

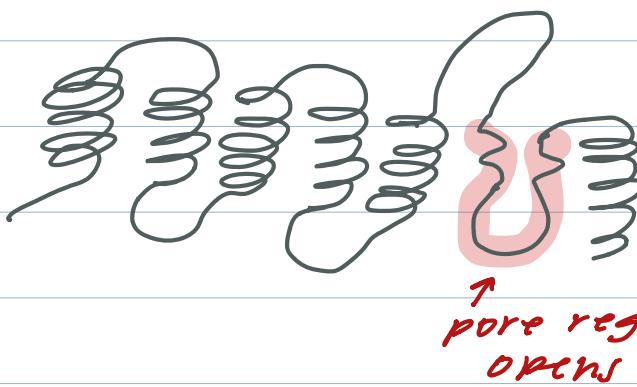
# Newer SD Lecture 7

Sept 25, 2019

$K^+$  current outwards

## Voltage-gated $Na^+$ channels

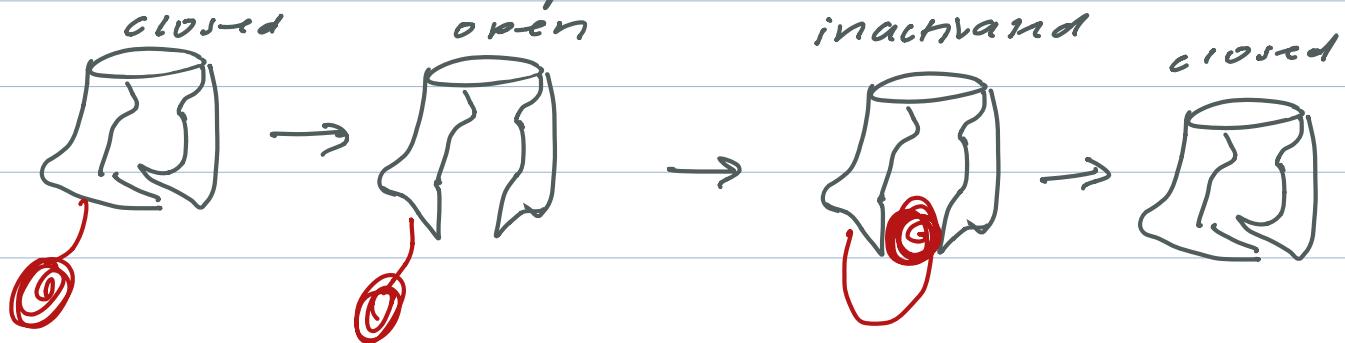
- single long peptide
- 12x more permeable to  $Na^+$  than  $K^+$
- 4 domains (I-IV) w/ 6 transmembrane  $\alpha$ -helices (S1-S6)



• S4 = voltage sensor,  
twists away from  
inside. Channel opens  
and  $Na^+$  move inside

## $Na^+$ channel inactivation

- "ball and chain" process



- No direct ATP usage

## $Na^+$ channel blockers

- Tetrodotoxin (puffer fish) - blocks  $Na^+$  entry to pore
- Lidocaine - blocks pore from outside

- Saxitoxin - Red tide, like TTX
- Scorpion Toxin - blocks inactivation step

Symptoms: physical discomfort, prickling, anything related to action potential

## Voltage-gated ion channels

$\text{Na}^+$ : 9 genes

$\text{Ca}^{2+}$ : 21 genes

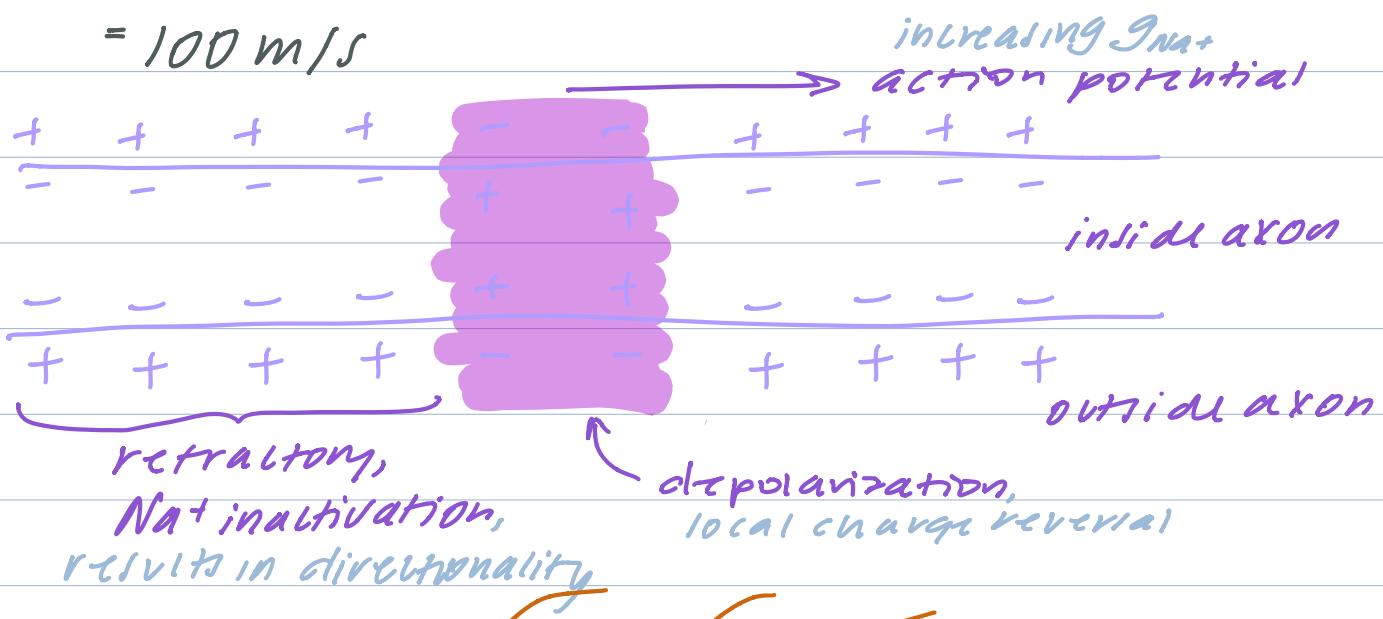
$\text{K}^+$ : 78 genes

"Channelpathy": new congenital disease associated w/ mutant ion selective channels

## Action Potential Conduction

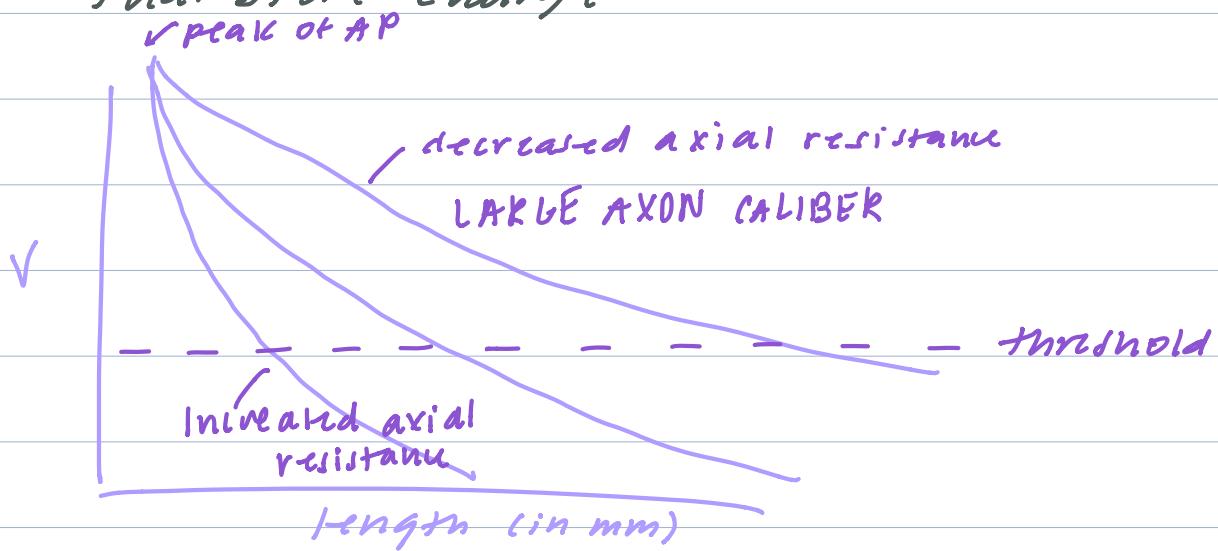
In axon, 10 ms time constraint

$$= 100 \text{ m/s}$$



## Passive Cable Properties of the Axon

- properties similar to telephone wires
- axial resistance inversely related to diameter
- membrane resistance inversely related to # of leak channels (open channels)
- membrane capacitance inversely related to distance between extra- and intra-cellular sites that store charge

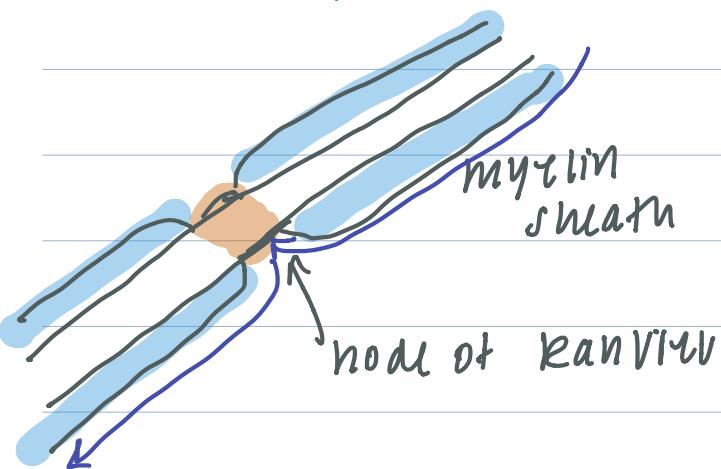


Resistance /capacitance can be changed

- with myelin, approx ~10 microns
- glial membrane from schwann cell (PNS) or oligodendrocytes (CNS)
- capacitors in series  $\rightarrow$  low membrane capacitance
- resistors in series  $\rightarrow$  high membrane resistance

<u>cable property</u>	unmyelinated	myelinated
Capacitance	1	0.05
membrane Resistance	1000	500,000,000

## Saltatory conduction



- Action potential "recharges" at nodes
- Spaced 100's of mm apart
- Na<sup>+</sup> channels concentrated at nodes

## Multiple Sclerosis

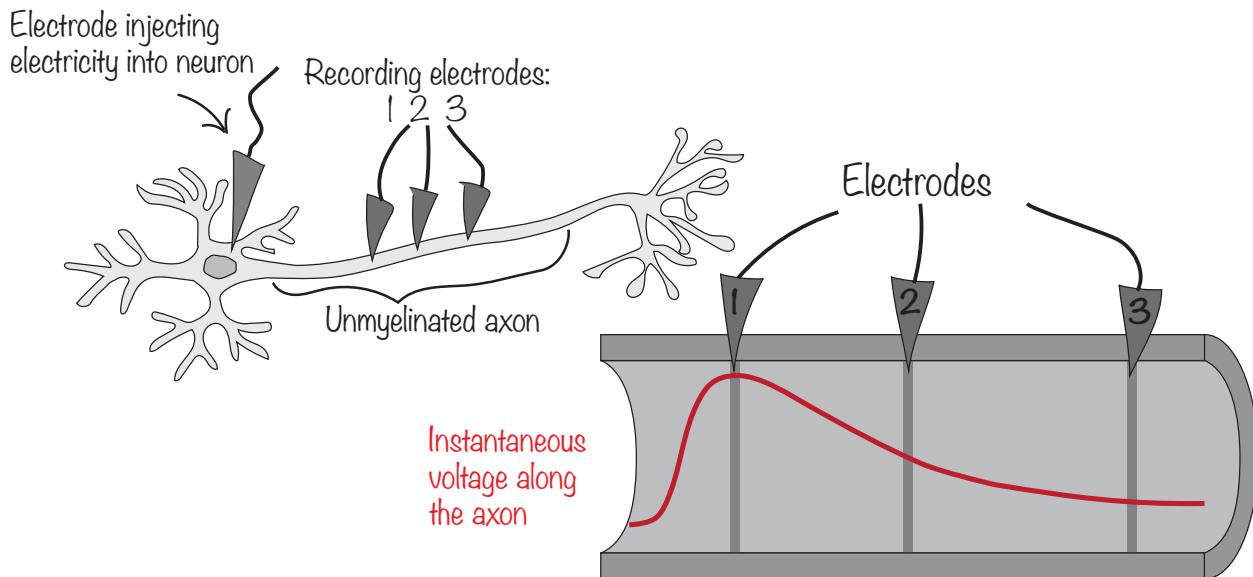
- demyelination spread out in time and space

## Lecture 7 - Channels and Conduction of Action Potentials

Pre-class notes for September 25, 2019

Reading: *Neuroscience* by Purves et al., pages 57-62

Action potentials typically begin at the initial segment of the axon and propagate in one direction. **Conduction**, is the movement or traveling of an action potential along the axon. During an action potential,  $\text{Na}^+$  ions enter and cause a local charge reversal (depolarization). If we look at a section of axon, we see the positive charges displace negative charges on the membrane both locally at the site of charge entry and to a lesser extent in both directions along the axon cylinder. This spread of charge occurs in the backward direction (toward the soma) where  $\text{Na}^+$  channels have already opened and inactivated (the membrane is refractory), and the forward direction where  $\text{Na}^+$  channels are simply closed (not inactivated). Within a few msec, the  $\text{Na}^+$  channels inactivate at the site of  $\text{Na}^+$  entry and that region of the axon membrane becomes refractory to further depolarization (temporarily). But in the forward direction the positive charges change the membrane potential causing an increase in  $g_{\text{Na}^+}$  (additional channels opening) to allow local  $\text{Na}^+$  entry and action potential propagation.



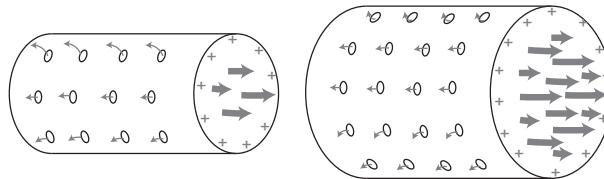
The distance over which the local sodium entry affects  $V_m$  is related to the axon's **Cable properties** - describe the passive flow of current (not taking into account voltage-gated channels). Passive signals become reduced (attenuated) over distance. **Attenuation** is the reduction in current magnitude due to distance and/or time. The loss of current is due to multiple factors including:

**Membrane resistance ( $R_m$ )** - the opposition of ionic flow across the membrane. The more channels in the membrane, the lower the membrane resistance. The lower the membrane resistance, the more the signal will attenuate over distance.

**Axial resistance ( $R_a$ )** - the opposition of ionic flow down the axon or neurite. The greater the diameter of the neurite, the lower the axial resistance. The greater the axial resistance, the more the signal will attenuate over distance.

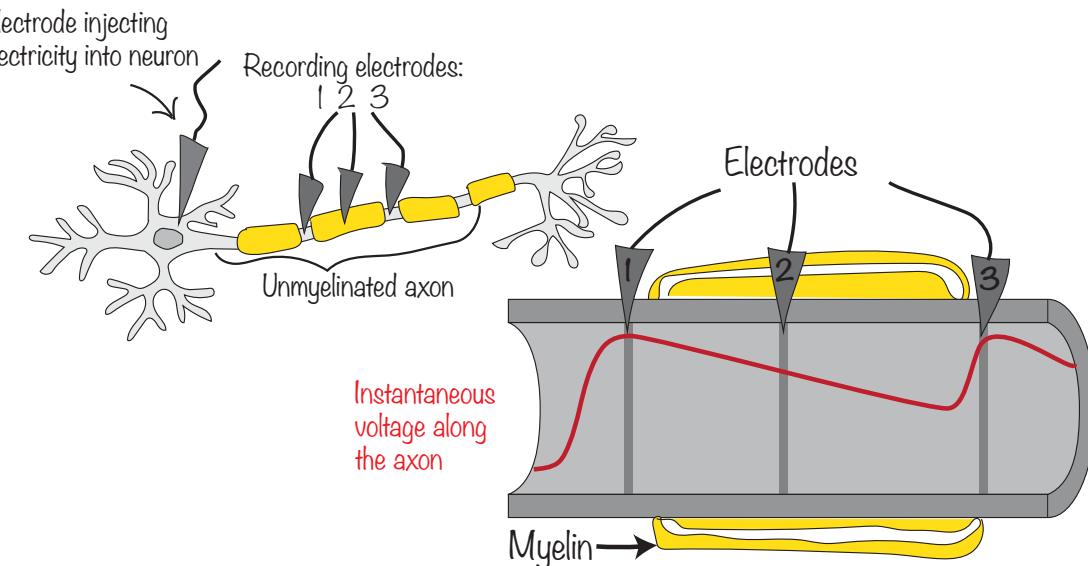
**Membrane capacitance ( $C_m$ )** - property of the membrane that allows for the storage of charge. Determines how quickly a neuron's membrane potential can respond to changes in current. The membrane capacitance is proportional to the surface area. The greater the capacitance, the more the signal will attenuate over distance.

**Diameter** - also known as *caliber*. As diameter increase,  $R_m$  decreases,  $R_a$  decreases and  $C_m$  increases.  $R_a$  is proportional to the radius<sup>2</sup>, whereas  $R_m$  and  $C_m$  are proportional to the radius.



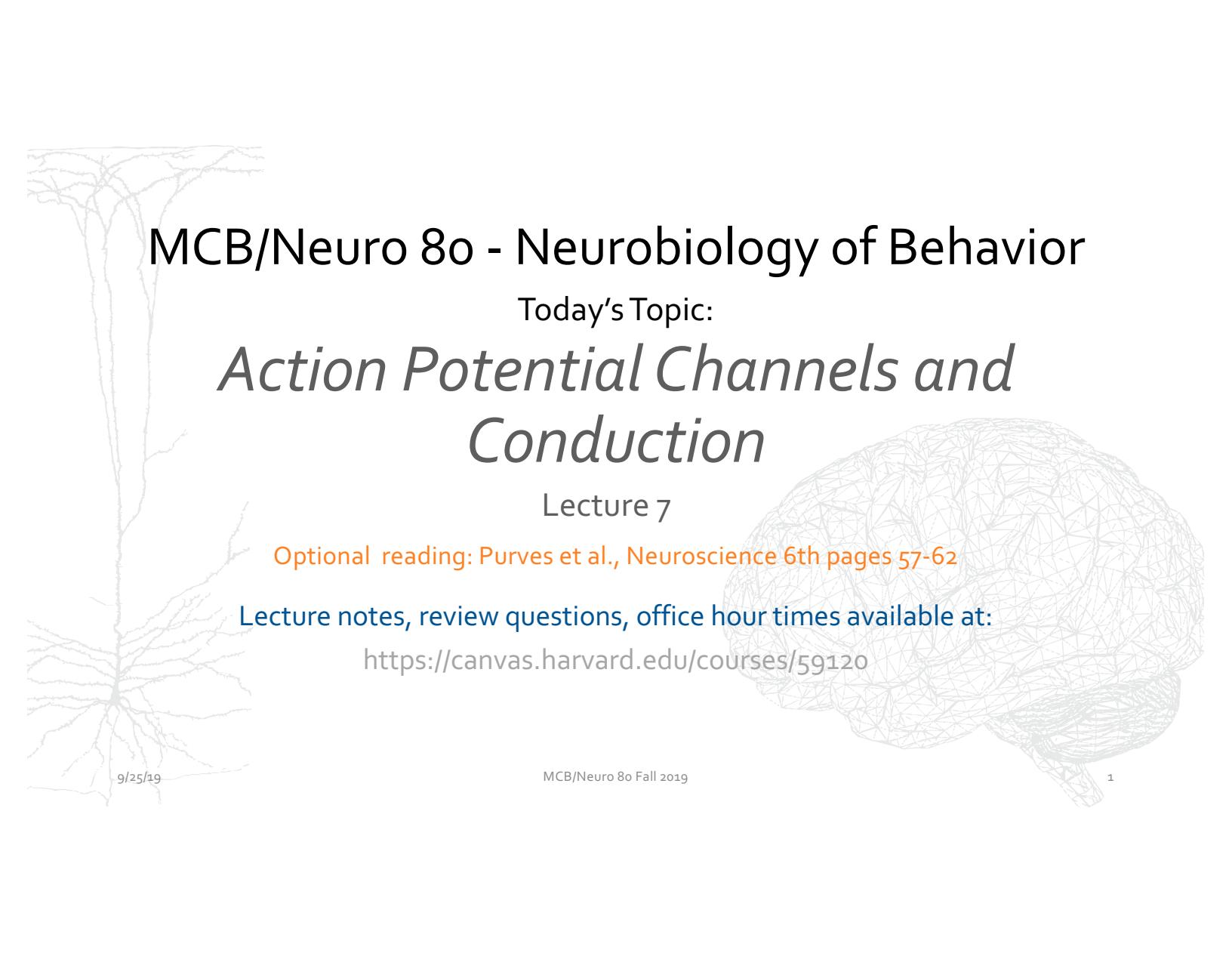
The diameter also plays an important role in the speed of action potential propagation, the larger the axon, the faster the action potential will travel.

The time consuming part of action potential conduction is the opening voltage-gated channels, so the more distance that can be depolarized without channel opening the better. **Myelin**, the intermittent wrappings around an axon formed by glia (oligodendrocytes in the CNS and Schwann cells in the PNS). The additional layers of membrane (high in lipid content) act as an insulator (decreases  $C_m$ ) and increases the distance along the axon a signal can travel passively (increases  $R_m$ ). However, even with myelination, the signal would attenuate, so there are gaps in the myelin: **Nodes of Ranvier**. Many voltage-gated sodium channels are located within the nodes that boost the signal. **Saltatory conduction** - describes the propagation of an action potential along a myelinated axon from one node to the next.



**Learning Objectives:** (By the end of Lecture 7 you should be able answer the following)

1. How does an action potential alter the membrane potential along an axon (voltage vs distance)?
2. Explain the ways in which an axon's passive properties: membrane resistance, membrane capacitance, and internal resistance alter a voltage change with distance from the site where an action potential is peaking.
3. How and why does axon caliber affect conduction velocity?
4. How does myelin affect cable properties and conduction velocity? Why are nodes of Ranvier necessary?
5. Describe multiple sclerosis, including biologic and physiologic symptoms.



# MCB/Neuro 80 - Neurobiology of Behavior

Today's Topic:

## *Action Potential Channels and Conduction*

Lecture 7

Optional reading: Purves et al., Neuroscience 6th pages 57-62

Lecture notes, review questions, office hour times available at:

<https://canvas.harvard.edu/courses/59120>

## Mt. Potential

- Myelin
- Cable Properties
- Conduction
- VGICs
- Ohm's Law



today: action potential conduction

- $\text{Na}^+$   $\text{K}^+$  Pump
- GHK Equation
- Nernst Equation
- Impermeable anions & cation-selective channels

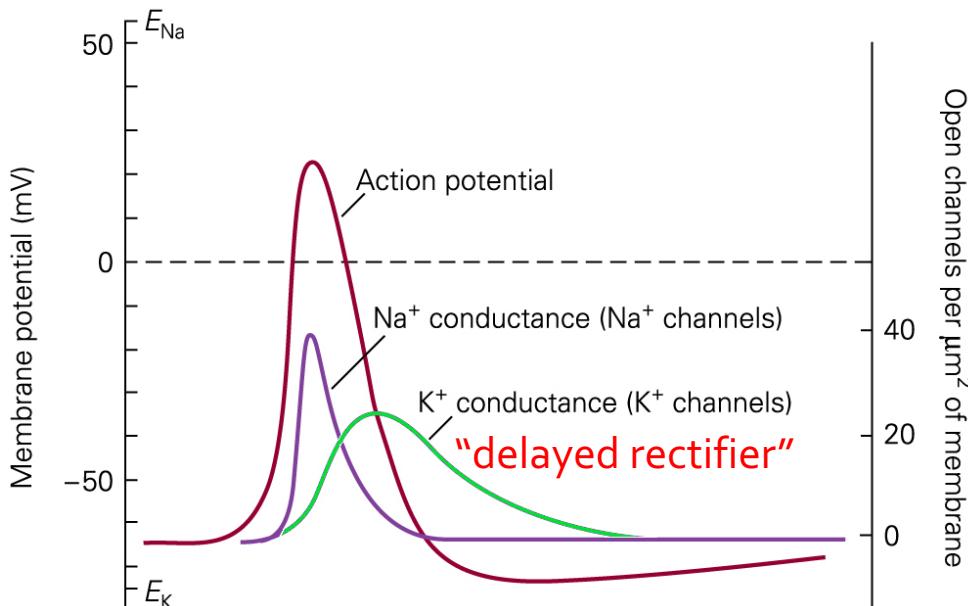
9/23/19

## Synaptic Potential

## Action Potential

## Resting Potential

# Na and K conductances change over time



Q: Why does  $g_{\text{Na}}$  go up & then go back down?  
A: Voltage-gated Na channels open & then inactivate

## Which response best characterizes the role of ion channels in explaining the action potential undershoot?

Chloride channels close

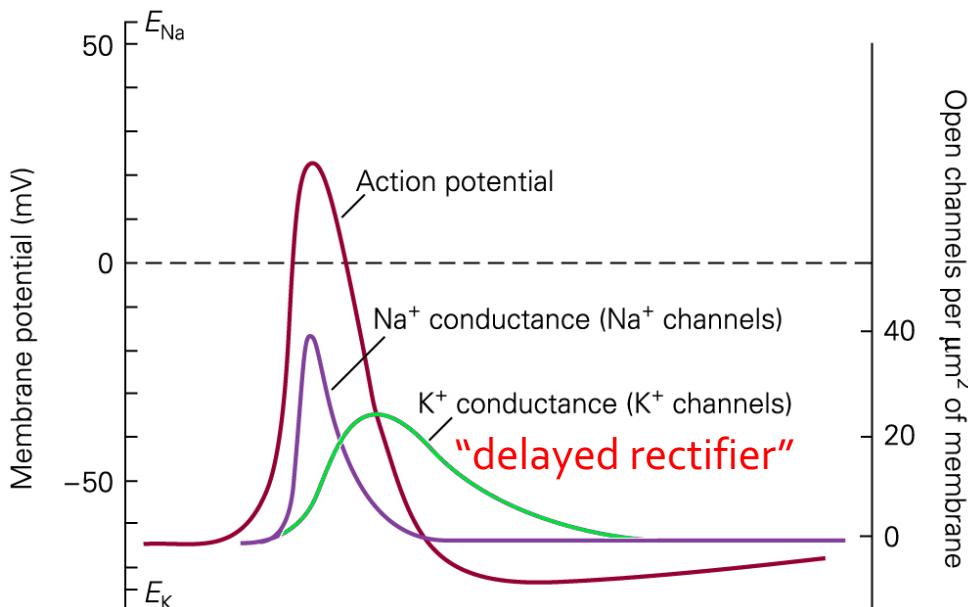


There is high potassium conductance of the delayed rectifier channel coupled with na inactivation beginning during the falling phase of the action potential

The Na-K pump (ATPase) is electrogenic and as sodium enters during rising phase the pump removes the Na but doesn't add as much K back into the cell

Another idea

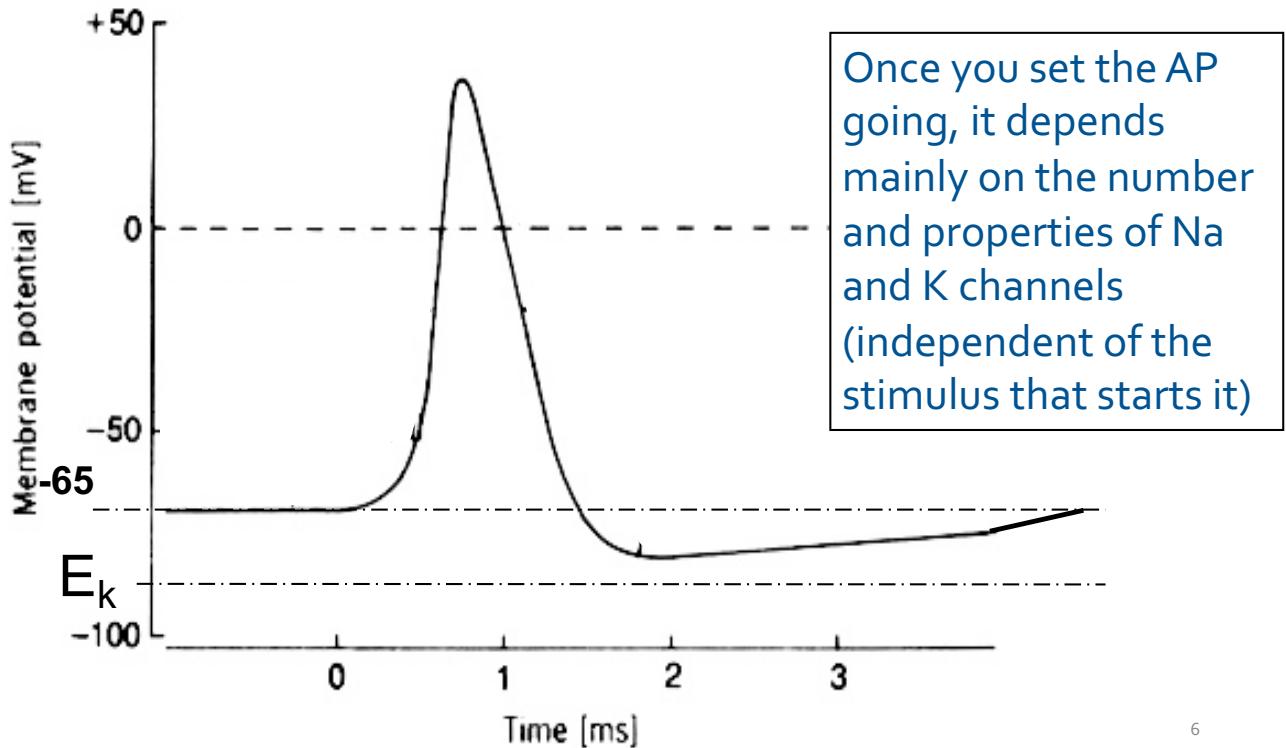
# Na and K conductances change over time



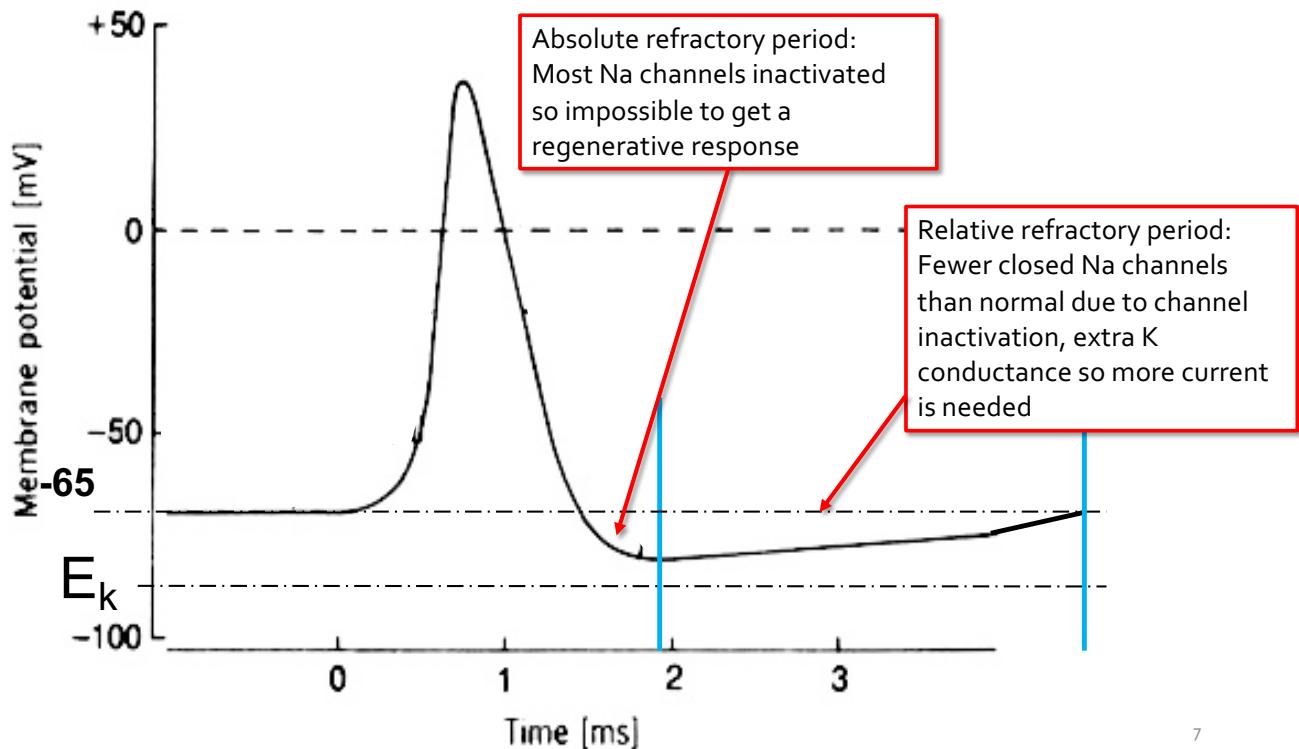
Q: Why is there an undershoot?

A: Delayed Rectifier Channel

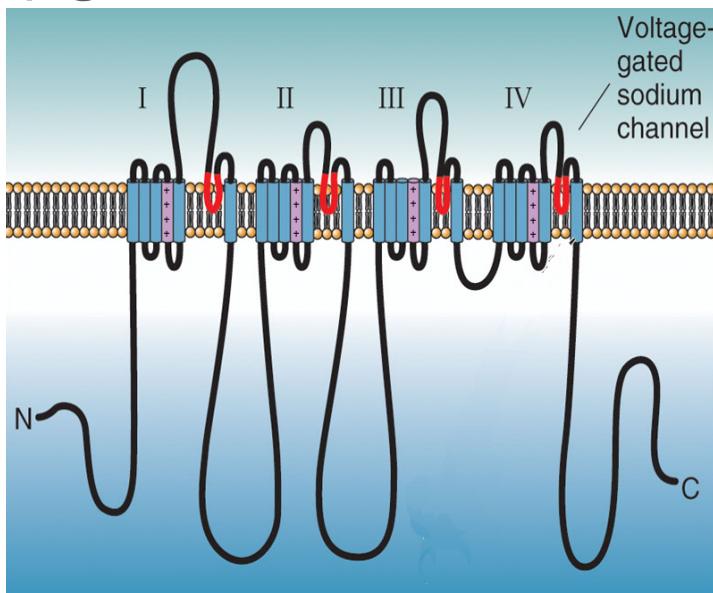
# All-or-none property of action potentials



# Refractory Period

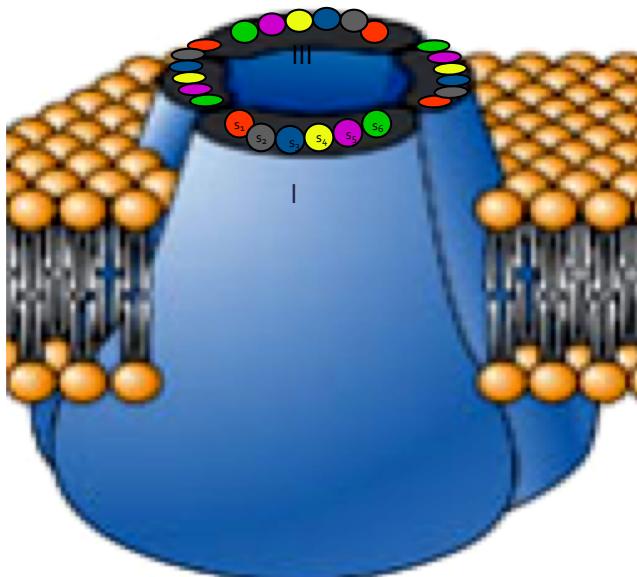


# Voltage gated Na channels: why $g_{Na}$ increases with depolarization



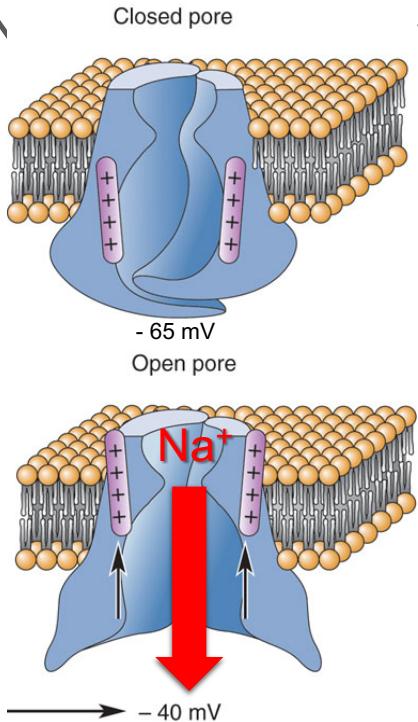
- Single long polypeptide
- 12 times more permeable to  $Na^+$  than  $K^+$
- 4 domains (I-IV)
- Each domain has 6 transmembrane  $\alpha$ -helices (S1-S6)
- **Voltage sensor** is S4. It twists away from the inside when cell is depolarized (from rest  $\sim -65$ mV to  $\sim -40$  mV)
- The twist causes the channel to open and allows an inrush of  $Na^+$  to depolarize the neuron

# Voltage gated Na channels: why $g_{Na}$ increases with depolarization



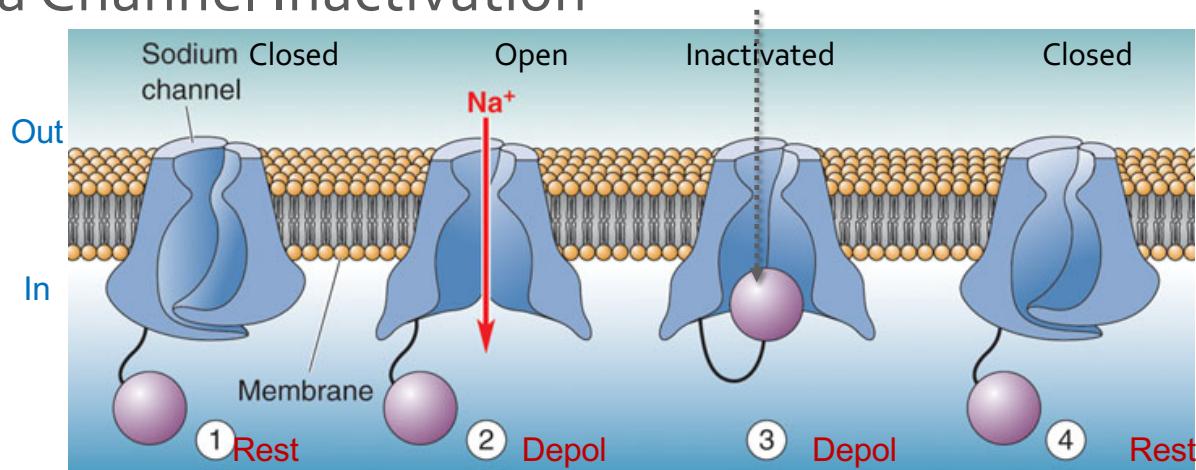
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# Voltage gated Na channels: why $g_Na$ ↑ with depolarization



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- The twist causes the channel to open and allows an inrush of  $\text{Na}^+$  to depolarize the neuron

# Why does $g_{Na}$ go down after depolarization?: Na Channel Inactivation



- At  $V_{rest}$  channel is closed but not inactivated (1)
- Depolarization not only opens the channel (2) ,
- but with a delay inactivates it (3). ( $\text{K}^+$  channels are V sensitive but don't inactivate-they close when  $V_{membrane}$  returns to negative values)
- Repolarization to  $V_{rest}$  de-inactivates the channel but it is closed (4)
- **Time until de-inactivation occurs sets the absolute refractory period**

# A variety of Na channel blockers



# A variety of Na channel blockers

- Tetrodotoxin (puffer fish)- blocks  $\text{Na}^+$  entry into pore (from outside)
- Lidocaine- blocks pore (from inside)
- Saxitoxin- Red tide, like TTX
- Scorpion toxin- blocks inactivation step

# A variety of Na channel blockers

Some of the fish's organs - the ovaries, testicles, skin, muscles and particularly the liver - contain tetrodotoxin, a powerful poison. Tetrodotoxin is 1,200 times deadlier than cyanide, and one fish contains enough poison to kill 30 people. Acting mainly on the nervous system, the symptoms in order of severity are:

Physical discomfort	Subnormal temperature
Pallor	Hypotension
Dizziness	Rapid weak pulse
Prickling or tingling of the mouth	Respiratory distress/arrest
Vomiting	Death
Diarrhea	<i>There is no known antidote</i>
Numbness	
Hypersalivation	
Sweating	
Weakness	

# Diversity of Voltage-Gated Ion Channels

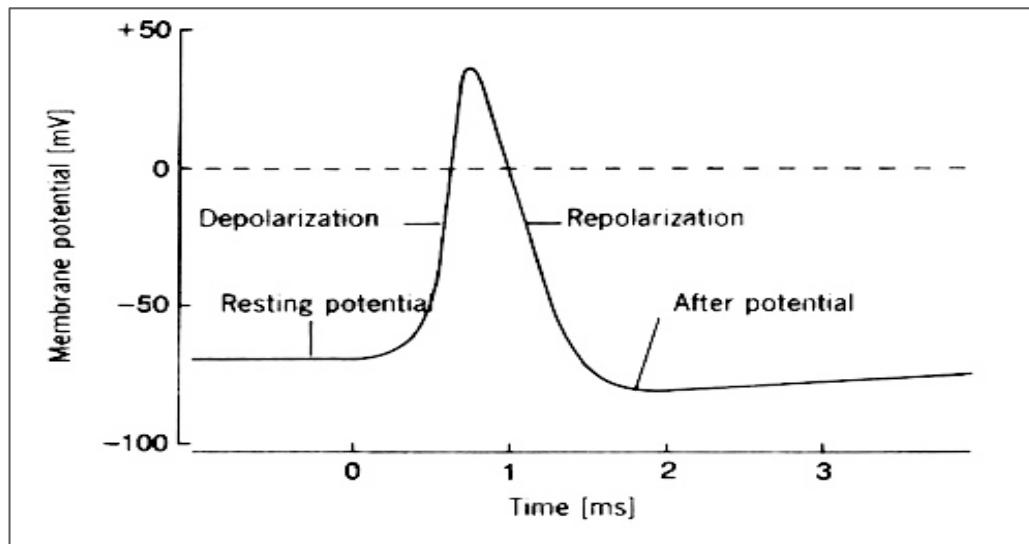
Voltage-gated sodium channels: 9 genes

Voltage-gated calcium channels: 21 genes

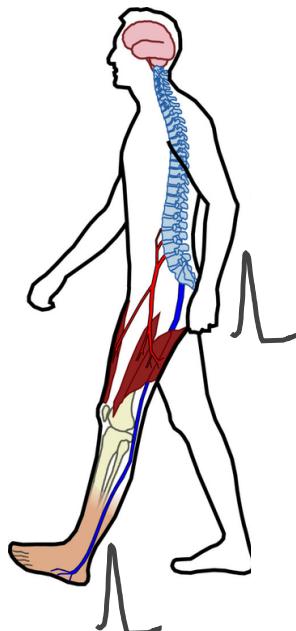
Voltage-gated potassium channels: 78 genes

**“Channelopathies”:** *new congenital diseases associated with mutant ion selective channel genes.* Includes certain neurological conditions with seizures and migraines.

# Action Potential Conduction



# Action Potential Conduction



Let's calculate:

Length of axon: 1m

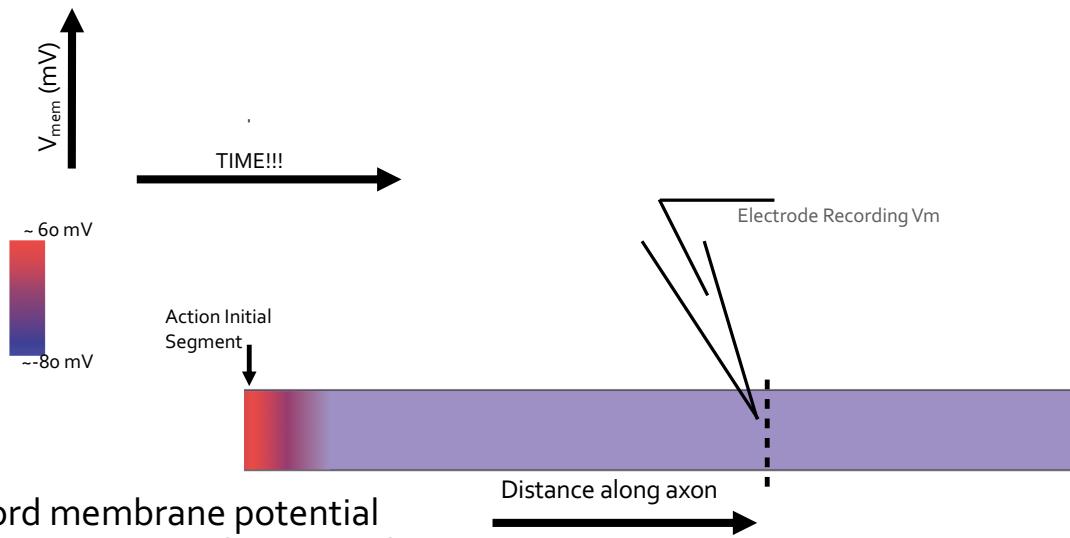
Time constraint: 10ms

Speed: ??

If an action potential travels 1 meter in 10 milliseconds, what is the speed?

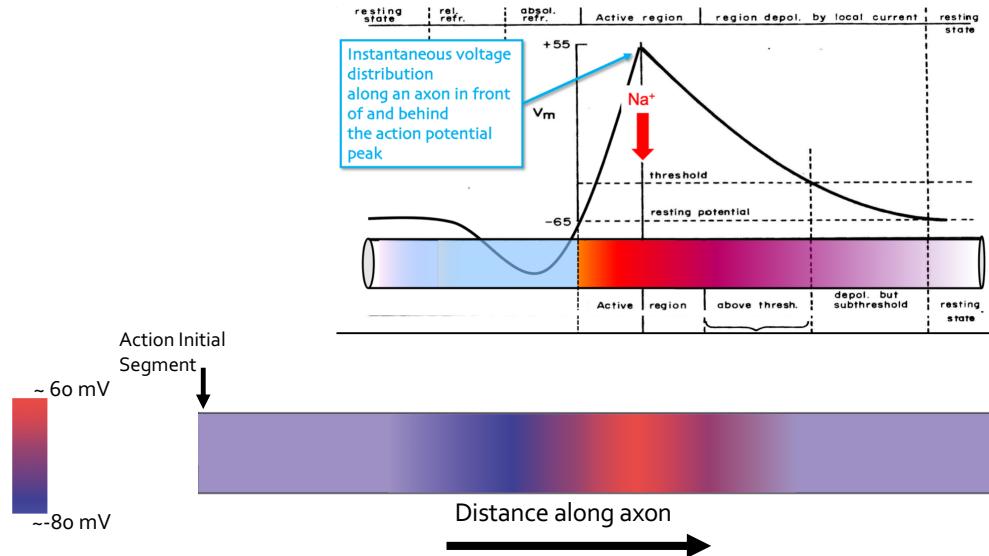
- 1 meter/second
- 100 meters/second 
- 10 meters/second
- Yikes, cannot calculate!

# Action Potential Conduction



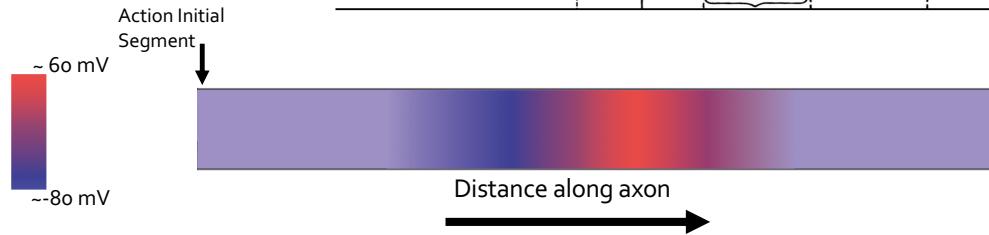
- If you record membrane potential at a single location as a function of time, the rising phase will be recorded first

# Spatial distribution of an Action Potential



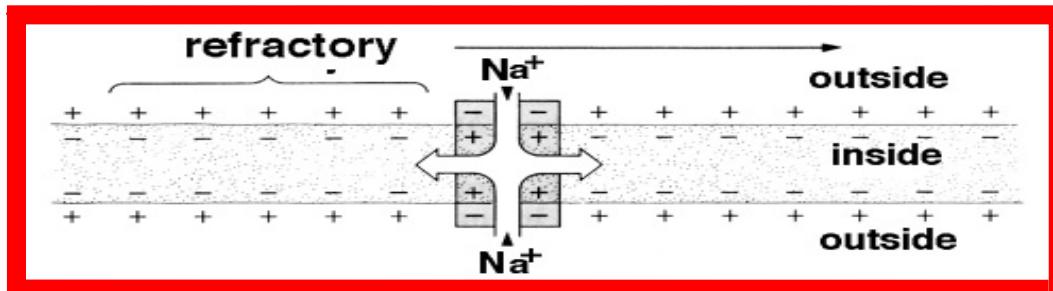
# Spatial distribution of an Action Potential

- Why does it appear backwards?
- The leading edge (rising phase) is furthest from the initial segment



# How is an action potential conducted?

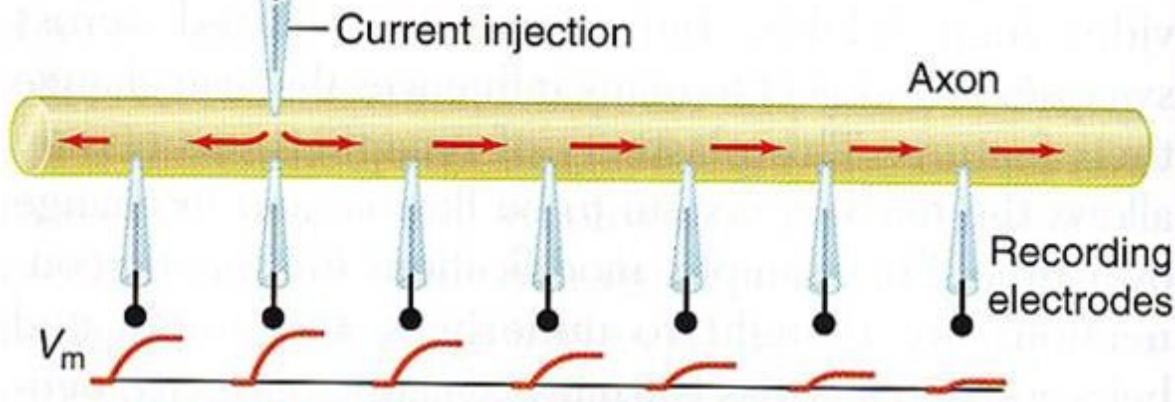
Local Current Flow



- $\text{Na}^+$  enters and causes a local charge reversal (inside positive)
- The positive charge displaces negative charges on the membrane both locally at the site of charge entry and to a lesser extent in both directions along the axon cylinder (in the backward direction where the membrane is refractory and the forward direction where  $\text{Na}^+$  channels are closed but not inactivated)
- Within a few msec, the  $\text{Na}^+$  channels inactivate at the site of  $\text{Na}^+$  entry and that region of the axon membrane becomes refractory to further depolarization (temporarily)
- But in the forward direction the positive charges change the membrane potential causing an increase in  $g_{\text{Na}^+}$  to allow local  $\text{Na}^+$  entry and action potential propagation

Site of  $I_{Na^+}$   
during rising  
phase of action  
potential

The distance over which the local sodium entry affects  $V_m$  is related to the axon's cable properties—this is the physics of local potentials



Traces show  $V_{memb}/time$   
measured simultaneously at  
many progressively more  
distant sites along an axon

# Passive cable properties of the Axon

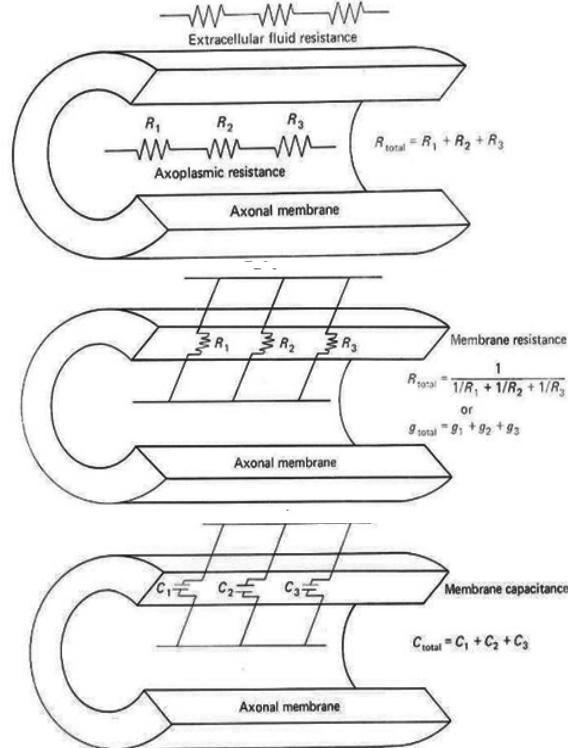
Axons (and dendrites) have cable properties just like telephone wires or water hoses.

The have axial resistance inversely related to their caliber (diameter)

They have membrane resistance inversely related to the number of open channels (leak channels)

They have membrane capacitance inversely related to the distance between the intra and extracellular sites that store charge

9/25/19

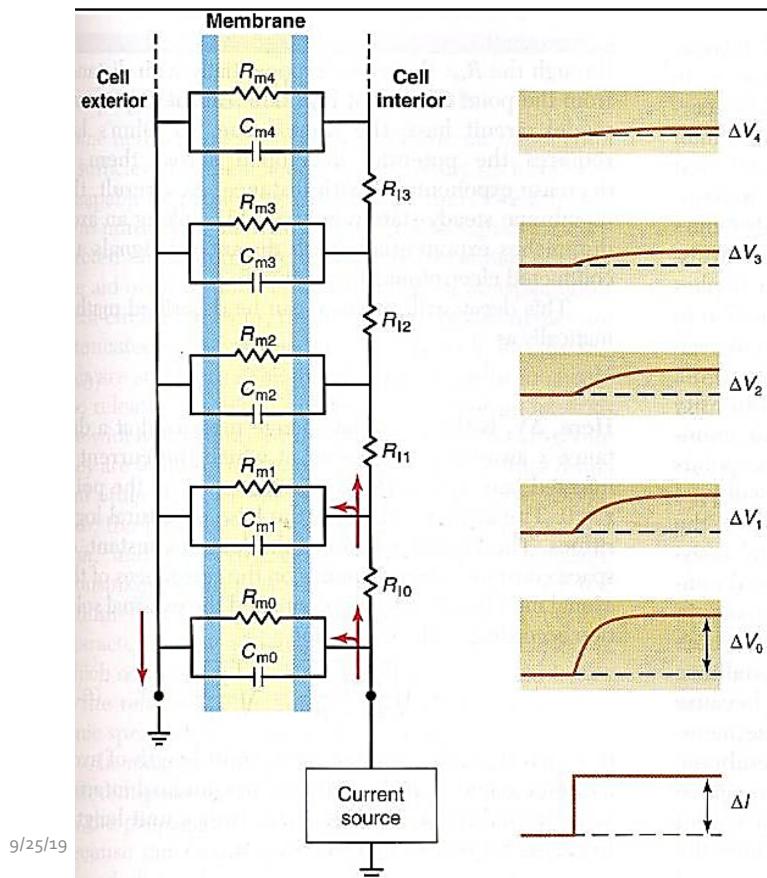


<http://www.humanneurophysiology.com/membranepotentials.htm>

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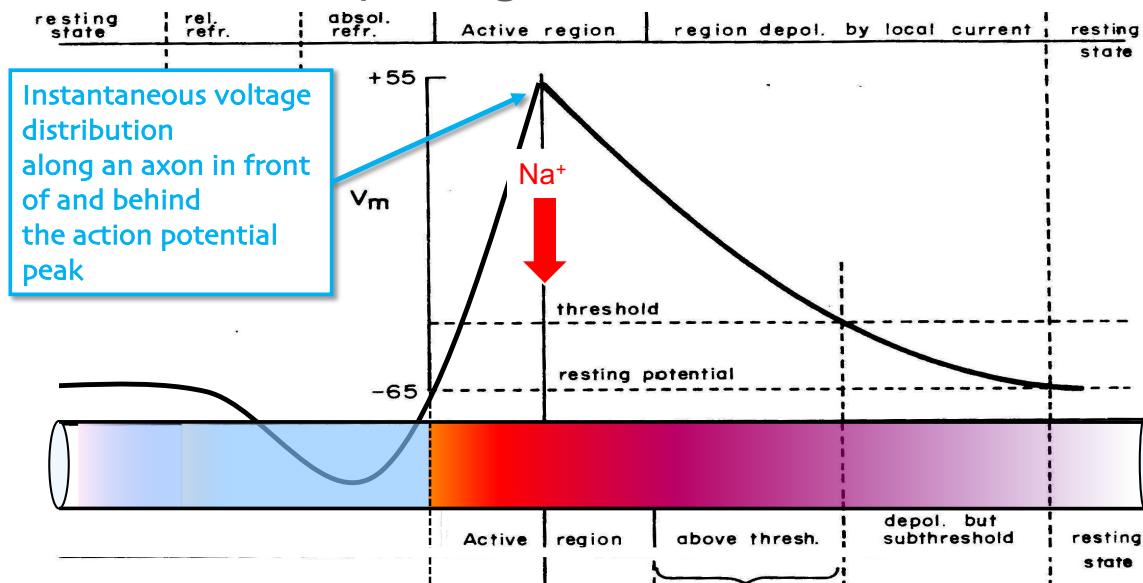
# The change in voltage due to Na<sup>+</sup> entry attenuates with distance due to cable properties

- At site of rising phase of action potential Na flows in causing a nearly instantaneous change in membrane potential along the axon (think of the effect of injecting water into one point along a leaky hose that is already filled with water)
- The voltage (equivalent to water pressure) is largest at the site of Na entry and gradually weakens over distance due to:
  - the axial resistance
  - the passive leak channels
  - the membrane capacitance



With distance away from a current pulse (i.e., the  $I_{Na}$  of the rising phase of an action potential) the recorded voltage amplitude gets smaller and the rise time of the voltage gets longer

Time consuming part of conduction is opening V-gated channels, so the more distance that can be depolarized without channel opening the better



Therefore, conduction velocity be changed by  
modifying cable properties

## How would a larger axonal caliber affect conduction velocity

The positive charge entering at the peak of the action potential would spread further because internal resistance would be lower this would mean a greater distance would be above threshold sp



The positive charge entering at the peak of the action potential would go less far if the axon caliber was larger and conduction velocity would be slowed

I can't figure this out...HELP!!!!

Peak  
Of AP

Therefore, conduction velocity be changed by modifying cable properties

Decreased Axial Resistance

**Large Axon Caliber**

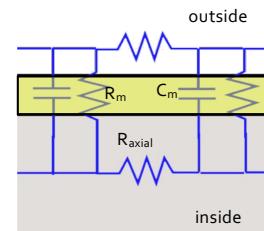
V

Increased  
Axial  
Resistance

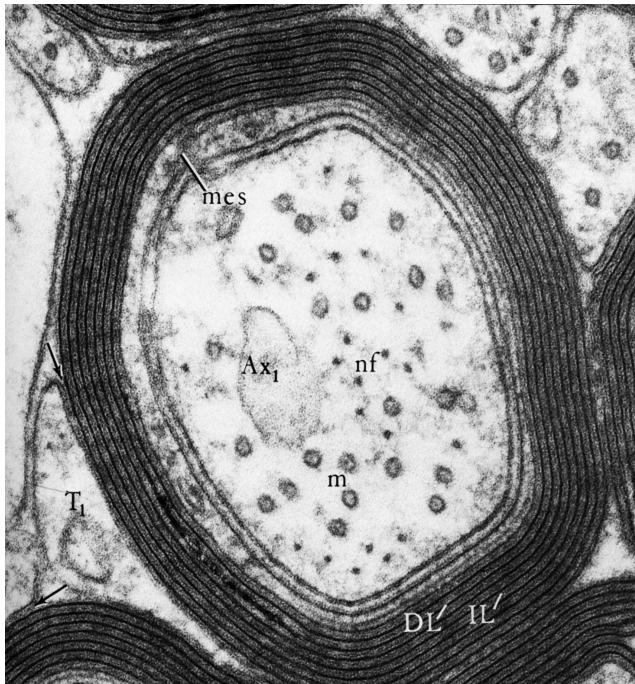
Threshold

**Small Caliber**

Length (mm)



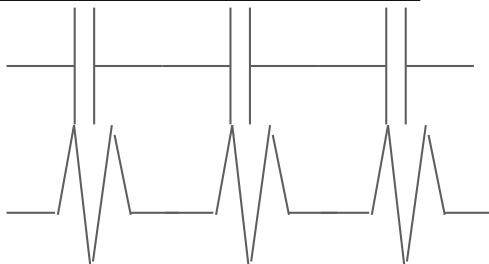
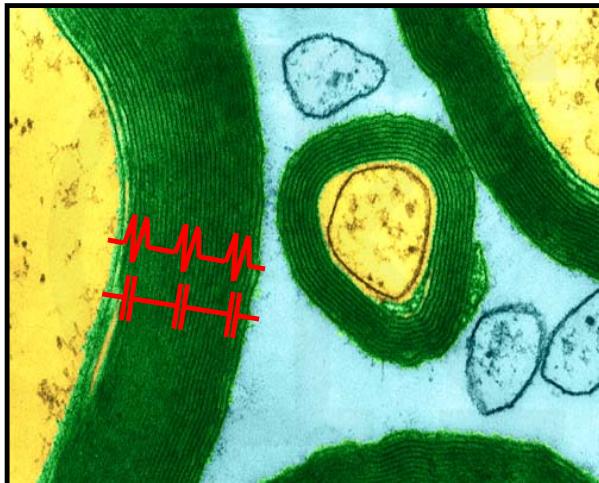
# Axonal membrane resistance and capacitance can be altered



with **myelin**

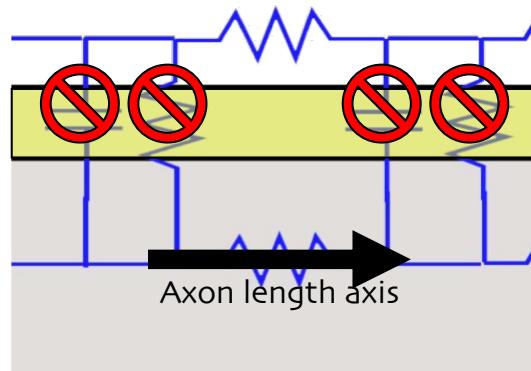
- Glial membrane from Schwann cells (PNS) or oligodendrocytes (CNS) wrapped around axons

# Myelin's effect on cable properties



9/25/19

- Capacitors in series so very low membrane **capacitance** (analogous to duct-taping a hose to decrease bulgeability)
- Resistors in series so very high membrane resistance (i.e., plug the leaks)
- Thus current flow mainly along axon **length** (equivalent to water pressure stays high for longer distance in taped hose)

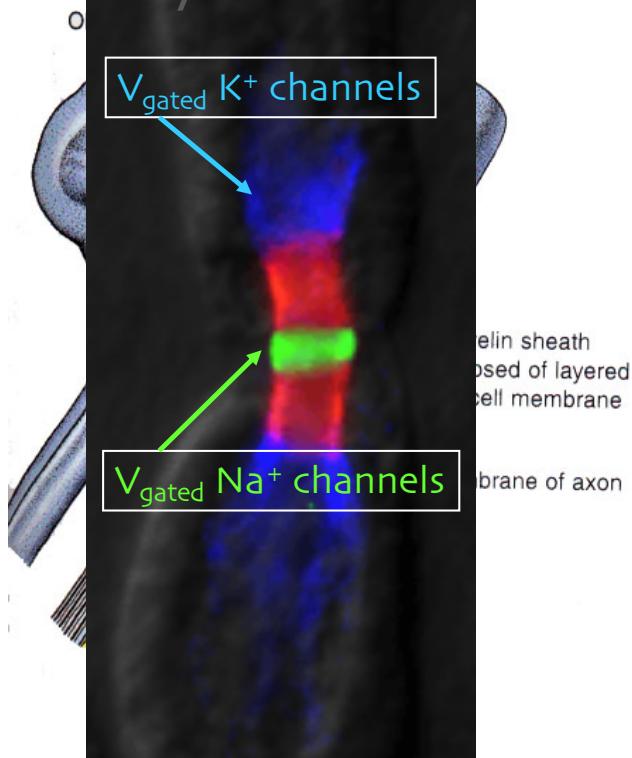


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# Myelin's effects on cable properties

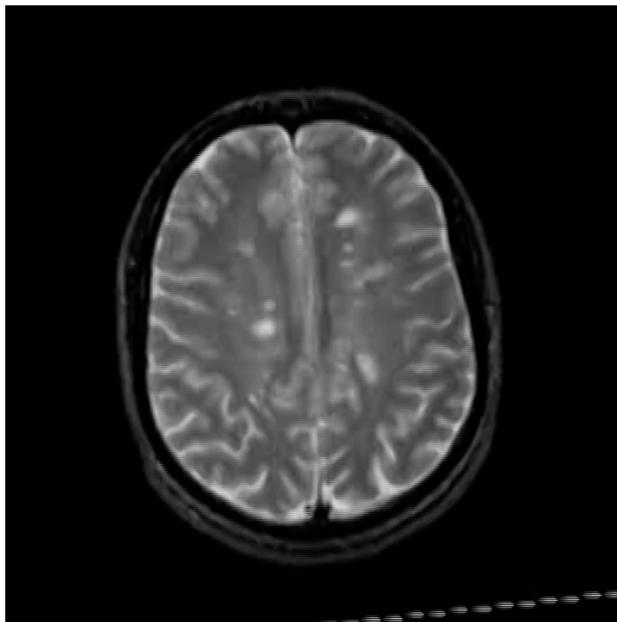
Cable property	Unmyelinated axon	Myelinated axon
Capacitance ( $\text{mF/cm}^2$ )	1	0.005
Membrane Resistance ( $\text{ohm}\cdot\text{cm}^2$ )	1000	500,000,000

# Saltatory Conduction



- Action potential “recharges” at the nodes
- Spaced hundreds of mms apart
- Na<sup>+</sup> channels concentrated at nodes
- K<sup>+</sup> channels along internodes (not sure why, any ideas?)

# Multiple Sclerosis - a demyelinating disease



1 year in the life of an MS patient as seen with transverse MRI of cerebral cortex

Episodes of demyelination spread out in time and space

# Learning Objectives

1. Define and describe the biological mechanism for each of the following:
  - threshold
  - all-or-none property of action potentials
  - absolute refractory period
2. Basic properties of ion channels (activation, inactivation, open, close)
3. Know how an action potential alters the membrane potential along an axon (voltage vs distance)
4. Explain the ways in which an axon's passive properties (membrane resistance, membrane capacitance, and internal resistance) alter a voltage change with distance from the site where an action potential is peaking.
5. How and why does axon caliber affect conduction velocity?
6. How does myelin affect cable properties and conduction velocity? Why are nodes of Ranvier necessary?