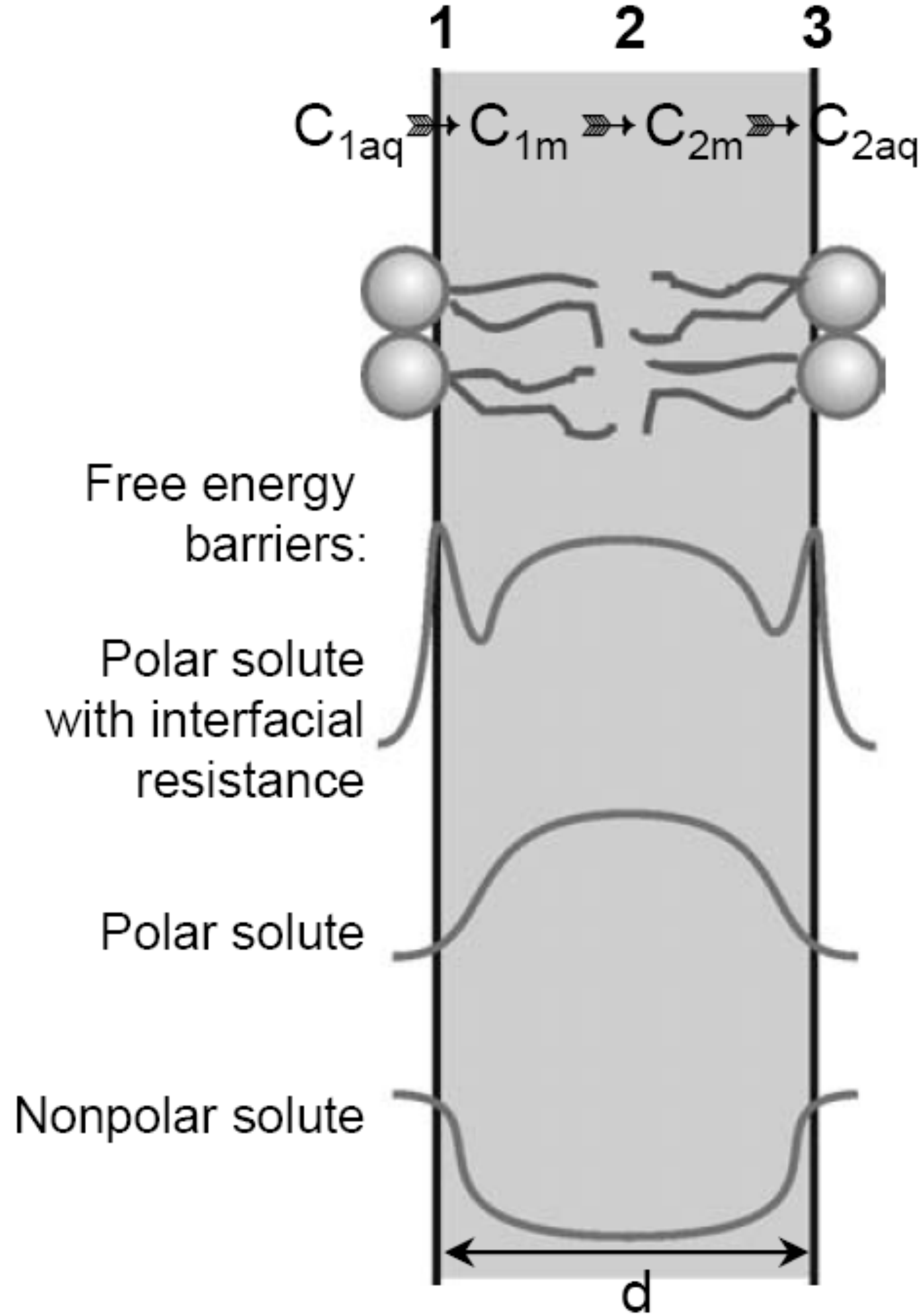
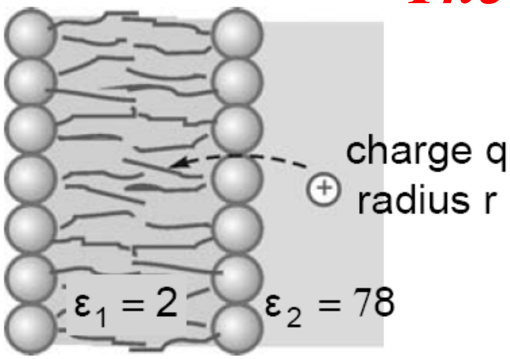
*Ion transport across the cell membrane underlies cellular **Homeostasis** and electrical activity.*

- the regulation of heart beat
- movement of muscle
- regulation of hormone release from pancreatic cells
- the generation of thought



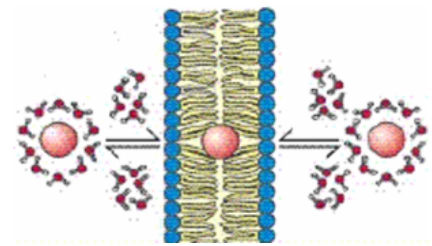
Membrane permeability to ions

The energy needed to move an ion into the membrane lipid phase is nearly 100 kT.



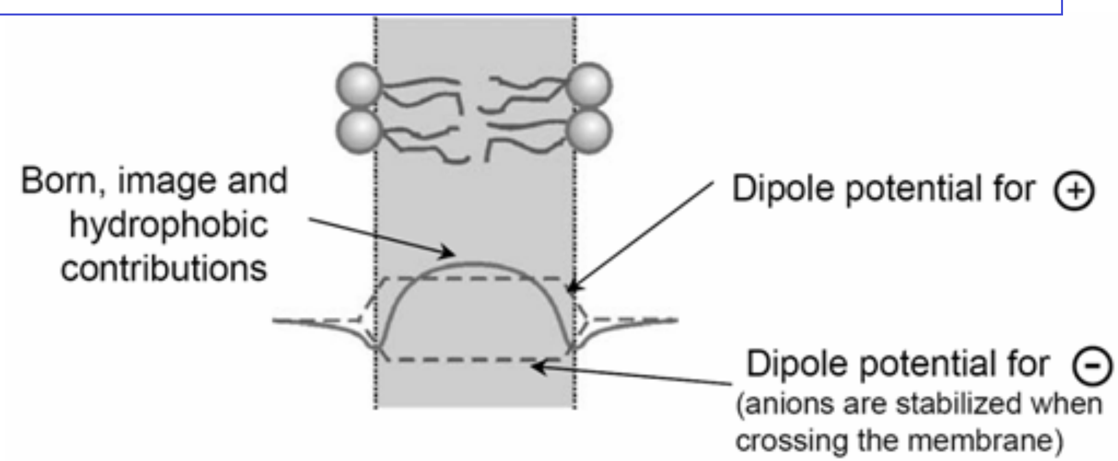
$$\boxed{\Delta E_B = \left(\frac{q^2}{8\pi\varepsilon_0 r}\right)\left(\frac{1}{\varepsilon_{hc}} - \frac{1}{\varepsilon_w}\right)}$$

Image forces reduce ΔE_B by 10 - 15%



Born energy concept makes no difference between „-" and „+".

$$P_{neutral\quad molecules} \overset{\approx 10^8\ times}{>>} P_{anions} \overset{20\text{-}1000\ times}{>>} P_{cations}$$



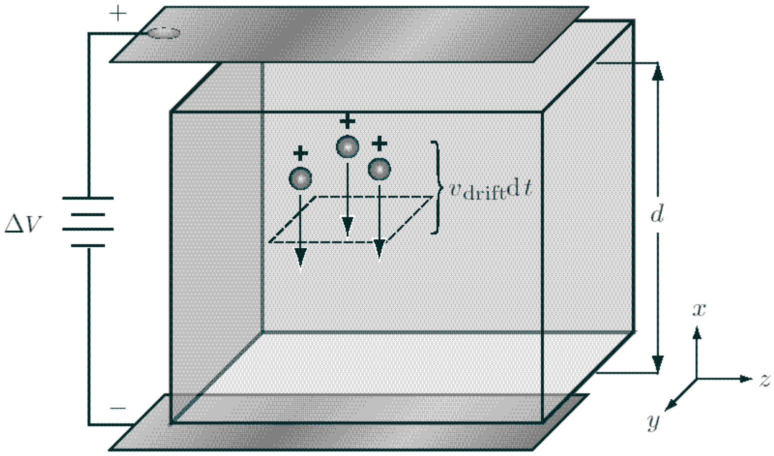
The movement of ions.

Diffusion

$$J = -D\frac{dc}{dx}$$

Electrophoresis

$$J = -uc\frac{d\psi}{dx}$$

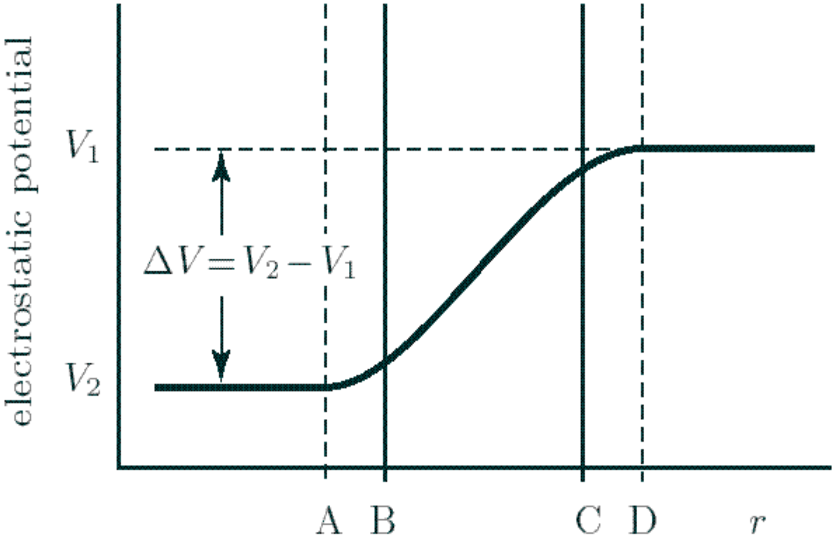


$$J = -D\frac{dc}{dx} - uc\frac{d\psi}{dx}$$

Nerst-Einstein relation $D = \frac{uRT}{zF}$ Faraday's constant $I = JzF$

The current across the membrane $I = -zFD\frac{dc}{dx} - zF\frac{DzF}{RT}c\frac{d\psi}{dx}$

Nerst-Plank relationship $I = -zFD\left[\frac{dc}{dx} + \frac{zF}{RT}c\frac{d\psi}{dx}\right]$



At equilibrium

$$I = 0 \qquad -\frac{RT}{zF}\frac{1}{c}\frac{dc}{dx} = \frac{d\psi}{dx}$$

Integrating across the membrane

$$\psi_i - \psi_o = \frac{RT}{zF}\ln\frac{[c]_o}{[c]_i}$$

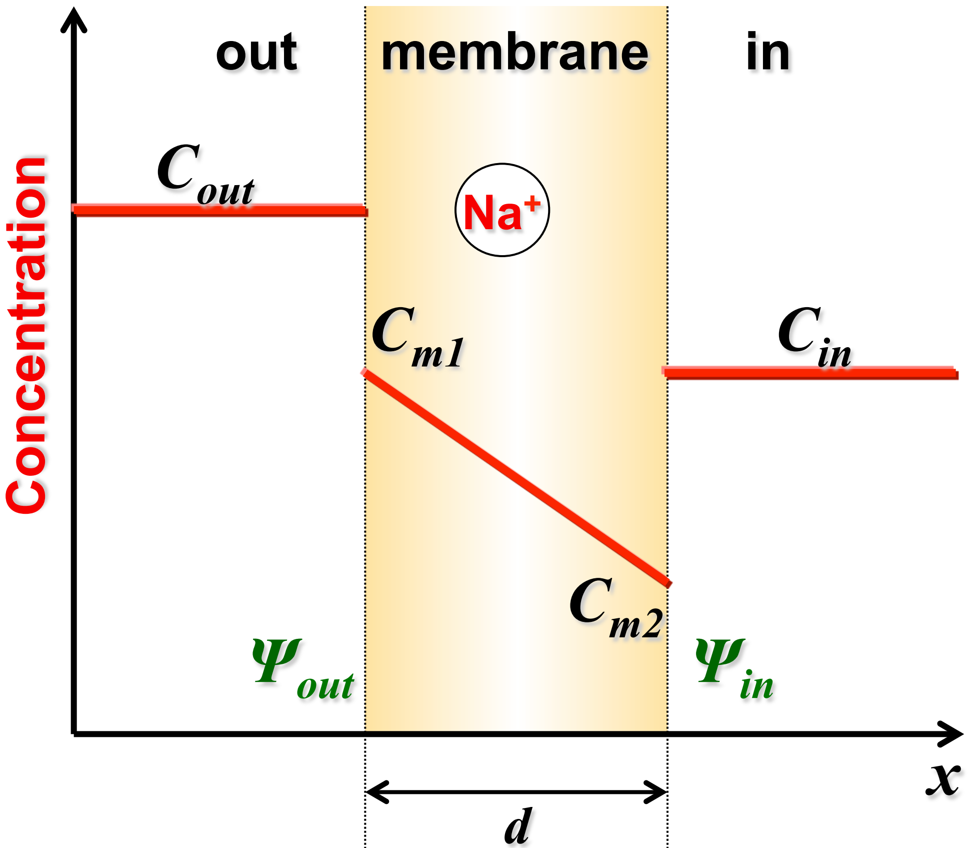
the Nernst Equation

Walther Hermann Nernst
Nobel Prize 1920

Transport of sodium ions

$$\mu_{Na^+} = \mu^0{}_{Na^+} + RT\ln[Na^+] + z^{Na}F\Psi$$

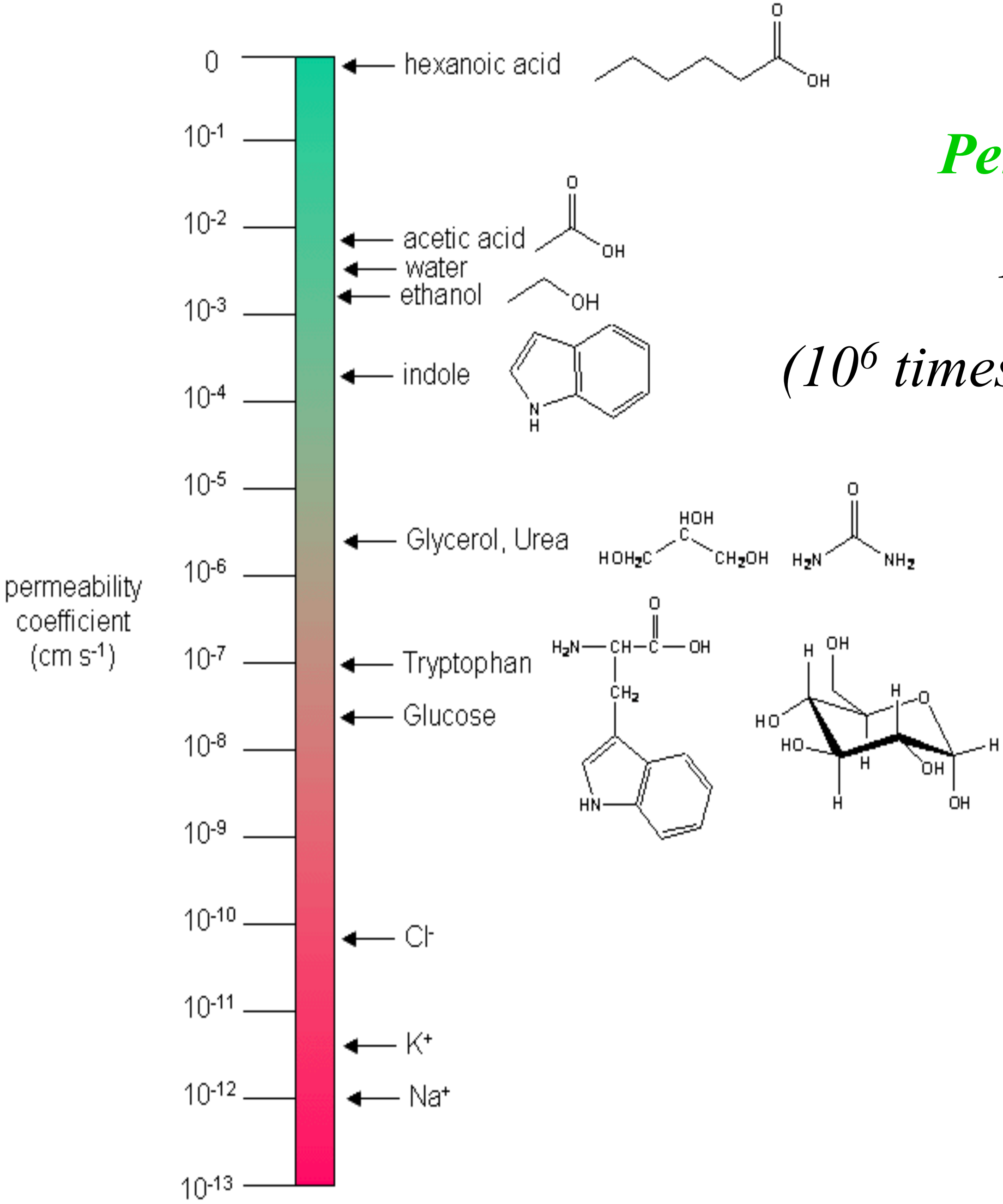
$$\Delta G = \mu_{Na^+(in)} - \mu_{Na^+(out)} = RT\ln\frac{[Na^+]_{in}}{[Na^+]_{out}} + F\Delta\Psi_{(in/out)}$$



Nernst equation:

$$\underbrace{-\frac{RT}{F}\ln\frac{[Na^+]_{in}}{[Na^+]_{out}}}_{\text{Nernst potential}} = \Delta\Psi_{in/out} \leftrightarrow \Delta\Psi_{Na}$$

Membrane permeability coefficient



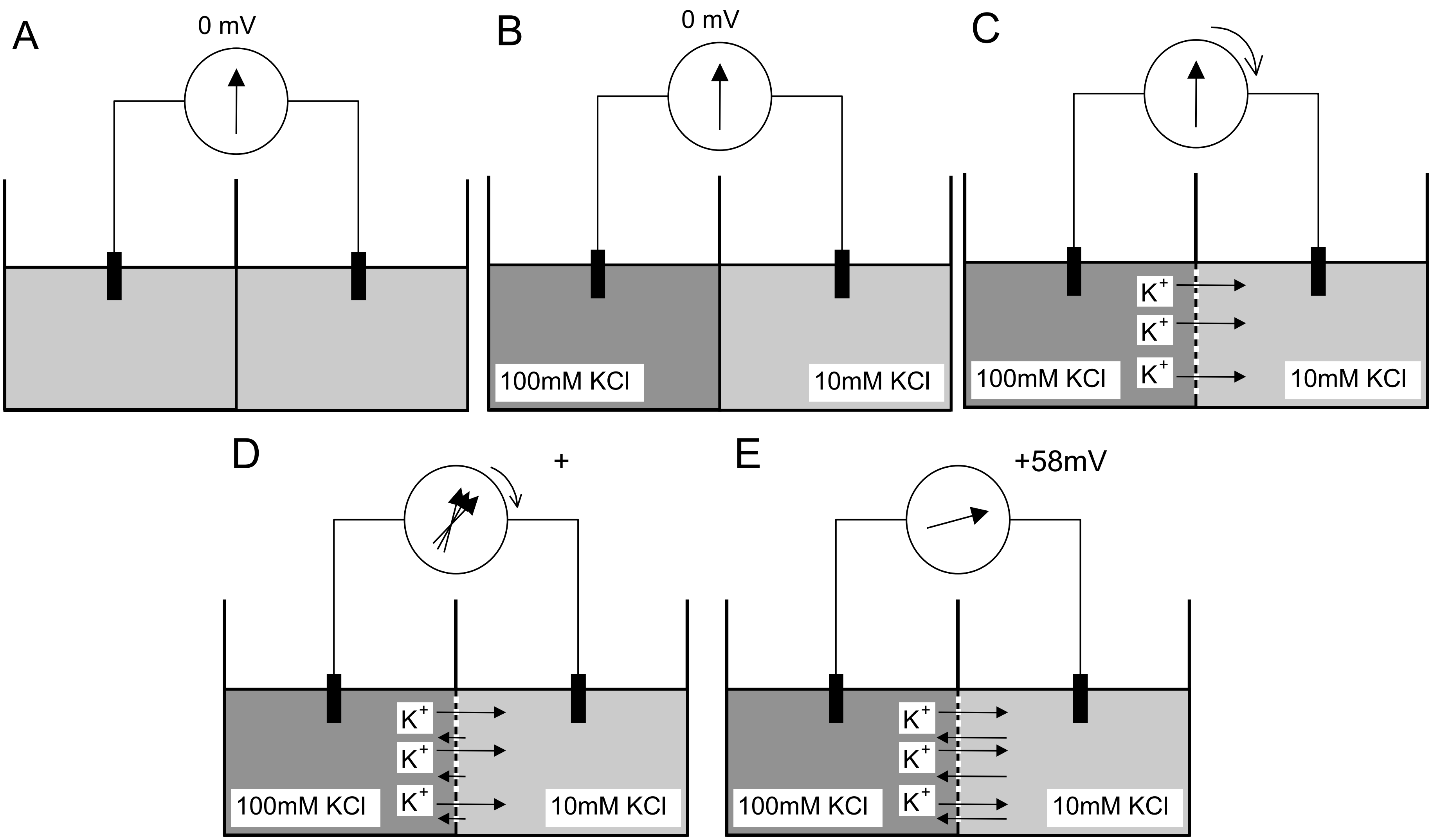
Permeability to protons,

$P = 10^{-4} - 10^{-8}$ cm/s

(10^6 times greater than for other ions)

$$\boxed{P = \frac{DK_P}{d}}$$

Equilibrium potentials



Flux due to conentration gradient = flux due to electrical potential

The factors affecting the size of the potential.

Concentration gradient *: larger gradient = larger voltage*

Higher temperature causes greater voltage.
At 0K (-273oC) there is no movement of ions, therefore no voltage is required to balance the flux. As the temperature goes up, random thermal motion increases and a higher voltage is required to reach equilibrium.

If the permeant ion has a high charge *(e.g. +2, +3) then it will be influenced more by the electrical potential. Hence a smaller electrical potential will be necessary to balance the flux.*

$$\frac{c_i}{c_o} = \exp\left(\frac{-zF\psi_{nerst}}{RT}\right)$$

Nerst equation gives the value of membrane potential ψ_{nerst} at which the ion is in steady-state equilibrium.

At the value of ψ_{nerst}, the electrostatic energy per mole ($zF\psi_m$) is exactly counterbalanced by the chemical energy per mole ($RT\ln(c_i/c_o)$).

The value of V_m is independent of the concentration or voltage profile within the membrane!

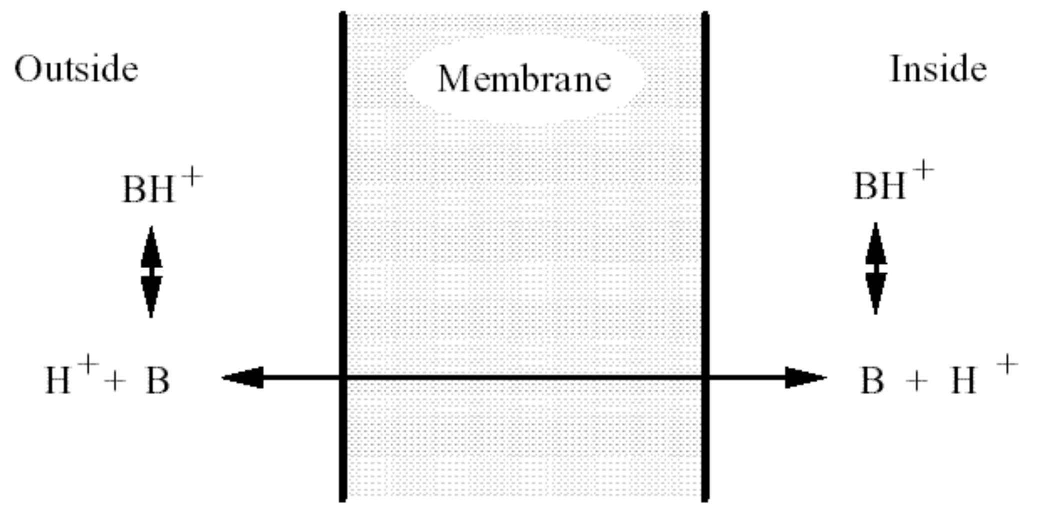
Equilibria of weak acids and weak bases

- At neutral pH, weak acids and weak bases are predominantly in their charged forms (A^- and BH^+).

- The charged species do not permeate across the membrane's hydrophobic barrier.

- The charged species are in equilibrium with uncharged species that will permeate the membrane.

- The uncharged species (B) will reach the equilibrium ($B_o = B_i$).



For a weak base

$$B + H^+ \leftrightarrow BH^+$$

Henderson - Hassalbach theory of dissociation

$$\boxed{\log\frac{[\mathrm{B}]}{[BH^+]} = pH - pK_a}$$

where, [BH⁺] = molar concentration of the salt of the base [B] = molar concentration of the weak base.

Unprotonated species are in equilibrium with the protonated form:

$$K = \frac{[B]_0[H^+]_o}{[BH^+]_o} = \frac{[B]_i[H^+]_i}{[BH^+]_i}$$

Since $[\mathrm{B}]_o = [\mathrm{B}]_i$

$$\frac{[BH^+]_i}{[BH^+]_o} = \frac{[H^+]_i}{[H^+]_o}$$

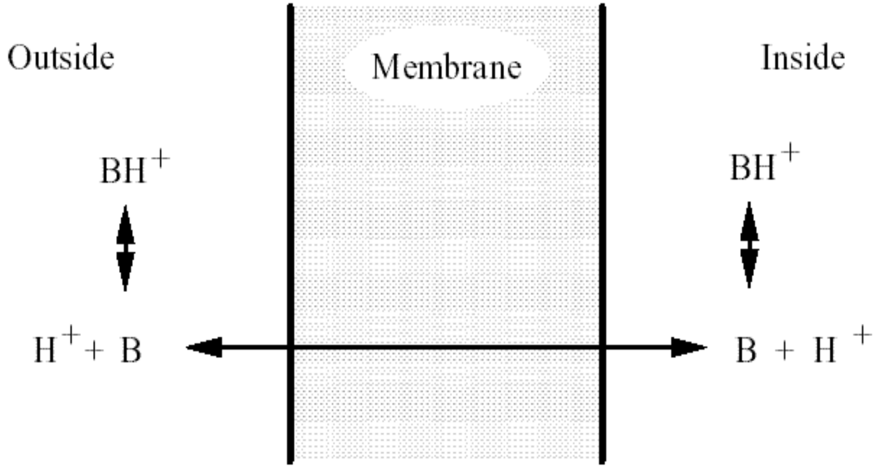
For a weak acid.

$$A^- + H^+ \leftrightarrow A$$

$$\boxed{\log\frac{[\mathrm{A}^-]}{[HA]} = pH - pKa}$$

where, [A⁻] = molar concentration of the salt of the acid [HA] = molar concentration of the weak acid.

$$\frac{[A^-]_i}{[A^-]_o} = \frac{[H^+]_o}{[H^+]_i}$$



Example

What will the % ionization be for a weak acidic drug with a pKa of 3.0;

(a) ***in the stomach which has a pH of 2.25?***
(b) ***in the blood which has a pH of 7.4?***

Percentage of drug ionized in trhe stomach

$$\log \frac{[A^-]}{[HA]} = 2.25 - 3 = -0.75$$

$$\frac{[A^-]}{[HA]} = \frac{0.1778}{1}$$

$$[A^-] = \frac{0.1778}{1 + 0.1778} x \frac{100}{1} = 15.09\%$$

Percentage of drug ioznized in the blood

$$\log \frac{[A^-]}{[HA]} = 7.4 - 3 = 4.4$$

$$\frac{[A^-]}{[HA]} = \frac{25119}{1}$$

$$[A^-] = \frac{25119}{1 + 25119} x \frac{100}{1} = 99.996\%$$