Introduction to Physiology II: Control of Cell Volume and Membrane Potential

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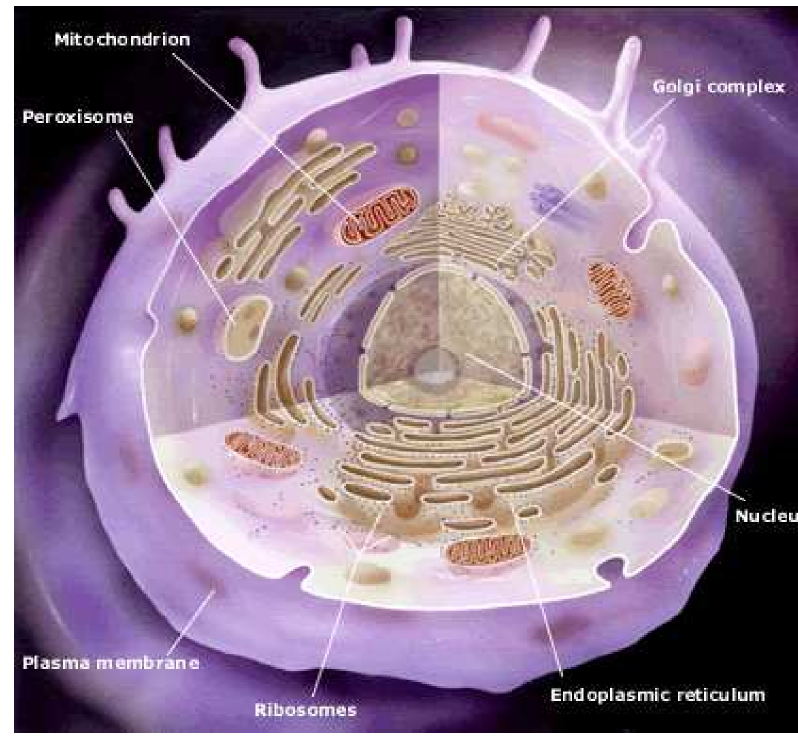
Basic Problem

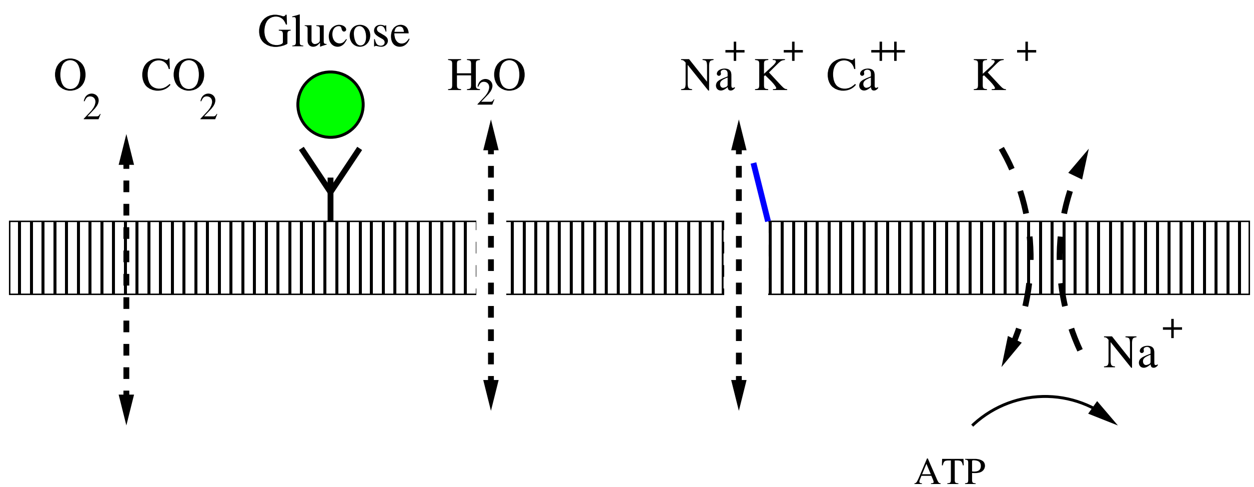
- The cell is full of stuff: Proteins, ions, fats, etc.
- The cell membrane is semipermeable, and these substances create osmotic pressures, sucking water into the cell.
- The cell membrane is like soap film, has no structural strength to resist bursting.



Basic Solution

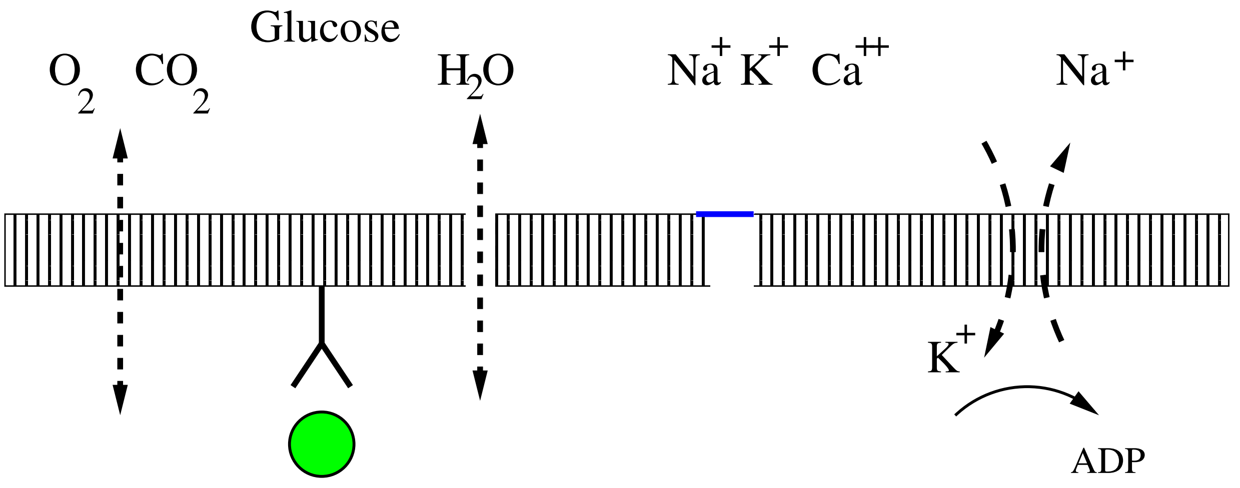
- Carefully regulate the intracellular ionic concentrations so that there are no net osmotic pressures.
- As a result, the major ions (Na^+, K^+, Cl^- and Ca^{++}) have different intracellular and extracellular concentrations.
- Consequently, there is an electrical potential difference across the cell membrane, the membrane potential.

Membrane Transporters



- transmembrane diffusion - carbon dioxide, oxygen

Membrane Transporters



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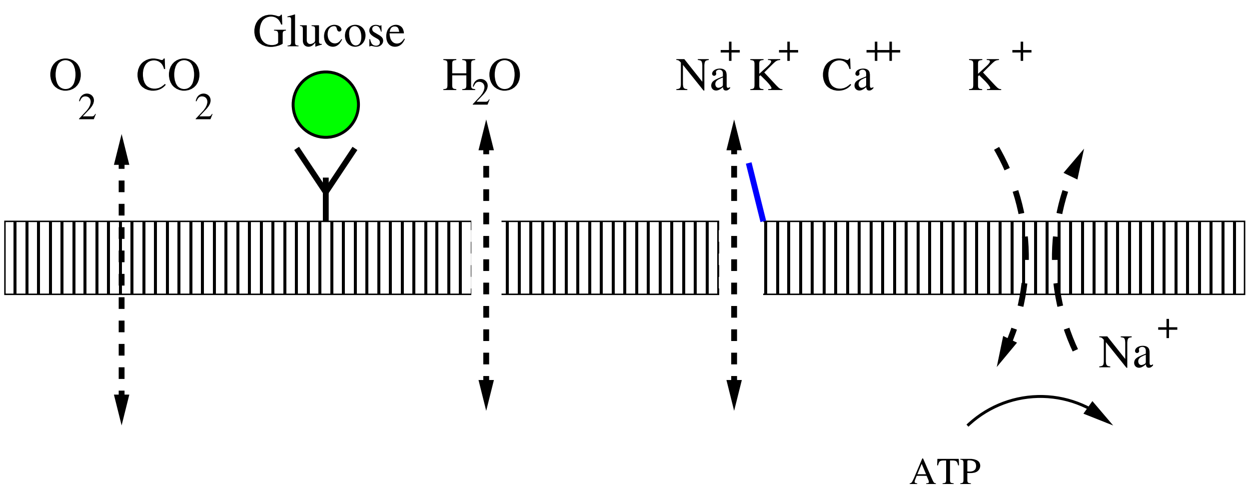
Membrane Transporters



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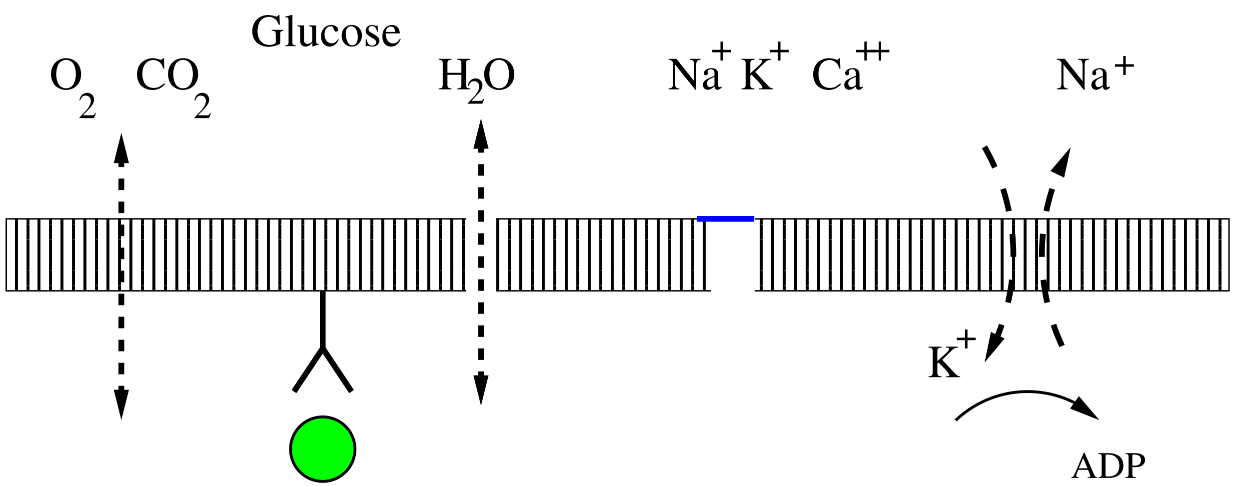
Membrane Transporters



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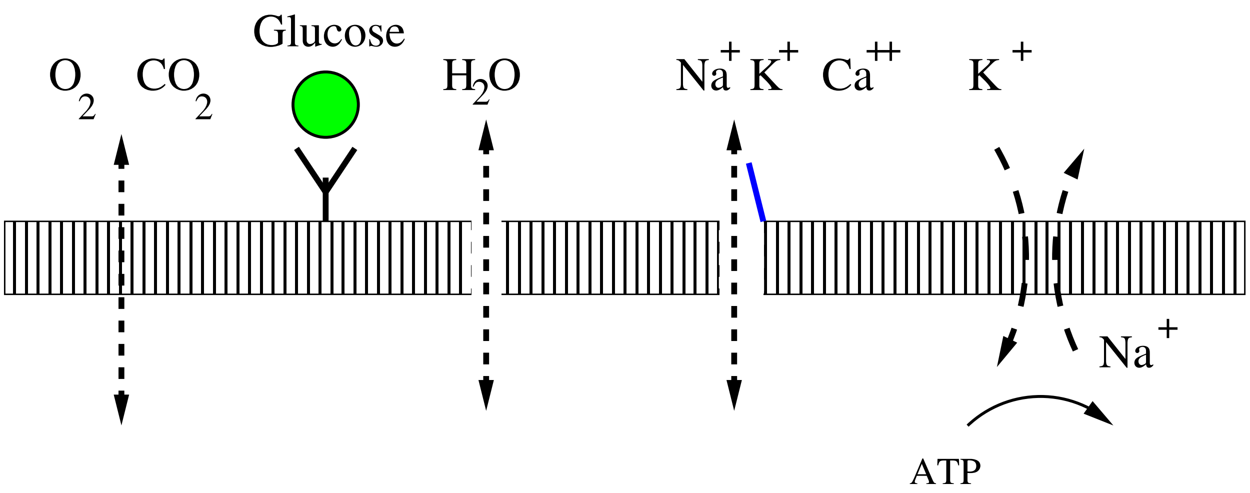
Membrane Transporters



- transmembrane diffusion - carbon dioxide, oxygen
- transporters - glucose, sodium-calcium exchanger
- pores - water
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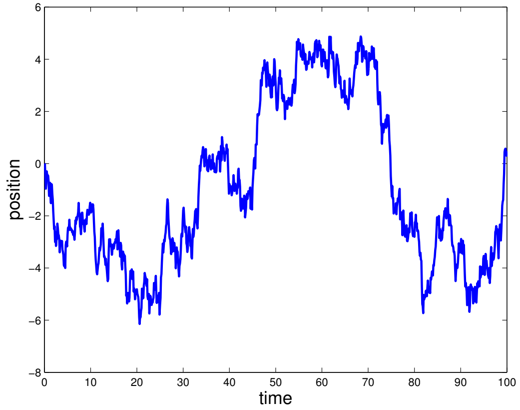
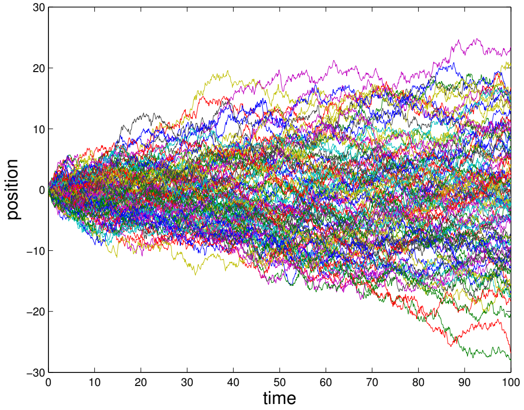
- ATPase exchangers - sodium-potassium ATPase, SERCA

How Things Move

Most molecules move by a random walk:





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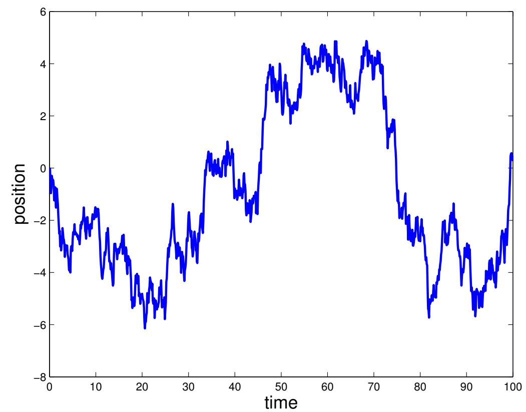

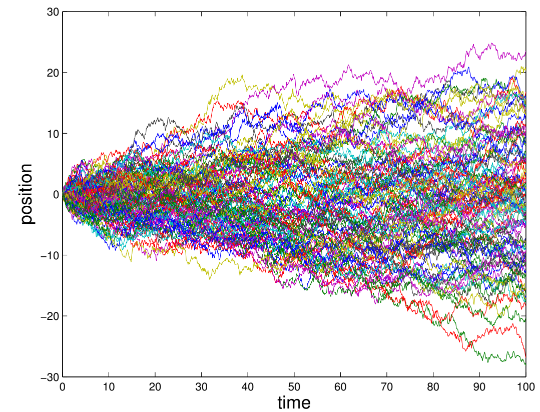

Fick's *law*: When there are a large number of these molecules, their motion can be described by

$$J = -D \frac{\partial C}{\partial x}$$

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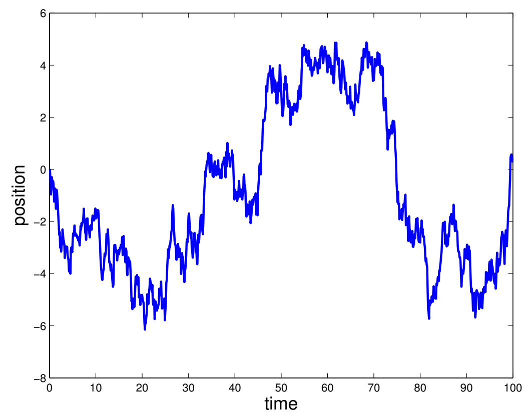

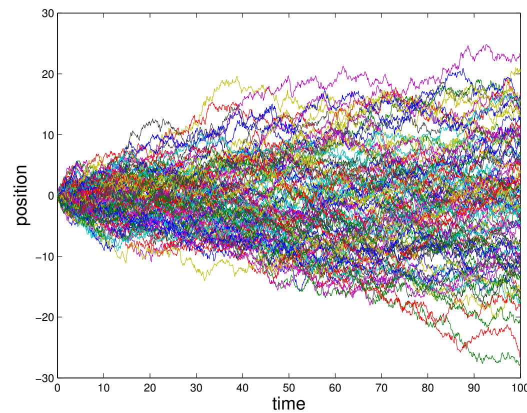

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molecular flux,

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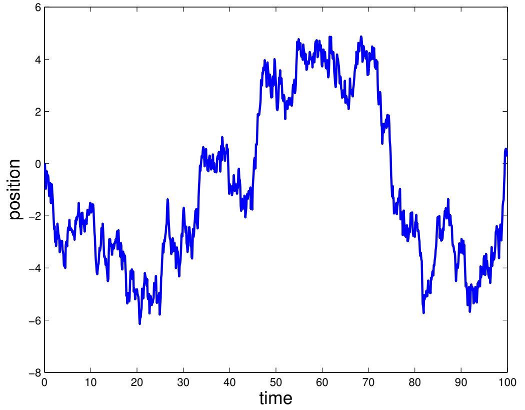

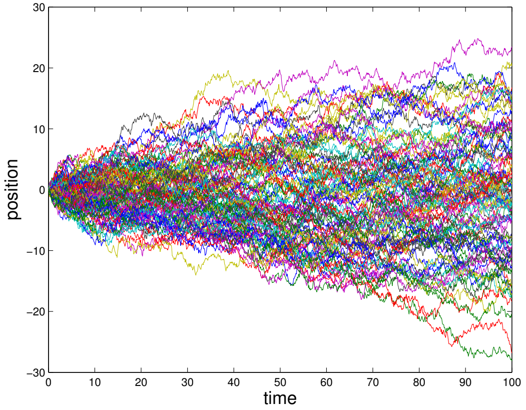

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molecular flux, diffusion coefficient,

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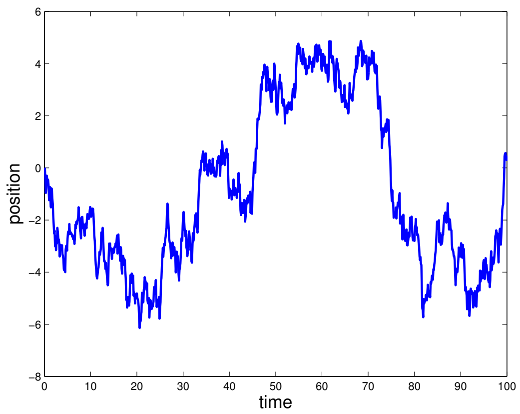
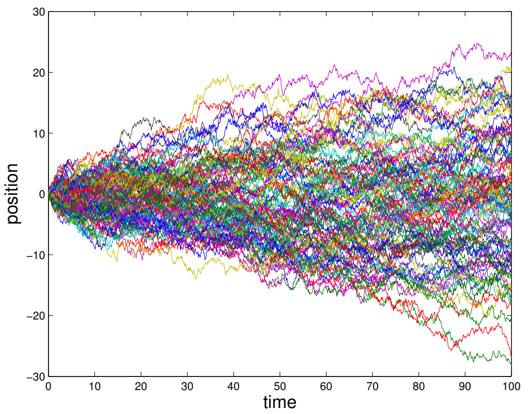




Fick's *law*: When there are a large number of these molecules, their motion can be described by

$$J = - D \boxed{\frac{\partial C}{\partial x}}$$

molecular flux, diffusion coefficient, concentration gradient.

Conservation Law

Conservation:

$$\frac{\partial C}{\partial t} + \frac{\partial J}{\partial x} = 0$$

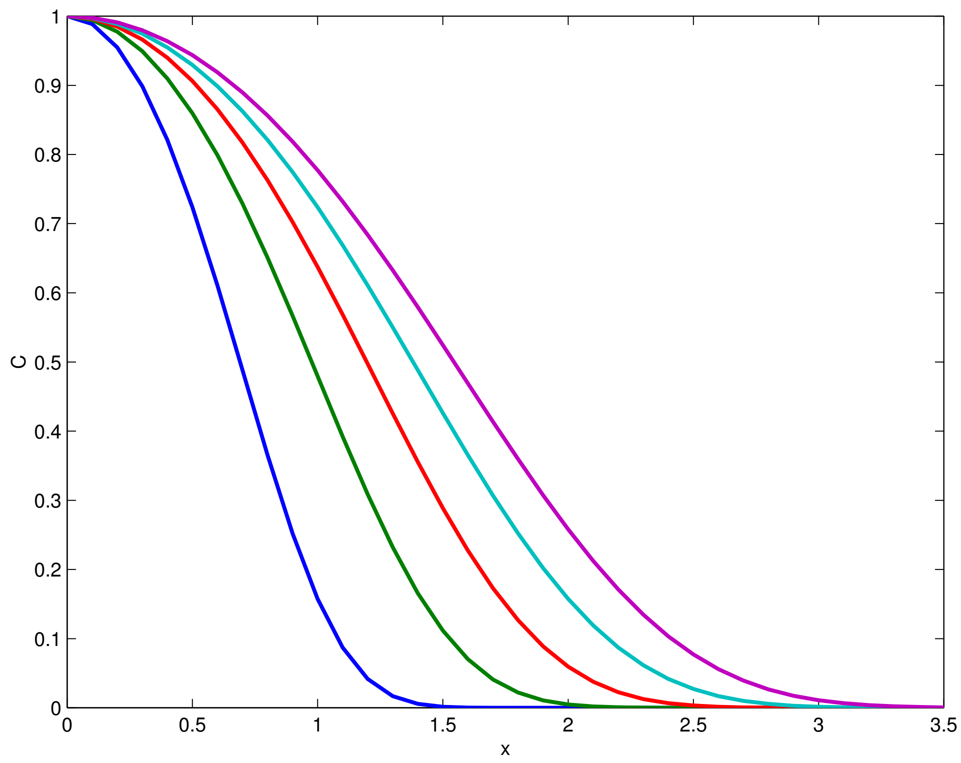
leading to the Diffusion Equation

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}(D\frac{\partial C}{\partial x}).$$

Basic Consequences - I

Diffusion in a tube fed by a reservoir

$$C(x,t) = f(\frac{x^2}{Dt})$$



Basic Consequences - II

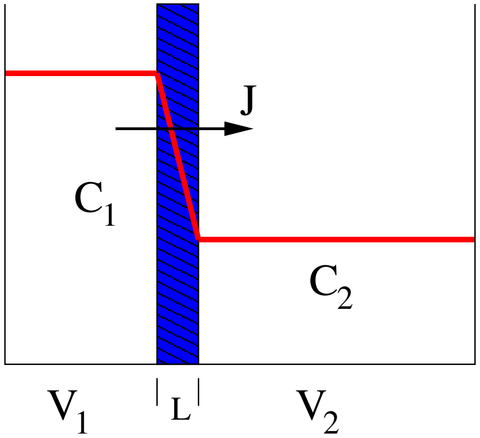
Diffusion time: $t = \frac{x^2}{D}$ for hydrogen ($D = 10^{-5}$cm^2/s).

x	t	Example
10 nm	100 ns	cell membrane
1 μm	1 ms	mitochondrion
10 μm	100 ms	mammalian cell
100 μm	10 s	diameter of muscle fiber
250 μm	60 s	radius of squid giant axon
1 mm	16.7 min	half-thickness of frog sartorius muscle
2 mm	1.1h	half-thickness of lens in the eye
5 mm	6.9 h	radius of mature ovarian follicle
2 cm	2.6 d	thickness of ventricular myocardium
1 m	31.7 yrs	length of sciatic nerve

Basic Consequences - Ohm's Law

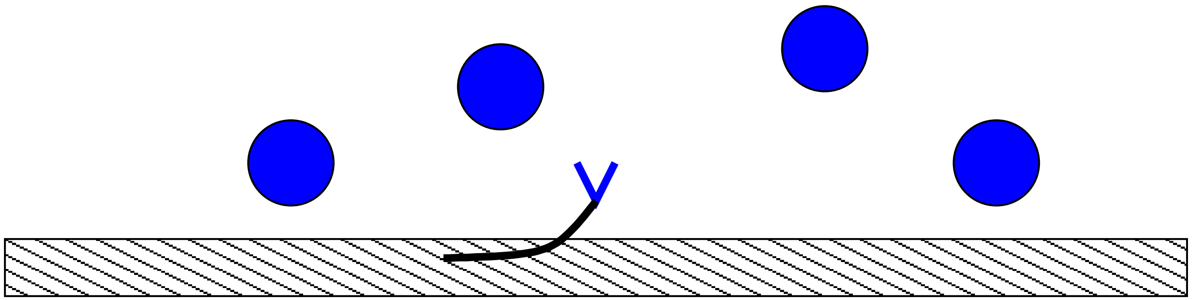
Diffusion across a membrane

$$J = \frac{AD}{L}(C_1 - C_2)$$



Flux changes as things like C_1, C_2 and L change.

Carrier Mediated Diffusion



$$C_e \rightleftarrows C_i$$

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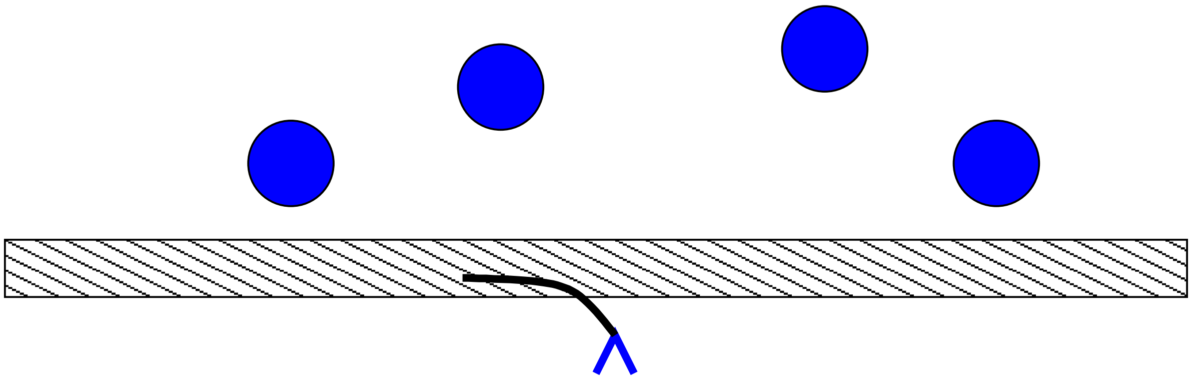

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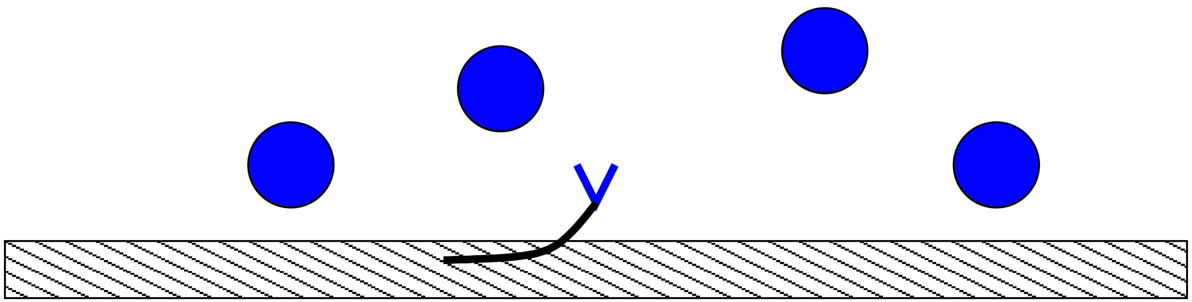

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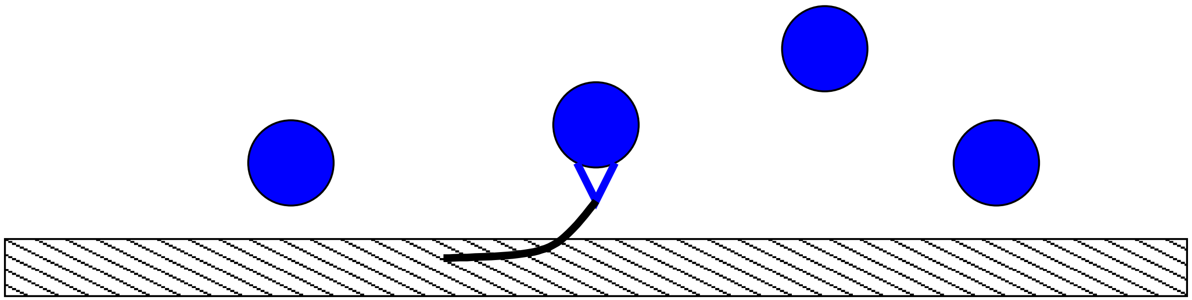
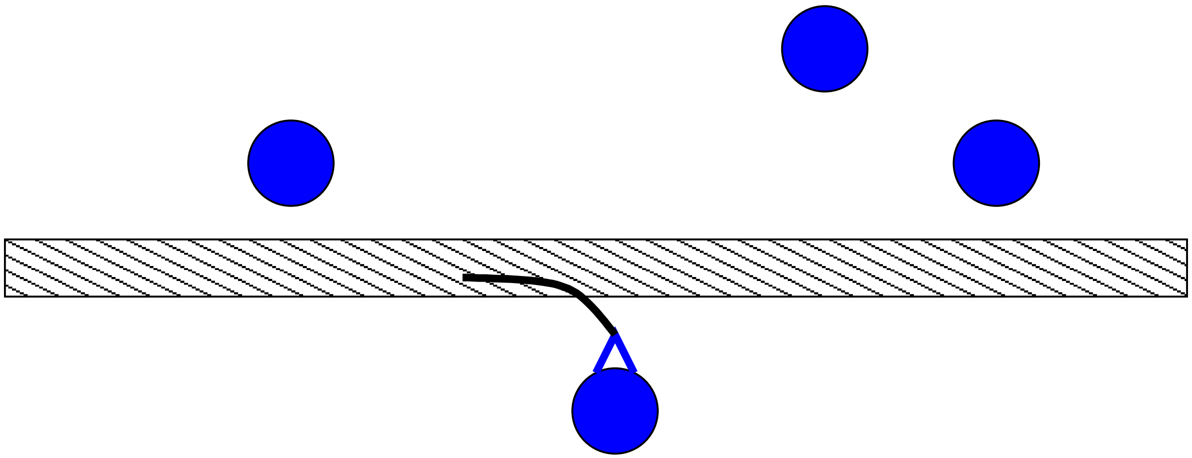


$$C_e \underset{}{\overset{\longrightarrow}{\longleftarrow}} C_i$$

$$S_e + C_e \overset{\rightarrow}{\leftarrow} P_e$$

Carrier Mediated Diffusion



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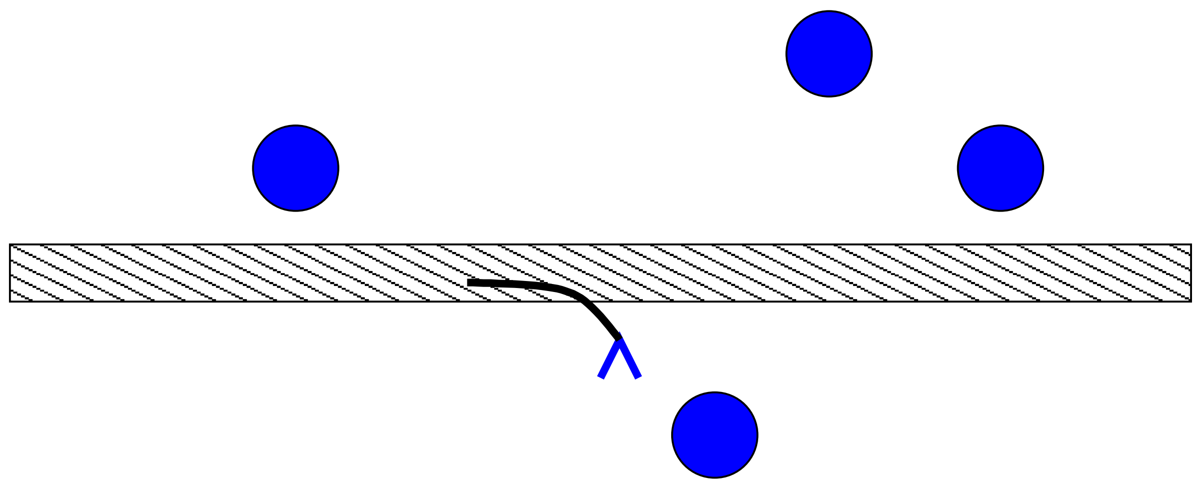

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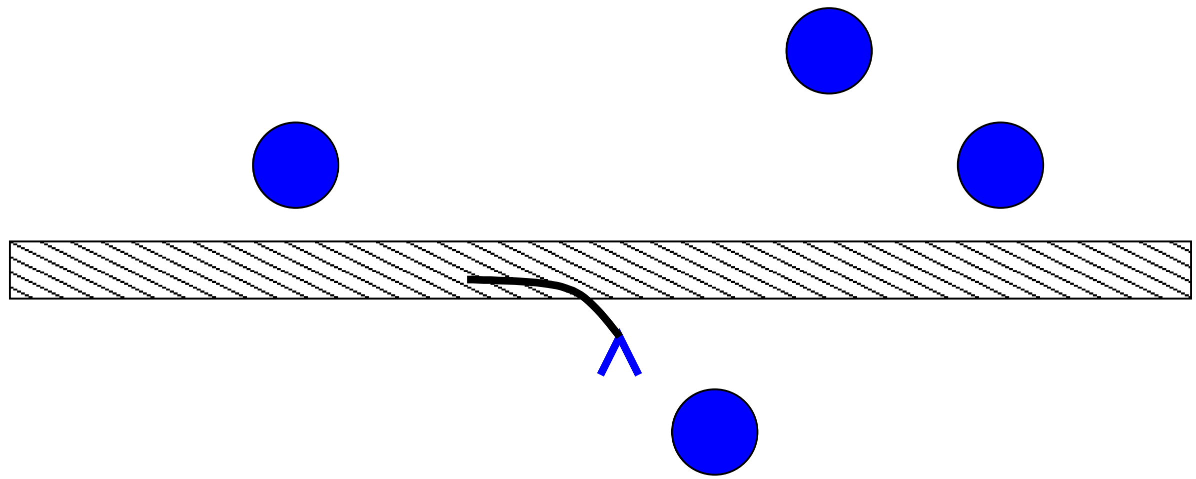


$$C_e \rightleftarrows C_i$$

$$S_e + C_e \rightleftarrows P_e \rightleftarrows P_i \rightleftarrows S_i + C_i$$

For this system,

$$J = J_{max} \frac{S_e - S_i}{(S_e + K_e)(S_i + K_i)}.$$

.... a saturating Fick's law

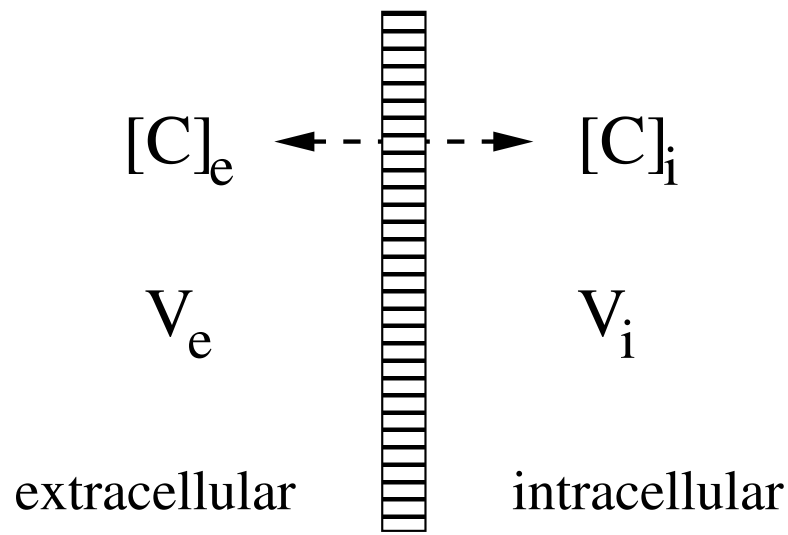
Ion Movement

Ions move according to the Nernst-Planck equation

$$J = -D(\nabla C + \frac{Fz}{RT}\nabla\phi)$$

Consequently, at equilibrium

$$V_N = V_i - V_e = \frac{RT}{zF}\ln\left(\frac{[C]_e}{[C]_i}\right)$$



This is called the Nernst Potential or Reversal Potential.

Ion Current Models

There are many different possible Models of I_{ionic}.

- Barrier models, binding models, saturating models, PNP equations, etc.
- Constant field assumption:

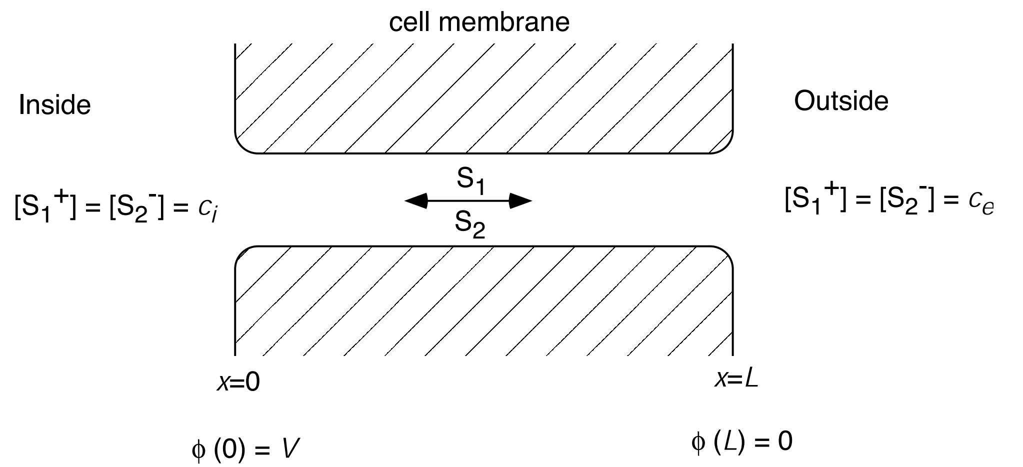
$$I_{ion} = P\frac{F^2}{RT}V\left(\frac{[C]_i - [C]_e\exp(\frac{-zVF}{RT})}{1-\exp(\frac{-zVF}{RT})}\right), \qquad \text{GHK Model}$$

- Long Channel limit (used by HH)

$$I_{ion} = g(V - V_N) \qquad \text{Linear Model}$$

All of these have the same reversal potential, as they must.

Electrodiffusion Models



$$\begin{aligned} \frac{d^2\phi}{dx^2} &= -\lambda^2(c_1 - c_2), && \text{Poisson Equation} \\ J_1 &= -D_1\left(\frac{dc_1}{dx} + \frac{F}{RT}c_1\frac{d\phi}{dx}\right), && \text{Nernst Planck Equations} \\ J_2 &= -D_2\left(\frac{dc_2}{dx} - \frac{F}{RT}c_2\frac{d\phi}{dx}\right), && \end{aligned}$$

Short Channel Limit

If the channel is short, then $L \approx 0 \Rightarrow \lambda \approx 0$. Then $\frac{d^2\phi}{dx^2} = 0$ implies the field is constant:

$$\begin{aligned}\frac{d\phi}{dx} = v \quad \Rightarrow \quad & \frac{dc_1}{dx} - vc_1 = -J_1 \\ \Rightarrow \quad & J_1 = v\frac{c_i - c_e e^{-v}}{1 - e^{-v}} \\ \Rightarrow \quad & I_{ion} = P\frac{F^2}{RT}V\left(\frac{[C]_i - [C]_e \exp(\frac{-zVF}{RT})}{1 - \exp(\frac{-zVF}{RT})}\right)\end{aligned}$$

This is the Goldman-Hodgkin-Katz equation.

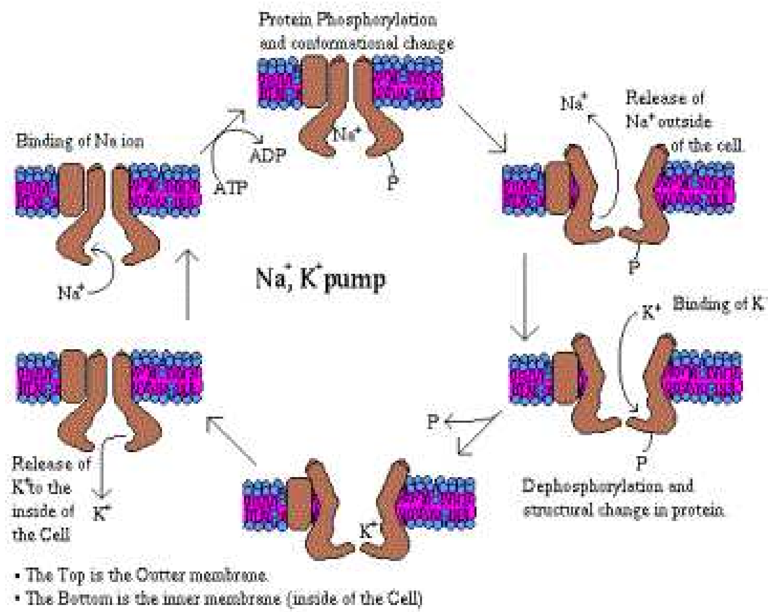
Long Channel Limit

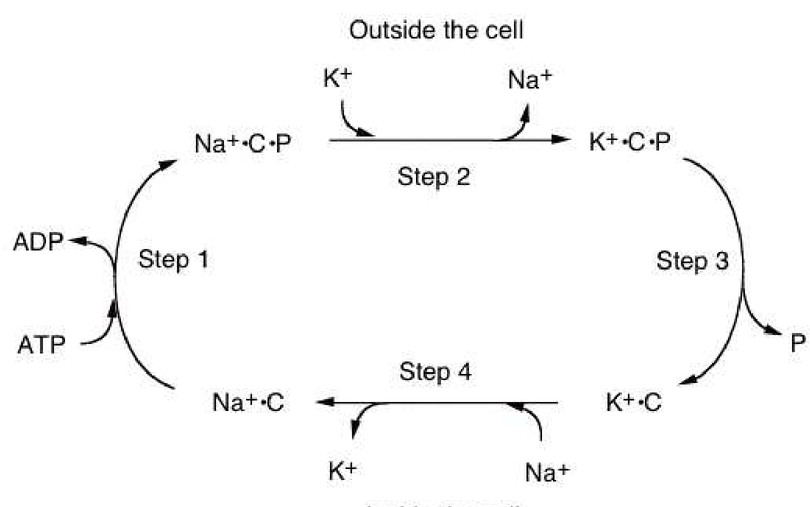
If the channel is long, then $\frac{1}{L} \approx 0 \Rightarrow \frac{1}{\lambda} \approx 0$. Then $c_1 \approx c_2$ throughout the channel:

$$
\begin{aligned}
c_1 = c_2 \quad &\Rightarrow \quad 2\frac{dc_1}{dx} = -J_1 - J_2 \\
&\Rightarrow \quad c_1 = c_2 + (c_e - c_i)x \\
&\Rightarrow \quad \phi = -\frac{v}{v_1} \ln\left(\frac{c_i}{c_e} + (1 - \frac{c_i}{c_e})x\right) \qquad v_1 = \text{Nernst potentia} \\
&\Rightarrow \quad J_1 = \frac{c_e - c_i}{v_1}(v - v_1)
\end{aligned}
$$

This is the linear I-V curve used by Hodgkin and Huxley.

Sodium-Potassium ATPase

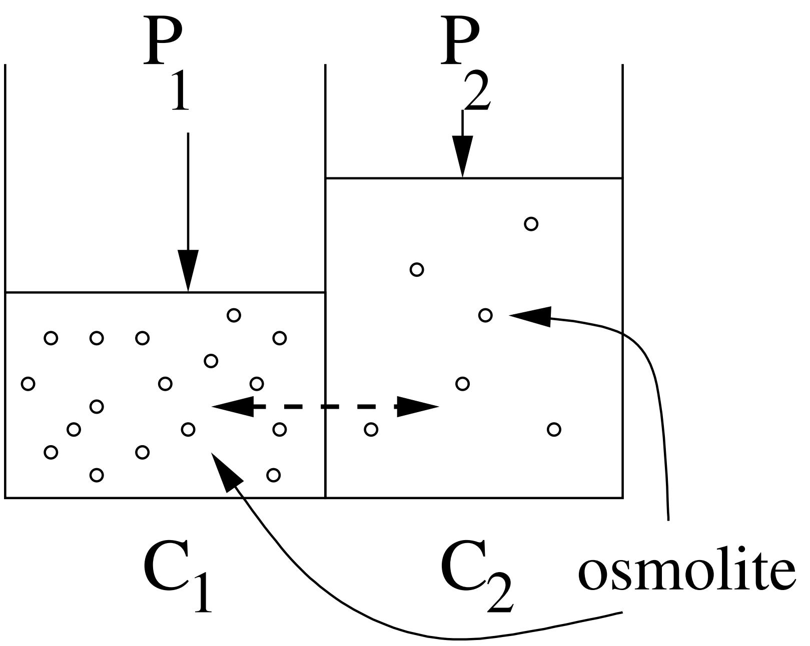




Osmotic Pressure and Flux

$$rQ = P_1 - P_2 - \pi_1 + \pi_2$$

$$\pi_i = kTC_i$$



Volume Control; Pump-Leak Model

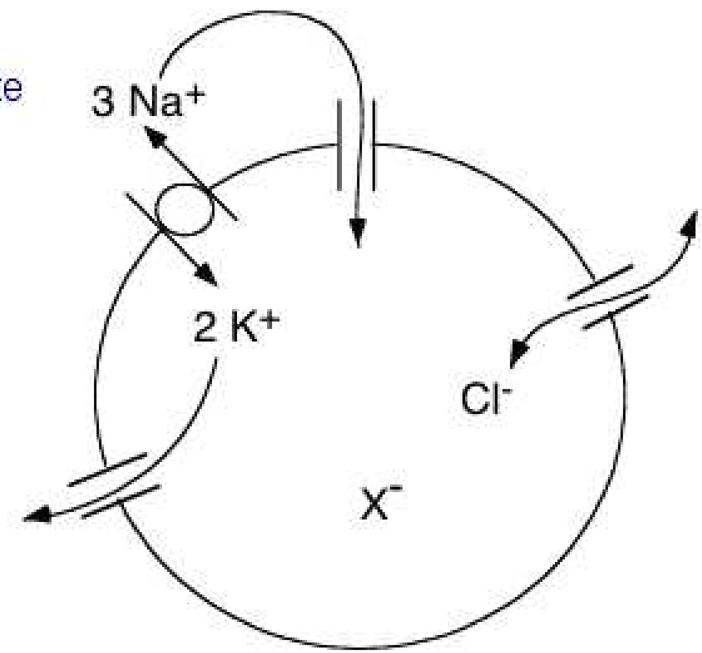
Na^{+} is pumped out, K^{+} is pumped in, Cl^{-} moves passively, negatively charged macromolecules are trapped in the cell.

cell volume $[Na]_i$ pump rate

$$-\frac{d}{dt}(qwN_i) = g_{Na}\left[V - \frac{RT}{F}\ln\left(\frac{N_e}{N_i}\right)\right] + 3pq$$

$$-\frac{d}{dt}(qwK_i) = g_{K}\left[V - \frac{RT}{F}\ln\left(\frac{K_e}{K_i}\right)\right] - 2pq$$

$$-\frac{d}{dt}(qwC_i) = g_{Cl}\left[V + \frac{RT}{F}\ln\left(\frac{C_e}{C_i}\right)\right]$$



Charge Balance and Osmotic Balance

- Inside and outside are both electrically neutral, macromolecules have negative charge z_x.

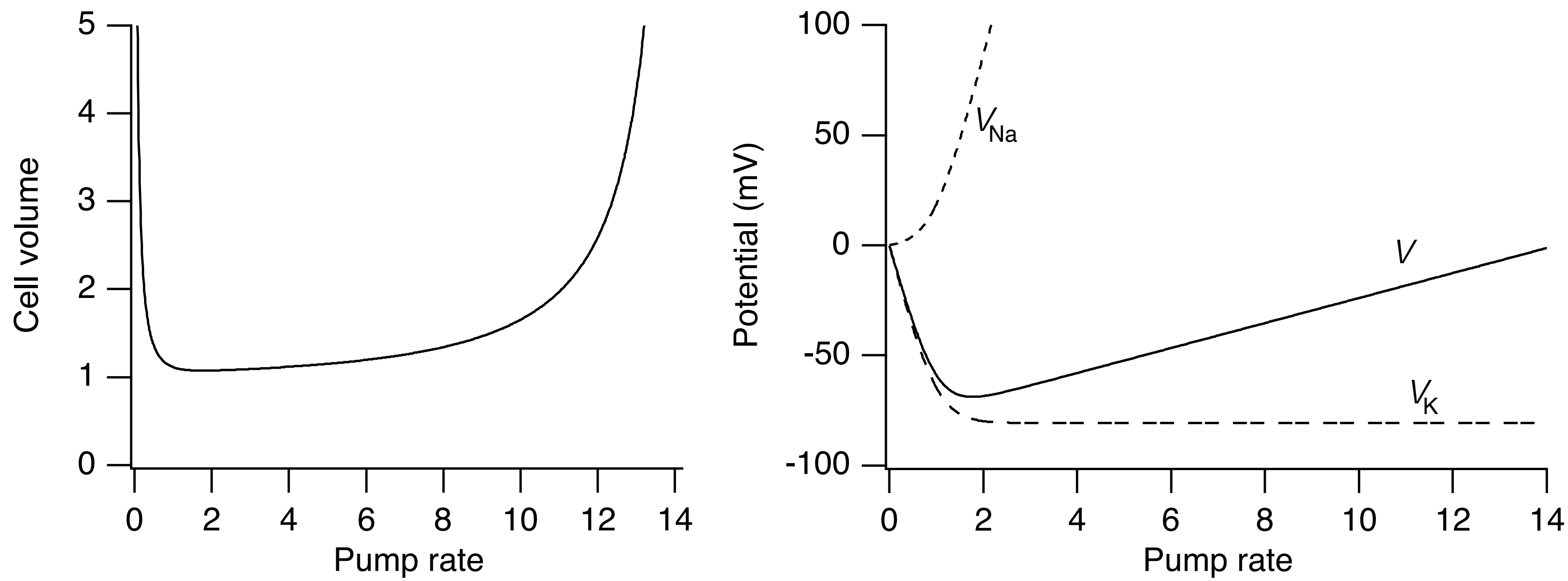
$$qw(N_i+K_i-C_i)+z_xqX = qw(N_e+K_e-C_e) = 0, \qquad \text{(charge bala}$$

- Total amount of osmolyte is the same on each side.

$$N_i + K_i + C_i + \frac{X}{w} = N_e + K_e + C_e \qquad \text{(osmotic balance)}$$

The Solution

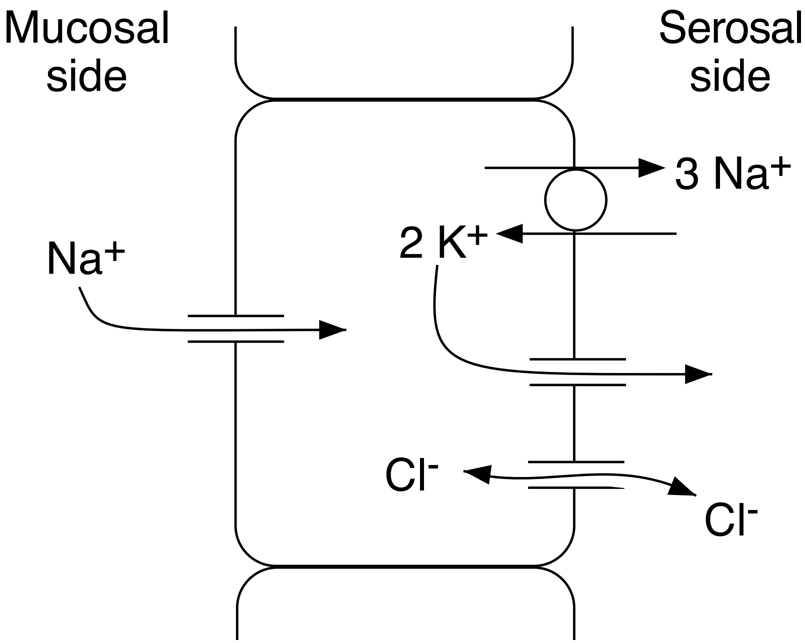
The resulting system of algebraic equations is readily solved



- If the pump stops, the cell bursts, as expected.
- The minimal volume gives approximately correct membrane potential (although there are MANY deficiencies with this model.)

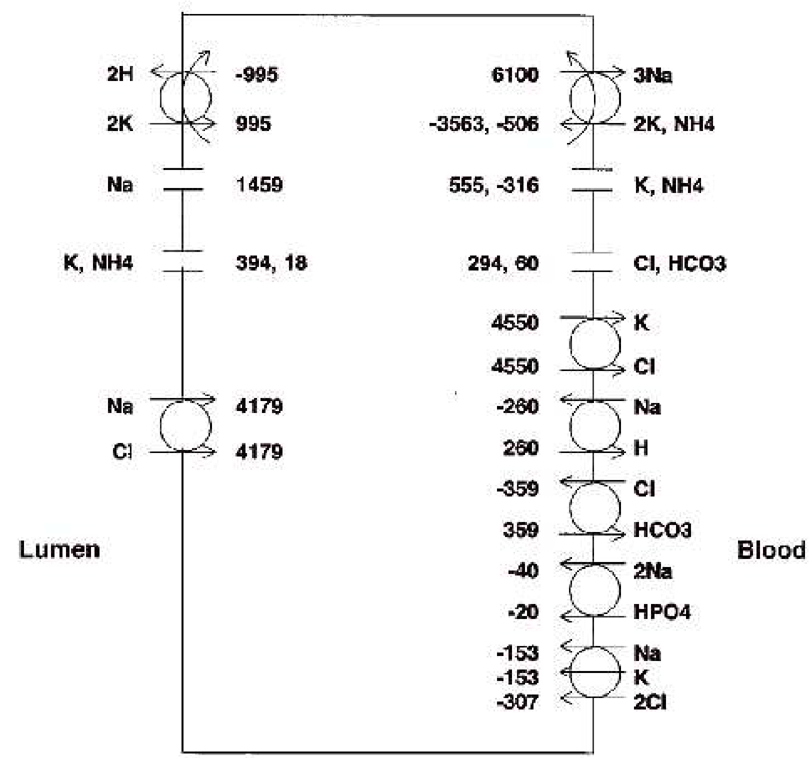
Volume Control and Ion Transport

- How can epithelial cells transport ions and water while maintaining constant cell volume under widely varying conditions?
- Spatial separation of leaks and pumps?
- Other intricate control mechanisms are needed.
- Lots of interesting problems (A. Weinstein, BMB 54, 537, 1992.)



Inner Meduullary Collecting Duct

- Real cells are far more complicated
- Notice the large Na^+ flux from the lumen.
- cf. A. Weinstein, Am. J. Physiol. 274, F841-F855, 1998.



Interesting Problems (suitable for projects)

- How do organism (e.g., T. Californicus living in tidal basins) adjust to dramatic environmental changes?
- How do plants in arid, salty regions, prevent dehydration? (They make proline)
- How do fish (e.g., salmon) adjust to both freshwater and salt water?
- What happens to a cell and its environment when there is ischemia (loss of ATP)?
- How do cell in high salt environments (epithelial cell in kidney) maintain constant volume?