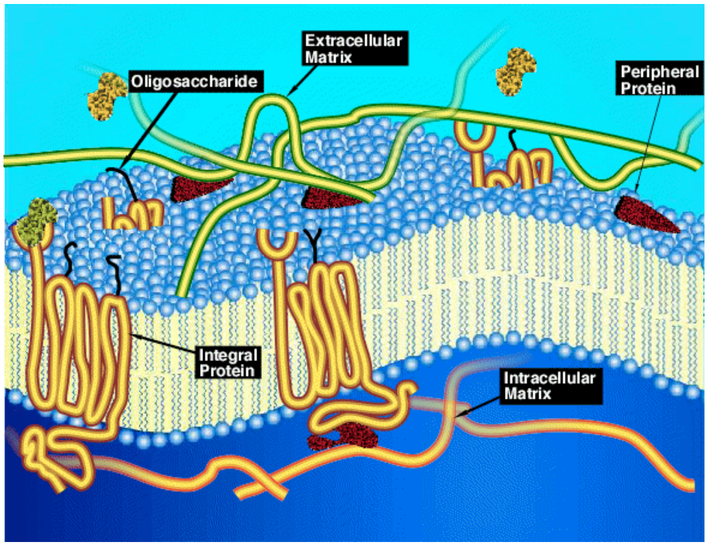
Transport, Resting Potential, and Cellular Homeostasis

John A. White
john.white@utah.edu
BIOEN 6003

Overview: Week 2

- Membrane structure
- Membrane transport, esp. diffusion
- “Electrodiffusion” of a charged particle in an electric field
- Electrodiffusion across a semi-permeable membrane
  - Single ionic species in equilibrium
  - Multiple ionic species in steady-state
- Pumps
- Osmotic effects

Membrane structure



http://telstar.ote.cmu.edu/biology/downloads/membranes/index.html

Methods of membrane transport

- Endocytosis (requires energy)
- Exocytosis
- Diffusion
- Protein-mediated transport
  - Active transport (requires energy)
  - Facilitated (passive) transport

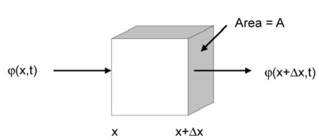
Diffusion: Fick's first law

In general: $\vec{\varphi}_n = -D_n \nabla c_n$, ∇c_n = gradient of $c_n = \frac{\partial c_n}{\partial x}\mathbf{i} + \frac{\partial c_n}{\partial y}\mathbf{j} + \frac{\partial c_n}{\partial z}\mathbf{k}$

In 1D steady-state: $\varphi_n = -D_n \frac{dc_n}{dx}$

c_n [=] mol/ L = M φ_n [=] mol/(s m^2) D_n [=] m^2/s

Add in continuity to get the diffusion equation



Net influx of particles in interval (t,t+Δt):

$$[\varphi(x,t) - \varphi(x+\Delta x,t)]\times A\times \Delta t = [c(x+\Delta x/2,t+\Delta t) - c(x+\Delta x/2,t)] \times A\times \Delta x$$

(assuming flux is constant during Δt and concentration is constant in Δx)

Rearrange to put like terms on each side:

$$[\varphi(x+\Delta x,t) - \varphi(x,t)] / \Delta x = - [c(x+\Delta x/2,t+\Delta t) - c(x+\Delta x/2,t)] / \Delta t$$

Take limit as Δx, Δt → 0:

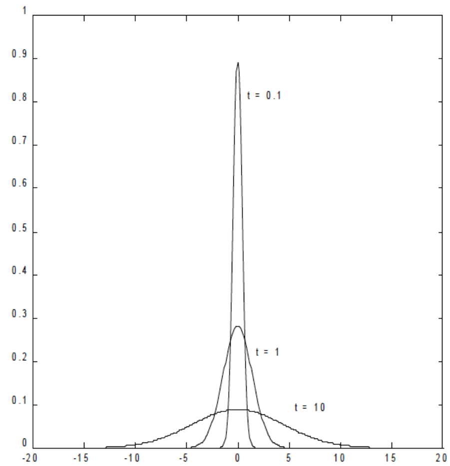
$$\frac{\partial \varphi(x,t)}{\partial x} = -\frac{\partial c(x,t)}{\partial t}$$

Combine Fick's first law and the continuity equation:

1. Take ∂/∂x of Fick's first law: $\frac{\partial \varphi}{\partial x} = -D\frac{\partial^2 c}{\partial x^2}$

2. Combine to get rid of φ: $D\frac{\partial^2 c}{\partial x^2} = \frac{\partial c(x,t)}{\partial t}$

Analytic solution of the diffusion equation



$$\text{Initial conditions}: c(x,0) = \delta(x) \Rightarrow c(x,t) = \frac{u(t)}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}$$

Nernst-Planck equation

- Key assumption: linear summation of diffusion and force-induced drift with friction (i.e., velocity proportional to force)

$\varphi_{n(F)} = c_n v_n$, where v_n [=] m/s is the *drift velocity* of species n

If f is the force per mole, and we assume that collisions between particles make the system frictional, the system acts like a dashpot, with velocity proportional to force:

$v = u_n f$, where u_n [=] (m mol)/(N s) is the *molar mechanical mobility of n.*

The total steady-state flux is the sum of the fluxes due to diffusion and the force:

$$\varphi_n = \varphi_{n(D)} + \varphi_{n(F)} = -D_n \frac{dc_n}{dx} + u_n f c_n(x,t)$$

Nernst-Planck equation

$$\varepsilon = -\frac{d\psi}{dx}, \text{ where } \psi \, [=] \, \text{V}$$

$$f = \varepsilon z_n F = -z_n F \frac{d\psi}{dx}$$

$$\varphi_n = -D_n \frac{dc_n}{dx} - u_n z_n F c_n(x,t) \frac{d\psi(x)}{dx}$$

$$u_n = \frac{D_n}{RT}$$

3 dependent variables, but only 1 equation, per ion. Not good!

Additional constraints make Nernst-Planck (theoretically) solvable

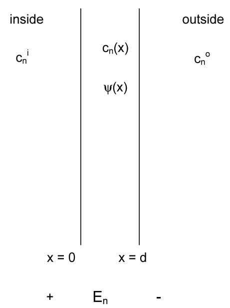
$$\text{Continuity: } \frac{\partial \phi_n}{\partial x} = -\frac{\partial c_n}{\partial t}$$

$$\text{Poisson's equation: } \frac{\partial^2 \psi}{\partial x^2} = \frac{-\rho(x,t)}{\varepsilon}$$

ε = permittivity of medium [=] C/(m V)
$\rho(x,t)$ = density of mobile & fixed charge within the medium

Still not good! A big pool of interlinked, nonlinear PDEs!

Nernst-Planck can be solved for one ion in steady-state equilibrium



$$\varphi_n(x) = 0 \Rightarrow u_n z_n F c_n(x) \frac{d\psi(x)}{dx} = -D_n \frac{dc_n(x)}{dx}$$

Because $D_n = u_n RT$ (this is the *Einstein relationship,* which relates the diffusion coefficient to molar molecular mobility), we can write:

$$RT \frac{dc_n(x)}{dx} = -z_n F c_n(x) \frac{d\psi(x)}{dx}$$

$$\Rightarrow RT \frac{1}{c_n(x)} \frac{dc_n(x)}{dx} = -z_n F \frac{d\psi(x)}{dx}$$

Integrate both sides over [0,d] to give the ***Nernst Equation***:

$$E_n = \frac{RT}{z_n F} \ln \frac{c_n^o}{c_n^i} = \frac{RT}{z_n F} \frac{1}{\log e} \log \frac{c_n^o}{c_n^i}$$

Getting a feel for the Nernst equation

$$E_n = \frac{RT}{z_n F} \frac{1}{\log e} \log \frac{c_n^o}{c_n^i}$$

$$\approx \frac{59 \text{ mV}}{z_n} \log \frac{c_n^o}{c_n^i} \text{ (at 24 C)}$$

$$\approx \frac{61 \text{ mV}}{z_n} \log \frac{c_n^o}{c_n^i} \text{ (at 37 C)}$$

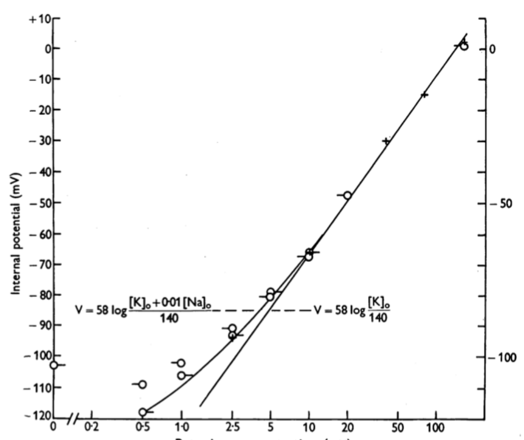
For frog muscle:

c_K^o = 2.25 mM, c_K^i = 124 mM, E_K =-101 mV
c_{Na}^o = 109 mM, c_{Na}^i = 10.4 mM, E_{Na} =+59 mV
c_{Cl}^o = 77.5 mM, c_{Cl}^i = 1.5 mM, E_{Cl} =-99 mV

Resting potential: hypotheses

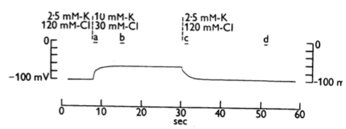
- Potassium is the only permeable ion at rest: $V_{rest} = E_K$
- Multiple ions lie in simultaneous *Donnan equilibrium*: e.g., $V_{rest} = E_K = E_{Cl}$
- <u>No</u> ion is in equilibrium; resting potential is a combination

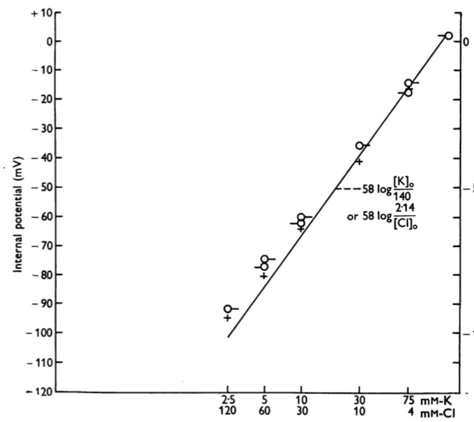
In the absence of chloride, resting muscle fibers can act something like "potassium electrodes"



Hodgkin and Horowicz, 1959

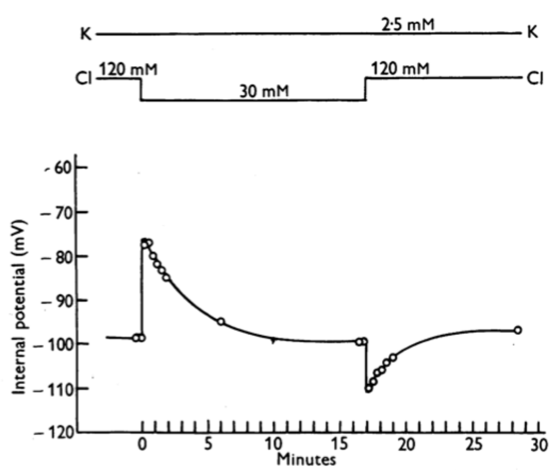
Simultaneous changes in c_{Cl}^{o} and c_{K}^{o} that allow simultaneous equilibrium suggest Donnan eq.





Hodgkin and Horowicz, 1959

Pushing the muscle cell out of equilibrium leads to osmotic changes that re-establish Donnan eq.



Hodgkin and Horowicz, 1959

Additional assumptions are typically made to solve Nernst-Planck for multiple ions in steady-state

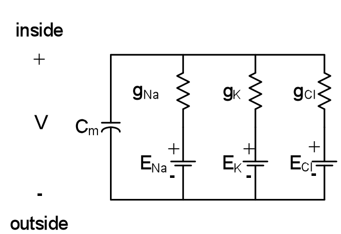
- *Constant-field assumption:* Assuming that the voltage profile varies linearly through the membrane allows one to derive the Goldman-Hodgkin-Katz (GHK) equation, which looks like a multi-ion version of the Nernst equation

$$V_{rest} = \frac{RT}{F} \ln \frac{P_{Na} c^{o}_{Na} + P_K c^{o}_{Na} + P_{Cl} c^{i}_{Cl}}{P_{Na} c^{i}_{Na} + P_K c^{i}_{Na} + P_{Cl} c^{o}_{Cl}}$$

$P_n = \frac{D_n}{d}$ (assuming continuous concentrations at boundaries)

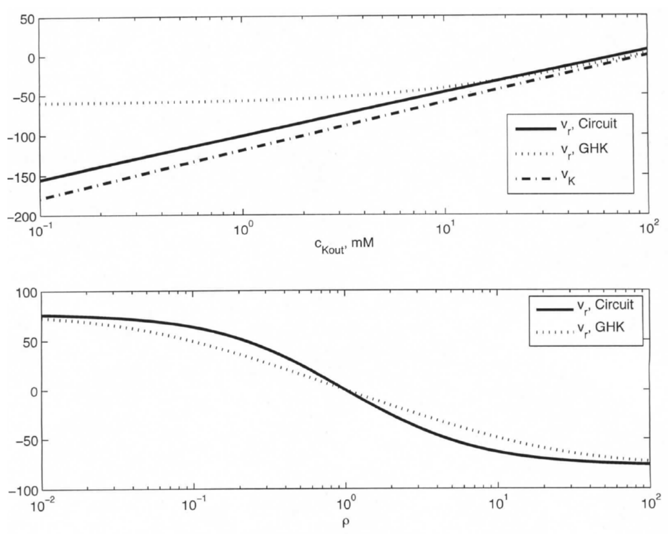
Additional assumptions are typically made to solve Nernst-Planck for multiple ions in steady-state

- *Linear I-V assumption:* Assuming that current flow depends linearly on *V* for each ion, as long as permeability (conductance) does not change, gives us a circuit model:



$$V_{rest} = \frac{g_{Na} E_{Na} + g_K E_{Na} + g_{Cl} E_{Cl}}{g_{Na} + g_K + g_{Cl}}$$

GHK and circuit give different outcomes



Electrogenic pumps affect membrane potential