Imagine the Possibilities

Mathematical Biology
University of Utah

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

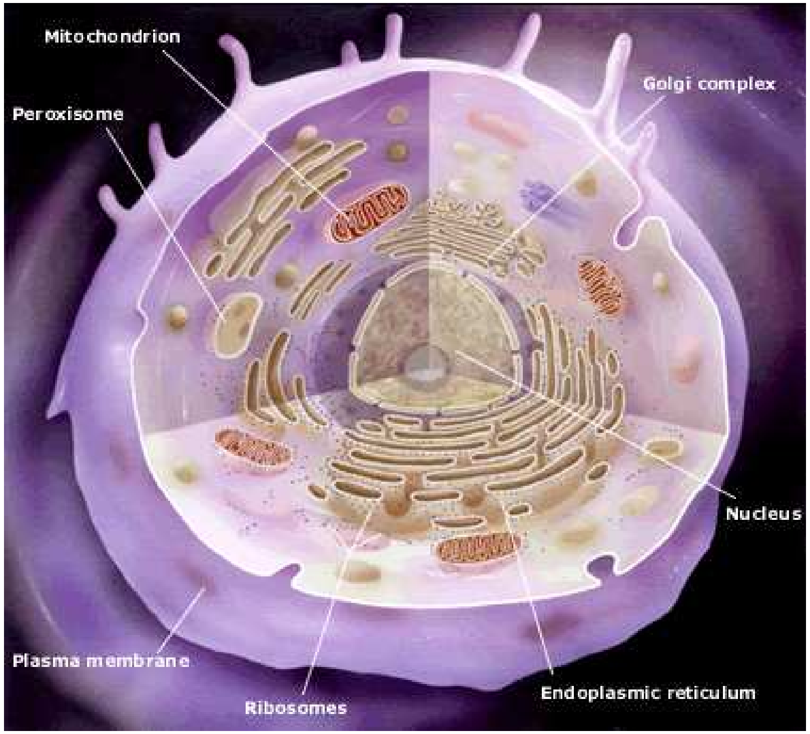
J. P. Keener

Mathematics Department

University of Utah

Basic Problem

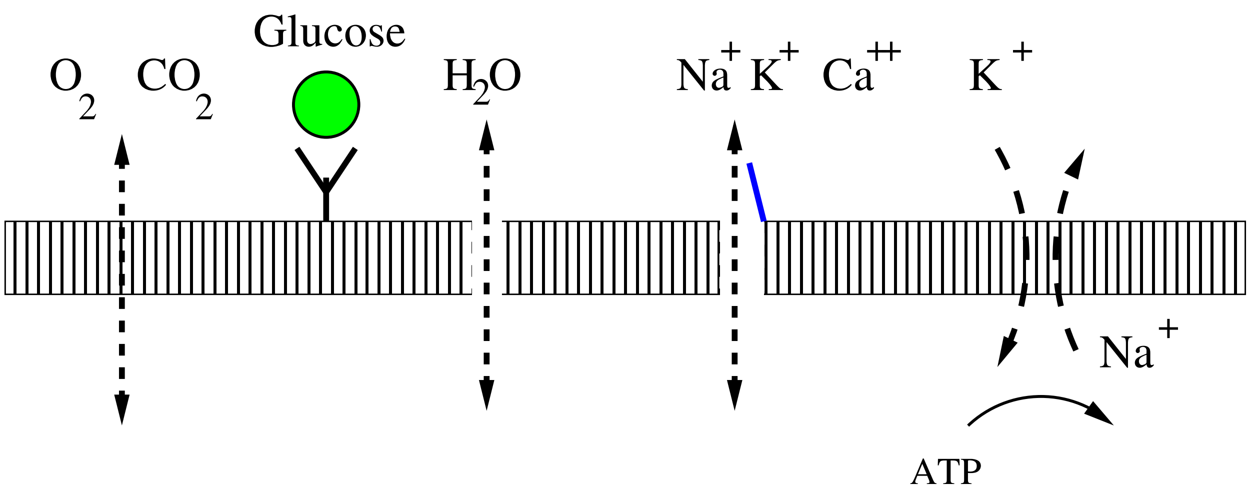
- The cell is full of stuff: Proteins, ions, fats, etc.
- The cell membrane is semipermeable, and these substances create osmotic pressures, sucking water into the cell.
- The cell membrane is like soap film, has no structural strength to resist bursting.



Basic Solution

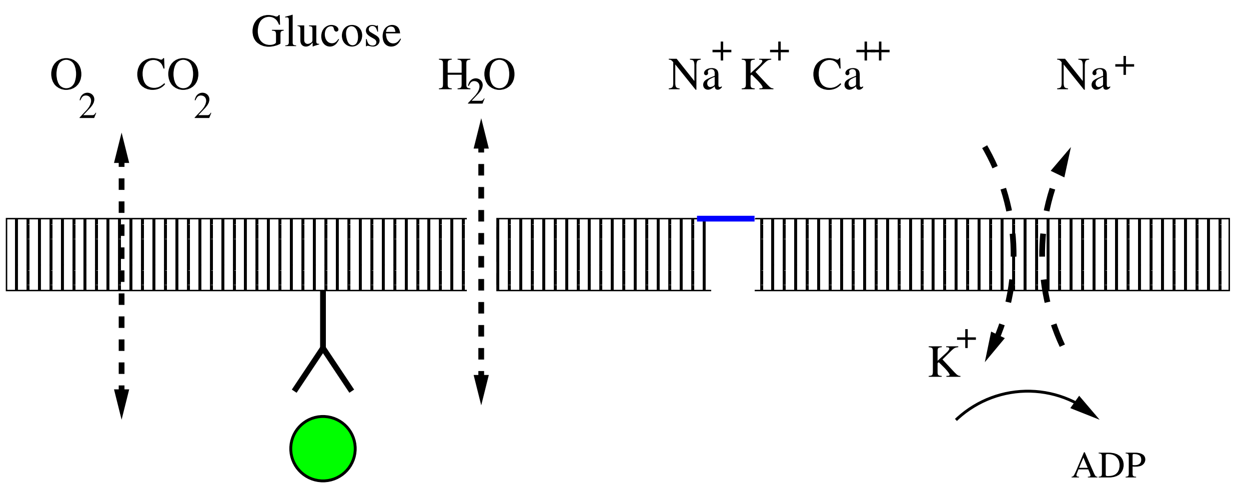
- Carefully regulate the intracellular ionic concentrations so that there are no net osmotic pressures.
- As a result, the major ions (Na^{+}, K^{+}, Cl^{-} and Ca^{++}) have different intracellular and extracellular concentrations.
- Consequently, there is an electrical potential difference across the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

Membrane Transporters



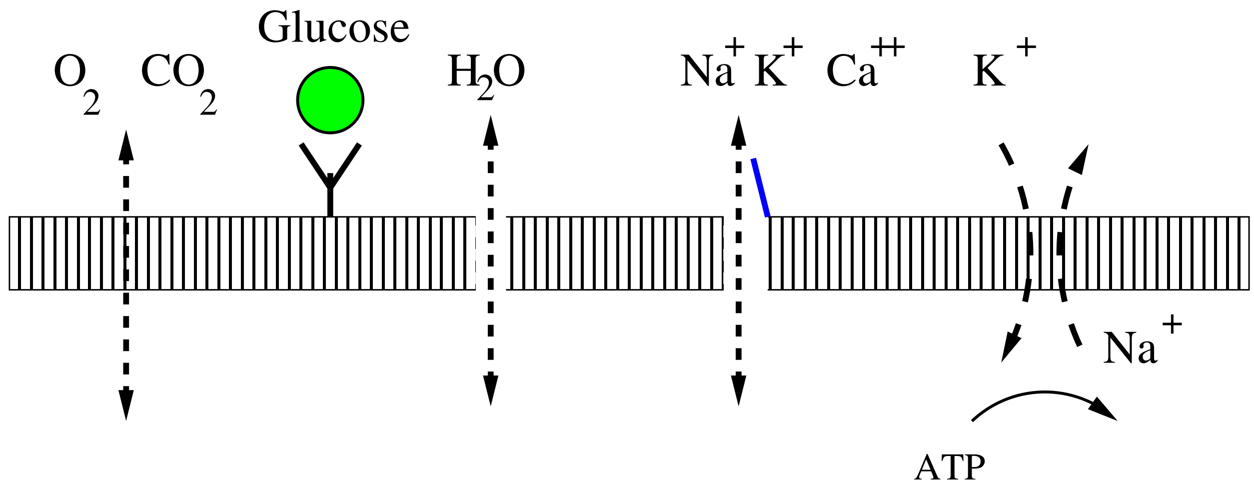
- transmembrane diffusion - carbon dioxide, oxygen

Membrane Transporters



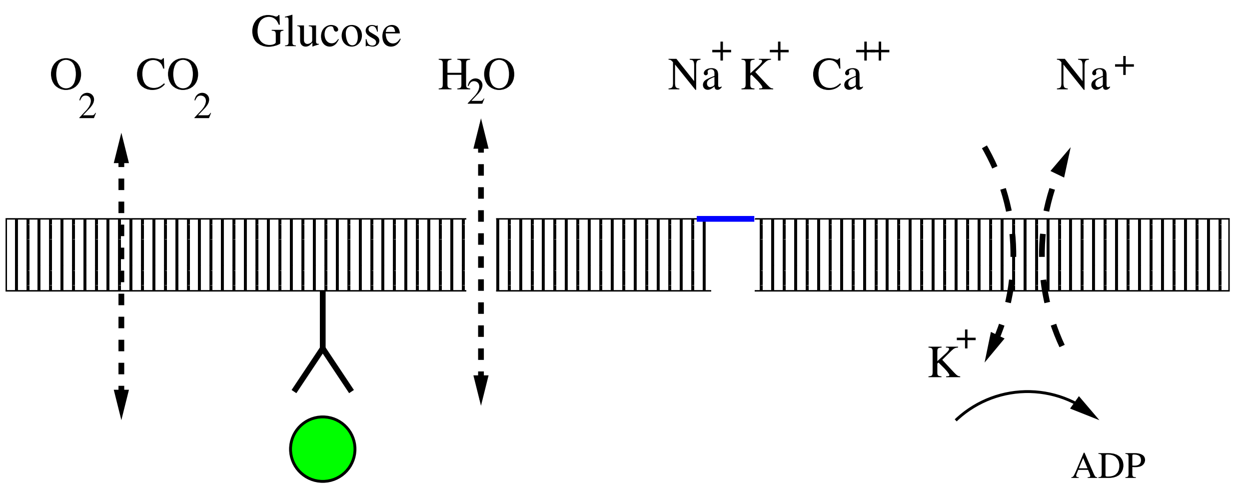
- transmembrane diffusion - carbon dioxide, oxygen
- transporters - glucose, sodium-calcium exchanger

Membrane Transporters



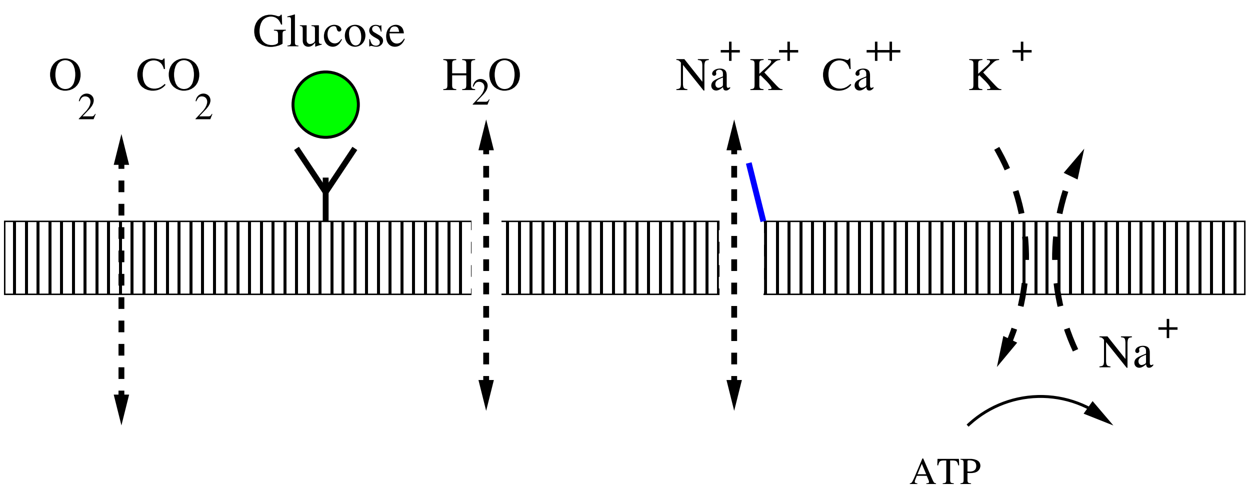
- transmembrane diffusion - carbon dioxide, oxygen
- transporters - glucose, sodium-calcium exchanger
- pores - water

Membrane Transporters



- transmembrane diffusion - carbon dioxide, oxygen
- transporters - glucose, sodium-calcium exchanger
- pores - water
- ion-selective, gated channels - sodium, potassium, calcium

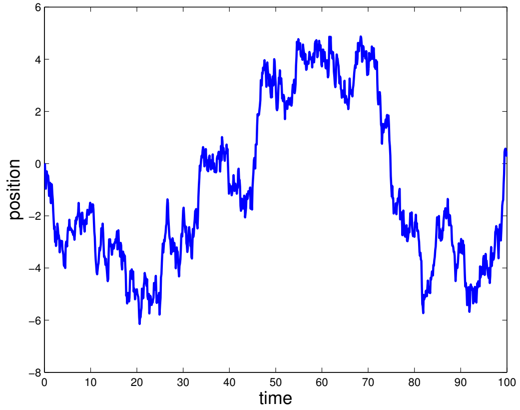
Membrane Transporters

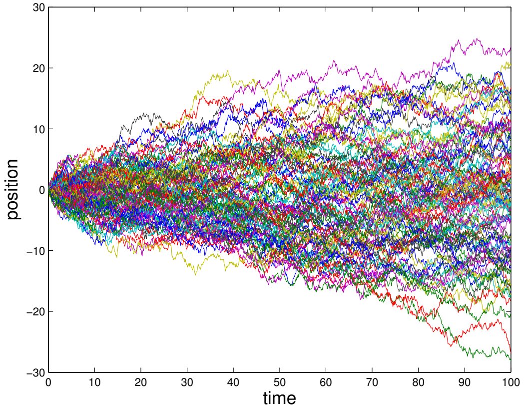


- transmembrane diffusion - carbon dioxide, oxygen
- transporters - glucose, sodium-calcium exchanger
- pores - water
- ion-selective, gated channels - sodium, potassium, calcium
- ATPase exchangers - sodium-potassium ATPase, SERCA

How Things Move

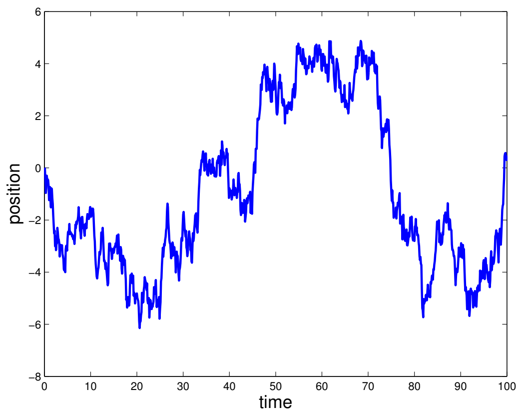
Most molecules move by a random walk:

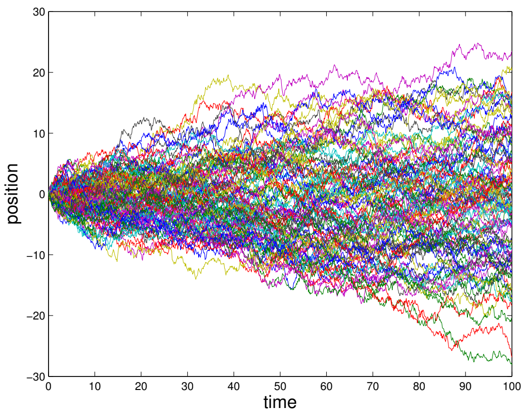




How Things Move

Most molecules move by a random walk:



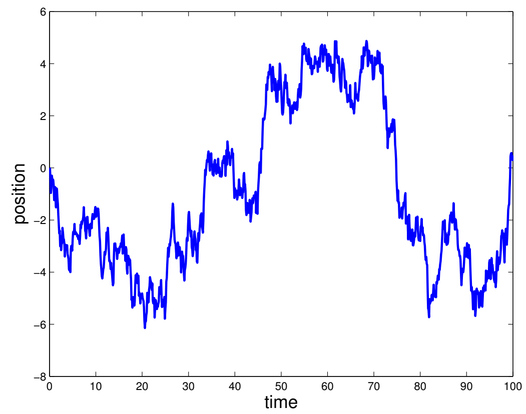


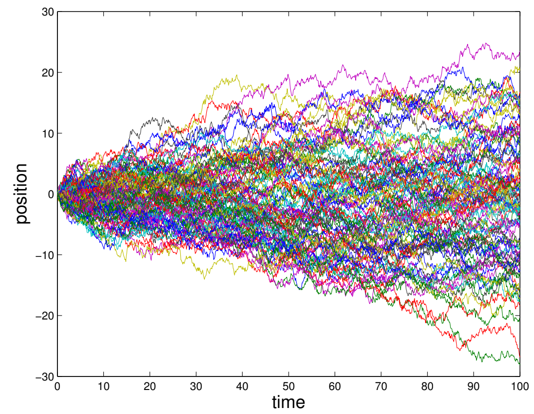
Fick's *law*: When there are a large number of these molecules, their motion can be described by

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

How Things Move

Most molecules move by a random walk:





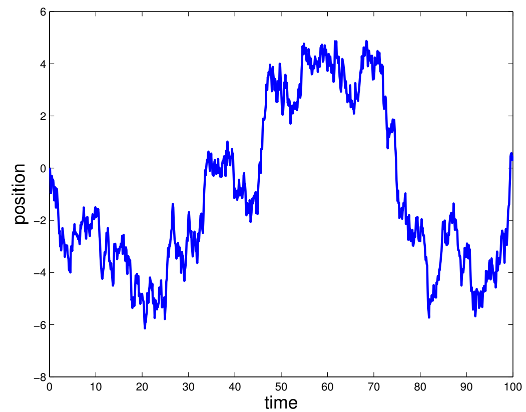
Fick's *law*: When there are a large number of these molecules, their motion can be described by

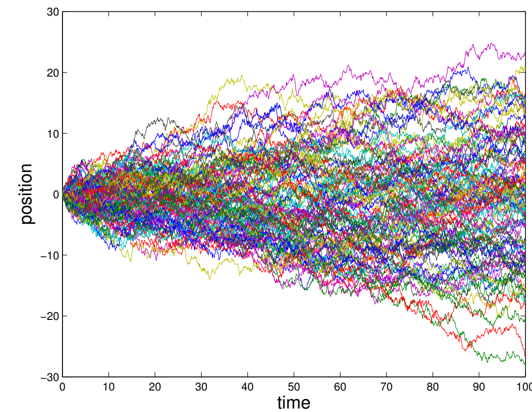
$$\boxed{J} = - D \frac{\partial C}{\partial x}$$

molecular flux,

How Things Move

Most molecules move by a random walk:





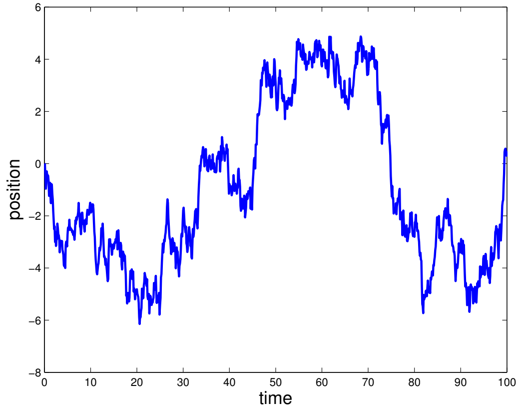
Fick's *law*: When there are a large number of these molecules, their motion can be described by

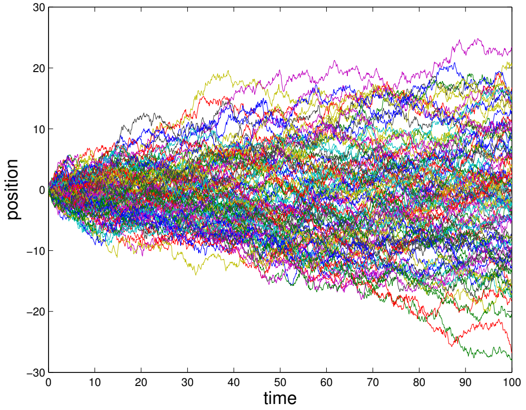
$$J = -\boxed{D}\,\frac{\partial C}{\partial x}$$

molecular flux, diffusion coefficient,

How Things Move

Most molecules move by a random walk:





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:

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

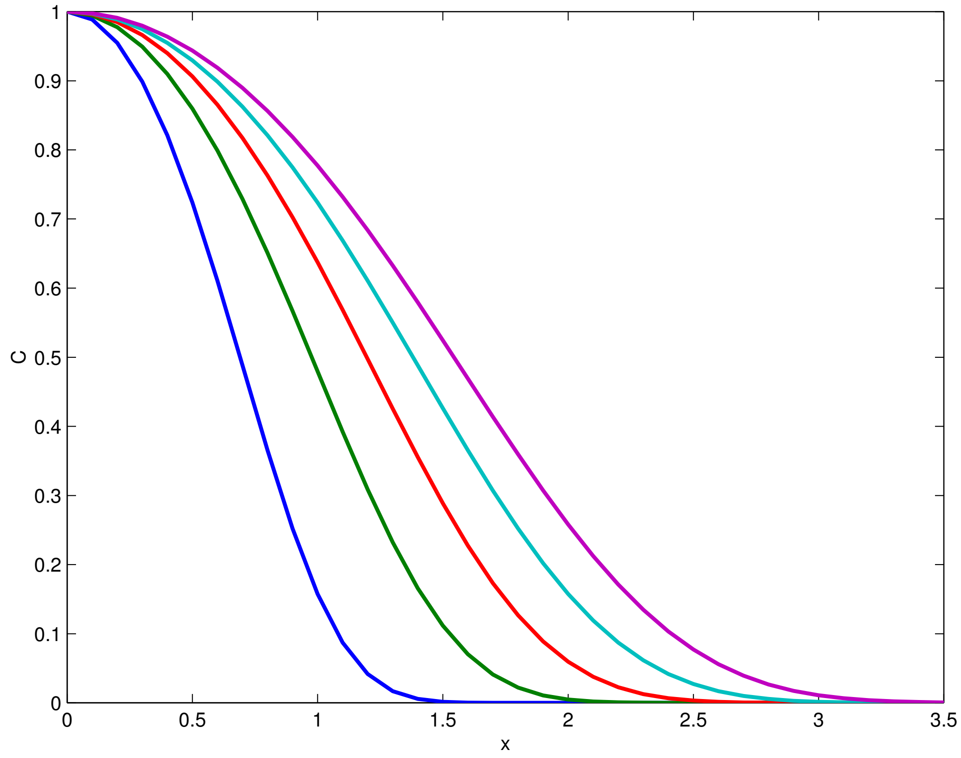
leading to the Diffusion Equation

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

Basic Consequences - I

Diffusion in a tube fed by a reservoir

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



Basic Consequences - II

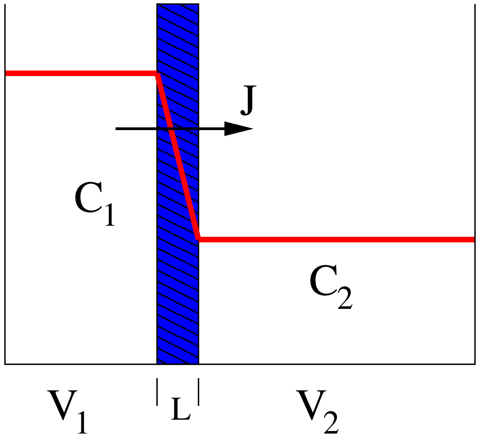
Diffusion time: $t = \frac{x^2}{D}$ for hydrogen ($D = 10^{-5}$cm^2/s).

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

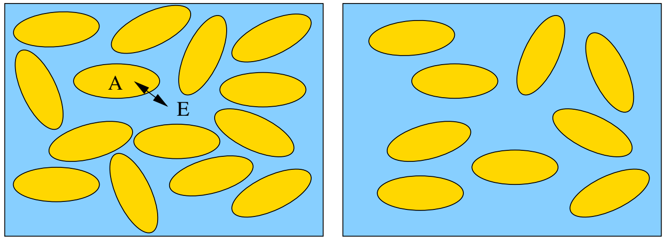
$$J = \frac{AD}{L}(C_1 - C_2)$$



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

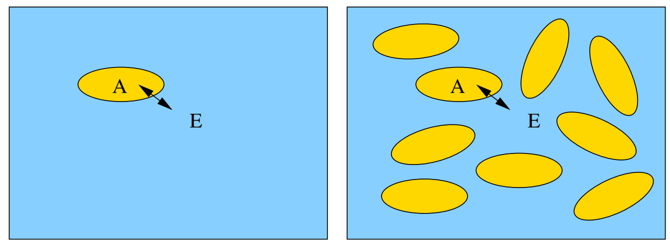
Quorum Sensing

Quorum sensing: The ability of bacteria to respond to their population size. Question: How do bacteria conduct a census?

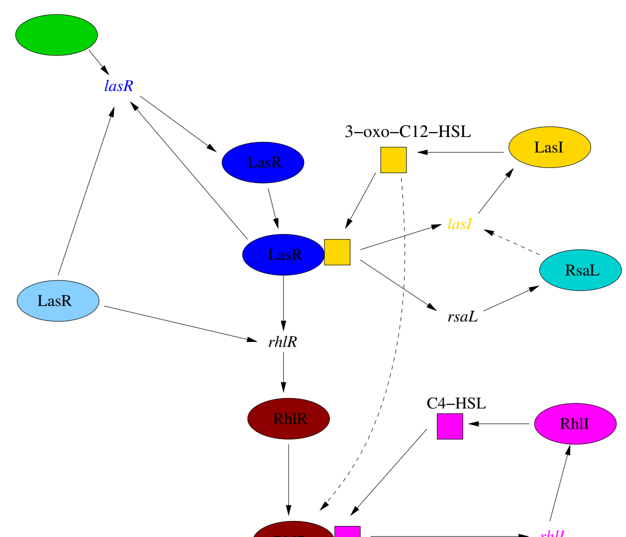


Quorum Sensing

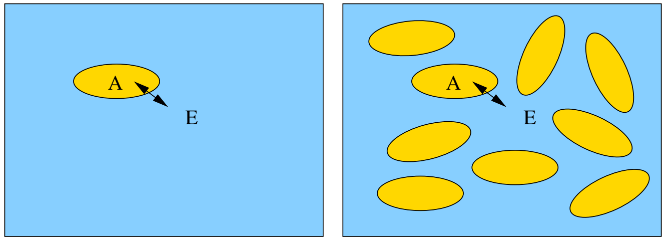
Quorum sensing: The ability of bacteria to respond to their population size. Question: How do bacteria conduct a census?



Solution: Autoinducer (HSL)- a freely diffusing chemical with auto-catalytic (positive feedback) production.

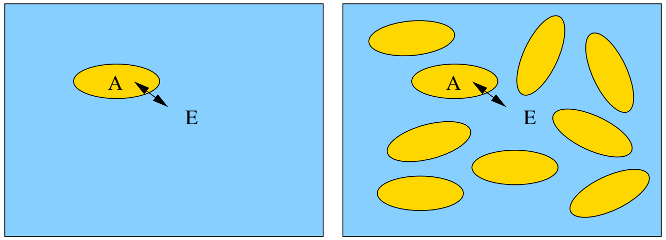


Quorum Sensing-II



$$\frac{dA}{dt} = F(A) + \delta(E - A)$$

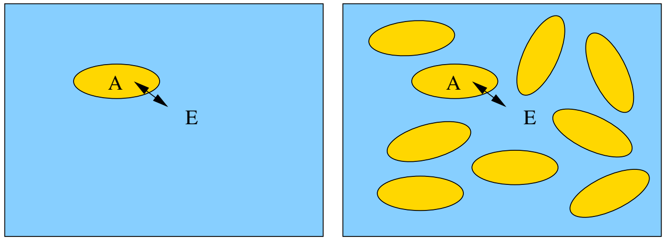
Quorum Sensing-II



$$\boxed{\frac{dA}{dt}} = F(A) + \delta(E - A)$$

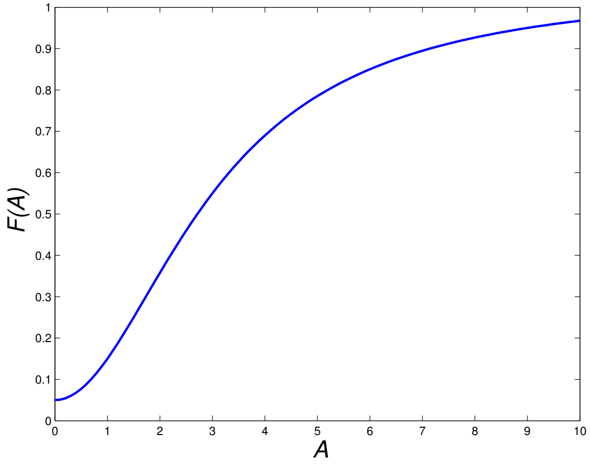
rate of change of A,

Quorum Sensing-II

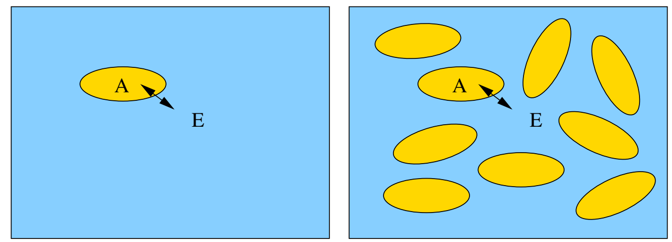


$$\frac{dA}{dt} = \boxed{F(A)} + \delta(E - A)$$

rate of change of A, production rate,

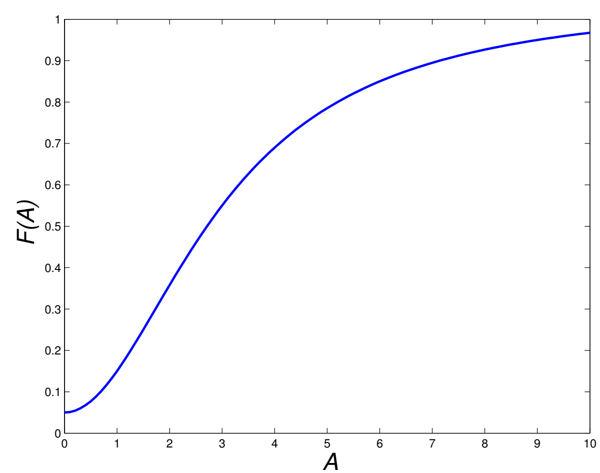


Quorum Sensing-II



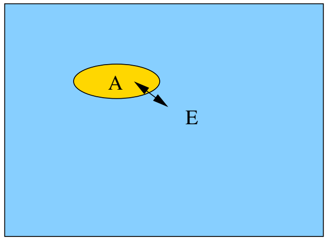
$$\frac{dA}{dt} = F(A) + \boxed{\delta(E-A)}$$

rate of change of A, production rate, diffusive loss.



Quorum Sensing-III

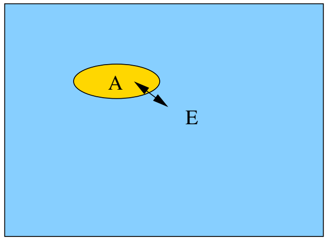
Extracellular Autoinducer E:



$$\frac{dE}{dt} = -\, k_E E \, + \, \delta(A - E)$$

Quorum Sensing-III

Extracellular Autoinducer E:

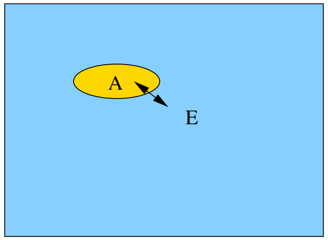


$$\boxed{\frac{dE}{dt}} = - \, k_E E \; + \; \delta(A - E)$$

rate of change of E,

Quorum Sensing-III

Extracellular Autoinducer E:

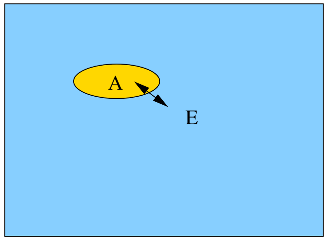


$$\frac{dE}{dt} = -\boxed{k_E E} + \delta(A - E)$$

rate of change of E, degradation rate,

Quorum Sensing-III

Extracellular Autoinducer E:

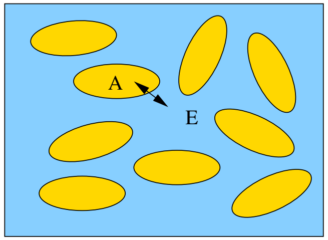


$$\frac{dE}{dt} = - k_E E + \boxed{\delta(A - E)}$$

rate of change of E, degradation rate, diffusive source,

Quorum Sensing-III

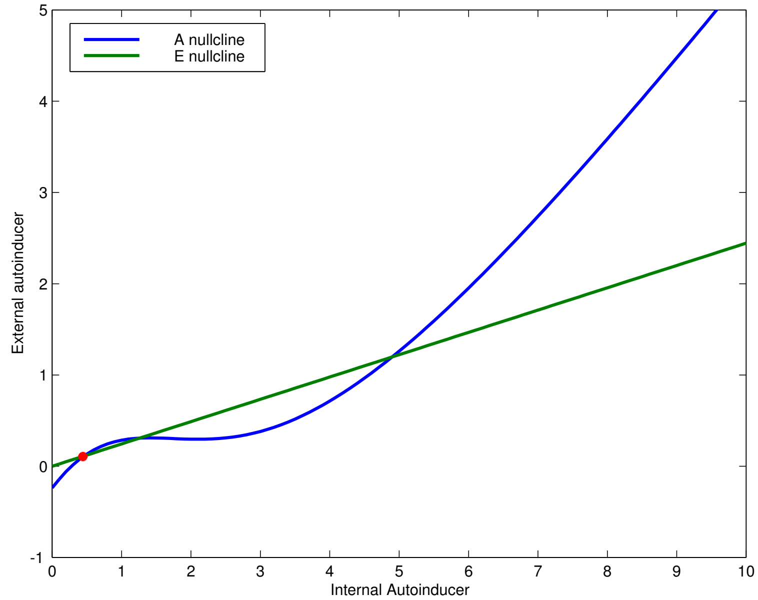
Extracellular Autoinducer E:



$$\boxed{(1-\rho)}\left(\frac{dE}{dt}+K_E E\right) = \boxed{\rho}\,\delta(A-E)$$

rate of change of E, degradation rate, diffusive source, density dependence.

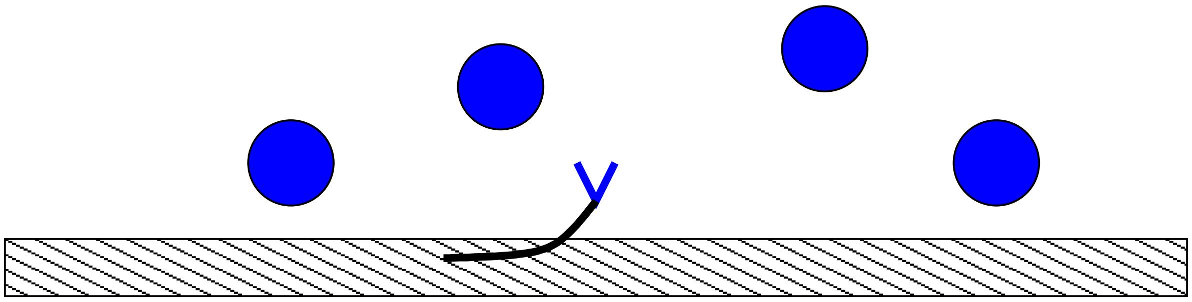
Quorum Sensing-IV



$$\frac{dA}{dt} = F(A) + \delta(E - A), \qquad E = A - \frac{1}{\delta}F(A)$$

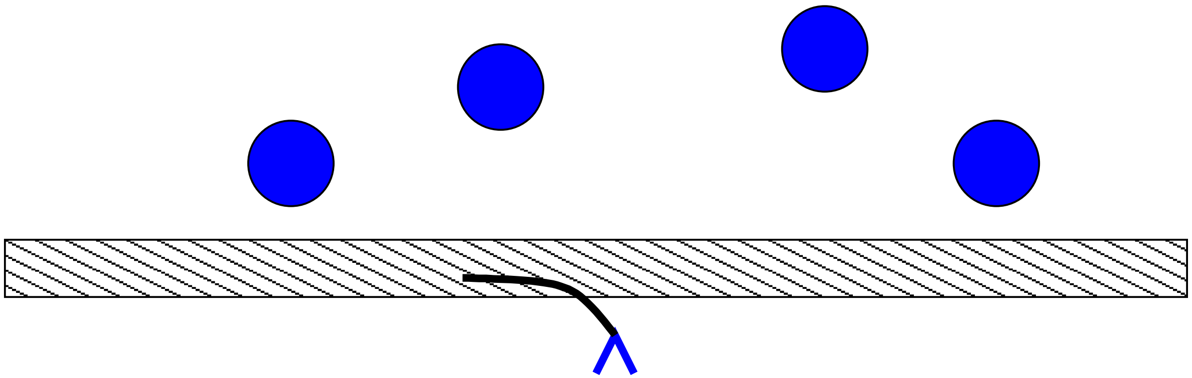
$$\frac{dE}{dt} = -k_E E + \frac{\rho}{1-\rho}\delta(A - E) \qquad A = (\frac{1-\rho}{\rho\delta}k_E + 1)E$$

Carrier Mediated Diffusion



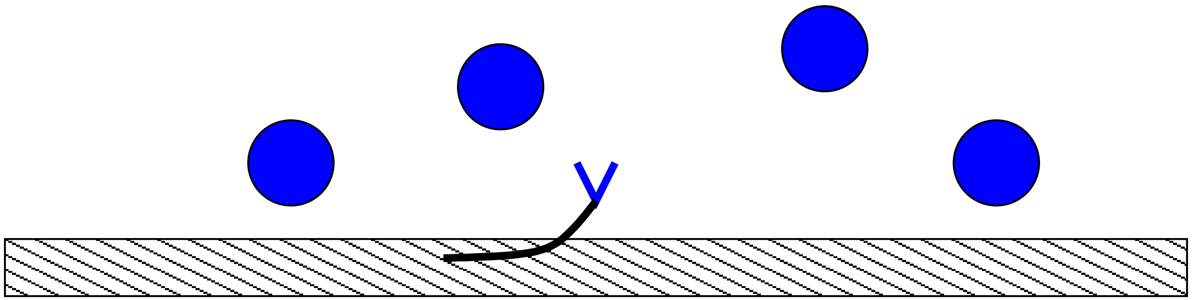
$$C_e \rightleftarrows C_i$$

Carrier Mediated Diffusion



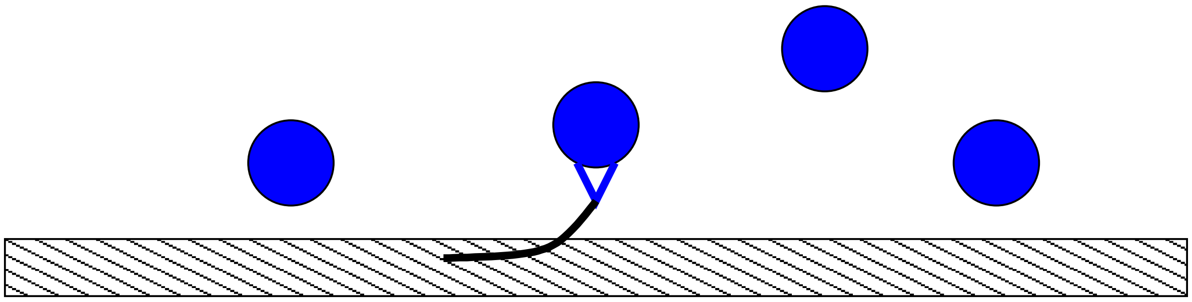
$$C_e \rightleftarrows C_i$$

Carrier Mediated Diffusion



$$C_e \rightleftarrows C_i$$

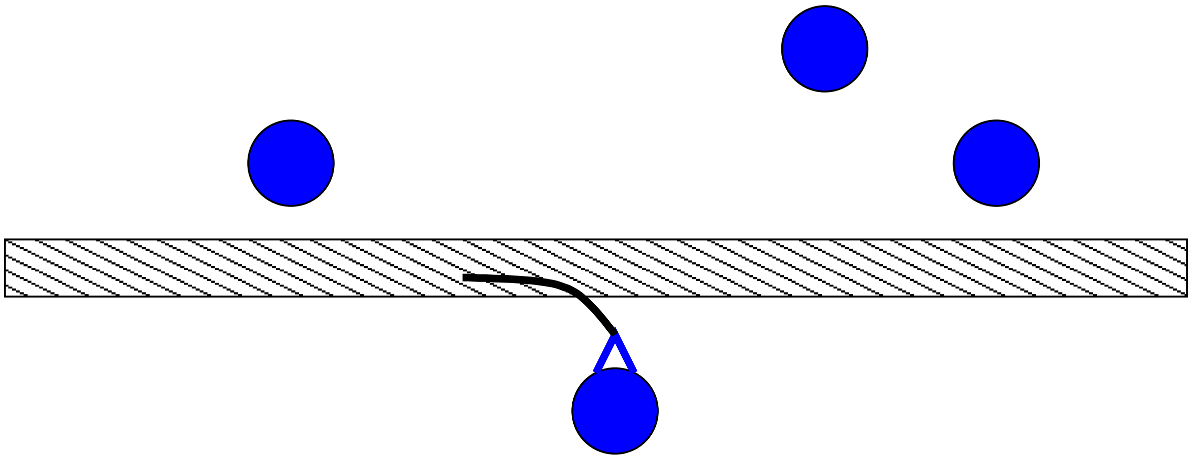
Carrier Mediated Diffusion



$$C_e \rightleftarrows C_i$$

$$S_e + C_e \rightleftarrows P_e$$

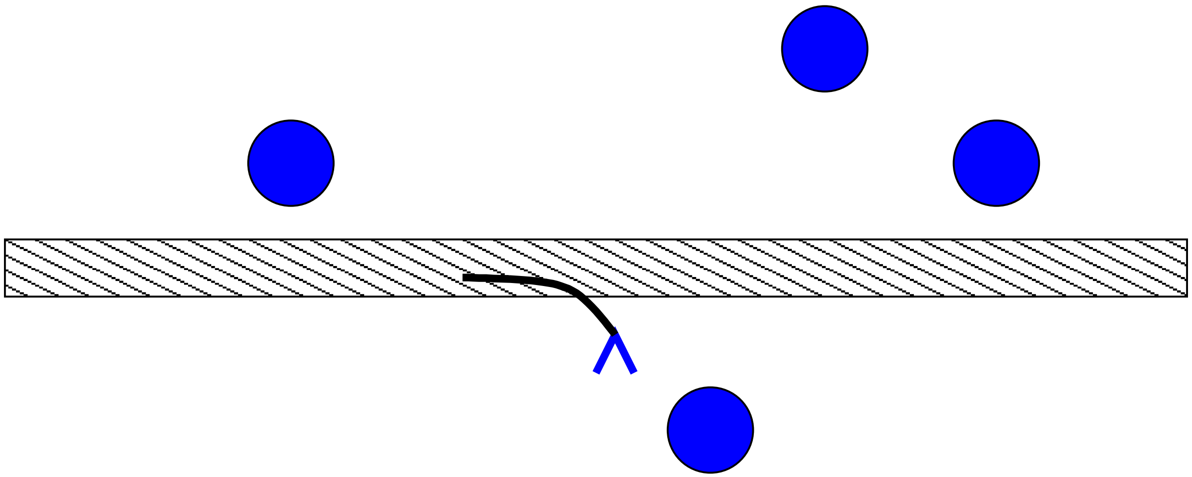
Carrier Mediated Diffusion



$$C_e \rightleftarrows C_i$$

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

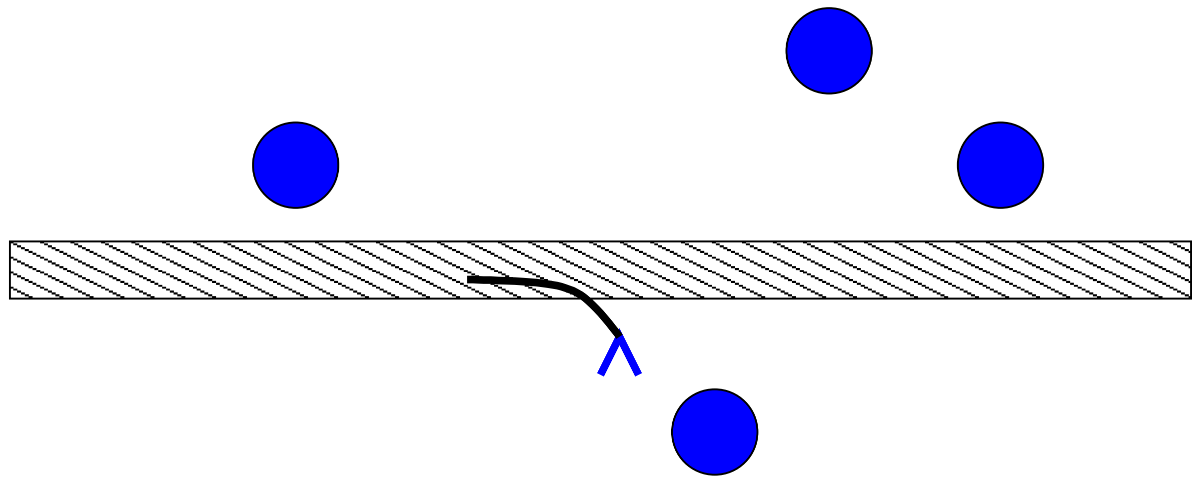
Carrier Mediated Diffusion



$$C_e \rightleftarrows C_i$$

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

Carrier Mediated Diffusion



$$C_e \rightleftarrows C_i$$

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

For this system,

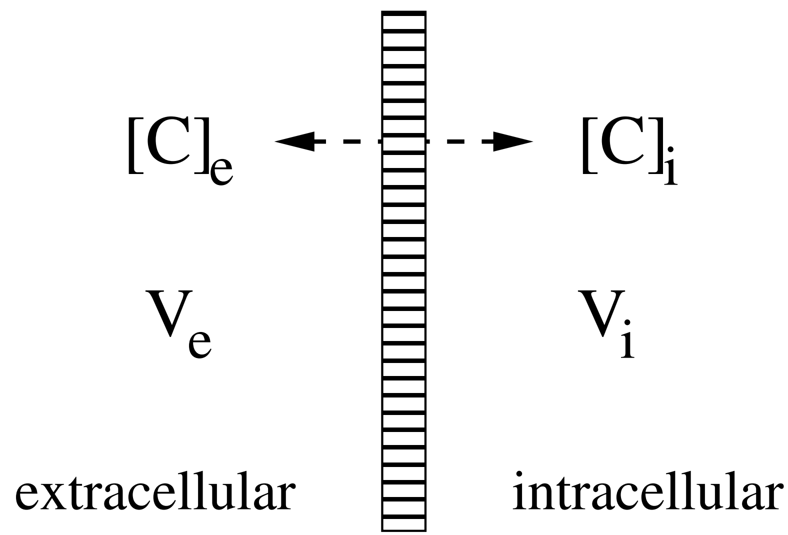
$$J = J_{max} \frac{S_e - S_i}{(S_e + K_e)(S_i + K_i)}.$$

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

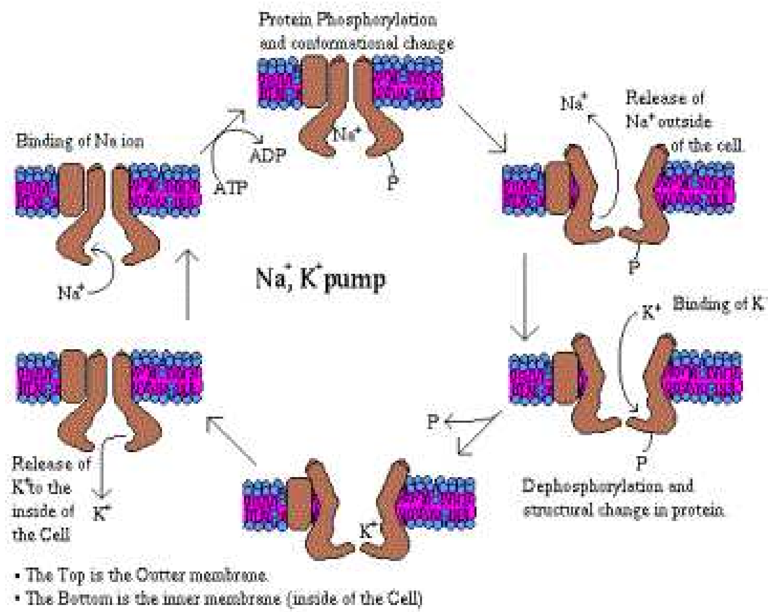
The two most popular ion current models

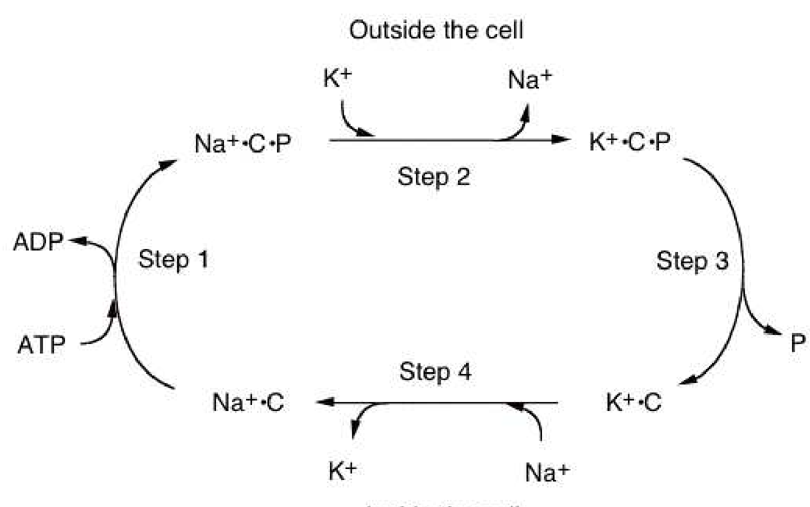
$$I_{ion} = g(V - V_N) \qquad \text{Linear Model}$$

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

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

Sodium-Potassium ATPase

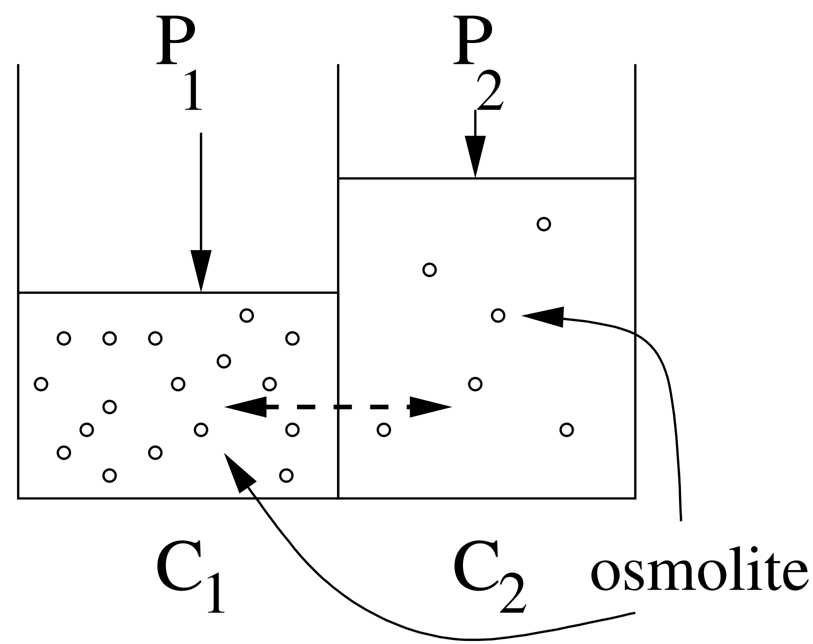




Osmotic Pressure and Flux

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

$$\pi_i = kTC_i$$



Volume Control; Pump-Leak Model

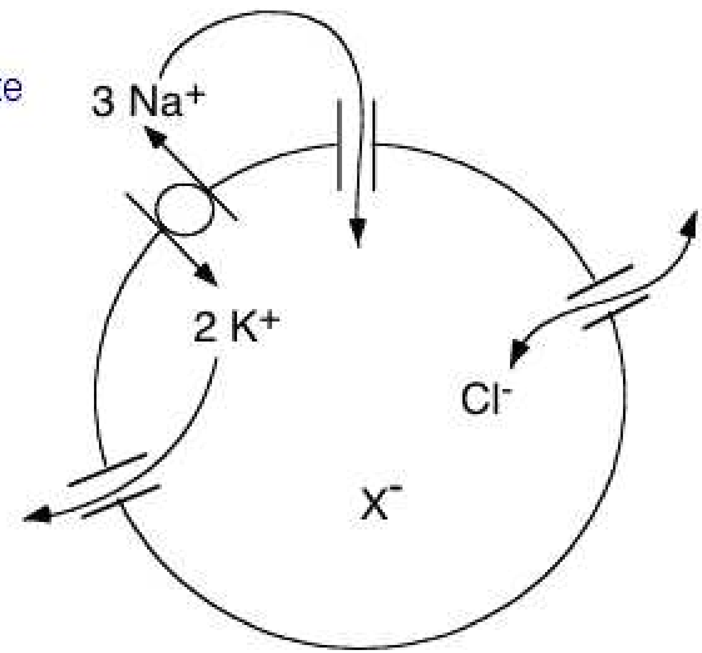
Na^+ is pumped out, K^+ is pumped in, Cl^- moves passively, negatively charged macromolecules are trapped in the cell.

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.

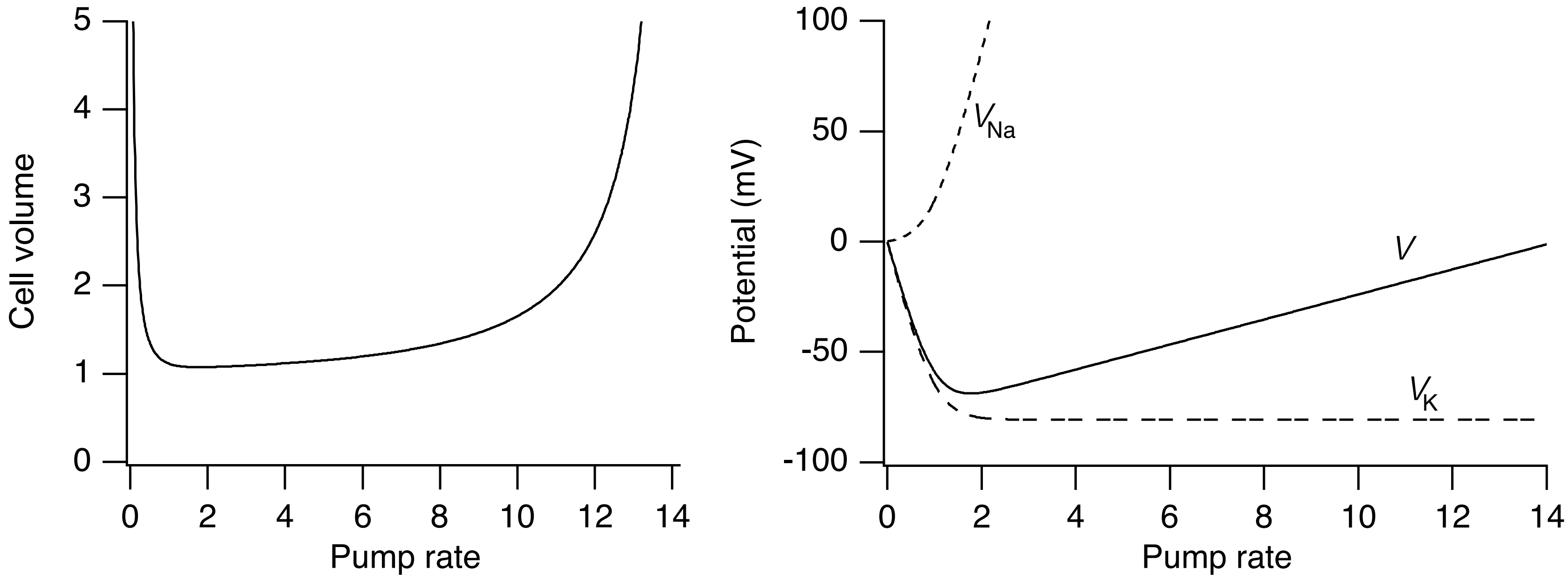
$$qw(N_i+K_i-C_i)+z_xqX = qw(N_e+K_e-C_e) = 0, \qquad \text{(charge bala}$$

- 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.)

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?