

# Introduction to Neural Computation – 9.40

- Prof. Michale Fee, Instructor
- Daniel Zysman, Technical instructor

## Texts: Selected readings

- Berg, Random Walks in Biology
- Dayan & Abbott, Theoretical Neuroscience.
- Hille, Ionic Channels of Excitable Membranes  
...and others

# What is neural computation?

- Brain and cognitive sciences are no longer primarily descriptive
  - Engineering-level descriptions of brain systems.

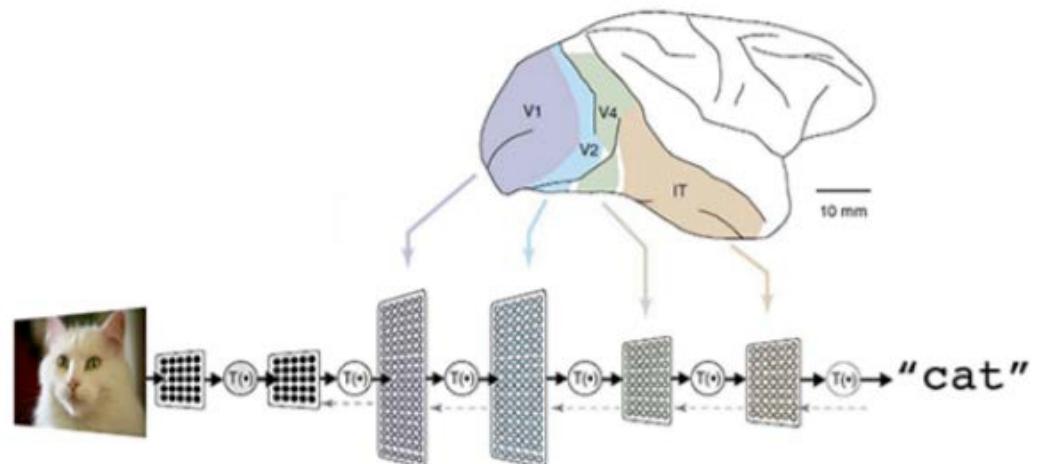
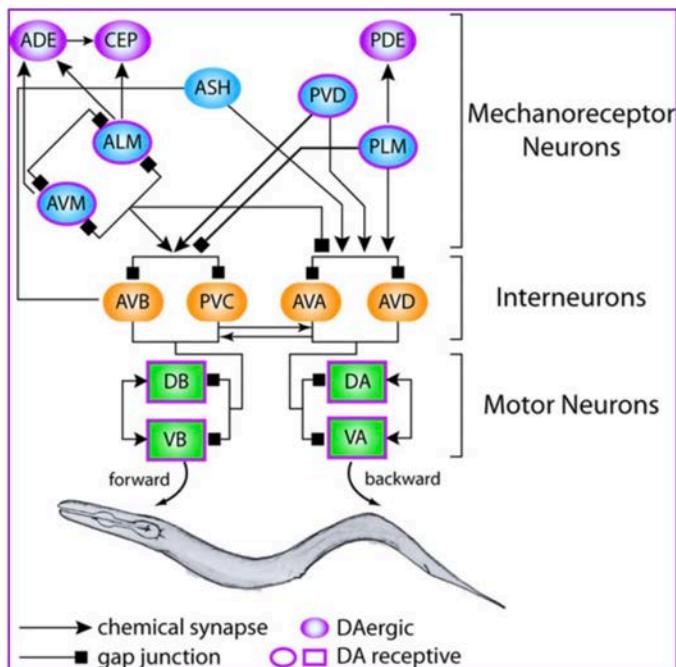


Diagram © Jeff Dean (adapted from DiCarlo & Cox, 2007). All rights reserved. This content is excluded from our Creative Commons License. For more information see <https://ocw.mit.edu/help/faq-fair-use/>.

# New technologies for neuronal activity measurements

*Video*

YaleCampus. "[Imaging Brain Activity Across the Mouse Cortex.](#)" YouTube.

Crair Lab, Yale Univ

# What is neural computation?

- Brain and cognitive sciences are no longer primarily descriptive
  - Engineering-level descriptions of brain systems.
- Use mathematical techniques to analyze neural data in a way that allows us to relate it to mathematical models.
- In this course we will have the added component that we will apply these techniques to understand the circuits and computational principles that underlie animal behavior.

# Neural circuits that control bird song

See Lecture 1 video recording for playback

# What is neural computation?

- Computational and quantitative approaches are also important in cognitive science.
- Importance of computation and quantitation in medical sciences

# Course Goals

- Understand the basic biophysics of neurons and networks and other principles underlying brain and cognitive functions
- Use mathematical techniques to
  - analyze simple models of neurons and networks
  - do data analysis of behavioral and neuronal data (compact representation of data)
- Become proficient at using numerical methods to implement these techniques (MATLAB®)

# Topics

Neuronal biophysics and model neurons	Differential equations
Neuronal responses and tuning curves	Spike sorting, PSTHs and firing rates
Neural coding and receptive fields	Correlation and convolution
Feed forward networks and perceptrons	Linear algebra
Data analysis, dimensionality reduction	Principle Component Analysis and SVD
Short-term memory, decision making	Recurrent networks, eigenvalues
Sensory integration	Bayes rule

# Skills you will have

- Translate a simple model of neurons and neural circuits into a mathematical model
- Be able to simulate simple models using MATLAB®
- Be able to analyze neuronal data (or model output) using MATLAB®
- Be able to visualize high dimensional data.
- Be able to productively contribute to research in a neuroscience lab!

# Problem sets

- MATLAB® will be used extensively for the problem sets.
  - Free for students. Please install on your laptop.
- We will use live scripts for Pset submissions.

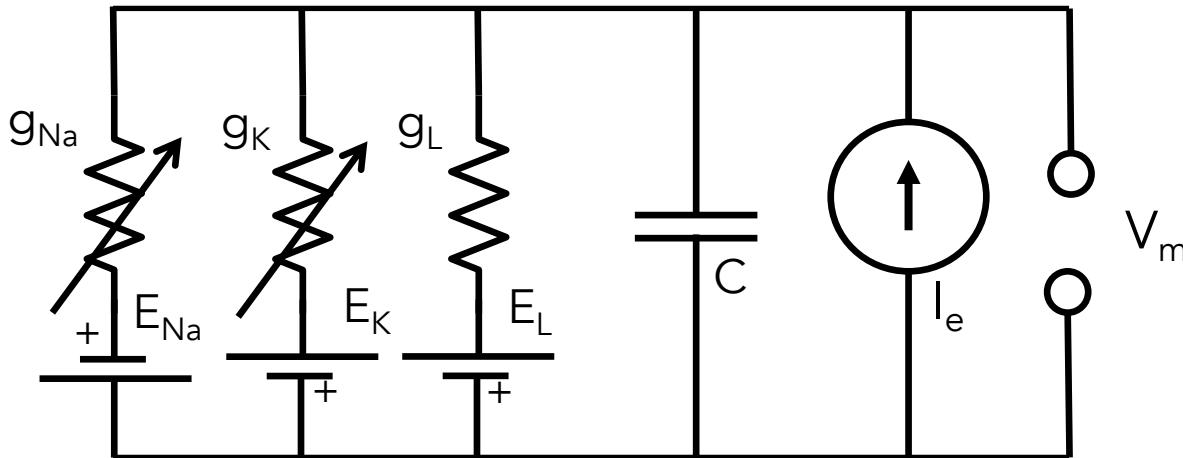
# Introduction to Neural Computation

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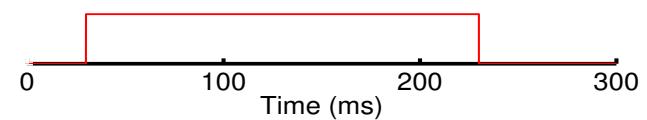
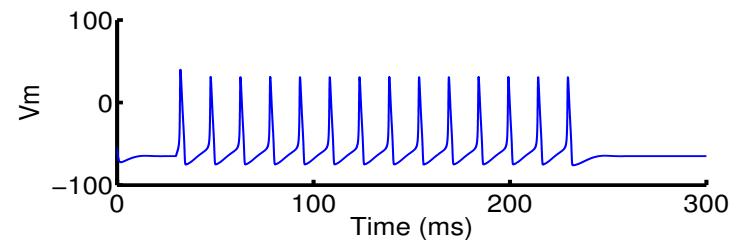
Michale Fee  
MIT BCS 9.40 — 2018  
Lecture 1 – Ionic Currents

# A mathematical model of a neuron

- Equivalent circuit model



- A conceptual model based on simple components from electrical circuits
- A mathematical model that we can use to calculate properties of neurons



# Why build a model of a neuron?

- Neurons are very complex.
- Different neuron types are defined by the genes that are expressed and their complement of ion channels
- Ion channels have dynamics at different timescales, voltage ranges, inactivation

Figures removed due to copyright restrictions. Left side is Figure 3a: Spectral tSNE plot of 13,079 neurons, colored according to the results of iterative subclustering. Campbell, J., et al. "[A molecular census of arcuate hypothalamus and median eminence cell types](#)." Nature Neuroscience 20, pages 484–496 (2017). Right side is Figure 1: Representation of the amino acid sequence relations of the minimal pore regions of the voltage-gated ion channel superfamily. Yu, F.H. and W.A. Catterall. "[The VGL-Chanome: A Protein Superfamily Specialized for Electrical Signaling and Ionic Homeostasis](#)." Science's STKE05 Oct 2004: re15.

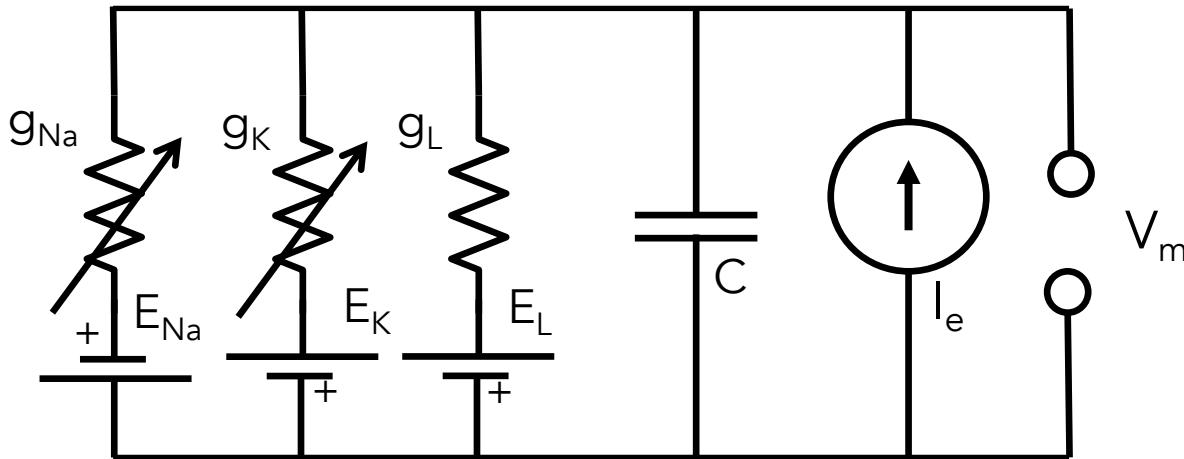
# Neurons are extremely complex

- Ion channel and morphological diversity lead to diversity of firing patterns
- It's hard to guess how morphology and ion channels lead to firing patterns
- ... and how firing patterns control circuit behavior

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[Multiple firing patterns in cortical neurons](#). In: Gerstner, W., et al. Neuronal Dynamics. Cambridge University Press.

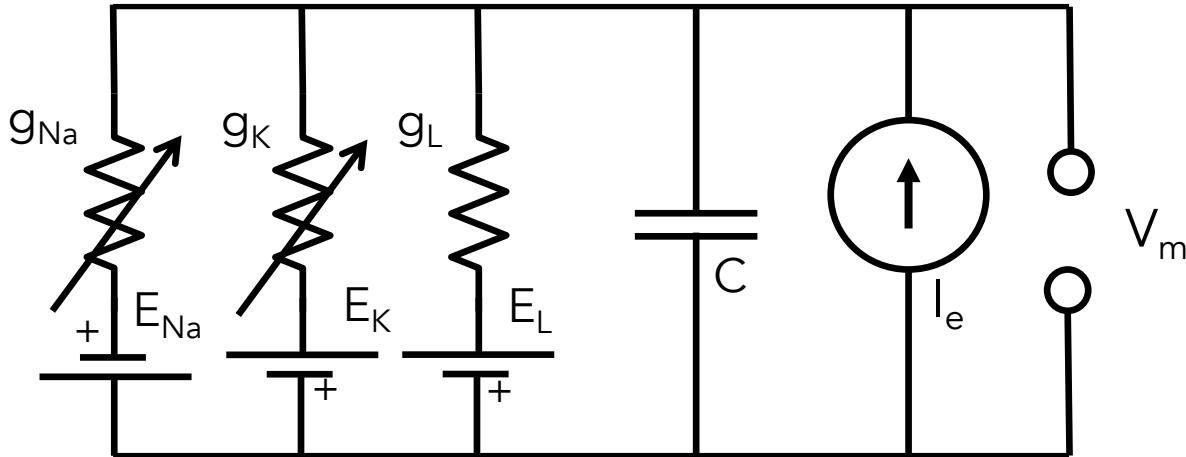
# A mathematical model of a neuron

- Equivalent circuit model



- Different parts of this circuit do different interesting things
  - Power supplies
  - Integrator of past inputs
  - Temporal filter to smooth inputs in time
  - Spike generator
  - Oscillator

# Ionic currents

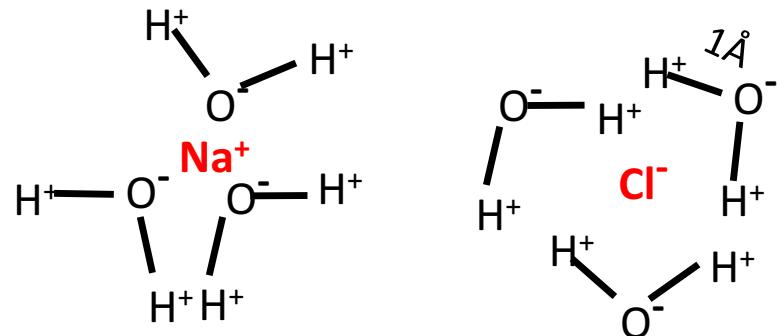


What are the wires of the brain?

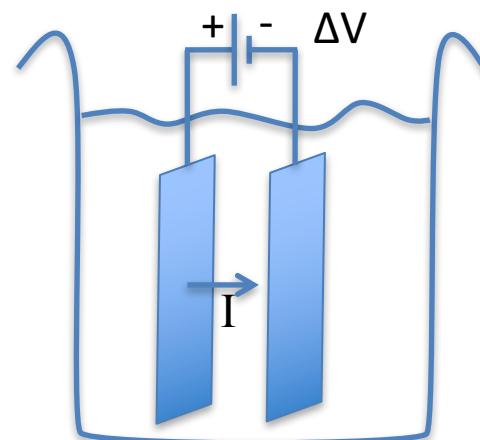
In the brain (in neurons), current flow results from the movement of ions in aqueous solution (water).

# Basic electrochemistry

- Water is a polar solvent
- Intracellular and extracellular space is filled with salt solution (~100mM)
  - $6 \times 10^{19}$  ions per  $\text{cm}^3$  ( $25\text{\AA}$  spacing)



- Currents flow through a salt solution by two key mechanisms:
  - Diffusion
  - Drift in an electric field



# Learning objectives for Lecture 1

- To understand how the timescale of diffusion relates to length scales
- To understand how concentration gradients lead to currents (Fick's First Law)
- To understand how charge drift in an electric field leads to currents (Ohm's Law and resistivity)

# Thermal energy

- Every degree of freedom comes to thermal equilibrium with an energy proportional to temperature (Kelvin, K)
- The proportionality constant is the Boltzmann constant (k)  
 $kT = 4 \times 10^{-21} \text{ Joules}$  at 300K)

- Kinetic energy :  $\left\langle \frac{1}{2}mv_x^2 \right\rangle = \frac{1}{2}kT \quad \left\langle v_x^2 \right\rangle = \frac{kT}{m}$

- The mass of a sodium ion is  $3.8 \times 10^{-26} \text{ kg}$

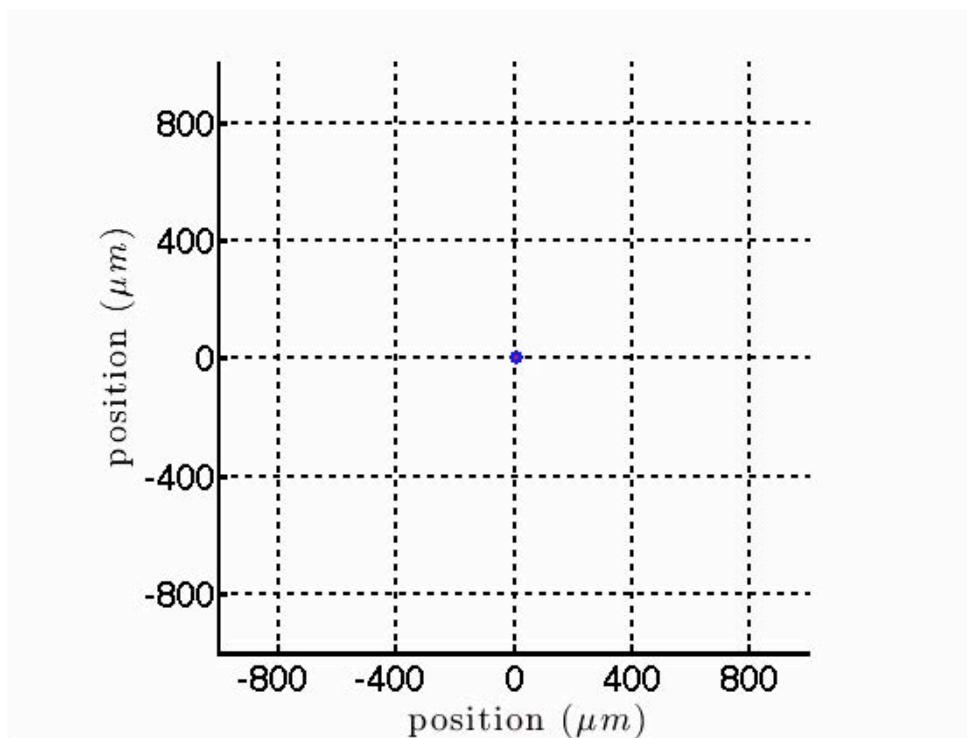
$$\left\langle v_x^2 \right\rangle = 10^5 \text{ m}^2 / \text{s}^2 \Rightarrow \bar{v}_x = 3.2 \times 10^2 \text{ m/s}$$

This would cross this 10m classroom in 3/10 second!

# What is diffusion?

- A particle in solution undergoes collisions with water molecules very often ( $\sim 10^{13}$  times per second!) that constantly change its direction of motion.

Collisions produce a ‘random walk’ in space



# Spatial and temporal scales

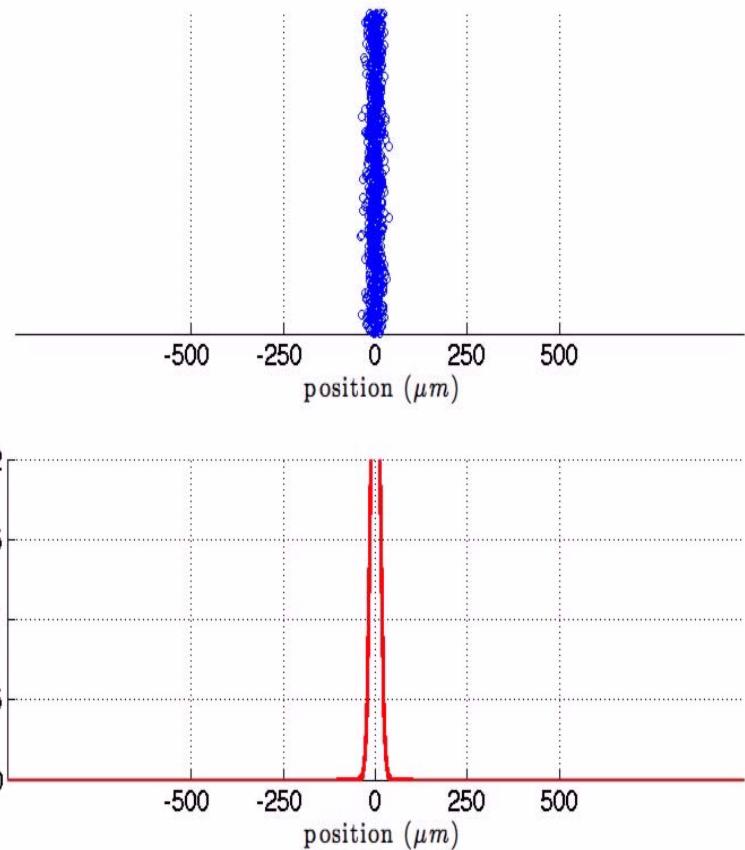
Diffusion is fast at short length scales and slow at long length scales.

- To diffuse across a cell body (10um) it takes an ion 50ms
- To diffuse down a dendrite (1mm) it takes about 10min
- How long does it take an ion to diffuse down a motor neuron axon (1m)?

10 years!

# Distribution of particles resulting from diffusion in 1-D

- On average particles stay clustered around initial position
- Particles spread out around initial position
- We can compute analytically properties of this distribution!

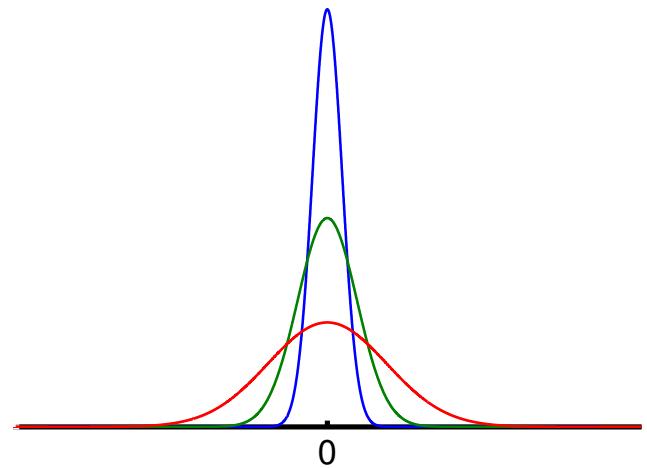


- An ensemble of particles diffusing from a point acquires a Gaussian distribution
- This arises from a binomial distribution for large number of time-steps (The probability of the particle moving exactly  $k$  steps to the right in  $n$  steps will be:

$$P(k; n, p) = \binom{n}{k} p^k (1-p)^{n-k}$$

$$\lim_{np \rightarrow \infty} P(k; n, p) = \frac{1}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}$$

## Gaussian Distribution



# Random walk in one dimension

- We can mathematically analyze the properties of an ensemble of particles undergoing a random walk
- Consider a particle moving left or right at a fixed velocity  $v_x$  for a  $\tau$  time before a collision.
- Imagine that each collision randomly resets the direction
- Thus, on every time-step,
  - half the particles step right by a distance  $\delta = +v_x \tau$
  - and half the particles step to the left by a distance  $\delta$

# Random Walk in 1-D

- Assume that we have  $N$  particles that start at position  $x=0$  at time  $t=0$
- $x_i(n)$  = the position of the  $i^{\text{th}}$  particle on time-step  $n$ :  $n = t / \tau$
- Assume the movement of each particle is independent
- Thus, we can write the position of each particle at time-step  $n$  as a function of the position at previous time-step

$$x_i(n) = x_i(n-1) \pm \delta$$

- Use this to compute how the distribution evolves in time!

# Average displacement is zero

- What is the average position of our ensemble?

$$\langle x_i(n) \rangle_i = \frac{1}{N} \sum_i x_i(n)$$
$$x_i(n) = x_i(n-1) \pm \delta$$

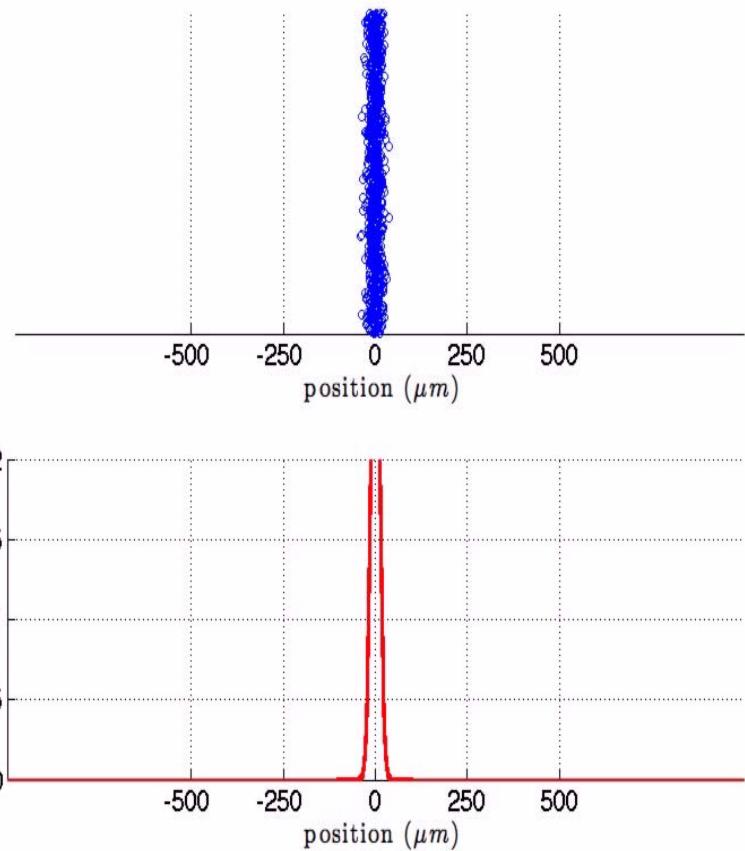
$$= \frac{1}{N} \sum_i [x_i(n-1) \pm \delta]$$

$$= \frac{1}{N} \sum_i [x_i(n-1)] + \frac{1}{N} \sum_i (\pm \delta)$$

$$\langle x_i(n) \rangle_i = \langle x_i(n-1) \rangle_i$$

# Distribution of particles resulting from diffusion in 1-D

- On average particles stay clustered around initial position
- Particles spread out around initial position
- We can compute analytically properties of this distribution!



# How far does a particle travel due to diffusion?

- We want to compute an average 'absolute value' distance from origin... Root mean square distance

$$\langle |x(n)| \rangle \rightarrow \sqrt{\langle x^2(n) \rangle}$$

Compute variance

$$x_i(n) = x_i(n-1) \pm \delta$$

$$x_i^2(n) = (x_i(n-1) \pm \delta)^2$$

$$\langle x^2(n) \rangle = \frac{1}{N} \sum_i x_i^2(n) = x_i^2(n-1) \pm 2\delta x_i(n-1) + \delta^2$$

$$\langle x^2(n) \rangle = \langle x^2(n-1) \rangle + \langle \pm 2\delta x_i(n-1) \rangle + \langle \delta^2 \rangle$$

$$\langle x^2(n) \rangle = \langle x^2(n-1) \rangle + \delta^2$$

# How far does a particle travel due to diffusion?

$$\langle x^2(n) \rangle = \langle x^2(n-1) \rangle + \delta^2$$

- Note that at each time-step, the variance grows by  $\delta^2$

$$\langle x^2(0) \rangle = 0 , \quad \langle x^2(1) \rangle = \delta^2 , \quad \langle x^2(2) \rangle = 2\delta^2 , \dots \quad \langle x^2(n) \rangle = n\delta^2$$

$$\langle x_i^2(t) \rangle = \frac{\delta^2 t}{\tau}, \quad n = t / \tau$$

$$\langle x_i^2 \rangle = 2Dt, \quad D = \delta^2 / 2\tau \quad (\text{Diffusion coefficient})$$

$$\sqrt{\langle x^2 \rangle} = \sqrt{2Dt}$$

# Spatial and temporal scales

$$L = \sqrt{2Dt}$$

$$L^2 = 2Dt$$

$$t = L^2/2D$$

Diffusion is fast at short length scales and slow at long length scales.  
Typical diffusion constants for small molecules and ions are  $\sim 10^{-5}$  cm $^2$ /s

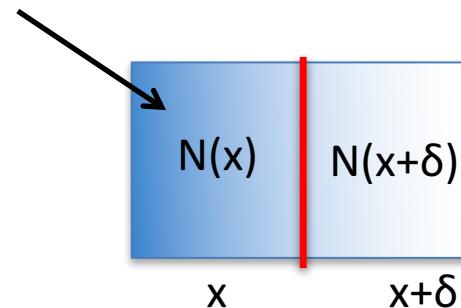
- $L = 10\mu\text{m} = 10^{-3} \text{ cm} \quad t = 10^{-6}(\text{cm}^2)/2 \times 10^{-5}(\text{cm}^2/\text{s}) = 50 \text{ ms}$
- $L = 1\text{mm} = 10^{-1} \text{ cm} \quad t = 10^{-2}(\text{cm}^2)/2 \times 10^{-5}(\text{cm}^2/\text{s}) = 500 \text{ s}$
- $L = 1000\text{mm} = 10^2 \text{ cm} \quad t = 10^4(\text{cm}^2)/2 \times 10^{-5}(\text{cm}^2/\text{s}) =$   
  
 $500,000,000 \text{ seconds!!}$

# Fick's first law

- Diffusion produces a net flow of particles from regions of high concentration to regions of lower concentration.
- The flux of particles is proportional to the concentration gradient.

$N(x)$  is the number of particles in  
the box at position  $x$

$$J_x = -D \frac{1}{\delta} [\varphi(x + \delta) - \varphi(x)]$$

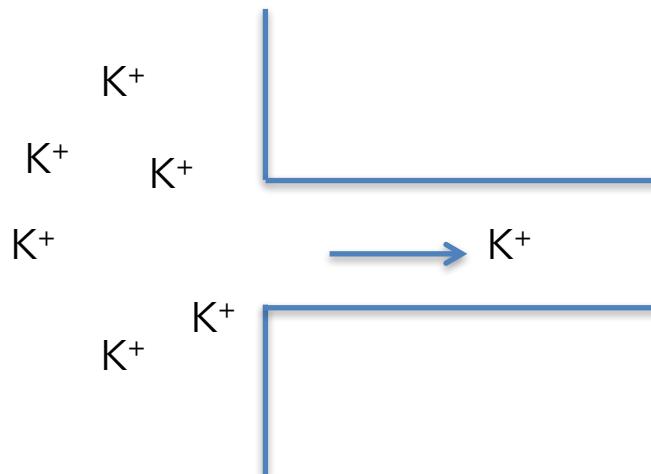
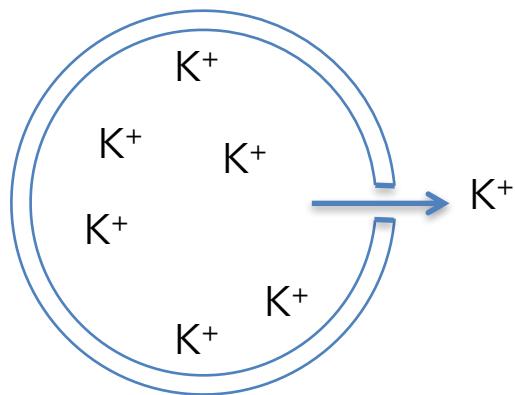


$$J_x = -D \frac{\partial \varphi}{\partial x}$$

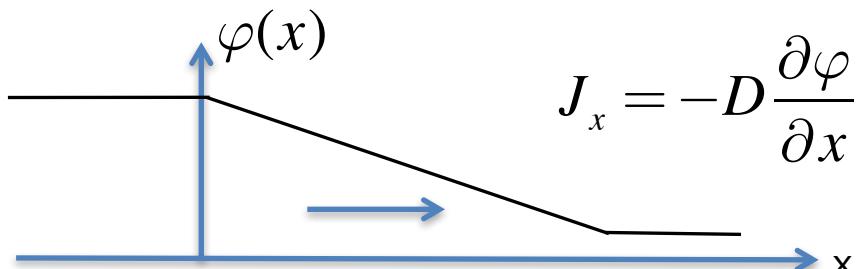
$$\frac{1}{2}N(x) \longrightarrow \frac{1}{2}N(x+\delta)$$

$\frac{1}{2}[N(x) - N(x + \delta)]$  is the net number of particles moving to the right in an interval of time  $\tau$

# Diffusion produces a net flux of particles down a gradient



- Each particle diffuses independently and randomly!
- And yet concentration gradients produce currents!
- Eventually all concentration gradients go away...

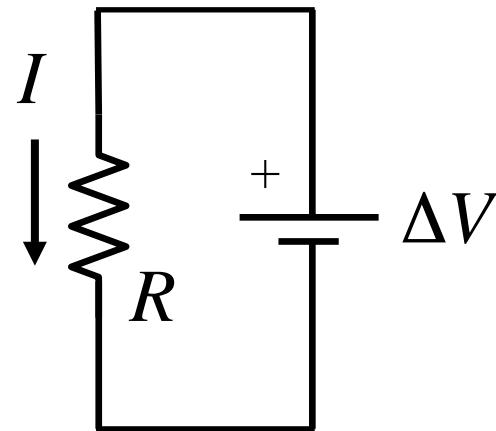


# Current flow in neurons obeys Ohm's Law

In a wire, current flow is proportional to voltage difference

Ohm's Law

$$I = \frac{\Delta V}{R}$$



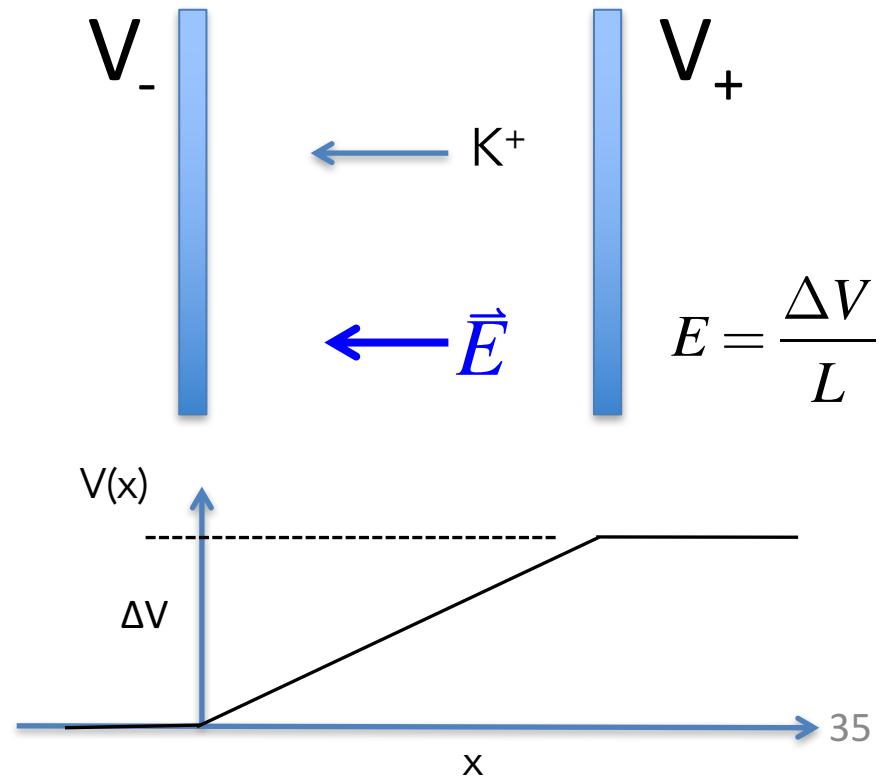
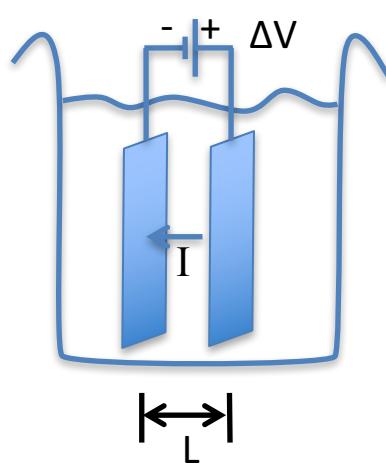
where

- I is current (Amperes, A)
- $\Delta V$  is voltage (Volts, V)
- R is resistance (Ohms,  $\Omega$ )

# Where does Ohm's Law come from?

Consider a beaker filled with salt solution, two electrodes, and a battery that produces a voltage difference between the electrodes.

- The electric field produces a force which, in a solution, causes an ion to drift with a constant velocity — a current

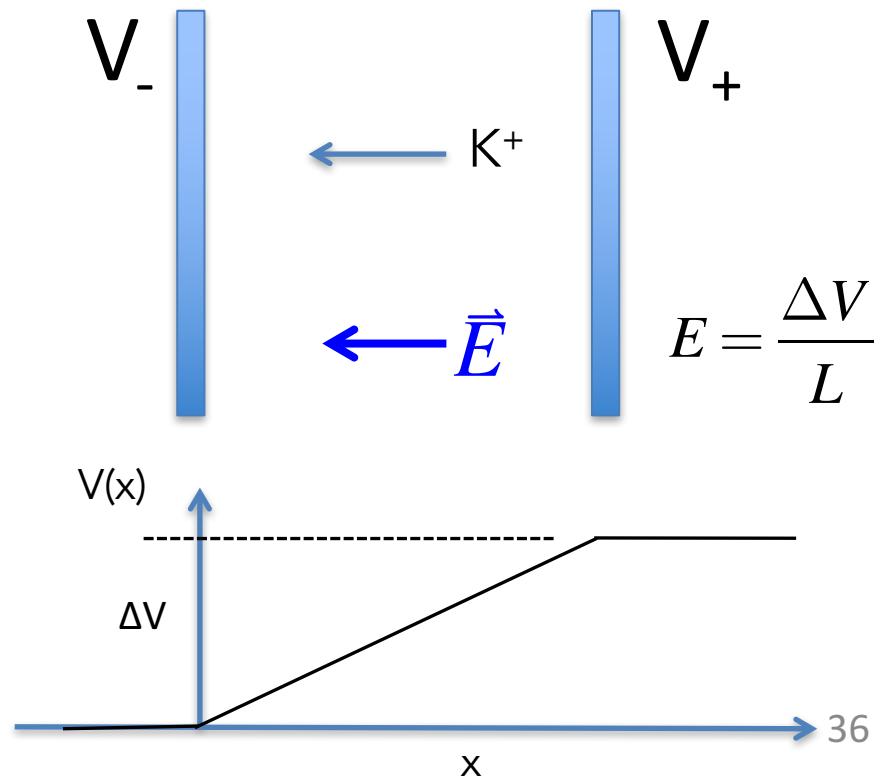
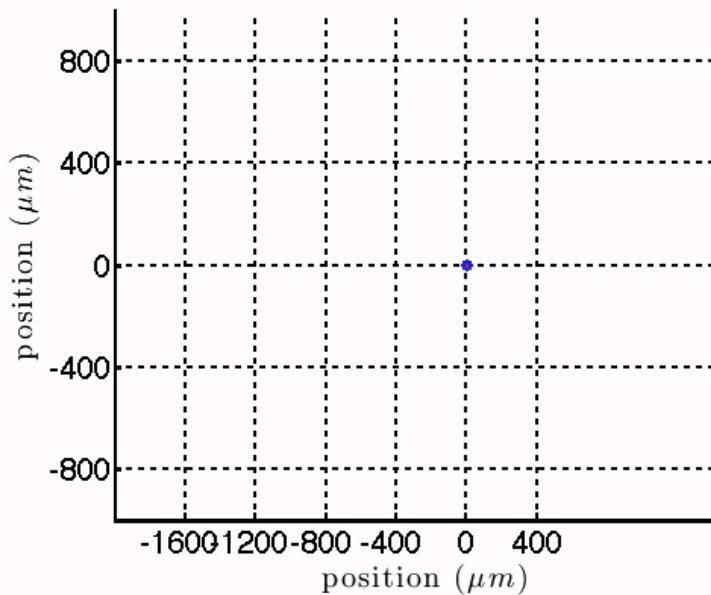


- Force:  $\vec{F} = q\vec{E}$

# Ion currents in an electric field

Currents are also caused by the drift of ions in the presence of an electric field.

- The electric field produces a force which, in a solution, causes an ion to drift with a constant velocity — a current



- Why constant velocity?

# Ion currents in an electric field

Currents are also caused by the drift of ions in the presence of an electric field.

- Einstein realized that this is just a result of viscous drag (or friction)

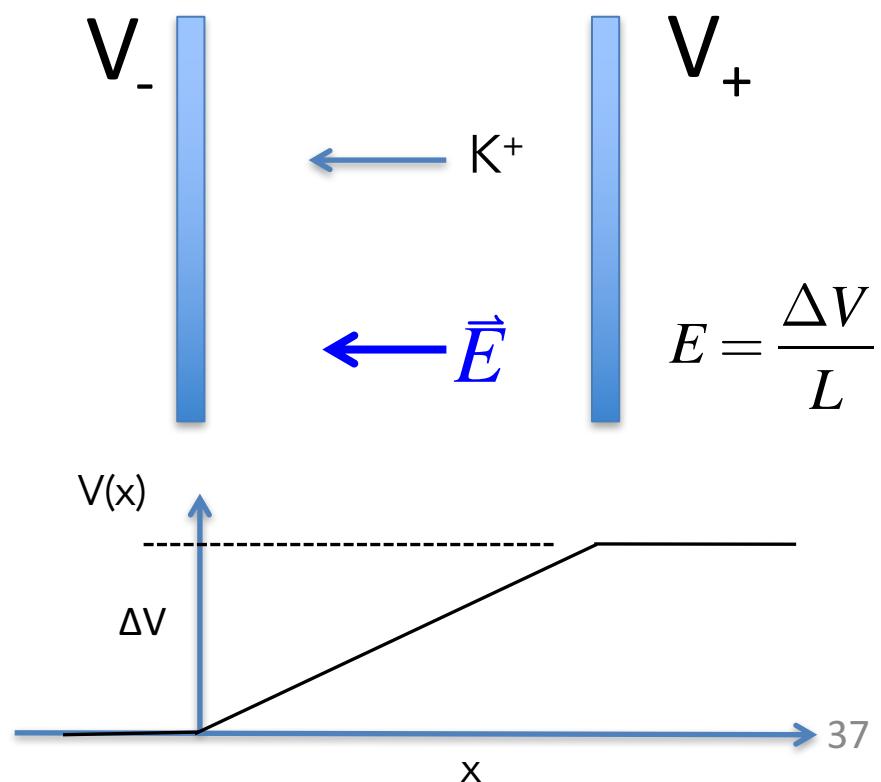
$$\vec{F} = f \vec{v}_d$$

- Einstein –Smoluchovski relation

$$f = kT / D$$

- Drift velocity is given by

$$\vec{v}_d = \frac{D}{kT} \vec{F} = \frac{D}{kT} (q \vec{E})$$



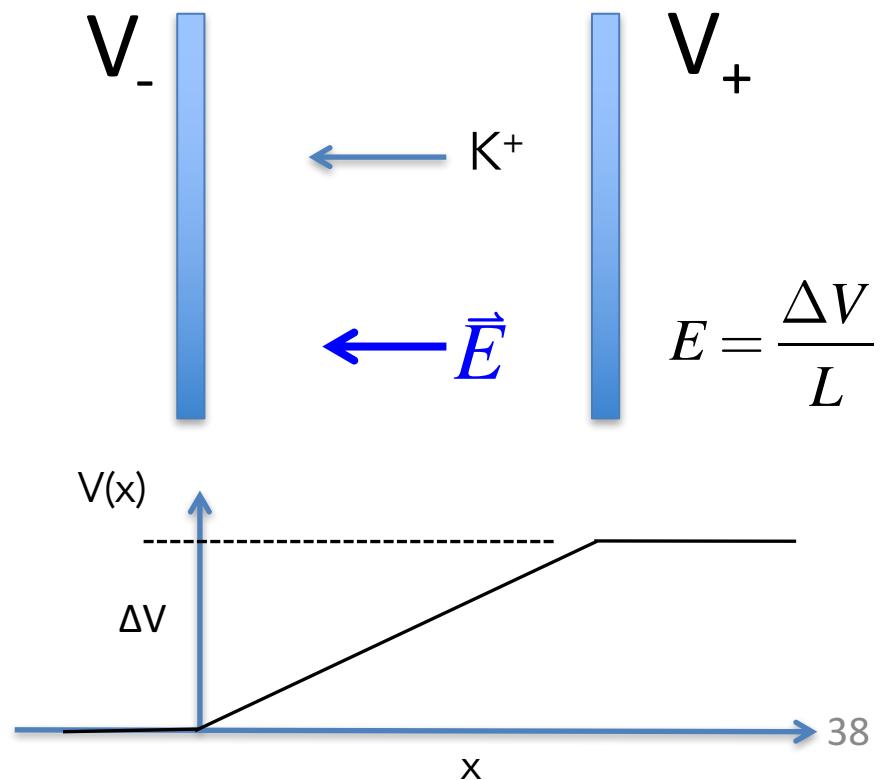
# Ion currents in an electric field

Currents are also caused by the drift of ions in the presence of an electric field.

- The electric field produces a force which, in a solution, causes an ion to drift with a constant velocity — a current

$$I \propto v_d A$$

$$I \propto E A = \frac{\Delta V}{L} A$$



# Ohm's Law in solution

In a solution, current flow per unit area is proportional to voltage gradients

$$I = \left( \frac{1}{\rho} \right) \frac{\Delta V}{L} A$$

$\rho$  = resistivity ( $\Omega \cdot \text{m}$ )

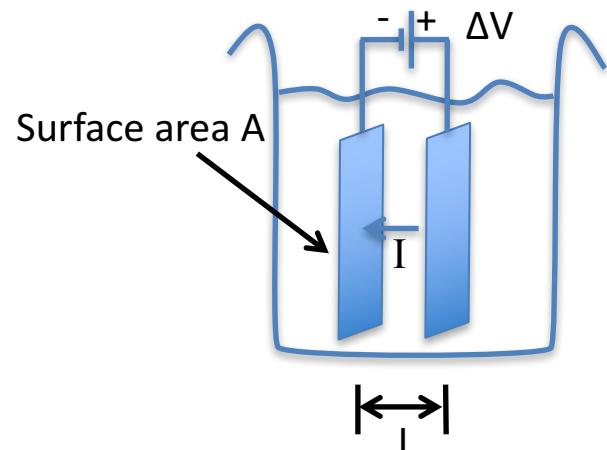
$$I = \frac{1}{R} \Delta V$$

- Let's make this look more like Ohm's Law

$$I = \left( \frac{A}{\rho L} \right) \Delta V$$

- Thus the resistance is given by:

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

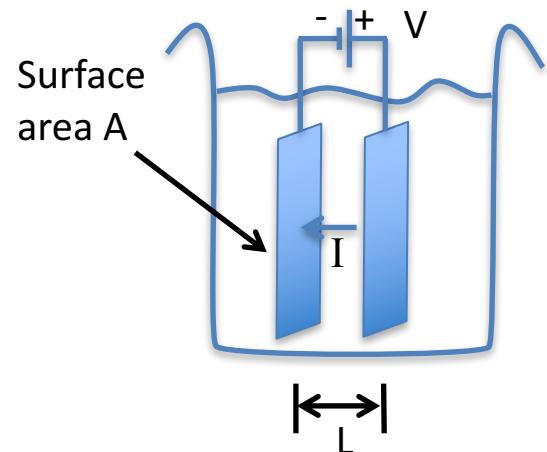


# Resistivity of intra/extracellular space

- Resistance of a volume of conductive medium is given by

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

- $\rho = 1.6 \mu\Omega\cdot\text{cm}$  for copper
- $\rho = \sim 60 \Omega\cdot\text{cm}$  for mammalian saline – the brain has lousy conductors!
- The brain has many specializations to deal with lousy wires...



# Learning objectives for Lecture 1

- To understand how the timescale of diffusion relates to length scales
  - Distance diffused grows as the square root of time
- To understand how concentration gradients lead to currents (Fick's First Law)
  - Concentration differences lead to particle flux, proportional to gradient
- To understand how charge drift in an electric field leads to currents (Ohm's Law and resistivity)

# (Extra slide) Derivation of resistivity

Current density (Coulombs per second per unit area) is just drift velocity times the density of ions times the charge per ion.

$$\frac{I}{A} = q\varphi v_d$$

$\varphi$  = ion density (ions per m<sup>3</sup>)  
 $q = ze$  = ionic charge (Coulombs per ion)  
= ion valence times 1.6x10<sup>-19</sup> Coulombs

- Plugging in drift velocity from above, we get:

$$\frac{I}{A} = q\varphi \frac{D}{kT}(qE)$$

# Derivation of resistivity

- Thus, the current density (coulombs per second per unit area) is just proportional to the electric field:

$$\frac{I}{A} = \frac{q^2 \varphi D}{kT} E$$

$$\frac{I}{A} = \left( \frac{1}{\rho} \right) E$$

- Solving for  $\rho$  we get:

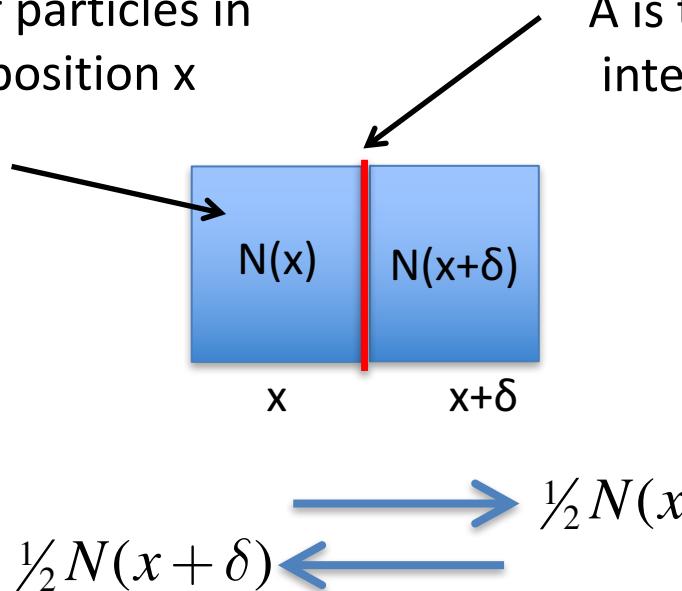
$$\rho = \frac{kT}{q^2 \varphi D} = \text{resistivity } (\Omega \cdot \text{m})$$

# Extra slides on derivation of Fick's first law

We will now use a similar approach to derive a macroscopic description of diffusion – a differential equation that describes the flux of particles from the spatial distribution of their concentration.

$N(x)$  is the number of particles in a box (of length  $\delta$ ) at position  $x$

$A$  is the area of the interface between the boxes

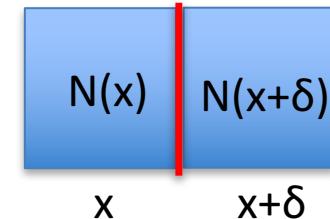


$\frac{1}{2}[N(x) - N(x + \delta)]$  is the net number of particles moving to the right in an interval of time  $\tau$

# Extra slides on derivation of Fick's first law

We can calculate the flux in units of particles per second per area

$$J_x = -\frac{1}{A\tau} \frac{1}{2} [N(x + \delta) - N(x)]$$



multiply by  $\delta^2 / \delta^2$

$$J_x = -\frac{\delta^2}{2\tau} \frac{1}{\delta} \left[ \frac{N(x + \delta)}{A\delta} - \frac{N(x)}{A\delta} \right]$$

Particles per unit volume

$$J_x = -D \frac{1}{\delta} [\varphi(x + \delta) - \varphi(x)]$$

Density - particles per unit volume

$$J_x = -D \frac{\partial \varphi}{\partial x}$$

Note: To get density ( $\text{ions}/\text{m}^3$ ) from molar concentration ( $\text{mol}/\text{L}$ ), you have to multiply by  $N_A \times 10^{-3}$ . ( $N_A$  is Avagadro's Number =  $6.02 \times 10^{23}$ )

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Spring 2018

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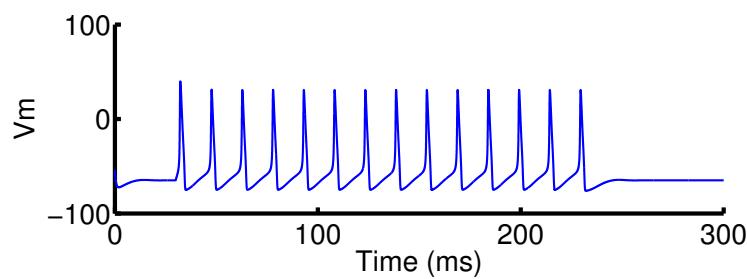
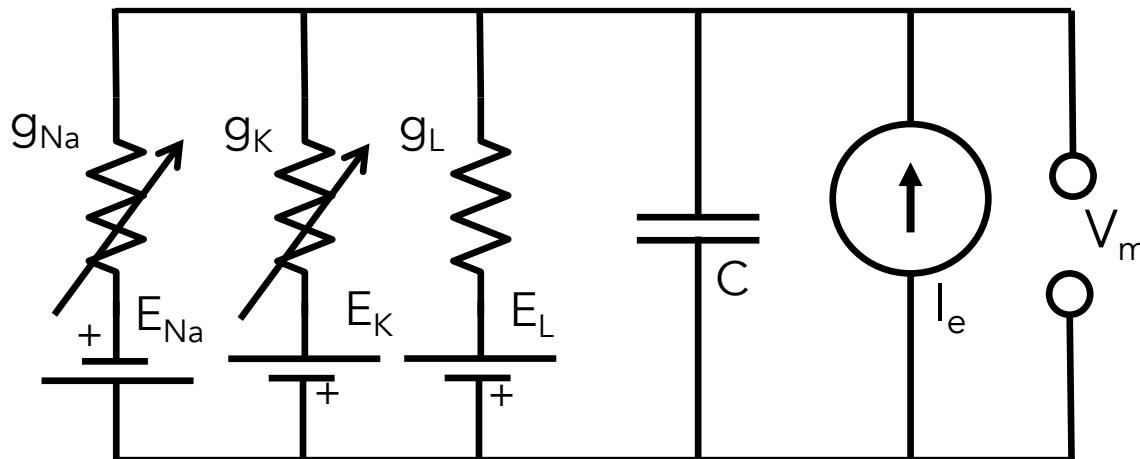
# Introduction to Neural Computation

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Michale Fee  
MIT BCS 9.40 — 2018  
Video Module on Nernst Potential  
Part 1

# A mathematical model of a neuron

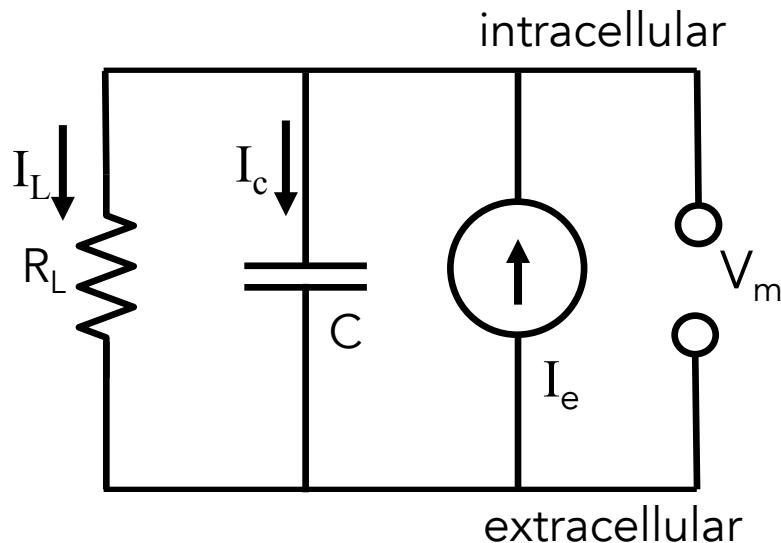
- Equivalent circuit model



Alan Hodgkin  
Andrew Huxley, 1952



# A neuron is a leaky capacitor



$I_c$  = membrane capacitive current

$I_L$  = membrane ionic current

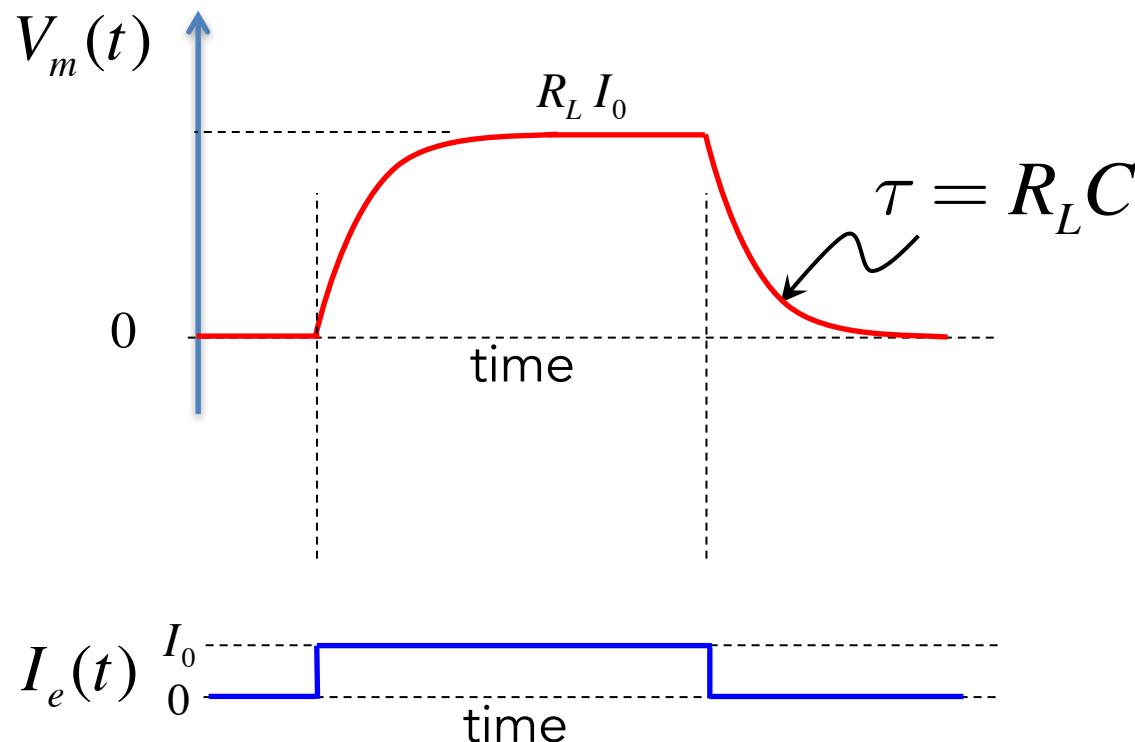
$$V_m + \tau \frac{dV_m}{dt} = V_\infty$$

$$\text{where } \tau = R_L C$$

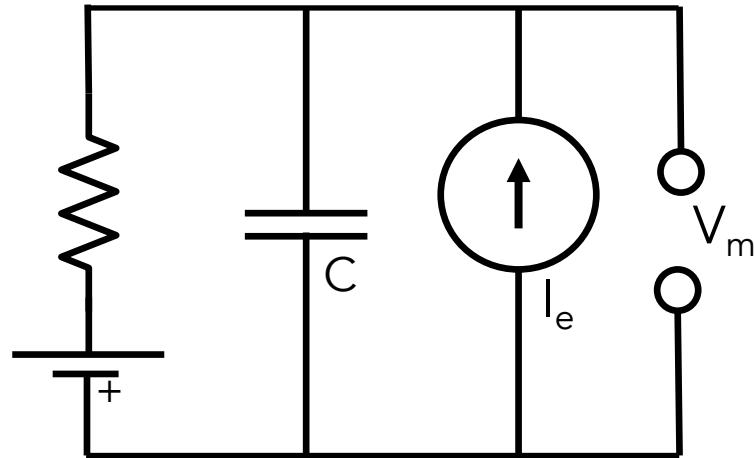
$$V_\infty(t) = R_L I_e(t)$$

# Response to current injection

Let's see what happens when we inject current into our model neuron with a leak conductance.

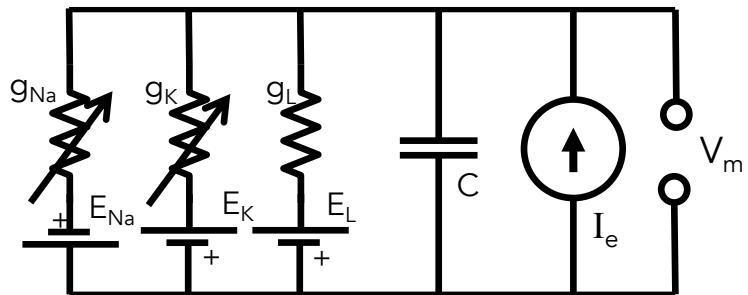
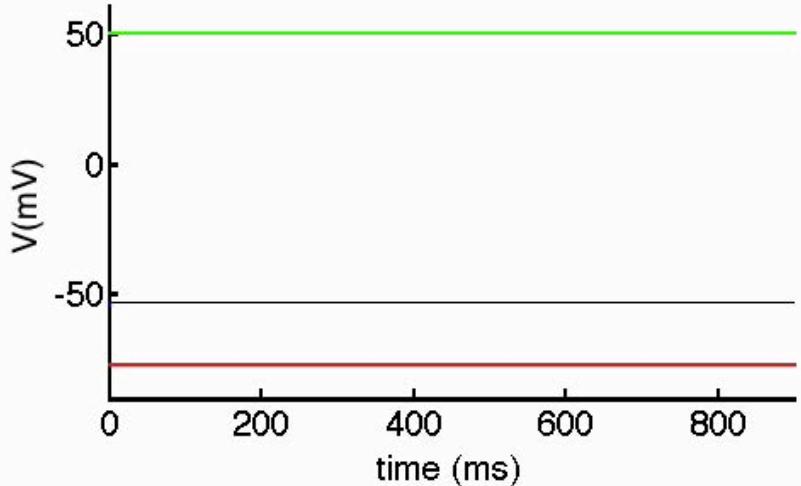


# A neuron is a leaky capacitor



# Outline of HH model

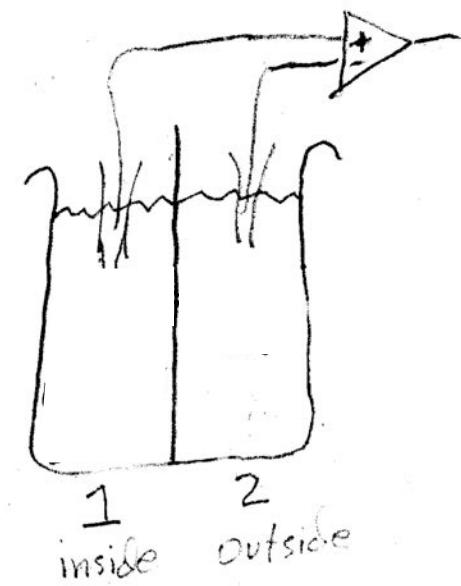
Voltage and time-dependent ion channels are the 'knobs' that control membrane potential.



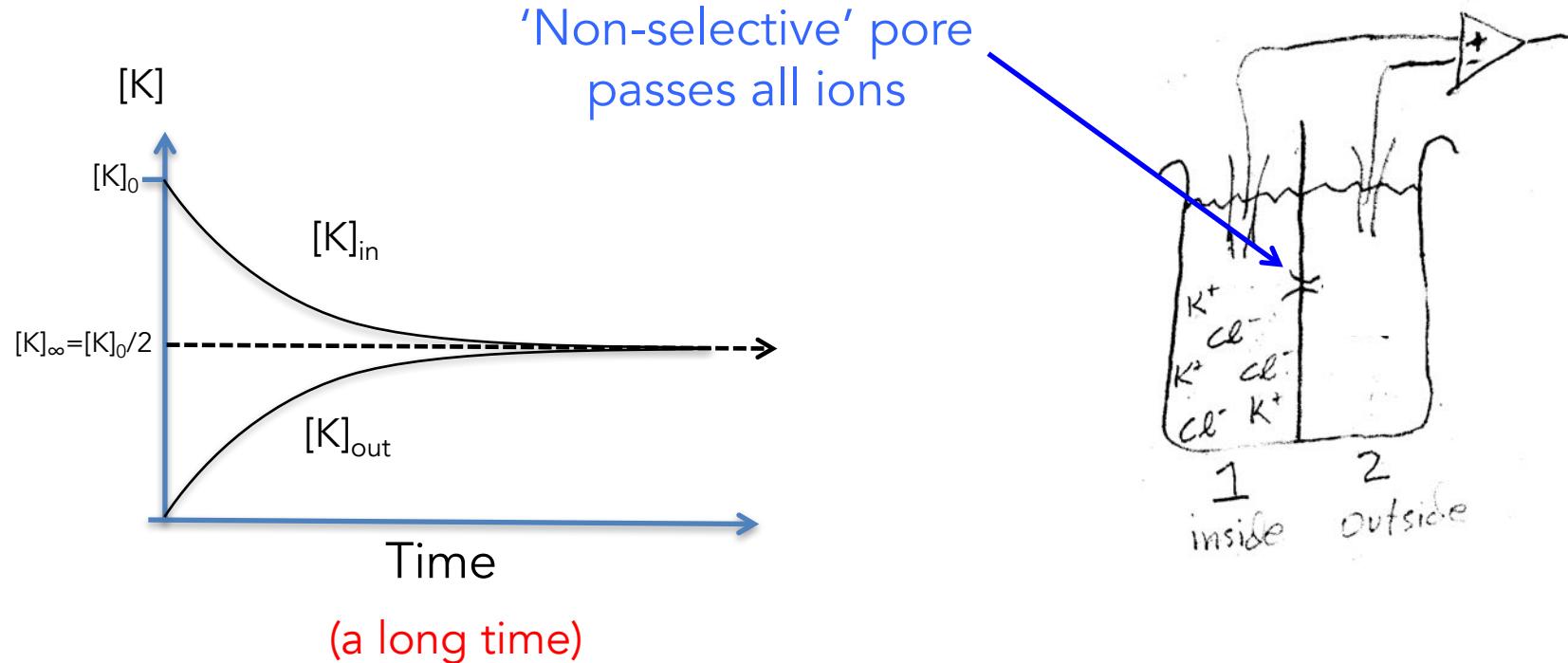
- Some ion channels push the membrane potential positive.
- Other ion channels push the membrane potential negative.
- Together these channels give the neural machinery flexible control of voltage!

# Where do the batteries of a neuron come from?

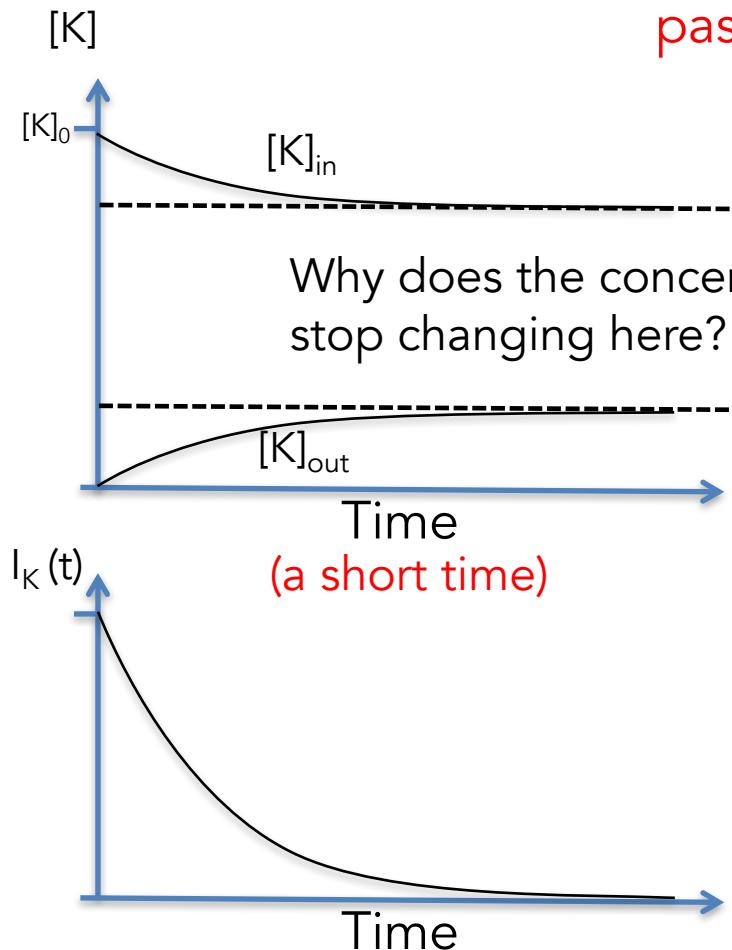
- 1) Ion concentration gradients
- 2) Ion-selective permeability of ion channels



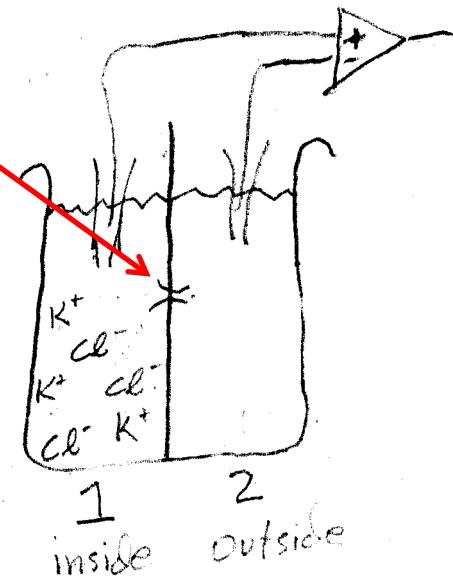
# Neurons have batteries



# Neurons have batteries

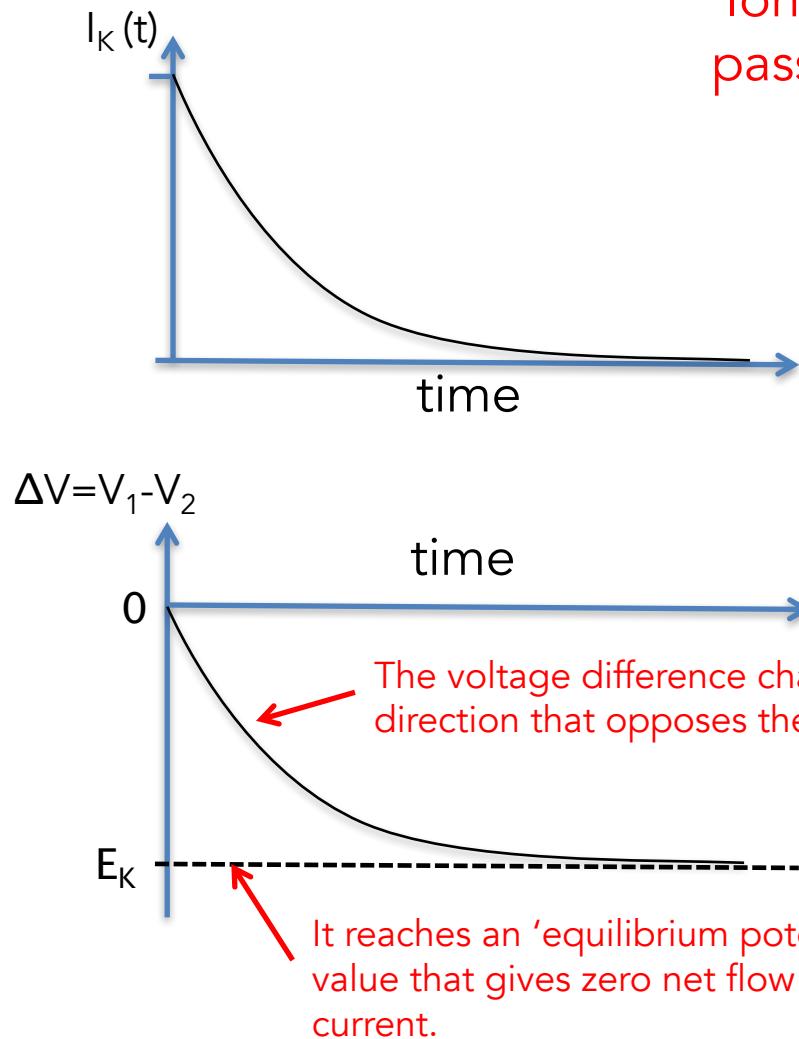


'Ion-selective' pore  
passes only  $K^+$  ions

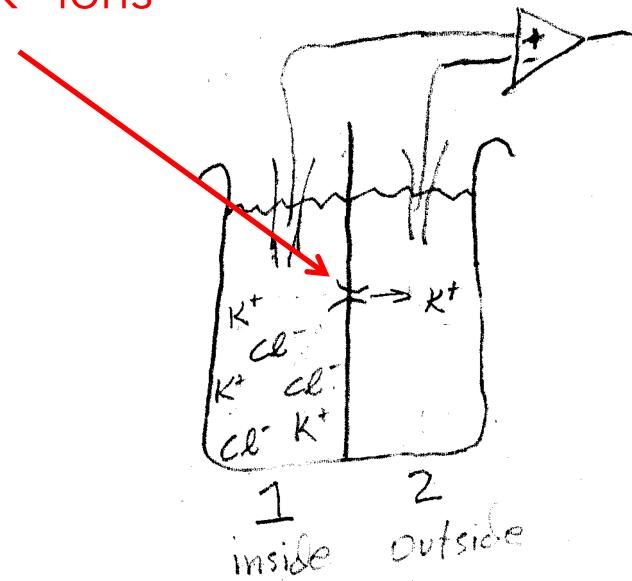


Why do the ions stop flowing  
from side 1 to side 2?

# Neurons have batteries

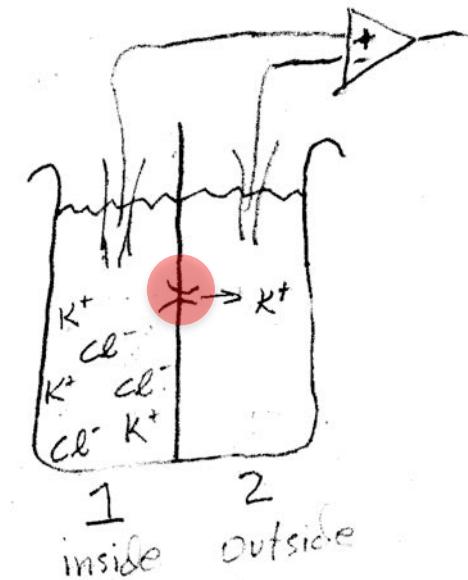
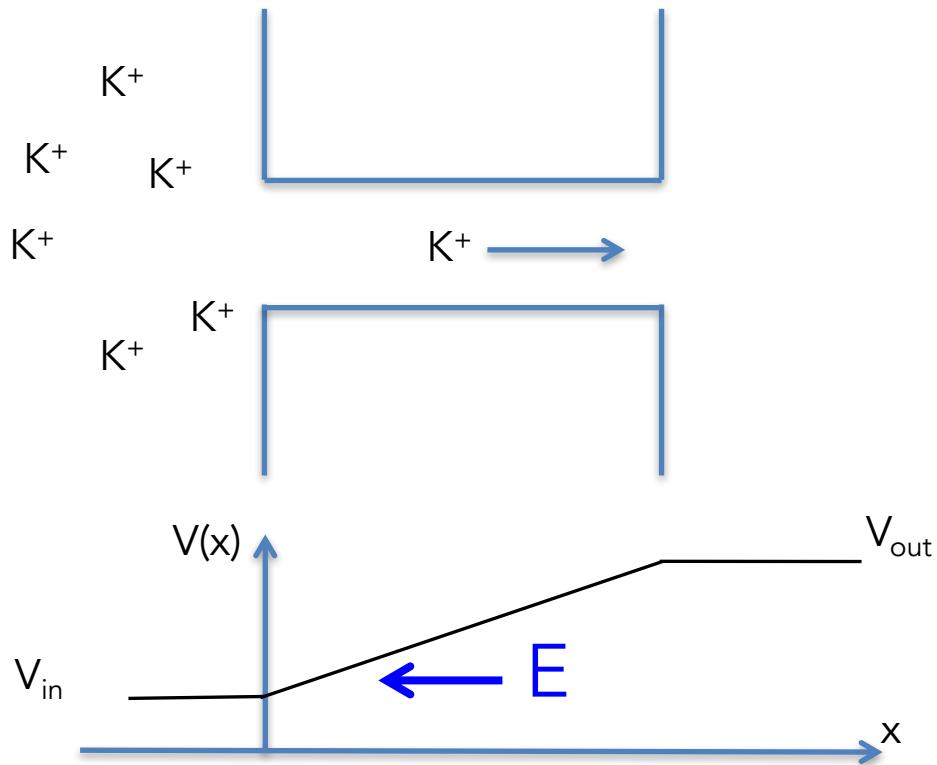


'Ion-selective' pore  
passes only  $K^+$  ions



This voltage difference is a battery for our model neuron!!

# Neurons have batteries



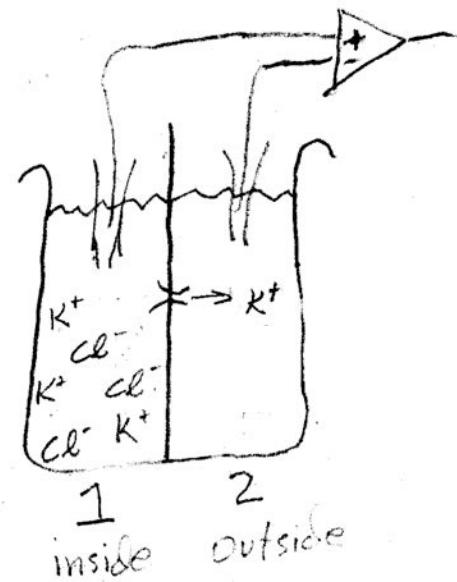
There will be some electric field strength such that the 'drift' will exactly balance the diffusion produced by the concentration gradient...

Nernst Potential

# Neurons have batteries

- Where do the 'batteries' of a neuron come from?
  - 1) Ion concentration gradients
  - 2) Ion-selective pores (channels)
- How big is the battery (how many volts?)

This is determined by a balance between diffusion down a concentration gradient balanced by 'drift' in the opposing electric field.



# Electrodiffusion and the Nernst Potential

One can use Ohm's law and Fick's first law to derive the Nernst potential

- At this voltage, the drift current in the electric field exactly balances current due to diffusion

$$I_{Tot} = I_{Drift} + I_{Diffusion} = 0$$

Ohm's Law

$$I_{Drift} = \frac{Aq^2\varphi(x)D}{kT} \frac{\Delta V}{L}$$

Fick's First Law

$$I_{Diffusion} = -AqD \frac{\partial \varphi}{\partial x}$$

$$\Delta V = \frac{kT}{q} \ln \left( \frac{\varphi_{out}}{\varphi_{in}} \right)$$

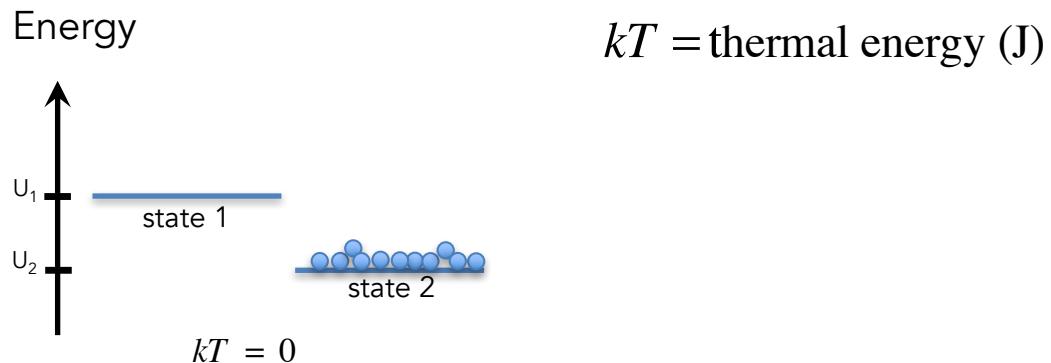
at equilibrium

# Derive Nernst potential using the Boltzmann equation

The Boltzmann equation describes the ratio of probabilities of a particle being in any two states, at thermal equilibrium:

$$\frac{P_{state1}}{P_{state2}} = e^{-\left(\frac{U_1-U_2}{kT}\right)}$$

$k$  = Boltzmann constant (J/K)  
 $T$  = temperature (K) = 273 + T<sub>C</sub>



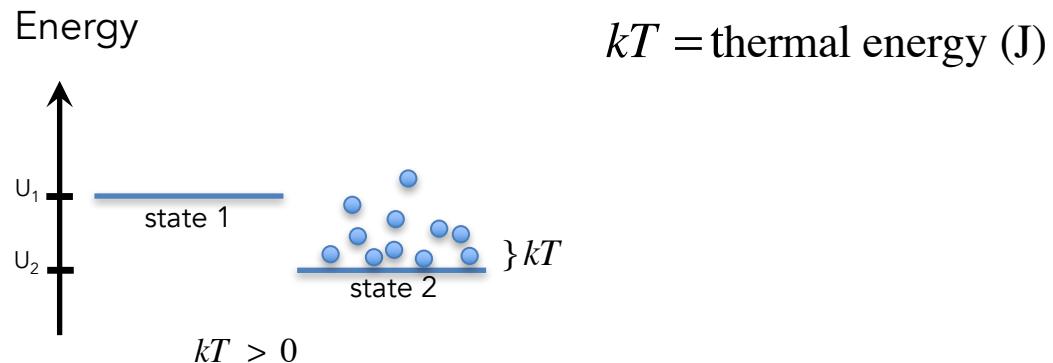
$$\frac{P_{state1}}{P_{state2}} = 0$$

# Derive Nernst potential using the Boltzmann equation

The Boltzmann equation describes the ratio of probabilities of a particle being in any two states, at thermal equilibrium:

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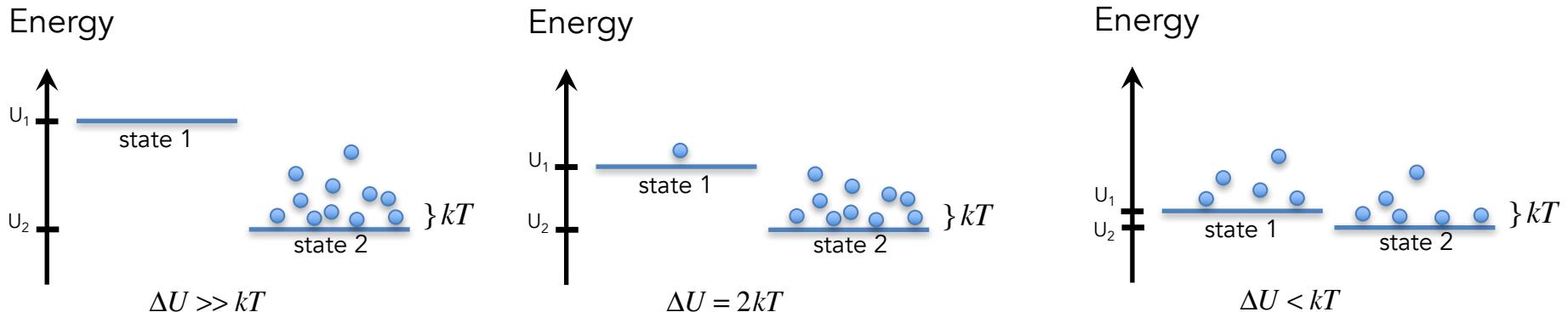


$$\frac{P_{state1}}{P_{state2}} > 0$$

# Derive Nernst potential using the Boltzmann equation

The Boltzmann equation describes the ratio of probabilities of a particle being in any two states, at thermal equilibrium:

$$\frac{P_{state1}}{P_{state2}} = e^{-\left(\frac{U_1-U_2}{kT}\right)}$$



$$\frac{P_{state1}}{P_{state2}} \approx 0$$

$$\frac{P_{state1}}{P_{state2}} = e^{-2}$$

$$\frac{P_{state1}}{P_{state2}} \approx 1.0$$

# Nernst Potential

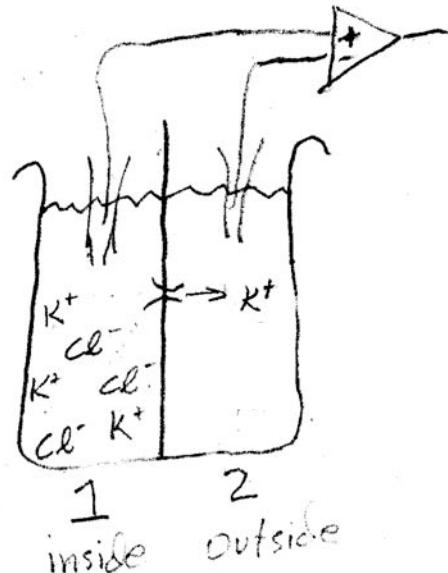
We can compute the equilibrium potential using the Boltzmann equation:

$$\frac{P_{in}}{P_{out}} = e^{-\frac{U_{in}-U_{out}}{kT}} = e^{-\frac{q(V_{in}-V_{out})}{kT}}$$

$U = qV$  = electrical potential (J)

$q$  = charge of ion

$q = 1.6 \times 10^{-19} \text{ C}$  for monovalent ion



# Nernst Potential

We can compute the equilibrium potential using the Boltzmann equation:

$$\frac{P_{in}}{P_{out}} = e^{-\frac{U_{in}-U_{out}}{kT}} = e^{-\frac{q(V_{in}-V_{out})}{kT}}$$

$U = qV$  = electrical potential (J)

$q$  = charge of ion

$$V_{in} - V_{out} = -\frac{kT}{q} \ln\left(\frac{P_{in}}{P_{out}}\right)$$

$q = 1.6 \times 10^{-19}$  C for monovalent ion

$$\Delta V = V_{in} - V_{out} = 25mV \ln\left(\frac{P_{out}}{P_{in}}\right)$$

$$\frac{kT}{q} = 25mV \text{ for monovalent ion}$$

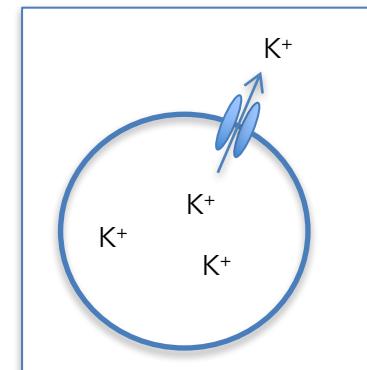
$$\Delta V = 25mV \ln\left(\frac{[K]_{out}}{[K]_{in}}\right) = E_K$$

Don't get confused by this notation.  $E_K$  is the equilibrium potential (voltage) for the K ion. 'E' here does not refer to an electric field.

# The Nernst potential for potassium

Intracellular and extracellular concentrations of ionic species, and the Nernst potential

Ion	Cytoplasm (mM)	Extracellular (mM)	Nernst (mV)
K <sup>+</sup>	400	20	-75

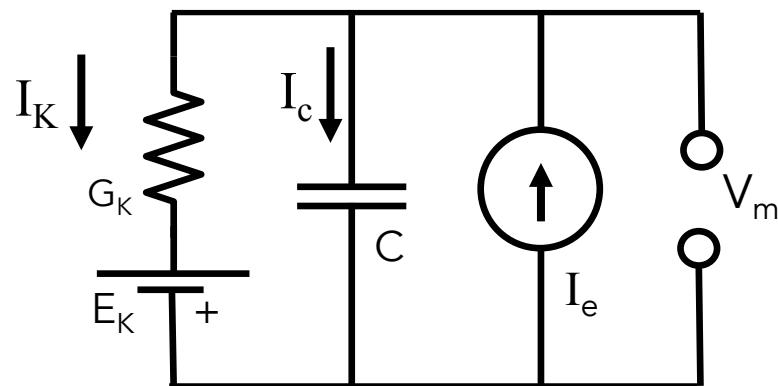


$$E_k = \frac{kT}{q} \ln\left(\frac{20}{400}\right) \quad \frac{kT}{q} = 25\text{mV at 300K (room temp)}$$

for monovalent ion

$$E_K = 25\text{mV}(-3.00) = -75\text{mV}$$

# How to implement an ion specific conductance as a battery in our model neuron



# Introduction to Neural Computation

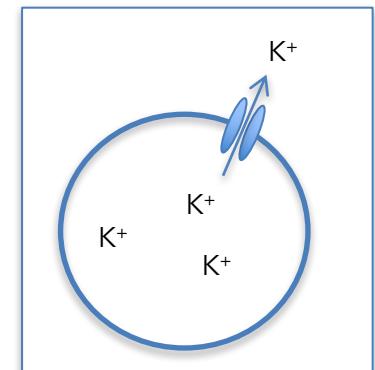
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Michale Fee  
MIT BCS 9.40 — 2018  
Video Module on Nernst Potential  
Part 2

# The Nernst potential for potassium

Intracellular and extracellular concentrations of ionic species, and the Nernst potential

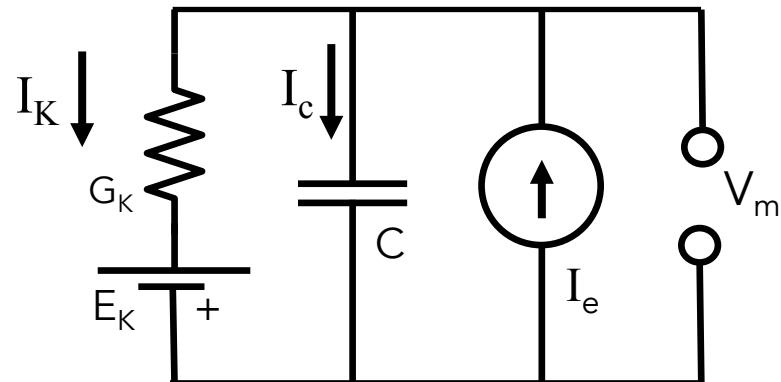
Ion	Cytoplasm (mM)	Extracellular (mM)	Nernst (mV)
K <sup>+</sup>	400	20	-75



$$\Delta V = \frac{kT}{q} \ln \left( \frac{[K]_{out}}{[K]_{in}} \right) \quad \frac{kT}{q} = 25\text{mV at } 300\text{K (room temp)} \\ \text{for monovalent ion}$$

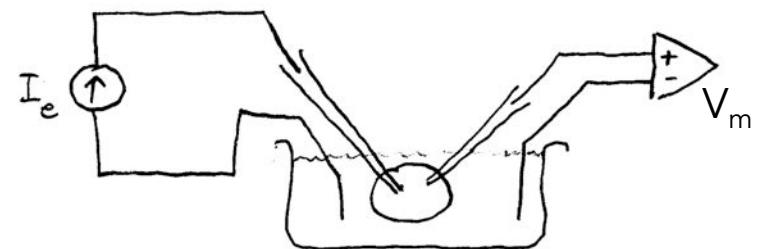
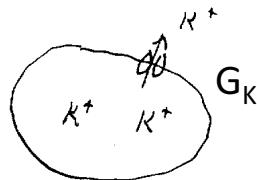
$$E_K = 25\text{mV}(-3.00) = -75\text{mV}$$

# How to implement an ion specific conductance as a battery in our model neuron



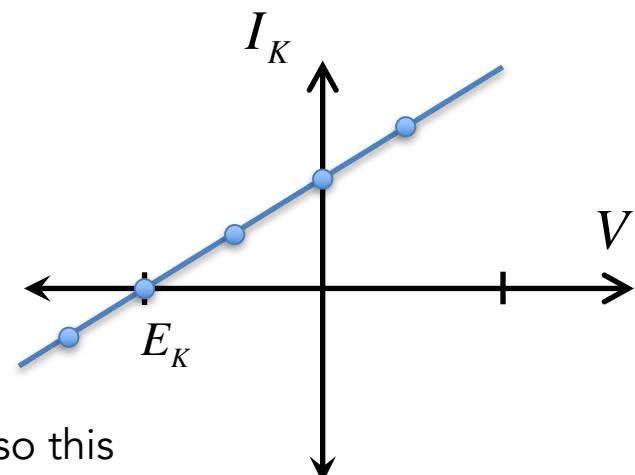
# Potassium I-V relation

One of the best ways to study the function of an ion channel is to plot the current-voltage relation (I-V curve). This can be measured as the current required to hold the neuron at a given voltage.



For a potassium conductance

- If you hold the voltage above the equilibrium potential, K current will flow out through the membrane (positive current)
- If you hold the cell below  $E_K$ , then the current will flow into the cell.

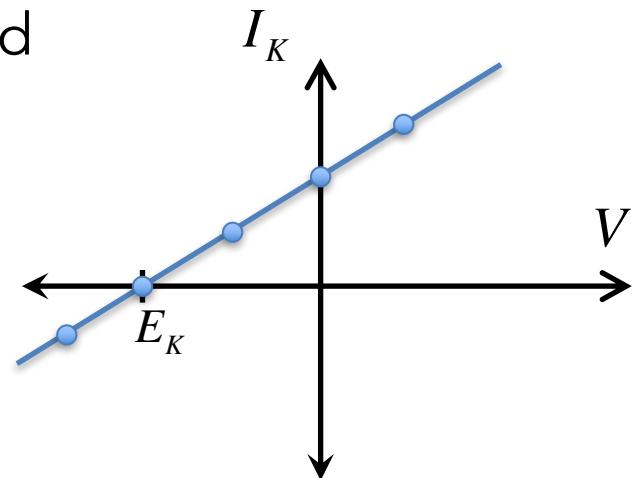


Note that the current reverses at the equilibrium potential, so this is often referred to as the 'reversal potential'

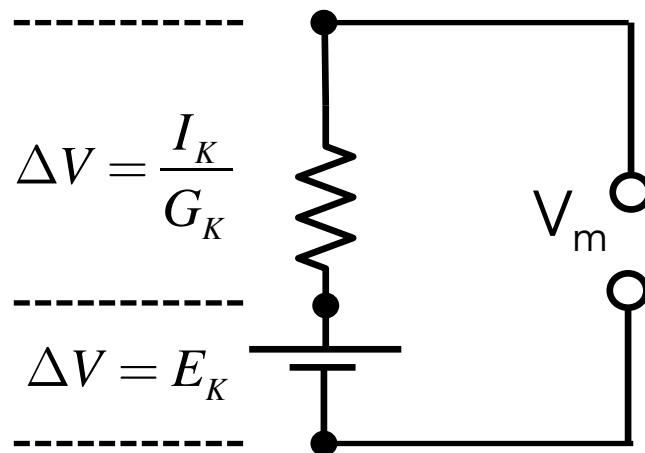
# I-V relation

This relation turns out to be monotonic and roughly linear for ion channels in the open state. So we can write:

$$I_K = G_K(V - E_K) , \quad G_K = R_K^{-1}$$



We can model this as a battery in series with a resistor! Why?

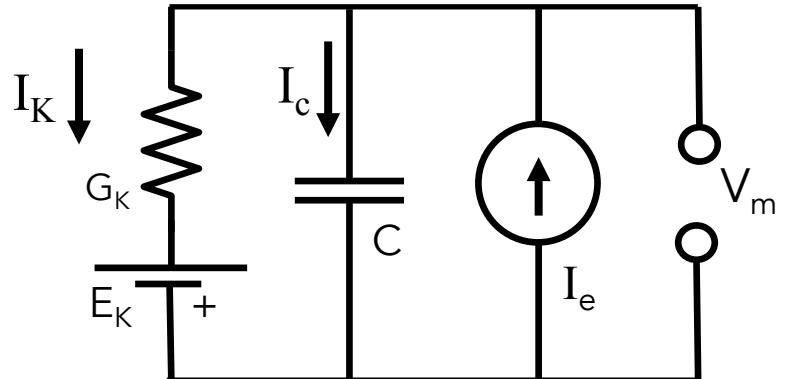


$$V_m = E_K + \frac{I_K}{G_K} \rightarrow I_K = G_K(V - E_K)$$

driving potential

Our equation is now:

$$I_K + C \frac{dV}{dt} = I_e$$

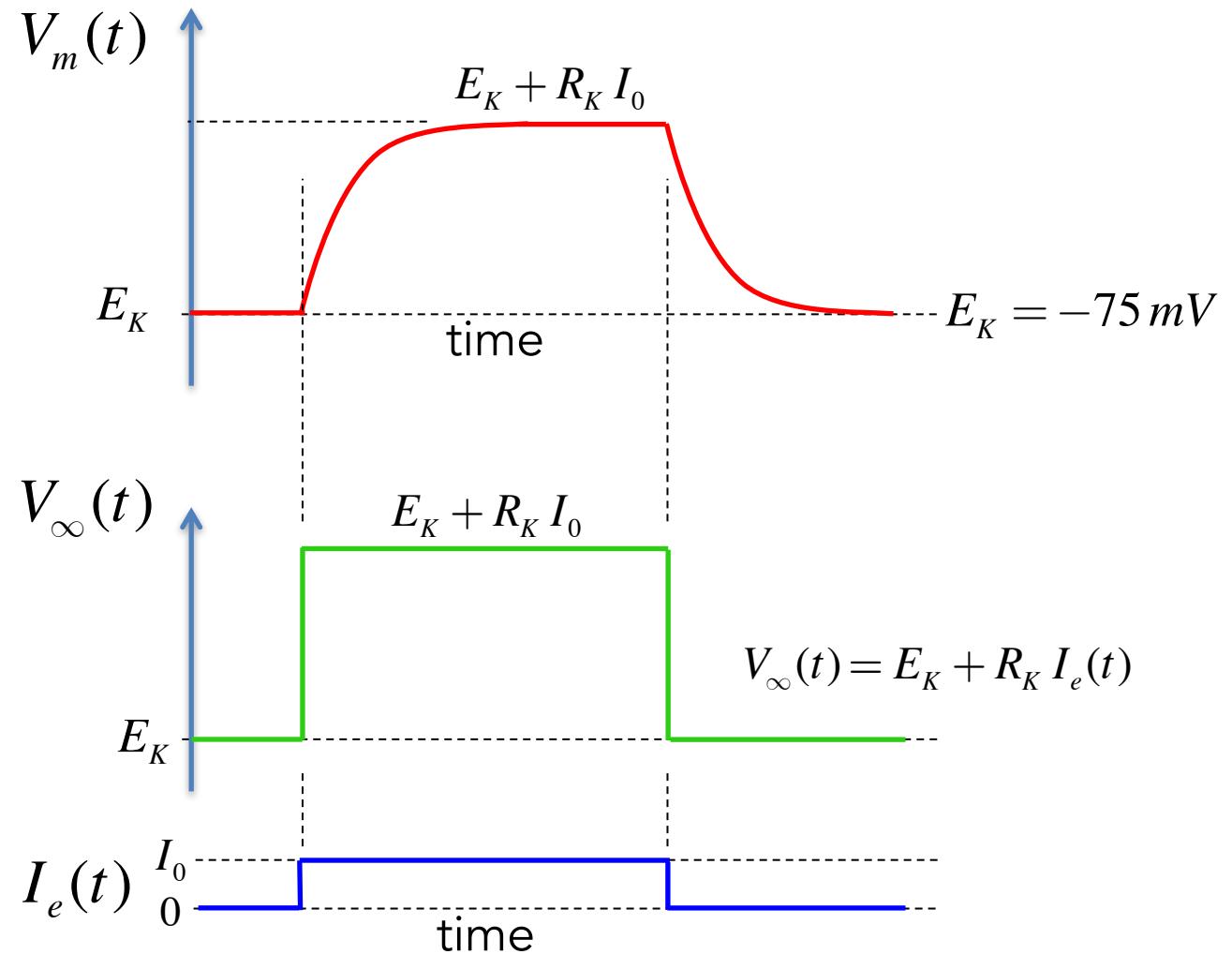


$$G_K(V - E_K) + C \frac{dV}{dt} = I_e , \quad R_K = G_K^{-1} , \quad \tau = R_K C$$

$$V + \tau \frac{dV}{dt} = \underbrace{E_K + R_K I_e}_{V_\infty}$$

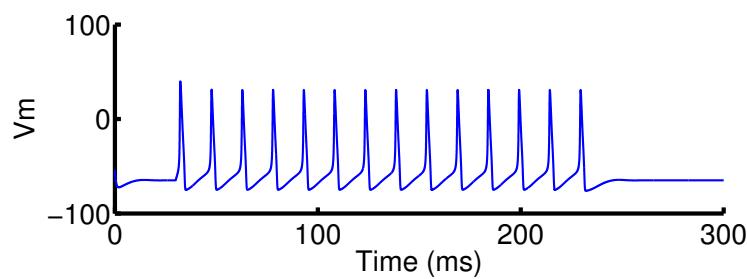
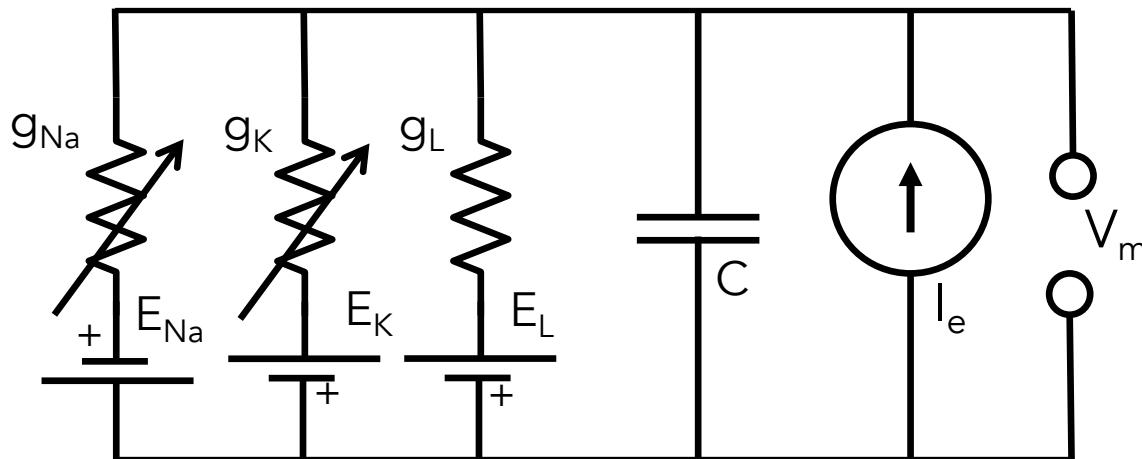
$$V + \tau \frac{dV}{dt} = V_\infty , \quad V_\infty = E_K + R_K I_e$$

# Response to current injection



# A mathematical model of a neuron

- Equivalent circuit model



Alan Hodgkin  
Andrew Huxley, 1952

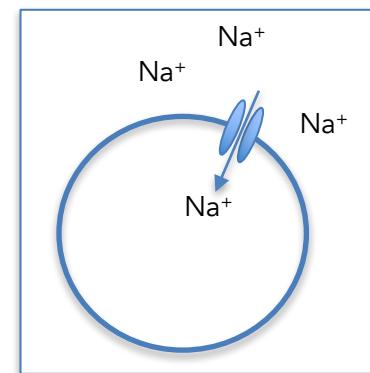


# The Nernst Potential is different for different ions

Intracellular and extracellular concentrations of ionic species, and the Nernst potential

Ion	Cytoplasm (mM)	Extracellular (mM)	Nernst (mV)
K <sup>+</sup>	400	20	-75
Na <sup>+</sup>	50	440	

$$E_{Na} = 25mV \ln\left(\frac{440}{50}\right) = 25mV(2.17) = 54.3mV$$



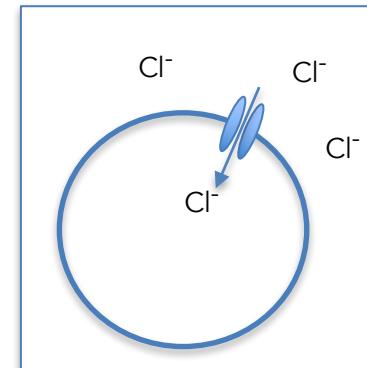
# The Nernst Potential is different for different ions

Intracellular and extracellular concentrations of ionic species, and the Nernst potential

Ion	Cytoplasm (mM)	Extracellular (mM)	Nernst (mV)
K <sup>+</sup>	400	20	-75
Na <sup>+</sup>	50	440	+54
Cl <sup>-</sup>	52	560	

$$E_{Cl} = -25mV \ln\left(\frac{560}{52}\right) = -25mV(2.38) = -59.4mV$$

The negative here comes from the negative charge of the Cl<sup>-</sup> ion (q=-e)



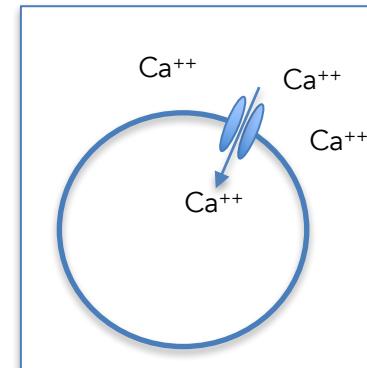
# The Nernst Potential is different for different ions

Intracellular and extracellular concentrations of ionic species, and the Nernst potential

Ion	Cytoplasm (mM)	Extracellular (mM)	Nernst (mV)
K <sup>+</sup>	400	20	-75
Na <sup>+</sup>	50	440	+55
Cl <sup>-</sup>	52	560	-59
Ca <sup>++</sup>	10 <sup>-4</sup>	2	+124

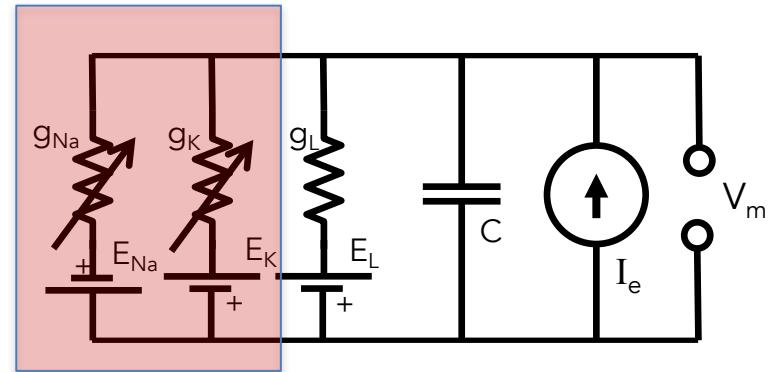
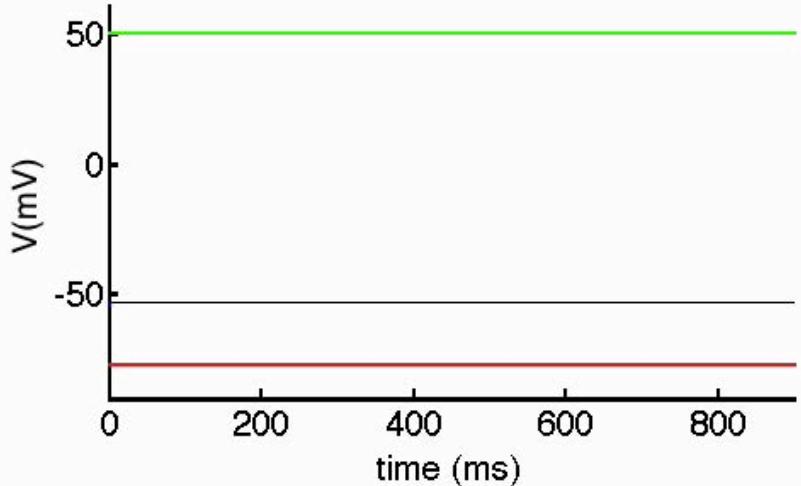
$$E_{Ca} = 12.5mV \ln\left(\frac{2}{.0001}\right) = 124mV$$

Why is this 12.5mV?



# Outline of HH model

Voltage and time-dependent ion channels are the 'knobs' that control membrane potential.



- $\text{Na}^+$  channels push the membrane potential toward +50mV.
- $\text{K}^+$  channels push the membrane potential toward -80mV.
- Together these channels give the neural machinery flexible control of voltage!
  - for example to generate an action potential

# Introduction to Neural Computation

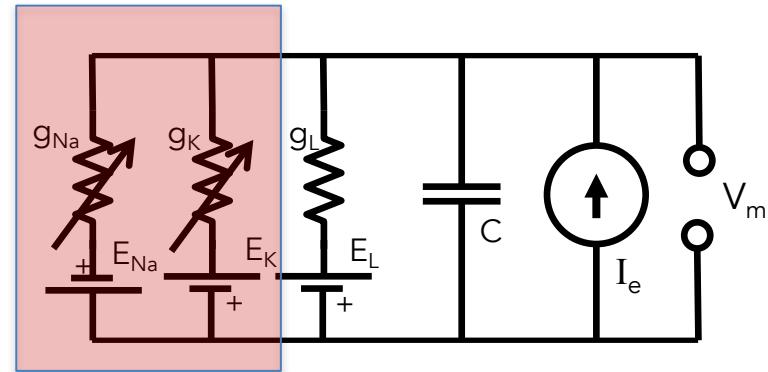
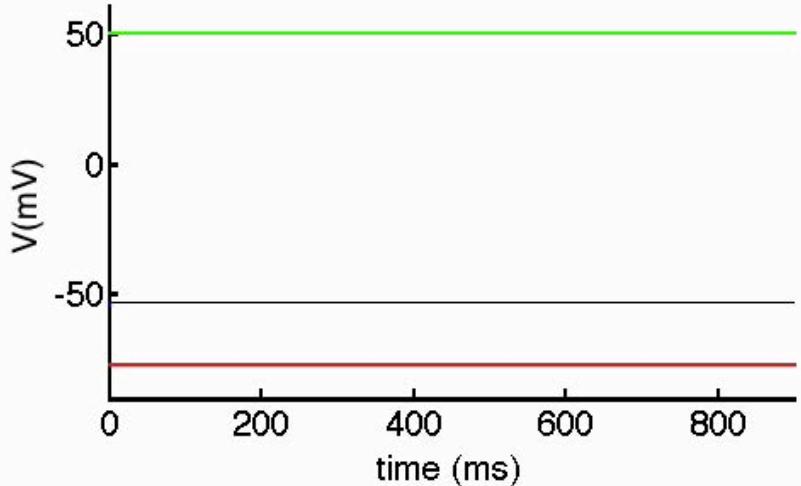
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Michale Fee  
MIT BCS 9.40

Video Module on Integrate and Fire  
Neuron

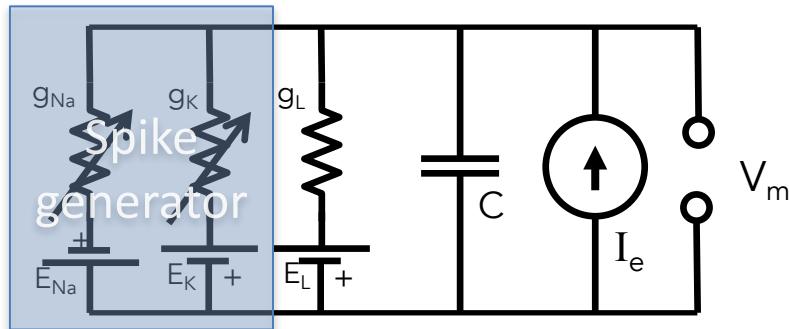
# Outline of HH model

Voltage and time-dependent ion channels are the 'knobs' that control membrane potential.

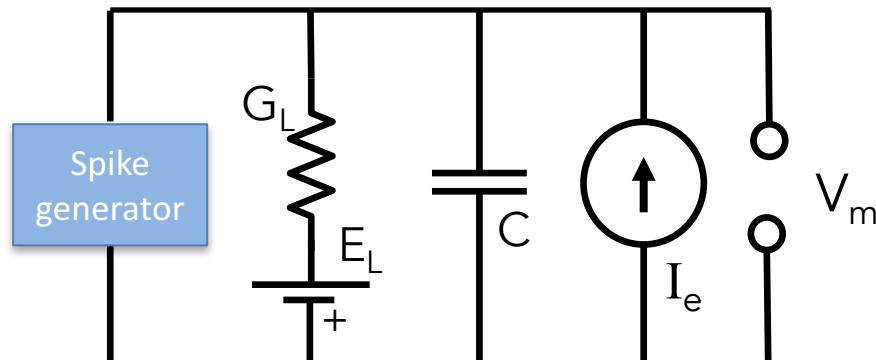


- $\text{Na}^+$  conductance pushes the membrane potential toward +55mV.
- $\text{K}^+$  conductance pushes the membrane potential toward -75mV.
- Together these conductances (and batteries) give the neuron flexible control of voltage!
  - for example to generate an action potential

# Integrate and Fire model of a neuron

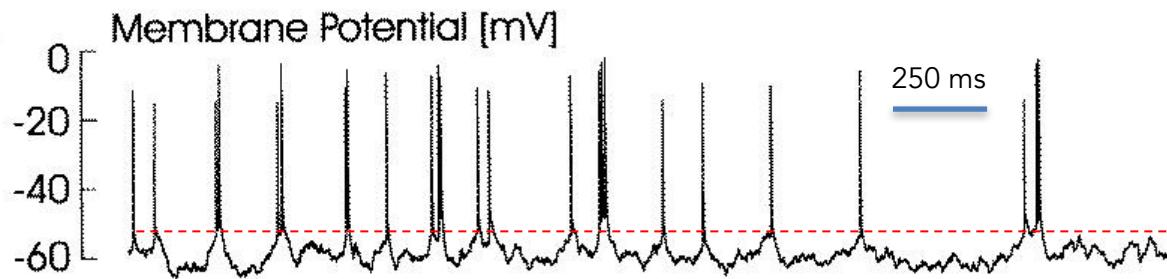


We are going to replace the fancy spike generating mechanism in a real neuron with a simplified 'spike generator'.



Louis Lapique, 1907  
Knight, 1972

# A simplified model of a neuron

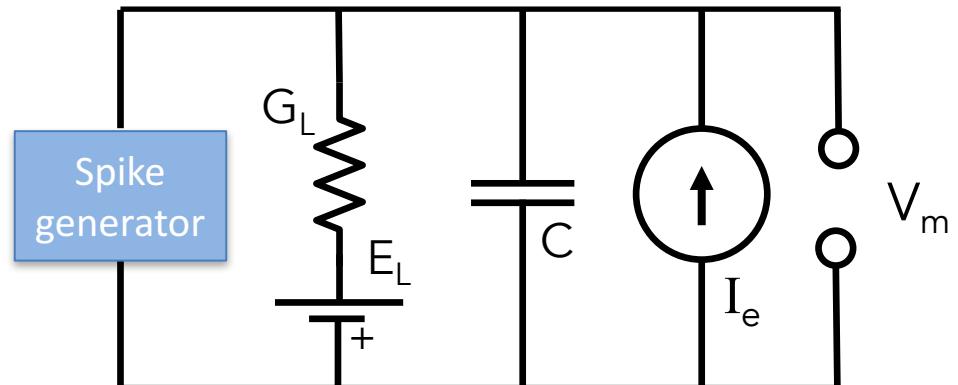


## *spikes as $\delta$ – functions*

- While APs (spikes) are important, they are not what neurons spend most of their time doing. Spikes are very fast (~1ms in duration).
- This is much shorter than the typical interval between spikes (~100ms). Most of the time, a neuron is 'integrating' its inputs. (Separation of timescales)
- All spikes are the same. (No information carried in the details of action potential waveforms.)
- Spikes tend to occur when the voltage in a neuron reaches a particular membrane potential, called the **spike threshold**.

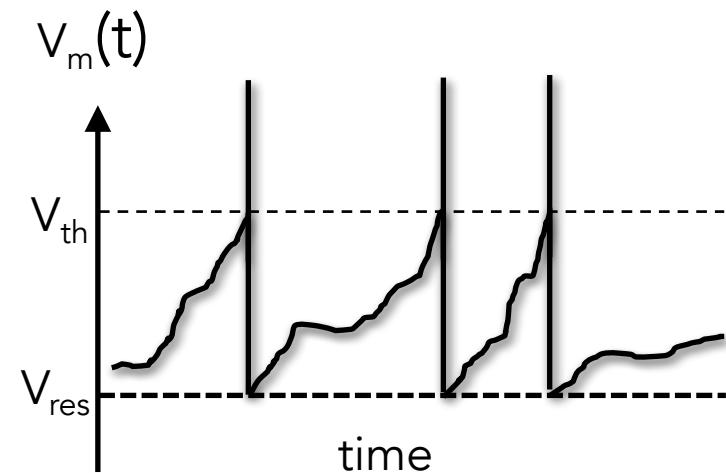
# Integrate and Fire model of a neuron

The spike generator is very simple. When the voltage reaches the threshold  $V_{th}$ , it resets the neuron to a hyperpolarized voltage  $V_{res}$ .



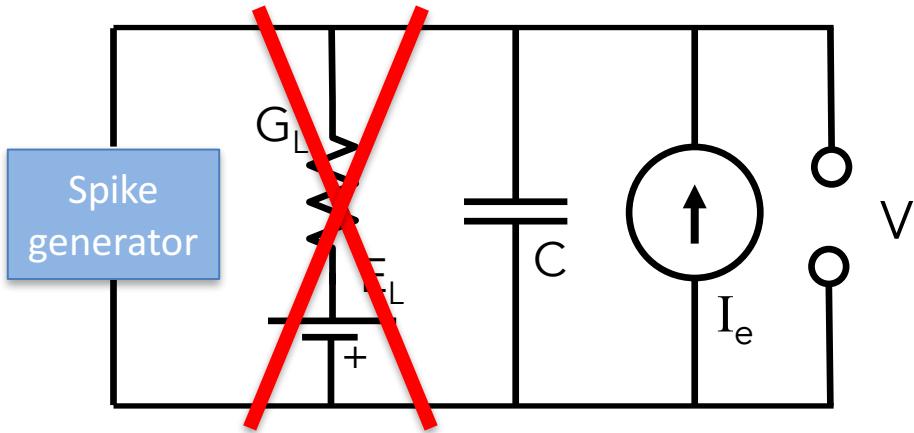
Louis Lapique, 1907

Removed due to copyright restrictions: Figure 2D1: Subthreshold membrane potential oscillations in RA neuron. Mooney, R. "[Synaptic basis for developmental plasticity in a birdsong nucleus](#)." Journal of Neuroscience 1 July 1992, 12 (7) 2464-2477.



# Integrate and Fire model of a neuron

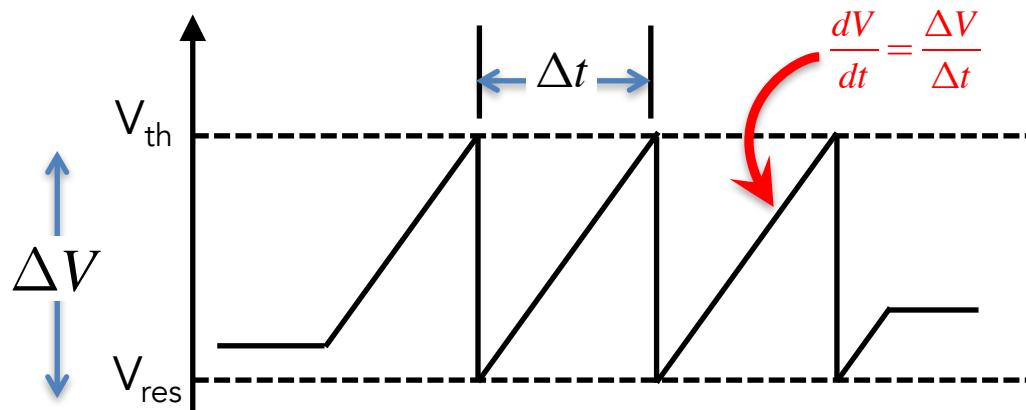
- Let's calculate the firing rate of our neuron



We'll first consider the case where there is no leak.

$$f.r. = \frac{1}{\Delta t}$$

$$\Delta V = V_{th} - V_{res}$$



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

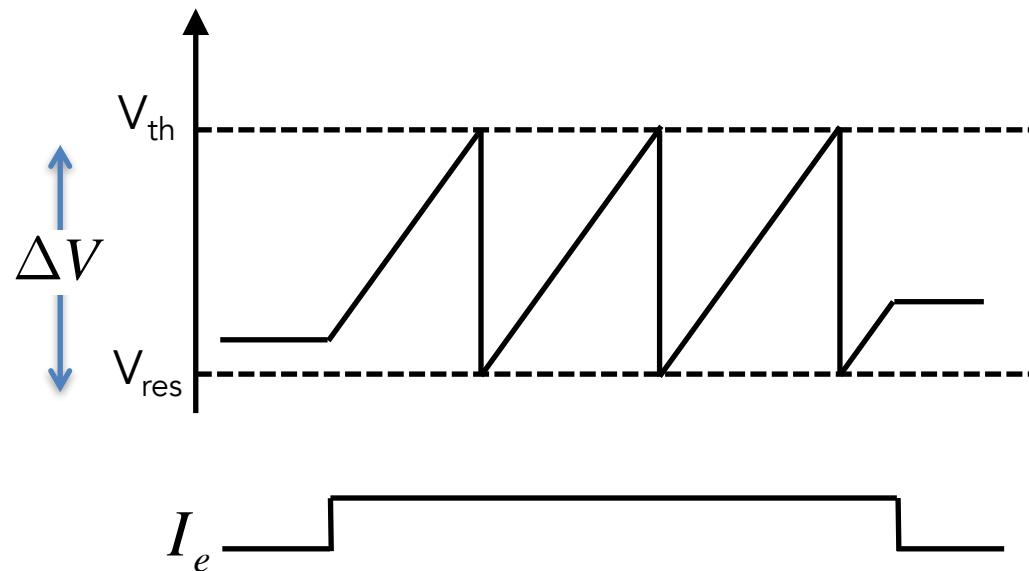
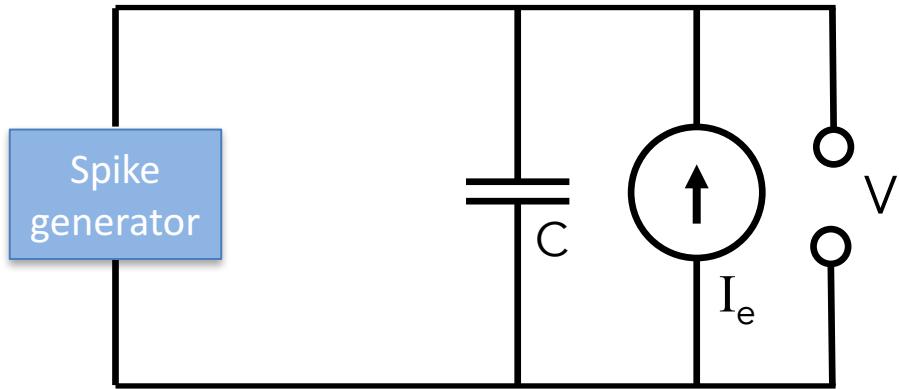
$$C \frac{\Delta V}{\Delta t} = I_e$$

$$f = \frac{1}{\Delta t} = \left( \frac{1}{C \Delta V} \right) I_e$$

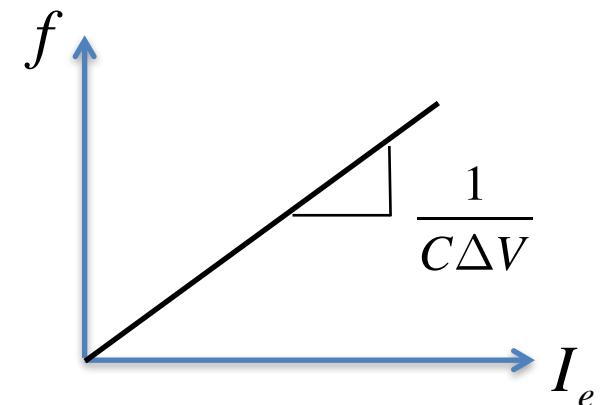


# Integrate and Fire model of a neuron

- Let's calculate the firing rate of our neuron



We'll first consider the case where there is no leak.

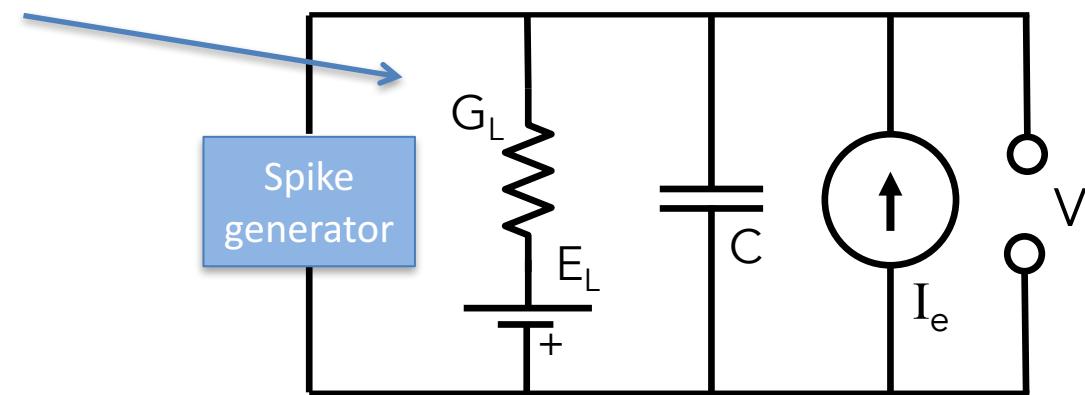


$$f = \left( \frac{1}{C\Delta V} \right) I_e$$

# Integrate and Fire model of a neuron

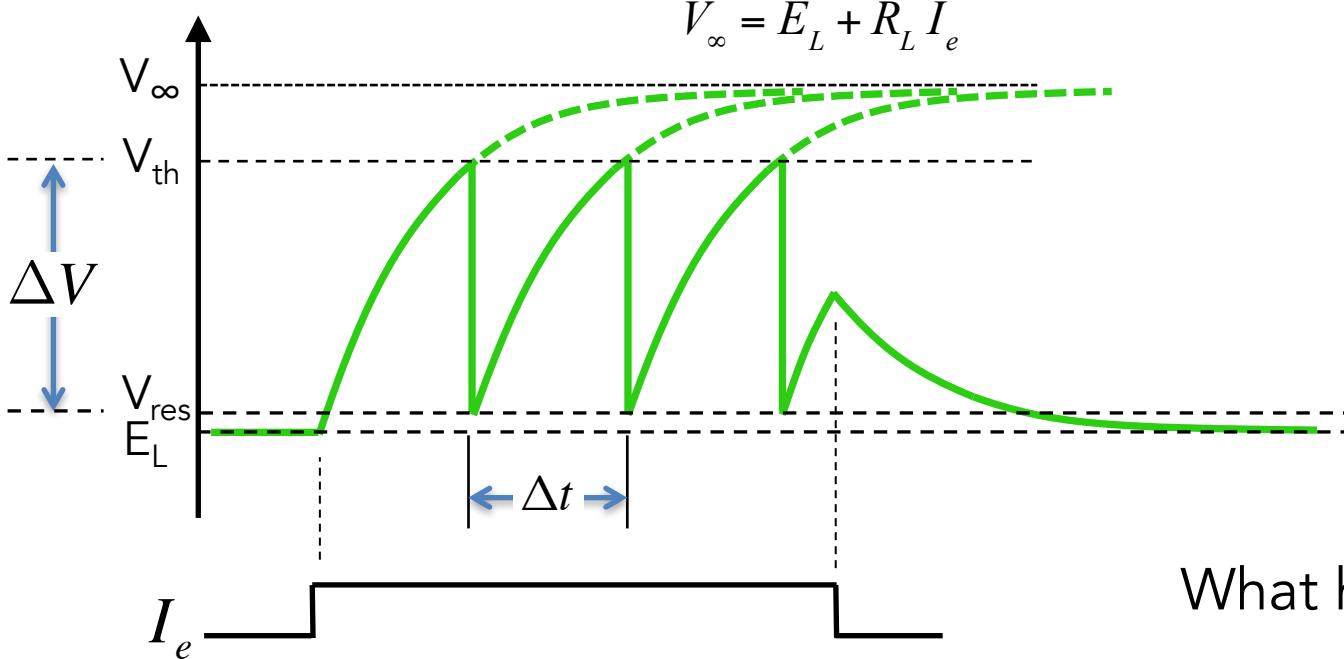
Now we'll put our leak conductance back in.

Think of this  $G_L$  like a small potassium conductance that is constantly on. It has no voltage dependence and no time dependence.  $E_L = -75\text{mV}$ .



$$V_\infty = E_L + R_L I_e$$

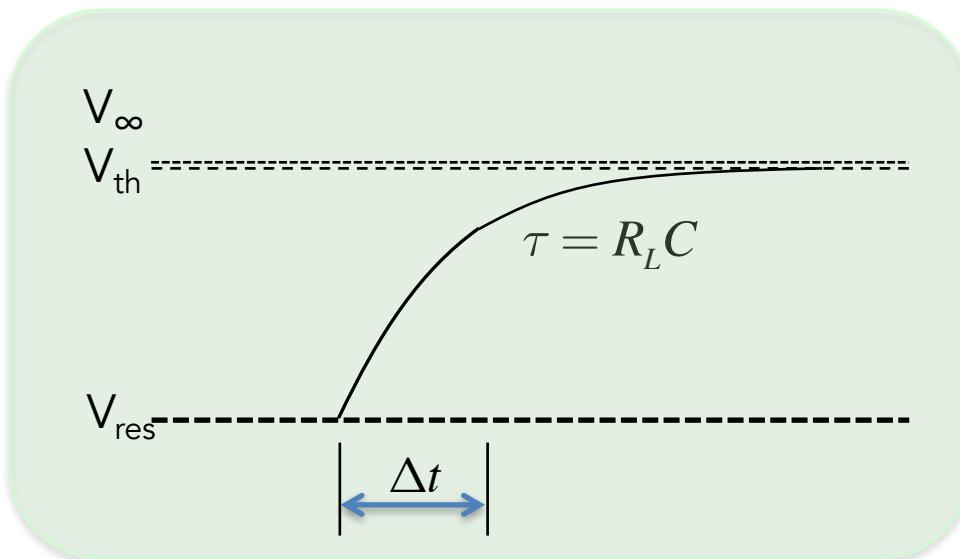
$$f.r. = \frac{1}{\Delta t}$$



What happens when  
 $V_\infty < V_{th}$  ?

# Integrate and fire with leak

What happens just at threshold?



Lets calculate the injected current required to reach threshold (rheobase).

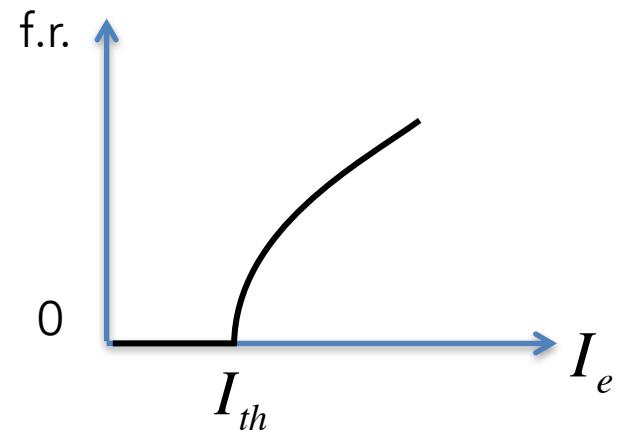
$$V_\infty = V_{th}$$

$$E_L + R_L I_e = V_{th}$$

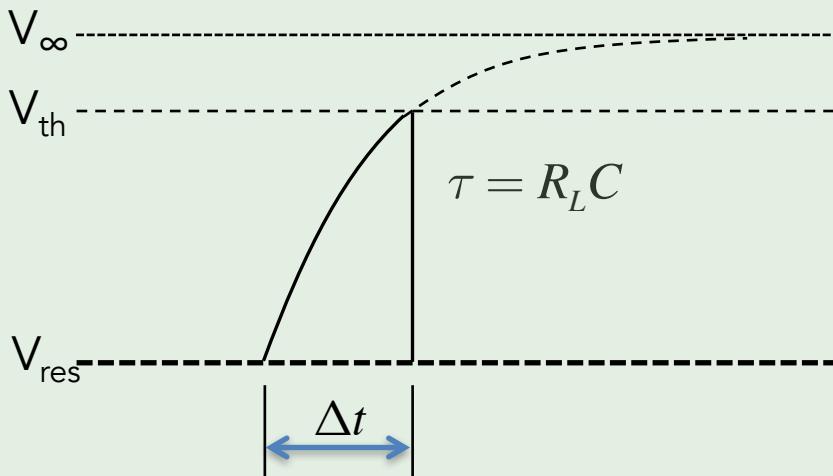
$$I_{th} = I_e = G_L(V_{th} - E_L)$$

The time to reach threshold ( $\Delta t$ ) is:

- very long
- very sensitive to injected current



# Integrate and fire with leak



$$e^{-\Delta t/\tau} = \frac{V_\infty - V_{th}}{V_\infty - V_{res}}$$

$$\Delta t = -\tau \ln \left( \frac{V_\infty - V_{th}}{V_\infty - V_{res}} \right)$$

$$V(t) - V_\infty = (V_0 - V_\infty) e^{-t/\tau}$$
$$V_{th} - V_\infty = (V_{res} - V_\infty) e^{-\Delta t/\tau}$$

$$f = \Delta t^{-1} = \left[ \tau \ln \left( \frac{V_\infty - V_{res}}{V_\infty - V_{th}} \right) \right]^{-1}$$

# Integrate and fire

At high input currents, the solution has a simple approximation

$$V_\infty \gg V_{th}, V_{res}$$

$$f = \left[ \tau \ln \left( \frac{V_\infty - V_{res}}{V_\infty - V_{th}} \right) \right]^{-1}$$

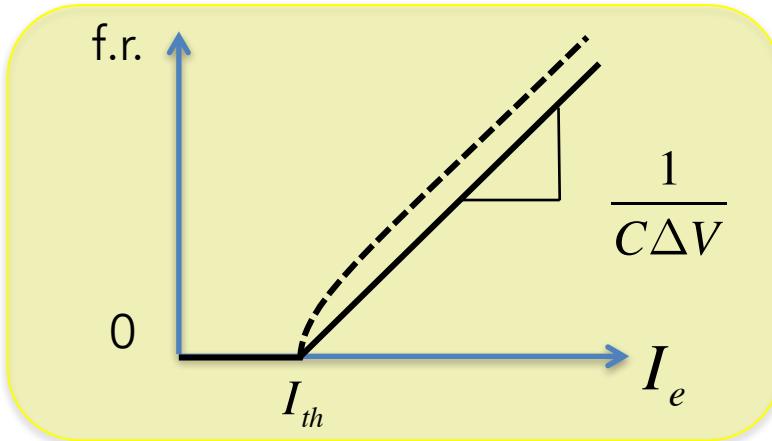
$$\ln(1 + \alpha) \sim \alpha$$

$$f = \frac{1}{C\Delta V} (I_e - I_{th})$$

$$I_{th} = G_L (V_{th} - E_L)$$

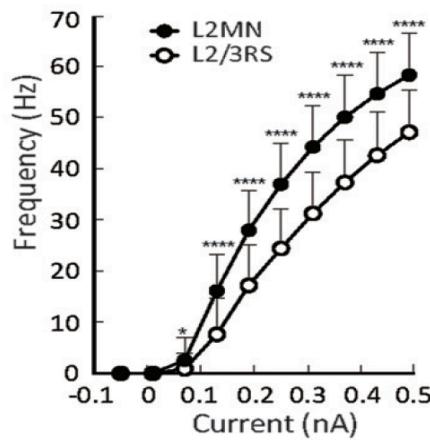
# Integrate and fire

This equation is linear in injected current  $I_e$ , just like the case of no leak!



$$f = \frac{1}{C\Delta V} (I_e - I_{th})$$

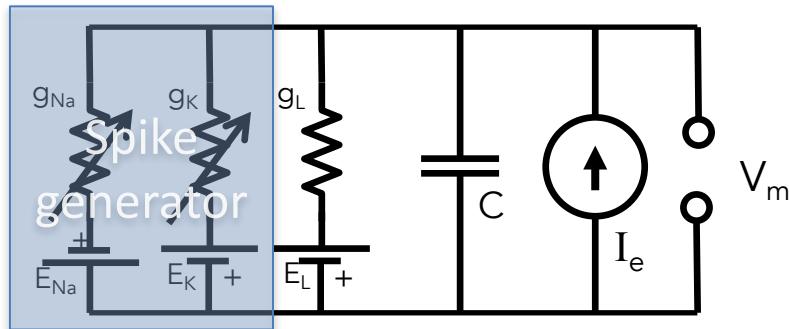
The F-I curve of many neurons look approximately like this!



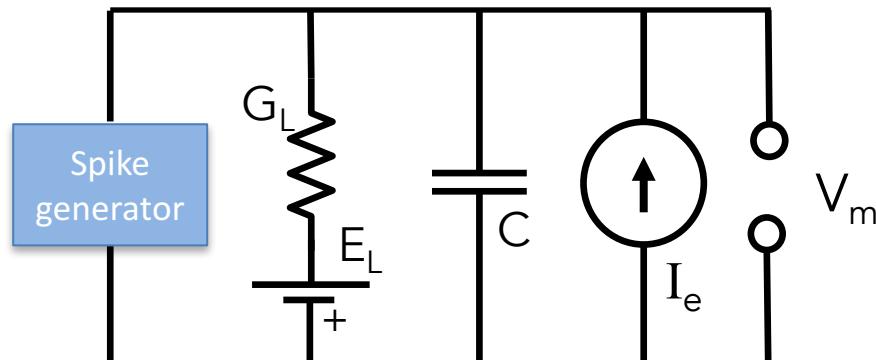
Luo et al 2017

Figure courtesy of Luo, et al. License: CC BY. Source: "[Comparison of the Upper Marginal Neurons of Cortical Layer 2 with Layer 2/3 Pyramidal Neurons in Mouse Temporal Cortex](#)." *Front. Neuroanat.*, 21 December 2017.

# Integrate and Fire model of a neuron



We have replaced the fancy spike generating mechanism in a real neuron with a simplified 'spike generator'.



Louis Lapicque, 1907  
Knight, 1972

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<https://ocw.mit.edu/>

9.40 Introduction to Neural Computation  
Spring 2018

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# Introduction to Neural Computation

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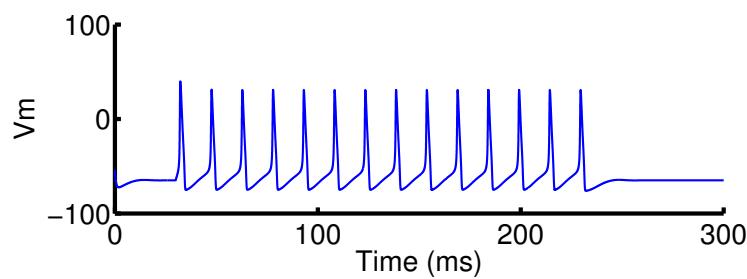
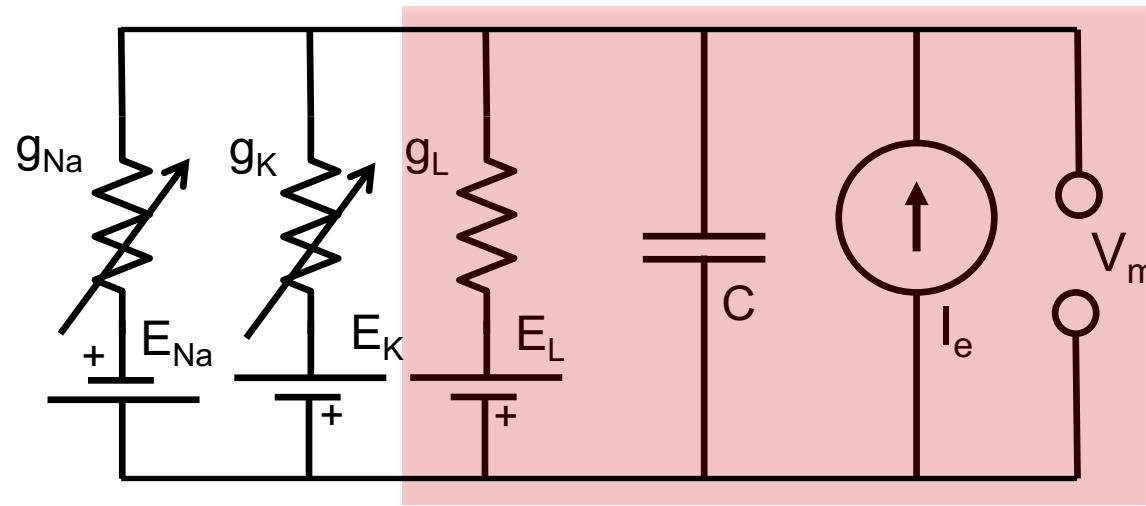
Michale Fee

MIT BCS 9.40 — 2018

Lecture 2 – RC Neuron Model

# A mathematical model of a neuron

- Equivalent circuit model



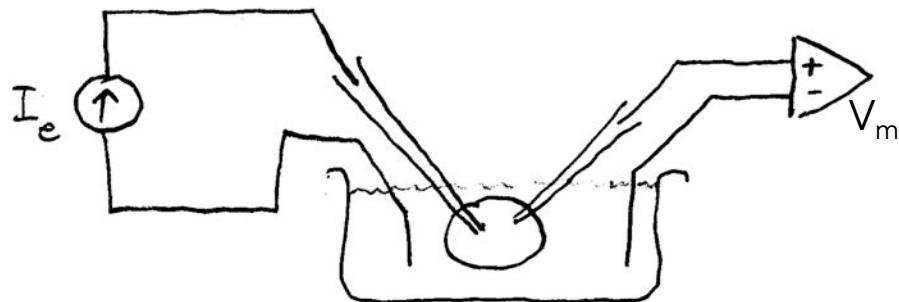
Alan Hodgkin  
Andrew Huxley, 1952



# Learning objectives for Lecture 2

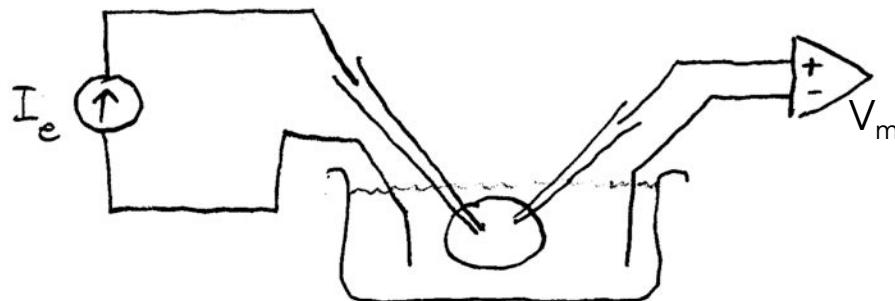
- To understand how neurons respond to injected currents
- To understand how membrane capacitance and resistance allows neurons to integrate or smooth their inputs over time (RC model)
- To understand how to derive the differential equations for the RC model
- To be able to sketch the response of an RC neuron to different current inputs
- To understand where the ‘batteries’ of a neuron come from

# Why understand how neurons respond to injected current?



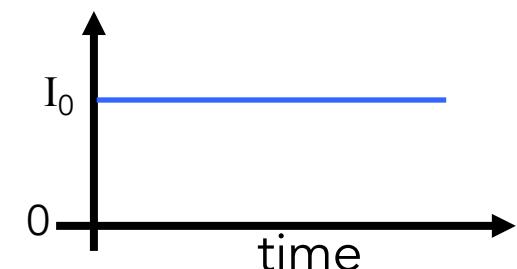
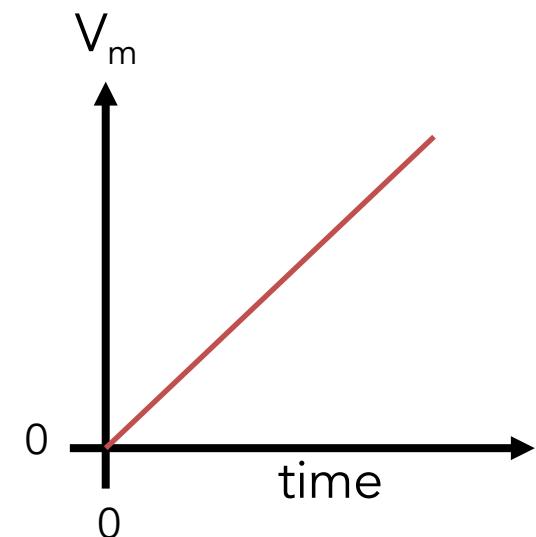
- First, because nearly every aspect of computation and signaling in a neuron is controlled by voltage. This control is almost entirely mediated by the voltage sensitivity of ion channels.
- In the brain, neurons have current injected into them:
  - Through synapses from other neurons
  - Or as a result of sensory stimuli

# Why understand how neurons respond to injected current?



Neurons can perform analog numerical integration over time

$$\text{Voltage}(t) = \int_0^t \text{Current}(\tau) d\tau$$



# A neuron is a capacitor

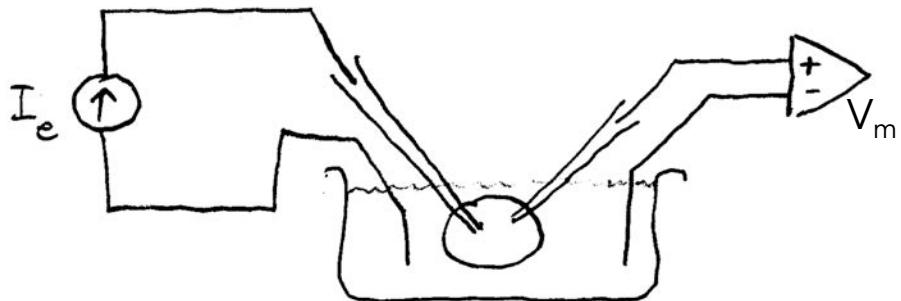
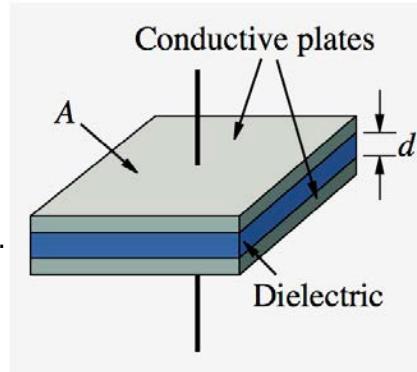
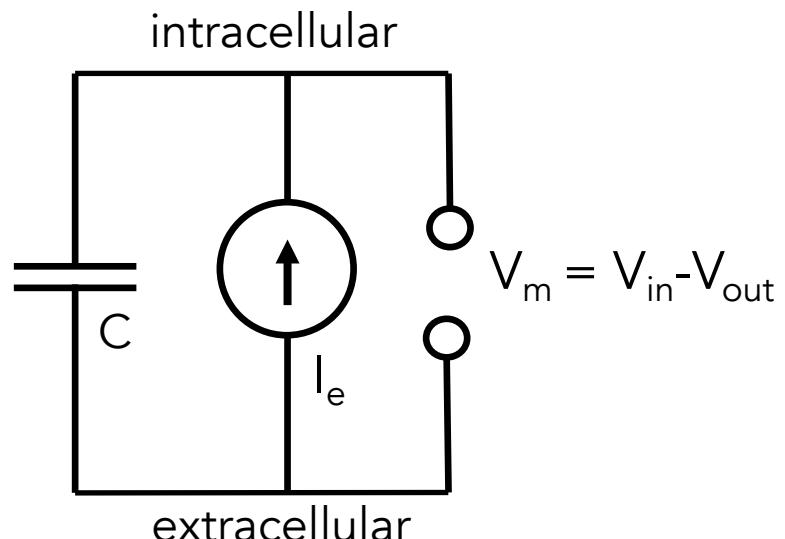


Image of a parallel plate capacitor is in the public domain. Source: [Wikimedia](#).

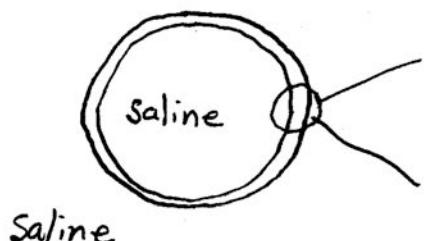


## Equivalent circuit



## Why is this a capacitor?

A capacitor is two conductors separated by an insulator

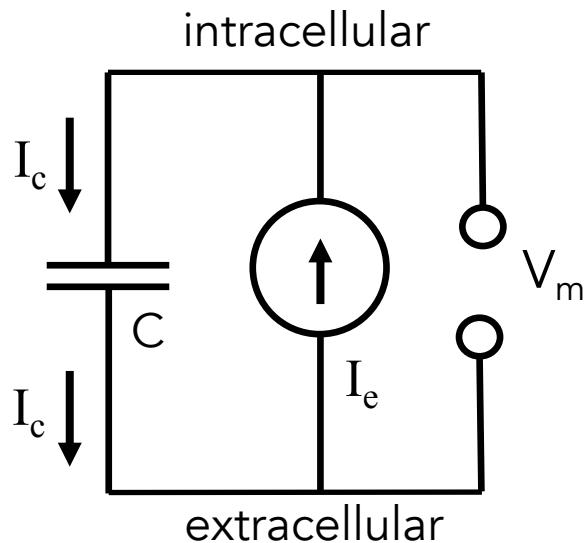


○  
○  
○  
○  
○  
 $\leftarrow 23\text{\AA} \rightarrow$   
 $\text{\AA} = 10^{-8}\text{ cm}$

Phospholipid bilayer:  
—polar head  
—non-polar tail

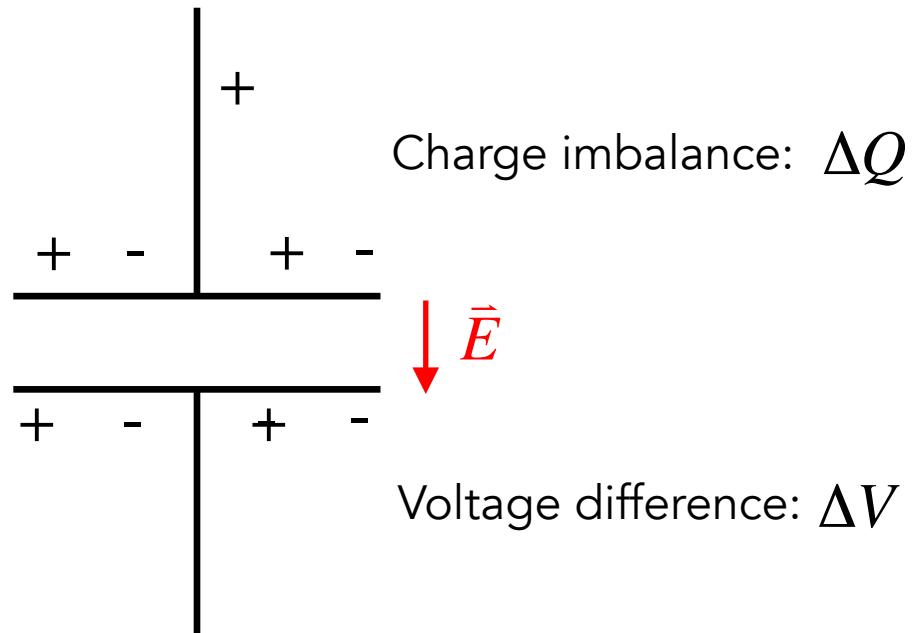
What happens when we inject current into our neuron?

# A neuron is a capacitor



As positive charges build up on the inside of the membrane, they repel positive charges away from the outside of the membrane...

This looks like a current flowing through the capacitor!



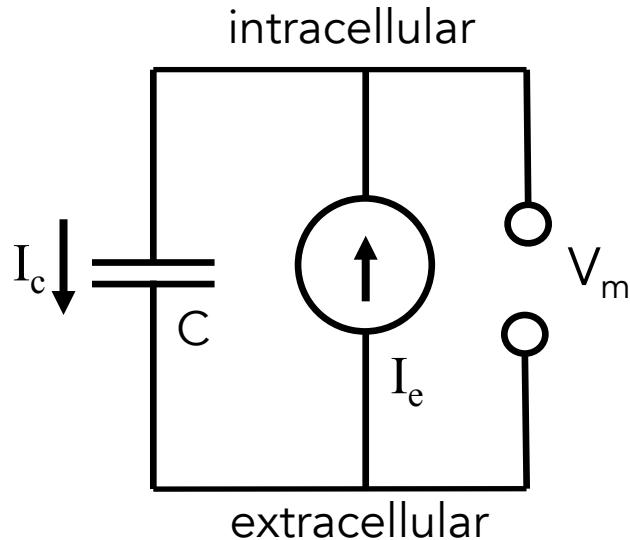
$$\Delta Q = C \cdot \Delta V$$

Q: charge (Coulombs, C =  $6 \times 10^{18}$  charges)

C: capacitance (Farads, F)

V: voltage difference across capacitor (Volts, V)

# A neuron is a capacitor



$$\Delta Q = C \cdot \Delta V$$

Definition of capacitive current

$$I_c(t) = \frac{dQ}{dt} = C \frac{dV_m}{dt}$$

But, Kirchoff's current law tells us that the sum of all currents into a node is zero

$$-I_c + I_e = 0$$

Thus, we can write the differential equation that describes the change in voltage of our neural capacitor with injected current

$$I_e(t) = C \frac{dV_m}{dt}$$

$I_e$  has units of Amperes, which is Coulombs per second

# capacitor

## Response of a ~~neuron~~ to injected current

$$I_e(t) = C \frac{dV_m}{dt}$$

We can integrate this differential equation over time, starting with initial voltage  $V_0$  at time zero.

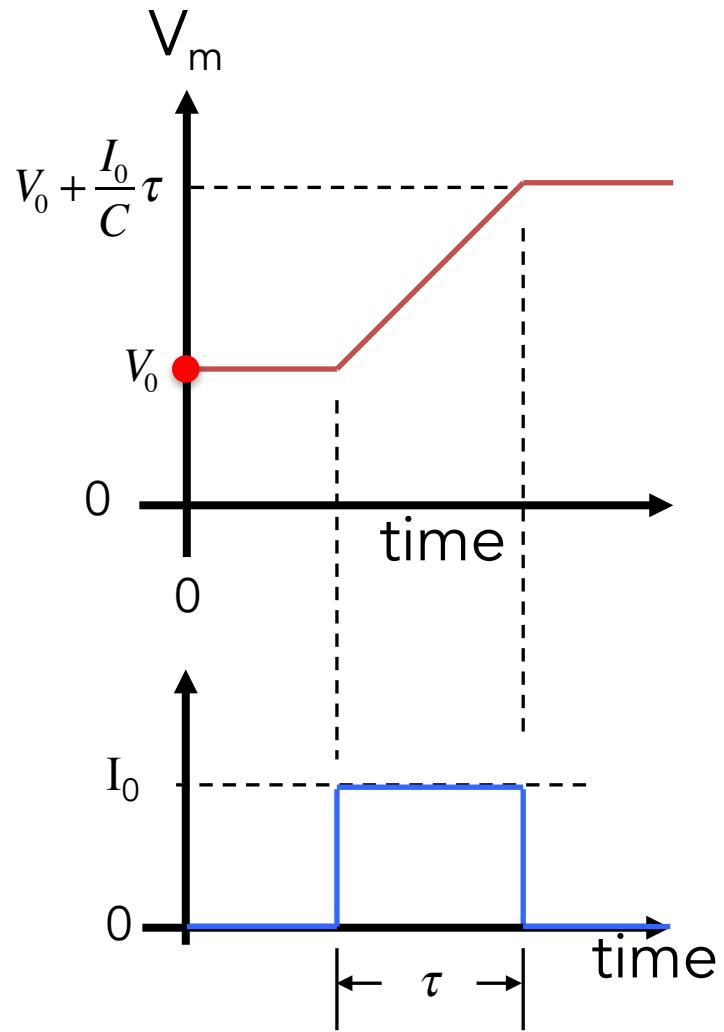
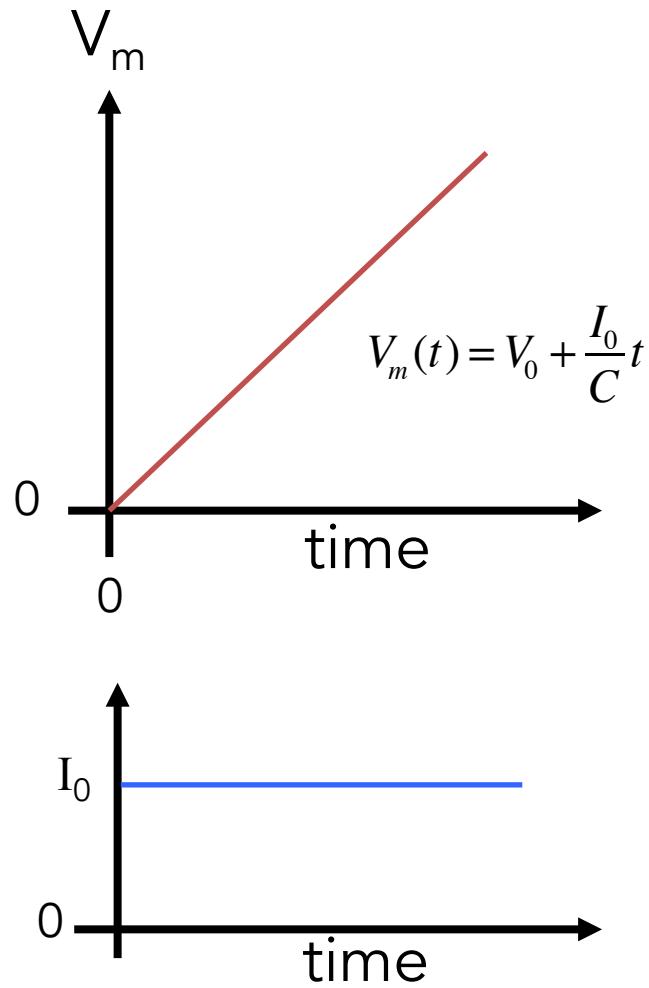
$$V_m(t) = V_0 + \frac{1}{C} \int_0^t I_e(\tau) d\tau$$
$$\int_0^t I_e(\tau) d\tau = \Delta Q$$


Think about the integral as adding up all the current from time 0 to time  $t$

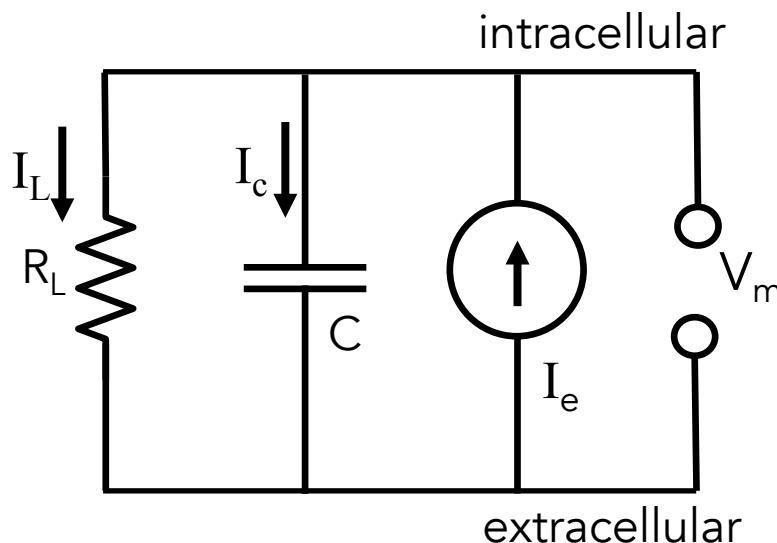
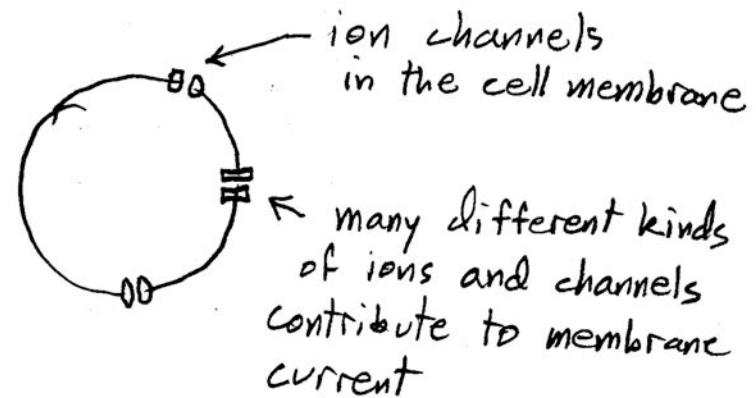
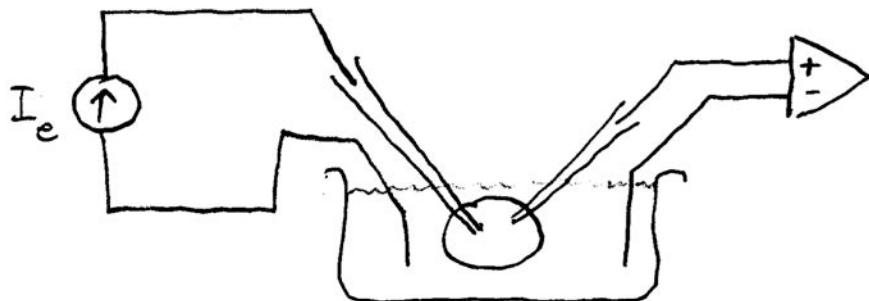
Thus, the total change in voltage is just given by

$$\Delta V = \frac{1}{C} \Delta Q$$

# Some examples



# A neuron is a **leaky** capacitor



$I_c$  = membrane capacitive current

$I_L$  = membrane ionic current

# Our equation for our model becomes:

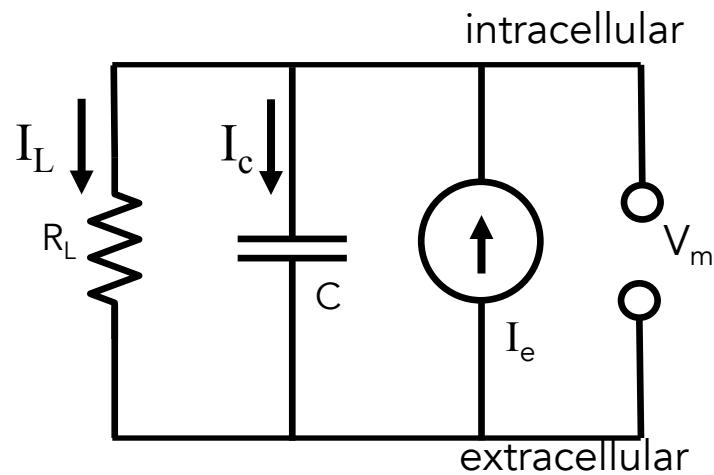
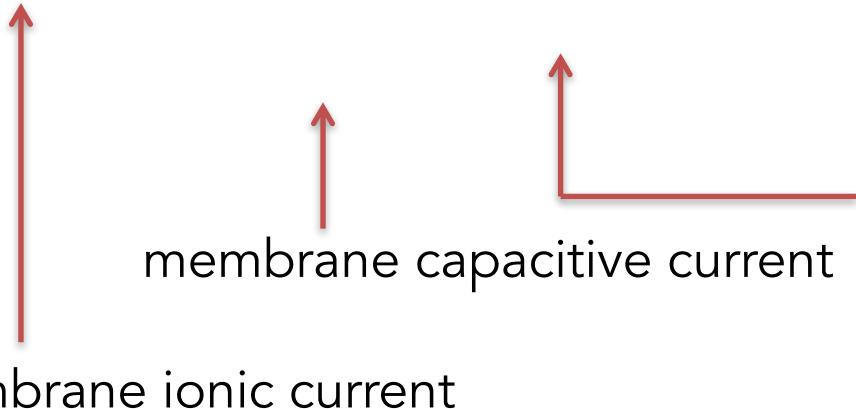
$$I_L + I_c = I_e$$

$$I_L + C \frac{dV}{dt} = I_e$$

membrane ionic current

membrane capacitive current

electrode current



outward current  
‘+’ leaving the cell  $\Rightarrow$  positive

inward current  
‘+’ entering the cell  $\Rightarrow$  negative

# Simple case: a leak

- We are going to begin by considering the simplest case of a membrane current – a simple leak (like a hole in the membrane)
- In this case, the current through the ion channel can be modeled using Ohm's Law

$$I_L = \frac{V_m}{R_L}$$

Plugging this into our equation above, we get

$$I_L + I_c = I_e$$

$$\frac{V_m}{R_L} + C \frac{dV_m}{dt} = I_e$$

Multiplying by  $R_L$ , we get:

$$V_m + R_L C \frac{dV_m}{dt} = R_L I_e$$

$$V_m + R_L C \frac{dV_m}{dt} = R_L I_e$$

What is the steady-state solution to this equation?

$$\text{Set } dV_m/dt = 0$$

We find that:

$$V_m \Rightarrow V_\infty = R_L I_e$$

Thus, we can rewrite our equation as follows

$$V_m + \tau \frac{dV_m}{dt} = V_\infty \quad \text{where } \tau = R_L C$$

# An aside about first-order linear differential equations

We can rewrite our equation in the following form:

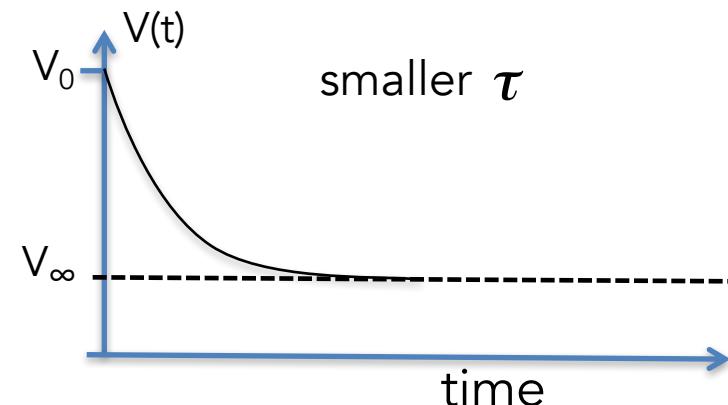
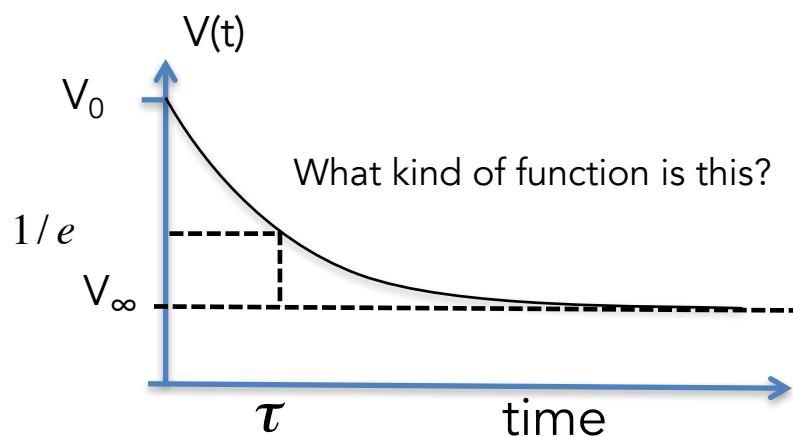
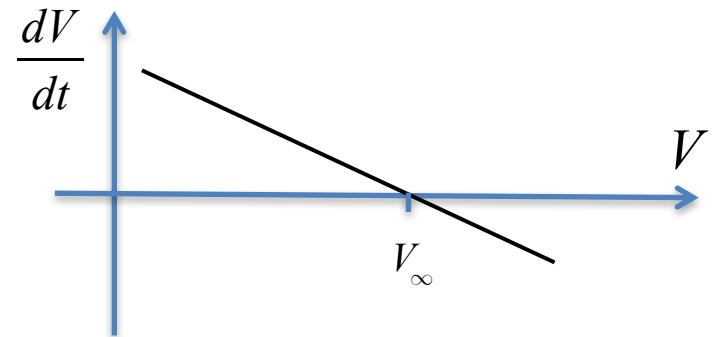
$$\frac{dV}{dt} = -\frac{1}{\tau}(V - V_\infty)$$

Thus, the voltage always approaches the value  $V_\infty$

And it approaches at a rate proportional to how far  $V$  is from  $V_\infty$

We see that the derivative is

- negative if  $V > V_\infty$
- positive if  $V < V_\infty$



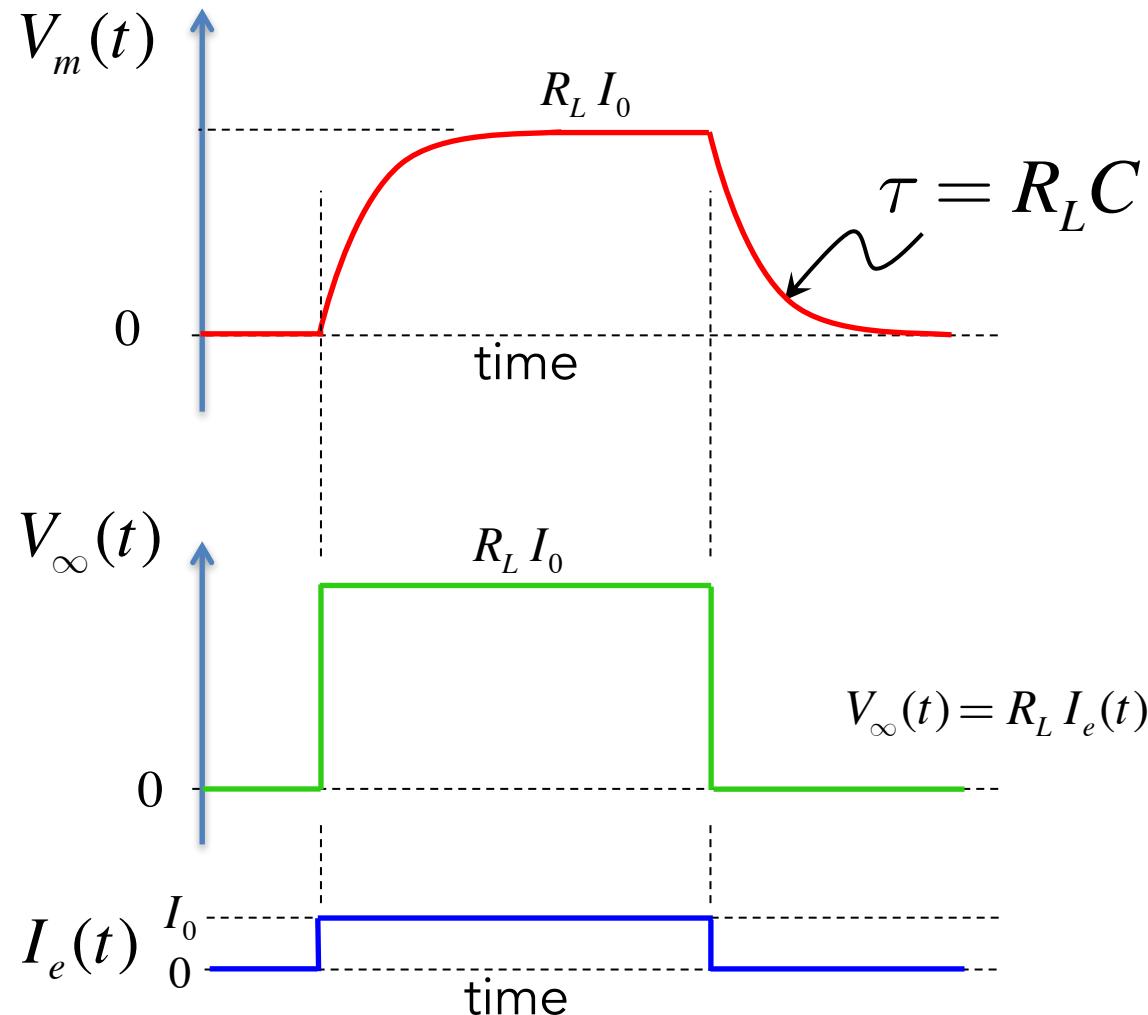
Thus, under the condition that  $I_e$  is constant (and thus  $V_\infty$ ) is constant:

$$V(t) - V_\infty = (V_0 - V_\infty)e^{-t/\tau}$$

While this solution applies only in the case of constant  $V_\infty$ , it can be very useful

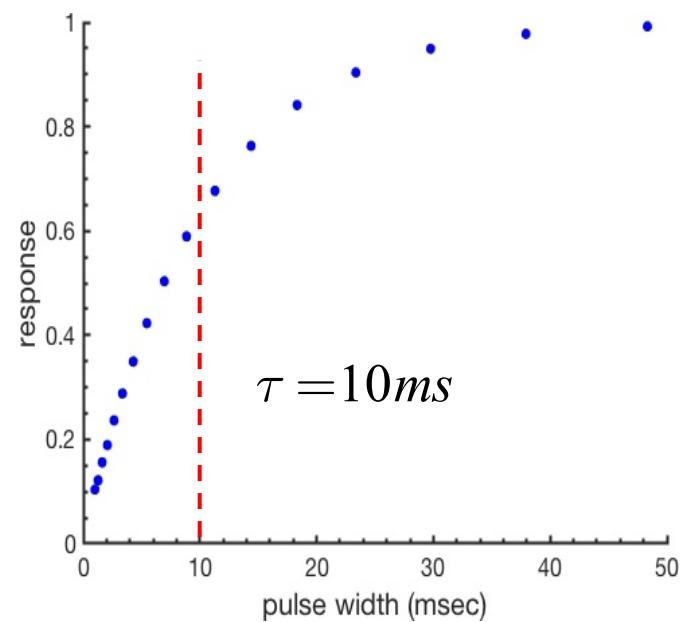
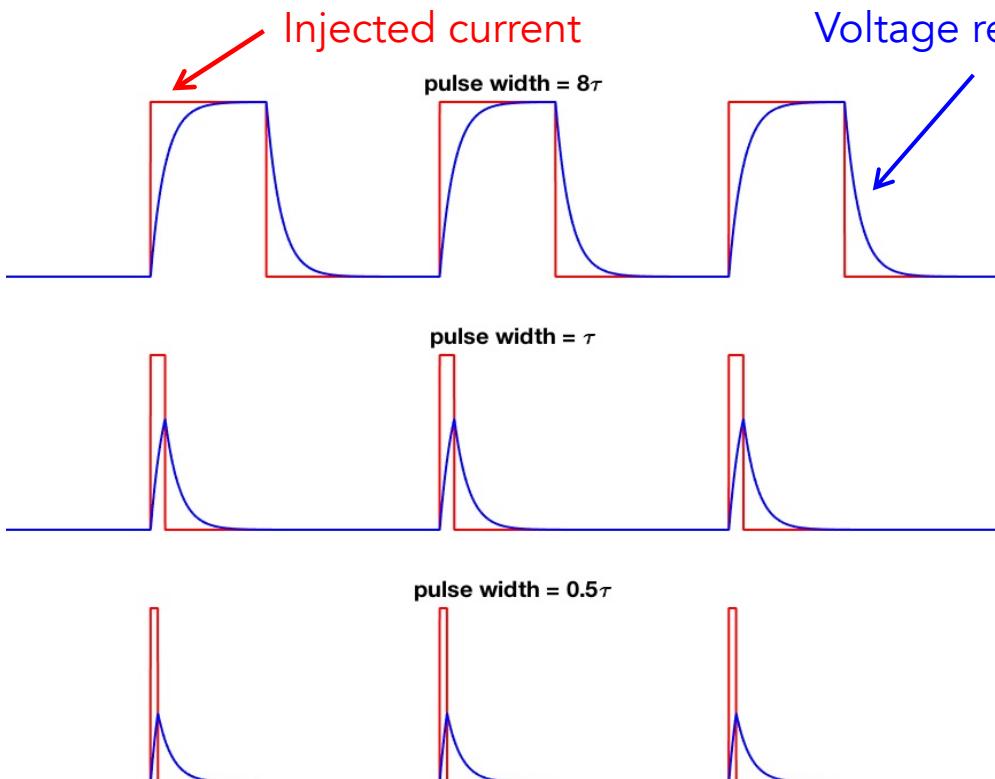
# Response to current injection

Let's see what happens when we inject current into our model neuron with a leak conductance.



# An RC neuron acts like a filter

Responding well to inputs slower than  $\tau$ , but not to inputs faster than  $\tau$



The first-order linear differential equation is fundamental to understanding many processes in physics, chemistry, biology and neural computation

$$V + \tau \frac{dV}{dt} = V_\infty$$

$$V(t) = V_\infty + (V_0 - V_\infty)e^{-t/\tau}$$

Even more complex systems involve differential equations that are not (much) more difficult to understand and solve.

# Origin of 10 millisecond time scale

$$R \approx 10^8 \Omega = 100 M\Omega$$

$$C \approx 10^{-10} F$$

$$\tau = RC \sim 10ms$$

# A closer look at membrane resistance

We have described the relation between voltage and current using Ohms Law ( $V=I_L R_L$ )

$$I_L = R_L^{-1} V$$

We can rewrite Ohm's Law in terms of a quantity called  
'conductance.'

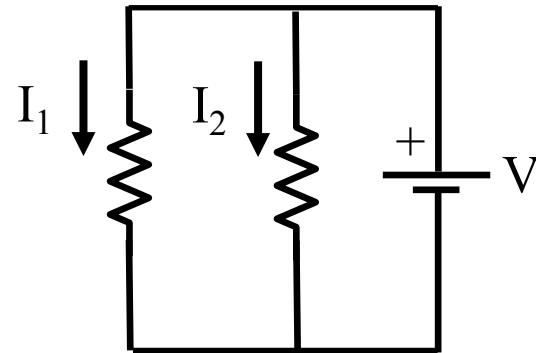
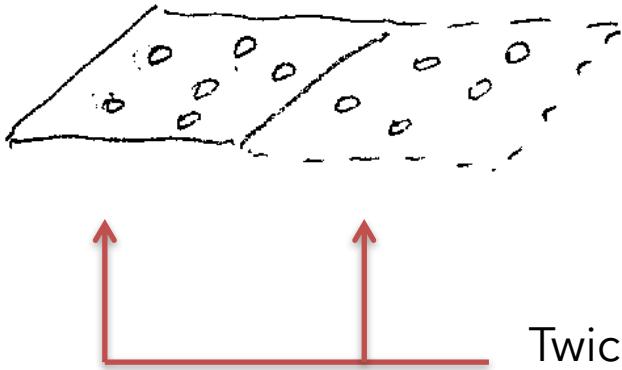
$$G_L = R_L^{-1}$$

$$I_L = G_L V$$

$R_L$  has units of Ohms ( $\Omega$ )

$G_L$  has units of Ohms $^{-1}$  or Siemens (S)

# Conductances in parallel add



$$I_{tot} = I_1 + I_2$$

$$I_{tot} = G_1 V + G_2 V$$

$$I_{tot} = (G_1 + G_2)V$$

$$G_{tot} = G_1 + G_2$$

Twice the area, twice the holes,  
twice the conductance, twice the  
current at a given voltage

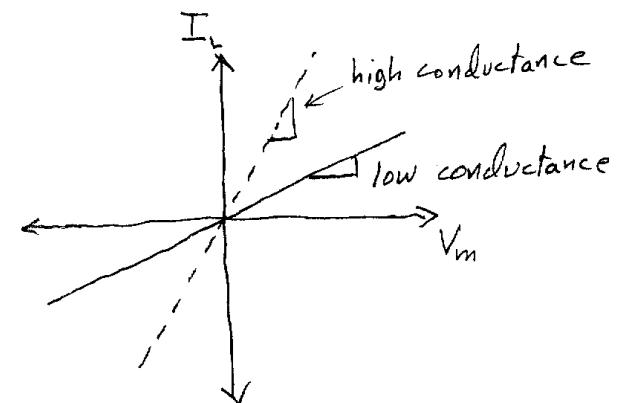
$$I_L = G_L V_m$$

$$= A g_L V_m$$

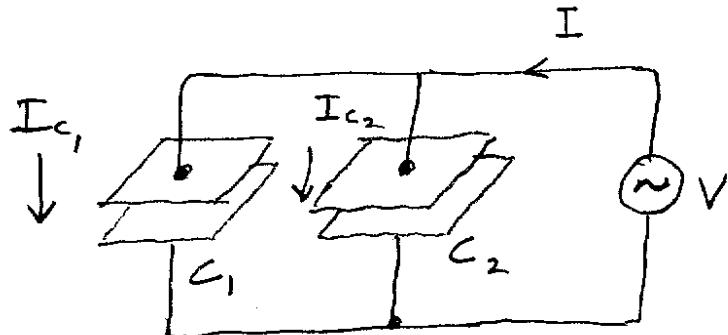
↑  
↑

Specific leak conductance ( $\text{mS/mm}^2$ )

Membrane area ( $\text{mm}^2$ )



# A closer look at membrane capacitance



$$I_{C_{tot}} = I_{C1} + I_{C2}$$

$$I_{C_{tot}} = C_1 \frac{dV}{dt} + C_2 \frac{dV}{dt}$$

$$I_{C_{tot}} = (C_1 + C_2) \frac{dV}{dt}$$

$$C_{tot} = C_1 + C_2$$

Capacitances in parallel add!

Thus, the capacitance of a cell depends linearly on surface area

$$C = c_m A \quad A = 4\pi r^2$$



specific capacitance ( $10 \text{ nF/mm}^2$ )



membrane area

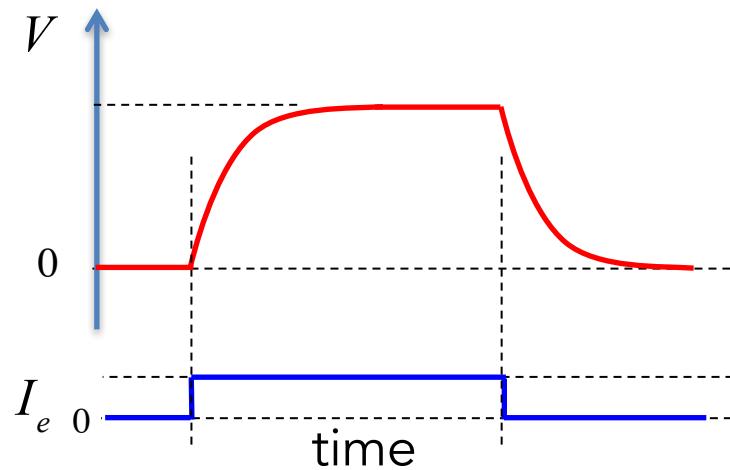
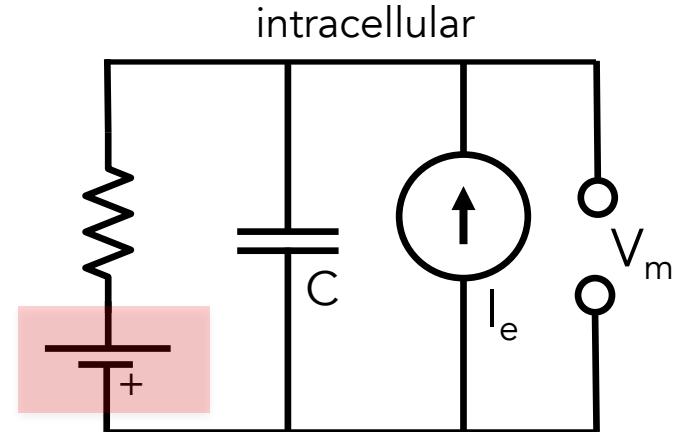
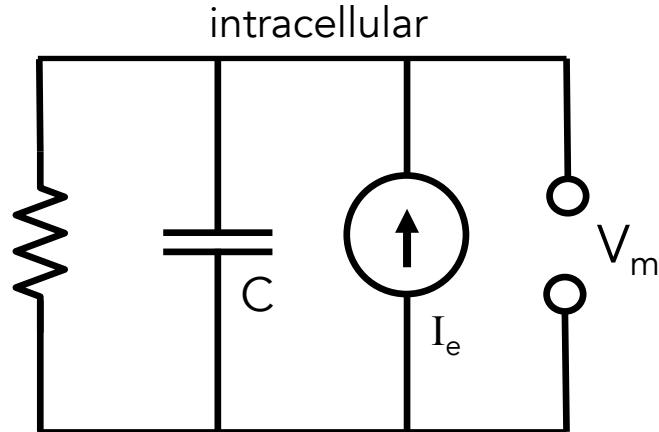
# Membrane time constant

Neuron time constant:

$$\begin{aligned}\tau_m &= R_L C \\ &= \frac{C}{G_L} = \frac{c_m A}{g_L A} = \frac{c_m}{g_L}\end{aligned}$$

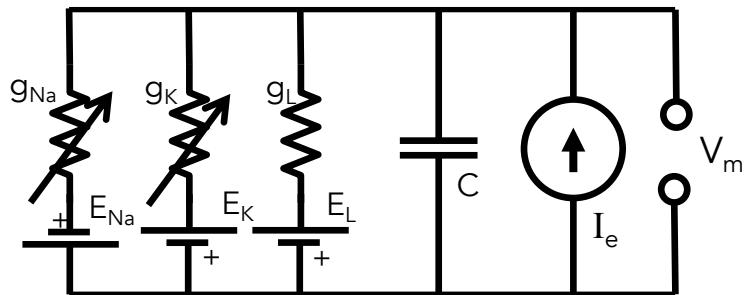
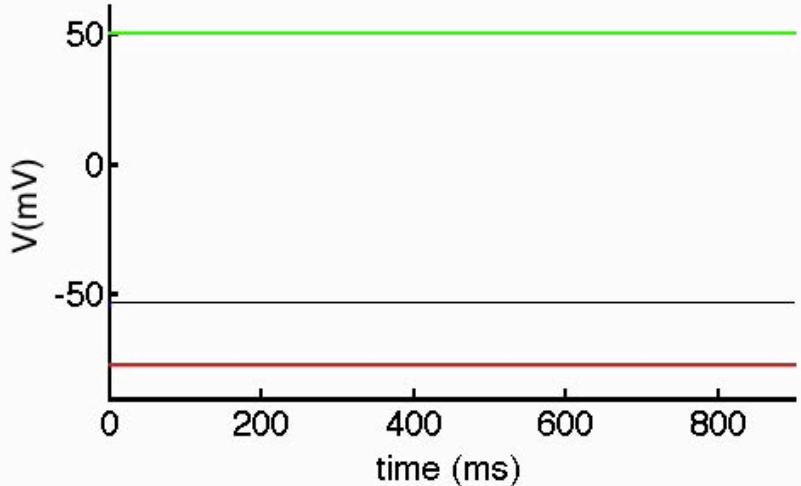
Thus, the time constant of a neuron is a property of the membrane, not dependent on cell geometry (size, shape, etc!).

# Let's add a battery to our neuron!



# Outline of HH model

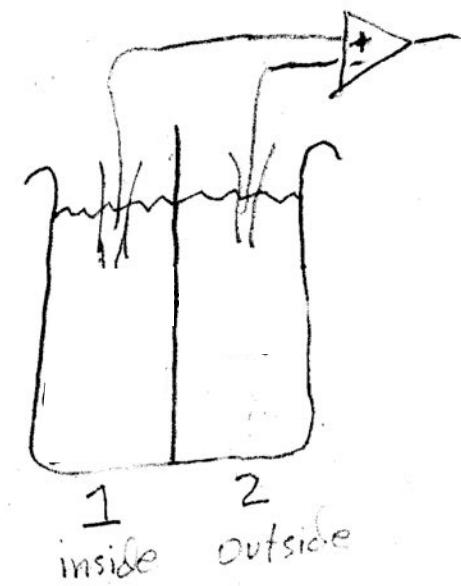
Voltage and time-dependent ion channels are the 'knobs' that control membrane potential.



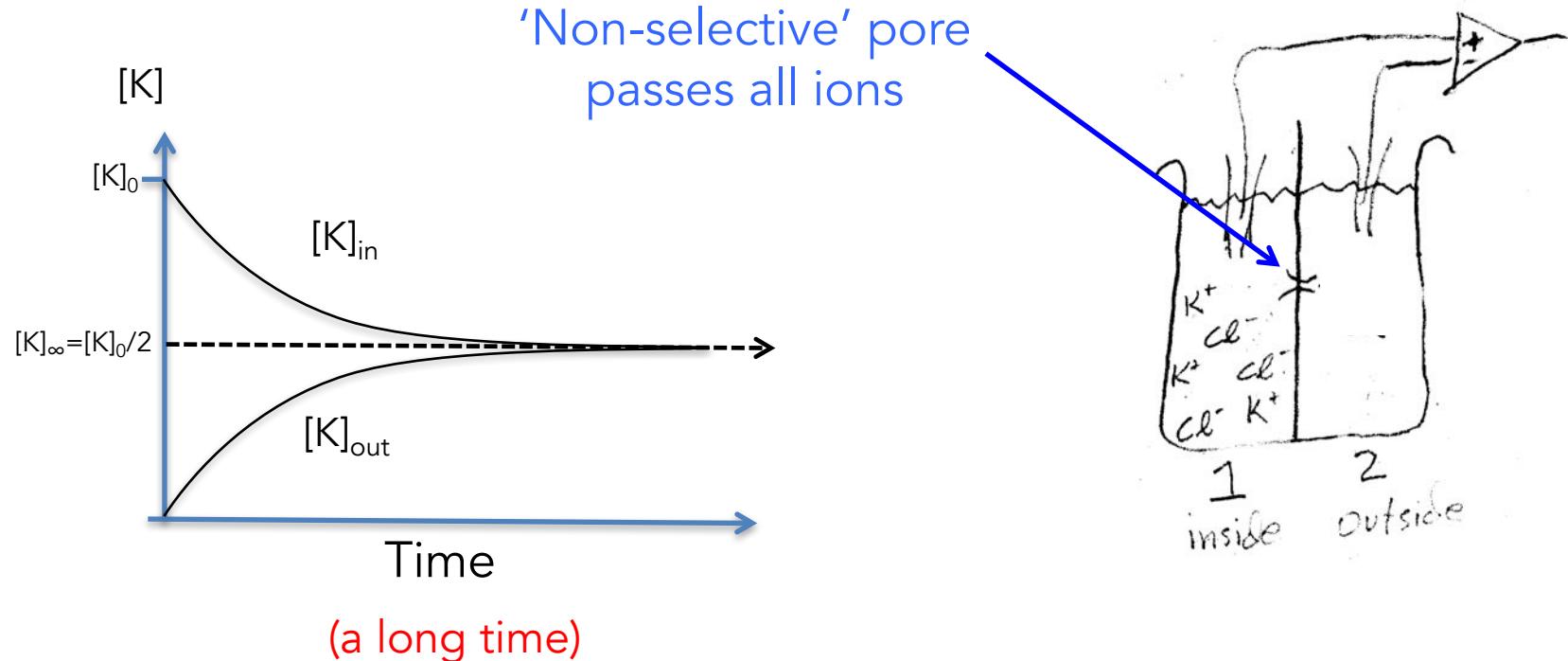
- Some ion channels push the membrane potential positive.
- Other ion channels push the membrane potential negative.
- Together these channels give the neural machinery flexible control of voltage!

# Where do the batteries of a neuron come from?

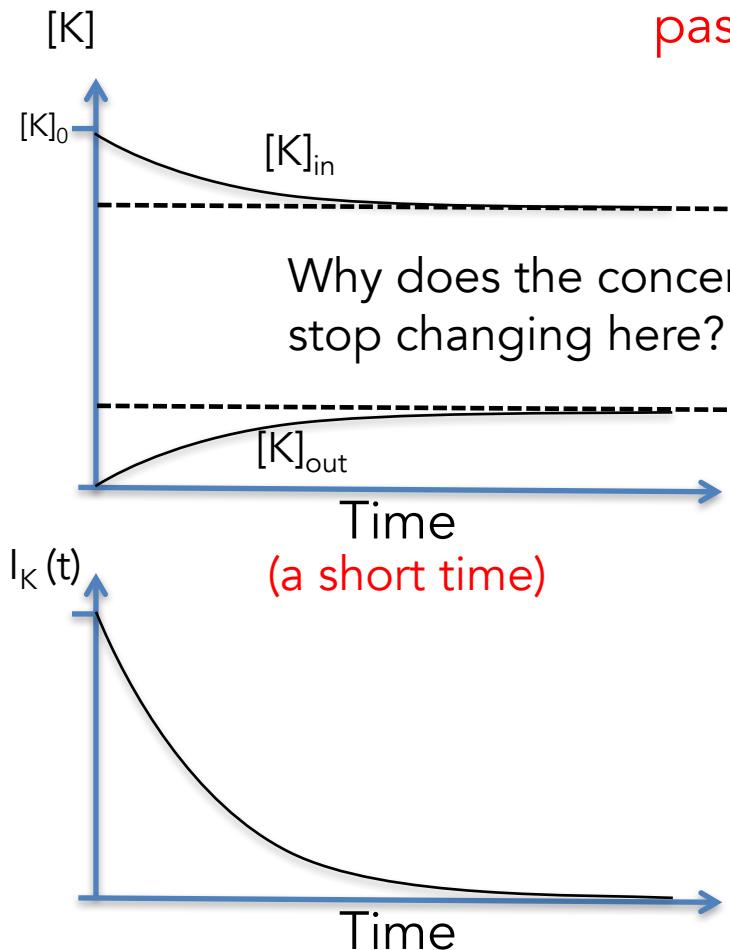
- 1) Ion concentration gradients
- 2) Ion-selective permeability of ion channels



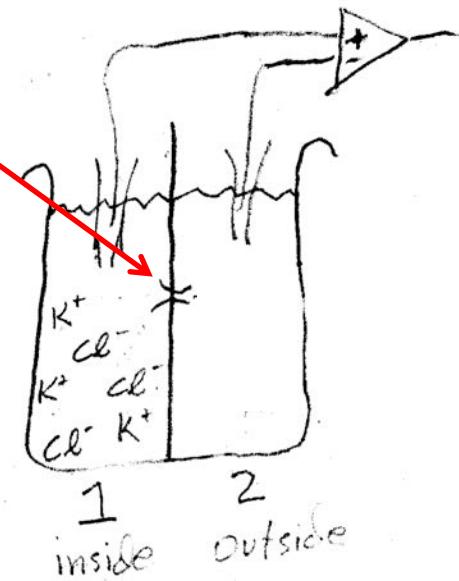
# Neurons have batteries



# Neurons have batteries

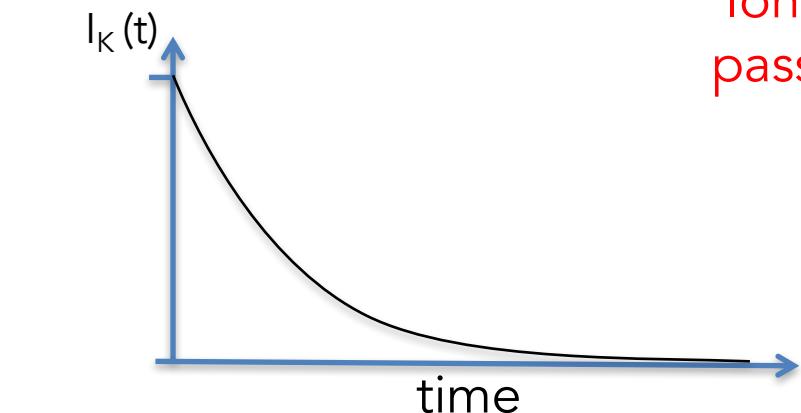


'Ion-selective' pore  
passes only  $K^+$  ions

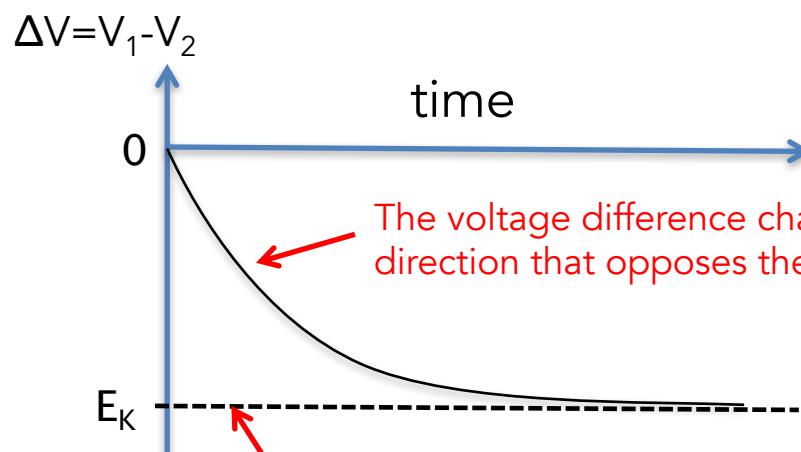


Why do the ions stop flowing  
from side 1 to side 2?

# Neurons have batteries

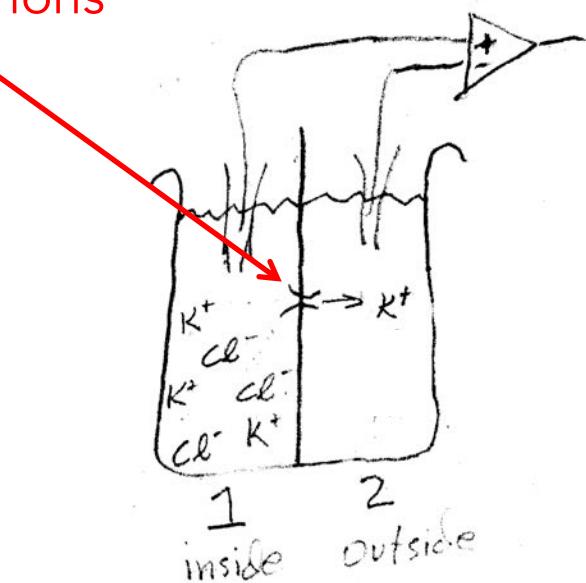


'Ion-selective' pore  
passes only  $K^+$  ions



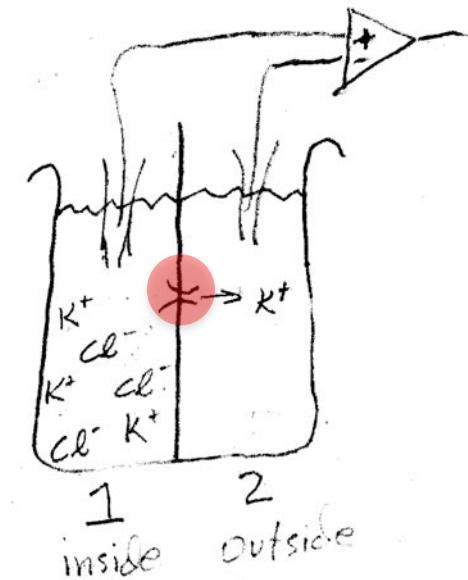
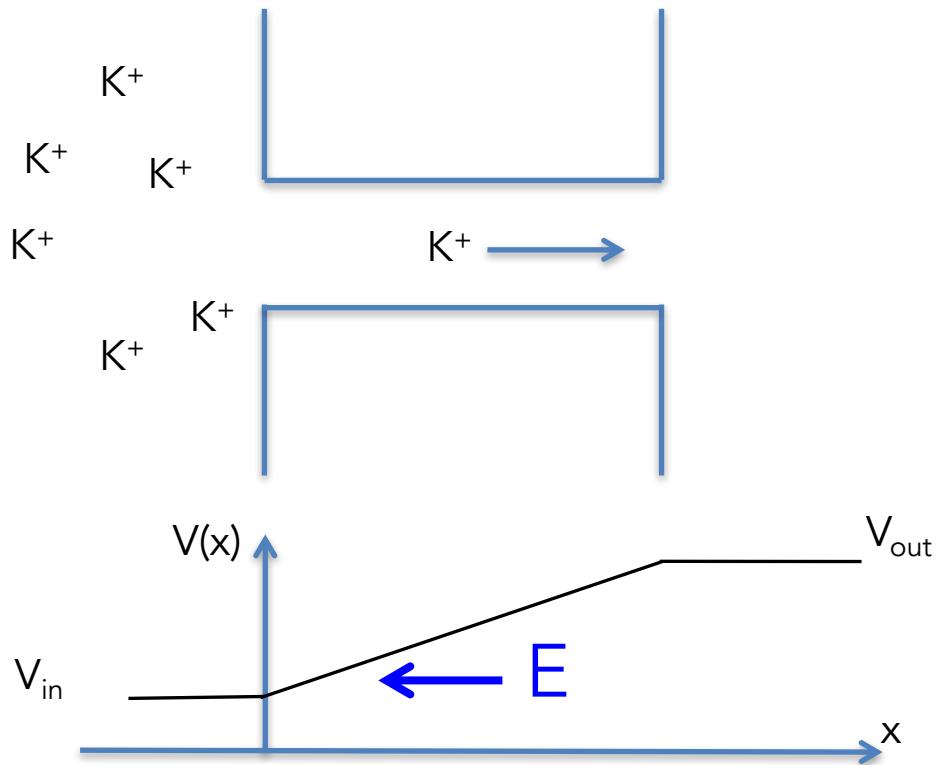
The voltage difference changes in a direction that opposes the flow of ions.

It reaches an 'equilibrium potential' at a value that gives zero net flow of ionic current.



This voltage difference is a battery for our model neuron!!

# Neurons have batteries



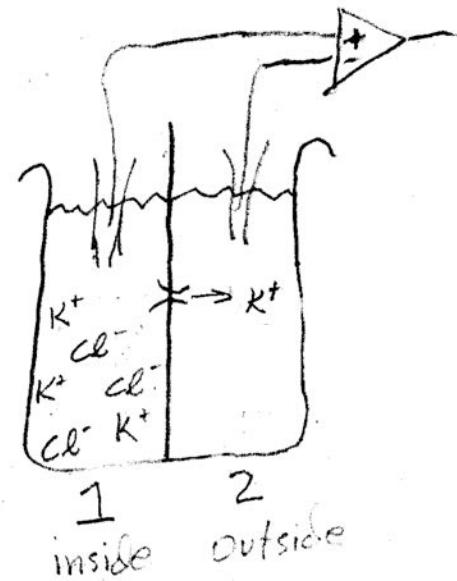
There will be some electric field strength such that the 'drift' will exactly balance the diffusion produced by the concentration gradient...

Nernst Potential

# Neurons have batteries

- Where do the 'batteries' of a neuron come from?
  - 1) Ion concentration gradients
  - 2) Ion-selective pores (channels)
- How big is the battery (how many volts?)

This is determined by a balance between diffusion down a concentration gradient balanced by 'drift' in the opposing electric field.



# Electrodiffusion and the Nernst Potential

One can use Ohm's law and Fick's first law to derive the Nernst potential

- At this voltage, the drift current in the electric field exactly balances current due to diffusion

$$I_{Tot} = I_{Drift} + I_{Diffusion} = 0$$

Ohm's Law

$$I_{Drift} = \frac{Aq^2\varphi(x)D}{kT} \frac{\Delta V}{L}$$

Fick's First Law

$$I_{Diffusion} = -AqD \frac{\partial \varphi}{\partial x}$$

$$\Delta V = \frac{kT}{q} \ln \left( \frac{\varphi_{out}}{\varphi_{in}} \right)$$

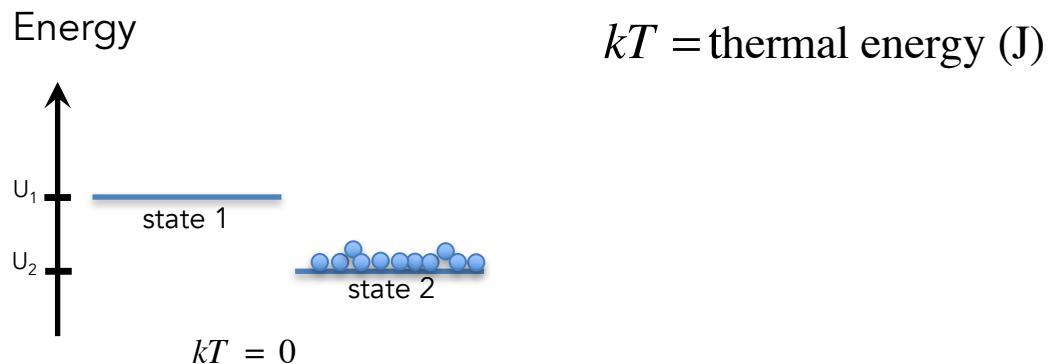
at equilibrium

# Derive Nernst potential using the Boltzmann equation

The Boltzmann equation describes the ratio of probabilities of a particle being in any two states, at thermal equilibrium:

$$\frac{P_{state1}}{P_{state2}} = e^{-\left(\frac{U_1-U_2}{kT}\right)}$$

$k$  = Boltzmann constant (J/K)  
 $T$  = temperature (K) = 273 + T<sub>C</sub>



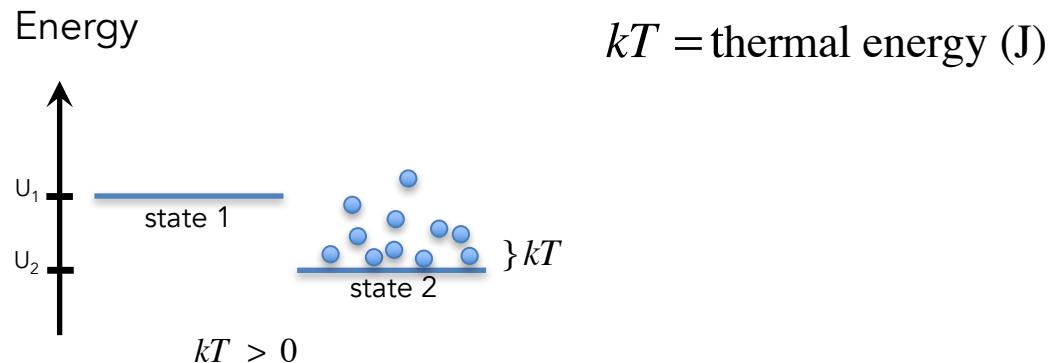
$$\frac{P_{state1}}{P_{state2}} = 0$$

# Derive Nernst potential using the Boltzmann equation

The Boltzmann equation describes the ratio of probabilities of a particle being in any two states, at thermal equilibrium:

$$\frac{P_{state1}}{P_{state2}} = e^{-\left(\frac{U_1-U_2}{kT}\right)}$$

$k$  = Boltzmann constant (J/K)  
 $T$  = temperature (K)

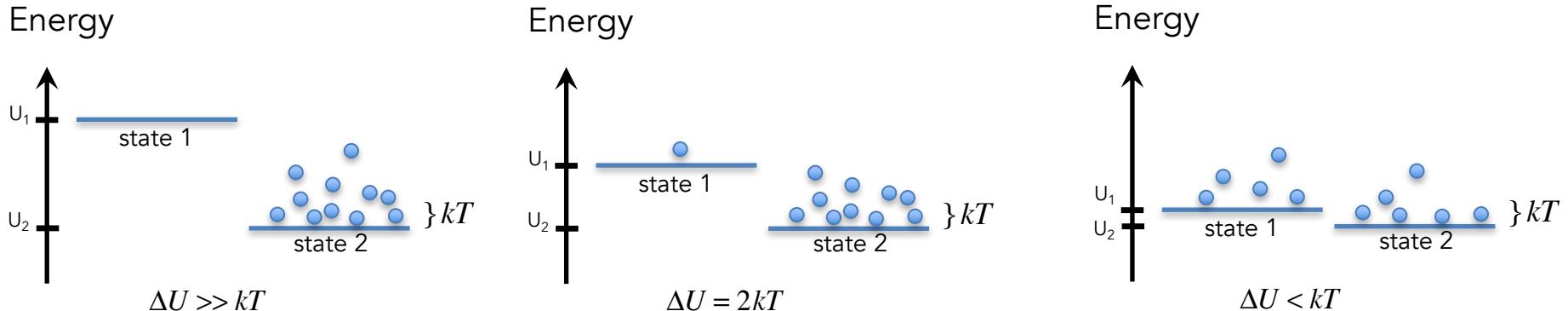


$$\frac{P_{state1}}{P_{state2}} > 0$$

# Derive Nernst potential using the Boltzmann equation

The Boltzmann equation describes the ratio of probabilities of a particle being in any two states, at thermal equilibrium:

$$\frac{P_{state1}}{P_{state2}} = e^{-\left(\frac{U_1 - U_2}{kT}\right)}$$



$$\frac{P_{state1}}{P_{state2}} \approx 0$$

$$\frac{P_{state1}}{P_{state2}} = e^{-2}$$

$$\frac{P_{state1}}{P_{state2}} \approx 1.0$$

# Nernst Potential

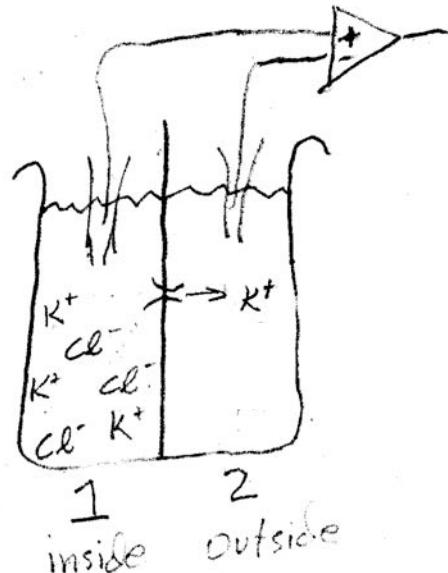
We can compute the equilibrium potential using the Boltzmann equation:

$$\frac{P_{in}}{P_{out}} = e^{-\frac{U_{in}-U_{out}}{kT}} = e^{-\frac{q(V_{in}-V_{out})}{kT}}$$

$U = qV$  = electrical potential (J)

$q$  = charge of ion

$q = 1.6 \times 10^{-19} \text{ C}$  for monovalent ion



# Nernst Potential

We can compute the equilibrium potential using the Boltzmann equation:

$$\frac{P_{in}}{P_{out}} = e^{-\frac{U_{in}-U_{out}}{kT}} = e^{-\frac{q(V_{in}-V_{out})}{kT}}$$

$U = qV$  = electrical potential (J)

$q$  = charge of ion

$$V_{in} - V_{out} = -\frac{kT}{q} \ln\left(\frac{P_{in}}{P_{out}}\right)$$

$q = 1.6 \times 10^{-19}$  C for monovalent ion

$$\Delta V = V_{in} - V_{out} = 25mV \ln\left(\frac{P_{out}}{P_{in}}\right)$$

$$\frac{kT}{q} = 25mV \text{ for monovalent ion}$$

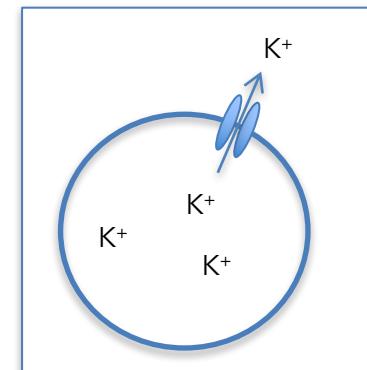
$$\Delta V = 25mV \ln\left(\frac{[K]_{out}}{[K]_{in}}\right) = E_K$$

Don't get confused by this notation.  $E_K$  is the equilibrium potential (voltage) for the K ion. 'E' here does not refer to an electric field.

# The Nernst potential for potassium

Intracellular and extracellular concentrations of ionic species, and the Nernst potential

Ion	Cytoplasm (mM)	Extracellular (mM)	Nernst (mV)
K <sup>+</sup>	400	20	-75

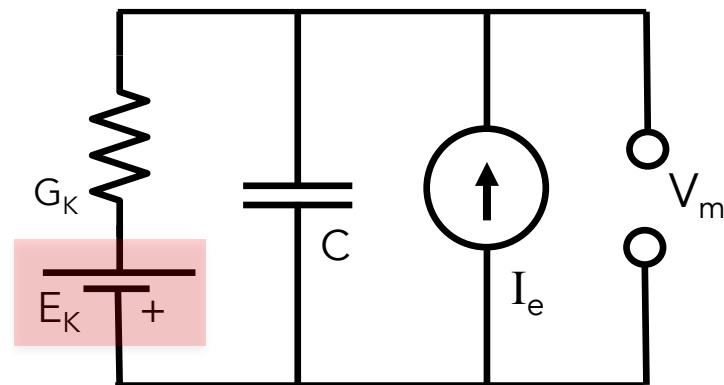


$$E_k = \frac{kT}{q} \ln\left(\frac{20}{400}\right) \quad \frac{kT}{q} = 25\text{mV at 300K (room temp)}$$

for monovalent ion

$$E_K = 25\text{mV}(-3.00) = -75\text{mV}$$

# How to implement an ion specific conductance as a battery in our model neuron



# Learning objectives for Lecture 2

- To understand how membrane capacitance and resistance allows neurons to integrate or smooth their inputs over time (RC model)
- To understand how to derive the differential equations for the RC model
- To be able to sketch the response of an RC neuron to different current inputs
- To understand where the 'batteries' of a neuron come from.

Extra notes on how to derive the Nernst potential  
using the equations for electrodiffusion

# Electrodiffusion and the Nernst Potential

In the last lecture, we found that the relation between drift velocity and force for an ion in an electric field is:

$$\vec{F} = \frac{kT}{D} \vec{v}_d$$

where  $f = kT/D$  is just the coefficient of friction given by the Einstein-Smoluchovski relation.

$\vec{F} = q\vec{E}$  = electric force on ion due to electric field E

$q$  = total ion charge in Coulombs

$\vec{E}$  = electric field (V/m)

$k$  = Boltzmann constant (J/K)

$T$  = temperature (K)

$kT$  = thermal energy (J)

$D$  = diffusion constant ( $m^2/s$ )

# Electrodiffusion and the Nernst Potential

Thus, we can write the drift velocity as:

$$v_d = \frac{qD}{kT} E$$

$\frac{qD}{kT}$  is the ion mobility, which describes how fast an ion will move in an electric field - (m/s)/(V/m)

We can find the total current density (amperes per unit area) as

$$\frac{I}{A} = q N_A c v_d$$

$N_A c$  = ion density (ions/m<sup>3</sup>)  
 $c$  = molar ion concentration (mol/m<sup>3</sup>)  
 $N_A$  = Avagadro's number (ions/mol)

Substituting  $v_d$  from above, we get that:

$$\frac{I}{A} = \frac{q^2 N_A D}{kT} c E$$

# Electrodiffusion and the Nernst Potential

Next we use the fact the the electric field is the spatial derivative of the electrical potential (voltage)

$$\vec{E} = -\vec{\nabla}V, \quad E_x = \frac{\partial V}{\partial x}$$

We can find the total current density (amperes per unit area) due to the electric field:

$$\frac{I}{A} = -\frac{q^2 N_A D}{kT} c \frac{\partial V}{\partial x}$$

# Electrodiffusion and the Nernst Potential

Put it all together and we get

$$\left[ \frac{I}{A} \right]_{Tot} = -qN_A D \left[ \frac{q}{kT} c \frac{\partial V}{\partial x} + \frac{\partial c}{\partial x} \right]$$

This has units of current per unit area  
(Amperes/m<sup>2</sup>)

We know that at equilibrium, the total current is zero. Thus,

$$\frac{q}{kT} c \frac{\partial V}{\partial x} + \frac{\partial c}{\partial x} = 0$$

$q$  = charge of a single ion  
 $c$  = molar concentration (mol/m<sup>3</sup>)  
 $N_A$  = Avagadro's number

A good reference for this derivation is Hille's chapter on 'Elementary Properties of Ions in Solution' (p. 261-269 of the second edition)

# Electrodiffusion and the Nernst Potential

Divide through by  $c$  and  $q/kT$  and we get

$$\frac{\partial V}{\partial x} + \left( \frac{kT}{q} \right) \frac{1}{c} \frac{\partial c}{\partial x} = 0$$

Use the fact that  $\frac{\partial \ln c(x)}{\partial x} = \frac{1}{c(x)} \frac{\partial c(x)}{\partial x}$

$$\frac{\partial V}{\partial x} + \left( \frac{kT}{q} \right) \frac{\partial \ln c(x)}{\partial x} = 0$$

# Electrodiffusion and the Nernst Potential

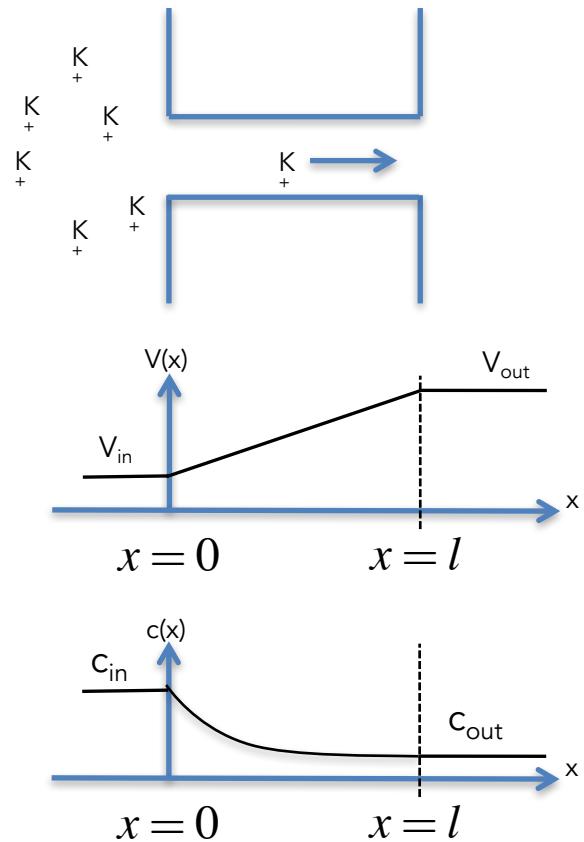
Now we can integrate both terms

$$V(x) \Big|_{x=0}^{x=l} + \left( \frac{kT}{q} \right) \ln c(x) \Big|_{x=0}^{x=l} = 0$$

$$V_{out} - V_{in} = - \left( \frac{kT}{q} \right) [\ln c_{out} - \ln c_{in}]$$

$$\Delta V = \frac{kT}{q} \ln \left( \frac{c_{out}}{c_{in}} \right), \text{ where } \Delta V = V_{in} - V_{out} \text{ at equilibrium}$$

Don't get confused by this notation.  $E_K$  is the equilibrium potential (voltage) for the K ion. 'E' here does not refer to an electric field.



$$c(x) = c_{in} e^{-\frac{x}{l} \ln \left( \frac{c_{out}}{c_{in}} \right)}$$

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9.40 Introduction to Neural Computation  
Spring 2018

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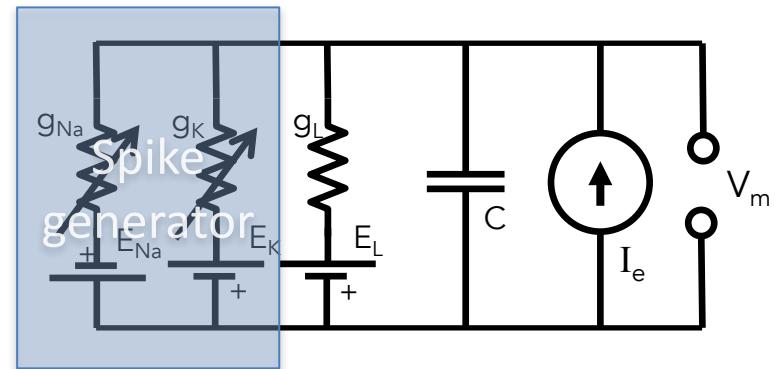
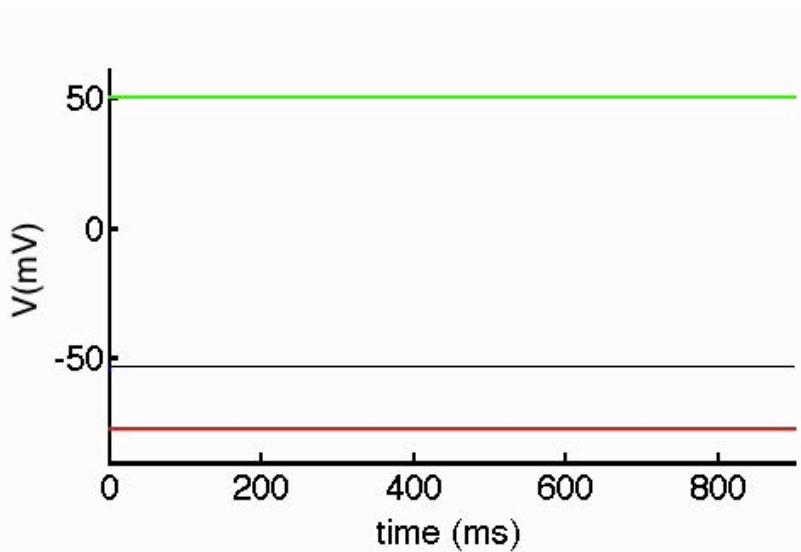
# Introduction to Neural Computation

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Prof. Michale Fee  
MIT BCS 9.40 — 2018  
Lecture 4

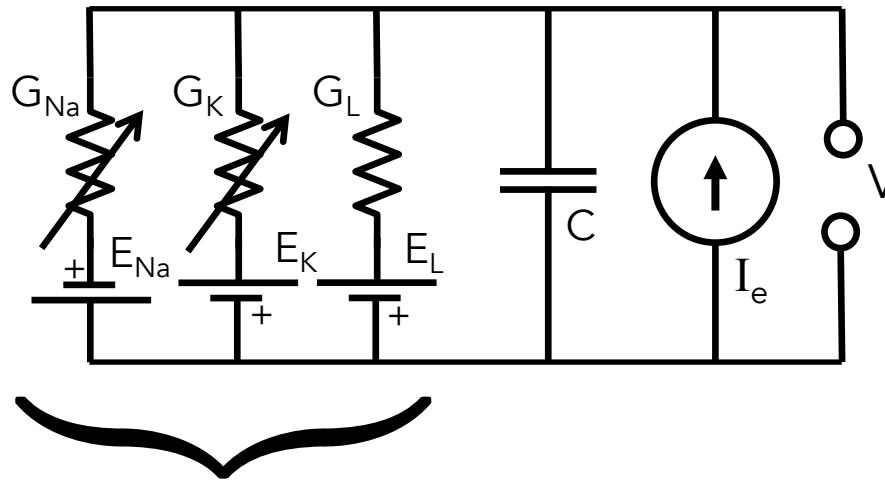
# Hodgkin-Huxley model of action potential generation

Voltage and time-dependent ion channels are the 'knobs' that control membrane potential.



Removed due to copyright restrictions: Figure 1a: The first intracellular recording of an action potential, from squid axon. Häusser, M. "The Hodgkin-Huxley theory of the action potential." *Nature Neuroscience* 3 (2000).

# Hodgkin-Huxley model of action potential generation



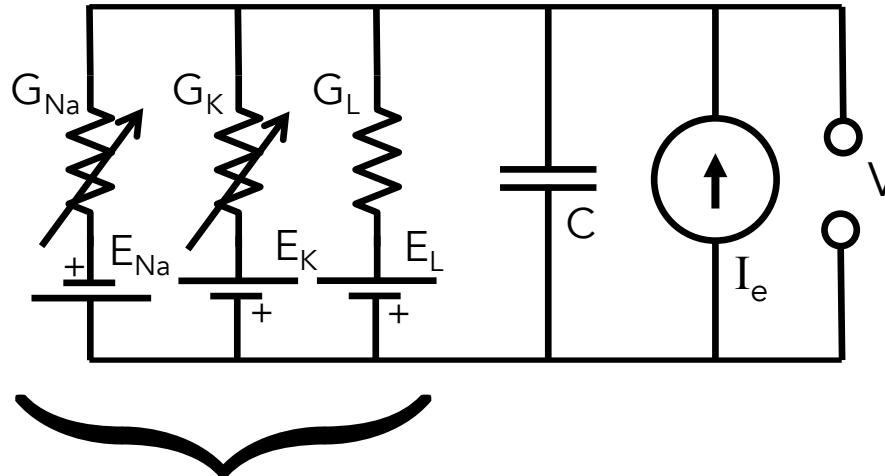
$$I_m = I_{Na} + I_K + I_L$$

This is the total membrane ionic current, and it includes the contribution from —sodium channels, potassium channels and a 'leak' conductance.

The equation for our HH model neuron is

$$I_m(t) + C \frac{dV(t)}{dt} = I_e(t)$$

# Hodgkin-Huxley model of action potential generation



$$I_m = I_{Na} + I_K + I_L \quad I_m(t) + C \frac{dV(t)}{dt} = I_e(t)$$

$$I_{Na} = G_{Na}(V,t)(V - E_{Na}) \quad I_K = G_K(V,t)(V - E_K) \quad I_L = G_L(V - E_L)$$

We can see that the membrane potential depends on current  
...which depends on all the conductances  
...which depend on the membrane potential

# We are going to write down an algorithm for how a neuron spikes!

Start with  $V_m$  :

→ Compute voltage-dependent parameters using  $V_m$

Compute conductance using voltage-dependent parameters

Compute sodium and potassium current from conductances

Compute total membrane current

Compute  $V_\infty$  and  $\tau_{mem}$

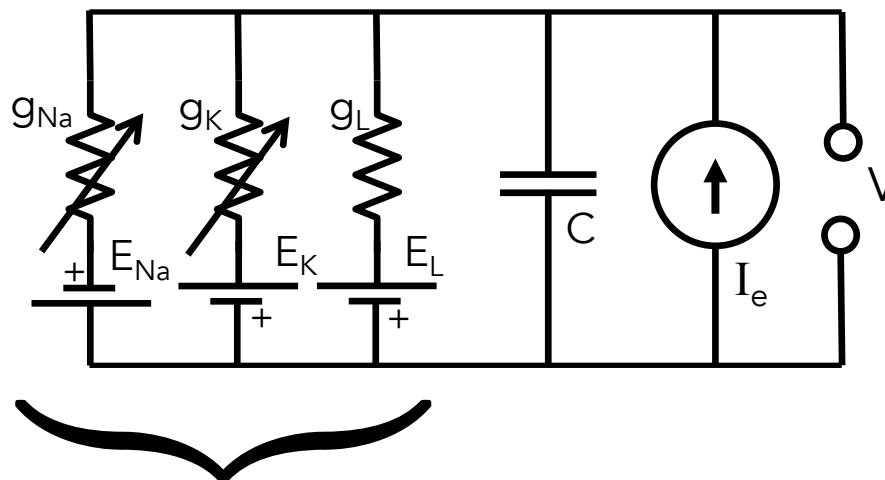
Compute membrane potential

$$V_m + \tau \frac{dV_m}{dt} = V_\infty$$

# Learning objectives for Lecture 2

- To be able to draw the circuit diagram of the HH model
- Understand what a voltage clamp is and how it works
- Be able to plot the voltage and time dependence of the potassium current and conductance
- Be able to explain the time and voltage dependence of the potassium conductance in terms of Hodgkin-Huxley gating variables

# Outline of HH model



$$I_m = I_{Na} + I_K + I_L$$

$$I_X = G_X \cdot (V - E_X)$$

$$I_{Na} = G_{Na}(V, t)(V - E_{Na})$$

$$I_K = G_K(V, t)(V - E_K)$$

$$I_L = G_L(V - E_L)$$

The sodium conductance is time-dependent and voltage-dependent

The potassium conductance is time-dependent and voltage-dependent

The leak conductance is neither time-dependent nor voltage-dependent

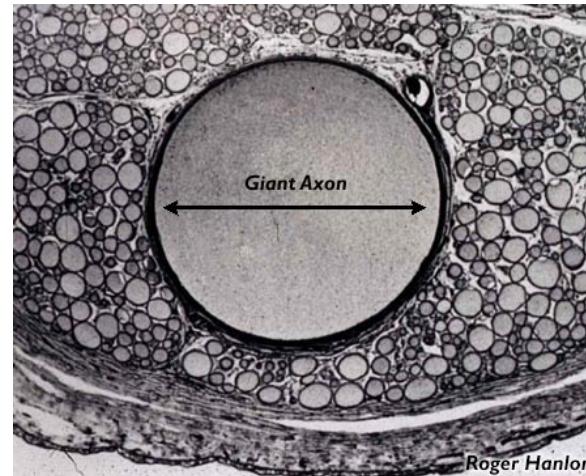
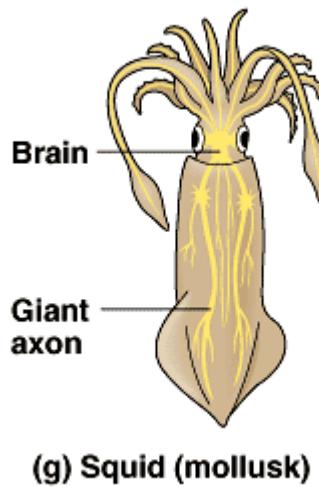
$$E_{Na} = +55mV$$

$$E_K = -75mV$$

$$E_L = -50mV$$

# Voltage and Time dependence

- Voltage and time-dependent ion channel **conductances** are the 'knobs' that control membrane potential.
- H&H studied the properties of K and Na channels in the squid giant axon. In particular they wanted to study the voltage and time dependence of the K and Na channels.



1mm diameter!

Squid diagram from [The CellularScale](#).  
License CC BY-NC-SA.

Image of squid giant axon © Kay Cooper and Roger Hanlon. Used with permission.

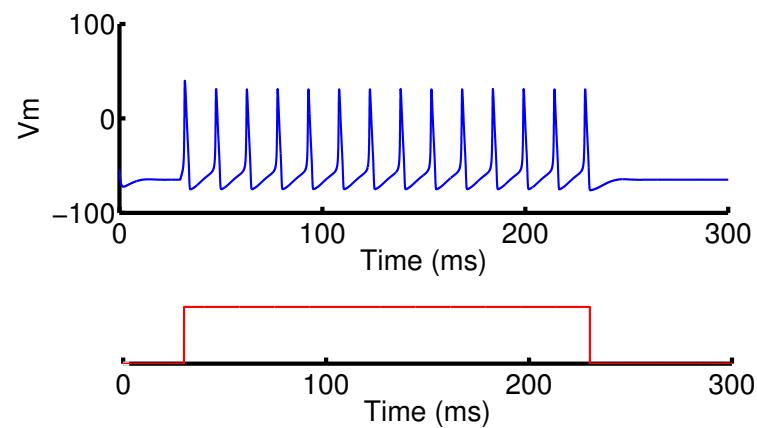
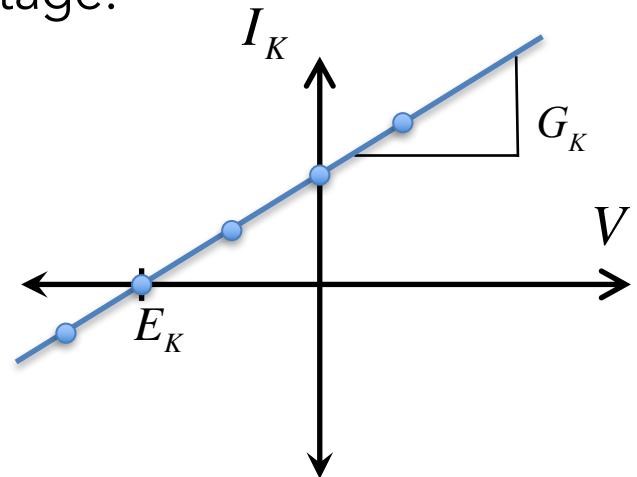
Most axons in our brain are 1um dia

# Outline of HH model

The best way study the time and voltage dependent **conductance** of ionic channels is to suddenly 'set' the voltage at different values and measure the current required to hold that voltage.

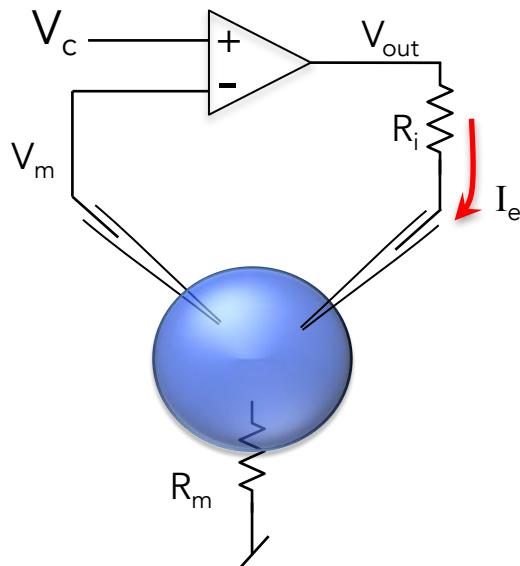
Then plot the I-V curve.

This not easy, because as soon as you depolarize the axon, the axon begins to spike!

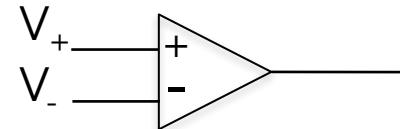


# Voltage Clamp

A voltage clamp is a device that holds the membrane potential of a cell to any desired 'command' voltage  $V_c$ , and measures the current required to hold that voltage.



The key component is an operational amplifier (op-amp)



The basic equation of an op-amp is:

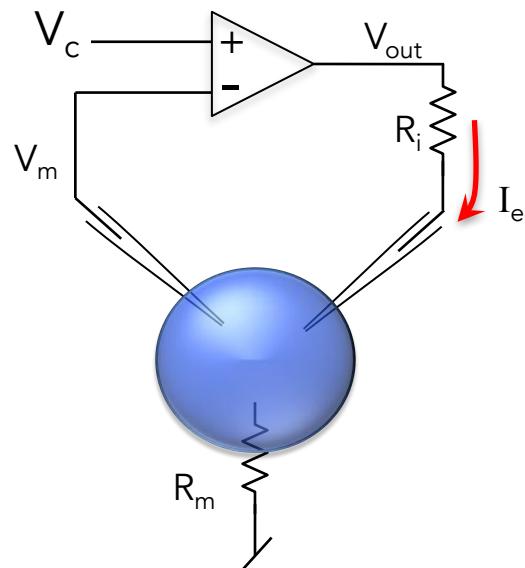
$$V_{out} = G(V_+ - V_-)$$

where  $G$  is the gain, typically  $\sim 10^5$  or  $10^6$ ,

Don't get confused here.  $G$  is gain, not conductance!

# Voltage Clamp

$$V_{out} = G(V_c - V_m)$$



If  $V_m < V_c$  then  $V_{out} \gg 0$

- Drives current into neuron
- Increases membrane potential

If  $V_m > V_c$  then  $V_{out} \ll 0$

- Pulls current out of neuron
- Decreases membrane potential

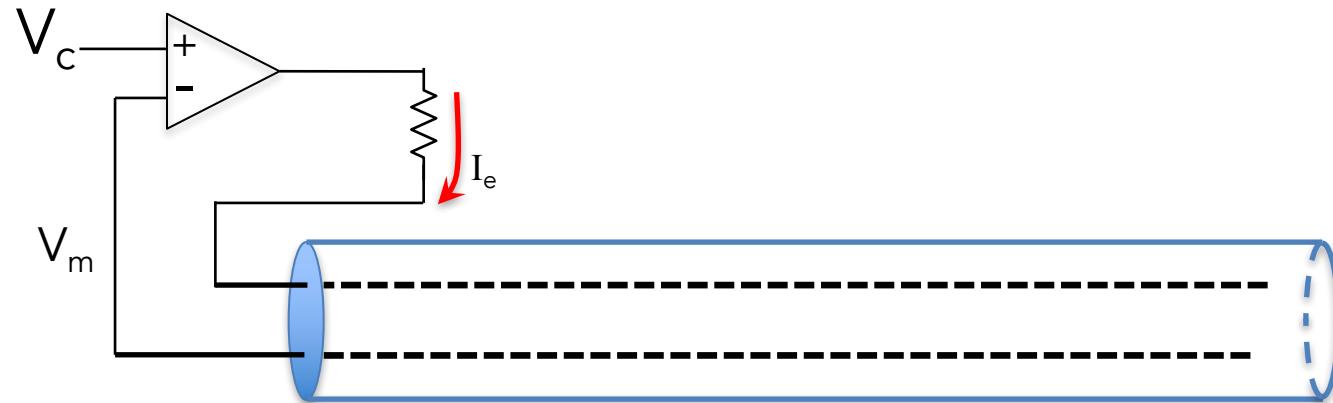
This is called 'negative feedback'.

- It is easy to show that, for large gain:

$$V_m \simeq V_c$$

- Thus, the voltage clamp circuit drives whatever current ( $I_e$ ) is necessary to 'clamp' the voltage of the neuron to the command voltage.
- During a voltage clamp experiment, we step the  $V_c$  around within the voltage range of interest and measure  $I_e$ .

# Ionic currents

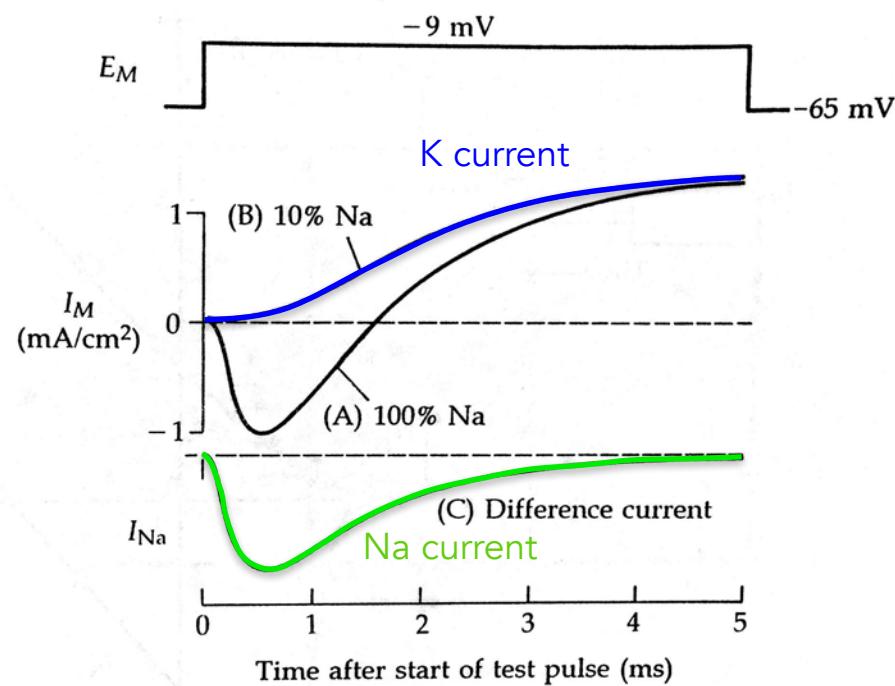


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# Ionic currents

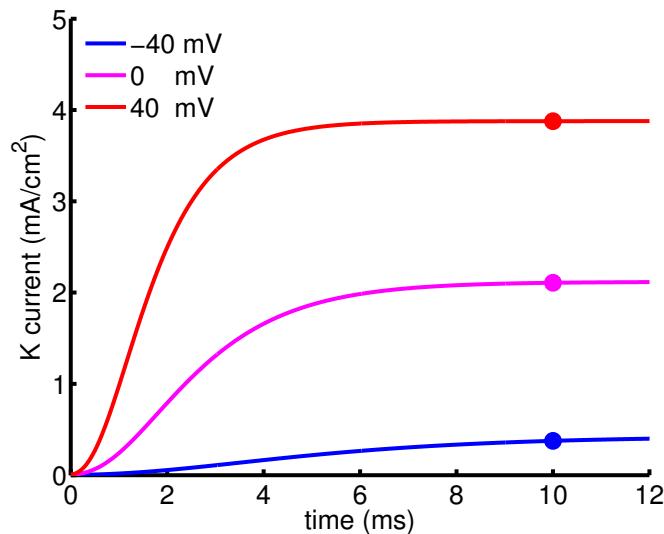
How do we figure out the contribution of Na and the contribution of K?

Ionic substitution (e.g. replace NaCl with choline chloride)

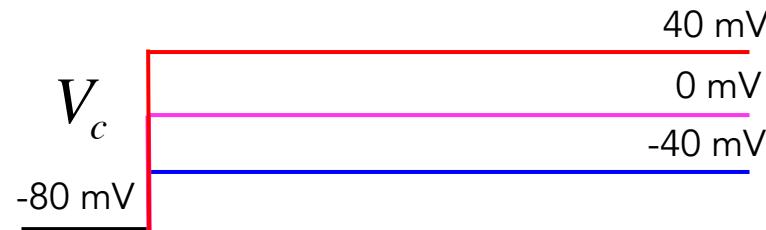
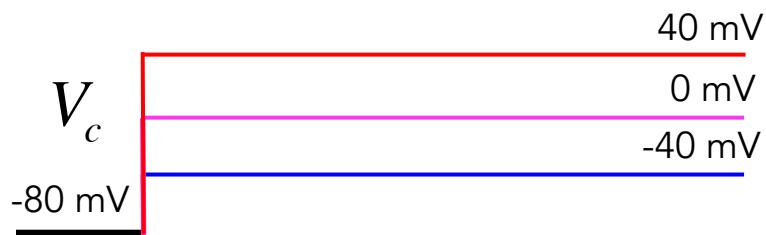
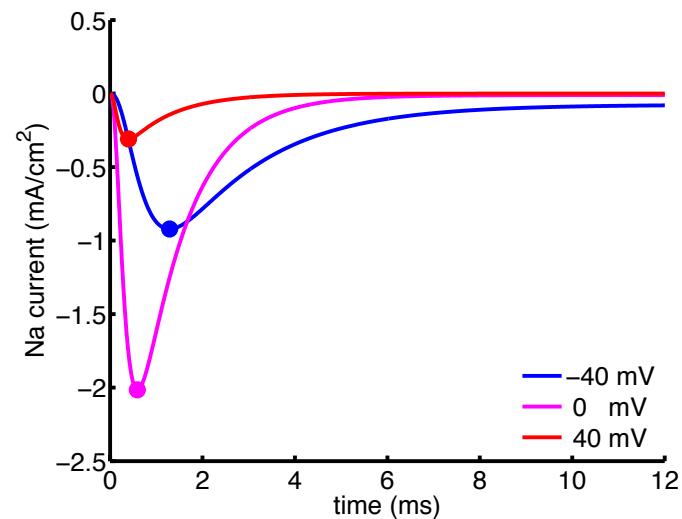


# Ionic currents

K current

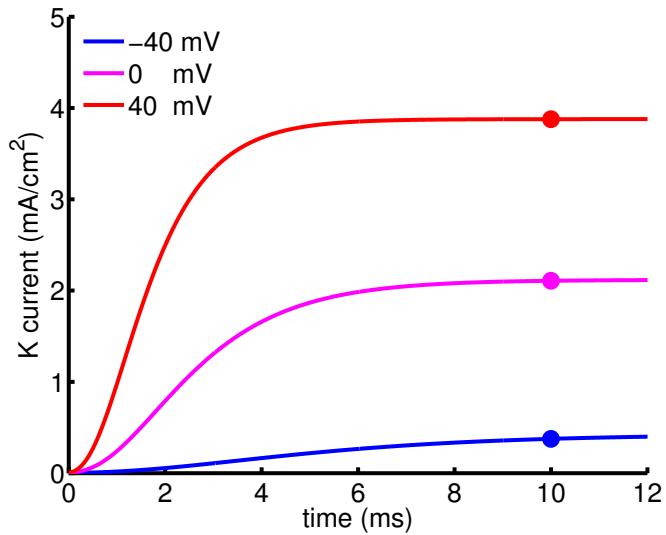


Na current

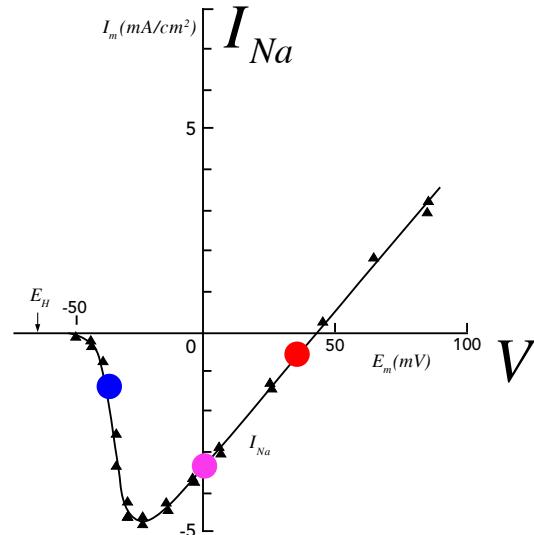
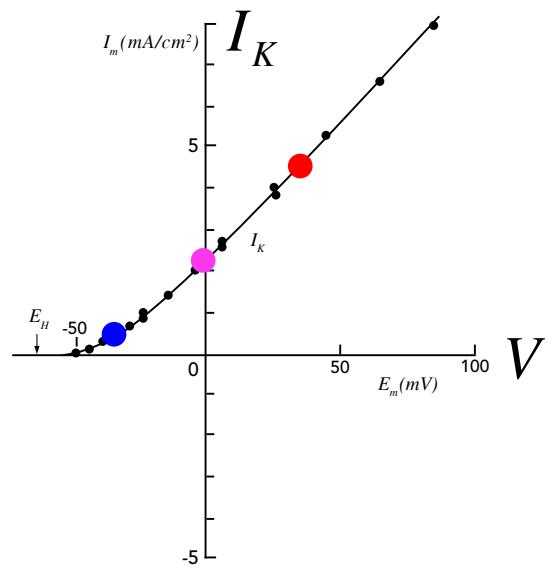
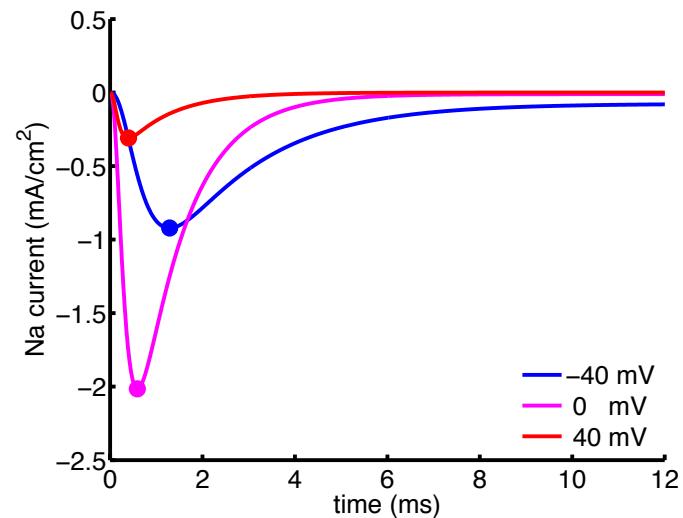


# Ionic currents

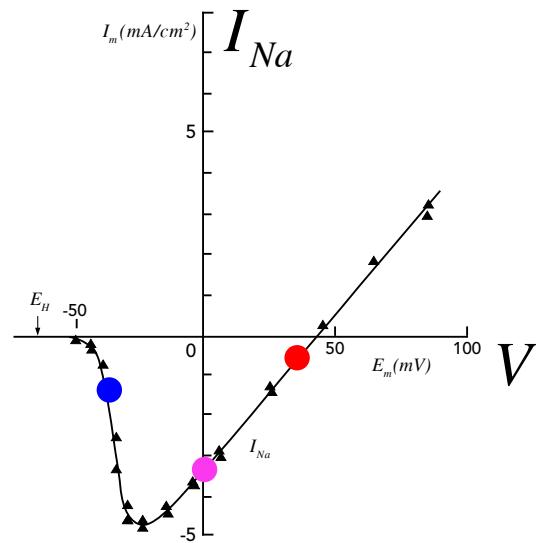
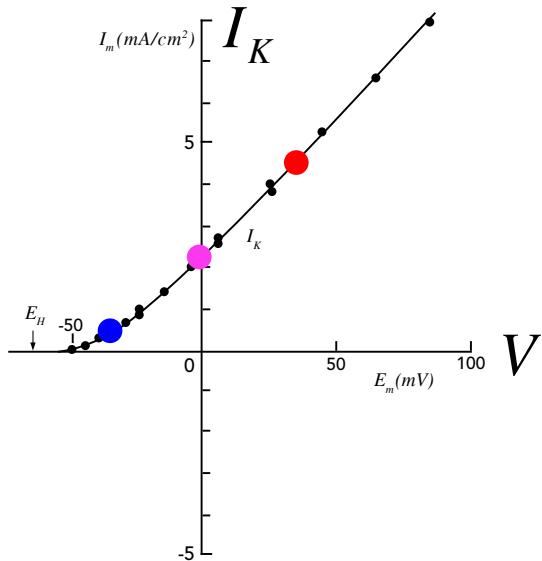
K current



Na current



# Ionic currents (voltage dependence)



We used the voltage clamp to measure **current** as a function of voltage.

But what we are really trying to extract is **conductance** as a function of voltage!

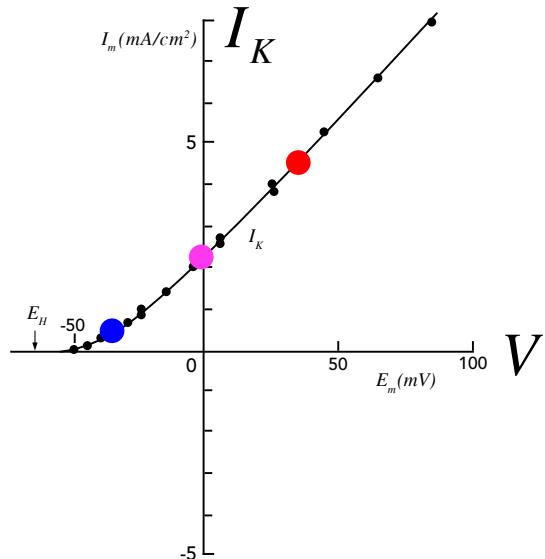
$$I_K(V) = G_K(V)(V - E_K)$$

$$I_{Na}(V) = G_{Na}(V)(V - E_{Na})$$

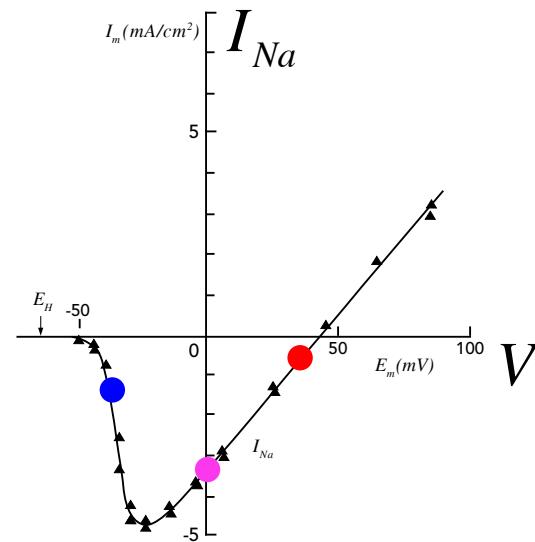
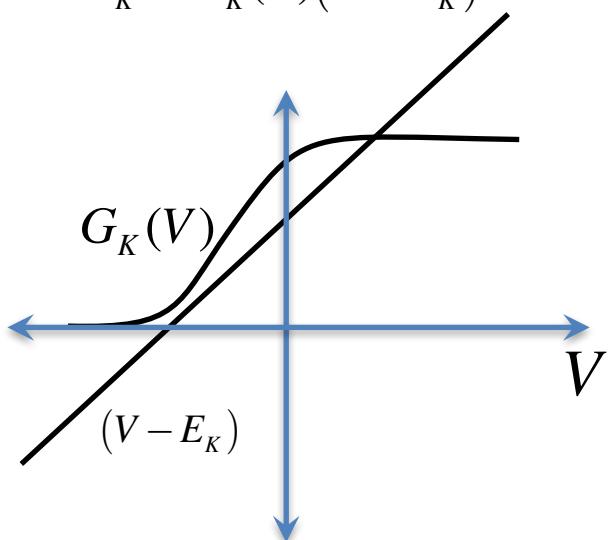
$$G_K(V) \equiv \frac{I_K(V)}{(V - E_K)}$$

$$G_{Na}(V) \equiv \frac{I_{Na}(V)}{(V - E_{Na})}$$

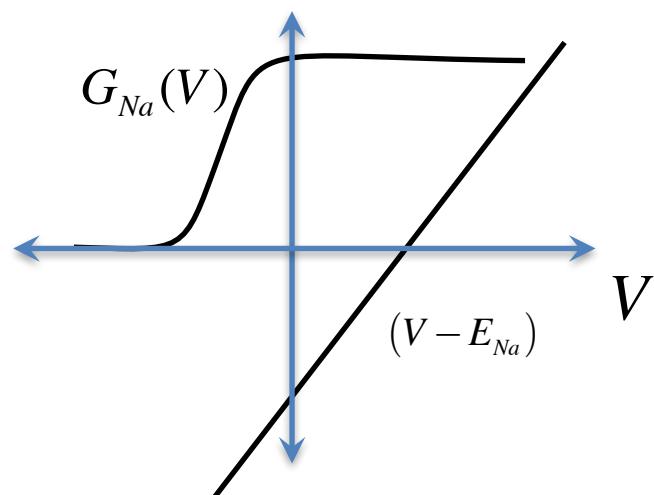
# Ionic currents (voltage dependence)



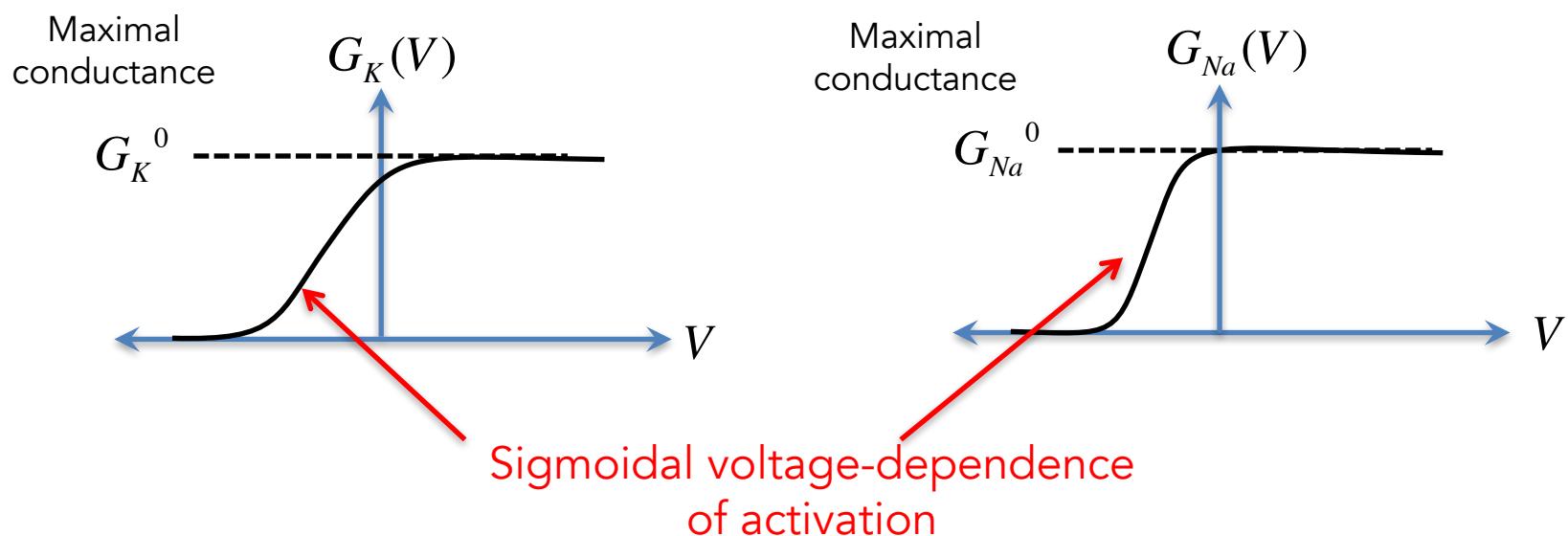
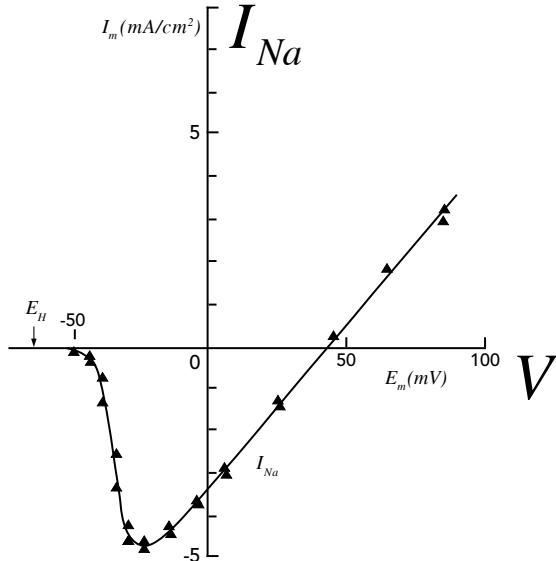
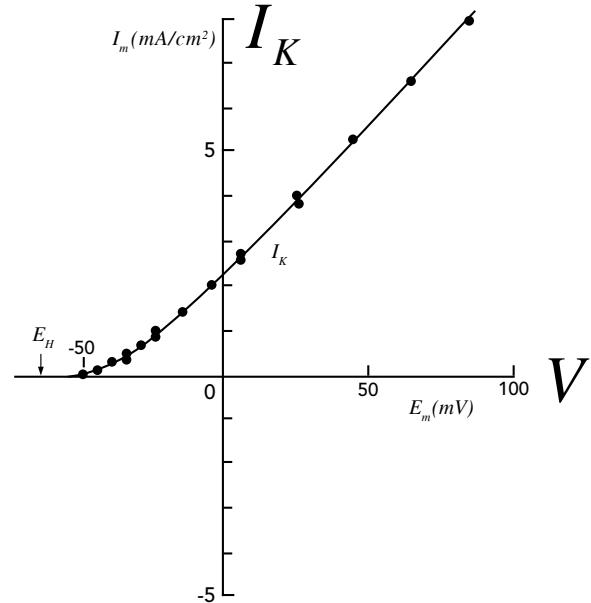
$$I_K = G_K(V)(V - E_K)$$



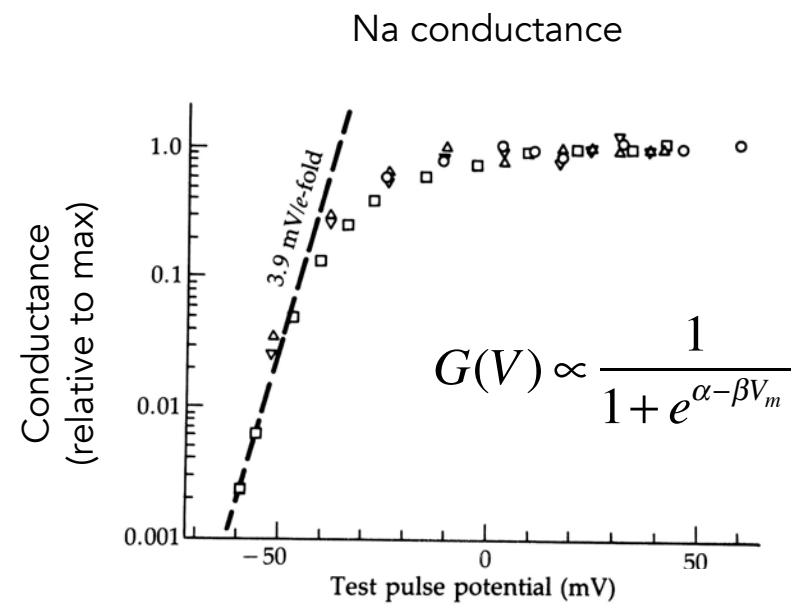
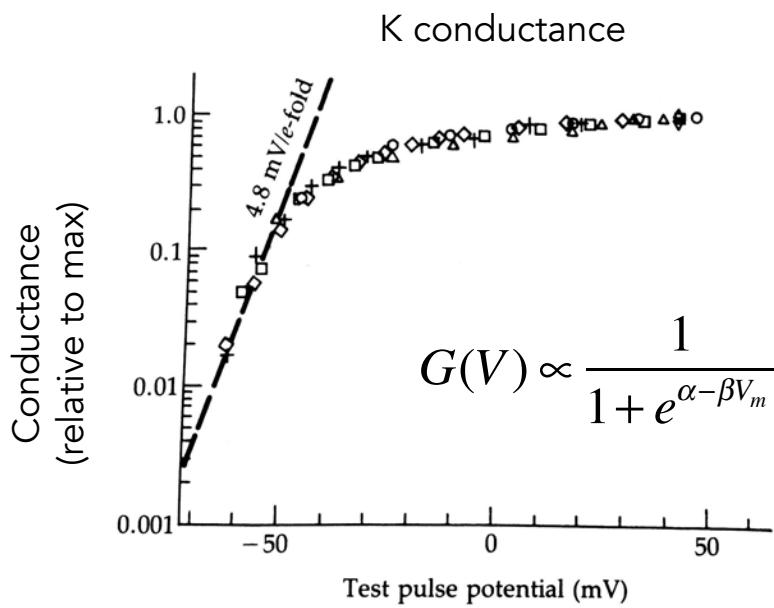
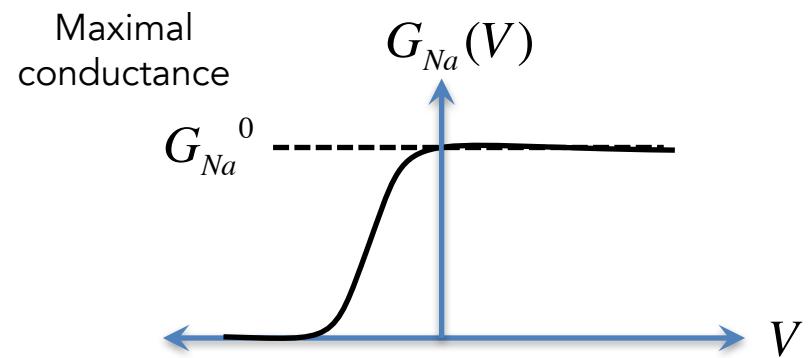
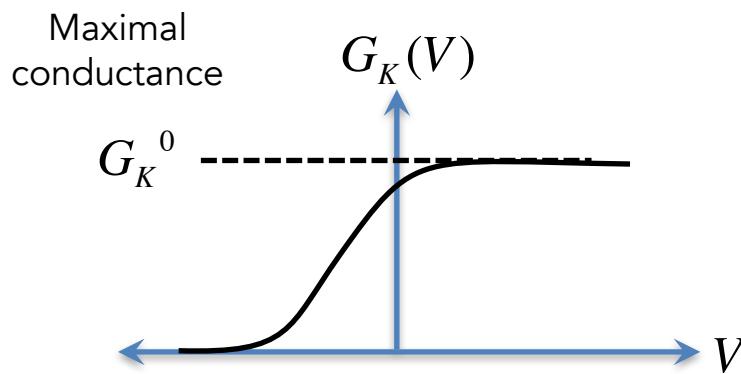
$$I_{Na} = G_{Na}(V)(V - E_{Na})$$



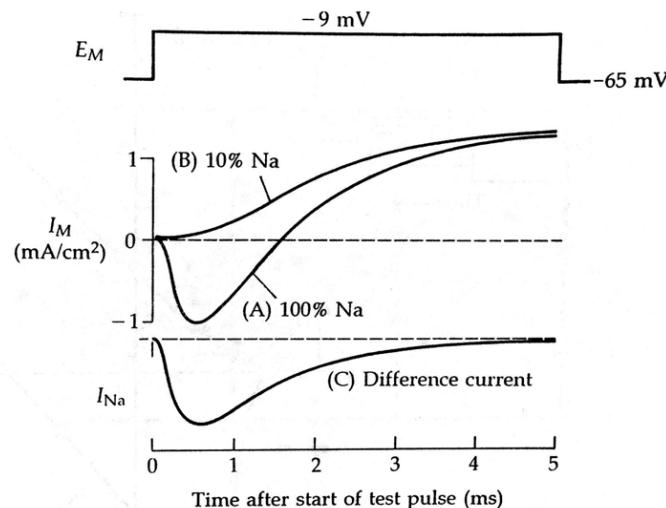
# Ionic currents (voltage dependence)



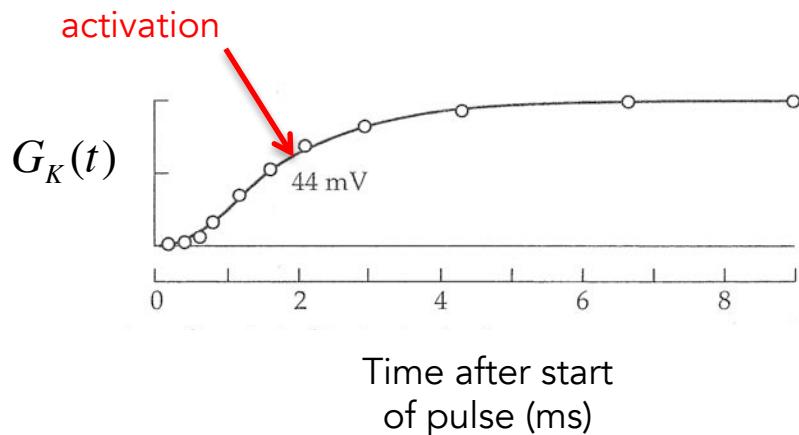
# Ionic currents (Voltage dependence)



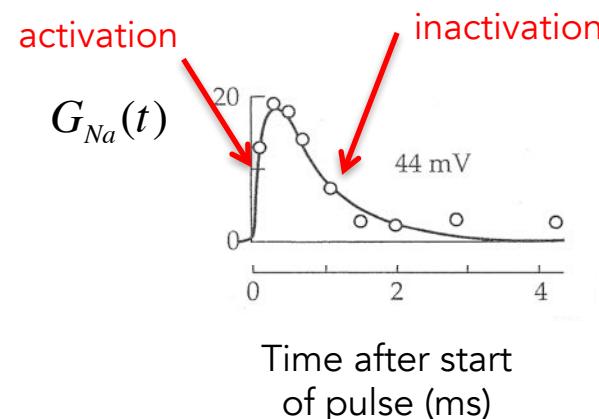
# Ionic currents (time dependence)



$$I_K(t) = G_K(t)(V - E_K)$$

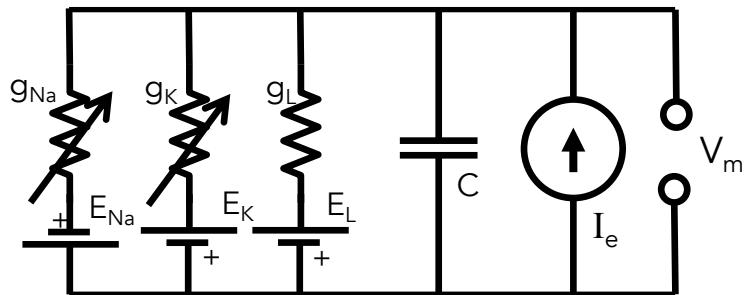
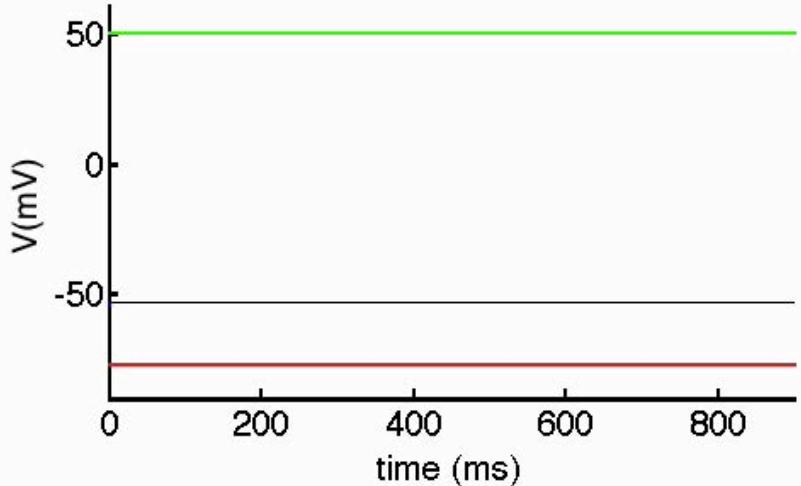


$$I_{Na}(t) = G_{Na}(t)(V - E_{Na})$$



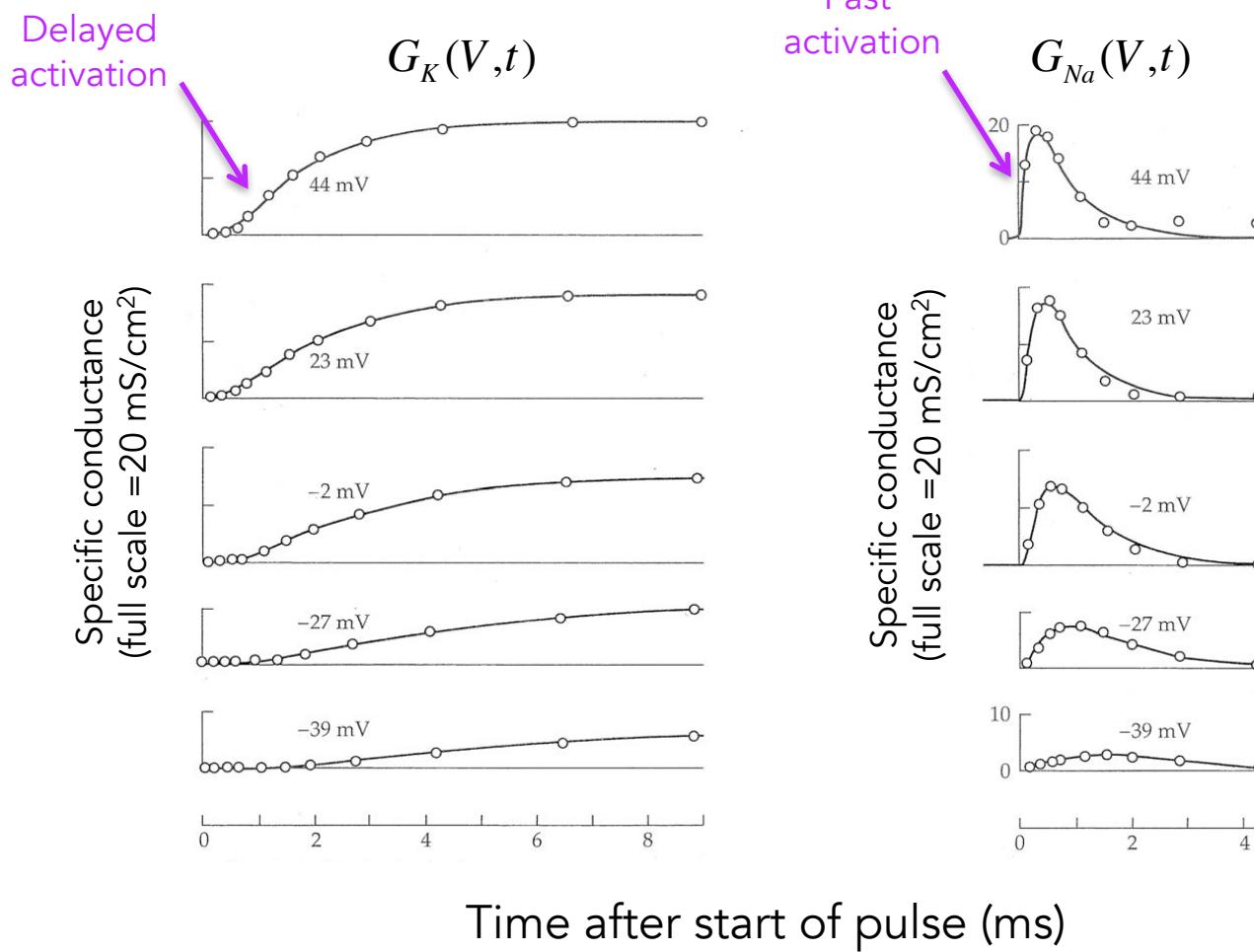
# Outline of HH model

Voltage and time-dependent ion channels are the 'knobs' that control membrane potential.



- Some ion channels push the membrane potential positive.
- Other ion channels push the membrane potential negative.
- Together these channels give the neural machinery flexible control of voltage!

# Ionic currents (time and voltage dependence)

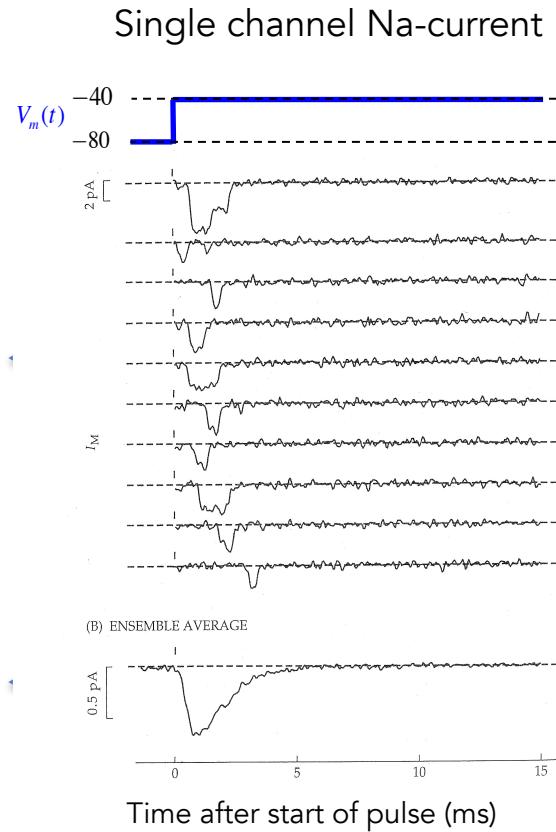
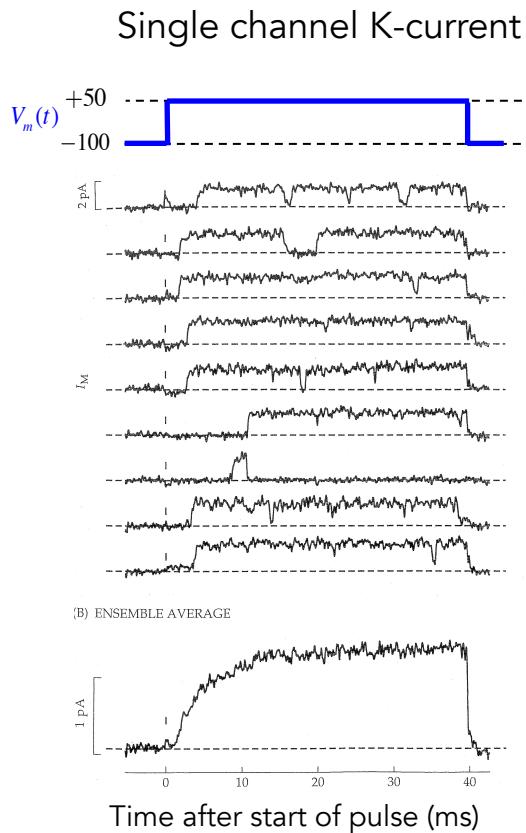


# Ionic Currents (time and voltage dependence)

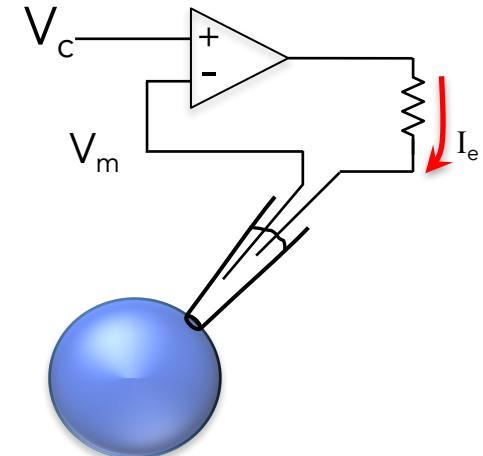
- Now we are going to develop a detailed understanding of where these voltage and time-dependencies come from!
- We are going to derive equations for the voltage dependence
- And differential equations for the time dependence.
- Once we do that, we will be able to write down a system of equations that allows us to simulate an action potential!

# Single Channels

So far, we have been discussing total currents into a neuron. However, these total currents result from ionic flow through thousands of individual ion channels.



It is possible to record from single ion channels using a 'patch clamp'.



Neher & Sakmann

# Ionic conductance in terms of single channels

Individual ion channels are either OPEN or CLOSED.

The total conductance through a membrane is given by the total number of open channels times the conductance one ion channel.

$P_K$  = probability of being 'open'

Number of 'open' ion

$N_K$  = total number of ion channels

channels =  $P_K N_K$

$\hat{g}_K$  = unitary conductance

Total K conductance:

$$G_K = P_K(V, t) N_K \hat{g}_K$$



Remember, K current is:

$$I_K = G_K(V, t) (V - E_K)$$

All of the interesting time and voltage dependence  
comes from here

# Ionic conductance in terms of single channels

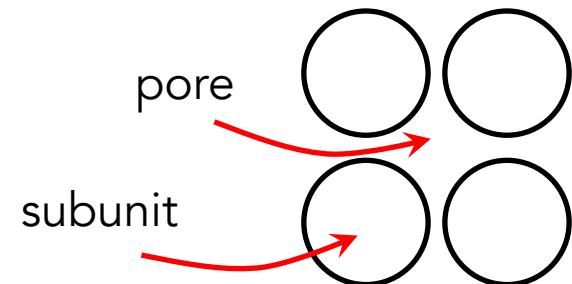
How do we describe the probability that a channel is open?

Lets start with the K channel.

The pore of a  $K^+$  channel is formed by 4 identical subunits.

Each subunit has a voltage sensor and gate to turn the channel on and off.

Each subunit has two states: 'open' and 'closed'.  
'n' is the probability that a subunit is open.

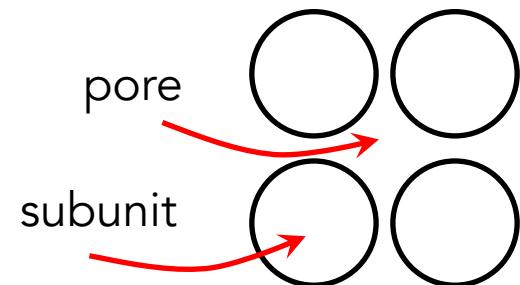


Finally, all subunits must be in the 'open' state for the channel to be permeable.

# Ionic conductance in terms of single channels

How do we describe the probability that a channel is open?

If 'n' is the probability that one subunit is open, then the probability that all four subunits is open is given by:



$$P_K = n^4 \quad \text{Assuming independence}$$

We can now write down the conductance of our K channels as:

$$G_K = \bar{G}_K n^4$$

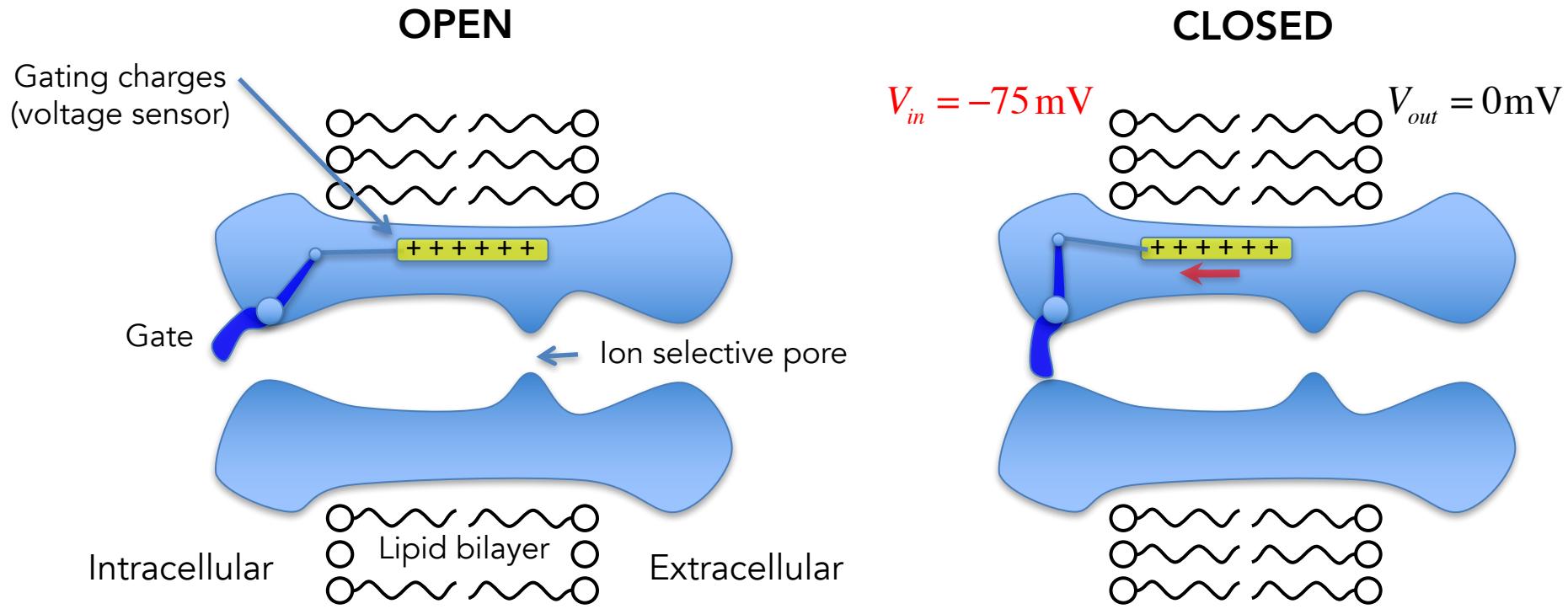
$\bar{G}_K$  is the maximal open conductance

And we can write the K current as:

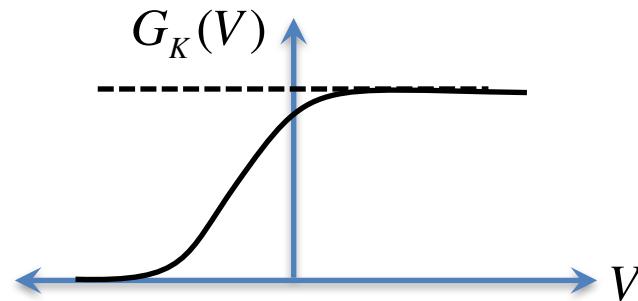
$$I_K = \bar{G}_K n^4 (V - E_K)$$

H & H called  $n$  the 'gating variable' for the potassium current

# Ionic conductance in terms of single channels



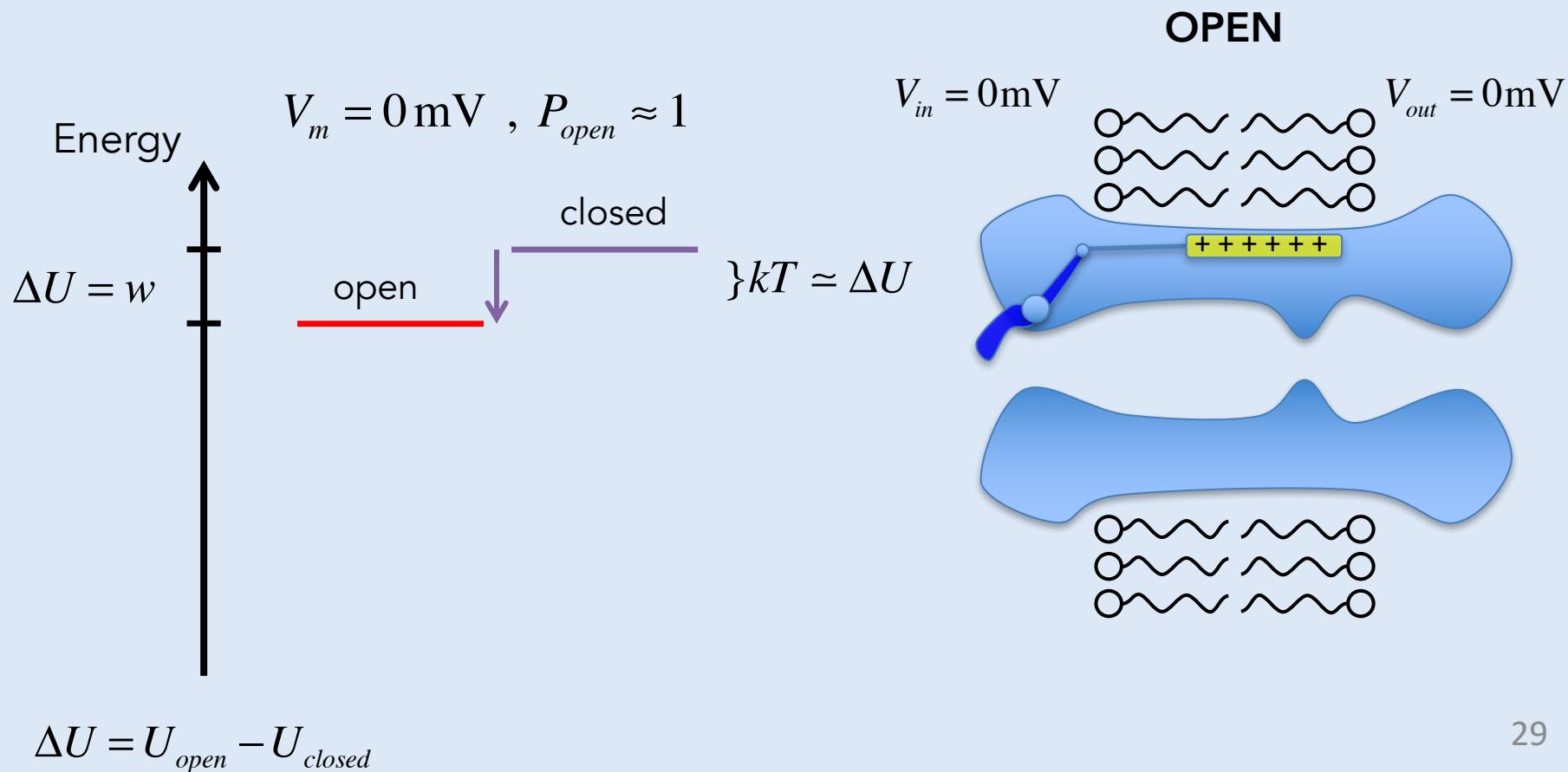
We are going see how to derive  
the voltage-dependence from first  
principles!



# Ionic conductance in terms of single channels

Ion channels are stochastic. They are either open or closed, and flicker back and forth between the open and closed states.

Lets see if we can predict the voltage-dependence of an ion channel!

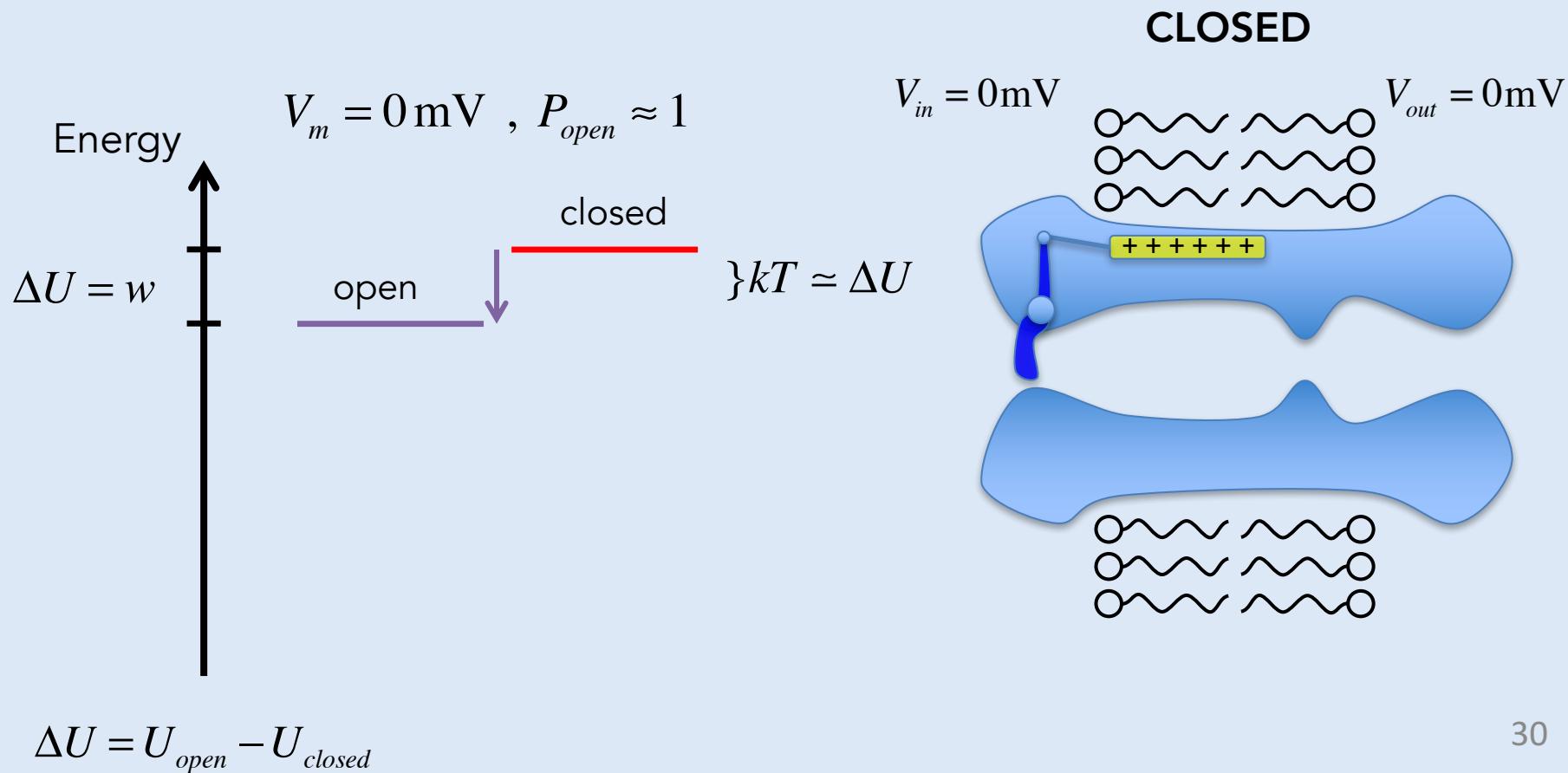


$$\Delta U = U_{open} - U_{closed}$$

# Ionic conductance in terms of single channels

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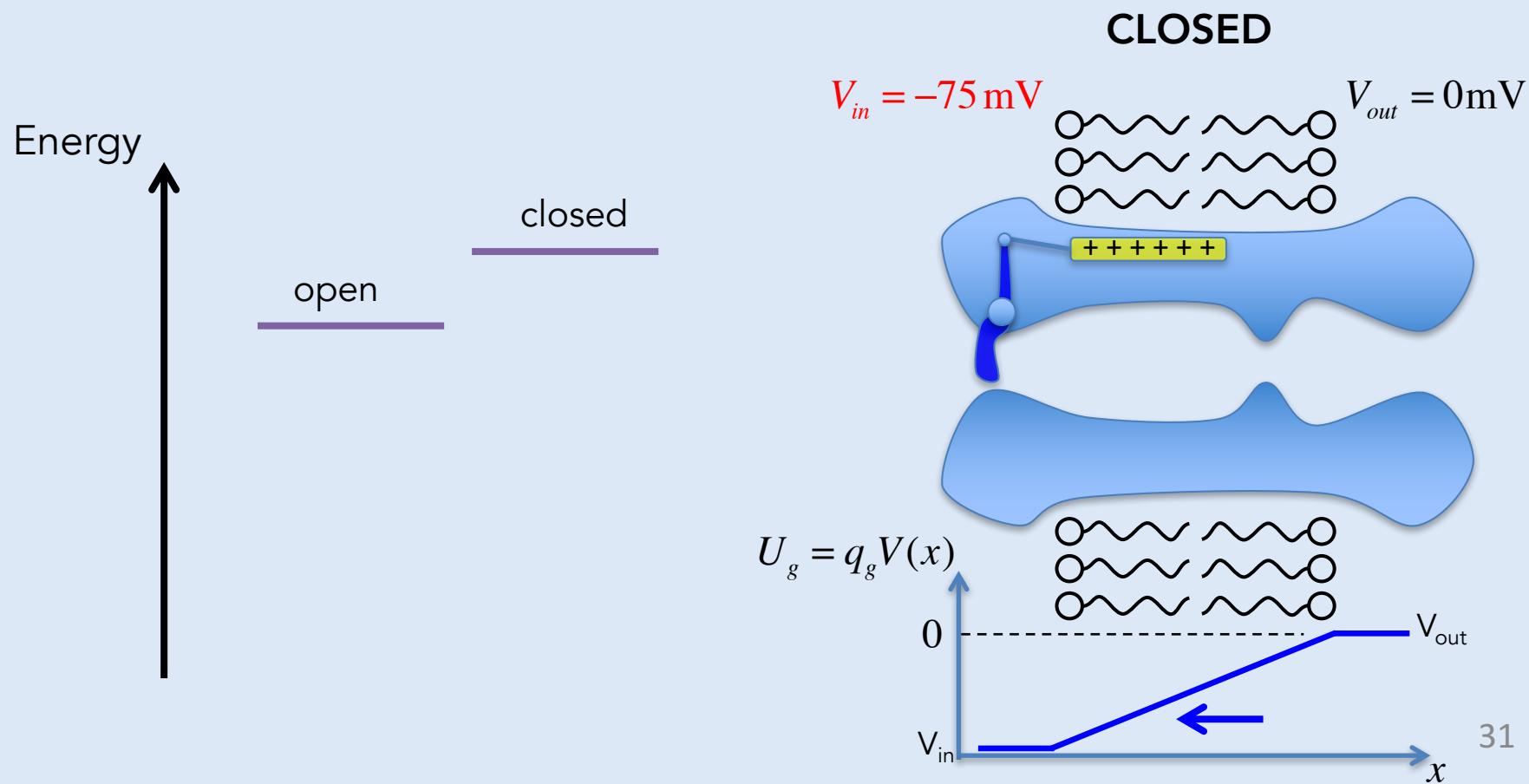


$$\Delta U = U_{open} - U_{closed}$$

# Ionic conductance in terms of single channels

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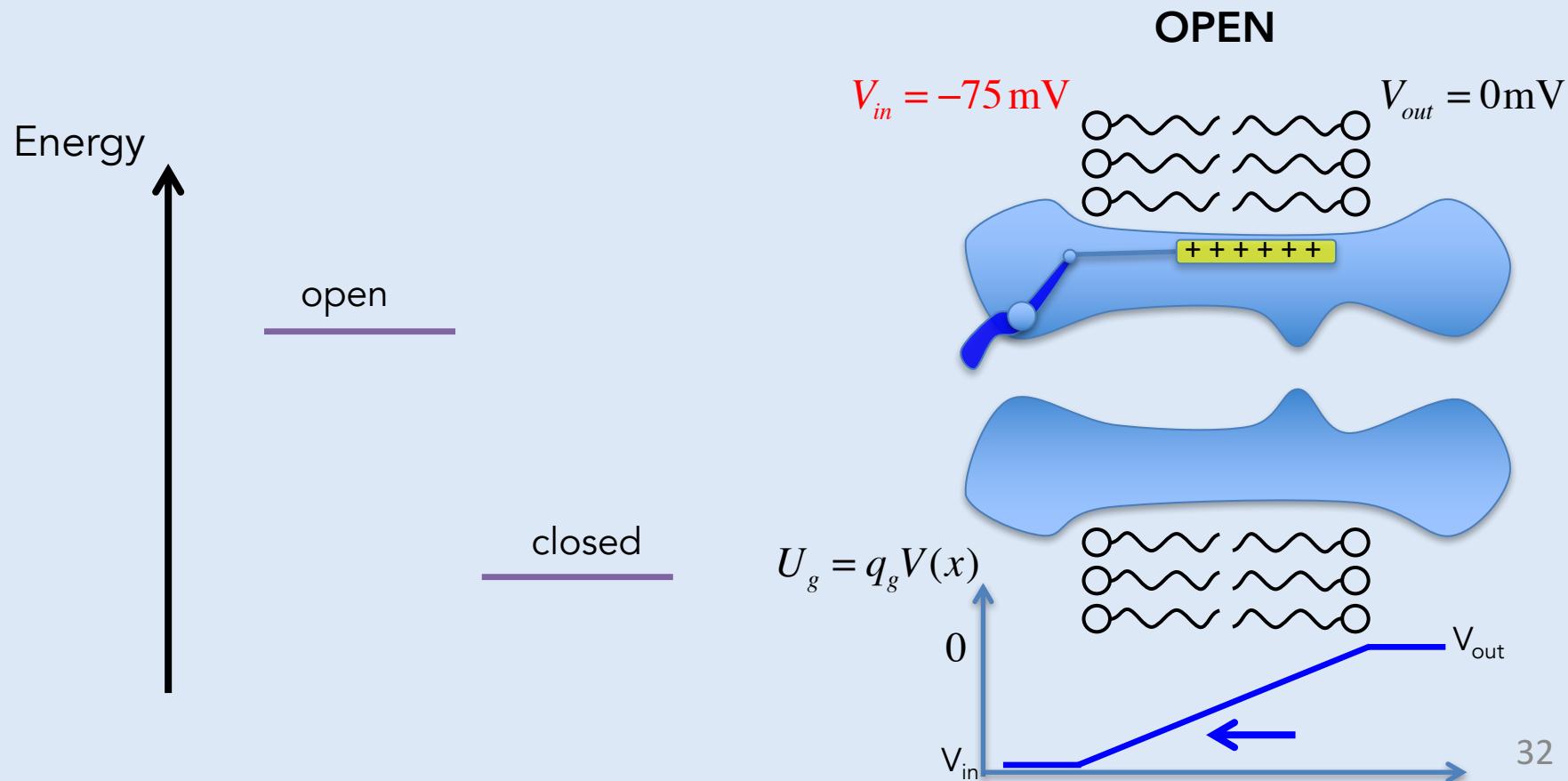
Lets see if we can predict the voltage-dependence of an ion channel!



# Ionic conductance in terms of single channels

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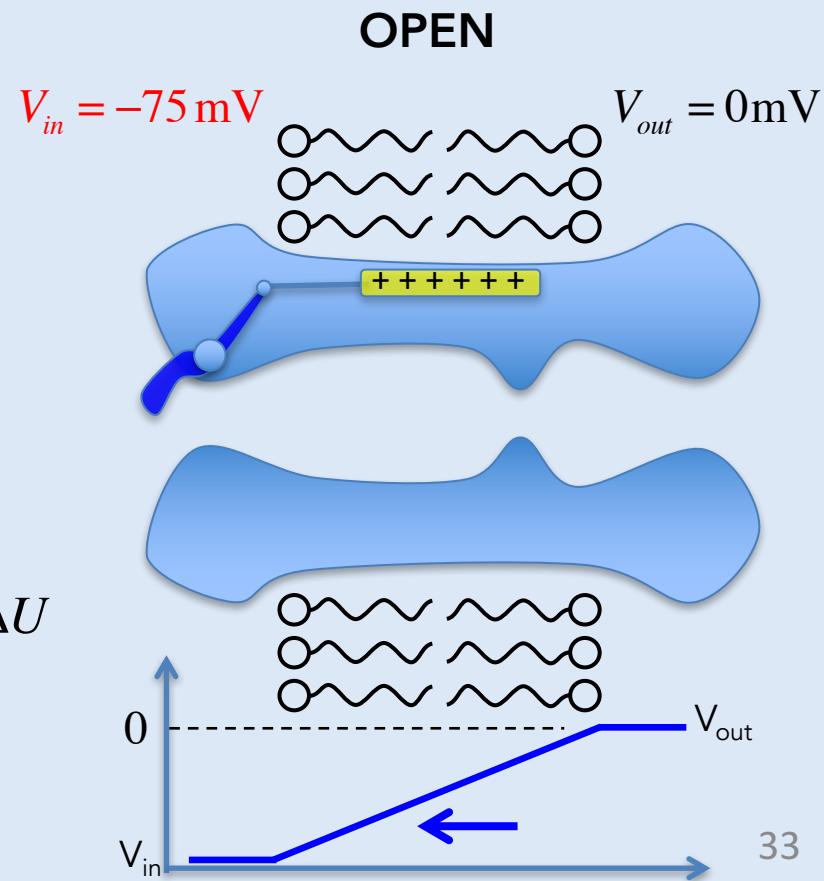
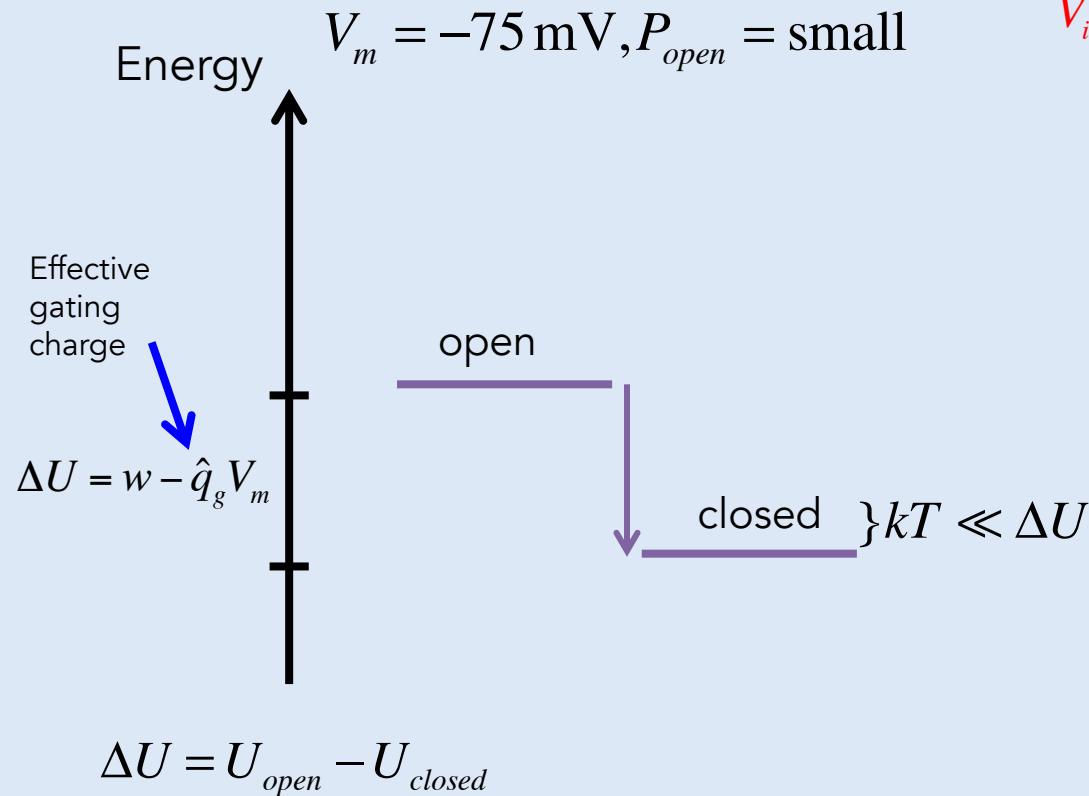
Lets see if we can predict the voltage-dependence of an ion channel!



# Ionic conductance in terms of single channels

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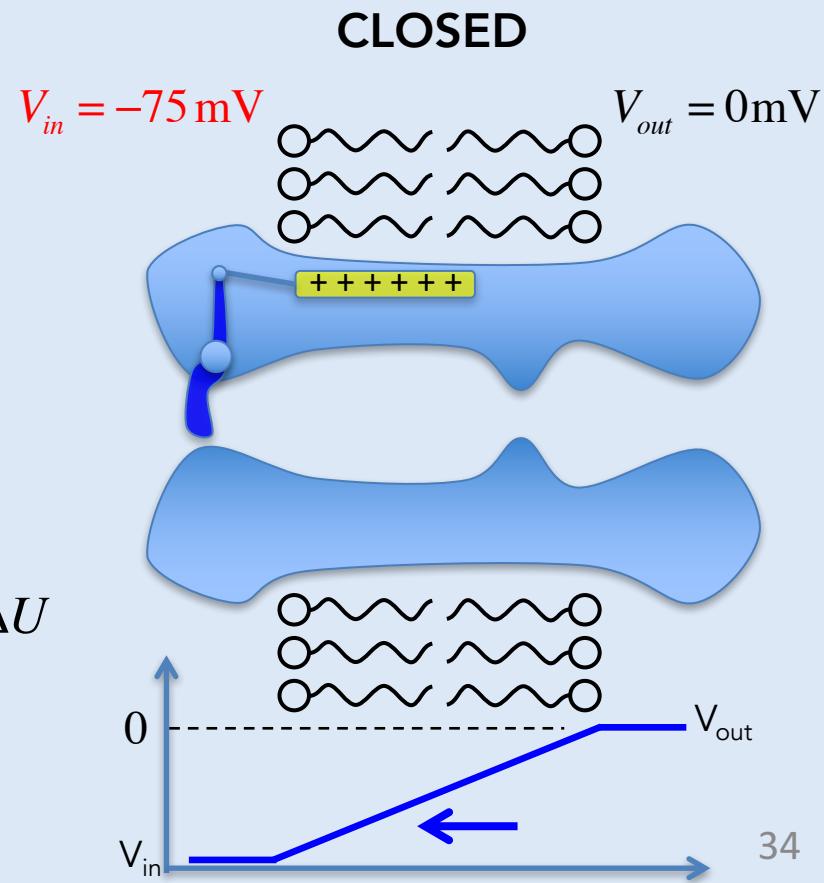
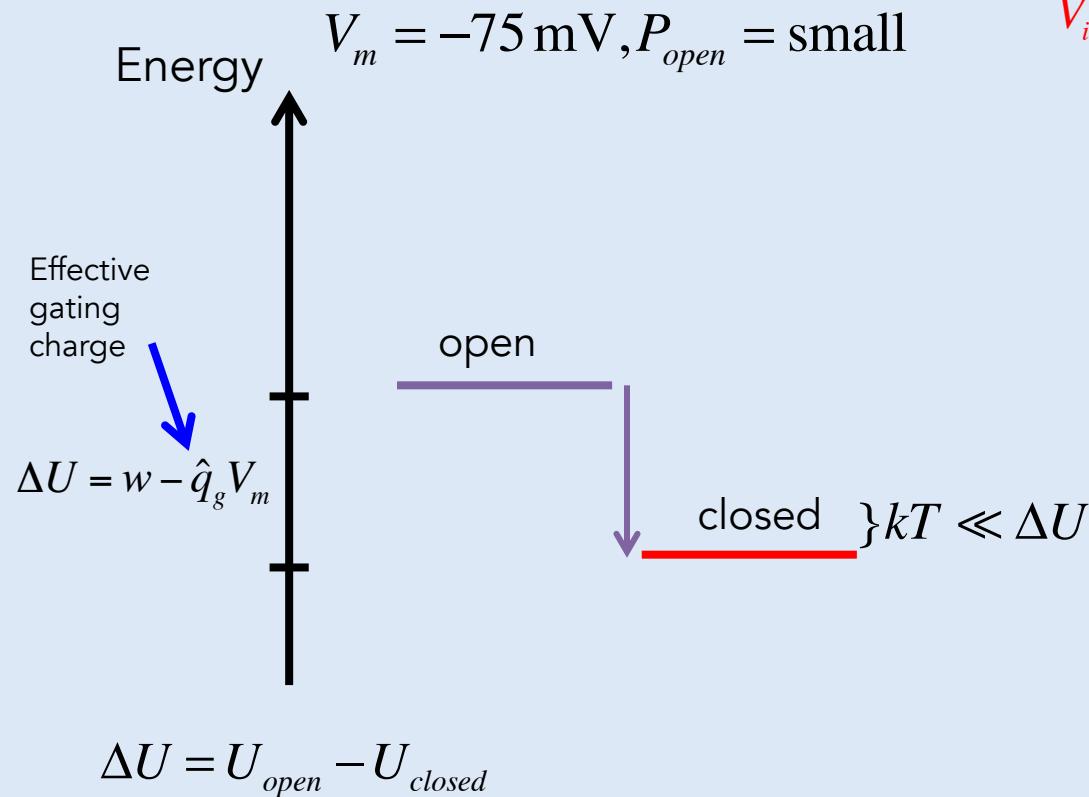
Lets see if we can predict the voltage-dependence of an ion channel!



# Ionic conductance in terms of single channels

Ion channels are stochastic. They are either open or closed, and flicker back and forth between the open and closed states.

Lets see if we can predict the voltage-dependence of an ion channel!



# To derive the voltage dependence: boltzmann equation

We can use the Boltzmann equation to describe the ratio of probabilities of being in the open or closed state:

$$\frac{P_{open}}{P_{closed}} = e^{-\left(\frac{U_{open}-U_{closed}}{kT}\right)}$$

$$\frac{P_{open}}{P_{closed}} = e^{-\left(\frac{w-q_g V_m}{kT}\right)}$$

The probability of having an open subunit is:

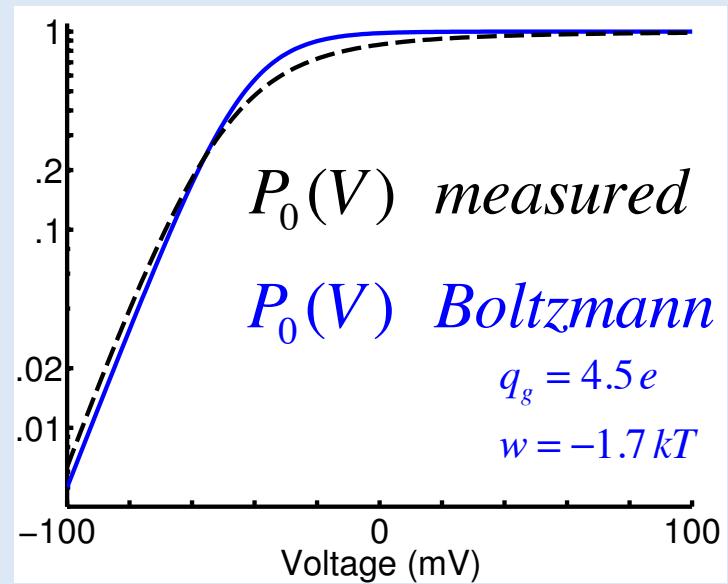
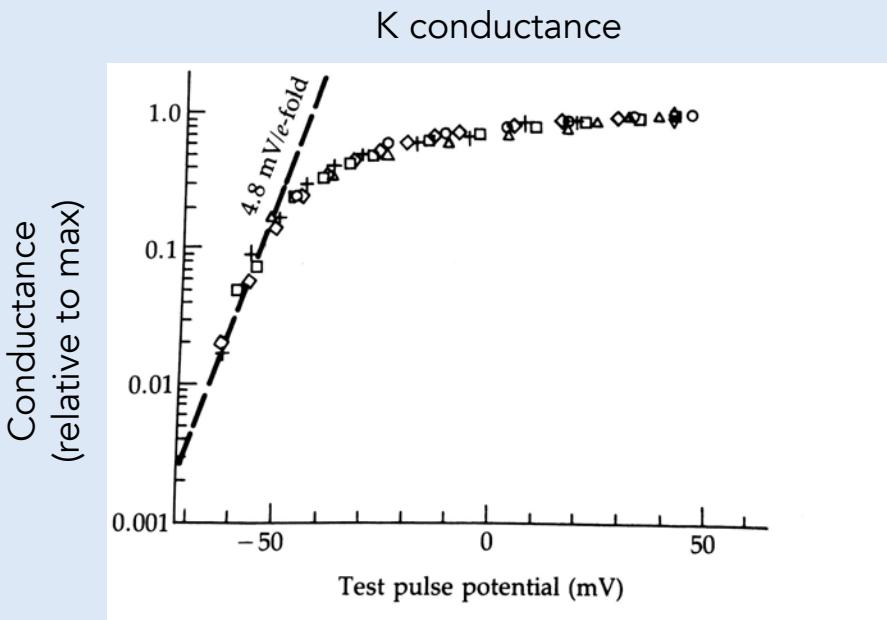
$$n = P_0 = \frac{P_o}{P_o + P_c} = \frac{1}{1 + \frac{P_c}{P_o}} = \frac{1}{1 + e^{(w-q_g V_m)/kT}}$$

# To derive the voltage dependence: boltzmann equation

$$P_o(V) = \frac{1}{1 + e^{(w - q_g V_m)/kT}}$$

Is this the observed voltage-dependence?

YES!

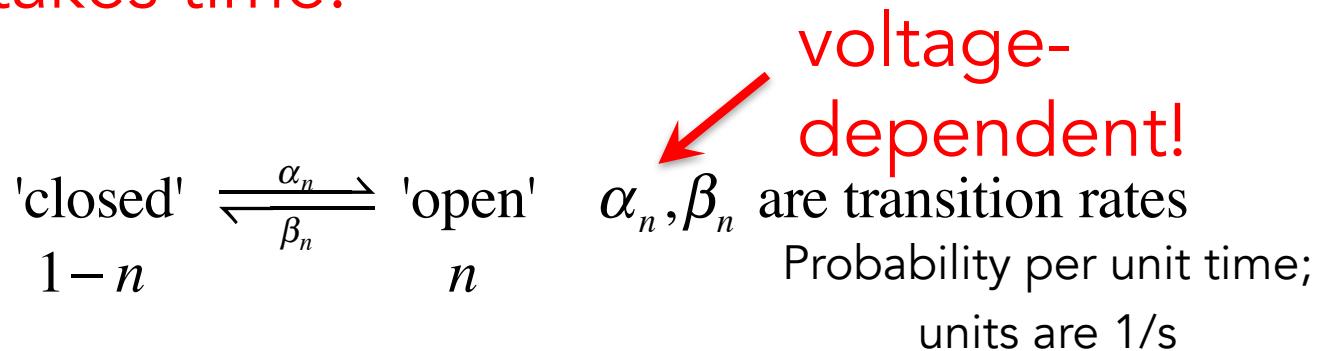


# Now get the time dependence!

Note that for any given subunit or channel, when we change the voltage, the energy levels shift (nearly) instantaneously. The probability of making a transition changes instantly, however the number of open channels does not change instantly.

We still have to wait for thermal fluctuations to kick the channel or subunit open, or wait for the subunit to make a conformational change.

This takes time!



We are going to model the transitions between open and closed states with a simple rate equation. We can do this because we have many channels to average over.

'closed'  $\xrightleftharpoons[\beta_n]{\alpha_n}$  'open'  $\alpha_n, \beta_n$  are transition rates

$1-n$                            $n$

Change in the number of open subunits = The number of closed subunits that open — The number of open subunits that close

Change in the number of open subunits per unit time = The number of closed subunits  $(1-n)$  times the probability that a closed subunit opens per unit time  $(\alpha_n)$  — The number of open subunits  $(n)$  times the probability that an open subunit closes per unit time  $(\beta_n)$

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

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

Let's rewrite this equation as follows:

$$= \alpha_n - \alpha_n n - \beta_n n$$

$$= \alpha_n - (\alpha_n + \beta_n)n$$

$$\underbrace{\frac{1}{(\alpha_n + \beta_n)} \frac{dn}{dt}}_{\text{red bracket}} = \underbrace{\frac{\alpha_n}{(\alpha_n + \beta_n)}}_{\text{red bracket}} - n$$

Thus, we can rewrite this equation in terms of the steady state open probability and a time constant:

$$\tau_n \frac{dn}{dt} = n_\infty - n$$

Remember:  $n$  is the probability that a subunit is open.

The steady state solution!

$$n_\infty = \frac{\alpha_n}{(\alpha_n + \beta_n)}$$

A time constant!

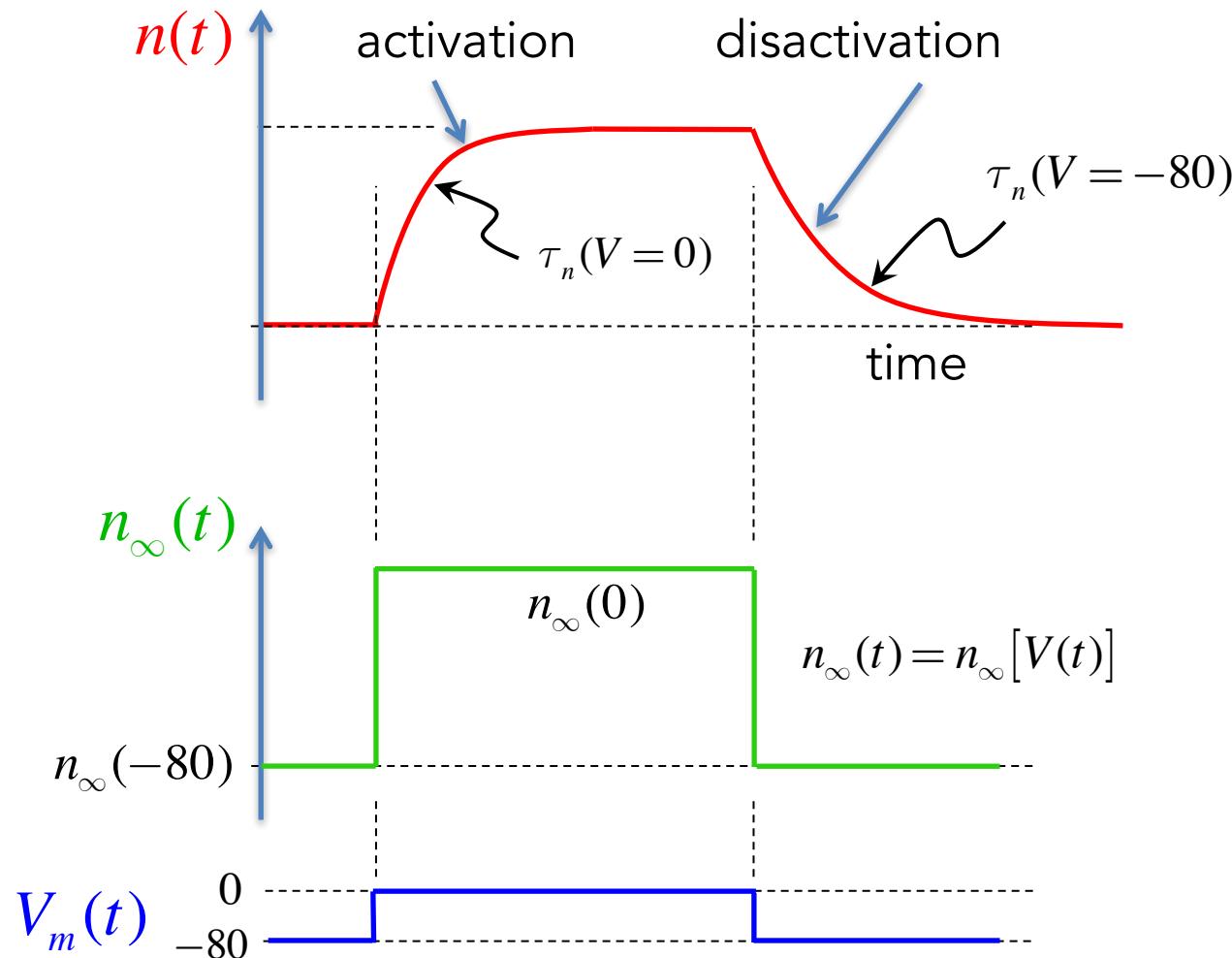
$$\tau_n = \frac{1}{(\alpha_n + \beta_n)}$$

But we just derived  $n_\infty(V)$  !

Remember...  $\alpha_n, \beta_n, n_\infty, \tau_n$  are all voltage dependent

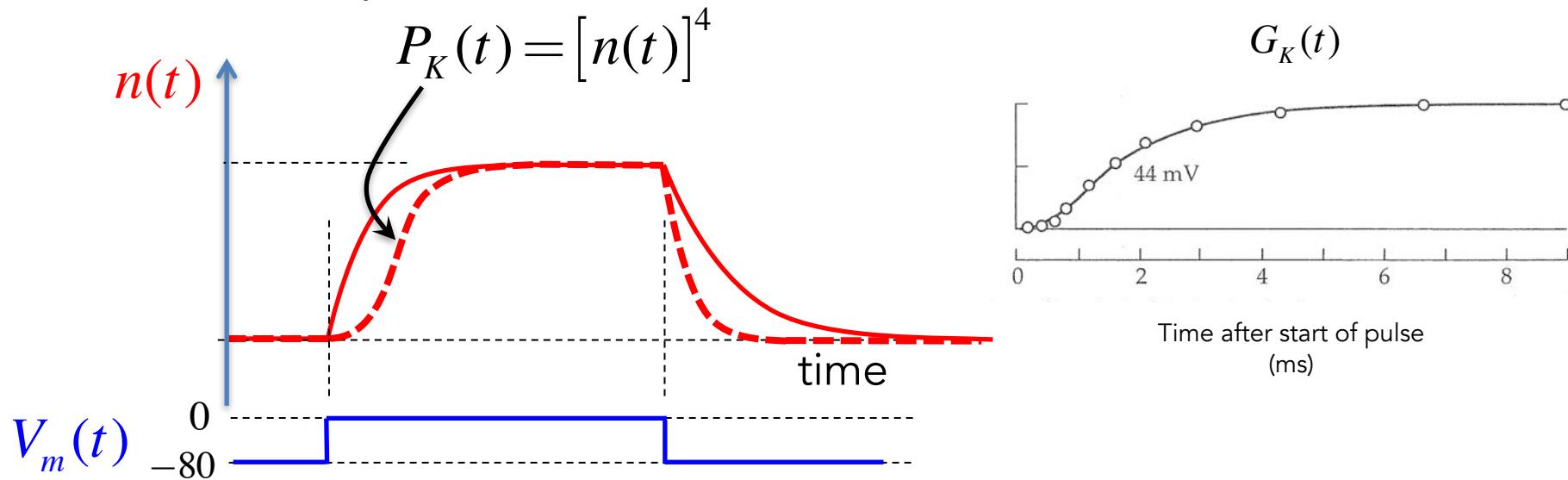
# Response to voltage change

How does the gating variable 'n' change as we step the membrane potential?



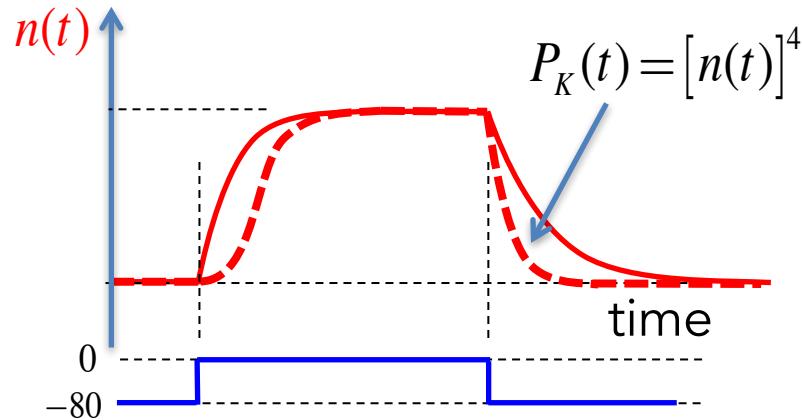
# Response to voltage change

How does the 'open' probability change as we step the membrane potential?

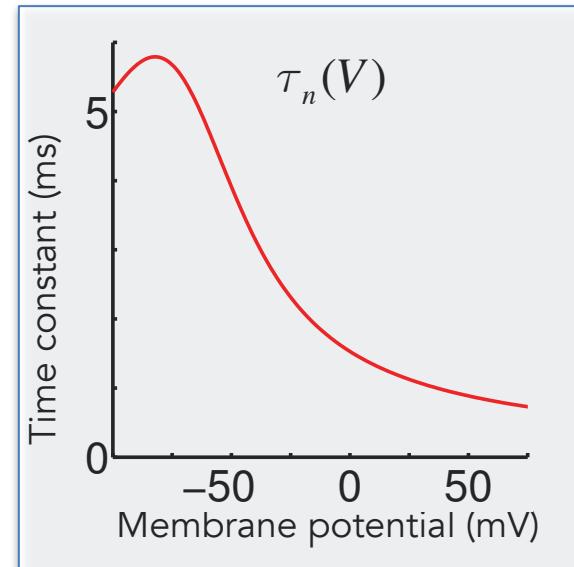
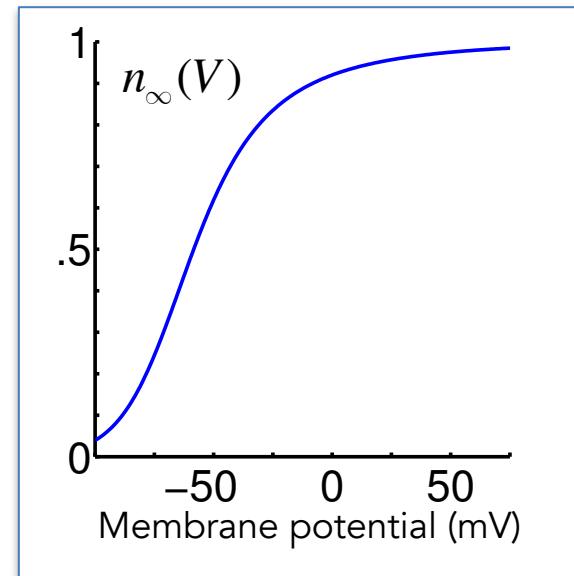


- The shape of the K conductance was well fit by a rising exponential raised to the fourth power.
- H & H inferred from this that the K-current was governed by four independent first-order processes! (They didn't know about the structure of K-channels at the time!)

# Measuring the parameters



- By measuring the persistent conductance at different voltages, they were able to measure  $n_\infty$  as a function of voltage.
- By measuring the time course of the conductance at onset and offset of the voltage steps, they were able to measure  $\tau_n$  as a function of voltage.



# Measuring the parameters

Hodgkin and Huxley summarized their data using algebraic expressions for the rate functions  $\alpha_n(V)$  ,  $\beta_n(V)$

$$\alpha_n(V) = \frac{1}{1 - \exp(-0.1(V + 55))}$$

$$\beta_n(V) = 0.125 \exp(-0.0125(V + 65))$$

$V$  is in mV

$\alpha_n, \beta_n$  are in  $\text{ms}^{-1}$

Remember that...

$$n_\infty = \frac{\alpha_n}{(\alpha_n + \beta_n)}$$

$$\tau_n = \frac{1}{(\alpha_n + \beta_n)}$$

# Measuring the parameters

Why did we do all of this?

Because once we have expressions for  $n_\infty(V)$  and  $\tau_n(V)$ , we can integrate the differential equation for  $n$  :

$$\tau_n \frac{dn}{dt} = n_\infty - n$$

to get the potassium conductance:

$$G_K = \bar{G}_K n^4$$

and the potassium current:

$$I_K = \bar{G}_K n^4 (V - E_K)$$

# We are going to write down an algorithm for how a neuron spikes!

For now here the parts related to the potassium current...

Start with  $V_m$  at time step t

→ Compute  $n_\infty(V)$  and  $\tau_n(V)$

Integrate  $\frac{dn}{dt}$  one time step to get  $n(t)$

Compute K current:  $I_K = \bar{G}_K n^4 (V - E_K)$

Compute total membrane current  $I_m = I_K + I_{Na} + I_L$

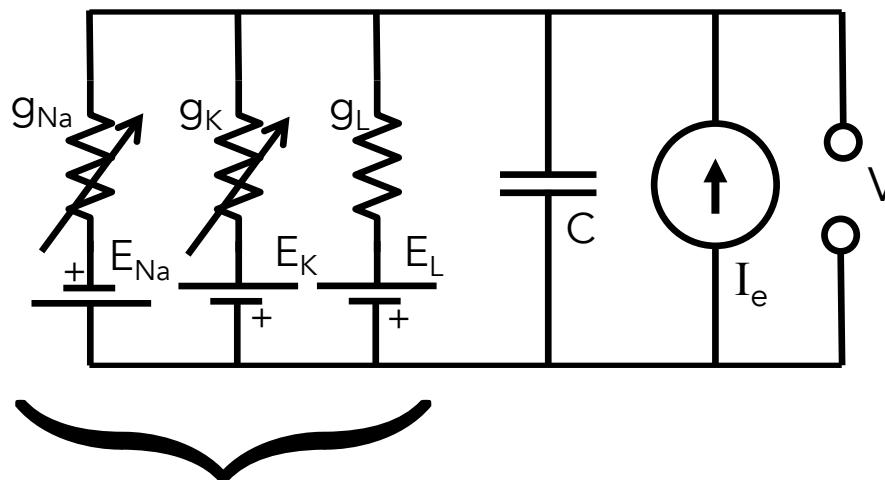
Compute  $V_\infty$

Integrate  $\frac{dV_m}{dt}$  to get  $V_m$  at next time step

# Learning objectives for Lecture 2

- To be able to draw the circuit diagram of the HH model
- Understand what a voltage clamp is and how it works
- Be able to plot the voltage and time dependence of the potassium current and conductance
- Be able to explain the time and voltage dependence of the potassium conductance in terms of Hodgkin-Huxley gating variables

# Outline of HH model



$$I_m = I_{Na} + I_K + I_L$$

$$I_m(t) + C \frac{dV(t)}{dt} = I_e(t)$$

$$I_{Na} = G_{Na}(V,t)(V - E_{Na})$$

The sodium conductance is time-dependent and voltage-dependent

$$E_{Na} = +55\text{mV}$$

$$I_K = G_K(V,t)(V - E_K)$$

The potassium conductance is time-dependent and voltage-dependent

$$E_K = -75\text{mV}$$

$$I_L = G_L(V - E_L)$$

The leak conductance is neither time-dependent nor voltage-dependent

$$E_L = -50\text{mV}$$

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