$$

1. Increase it's diameter – will increase the length constant and thus propagation

2. Myelin increases membrane resistance by factor of 5,000. Decreases capacitance by factor of 50.

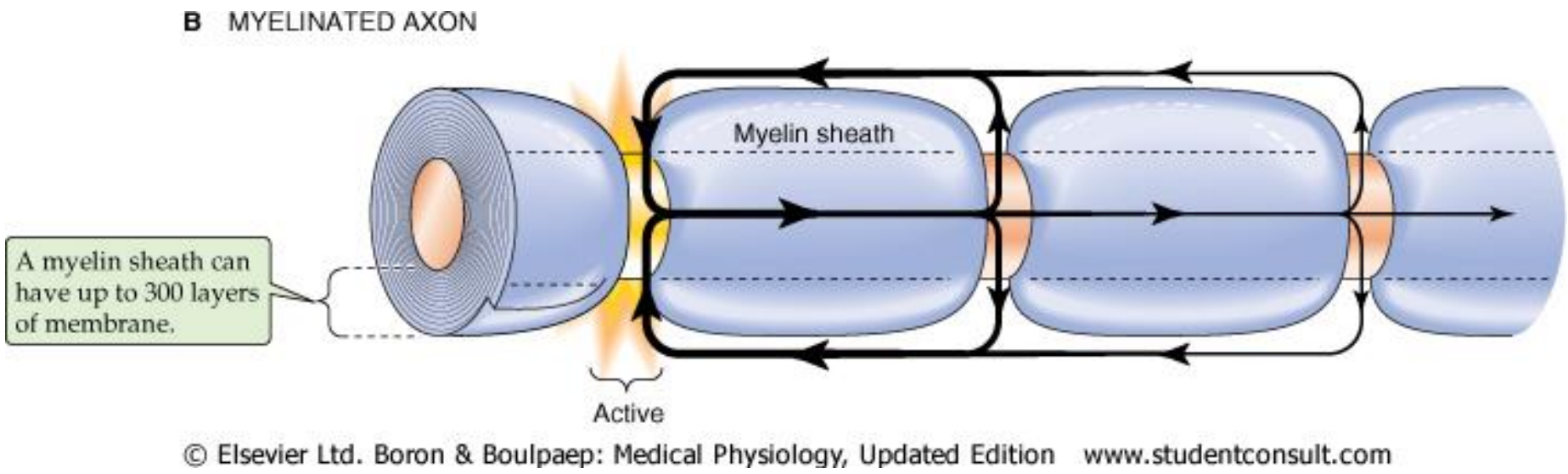


Typical resistance 500-800 MΩcm
Capacitance 0.0025-0.005 µF/cm2



The cable theory

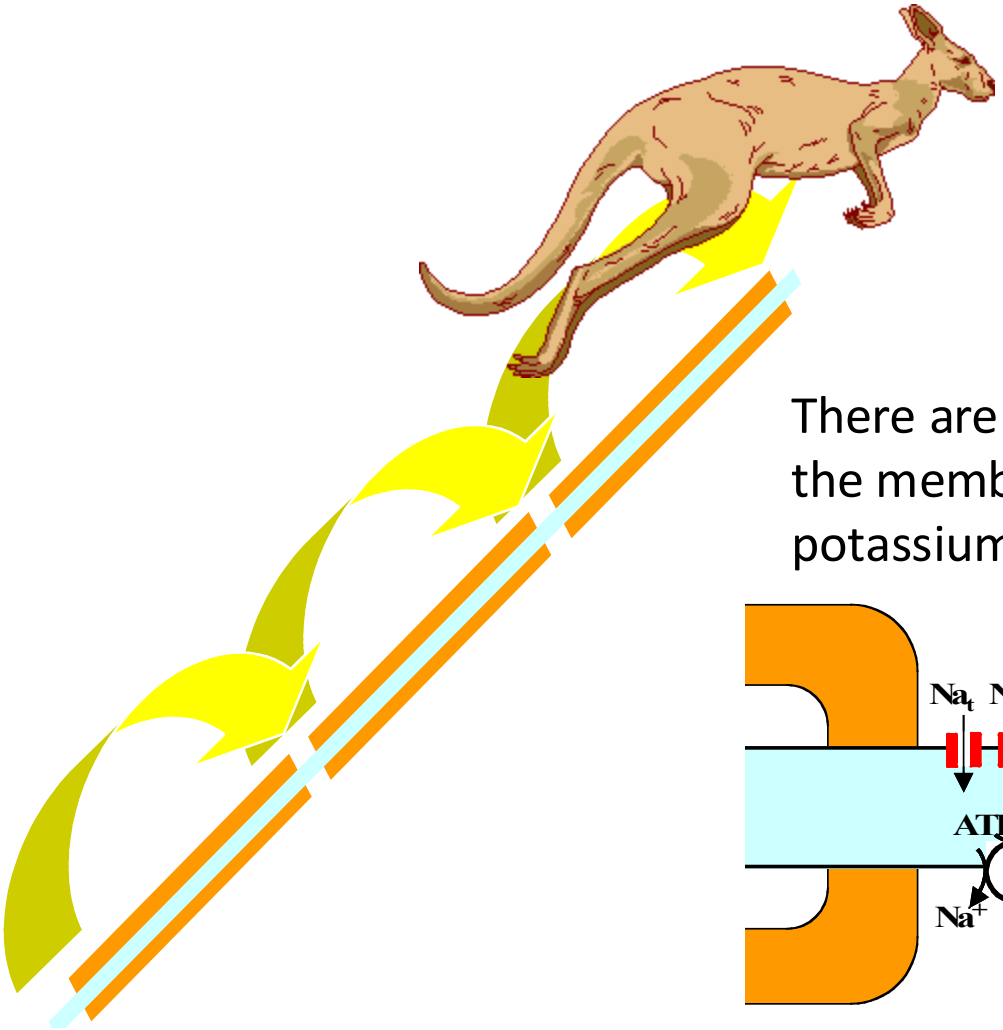
The ionic fluxes associated with the action potentials occur only at the ***nodes of Ranvier*** - the gaps in the insulating myelin sheath



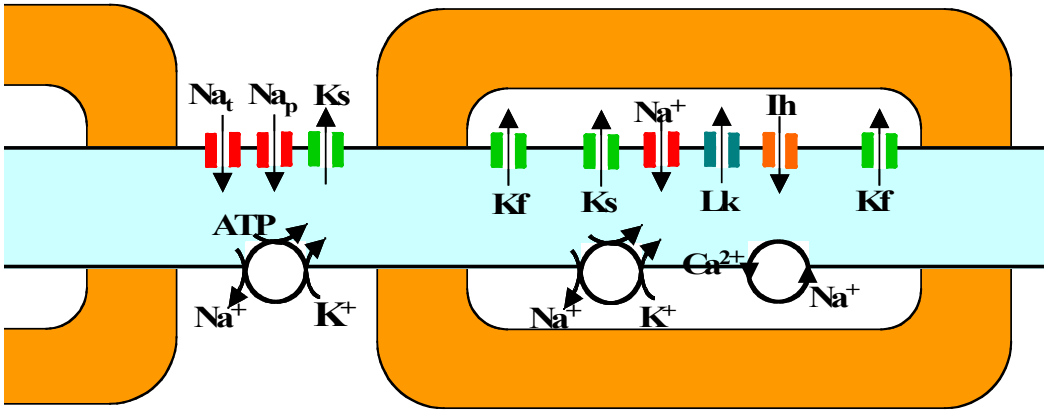
Action potentials that propagate along myelinated axons conduct rapidly (~80 m/s)

APENDIX

Action potentials jump from one node to the next, in a manner termed ***salutatory conduction***



There are voltage-gated channels within the membrane that allow sodium or potassium ions through



The cable theory

Summary

The spread of local graded potentials in neurons depend on the electrical properties of the cytoplasm and the cell membrane.

Propagation of action potentials along the axon/dendrites depends on the ***passive spread o***f current from one active region to the next segment.

The ***length constant*** increase with the fiber diameter

The propagation velocity depends on the ***time constant*** and ***length constant*** of the membrane and is proportional to fiber diameter

Propagation of action potential occur through ***regeneration*** of the depolarizing current along the axon.

To increase ***propagation velocity***, neurons can either ***increase the diameter*** of their axon, or ask a glial cell (Schwan/Oligo) to cover them with myelin sheath.

The cable theory

The fastest conducting myelinated axons in the human body are the sensory axons from mechanoreceptors in the skin and muscles (~80 m/s)

The next fastest are the motor axons, which innervate the muscle fibres (~50 m/s)

The unmyelinated sensory axons, which convey heat and pain information, are the slowest (~1 m/s)