# Mathematical models of action potentials

## Part 6: propagation of action potentials

Icahn School of Medicine at Mount Sinai

SBCNY

# 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**

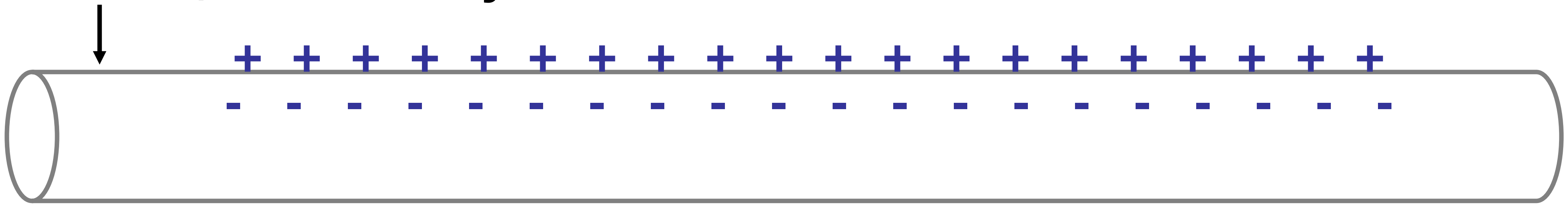
**This is where we transition from ODEs to PDEs**

**PDE = Partial Differential Equation**

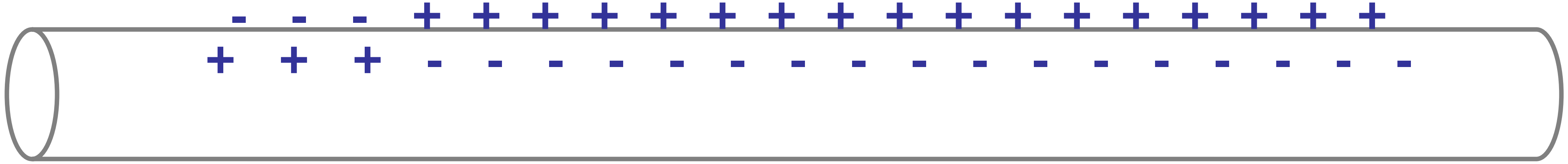
# Electrical propagation results from spatial voltage gradients

## Imagine a long, one-dimensional axon

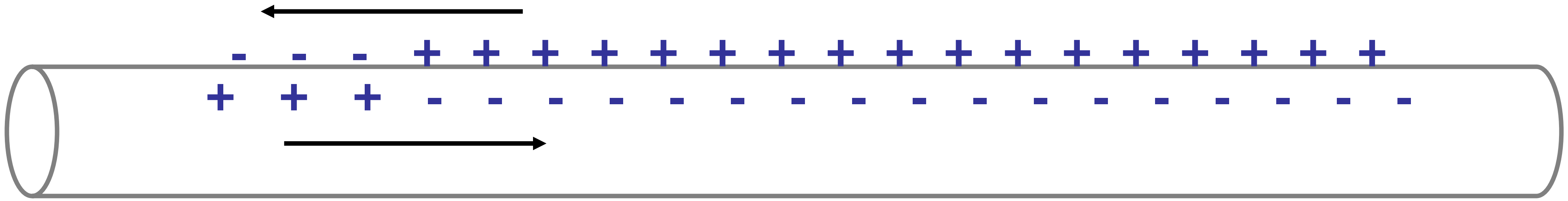
**(1) Starts at rest, then locally stimulated**



**(2) Depolarized on left, resting on right**



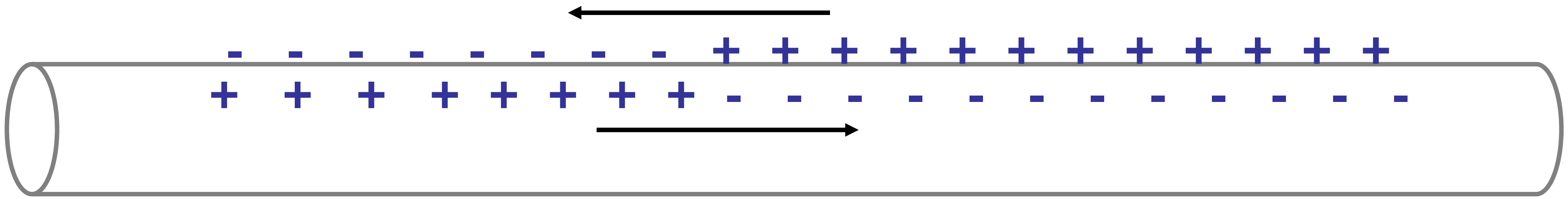
**(3) Electrical current will flow both inside and outside**



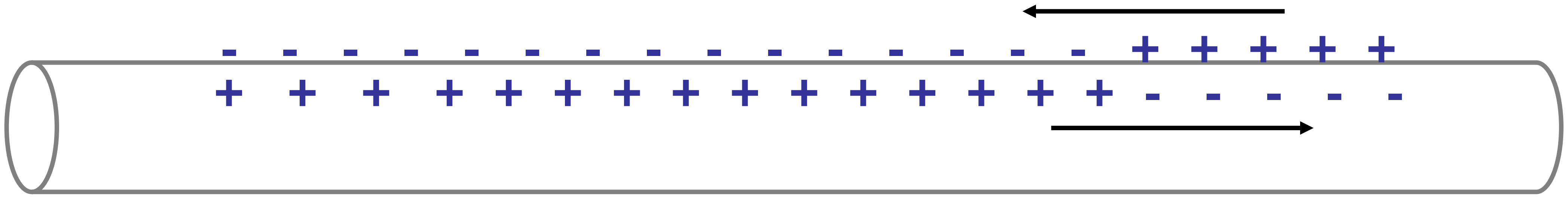
# Electrical propagation results from spatial voltage gradients

## Imagine a long, one-dimensional axon

**(4) More tissue will become depolarized**



**(5) Etc.**

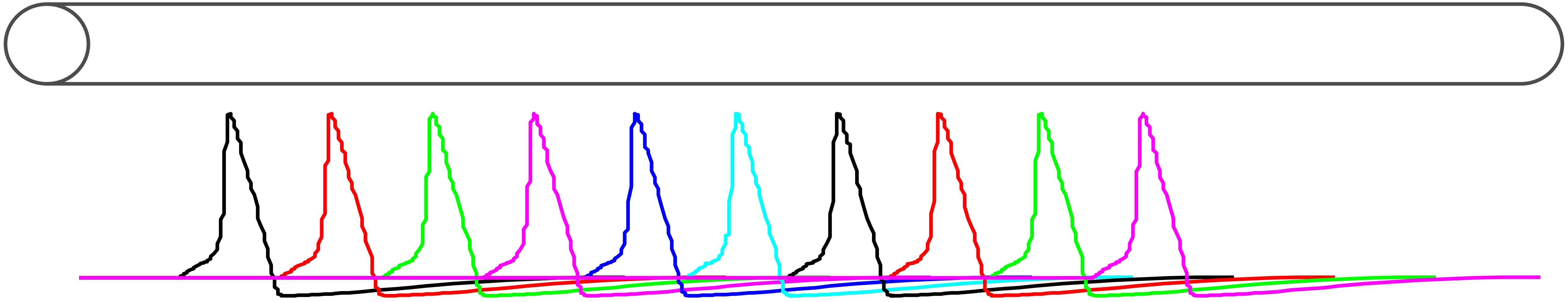


**This is the basic mechanism by which action potentials propagate**

**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

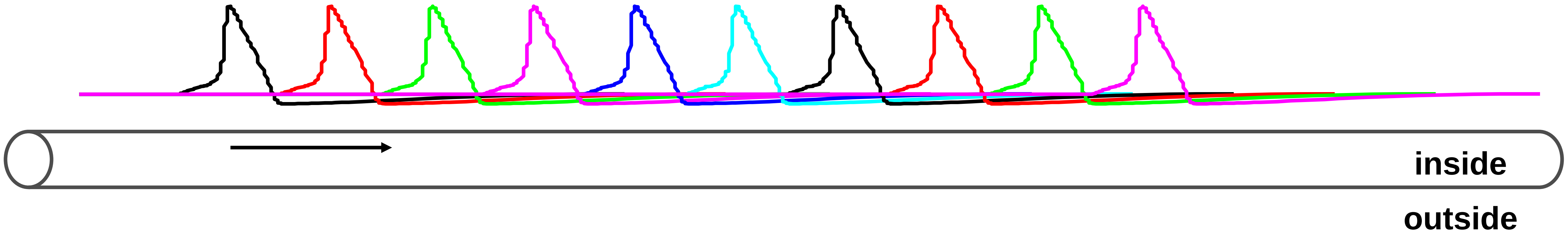
**Pertinent questions:**

1) Where does this equation come from?

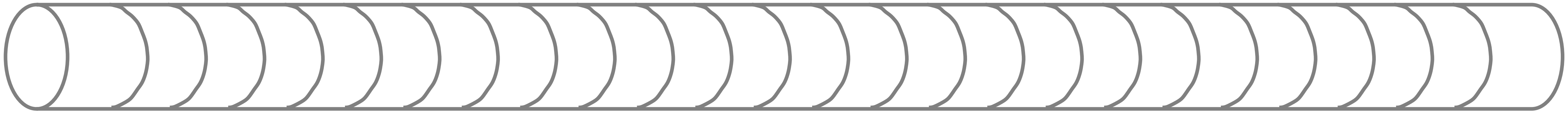
2) How do we solve this in practice? (subsequent lectures)

# One dimensional electrical propagation

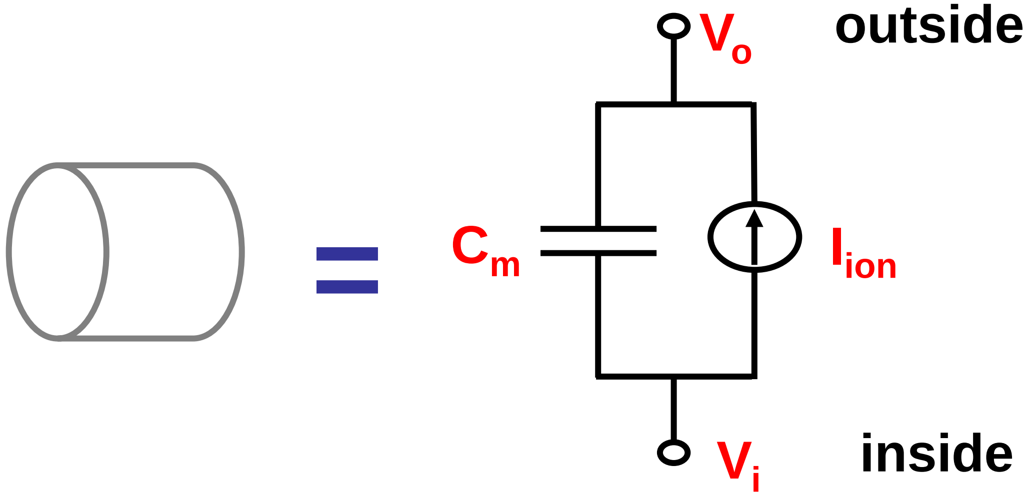
## AP propagating down a uniform cable




## Divide the cable into discrete segments

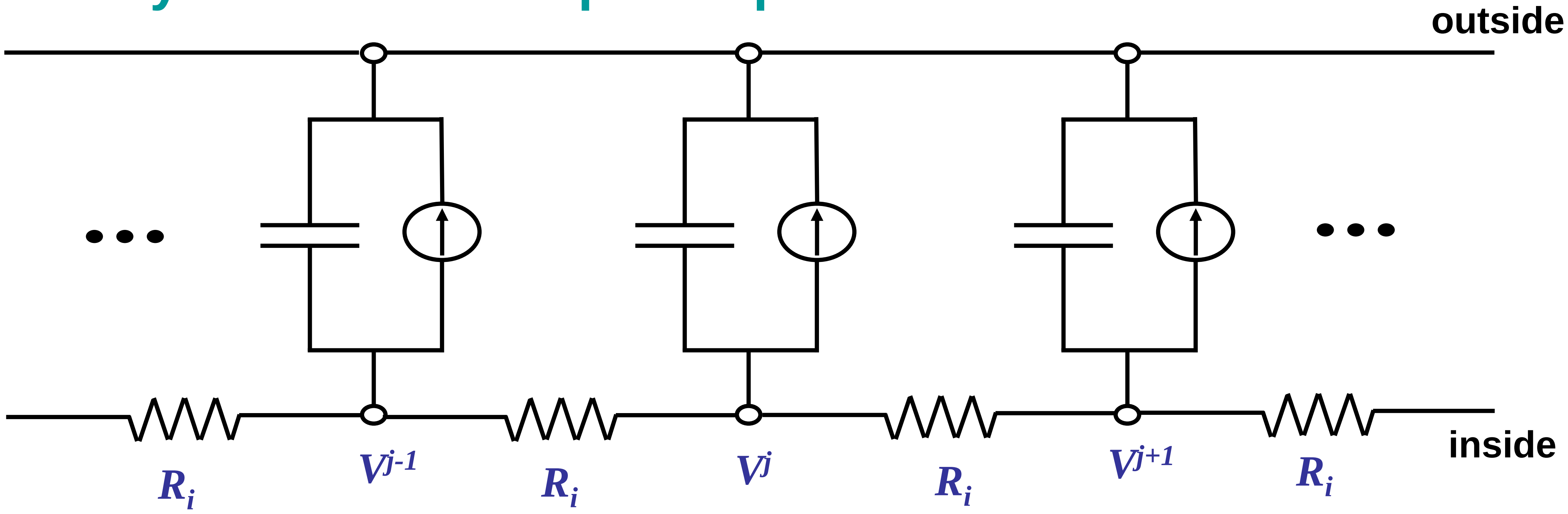


## Analyze the cable as coupled equivalent circuits



# One dimensional cable theory

## Analyze cable as coupled equivalent circuits



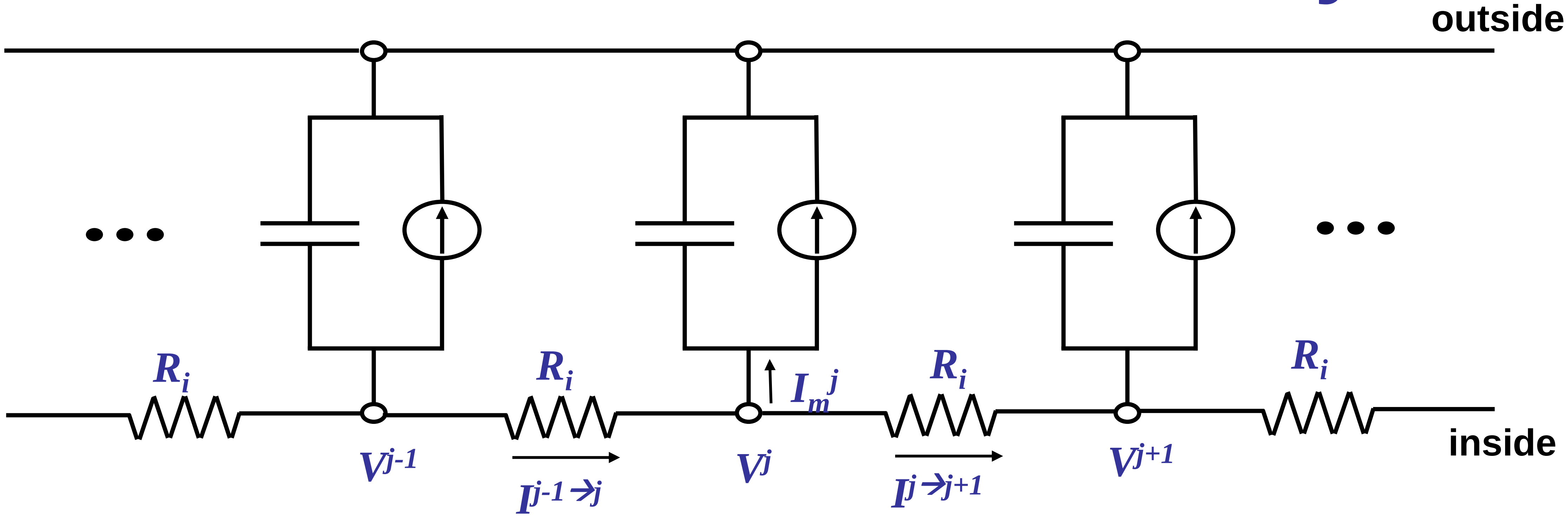

$R_i$=intracellular resistance

$V^j$=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 jth element of the cable?**

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

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

**Ohm's law**

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

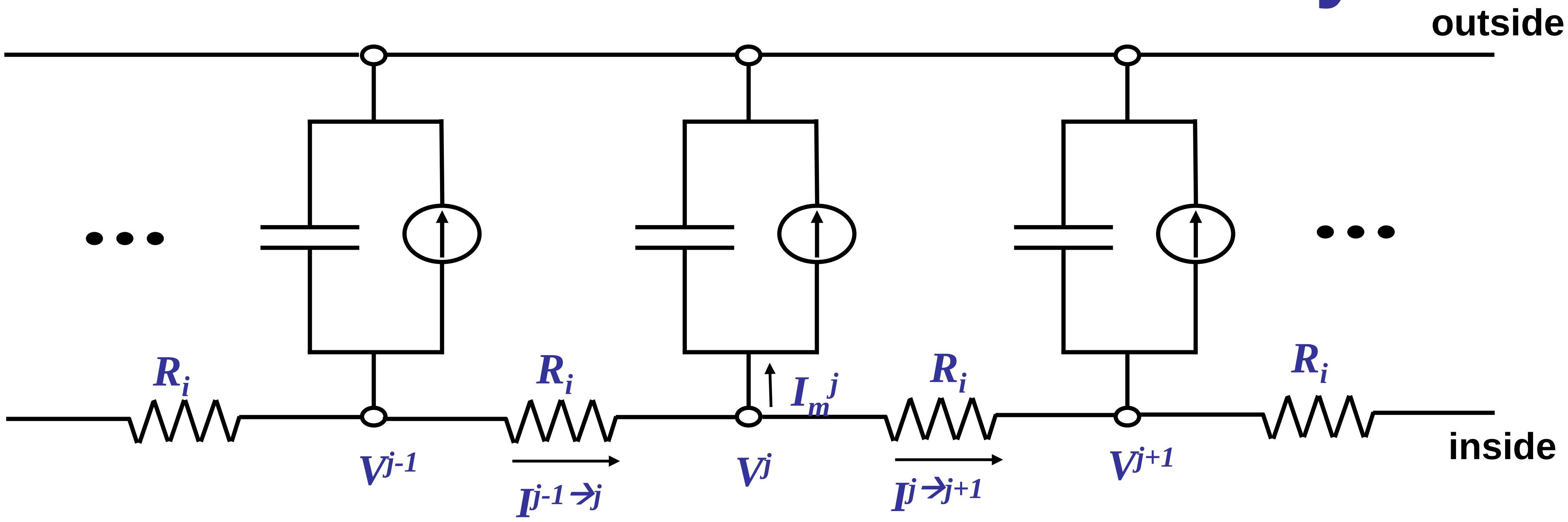
**Kirchoff's current law**

**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




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

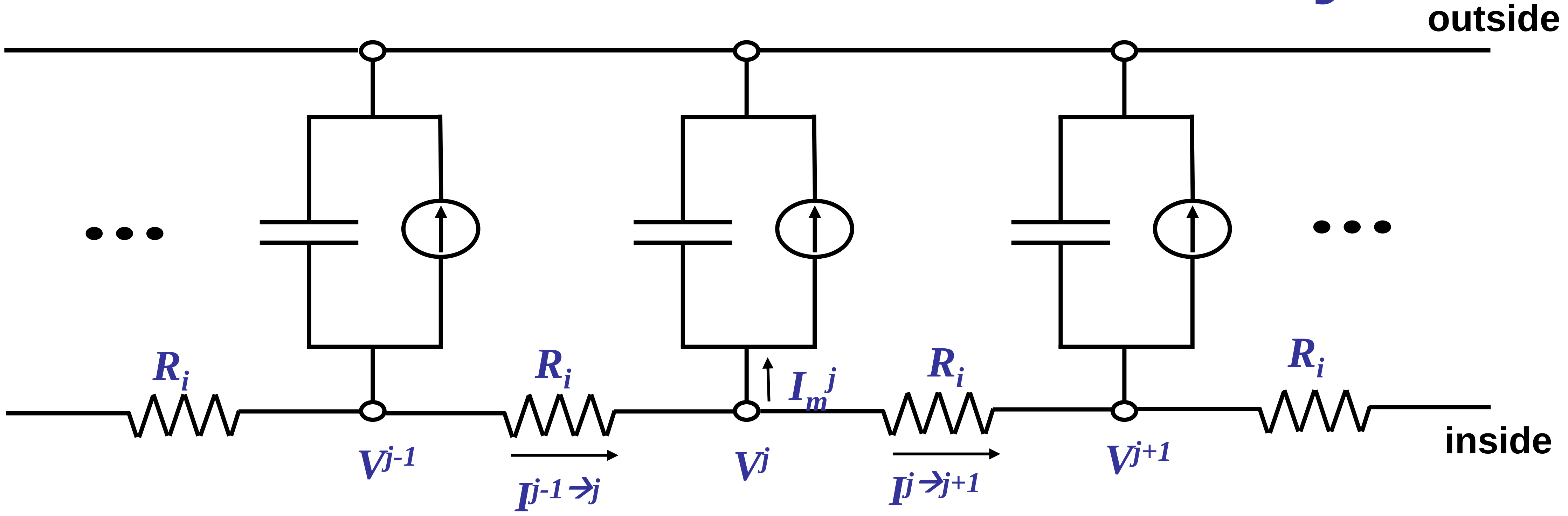
**Substitute into this:**

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

**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:

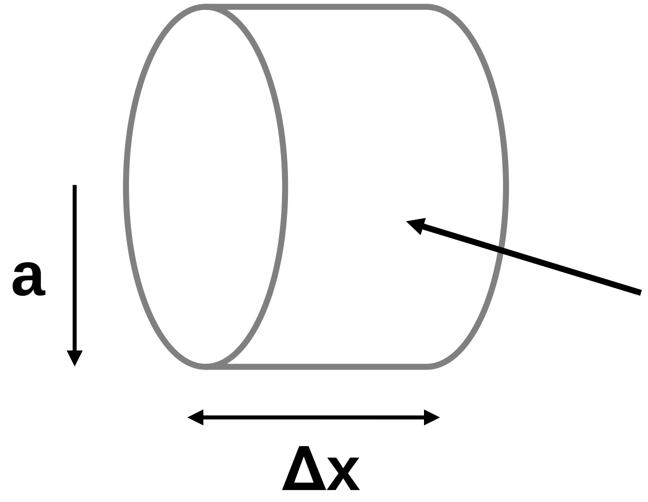
$$(V^{j-1} - V^j)/R_i = (V^j - V^{j+1})/R_i + A\left[C_m \frac{dV^j}{dt} + I_{ion}^j\right]$$

## 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?




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

$\rho_i$ = 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 $\Delta x$ → 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.**

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

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

# 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

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

**This is a matrix equation Ax = b**

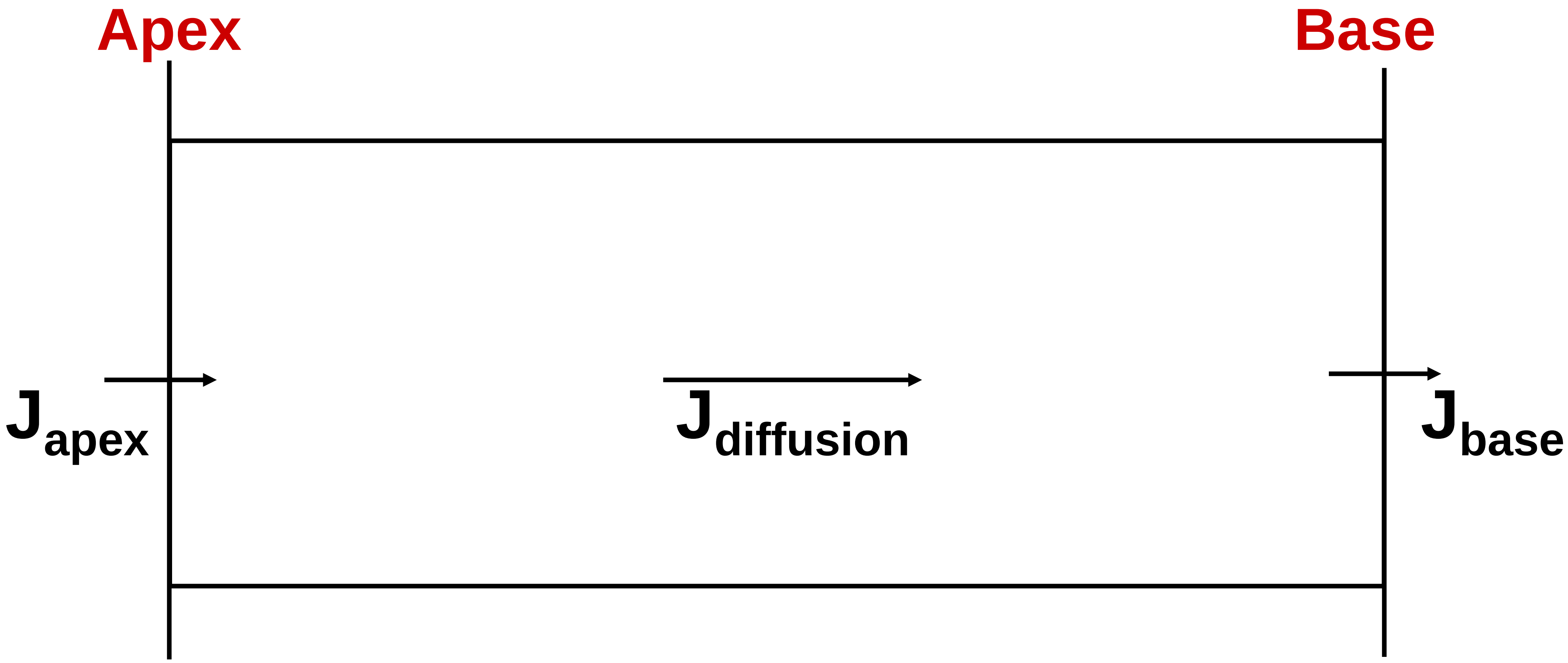
**$x = A^{-1}b$**

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

# Supplementary Slides

# Diffusion across an epithelial cell

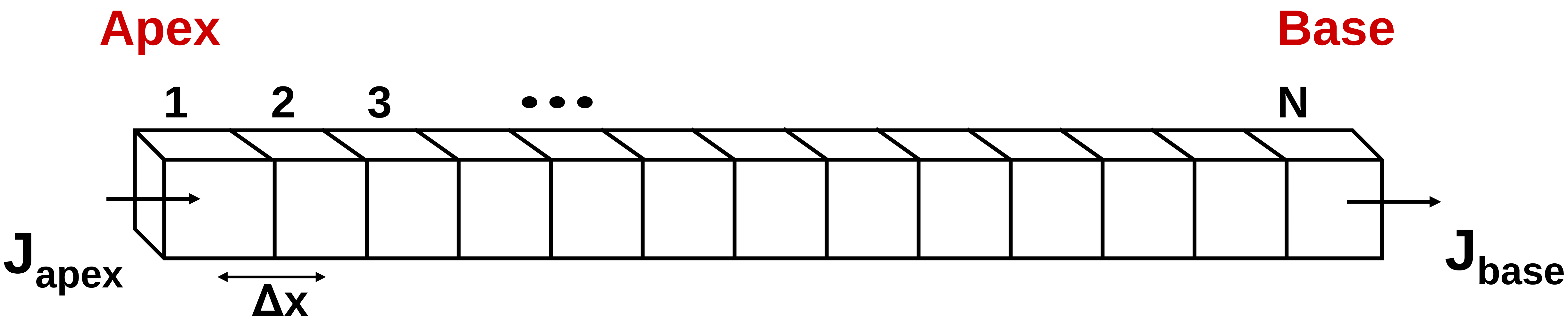
## Consider example of $HCO_3^-$ in proximal tubule




**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




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

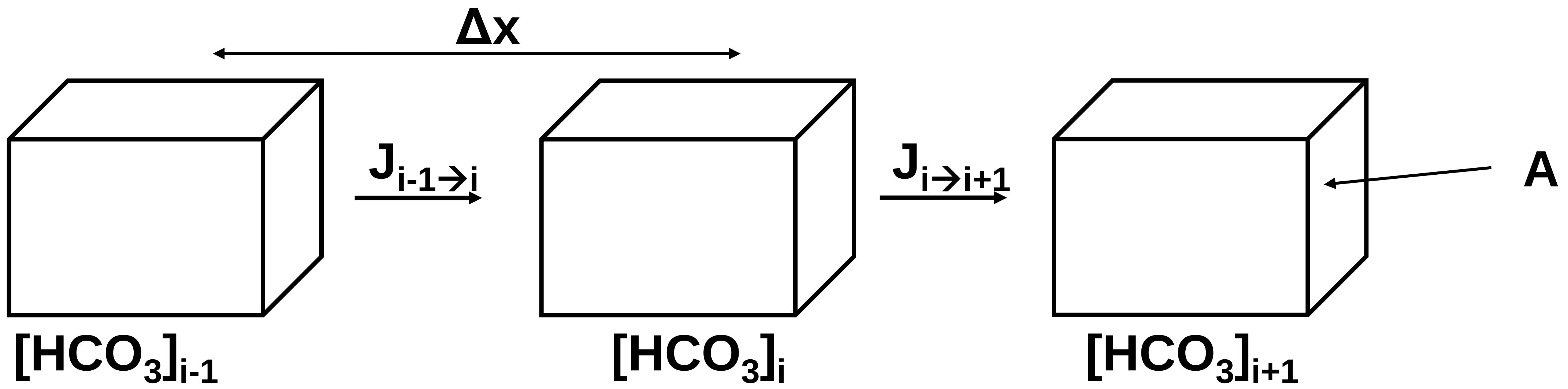
$D_{HCO3}$ = intracellular diffusion constant

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



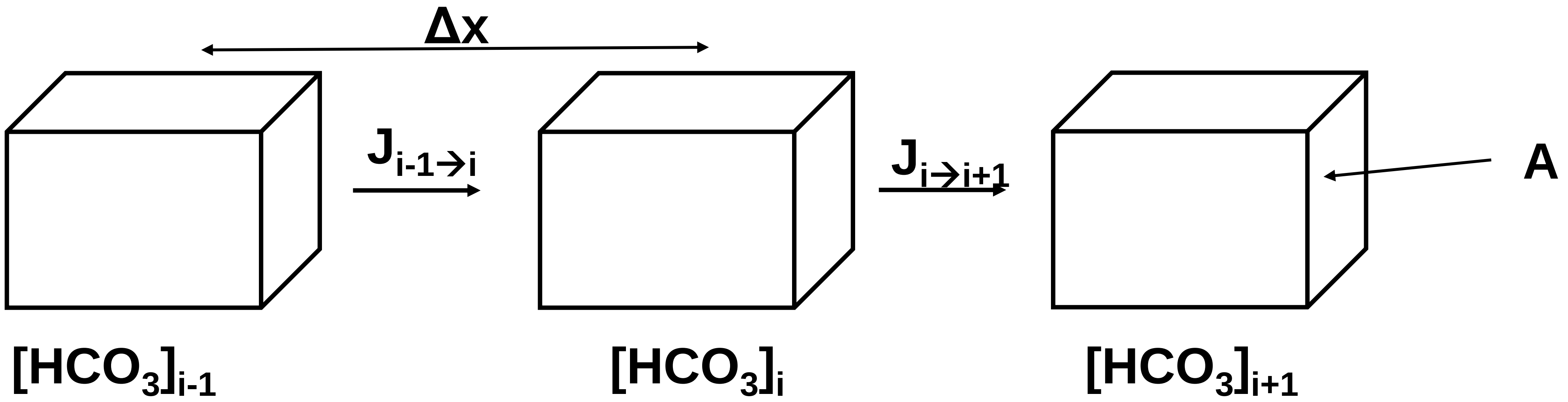

$$J_{i-1\to i} = D_{HCO_3} \frac{([HCO_3]_{i-1} - [HCO_3]_i)}{\Delta x}$$

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

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**

**$\Delta x$: 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/(cm² s) to μmol/(cm³ s)

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

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

**But** $V_i = A\Delta x$ **So** $$\frac{d[HCO_3]_i}{dt} = \frac{(J_{i-1\to i} - J_{i\to i+1})}{\Delta x}$$

**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?

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

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

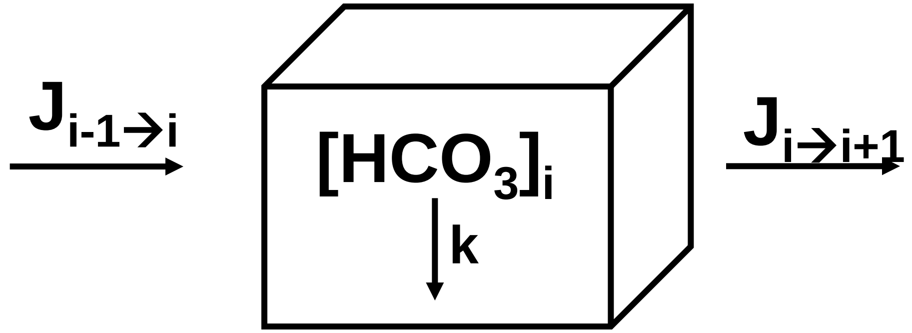
**So, in the limit of small Δx, our equation becomes**

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

**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?**