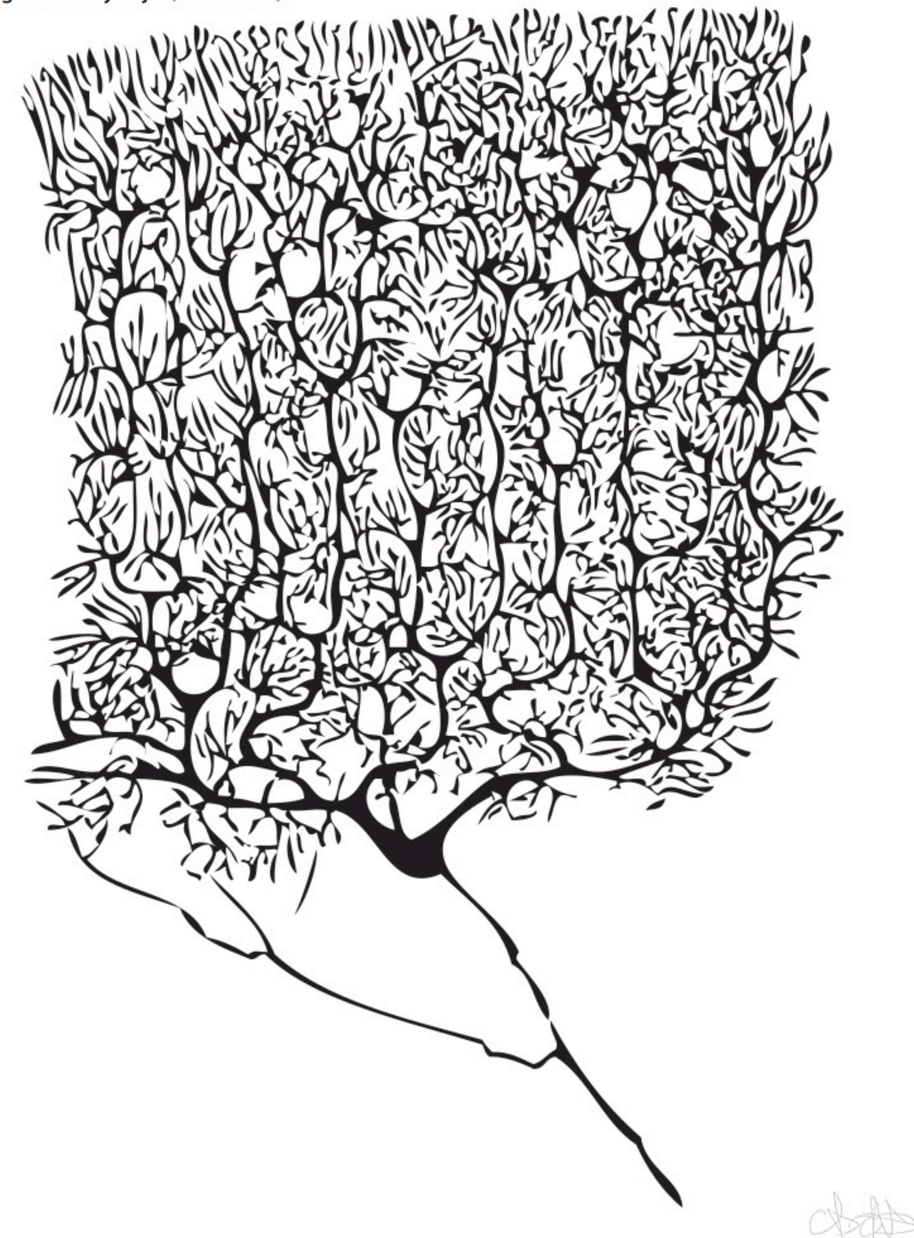
Cellular Electrodynamics

Santiago Ramón y Cajal (1852-1934)



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York University

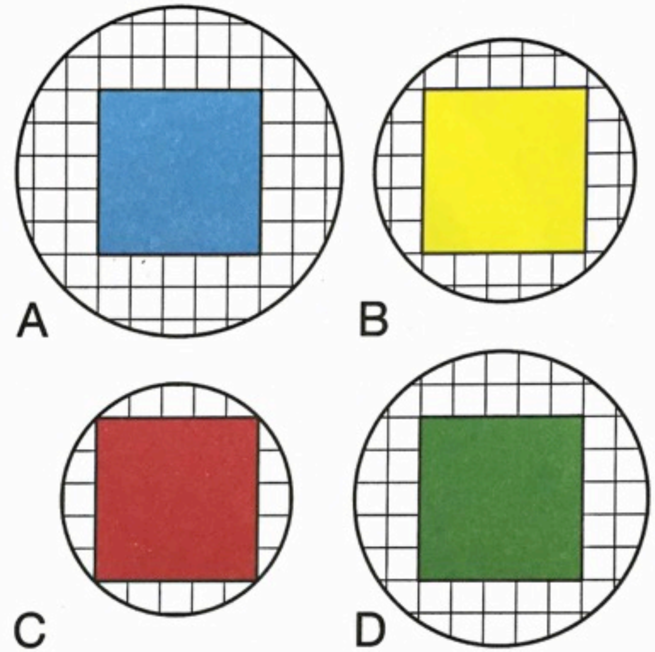
Winter 2020

BPHS 4080 Lecture 9

Reference/Acknowledgement:

- TF Weiss (Cellular Biophysics)
- D Freeman

222. Circle the Squares



Which circle's area is closest to twice the area of the square contained within it?

A B C D

Electrical properties of cells

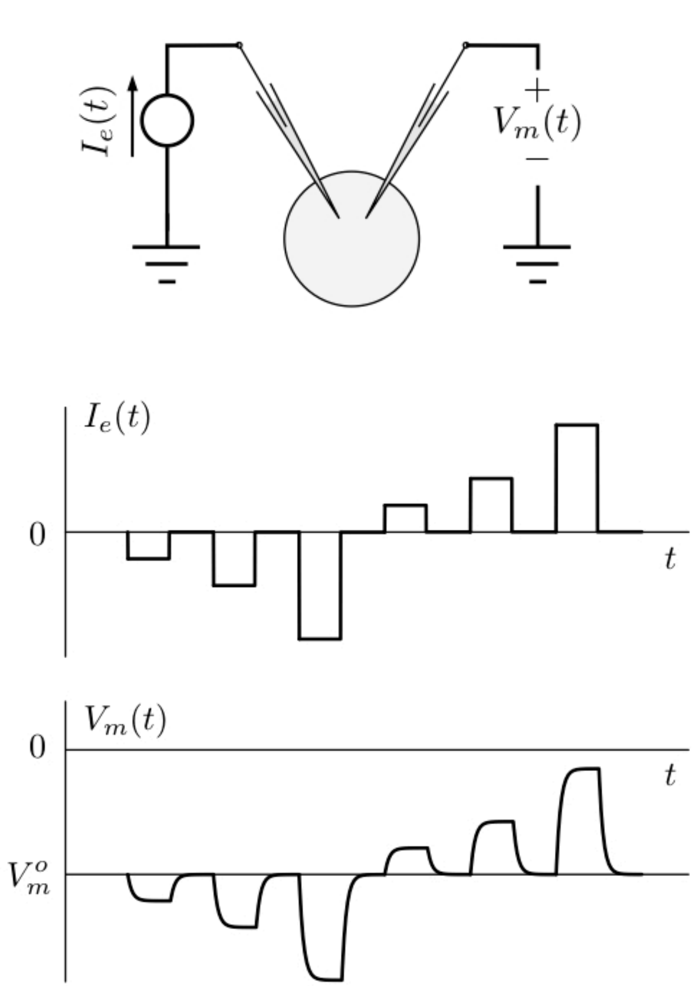


Figure 1.1

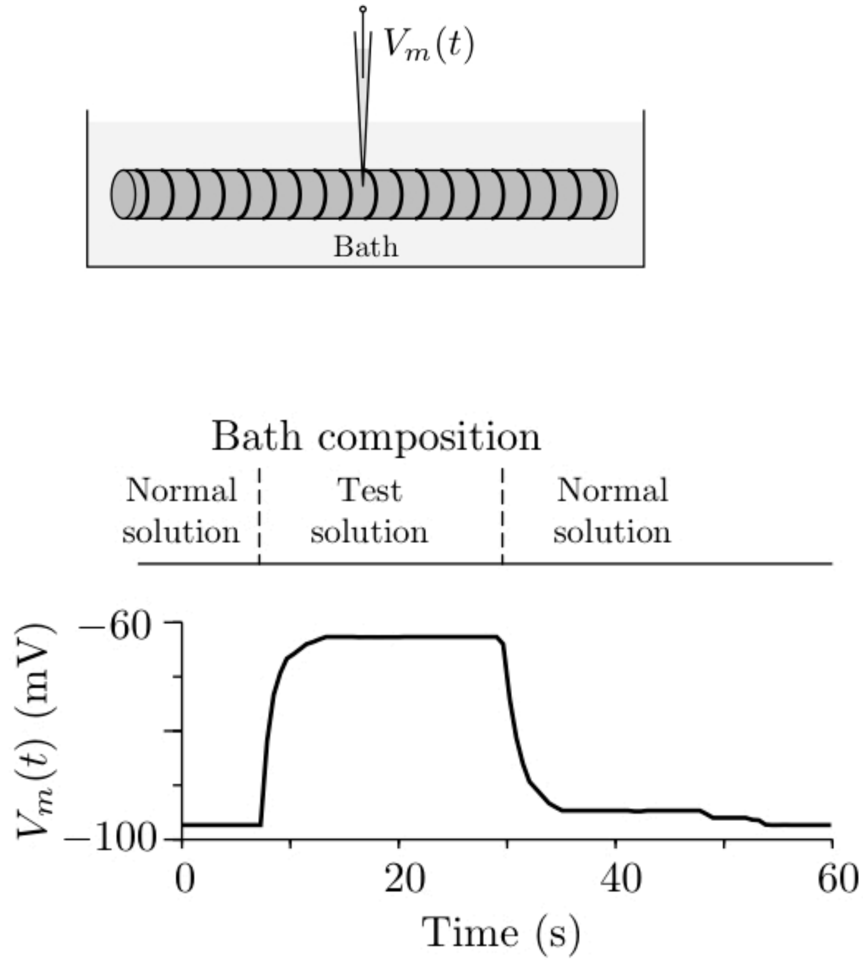
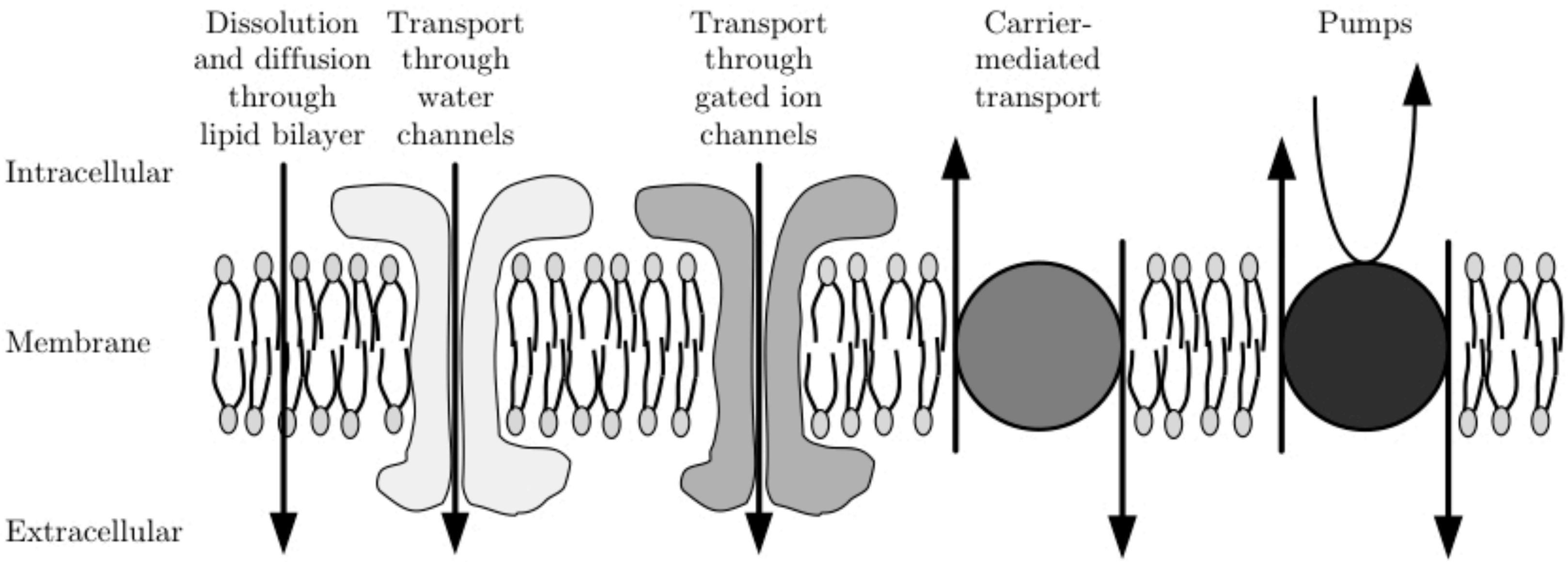


Figure 1.2

Graded potentials (note RC time constant!)

Extracellular solution can have a big effect

Weiss (1996)


Dissolution and diffusion through lipid bilayer
Transport through water channels
Transport through gated ion channels
Carrier-mediated transport
Pumps
Intracellular
Membrane
Extracellular
Figure 2.19

Equations of Electrodiffusion

Nernst-Plank Equation

$$J_n(x,t) = -z_n F D_n \frac{\partial c_n(x,t)}{\partial x} - u_n z_n^2 F^2 c_n(x,t) \frac{\partial \psi(x,t)}{\partial x}$$

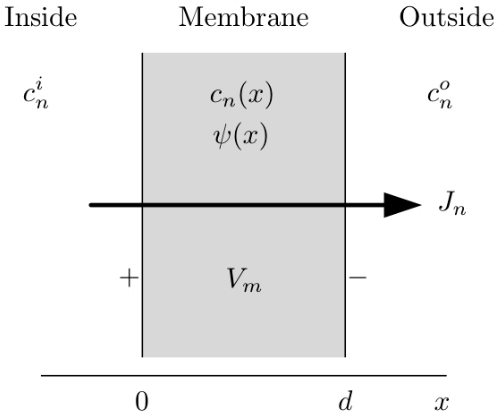
Continuity

$$\frac{\partial J_n(x,t)}{\partial x} = -z_n F \frac{\partial c_n(x,t)}{\partial t}$$

Poisson’s Equation

$$\frac{\partial^2 \psi(x,t)}{\partial x^2} = -\frac{1}{\epsilon} \sum_n z_n F c_n(x,t)$$

Steady-State Electrodiffusion through Membranes



Steady-state

$$\rightarrow \frac{\partial c_n(x,t)}{\partial t} = 0$$

$$\rightarrow \frac{\partial J_n(x,t)}{\partial x} = 0$$

$$\rightarrow J_n = \text{constant}$$

Note: $\ln x = 2.303 \log_{10} x$
& $\log_{10} e = 1/2.303$

$$J_n \frac{1}{G_n} = -\overbrace{\frac{RT}{z_nF} \ln \frac{c_n(d)}{c_n(0)}}^{V_n} + \overbrace{\psi(0) - \psi(d)}^{V_m}$$

$$J_n = G_n(V_m - V_n)$$

→ Like Ohm's law!

Nernst Equilibrium Potential

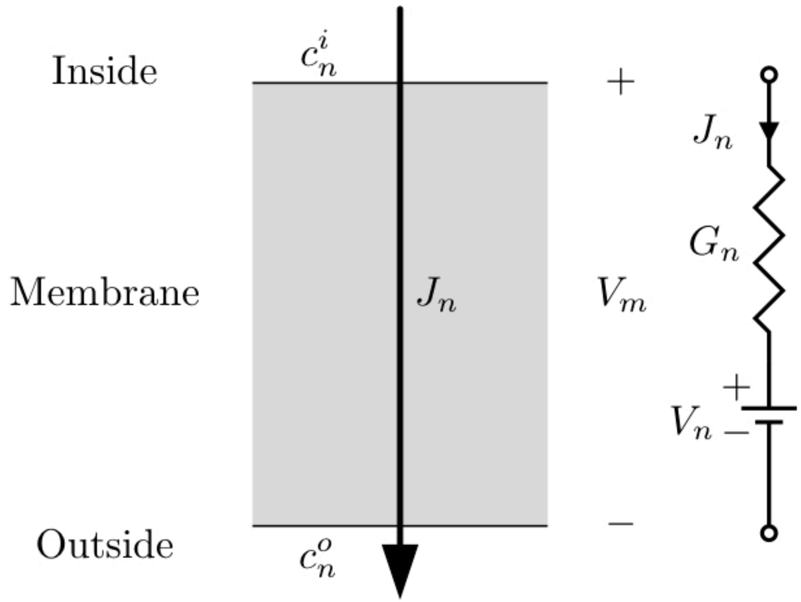
$$V_n = \frac{RT}{z_nF} \ln \frac{c_n(d)}{c_n(0)} = \frac{RT}{z_nF} \ln \frac{c_n^o}{c_n^i}$$

$$G_n = \frac{1}{\int_o^d \frac{dx}{u_n z_n^2 F^2 c_n(x)}} \geq 0$$

$$\frac{RT}{z_nF \log_{10} e}$$ ~ 59 mV

(for z_n=+1, room temp.)

Model of Steady-State Electrodiffusion through Membranes



$$\text{Nernst Equilibrium Potential } V_n = \frac{RT}{z_n F} \ln \frac{c_n^o}{c_n^i}$$

$$\text{Electrical Conductivity } G_n = \frac{1}{\displaystyle\int_o^d \frac{dx}{u_n z_n^2 F^2 c_n(x)}} \geq 0$$

How is the Nernst potential generated?

Assumption: Single permeable ionic species (positively charged)

$c_1 < c_2$

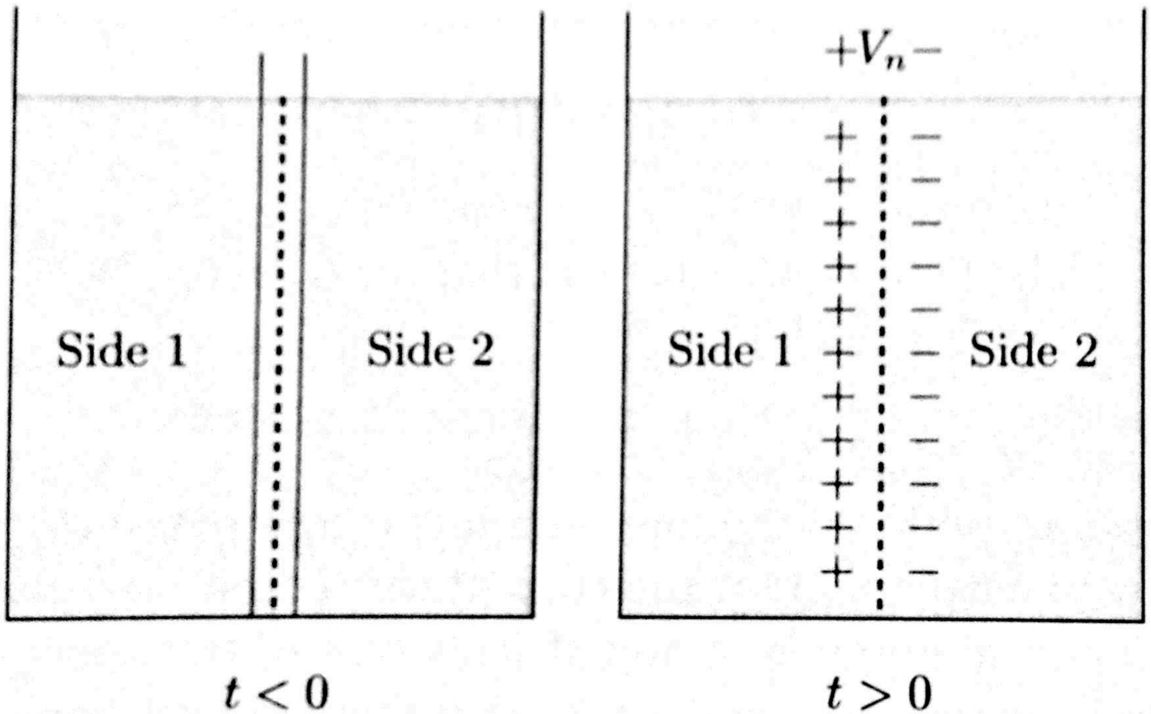
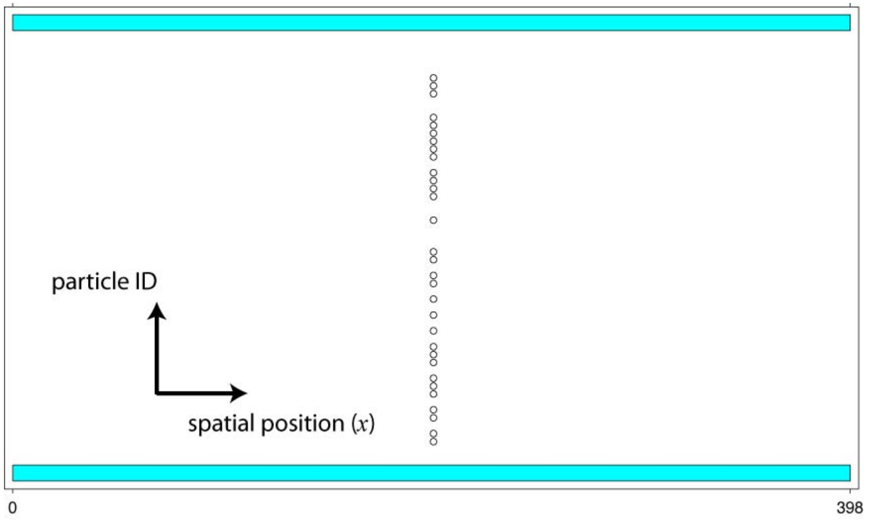


Figure 7.16 Illustration of the generation of the Nernst equilibrium potential. A bath is separated into two compartments by a membrane permeable only to ion n.

→ Note that the creation of a significant V_n need not require significant concentration changes

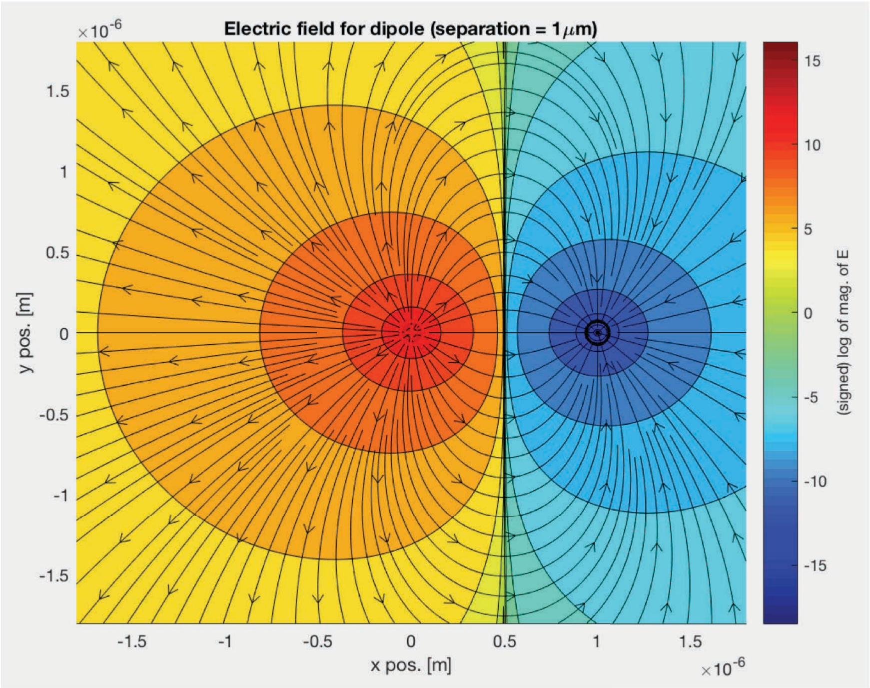
Key Idea: Charged random walkers?



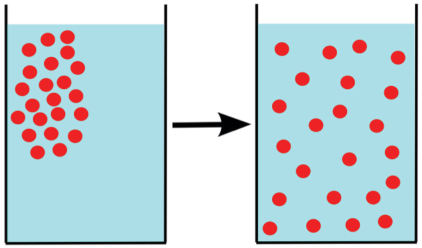
- Up until this point, we have considered our walkers to not be interacting

$$x_i(n) = x_i(n-1) \pm \delta.$$

→ But what if they were (electrically) charged?



Electrodiffusion



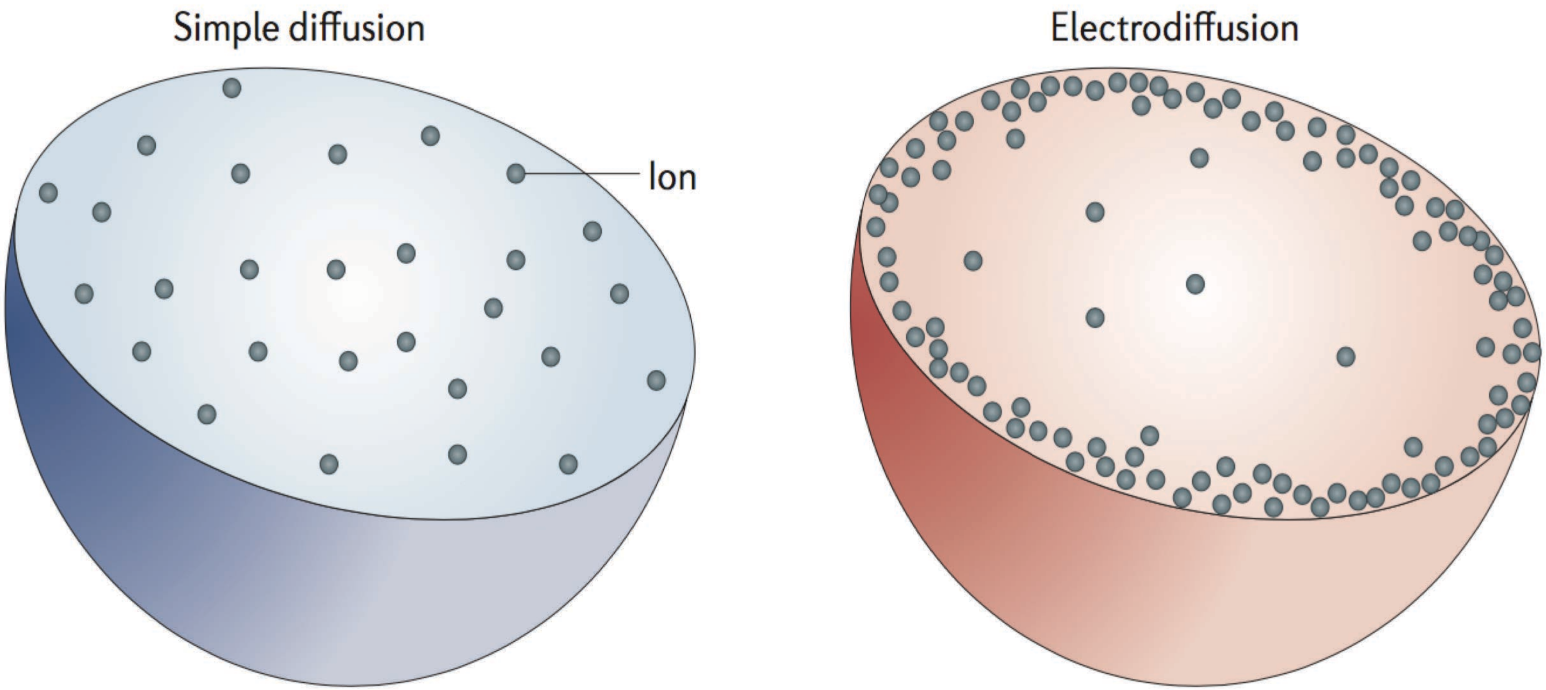


Figure 3 | **Comparison of simple diffusion and electrodiffusion theories.** Traditional diffusion theories and electrodiffusion theories make very different predictions about the distribution of ions within a three-dimensional structure such as a dendritic spine head.

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Electrodiffusion phenomena in neuroscience: a neglected companion

Leonid P. Savtchenko[1], Mu Ming Poo[2] and Dmitri A. Rusakov[1]

Abstract | The emerging technological revolution in genetically encoded molecular sensors and super-resolution imaging provides neuroscientists with a pass to the real-time nano-world. On this small scale, however, classical principles of electrophysiology do not always apply. This is in large part because the nanoscopic heterogeneities in ionic concentrations and the local electric fields associated with individual ions and their movement can no longer be ignored. Here, we review basic principles of molecular electrodiffusion in the cellular environment of organized brain tissue. We argue that accurate interpretation of physiological observations on the nanoscale requires a better understanding of the underlying electrodiffusion phenomena.

“We also endeavour to dispel some common misconceptions regarding the nature of the membrane potential while trying not to dwell too much on the well-established electrophysiological postulates."

“…discuss where and how electroneutrality could be violated and what consequences this may have for our interpretation of empirical observations“

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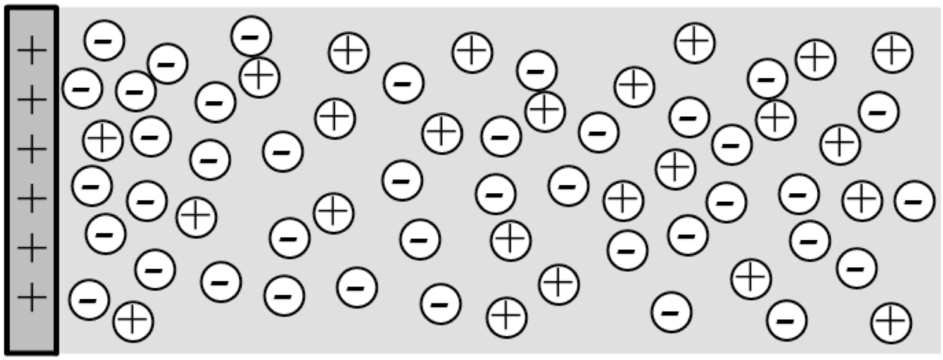
Assumptions re membrane electrodiffusion

- **Electrolytic solutions** → Fluids inside and outside cell are a stew of dissociated ionic species (e.g., K^+, Na^+, Ca^+, etc…)

- **Electroneutrality** → Total charge per unit volume is zero



Clearly this is only going to be valid on a suitable set of scales…

→ Validity of these assumptions depends upon both a temporal scale (*charge relaxation time*) and spatial scale (*Debye length*)

Assumptions re membrane electrodiffusion

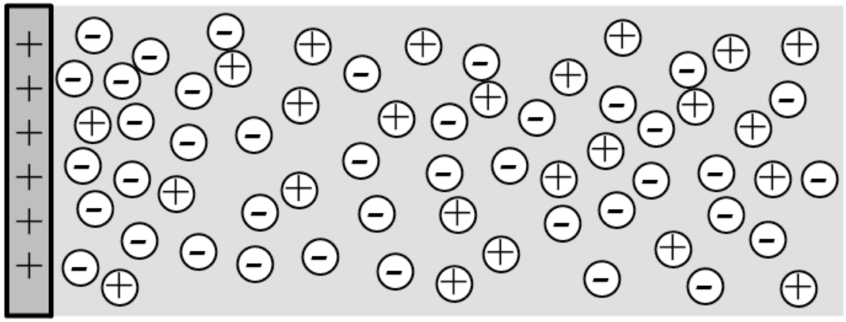
Electrolyte solutions → Electroneutrality

$$\text{if} \quad t >> \tau_r \quad \text{and} \quad x >> \Lambda_D \quad \text{then} \qquad \sum_n z_n F c_n(x,t) = 0$$

- Charge Relaxation Time τ_r

Measures temporal change in charge density
(i.e., relaxation time of charge distribution)

- Debye Length Λ_D



Measures spatial extent of electric potential
(i.e., distance over which electroneutrality is violated)

→ Both are very small (1 ns and 1 nm respectively; see Weiss v.1 7.2.3), justifying that ionic solutions obey electroneutrality

Freeman

(further) Aside: Deviations from the ideal model....

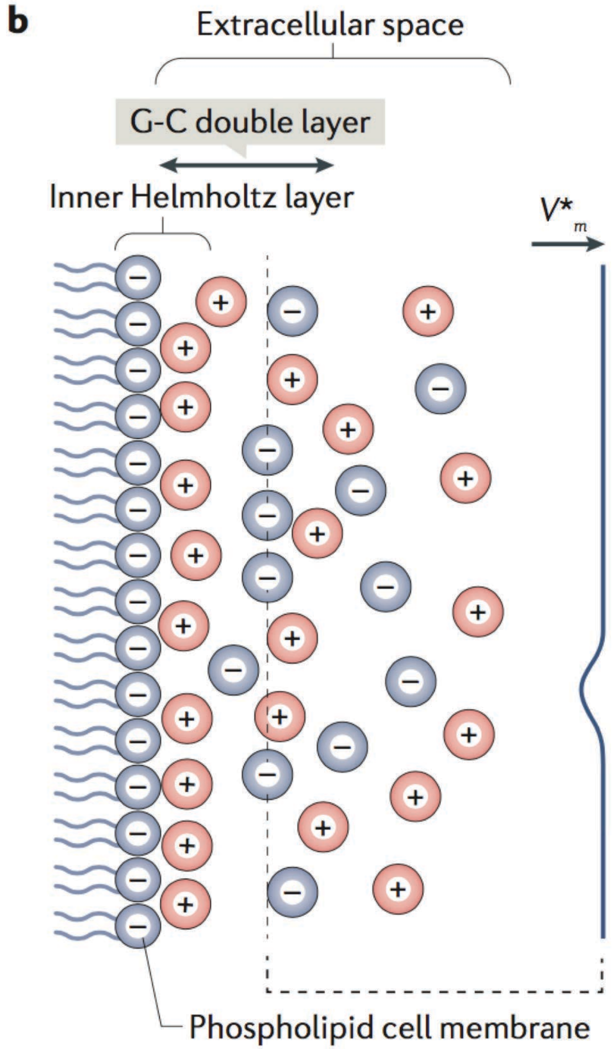
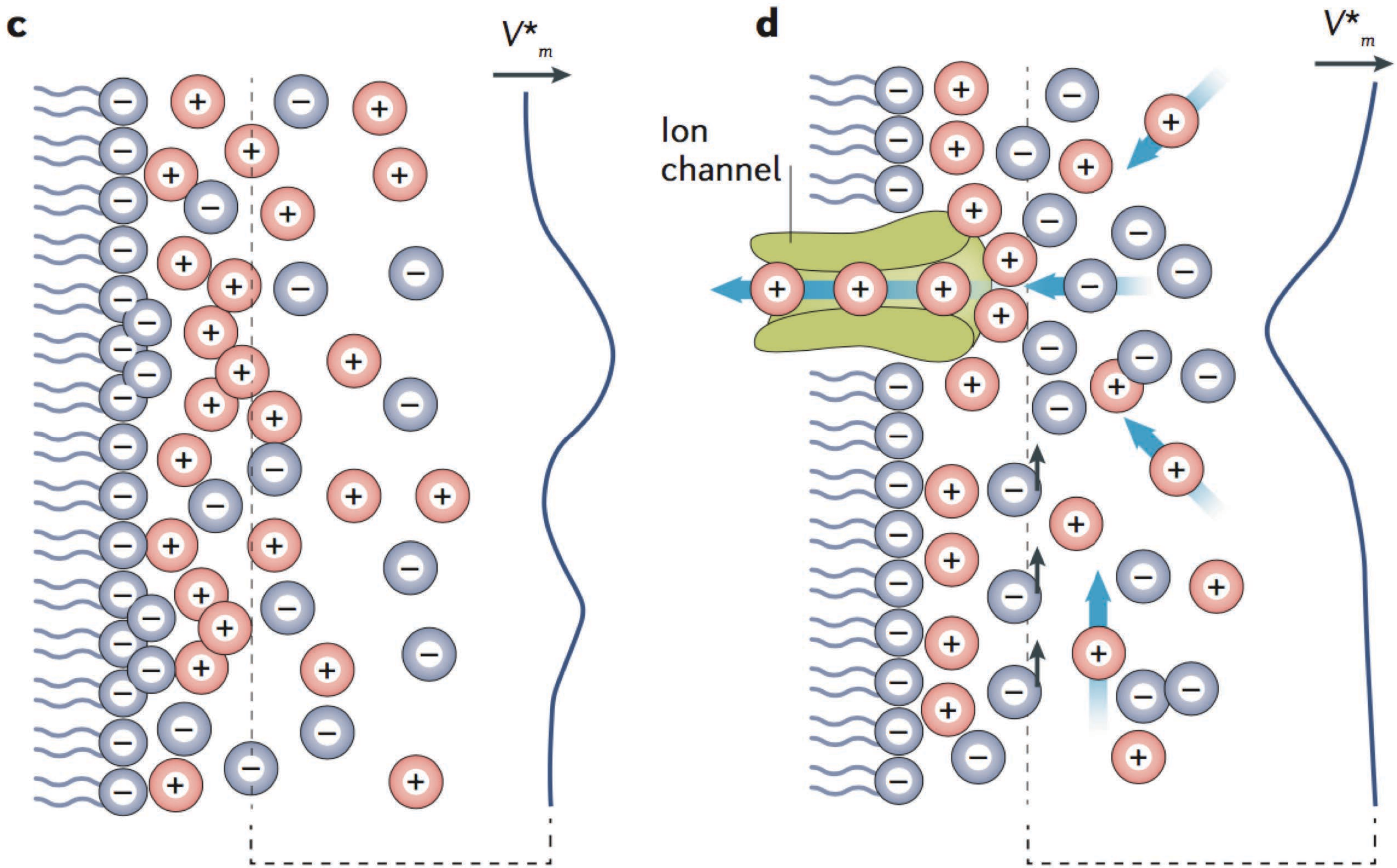


Figure 1 | **Electric charges and their fields in brain tissue: basic principles and two common deviations from common electrophysiological postulates. a** | The schematic depicts electrostatic electric fields generated by a local (point) charge and a charged plane, in either a vacuum (dielectric medium, top) or an electrolyte (bottom). The colour intensity illustrates the field strength. Whereas the field (depicted by arrows) in a vacuum extends into infinity, fields in electrolytes are highly localized. **b** | The panel shows ion distributions and the local voltage profile near a negatively charged phospholipid cell membrane surface; the inner Helmholtz layer (a layer of cations lined up next to the negatively charged membrane) and Gouy–Chapman double layer (G-C; includes the Helmholtz layer and a loose layer of anions adjacent to it) are indicated. V^*_m depicts the voltage profile (arrow indicates voltage scale) at a short distance from the membrane (dotted line, not to scale) from which signalling proteins such as ion channels may sense local electric fields (see below). The V^*_m profile shows a canonical case of a nearly evenly charged membrane. **c** | The schematic depicts heterogeneity in sub-membrane ion distribution and local voltage owing to excessive membrane charges (carried by either phospholipids or membrane proteins). The uneven occurrence of cations (red) and anions (blue) reflects the variable density of local electric fields and hence the heightened variability of the sub-membrane voltage V^*_m compared with that in part **b**. **d** | This panel depicts heterogeneity in sub-membrane ion distribution and local voltage owing to ion channel currents. Blue arrows depict the current direction (an ion channel is shown in green). Black arrows depict drag forces exerted by the cation current flow; these forces tend to drag particles alongside the sub-membrane ion layers.

Savtchenko et al

(further) Aside: Deviations from the ideal model….



Problems

7.5 Describe the distinctions between the following terms that refer to ion transport across a cellular membrane: electrodiffusive equilibrium, steady state, resting conditions, and cellular quasi-equilibrium.

7.6 The following is a discussion of electroneutrality (Nicholls et al., 1992):

The intracellular and extracellular solutions must each be electrically neutral. For example, a solution of chloride ions alone cannot exist; their charges must be balanced by an equal number of positive charges on cations such as sodium or potassium (otherwise electrical repulsion would literally blow the solution apart).

Briefly critique this discussion of electroneutrality.

Exercise 7.5 In steady state the ionic flux through the membrane, the concentration of ions in the membrane, and the voltage across the membrane are all constant with respect to time. Electrodiffusive equilibrium requires all of the conditions for steady state plus the condition that the ionic flux through the membrane is zero. At equilibrium, the potential across the membrane equals the Nernst equilibrium potentials of each permeant ionic species. Rest requires all of the conditions for steady state plus the condition that the net current through the membrane (total across ionic species) is zero. Quasi-equilibrium requires all of the conditions for steady state plus that the net flux of each ionic species (summed across all of the transport mechanisms for that species) is zero.

As an example, suppose external electrodes pass a constant current through the membrane of a cell. For this case, the membrane could come to a steady-state condition. It could be at electrodiffusive equilibrium if the membrane contains active transport mechanisms to carry all of the current from the external electrodes through the membrane. By definition, the cell is not at rest. Furthermore, the cell could not be in quasi-equilibrium, since the external current must be carried through the membrane by some ionic species.

Exercise 7.6 The statement is largely correct except for the parenthetical phrase. The solution would not blow up. The excess charges would repel each other and would ultimately reside on the boundaries of the vessel enclosing the solution.

Resting Potential

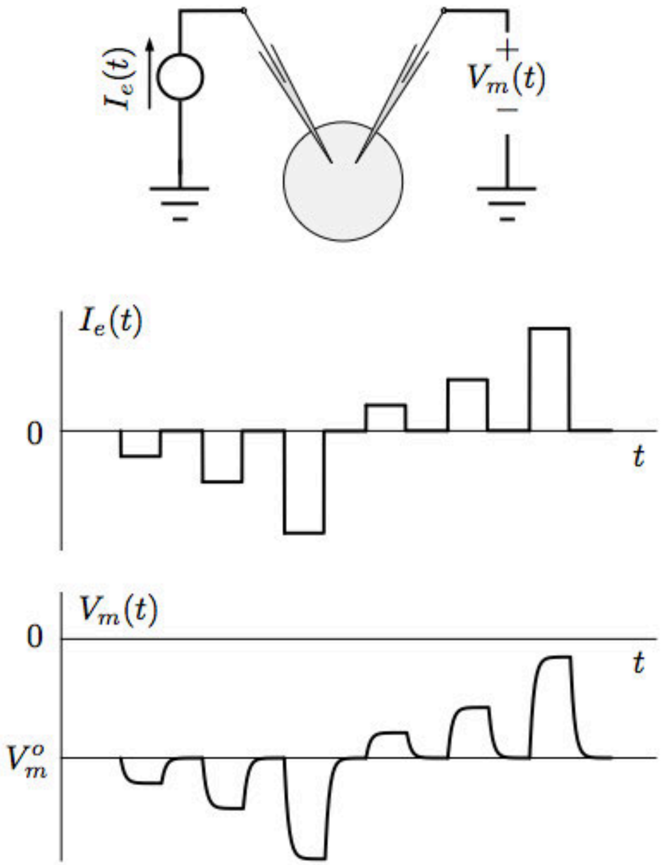


Figure 1.1

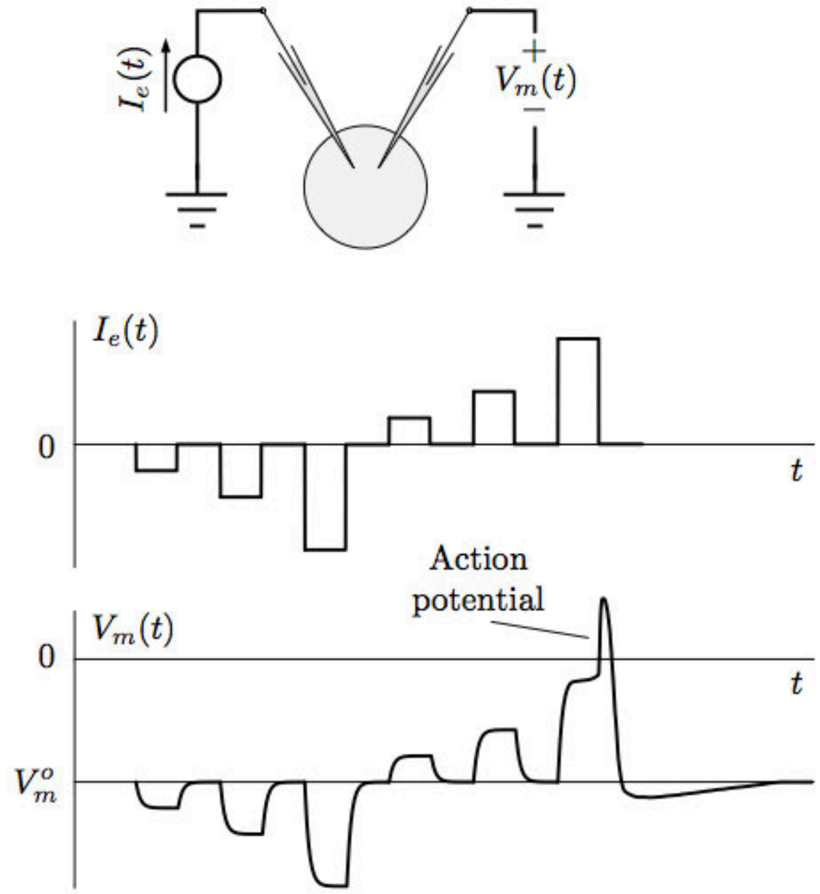


Figure 1.8

→ Independent of whether a cell "fires" an action potential or not, note that there is a baseline trans-membrane potential ("resting potential") V_m^o

Resting Potential

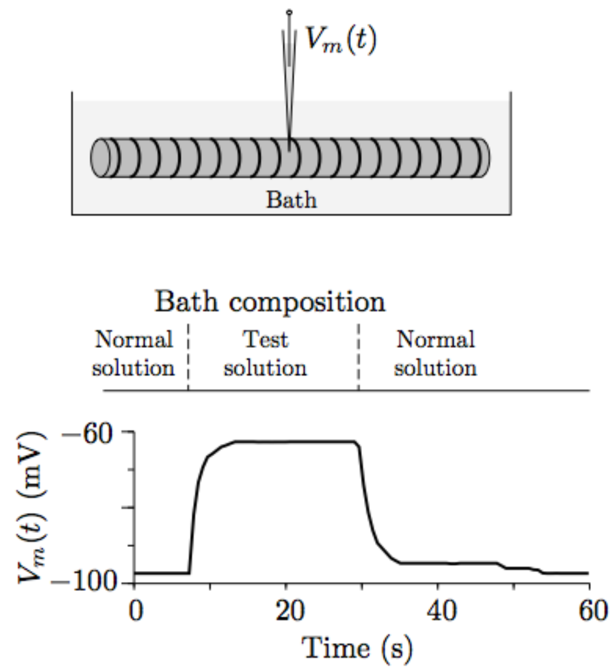


Figure 1.2

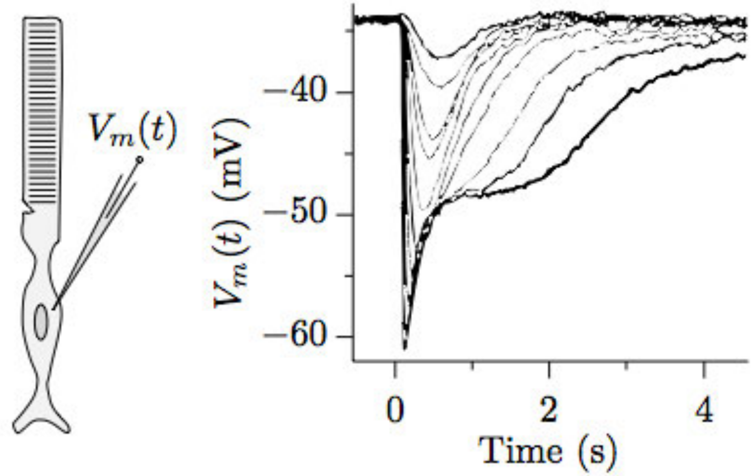


Figure 1.3

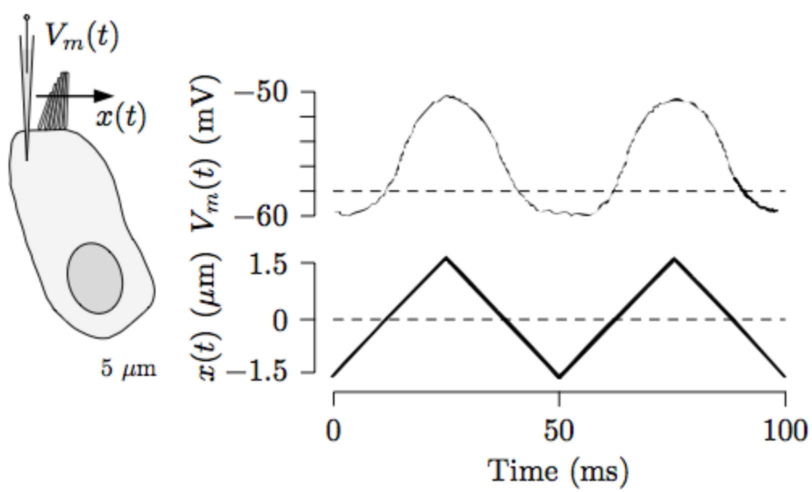


Figure 1.5

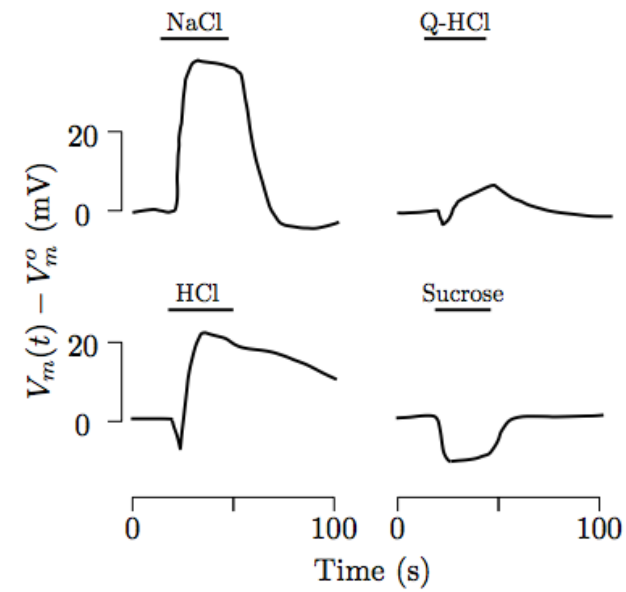


Figure 1.6

→ What is the basis for such a resting potential?

Resting Potential: Model considering only a *single permeant ion*

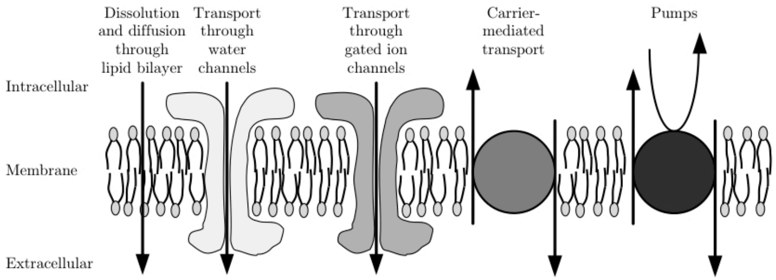


Figure 2.19

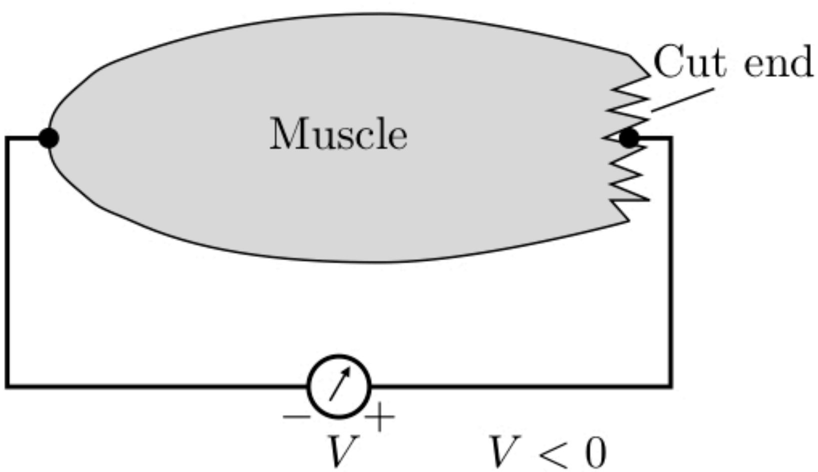


Figure 7.17

Emipirical observation:
Inside cell: high [K+], low [Na+]
Outside cell: low [K+], high [Na+]

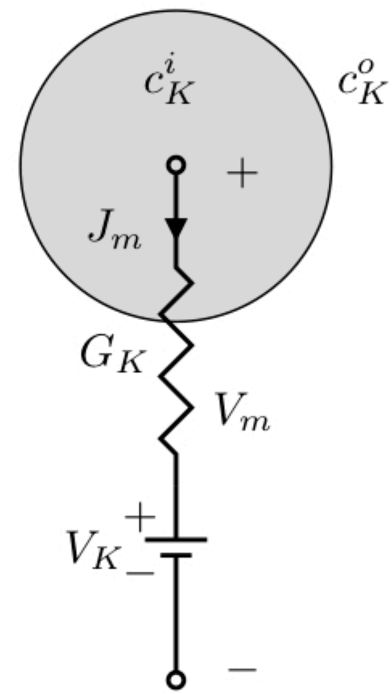


Figure 7.18

→ Bernstein's idea (1902) was that membrane was permeable to potassium only, thereby K^+ determined resting potential

Resting Potential: Model considering only a *single permeant ion*

Nernst Equilibrium Potential

$$V_n = \frac{RT}{z_n F} \ln \frac{c_n(d)}{c_n(0)} = \frac{RT}{z_n F} \ln \frac{c_n^o}{c_n^i}$$

$$G_n = \frac{1}{\int_o^d \frac{dx}{u_n z_n^2 F^2 c_n(x)}} \geq 0$$

Bernstein model:

$$V_m^o = V_K = \frac{RT}{F \log_{10} e} \log_{10} \left(\frac{c_K^o}{c_K^i} \right)$$

$$\frac{RT}{z_n F \log_{10} e}$$ ~ 59 mV

(for z_n=+1, room temp.)

Inside cell: high [K+], low [Na+]
Outside cell: low [K+], high [Na+]

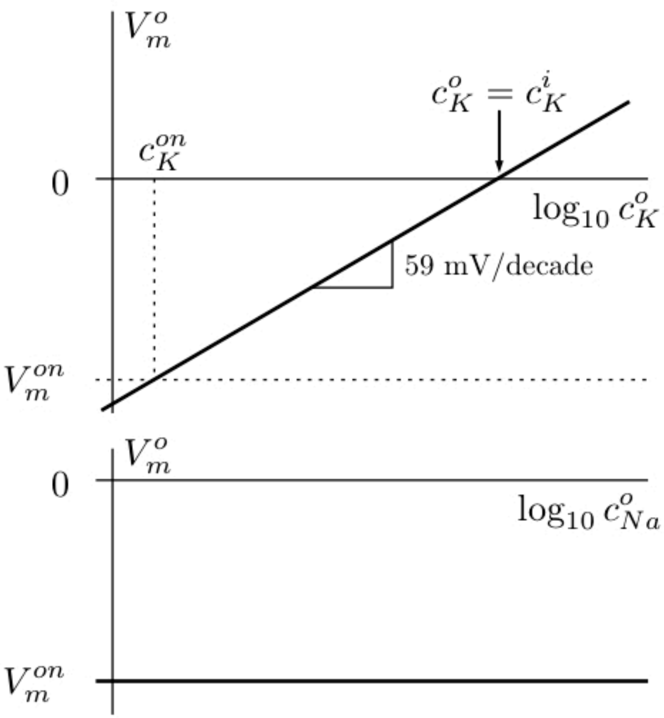


Figure 7.19

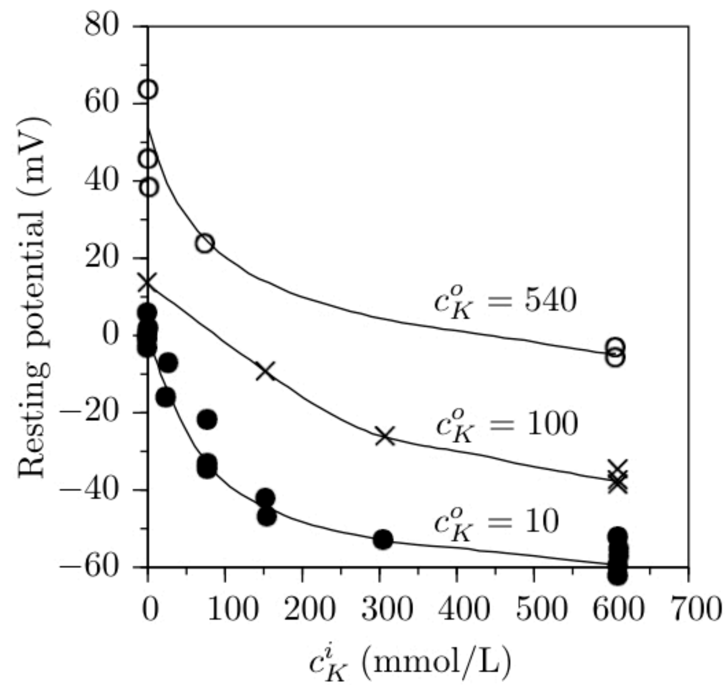


Figure 7.20

Resting Potential: Model considering only a *single permeant ion*

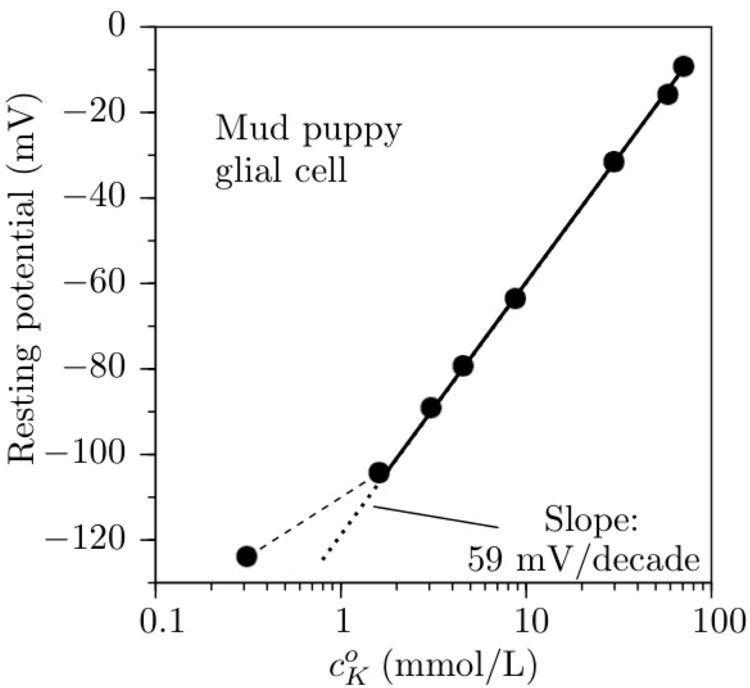


Figure 7.21

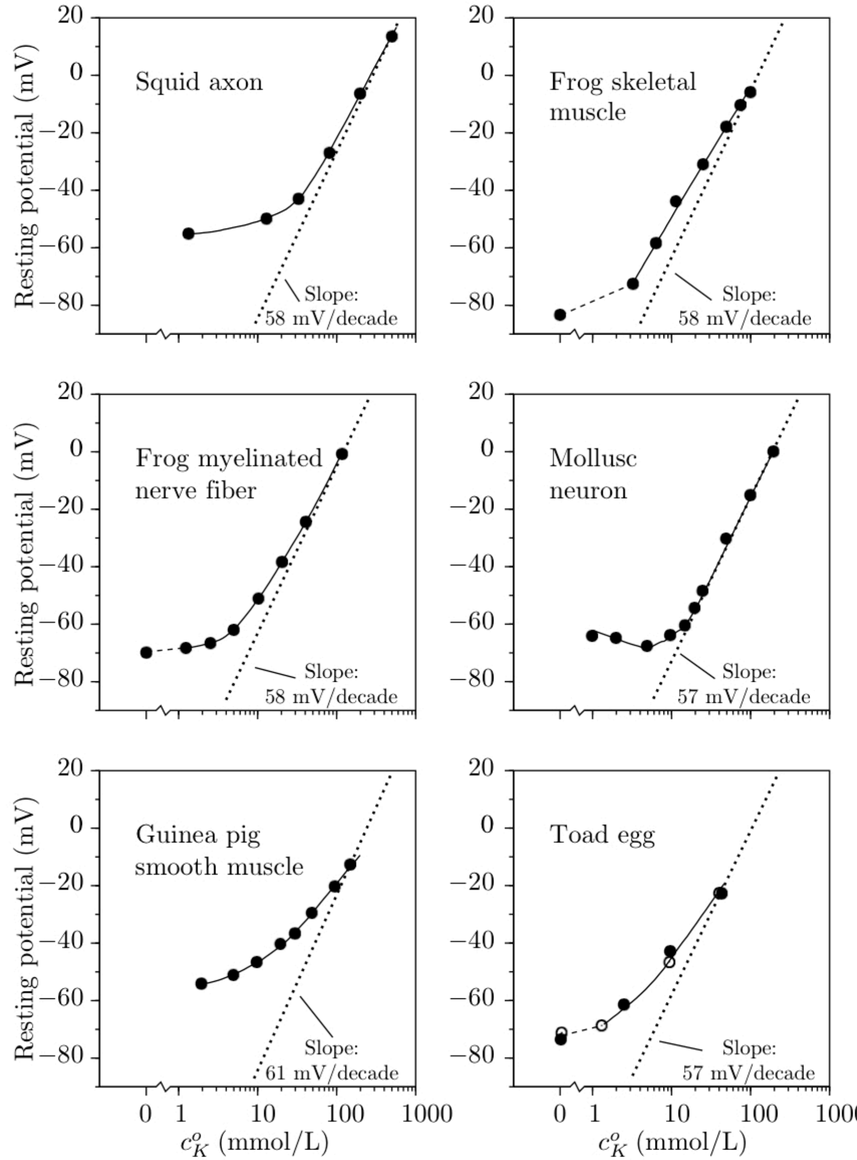
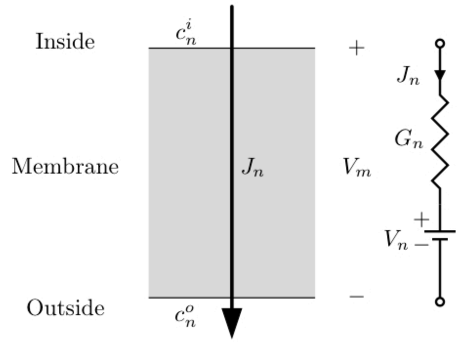


Figure 7.22

→ Model does a decent job, but deviations apparent (e.g., low c_K, Na^+ does matter re Fig.7.23)

Stepping back a moment....



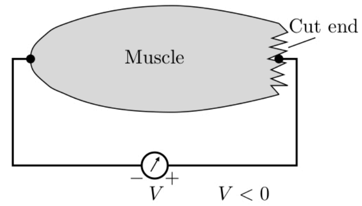


Figure 7.17

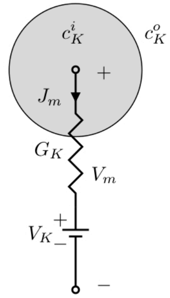
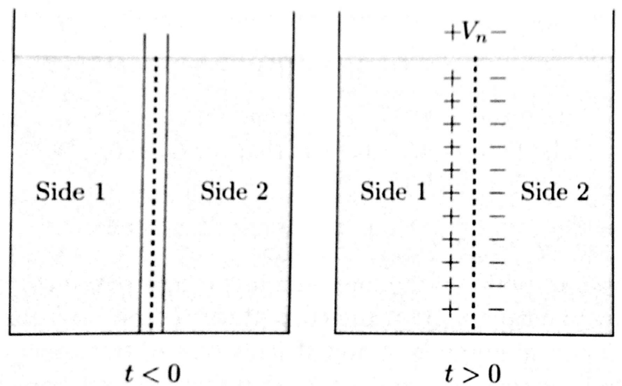
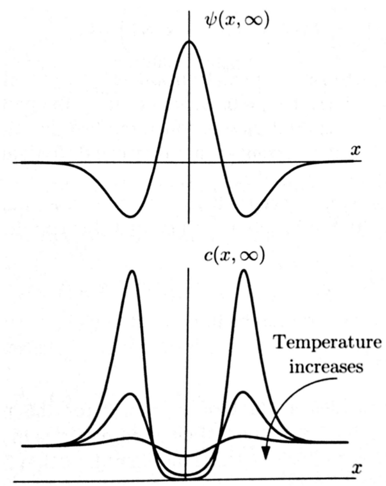


Figure 7.18

$$J_n(x,t) = -z_n F D_n \frac{\partial c_n(x,t)}{\partial x} - u_n z_n^2 F^2 c_n(x,t) \frac{\partial \psi(x,t)}{\partial x}$$





$$V_m^o = V_K = \frac{RT}{F \log_{10} e} \log_{10}\left(\frac{c_K^o}{c_K^i}\right)$$

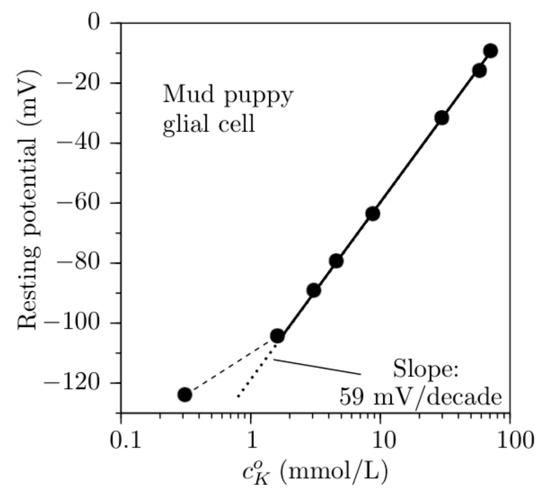


Figure 7.21

→ Different ways of looking at/describing the same thing!

Resting Potential: Model considering only a ***multiple*** *permeant ions*

→ What if different ions are able to diffuse?

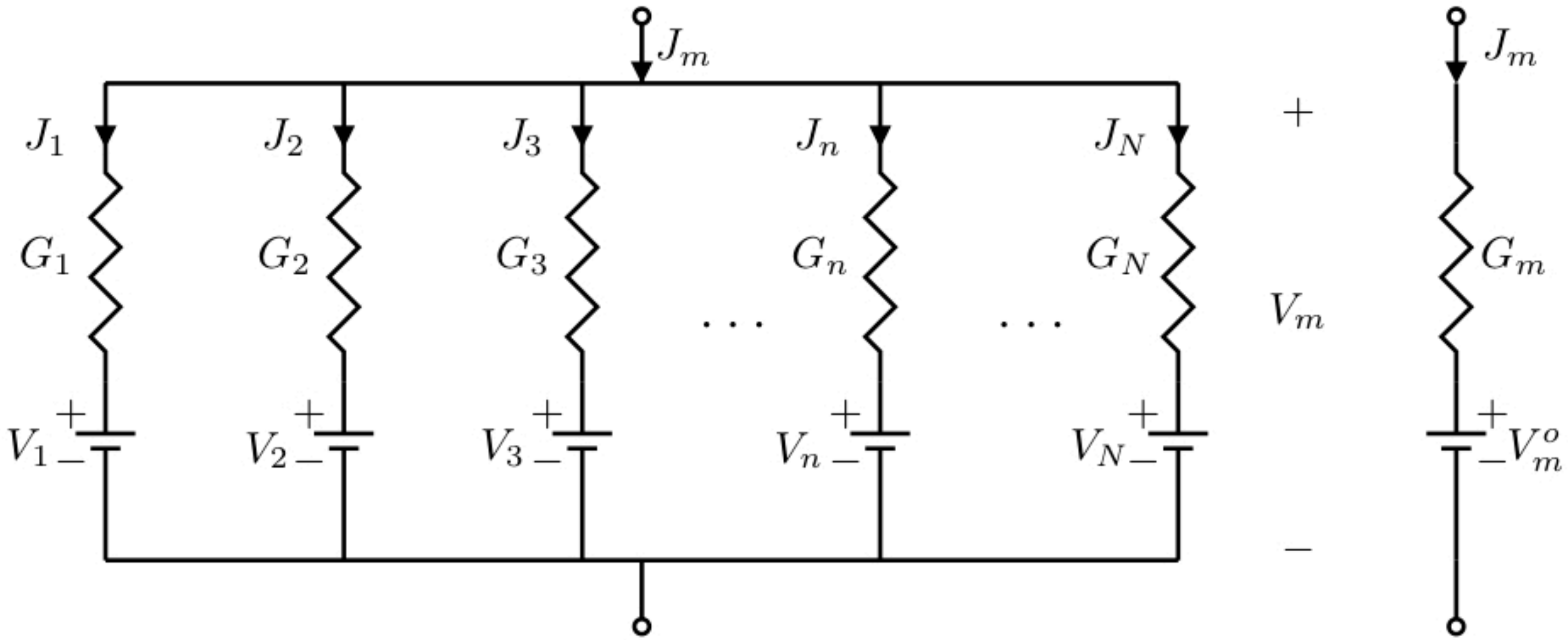


Figure 7.24

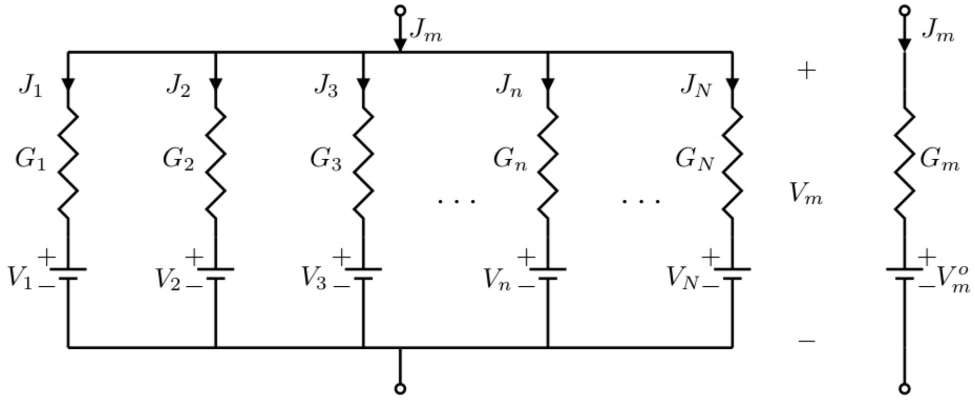


Figure 7.24

<u>At electrodiffusive equilibrium...</u> (i.e., zero current densities concurrently)

$$\frac{RT}{z_1F}\ln\left(\frac{c_1^o}{c_1^i}\right)=\frac{RT}{z_2F}\ln\left(\frac{c_2^o}{c_2^i}\right)=\cdots=\frac{RT}{z_nF}\ln\left(\frac{c_n^o}{c_n^i}\right)$$

Nernst potentials must be equal

$$\left(\frac{c_1^o}{c_1^i}\right)^{1/z_1}=\left(\frac{c_2^o}{c_2^i}\right)^{1/z_2}=\cdots=\left(\frac{c_n^o}{c_n^i}\right)^{1/z_n}$$

Possible concentrations are constrained!

e.g., $c_K^o/c_K^i = c_{Cl}^i/c_{Cl}^o$ or that $c_K^o c_{Cl}^o = c_K^i c_{Cl}^i$

Donnan relation

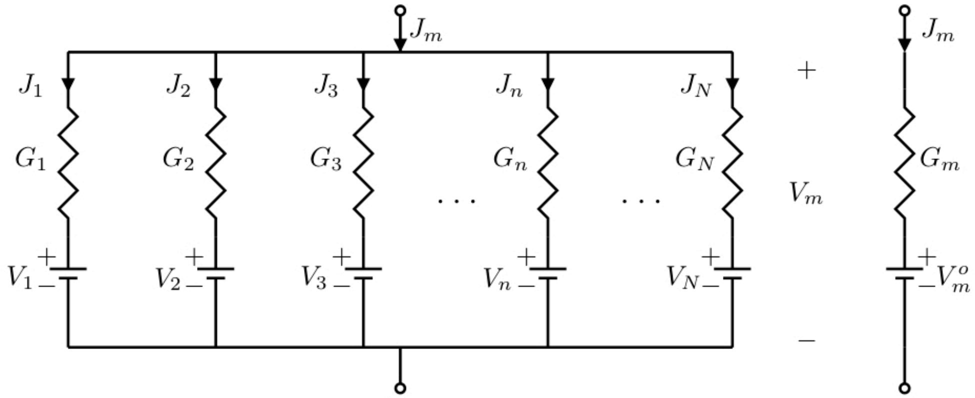


Figure 7.24

More general case

$$J_m = \sum_n J_n$$

total membrane current is sum of all permeant charged species

$$\rightarrow \quad J_m = \sum_n G_n (V_m - V_n)$$

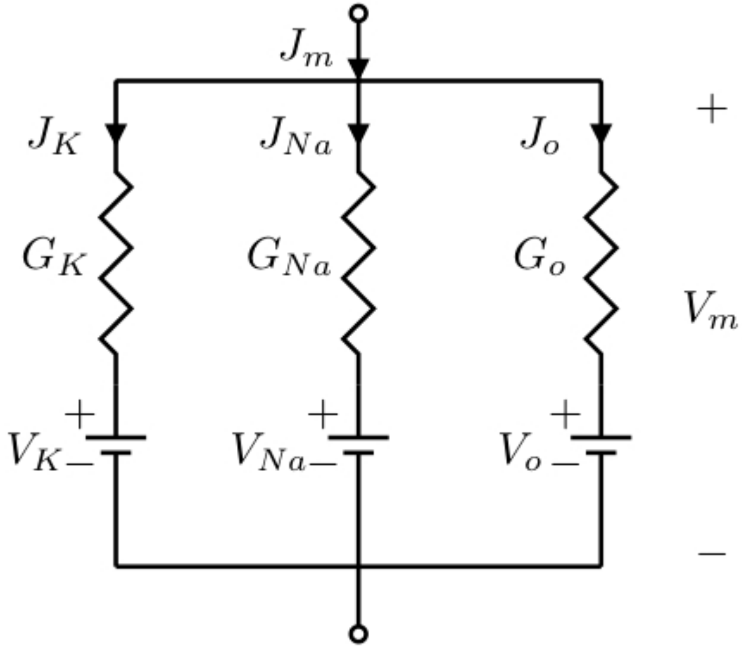
$$\sum_n G_n (V_m^o - V_n) = 0$$

'resting state' condition such that membrane potential is const. (i.e., no net charge entering/leaving cell)

$$V_m^o = \sum_n \frac{G_n}{G_m} V_n$$

where $G_m = \sum_n G_n$

(total conductance per unit area of membrane)



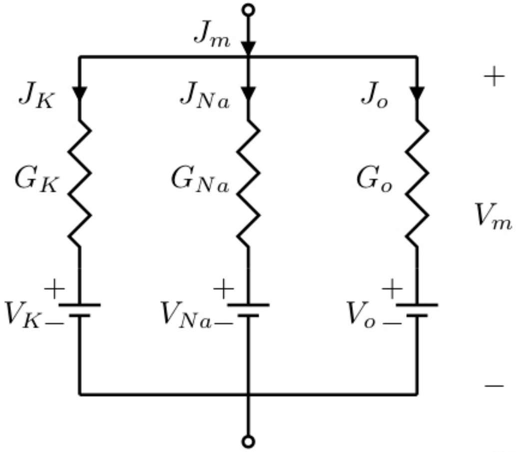
Model with three relevant "paths":

1. K^+
2. Na+
3. Other/Leakage (e.g., Cl^-, Ca^{++})

$$V_m^o = \sum_n \frac{G_n}{G_m} V_n$$

Ion	G_n (S/cm^2)	G_n/G_m	c_n^o/c_n^i	V_n (mV)
K^+	3.7×10^{-4}	0.55	0.05	−72
Na^+	1×10^{-5}	0.016	9.8	+55
leakage	3.0×10^{-4}	0.44	—	−49

'resting' values for squid giant axon (determined empirically)



Ion	G_n (S/cm^2)	G_n/G_m	c_n^o/c_n^i	V_n (mV)
K^+	3.7×10^{-4}	0.55	0.05	−72
Na^+	1×10^{-5}	0.016	9.8	+55
leakage	3.0×10^{-4}	0.44	—	−49

$$V_m^o = \frac{RT}{F}\left(\frac{G_K}{G_m}\right)\ln\left(\frac{c_K^o}{c_K^i}\right) + \sum_{n \neq K}\frac{G_n}{G_m}V_n$$

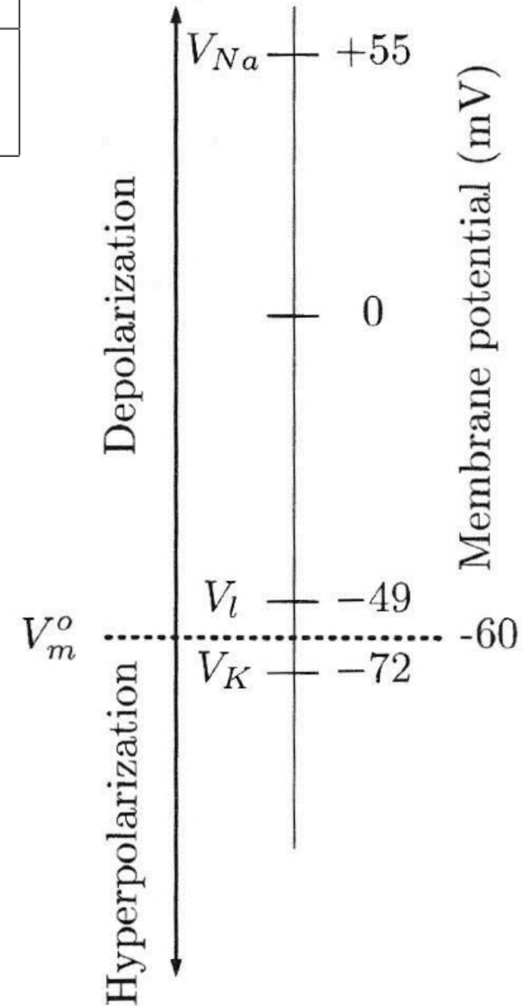


Figure 7.27

K$^+$ contribuition?

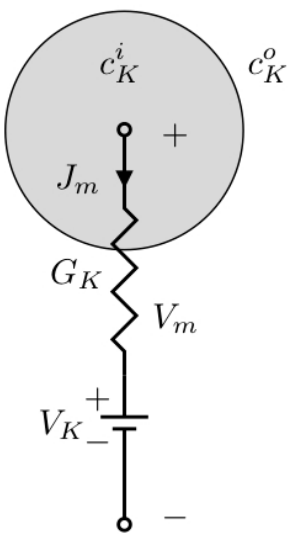


Figure 7.18

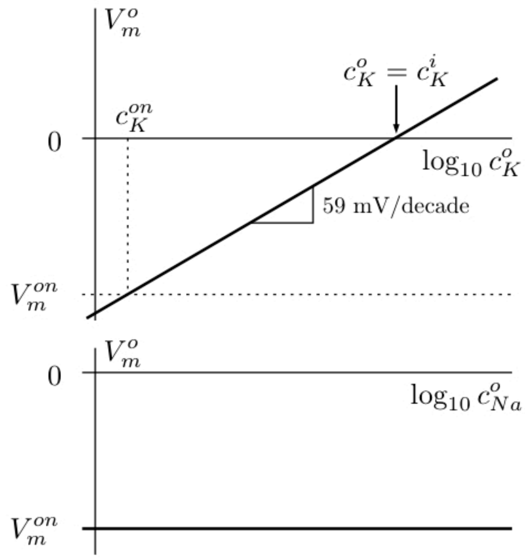


Figure 7.19

→ Multiple ion model seems to take us one step closer, but still doesn't explain everything....

K⁺ contribuition?

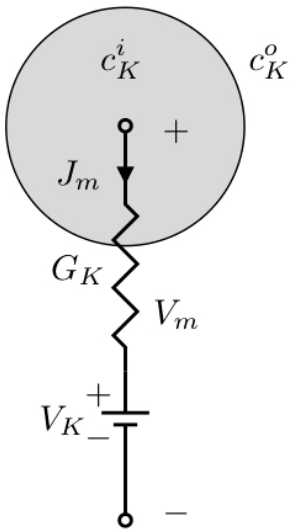


Figure 7.18

$$V_m^o = \frac{RT}{F}\left(\frac{G_K}{G_m}\right)\ln\left(\frac{c_K^o}{c_K^i}\right) + \sum_{n \neq K} \frac{G_n}{G_m} V_n$$

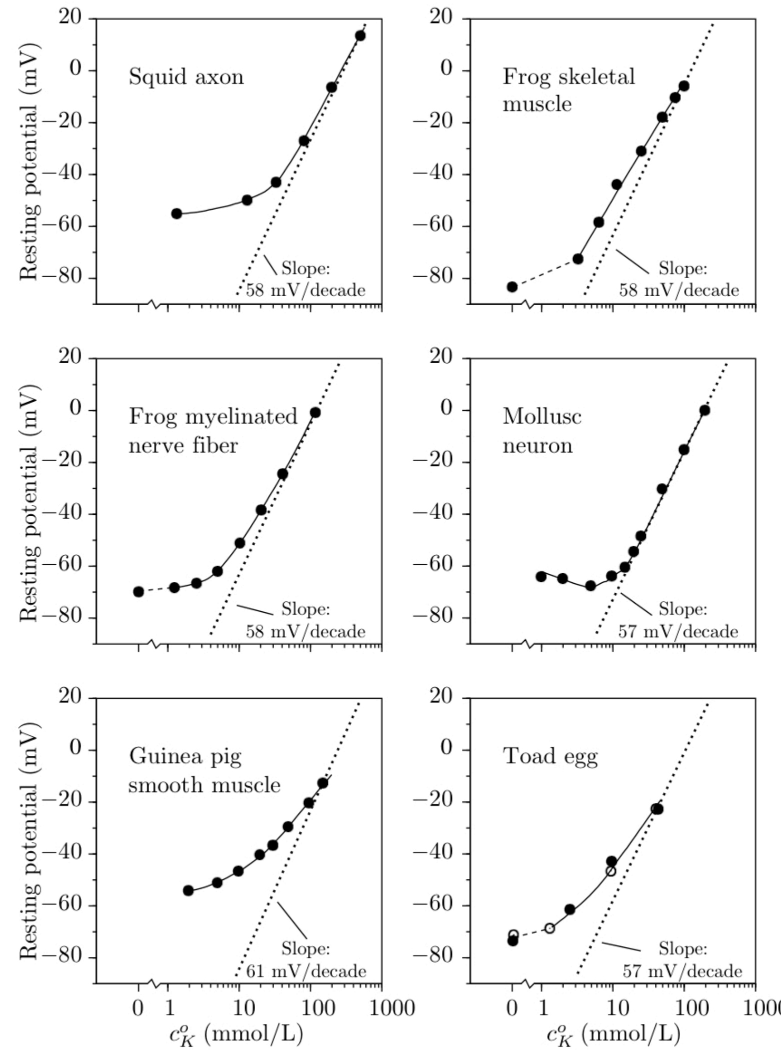


Figure 7.22

→ Chief issue is deviations at lower K⁺ concentrations (i.e., saturation in resting potential)

What if conductances were voltage-dependent?

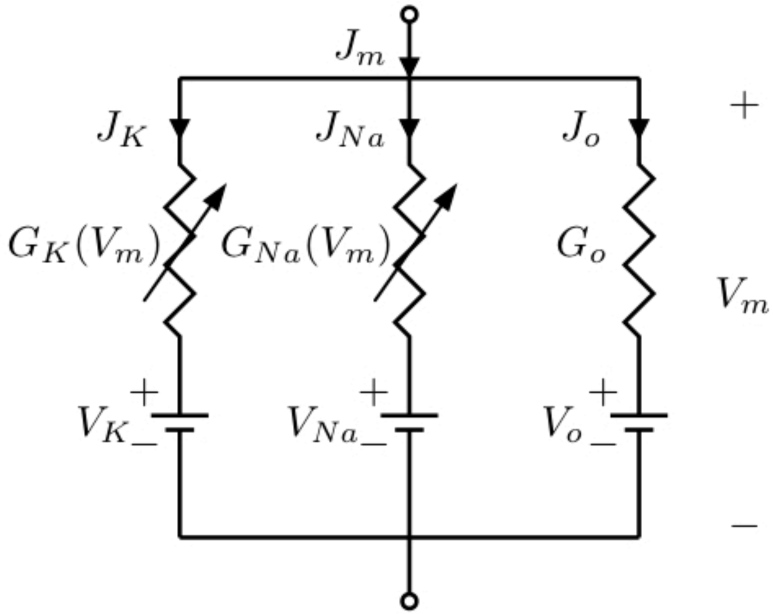
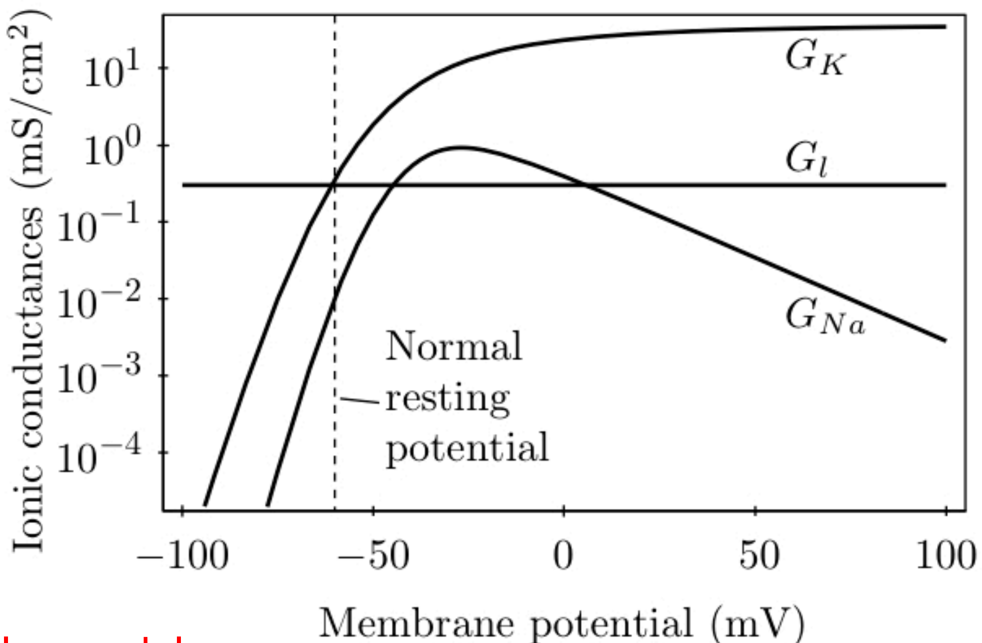


Figure 7.32

i.e., voltage-gated ion channels
(more detail in vol.2 ch.6)



Hodgkin-Huxley model conductances

Figure 7.28

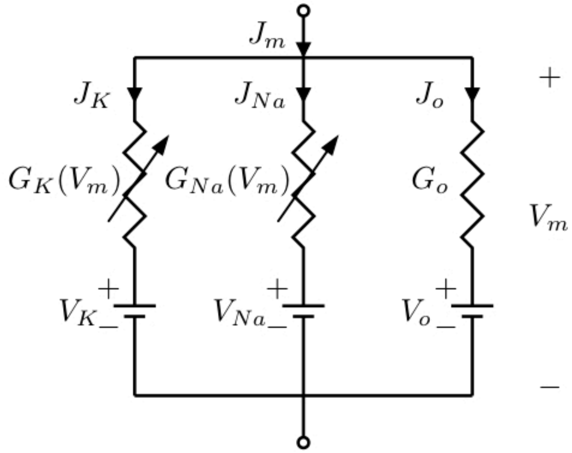


Figure 7.32

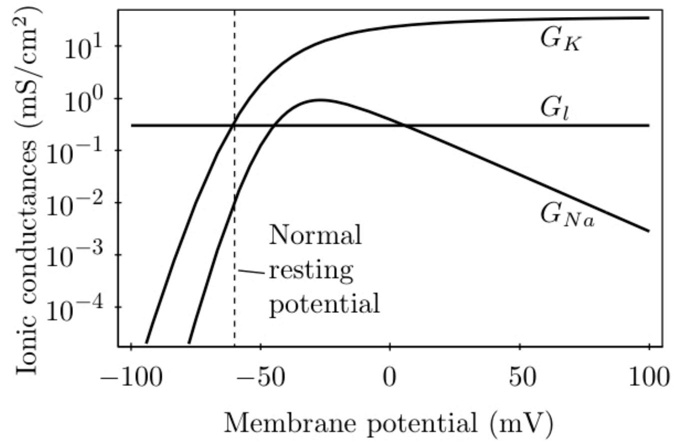


Figure 7.28

$$\sum_n G_n(V_m^o - V_n) = 0$$

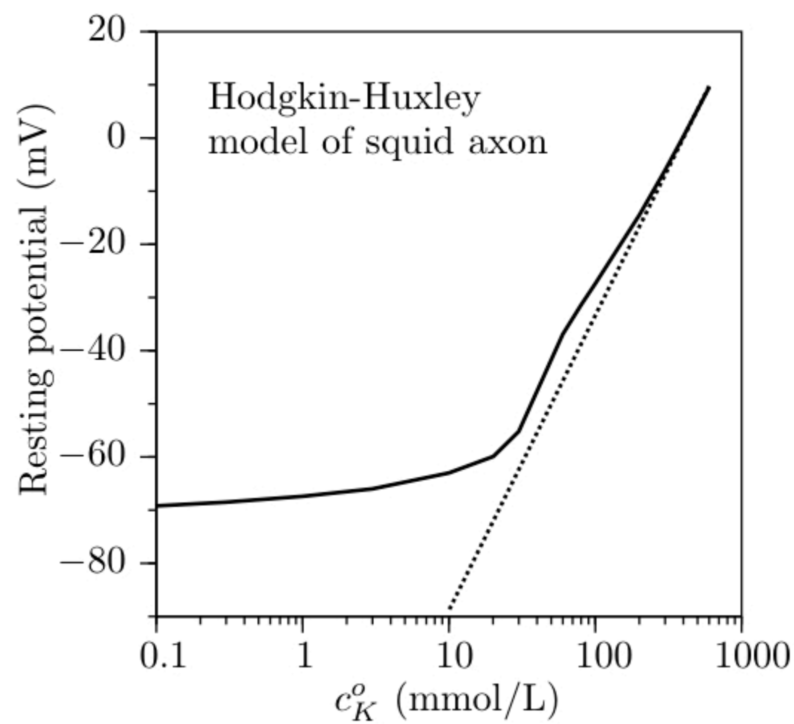


Figure 7.29

Problem

7.9 Figure 7.55 shows three panels in which the distributions of Na^+, K^+, Cl^-, and an impermeant anion A^- are shown schematically in two rigid compartments separated by a rigid semipermeable membrane. The problem concerns the distributions at electrodiffusive equilibrium for different membrane characteristics.

a. If the membrane were permeable only to K^+, which of the three distributions would be possible at electrodiffusive equilibrium?

b. If the membrane were permeable to both K^+ and Cl^-, which of the three distributions would be possible at electrodiffusive equilibrium?

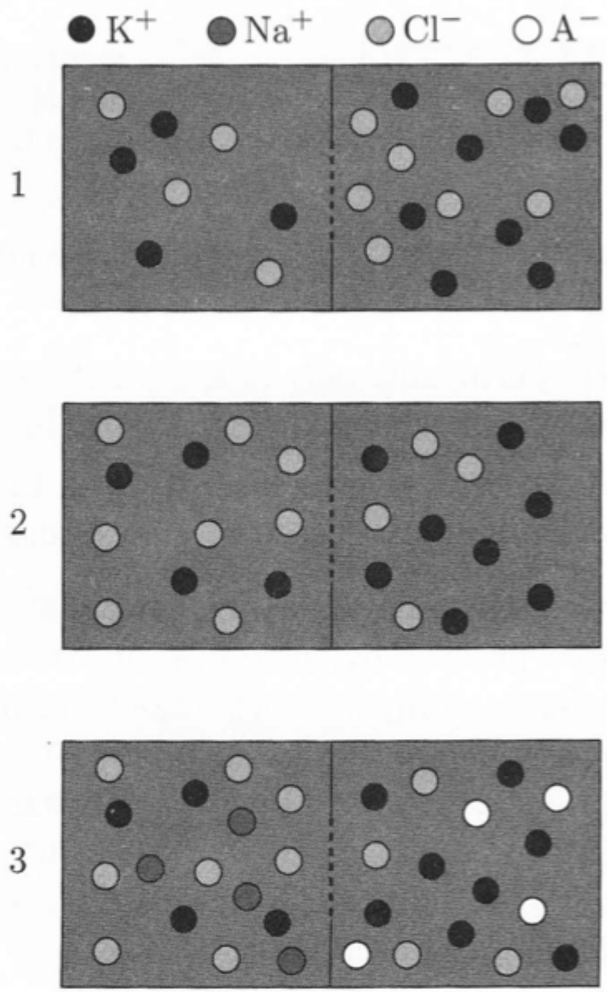


Figure 7.55 Two compartments separated by a membrane with different ions on the two sides of the membrane (Exercise 7.9). The three panels show different distributions of ions. The diagrams represent the compositions of the bulk solutions on the two sides of the membrane.

Problem

7.14 The intracellular and extracellular ion concentrations are given in Table 7.7 for four cells. The permeant ions are also listed for each cell. You may assume that the permeant ions are transported passively only and that there are no mechanisms of active ion transport in these cells. The temperature is 24°C. For each cell, determine whether the solutions are in electrodiffusive equilibrium across the membrane, and if they are, determine the resting membrane potential.

Table 7.7 The table shows the compositions of intracellular and extracellular ions in four different cells and also indicates which ions are permeant through the cell membranes (Exercise 7.14). Ion A is an impermeant anion.

Cell number	Permeant ions	*Composition (mmol/L)*					
		Intracellular			*Extracellular*		
		KCl	NaCl	KA	KCl	NaCl	KA
1	K^+	150	10	0	10	150	0
2	Cl^-	150	10	0	10	150	0
3	K^+ & Cl^-	150	10	0	10	150	0
4	K^+ & Cl^-	0	10	150	0	150	10

Problem SOL

Exercise 7.9 The two solutions in (1) and (3) are electrically neutral whereas those in (2) are not. Solution 2 is an unphysical ionic solution — you cannot obtain such a solution by dissolving salts in water! Therefore, case (2) is not a possible answer to either part a or part b.

a. Both (1) and (3) are possible distributions of ions at equilibrium. In both cases, a potential appears across the membrane so that the left compartment is at a higher potential than the right compartment in order to prevent diffusion of the potassium ions from the right to the left compartment. It is interesting to note that the osmolarity of the solution in the right compartment is larger than that in the left compartment for (1). Therefore, since the walls and the membrane are rigid, a hydraulic pressure appears across the membrane such that the right compartment is at a higher hydraulic pressure than the left compartment.

b. Since both potassium and chloride are permeant, at equilibrium the potential across the membrane must equal both the potassium and the chloride equilibrium potential. But, the valences have different signs, so that

$$V_K = \frac{RT}{F}\ln\left(\frac{c_K^r}{c_K^l}\right) = V_{Cl} = -\frac{RT}{F}\ln\left(\frac{c_{Cl}^r}{c_{Cl}^l}\right),$$

which implies that

$$\frac{c_K^r}{c_K^l} = \frac{c_{Cl}^l}{c_{Cl}^r},$$

where c_K^l, c_K^r, c_{Cl}^l, and c_{Cl}^r are the concentration in the left and right compartments for potassium and for chloride. Thus, the concentration ratios of potassium and chloride must be reciprocal. Therefore, only distribution (3) is possible.

Problem SOL

Exercise 7.14 Cell #1 is permeable to K^+ only. The resting membrane potential will be the Nernst equilibrium potential for potassium $V_m^o = V_K = 59\log_{10}(10/150) = -69$ mV. Cell #2 is permeable to Cl^- only. The resting membrane potential will be the Nernst equilibrium potential for chloride $V_m^o = V_{Cl} = -59\log_{10}(160/160) = 0$ mV. Cell#3 is permeable of both K^+ and Cl^-. Since the compositions of the solutions are the same as for Cell#1 and Cell#2, the Nernst potentials are the same as for those cells, i.e., $V_K = -69$ mV and $V_{Cl} = 0$ mV. Therefore, both ions cannot be in equilibrium and there will be net transport of each ion down its concentration gradient, and the potential across the membrane will change with time. Cell#4 is also permeable to both K^+ and Cl^-, but the compositions of these ions are different. The two Nernst equilibrium potentials are $V_K = 59\log_{10}(10/150) = -69$ mV and $V_{Cl} = -59\log_{10}(150/10) = -69$ mV. Therefore, both Nernst equilibrium potentials are the same and both ions will be at equilibrium at the potential $V_m^o = -69$ mV.