BME 5742 Biosystems Modeling and Control

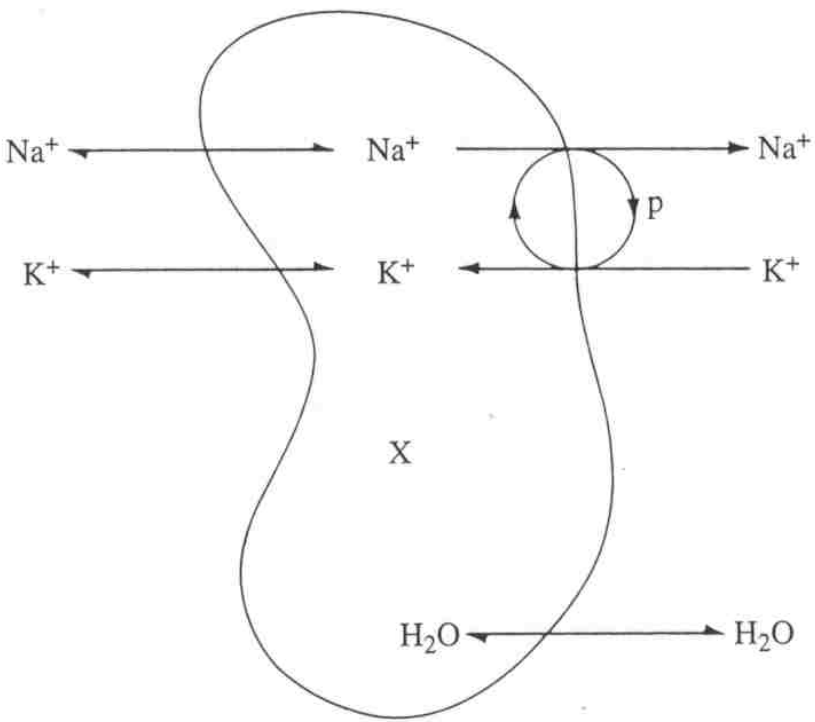
Lecture 33

Ion Movement across Cell Membrane
Interaction of Electrical and Osmosis Effects

Recall: Cell Volume Control – Osmosis and Pump Effects Only

Fluxes ←→ f

Passive permeabilities←→α



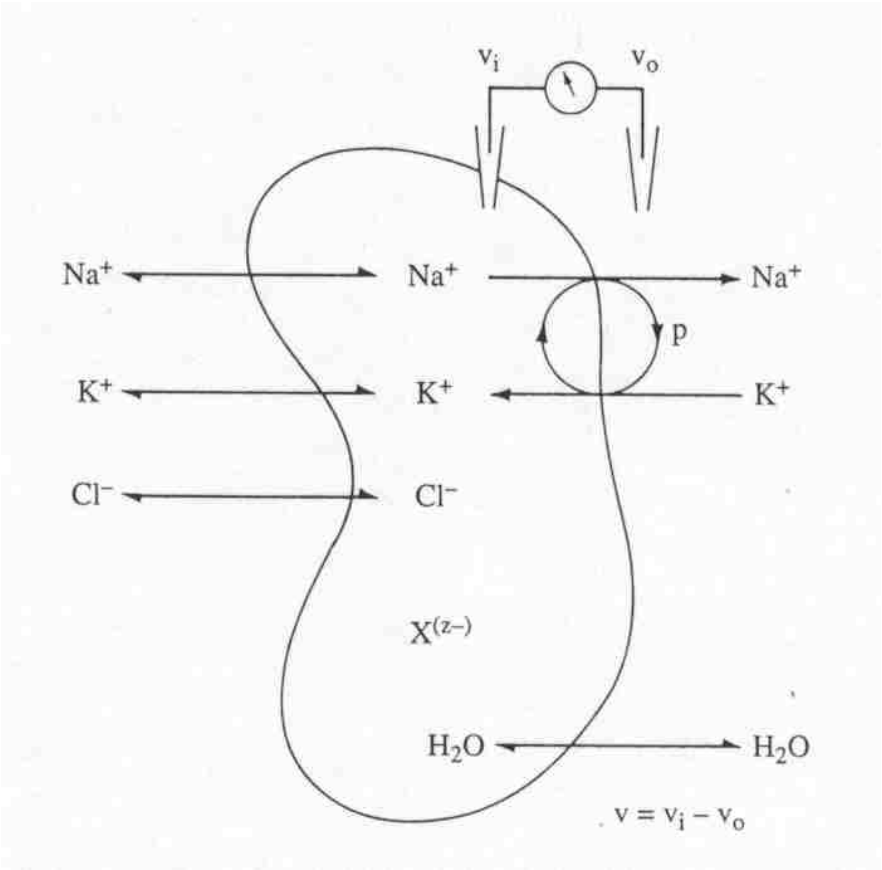
$$f_{Na} = \alpha_{Na}([Na^+]_i - [Na^+]_o) + p$$

$$f_K = \alpha_K([K^+]_i - [K^+]_o) - p$$

$$R_{H_2O}Q = -KT([Na^+]_i + [K^+]_i + \frac{X}{V} - [Na^+]_o - [K^+]_o)$$

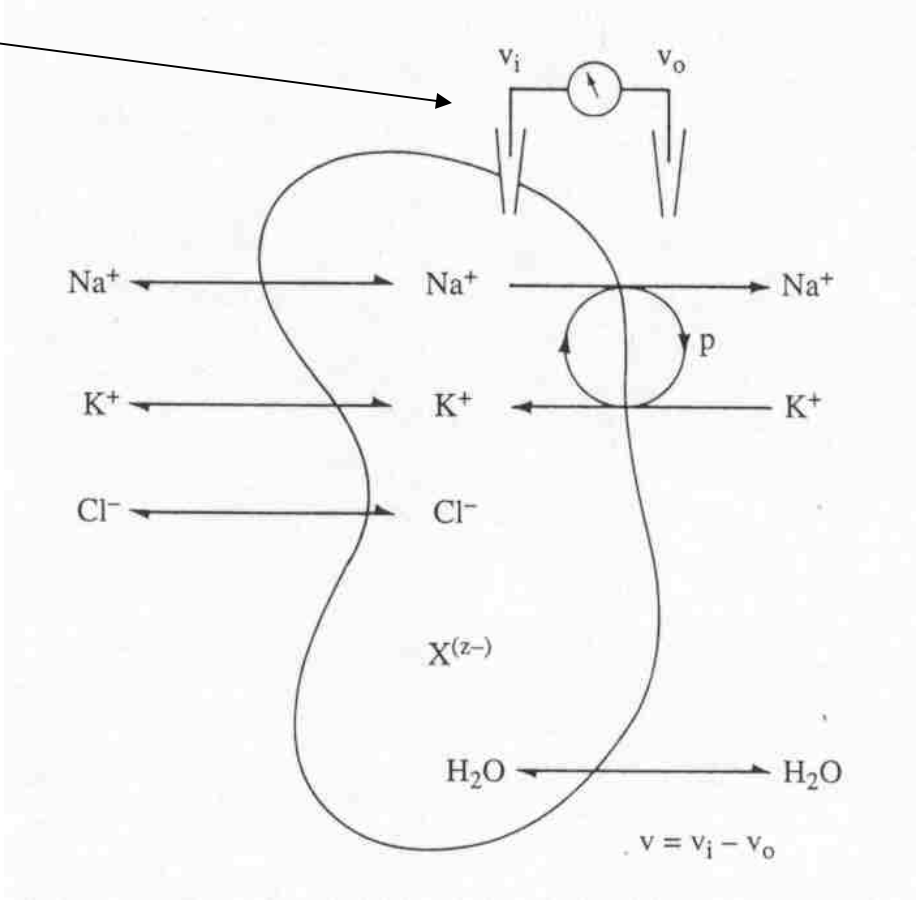
Model Extension

- Need to add the electrical effects.
- That's why it's necessary to account for Cl^- ions and for the negative charges associated with the large macro-molecules X^{z-}



Membrane Voltage and Ionic Currents Sign Convention

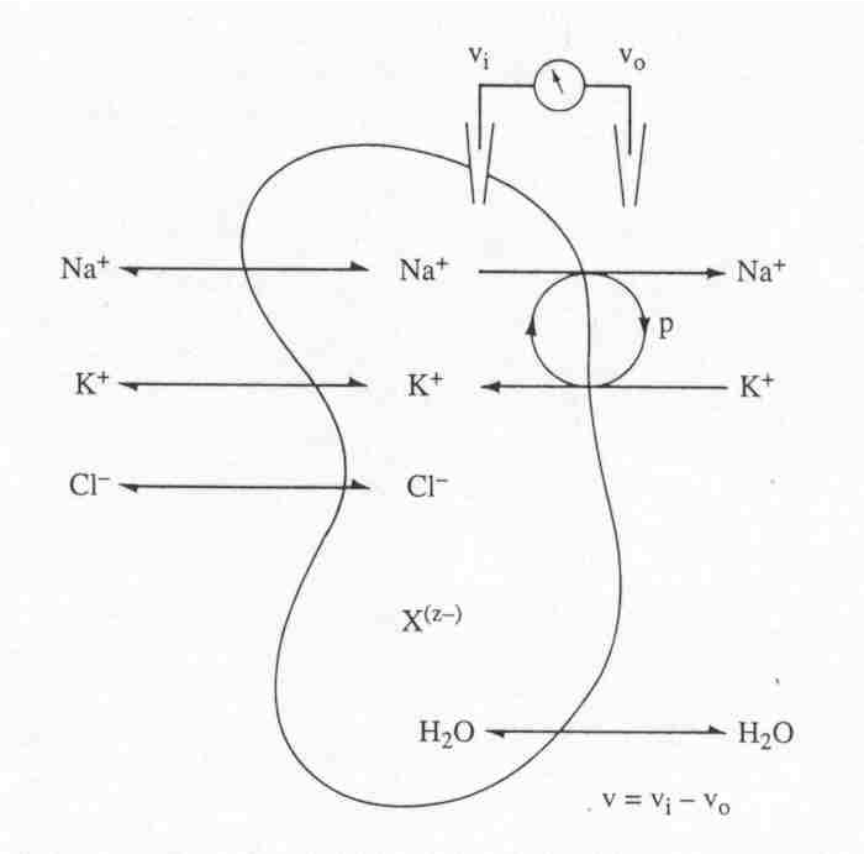
- Cell membrane voltage $v = v_i - v_o$ is considered unknown.
- For each ionic current, positive direction is defined as outwards.



Ionic Currents

Recall:

$$E_S = v_i - v_o = \frac{KT}{zq}\ln\left(\frac{[S]_o}{[S]_i}\right)$$



S Ion Current = (membrane S conductance) x (v – E_S) + S-pump current

S is either Na^+, K^+ or Cl^-. For Cl^- though there is no pumping

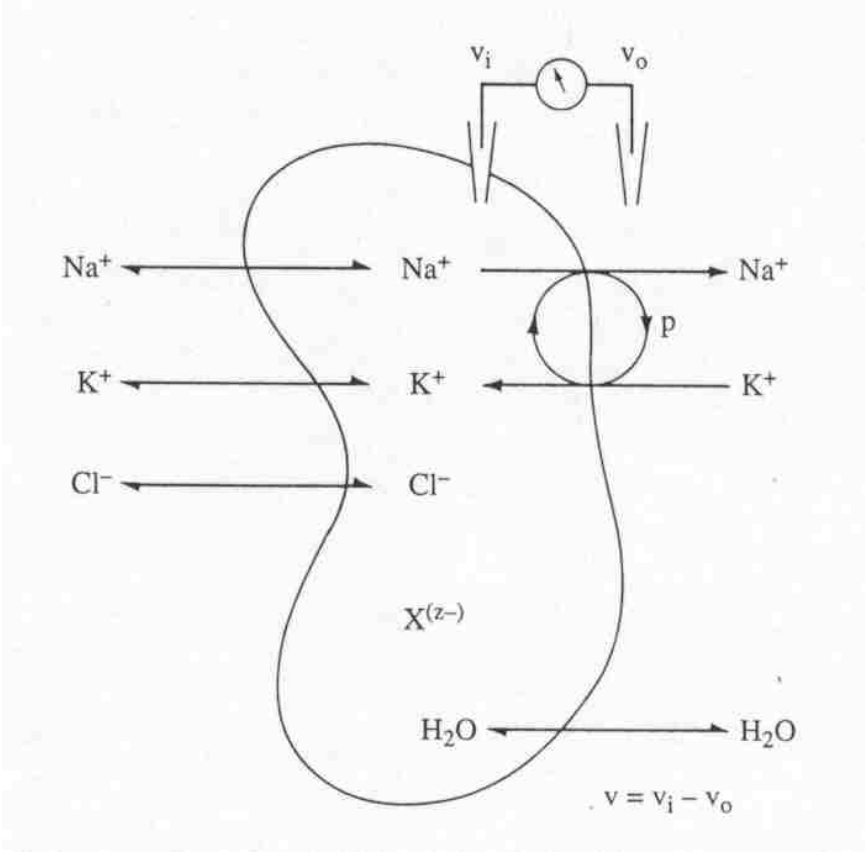
Sodium Ionic Current

$$E_S = v_i - v_o = \frac{KT}{zq}\ln(\frac{[S]_o}{[S]_i}) \Rightarrow$$

$$\Rightarrow I_{Na} = g_{Na}(v - E_{Na}) + pq =$$

$$= g_{Na}(v - \frac{KT}{q}\ln(\frac{[Na^+]_o}{[Na^+]_i})) + pq$$

Since $[Na^+]_o >> [Na^+]_i$ the potential $E_{Na} > 0$. As an approximation, we neglect the 3:2 pumping ratio, replacing it with 1:1.



Pump Na current is positive (outwards) = +pq

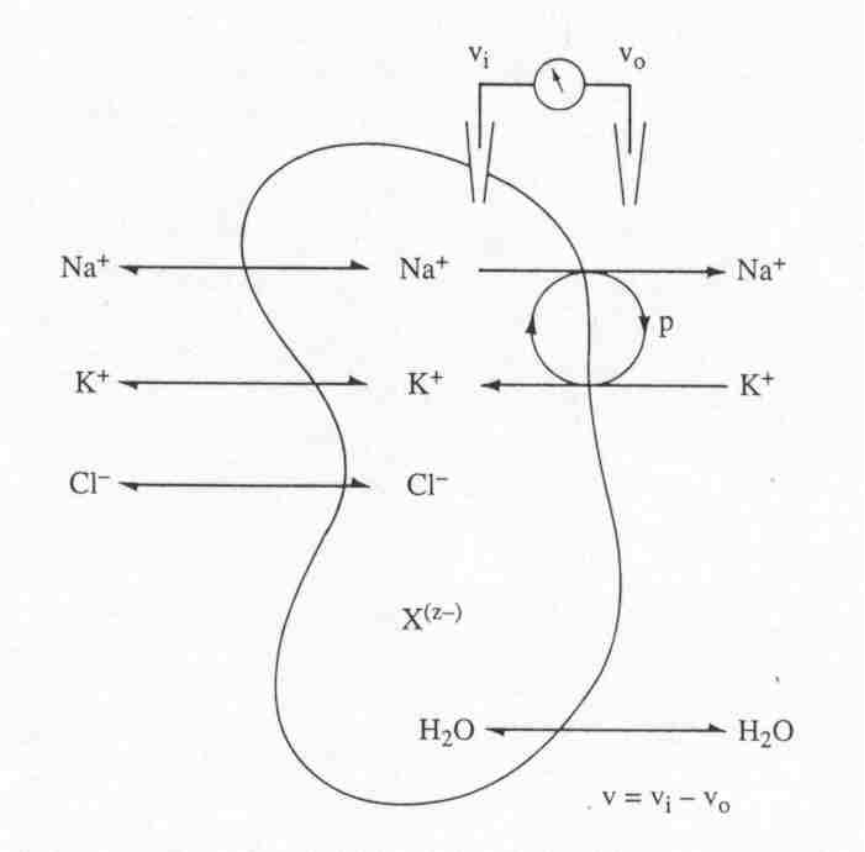
Potassium Ionic Current

$$E_S = v_i - v_o = \frac{KT}{zq}\ln\left(\frac{[S]_o}{[S]_i}\right) \Rightarrow$$

$$\Rightarrow I_K = g_K(v - E_K) - pq =$$

$$= g_K\left(v - \frac{KT}{q}\ln\left(\frac{[K^+]_o}{[K^+]_i}\right)\right) - pq$$

Since $[K^+]_o << [K^+]_i$ the potential $E_K < 0$. As an approximation, we neglect the 3:2 pumping ratio, replacing it with 1:1.



Pump K current is negative (inwards) = -pq

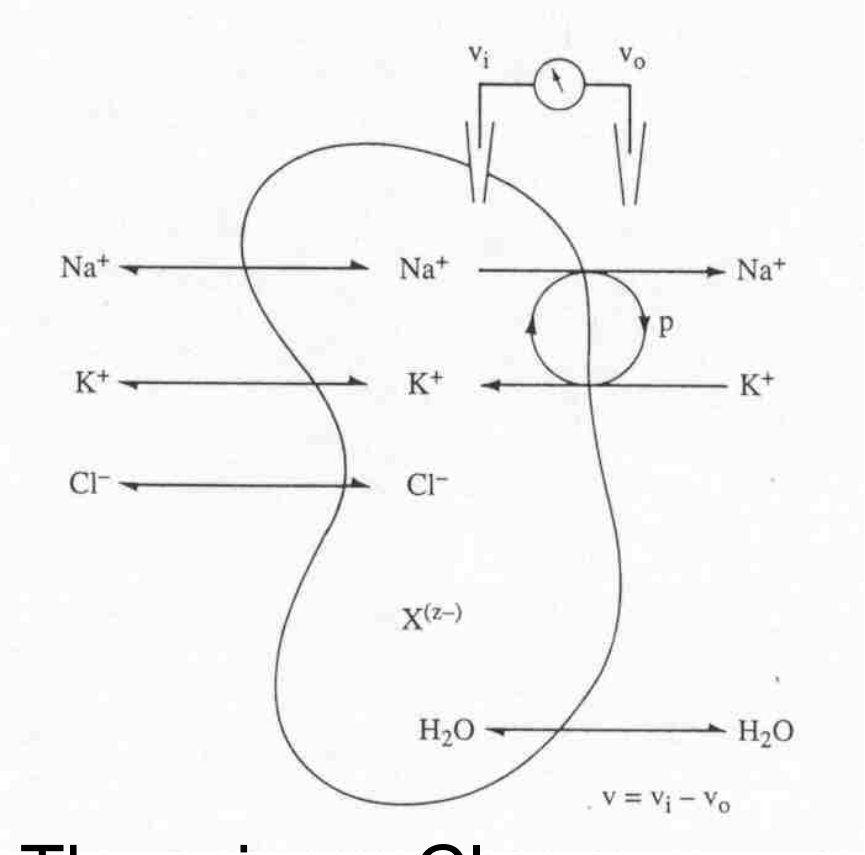
Chloride Ionic Current

$$E_S = v_i - v_o = \frac{KT}{zq}\ln\left(\frac{[S]_o}{[S]_i}\right) \Rightarrow$$

$$\Rightarrow I_{Cl} = g_{Cl}(v + E_{Cl}) =$$

$$= g_{Cl}\left(v + \frac{KT}{q}\ln\left(\frac{[Cl^-]_o}{[Cl^-]_i}\right)\right)$$

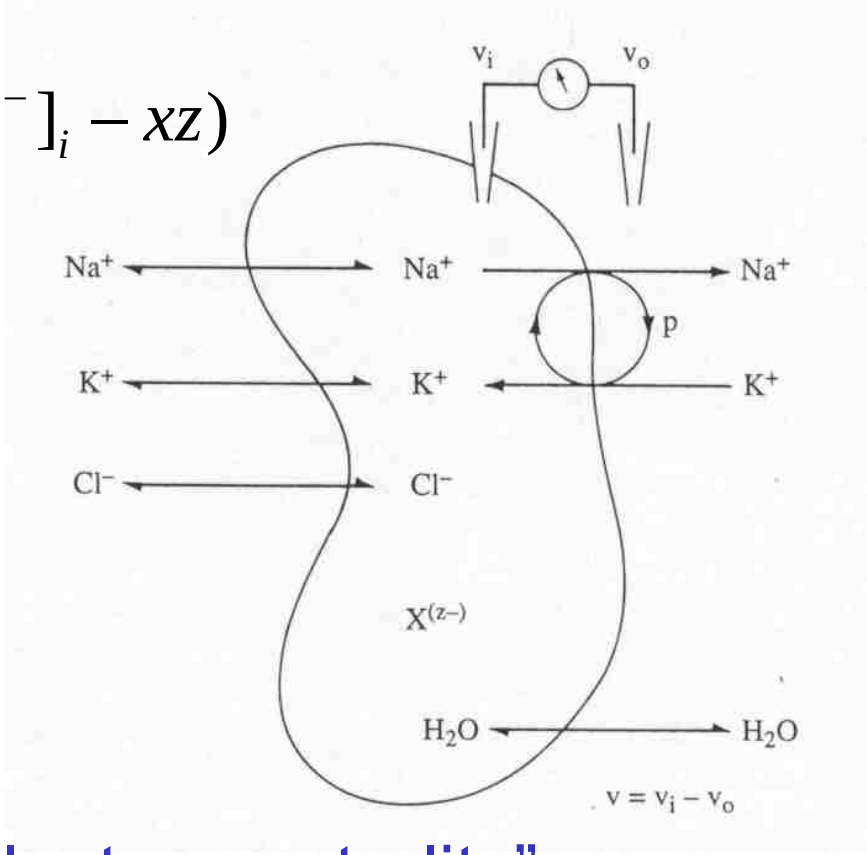
Since $[Cl^-]_o >> [Cl^-]_i$ the potential $E_{Cl} < 0$, because z= -1. This potential is opposite to the Na^+ and K^+ potentials



There is no Cl^- pump. Current is opposite to actual flow of (-) charge

Cell Membrane Capacitance

$$Cv = q(V[Na^+]_i + V[K^+]_i - V[Cl^-]_i - xz)$$



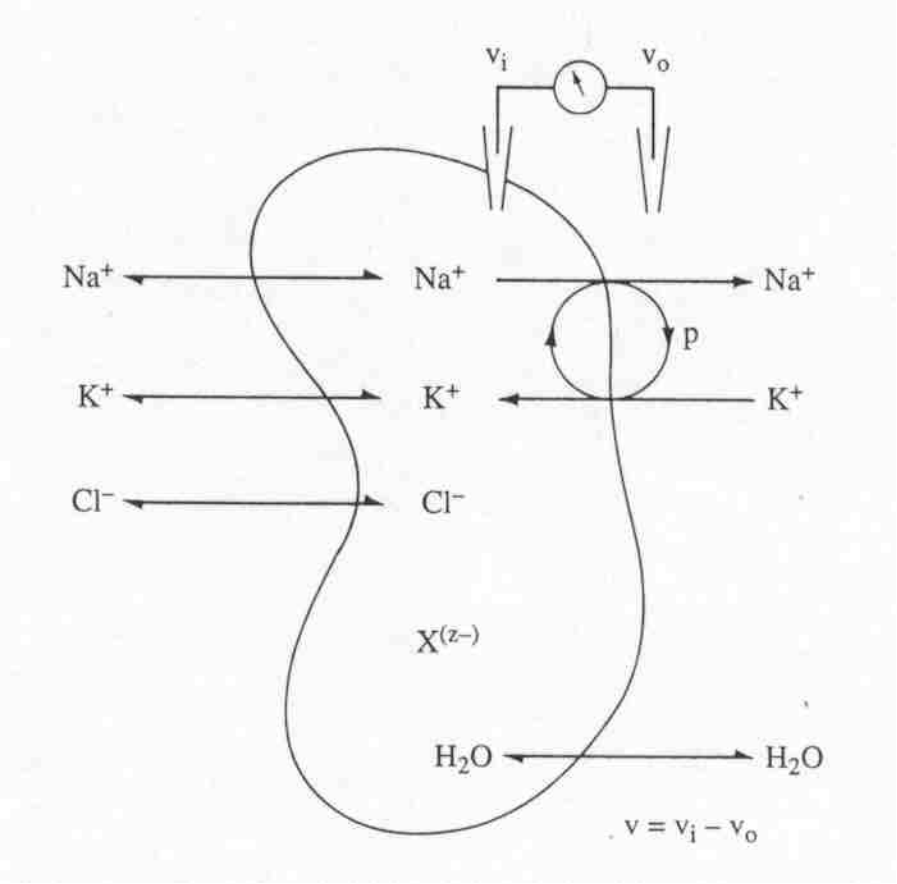
Much of the charge is either outside or inside the cell. Only very little charge accumulates at the membrane itself. We denote the equivalent ion voltage to each ion's excess charge by v.

"Electro-neutrality" assumption is to take C→0.

Water Osmotic Flux

Osmotic water positive direction is defined as outwards.

It is assumed that internal and external hydrostatic pressures must be equal.

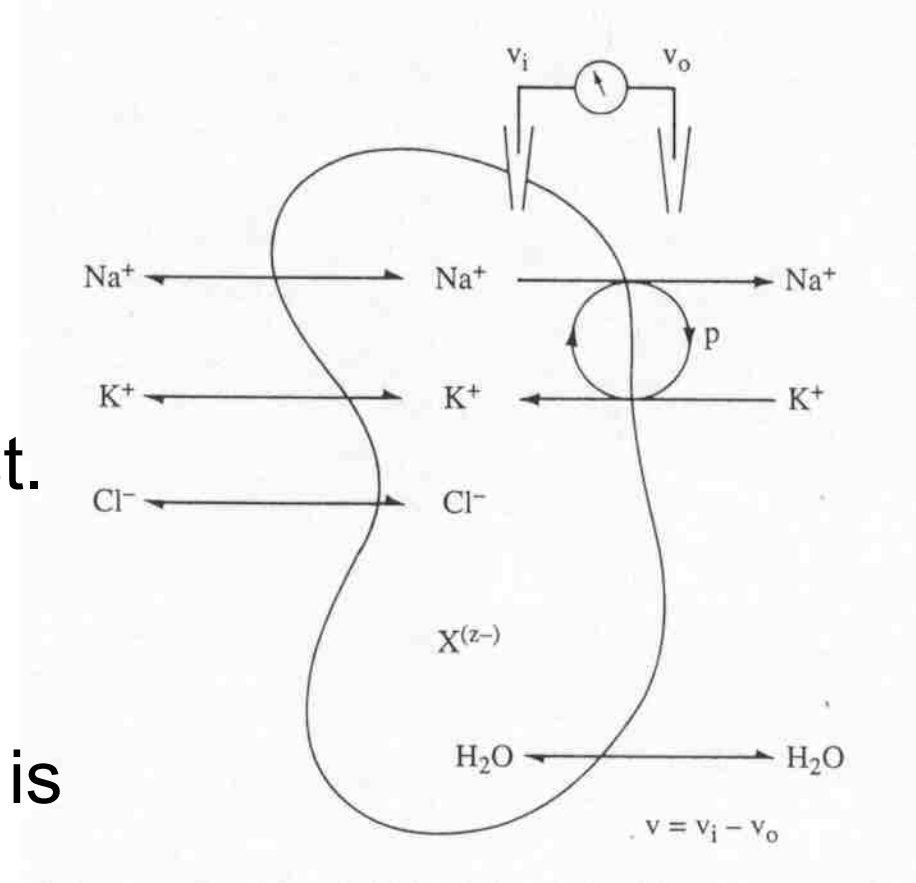


$$R_{H_2O}Q = -KT([Na^+]_i + [K^+]_i + [Cl^-]_i + \frac{x}{V} - [Na^+]_o - [K^+]_o) - [Cl^-]_o)$$

Water Osmotic Flux – Large X^{z-} effect?? -1

Let xz=N, where N is the total number of negative charges trapped in cell. Let z→∞,x→0,xz=N=const.

←→Small number of large molecules but each negative charge is large.

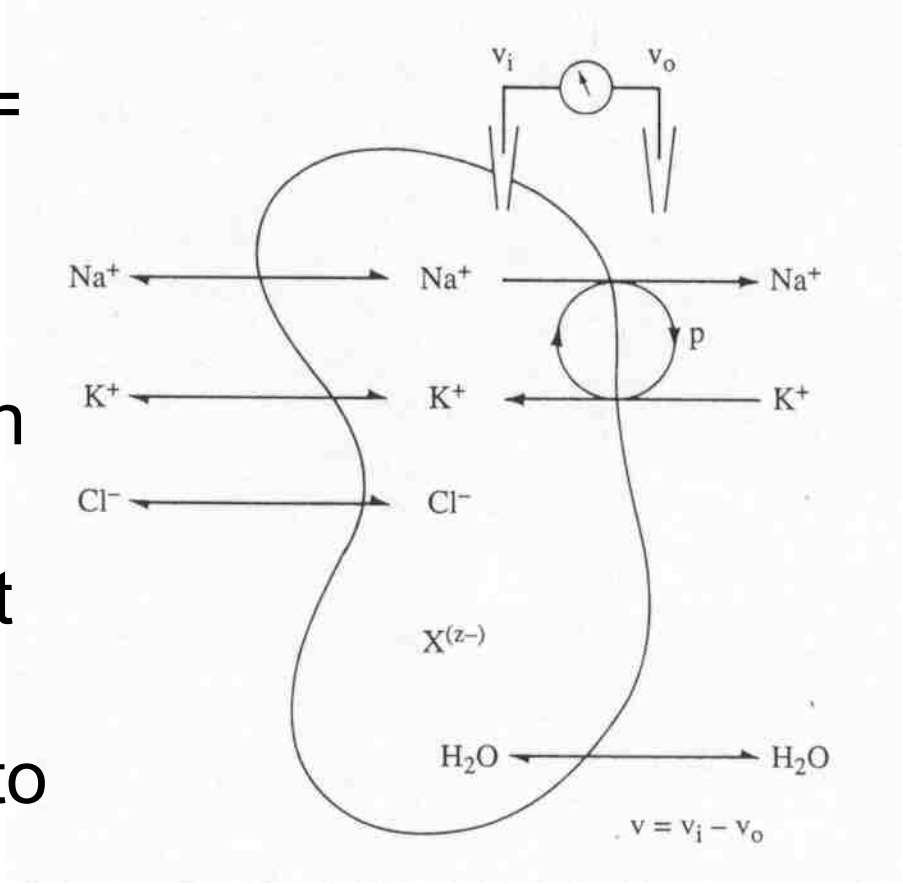


$$R_{H_2O}Q = -KT([Na^+]_i + [K^+]_i + [Cl^-]_i + \frac{x}{V} - [Na^+]_o - [K^+]_o) - [Cl^-]_o)$$

Water Osmotic Flux – Large X^{z-} effect?? -2

Let z → ∞ , x → 0, xz = N = const.

←→ That's why X^{z-} is typically not included in water osmotic flux (since x is small), but it influences the excess charge equation (due to -xz).



$$R_{H_2O}Q = -KT([Na^+]_i + [K^+]_i + [Cl^-]_i + \frac{x}{V} - [Na^+]_o - [K^+]_o) - [Cl^-]_o)$$

Steady-State Relationships and Approximations

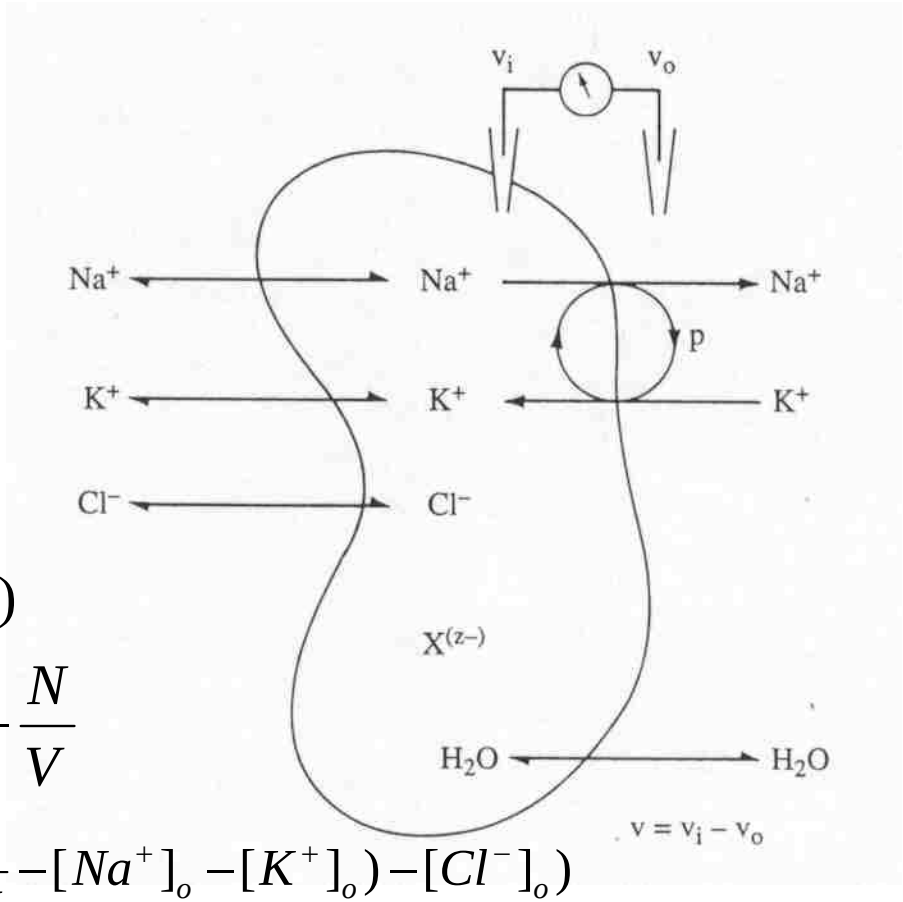
$$0 = I_{Na} = g_{Na}(v - \frac{KT}{q}\ln(\frac{[Na^+]_o}{[Na^+]_i})) + pq$$

$$0 = I_K = g_K(v - \frac{KT}{q}\ln(\frac{[K^+]_o}{[K^+]_i})) - pq$$

$$0 = I_{Cl} = g_{Cl}(v + \frac{KT}{q}\ln(\frac{[Cl^-]_o}{[Cl^-]_i}))$$

$$Cv = q(V[Na^+]_i + V[K^+]_i - V[Cl^-]_i - xz)$$

$$\Leftrightarrow C = 0 \Rightarrow 0 = [Na^+]_i + [K^+]_i - [Cl^-]_i - \frac{N}{V}$$



$$R_{H_2O}Q = -KT([Na^+]_i + [K^+]_i + [Cl^-]_i + \frac{x}{V} - [Na^+]_o - [K^+]_o) - [Cl^-]_o)$$

$$\Leftrightarrow R_{H_2O}Q = 0, x \to 0 \Rightarrow$$

$$0 = [Na^+]_i + [K^+]_i + [Cl^-]_i - [Na^+]_o - [K^+]_o) - [Cl^-]_o$$

Steady-State Equations

- Five equations with 5 unknowns – $[Na^+]_i$, $[K^+]_i$, $[Cl^-]_i$, v and V.
- ECF concentrations are assumed known.
- ECF is assumed electrically neutral:
- $[Na^+]_o+[K^+]_o=[Cl^-]_o$

$$0 = g_K(v - \frac{KT}{q}\ln(\frac{[K^+]_o}{[K^+]_i})) - pq$$

$$0 = g_{Cl}(v + \frac{KT}{q}\ln(\frac{[Cl^-]_o}{[Cl^-]_i}))$$

$$0 = g_{Na}(v - \frac{KT}{q}\ln(\frac{[Na^+]_o}{[Na^+]_i})) + pq$$

$$0 = [Na^+]_i + [K^+]_i - [Cl^-]_i - \frac{N}{V}$$

$$0 = [Na^+]_i + [K^+]_i + [Cl^-]_i - [Na^+]_o - [K^+]_o) - [Cl^-]_o$$

Steady-State Equations – Solution Approach

- <u>Step 1:</u> From first three equations, express ICF concentrations as functions of v.
- <u>Step 2:</u> Substitute into the last two equations, and solve for v and V.

$$0 = g_K (v - \frac{KT}{q} \ln(\frac{[K^+]_o}{[K^+]_i})) - pq$$

$$0 = g_{Cl} (v + \frac{KT}{q} \ln(\frac{[Cl^-]_o}{[Cl^-]_i}))$$

$$0 = g_{Na} (v - \frac{KT}{q} \ln(\frac{[Na^+]_o}{[Na^+]_i})) + pq$$

$$0 = [Na^+]_i + [K^+]_i - [Cl^-]_i - \frac{N}{V}$$

$$0 = [Na^+]_i + [K^+]_i + [Cl^-]_i - [Na^+]_o - [K^+]_o) - [Cl^-]_o$$

Steady-State Equations – ICF Concentration Expressions

$$0 = g_{Na}(v - \frac{KT}{q}\ln(\frac{[Na^+]_o}{[Na^+]_i})) + pq \Rightarrow \frac{[Na^+]_i}{[Na^+]_o} = e^{-\frac{qv}{KT} - \frac{pq^2}{g_{Na}KT}}$$

$$0 = g_K(v - \frac{KT}{q}\ln(\frac{[K^+]_o}{[K^+]_i})) - pq \Rightarrow \frac{[K^+]_i}{[K^+]_o} = e^{-\frac{qv}{KT} + \frac{pq^2}{g_K KT}}$$

$$0 = g_{Cl}(v + \frac{KT}{q}\ln(\frac{[Cl^-]_o}{[Cl^-]_i})) \Rightarrow \frac{[Cl^-]_i}{[Cl^-]_o} = e^{\frac{qv}{KT}}$$

Steady-State Equations – ICF Concentration Expressions with Simplified Notation

$$\frac{[Cl^-]_i}{[Cl^-]_o} = e^{\frac{qv}{KT}} = \gamma \qquad \beta_{Na} = e^{-\frac{pq^2}{g_{Na}KT}} \qquad \beta_K = e^{\frac{pq^2}{g_K KT}}$$

$$\frac{[Na^+]_i}{[Na^+]_o} = e^{-\frac{qv}{KT} - \frac{pq^2}{g_{Na}KT}} \Rightarrow [Na^+]_i = \frac{\beta_{Na}[Na^+]_o}{\gamma}$$

$$\frac{[K^+]_i}{[K^+]_o} = e^{-\frac{qv}{KT} + \frac{pq^2}{g_K KT}} \Rightarrow [K^+]_i = \frac{\beta_K[K^+]_o}{\gamma}$$

$$[Cl^-]_i = \gamma[Cl^-]_o$$

Steady-State Equations – Capacitance and Water Osmosis Equations

Substitute:

$$[Cl^-]_i = \gamma[Cl^-]_o = \gamma([Na^+]_o + [K^+]_o)$$

$$[Na^+]_i = \frac{\beta_{Na}[Na^+]_o}{\gamma} \quad [K^+]_i = \frac{\beta_K[K^+]_o}{\gamma}$$

Into:

$$0 = [Na^+]_i + [K^+]_i - [Cl^-]_i - \frac{N}{V} \Rightarrow$$

$$\Rightarrow \frac{\beta_{Na}[Na^+]_o}{\gamma} + \frac{\beta_K[K^+]_o}{\gamma} = \gamma([Na^+]_o + [K^+]_o) + \frac{N}{V}$$

$$0 = [Na^+]_i + [K^+]_i + [Cl^-]_i - [Na^+]_o - [K^+]_o) - [Cl^-]_o \Rightarrow$$

$$\Rightarrow \frac{\beta_{Na}[Na^+]_o}{\gamma} + \frac{\beta_K[K^+]_o}{\gamma} + (\gamma - 2)([Na^+]_o + [K^+]_o) = 0$$

Steady-State Equations – Capacitance and Water Osmosis Equations (Simplified)

$$\frac{\beta_{Na}[Na^+]_o}{\gamma} + \frac{\beta_K[K^+]_o}{\gamma} = \gamma([Na^+]_o + [K^+]_o) + \frac{N}{V}$$

$$\frac{\beta_{Na}[Na^+]_o}{\gamma} + \frac{\beta_K[K^+]_o}{\gamma} + (\gamma - 2)([Na^+]_o + [K^+]_o) = 0$$

$$\beta = \frac{\beta_{Na}[Na^+]_o + \beta_K[K^+]_o}{[Na^+]_o + [K^+]_o}$$

$$b = \frac{N}{2V([Na^+]_o + [K^+]_o)}$$

$$\boxed{\begin{aligned} &\frac{\beta}{2\gamma} - \frac{\gamma}{2} - b = 0 \\ &\frac{\beta}{2\gamma} + \frac{\gamma}{2} - 1 = 0 \end{aligned}}$$

Recall variables physical meaning:

$$\beta = \frac{\beta_{Na}[Na^+]_o + \beta_K[K^+]_o}{[Na^+]_o + [K^+]_o}$$

It represents p, conductances and ECF concentrations

$$b = \frac{N}{2V([Na^+]_o + [K^+]_o)}$$

Volume is represented by b

$$e^{\frac{qv}{KT}} = \gamma$$

Voltage is represented by γ

$$\frac{\beta}{2\gamma} - \frac{\gamma}{2} - b = 0$$

$$\frac{\beta}{2\gamma} + \frac{\gamma}{2} - 1 = 0$$

First, let us try to find γ (voltage) in terms of β.

A dead-end solution approach:

$$e^{\frac{qv}{KT}} = \gamma$$

$$\frac{\beta}{2\gamma} + \frac{\gamma}{2} - 1 = 0 \Rightarrow \gamma^2 - 2\gamma + \beta = 0 \Rightarrow$$

$$\Rightarrow \gamma = 1 \pm \sqrt{1-\beta}$$

At this point, it's unclear which of the two solutions is correct

Alternate Steady-State Membrane Voltage and Cell Volume Solution Approach

$$\beta = \frac{\beta_{Na}[Na^+]_o + \beta_K[K^+]_o}{[Na^+]_o + [K^+]_o}$$

It represents p, conductances and ECF concentrations

$$b = \frac{N}{2V([Na^+]_o + [K^+]_o)}$$

Volume is represented by b

$$e^{\frac{qv}{KT}} = \gamma$$

Voltage is represented by γ

$$\frac{\beta}{2\gamma} - \frac{\gamma}{2} - b = 0$$

$$\frac{\beta}{2\gamma} + \frac{\gamma}{2} - 1 = 0$$

Next, let us find γ (voltage) in terms of b (volume).

Unique voltage solution (dependent on volume)

$$e^{\frac{qv}{KT}} = \gamma$$

$$\frac{\beta}{2\gamma} - \frac{\gamma}{2} - b = 0 \Rightarrow \gamma^2 + 2b\gamma - \beta = 0 \Rightarrow$$

$$\Rightarrow \gamma = -b \pm \sqrt{b^2 + \beta} \Rightarrow \gamma = -b + \sqrt{b^2 + \beta}$$

The variable $b=N/(2[Cl^-]_oV)$ is positive. Now, it is obvious which of the two solutions here is to be adopted, as γ must not be negative.

Unique volume solution

$$\gamma = -b + \sqrt{b^2 + \beta} \Leftrightarrow \frac{1}{\gamma} = \frac{b + \sqrt{b^2 + \beta}}{\beta}$$

$$\frac{\beta}{2\gamma} + \frac{\gamma}{2} - 1 = 0 \Rightarrow \sqrt{b^2 + \beta} = 1 \Rightarrow$$

$$\Rightarrow b = \sqrt{1 - \beta}$$

From the osmotic balance equation we get the solution for b, which leads to the volume formula

Steady-State Cell Volume Solution

$$\beta = \frac{\beta_{Na}[Na^+]_o + \beta_K[K^+]_o}{[Na^+]_o + [K^+]_o}$$

$$b = \frac{N}{2V([Na^+]_o + [K^+]_o)} = \frac{N}{2V[Cl^-]_o}$$

$$b = \sqrt{1-\beta}$$

$$\boxed{V = \frac{N}{2[Cl^-]_o\sqrt{1-\beta}}}$$

Cell Volume Solution

It is necessary that β<1, or cell swells until it bursts

Properties of β

$$\beta = \frac{\beta_{Na}[Na^+]_o + \beta_K[K^+]_o}{[Na^+]_o + [K^+]_o} = \frac{[Na^+]_o e^{-\frac{pq^2}{g_{Na}KT}} + [K^+]_o e^{\frac{pq^2}{g_K KT}}}{[Na^+]_o + [K^+]_o}$$

- We see that as function of the pump rate p β(0)=1 and β(∞)=∞.
- Because we must have β<1, it's important that dβ/dp< 0 at p=0. Then there exist a range of pump rates p, for which cell volume can be controlled.

More properties of β

$$\beta = \frac{\beta_{Na}[Na^+]_o + \beta_K[K^+]_o}{[Na^+]_o + [K^+]_o} = \frac{[Na^+]_o e^{-\frac{pq^2}{g_{Na}KT}} + [K^+]_o e^{\frac{pq^2}{g_K KT}}}{[Na^+]_o + [K^+]_o}$$

$$\frac{d\beta}{dp} = a\left(-\frac{[Na^+]_o \beta_{Na}}{g_{Na}} + \frac{[K^+]_o \beta_K}{g_K}\right) \Rightarrow$$

$$\Rightarrow \frac{d\beta}{dp}(0) = a\left(-\frac{[Na^+]_o}{g_{Na}} + \frac{[K^+]_o}{g_K}\right)$$

The constant a is independent of p.

Finite Cell Volume Condition

$$\beta = \frac{\beta_{Na}[Na^+]_o + \beta_K[K^+]_o}{[Na^+]_o + [K^+]_o} = \frac{[Na^+]_o e^{-\frac{pq^2}{g_{Na}KT}} + [K^+]_o e^{\frac{pq^2}{g_K KT}}}{[Na^+]_o + [K^+]_o} < 1$$

$$\frac{d\beta}{dp}(0) = a\left(-\frac{[Na^+]_o}{g_{Na}} + \frac{[K^+]_o}{g_K}\right) < 0 \Rightarrow$$

$$\Rightarrow \boxed{\frac{[Na^+]_o}{g_{Na}} > \frac{[K^+]_o}{g_K}}$$

Necessary condition for controlled cell volume. If condition is not satisfied, then β>1 for all p.

Optimum Pumping Rate

$$\beta = \frac{\beta_{Na}[Na^+]_o + \beta_K[K^+]_o}{[Na^+]_o + [K^+]_o} = \frac{[Na^+]_o e^{-\frac{pq^2}{g_{Na}KT}} + [K^+]_o e^{\frac{pq^2}{g_K KT}}}{[Na^+]_o + [K^+]_o} < 1$$

$$\frac{[Na^+]_o}{g_{Na}} > \frac{[K^+]_o}{g_K}$$

$$\frac{d\beta}{dp} = 0 \Rightarrow \beta = \beta_{\min} \Leftrightarrow p_{opt} = \frac{\frac{KT}{q^2} g_{Na} g_K}{g_{Na} + g_K} \ln\left(\frac{[Na^+]_o g_K}{[K^+]_o g_{Na}}\right)$$

For $\beta=\beta_{min}$ we have $V=V_{min}$. It turns out that sensitivity of V to p is low when p is near p_{opt}.

Cell Volume Dependencies

$$\beta = \frac{\beta_{Na}[Na^+]_o + \beta_K[K^+]_o}{[Na^+]_o + [K^+]_o} \qquad V = \frac{N}{2[Cl^-]_o\sqrt{1-\beta}}$$

- If p is constant, then V depends on N (the number of trapped negative charges)
- Recall: $2[Cl^-]_o=[Cl^-]_o+[Na^+]_o+[K^+]_o$. This is the total ECF ions concentration. If it becomes smaller, then V increases.
- The constant β depends on $[Na^+]_o/[K^+]_o$. If ratio reduces, V increases.

Membrane Voltage Unique Solution

$$\gamma = -b + \sqrt{b^2 + \beta} \qquad b = \sqrt{1-\beta}$$

$$\Rightarrow \gamma = 1 - \sqrt{1-\beta}$$

Now we know what the correct sign is.

From here we can write the membrane voltage→

Membrane Voltage Solution

$$\gamma = 1 - \sqrt{1-\beta}$$

$$\Rightarrow v = \frac{KT}{q}\ln\gamma = \frac{KT}{q}\ln(1-\sqrt{1-\beta})$$

- Because γ<1 we have that v< 0!
- The negative animal cell membrane potential is a by-product of the mechanism that regulates cell volume.