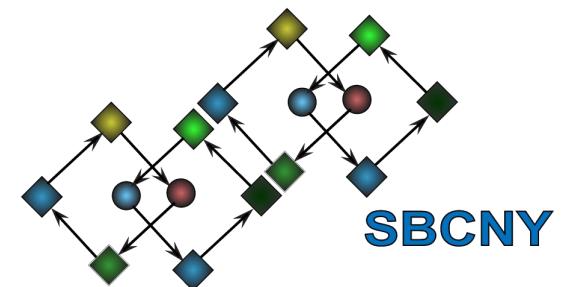


Mathematical models of action potentials

Part 1

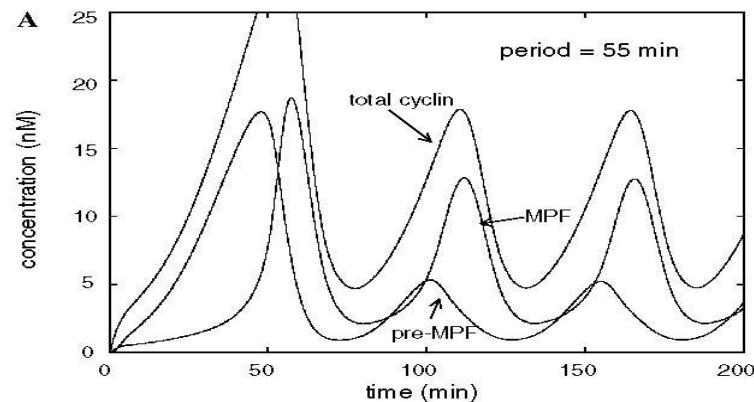


Icahn School of Medicine at Mount Sinai

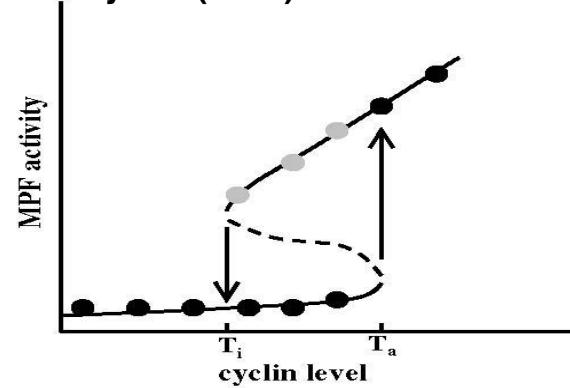


Relating to previous lectures

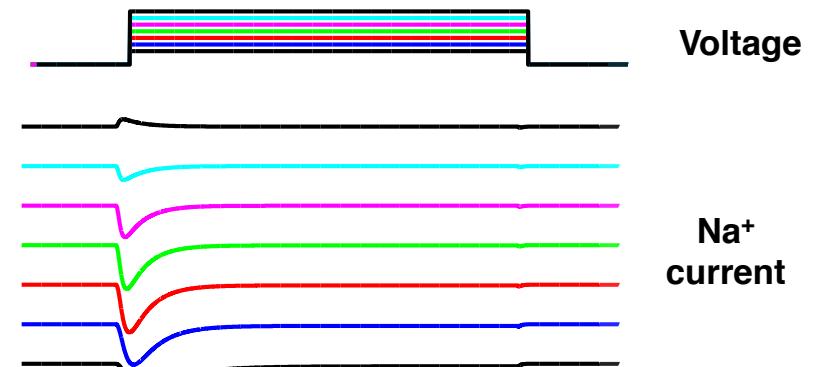
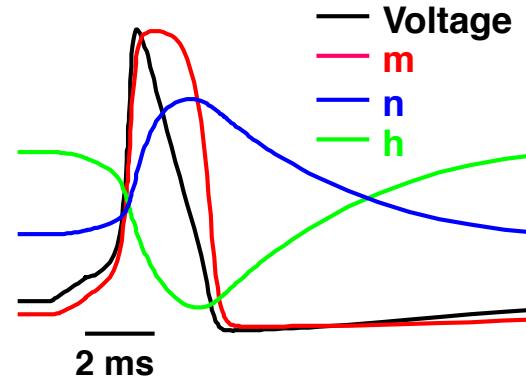
Cell cycle model



Sible & Tyson (2007) *Methods* 41:238-247



Action potential model



Simulation of simplified experiment was critical for both model development and understanding

Outline: Part 1

Biology

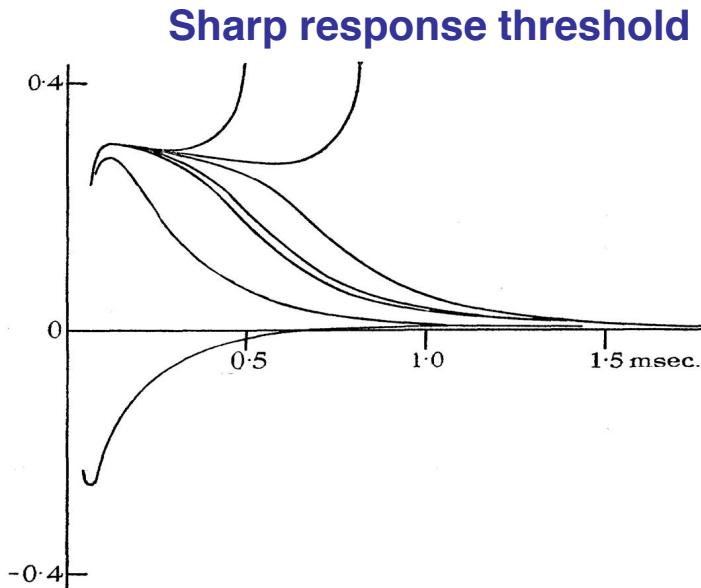
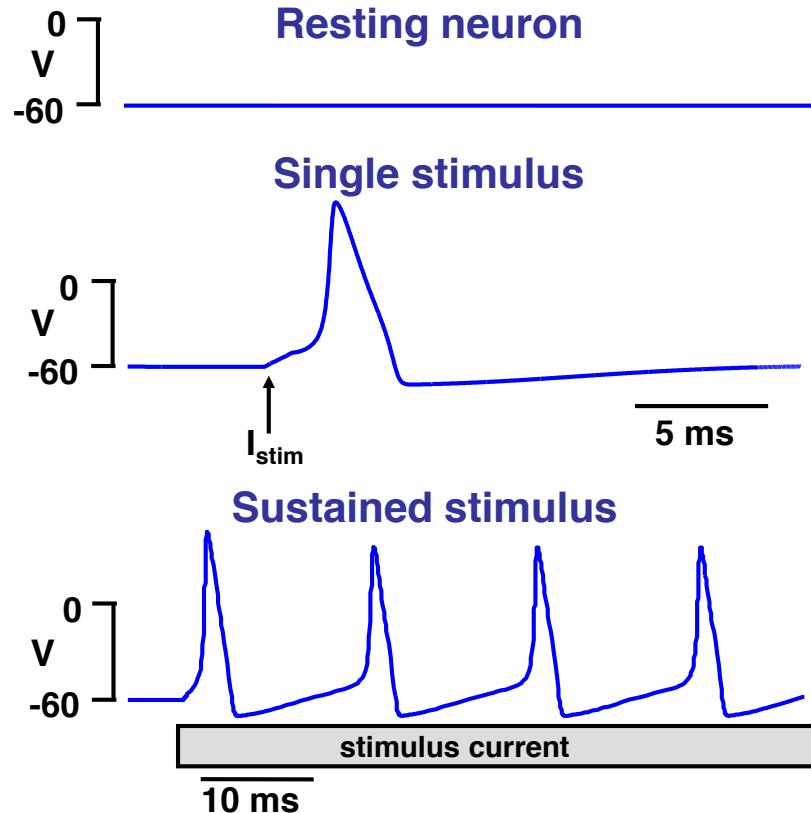
Interesting nonlinear behaviors of excitable cells

Definitions of terms

Electrochemical potential and driving force

Action potentials in squid giant axon

They exhibit unusual nonlinear behavior



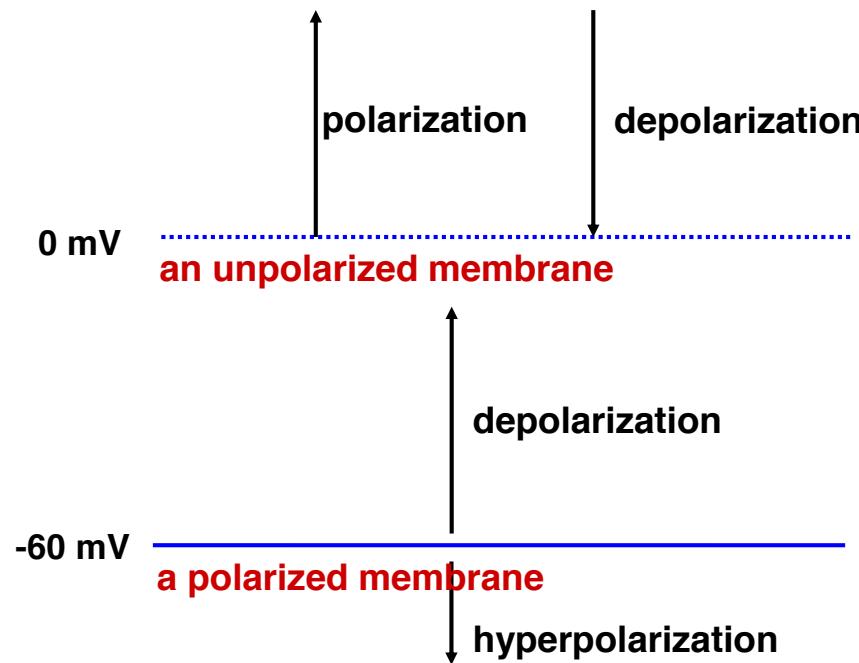
Hodgkin (1938), *Proc. Roy. Soc. B* 126:87-121.

How can we account for this behavior quantitatively?

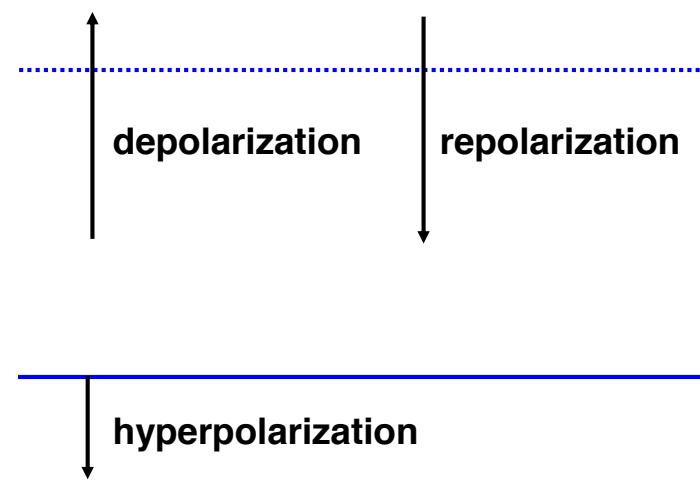
Important definition of terms

Depolarization, repolarization, and hyperpolarization

Technically correct



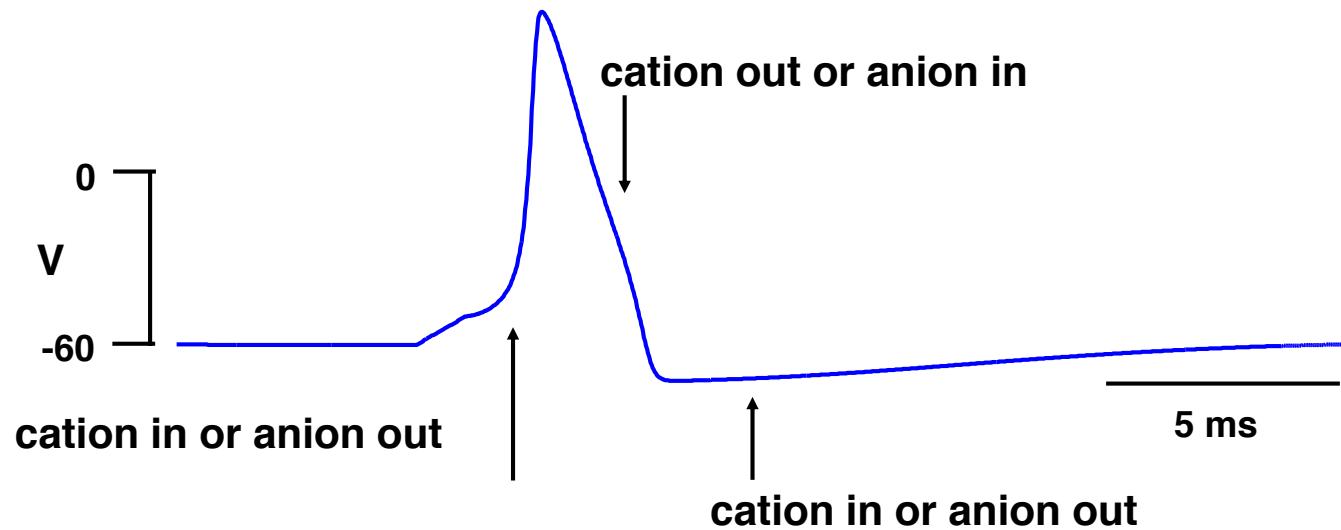
Colloquial



Voltage changes result from ion movements

Cations flowing in depolarize the membrane

Cations flowing out repolarize/hyperpolarize the membrane



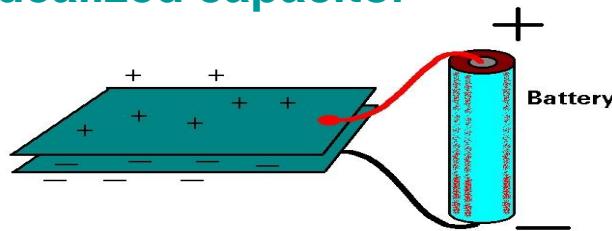
Two questions:

- (1) How to describe depolarization/repolarization quantitatively?
- (2) Which ions are the most likely candidates?

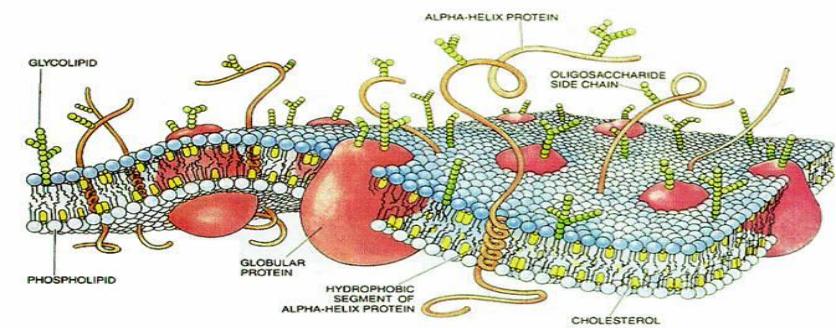
The cell membrane is a capacitor

Idealized capacitor

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



Cell membrane

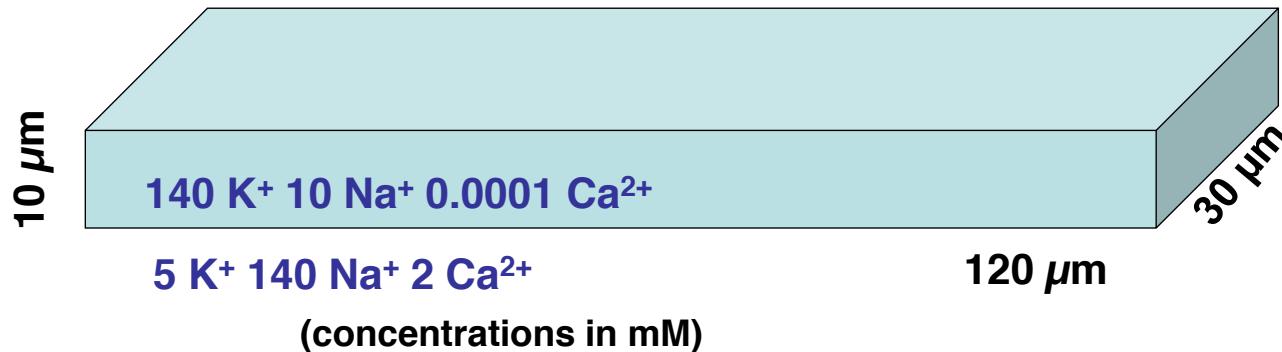


This is where we get our differential
equation for membrane voltage

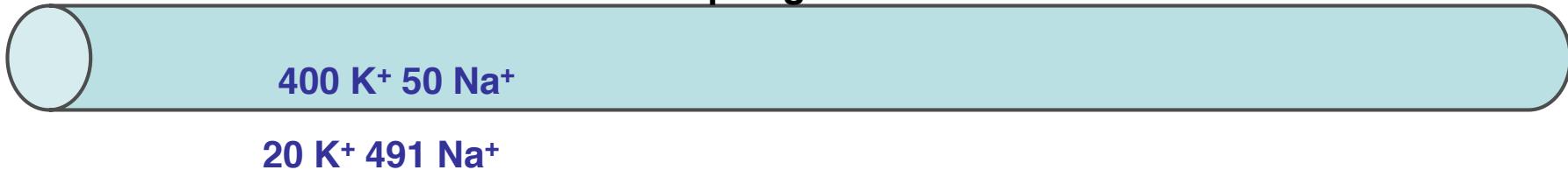
$$C_m \frac{dV}{dt} = -I_{ion}$$

Ionic concentrations in cells

Mammalian ventricular myocyte

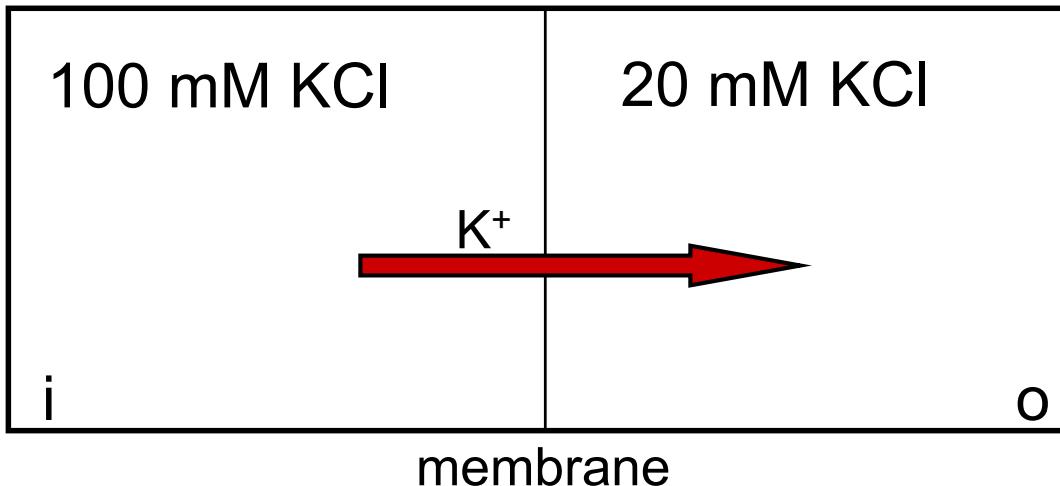


Squid giant axon



Thus, diffusion will drive Na⁺ inward, K⁺ outward
These movements will depolarize or hyperpolarize the membrane, respectively

Concentration Cell



Membrane permeable to K⁺ but not to Cl⁻

Qualitatively, what happens when [KCl] on left is increased?

- 1) K⁺ ions flow from left to right.
- 2) Excess positive ions on right produce voltage difference
- 3) Voltage difference opposes left→right movement of K⁺
- 4) Eventually, an equilibrium is reached.

How can we understand this more quantitatively?

Electrochemical potential

$$\mu = \mu^0 + RT \ln C + zFV$$

What is the significance of each term?

μ^0

this is the "standard" electrochemical potential
(same on both sides, can ignore)

$RT \ln C$

this term describes diffusion: a higher concentration leads to a higher electrochemical potential

zFV

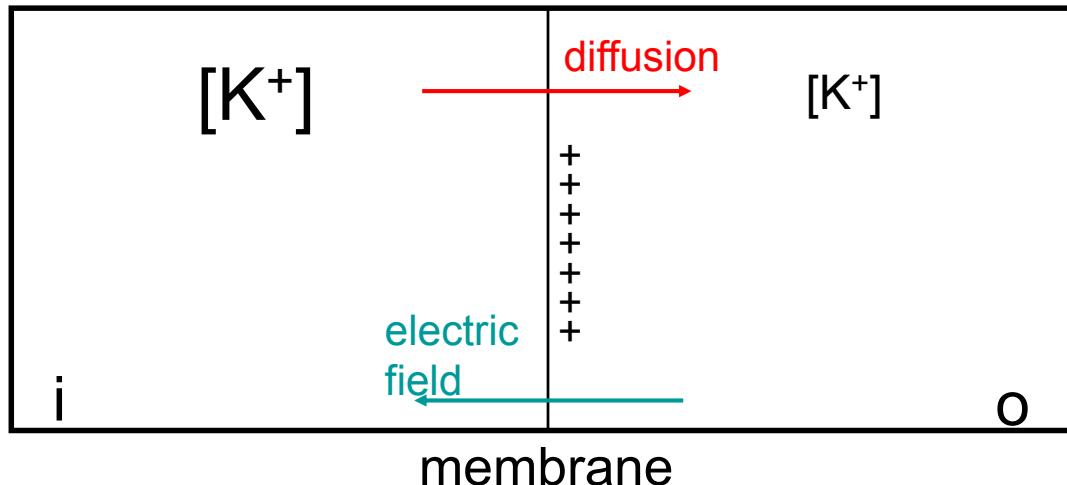
this term describes electrical effects: greater voltage means greater electrochemical potential, for positively charged species only ($z > 0$)

Like a ball rolling down a hill, species want to move from higher to lower electrochemical potential

Units are J/mol

Energy, normalized by how much is present

Electrochemical potential



At equilibrium, $\mu_i = \mu_o$

$$RT \ln C_i + zFV_i = RT \ln C_o + zFV_o$$

Then, rearranging terms:

$$zF(V_i - V_o) = RT(\ln C_o - \ln C_i)$$

$$V_i - V_o = \frac{RT}{zF} \ln \frac{C_o}{C_i}$$

This is definition of equilibrium or Nernst potential

So in the squid giant axon

Squid giant axon

400 K⁺ 50 Na⁺

20 K⁺ 491 Na⁺

Each ion associated with a Nernst potential

$$E_x = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i}$$

$$E_K = -72 \text{ mV} \quad E_{Na} = +55 \text{ mV}$$

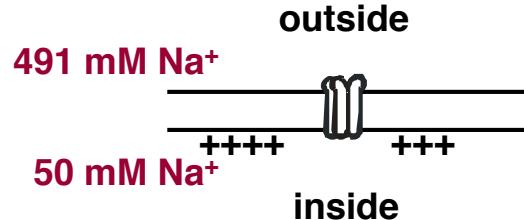
The distance away from the reversal potential, V-E_x is the "driving force" for ion X.

This is basically converting electrochemical potential from units of J/mol to units of volts (J/C), i.e.

$$V - E_x = \frac{\Delta\mu_x}{F}$$

Driving force and ionic currents

Defined as: $V - E_{Na}$



If $V - E_{Na} > 0$, $\Delta\mu_{Na} > 0$, Na^+ moves out of the cell

If $V - E_{Na} < 0$, $\Delta\mu_{Na} < 0$, Na^+ moves into the cell

Ionic current, then, can be calculated as:

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

Units:

V, E_{Na} : mV

I_{Na} : $\mu A/cm^2$ ($\mu A/\mu F$)

g_{Na} : mS/cm^2 ($mS/\mu F$)

By convention, inward current is negative

In general, g_x can be dependent on both V and time

Summary

Neurons exhibit complex non-linear behavior that is challenging to describe mathematically.

Changes in membrane potential (voltage) result from ion movements across the cell membrane.

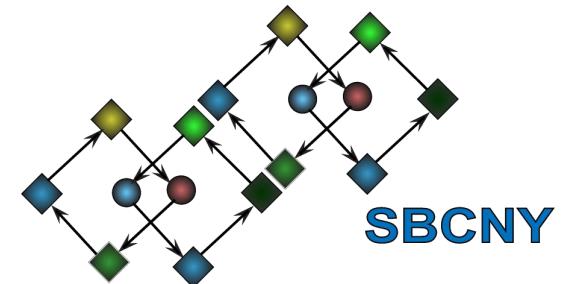
Electrochemical potentials determine which direction ions move, with the Nernst potential representing equilibrium.

Mathematical models of action potentials

Part 2



Icahn School
of Medicine at
Mount
Sinai



Outline: Part 2

Biology

The challenges in understanding neuronal electrophysiology

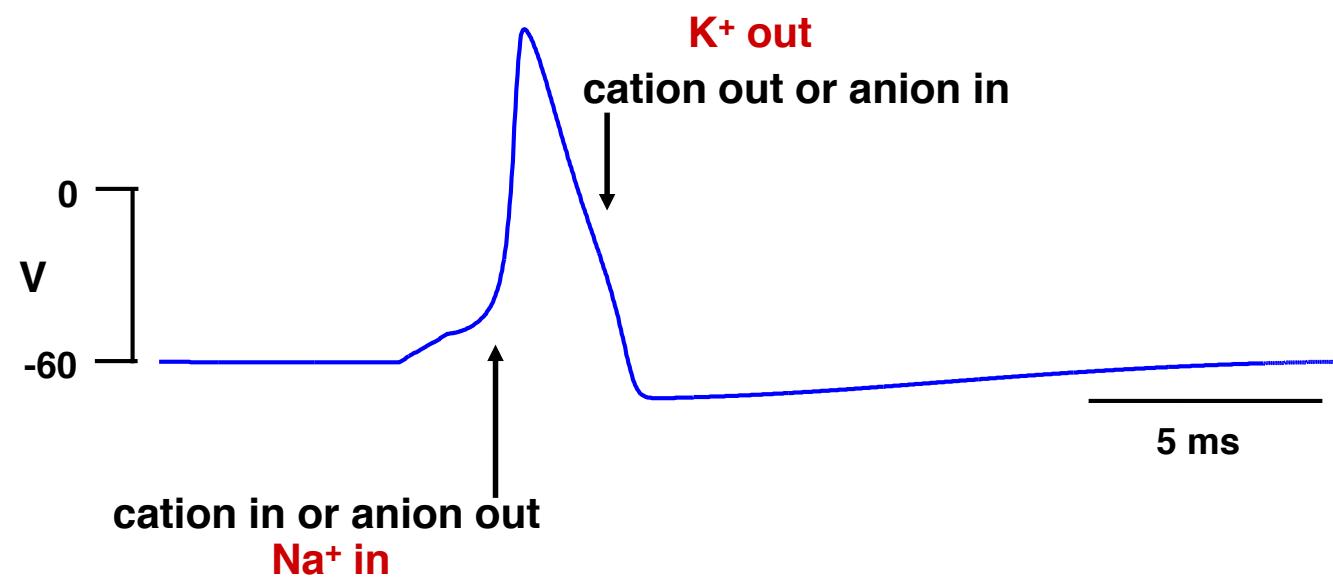
The importance of the voltage-clamp technique

Separating Na^+ and K^+ currents

Theme

**Voltage clamp was the key advance that made the
Hodgkin-Huxley model possible**

Voltage changes result from ion movements



Why do we call this the Hodgkin-Huxley model?

Sir Alan Hodgkin



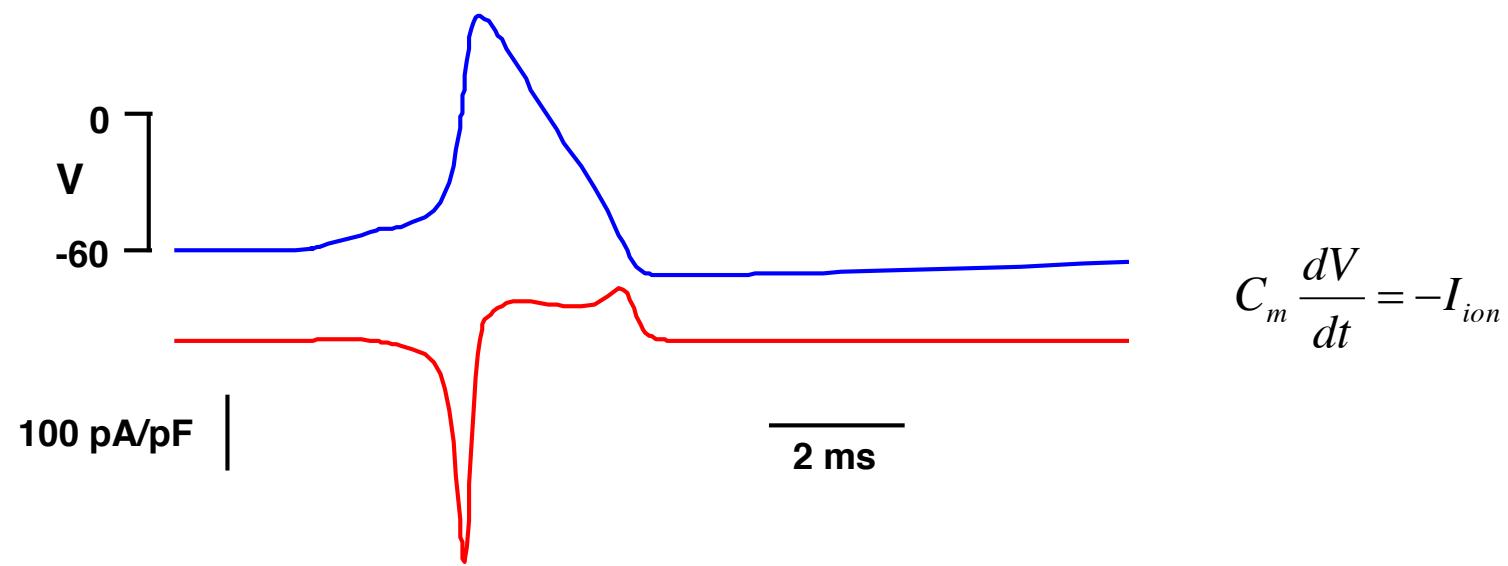
1914-1998
Nobel Prize 1963

Sir Andrew Huxley



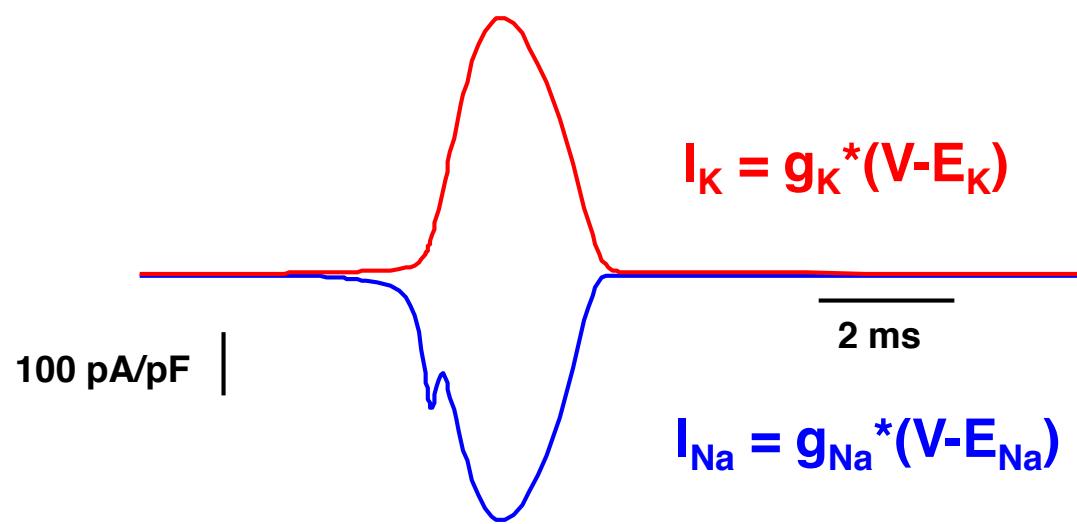
1917-2012
Nobel Prize 1963

What if Hodgkin & Huxley knew the currents?



Imagine that we can magically separate Na^+ and K^+ currents

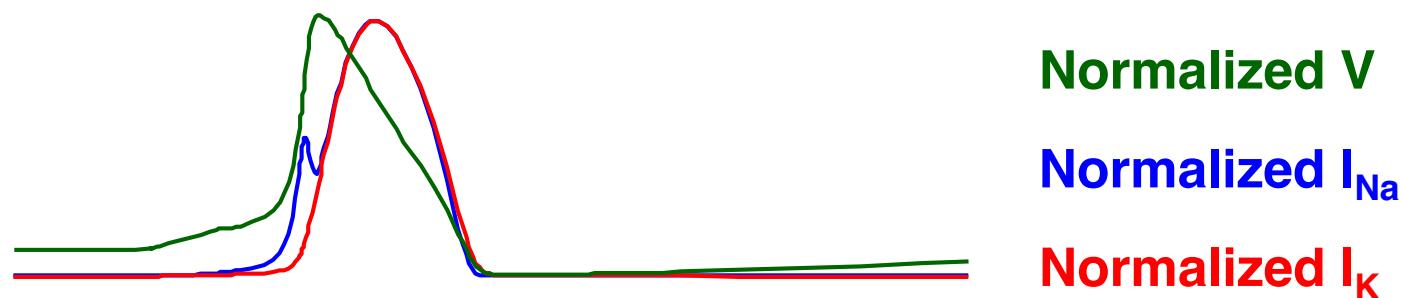
What if Hodgkin & Huxley knew the currents?



Change in current could result from:
change in conductance g_x , or
change in driving force $V-E_x$

Now let's plot V , I_K , and I_{Na} all on the same scale

What if Hodgkin & Huxley knew the currents?



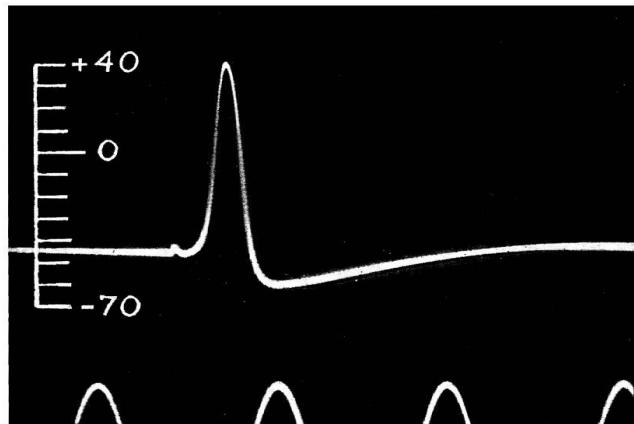
So the problem is:

- (1) a change in voltage causes a change in current
- (2) a change in current causes a change in voltage

This makes it difficult to separate

Brief historical note

Action potential recorded at Marine Biological Association at Plymouth



Hodgkin & Huxley (1939) *Nature* 144:710-711

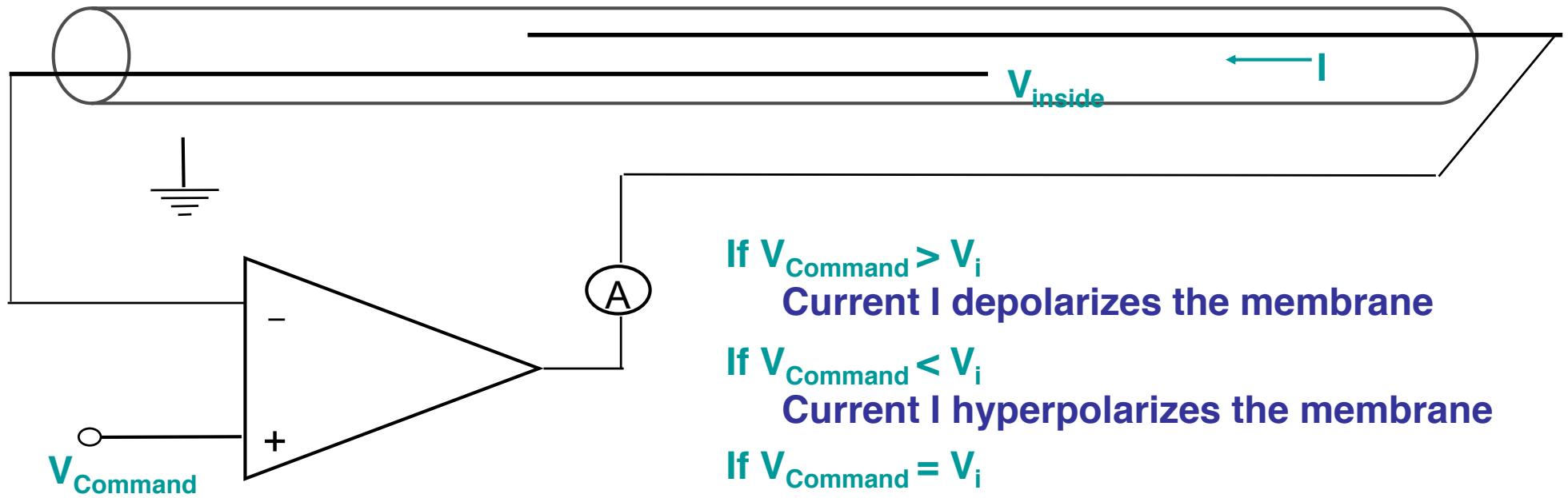
Hodgkin & Huxley left Plymouth: August 30, 1939

Hitler invaded Poland: September 1, 1939

“We published this result in a letter in *Nature* (1939) with no discussion or explanation. In a full paper (1945) we gave four possible explanations, all wrong.”

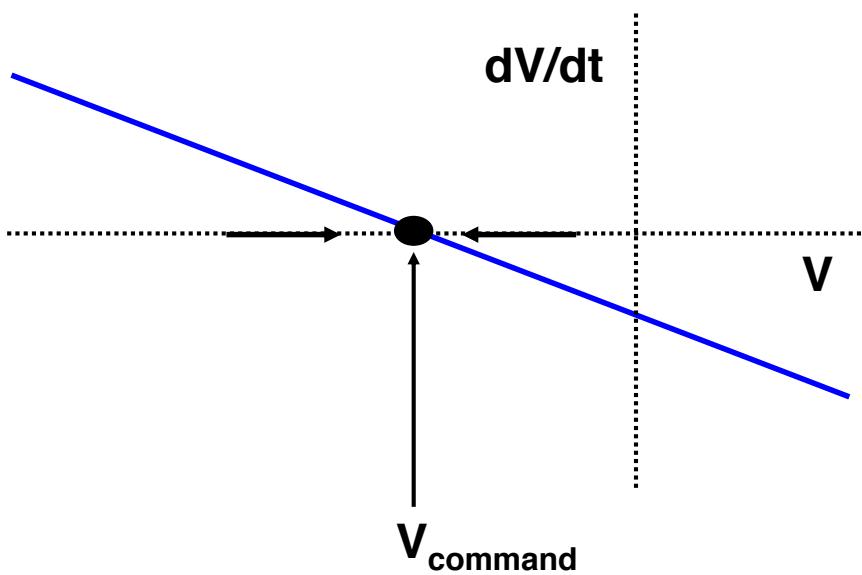
Huxley (2002) *J. Physiol.* 539:2

Voltage clamp of squid giant axon



Current I required to keep $V_{command}=V_i$ is equal in magnitude to current flowing across the membrane

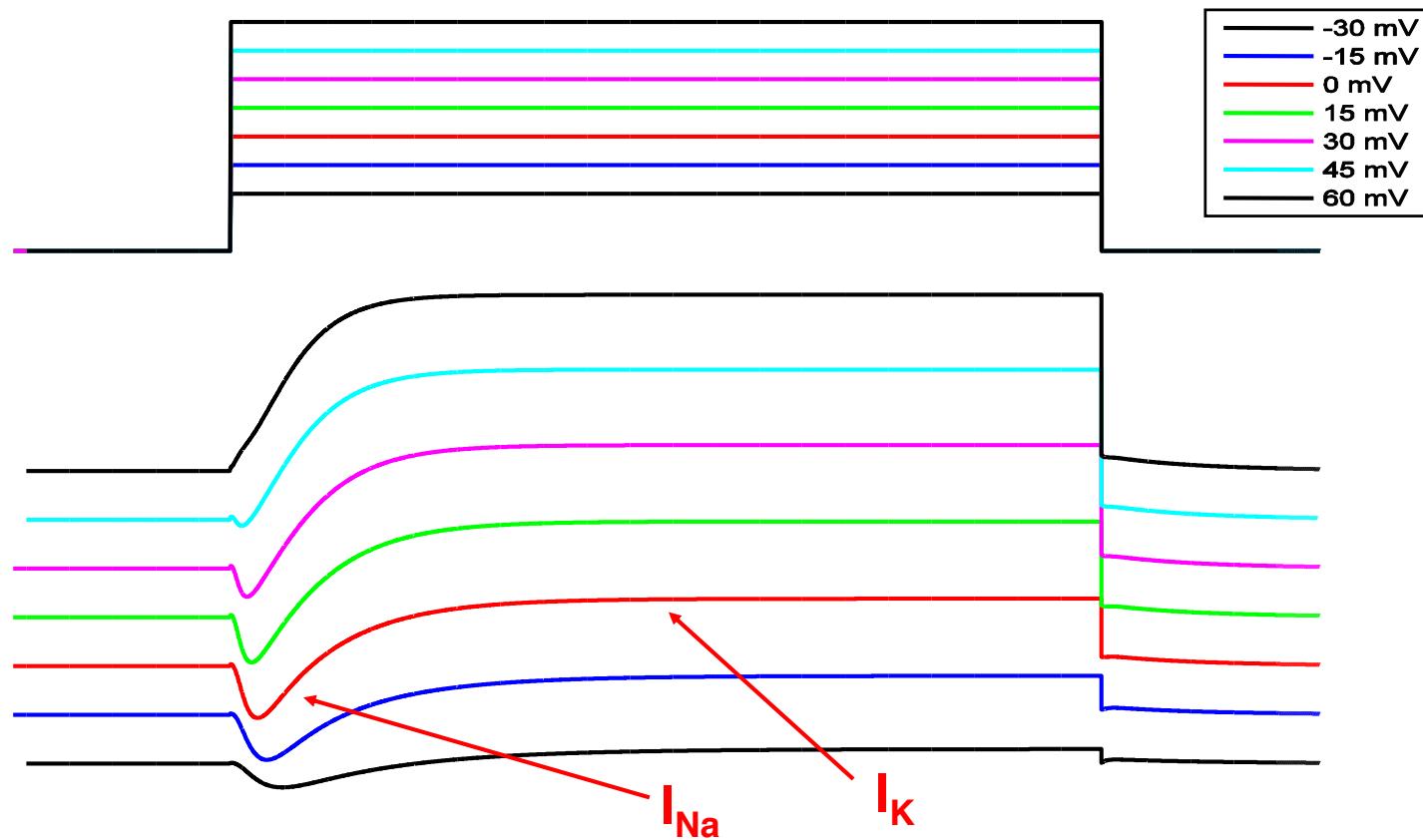
Voltage clamp as 1D dynamical system



- If $V_{\text{Command}} > V_i$
Current I depolarizes the membrane
- If $V_{\text{Command}} < V_i$
Current I hyperpolarizes the membrane
- If $V_{\text{Command}} = V_i$
Current I is zero

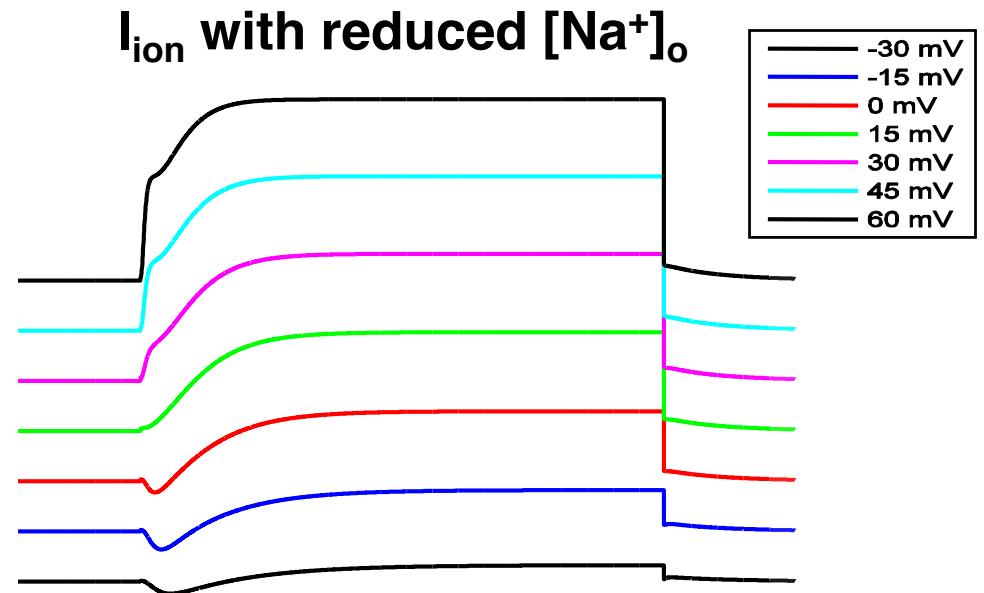
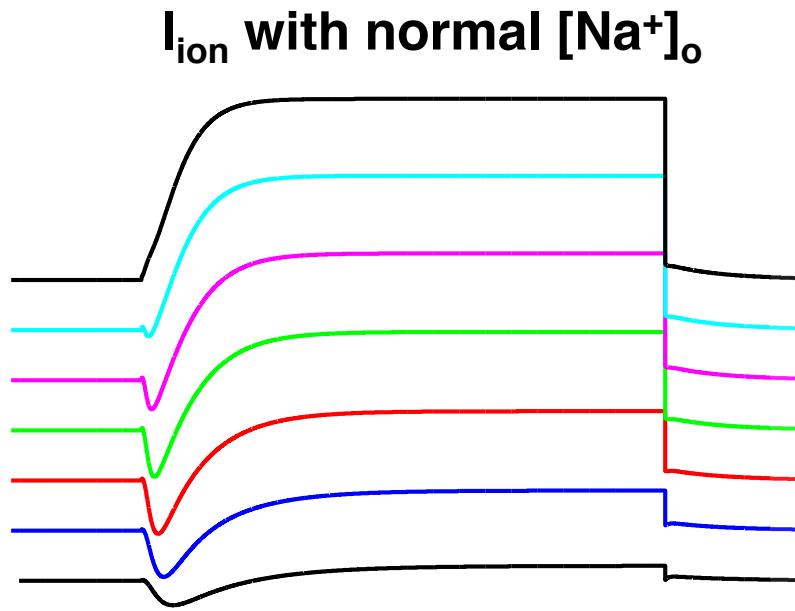
Command voltage therefore constitutes a stable fixed point

Currents recorded under voltage clamp



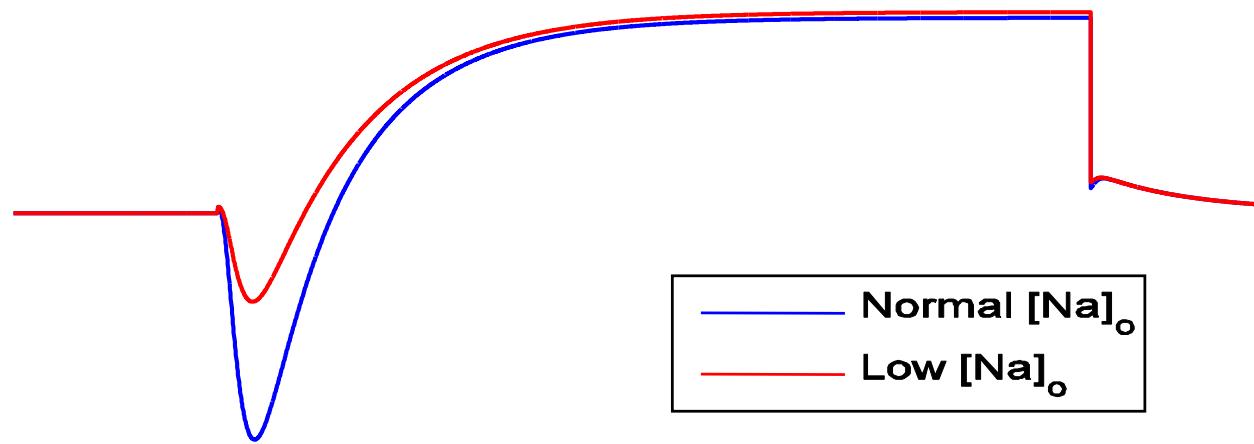
How can I_{Na} and I_K be separated?

A clever technique for separating I_{Na} and I_K



Assume that changing $[Na^+]_o$ only affects I_{Na} , not I_K

A clever technique for separating I_{Na} and I_K



$$I_{ion} = I_{Na} + I_K$$

$$I'_{ion} = I'_{Na} + I'_{K}$$

Assume that:

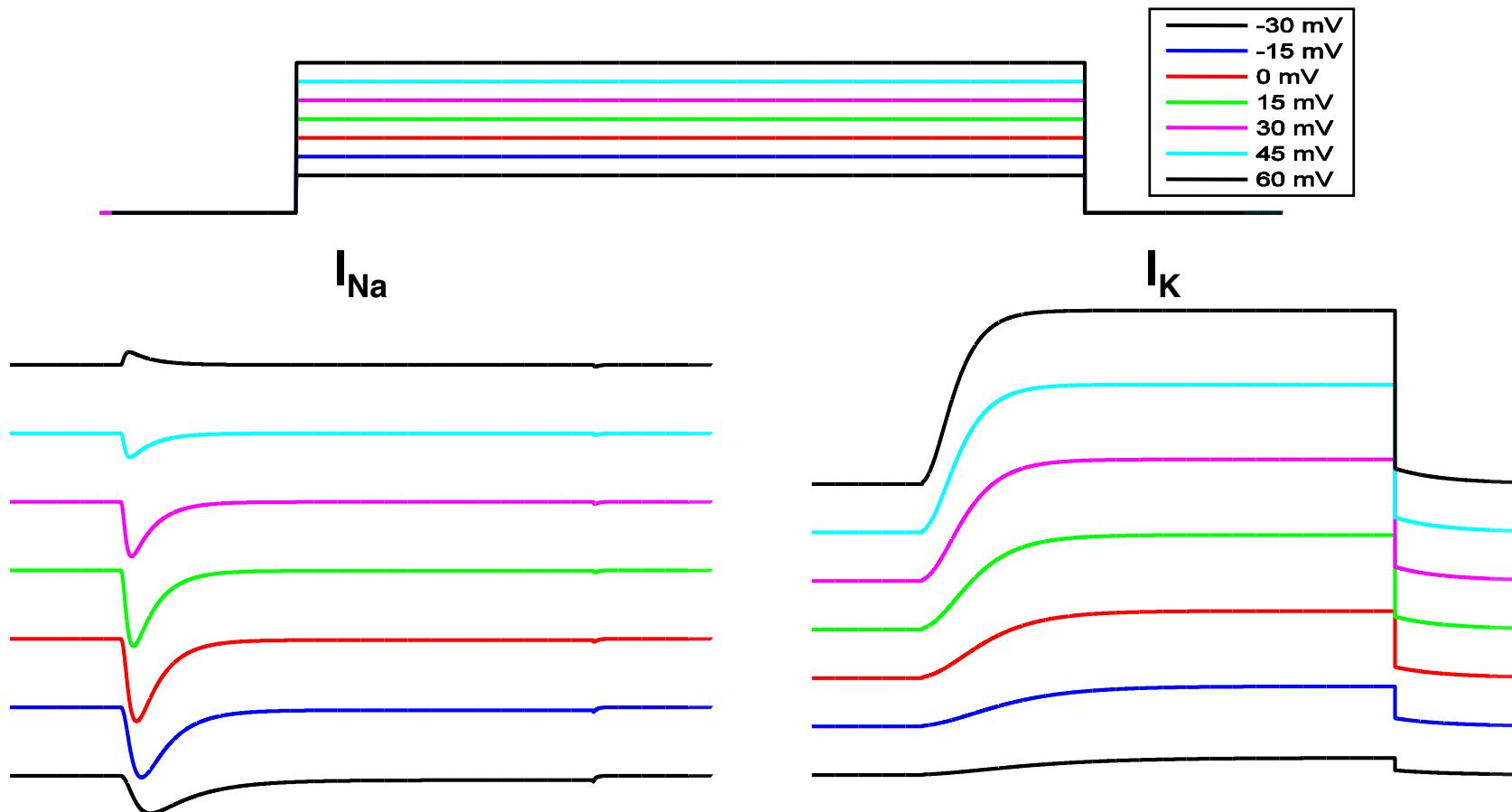
$$I'_K = I_K$$

$$I'_{Na} = K^* I_{Na}$$

It follows that:

$$I_{Na} = (I_{ion} - I'_{ion}) / (1 - K) \quad I_K = (I'_{ion} - K^* I_{ion}) / (1 - K)$$

I_{Na} and I_K at different membrane potentials



How do we go from these recordings to the famous equations?

Summary

Membrane voltage and ionic currents in neurons are interdependent, which makes it difficult to develop mathematical representations.

The voltage clamp method, pioneered by Hodgkin and Huxley, allows for the currents to be recorded while voltage is controlled.

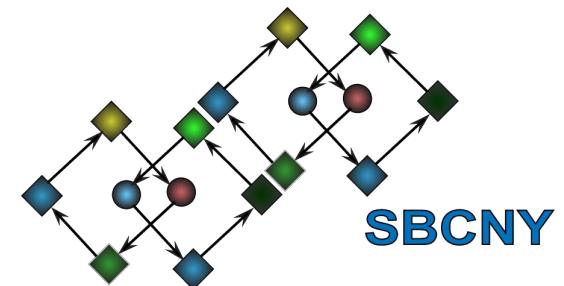
Voltage clamp was the key advance that made the Hodgkin-Huxley model possible.

Mathematical models of action potentials

Part 3



Icahn School
of Medicine at
**Mount
Sinai**



Outline: Part 3

The Hodgkin-Huxley (1952) action potential model

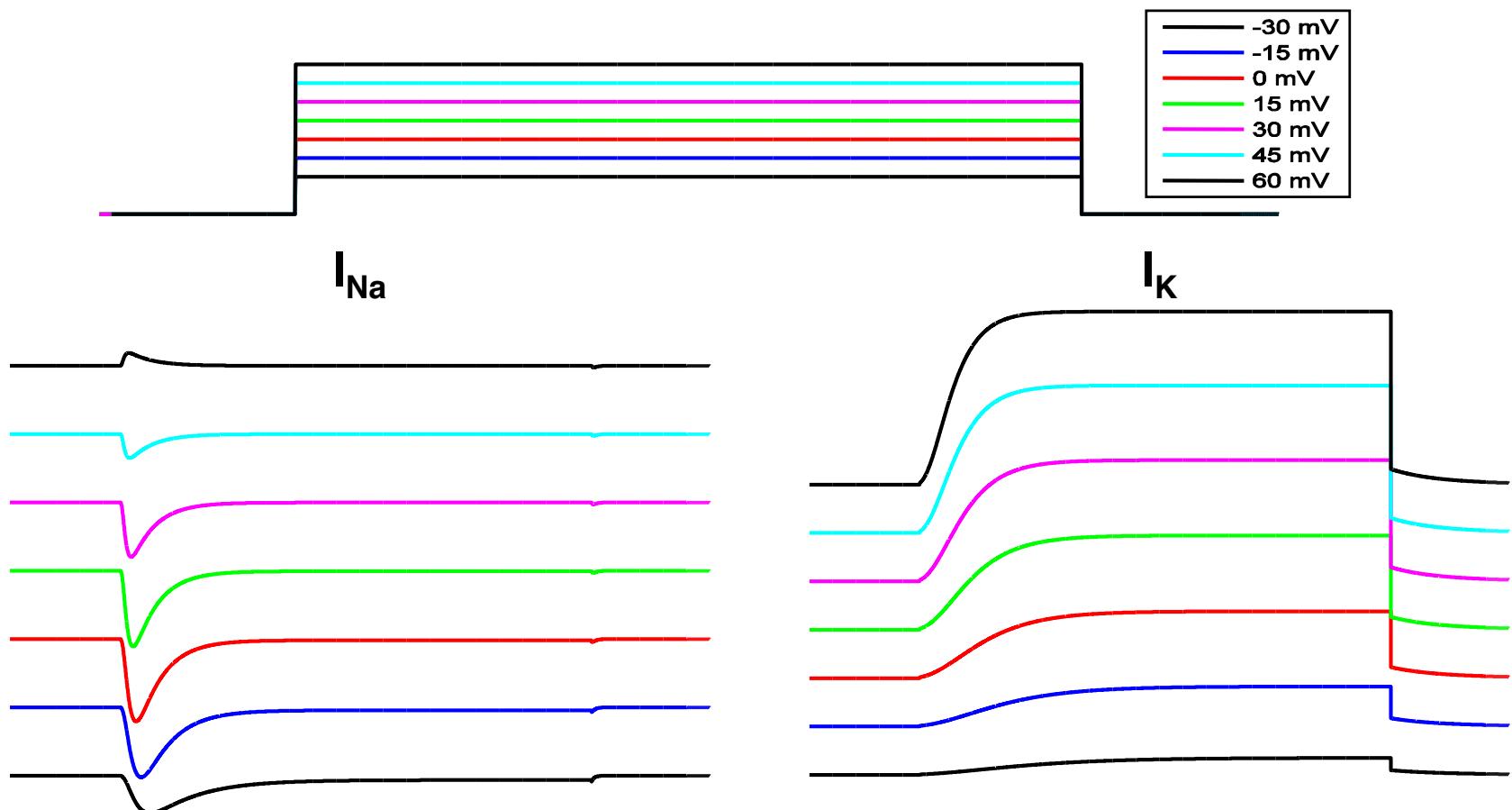
Deriving the model equations from the experimental records

Converting from currents to conductances

K⁺ conductance: increases with a delay

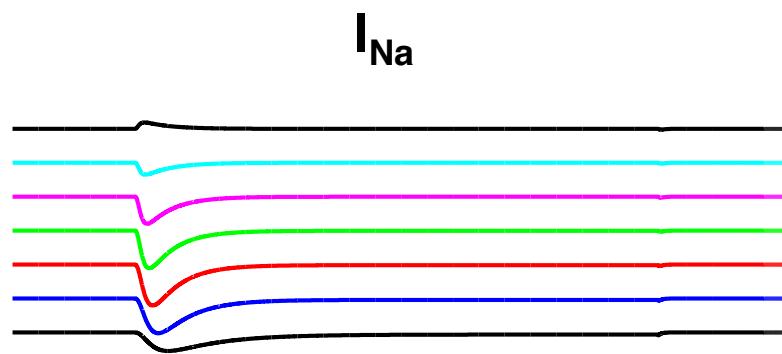
Na⁺ conductance: increases then decreases (inactivates)

I_{Na} and I_K at different membrane potentials



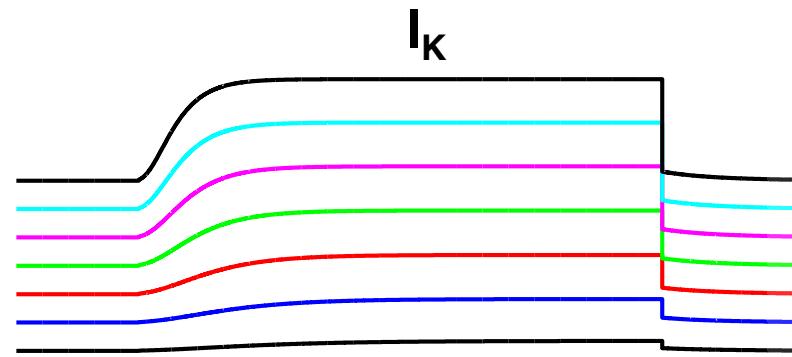
$I_x = g_x^*(V - E_x)$, change in current can reflect conductance or driving force

Convert from currents to conductances



$$I_{Na} = g_{Na} * (V - E_{Na})$$

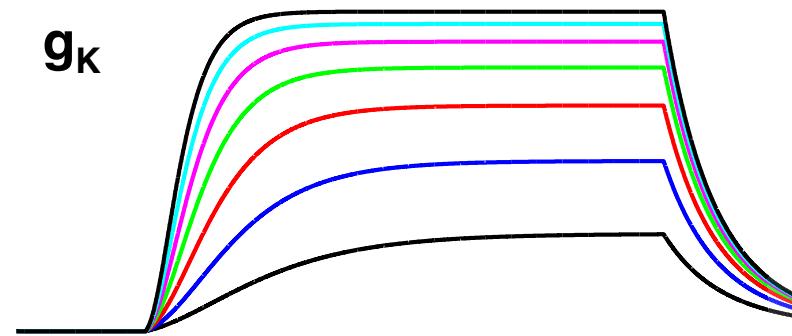
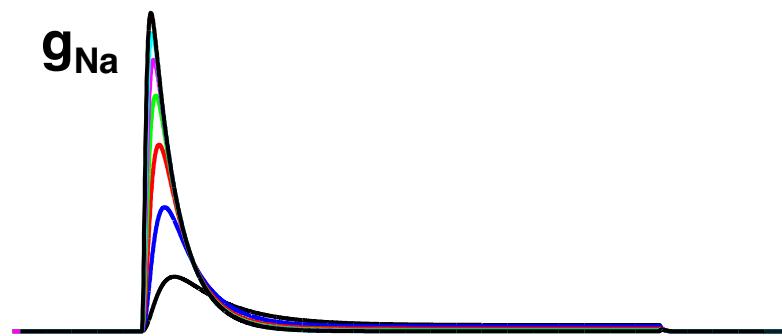
$$g_{Na} = I_{Na} / (V - E_{Na})$$



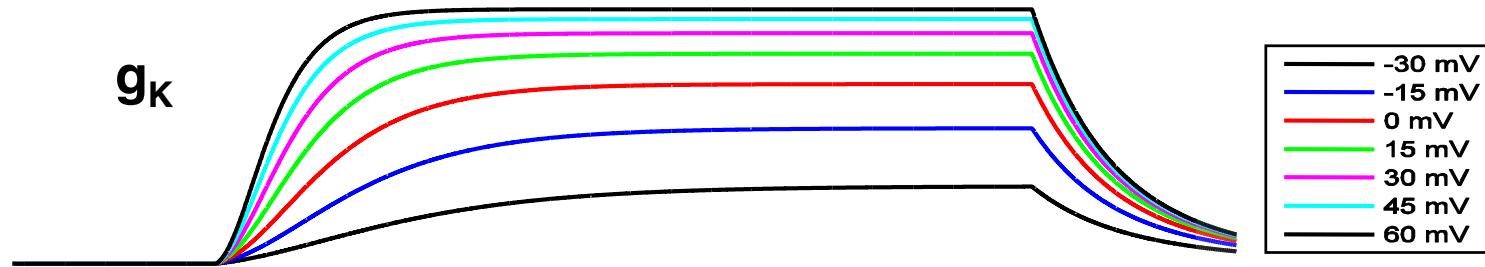
$$I_K = g_K * (V - E_K)$$

$$g_K = I_K / (V - E_K)$$

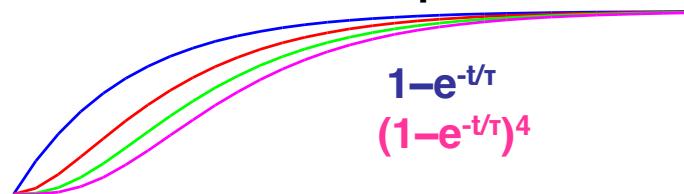
therefore:



Focus on potassium conductance



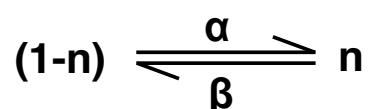
- 1) Changing V changes both steady-state g_K and rate of rise
- 2) Time course of g_K increase similar to an exponential raised to a power



These facts suggest the following model:

n = fraction of particles in "permissive" state
conductance proportional to n^4

$$g_K = g_{K,\max} n^4$$



$$\frac{dn}{dt} = \alpha(1-n) - \beta n$$

α and β are functions of voltage

gating variable n
always between 0 and 1

How are the functions for $\alpha(V)$ and $\beta(V)$ determined?

$$dn/dt = \alpha(1-n) - \beta n = \alpha - (\alpha + \beta)n$$

This equation has the steady-state ($t=\infty$) solution:

$$n_{\infty} = \alpha/(\alpha + \beta)$$

The steady-state value is reached with a time constant:

$$\tau = 1/(\alpha + \beta)$$

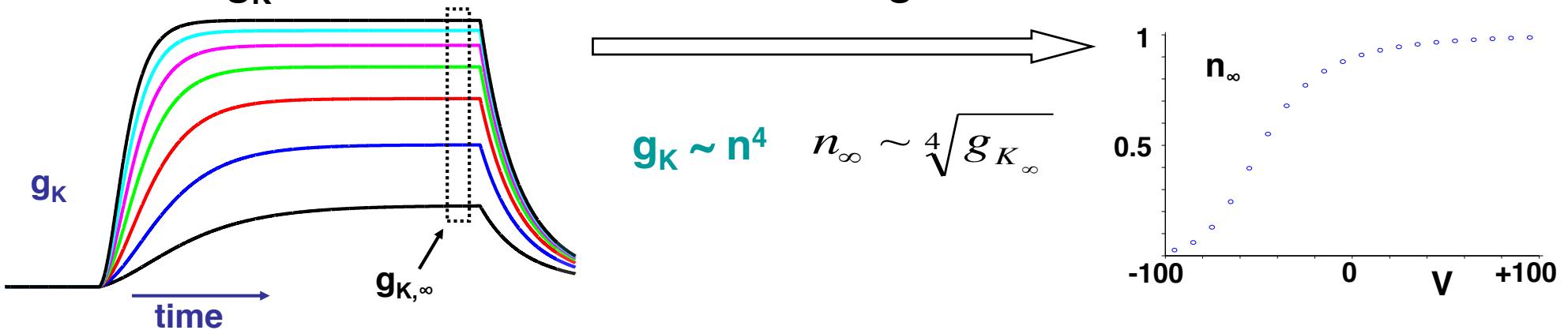
Rearranging terms: $\alpha=n_{\infty}/\tau$ $\beta=(1 - n_{\infty})/\tau$

So if we know $n_{\infty}(V)$ and $\tau(V)$, we can determine $\alpha(V)$ and $\beta(V)$

$n_{\infty}(V)$ and $\tau(V)$ can be extracted from the data. How?

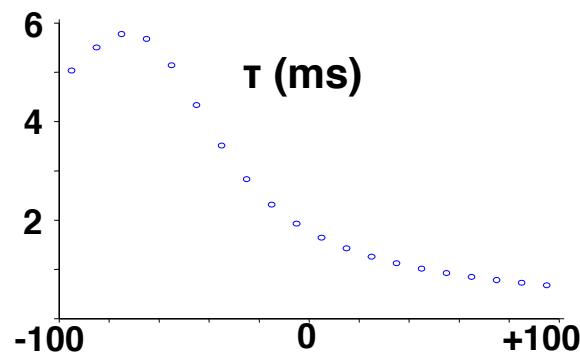
How are the functions for $\alpha(V)$ and $\beta(V)$ determined?

g_K as a function of time and voltage tells us n_∞ and τ



$$g_K \sim n^4 \quad n_\infty \sim \sqrt[4]{g_{K,\infty}}$$

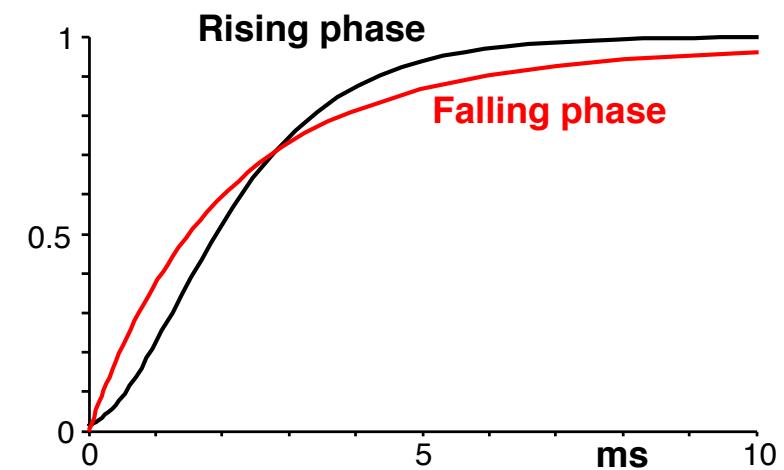
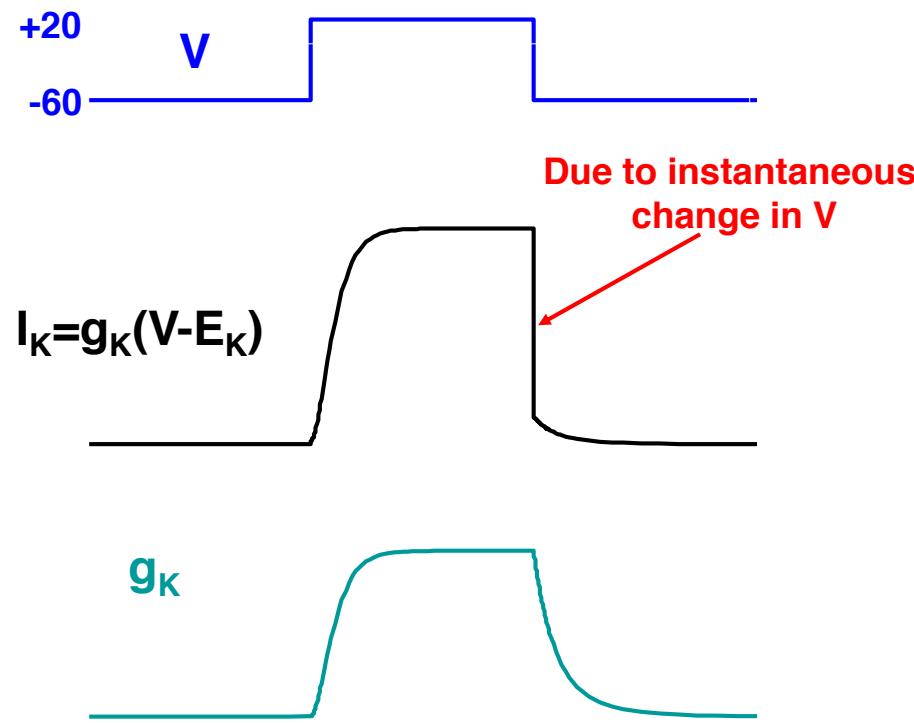
To determine $\tau(V)$, plot $(1 - e^{-t/\tau})^4$ for different τ , choose best fit



Then solve: $\alpha = n_\infty / \tau$ $\beta = (1 - n_\infty) / \tau$

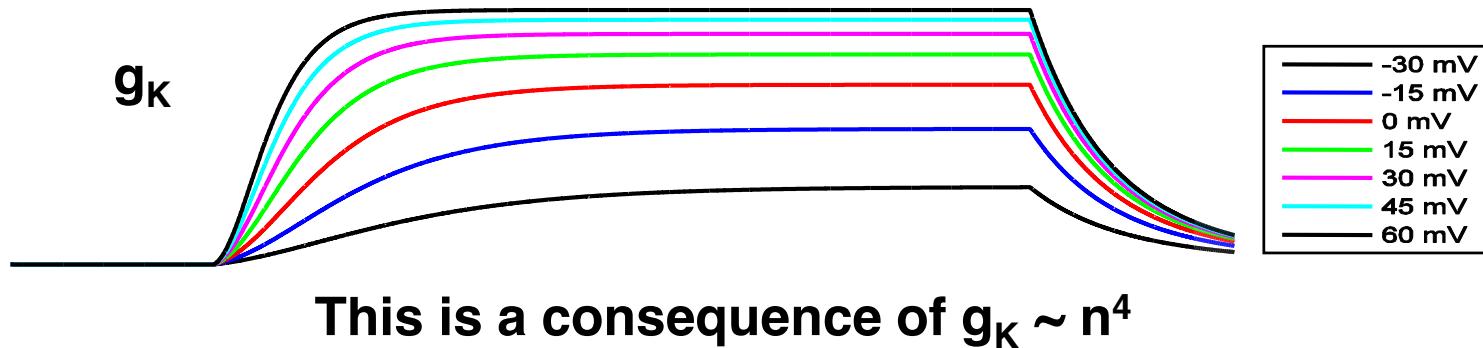
Time course of conductance changes

Rising phase has a delay, falling phase does not!

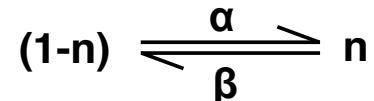


Time course of conductance changes

Rising phase has a delay, falling phase does not!



This is a consequence of $g_K \sim n^4$



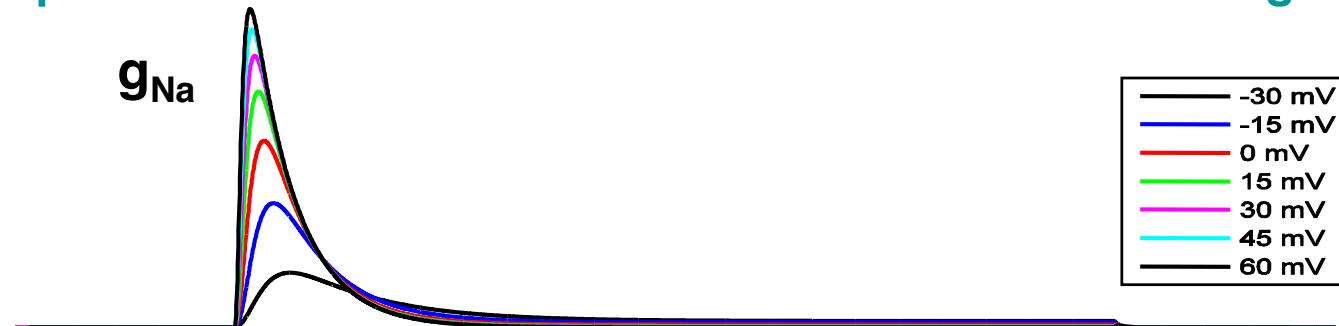
When conductance increases, all 4 charged particles must move
When conductances decreases, 1 out of 4 is sufficient

This model now has a well-established physical basis, namely
that as most ion channels are tetramers.

Focus on sodium conductance

Slightly more complicated than g_K

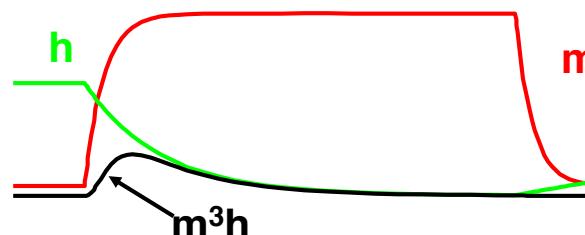
How to explain both the increase and decrease at constant voltage?



H & H postulated separate activation and inactivation processes

$$g_{Na} \sim m^3 h$$

Both must be > 0 for appreciable g_{Na}



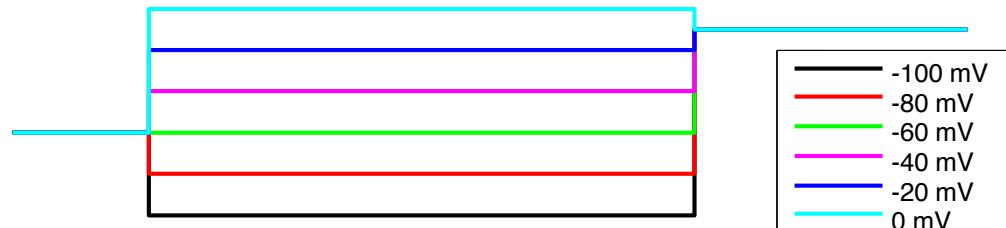
m must be faster than h

This idea also now has a physical basis, "ball-and-chain" inactivation.

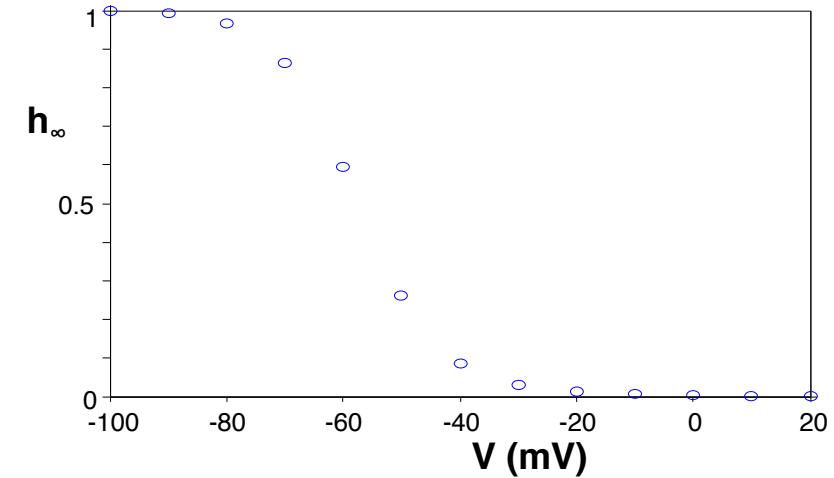
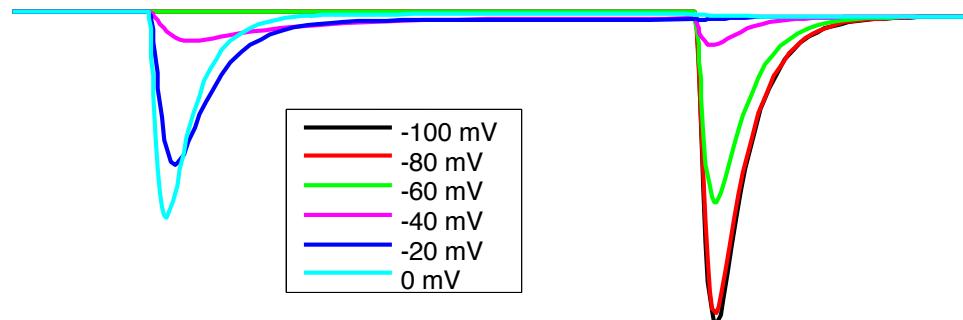
Focus on sodium conductance

How to derive both m and h from the data?

A clever experiment to measure steady-state value of h



Measure I_{Na} due to *second* pulse



If first pulse is long, this gives value of steady-state inactivation, h_∞ .

Summary

Changes in K⁺ conductance and Na⁺ conductance can be described by “gating variables” that range from 0 to 1.

K⁺ conductance is described by a single variable (n). Na⁺ conductance is described by the product of an activation variable (m) and an inactivation variable (h).

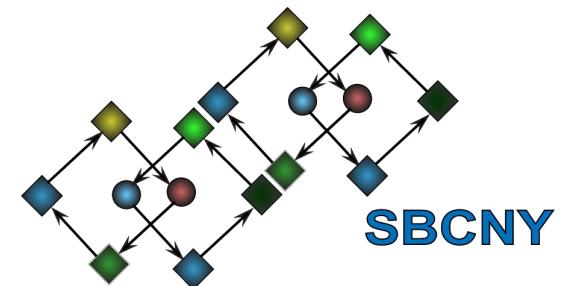
The terms describing how gating variables depend on voltage are extracted directly from the experimental voltage clamp data.

Mathematical models of action potentials

Part 4



Icahn School
of Medicine at
Mount
Sinai



Outline: Part 4

Example results with Hodgkin-Huxley model

Sub-threshold and supra-threshold responses

Refractoriness

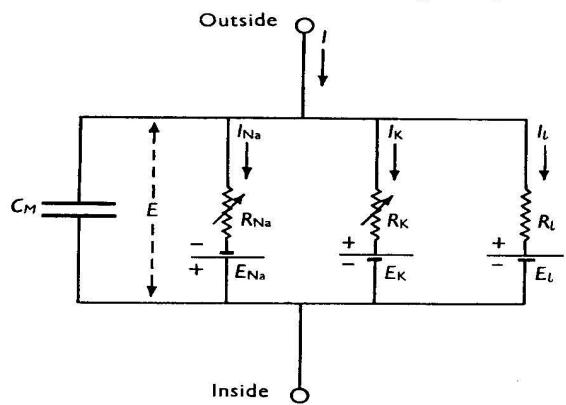
Anode break excitation

Theme

**Each of these simulations represented an independent
validation of the model.**

Overall Hodgkin-Huxley model

Membrane represented as parallel conductances



Hodgkin & Huxley (1952), *J. Physiol.* 117:400.

Four ODEs

$$C_m \frac{dV}{dt} = -g_L(V - V_L) - \bar{g}_{Na} m^3 h (V - V_{Na}) - \bar{g}_K n^4 (V - V_K)$$

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

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

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

Voltage-dependent rate constants

$$\alpha_m = 0.1(V_m + 35.0)/(1 - e^{-(V_m + 35.0)/10.0})$$

$$\beta_m = 4.0 e^{-(V_m + 60.0)/18.0}$$

$$\alpha_h = 0.07 e^{-(V_m + 60.0)/20.0}$$

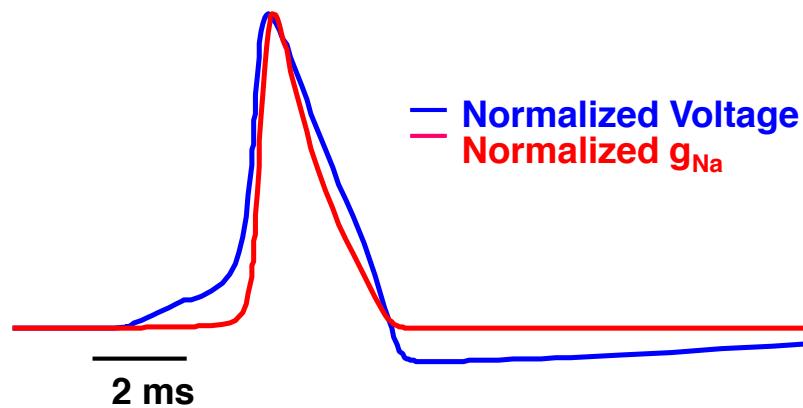
$$\beta_h = 1. / (1 + e^{-(V_m + 30.0)/10.0})$$

$$\alpha_n = 0.01(V_m + 50.0)/(1 - e^{-(V_m + 50.0)/10.0})$$

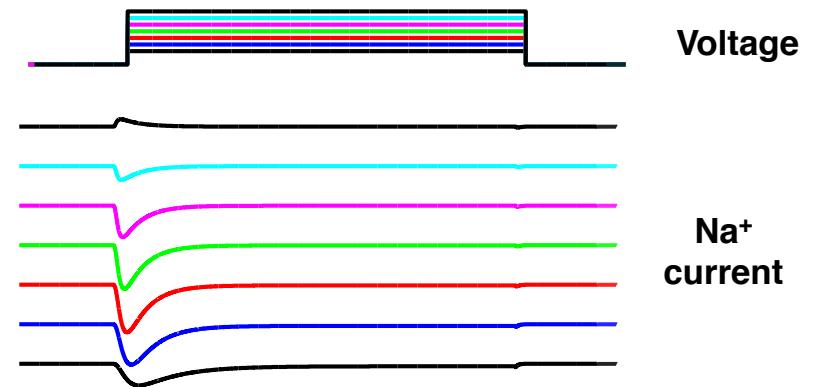
$$\beta_n = 0.125 e^{-(V_m + 60.0)/80.0}$$

Why was voltage clamp transformative?

Voltage and conductance changing together



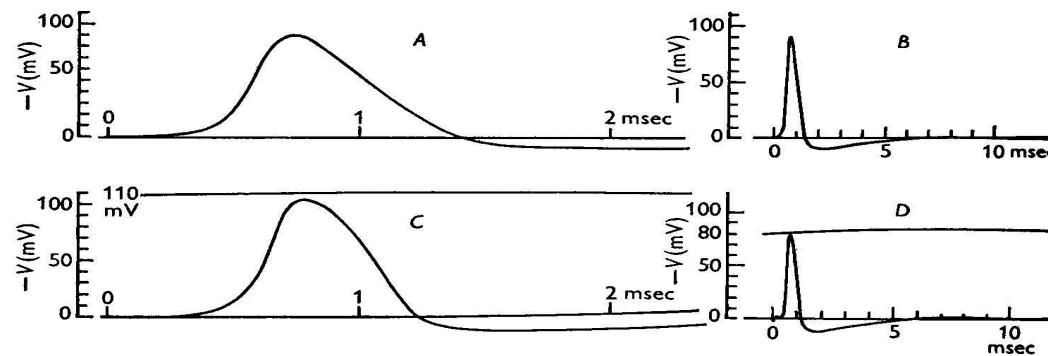
Voltage controlled. Conductance changes can be quantified.



Simulation of simplified experiment was critical for both model development and understanding

Behavior of Hodgkin-Huxley model

Important note: equations and parameters were derived from voltage-clamp data, action potential simulations were an independent test



Experiment

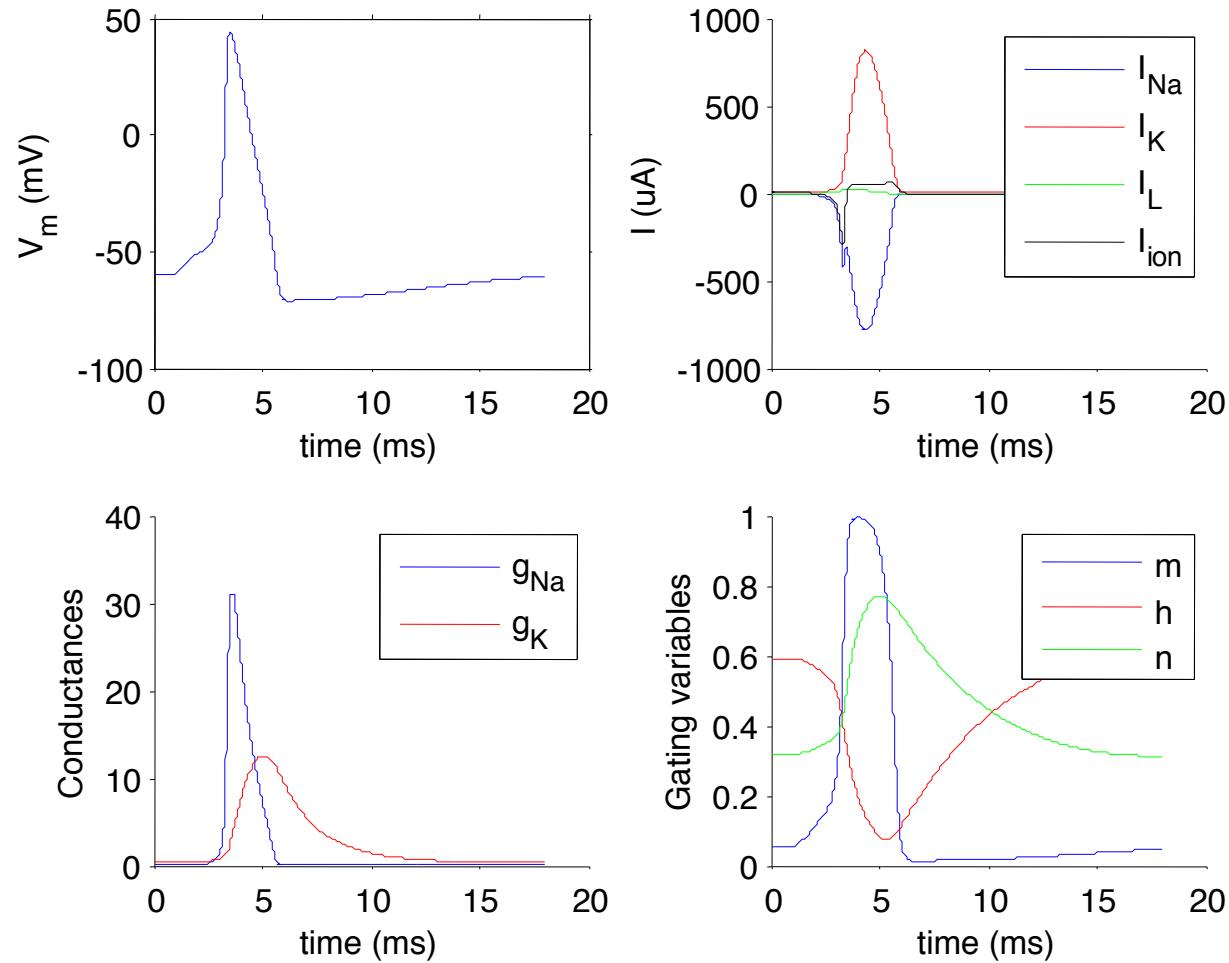
Simulation

In addition to producing realistic action potentials, the model:

- 1) exhibits sub-threshold and supra-threshold responses
- 2) correctly reproduces refractoriness
- 3) reproduces “anode break” excitation

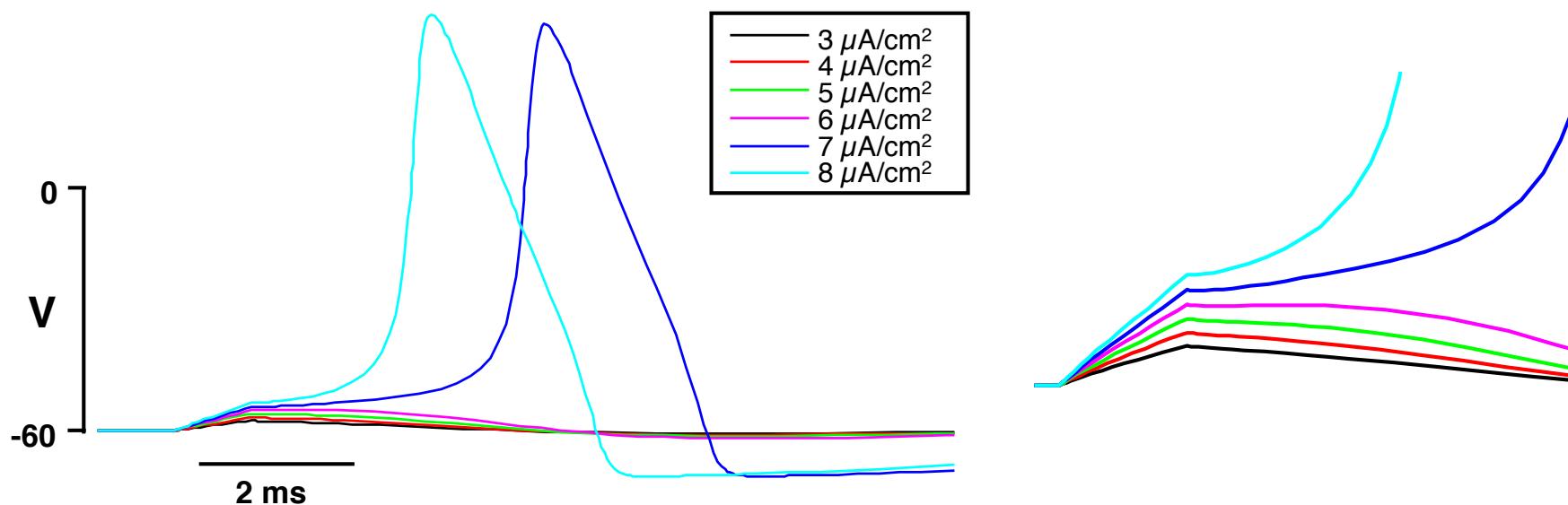
Behavior of Hodgkin-Huxley model

Response to brief injected current



Behavior of Hodgkin-Huxley model

The model exhibits sub-threshold and supra-threshold responses

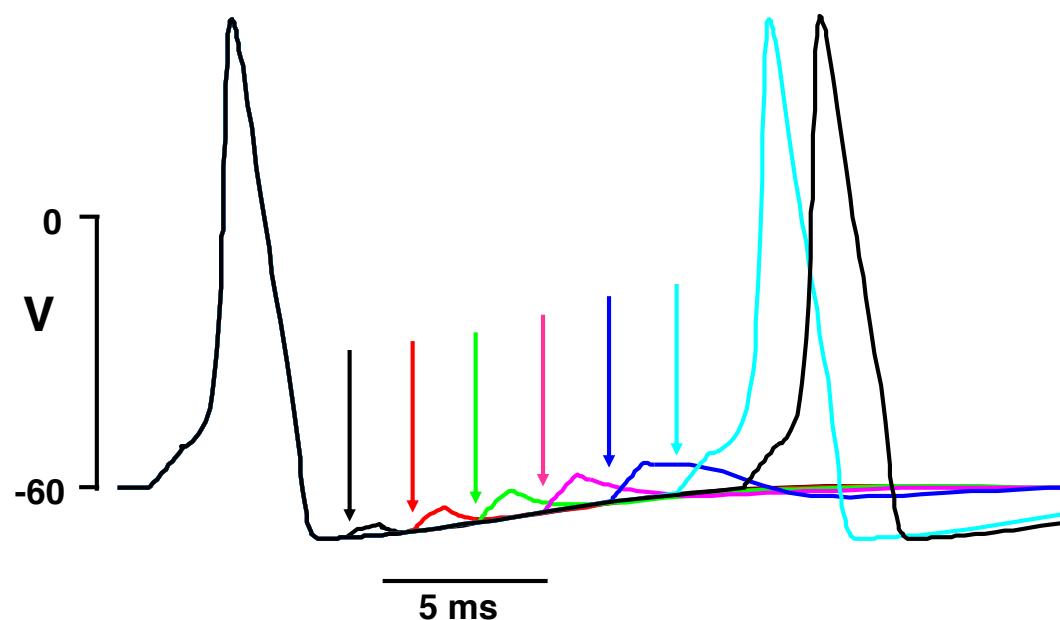


The threshold results from the positive feedback between V and I_{Na}
 $\uparrow V$ leads to $\uparrow I_{\text{Na}}$ leads to $\uparrow V$, etc.

In other words, bistability

Behavior of Hodgkin-Huxley model

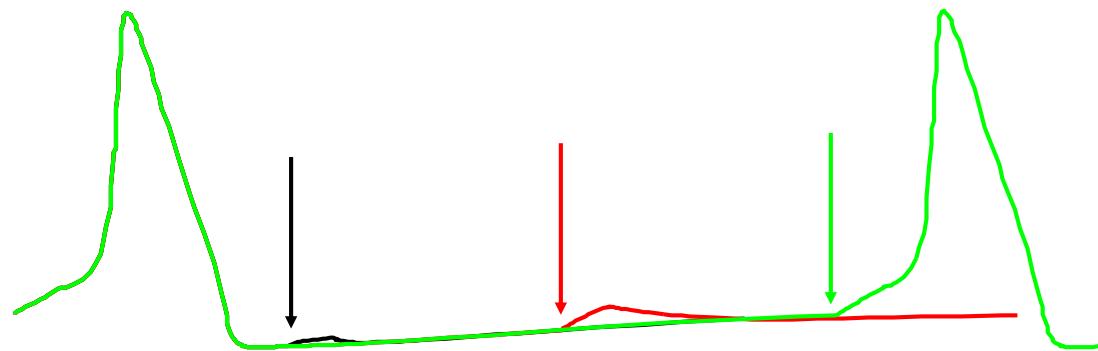
The model correctly reproduces refractoriness



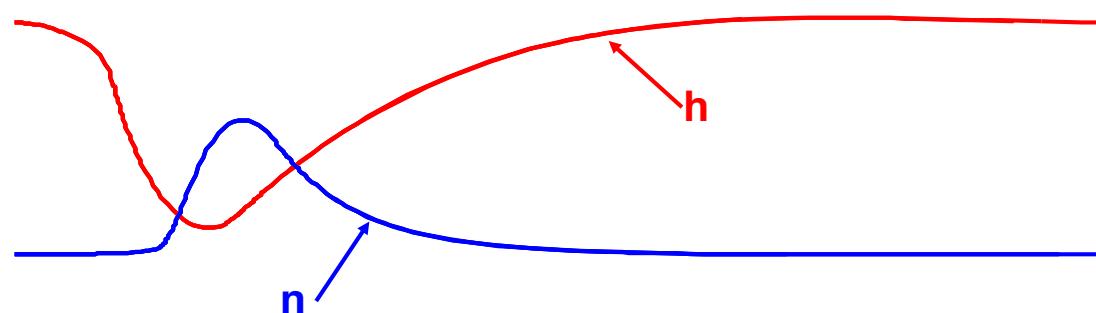
Stimuli given soon after an initial AP will fail to induce a second AP, until the refractory period is over.

Behavior of Hodgkin-Huxley model

Mechanism of refractoriness
Increase in g_K as well as decrease in g_{Na}



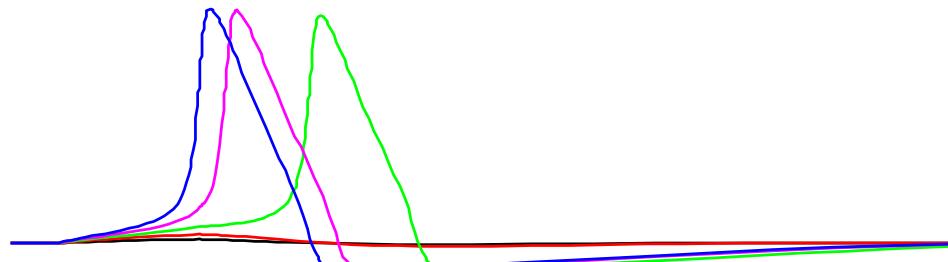
Remember: $g_K \sim n^4$, $g_{Na} \sim m^3 h$



Behavior of Hodgkin-Huxley model

The model reproduced and explained "anode break" excitation.

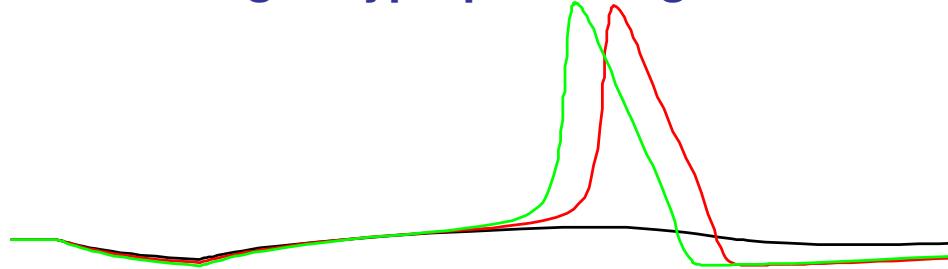
Depolarizing (cathodal) stimuli



Hyperpolarizing (anodal) stimuli



Stronger hyperpolarizing stimuli



Because this comes about after the stimulus, this is called "break" excitation

Summary

The Hodgkin-Huxley equations were derived entirely from voltage-clamp data. Simulations of action potentials represented an independent test of the model.

The model was able to reproduce several observed phenomena:

threshold behavior

refractoriness

anode break excitation

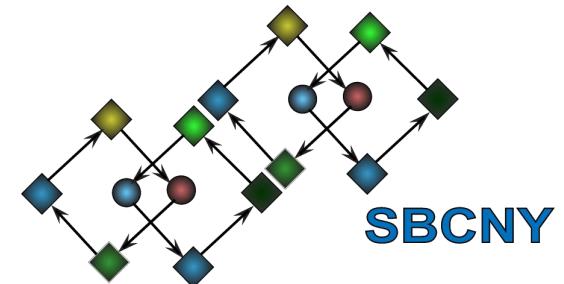
The simulations of these phenomena generated new predictions about the underlying biological mechanisms.

Mathematical models of action potentials

Part 5



Icahn School
of Medicine at
Mount
Sinai



Outline: Part 5

Theme: Phenomenology versus Mechanism

Is the Hodgkin-Huxley model mechanistic or phenomenological?

Some aspects are clearly mechanistic

Other aspects may appear phenomenological

When mechanism is known, can a phenomenological model be useful?

The Fitzhugh-Nagumo model

Phenomenology versus Mechanism

Is the Hodgkin-Huxley model mechanistic or phenomenological?

Answer: both

Mechanism: Separation of I_{ion} into I_{Na} and I_K

Phenomenology: Functions describing $\alpha(V)$, $\beta(V)$

$$\beta_m(V) = 4.0e^{\frac{-(V+60)}{20}}$$

No physical basis for exponential function

Numbers 4, 60, 20, chosen simply to fit the data

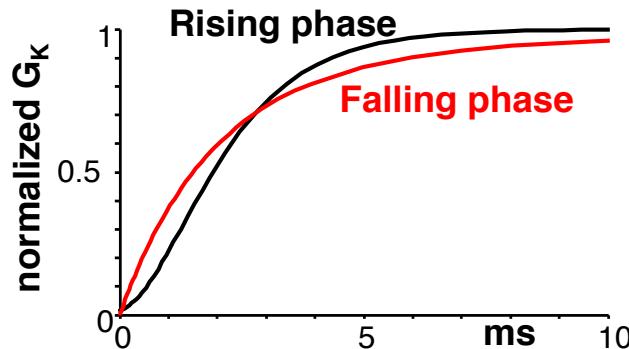
Phenomenology begets mechanism: $I_K = G_K n^4 (V - E_K)$

Four particle model based on curve fitting

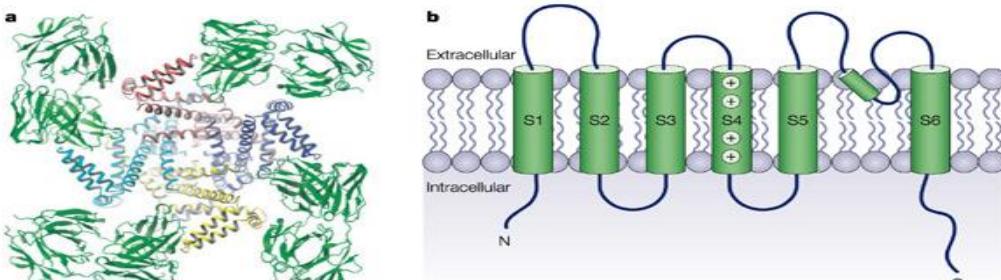
Tetrameric ion channel structure is now a rigorous physical basis

Phenomenology begets Mechanism

Hodgkin-Huxley model

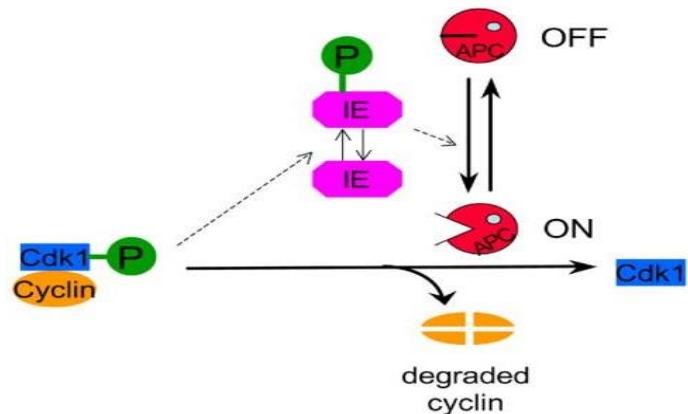


Tetrameric ion channel structure



Nature Reviews | Drug Discovery

Novak & Tyson model

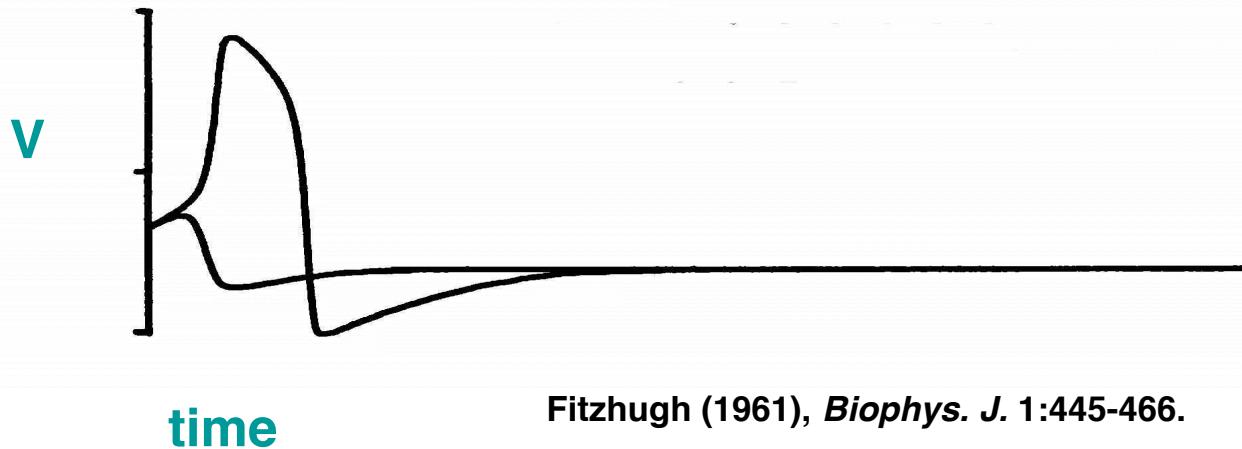


IE = intermediate enzyme

This is now known to correspond to Fizzy/cdc20

Phenomenology versus Mechanism

An extreme case: the Fitzhugh-Nagumo model



Fitzhugh (1961), *Biophys. J.* 1:445-466.



Dr. Richard Fitzhugh

$$\frac{dV}{dt} = V - V^3 - W - I$$

$$\frac{dW}{dt} = 0.08*(V + 0.7 - 0.8W)$$

V : voltage-like variable

W : recovery variable

The Fitzhugh-Nagumo model

An abstract and clearly phenomenological model

$$\frac{dV}{dt} = V - V^3 - W - I$$

$$\frac{dW}{dt} = 0.08*(V + 0.7 - 0.8W)$$

Only 2 variables

No explicit ionic currents included

Recovery variable W not related to any specific biological process

This model was published 9 years after Hodgkin-Huxley.
Can it have any value?

The Fitzhugh-Nagumo model

Why would anyone care about a two-variable phenomenological model when a “better” more mechanistic, four-variable model already exists?

One reason: In the pre-digital era, this model was much easier to implement



Nagumo et al., (1962) Proc. IRE. 50:2061–2070

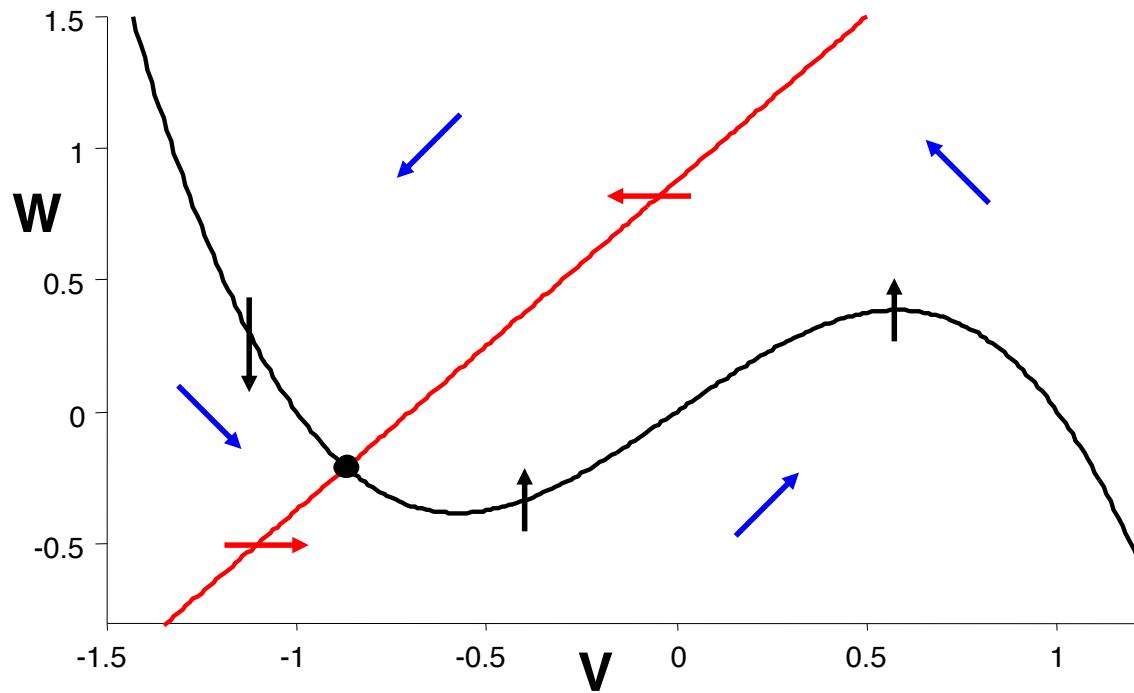


Dr. Jin-Ichi Nagumo

Electronic circuit built using tunnel diodes

The Fitzhugh-Nagumo model

Benefits of a generic two-variable model



V nullcline:

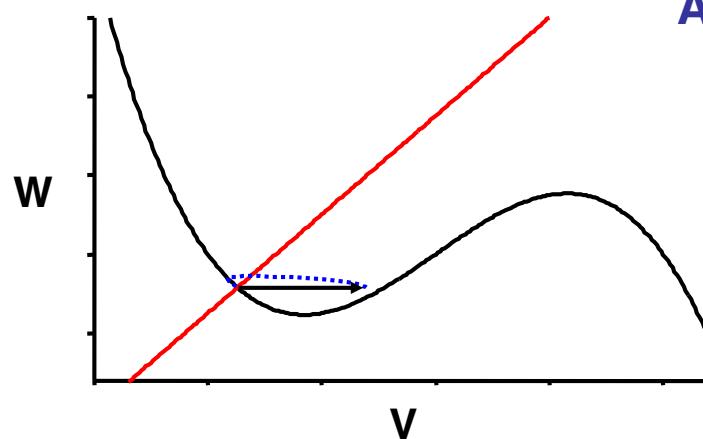
$$W = V - V^3 - I$$

W nullcline:

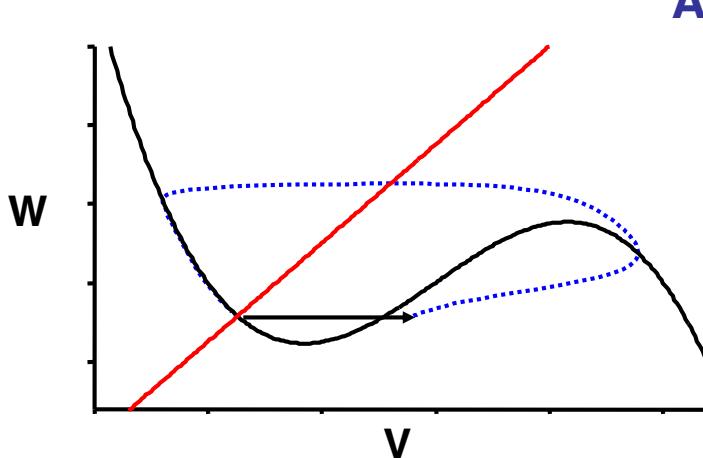
$$W = (V + 0.7)/0.8$$

The Fitzhugh-Nagumo model

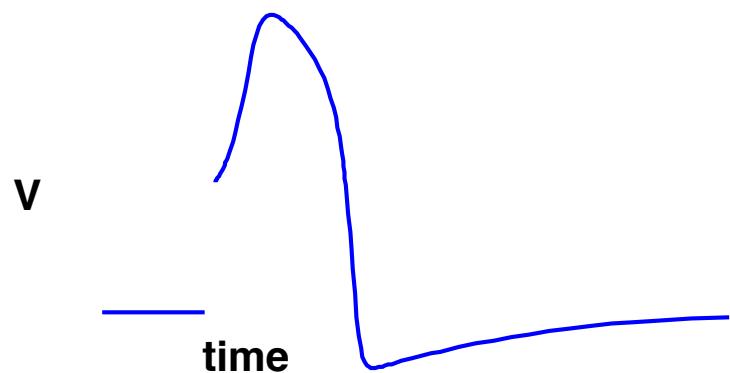
Electrical stimulus: an instantaneous increase in V



A small increase in V



A larger increase in V

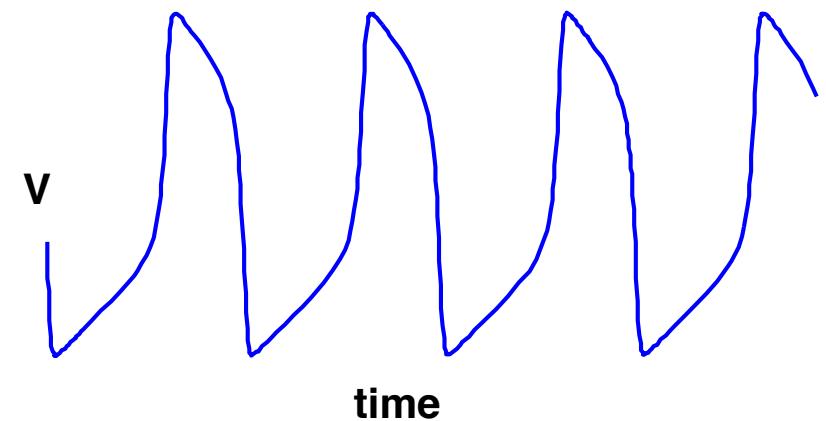
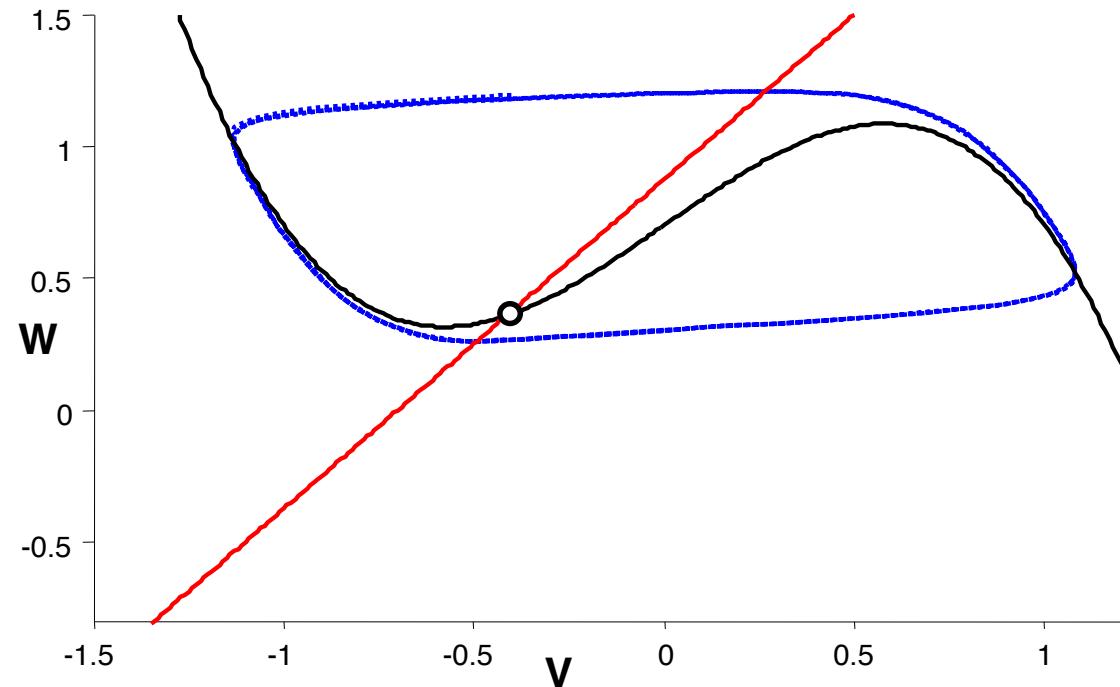


The Fitzhugh-Nagumo model

Constant current injection (negative I) will shift V nullcline up

V nullcline: $W = V - V^3 - I$

$I = -0.7$



Repetitive action potentials with constant current = conversion from stable fixed point to stable limit cycle

This fixed point is now unstable!

Summary

The Hodgkin-Huxley model, like most mathematical models, contains a mixture of mechanistic and phenomenological elements.

When a phenomenological representation is later found to have a mechanistic basis, this is usually a modeling success.

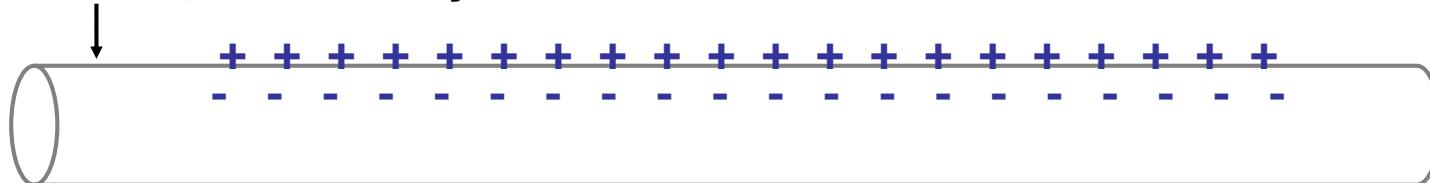
**When mechanism is known, phenomenological representations can nonetheless be very useful for the general insight they provide
A prominent example: the Fitzhugh-Nagumo model**

Simulating a propagating action potential

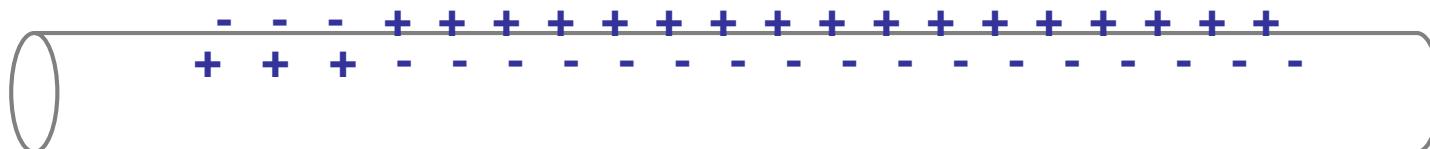
Electrical propagation involves spatial voltage gradients

Imagine a long, one-dimensional axon

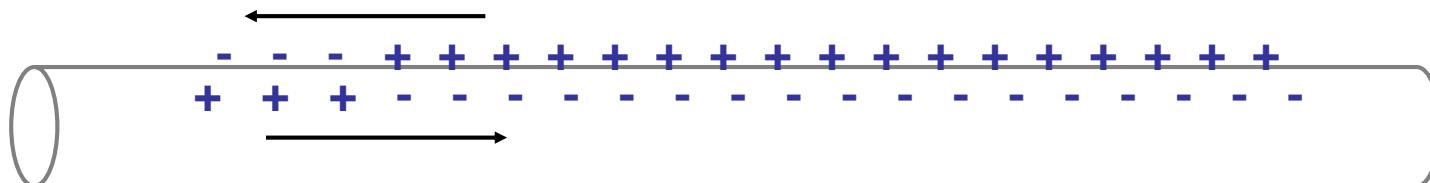
(1) Starts at rest, then locally stimulated



(2) Depolarized on left, resting on right



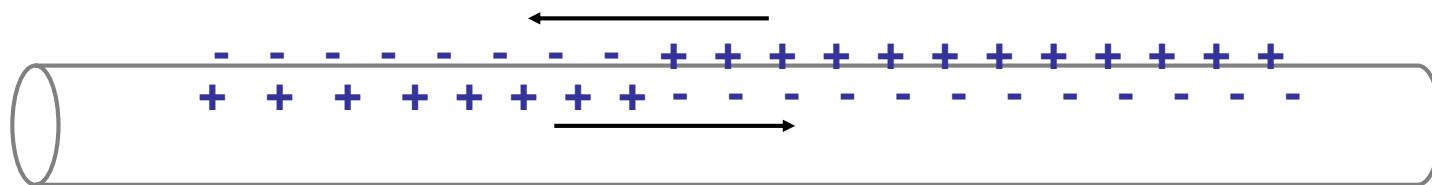
(3) Electrical current will flow both inside and outside



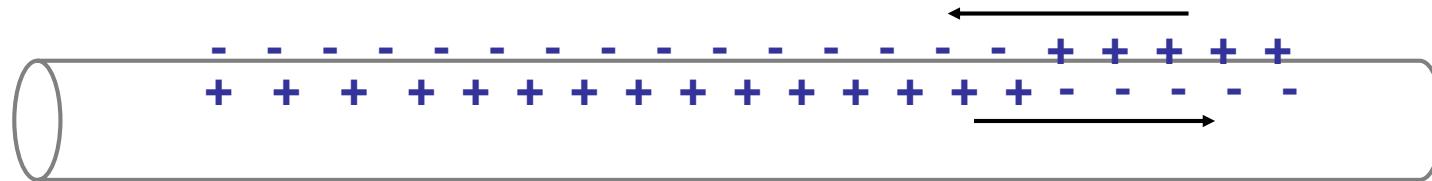
Electrical propagation results from spatial voltage gradients

Imagine a long, one-dimensional axon

(4) More tissue will become depolarized



(5) Etc.

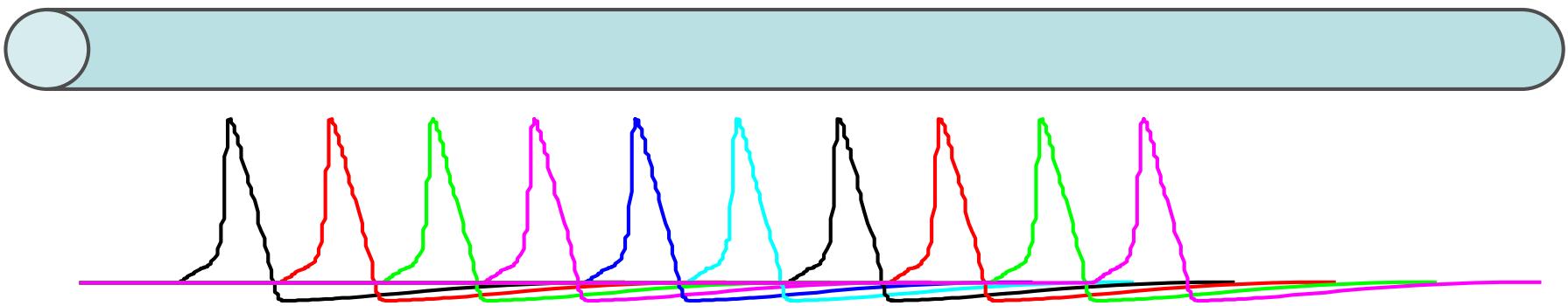


This is the basic mechanism by which action potentials propagate

But now voltage depends on both time and location

We need to solve a system of Partial Differential Equations (PDEs)

A propagated action potential



V, m, h, n, now functions of both time and location

The relevant equation for voltage is:

$$C_m \frac{\partial V}{\partial t} = \frac{a}{2\rho_i} \frac{\partial^2 V}{\partial x^2} - I_{ion}$$

a "partial" rather than an "ordinary" differential equation

Pertinent questions:

1) Where does this equation come from?

(provided in supplementary slides)

2) How do we solve this in practice?

Notes on the 1-D cable equation

$$C_m \frac{\partial V}{\partial t} = \frac{a}{2\rho_i} \frac{\partial^2 V}{\partial x^2} - I_{ion}$$

1) This is a reaction-diffusion equation.

These equations appear in other contexts, e.g. sub-cellular diffusion of Ca^{2+} and other second messengers.

2) This is a partial differential equation (PDE).

To obtain a numerical solution, must convert to discrete form in both space and time.

$$\left. \frac{\partial V}{\partial t} \right|_j^t \approx \frac{V_j^{t+\Delta t} - V_j^t}{\Delta t}$$

$$\left. \frac{\partial^2 V}{\partial x^2} \right|_j^t \approx \frac{V_{j+1}^t - 2V_j^t + V_{j-1}^t}{\Delta x^2}$$

PDE solvers, like ODE solvers, are based on such discrete approximations.

Explicit versus Implicit Solutions

$$C_m \frac{\partial V}{\partial t} = \frac{a}{2\rho_i} \frac{\partial^2 V}{\partial x^2} - I_{ion}$$

Explicit solutions

Solve for each future value of V based on current values of V

$$C_m \frac{V_j^{t+\Delta t} - V_j^t}{\Delta t} = \frac{a}{2\rho_i} \frac{V_{j+1}^t - 2V_j^t + V_{j-1}^t}{\Delta x^2} - I_{ion}^t$$

Implicit solutions

Solve for future values of V based on future values of V

$$C_m \frac{V_j^{t+\Delta t} - V_j^t}{\Delta t} = \frac{a}{2\rho_i} \frac{V_{j+1}^{t+\Delta t} - 2V_j^{t+\Delta t} + V_{j-1}^{t+\Delta t}}{\Delta x^2} - I_{ion}^{t+\Delta t}$$

Explicit versus Implicit Solutions

Explicit solutions are simple to implement

Rearrange so that future is on LHS, present on RHS

$$V_j^{t+\Delta t} = V_j^t + \Delta t \frac{a}{2\rho_i C_m} \left[\frac{V_{j+1}^t - 2V_j^t + V_{j-1}^t}{\Delta x^2} - I_{ion}^t \right]$$

plus similar equations for $V_{j+1}^{t+\Delta t}$ $V_{j-1}^{t+\Delta t}$ etc.

This just converts the PDE into large system of ODEs

Advantage: simple

Disadvantage: for stability $\Delta t \sim \Delta x^2$, must be very small

Explicit solutions of PDEs can take a very long time to run.

Explicit versus Implicit Solutions

Implicit solutions are conceptually more difficult

$$C_m \frac{V_j^{t+\Delta t} - V_j^t}{\Delta t} = \frac{a}{2\rho_i} \frac{V_{j+1}^{t+\Delta t} - 2V_j^{t+\Delta t} + V_{j-1}^{t+\Delta t}}{\Delta x^2} - I_{ion}^{t+\Delta t}$$

Computing $I_{ion}^{t+\Delta t}$ requires knowing $m^{t+\Delta t}$, $h^{t+\Delta t}$, $n^{t+\Delta t}$.

In practice, reaction treated explicitly, diffusion implicitly.

$$C_m \frac{V_j^{t+\Delta t} - V_j^t}{\Delta t} = \frac{a}{2\rho_i} \frac{V_{j+1}^{t+\Delta t} - 2V_j^{t+\Delta t} + V_{j-1}^{t+\Delta t}}{\Delta x^2} - I_{ion}^t$$

Even with this simplification, the equation still has 3 unknowns!

$$-\frac{a}{2\rho_i \Delta x^2} V_{j+1}^{t+\Delta t} + \left[\frac{a}{\rho_i \Delta x^2} + \frac{C_m}{\Delta t} \right] V_j^{t+\Delta t} - \frac{a}{2\rho_i \Delta x^2} V_{j-1}^{t+\Delta t} = \frac{C_m}{\Delta t} V_j^t - I_{ion}^t$$

Must solve for the three unknowns simultaneously.
This requires inverting a matrix.

Implicit Solution of HH Equations

$$\begin{bmatrix} \ddots & \ddots & & \\ -a & \left(\frac{a}{\rho_i \Delta x^2} + \frac{C_m}{\Delta t}\right) & -a & \\ & \frac{-a}{2\rho_i \Delta x^2} & \left(\frac{a}{\rho_i \Delta x^2} + \frac{C_m}{\Delta t}\right) & -a \\ & & \frac{-a}{2\rho_i \Delta x^2} & \left(\frac{a}{\rho_i \Delta x^2} + \frac{C_m}{\Delta t}\right) & -a \\ & & & \ddots & \ddots \end{bmatrix} \cdot \begin{bmatrix} \vdots \\ V_{j-1}^{t+\Delta t} \\ V_j^{t+\Delta t} \\ V_{j+1}^{t+\Delta t} \\ \vdots \end{bmatrix} = \frac{C_m}{\Delta t} \begin{bmatrix} \vdots \\ V_{j-1}^t \\ V_j^t \\ V_{j+1}^t \\ \vdots \end{bmatrix} - \begin{bmatrix} \vdots \\ I_{ion,j-1}^t \\ I_{ion,j}^t \\ I_{ion,j+1}^t \\ \vdots \end{bmatrix}$$

This is a matrix equation $\mathbf{Ax} = \mathbf{b}$

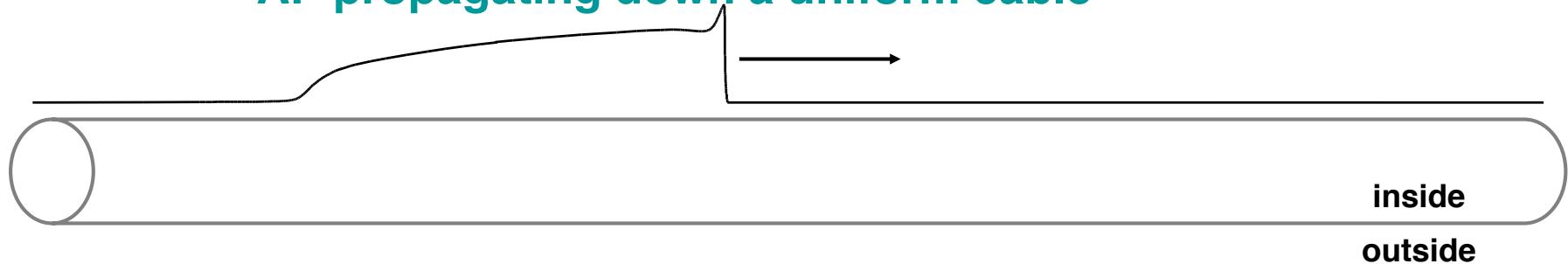
$$\mathbf{x} = \mathbf{A}^{-1}\mathbf{b}$$

Thus, implicit solutions involve inverting a matrix
at each time step

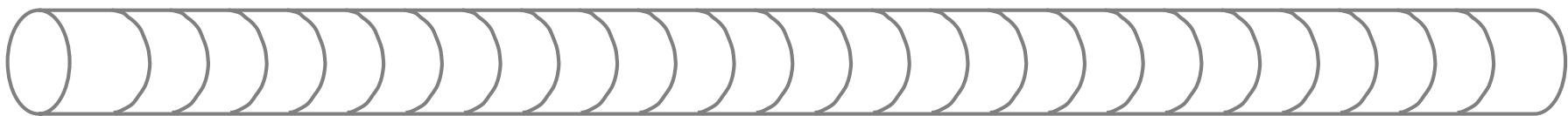
Supplementary Slides

One dimensional electrical propagation

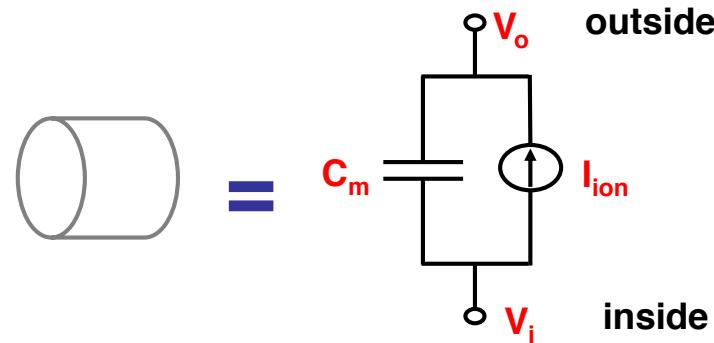
AP propagating down a uniform cable



Divide the cable into discrete segments

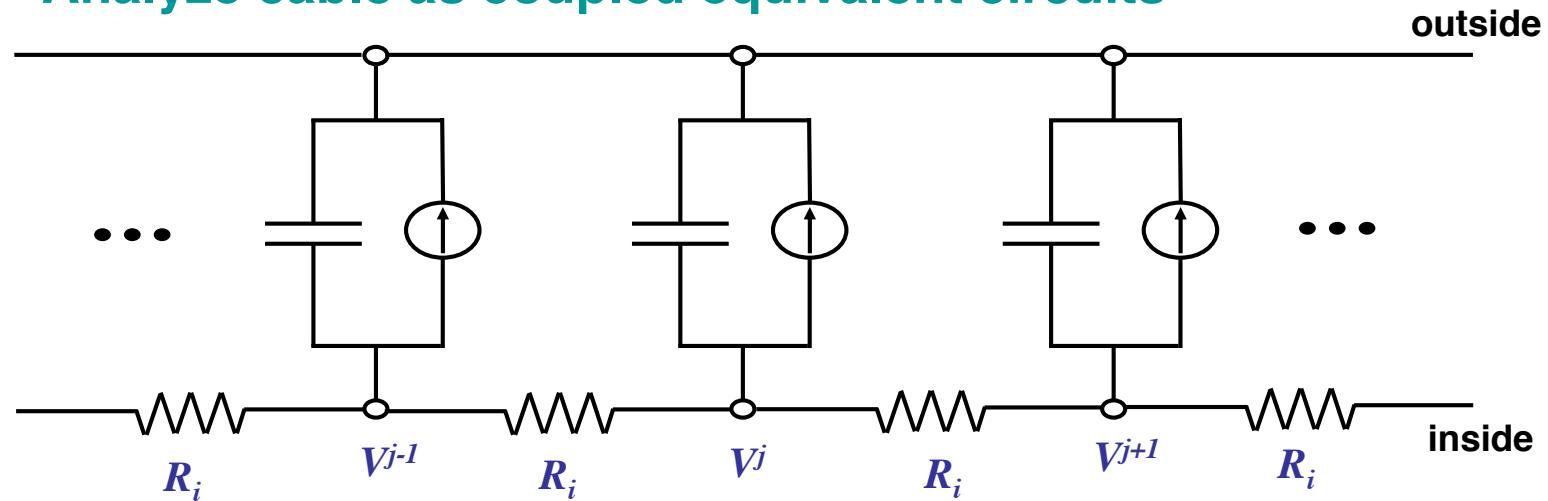


Analyze the cable as coupled equivalent circuits



One dimensional cable theory

Analyze cable as coupled equivalent circuits



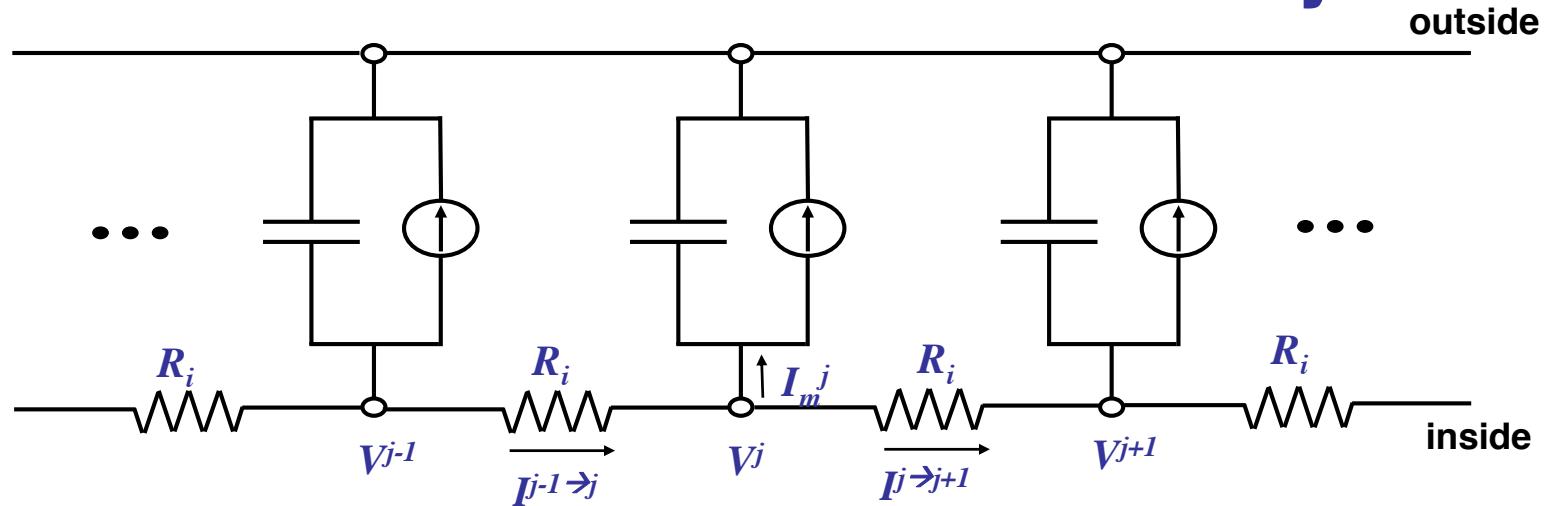
R_i =intracellular resistance

V_j =voltage at the j th element of the cable

For simplicity, assume that $R_e=0$ so that all extracellular voltages are grounded. Then intracellular potential = transmembrane potential at all elements.

A reasonable assumption for an isolated fiber in a bath.

One dimensional cable theory



What equations describe the j th element of the cable?

$$I^{j-1 \rightarrow j} = (V^{j-1} - V^j) / R_i$$

Ohm's law

$$I^{j \rightarrow j+1} = (V^j - V^{j+1}) / R_i$$

$$I^{j-1 \rightarrow j} = I^{j \rightarrow j+1} + A I_m^j$$

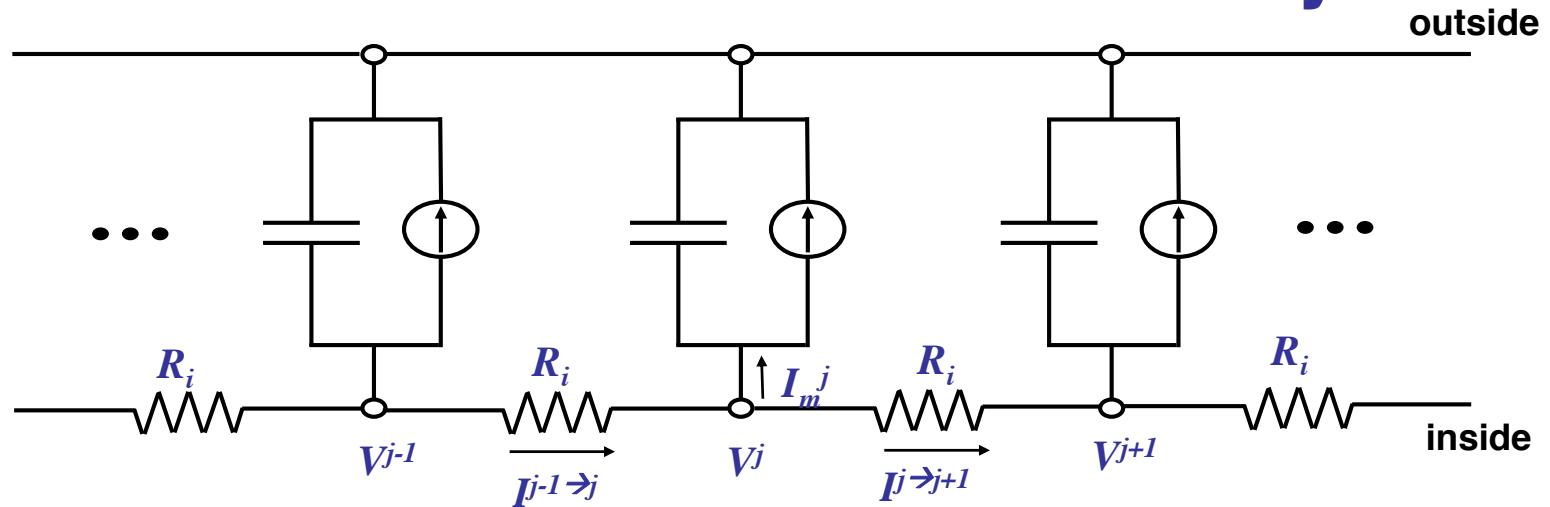
Kirchoff's current law

where **A** is the surface area of the j th element

$$I_m^j = C_m \frac{dV^j}{dt} + I_{ion}^j$$

Membrane currents are normalized per unit area.

One dimensional cable theory



Putting the equations together:

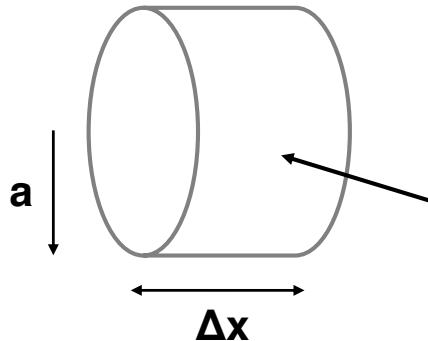
$$(V^{j-1} - V^j) / R_i = (V^j - V^{j+1}) / R_i + A \left[C_m \frac{dV^j}{dt} + I_{ion}^j \right]$$

Rearranging yields:

$$C_m \frac{dV^j}{dt} = \frac{(V^{j-1} - 2V^j + V^{j+1})}{AR_i} - I_{ion}^j$$

One dimensional cable theory

How can we relate R_i to cable geometry?



$$R_i = \frac{\rho_i \Delta x}{\pi a^2}$$

$$A = 2\pi a \Delta x$$

ρ_i = intracellular resistivity

Thus,

$$AR_i = 2\pi a \Delta x \frac{\rho_i \Delta x}{\pi a^2} = \frac{2\rho_i \Delta x^2}{a}$$

Substituting yields:

$$C_m \frac{dV^j}{dt} = \frac{a}{2\rho_i} \frac{(V^{j-1} - 2V^j + V^{j+1})}{\Delta x^2} - I_{ion}^j$$

As $\Delta x \rightarrow 0$, this becomes:

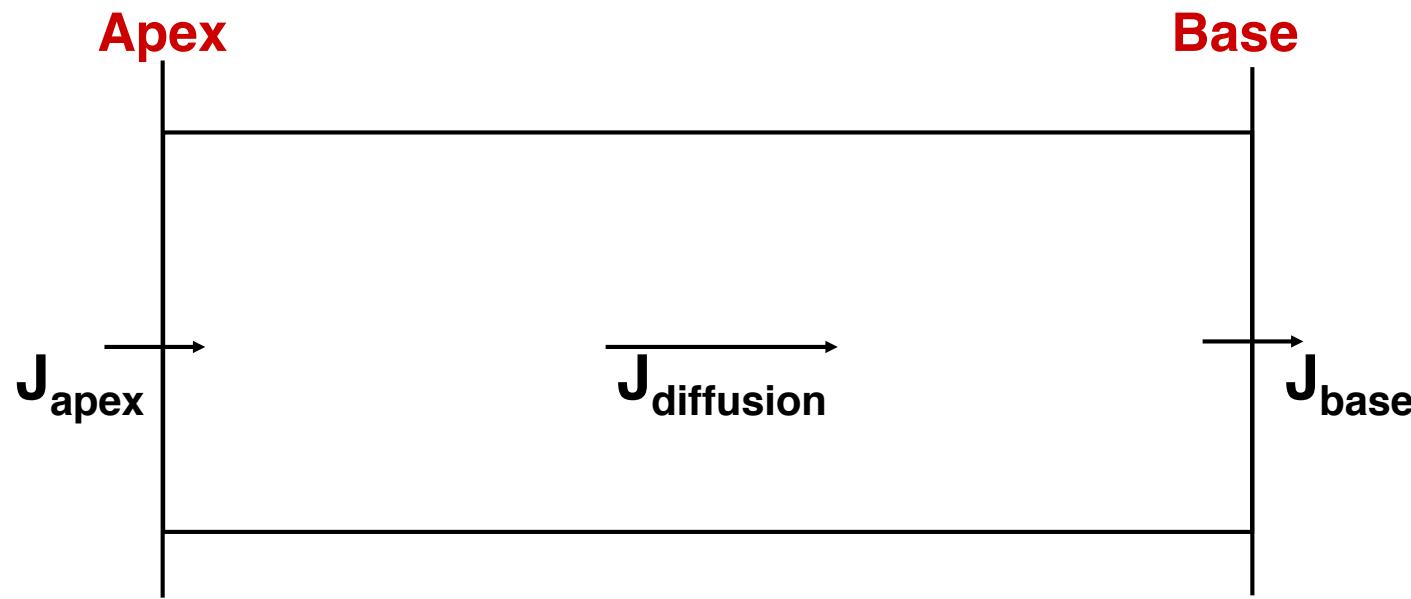
$$C_m \frac{\partial V}{\partial t} = \frac{a}{2\rho_i} \frac{\partial^2 V}{\partial x^2} - I_{ion}$$

Dropped the j superscript.
This applies for all j

This is the nonlinear cable equation

Diffusion across an epithelial cell

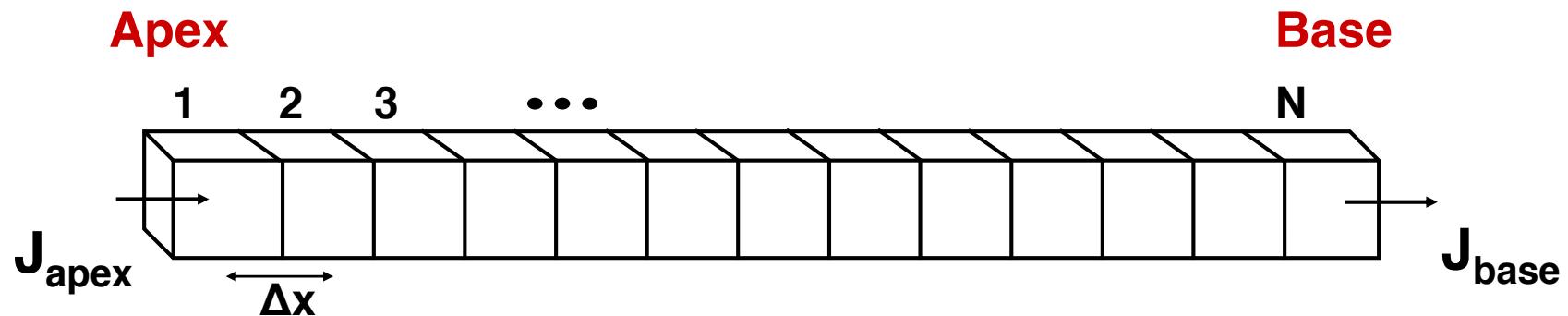
Consider example of HCO_3^- in proximal tubule



How do we describe diffusion of HCO_3^- from apex to base?

Diffusion across an epithelial cell

Represent cell as a series of discrete segments



$[\text{HCO}_3]_i$ = concentration in sub-cube i

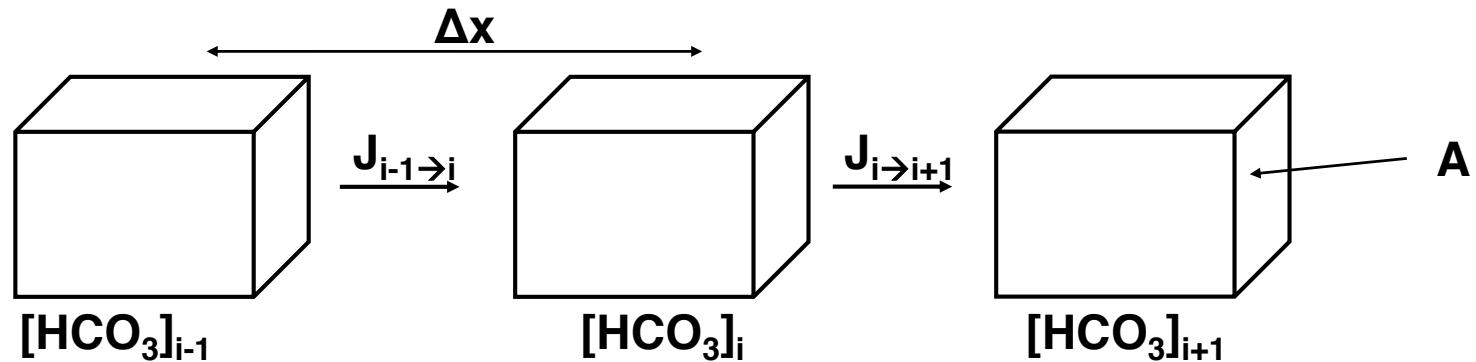
D_{HCO_3} = intracellular diffusion constant

Δx = distance between adjacent sub-cubes

What are the equations that describe diffusion
from apex to base?

Diffusion across an epithelial cell

First consider diffusion within three sub-cubes



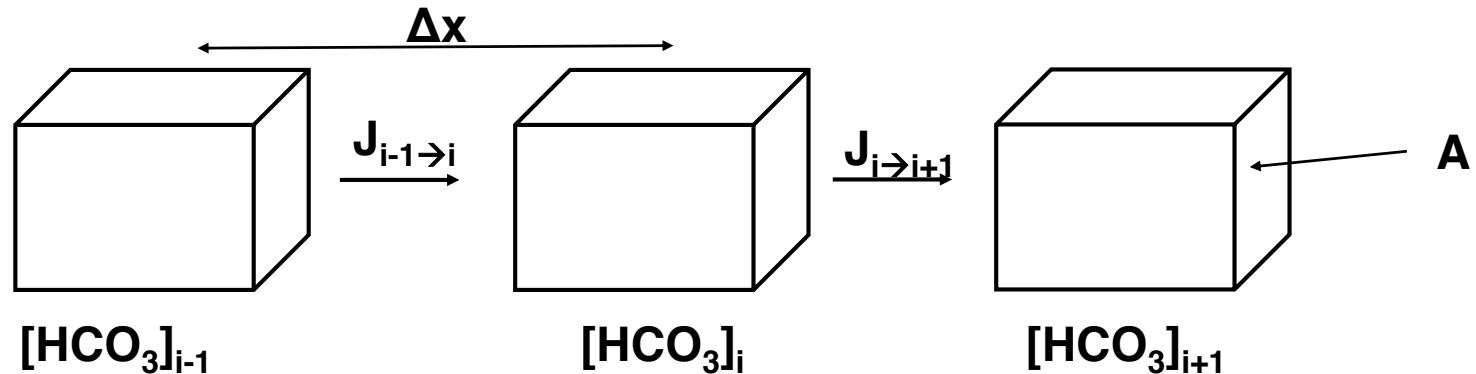
$$J_{i-1 \rightarrow i} = D_{HCO_3} \frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x}$$

$$J_{i \rightarrow i+1} = D_{HCO_3} \frac{([HCO_3]_i - [HCO_3]_{i+1})}{\Delta x}$$

Fick's first law of diffusion

Diffusion across an epithelial cell

How to relate to changes in $[HCO_3^-]_i$?



Intuitively, $d[HCO_3]_i/dt$ depends on inflow vs. outflow, $J_{i-1 \rightarrow i} - J_{i \rightarrow i+1}$

Need to consider units to express this precisely

Δx : cm

$[HCO_3]$: mM;

equivalent to $\mu\text{mol}/\text{cm}^3$

D_{HCO_3} : cm^2/s

$$J_{i-1 \rightarrow i} = D_{HCO_3} \frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x}$$

$J_{i \rightarrow i+1}$: $\mu\text{mol}/(\text{cm}^2 \text{ s})$

Therefore we must convert from $\mu\text{mol}/(\text{cm}^2 \text{ s})$ to $\mu\text{mol}/(\text{cm}^3 \text{ s})$

Diffusion across an epithelial cell

Need to convert from $\mu\text{mol}/(\text{cm}^2 \text{ s})$ to $\mu\text{mol}/(\text{cm}^3 \text{ s})$

Multiply by inter-cube surface area A, then divide by volume (V_i)

$$\frac{d[HCO_3]_i}{dt} = \frac{A(J_{i-1 \rightarrow i} - J_{i \rightarrow i+1})}{V_i}$$

But $V_i = A\Delta x$

So $\frac{d[HCO_3]_i}{dt} = \frac{(J_{i-1 \rightarrow i} - J_{i \rightarrow i+1})}{\Delta x}$

Thus:

$$\frac{d[HCO_3]_i}{dt} = D_{HCO_3} \left[\frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x} - \frac{([HCO_3]_i - [HCO_3]_{i+1})}{\Delta x} \right]$$

Diffusion across an epithelial cell

What is the limit as $\Delta x \rightarrow 0$?

$$\lim_{\Delta x \rightarrow 0} \frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x} = \frac{d[HCO_3]}{dx}$$

$$\lim_{\Delta x \rightarrow 0} \left[\frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x} - \frac{([HCO_3]_i - [HCO_3]_{i+1})}{\Delta x} \right] = \frac{d^2[HCO_3]}{dx^2}$$

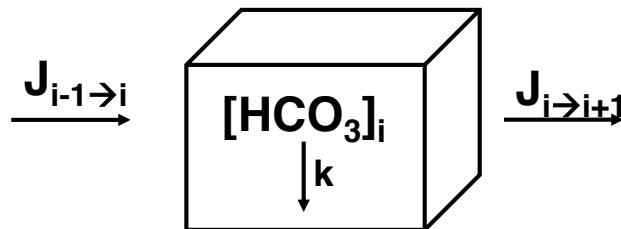
So, in the limit of small Δx , our equation becomes

$$\frac{\partial[HCO_3]_i}{\partial t} = D_{HCO_3} \frac{\partial^2[HCO_3]}{\partial x^2}$$

This is a one-dimensional diffusion equation

Diffusion across an epithelial cell

What if some first order intracellular process is also consuming HCO_3 ?



Then,

$$\frac{d[\text{HCO}_3]_i}{dt} = \frac{J_{i-1 \rightarrow i}}{\Delta x} - \frac{J_{i \rightarrow i+1}}{\Delta x} - k[\text{HCO}_3]_i$$

In the continuum limit:

$$\frac{\partial [\text{HCO}_3]_i}{\partial t} = D_{\text{HCO}_3} \frac{\partial^2 [\text{HCO}_3]}{\partial x^2} - k[\text{HCO}_3]$$

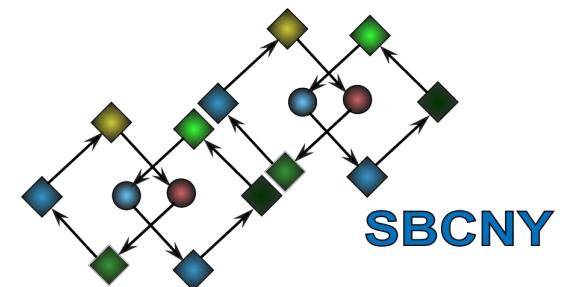
This is a reaction-diffusion equation.
Where have we seen this before?

Mathematical models of action potentials

Part 6: propagation of action potentials



Icahn School
of Medicine at
**Mount
Sinai**



Outline: Part 6

In all the equations we discussed to this point: voltage, m, h, and n were assumed to be spatially-uniform

What do we do if voltages vary with time and location?

Electrical propagation in conceptual terms

Derivation of the relevant reaction-diffusion

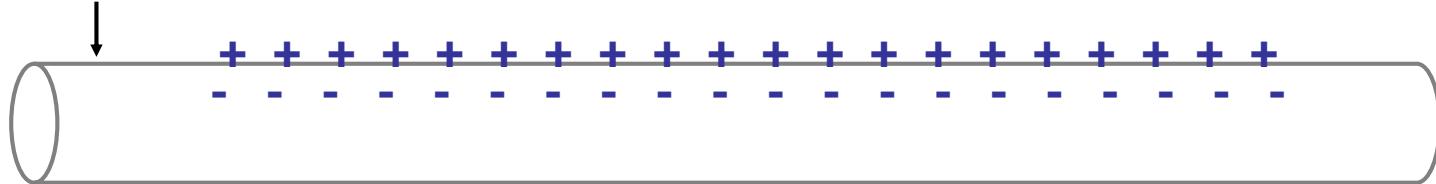
This is where we transition from ODEs to PDEs

PDE = Partial Differential Equation

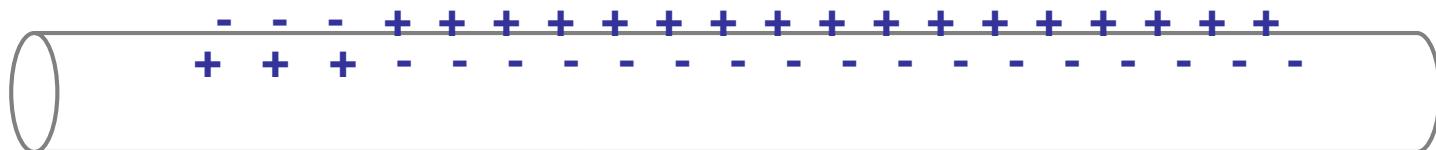
Electrical propagation results from spatial voltage gradients

Imagine a long, one-dimensional axon

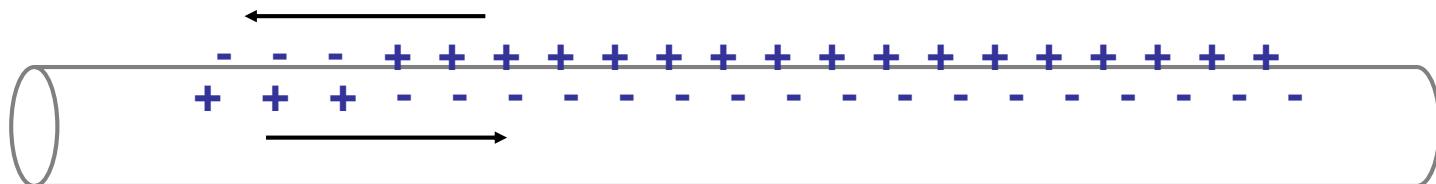
(1) Starts at rest, then locally stimulated



(2) Depolarized on left, resting on right



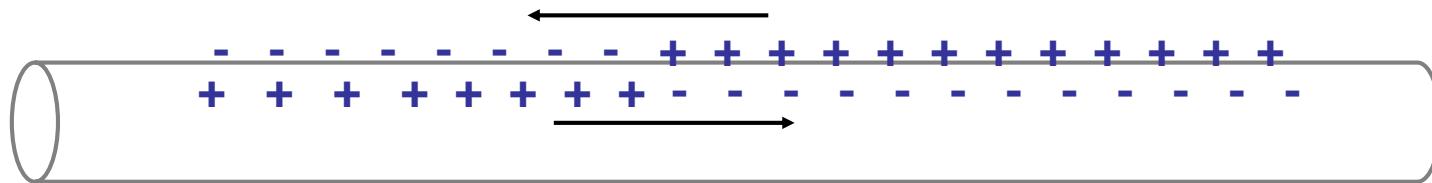
(3) Electrical current will flow both inside and outside



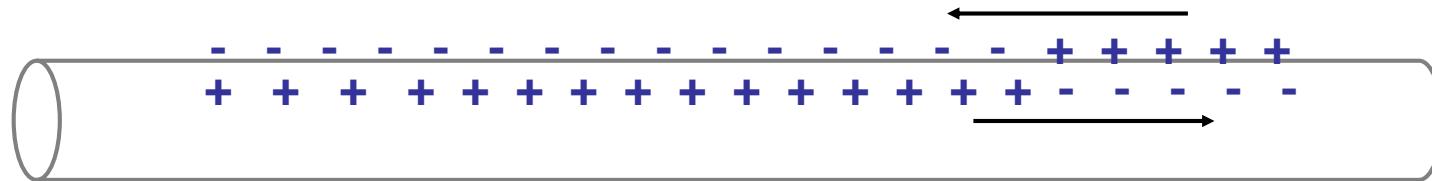
Electrical propagation results from spatial voltage gradients

Imagine a long, one-dimensional axon

(4) More tissue will become depolarized



(5) Etc.

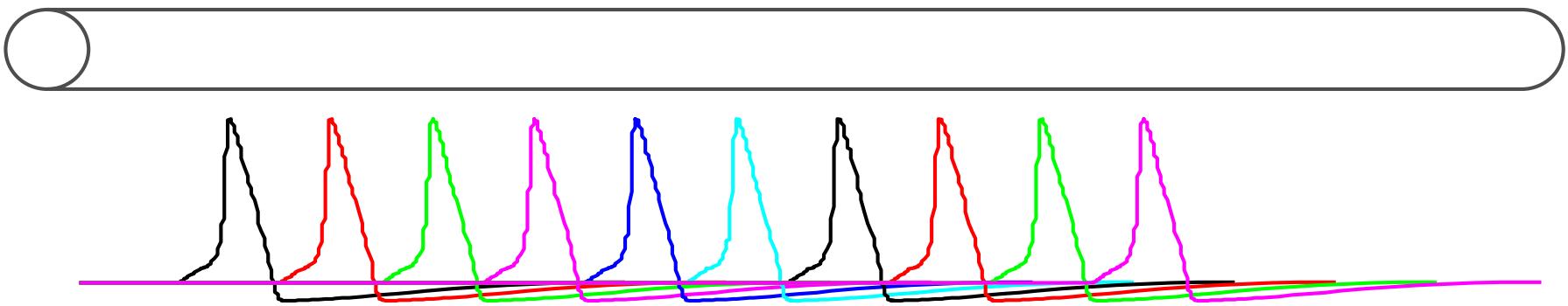


This is the basic mechanism by which action potentials propagate

But now voltage depends on both time and location

We need to solve a system of Partial Differential Equations (PDEs)

A propagated action potential



V, m, h, n, now functions of both time and location

The relevant equation for voltage is:

$$C_m \frac{\partial V}{\partial t} = \frac{a}{2\rho_i} \frac{\partial^2 V}{\partial x^2} - I_{ion}$$

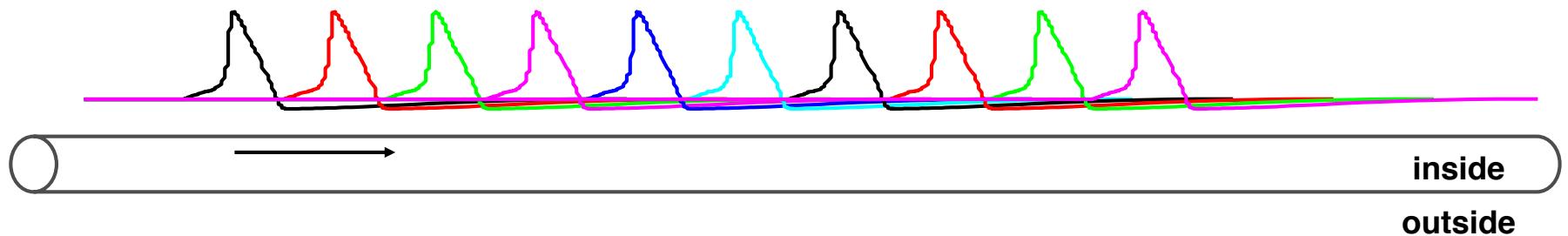
a "partial" rather than an "ordinary" differential equation

Pertinent questions:

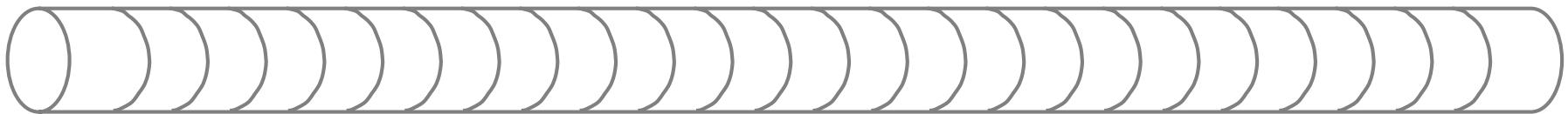
- 1) Where does this equation come from?**
- 2) How do we solve this in practice? (subsequent lectures)**

One dimensional electrical propagation

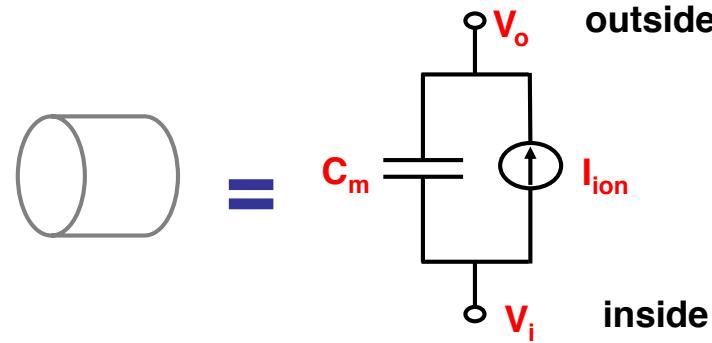
AP propagating down a uniform cable



Divide the cable into discrete segments

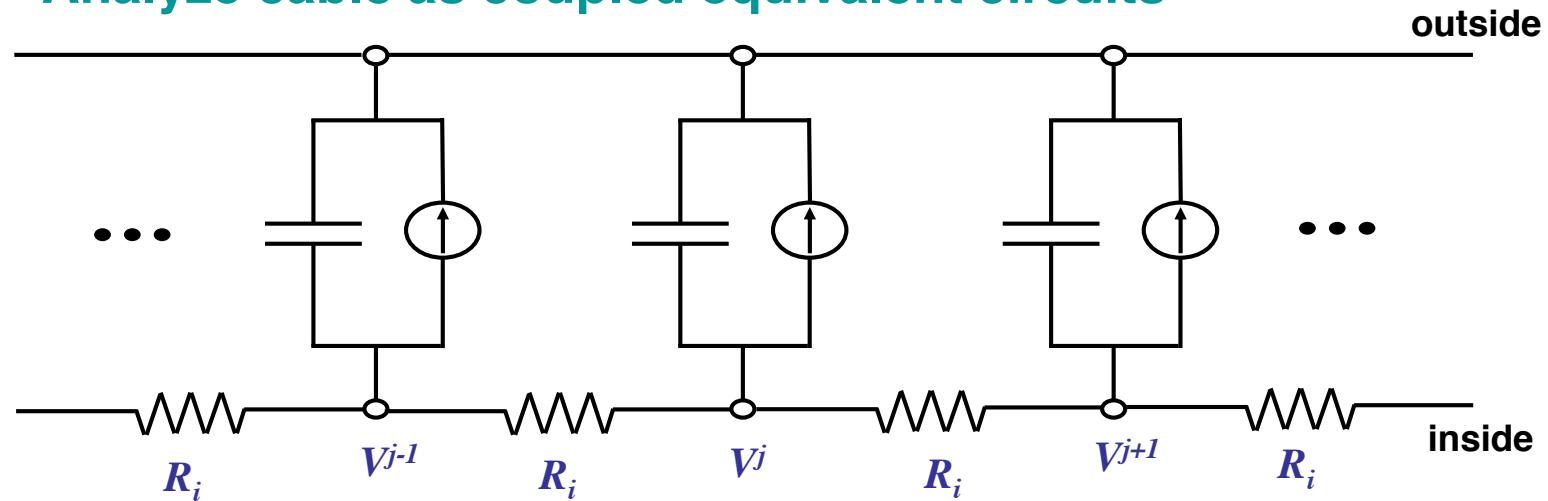


Analyze the cable as coupled equivalent circuits



One dimensional cable theory

Analyze cable as coupled equivalent circuits



R_i =intracellular resistance

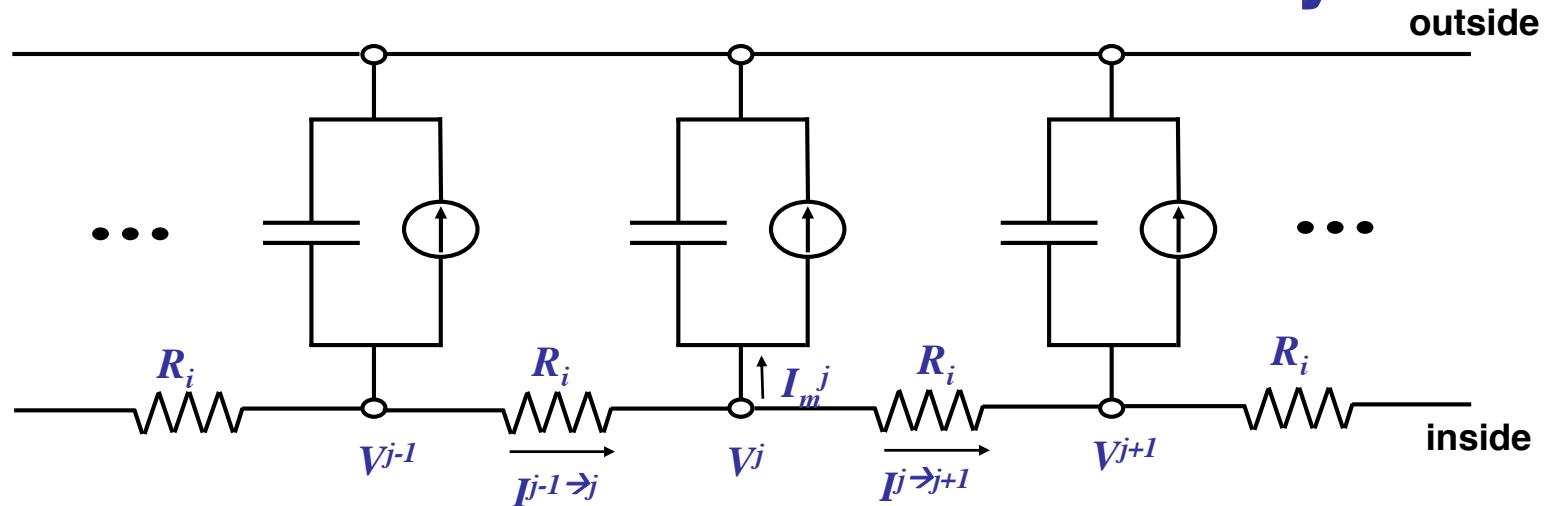
V^j =voltage at the jth element of the cable

We assume that $R_e=0$ so that all extracellular voltages are grounded.

Then intracellular potential = transmembrane potential at all elements.

A reasonable assumption for an isolated fiber in a bath.

One dimensional cable theory



What equations describe the j th element of the cable?

$$I^{j-1 \rightarrow j} = (V^{j-1} - V^j) / R_i$$

Ohm's law

$$I^{j \rightarrow j+1} = (V^j - V^{j+1}) / R_i$$

$$I^{j-1 \rightarrow j} = I^{j \rightarrow j+1} + A I_m^j$$

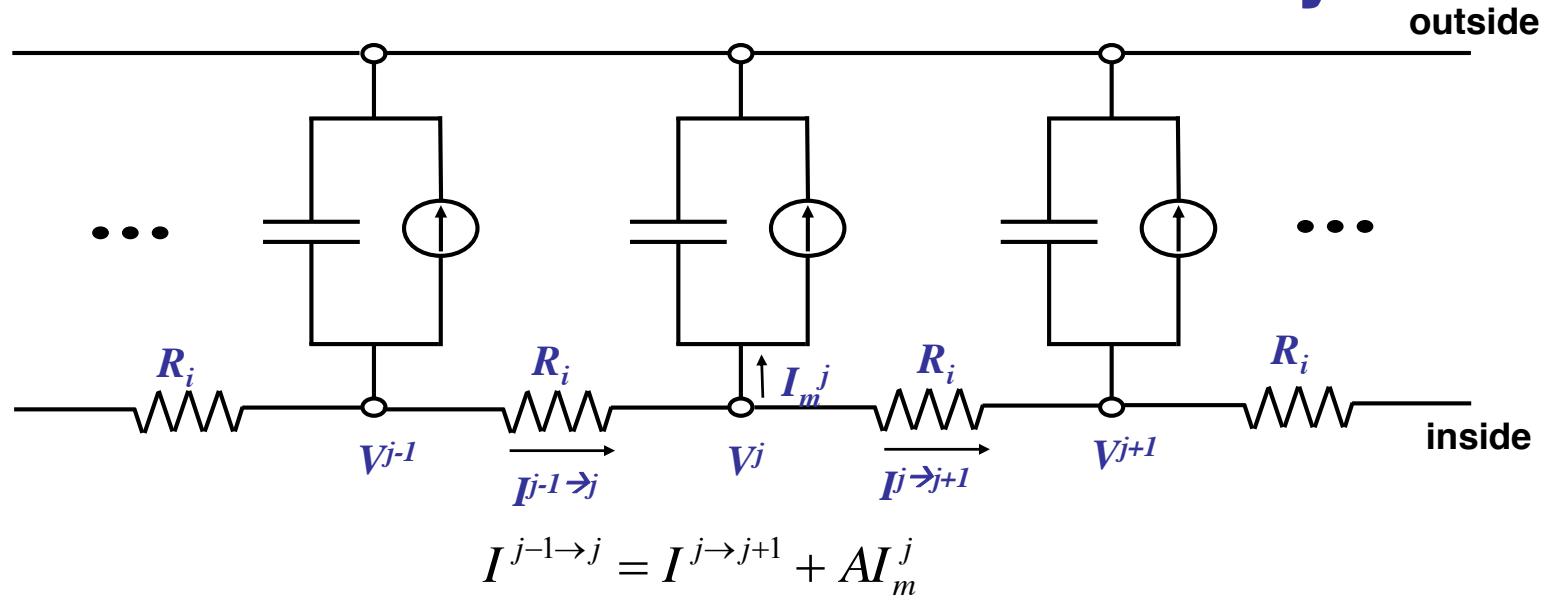
Kirchoff's current law

where **A** is the surface area of the j th element

$$I_m^j = C_m \frac{dV^j}{dt} + I_{ion}^j$$

Membrane currents are normalized per unit area.

One dimensional cable theory



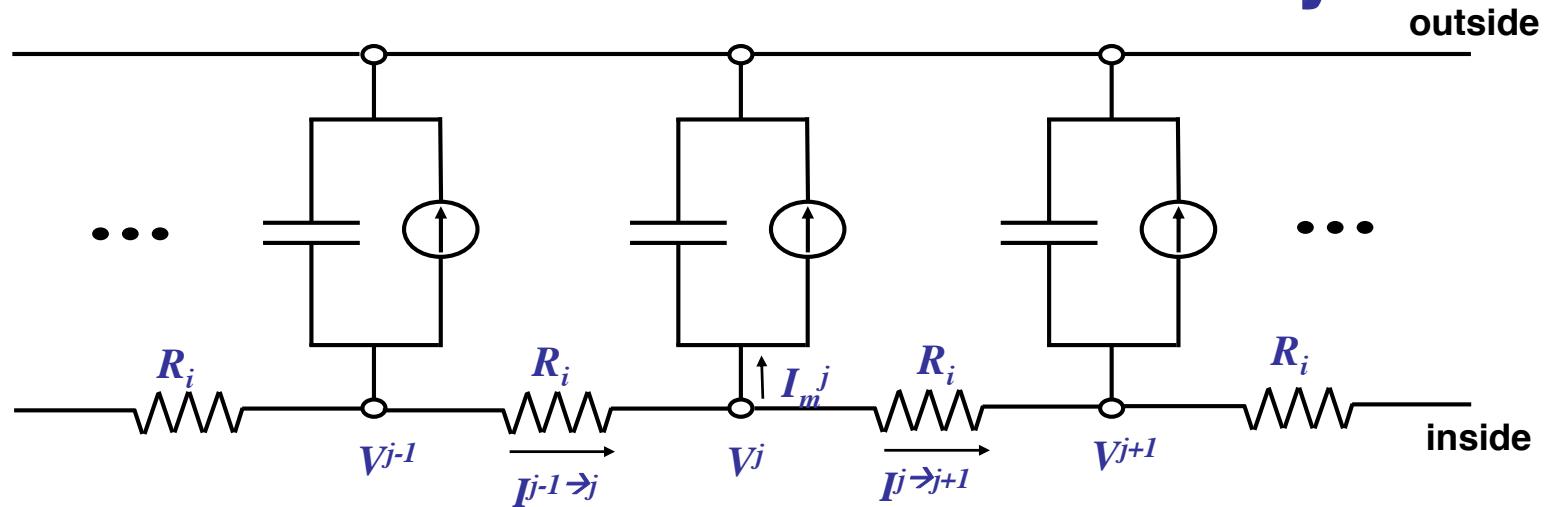
Substitute into this:

$$I^{j-1 \rightarrow j} = (V^{j-1} - V^j) / R_i \quad I^{j \rightarrow j+1} = (V^j - V^{j+1}) / R_i \quad I_m^j = C_m \frac{dV^j}{dt} + I_{ion}^j$$

This yields:

$$(V^{j-1} - V^j) / R_i = (V^j - V^{j+1}) / R_i + A \left[C_m \frac{dV^j}{dt} + I_{ion}^j \right]$$

One dimensional cable theory



Putting the equations together:

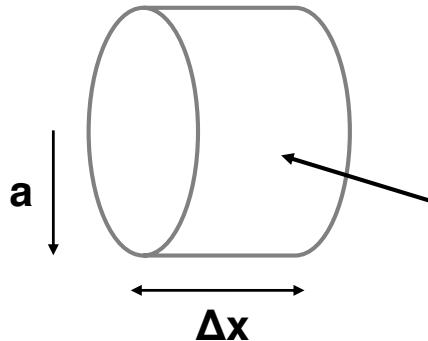
$$(V^{j-1} - V^j)/R_i = (V^j - V^{j+1})/R_i + A \left[C_m \frac{dV^j}{dt} + I_{ion}^j \right]$$

Rearranging yields:

$$C_m \frac{dV^j}{dt} = \frac{(V^{j-1} - 2V^j + V^{j+1})}{AR_i} - I_{ion}^j$$

One dimensional cable theory

How can we relate R_i to cable geometry?



$$R_i = \frac{\rho_i \Delta x}{\pi a^2}$$

$$A = 2\pi a \Delta x$$

ρ_i = intracellular resistivity

Thus,

$$AR_i = 2\pi a \Delta x \frac{\rho_i \Delta x}{\pi a^2} = \frac{2\rho_i \Delta x^2}{a}$$

Substituting yields:

$$C_m \frac{dV^j}{dt} = \frac{a}{2\rho_i} \frac{(V^{j-1} - 2V^j + V^{j+1})}{\Delta x^2} - I_{ion}^j$$

As $\Delta x \rightarrow 0$, this becomes:

$$C_m \frac{\partial V}{\partial t} = \frac{a}{2\rho_i} \frac{\partial^2 V}{\partial x^2} - I_{ion}$$

Dropped the j superscript.
This applies for all j

This is the nonlinear cable equation

Notes on the 1-D cable equation

$$C_m \frac{\partial V}{\partial t} = \frac{a}{2\rho_i} \frac{\partial^2 V}{\partial x^2} - I_{ion}$$

1) This is a reaction-diffusion equation.

These equations appear in other contexts

For instance, sub-cellular diffusion of Ca^{2+}

We will discuss other examples of reaction-diffusion

2) This is a partial differential equation (PDE).

To obtain a numerical solution, must convert to discrete form in both space and time.

$$\left. \frac{\partial V}{\partial t} \right|_j^t \approx \frac{V_j^{t+\Delta t} - V_j^t}{\Delta t} \quad \left. \frac{\partial^2 V}{\partial x^2} \right|_j^t \approx \frac{V_{j+1}^t - 2V_j^t + V_{j-1}^t}{\Delta x^2}$$

PDE solvers, like ODE solvers, are based on such discrete approximations.

Summary

In neurons, voltage is typically not spatially uniform but instead varies as a function of time and location.

Partial Differential Equations (PDEs) are used to mathematically describe such spatially non-uniform systems.

The "cable equation" is an example of a reaction-diffusion equation, a type of PDE that is frequently encountered in biology.

Explicit versus Implicit Solutions

$$C_m \frac{\partial V}{\partial t} = \frac{a}{2\rho_i} \frac{\partial^2 V}{\partial x^2} - I_{ion}$$

Explicit solutions

Solve for each future value of V based on current values of V

$$C_m \frac{V_j^{t+\Delta t} - V_j^t}{\Delta t} = \frac{a}{2\rho_i} \frac{V_{j+1}^t - 2V_j^t + V_{j-1}^t}{\Delta x^2} - I_{ion}^t$$

Implicit solutions

Solve for future values of V based on future values of V

$$C_m \frac{V_j^{t+\Delta t} - V_j^t}{\Delta t} = \frac{a}{2\rho_i} \frac{V_{j+1}^{t+\Delta t} - 2V_j^{t+\Delta t} + V_{j-1}^{t+\Delta t}}{\Delta x^2} - I_{ion}^{t+\Delta t}$$

Explicit versus Implicit Solutions

Explicit solutions are simple to implement

Rearrange so that future is on LHS, present on RHS

$$V_j^{t+\Delta t} = V_j^t + \Delta t \frac{a}{2\rho_i C_m} \left[\frac{V_{j+1}^t - 2V_j^t + V_{j-1}^t}{\Delta x^2} - I_{ion}^t \right]$$

plus similar equations for $V_{j+1}^{t+\Delta t}$ $V_{j-1}^{t+\Delta t}$ etc.

This just converts the PDE into large system of ODEs

Advantage: simple

Disadvantage: for stability $\Delta t \sim \Delta x^2$, must be very small

Explicit solutions of PDEs can take a very long time to run.

Explicit versus Implicit Solutions

Implicit solutions are conceptually more difficult

$$C_m \frac{V_j^{t+\Delta t} - V_j^t}{\Delta t} = \frac{a}{2\rho_i} \frac{V_{j+1}^{t+\Delta t} - 2V_j^{t+\Delta t} + V_{j-1}^{t+\Delta t}}{\Delta x^2} - I_{ion}^{t+\Delta t}$$

Computing $I_{ion}^{t+\Delta t}$ requires knowing $m^{t+\Delta t}$, $h^{t+\Delta t}$, $n^{t+\Delta t}$.

In practice, reaction treated explicitly, diffusion implicitly.

$$C_m \frac{V_j^{t+\Delta t} - V_j^t}{\Delta t} = \frac{a}{2\rho_i} \frac{V_{j+1}^{t+\Delta t} - 2V_j^{t+\Delta t} + V_{j-1}^{t+\Delta t}}{\Delta x^2} - I_{ion}^t$$

Even with this simplification, the equation still has 3 unknowns!

$$-\frac{a}{2\rho_i \Delta x^2} V_{j+1}^{t+\Delta t} + \left[\frac{a}{\rho_i \Delta x^2} + \frac{C_m}{\Delta t} \right] V_j^{t+\Delta t} - \frac{a}{2\rho_i \Delta x^2} V_{j-1}^{t+\Delta t} = \frac{C_m}{\Delta t} V_j^t - I_{ion}^t$$

Must solve for the three unknowns simultaneously.
This requires inverting a matrix.

Implicit Solution of HH Equations

$$\begin{bmatrix} \ddots & \ddots & & \\ -a & \left(\frac{a}{\rho_i \Delta x^2} + \frac{C_m}{\Delta t}\right) & -a & \\ & \frac{-a}{2\rho_i \Delta x^2} & \left(\frac{a}{\rho_i \Delta x^2} + \frac{C_m}{\Delta t}\right) & -a \\ & & \frac{-a}{2\rho_i \Delta x^2} & \left(\frac{a}{\rho_i \Delta x^2} + \frac{C_m}{\Delta t}\right) & -a \\ & & & \ddots & \ddots \end{bmatrix} \cdot \begin{bmatrix} \vdots \\ V_{j-1}^{t+\Delta t} \\ V_j^{t+\Delta t} \\ V_{j+1}^{t+\Delta t} \\ \vdots \end{bmatrix} = \frac{C_m}{\Delta t} \begin{bmatrix} \vdots \\ V_{j-1}^t \\ V_j^t \\ V_{j+1}^t \\ \vdots \end{bmatrix} - \begin{bmatrix} \vdots \\ I_{ion,j-1}^t \\ I_{ion,j}^t \\ I_{ion,j+1}^t \\ \vdots \end{bmatrix}$$

This is a matrix equation $\mathbf{Ax} = \mathbf{b}$

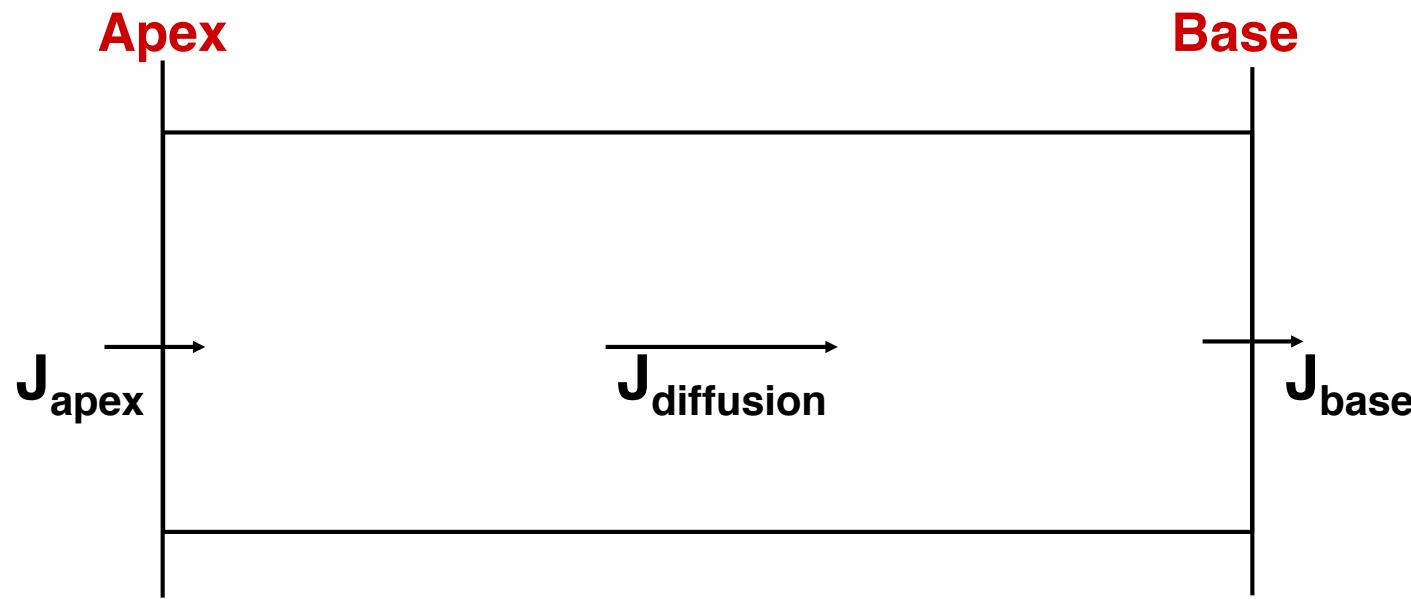
$$\mathbf{x} = \mathbf{A}^{-1}\mathbf{b}$$

Thus, implicit solutions involve inverting a matrix
at each time step

Supplementary Slides

Diffusion across an epithelial cell

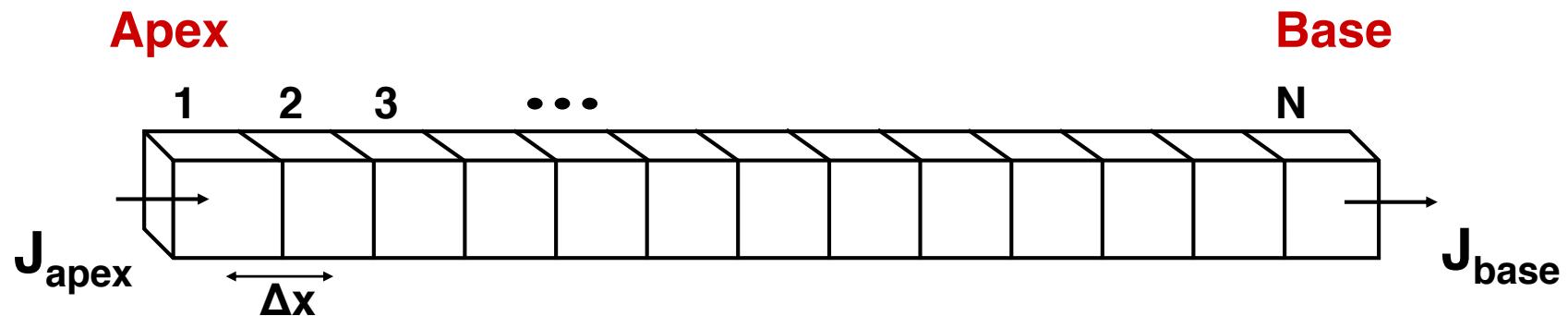
Consider example of HCO_3^- in proximal tubule



How do we describe diffusion of HCO_3^- from apex to base?

Diffusion across an epithelial cell

Represent cell as a series of discrete segments



$[\text{HCO}_3]_i$ = concentration in sub-cube i

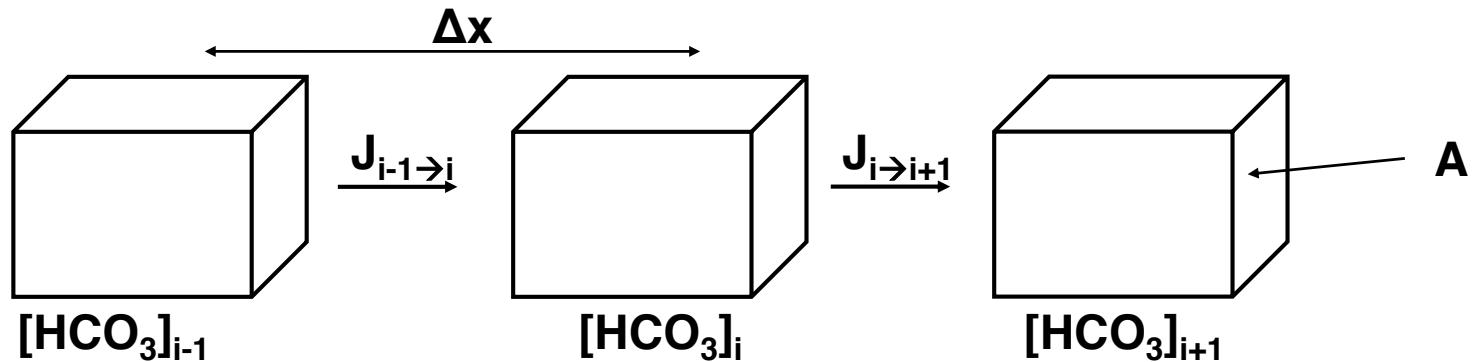
D_{HCO_3} = intracellular diffusion constant

Δx = distance between adjacent sub-cubes

What are the equations that describe diffusion
from apex to base?

Diffusion across an epithelial cell

First consider diffusion within three sub-cubes



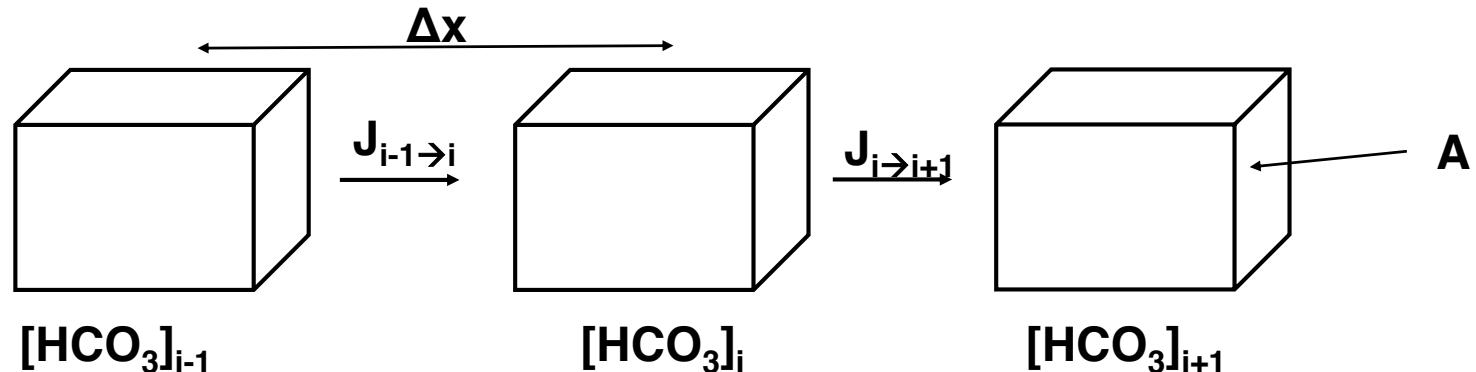
$$J_{i-1 \rightarrow i} = D_{HCO_3} \frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x}$$

$$J_{i \rightarrow i+1} = D_{HCO_3} \frac{([HCO_3]_i - [HCO_3]_{i+1})}{\Delta x}$$

Fick's first law of diffusion

Diffusion across an epithelial cell

How to relate to changes in $[HCO_3^-]_i$?



Intuitively, $d[HCO_3]_i/dt$ depends on inflow vs. outflow, $J_{i-1 \rightarrow i} - J_{i \rightarrow i+1}$

Need to consider units to express this precisely

Δx : cm

$[HCO_3]$: mM;

equivalent to $\mu\text{mol}/\text{cm}^3$

D_{HCO_3} : cm^2/s

$$J_{i-1 \rightarrow i} = D_{HCO_3} \frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x}$$

$J_{i \rightarrow i+1}$: $\mu\text{mol}/(\text{cm}^2 \text{ s})$

Therefore we must convert from $\mu\text{mol}/(\text{cm}^2 \text{ s})$ to $\mu\text{mol}/(\text{cm}^3 \text{ s})$

Diffusion across an epithelial cell

Need to convert from $\mu\text{mol}/(\text{cm}^2 \text{ s})$ to $\mu\text{mol}/(\text{cm}^3 \text{ s})$

Multiply by inter-cube surface area A, then divide by volume (V_i)

$$\frac{d[HCO_3]_i}{dt} = \frac{A(J_{i-1 \rightarrow i} - J_{i \rightarrow i+1})}{V_i}$$

But $V_i = A\Delta x$

So $\frac{d[HCO_3]_i}{dt} = \frac{(J_{i-1 \rightarrow i} - J_{i \rightarrow i+1})}{\Delta x}$

Thus:

$$\frac{d[HCO_3]_i}{dt} = D_{HCO_3} \left[\frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x} - \frac{([HCO_3]_i - [HCO_3]_{i+1})}{\Delta x} \right]$$

Diffusion across an epithelial cell

What is the limit as $\Delta x \rightarrow 0$?

$$\lim_{\Delta x \rightarrow 0} \frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x} = \frac{d[HCO_3]}{dx}$$

$$\lim_{\Delta x \rightarrow 0} \left[\frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x} - \frac{([HCO_3]_i - [HCO_3]_{i+1})}{\Delta x} \right] = \frac{d^2[HCO_3]}{dx^2}$$

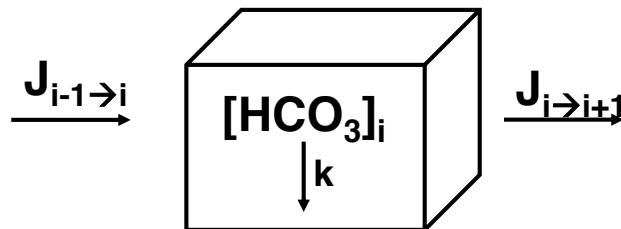
So, in the limit of small Δx , our equation becomes

$$\frac{\partial[HCO_3]_i}{\partial t} = D_{HCO_3} \frac{\partial^2[HCO_3]}{\partial x^2}$$

This is a one-dimensional diffusion equation

Diffusion across an epithelial cell

What if some first order intracellular process is also consuming HCO_3 ?



Then,

$$\frac{d[\text{HCO}_3]_i}{dt} = \frac{J_{i-1 \rightarrow i}}{\Delta x} - \frac{J_{i \rightarrow i+1}}{\Delta x} - k[\text{HCO}_3]_i$$

In the continuum limit:

$$\frac{\partial [\text{HCO}_3]_i}{\partial t} = D_{\text{HCO}_3} \frac{\partial^2 [\text{HCO}_3]}{\partial x^2} - k[\text{HCO}_3]$$

This is a reaction-diffusion equation.
Where have we seen this before?