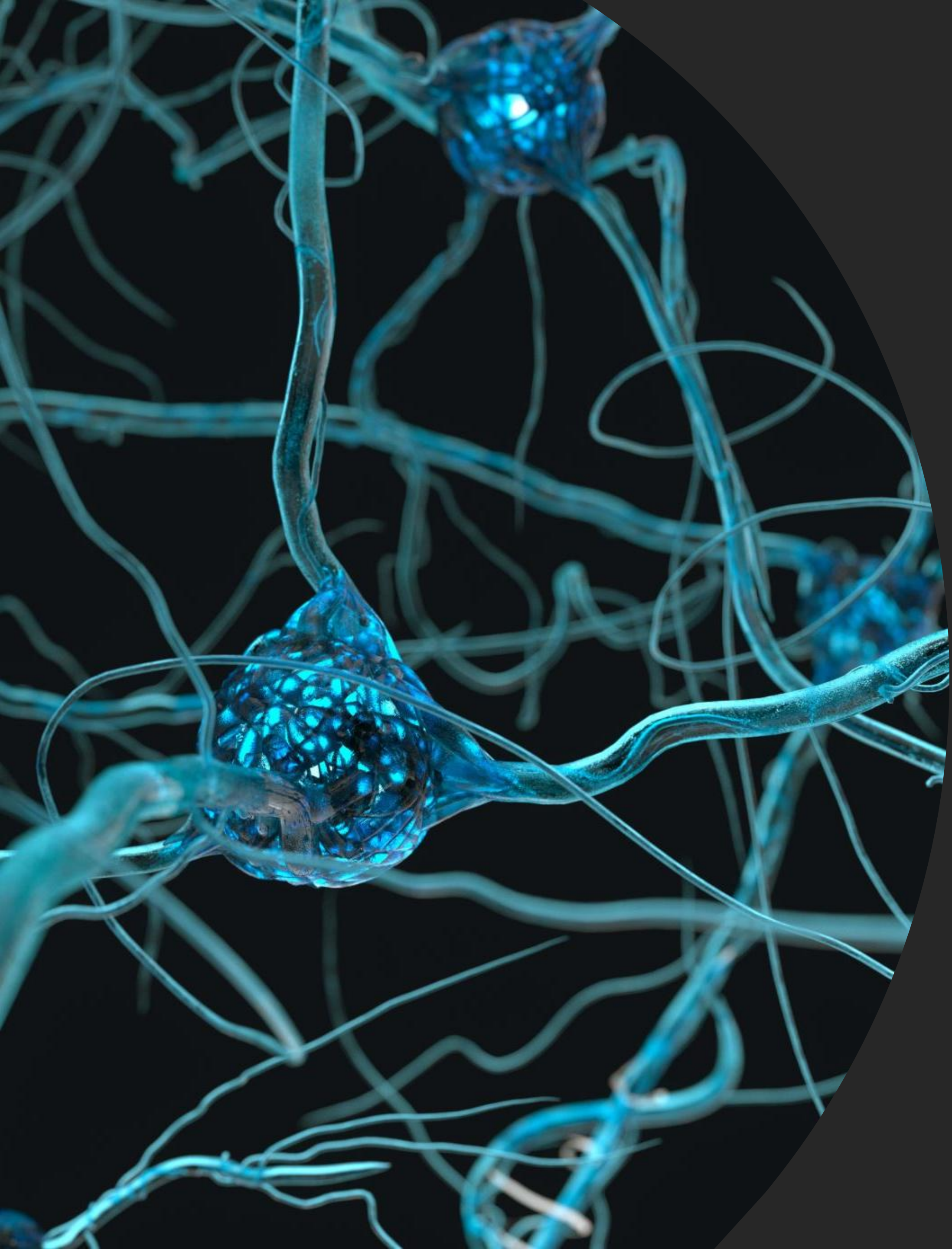
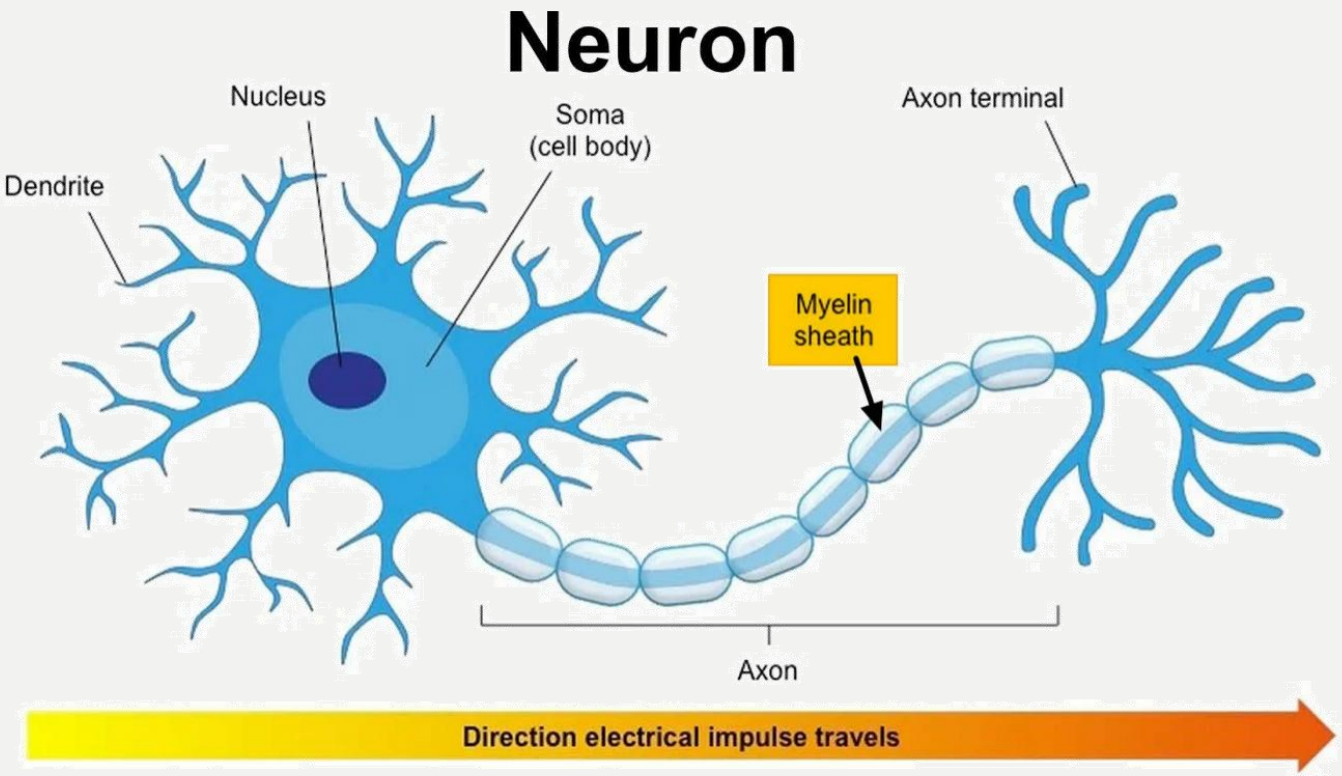


Neural Circuitry

Nino Koci

What is a Neuron

- A type of cell that is specialized with sending signals within the nervous system
- Neurons have many shapes and sizes. However, all neurons contain specific structures that allow them to propagate signals



Neuronal Properties

- Neurons are unique in that they maintain ion gradients

  High K^+ and Cl^- inside, High Na^+ outside

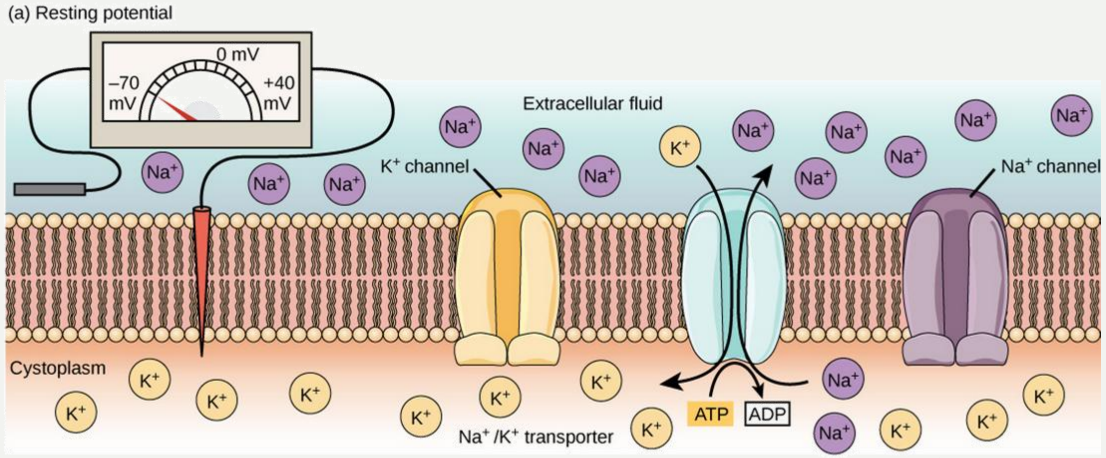
- The cellular phospholipid bilayer separates these ions

  Each ion has its potential that we can measure through the Nerst equation

  This creates a membrane potential that can be measured through the Goldman equation

- For these ions to diffuse and achieve equilibrium, they require the assistance of ion channels

  These channels are voltage-gated and will only open once the membrane potential changes



$$V_{\text{Eq.}} = \frac{RT}{zF} \ln\left(\frac{[X]_{\text{out}}}{[X]_{\text{in}}}\right)$$

$$V_{\text{m}} = \frac{RT}{F} \ln\left(\frac{p_{\text{K}}[\text{K}^+]_{\text{o}} + p_{\text{Na}}[\text{Na}^+]_{\text{o}} + p_{\text{Cl}}[\text{Cl}^-]_{\text{i}}}{p_{\text{K}}[\text{K}^+]_{\text{i}} + p_{\text{Na}}[\text{Na}^+]_{\text{i}} + p_{\text{Cl}}[\text{Cl}^-]_{\text{o}}}\right)$$

Action Potentials

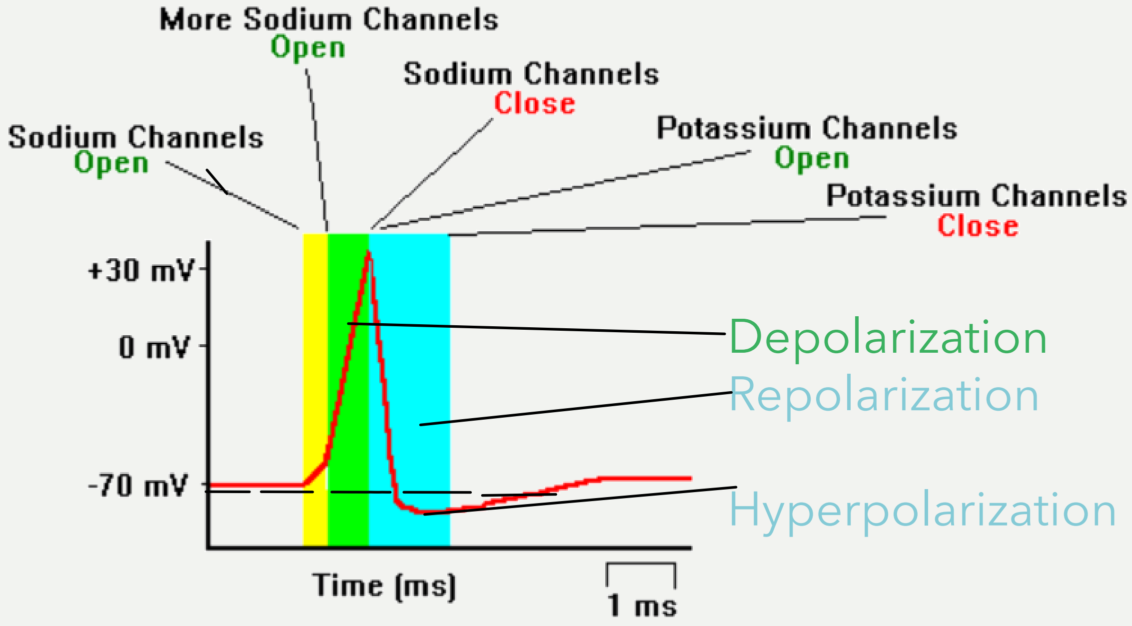
- Neurons propagate action potentials to send signals
- Depolarization occurs as Na^+ enters the cell

  The membrane becomes more positive

- At peak Na^+ voltage-gated channels deactivate and K^+ voltage-gated channels open

  Na^+ channels lock once the membrane potential is high

- After the peak, the cell polarizes until it hyperpolarizes when the K^+ exits the cell
- Potential is re-established through the Na^+/K^+ pump



How does this Translate into Circuits?

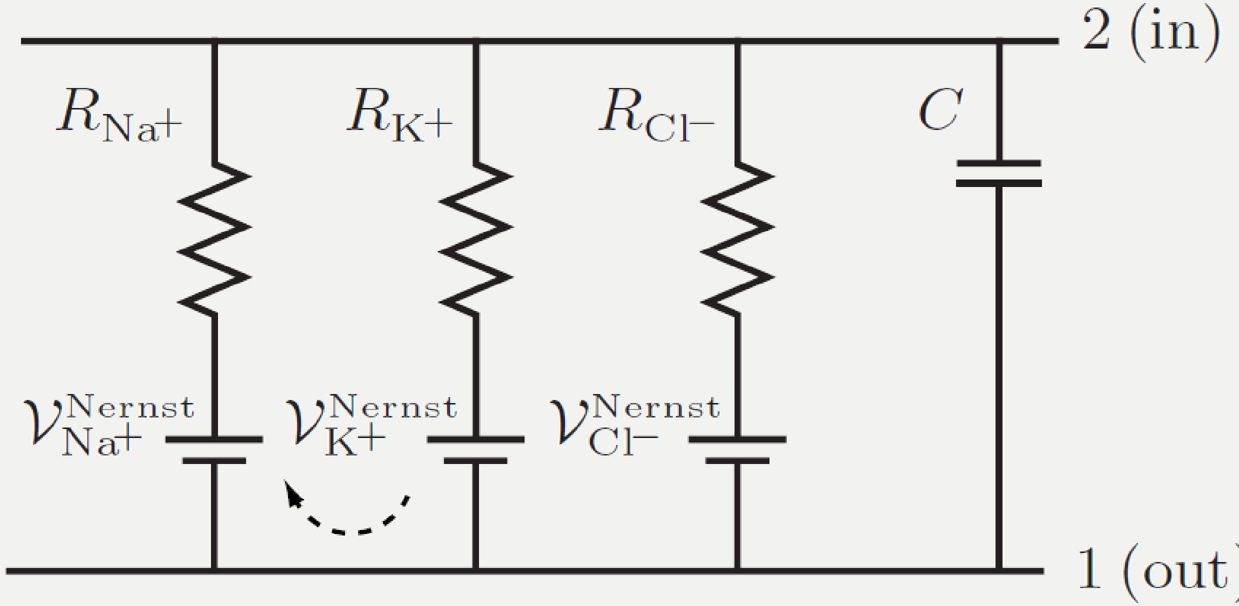
- We can translate the neuronal properties into the same proprieties that a circuit would have

  Voltage(V) is equivalent to the membrane potential, driving the energy in the membrane like a battery

  Ion channels determine the flow of ions and can stand for resistance(R) or conductance (g=1/R)

  Since the membrane separates the charges and acts like a capacitor, it can stand for capacitance(C)

  Ionic flow stands for current(I)



Driving Force

- Each ionic current(I_{ion}) is influenced by diffusion equilibrium (E_{ion})and the membrane potential (V_m)

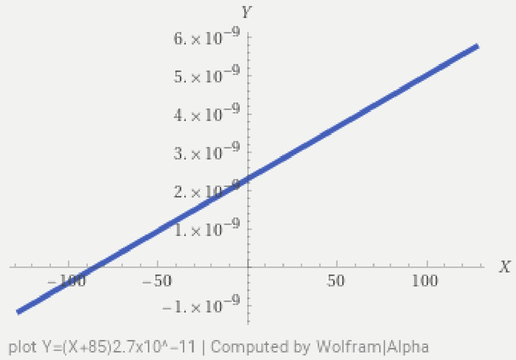
  Ohms law: $I=V/R=gV \Rightarrow I_{ion}=g_{ion}V_m$

  At equilibrium: $I_{ion}=g_{ion}E_{ion}$

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

- This combination is the driving force of an ion

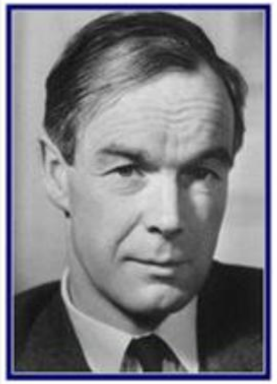
I_{Na+} vs. V_m plot

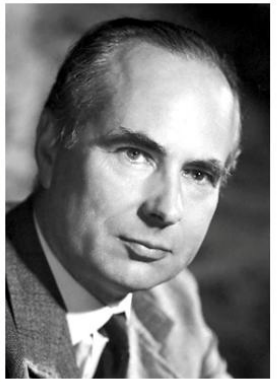


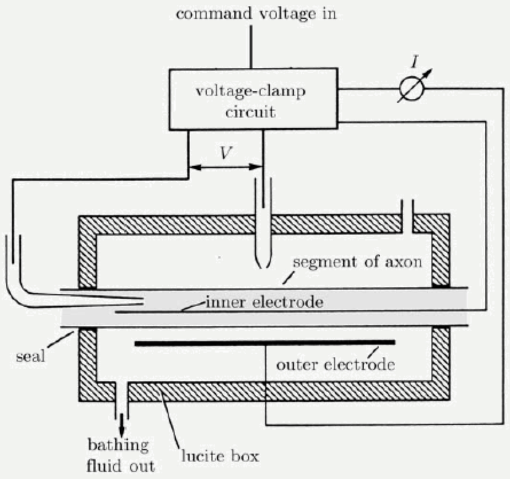
I_{K+} vs. V_m plot

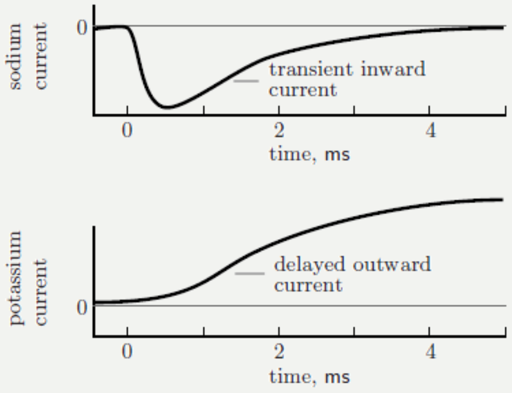
Hodgkin & Huxley

- Tested the strength of the currents present in the giant squid axon through voltage clamping
- They discovered that there is an initial interior Na^+ current that is then followed by an exiting K^+ current
- Therefore, Na^+ ions will begin to enter and depolarize the neuron until its deactivated
- K^+ ions leave following the opening of their voltage-gated channels









Single RC Circuit

- Let's consider the membrane as a RC circuit
- We have the membrane as a capacitor(C), and ions will flow out due to the leakiness of the membrane($1/R_r=g_r$)
- We know that we will have three currents

  Capacitive(I_C) and Leak(I_r) leave, and Sodium(I_{Na+})goes into the cell

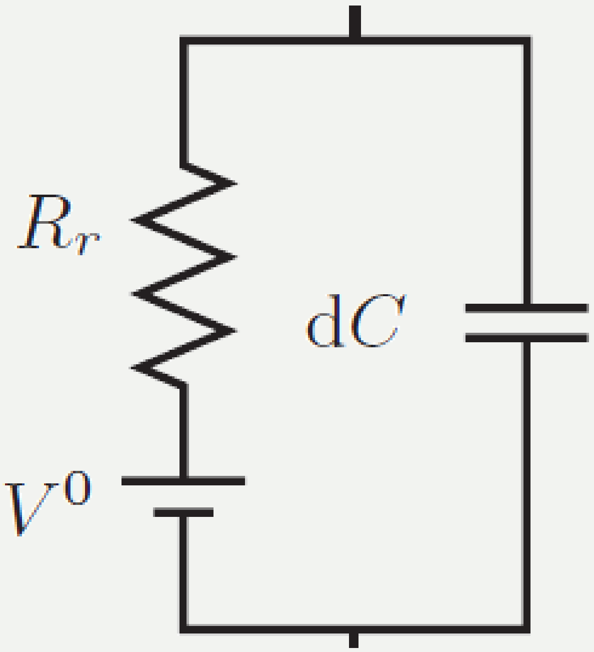
  $I_C+I_r= I_{Na}$
- Now, let's calculate the potential when the driving current flows

  $I_{Na}=C_m\,(\frac{dV}{dt})+V_m g_r \Rightarrow \frac{I_{Na}}{g_r} = \frac{C_m}{g_r}(\frac{dV}{dt})+V_m$

  Assume steady state: $(\frac{dV}{dt})=0 \Rightarrow \frac{I_{Na}}{g_r}=V_{max}$

  Substitute $\frac{C_m}{g_r}$ *for* τ *and solve for* $(\frac{dV}{dt})$

  $V_m(t)=V_{max}[1-(e^{-t/\tau})]$*(the capacitor is charging)*



Single RC Circuit(cont.)

- Assume the ion flow is successful and there is now no more sodium flow(I_{Na}=0)

  $0=C_m(\frac{dV}{dt})+V_m g_r=\frac{C_m}{g_r}(\frac{dV}{dt})+V_m$

  Substitute C_m/g_r for τ

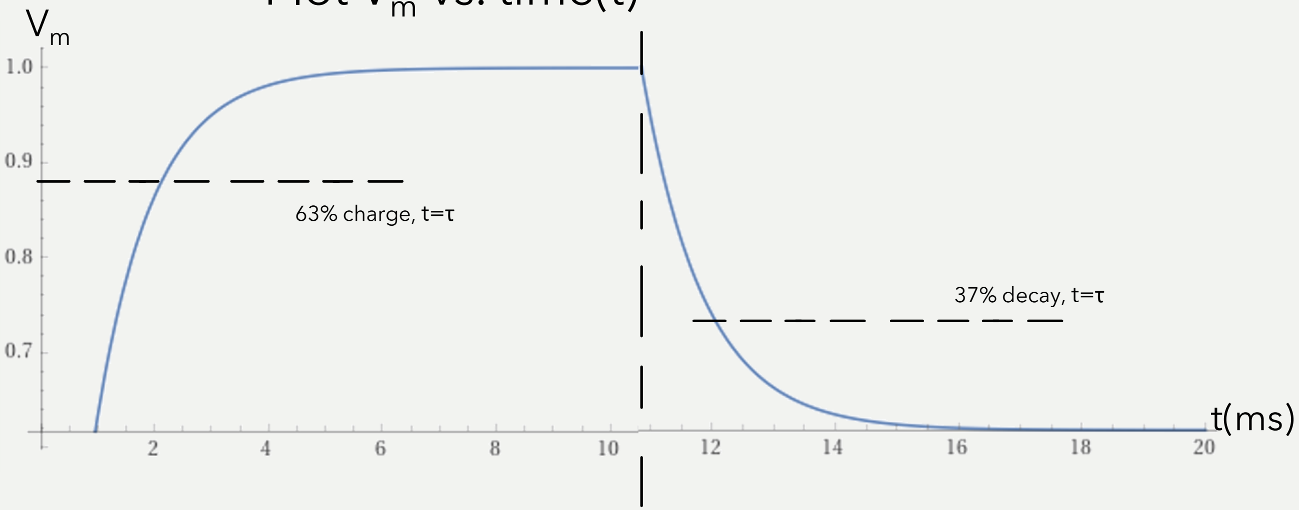
  Solve for $(\frac{dV}{dt})$ ➡ $V_m(t)= V_{max}[e^{-t/\tau}]$, the capacitor is discharging

- The τ constant will be the innate time factor that will determine how long the membrane potential can increase, or decay while maintaining its potency

  In charging when $t=\tau$, V_0 reaches to 63% of V_{max}

  In discharging when $t=\tau$, V_{max} decays to 37%

Plot V_m vs. time(t)



The Neuron as a Cable

- Let's consider the neuron a cylindrical cable with multiple connected RC circuits, with the cytoplasm acting as a buffer that offers resistance
- Let's derive an equation based on a junction(Nelson eq.12.6)

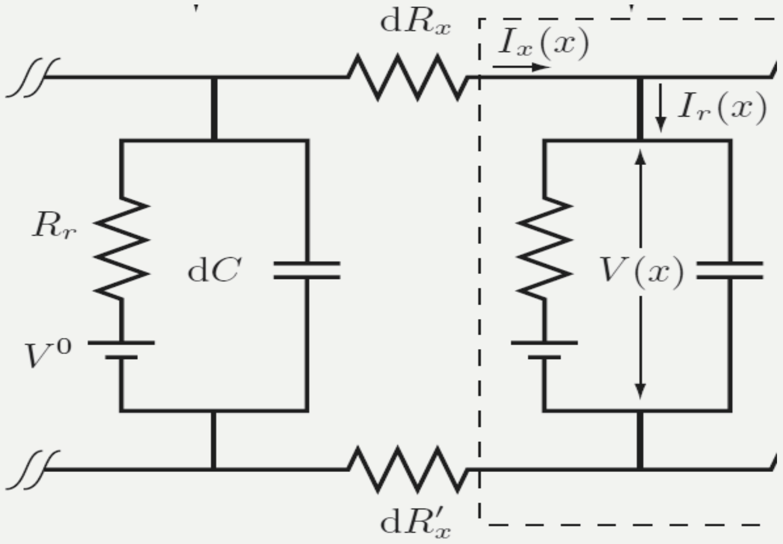
$$I_x(x) - I_x(x+dx) = -dI = 2\pi r(j_{q,r}(x) + C_m(\frac{dV}{dt}))\ dx$$

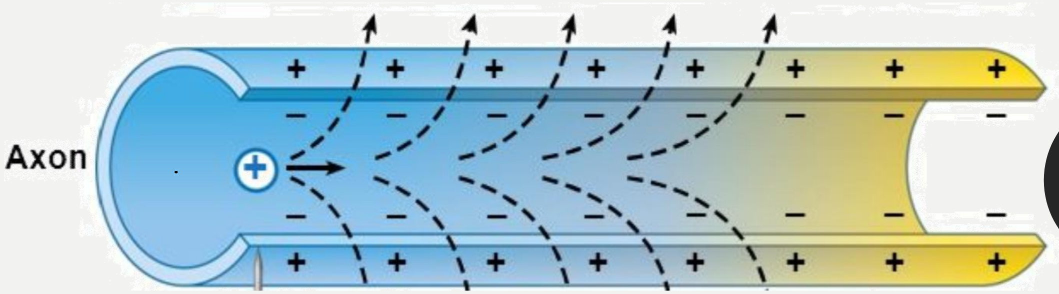
- Let's solve the equation and assume $j_{q,r}=g_r(V_m-V_0)$

$$r^2\pi\kappa\ (\frac{d^2V}{dx^2})=2\pi r(g_r(V_m-V_0)+C_m(\frac{dV}{dt}))\ \text{(Nelson Eq. 12.7)}$$

$$\frac{r\kappa}{2g_r}(\frac{d^2V}{dx^2})=(V_{max}-V_0)+\frac{C_m}{g_r}(\frac{dV}{dt}) \Rightarrow \lambda^2(\frac{d^2V}{dx^2})=(V_m-V_0)+\tau(\frac{dV}{dt})$$

Where $\frac{r\kappa}{2}$ is the axial cytoplasmic conductance and g_r is the total membrane conductance for ions





The Neuron as a Cable(cont.)

- Since we know τ, let's look at how λ impacts voltage

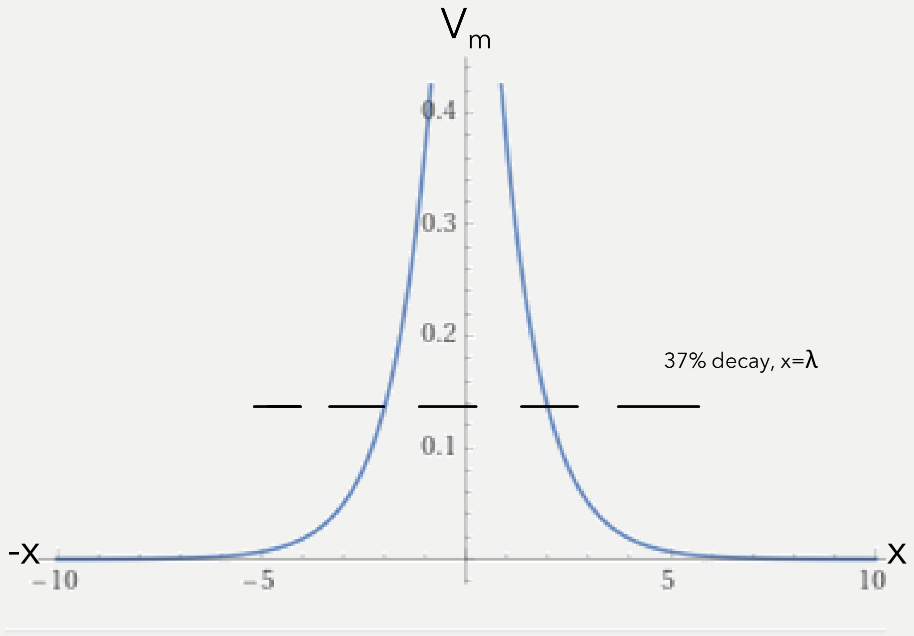
  $\lambda^2(\frac{d^2V}{dx^2})=(V_m\text{-}V_0)+\tau(\frac{dV}{dt})$, *assume* $\tau=0$ *and solve for* $\frac{d^2V}{dx^2}$

  $V_m=V_0\,(e^{-|x|/\lambda})$

- λ, like τ, will represent a space constant innate within a cell that determines how far will the membrane potential go while maintaining its potency

  In this case, λ will represent the distance(x) when V_m *decays to 37% of its original value*

Plot V_m vs. distance(x)



Putting this Together

- We can now establish a good model that explains the conductivity of a current inside a neuron
- We can see from our space and time factors (λ and τ) that when the initial current carries the Na^+ ions come in, they behave similarly to a diffusion response and spread passively in the membrane

  Passive spread derivation: $v(x, t) = (e^{-t/\tau})(t^{-1/2})(e_{-}^{x^2/(4t\lambda 2/\tau)})$ (Nelson Eq.12.10)
- Through passive spread, these ions can be quick in traveling and depolarizing a cell and, therefore, initiating future action potentials down the cell

Biological Optimizations: Giant Squid Axon

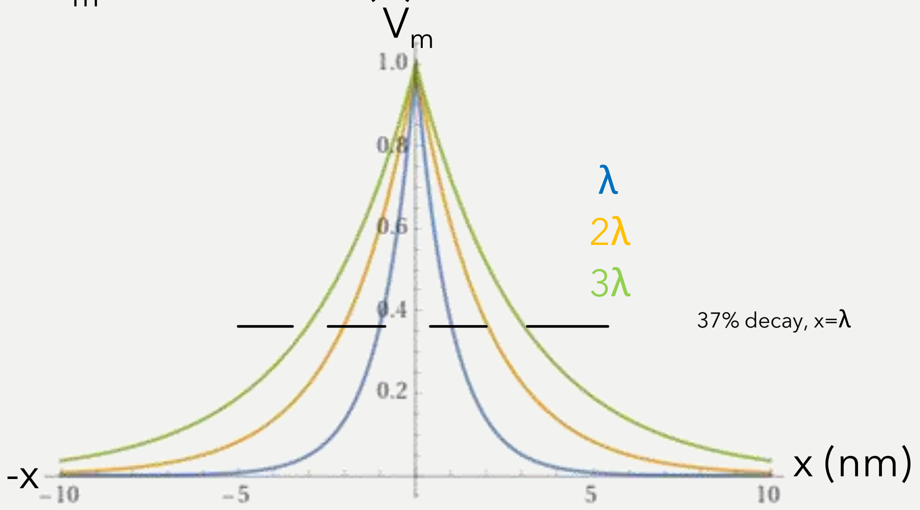
- Why do squid have such fast responses?
- Squids have large axons that carry the signal fast
- We know that the λ constant will increase with an increase in cytoplasmic conductivity as $\frac{r\kappa}{2}$ increases

  g_r also increases, but this is countered by an increase in Na^+ channels too

- This would make the charge move further down the axon without any cytoplasmic interference or risk of losing potential due to leakiness

  Na^+ can move further along the axon and depolarize the membrane faster and with greater coverage

Plot V_m vs. distance(x) for different λ values

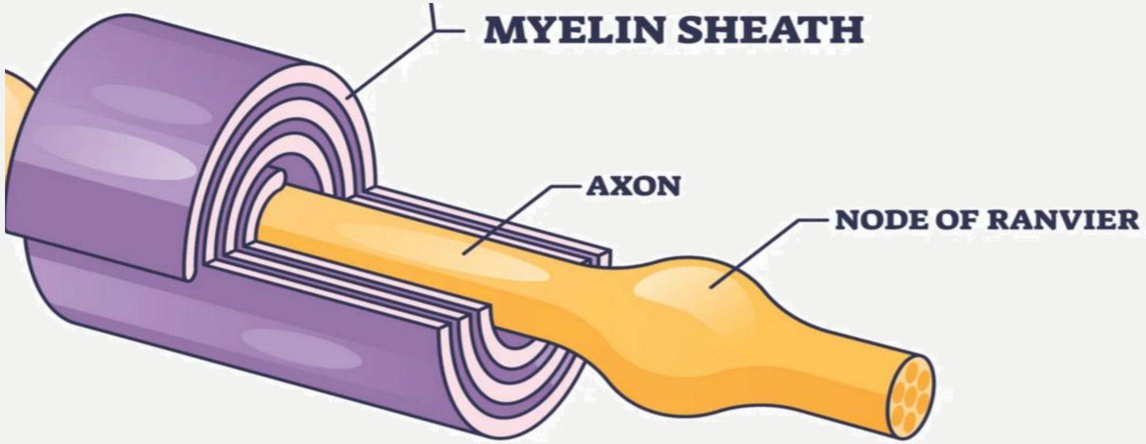


Biological Optimizations: Myelin

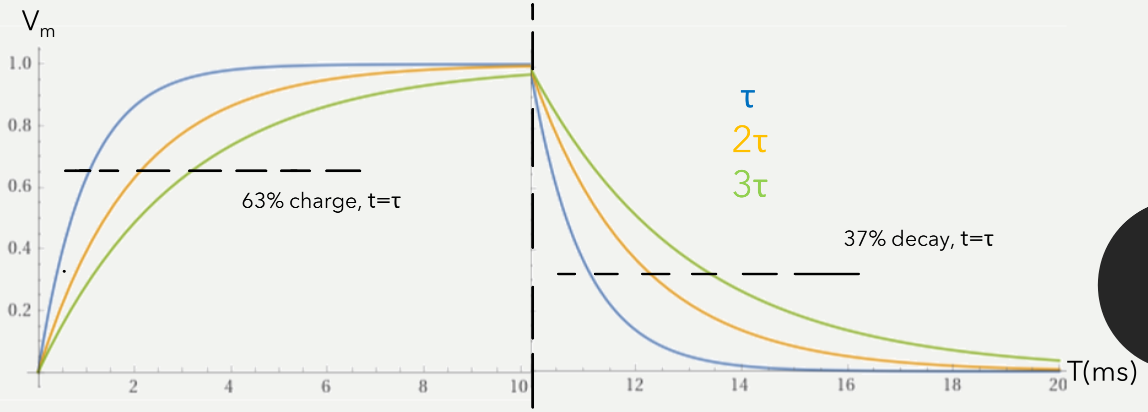
- Let's consider our cells compared to the squid

  If our optical neuron were on scale with the giant squid axon, it would end up being 1m long

- How do we solve this issue? Myelin
- Myelin is a coating of cells in a neuron that leaves small relay junctions to generate APs
- Schwann cells act like parallel capacitors and insulation, increasing C_m and g_r and, therefore, τ
- With a higher τ value, the current can propagate faster without losing its potency
- In disorders that involve loss of myelin, like multiple sclerosis, patients often experience sudden paralysis as the signal is not fast enough to relay



Plot V_m vs. time(t) for different τ values



Acknowledgments

- I would like to thank my group for helping me assemble this presentation (You guys rock!!!!)
- I would also like to thank my mom, sis, and gf for sitting through and hearing me prepare for this presentation
- I also would like to thank Professor Cebe for supporting and permitting me to present this fascinating topic
- Finally, I would thank Dr. Barry Trimmer for giving me much background on this topic in Neurobiology

References

- https://www.simplypsychology.org/myelin-sheath.html
- https://www.physiologyweb.com/calculators/nernst_equation_calculator.html
- https://www.physiologyweb.com/calculators/ghk_equation_calculator.html
- https://openbooks.lib.msu.edu/neuroscience/chapter/membrane-potential/
- https://courses.lumenlearning.com/wm-biology2/chapter/resting-membrane-potential/
- https://mrgreene09.github.io/computational-neuroscience-textbook/Ch4.html
- http://pittmedneuro.com/synaptic.html
- Nelson *Biological Physics: Energy, Information, Life* Chapter 12
- Montanino, A., Deryckere, A., Famaey, N. *et al.* Mechanical characterization of squid giant axon membrane sheath and influence of the collagenous endoneurium on its properties. *Sci Rep* **9**, 8969 (2019). https://doi.org/10.1038/s41598-019-45446-y
- Sakmann B, Trube G. Conductance properties of single inwardly rectifying potassium channels in ventricular cells from guinea-pig heart. J Physiol. 1984 Feb;347:641-57. doi: 10.1113/jphysiol.1984.sp015088. PMID: 6323703; PMCID: PMC1199469
- Milburn T, Saint DA, Chung SH. The temperature dependence of conductance of the sodium channel: implications for mechanisms of ion permeation. Recept Channels. 1995;3(3):201-211. PMID: 8821793.