

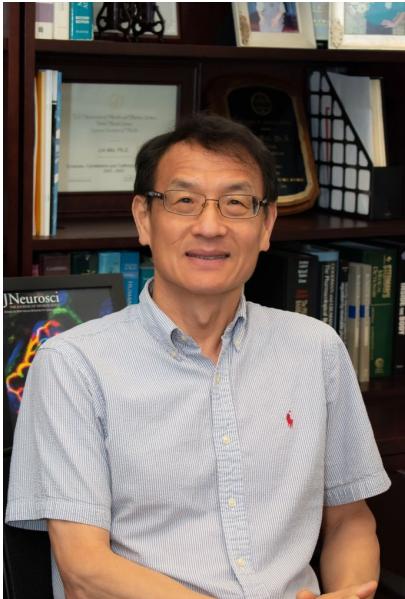
Computational Neuroscience: Introduction and Neuronal Models

Heath Robinson, Ph.D

CWRU Undergraduate Neuroscience

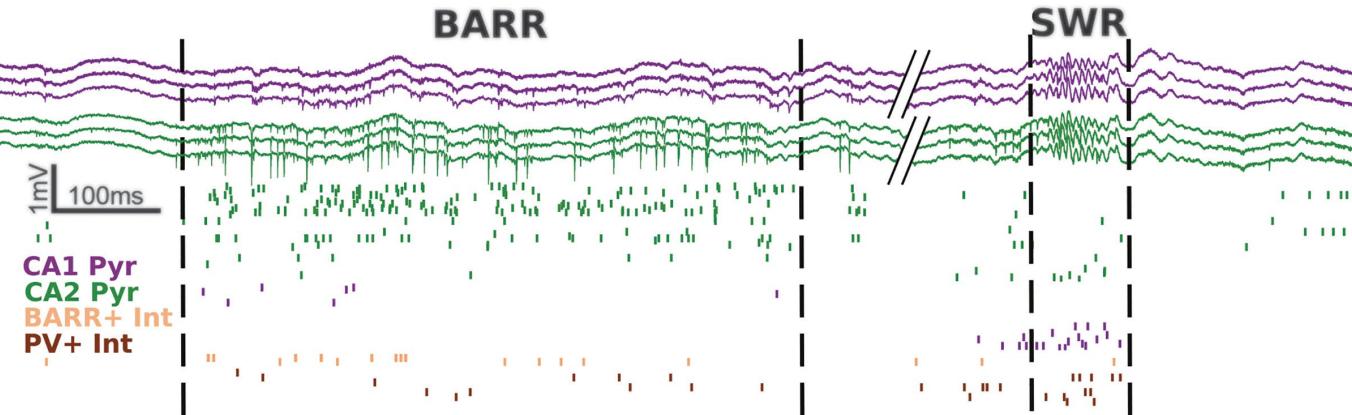
Who I am:

- Postdoctoral fellow at Cornell in the labs of Drs. Azahara Oliva and Antonio Fernandez-Ruiz (braincomputations.org)
- Did my PhD under Lin Mei MD,PhD at CWRU Neuroscience Department
- Currently using large-scale electrophysiology recordings in freely moving animals, using closed-loop optogenetics to understand the physiology of memory consolidation in the cortex
- I love electrophysiology and hate how it is normally taught, so here I am!



I am currently studying:

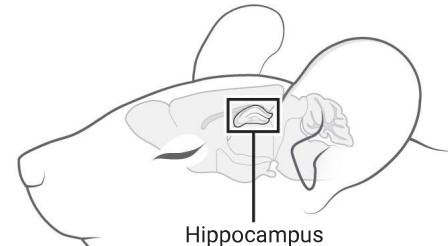
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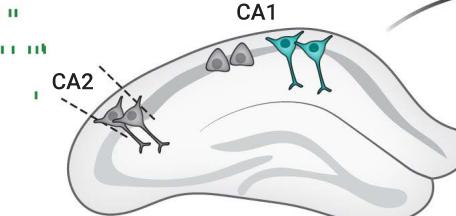
Karaba, Robinson et al. *Science* 2024

Excitatory neurons
Inhibitory interneurons (CCK+ basket cells)

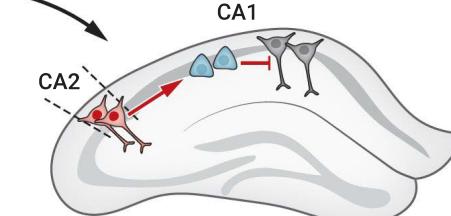
● SWR ● Low-level activity ● BARR



Reactivation



Rebalancing



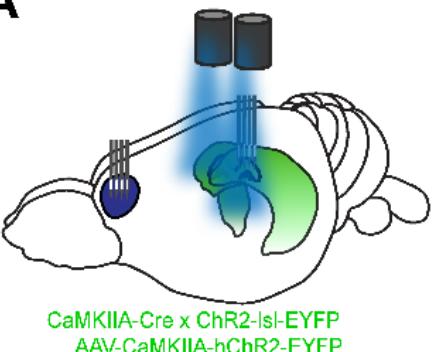
80 ms

100 ms

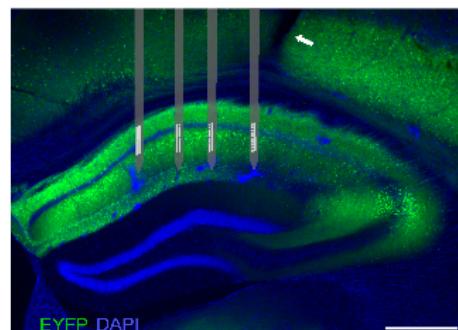
Plots are firing spike raster of individual neurons (each row is a neuron), which are not actual data, but representational.

Mou and Ji. *Science* 2024

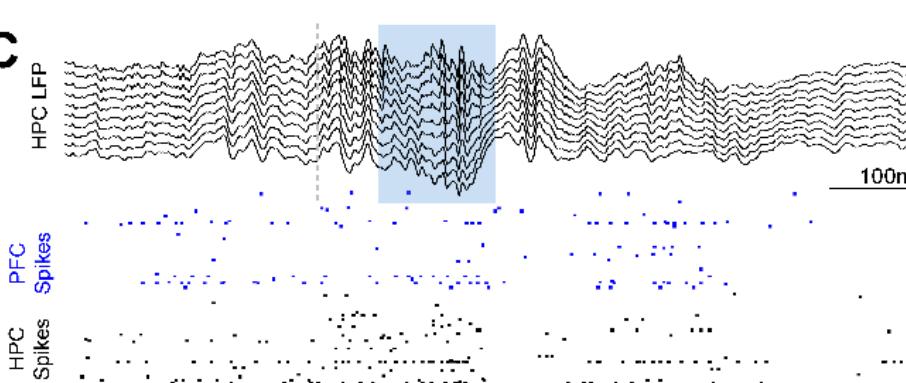
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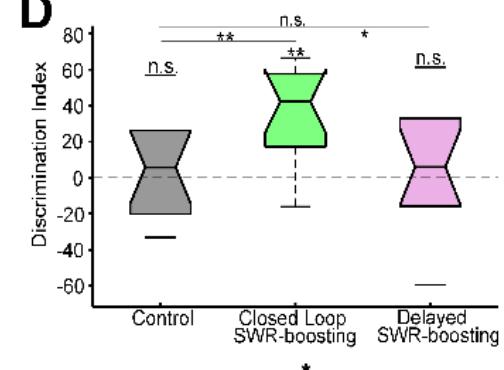
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C

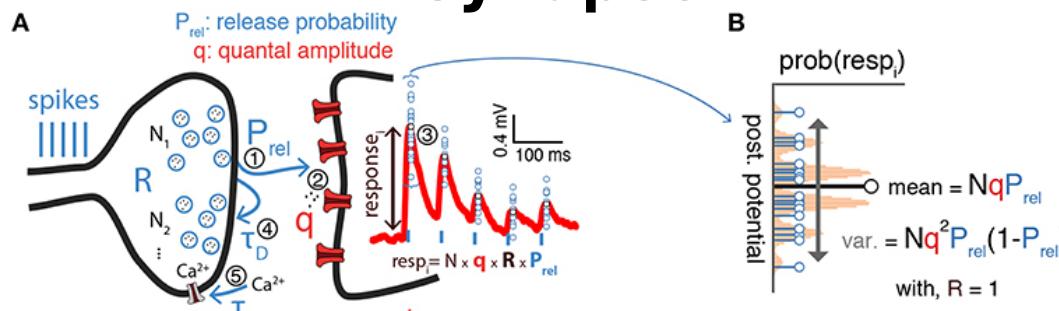


D



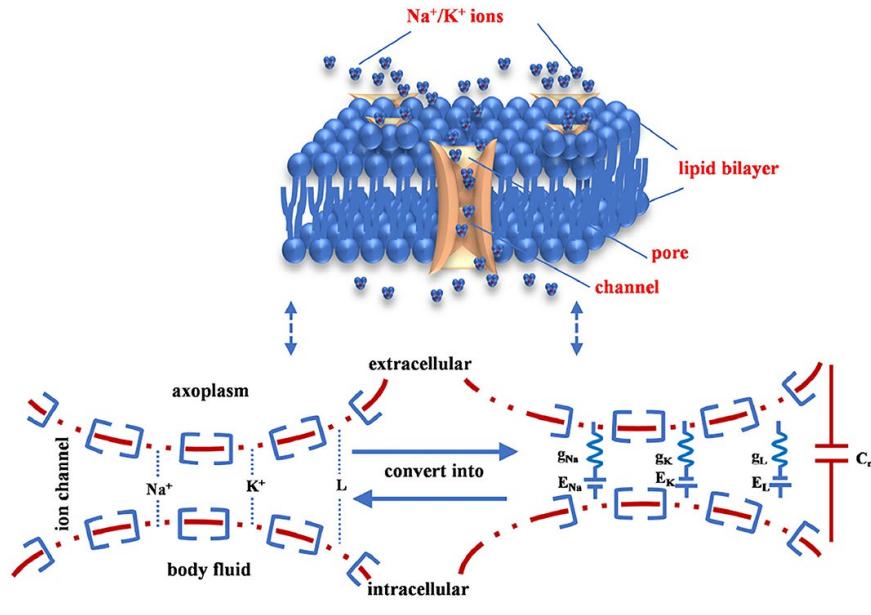
Modelling at different levels of neuroscience

Synapse



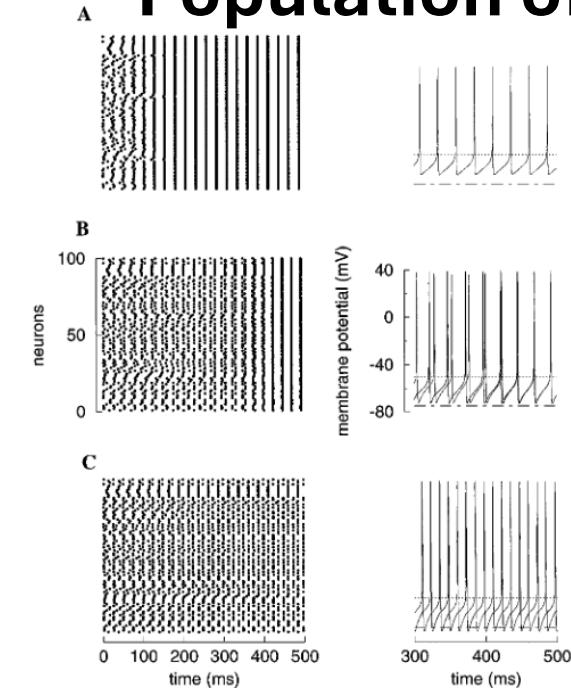
Bykowska et al. *Frontiers in Synaptic Neuroscience* 2019

Individual Cell



Fang, Duan, Wang *Frontiers in Neuroscience* 2021

Population of neurons



Wang and Buzsaki *The Journal of Neuroscience* 1996

Modeling at different levels of neuroscience: Outside-in modelling (modeling findings to understand experimental findings)

Place Cells emerge in RNN as an agent exploring an environment with sensory input

The Nobel Prize in Physiology or Medicine 2014



John O'Keefe

John O'Keefe discovered, in 1971, that certain nerve cells in the brain were activated when a rat assumed a particular place in the environment. Other nerve cells were activated at other places. He proposed that these "place cells" build up an inner map of the environment. Place cells are located in a part of the brain called the hippocampus.

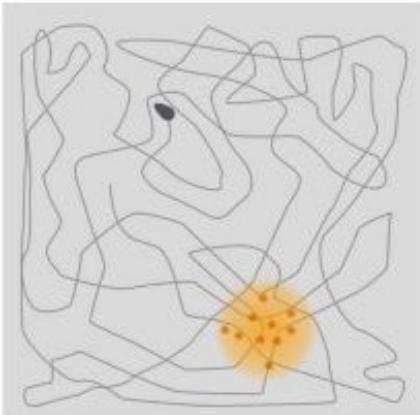
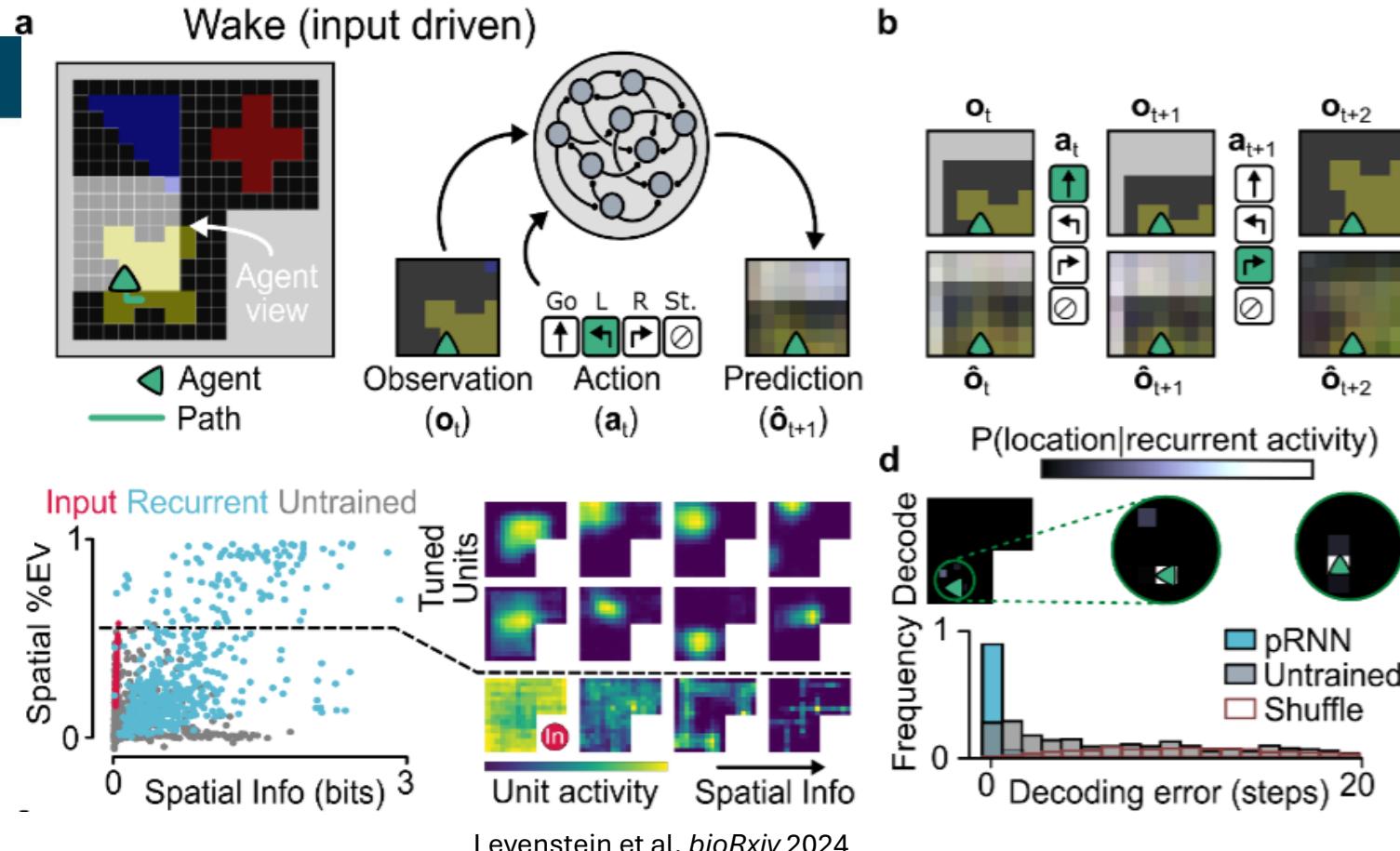
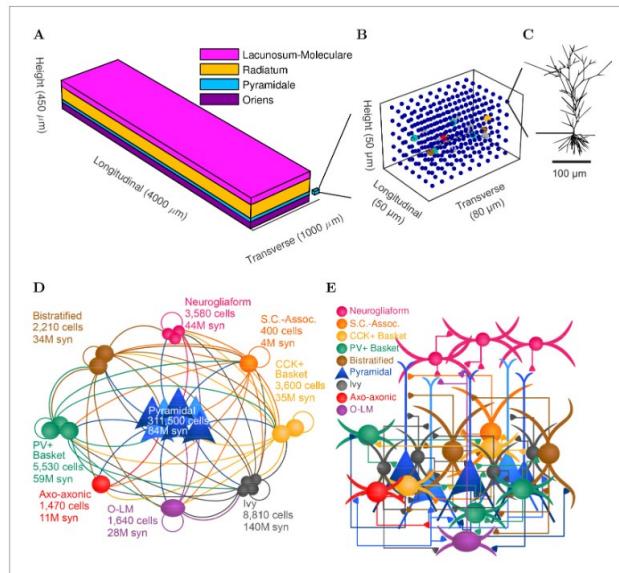


Fig. 1



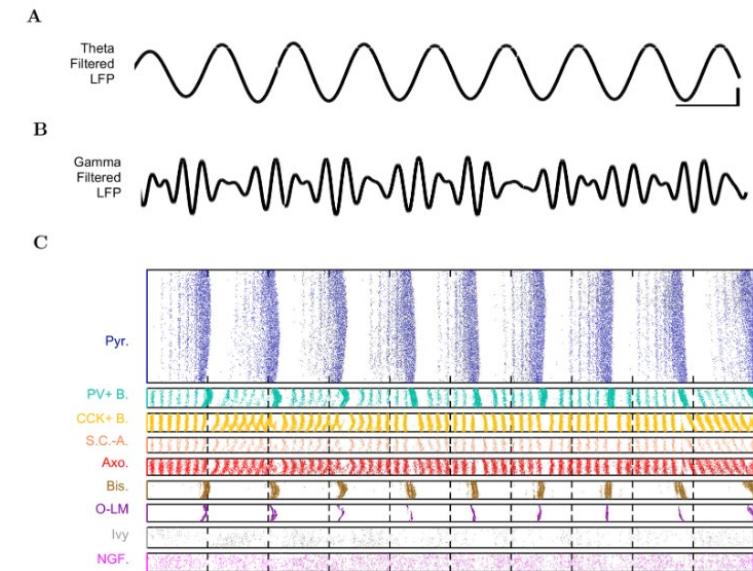
The MOST important question is your scientific hypothesis

- What determines your use of a model is the question you are asking and at what level
- Identify the level your question is at, **then** identify the ideal model
- You **cannot** have it all – models at full scale are still not feasible



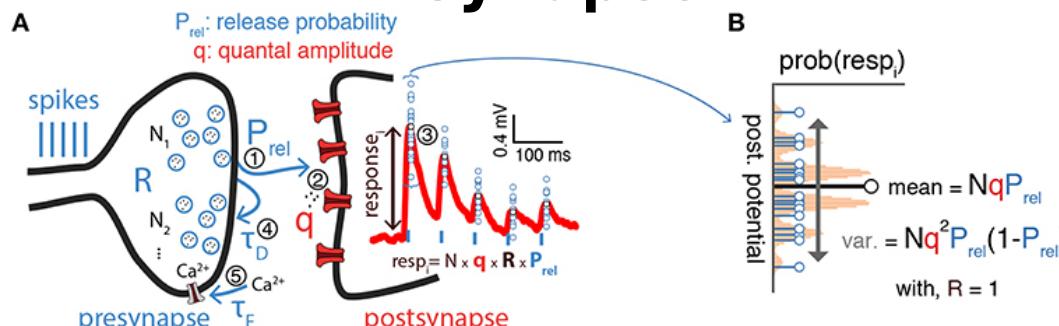
Development of a data-driven, full-scale model of the isolated CA1

Details of the full-scale model are described in the Methods, and the most important features are illustrated in *Figures 1* and *2* and summarized here. Briefly, CA1 model cells were evenly distributed within their respective layers in a 3-dimensional prism with realistic dimensions for the rodent hippocampal CA1 region (*Figure 1A and B*). The model network contained 338,740 cells (similar to the biological CA1 in rats, including 311,500 pyramidal cells and 27,240 interneurons) (*Figure 1D–E* and *Figure 1—figure supplement 1*). In addition, the network also incorporated 434,700 artificial stimulating cells (spiking units with random, Poisson-distributed interspike intervals) to simulate afferents to CA1; the cell type-specific distribution, dendritic position, amplitude and kinetics of the excitatory input synapses were all experimentally constrained by afferent CA3 and entorhinal cortical data. Cell type-specific connectivity data, including cell numbers (*Figure 1D*) and convergence and divergence values (*Figure 1E*; *Figure 1—figure supplement 1* and *Table 1*) were taken without alteration from our previously published, in-depth, quantitative assessment of the CA1 circuit (Bezaire and Soltesz, 2013). Anatomical constraints of the connectivity were implemented in the model by accounting for the distribution of the axonal boutons as a function of longitudinal and transverse distance from the presynaptic cell soma (*Figure 1—figure supplement 2*). The afferent divergence and convergence onto the cells were also anatomically patterned, maintaining the topographical arrangement seen experimentally (Hongo et al., 2015), for a total of 5.19 billion synaptic connections in the model network. In addition, the remaining parameters that could not be constrained by experimental data were documented, with the assumptions used to arrive at them explicitly listed in Table 2 of Bezaire and Soltesz (2013) and additional parameter calculations described in the Appendix of the present paper, section ‘Inhibitory connectivity’. To highlight the many constraints applied in the current work and address the unconstrained model parameters, we characterized all model components (constrained and unconstrained) in experimental terms, comparing with experimental data where possible (*Figure 2*; Appendix). For a four second simulation, the full-scale model required 3–4 terabytes (TB) of RAM and four hours of execution time on a supercomputer using ~3000 processors (or up to 12 hr for simulations calculating a high-accuracy local field potential (LFP) analog). Additional details and data about model performance are available in *Table 2* and Bezaire et al. (2016a).



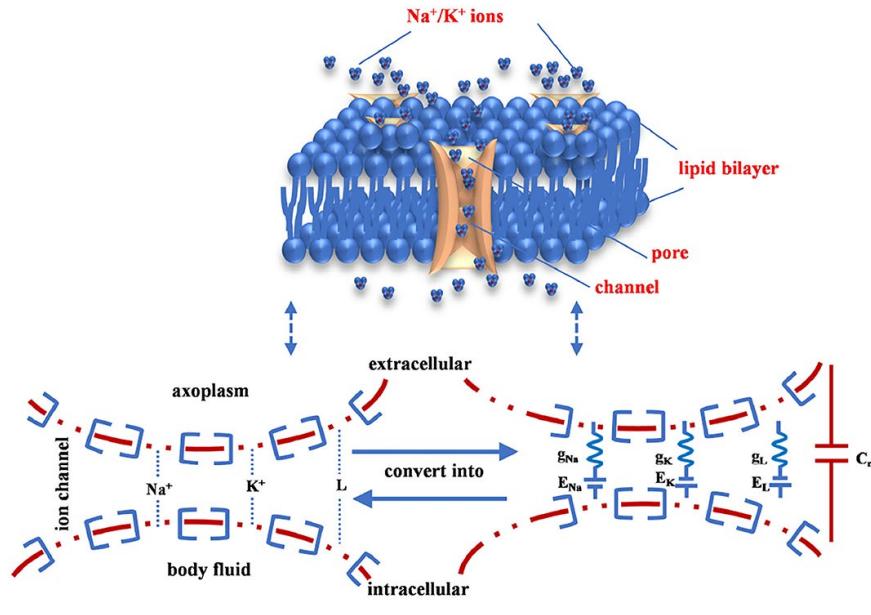
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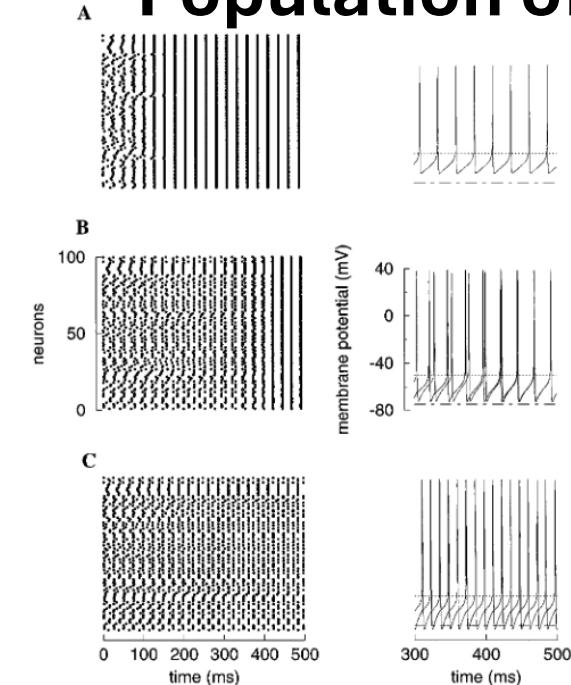
Bykowska et al. *Frontiers in Synaptic Neuroscience* 2019

Individual Cell



Fang, Duan, Wang *Frontiers in Neuroscience* 2021

Population of neurons



Wang and Buzsaki *The Journal of Neuroscience* 1996

So, what is our **scientific question**?

To gain an understanding of single compartment and approximated models to understand:

1. Electrophysiology of a single neuron (Hodgkin-Huxley model)
2. Neural network understanding of brain oscillations (Leaky Integrate and Fire model, PING model)

In this lecture and Wednesday's lab:

Spoiler 1 – We will see the complexity of a Hodgkin-Huxley model for gaining a mechanistic understanding of how different ions contribute to AP

Spoiler 2 – We will see how Leaky Integrate and Fire models or single-ohmic models are better at network modeling

Spoiler 3 – Use PING model to observe how networks of inhibitory and excitatory neurons lead to oscillations that we observe in the brain (Outside-In Modelling)

A quick guide to excitable membranes and action potentials – lipid membranes

- Forms spontaneously a bilayer in water
- Impermeable to “**non-lipid**” things – such as water molecules
- **GREAT** for not allowing ions in....

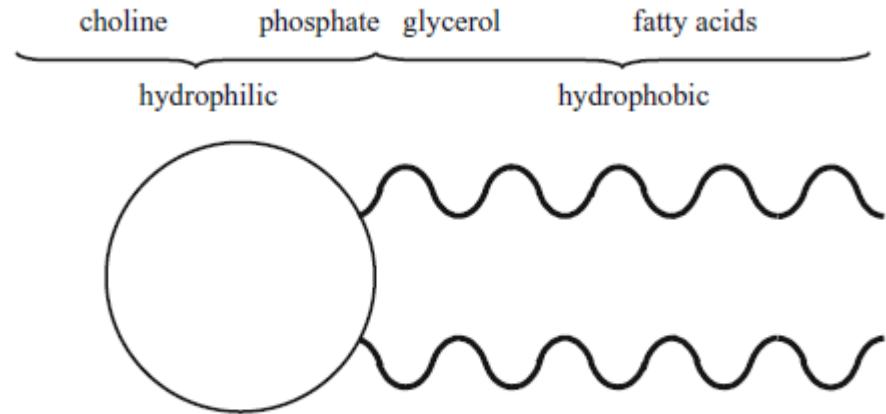


Figure 2.1 Phosphatidyl choline, which is a typical membrane phospholipid, has a polarised head and fatty tails. Phospholipids are often represented as shown at the bottom

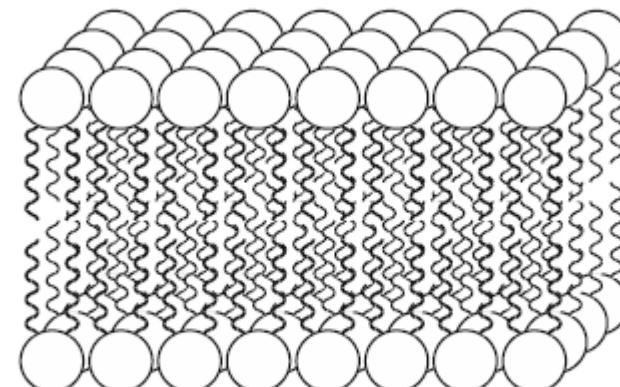


Figure 2.2 Bilayer arrangement of phospholipids in a watery environment

A quick guide to excitable membranes and action potentials – ion distribution

- Take a moment and look at the disparity of ions
- **No matter which you choose you see there is a concentration barrier**
- We can thank are hard working lipid membrane for this!
- This is showing the **chemical gradient** of ions
- But ions also have a **charge**

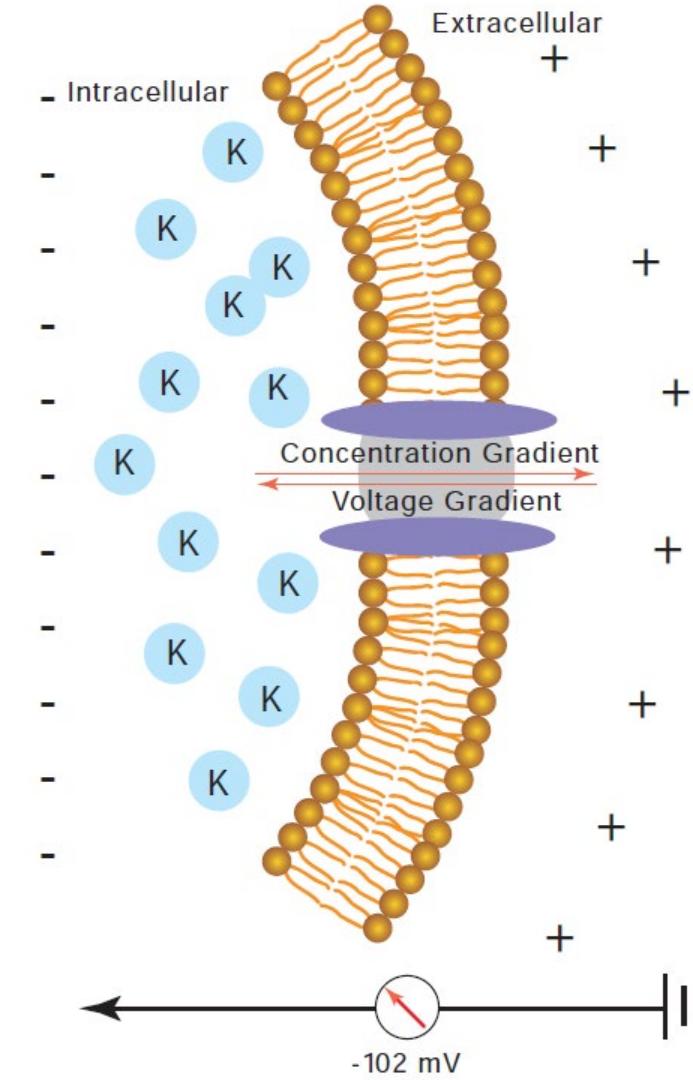
Table 2.1 Intracellular and extracellular distribution of the main ions found in animal fluids

Ion	Intracellular range (mM)	Extracellular range (mM)
Na^+	5–20	130–160
K^+	130–160	4–8
Ca^{2+}	50–1000 nM ^a	1.2–4
Mg^{2+}	10–20	1–5
Cl^-	1–60	100–140
HCO_3^-	1–3	20–30

^a Given as nanomolar rather than millimolar.

A quick guide to excitable membranes and action potentials – ion distribution

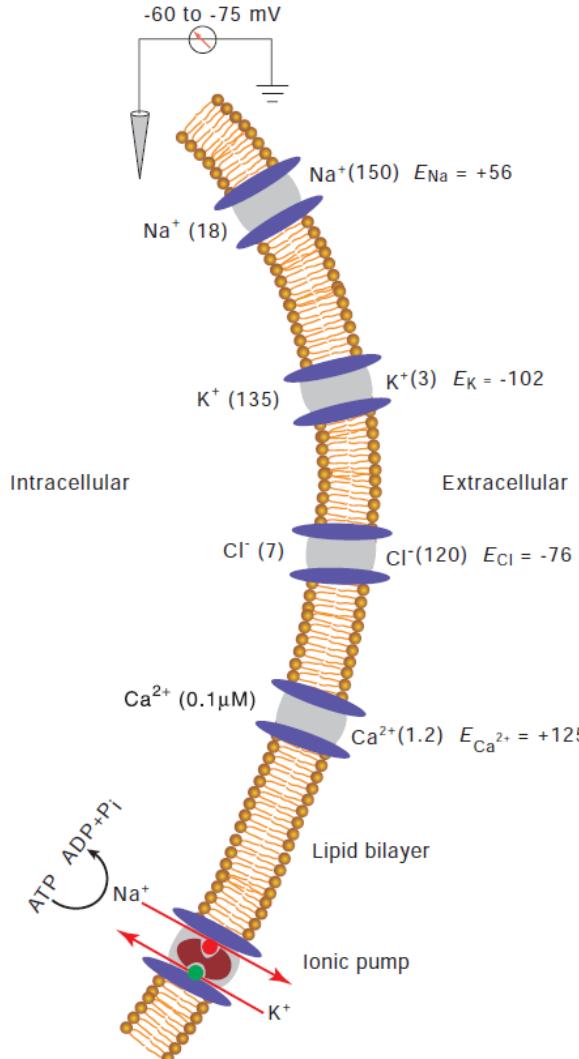
- But ions also have a **charge**
- **If you set up a chemical gradient of ions, you will inherit their charge**
- **This is what Neuroscience means when it says there is an electrochemical gradient**
- It is important to remember that both the charge disparity of the membrane and natural gradient of concentration both will determine flow of these ions (the electrochemical aspects are linked)



A quick guide to excitable membranes and action potentials – ion distribution all together

- Each ion has channels that can allow the ions to flow down their **concentration gradients**
- **What factors control diffusion of concentration down its gradient?** (thanks to **thermodynamics** and Walther Hermann **Nernst** we know this!)
- **Nernst equation** describes the electrical potential of a concentration of ions
 - It solves the electrical potential (or disparity) for an ion given the concentration gradient
 - It needs thermodynamic parameters that **impact concentration gradients of ions**
 - **z** (charge of ion)
 - **T** (temperature)
 - **R** (universal gas constant)
 - **F** (Faraday constant)

$$E = \frac{RT}{zF} \ln \frac{\text{ion concentration outside}}{\text{ion concentration inside}}$$

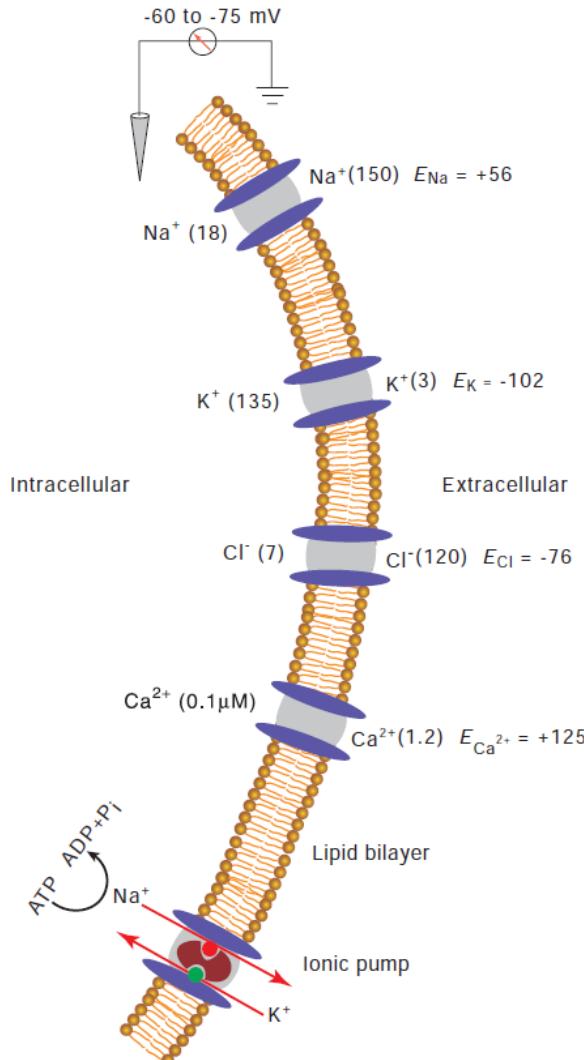


A quick guide to excitable membranes and action potentials – ion distribution all together

- Each ion has channels that can allow the ions to flow down their **concentration gradients**
- **The combination of all these ion gradients together is imbalanced at equilibrium**
 - This equilibrium is the **resting voltage of a membrane**

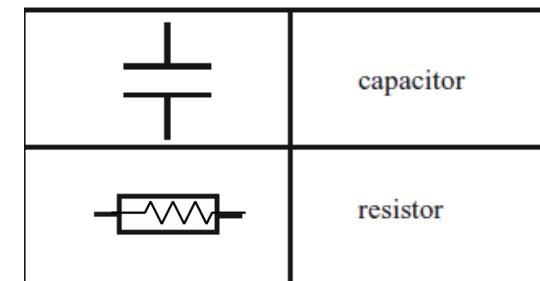
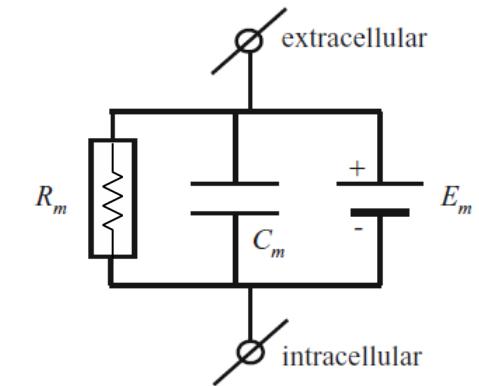
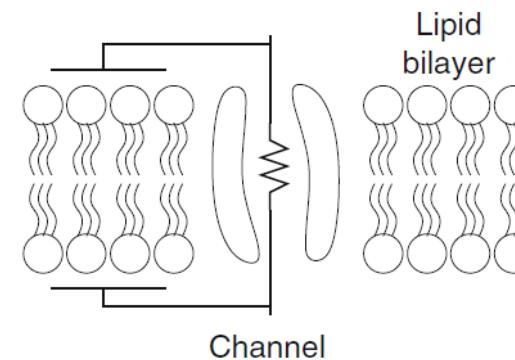
$$V_m = V_{\text{inside cell}} - V_{\text{outside cell}}$$

- There is an actual **charge** to neuronal membranes
- This charge is the same that underlies batteries!
- **Note that for multiple ions, we use Goldman-Hodgkin-Katz (GHK) equation**
 - Not to worry, this is taking **Nernst equation** and applying it for **multiple ions in a permeable membrane**, which we will revisit later

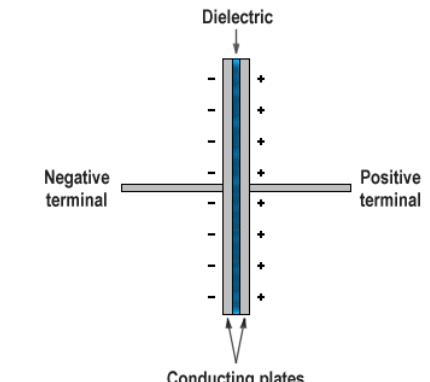


A quick guide to excitable membranes and action potentials – electrical engineering view

- Due to the electrical nature of neuronal membranes, they are often diagrammed as an electrical circuit
- This helps us understand different parts of electrical charges
- A **resistor** a device that **resists electrical flow**
- A **capacitor** is electoral device that stores charges by the natural thermodynamic law that if you have charge disparity the opposing charged ions will align as close to each other as possible



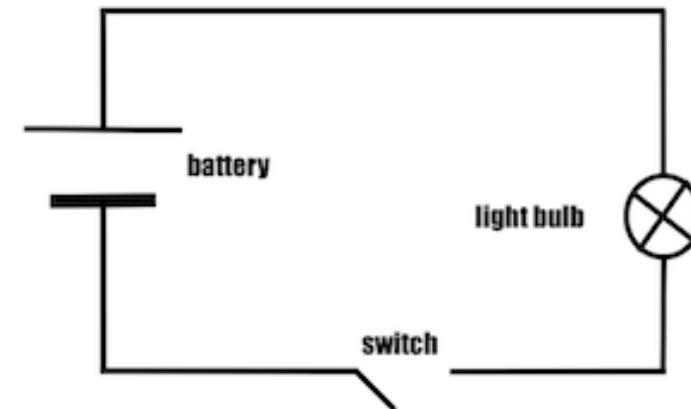
Capacitor



A quick guide to excitable membranes and action potentials – electrical engineering view

- The **membrane** is a **natural resistor** and **capacitance naturally occurs**
 - Resistor + capacitor + battery (our electrochemical gradient) = simple circuit with a battery

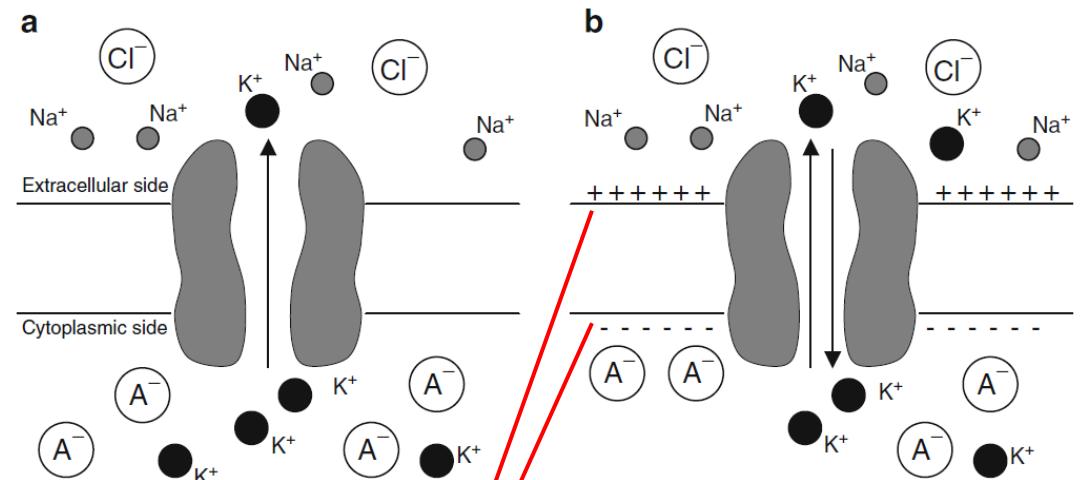
Simple Electric Circuit



What is the “Switch” though in our membrane?

A quick guide to excitable membranes and action potentials – **Voltage-gated permeable ion channels**

- The **switch is permeable ion channels**
- When open they allow ions to flow down their electro-chemical gradient
- **These aren't just permeable channels; they are triggered by voltage changes in the membrane**

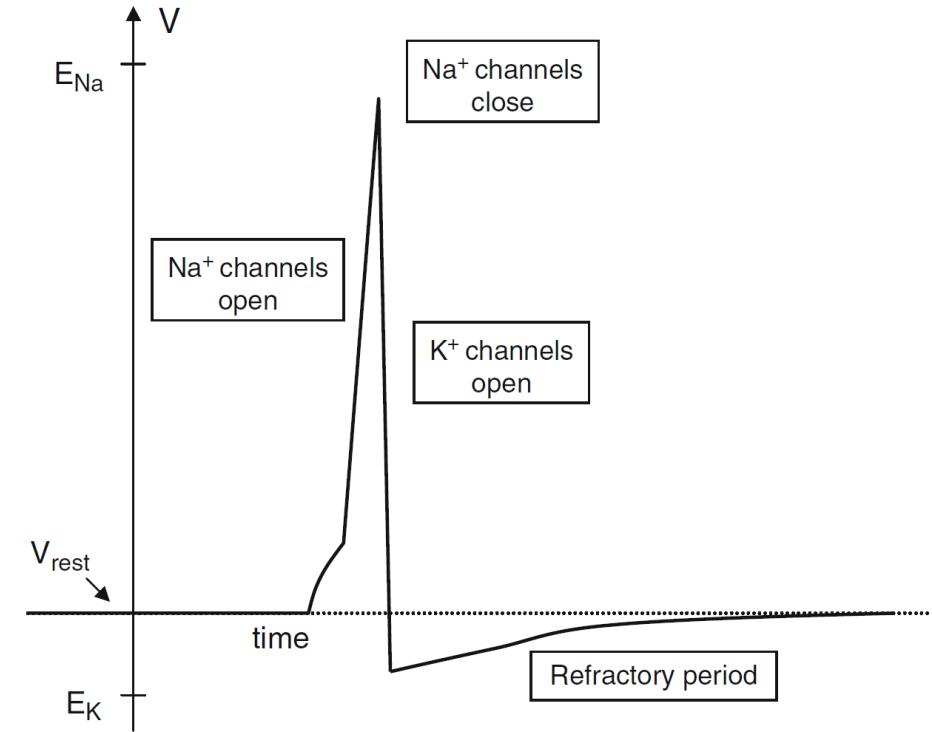


Look at the capacitance that is naturally occurring at this membrane!

A quick guide to excitable membranes and action potentials – Action Potentials

- As **calcium** is increasing, **neurotransmitters** are being released from presynaptic neuron
- **Neurotransmitters** bind to postsynaptic neuron's receptors and start depolarizing the postsynaptic neuron
- Enough depolarization activates depolarization of **voltage-gated Na⁺ channels** that allows **Na⁺ to go down its concentration gradient**
- **Na⁺** going down its gradient (flowing into the neuron) is also a **positive ion** that **increases the membrane further**
- The large voltage increase activates **K⁺ channels** that allow **K⁺** to flow down its gradient (flowing out of the neuron) and **repolarize the neuron**
- The **K⁺ channels** remain open **past** the neurons **resting membrane potential** known as the **refractory period**

Depolarization = away from resting potential
Repolarization = towards resting potential

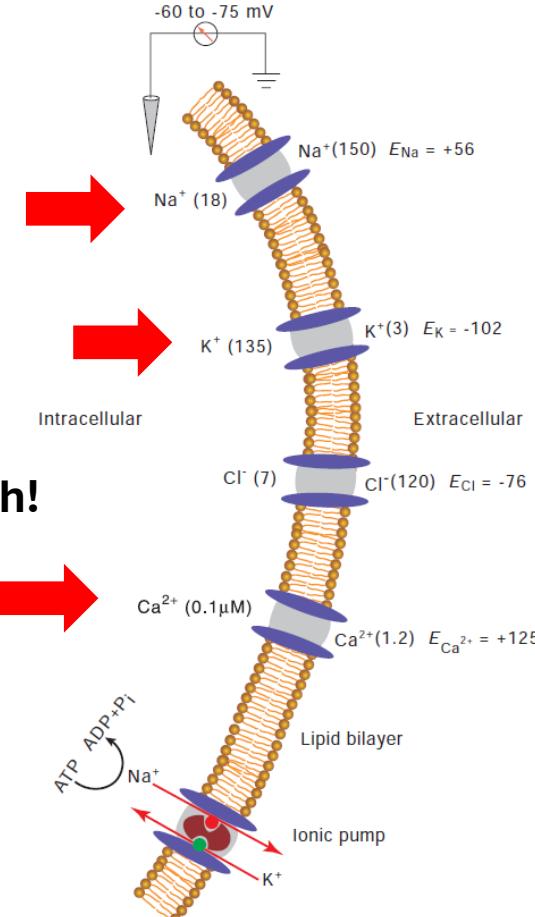


Going from Nernst to GSK equations – a full equation including all ions

- Earlier we talked about **Nernst Equation**
- **Nernst equation** describes the electrical potential of a concentration of ions
 - It solves the electrical potential (or disparity) **for an ion** given the concentration gradient
 - It needs thermodynamic parameters that **impact concentration gradients of ions**
 - **z** (charge of ion)
 - **T** (temperature)
 - **R** (universal gas constant)
 - **F** (Faraday constant)

$$V_m = \frac{RT}{zF} \ln \frac{\text{ion concentration outside}}{\text{ion concentration inside}}$$

**There is an issue though!
We have multiple ions!**

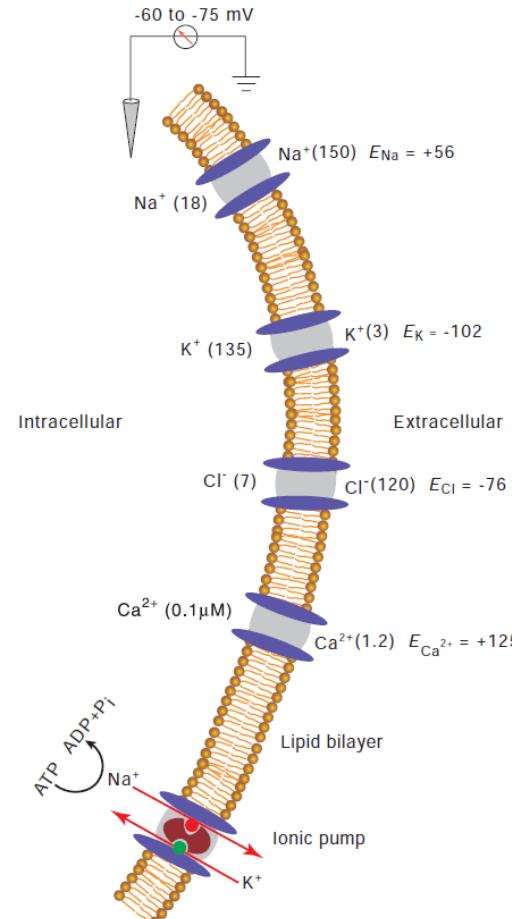


Going from Nernst to GSK equations – a full equation including all ions

- For multiple ions, we use **Goldman-Hodgkin-Katz (GHK) equation**
- **GHK is Nernst equation applied for multiple ions in a permeable membrane**
- We will add **permeability** now that we know that voltage-gated **ion channels are permeable to certain ions.**
- **GHK:**

$$V_M = \frac{RT}{F} \ln \frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{out}}$$

- **Note:** P_{ion} is the permeability at any time for a given ion (depending on the state of the voltage gated ion channels)
- Now we have an equation that gives us the terms of V_m since it is the **electrical potential across the whole membrane**
- Z is also gone because we assign charge differently for each ion (it is within the calculation for **Permeability (P_{ion})**)



Quick Summary

Science

Ions carry a charge + concentration

Lipid Blocks ion movement

Neuronal membranes have ion disparity across the membrane (i.e. voltage)

Action Potentials change permeability to sodium then potassium via voltage gated ion permeable channels

Modelling

Nernst Equation

describes the electrical potential of a concentration of individual ions

$$V_m = \frac{RT}{zF} \ln \frac{\text{ion concentration outside}}{\text{ion concentration inside}}$$

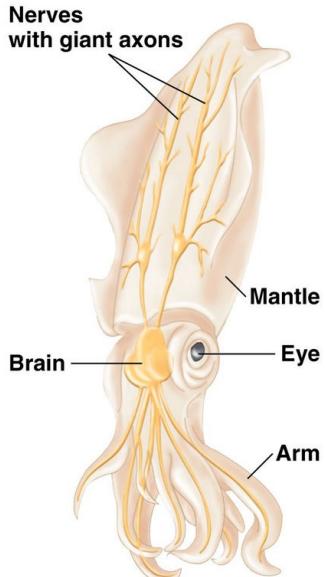
GHK Equation

GHK is Nernst equation applied for multiple ions in a permeable membrane

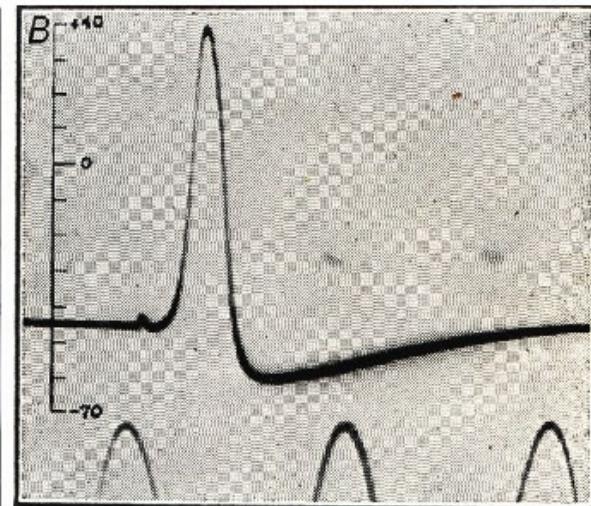
$$V_M = \frac{RT}{F} \ln \frac{P_K[K^+]_{\text{out}} + P_{Na}[Na^+]_{\text{out}} + P_{Cl}[Cl^-]_{\text{in}}}{P_K[K^+]_{\text{in}} + P_{Na}[Na^+]_{\text{in}} + P_{Cl}[Cl^-]_{\text{out}}}$$

Where are we in time...

1937 - Hodgkin works with KS Cole and HJ Curtis at Wood Hole Marine Biological Lab in Massachusetts. **Hodgkin introduced to giant nerve fiber of the squid**



1939 – Hodgkin and Huxley publish **first recorded Action Potential in Nature**. Hodgkin noted "...the membrane potential at the peak of the nerve impulse reversed by 40 mV instead of falling to zero as assumed in the classical theory"



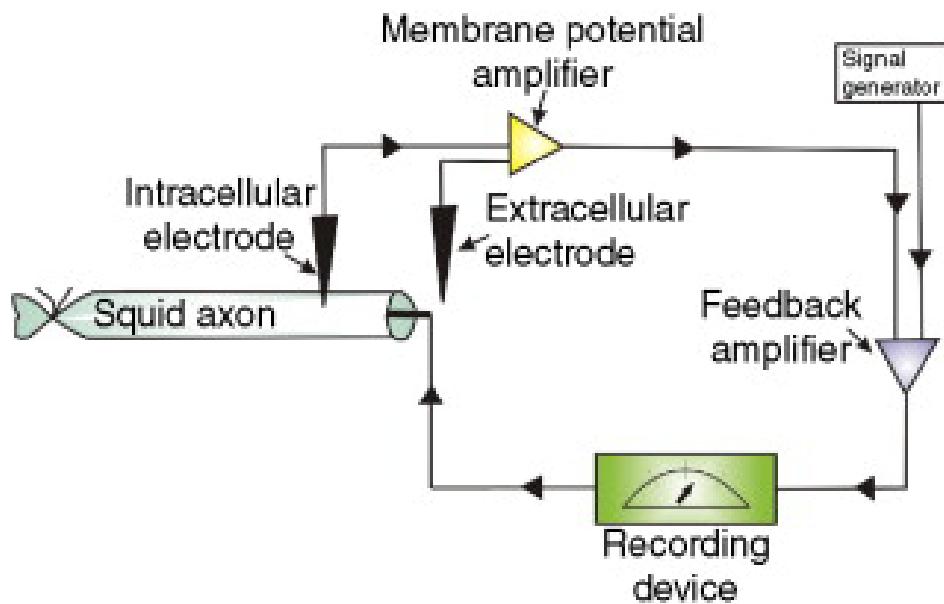
Hitler invades Poland, escalating into WW2.



Where are we in time...

1946– John Eccles used a voltage clamp and found that action potential overshoot was **NOT** due to sodium.

Hodgkin and Huxley could not perform voltage clamp at first returning from the war due to damaged equipment during the war.



1949– Hodgkin and Huxley now record voltage clamp and gain insight into **gating variables** via fitting sodium and potassium channel dynamics

“At first, the response of a nerve to different electrical stimuli is too complicated and varied to be explained by these relatively simple conclusions. Partly for this reason, Huxley and I spent a long time developing what are sometimes known as the Hodgkin-Huxley equations, which are given in outline below. **In using the equations it should be emphasized that there are no arbitrary constants, as the voltage-clamp results were used to supply the numerical data required.”**

Hodgkin-Huxley equation contextualized

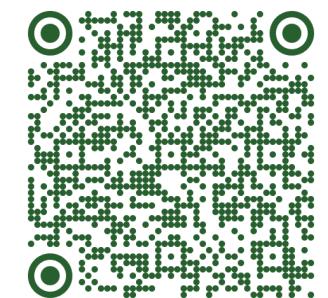
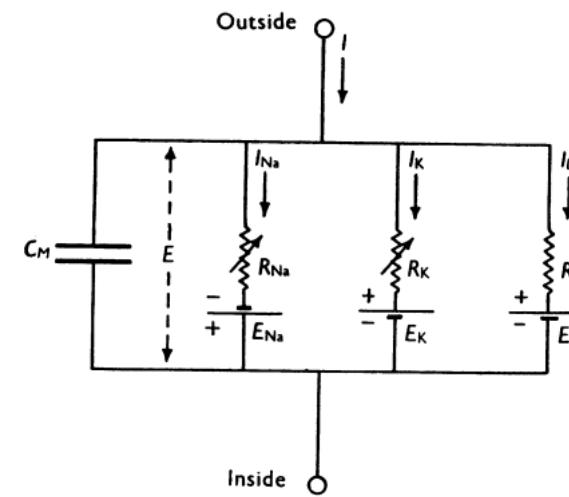
- GSK equation has allowed for finding the resting membrane potential (V_m)
- Hodgkin-Huxley equation is now going to try and look at how these **voltage potentials change during an action potential**
- The **GSK equation has an issue – it assumes no changes in permeability, which you know changes during an action potential!**

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

BY A. L. HODGKIN AND A. F. HUXLEY

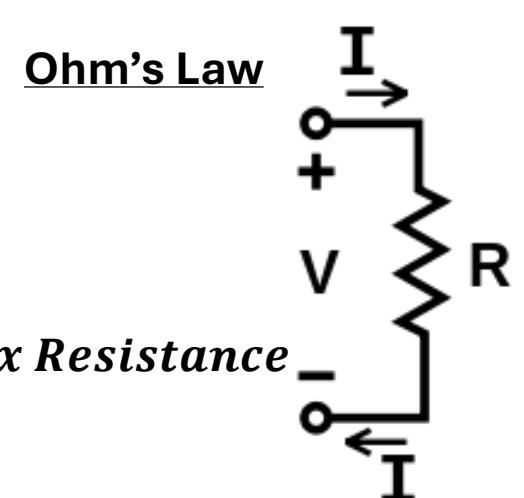
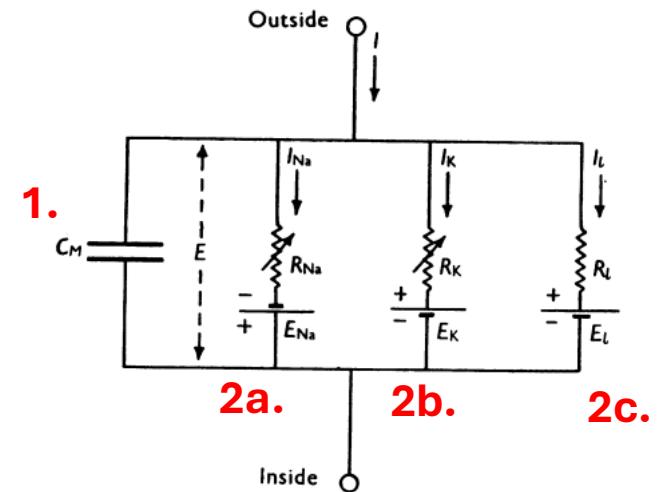
From the Physiological Laboratory, University of Cambridge

(Received 10 March 1952)



Hodgkin-Huxley equation

- We are hoping to find out about the change of **voltage over time during an action potential**
- If we are talking about changes in voltage, we are really talking about **ions moving = current**
 - Both **Nernst and GHK equations set the current = 0**
 - This isn't a mistake, but the goal of these equation was to find the total **electrical potential across the membrane at rest**
 - These equations provided the **reversal potential of each ion, something we now need**
- **Ohms Law is a simple equation on which we start to build, as it is ideal situations when current $\neq 0$**
- We can use **Ohms law** to find **I (current)** for each part of our circuit in hopes of finding overall **current changes during an action potential:**
 1. Current of a simple membrane
 2. Current for each ion



$$\text{Voltage} = \text{Current} \times \text{Resistance}$$

Hodgkin-Huxley equation – Coulomb's Law of Capacitance

- We can use **Ohms law** to find **I (current)** for each part of our circuit
 1. Current of a simple membrane = **capacitance current**
 2. Current for each ion
- We know we can get **Voltage, Current, and Resistance if we have the other two, but what about capacitance**
- Capacitance can be derived (thanks to Nernst, Einstein, and others) as **Coulomb's Law of Capacitance**
- We can change 1. and 2. to the following:
 1. $I_C = C_m \frac{dV_m}{dt}$
- **One more important note before 2 –**

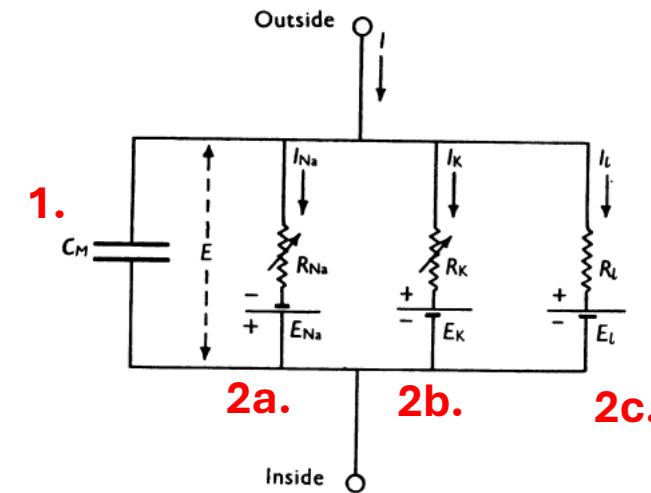
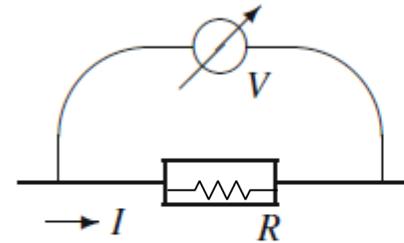


Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_L = 1/\bar{g}_L$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.

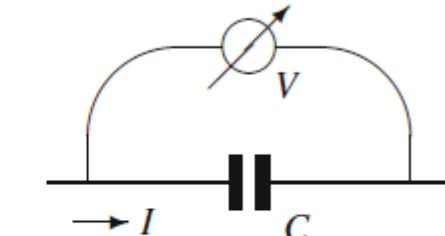
Ohm's Law



a.

$$V = RI$$

Coulomb's Law



b.

$$C \frac{dV}{dt} = I$$

Hodgkin-Huxley equation – Ohms law in resistors in parallel

- One more important note before 2 – In our **circuit diagram**, the **resistors are set in parallel**
- It is easier to discuss then **conductance (g)**, because:

$$\text{conductance } (g) = \frac{1}{R}$$

- You can now exchange in **rearranged Ohms law**:

$$\text{Current} = \frac{\text{Voltage}}{\text{Resistance}}$$

- and now you get:

$$\text{Current } (I) = \text{conductance } (g) \times \text{voltage } (V)$$

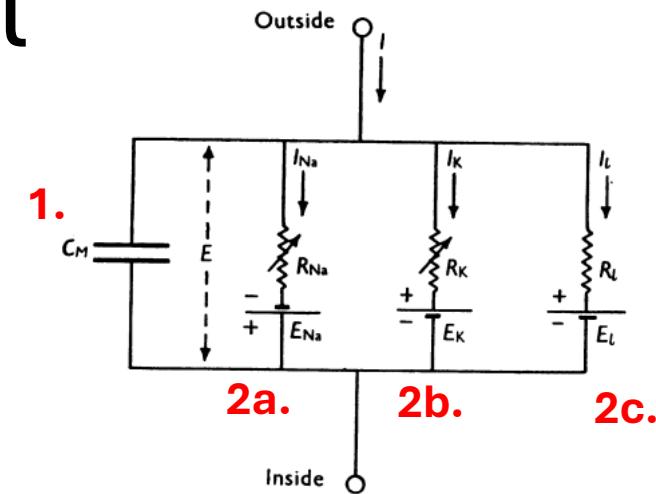
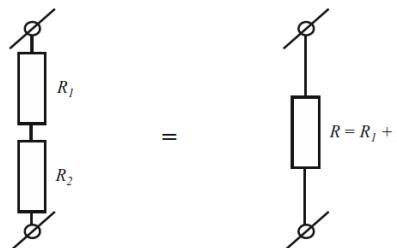
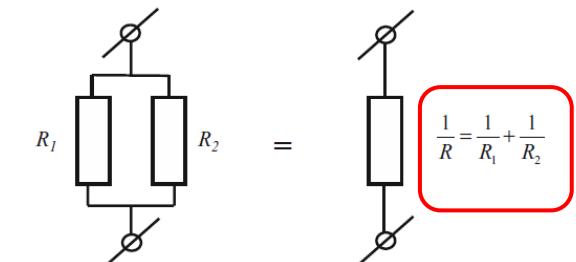


Fig. 1. Electrical circuit representing membrane. $R_{\text{Na}} = 1/g_{\text{Na}}$; $R_{\text{K}} = 1/g_{\text{K}}$; $R_{\text{L}} = 1/\bar{g}_{\text{L}}$. R_{Na} and R_{K} vary with time and membrane potential; the other components are constant.

Resistors in series



Resistors in parallel



Hodgkin-Huxley equation

- We can change **1.** and **2.** to the following:

$$1. \quad I_C = C_m \frac{dV_m}{dt}$$

Coulomb's law

$$2. \quad I_{ion} = g_{ion}(V_m - V_{ion})$$

Trick to use Ohm's law
with resistors in series

- Where V_m is the **resting membrane potential**:

$$V_m = V_{\text{inside cell}} - V_{\text{outside cell}}$$

- And V_{ion} is the **reversal potential** for that ion
- Reversal potential** is the voltage at which the ion will be at **equilibrium (no movement across the membrane)**
- Thankfully, we have all of those for each ion thanks to **Nernst and GHK equations which solved for this**

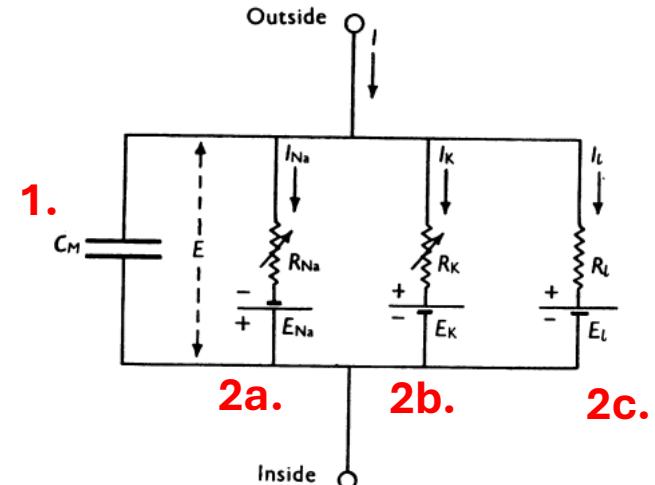
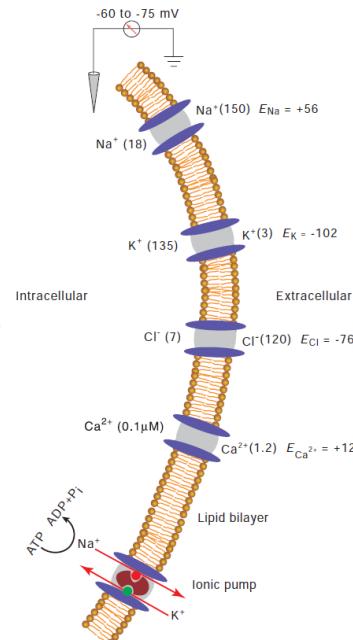


Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_L = 1/\bar{g}_L$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.



Hodgkin-Huxley equation

- We can change **2.** for each ion (**2a,b,c**):

$$1. \quad I_C = C_m \frac{dV_m}{dt}$$

$$2. \quad I_{ion} = g_{Na}(V_m - V_{Na}) + g_K(V_m - V_K) + g_l(V_m - V_l)$$

- The total current across the membrane (**I**) would then be:

$$I = I_C + I_{ion}$$

or

$$I = I_C + I_{Na} + I_K + I_l$$

- Now it simply plugging in **1.** and **2.**

$$I = C_m \frac{dV_m}{dt} + g_{Na}(V_m - V_{Na}) + g_K(V_m - V_K) + g_l(V_m - V_l)$$

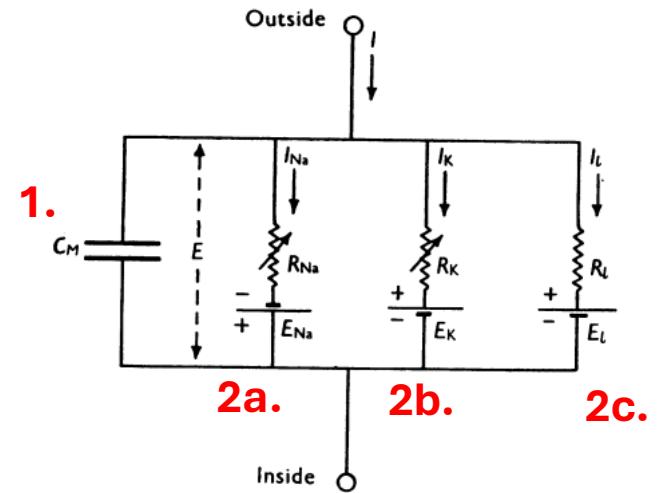


Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_l = 1/g_l$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.

Hodgkin-Huxley equation

- The most important part of the equation is done!
- **The remained of the Hodgkin-Huxley model is channel gating variable equations**
- The equations are to **model** the dynamics of **Na⁺** and **K⁺** channels in response to voltage as:
 - **K⁺ activation (n)**: delayed response to depolarization
 - **Na⁺ activation (m)**: opens rapidly in response to depolarization
 - **Na⁺ inactivation (h)**: inactivation period, where the **Na⁺** channel cannot re-open for a period after opening (i.e. refractory period)
- These equations can be summarized by:

$$\frac{dx}{dt} = \alpha_x(V_m)(1 - x) - \beta_x(V_m)x$$

- Where **x** is equal to our **gating variables n, m, h**
- α_x and β_x are **rate constants** that are enforcing the **activation of these channels to incoming voltage**
- Specifically:
 - $\alpha_n(V_m)$ increases V_m with depolarization, but with **delayed response – K⁺ channel activation**
 - $\beta_n(V_m)$ decrease V_m with depolarization to bring back to equilibrium- **K⁺ channel inactivation**
 - $\alpha_m(V_m)$ increase V_m **rapidly** with depolarization – **Na⁺ channel activation**
 - $\beta_m(V_m)$ increase as V_m decrease – **Na⁺ channel inactivation (due to K⁺ delayed response)**
 - $\alpha_n(V_m)$ decreases as V_m increases – **Na⁺ channel refractory period**
 - and $\beta_n(V_m)$ increase as V_m returns to V_m in **resting state** (towards V_m at rest) – **Na⁺ channel reset**

Hodgkin-Huxley equation

- Here are the four equations:

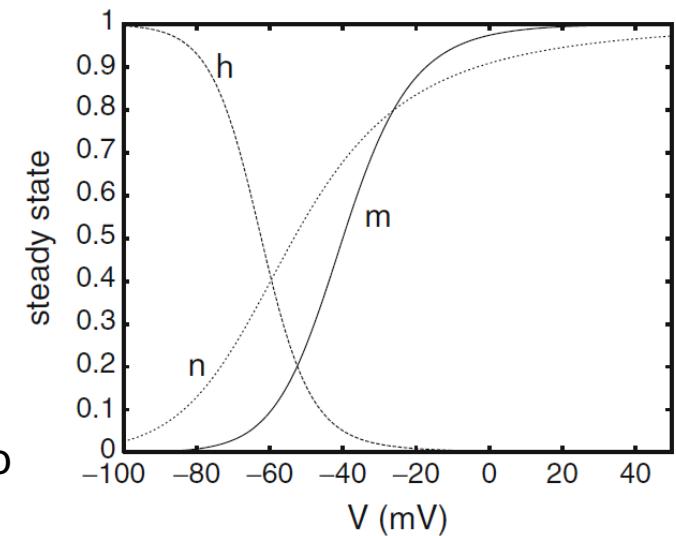
$$I = C_m \frac{dV_m}{dt} + g_{Na} m^3 h (V_m - V_{Na}) + g_K n^4 (V_m - V_K) + g_l (V_m - V_l)$$

$$\frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n$$

$$\frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m$$

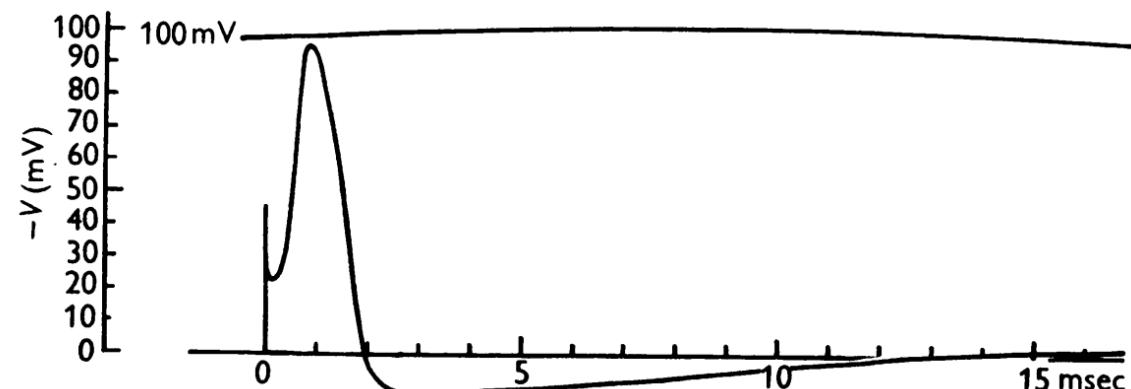
$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$

- Note that our original **equation 1** did not incorporate our **channel gate variables**. No worries, as constant we just add them to the beginning of their respective I_{ion} equations.
- The exponents are **empirically driven (found from experiments)**
- They are trying to mirror how these channels function:
 - K+ channel has 4 gates that must be open to allow K+ = n^4
 - Na+ channel has 3 gates that must be open to allow Na+ = n^3
 - Na+ channel has 1 gate that must be open to inactivate Na+ = h



Hodgkin-Huxley equation

- We have the equations. Now what?
- This is exactly what **differential equations** mathematically solves!
- **Calculus** is the mathematics of change – **voltage over time** ($\frac{dV_m}{dt}$)
 - It allows looking at how **voltage changes over time**
 - But this is where **Calculus breaks down**
 - What about all the **factors?**
- **Differential equations** solves exactly that
 - It extends **Calculus to multiple dynamic variables**
 - We can model multiple variables and if they are **interdependent** than we can calculate these variables **in discrete steps over time** when given **different input parameters**
- For the **Hodgkin-Huxley** model this allows us to test whether if we are given **an input of current** do we see the **V_m** response that correlates to the **V_m** from a recorded **AP?**
- We modeled the individual **ions** and their **voltage-gated** according to **values recorded experimentally (empirical values)**, so if the model recapitulates the **V_m** dynamics it would support **Hodgkin and Huxley's hypothesis that Na⁺ and K⁺ conductance's underly an AP**



Hodgkin-Huxley equation results

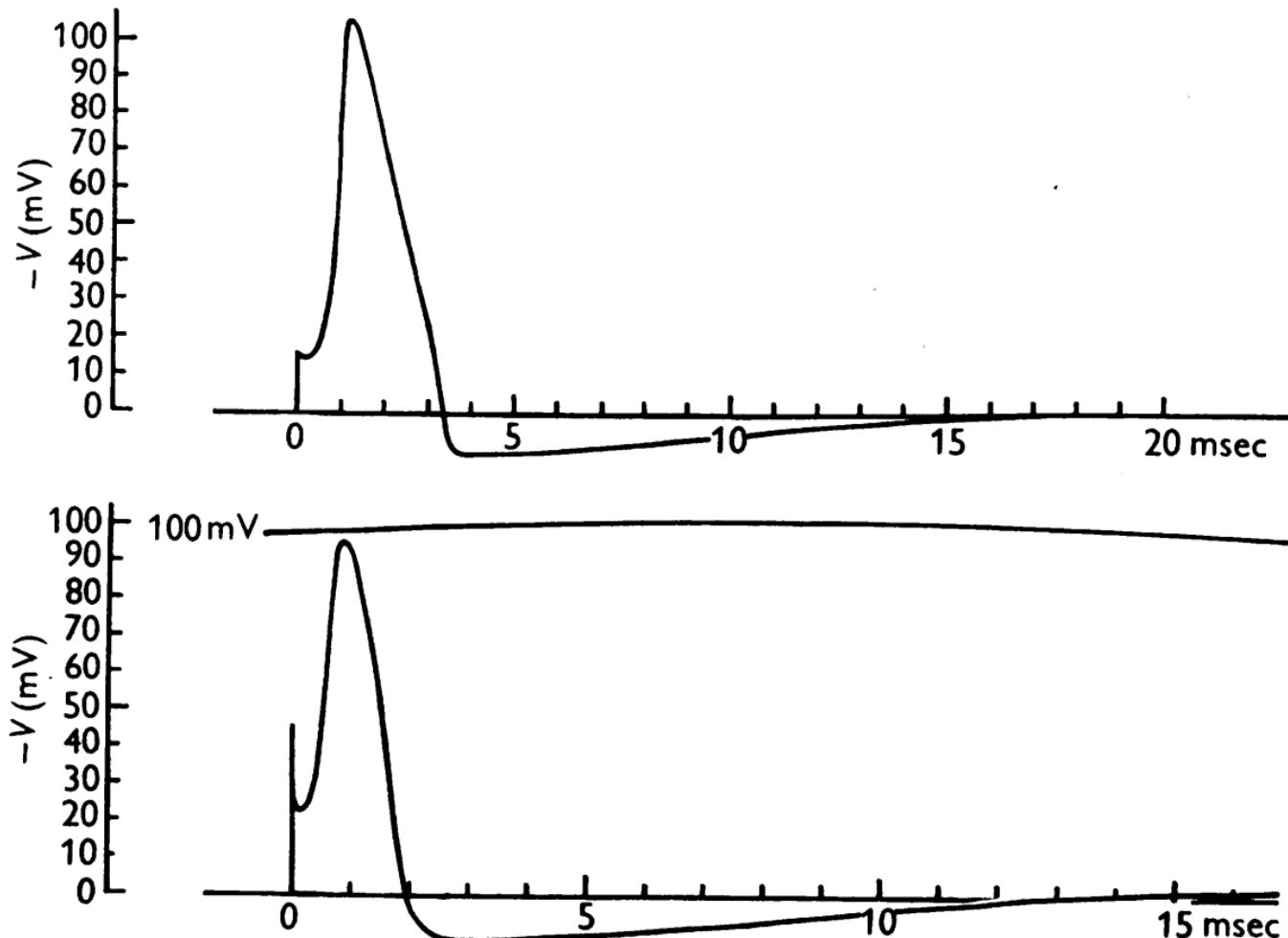


Fig. 13. Upper curve: solution of eqn. (26) for initial depolarization of 15 mV, calculated for 6° C. Lower curve: tracing of membrane action potential recorded at 9.1° C (axon 14). The vertical scales are the same in both curves (apart from curvature in the lower record). The horizontal scales differ by a factor appropriate to the temperature difference.

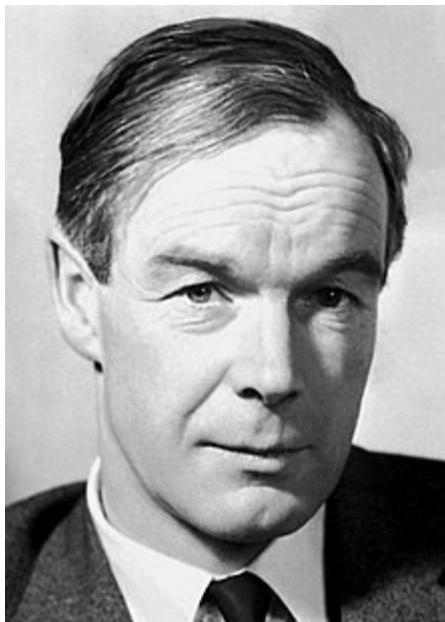
At the footsteps of greatness...

An **Equation(s)** that fully explains the ionic mechanisms underlying the **Action Potential**

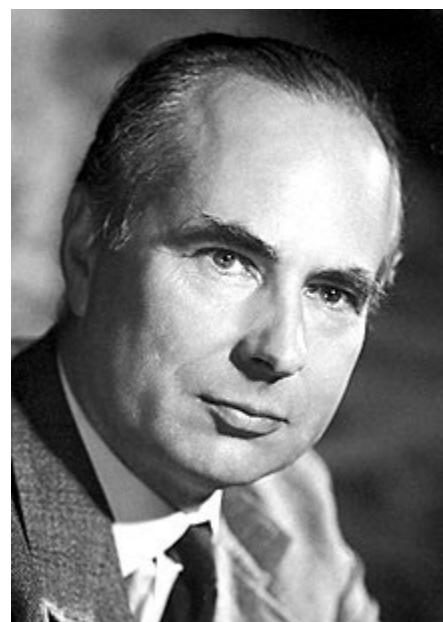
A model that recapitulates a neuron firing!



John Eccles



Alan Hodgkin



Andrew Huxley



The **MOST** important question is your scientific hypothesis

- What determines your use of a model is the question you are asking and at what level
- Identify the level your question is at, **then** identify the ideal model
- You **cannot** have it all – models at full scale are still not feasible
- **Hodgkin-Huxley model**
 - is a **model perfectly at its level** – ions electrochemical gradients linked to membrane voltage
 - It **models** what was known about the **two major ions, Na⁺ and K⁺**
 - **Show what models aim to do - integrate multiple factors to model how well it explains the mechanism being investigated**
 - **One factor included is the leak current (I_L)**, which is the current that leaks across the membrane due to leaky ion channels (something that naturally occurs in neurons)

Quick Summary – the full path to HH equations

Nernst Equation

describes the electrical potential of a concentration of individual ions

$$V_m = \frac{RT}{zF} \ln \frac{\text{ion concentration outside}}{\text{ion concentration inside}}$$

GHK Equation

GHK is Nernst equation applied for multiple ions in a permeable membrane

$$V_M = \frac{RT}{F} \ln \frac{P_K[K^+]_{\text{out}} + P_{Na}[Na^+]_{\text{out}} + P_{Cl}[Cl^-]_{\text{in}}}{P_K[K^+]_{\text{in}} + P_{Na}[Na^+]_{\text{in}} + P_{Cl}[Cl^-]_{\text{out}}}$$

Passive Membrane (i.e., resting membrane)

Coulombs Law

Capacitance can be derived as Coulomb's Law of Capacitance

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

Ohms Law for resistors in series

Finding for current across membrane for ions (remember why we can model as resistors in series)

$$I_{ion} = g_{ion}(V_m - V_{ion})$$

Combine Coulombs Law + Ohms Law for resistors in series for all ions

Capacitance can be derived as Coulomb's Law of Capacitance

$$I = C_m \frac{dV_m}{dt} + g_{Na}(V_m - V_{Na}) + g_K(V_m - V_K) + g_l(V_m - V_l)$$

Active Membrane (i.e., during an action potential)

Quick Summary – the full path to HH equations

**Combine Coulomb's Law + Ohm's Law for resistors in series
for all ions**

Combine now capacitance calculation with Ohm's law for each ion

$$I = C_m \frac{dV_m}{dt} + g_{Na}(V_m - V_{Na}) + g_K(V_m - V_K) + g_l(V_m - V_l)$$



**Hodgkin-Huxley Equation combining Coulomb's Law, Ohm's
Law and Gating variables**

Adding in gating variables

$$I = C_m \frac{dV_m}{dt} + g_{Na}m^3h(V_m - V_{Na}) + g_Kn^4(V_m - V_K) + g_l(V_m - V_l)$$

$$\frac{dn}{dt} = \alpha_n(V_m)(1 - n) - \beta_n(V_m)n$$

$$\frac{dm}{dt} = \alpha_m(V_m)(1 - m) - \beta_m(V_m)m$$

$$\frac{dh}{dt} = \alpha_h(V_m)(1 - h) - \beta_h(V_m)h$$

Hodgkin-Huxley in the context of compartmental models and passive membrane properties

- We have been dealing with a small isolated portion of a neuronal membrane
- **We can extend our model to a compartment of models with repeated motifs of our isolated membrane**
- If we do so we need to include **passive (native) properties**
- **Cable theory** is the area of computational neuroscience that models these properties
- Here is an equation that we can integrate **into our other equations to relate current (I) and resistance (R)** to the rest of our equations (remember **interdependence?**)

$$I = \frac{a}{2R} \frac{\partial^2 V}{\partial x^2}$$

- Where **a** is the radius of the axon, **R** the cytoplasm resistance, **x** the position on the nerve
- **∂** indicates a partial derivative, which is a **differential equations tool** used to figure out how a quantity that depends on more than one factor changes when you adjust one of these factors

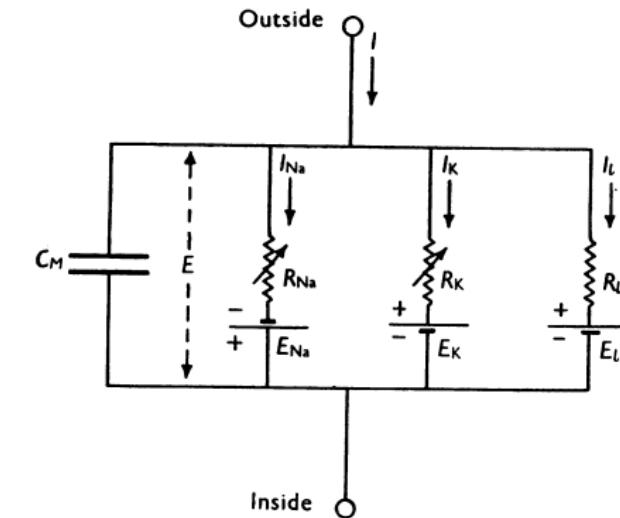


Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_L = 1/\bar{g}_L$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.

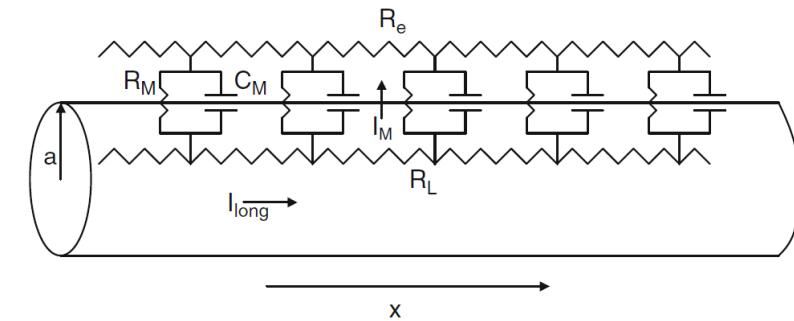
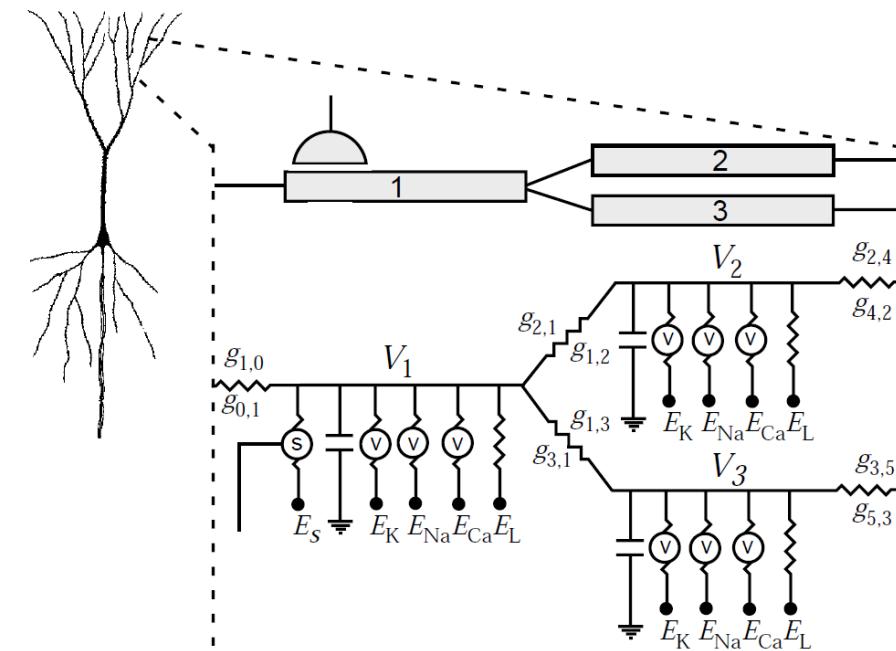
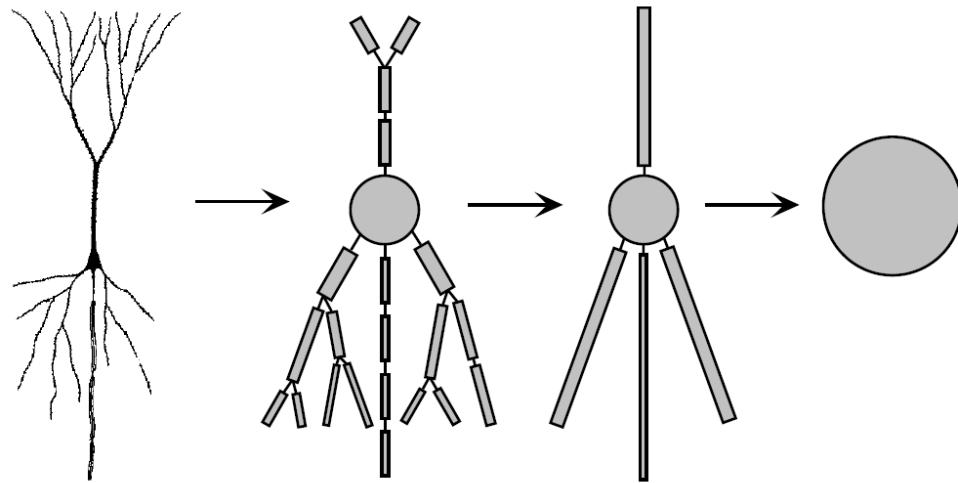


Fig. 1.5 Equivalent circuit for a uniform passive cable. I_{long} is the current along the inside of the cable, I_M is the current across the membrane, R_L is the resistance of the cytoplasm, R_e is the resistance of the extracellular space, R_M is the membrane resistance, and C_M is the membrane capacitance

Multicompartmental models

- These are large-scale models where every portion of the neuron is modeled with a compartment
- These can be very exhaustive, and even the passive membrane properties changed in the axons versus the dendrites that are well identified experimentally



Let us take a moment to see what parts of the Hodgkin-Huxley model show us other computational areas in Neuroscience

- We could model **ion channel dynamics**
- We could model **passive membrane properties**
- We could model **how different ion channels impact action potentials**
- You know (and Wednesday especially) how **Na and K channels are activated during an AP**
- You know how **the electrochemical gradient of neuronal membranes is established**
- You know how **ions' electrochemical nature allows them to regulate the neuronal membrane and action potentials**

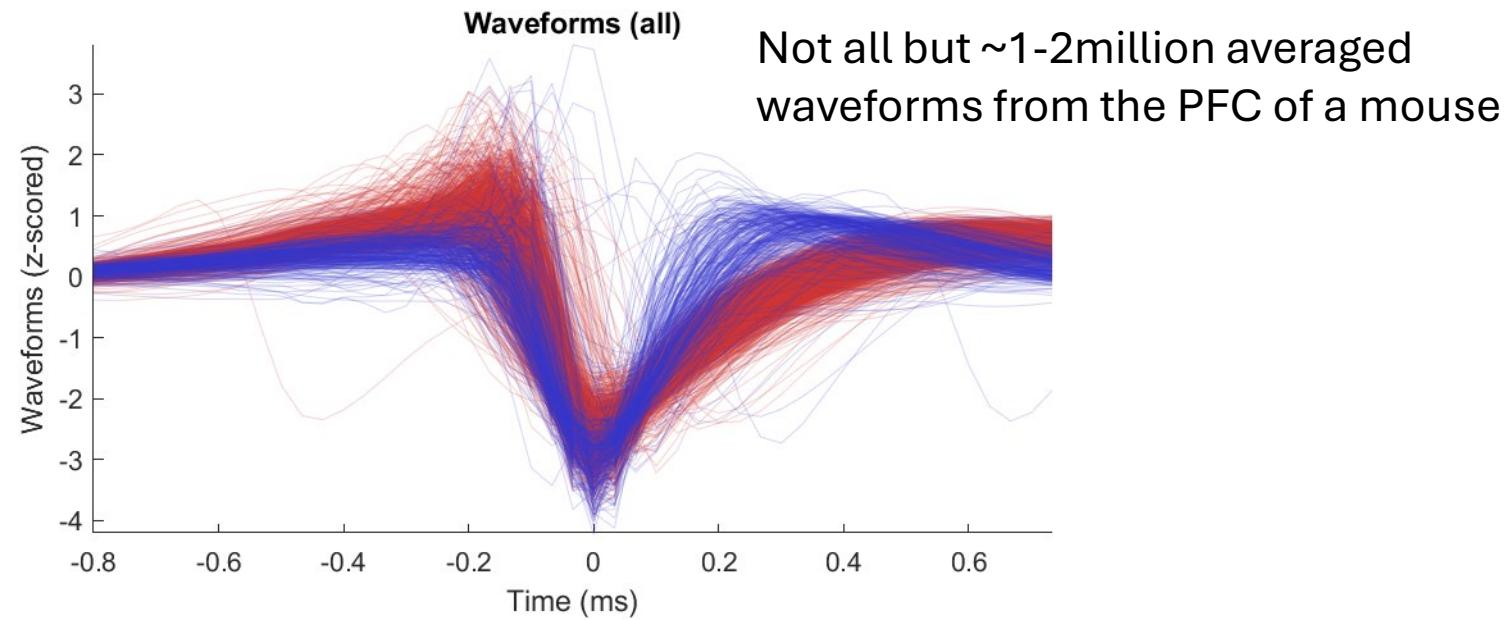
The **MOST** important question is your scientific hypothesis

- What determines your use of a model is the question you are asking and at what level
- Identify the level your question is at, **then** identify the ideal model
- You **cannot** have it all – models at full scale are still not feasible

What about modeling networks of neurons?

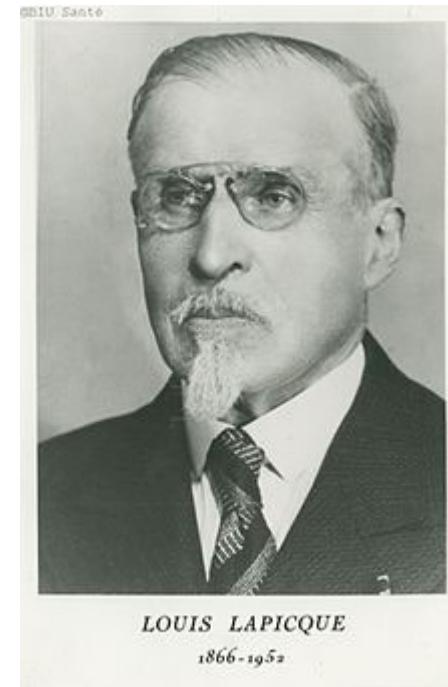
Approximating the dynamics of action potentials

- A neurons threshold for an AP is about -55 to -50mv
- AP are a very stereotyped event where the **V_m** is depolarized-hyperpolarized-refractory period
- **What if we... what if we just... modeled these dynamics? Wouldn't that be computationally easier?**



Approximating the dynamics of action potentials – Leaky-integrate and Fire neuron models

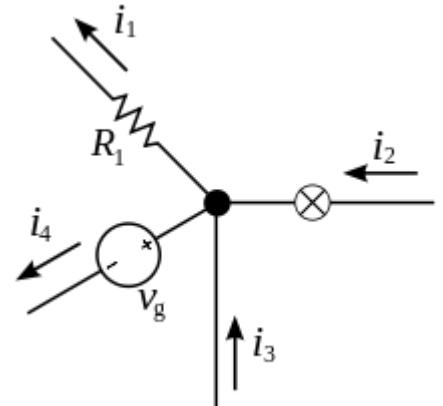
- **Leaky-integrate and Fire (LIF) neuron models** are one of many varieties of neuronal models that approximate AP dynamics
- **LIF models** state that an AP occurs when the **V_m reaches a threshold**
- By avoiding biophysical modelling aspects, **LIF models** only need to model **subthreshold dynamics of V_m**
- We aren't going to throw away all the parts from **Hodgkin-Huxley, the passive membrane properties (capacitance and resistance)**, because that is what makes our neuron models **realistic**



Leaky-integrate and Fire neuron models – derivation

- We start just where we started for **Hodgkin-Huxley**
- **We start by modeling the entire current (I_{total}) of the system**
$$I_{total} = I_C + I_{RL} + I_{ext}$$
- We used this trick earlier, but how do we justify it?
- **Kirchoff's current law** – the total current (I_{total}) entering a system (node/junction) is equal to that flowing out of the system
- The key to understanding **Kirchoff's current law** is that the **current of any electrical system has to go somewhere. If the current cannot go to I_1 and I_4 then the current will not enter the node at I_2 and I_3**
- **Therefore, the sum of the current in the node $I_{total}(I_k)$ is always balanced (input and output current sum together = 0)**
- Note that the I_C is **current of capacitance**, I_{RL} **current of leak resistance** (previously this was I_l - as we are referring to the **leak current across the membrane**) I_{Ext} is **current applied externally** (think injected neuron with current or inputting synapses to a neuron)
- This is an **RC circuit** which is a **resistor-capacitance circuit**

Kirchoff's current law



$$I_2 + I_3 = I_1 + I_4$$

$$\sum_{k=1}^n I_k = 0$$

Leaky-integrate and Fire neuron models – derivation

- Now we have modeled everything for the passive membrane properties
- The **AP dynamics** of the model will be explicitly stated later; **therefore we are done:**

$$I_{total} = I_C + I_{RL} + I_{ext}$$

- Let's be good mathematicians and substitute in equations we know for the above variables

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

$$I_{RL} = \frac{V_m - V_{rest}}{R_m}$$

C_m is the **membrane capacitance**

V_m is the **membrane potential at any given time** (previously meant resting membrane potential when we weren't talking about action potentials so $V_m = V_{rest}$)

Now we know, for instance during an action potential $V_m \neq V_{rest}$ so we denote resting membrane potential as V_{rest}

Leaky-integrate and Fire neuron models – derivation

- Let's substitute in new values for I_C and I_{RL}

$$I_{total} = C_m \frac{dV_m}{dt} + \frac{V_m - V_{rest}}{R_m} + I_{ext}$$

- Moving $\frac{dV_m}{dt}$ to the left side and **recognize that according to Kirchoff's law that current into a neuron will equal current out of a neuron, so $I_{total} - I_{ext} = 0$**
- Now we have:

$$\frac{dV_m}{dt} = \frac{-(V_m - V_{rest})}{R_m C_m} + \frac{I_{ext}}{C_m}$$

Leaky-integrate and Fire neuron models – derivation

- Often the following value is replaced in **LIF** equations because it is commonly found experimentally so is easier to simply input:
 - **The Tau membrane constant:**

$$\tau_m = R_m C_m$$

- Replace our update equation with τ_m

$$\frac{dV_m}{dt} = \frac{-(V_m - V_{rest})}{\tau_m} + \frac{I_{ext}}{C_m}$$

Leaky-integrate and Fire neuron models – implementation

- Let us think through our equation:

$$\frac{dV_m}{dt} = \frac{-(V_m - V_{rest})}{\tau_m} + \frac{I_{ext}}{C_m}$$

- Now we implement these equations to produce an AP:
 - Voltage threshold (V_{thr})** the voltage where an action potential occurs
 - The amount of I_{ext} needed to elicit an AP is $I_{threshold}$ - the amount of current needed to elicit an AP

$$I_{thr} = \frac{V_{thr}}{R_m}$$

Leaky-integrate and Fire neuron models – implementation

- The following set function implements firing:

$$\text{firing}(I) = \begin{cases} 0 & I \leq I_{thr} \\ \left[t_{refr} - R_m C_m \log\left(1 - \frac{V_{thr}}{IR_m}\right) \right]^{-1}, & I > I_{thr} \end{cases}$$

- While seemingly complicated, the above states if the $I \leq I_{thr}$ then the **LIF neuron does not fire ($\text{firing}(I) = 0$)**
- If the $I > I_{thr}$ then the **LIF neuron reaches an AP by implementing:**

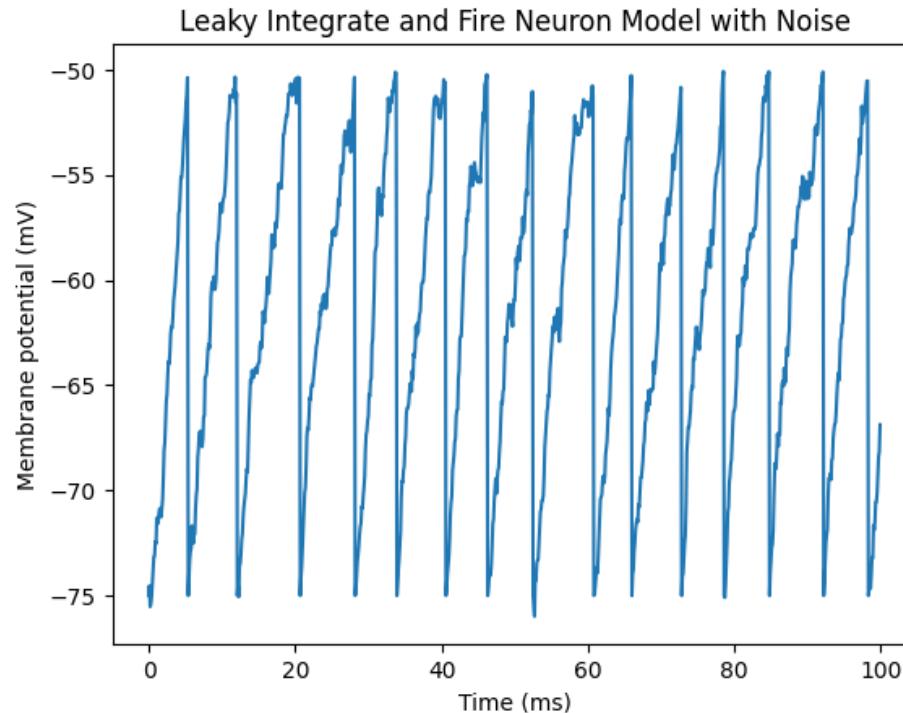
$$\left[t_{refr} - R_m C_m \log\left(1 - \frac{V_{thr}}{IR_m}\right) \right]^{-1}$$

Why does this AP not look like an AP in LIF

- Because we are simply mimicking the **nature of a neurons AP – that when inputting current increases V_m to above its AP V_{thr} then we have an AP**
- When you see the value reset, an AP has just occurred with LIF



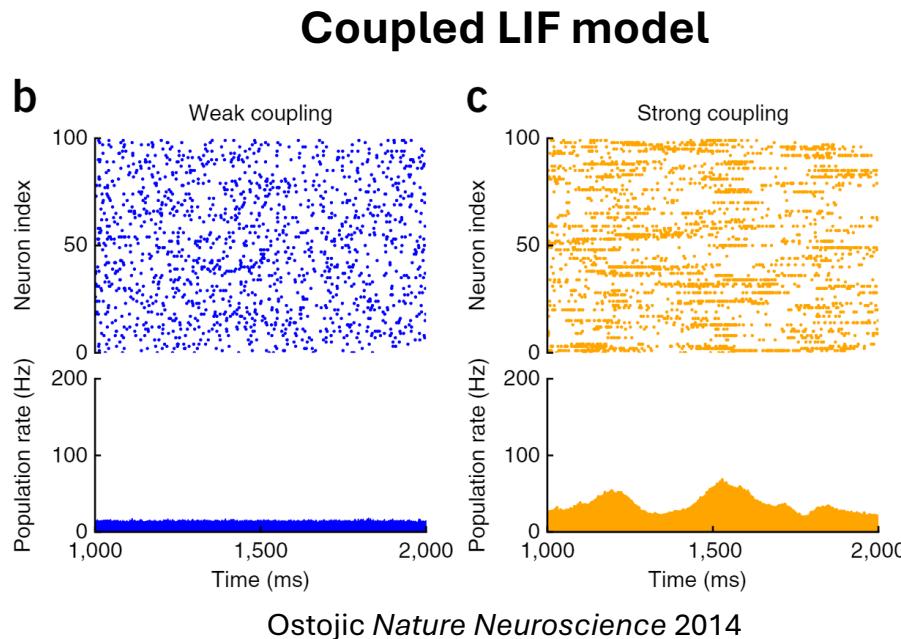
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```
V_rest = -75*mV          # Resting potential
V_threshold = -50*mV      # Threshold
R_m = 100*Mohm            # Membrane resistance
tau_m = 10*ms              # Membrane time constant
I = .5*nA                  # Input current
```

What can these models do:

- Large networks of **LIF neurons** or **Single-Ohmic HH models** to look at **network events in the brain such as oscillations**



Single-Ohmic Hodgkin-Huxley model (PING model)

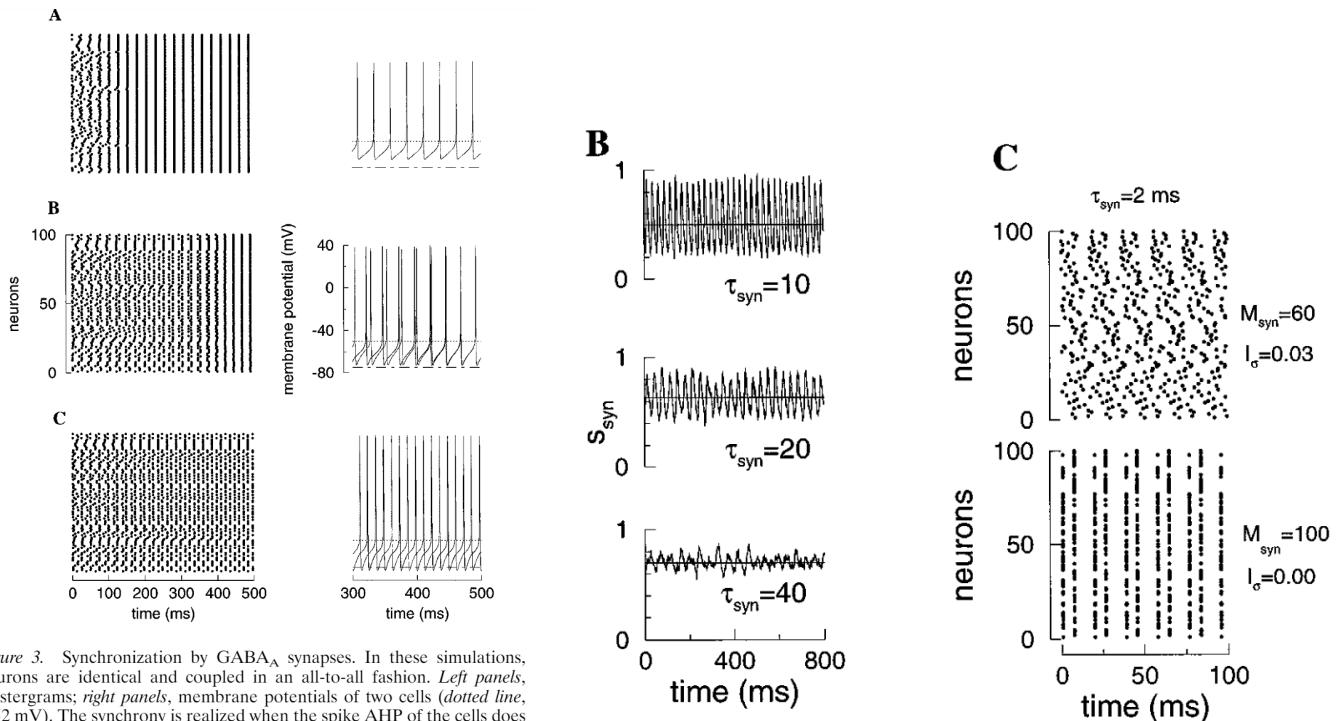


Figure 3. Synchronization by GABA_A synapses. In these simulations, neurons are identical and coupled in an all-to-all fashion. Left panels, Rastergrams; right panels, membrane potentials of two cells (dotted line, -52 mV). The synchrony is realized when the spike AHP of the cells does not fall below the synaptic reversal potential $E_{syn} = -75$ mV (dot-dashed line on the right panels). From A to C, $\phi = 5, 3.33$, and 2 respectively; $I_{app} = 1, 1.2$, and $1.4 \mu\text{A}/\text{cm}^2$ accordingly to preserve a similar oscillation frequency. With smaller ϕ values, I_K is slower and the AHP amplitude (V_{AHP}) is more negative. When $V_{AHP} < E_{syn}$, the full synchrony is lost (C).

Teaching References

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