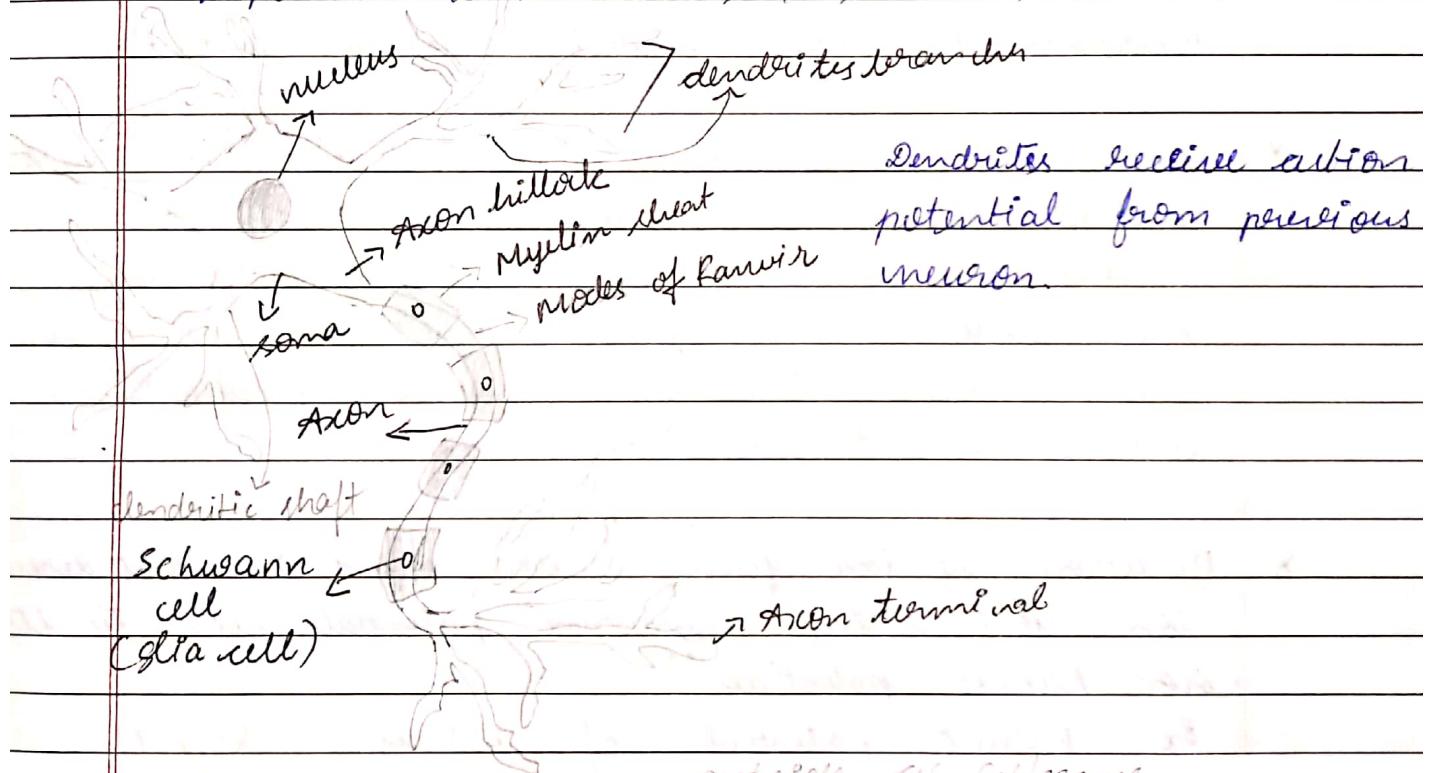


Fundamentals of Neuroscience, Part - 1

HarvardX : MCB 80.1x.

- Neurons at rest have potential across their membrane called resting potential. $\approx -70 \text{ mV}$ (approximately equal to -60 mV) \rightarrow proportional
- In neuroscience points inside and outside the cell is separated by membrane which is impermeable to charged particles. \rightarrow lipid membrane
- Voltage across membrane is measured relative to outside of the cell (Reference).
- Important ions. Na^+ , K^+ , Ca^{2+} , Cl^- .



- * Different potentials:
 - membrane potential: voltage across membrane at any time ($-90 \text{ mV} \rightarrow +60 \text{ mV}$)
 - Nernst potential: membrane potential at given condition
 - Resting potential: stable membrane potential that is determined by flow of ions. When we say a neuron is at rest we mean it is at resting potential ($-60 \text{ mV} \rightarrow -70 \text{ mV}$)

→ From Nernst equation, it's relative concentration between inside and outside matters, not their absolute values.

	Extracellular	Intracellular	(Nernst Em potential)
K ⁺ most permeable among all other ions	5 mM	100 mM	-90 -80 mV
Sodium	145 mM	5 mM	+55 +90 mV
Chloride	140 mM	10 mM	-65 -70 mV
Calcium	2 mM	0.0002 mM	+123 mV

* Driving force: "How hard the ion is getting pushed"

$$E_{\text{driving force}} = E_{\text{membrane}} - E_{\text{ion}}^{\text{(Nernst potential for an ion)}}$$

* Depolarization: +ve change in membrane potential
Hyperpolarization: -ve change in membrane potential.

* Consider: The concentration of K⁺ inside is 100 mM and K⁺ outside is 10 mM.

→ Diffusion will push K⁺ outside of the cell, this will build up +ve charge outside and -ve charge inside, and so electrostatic force will push K⁺ back into cell.

* Direction of ion flow: "Ions move in that direction that brings membrane potential closer to its own Nernst potential."

Ex: Nernst potential of K⁺ is -80 mV

Now consider membrane potential as -40 mV

According to above statement,

-40 is more +ve than -80 mV. ∴ Ions will move out to bring membrane potential closer to -80 mV. ∴ Membrane potential becomes more -ve.

* A system at equilibrium is said to be at a steady state

ionNernst equation

- * Equilibrium potential: Net flow of an individual ion in and out of the neuron will be equal and opposite.

Want, GILL equation, Resting potential.

- * Steady state (balancing point) :- No single ion will be at its equilibrium, but the total net flow of charges in and out of the cell will be equal and opposite. (ion movement balance) at resting potential.

- * Permeability: Ease with which the ions can pass through the channels and the lipid bilayer.

- * GILL Equation: (resting potential)

$$V_m = \frac{RT}{F} \ln \left[\frac{P_K [K]_o + P_{Na} [Na]_o + P_{Cl} [Cl]_i}{P_K [K]_i + P_{Na} [Na]_i + P_{Cl} [Cl]_o} \right]$$

T in Kelvin, R = 8.314 J/K·mol, F = 96,485 C/mol
where P is permeability.

- In actual neuron permeability of K⁺ is higher than Na⁺
- Changing permeability is easier than drastically changing ions' concentration.
- Portions in neuronal membrane will decide different ions are able to pass through membrane more or less easily (through size of the channel).
- Pumps are (K⁺/Na⁺ pumps) used to keep ions at particular concentration, ensuring that neurons are able to function properly. These pumps use lot of energy.
- Only when membrane potential reaches threshold value action potential is fired (i.e active).

→ more channels \Rightarrow less resistance

* membrane resistance: The resistance to the flow of ions across the membrane.

* axial resistance: The resistance to the flow of ions down the axon.

→ In neuroscience size of a cell effects resistance
total axial resistance / total membrane resistance
is used.

→ In neuroscience neuronal membrane acts as a capacitor, storing -ve charge on one side and +ve charge on the other.
"Capacitor = \Rightarrow ability to store charge".

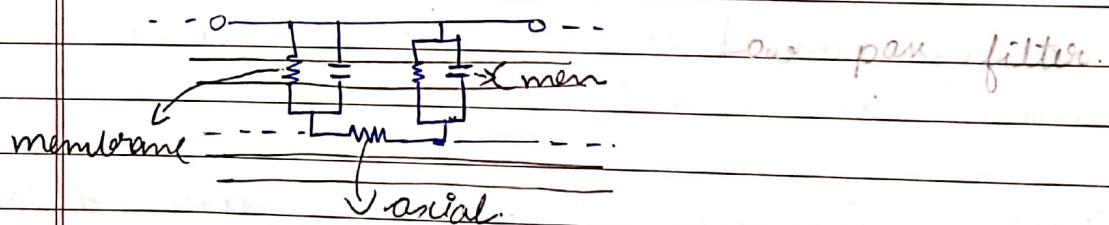
Factors affecting capacitance in a neuron,

a. Larger surface area $A = \pi r^2$

b. Thickness of the membrane = d

$$C = \frac{EA}{d}$$

*



* extracellular ↑ intracellular ↓ → 2 currents
extracellular. ↓ across the membrane

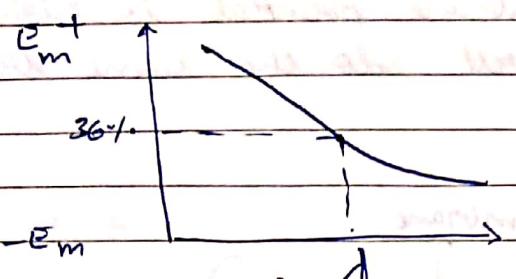
- a. Ion flow b/n membrane to axon
- b. Ion flow down to axon

→ Membrane potential won't be constant every where across the membrane

$$J = \frac{RA}{l}$$

$$\Rightarrow R = \frac{\rho l}{A}$$

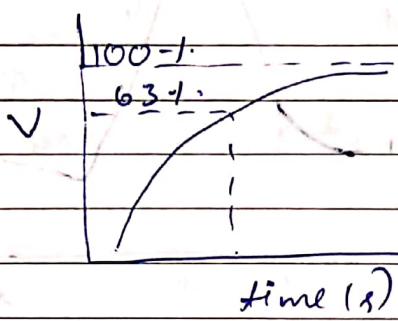
- * Fall of voltage down the axon. (how far)



Length constant =

$$\sqrt{\frac{R_{membrane}}{R_{series}}} \text{ cm}$$

- * Time constant - $T = R_{mem} C_{mem}$



"How long it takes a piece of membrane to charge upto 63% of its final value in response to a step change in its input voltage".

- * Length constant \Rightarrow "How far voltage change will travel until it reaches approximately 37% of its initial value".

Ex: V_i - Initial voltage, V_L is the voltage at length ' l ', ' λ ' is the length constant.

How far is ' l ' in terms of ' λ '?

$$k = \frac{l}{\lambda} \text{ times}$$

$$\therefore \text{Voltage at length } l : V_L = (V_i) \times (0.37)^k$$

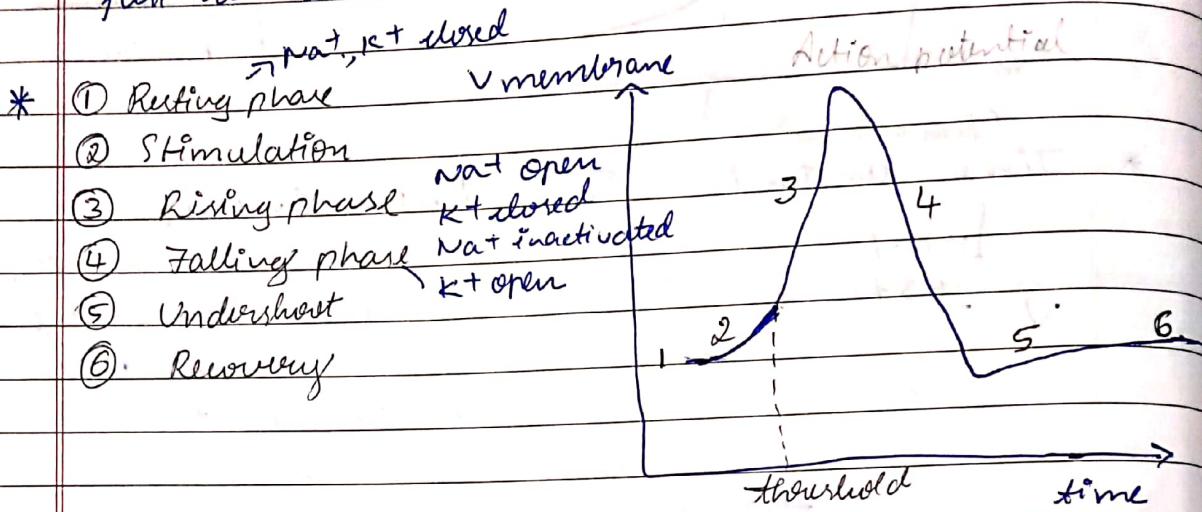
- \Rightarrow Na^+ ions are more concentrated outside of a typical neuron

- * Voltage gated ion channels and action potential

Open and close at particular times, creating ion flow that underlies the shape of the action potential. 2 main voltage gated channels,

- ① Na^+ channel } voltage gated.
② K^+ channel }

- Voltage-gated sodium channels are more likely to open when membrane potential is high.
- Voltage-gated K⁺ will do the same but just a bit slower.



"The action potential is a propagated change in the membrane potential of a neuron that begins with a depolarization of the membrane. If enough voltage-gated sodium channels open, then we enter the rising phase of the action potential. The rapid change is due to the sodium current from the rapidly opening channels. The next phase of the action potential, the falling phase, sees the membrane potential hyperpolarize due to opening of the voltage-gated channels."

? → Voltage-gated Na⁺ channel activation and deactivation is fast
Voltage-gated Na⁺ channel inactivation is slow

Voltage-gated K⁺ channel activation and deactivation is slow

→ If V_{GK} K⁺ channel activation were equally fast as voltage-gated Na⁺ channel activation then action potential wouldn't initiate

Nat channel have 2 gate

a. Activation gate
b. Inactivation gate

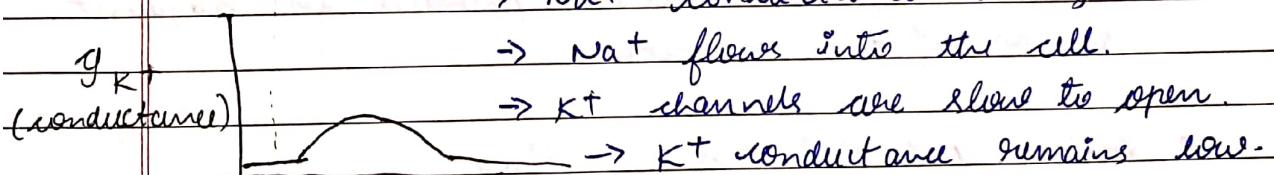
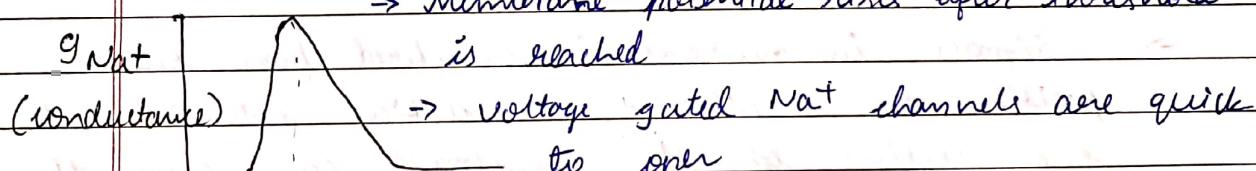
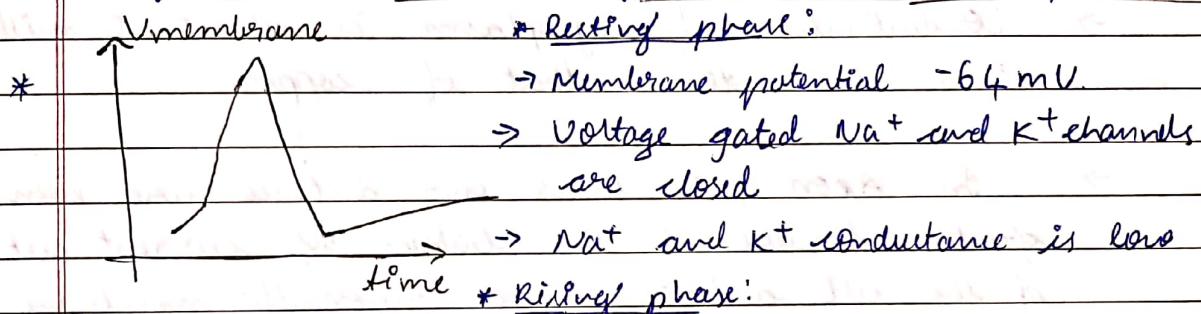
Page

? Because if both voltage-gated channels opened at the same time, the net flux of the K^+ and Nat ion would largely cancel each other out.

* 2 types of refractory period

- ① Relative Refractory period : of open gated K^+ channels, voltage gated Na^+ channels are active (threshold of action potential)
- ② Absolute refractory period : Voltage gated Na^+ channel inactivation. (Inactivation Kinetics)

* Action potential - " Signals characterized by large and rapid changes in membrane potential."



→ Membrane potential falls.
 → V_b K^+ channels are open.

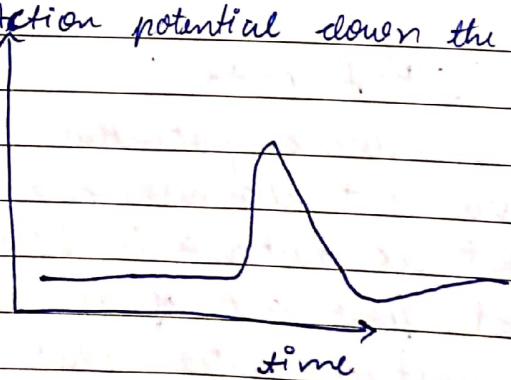
→ K^+ conductance is high.
 → K^+ flows out of the cell.
 → Voltage gated Na^+ channels become inactivated.

- Na^+ conductance drops
- Flow of Na^+ into the cell stops

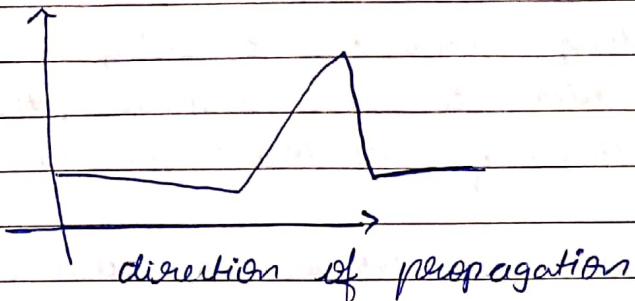
* Undershoot:

- Membrane potential becomes more -ve than at rest.
- Voltage gated K^+ channels begin to close
- K^+ conductance falls
- Flow of K^+ out of the cell begin to stop
- V. or Na^+ channels remains inactivated
- Na^+ conductance is low.
- Diffusion is slow compared to signal.
- Conductivity of cytoplasm is about 10 million times less than that of copper.
- In Axon, the losses over distance are even greater because of the leakage of current out of the cell and resistance across the membrane.
- Signals in neurons is transferred from one position to another - An action potential at one section of the membrane can cause the initiation of an action potential in adjacent section of the membrane.

* Action potential ^(propagates for time down the axon) versus time
Action potential down the axon.



* Action potential (down the axon) vs distance



* Initiation

Absolute refractory period

when Nat is
inactivated

Absolute Relative time.

→ when the action potentials meet, both of their leading edges are undergoing Na^+ channel opening and then inactivation. This Na^+ channel inactivation, which constitutes absolute refractory period prevents two propagating signals from depolarizing adjacent sections of membrane once they meet.

→ Diameter effect on membrane resistance

$\propto 2\pi r$ (circumference)

→ Diameter effect on axial resistance

$\propto \pi r^2$ (cross sectional area).

* Large axons need:

a. Lot of space

b. Larger axons require more energy to maintain a resting potential.

c. Large axons require more voltage-gated Na^+ channels

d. More mitochondria are needed to allow cellular

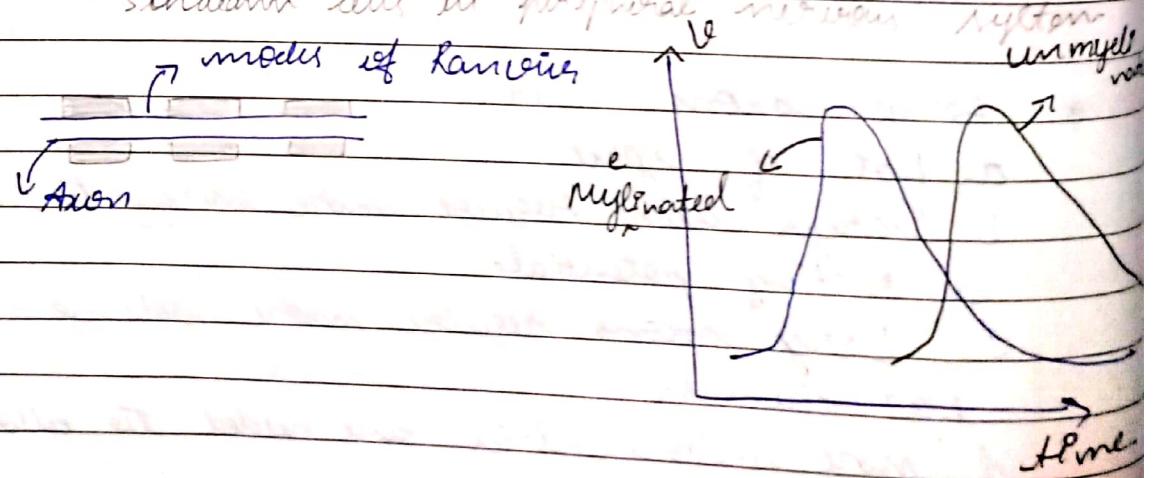
- process to occur
- Increase in decreasing capacitance is not more
- Myelin insulating segmented covering serves as a physical barrier to ion leakage, thus substantially increasing membrane resistance
 - a. myelin decreases number of ion channels thereby increasing membrane resistance
 - b. it increases the thickness thereby decreasing membrane capacitance
 - Gaint axons enable fast action potential propagation - ion by lowering axial resistance

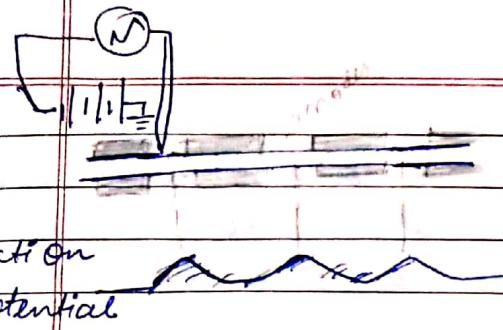
$$* C = \frac{\epsilon A}{d}$$

Neuron decreases the capacitance by increasing 'd'. myelin is wrapped around multiple times by supporting cell to make dielectric thicker.

- If we coat whole axon with myelin then there is no place to put voltage gate channel. In actual axon there is regularly spaced tiny little openings in the myelin. These are called nodes of Ranvier produced by supporting cell called glia
- Myelinated axon will travel faster

*





Jumping of action potential from one node to another is called "saltatory conduction".

Saltatory conduction is because myelin greatly increases length constant in internode region.

→ Adding myelin to the surface is more space efficient than having larger diameter axons, while still allowing signals to travel fast.

* Observation - Capacitance and resistance effect on speed of signal transmission

$C = 0$, $R = \text{max}$ - slow

$C = 0$, $R = 0$ - Fast ✓

$C = \text{max}$, $R = \text{min}$ - same

$C = \text{max}$, $R = \text{max}$ - very slow.

→ Damaged myelin.

- a. Stops the action potential in dead tracks.
- b. ↑ capacitance (membrane).
- c. Shortens length constant.

→ Myelin reduces capacitance ($C_{\text{membrane}} \downarrow$, $R_{\text{mem}} \uparrow$)

→ "As sodium (Na^+) rushes into the node it creates an electrical force (R_{membrane} is less at nodes) which pushes the ions already inside the axon".

- * Ions are able to move around (in and out) of the membrane, 2 important forces guiding this behaviour are
 - (1) Diffusion
 - (2) Electrostatics

? → Very few ions are needed to deal with charge imbalance therefore, concentration remains unchanged.

- * Nernst potential: which calculates the membrane potential at which the diffusion and electrostatic forces of an ion balance out, given particular concentrations in and out.

$$E_{ion} = \frac{RT}{zF} \ln \frac{[ion]_o}{[ion]_i}$$

T in Kelvin, $R = 8.314 \text{ J/K mol}$.

$F = 96,485 \text{ C/mol}$

\ln = natural log

z = valency (can be +ve or -ve).

→ (1) - Nernst potential \approx resting potential (-70mV)

→ "Ions independently wanting to approach Nernst potential".

→ "Voltage to further down the axon; $R_{membrane}$ should be larger and R_{axial} should be lower"

- * Length constant intuition:

Let $d = 2$, $V_A = 100 \text{ mV}$ (starting point)

B is at 2cm away, C at 4cm away and D at 6cm away.

$$L_B = 2 \text{ cm} = d = 2 \text{ cm} \therefore V_B = (V_A) (37-1)$$

$$V_B = 100 \times 0.37$$

$$V_C = 4 \text{ cm} \text{ in other words } 2 \text{ cm from B.}$$

$$\therefore V_C = (V_B) (37-1) = V_B \times 0.37.$$

$$\text{But } V_B = (V_A) (0.37)$$

$$\therefore V_C = (V_A) (0.37)(0.37) = (V_A) (0.37)^2$$

Same for $V_D \dots$

- ⇒ 'd' small ⇒ small distance travelled down the axon
- ⇒ Voltage gated channels have different conductance depending on the membrane potential, which allows neural signalling.
- ⇒ Passive channel have constant conductance
- ⇒ Increasing the speed of action potential propagation in an axon,
 - ① Decreasing axial resistance
 - ② Decreasing membrane capacitance
 - ③ Increasing the density of voltage gated Na^+ channels (Na^+ is key factor in action potential)?

* 'd' and 'C' intuition for myelinated axon:

$$d = \sqrt{\frac{R_{\text{mem}}}{R_{\text{axial}}}}, R_{\text{mem}} \uparrow, R_{\text{axial}} \text{ remains the same}$$

(Purple diameter is not changed)

$$C = R_{\text{mem}} C_{\text{mem.}} = \frac{S}{A} \cdot \frac{E_A}{d}$$

\hookrightarrow decreases more

this outcome ⇒ change in 'S' : of myelin layer is less than change in 'd', thickness

what happens when axial diameter \uparrow or outer surface

area \uparrow : Ans: Area \uparrow (A), d - remains same

d : depth here diameter \uparrow ∴ $\frac{S}{A} \frac{E_A}{d} \uparrow \rightarrow C_{\text{mem.}} \downarrow$.

* Relative refractory period:
After the first action potential, voltage gated Na⁺ channels are mostly de-inactivated (ball ed chain gate is removed) but K⁺ voltage gated channels are still open. If we want another action potential we need to provide more current in order to reach threshold.

→ Action potential can propagate in both directions.

Opposite stimulation - Antidromic stimulation

* Collision test: 2 colliding action potentials cancel out. When action potentials meet, both of their leading edges are undergoing Na⁺ channel opening and then inactivation. This Na⁺ channel inactivation, which constitutes the absolute refractory period, prevents the 2 propagating signals from depolarizing adjacent sections of membrane once they meet.

→ Delay in firing of action potential is due to very fast activated V_{IR} K⁺ channel because influx of this current will at first prevent the neuron from reaching threshold.

→ opening of Cl⁻ channel is a common mechanism for inhibiting a neuron, by preventing it from firing action potential.

→ As number of ion channels increases along the membrane that allows more current to flow which means a reduction in membrane resistance.