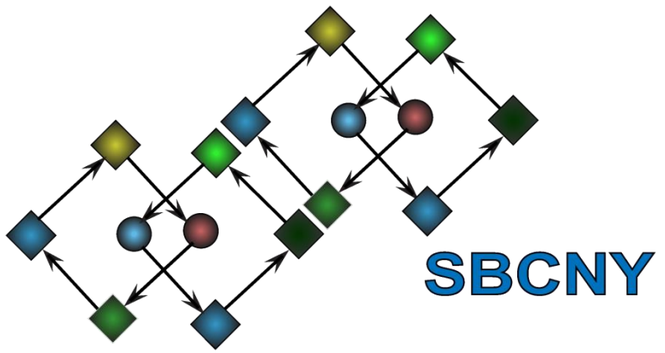
Mathematical models of action potentials

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 α(V), β(V)

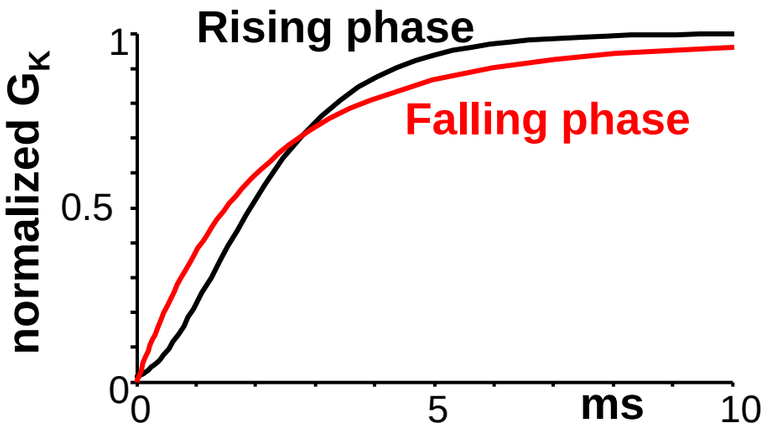
$$\beta_m(V) = 4.0e^{\frac{-(V+60)}{20}}$$

No physical basis for exponential function
Numbers 4, 60, 20, chosen simply to fit the data

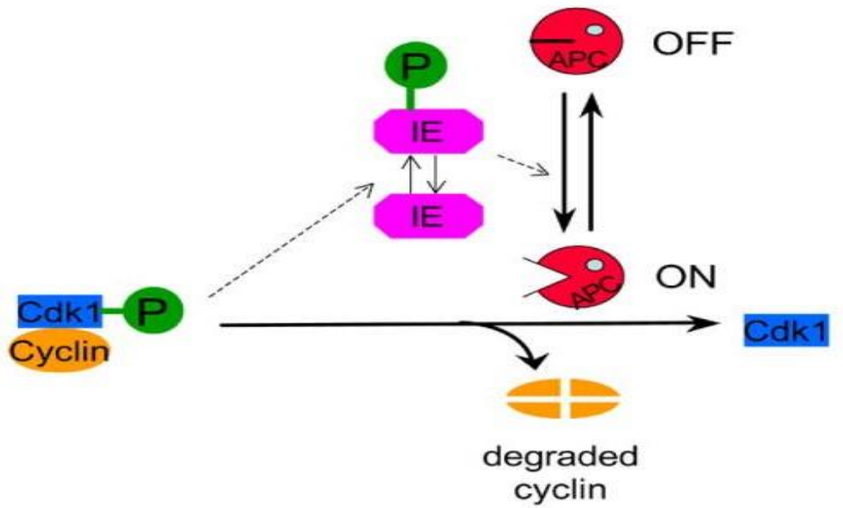
Phenomenology begets mechanism: $I_K = G_K n^4 (V - E_K)$
Four particle model based on curve fitting
Tetrameric ion channel structure is now a rigorous physical basis

Phenomenology begets Mechanism

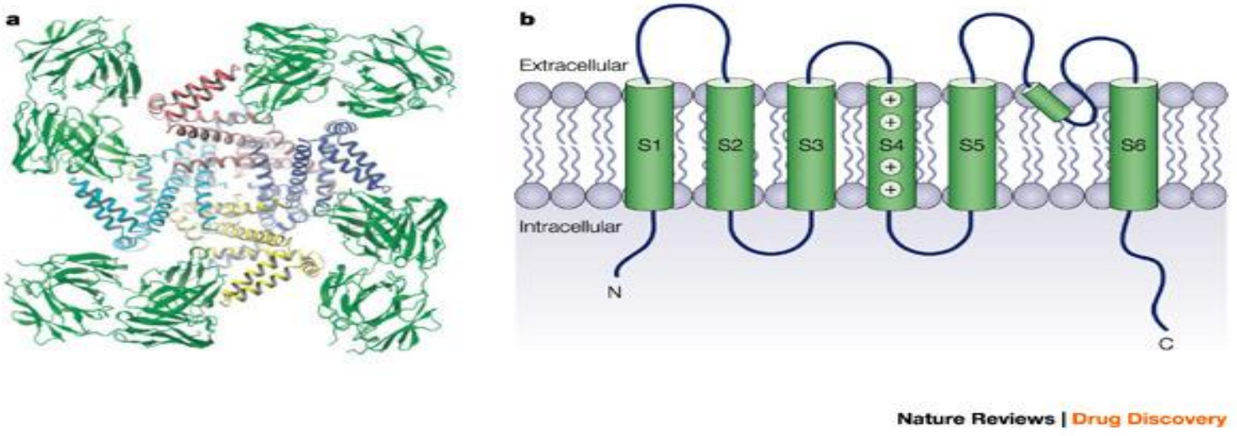
Hodgkin-Huxley model



Novak & Tyson model



Tetrameric ion channel structure



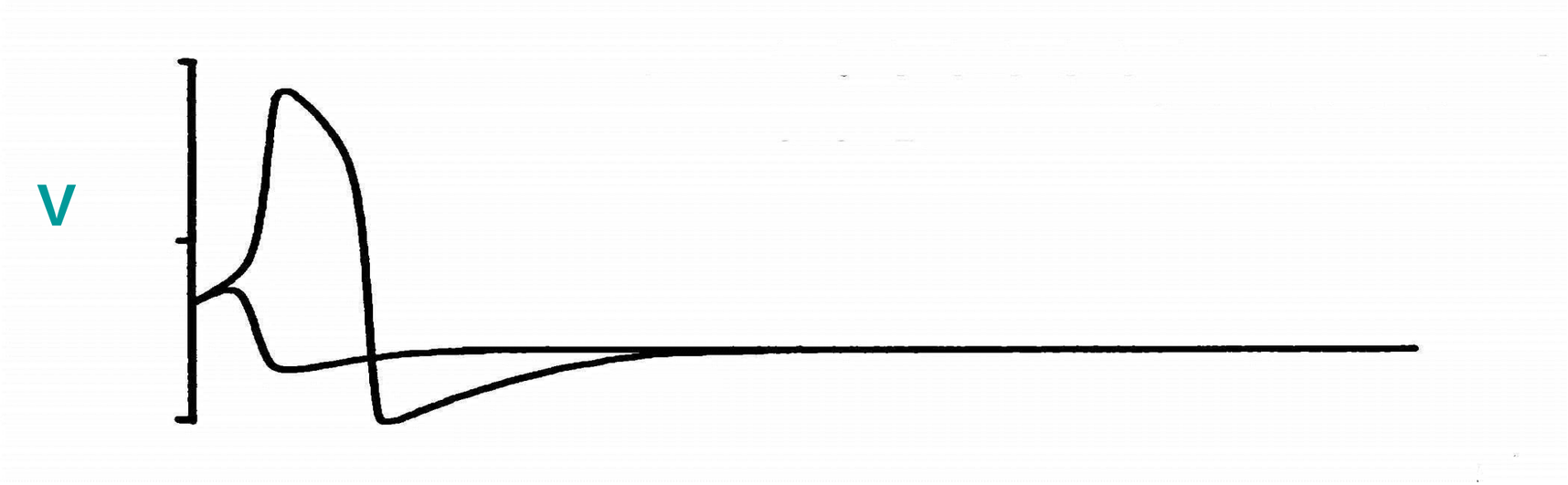
IE = intermediate enzyme

This is now known to correspond to Fizzy/cdc20

Nature Reviews Drug Discovery (2004) 3, 239-278

Phenomenology versus Mechanism

An extreme case: the Fitzhugh-Nagumo model



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

Dr. Richard Fitzhugh

$$dV/dt = V - V^3 - W - I$$

$$dW/dt = 0.08*(V + 0.7-0.8W)$$

V: voltage-like variable

W: recovery variable

The Fitzhugh-Nagumo model

An abstract and clearly phenomenological model

$$dV/dt = V - V^3 - W - I$$

$$dW/dt = 0.08*(V + 0.7-0.8W)$$

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

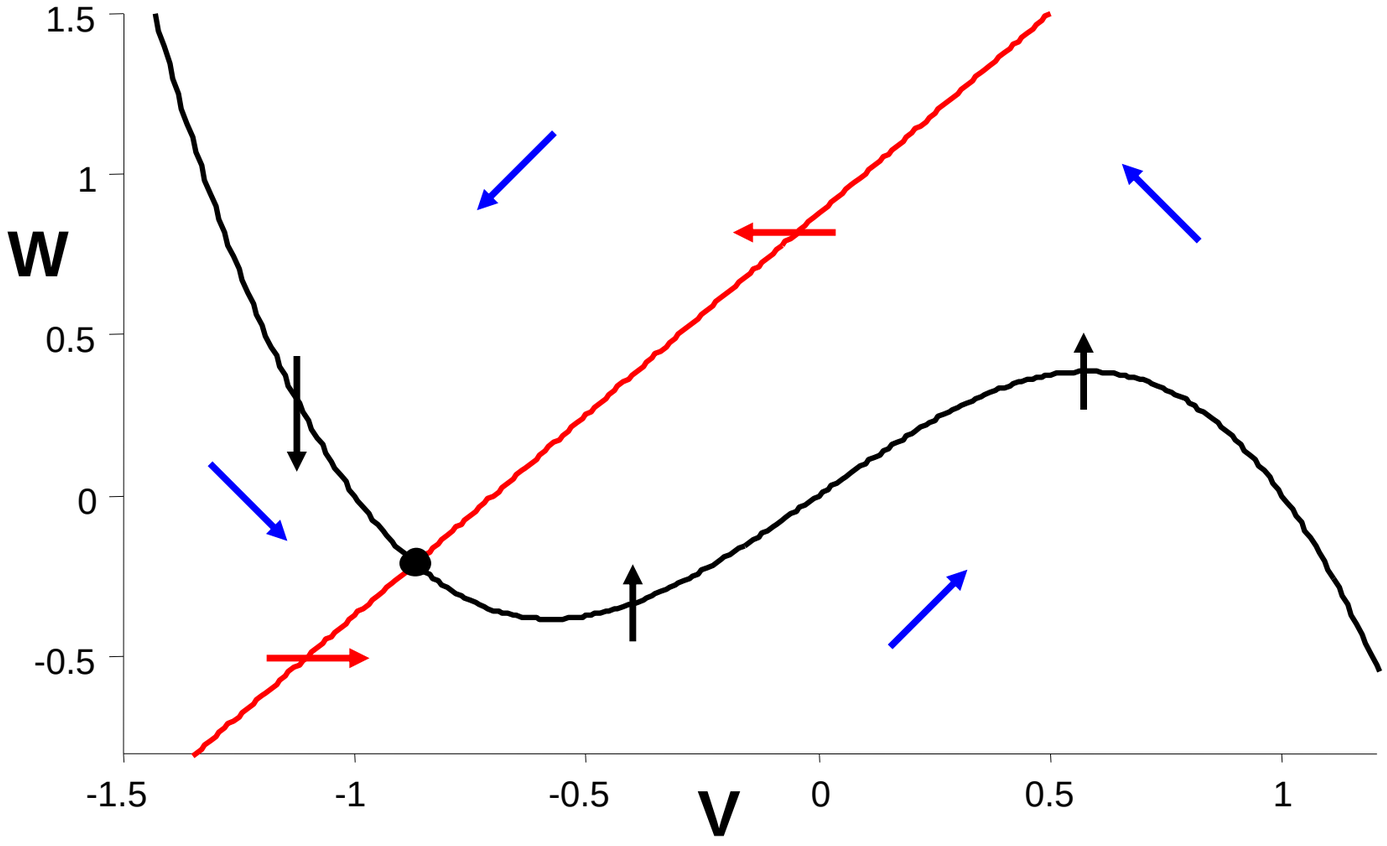
Nagumo et al., (1962) Proc. IRE. 50:2061–2070

Dr. Jin-Ichi Nagumo

Electronic circuit built using tunnel diodes

The Fitzhugh-Nagumo model

Benefits of a generic two-variable model



V nullcline:

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

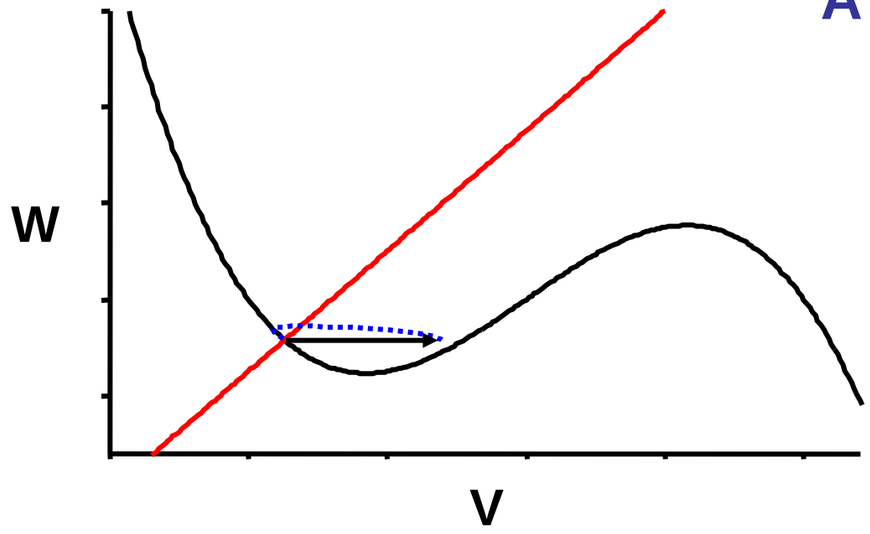
W nullcline:

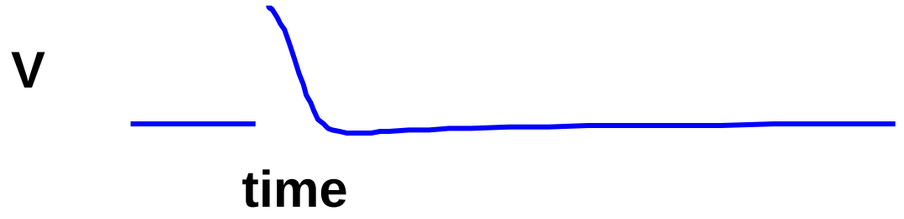
$$W = (V + 0.7)/0.8$$

The Fitzhugh-Nagumo model

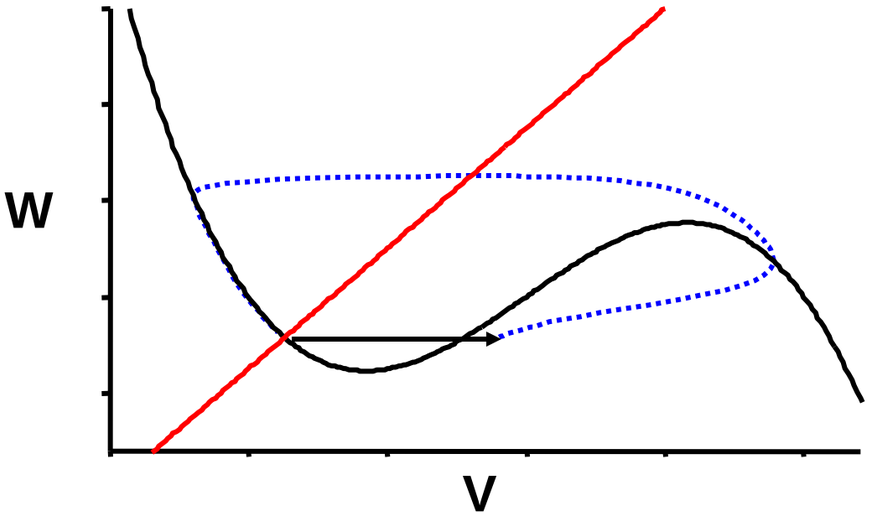
Electrical stimulus: an instantaneous increase in V

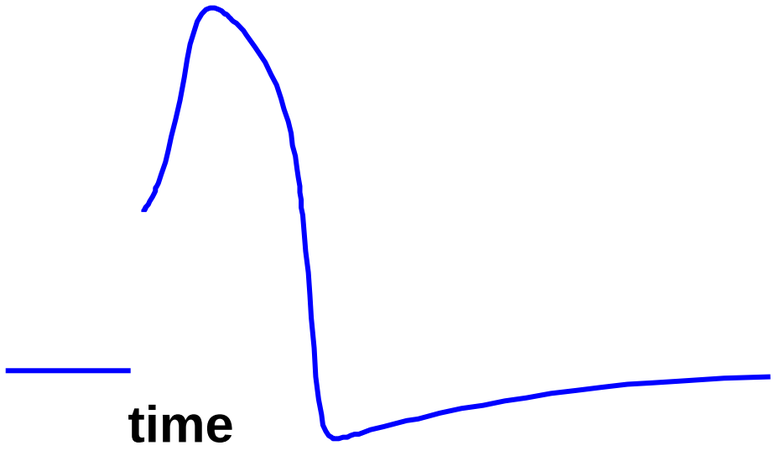
A small increase in V





A larger increase in V



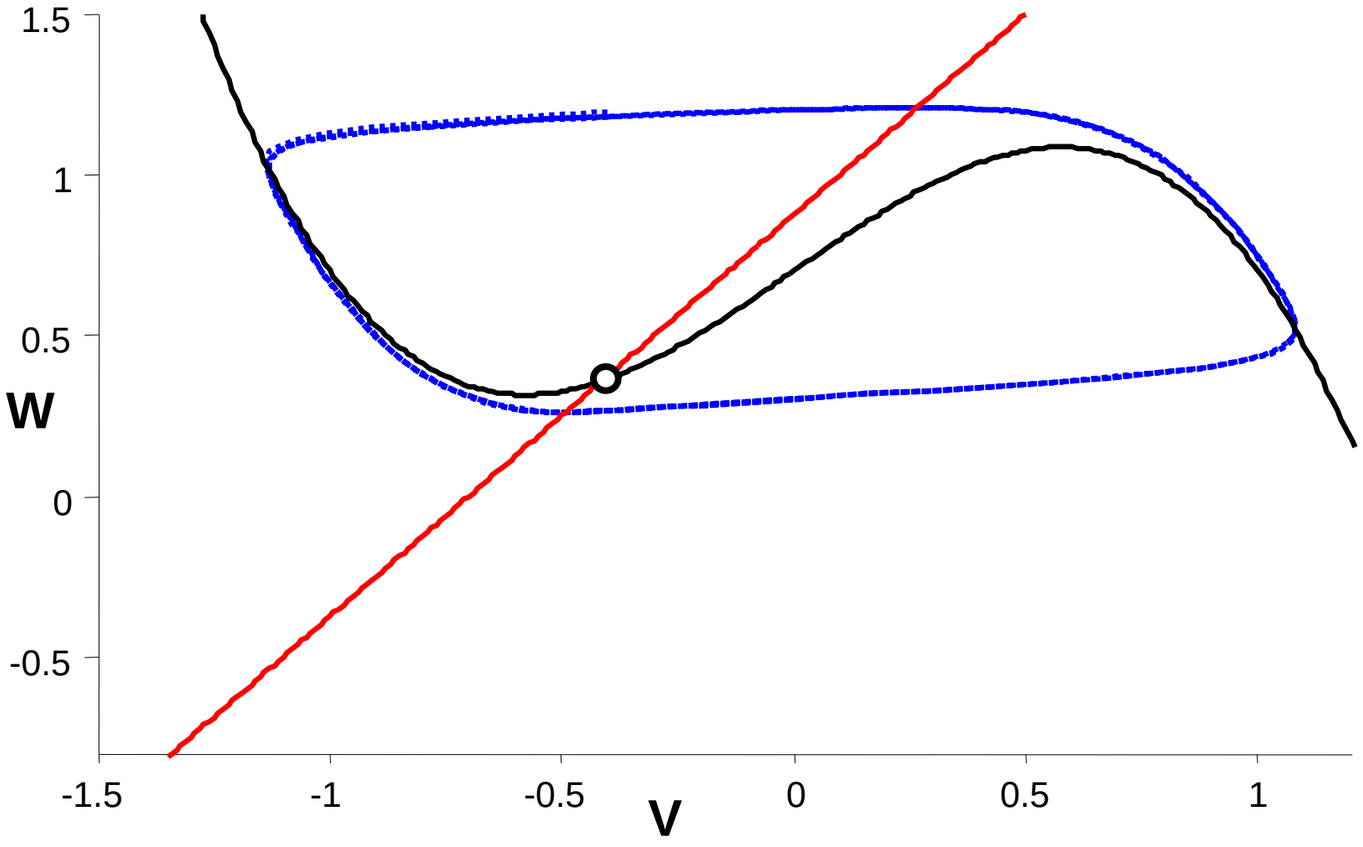


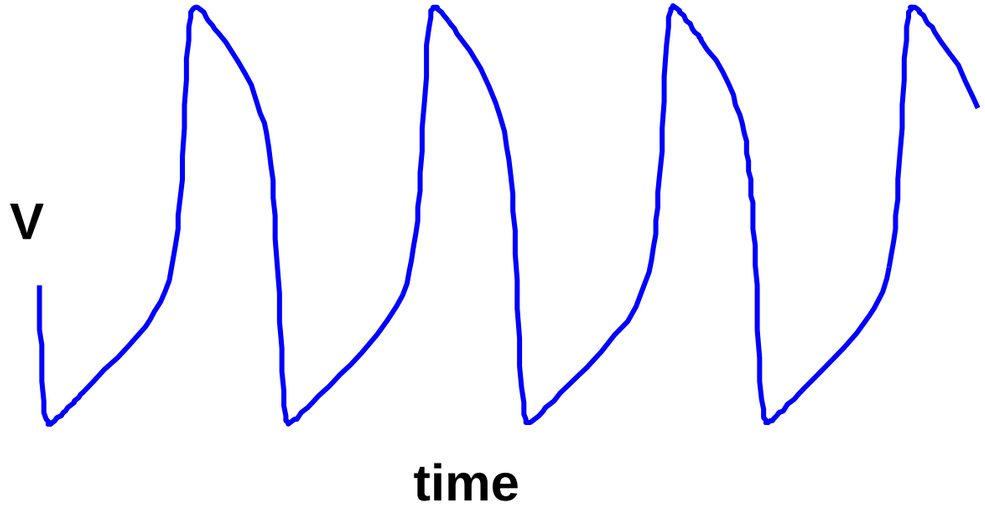
The Fitzhugh-Nagumo model

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

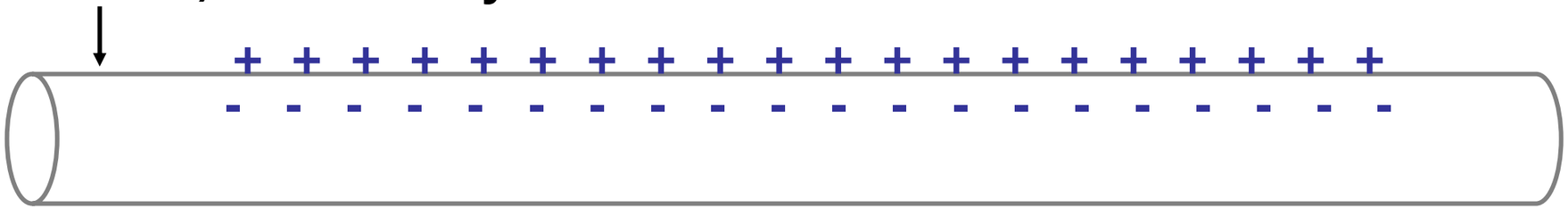
A prominent example: the Fitzhugh-Nagumo model

Simulating a propagating action potential

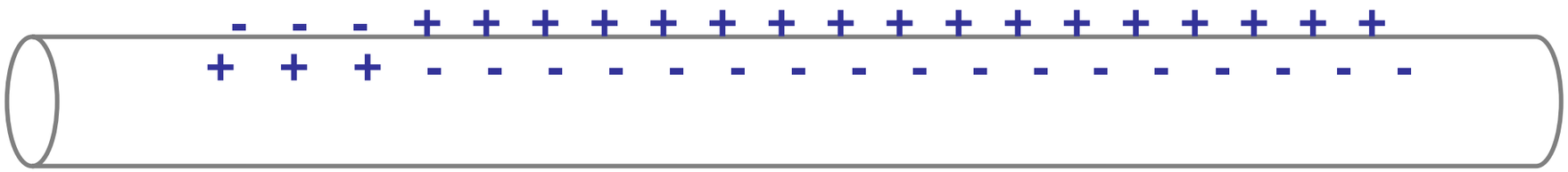
Electrical propagation involves spatial voltage gradients

Imagine a long, one-dimensional axon

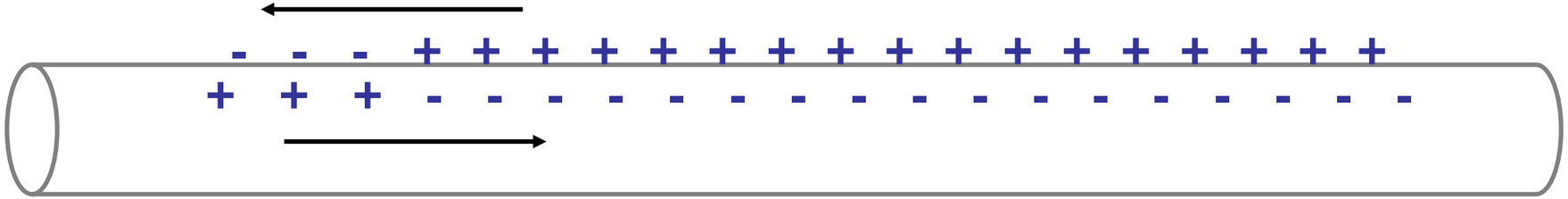
(1) Starts at rest, then locally stimulated



(2) Depolarized on left, resting on right



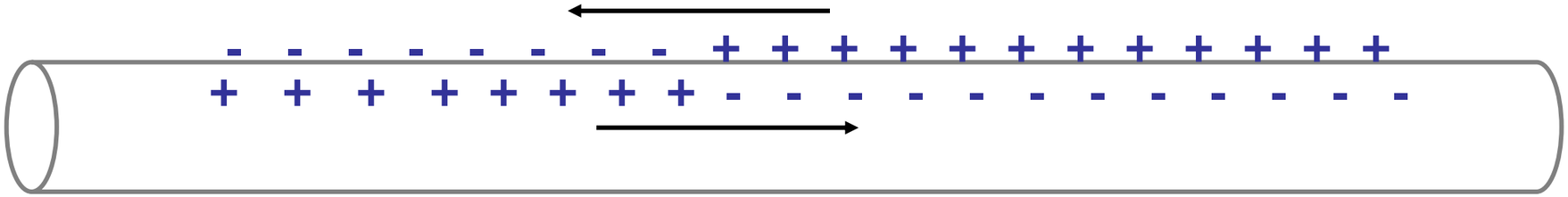
(3) Electrical current will flow both inside and outside



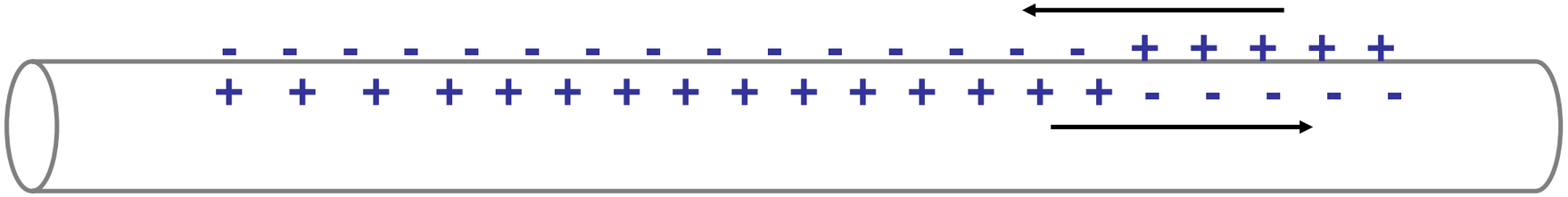
Electrical propagation results from spatial voltage gradients

Imagine a long, one-dimensional axon

(4) More tissue will become depolarized



(5) Etc.

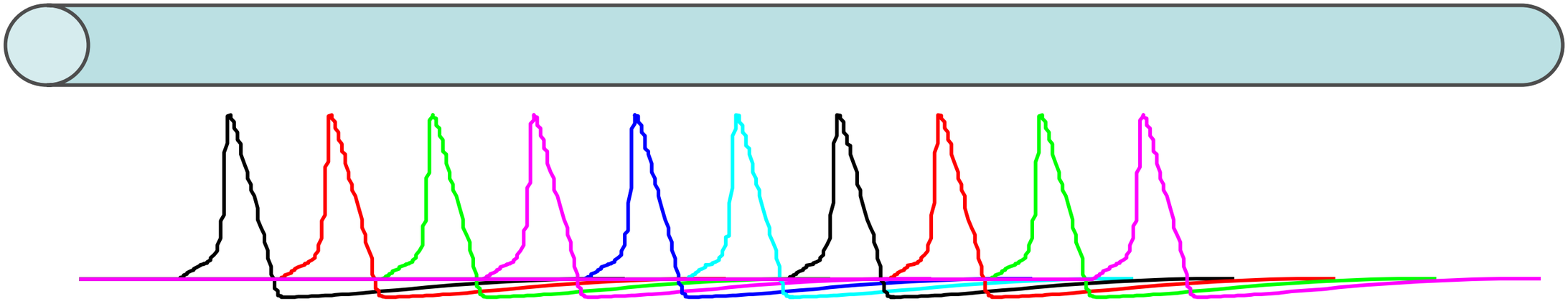


This is the basic mechanism by which action potentials propagate

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.

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

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

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

This is a matrix equation Ax = b

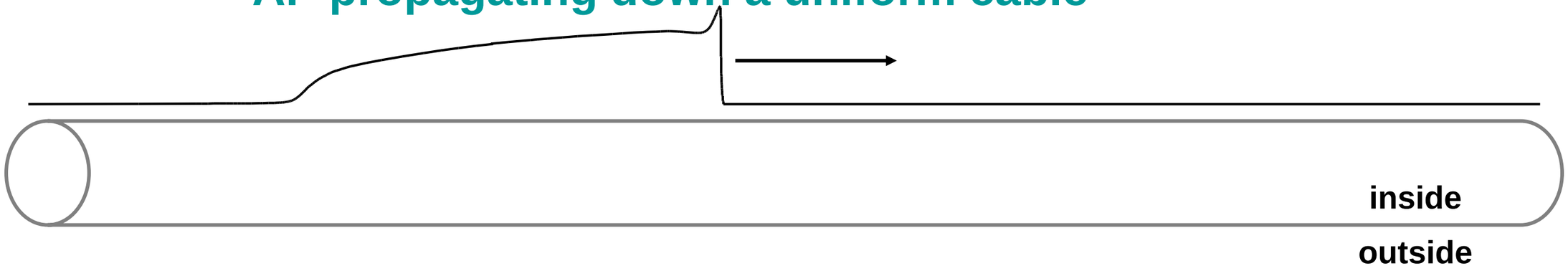
$x = A^{-1}b$

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

Supplementary Slides

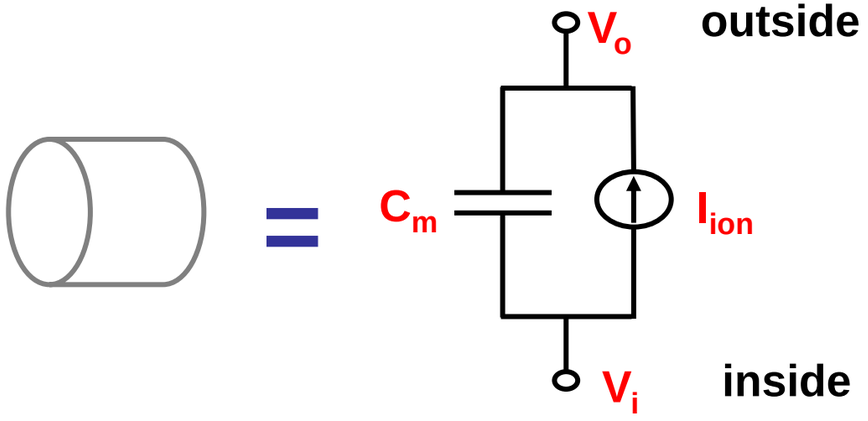
One dimensional electrical propagation

AP propagating down a uniform cable



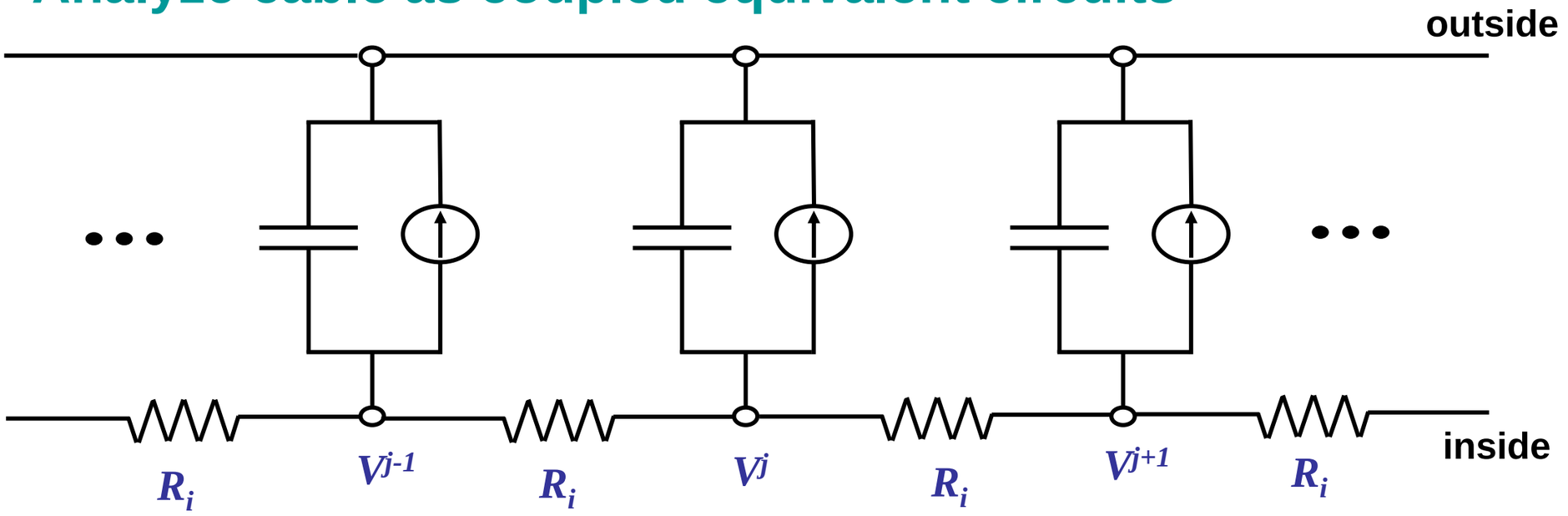
Divide the cable into discrete segments

Analyze the cable as coupled equivalent circuits



One dimensional cable theory

Analyze cable as coupled equivalent circuits



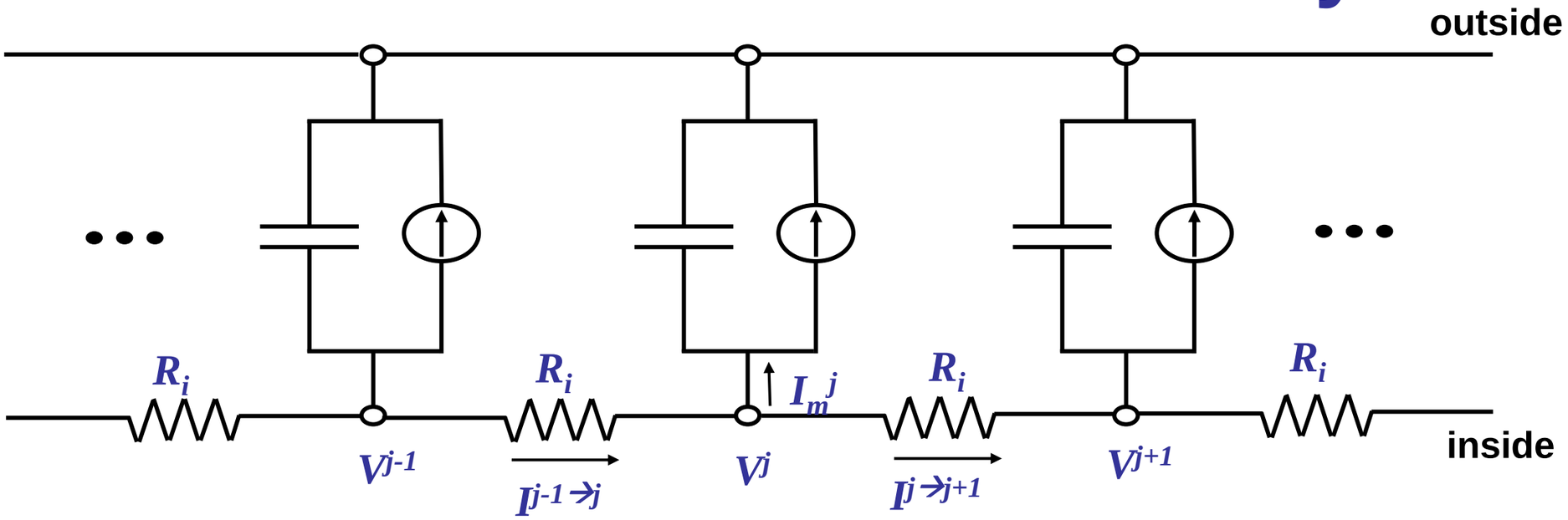
R_i=intracellular resistance

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

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

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

Ohm's law

$$I^{j-1\to j} = I^{j\to j+1} + AI_m^j$$

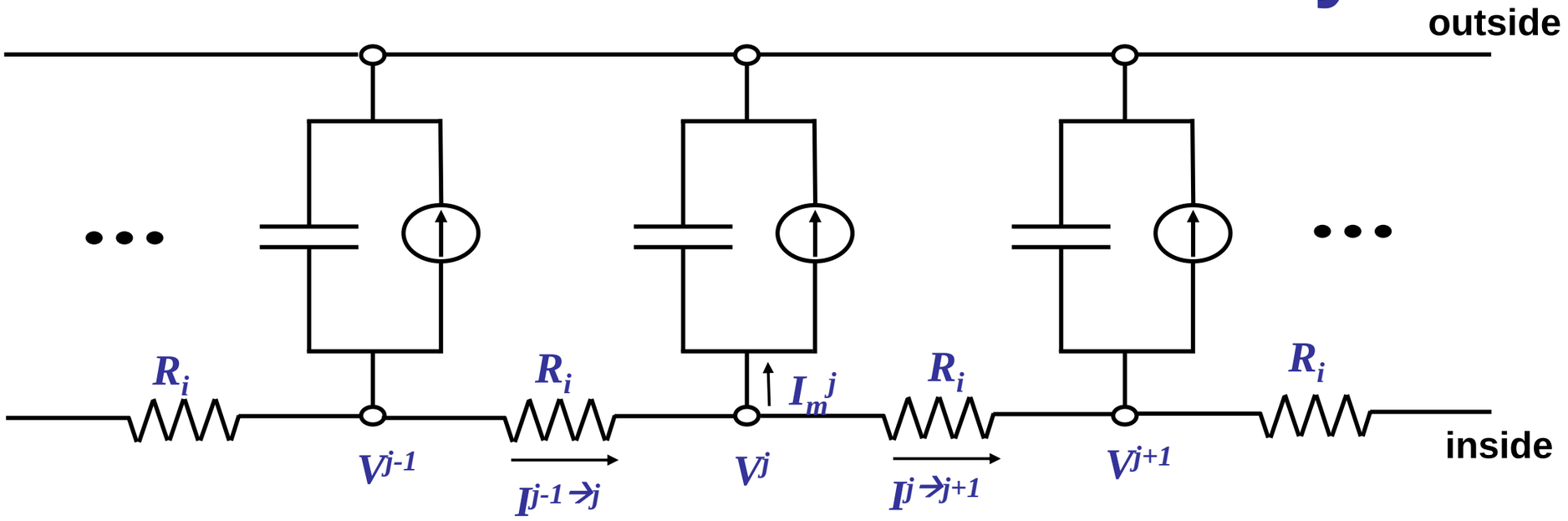
Kirchoff's current law

where A is the surface area of the jth 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:

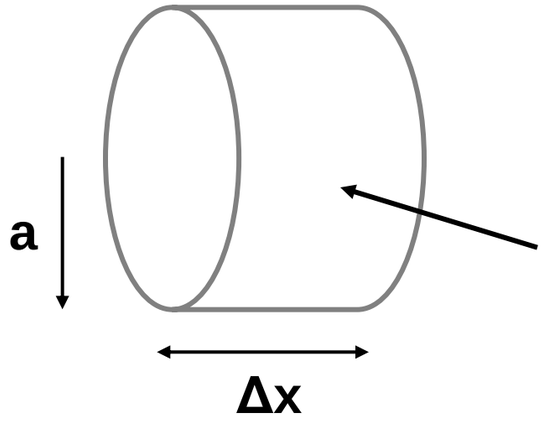
$$(V^{j-1} - V^j)/R_i = (V^j - V^{j+1})/R_i + A\left[C_m \frac{dV^j}{dt} + I_{ion}^j\right]$$

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?



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

ρ_i = intracellular resistivity

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

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:

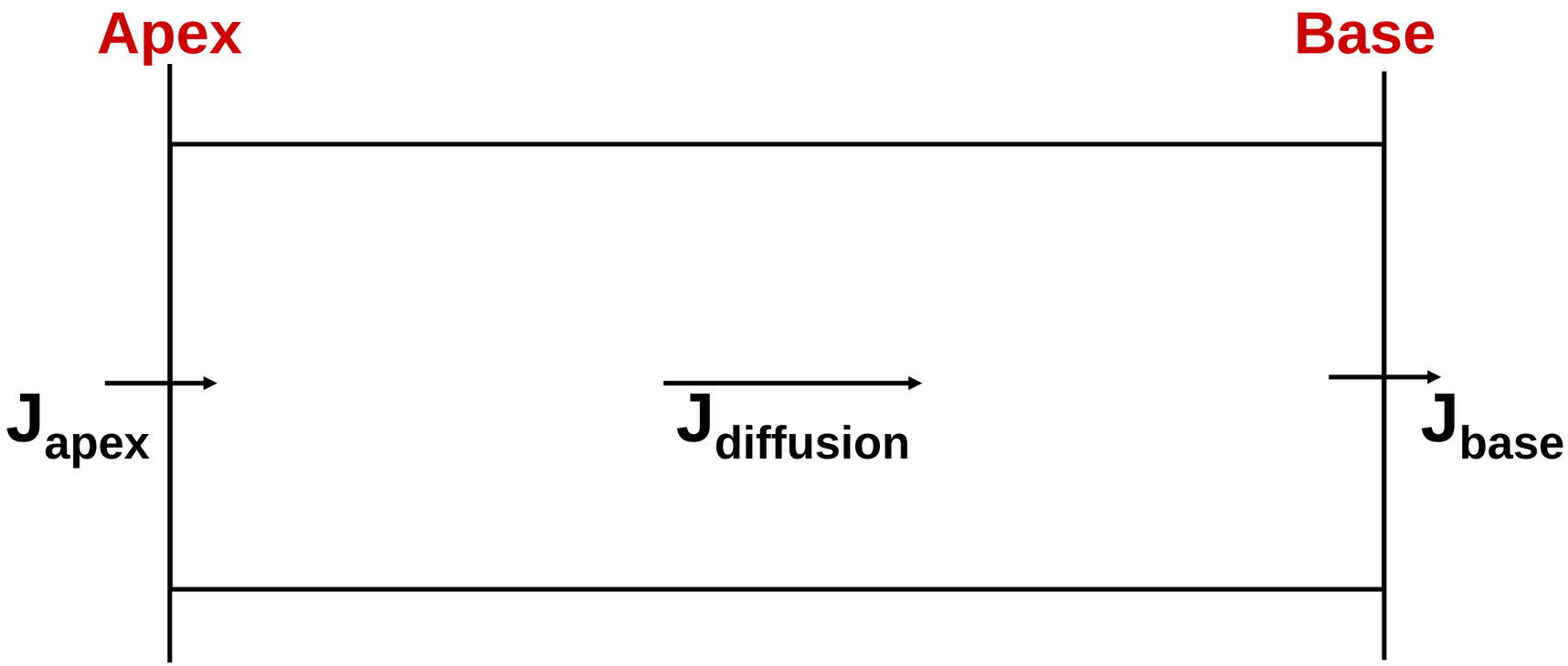
$$C_m \frac{\partial V}{\partial t} = \frac{a}{2\rho_i} \frac{\partial^2 V}{\partial x^2} - I_{ion}$$

Dropped the j superscript.
This applies for all j

This is the nonlinear cable equation

Diffusion across an epithelial cell

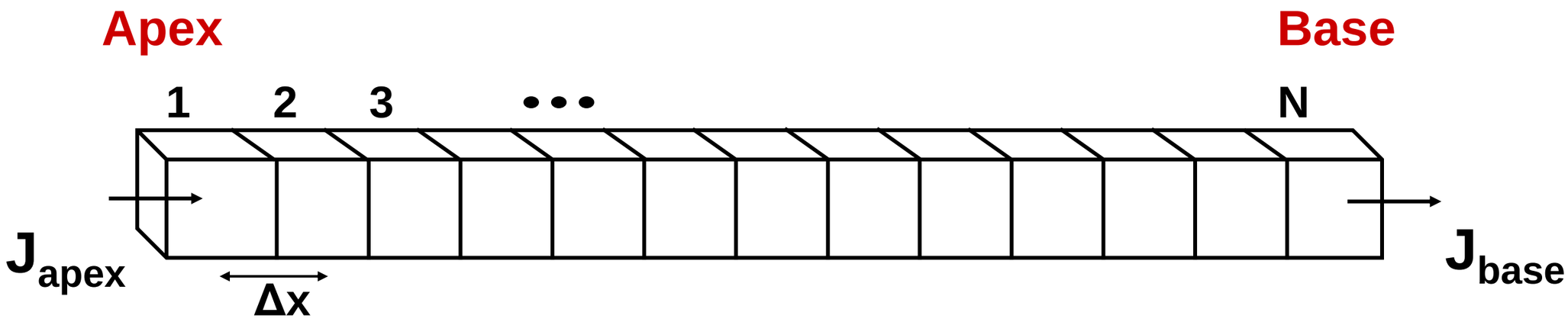
Consider example of HCO_3^- in proximal tubule



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



$[HCO_3]_i$ = concentration in sub-cube i

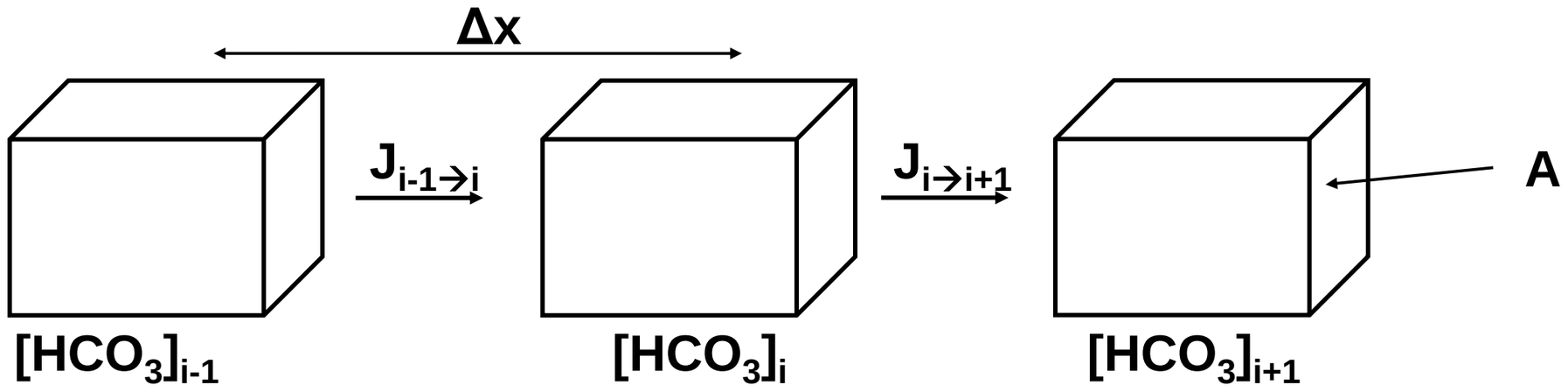
D_{HCO3} = intracellular diffusion constant

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



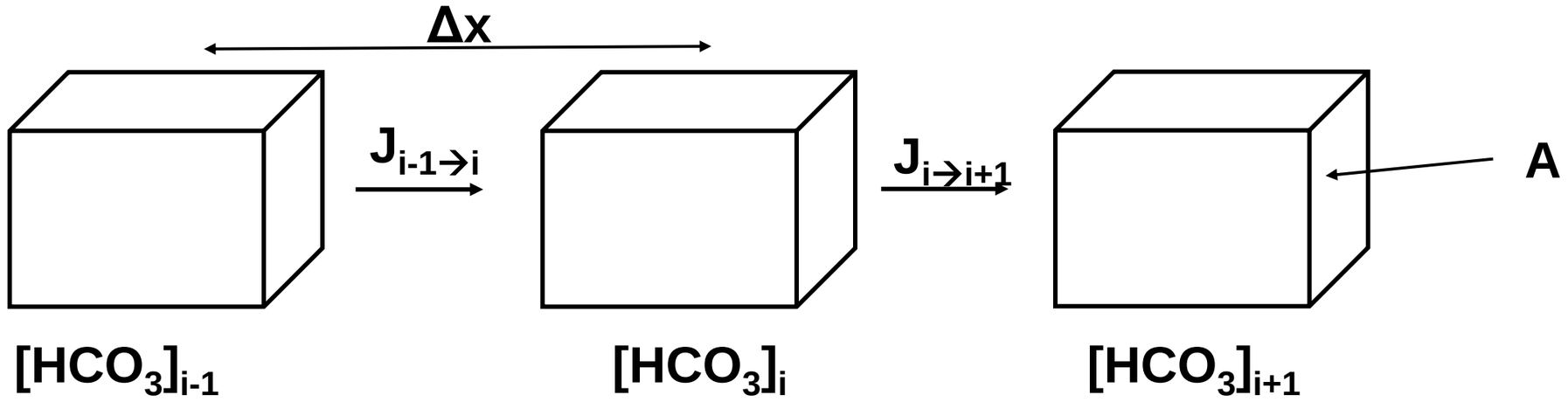
$$J_{i-1\rightarrow i} = D_{HCO_3} \frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x}$$

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

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 μmol/cm³
D_{HCO3}: cm²/s

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

$J_{i\rightarrow i+1}$: μmol/(cm² s)

Therefore we must convert from μmol/(cm² s) to μmol/(cm³ s)

Diffusion across an epithelial cell

Need to convert from μmol/(cm^2 s) to μmol/(cm^3 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:

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

Diffusion across an epithelial cell

What is the limit as Δx→0?

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

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

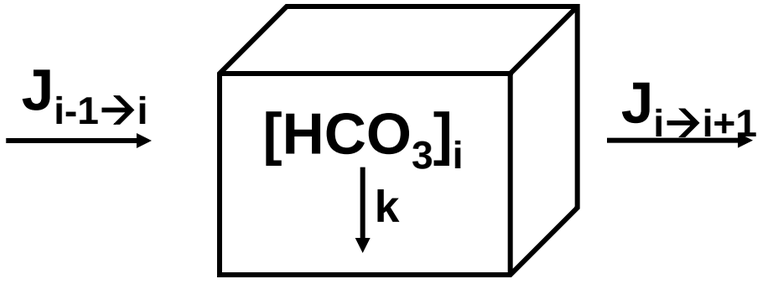
So, in the limit of small Δx, our equation becomes

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

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,

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

In the continuum limit:

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

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