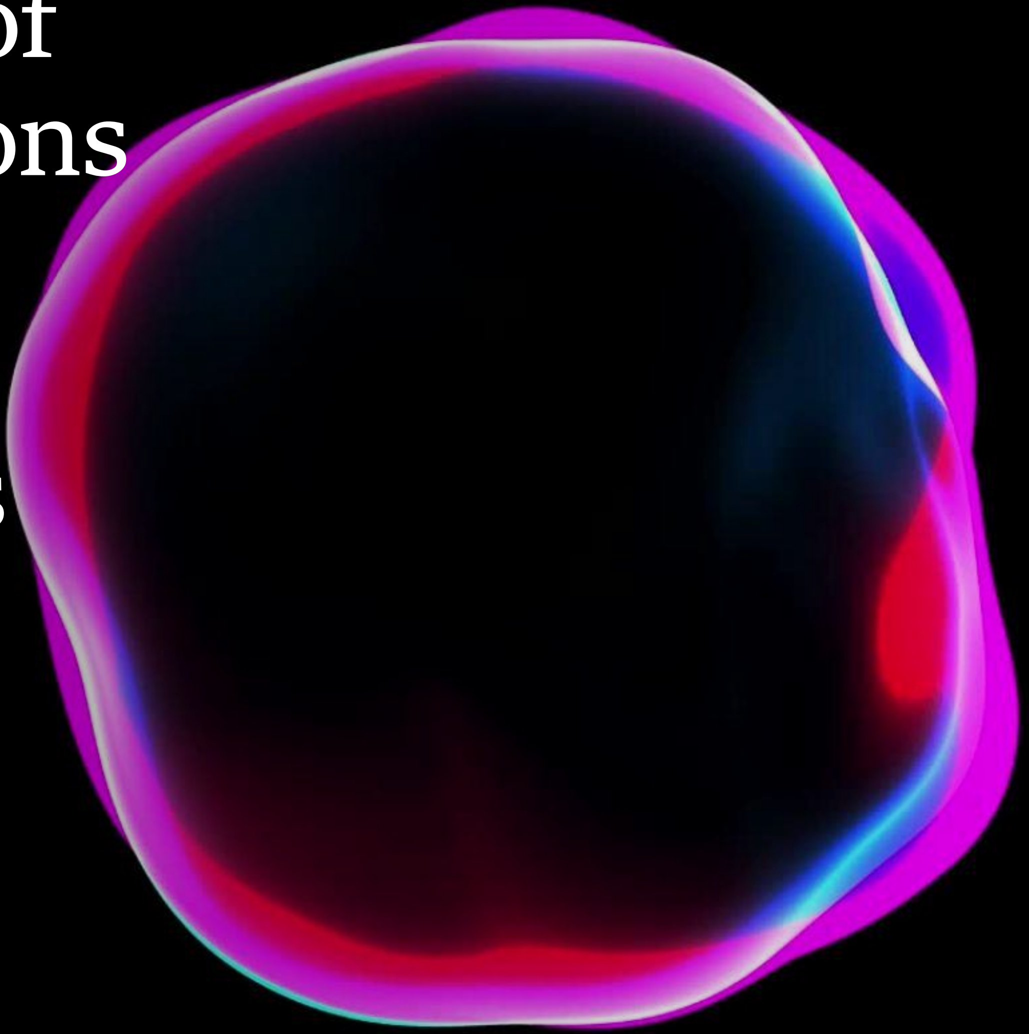
# Biophysics of single neurons and their modeling applications



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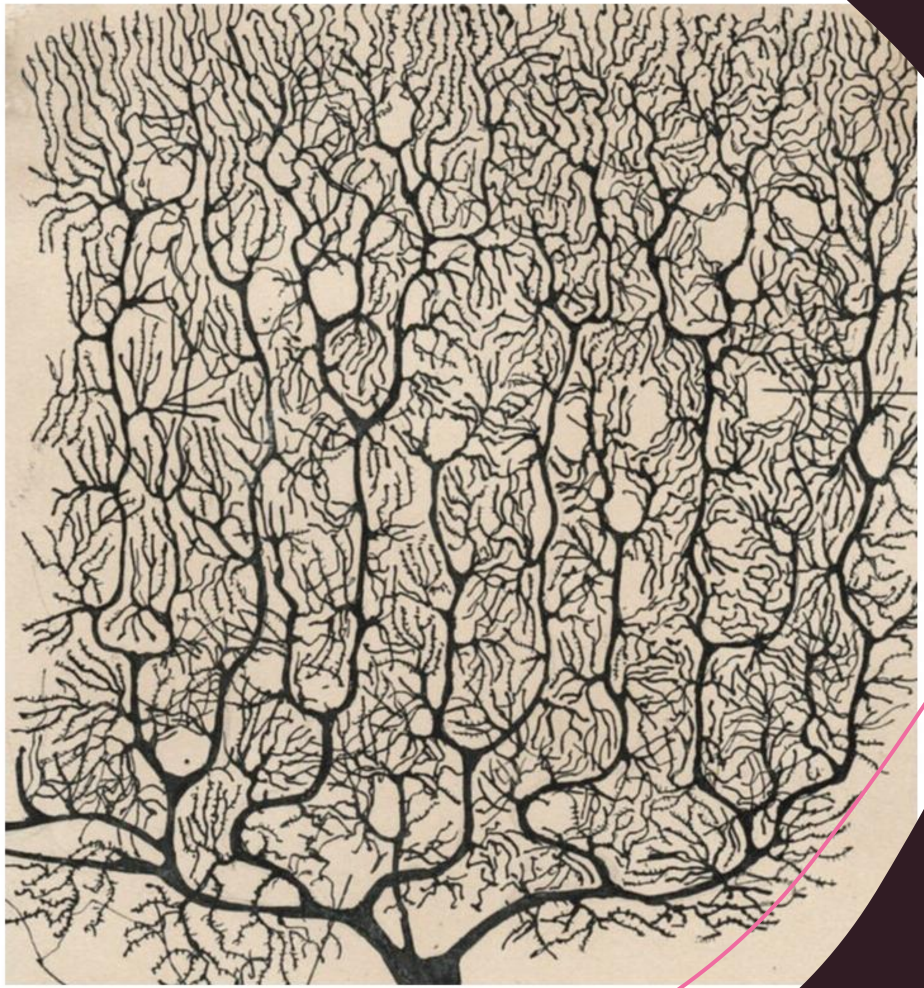
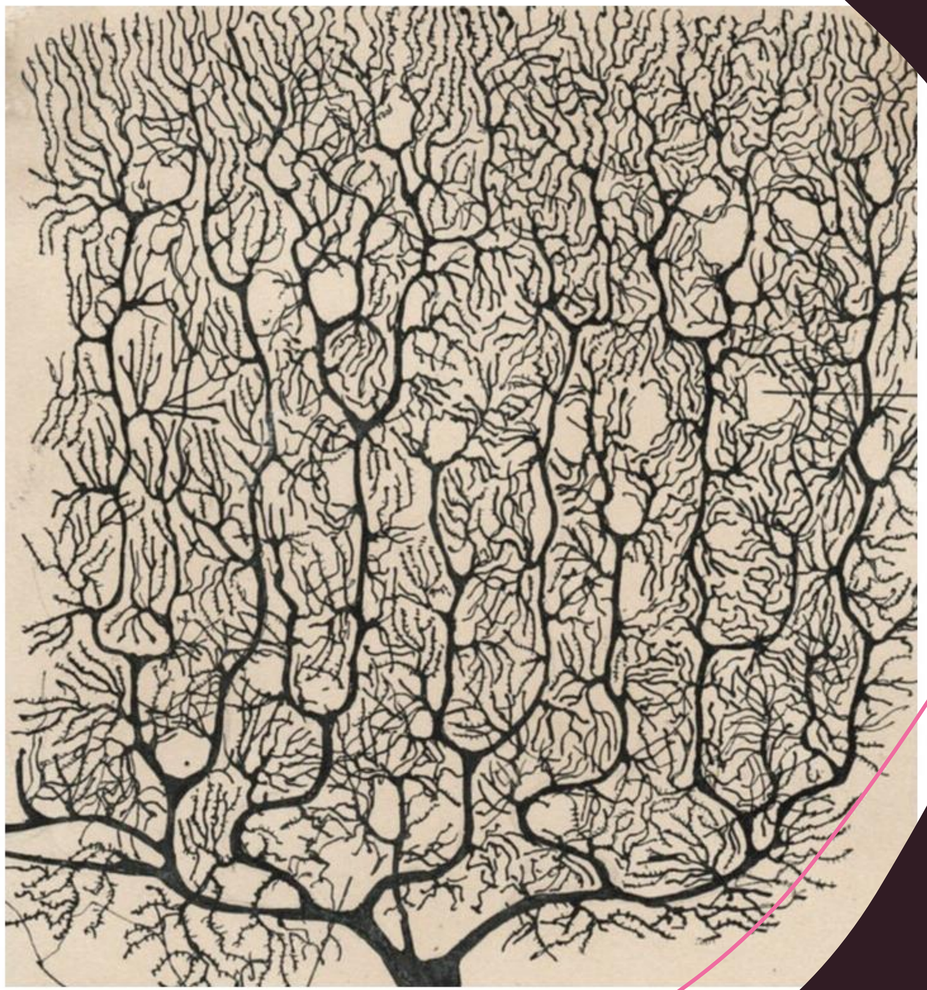
# Content

- Why neurons?
- Biophysics of a neuron
  - Treating a neuron as a passive circuit: model of equilibrium potential and resting potential
- Model neuronal firing using a dynamical system: LIF
- Maybe: model neuronal firing using voltage-dependent ion gates
- Maybe: using a GLM to infer synaptic connectivity changes from spiking data



Santiago Ramón y Cajal (Spanish, 1852 – 1934) a purkinje neuron from the human cerebellum 1899 ink and pencil on paper

# Why do we care (so much) about neurons?

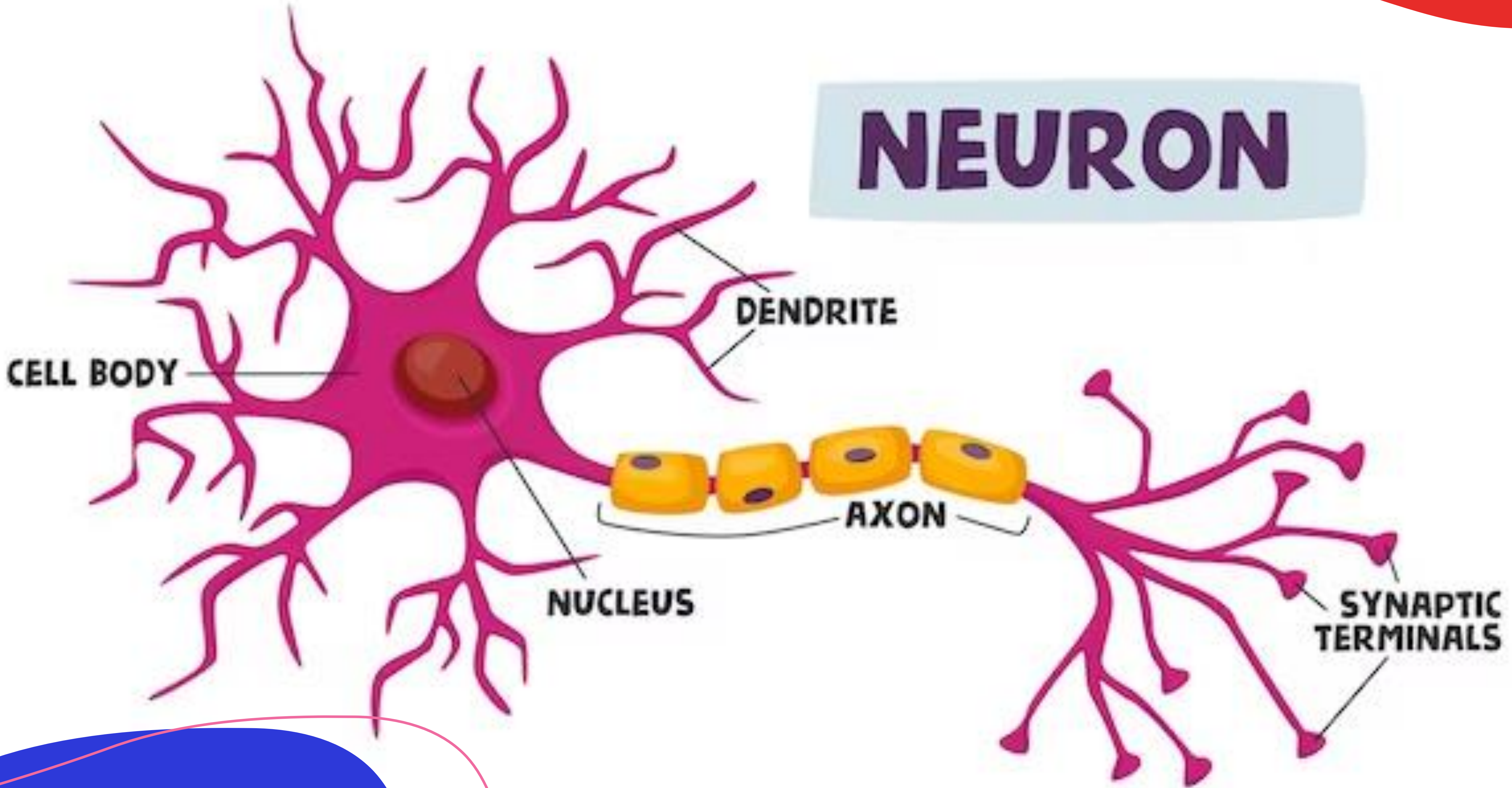


Santiago Ramón y Cajal (Spanish, 1852 – 1934) a purkinje neuron from the human cerebellum 1899 ink and pencil on paper

# Why do we care (so much) about neurons?

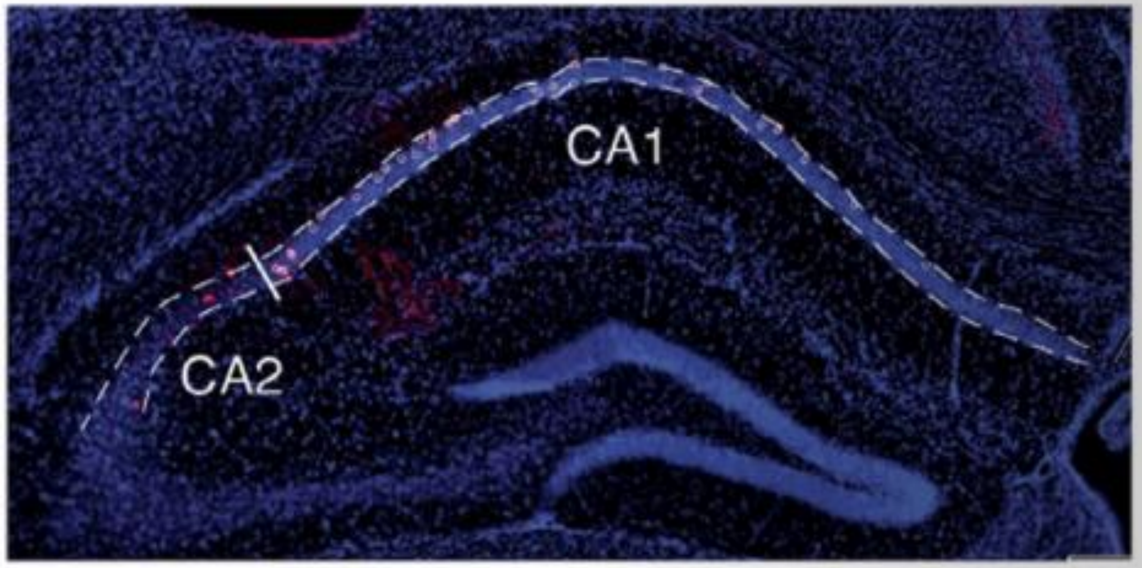
- Neuron doctrine: The view of nerve cells as the 'building blocks', and synapses as the one-way communication link between them, provided the structures upon which analysis of the long pathways of the vertebrate brain depended heavily for 50 years.

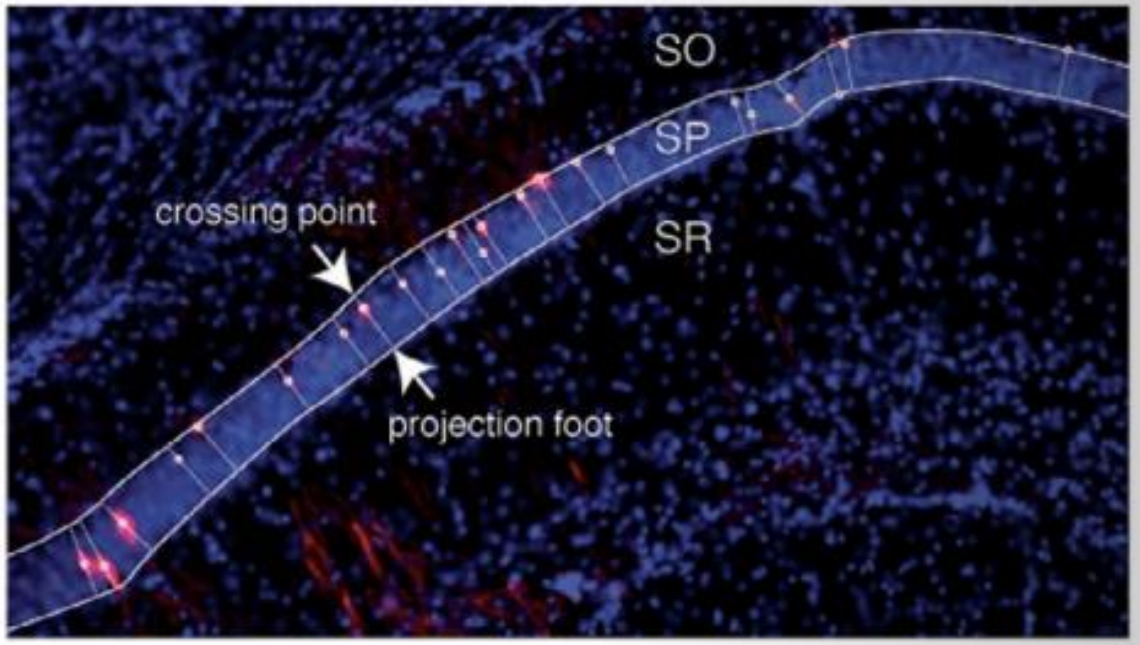
Guillery RW. Observations of synaptic structures: origins of the neuron doctrine and its current status. Philos Trans R Soc Lond B Biol Sci. 2005 Jun 29;360(1458):1281-307. doi: 10.1098/rstb.2003.1459. PMID: 16147523; PMCID: PMC1569502.


NEURON
DENDRITE
CELL BODY
AXON
NUCLEUS
SYNAPTIC
TERMINALS

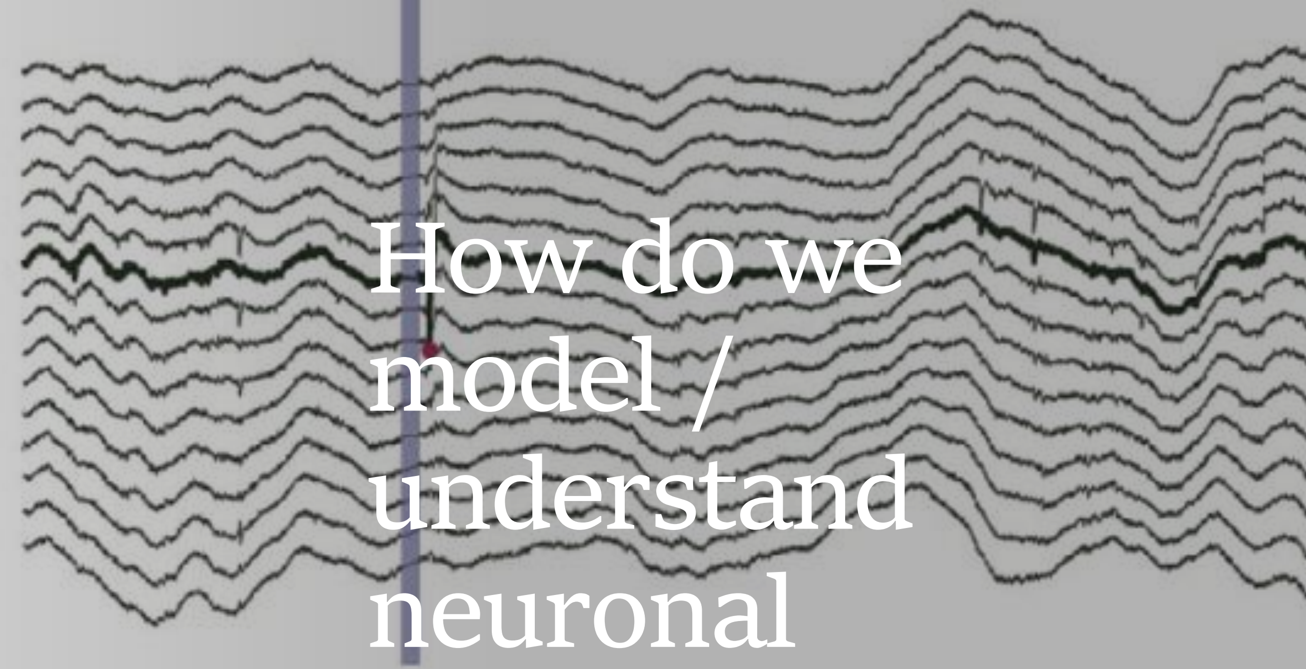
# Dimensions of Neurons

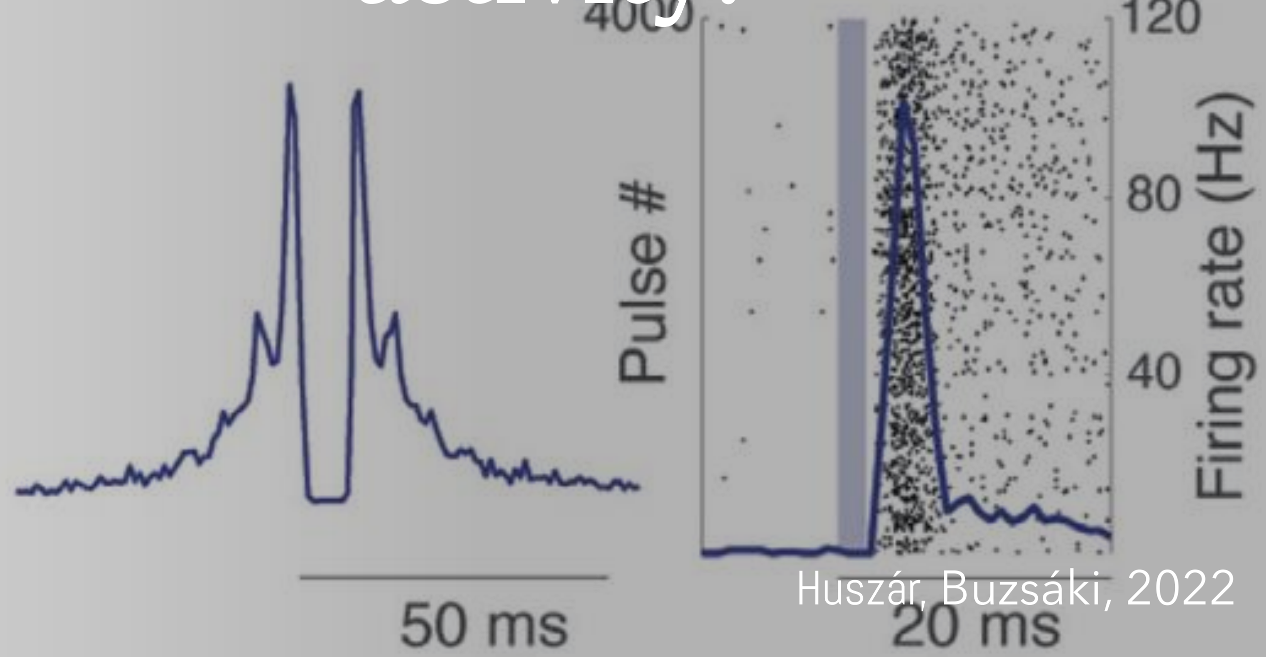
- Cell body diameter = 20 µm
- Dendrite length = up to 1 mm
- Dendritic width = 1 µm
- Spine size = 1 µm
- Axon length = up to 2 m
- Axon width = 1 µm
- Synapse size = 1 µm
- Vesicle size = 50 nm



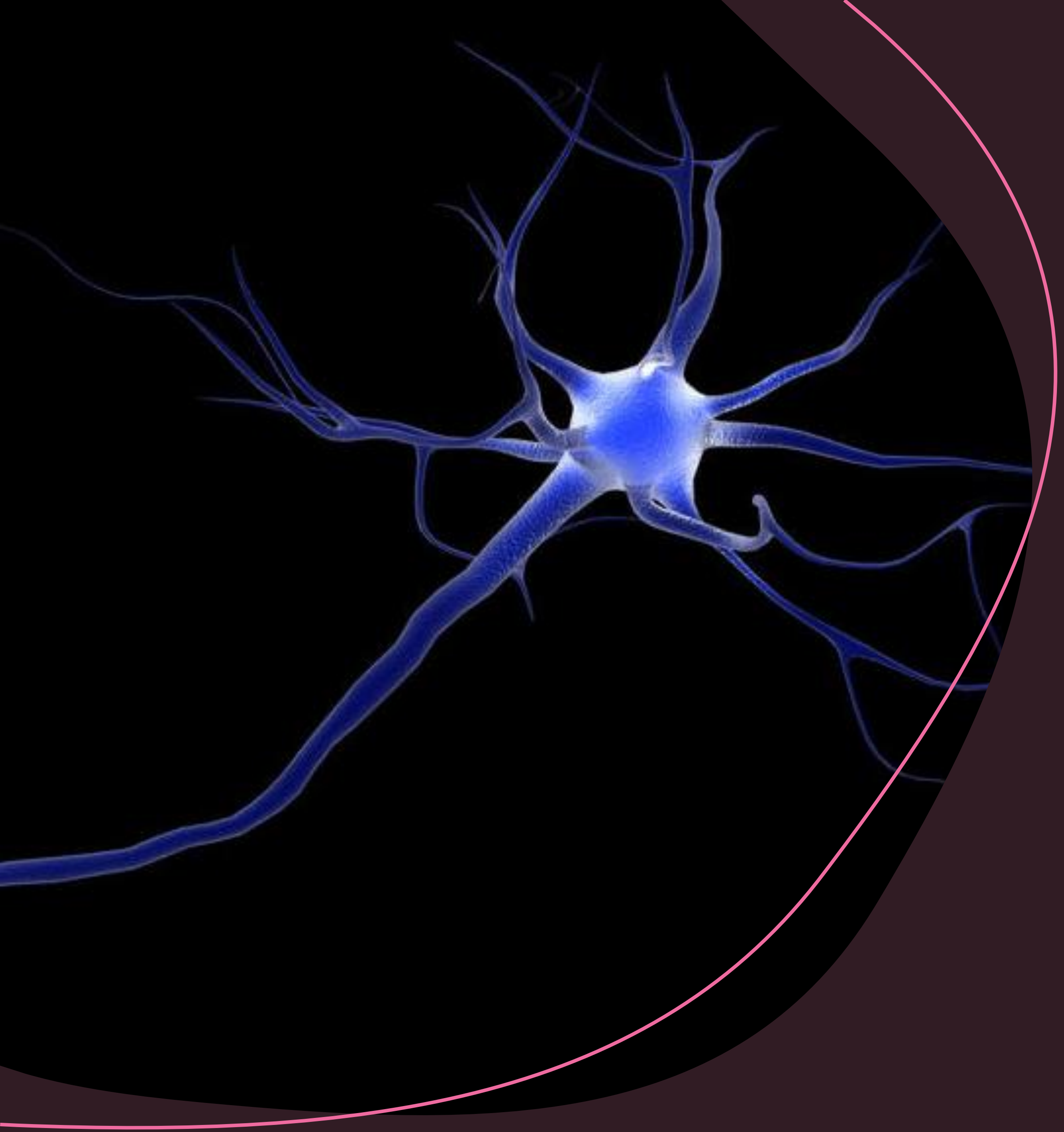




# How do we model / understand neuronal activity?

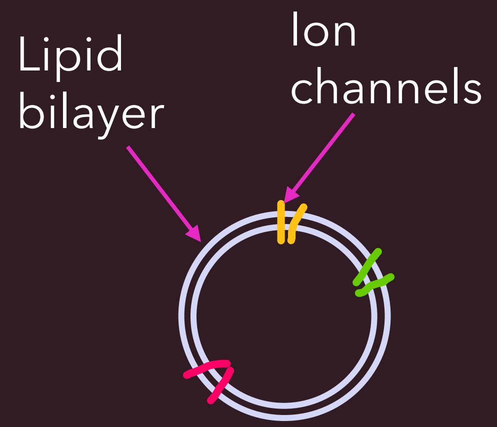




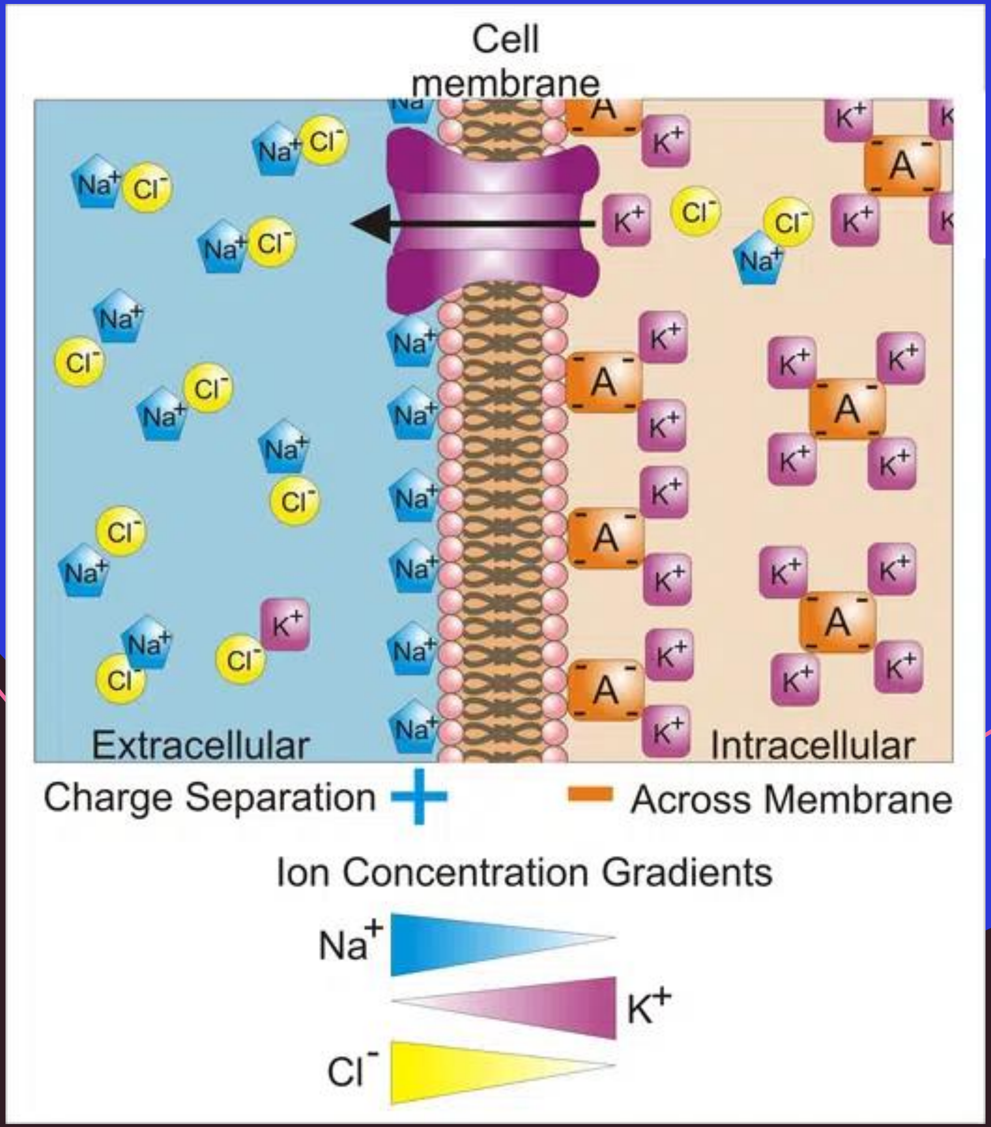

Huszár, Buzsáki, 2022



# Reduce a biological neuron to a "point neuron" model



# Equilibrium potential



# Equilibrium potential

- Basic definition and facts
  - Membrane potential:

$V_m = V_{in} - V_{out}$

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  - Ionic concentration across membrane (of a typical neuron):

| Ion | Intracellular (mM) | Extracellular (mM) |
|---|---|---|
| Na+ | 15 | 145 |
| K+ | 140 | 5 |
| Cl- | 7 | 110 |
| Ca2+ | 0.0001 | 2.5 |

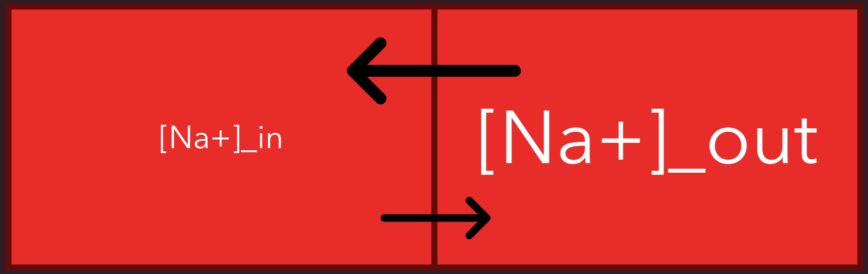
# Equilibrium potential


- Definition: Eq. potential of an ion is the **electrical potential difference** across the cell membrane that exactly balances the concentration gradient for an ion.

# Equilibrium potential


- Consider only one ion
- Let one side be "intracellular" and the other side be "extracellular"
- Both sides are electrically neutral (with equal number of positive and negative charges).

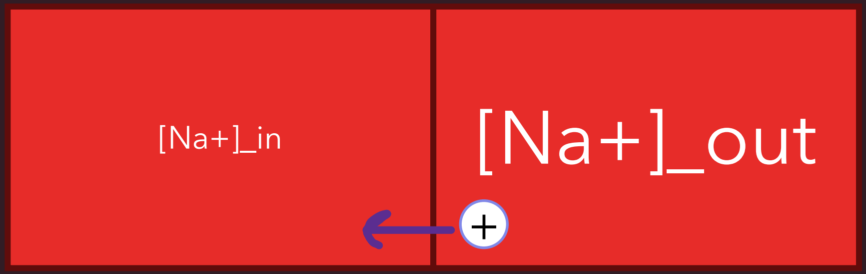
# Equilibrium potential




- Consider only one ion .
- Let one side be "intracellular" and the other side be "extracellular".
- Both sides are electrically neutral (with equal number of positive and negative charges).
- Now, make the membrane fully permeable to Na+ by opening the "leak channels".
- Intuition:
  - Ions tend to diffuse from its high concentration to low concentration (Law of diffusion), while positive / negative ions tend to move toward where the electric filed is low / high (Electrophoresis)

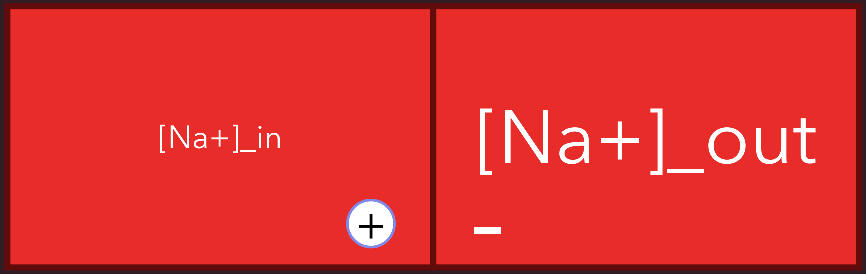
# Equilibrium potential

- **Law of diffusion**: the diffusive flux goes from a high-concentration area to a low-concentration area proportional to the concentration gradient



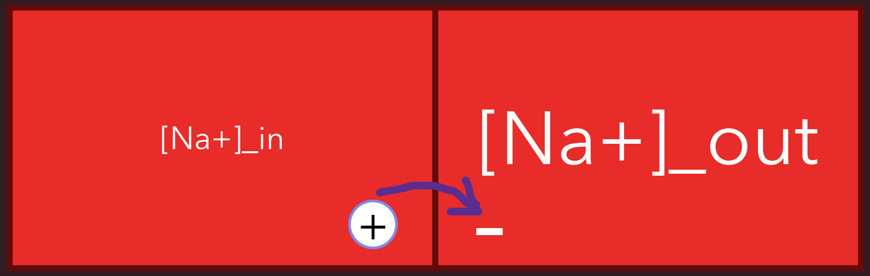
# Equilibrium potential

- Negative charge (and electrical field) created when Na+ left the right-hand side solution.

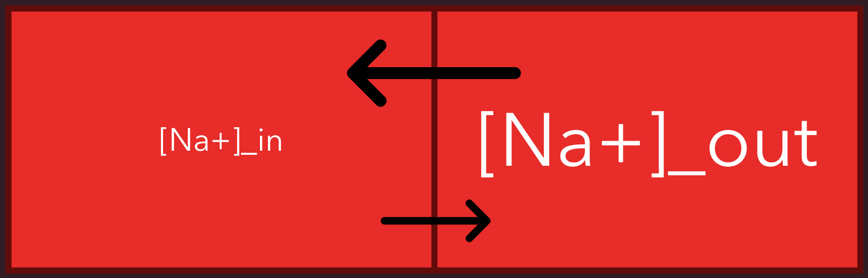


# Equilibrium potential

- **Columb's Law** predicts an electrostatic force on the Na+ ion that is against the concentration gradient



# Equilibrium potential

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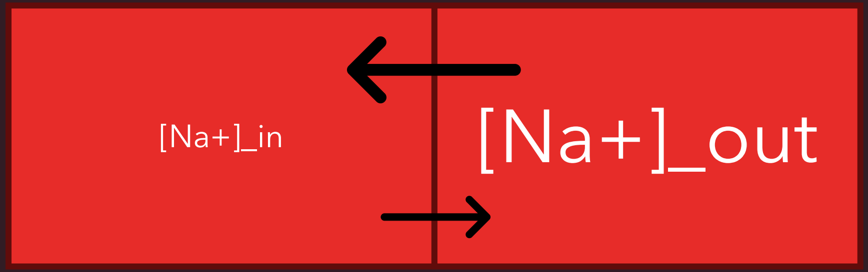
- Let one side be "intracellular" and the other side be "extracellular".
- Both sides are electrically neutral (with equal number of positive and negative charges).
- Now, make the membrane fully permeable to Na+ by opening the "leak channels".
- Intuition:
  - Ions tend to diffuse from its high concentration to low concentration (Law of diffusion), while positive / negative ions tend to move toward where the electric filed is low / high (Electrophoresis)
  - Two forces balance out -> the resulting membrane potential is the equilibrium potential
  - Experimentally find: $V_{Na^+ eq.} = +65\ mV$

# Equilibrium potential




- **Nernst equation** gives

$$V_{Na^+\ eq.} = \frac{RT}{zF} * ln\left(\frac{[Na^+]_{out}}{[Na^+]_{in}}\right)$$

  - Where z is the valency of the ion (1 for Na+), R is gas constant (8.314 J / mol), T is temperature (298.15 K), F is Faraday constant (elementary charge e times Avogadro constant N_A), [ .. ] is the concentration

# Resting potential

- But there are more than one type of ions in and outside a neuron!
- And, the membrane is <u>not fully</u> permeable to any ion under any conditions! Leak channels of different ions might have different permeability.

# Resting potential

- Consider the contribution of the three major ions (sodium, potassium, and chloride) and their permeability through the membrane, we have the Goldman-Hodgkin-Katz equation (**GHK equation**):

$$V_m = \frac{RT}{F} ln\left(\frac{p_{K^+}[K^+]_o + p_{Na^+}[Na^+]_o + p_{Cl^-}[Cl^-]_i}{p_{K^+}[K^+]_i + p_{Na^+}[Na^+]_i + p_{Cl^-}[Cl^-]_o}\right)$$

- Plugging in the permeability terms (can be experimentally measured), ionic concentrations, and the constants, we can estimate resting potential to be ~ -70mV, which aligns with experimental observations.

# Resting potential

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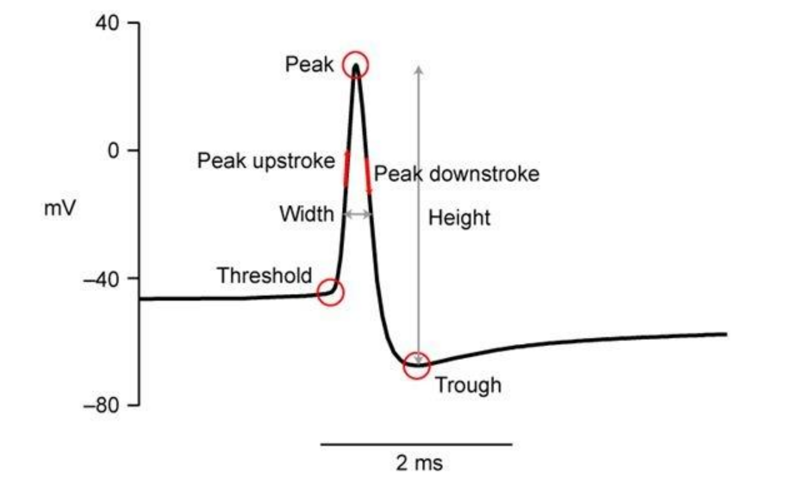
- The permeability terms can vary depending on the specific cell.

# Action potential




- Now we know the membrane potential of a neuron at "rest". But neurons are famous for their activity: spikes / action potentials

# Action potential

- What is the **cellular mechanism** underlying an action potential?

Schwiening CJ. A brief historical perspective: Hodgkin and Huxley. J Physiol. 2012 Jun 1;590(11):2571-5. doi: 10.1113/jphysiol.2012.230458. PMID: 22787170; PMCID: PMC3424716.

# Action potential

- What is the cellular mechanism underlying an action potential?
- Na+ channel opens -> depolarization -> K+ channel opens -> repolarization -> hyperpolarization -> K+ and Na+ channel closes ->back to resting potential and refractory period

Schwiening CJ. A brief historical perspective: Hodgkin and Huxley. J Physiol. 2012 Jun 1;590(11):2571-5. doi: 10.1113/jphysiol.2012.230458. PMID: 22787170; PMCID: PMC3424716.

# Action potential

- What is the cellular mechanism underlying an action potential?
- Na+ channel opens -> depolarization -> K+ channel opens -> repolarization -> hyperpolarization -> K+ and Na+ channel closes ->back to resting potential and refractory period
- But this is a super high-level description. **Alan Hodgkin and Andrew Huxley (HH)** worked out the mathematical model for describing AP
  - They provided hint for future discovery of ion channel structures without even knowing whether ion channel existed!

Schwiening CJ. A brief historical perspective: Hodgkin and Huxley. J Physiol. 2012 Jun 1;590(11):2571-5. doi: 10.1113/jphysiol.2012.230458. PMID: 22787170; PMCID: PMC3424716.

# Action potential

- HH model:
  - The total current through the membrane is the sum of capacitive current, voltage-gated ion channel current, and leak current

$$I = C_m \frac{dV_m}{dt} + \bar{g}_K n^4 \left( V_m - V_K \right) + \bar{g}_{Na} m^3 h \left( V_m - V_{Na} \right) + \bar{g}_l \left( V_m - V_l \right)$$

    - The conductance terms (g_..) are voltage-dependent, following their own differential equation.
    - "Driving force" is also voltage dependent: $V_m - V_{Na+\ eq.}$

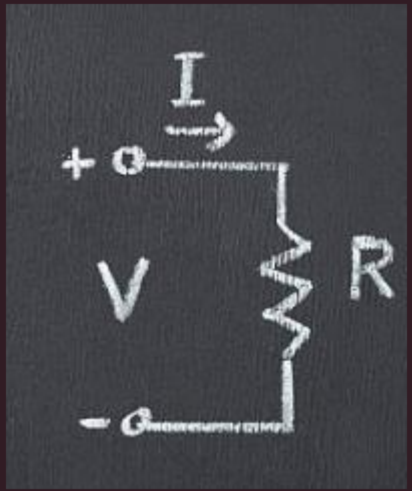
# Basic AP Physics C review

- **Ohm's law**: Current (I) is proportional to voltage (V) given the resistance R:

$$V = IR$$

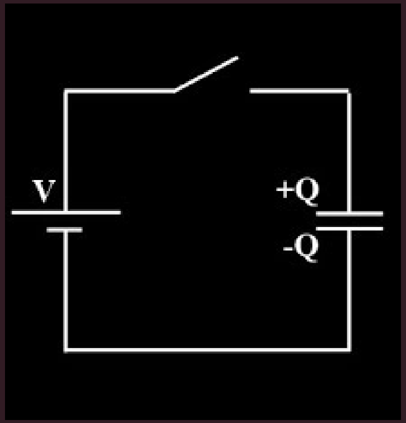
- Conductance (g) of a resistor is the inverse of its resistance:

$$g = \frac{1}{R}$$



# Basic AP Physics C review

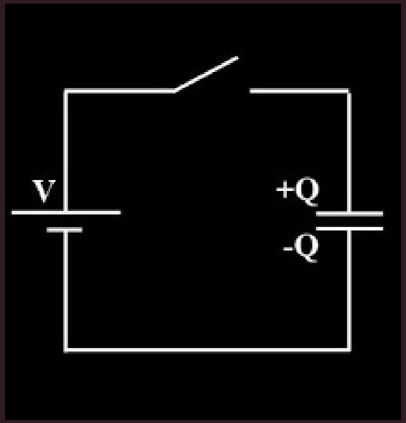
- **Capacitor**: a device that stores electrical energy in an electric field by accumulating electric charges on two closely spaced surfaces that are insulated from each other.



# Basic AP Physics C review

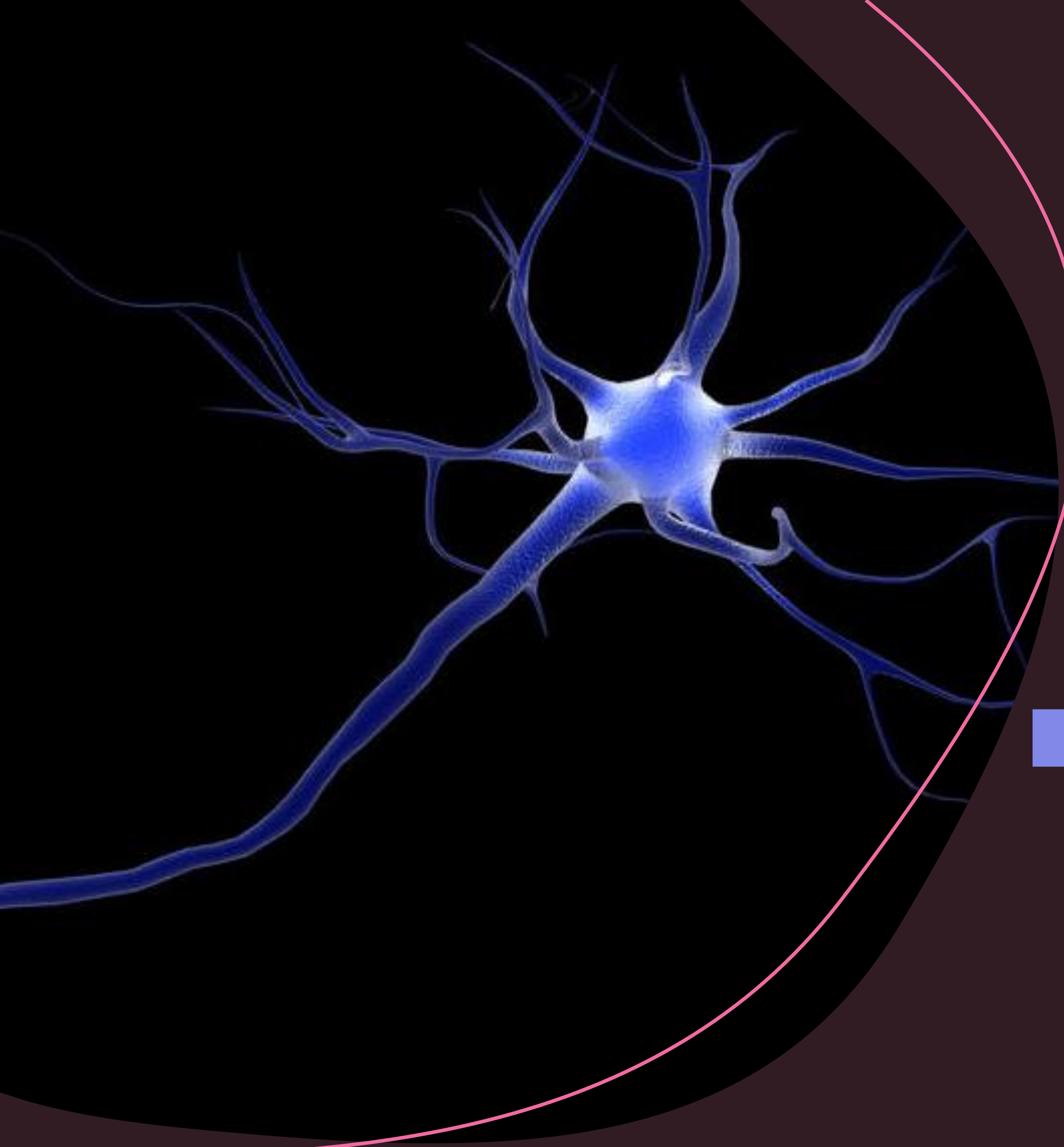
- Capacitor: a device that stores electrical energy in an electric field by accumulating electric charges on two closely spaced surfaces that are insulated from each other.
  - **Capacitance** (C): the capability of a capacitor to hold charges
    - defined as the ratio of the positive or negative charge (Q) on each conductor, to the voltage (V) difference between them
    - C = Q/V
  - **Capacitive current**: The current ($I_C$) flow onto a capacitor equals the product of the capacitance and the rate of change of the voltage (dV/dt):

$$I_C = C \cdot \frac{dV}{dt}$$



# Leaky Integrate-and-Fire (LIF) model

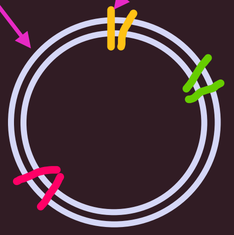
- HH is a detailed biophysical model, and it made great scientific predictions.
- But, to capture a neuron's response to external inputs (action potentials and subthreshold membrane potential), a simpler model might be enough.
- Why do we want simplicity?
  - Capturing the essence of the biological process without getting lost in the details.
  - Fewer parameters so that we can apply the model to make more predictions / run large-scale simulations.

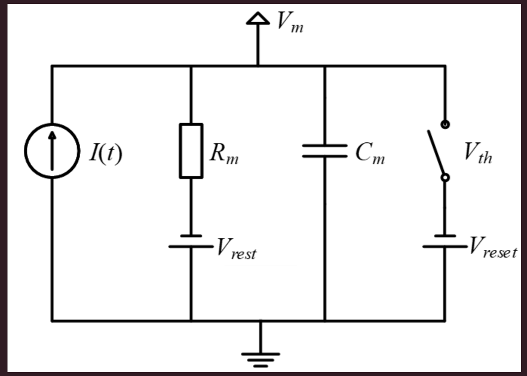


# Reduce a biological neuron to an equivalent circuit

Lipid bilayer

Ion channels

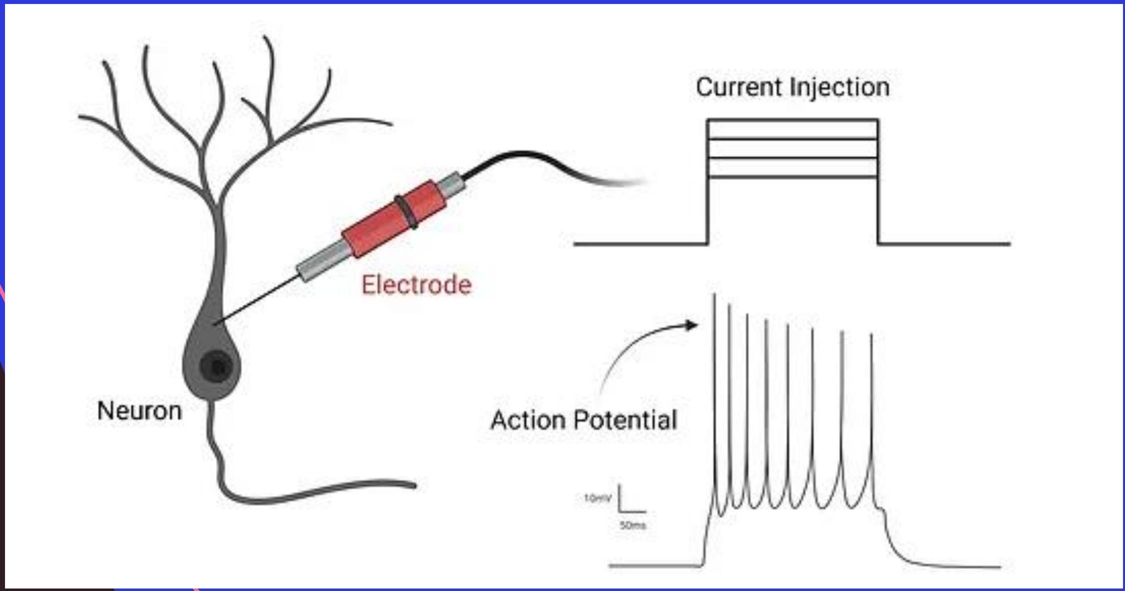





Equivalent circuit

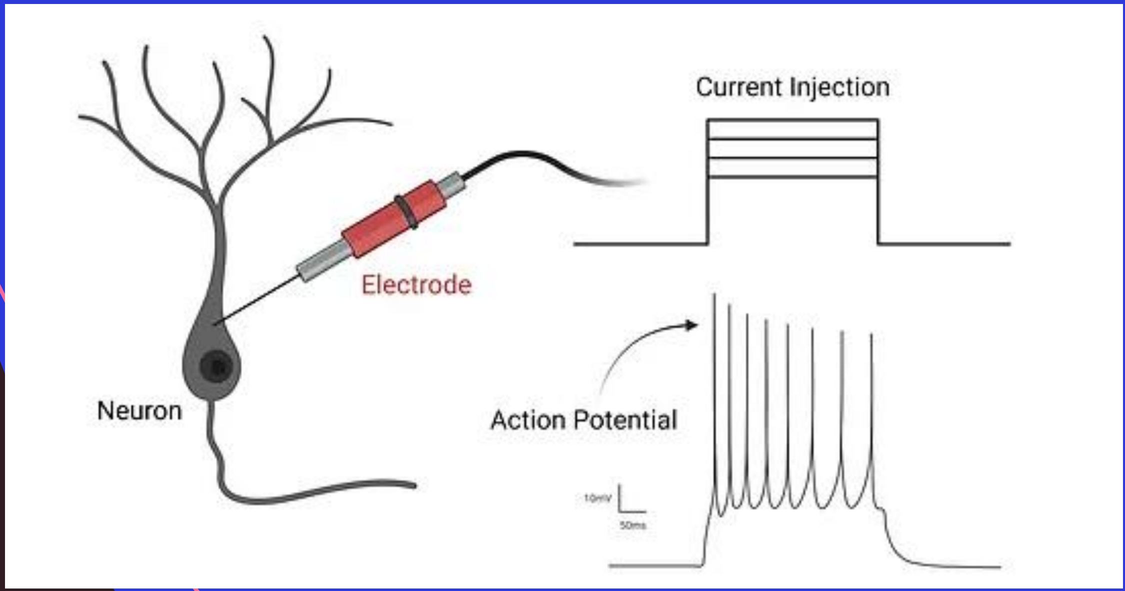
# Leaky Integrate-and-Fire (LIF) model

- Key assumptions:
  - Neuronal dynamics can be conceived as a summation process (sometimes also called 'integration' process) of external current input (I), combined with a mechanism that triggers action potentials above some critical voltage / threshold: $V_{th}$



# Leaky Integrate-and-Fire (LIF) model

- Key assumptions:
  - Action potentials of a given neuron always have roughly the same form -> we raise $V_m$ to some arbitrary high value (e.g. 50 mV) to denote an AP.
  - After an AP, we reset membrane potential to be around –65 mV to denote the undershoot.

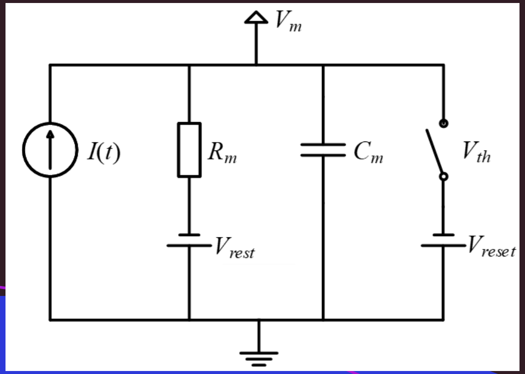


# Leaky Integrate-and-Fire (LIF) model

- Key assumptions:
  - Ionic current entering the cell must go somewhere, either charging up the membrane capacitance (C) or leak out of the cell through the leak channels (with resistance R) (Kirchhoff's circuit laws):

$$I(t) = I_R(t) + I_C(t)$$

  - External input might change temporally, i.e., *I* is a function of time.



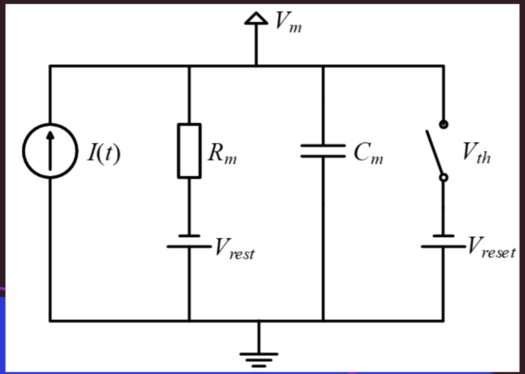
# Leaky Integrate-and-Fire (LIF) model

- From here, we can start to model how $V_m$ responses to some external current injections:
  - Because of Ohm's law:

$$I_R(t) = \frac{\left(V_m(t) - V_{rest}\right)}{R_m} = g_m \cdot \left(V_m(t) - V_{rest}\right)$$

  - Capacitive current:

$$I_C(t) = C_m \frac{dV_m(t)}{dt}$$

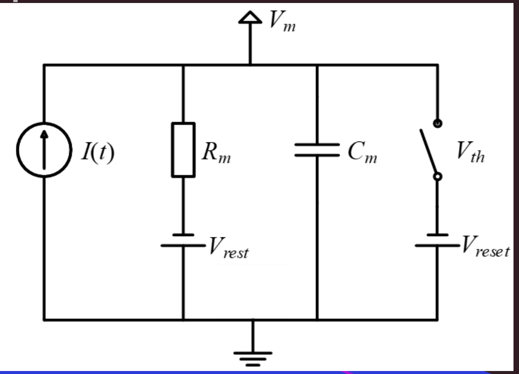


# Leaky Integrate-and-Fire (LIF) model

- From here, we can start to model how $V_m$ responses to some external current injections:
  - Then,

$$I(t) = g_m \cdot \left(V_m(t) - V_{rest}\right) + C_m \cdot \frac{dV_m(t)}{dt}$$

  - Arranging the equation, we have the relationship between instantaneous change of $V_m$, $V_m$ and current input!




$$C_m \cdot \frac{dV_m(t)}{dt} = \underbrace{-g_m\left(V_m(t) - V_{rest}\right)}_{\text{"Leak" term}} + I(t)$$

# Leaky Integrate-and-Fire (LIF) model

$$C_m \cdot \frac{dV_m(t)}{dt} = -g_m\left(V_m(t) - V_{rest}\right) + I(t)$$

- What does this ordinary differential equation entail?
  - Rate of change of $V_m$ is negatively proportional to the difference between $V_m$ and $V_{rest}$ -> Without external current input, $V_m$ tends to go back to $V_{rest}$.
  - Rate of change of $V_m$ is proportional to external current input without considering the leak term.

# LIF simulation: Euler method

- Euler method: a first-order numerical procedure for solving ordinary differential equations (ODEs)
  - Logic: Divide continuous time into small and discrete time bins. For each time bin ($\Delta$t), update the independent variable by the amount of change. For example:

$$V_m(t_1) = V_m(t_0) + \frac{dV(t_0)}{dt} \cdot \Delta t$$

$$V_m(t + \Delta t) = V_m(t) + \frac{dV(t)}{dt} \cdot \Delta t$$

- What we need to know/specify:
  - Initial condition of the independent variable (V_m)
  - Parameters of the equation, duration, and time bin size of the simulation
  - Update rule (here, first order Euler method)