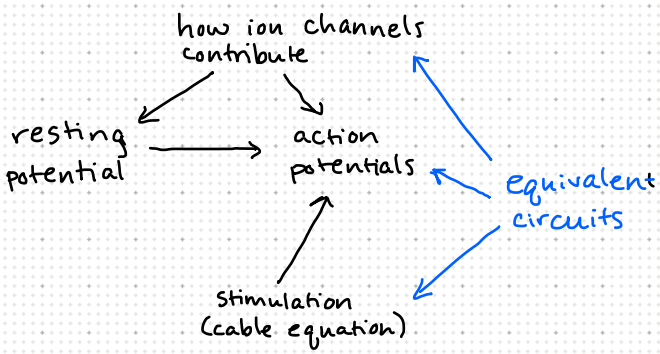
LECTURE 1: Current flow during action potentials (Stim Theory)

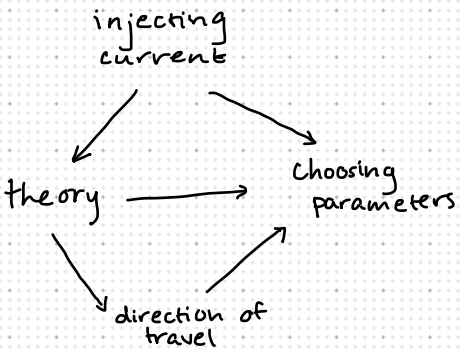
1. Membrane potential
2. Equivalent circuits
3. Kirchoff's and Ohm's Laws
4. Hodgkin & Huxley
   - conductance model
5. The Cable Equation
   - equivalent circuit

Concept Map



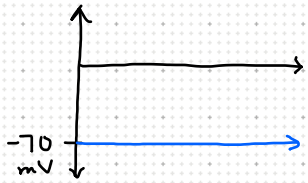
LECTURE 2: Using neurostimulation (Stim Applications)

1. External sources of current
   - current vs. voltage
   - activating function
2. Chronaxie and rheobase
3. Antidromic and orthodromic action potentials
4. Applying a stimulus pulse
   - location
   - shape



Additional resources: neuronaldynamics.epfl.ch/online/Ch2.html
neuromembrane.ualberta.ca
Brocher & Grill 2013 - Principles of electrical stimulation of neural tissue

1 Membrane Potential

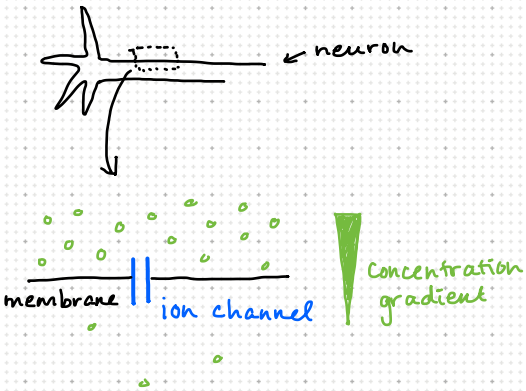


Ions flow to balance concentration gradient (diffusion) and due to electric field.

Neurons don't just sit around at rest.

* How and why is current flowing during action potential?

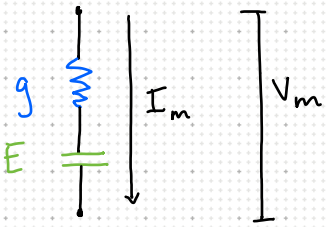
2 Equivalent Circuits



membrane components	electronics	purpose
membrane	capacitor	builds up charge without letting flow
conc. gradient	power source	provide power
ion channels	resistors *	let through charge a little at a time

*often described in terms of conductance $g = \frac{1}{r}$

So for EACH ION:



Each ion contributes to the circuit:

g = conductance (how easy it is for current to flow)

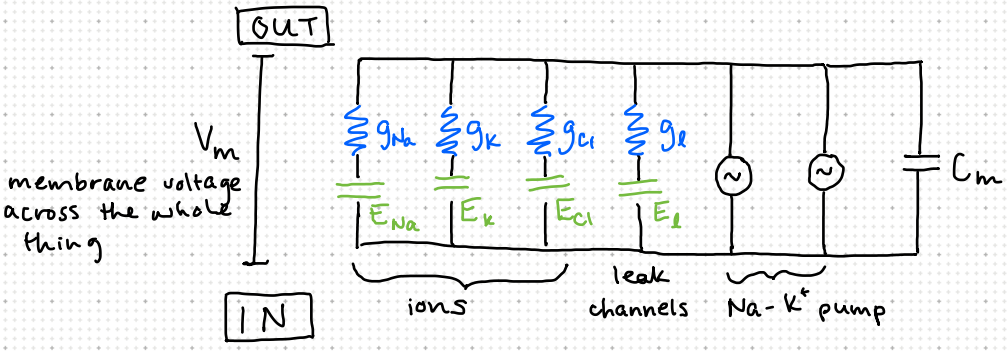
E = Nernst potential for an ion

$$= \frac{RT}{FZ} \ln\left(\frac{[S]_o}{[S]_i}\right) \approx \frac{25.693}{Z} \ln\left(\frac{[S]_o}{[S]_i}\right)$$

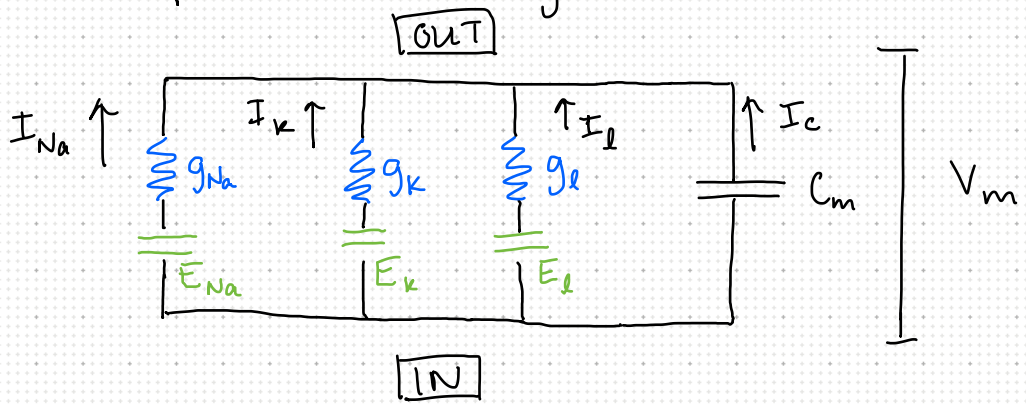
R: gas constant
T: temperature Kelvin
F: Faraday constant
Z: charge of ion
[S]: concentration of ion inside, outside cell

→ at room temperature, 25°C

For full circuit, include all ions and membrane capacitance:



In a simplified circuit, ignore Cl^- channels and Na-K pump.



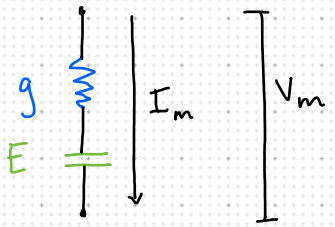
3 Kirchoff's and Ohm's Laws

Kirchoff: sum of all current into a node is the same as amount of current out of the node

$$I_m = I_{Na} + I_K + I_l + I_c$$

Ohm's Law: $V = IR$ and since $R = \frac{1}{g}$, $V = \frac{I}{g}$

For each <u>channel</u> (Na, K, leak) we want to find voltage drop.



Why? Because to understand how applying voltage affects the circuit (ie. how should we stimulate) we have to understand how it works normally.

From Ohm's Law, we know voltage drop across the resistor is

$$V = \frac{I}{g}$$

There is also extra voltage contributing since each channel has both a resistor <u>and</u> the Nernst potential.

$$V_m = \frac{I}{g} + E$$

Rearrange:

$$I = g(V_m - E)$$ for each channel.

The last part of that simplified circuit is capacitance of the membrane. Capacitance is related to the buildup of charge over time, so it's related to current (flow of charge) and membrane potential:

$$I_c = C_m \frac{dV_m}{dt}$$

∴ Substitute into Kirchoff's Current Law:

$$I_m = C_m \frac{dV}{dt} + g_{Na}(V_m - E_{Na}) + g_{ll}(V_m - E_{Na}) + g_l(V_m - E_l)$$

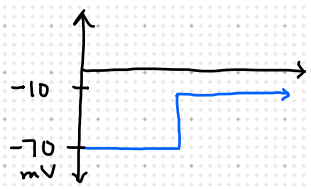
With <u>no</u> external sources of current, $I_m = 0$.

$$-C_m \frac{dV}{dt} = g_{Na}(V_m - E_{Na}) + g_{ll}(V_m - E_{Na}) + g_l(V_m - E_l)$$

4 Hodgkin and Huxley

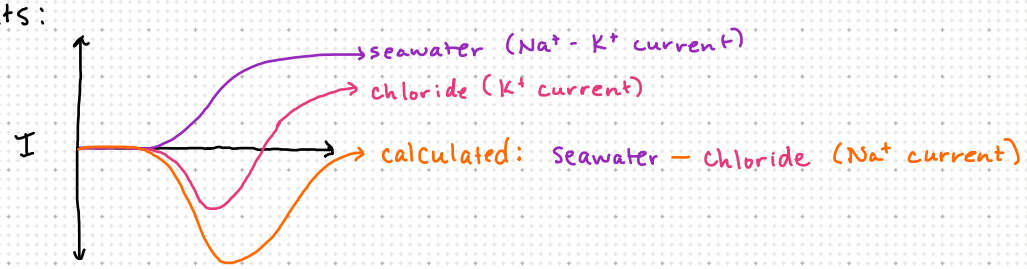
- Can measure V_m
- Can calculate Nernst potential E for an ion
- Want to know how different ion channels contribute to current flow in and out of cell. (Don't know how an action potential spreads until you know where the ions are.)
- Difficult to find conductance - changes over time and with different V_m
- Measure current to find conductance

Their experiment:



- Squid axons = very large
- Voltage clamp (control voltage of axon)
- in seawater: normal channel behavior
- in mix of seawater and isotonic chloride: almost no Na^+ current, purely K^+ current (too positive inside cell)

Results:



How much of an ion is moving across a membrane depends on:
- how likely the channel is to be open
- a channel has <u>gates</u>. All the right gates need to be open for the channel to be open.
  - → K^+: 4 gates to open
  - → Na^+: both activation and inactivation gates
    - (tend to open during action potential)
    - (tend to close during action potential)

Conductances are given by

$g_K = \overline{g_K}^{\text{max}} n^4$ $\quad g_{Na} = \overline{g_{Na}}\, m^3 h$

n, m, h = probability a gate is open

n, m = activation

h = inactivation

One more level of detail: How fast/slow do gates transition between states?

$$\text{CLOSED} \underset{\beta}{\overset{\alpha}{\rightleftarrows}} \text{OPEN}$$

α, β = transition rate constants

P = proportion of open gates

βP = fraction of gates closing

$\alpha(1-P)$ = fraction of gates opening

$$\frac{dP}{dt} = \alpha(1-P) - \beta P$$ Change in proportion of open gates over time

Solve for transition rates for activation and inactivation gates n, m, h.

activation gates:

$$\alpha_n = \frac{0.01(10-\Delta V)}{e^{(10-\Delta V)/10}-1} \qquad \beta_n = 0.125 e^{-\Delta V/80}$$

$$\alpha_m = \frac{0.1(25-\Delta V)}{e^{(25-\Delta V)/10}-1} \qquad \beta_m = 4 e^{-\Delta V/18}$$

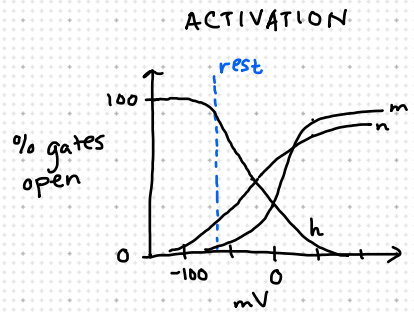
inactivation gates:

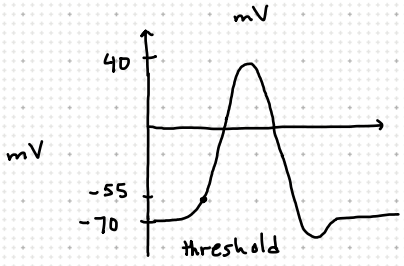
$$\alpha_h = 0.07 e^{-\Delta V/20} \qquad \beta_h = \frac{1}{e^{(30-\Delta V)/10}+1}$$

Since this is all varying over time, it's useful to understand activity in terms of a time constant.

$$\tau = \frac{1}{\alpha+\beta}$$ very small τ means with ΔV, it will reach new equilibrium quickly.

Gate Behavior



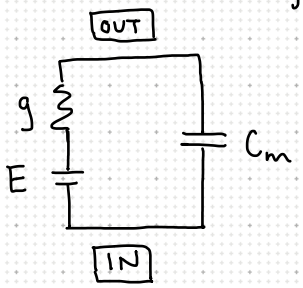


- At 55mV (threshold), m gates begin to open and h gates begin to swing closed (ball and chain) → Na^+ out
- As mV ↑, n gates open → K^+ into cell
- Because inactivation gates (h) take time to open again, there is a hyperpolarization period immediately after action potential. There is about 1ms refractory period while these gates are closed when it is impossible to produce another action potential

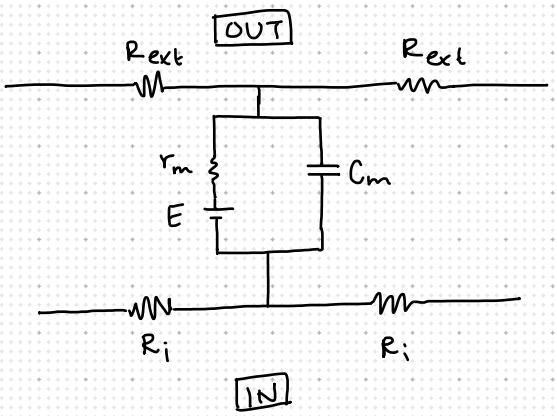
5 The Cable Equation - How does an action potential travel? (Undersea cables)

Ways to lose current during travel:
- resistance inside cell / cable
- leak through membrane

Equivalent circuit: typical patch of membrane



Equivalent circuit: including internal resistance



Ease of producing an action potential and how far/fast it travels:

$$\frac{r_m}{r_i} \cdot \frac{\partial^2 V}{\partial x^2} = c_m r_m \frac{dV}{dt} + V$$

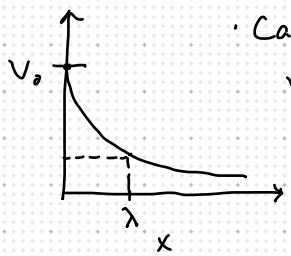
* derivation in extra notes

$\frac{r_m}{r_i} = \lambda^2$ — length constant

$c_m r_m = \tau$ — time constant

↑ CABLE EQUATION (without injected current)

- Also derived from Kirchoff's Current Law
- Can find steady-state solution to find voltage drop off with distance / time from stim electrode (example in extra notes)



- length and time constants change with axon diameter, myelination, # ion channels
- length constant - related to potential difference across the membrane and how it changes
  ↳ Does an action potential travel farther in larger or smaller axons?

$r_m \propto \frac{1}{2\pi a}$ $\quad r_i \propto \frac{1}{\pi a^2}$ $\quad \frac{r_m}{r_i} \propto a$ so there is a larger length constant in large cables

- time constant - how long does it take to "charge"? How quickly does it respond to external changes in voltage (stimulation)?

$c_m \propto 2\pi a \longrightarrow r_m c_m \propto 1$ so time constant is not affected by diameter

- myelination $\uparrow \lambda^2$, $\uparrow \tau$

- "ideal" neuron might respond instantly to stimulation and perfectly propogate action potential: $\lambda^2 = \infty$, $\tau = 0$. That is not possible...

Extra Notes: Deriving the Cable Equation

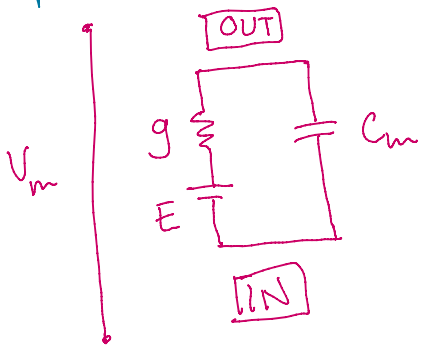
Just talked about giant squid and we've got a good thing going with that general underwater theme... what we should look at that would help describe how action potentials travel in neurons?

- How A.P. travel
- How injecting current causes A.P. to travel
- Practical realities of stimulation

→ underwater telephone cables! → conductive inside, insulator, saline outside

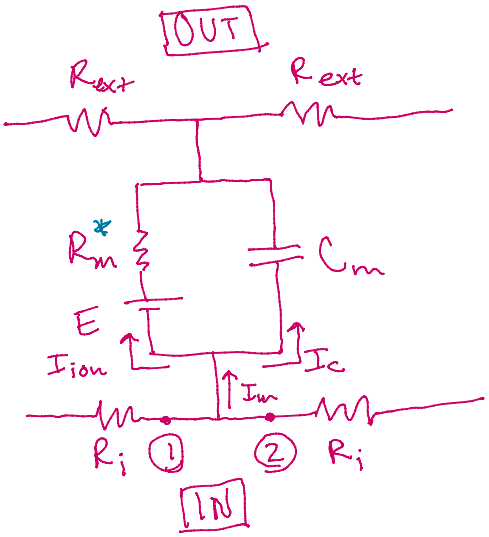
CABLE EQUATION

Remember how a patch of membrane looked in our equivalent circuit?



If we consider how this looks in a wider patch of membrane, also need to consider internal resistance of the axon:

So a new + improved equivalent circuit might look like this:



* looking at memb. resistivity instead of conductance this time-

What's the difference?

- g - ease of current travel
- R - difficulty "

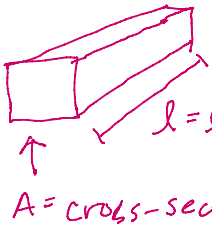
This time, we want to know more about memb. cap. & res., and R_i (internal resistance) because those affect how the action potential travels. Starting with internal resistance:

A block of material that is 1 cm on all sides has a certain...

ρ = specific resistance*

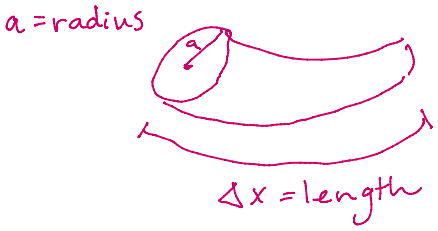
* get this value from a lookup table

Resistivity of that block of material is calculated by finding out how much of the material is there to do the resisting:



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

Then applying that to internal resistance of the axon:



resistivity of a little slice:

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

resistivity of the whole thing:

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

We also want to know how current changes as it passes through the axon, we can rearrange $V = IR$ to get

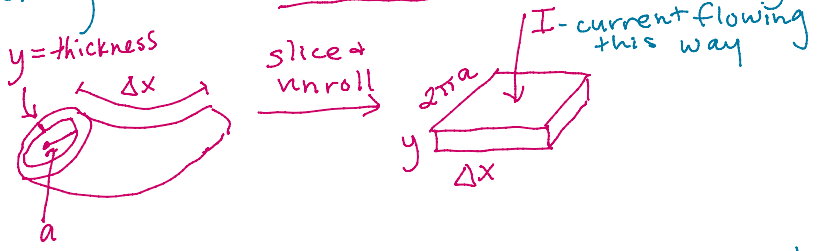
$$\Delta V = -I_i r_i \Delta x \quad \text{(negative because of the voltage drop)}$$

$$-I_i = \frac{\Delta V}{r_i \Delta x}$$

lim as $x \to 0$

$$-I_i = \frac{1}{r_i} \frac{\partial V}{\partial x}$$

Now looking at the membrane factors affecting charge:



We can do the same thing as before, where we look at a little slice:

$$r_m = \frac{\rho_m y}{2\pi a}$$

then at resistivity of the whole thing:

$$R_m = \frac{r_m}{\Delta x} = \frac{\rho_m y}{2\pi a \Delta x}$$

Similarly, we look at capacitance as a slice and for the whole thing:

$\mathcal{E}$ = specific capacitance

$$C = \frac{\mathcal{E} A}{l}$$

$$c_m = \frac{\mathcal{E}_m 2\pi a}{y}$$

$$C_m = c_m \Delta x = \frac{\mathcal{E}_m 2\pi a \Delta x}{y}$$

Now we know enough details to go back to equiv. circuit and derive cable equation!

Remember Kirchoff's Current Law? Current into node = current out

SO... $I_m = I_c + I_{ion}$

$I_m = \Delta I_i$ between pts. ① and ②

$I_c = C_m \frac{dV}{dt}$ * should sound familiar

$= c_m \Delta x \frac{dV}{dt}$ *want to look at how it changes in tiny slices

$I_{ion} = \frac{V}{R_m}$

$= \frac{V \Delta x}{r_m}$

Again negative due to voltage drop

$$-\Delta I_i = c_m \Delta x \frac{dV}{dt} + \frac{V \Delta x}{r_m}$$ divide by Δx

$$-\frac{\Delta I_i}{\Delta x} = c_m \frac{dV}{dt} + \frac{V}{r_m}$$

Take $\lim_{\Delta x \to 0}$

$$-\frac{\partial I_i}{\partial x} = c_m \frac{dV}{dt} + \frac{V}{r_m}$$

$$-I_i = \frac{1}{r_i}\frac{\partial V}{\partial x}$$

From before

$$\frac{-\partial I_i}{\partial x} = \frac{1}{r_i}\frac{\partial^2 V}{\partial x^2}$$

$$\frac{1}{r_i}\frac{\partial^2 V}{\partial x^2} = c_m \frac{dV}{dt} + \frac{V}{r_m}$$ multiply by r_m

$$\boxed{\frac{r_m}{r_i}\frac{\partial^2 V}{\partial x^2} = c_m r_m \frac{dV}{dt} + V}$$ Cable equation

Two constants in this equation.

(1) Length constant:

$$\lambda^2 = \frac{r_m}{r_i}$$. This can be rewritten a couple of ways.

$$\lambda = \sqrt{\frac{r_m}{r_i}} = \sqrt{\frac{1}{g_m r_i}} = \sqrt{\frac{R_m}{2R_i} \cdot a}$$

λ is proportional to $\sqrt{a}$ so potentials spread farther in larger cylinders.

② Time constant:

$$\tau = c_m r_m = \frac{c_m}{g_m}$$

↑ * NOTE this time constant is different from the one we discussed last time.

→ What Δ length / time constants? # ion channels, size of axon, myelination

If we find a steady state solution to the Cable Eq, we can see how the length constant affects membrane voltage.

Let $\frac{\partial V}{\partial t} = 0$ because no Δ in process

$\lambda^2 \frac{\partial^2 V}{\partial x^2} = V$ then use diff. eq. to find an analytical solution.

$V = Ae^{-|x|/\lambda} + Be^{|x|/\lambda}$ where A and B are constants

Look at it where $x \to \infty$

That means we're very far from the stim. electrode so $V \to 0$

$$0 = Ae^{-\infty/\lambda} + Be^{\infty/\lambda}$$

$$0 = 0 + Be^{\infty/\lambda}$$

$$\therefore B = 0$$

Then look at $x = 0$

No voltage drop because you're at the stim electrode so

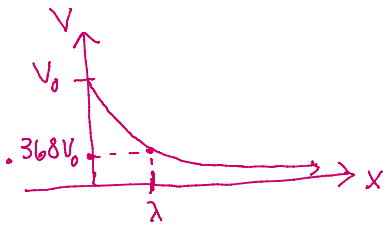
$$V = V_0 = Ae^{0/\lambda}$$

$$V_0 = A(1)$$

$$V_0 = A$$

Thus the steady-state solution is

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



Where $x = \lambda$

$$V = V_0 e^{-\lambda/\lambda}$$

$$V = V_0 e^{-1}$$

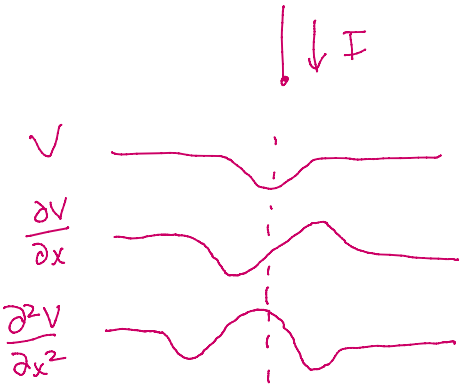
$$V = 0.368\, V_0$$

Now, if we want to add injected current into the Cable Equation, the difference is that we can't ignore I_{ext} anymore. So we have:

$$\lambda^2 \frac{\partial^2 V_m}{\partial x^2} - V_m - \tau \frac{\partial V_m}{\partial t} = \underbrace{-\lambda^2 \frac{\partial^2 V_{ext}}{\partial x^2}}_{\text{activating function}}$$

- Activating function allows us to see how injecting current affects the axon.
  → where axon is hyperpolarized/depolarized

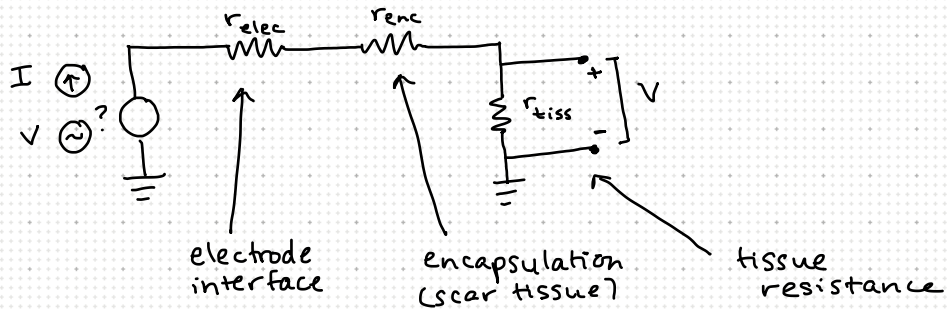
So what does happen when we stimulate? Let's make a graph.



- Similar math at play in Schrodinger's equation (if you're ever interested in particle physics...)
- Usually inject cathodal current (= negative) – why? To depolarize cell

* Act. Fn It's possible if you stimulate at very high currents to cause a current block on either side of injected I.

1 External Sources of Current

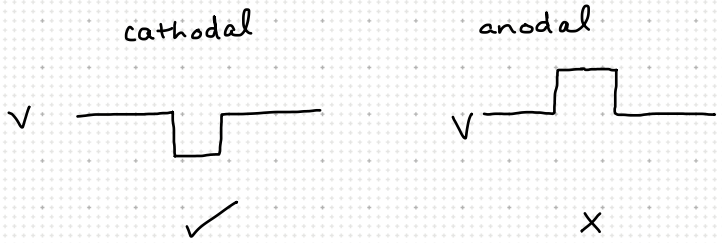


$$V = V_{source} - V_{elec} - V_{enc}$$

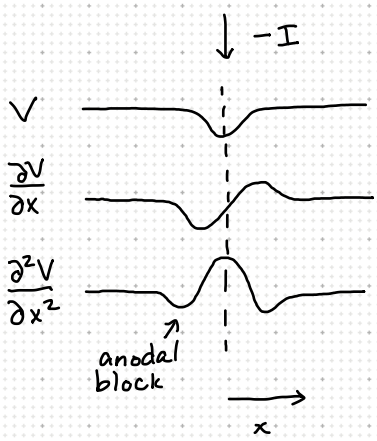
$$V = V_{source} - I_{source}(R_{elec} + R_{enc})$$

- R_{enc} changes over time, so I_{source} must increase, changing V
- With <u>current</u> stim, I_{source} stays constant so you always deliver same amount of charge

To depolarize the cell... cathodal or anodal stimulation?



Activating function: allows us to see how injecting current affects the cell (where axon is hyperpolarized / depolarized)



membrane potential along axon

change in membrane potential

* Activating function: describes locations most and least able to produce an action potential. Wells on either side of injected current can produce a block with sufficiently high stimulation amplitude.

Cable equation with injected current:

$$\lambda^2 \frac{\partial^2 V}{\partial x^2} - V_m - \tau \frac{\partial V_m}{\partial t} = -\lambda^2 \frac{\partial^2 V}{\partial x^2}$$

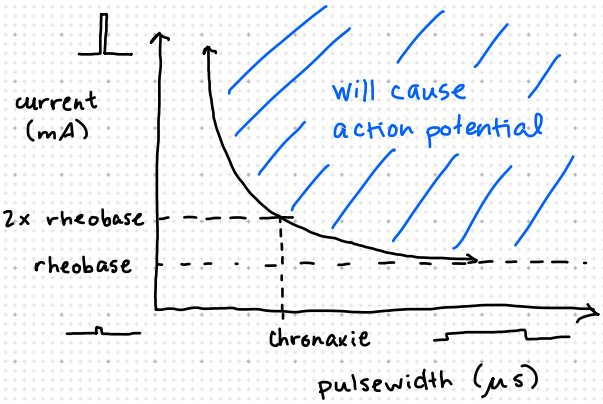
activating function

- refers to part of the equation
- How does this change with length constant? (bigger λ^2 → easier to activate)

2 Chronaxie and rheobase

Things you can change about a stim pulse:
- amplitude
- pulse width
- charge balance
- # repetitions
- frequency
- current vs. voltage

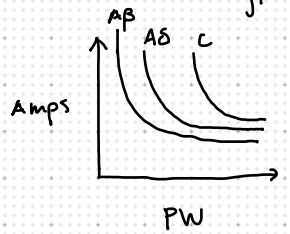
] most directly affect amount of current injected



RHEOBASE - below this amplitude, you will never cause action potential no matter how long you stimulate

CHRONAXIE - a good "minimum length of time", it's the point on curve at 2x rheobase.

Different nerve types have different curves.

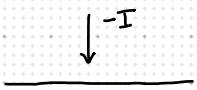


Aβ — larger axon, more myelin

↓

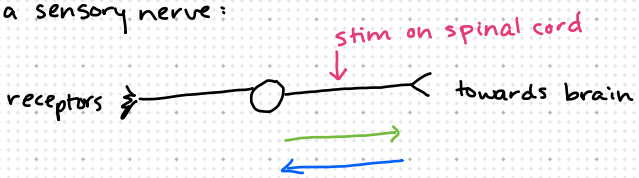
C — smaller axon, less myelin

3 Where does the action potential travel when you stimulate?



Action potentials travel <u>both</u> directions from the point of stimulation

In a sensory nerve:



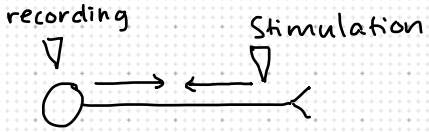
- Orthodromic - waves travel in the <u>normal</u> direction along a neuron
  in a sensory neuron, this is towards the brain
- antidromic - waves travel <u>backward</u> along neuron
  in a sensory neuron, this is towards the body

Examples: our experiments include peripheral nerve recording
stimulating motor neurons
↳ these produce action potentials in both directions but often we focus on one direction

★ Collision testing - if a cell produces an action potential and you stimulate to produce an action potential, they can cancel each other out.
- can determine how two areas are connected

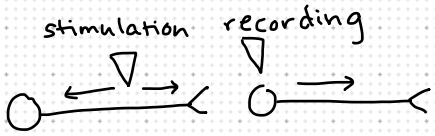
Given: recording electrode and stimulation electrode
recording electrode must record from cell body
stimulation electrode can be anywhere along the neuron

PASSING EXAMPLE (action potentials cancel)



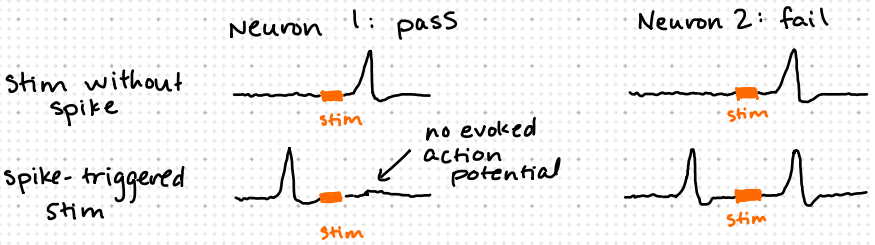
- Place a recording elec. in one area and a stim. elec. in another.
- Immediately after you record an action potential from rec. elec, stimulate on the other
- The action potential recorded will travel orthodromically along neuron
- If the stimulation electrode is on the axon of that nerve, the antidromic action potential will collide with the one already travelling orthodromically
- because the axon will still be in the refractory period, the action potentials cannot travel past each other

FAILING EXAMPLE (action potentials do not cancel)



- recorded spontaneous pulses are moving orthodromically away from stimulation electrode
- stim-evoked spikes that reach recording electrode are also moving orthodrom so they do <u>not</u> collide and by the time the arrive the refractory period is over.
- this stim-evokes spike crosses synapse - will have less consistent timing.

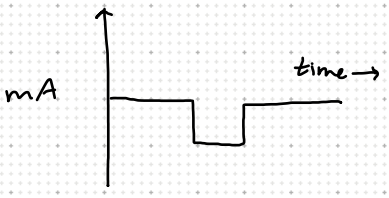
EXAMPLE RECORDINGS



4 Applying a stimulus pulse

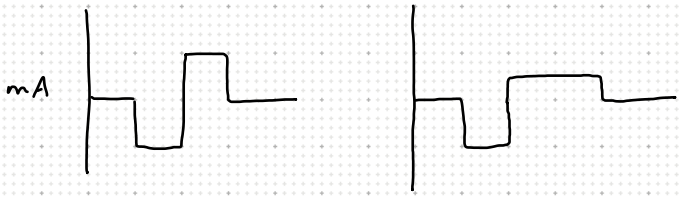
Stim locations include: on an organ
peripheral nerve (afferent, efferent)
dorsal root ganglion, ventral roots
epidural spinal cord
penetrating electrode in cord
brain (motor, sensory areas, collision testing)

Choosing a pulse:



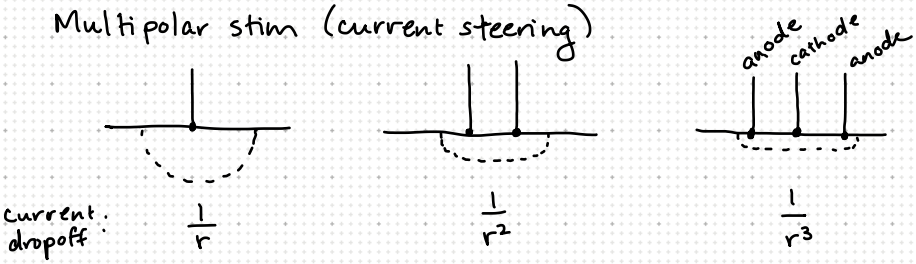
Simple cathodal stimulus (→ choose polarity)
- change amplitude
- change pulsewidth

To improve safety for tissue, add charge balancing. → reduces formation of toxic compounds due to corrosion at electrode



Vary frequency - often changes functional effect
- bladder
- biomimetic - sensory input

Multipolar stim (current steering)



★ For more info about dropoff, see steady-state solution in the additional notes with proof of the cable equation.

example (on spinal cord)