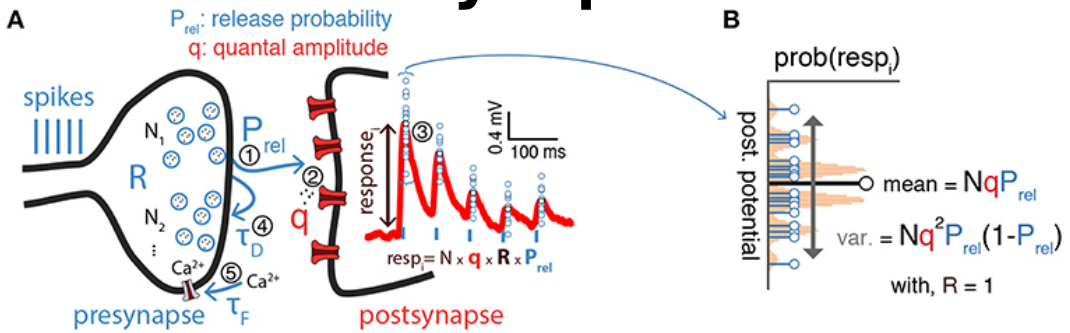
Computational Neuroscience: Introduction and Neuronal Models

Heath Robinson, Ph.D

CWRU Undergraduate Neuroscience

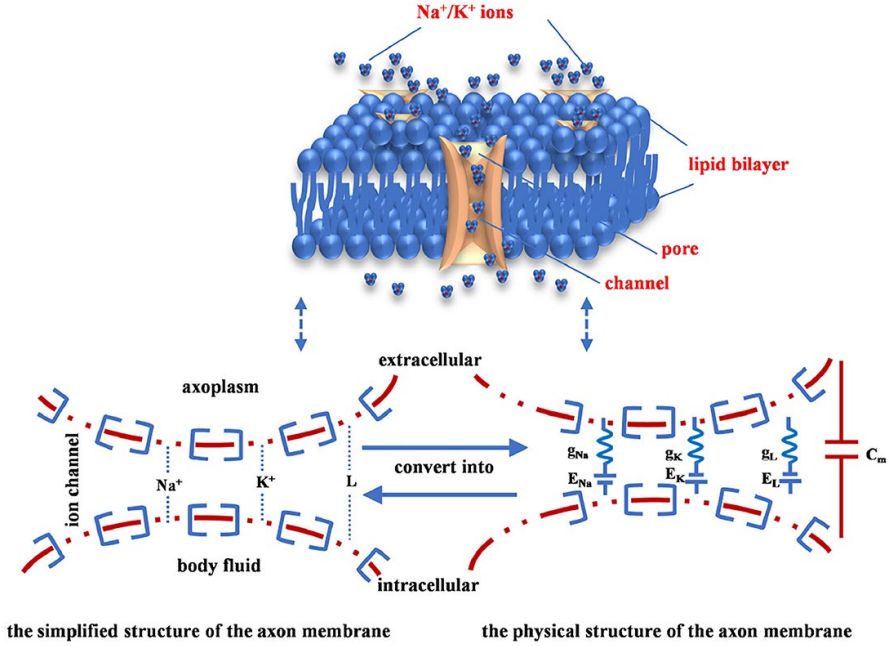
Modelling at different levels of neuroscience

Synapse



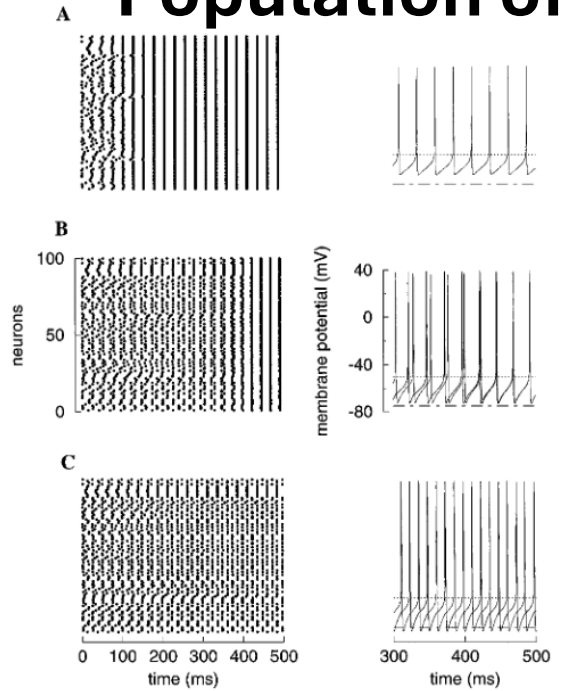
Bykowska et al. *Frontiers in Synaptic Neuroscience* 2019

Individual Cell



Fang, Duan, Wang *Frontiers in Neuroscience* 2021

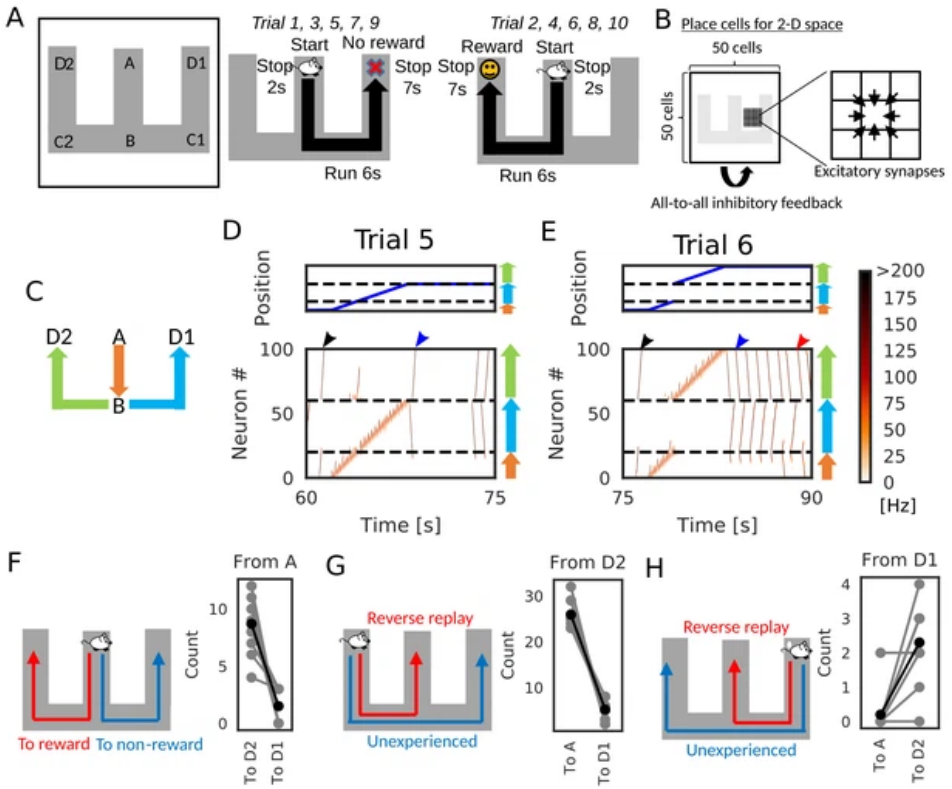
Population of neurons



Wang and Buzsaki *The Journal of Neuroscience* 1996

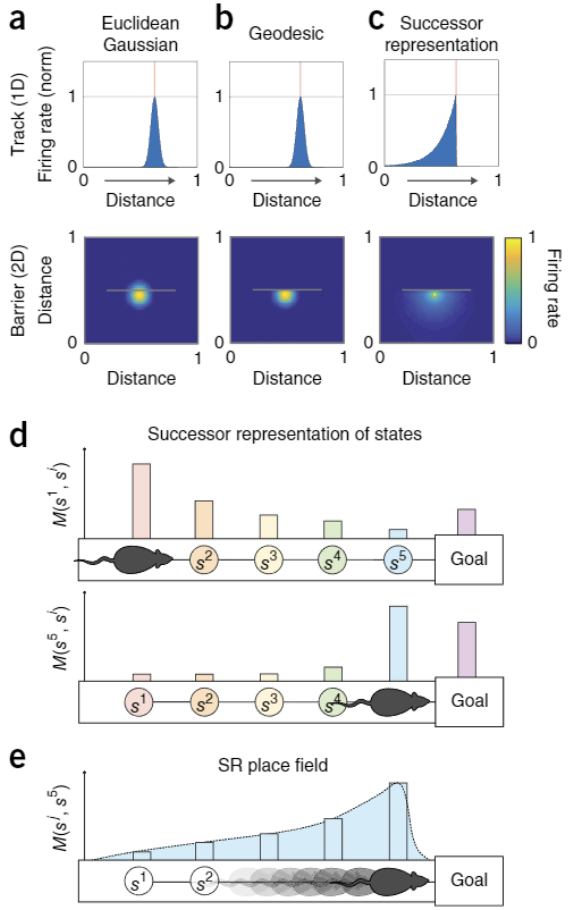
Modeling at different levels of neuroscience: Outside-in modelling (modeling findings to understand experimental findings)

Place Cells in RL Agent (more on that Friday)



Fang, Duan, Wang *Frontiers in Neuroscience* 2021

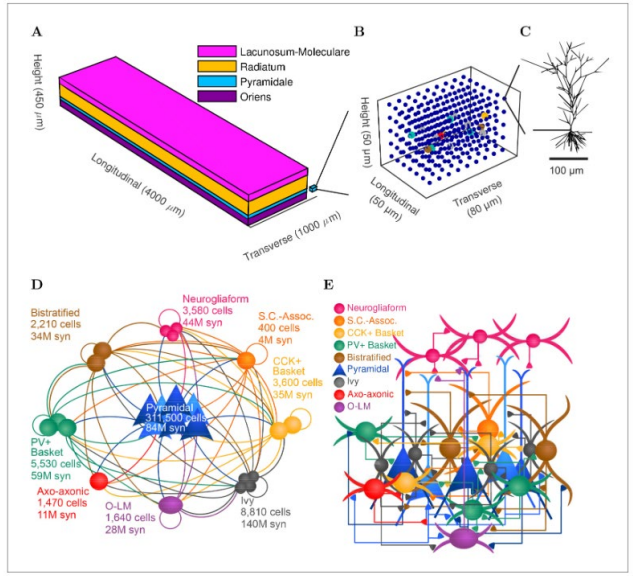
Place Cells in successful representation(more on that Friday)



Fang, Duan, Wang *Frontiers in Neuroscience* 2021

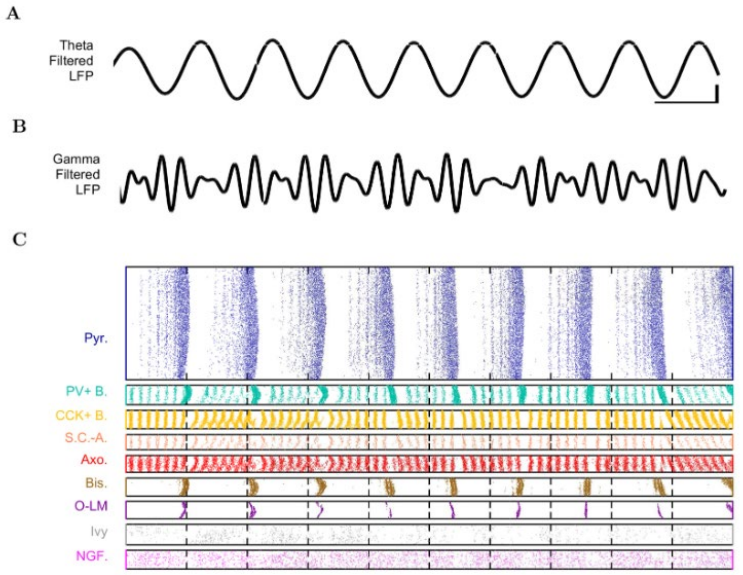
The **MOST** important question is your **scientific hypothesis**

- 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 454,700 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)***.



Bezaire et al. *eLife* 2016

Modelling at different levels of neuroscience

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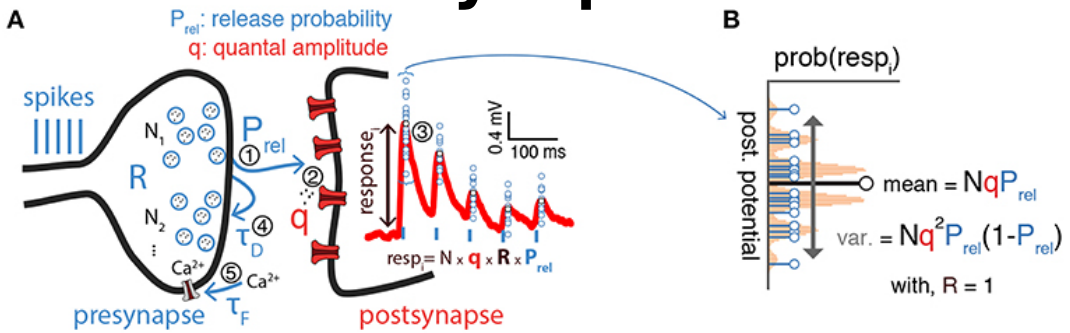

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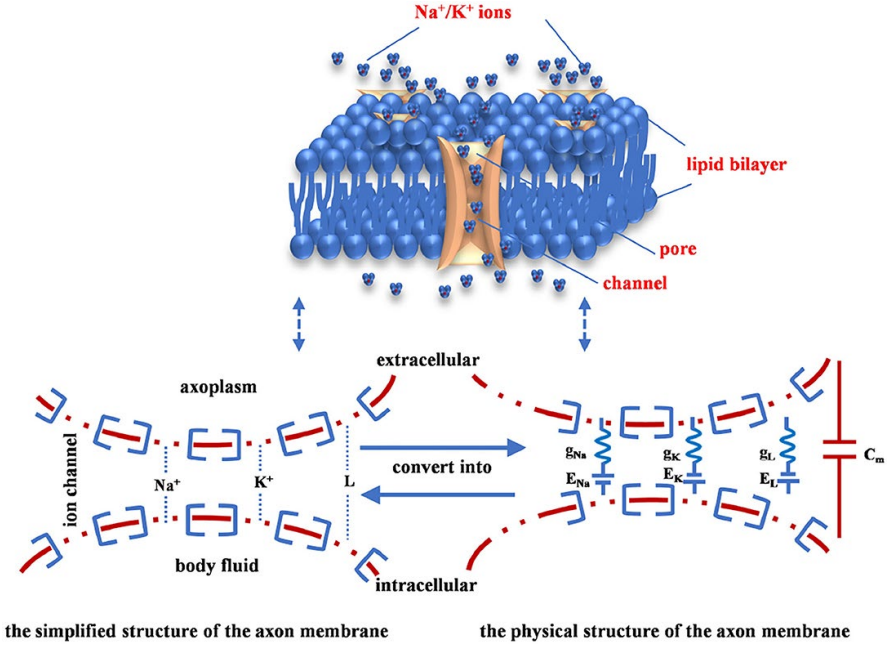
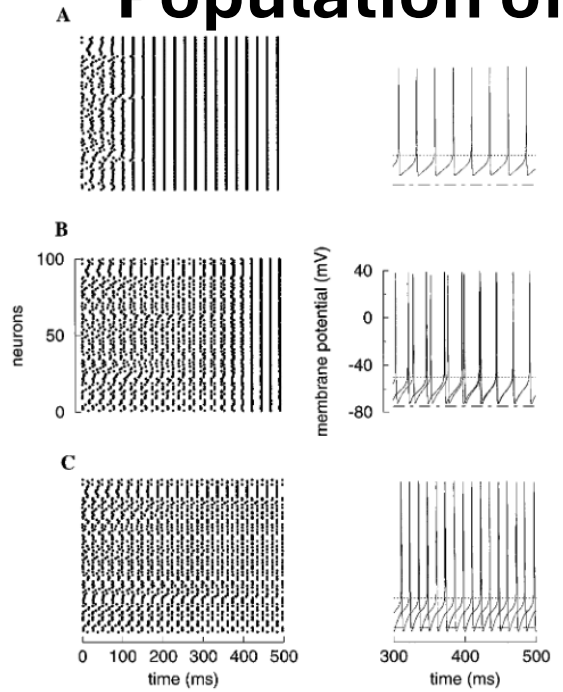


Fang, Duan, Wang *Frontiers in Neuroscience* 2021

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….

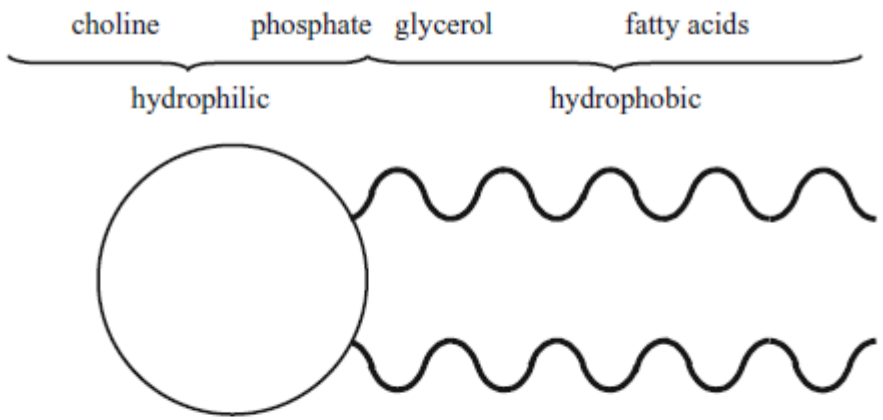


Figure 2.1 Phosphatidyl choline, which is a typical membrane phospholipid, has a polarised head and fatty tails. Phospholipids are often represented as shown at the bottom

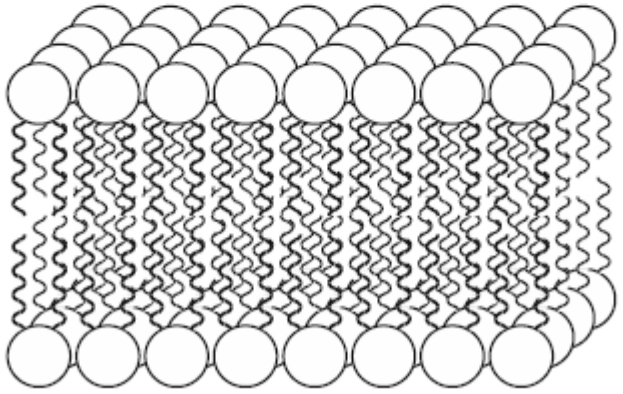


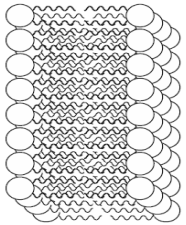
Figure 2.2 Bilayer arrangement of phospholipids in a watery environment

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

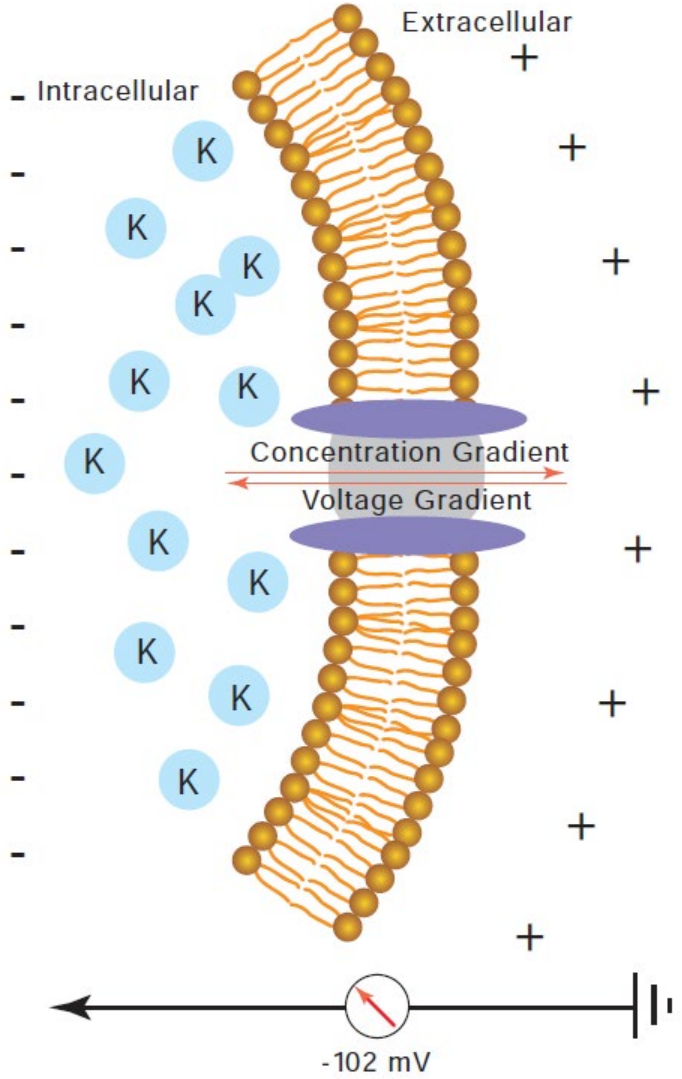
Ion	Intracellular range (mM)	Extracellular range (mM)
Na^+	5–20	130–160
K^+	130–160	4–8
Ca^{2+}	50–1000 nM[a]	1.2–4
Mg^{2+}	10–20	1–5
Cl^-	1–60	100–140
HCO_3^-	1–3	20–30



[a] Given as nanomolar rather than millimolar.

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

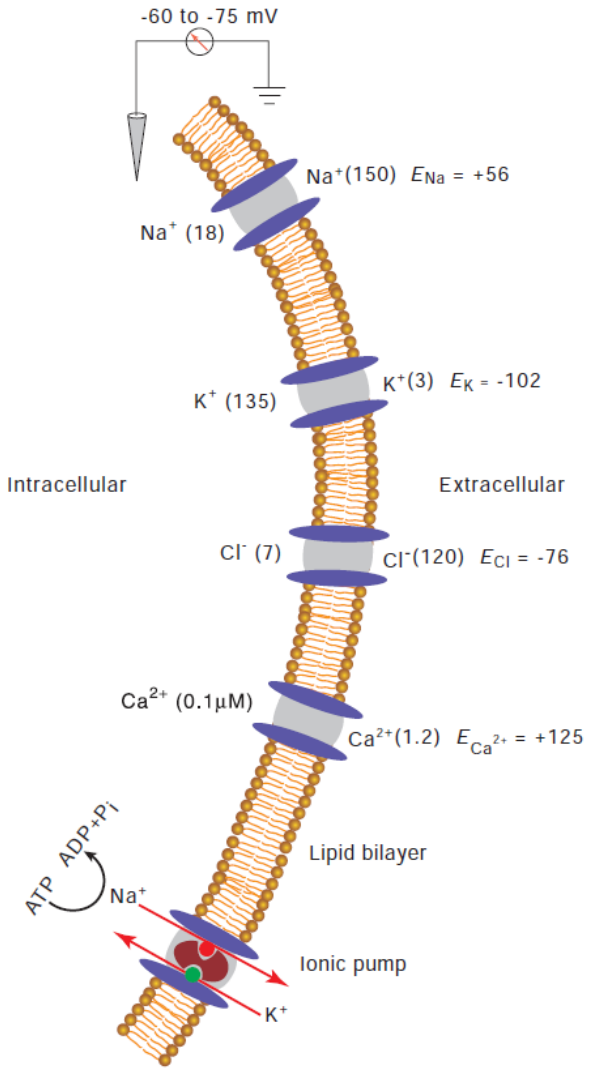
- But ions also have a **charge**
- **If you set up a chemical gradient of ions, you will <u>inherit their charge</u>**
- **<u>This is what Neuroscience means when it says there is an electrochemical gradient</u>**
- It is important to remember that both the charge disparity of the membrane and natural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

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

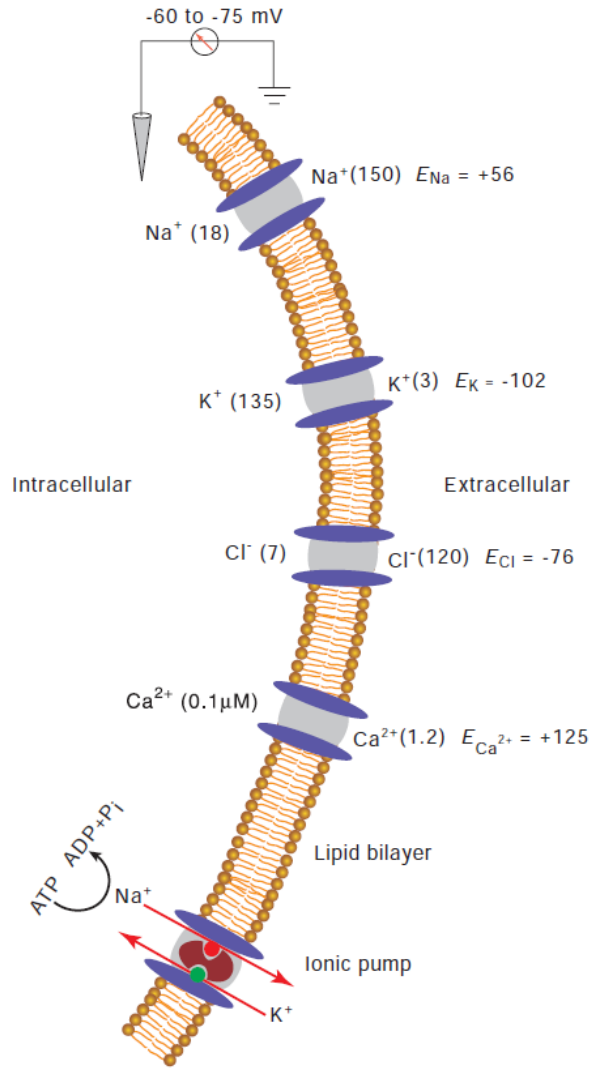


A quick guide to excitable membranes and action potentials – **ion distribution all together**

- 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**

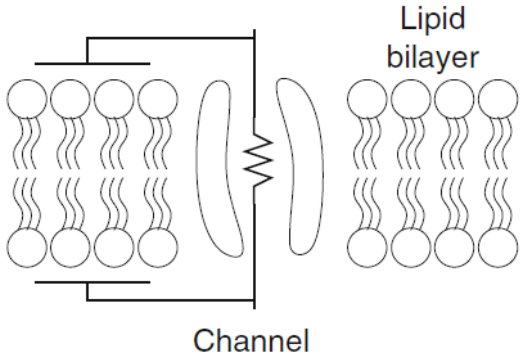
$$V_m = \mathbf{V}_{\text{inside cell}} - \mathbf{V}_{\text{outisde cell}}$$

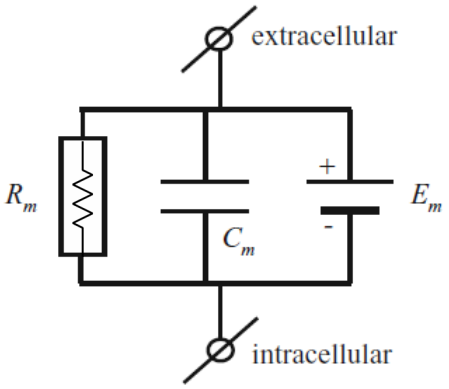
- There is an actual **charge** to neuronal membranes
- This charge is the same that underlies batteries!
- **Note that for multiple ions, we use Goldman-Hodgkin-Katz (GHK) equation**
  - Not to worry, this is taking **Nernst equation and applying it for multiple ions in a permeable membrane**, which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

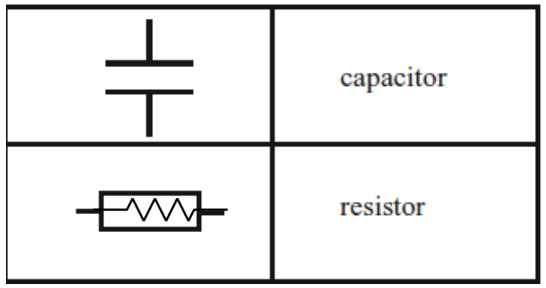


A quick guide to excitable membranes and action potentials – **electrical engineering view**

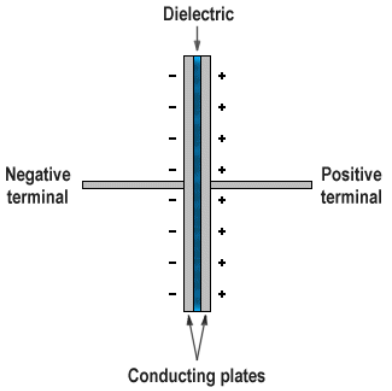
- Due to the electrical nature of neuronal membranes, they are often diagramed as an electrical circuit
- This helps us understand different parts of electrical charges
- A **resistor** a device that **resists electrical flow**
- A **capacitor** is electoral device that stores charges by the natural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





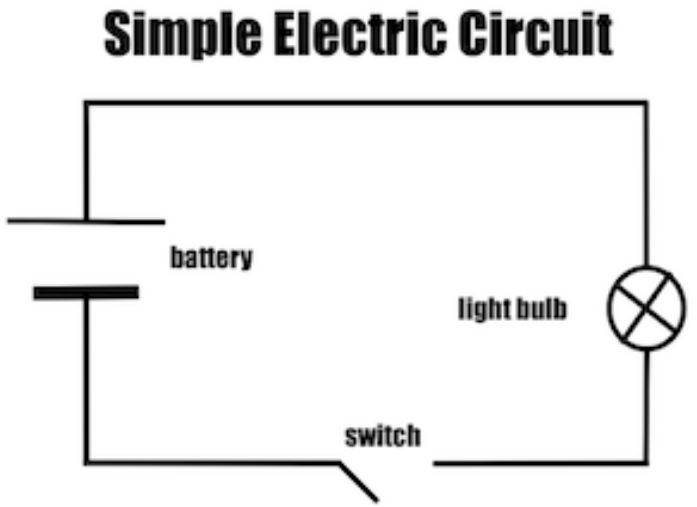


Capacitor



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

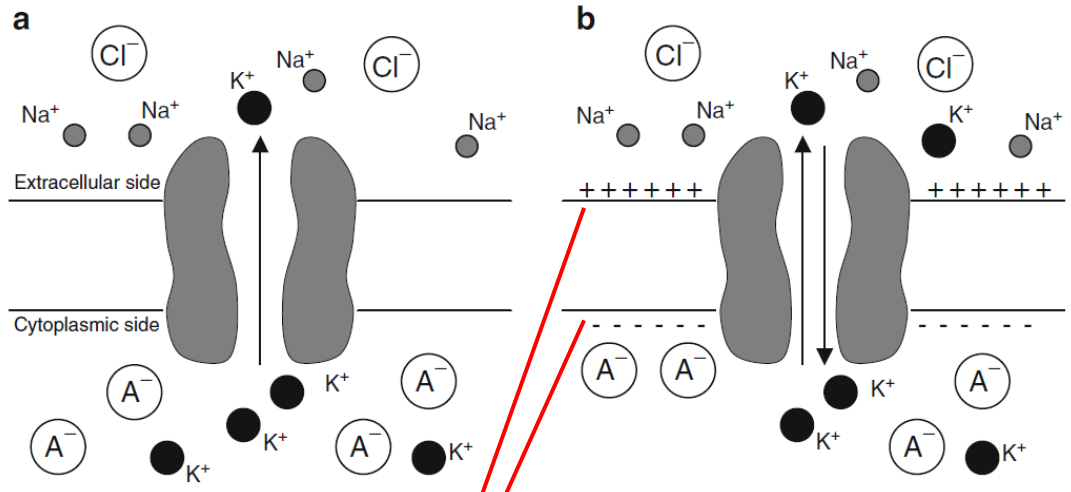
- The **membrane** is a **natural resistor** and **capacitance naturally occurs**
  - **Resistor + capacitor + battery (our electrochemical gradient) = simple circuit with a battery**



What is the “Switch” though in our membrane?

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

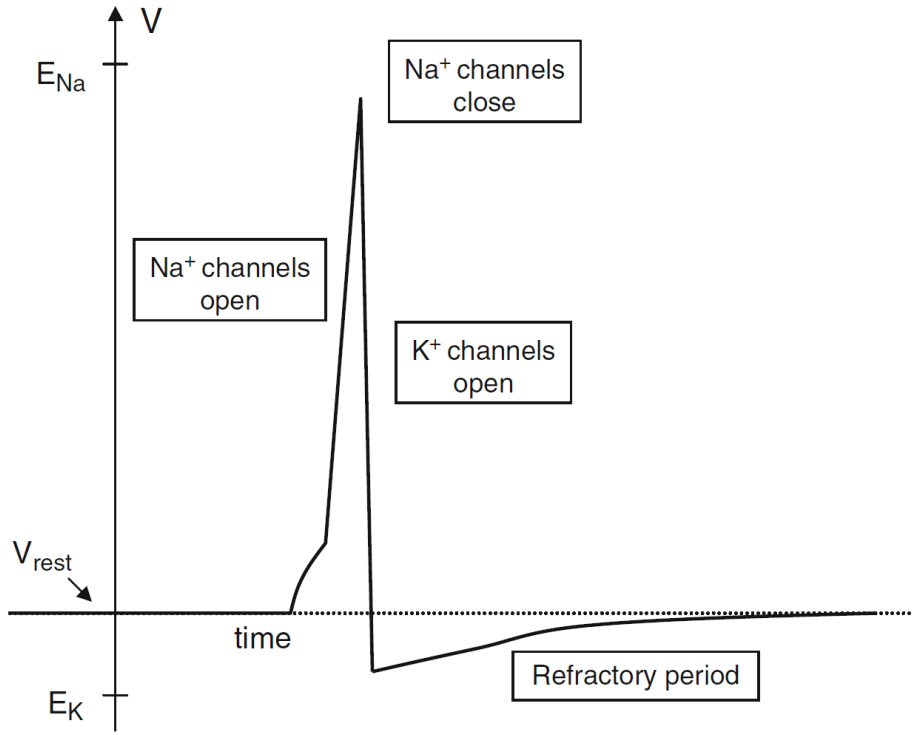
- The **switch** is **permeable ion channels**
- When open they allow ions to flow down their electro-chemical gradient
- **These aren't just permeable channels; they are triggered by <u>voltage changes in the membrane</u>**



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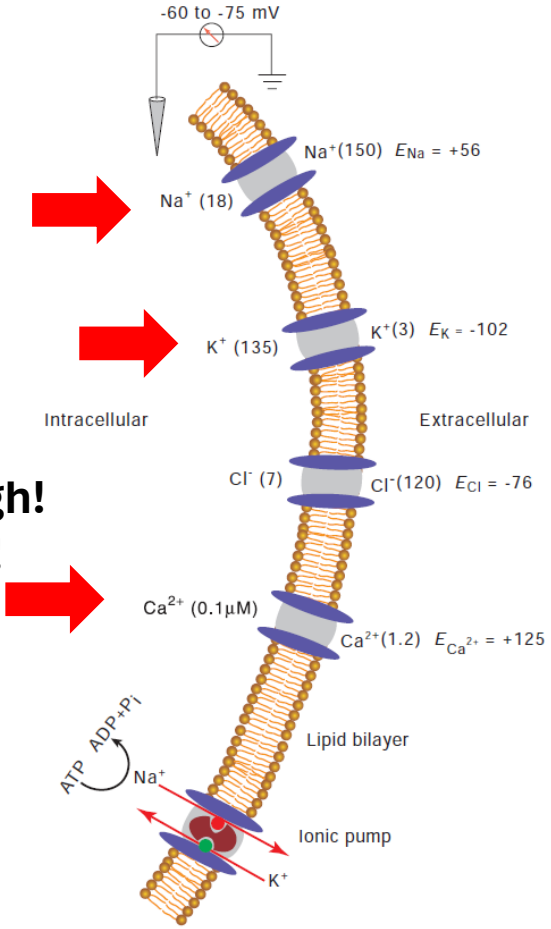
$$V_m = \frac{RT}{zF} ln \frac{ion\ concentration\ outside}{ion\ concentration\ inside}$$

There is an issue though!
We have multiple ions!

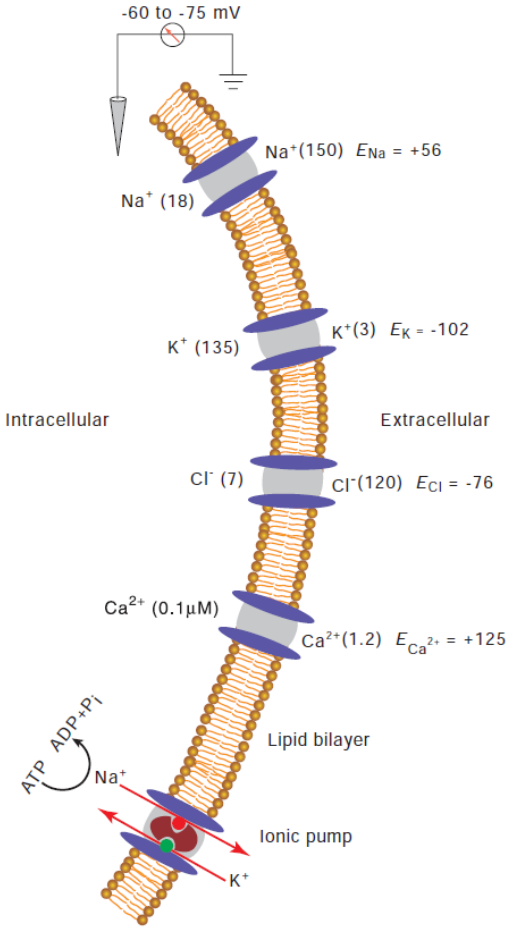


Going from Nernst to GSK equations – a full equation including all ions

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

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

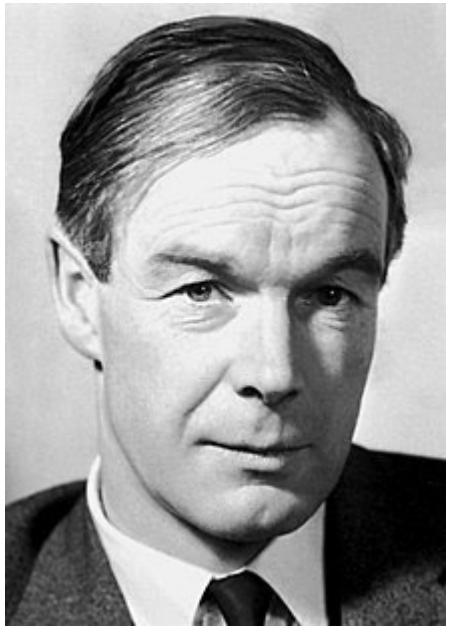
- **Note:** P_{ion} is the permeability at any time for a given ion (depending on the state of the voltage gated ion channels
- Now we have an equation that gives us the terms of **Vm** since it is the **electrical potential across the whole membrane**
- **Z** is also gone because we assign charge differently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

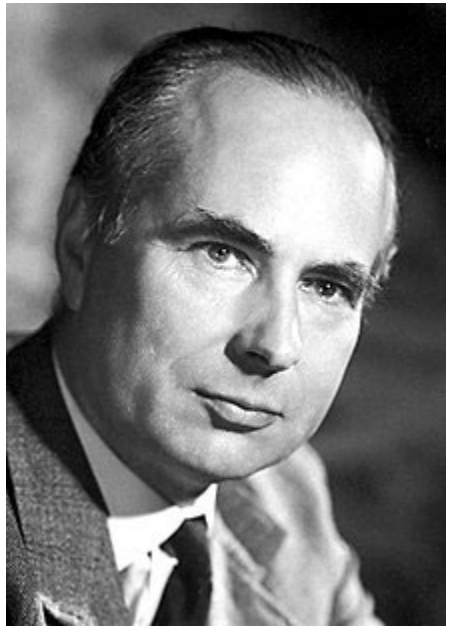


At the footsteps of greatness…
An Equation(s) that fully explains the ionic mechanisms underlying the **Action Potential**

A model that recapitulates a neuron firing!

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+**
  - **<u>Shows what models aim to do, explain a mechanism without all the factors</u>**
  - **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)

Hodgkin-Huxley equation contextualized

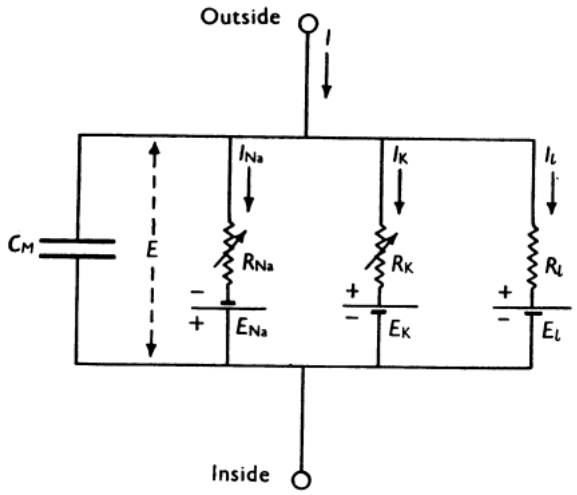
- GSK equation has allowed for finding the resting membrane potential (**Vm**)
- Hodgkin-Huxley equation is now going to try and look at how these **voltage potentials change during an action potential**
- The **GSK equation has an issue – it assumes no changes in permeability, <u>which you know changes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

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

By A. L. HODGKIN and A. F. HUXLEY

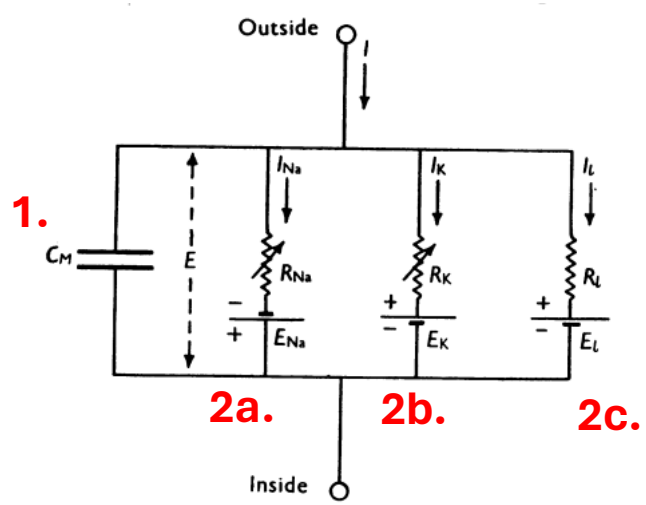
From the Physiological Laboratory, University of Cambridge

(*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 **<u>ions moving = current</u>**
  - 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 ≠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**



<u>Ohm's Law</u>

$$Voltage = Current\ x\ Resistance$$

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 –**

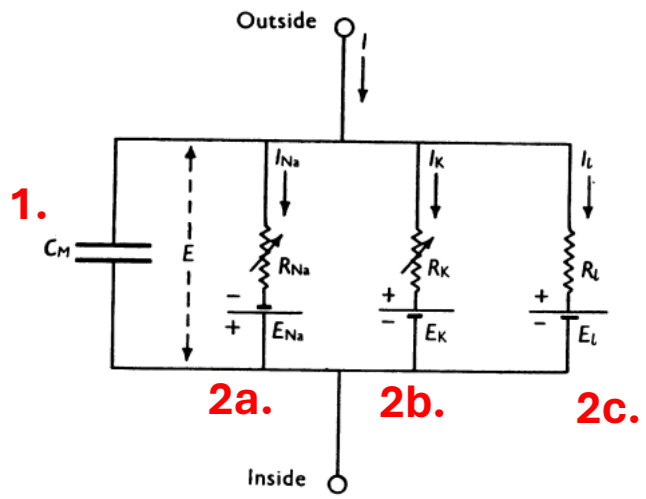
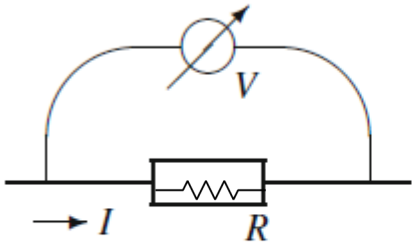


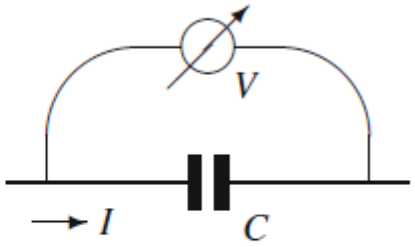
Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_l = 1/\bar{g}_l$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.

Ohm's Law



a. $V = R\,I$

Coulomb's Law



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

Hodgkin-Huxley equation – Ohms law in resistors in parallel

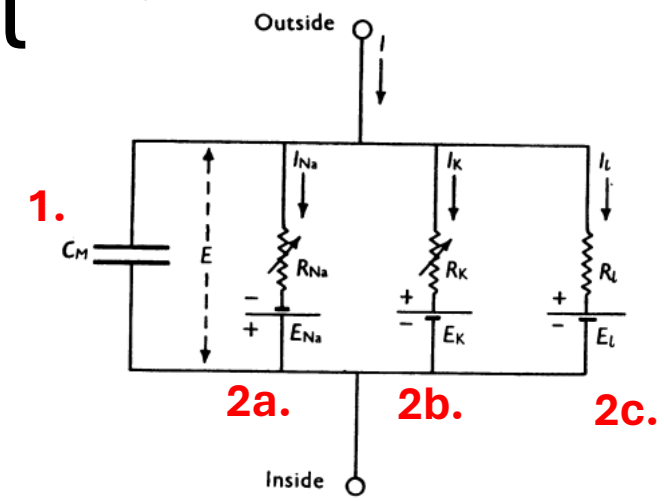


Fig. 1. Electrical circuit representing membrane. $R_{Na}=1/g_{Na}$; $R_K=1/g_K$; $R_l=1/\bar{g}_l$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.

- **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:

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

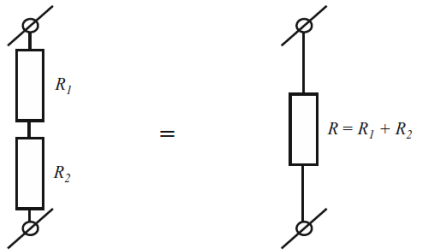
- You can now exchange in **rearranged Ohms law:**

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

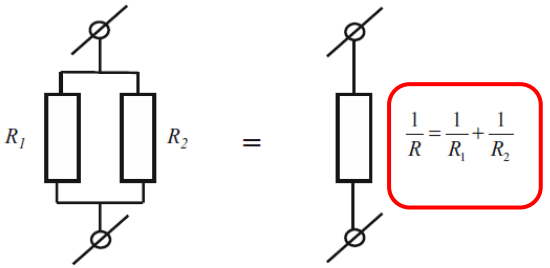
- and now you get:

$$\boldsymbol{Current\ (I) = conductance\ (g)\ x\ voltage\ (V)}$$

Resistors in series



Resistors in parallel



Hodgkin-Huxley equation

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

1. $I_C = C_m \frac{dV_m}{dt}$ **Coulomb's law**

2. $I_{ion} = g_{ion}(V_m - V_{ion})$ **Trick to use Ohm's law with resistors in series**

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

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

- 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**

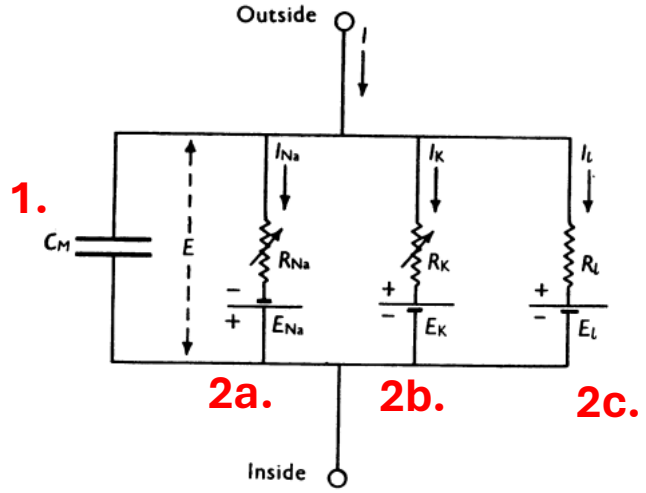
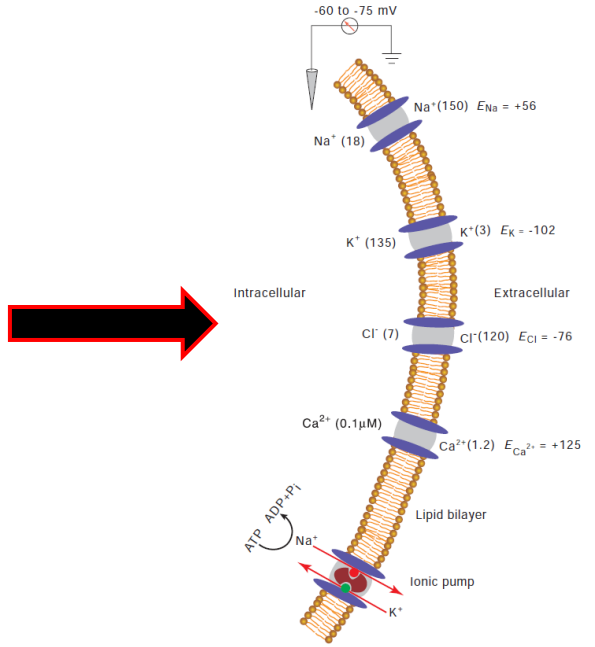


Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_l = 1/\bar{g}_l$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.



Hodgkin-Huxley equation

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

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

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

2a. 2b. 2c.

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

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

or

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

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

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

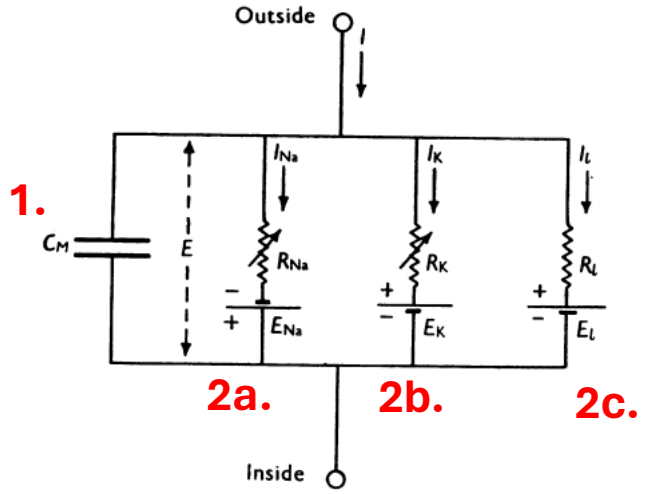


Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_l = 1/\bar{g}_l$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.

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**
  - $\beta_n(V_m)$ 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 retures to V_m in **resting state** (towards V_m at rest) – **Na+ channel reset**

Hodgkin-Huxley equation

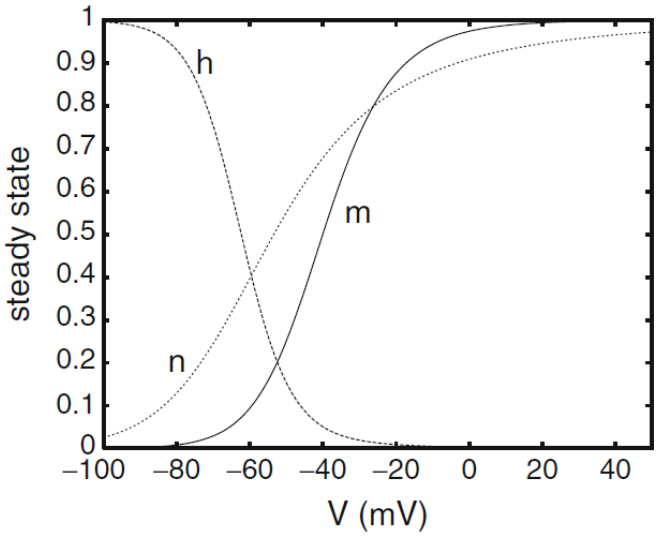
- Here are the four equations:

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

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

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

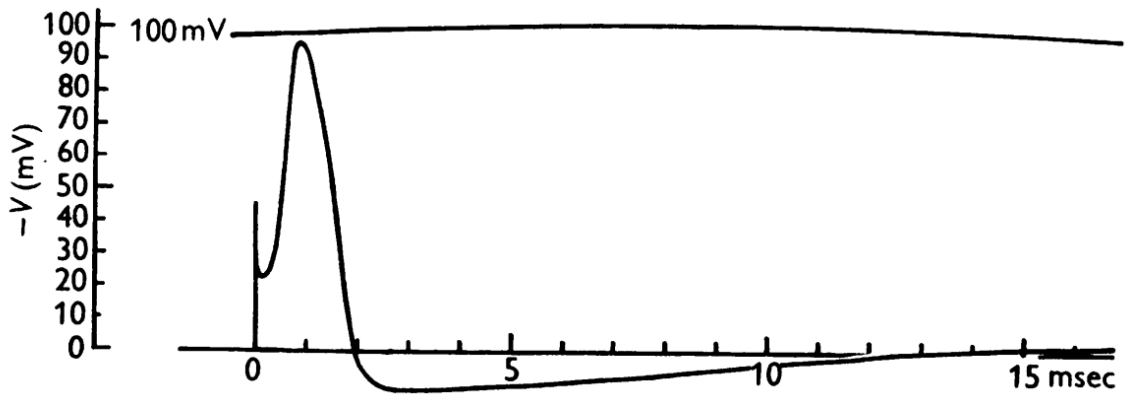
$$\frac{dh}{dt} = \alpha_h(V_m)(1 - h) - \beta_h(V_m) h$$



- **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 K+ = 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 **Hodking-Huxley** model this allows us to test whether if we are given **an input of current** dowe see the **Vm** response that correlates to the **Vm** 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 **Vm** dynamics it would support **Hodgkin and Huxley's hypothesis that Na+ and K+ conductance's underly an AP**



Hodgkin-Huxley equation results

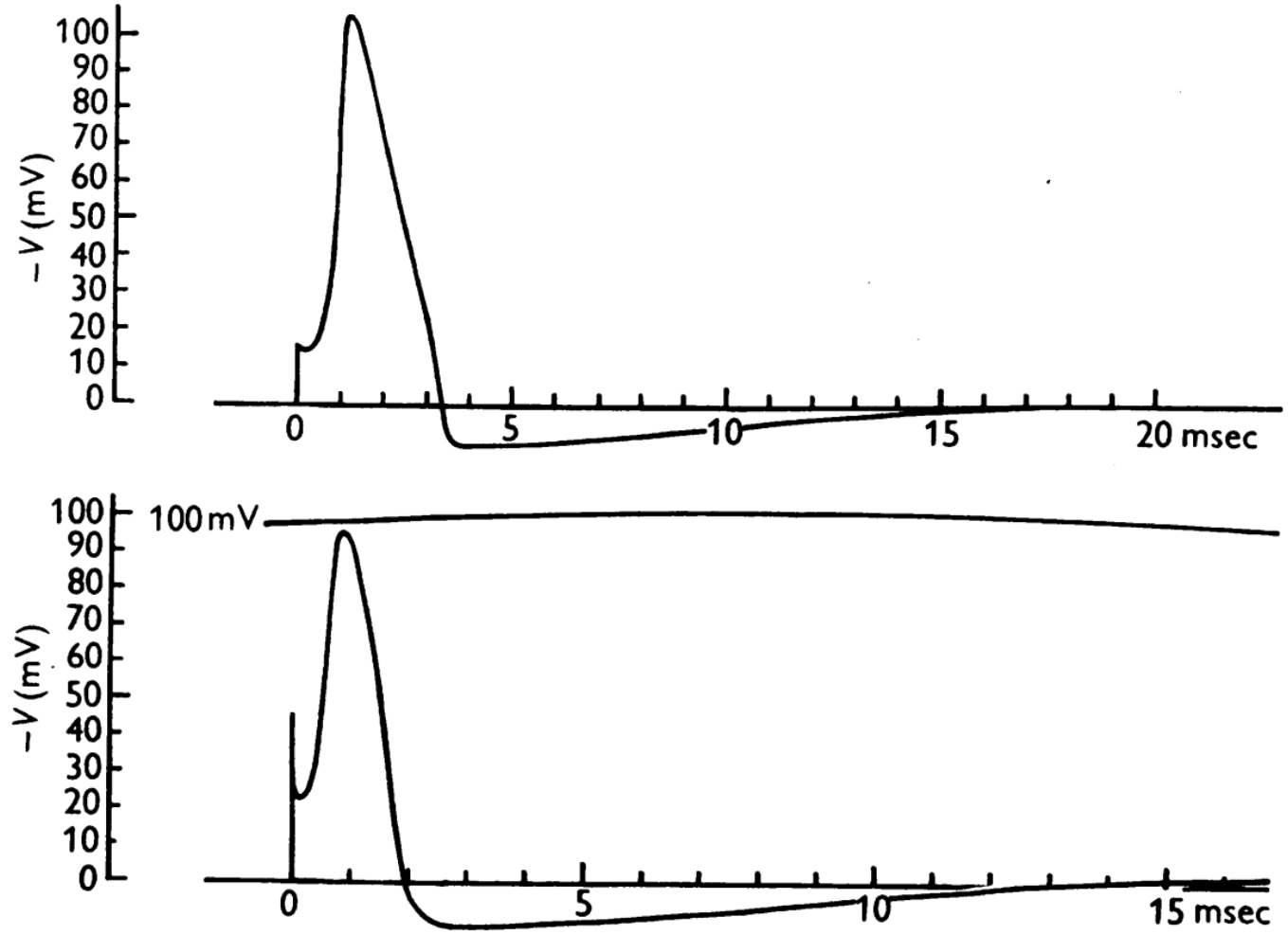


Fig. 13. Upper curve: solution of eqn. (26) for initial depolarization of 15 mV, calculated for 6° C. Lower curve: tracing of membrane action potential recorded at 9·1° C (axon 14). The vertical scales are the same in both curves (apart from curvature in the lower record). The horizontal scales differ by a factor appropriate to the temperature difference.

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 restistance (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

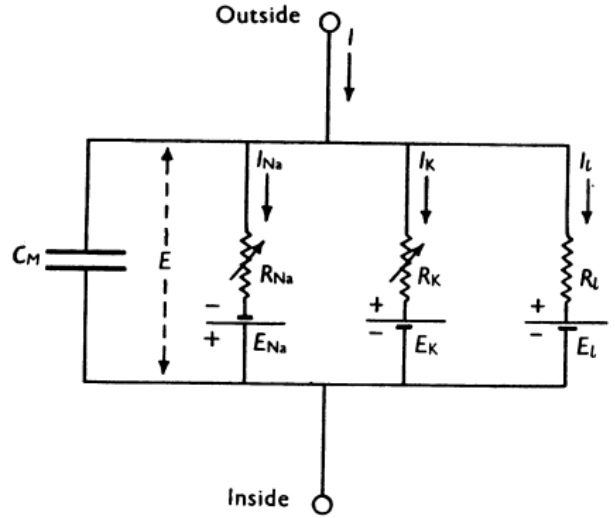


Fig. 1. Electrical circuit representing membrane. $R_{Na}=1/g_{Na}$; $R_K=1/g_K$; $R_l=1/\bar{g}_l$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.

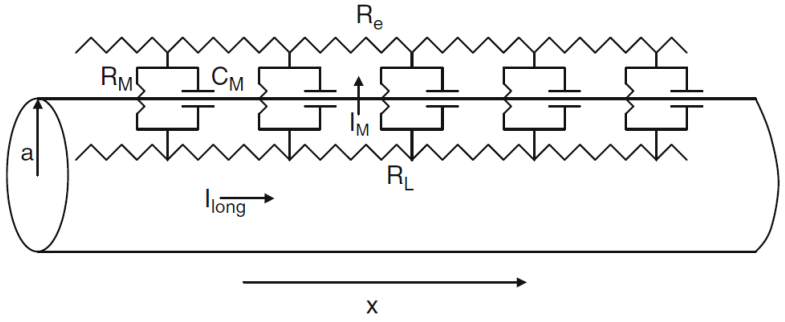
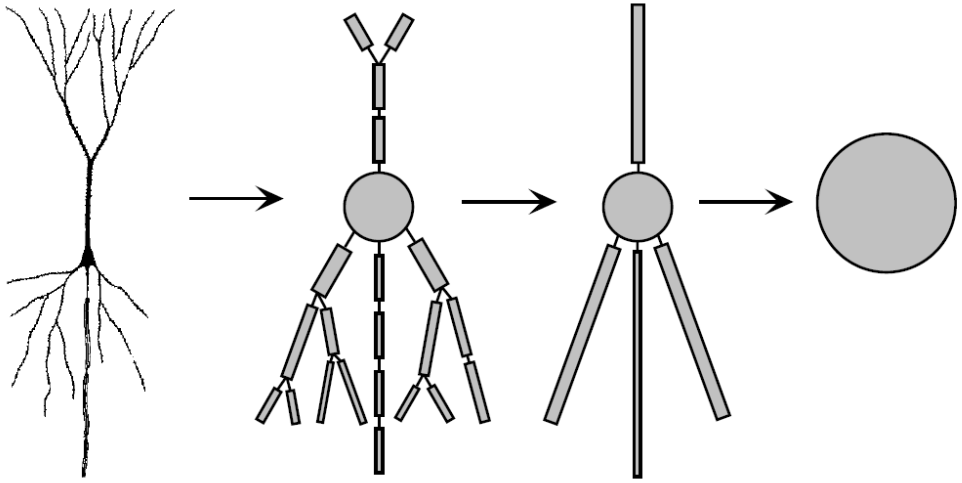
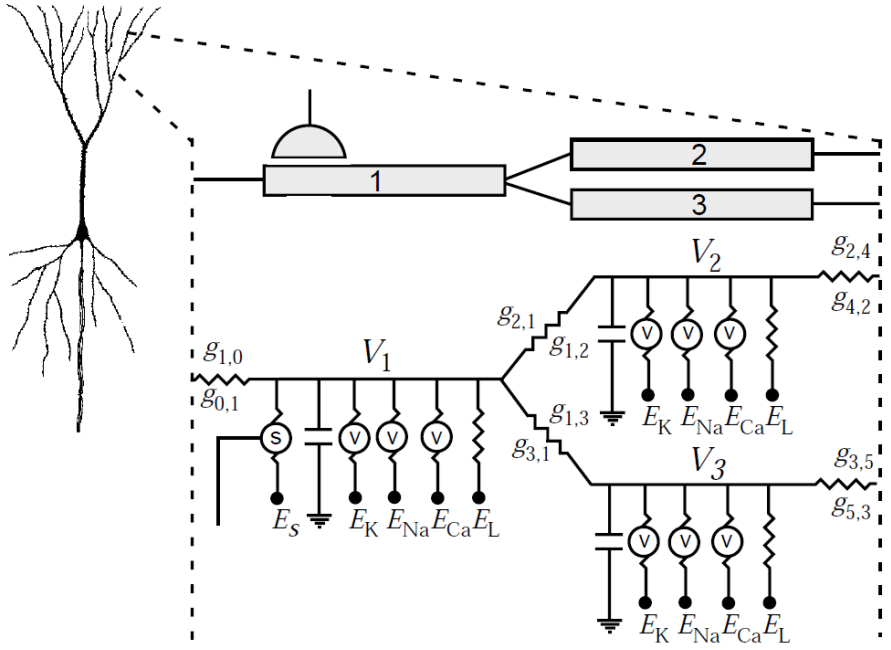


Fig. 1.5 Equivalent circuit for a uniform passive cable. I_{long} is the current along the inside of the cable, I_M is the current across the membrane, R_L is the resistance of the cytoplasm, R_e is the resistance of the extracellular space, R_M is the membrane resistance, and C_M is the membrane capacitance

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**

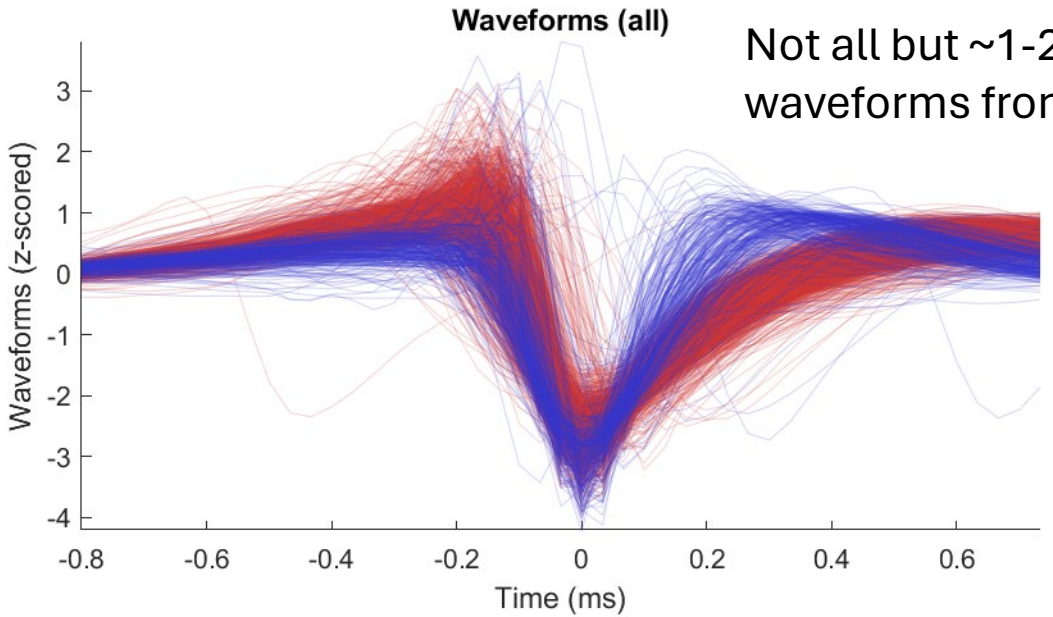
The **MOST** important question is your **scientific hypothesis**

- 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 **Vm** is depolarizated-hyperpolarizated-refractory period
- **What if we… what if we just… modeled these dynamics? Wouldn't that be computationally easier?**



Not all but ~1-2million averaged waveforms from the PFC of a mouse

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 **Vm reaches a threshold**
- By avoiding biophysical modelling aspects, **LIF models** only need to model **subthreshold dynamics of Vm**
- 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**

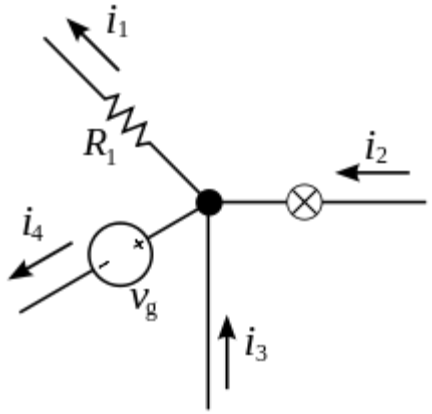
Leaky-integrate and Fire neuron models – derivation

- 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 $\boldsymbol{I_C}$ and $\boldsymbol{I_{RL}}$

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

- Moving $\frac{\boldsymbol{dV_m}}{\boldsymbol{dt}}$ 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** $\boldsymbol{I_{total} - I_{ext} = 0}$
- Now we have:

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

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:

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

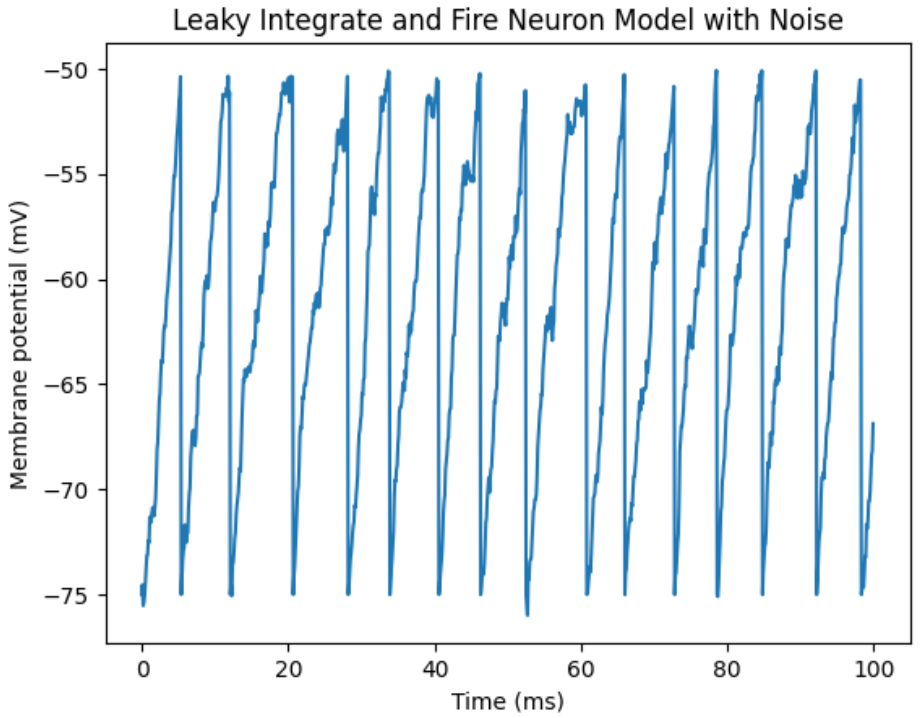
- While seemingly complicated, the above states if the $\boldsymbol{I \leq I_{thr}}$ then the **LIF neuron does not fire (firing (I) = 0)**
- If the $\boldsymbol{I > I_{thr}}$ then the **LIF neuron reaches an AP by implementing:**

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

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 Vm to above its AP Vthr then we have an AP**
- When you see the value reset, an AP has just occurred with LIF

⬇⬇ …

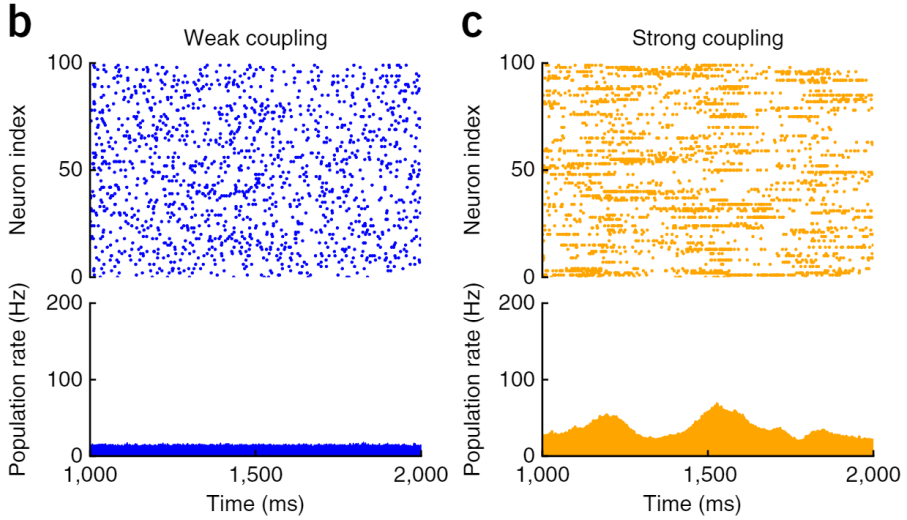



```
V_rest = -75*mV              # Resting
potential
V_threshold = -50*mV         # Threshold
potential
R_m = 100*Mohm               # Membrane
resistance
tau_m = 10*ms                # Membrane time
constant
I = .5*nA                     # Input current
```

What can these models do:

- Large networks of **LIF neurons** to look at **network events in the brain such as oscillations**

Coupled LIF model



Ostojic *Nature Neuroscience* 2014

Single-Ohmic Hodgkin-Huxley model (PING model)

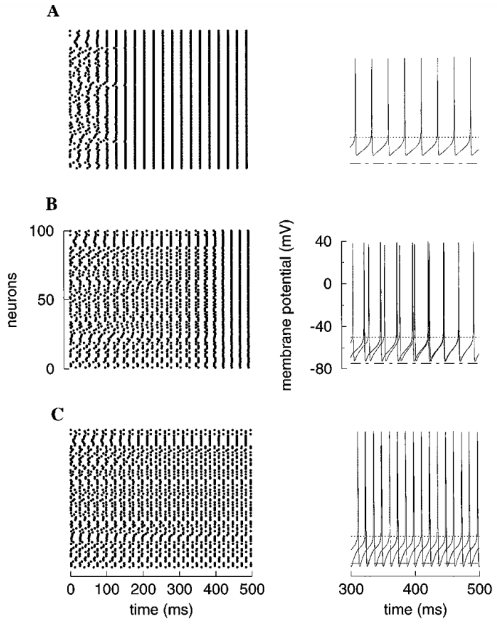
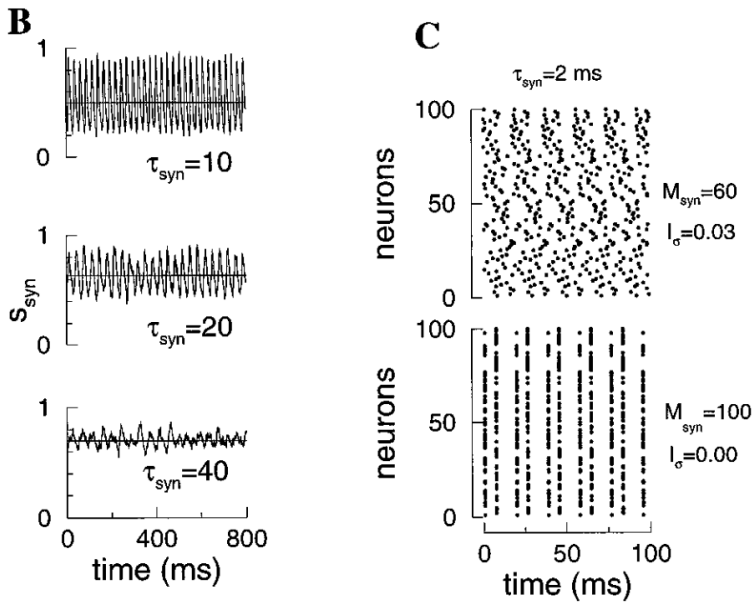


Figure 3. Synchronization by $GABA_A$ synapses. In these simulations, neurons are identical and coupled in an all-to-all fashion. *Left panels*, Rastergrams; *right panels*, membrane potentials of two cells (*dotted line*, −52 mV). The synchrony is realized when the spike AHP of the cells does not fall 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 $\mu A/cm^2$ 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*).



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Funding

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