To Aurice B, Max, Elisa, and Eric
PREFACE

The textbooks *Cellular Biophysics, Volume 1: Transport* (Weiss, 1996a) and *Cellular Biophysics, Volume 2: Electrical Properties* (Weiss, 1996b) contain a collection of exercises and problems that have been developed over many years. These problems and exercises allow students to test their comprehension of the material and they also extend the material contained in the textbooks. For learning the material, there is no substitute for attempting to solve problems — challenging problems. Solving problems can reveal which aspects of the material are understood and which are not yet grasped and require further study. This solution book contains solutions to all the exercises and problems in Volume 1; a companion solution book (Weiss, 1997) contains solutions to all the exercises and problems in Volume 2. The purpose of making the solutions available is to allow students to check their work. Properly used, these solutions can be helpful for learning the material. By comparing their solutions with those in the solution book, students can obtain an objective evaluation of their comprehension of the subject material. However, the solutions contained here are more extensive than would be expected for a typical student. Hopefully, these more extensive solutions further explicate the material. There is one caveat concerning a possible misuse of this solution book. If a problem is assigned in a subject that uses these textbooks, a student might be tempted to just reproduce the solution after only a cursory reading of the problem. This certainly saves time. However, it short-circuits the process of actively struggling with the problem. This is where learning takes place and the subject material is assimilated. My advice to students is: resist the temptation to use the solution texts in a counterproductive manner. Remember as you struggle to solve a problem, “no pain, no gain.”

The practice of the faculty has been to assign problems for homework one week and then to issue solutions to students the following week when the work was due. These solutions started out as handwritten and progressed over the years to more elaborate typeset solutions. Therefore, when I started the project of producing these solutions books, I gathered together all previous solutions — multiple solutions were typically available for the same problem assigned in different years. These solutions were written by various faculty who have taught the subject as well as by graduate student teaching assistants. In reviewing these solutions, I found with some chagrin that several solutions were incorrect despite the fact that they had been issued many times (by faculty including primarily myself), checked by several teaching assistants, and presumably read by many hundreds of students. I apologize to students who were led astray by errant solutions, but these same students should feel guilty for not having caught the errors. The solutions I have found in error, I have tried to fix. However, my experience with compiling past solutions has left me a bit pessimistic about eliminating all errors from these solutions. I invite the reader to communicate with me to point out any remaining errors. I can be reached via email at tfweiss@mit.edu. I will post errors in the texts and in the problem solution texts on my homepage on the world wide web whose current address is http://umech.mit.edu:80/weiss/home.html. My homepage can be reached through the MIT home page which links to the Department of Electrical Engineering and Computer Science homepage.

As with the textbooks, these solution books were typeset in \TeX with \LaTeX macros on a Macintosh computer using Textures. Spelling was checked with the \LaTeX spell
checker Excalibur. Theoretical calculations were done with Mathematica and MATLAB. Graphic files were imported to Adobe Illustrator for annotation and saved as encapsulated postscript files that were included electronically in the text. Mathematical annotations were obtained by typesetting the mathematical expressions with Textures and saving the typeset version as a file that was read by Adobe Illustrator. The subject is taught with the use of software (Weiss et al., 1992) designed to complement other pedagogic materials we have used. Some of the problems reflect access to this software, but the software is not required to solve any of the problems.

I wish to acknowledge support from a faculty professorship donated to MIT by Gerd and Tom Perkins. My secretaries (Susan Ross and Janice Balzer) were helpful in compiling the solutions from past years. Faculty who have taught the material also developed problems and solutions over the years. In particular, I wish to acknowledge the contributions of my colleagues Denny Freeman and Bill Peake. Finally, my immediate family (Aurice, Max, Elisa, Eric, Kelly, Nico, Sarah, Madison, and Phoebe), which has grown as the writing has progressed, has continued to support me despite my obsession with writing texts.
Chapter 1

INTRODUCTION TO MEMBRANES

Exercises

Exercise 1.1 Cellular membranes consist of lipid bilayers. Each bilayer contains phospholipids which in turn consist of fatty acids, glycerol, and an alcohol. The fatty acids have a hydrocarbon chain consisting typically of 16 or 18 carbon atoms. Since a carbon-carbon bond has a bond length of about 1.5 Å, the length of a fully stretched out chain of 18 carbon atoms is 25.5 Å. Therefore, the portion of the lipid bilayer that is due to the hydrocarbon chains of fatty acids has a maximum length of about 51 Å.

Exercise 1.2 Assume that each position in the protein sequence is equally likely to be any one of the 20 amino acids. Therefore, there are \( N = 20^{100} \) distinct sequences of 100 amino acids. This number can be expressed as a power of 10, i.e.,

\[
N = 10^{100 \log_{10} 20} \approx 10^{130}.
\]

Thus, the number of possible distinct protein sequences consisting of 100 amino acids greatly exceeds the number of atoms in the universe. Clearly, not all of the possible sequences of amino acids are found in nature.

Exercise 1.3

a. The membrane is assumed to be 75 Å thick. Therefore, there are \((75/5.4) \times 3.6 = 50\) amino acids in a membrane-spanning segment.

b. Figure 1.33 (Weiss, 1996a) shows the opacity of the membrane stained with a heavy metal that combines with the hydrophobic portion of the membrane. The distance between the peak opacities is 5.7 nm. Therefore, the hydrophobic domain is less than 5.7 nm. If the hydrophobic portion is assumed to span about half of this distance, then there are \((29/5.4) \times 3.6 = 19\) amino acids in a segment spanning the hydrophobic portion of the membrane.

Exercise 1.4

a. The structure is clearly seen if only two amino acids are used — isoleucine (I), which is hydrophobic, and arginine (R), which is hydrophilic. The sequence of 25 amino acids is displayed in an \( \alpha \) helix in Figure 1.1.
CHAPTER 1. INTRODUCTION TO MEMBRANES

Figure 1.1: An amphipathic α helix of 25 amino acids with hydrophobic amino acids on the left and hydrophilic amino acids on the right (Exercise 1.4). Each number gives the position of that amino acid in the sequence. The diagram shows the amino acids in the form of a helical wheel in which the view is down the axis of the helix.

Exercise 1.5 Both RNA and DNA consist of polymers of nucleotides. Each nucleotide consists of a pentose linked to an organic base and phosphates. In RNA the pentose is ribose; in DNA the pentose is 2-deoxyribose. The bases adenine, guanine, and cytosine are found in both RNA and DNA. The fourth base in RNA is uracil and in DNA is thymine.

Exercise 1.6 Phospholipids are amphipathic with a hydrophilic head and a hydrophobic tail. Therefore, they self-assemble into bilayers with the hydrophilic heads facing aqueous media; cytoplasm on one side and the extracellular solution on the other. These bilayers are relatively impermeable to solutes that dissolve in water. Hence, membranes made of phospholipid bilayers effectively isolate intracellular from extracellular compartments.

Exercise 1.7 All cells contain a cell membrane consisting of a lipid bilayer which is the permeability barrier that separates cytoplasm from the extracellular environment. The cell membrane is highly deformable. Plant cells and some bacteria contain an additional boundary outside the cell membrane, called the cell wall. The cell wall is relatively rigid and gives mechanical rigidity to the cell. The cell wall is highly permeant to most solutes and to water.

Exercise 1.8 The sequence · · · TCTAATAGC · · · corresponds to DNA since it contains thymine, and the sequence · · · UCUAAUAGC · · · corresponds to RNA since it contains uracil.

Exercise 1.9
a. Integral membrane proteins are bound tightly to the membrane and are not readily dislodged without the use of detergents that disrupt the membrane. Integral membrane proteins typically have one or more segments that insert into or span the membrane.

b. A procaryote is a single cell without a nucleus or cell organelles. The genetic material and protein synthesis machinery reside in the cytoplasm.

c. Cytosol is the liquid portion of the cytoplasm. The cytosol together with the organelles make up the cytoplasm.

d. In a covalent bond between dissimilar atoms, the electronic cloud is usually disposed asymmetrical about the two nuclei. The electronegativity of an atom reflects its ability to attract the electronic cloud. For example, consider a highly electronegative atom such as oxygen bound to a less electronegative atom. The center of gravity of the electronic cloud will be closer to the oxygen nucleus than to the nucleus of the less electronegative atom.

e. A hydrogen bond is a secondary chemical bond that forms between a hydrogen atom and two electronegative atoms each of which can separately bind hydrogen. The bond links the two electronegative atoms with an interposed hydrogen atom.

f. A pentose is a 5-carbon sugar.

g. The peptide bond is the bond that links two amino acids in a peptide or protein. The peptide bond is formed by a condensation reaction of the carboxyl group of one amino acid with the amino groups of another.

h. A saturated fatty acid has a hydrocarbon tail that includes the maximum possible number of hydrogen atoms. Each carbon atom in the tail is linked to two hydrogen atoms.

i. An amphipathic molecule has one portion that contains polar chemical groups and another that contains nonpolar chemical groups.

Exercise 1.10

a. This applies to procaryotes, as well as to both eucaryotic plant and animal cells.

b. This applies to none of these cell types.

c. This applies to eucaryotes.

d. This applies to eucaryotes.

e. This applies to procaryotes, as well as to both eucaryotic plant and animal cells.

Exercise 1.11

a. A hydrophobicity plot is a plot of the hydrophobicity of the amino acids’ side chains as a function of the amino acid position in the protein.
b. Regions of sufficient length (ca. 20 amino acids long) that have a high hydrophobicity have been found to be regions of the protein that reside in the lipid bilayer. These regions are separated by regions that are hydrophilic that reside either in the cytoplasmic or extracellular regions.
Chapter 2

INTRODUCTION TO TRANSPORT

Exercises

Exercise 2.1 While elimination of waste products of digestion is an important property of the digestive system, the absorption of nutrients derived from the ingested food is equally important.

Exercise 2.2 The surface area of the small intestine is $20 \times \pi (1.5/12) = 7.9 \text{ ft}^2$. The villi and microvilli have been estimated to increase the surface area by a factor of 600. Hence, the surface area available for absorption is about 4700 ft$^2$ which amounts to a surface area equal to 1.7 tennis courts.

Exercise 2.3 Villi are projections of the intestinal wall into its lumen. They have a length of about 1 mm. Microvilli are projection from the surface of an enterocyte and have a length of about 1 μm. Both serve to extend the surface area available for digestion and transport in the small intestine, but their dimensions differ by three orders of magnitude.

Exercise 2.4 The influx of glucose on the mucosal side of the enterocyte depends upon the sodium gradient across the membrane, because the protein carrier that transports the glucose transports sodium simultaneously. Since the concentration of sodium in the lumen of the intestine exceeds that in the cytoplasm of the enterocyte, sodium and glucose flow into the enterocyte on the mucosal surface. Since sodium will tend to accumulate in the enterocyte due to this mechanism, the role of the sodium/potassium pump is to remove the sodium from the cytoplasm. This pump maintains the difference in sodium concentration between the lumen of the intestine and the cytoplasm of the enterocyte upon which the influx of glucose into the enterocyte depends.

Exercise 2.5

a. Enterocytes are absorptive epithelial cells that line the wall of the intestine. They are responsible for the absorption of the end products of digestion.

b. The glycocalyx is a filamentous structure that coats the microvilli and is attached to the membrane of the enterocyte. The glycocalyx contains enzymes that are important in the final stages of digestion of nutrients just before they are transported into enterocytes.
c. Tight junctions link the membranes of neighboring epithelial cells. At tight junctions the outer leaflets of membranes of apposed cells are fused. These junctions provide a barrier to diffusion of substances in a paracellular route (between the cells) in an epithelium.

d. The lumen of the intestine is the region enclosed by the epithelium in which the products of digestion and the waste products travel in the course of digestion.

e. Amylase is an enzyme that digests carbohydrates and is secreted by both the salivary glands and the pancreas. Amylase hydrolyzes the $\alpha$1,4 linkage common in carbohydrates such as starch.

**Exercise 2.6** The pancreas secretes digestive enzymes into the intestines. These include trypsin, chymotrypsin, carboxypeptidase, lipase, and amylase. The pancreas also secretes several hormones, including insulin and glucagon, into the circulatory system. Insulin and glucagon are important in the utilization of the end products of carbohydrate metabolism.

**Exercise 2.7** Tight junctions provide a barrier to diffusion of substances in a paracellular route (between the cells) in an epithelium.

**Exercise 2.8** In the mouth, the potato is chewed and attacked enzymatically by salivary amylase which breaks chemical bonds in starch. The partially digested potato enters the stomach and then the small intestine where it is further digested by pancreatic amylase into glucose, maltose, and polysaccharide fragments. Maltase and sucrase, located in the glycocalyx of enterocytes, break down maltose into two glucose molecules and sucrose into glucose plus fructose, respectively. Glucose and fructose, are transported into enterocytes and then enter the circulatory system. Ultimately, glucose yields carbon dioxide and water and produces chemical energy in the phosphate bonds of ATP.

**Exercise 2.9** Physiological experiments in which intracellular solutions or the potential across the membrane (such as might be important in sodium-linked amino acid transport) need to be manipulated while the flux of amino acids are measure are probably more easily accomplished in the large invertebrate neurons. With presently available techniques, the transport would have to be studied on a population of bacteria although it could be studied on individual invertebrate neurons. It would be more difficult to discern if there were a population of amino acid transporters that differed subtly in their transport properties for experiments on bacteria than on the invertebrate neurons. Identifying the protein carrier may well be equally done on both cell types. However, genetic experiments in which the portions of the protein carrier are mutated to determine effects on transport are probably done more easily on bacteria which are plentiful, have a short life cycle, and are simpler to manipulate genetically.

**Exercise 2.10** Glucose is transported from the lumen of the small intestine into the circulatory system via membrane transport processes that occur on the apical and basolateral portions of enterocytes. In addition, the uptake of glucose by all cells in the body occurs via membrane resident carriers. Sugar transport into some cell types is
modulated by hormones (e.g., insulin and glucagon) which are released into the circulatory system by cells in the pancreas. The pancreatic cells also contain membrane bound glucose carriers. When the blood glucose concentration changes so does the glucose concentration in the interstitial fluid, which changes the uptake of glucose into the pancreatic cells. The change in intracellular glucose concentration leads to modulation of hormonal release. Thus, many of the important stages in carbohydrate utilization in the body involve membrane processes.
Chapter 3

DIFFUSION

Exercises

Exercise 3.1 The permeability of a membrane for a solute equals the ratio of the outward solute flux through the membrane to the difference between the inside and outside solute concentrations under the assumption that diffusion through the membrane is in steady state.

Exercise 3.2 Given two media 1 and 2 that are in communication with each other and that contain the solute \( n \). The 1:2 partition coefficient \( k_n \) is defined as the ratio of concentrations of \( n \) in liquid 1 to that in liquid 2 when these concentrations have come to equilibrium.

Exercise 3.3 The continuity equation expresses the conservation of a substance during the passage of time. When applied to a volume element, the continuity equation requires that the amount of substance that enters the volume element during some time interval must equal the increase in that substance contained within the volume during that time interval. When applied to a point in space, the continuity equation states that the rate of increase of flux with position equals the rate of decrease of concentration with time. Thus, if the flux is increasing with position at some point, then more flux leaves that point than enters it, and the concentration must be decreasing with time at that point.

Exercise 3.4 Equation 3.1 (Weiss, 1996a) is Fick’s first law which is a macroscopic relation and is independent of any microscopic model of diffusion. Equation 3.18 (Weiss, 1996a) is Fick’s first law derived from a particular microscopic model of diffusion — the one-dimensional random walk.

Exercise 3.5 The modern definition of permeability is given by

\[
P_n = \frac{\phi_n}{c_n^I - c_n^O}.\]

\( P_n \) is the ratio of the flux to the concentration difference across the membrane. The flux is the rate of transport of solute across a unit area of membrane. Thus, \( P_n \) is independent of the dimensions of cells for cells that have membranes made of identical material. As shown in Section 3.7 (Weiss, 1996a), diffusion through the membrane of
a cell can be represented as diffusion between two compartments. Conservation of particles yields

\[- \frac{d c_i^n(t)}{dt} = \frac{A P_n}{V_c} \left( c_i^n(t) - c_o^n(t) \right).\]

Therefore,

\[P_n' = \frac{A P_n}{V_c}.\]

Since \( P_n \) is by definition independent of the dimensions of a cell, \( P_n' \) must depend on cell dimensions. Thus, cells with identical membranes (except for dimensions) have different values of \( P_n' \) but the same values of \( P_n \). Early measurements of properties of membranes based on estimates of \( P_n' \) showed great scatter across different cells. Part of this scatter is attributable to the different dimensions of cells and not to intrinsic differences in their membranes.

**Exercise 3.6** In steady-state diffusion, the flux and concentration of particles are constant in time. In equilibrium, the flux and concentration of particles are constant in time and, in addition, the flux is zero.

**Exercise 3.7** The steady-state time constant (\( \tau_{ss} \)) in the membrane is a measure of the time required for the membrane to reach steady state. In steady state, the solute concentration depends linearly on position in the membrane. The equilibrium time constant (\( \tau_{eq} \)) for the two compartments is a measure of the time required for the baths to reach diffusive equilibrium. At diffusive equilibrium the concentrations of solute in both baths are equal.

**Exercise 3.8** Solutes that obey the **dissolve-diffuse theory** first dissolve in the membrane and then diffuse through it.

**Exercise 3.9** Collander plots relate the permeability of solutes through cellular membranes to the organic-solvent/water partition coefficient. Because of the large range of both variables, the data are normally plotted in logarithmic coordinates. Collander plots determine the relation between the permeability of a cellular membrane for a solute and the ratio of the solubility of that solute in an organic solvent to that in water. Collander plots have been used to test the dissolve-diffuse theory of diffusion through cellular membranes.

**Exercise 3.10** Figure 3.1 shows the concentration profile at the time that the membrane has just reached steady-state. The concentration in bath 1 is \( C \) and that in bath 2 is nearly zero (a small amount of solute will actually enter bath 2 while the membrane is approaching steady state, so the concentration in bath 2 is not exactly zero). The concentration in the membrane decreases linearly from \( 1.5C \) at \( x = 0 \) to near zero at \( x = d \). The value at \( x = 0 \) exceeds the value in bath 1 because the partition coefficient is 1.5.

**Exercise 3.11** Bath 2 will come to equilibrium with Bath 1 when \( c_{n}^{2}(\infty) = C \) and the concentration of bath 2 will change exponentially from \( c_{n}^{2}(0) = 0 \) to \( c_{n}^{2}(\infty) = C \), i.e.,

\[c_{n}^{2}(t) = C(1 - e^{-t/\tau_{eq}}) \text{ for } t \geq 0,
\]

where \( \tau_{eq} = V/(A P_n) \). The results are shown in Figure 3.2.
Exercise 3.12 A crude approximation can be obtained by computing the time \( t_{1/2} \) taken for 1/2 the particles released at a point to move at least 200 Å, which is

\[
t_{1/2} = \frac{x_{1/2}^2}{D} = \frac{(200 \times 10^{-8})^2}{5 \times 10^{-6}} = \frac{4}{5} \times 10^{-6} \approx 1 \text{ ms}.
\]

This calculation gives the order of magnitude of the time it takes for the transmitter to diffuse. This crude estimate does not take the geometry of the synaptic cleft into account.

Exercise 3.13 The equilibrium distribution of solute \( n \) results from two physical mechanisms — gravity which tends to pull the solute to the bottom of the cylinder and diffusion which tends to disperse the solute in the solution. The mass of Jupiter is \( 1.9 \times 10^{27} \text{ kg} \) and the mass of the Earth is \( 5.98 \times 10^{24} \text{ kg} \). Therefore, the force of gravity on the surface is 318 times larger on Jupiter than on Earth. Therefore, we expect intuitively that the solute will be located closer to the bottom of the cylinder on Jupiter than on Earth as indicated in Figure 3.3. A more quantitative analysis, which is required to obtain a more precise result, follows. The flux of particles due to diffusion and gravity-induced
convection in the $y$ direction is

$$\phi(y) = -D \frac{dc_n(y)}{dy} + uc_n(y)f$$

The molar force $f = -mg$ where $m$ is the mass of a mole of solute particles and $g$ is the acceleration of gravity. The Einstein relation relates the diffusion coefficient to the molar mechanical mobility, i.e., $D = uRT$. Combining all these relations and noting that at equilibrium $\phi(y) = 0$ yields the differential equation

$$\frac{dc_n(y)}{dy} + \frac{c_n(y)}{\lambda} = 0,$$

where $\lambda = RT/(mg)$. The solution to this equation is

$$c_n(y) = Ke^{-y/\lambda},$$

where $K$ is a constant to be determined by the boundary conditions. Suppose the cylinder on earth and on jupiter contained the same number of moles of solute. Then

$$AK \int_0^\infty e^{-y/\lambda} dy = N_n,$$

where $A$ is the cross-sectional area of the cylinder and $N_n$ is the total number of moles of solute $n$. Evaluation of the integral yields $K = N_n/(A\lambda)$ so that

$$c_n(y) = \frac{N_n}{A\lambda} e^{-y/\lambda}.$$

Thus, the spatial distribution of concentration is exponential in $y$ with space constant $\lambda$. The space constant is inversely related to $g$. Hence, the space constant is 318 times smaller than on earth and the concentration at the bottom of the cylinder is 318 times larger. From an earth based frame of reference, it appears that all the particles lie at the bottom of the cylinder on jupiter.

**Exercise 3.14** The impulse response $c_n(x, t)$ at $x_b$ is larger and reaches its maximum value more rapidly than at $x_a$. Therefore, $x_b$ is closer to the source than is $x_a$. Hence, $x_a > x_b$.

**Exercise 3.15** Cell $a$ equilibrates more rapidly than cell $b$. Therefore, the equilibrium time constant for cell $a$ is smaller than for cell $b$, i.e., $\tau_{eqa} < \tau_{eqb}$. Since $\tau_{eq} = V_e/(AP_n)$, $P^a_n > P^b_n$.

**Exercise 3.16** Consider the concentrations at the left-hand membrane interface. As shown in Figure 3.52 (Weiss, 1996a),

$$\frac{c_a(0)}{c_a^1} = k_a > 1 \text{ and } \frac{c_b(0)}{c_b^1} = k_b < 1,$$

where $c_a(0)$ and $c_b(0)$ are the concentrations of solutes $a$ and $b$ in the membrane at the left interface, and $c_a^1$ and $c_b^1$ are the concentrations of solutes $a$ and $b$ in bath 1. Therefore, $k_a > k_b$. The same conclusion can be reached by examining the concentrations at the right membrane interface.
Exercise 3.17  Since the concentration in compartment a changes less than that in compartment b, compartment a has the larger volume. More formally, Figure 3.53 (Weiss, 1996a) shows that \( c_a^a(0) - c_a^a(\infty) < c_b^b(\infty) - c_b^b(0) \). But \( c_a^a(\infty) = c_b^b(\infty) \) and \( c_b^b(0) = 0 \). Combining these relations yields \( c_a^a(0) < 2c_a^a(\infty) \). Let \( n_n^a \) be the number of moles of \( n \) in compartment \( a \). Then,

\[
\frac{n_n^a}{V_a} < 2 \frac{n_n^a}{V_a + V_b},
\]

from which it follows that

\[
V_a + V_b < 2V_a \text{ which implies that } V_b < V_a.
\]

Exercise 3.18  Based on Figure 3.54 (Weiss, 1996a), the concentration can be expressed as

\[
c(x, t_0) = (10 + 10 \cos(4\pi x)) \times 10^{-3} \text{ (mol/cm}^3\text{)},
\]

where \( x \) is expressed in cm. From Fick’s first law

\[
\phi(x, t_0) = -D \frac{\partial c(x, t_0)}{\partial x} = 4\pi D \times 10^{-2} \sin(4\pi x) \text{ (mol/(cm}^2\cdot\text{s})\text{)}.
\]

The concentration and flux are shown in Figure 3.4.

Problems

Problem 3.1  This problem explores the diffusion of a substance in a cellular process when that substance is used up in the cytoplasm.

a. The continuity equation is

\[
\frac{\partial \phi_n}{\partial z} = -\frac{\partial c_n}{\partial t} - \frac{\alpha_n}{A},
\]

and Fick’s first law is

\[
\phi_n = -D \frac{\partial c_n}{\partial z}.
\]

These two equations can be combined by taking \( \partial/\partial z \) of Fick’s first law to yield

\[
D \frac{\partial^2 c_n(z, t)}{\partial z^2} = \frac{\partial c_n}{\partial t} + \frac{\alpha_n}{A}.
\]
b. In the steady state $\partial c_n/\partial t = 0$. Therefore,

$$D \frac{d^2 c_n(z)}{dz^2} = \frac{\alpha_n}{A}.$$ 

Integrating twice yields

$$c_n(z) = \frac{\alpha_n}{2DA} z^2 + a_0 z + b_0.$$ 

The constants $a_0$ and $b_0$ are evaluated from the boundary conditions. At $z = 0$ this evaluation gives

$$c_n(0) = C_o = b_0.$$ 

At $z = l$, $\phi_n(l) = 0$. Therefore, from Fick’s first law

$$\phi_n(l) = -D \left( \frac{\partial c_n}{\partial z} \right)_{z=l} = -\frac{\alpha_n}{A} l - Da_o = 0.$$ 

Therefore,

$$a_0 = -\frac{\alpha_n l}{DA}.$$ 

c. The concentration can be expressed as

$$c_n(z) = \frac{\alpha_n}{DA} z \left( \frac{z}{2} - l \right) + C_o \text{ for } 0 < z < l.$$ 

This relation can be written as

$$\frac{c_n(z)}{C_o} = \frac{\alpha_n l^2}{DAC_o} \frac{z}{l} \left( \frac{z}{2l} - l \right) + 1 \text{ for } 0 < z < l,$$

which is plotted in Figure 3.5. The concentration must be positive at all positions along the process. Since the concentration has its smallest value at $z = l$,

$$c_n(l) = C_o - \frac{\alpha_n}{2DA} l^2 > 0.$$ 

The condition that the concentration is positive at its smallest value places an upper limit on the length of the process $l_{\text{max}}$ which is

$$l_{\text{max}} = \sqrt{\frac{2DAC_o}{\alpha_n}}.$$
This result shows that \( l_{\text{max}} \) increases if: the diffusion coefficient increases, the cross-sectional area of the process increases, the concentration at \( z = 0 \) increases, and the rate \( \alpha_n \) decreases. This makes intuitive sense. For example, we might expect that as the rate at which the substance \( n \) is removed increases, the length of the process over which steady state can be maintained decreases.

To illustrate the numerical consequences of this problem, we examine the expression for \( l_{\text{max}} \). The quantity \( AC_0 / \alpha_n \) has the units of time, since it is the ratio of the concentration per unit length to the rate of change of concentration per unit length. \( AC_0 / \alpha_n \) represents the time it takes to use up all of the metabolite. Suppose this time is 10 s and \( D = 10^{-5} \text{ cm}^2/\text{s} \) (Section 3.3). Then,

\[
l_{\text{max}} = \sqrt{2 \times 10^{-5} \text{ cm}^2/\text{s} \times 10 \text{ s}} = 0.014 \text{ cm}
\]

which is very short compared to the axons of many neurons, but is comparable to the flagellum of a sperm cell.

**Problem 3.2** Diffusion in the presence of both convection and a chemical reaction is described by Fick's first law, modified by the presence of convection, and by the continuity equation, modified by the effect of the chemical reaction,

\[
\phi = -D \frac{\partial c}{\partial x} + \nu c,
\]

\[
\frac{\partial \phi}{\partial x} = -\frac{\partial c}{\partial t} - \alpha c.
\]

If these equations are combined they yield a modified diffusion equation that incorporates both convection and the effect of the chemical reaction,

\[
\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - \nu \frac{\partial c}{\partial x} - \alpha c.
\]

a. If there is no chemical reaction to eliminate particles \( \alpha = 0 \).

i. At equilibrium, \( \phi = 0 \) and \( \partial c / \partial t = 0 \). Therefore, Fick’s first law becomes

\[
-D \frac{dc}{dx} + \nu c = 0.
\]

To determine the general form of the solution, try the solution \( c = Ae^{px} \) which yields

\[
-DAe^{px} + \nu Ae^{px} = 0,
\]

which can be divided by \( Ae^{px} \) to yield the characteristic equation

\[
-Dp + \nu = 0.
\]

The natural frequency is the root of the characteristic polynomial and is

\[
p = \nu / D.
\]

Therefore, the general solution at equilibrium has the form

\[
c(x) = Ae^{\nu x / D}.
\]

In the presence of convection, the equilibrium distribution of concentration is exponential in space.
ii. In the steady state, the flux need not be zero. However, $\partial c / \partial t = 0$. Under steady-state conditions, the diffusion equation becomes

$$0 = D \frac{d^2 c}{dx^2} - \nu \frac{dc}{dx}.$$  

To determine the form of the solution, try a solution of the form $c = Ae^{px}$, which yields

$$DAp^2e^{px} - vApe^{px} = 0.$$  

Since $Ae^{px} \neq 0$, the equation can be divided by this factor to yield the characteristic equation

$$Dp^2 - vp = 0.$$  

The characteristic polynomial has two roots $p = 0$ and $p = v/D$. Therefore, the general form of the solution is

$$c(x) = A_1 + A_2e^{vx/D}.$$  

The constants $A_1$ and $A_2$ are found by matching the boundary conditions $c(0) = 0$ and $c(1) = 1$ mol/cm$^3$. Application of the boundary condition at $x = 0$ yields $c(0) = 0 = A_1 + A_2$ which implies that $A_1 = A_2$. Therefore, the solution has the form

$$c(x) = A \left(1 - e^{vx/D}\right).$$  

Application of the boundary condition at $x = 1$ yields

$$c(1) = 1 = A \left(1 - e^{v/D}\right),$$  

so that

$$A = \frac{1}{1 - e^{v/D}}.$$  

Therefore, the solution is

$$c(x) = \frac{1 - e^{vx/D}}{1 - e^{v/D}}.$$  

The solution is shown in Figure 3.6 for a diffusion coefficient of $D = 10^{-5}$ cm$^2$/s and for convection velocities of $\pm 1$ cm/s. Note that $c(0) = 0$ and $c(1) = 1$ and the change in $c(x)$ occurs within a narrow range of $x$ because the exponent is $\nu x/D = \pm 10^5x$. Mathematically, for $\nu > 0$ $c(x)$ changes rapidly near $x = 1$, whereas for $\nu < 0$ $c(x)$ changes rapidly near $x = 0$. Physically, if the velocity is positive then particles are swept from the left to the right, whereas if the velocity is negative then the particles are swept from the right to the left.

b. Now assume that a chemical reaction removes particles at a rate $\alpha \neq 0$. At equilibrium the flux is zero and the diffusive variables are time independent. Note the continuity relation for these conditions reduces to

$$0 = -\alpha c.$$  

Therefore, the only solution is $c(x) = 0$. At equilibrium all of the particles are consumed.
Problem 3.3 Substitute the solution to the modified diffusion equation \( g(x, t) \) into the modified diffusion equation and differentiate by parts to obtain

\[
\frac{\partial f(x, t)}{\partial t}e^{-\alpha t} - \alpha e^{-\alpha t} f(x, t) = D \frac{\partial^2 f(x, t)}{\partial x^2} e^{-\alpha t} - \alpha e^{-\alpha t} f(x, t).
\]

Cancellation of common terms on the two sides of the equation and division of both sides of the equation by \( e^{-\alpha t} \) yields

\[
\frac{\partial f(x, t)}{\partial t} = D \frac{\partial^2 f(x, t)}{\partial x^2}
\]

which shows that since \( g(x, t) \) satisfies the modified diffusion equation, \( f(x, t) \) satisfies the diffusion equation. The method developed in this problem yields a transformation through which the modified diffusion equation can be transformed into the diffusion equation. Thus, a knowledge of the solution to one of these equations gives the solution to the other.

Problem 3.4 The chain rule of partial differentiation is used to relate the partial derivatives of \( g \) and \( f \). Since there are now 3 variables, a subscript is used to indicate which variables are held constant. The partial derivatives with respect to time are evaluated first.

\[
\left( \frac{\partial f(z, t)}{\partial t} \right)_z = \left( \frac{\partial g(x, t)}{\partial t} \right)_x + \left( \frac{\partial g(x, t)}{\partial x} \right)_t \left( \frac{\partial x}{\partial z} \right)_z,
\]

\[
\left( \frac{\partial f(z, t)}{\partial t} \right)_z = \left( \frac{\partial g(x, t)}{\partial t} \right)_x + \nu \left( \frac{\partial g(x, t)}{\partial x} \right)_t.
\]

The first partial derivatives with respect to space is evaluated as follows.

\[
\left( \frac{\partial f(z, t)}{\partial z} \right)_t = \left( \frac{\partial g(x, t)}{\partial z} \right)_t \left( \frac{\partial x}{\partial z} \right)_t,
\]

\[
\left( \frac{\partial f(z, t)}{\partial z} \right)_t = \left( \frac{\partial g(x, t)}{\partial x} \right)_t.
\]
Similarly, 

\[
\left( \frac{\partial^2 f(z,t)}{\partial z^2} \right)_t = \left( \frac{\partial^2 g(x,t)}{\partial x^2} \right)_t.
\]

Now these relations are substituted into the diffusion equation.

\[
\frac{\partial f(z,t)}{\partial t} = D \frac{\partial^2 f(z,t)}{\partial z^2},
\]

\[
\frac{\partial g(x,t)}{\partial t} + \nu \frac{\partial g(x,t)}{\partial x} = D \frac{\partial^2 g(x,t)}{\partial x^2}.
\]

Therefore,

\[
\frac{\partial g(x,t)}{\partial t} = D \frac{\partial^2 g(x,t)}{\partial x^2} - \nu \frac{\partial g(x,t)}{\partial x}.
\]

The method developed in this problem yields a transformation through which the modified diffusion equation can be transformed into the diffusion equation. Thus, a knowledge of the solution to one of these equations gives the solution to the other.

**Problem 3.5**

a. Diffusion from a point source in the absence of convection has the solution

\[
c(x,t) = \frac{1}{\sqrt{4\pi Dt}} e^{-x^2/4Dt}, \text{ for } t > 0.
\]

As shown in Problem 3.4, the solution with convection at velocity \( \nu \) is

\[
c(x,t) = \frac{1}{\sqrt{4\pi Dt}} e^{-(x-\nu t)^2/4Dt}, \text{ for } t > 0,
\]

where \( \nu = uf, u \) is the molar mechanical mobility, and \( f \) is the molar force.

b. The diffusion coefficient and the mobility can be estimated from the measurements shown in Figure 3.7. The peak concentration is about 450 mol/m\(^3\) and occurs at \( x = 1.6 \text{ mm} \). The half-width of the spatial distribution measured where the concentration is down to \( 1/e \approx 0.3679 \) of its peak value is about 1.3 mm. Note that the concentration is down \( 1/e \) when \( (x-\nu t)^2/4Dt = 1 \). Therefore, \( (1.3 \times 10^{-3})^2 = 4D \times 200 \) which implies that \( D \approx 2.1 \times 10^{-9} \text{ m}^2/\text{s} \).
c. The Einstein relation is \( D = uRT \). Therefore, the mobility is

\[
u = \frac{2.1 \times 10^{-9} \text{ m}^2/\text{s}}{(8.314 \text{ J/(mol \cdot K))}(300 \text{ K})} = 8.47 \times 10^{-13} \text{ (m/s)/(N/mol)}.\]

d. To obtain the force on a mole of particles, use the relation \( \nu = uf \). The convection velocity is determined from the displacement of the peak value of the concentration, i.e., \( \nu \cdot 200 = 1.6 \times 10^{-3} \) so that \( \nu = 0.8 \times 10^{-5} \text{ m/s} \). Therefore, \( f = \nu/u = (0.8 \times 10^{-5})/(8.47 \times 10^{-13}) = 9.45 \times 10^6 \text{ N/mol} \).

**Problem 3.6** The flux through both membranes is the same and steady state applies to both membranes. Since each membrane obeys Fick’s law for membranes, \( \phi_n = P_1 (c^1_n - c^n_0) = P_2 (c^n_0 - c^2_n) \) from which

\[
\frac{\phi_n}{P_1} + c^n_0 = c^1_n \quad \text{and} \quad \frac{\phi_n}{P_2} - c^n_0 = -c^2_n.
\]

Summing these two equations yields

\[
\phi_n \left(\frac{1}{P_1} + \frac{1}{P_2}\right) = c^1_n - c^2_n,
\]

which can be written as

\[
\phi_n = \frac{P_1 P_2}{P_1 + P_2} (c^1_n - c^2_n).
\]

Therefore,

\[
P = \frac{P_1 P_2}{P_1 + P_2},
\]

which demonstrates that the permeability of the two membranes in series is smaller than the smaller of the two permeabilities \( P_1 \) and \( P_2 \). By taking the reciprocal of this expression,

\[
\frac{1}{P} = \frac{1}{P_1} + \frac{1}{P_2},
\]

which shows that the reciprocal of the permeabilities add for two membranes in series (two membranes through which the same flux flows).

**Problem 3.7** Because steady state applies in the membrane, the flux through patch 1 is \( \phi^1_n = P_1 (c^1_n - c^n_0) \), and that through patch 2 is \( \phi^2_n = P_2 (c^n_0 - c^2_n) \). The total flux is the total quantity of solute flowing through both patches per unit area per unit time. Therefore,

\[
\phi = \frac{P_1 A_1 (c^1_n - c^n_0) + P_2 A_2 (c^n_0 - c^2_n)}{A_1 + A_2} = \frac{P_1 A_1 + P_2 A_2}{A_1 + A_2} (c^1_n - c^2_n)
\]

Thus,

\[
P = P_1 \left( \frac{A_1}{A_1 + A_2} \right) + P_2 \left( \frac{A_2}{A_1 + A_2} \right).
\]

The permeability of the membrane is a weighted sum of the permeabilities of the two types of membrane. Each weighting factor equals the fraction of the area occupied by that membrane type.
Problem 3.8

a. Let us call the concentration at the membrane surface on side 1, \(C_{s1}\), and on side 2, \(C_{s2}\). Then in the steady state, the flux can be expressed as

\[
\phi = P_m(C_1 - C_2) = P(C_{s1} - C_{s2}),
\]

and the problem is to determine the relation between \(P\) and \(P_m\) which can be determined from \(C_{s1}\) and \(C_{s2}\). Steady-state diffusion is assumed to occur in each unstirred layer. Therefore, in each of these regions, the flux and concentration are independent of time and satisfy Fick’s first law of diffusion, i.e.,

\[
\phi = -D \frac{dc(x)}{dx}.
\]

Integrating this relation yields

\[
\int_{c_a}^{c_b} dc = -\frac{\phi}{D} \int_a^b dx.
\]

Hence,

\[
c_b - c_a = -\frac{\phi}{D}(b - a).
\]

Application of this result to the two unstirred layers yields

\[
C_{s1} - C_1 = -\frac{\phi}{D_1}d_1,
\]

\[
C_2 - C_{s2} = -\frac{\phi}{D_2}d_2.
\]

Addition of these equations yields

\[
C_1 - C_2 = (C_{s1} - C_{s2}) + \phi \left(\frac{d_1}{D_1} + \frac{d_2}{D_2}\right).
\]

Division of this equation by \(\phi\) and identification of terms yields

\[
\frac{1}{P_m} = \frac{1}{P} + \frac{d_1D_2 + d_2D_1}{D_1D_2} = \frac{1}{P} + \frac{1}{P_l},
\]

where \(P_l\) is the equivalent permeability of the unstirred layer

\[
P_l = \frac{D_1D_2}{d_1D_2 + d_2D_1}.
\]

The measured permeability can also be expressed as

\[
P_m = \frac{PP_l}{P + P_l}.
\]

Define the reciprocal of the permeability as the diffusive resistance \(\mathcal{R}\). Then the measured diffusive resistance is the sum of the diffusive resistance of the membrane and the diffusive resistance of the unstirred layer \(\mathcal{R}_m = \mathcal{R} + \mathcal{R}_l\).
b. Note that when the permeability of the membrane is large compared to the permeability of the unstirred layer \( P \gg P_l \), the measured permeability approaches the permeability of the unstirred layer \( P_m \approx P_l \) and not the permeability of the membrane. If the permeability of the membrane is much lower than that of the unstirred layer, then the measured permeability approaches that of the membrane. Therefore, measurements of the permeability of highly permeant solutes are affected more by unstirred layers than are measurements of the permeability of poorly permeant solutes.

**Problem 3.9** Figure 3.36 (Weiss, 1996a) shows a plot of extracellular propanol concentration which according to the two-compartment diffusion theory should have the form

\[
\ln \left( \frac{c^n_p(t) - c^n_p(\infty)}{c^n_p(0) - c^n_p(\infty)} \right) = -t/\tau_{eq},
\]

where \( \tau_{eq} = V_e/(AP_p) \). \( V_e \) is the equivalent volume of the two compartments which approximately equals the volume of the erythrocyte since the extracellular volume is much greater than that of an erythrocyte. \( A \) is the surface area of the erythrocyte and \( P_p \) is the permeability of the membrane to propanol. Because the initial extracellular concentration is zero, the expression simplifies to

\[
\ln \left( 1 - \frac{c^n_p(t)}{c^n_p(\infty)} \right) = -t/\tau_{eq}.
\]

Thus, the two-compartment diffusion model predicts that the concentration plotted in these normalized, semi-logarithmic coordinates should be a straight line as a function of time. The measurements are consistent with this theory. Therefore, \( \tau_{eq} \) must be determined from the measurements, and the permeability computed from \( \tau_{eq} \) as well as the known surface area and volume of erythrocytes. The measurements indicate that in 15 ms, the normalized concentration has value 0.1. Therefore, \( \ln 0.1 = -15/\tau_{eq} \), where \( \tau_{eq} \) is in ms. Evaluation of this expression yields \( \tau_{eq} = 6.5 \) ms. The permeability is \( P_p = V_e/(A\tau_{eq}) \) which can be evaluated from

\[
P_p = \frac{104 \times (10^{-4})^3}{137 \times (10^{-4})^2 \times 6.5 \times 10^{-3}} = 1.2 \times 10^{-2} \text{ cm/s}.
\]

**Problem 3.10** This problem involves one-dimensional diffusion from a point source. Hence, the concentration is a Gaussian function of space and time,

\[
c(x, t) = \frac{n_0}{\sqrt{4\pi D t}} e^{-x^2/4Dt} \text{ for } t > 0.
\]

a. To find the maximum value of \( c(x, t) \) as a function of time for any fixed point in space, \( x_p \), set the partial derivative of \( c(x_p, t) \) with respect to \( t \) to zero.

\[
\frac{\partial c(x_p, t)}{\partial t} = \frac{n_0}{\sqrt{4\pi D}} e^{-x_p^2/4Dt} \left( -\frac{1}{2t^{3/2}} + \frac{(-x_p^2/4D)(-1/t^2)}{t^{1/2}} \right) = 0.
\]
Therefore,
\[ \frac{1}{2t_m^{3/2}} = \frac{x_p^2}{4Dt_m^{3/2}}, \]
which gives
\[ t_m = \frac{x_p^2}{2D}. \]

b. For \( x = 1 \) cm, \( D = 0.5 \times 10^{-5} \) cm\(^2\)/s, \( t_m = 10^5 \) s \( \approx 1 \) day. Therefore, if you want your coffee to be sweet this morning, stir it!

**Problem 3.11**

a. For steady-state conditions in the membrane,
\[ \phi_X = P_X(c_X^i - c_X^c). \]

From conservation of \( X \)
\[ \frac{d(c_X^i V)}{dt} = -A\phi_X, \]
and since \( V \) is constant,
\[ \frac{dc_X^i}{dt} = -\frac{A}{V}\phi_X. \]

Therefore
\[ \frac{dc_X^i}{dt} = -\frac{A}{V}P_X(c_X^i - c_X^c), \]
which can be written as
\[ \frac{dc_X^i}{dt} + \frac{AP_X}{V}c_X^i = \frac{AP_X}{V}c_X^c. \]

This is a first-order differential equation with constant coefficients. Hence, the solution is exponential of the form
\[ c_X^i(t) = c_X^i(\infty) + (c_X^i(0) - c_X^i(\infty))e^{-t/\tau_{eq}}. \]

The parameters of the exponential equation are obtained from the initial conditions and the differential equation and are
\[ c_X^i(0) = 0, \quad c_X^i(\infty) = c_X^c, \quad \tau_{eq} = \frac{V}{AP_X}. \]

Therefore, the solution is
\[ c_X^i(t) = c_X^c\left(1 - e^{-t/\tau_{eq}}\right). \]

The measurement shows that the time constant for equilibration is 100 s. Therefore,
\[ \tau_{eq} = \frac{V}{AP_X} = 100 = \frac{4\pi(30 \times 10^{-4})^3}{4\pi(30 \times 10^{-4})^2P_X}. \]

Solving for \( P_X \) yields
\[ P_X = \frac{30 \times 10^{-4}}{3 \times 10^{-2}} = 10^{-5} \text{ cm/sec}. \]
b. For steady-state diffusion in the membrane, the permeability is

\[ P_X = \frac{D_X k_X}{d}, \]

which can be solved for \( D_X \) to yield

\[ D_X = \frac{P_X d}{k_X} = \frac{(10^{-5})10^{-6}}{0.2} = 5 \times 10^{-11} \text{ cm}^2/\text{s}. \]

c. The time constant for the membrane to reach steady state \( \tau_{ss} \) is

\[ \tau_{ss} = \frac{d^2}{\pi^2 D} = \frac{(10^{-6})^2}{\pi^2 \times 5 \times 10^{-11}} \approx 2 \text{ ms}. \]

d. Since \( \tau_{ss} \ll \tau_{eq} \), the membrane will be equilibrated instantaneously relative to the time required for \( c_1^X \) to change appreciably. Therefore, the steady-state assumption is justified.

**Problem 3.12**

a. Since \( c_1(x, t) \) and \( c_2(x, t) \) are solutions,

\[ D \frac{\partial^2 c_1(x, t)}{\partial x^2} = \frac{\partial c_1(x, t)}{\partial t} \quad \text{and} \quad D \frac{\partial^2 c_2(x, t)}{\partial x^2} = \frac{\partial c_2(x, t)}{\partial t}. \]

The equations can be scaled by \( a \) and \( b \) to obtain

\[ D \frac{\partial^2 (ac_1(x, t) + bc_2(x, t))}{\partial x^2} = \frac{\partial (ac_1(x, t) + bc_2(x, t))}{\partial t}. \]

Addition of these two equations yields

\[ D \frac{\partial^2 (ac_1(x, t) + bc_2(x, t))}{\partial x^2} = \frac{\partial (ac_1(x, t) + bc_2(x, t))}{\partial t}, \]

which shows that \( ac_1(x, t) + bc_2(x, t) \) is a solution to the diffusion equation.

b. To determine if \( c(x, t) = C_0 + y(t) \cos(2\pi x/\lambda) \) is a solution to the diffusion equation, substitute this expression into the diffusion equation which requires evaluating the partial derivatives of this function.

\[ \frac{\partial c(x, t)}{\partial t} = \frac{dy(t)}{dt} \cos(2\pi x/\lambda) \]
\[ \frac{\partial^2 c(x, t)}{\partial x^2} = -y(t) \left( \frac{2\pi}{\lambda} \right)^2 \cos(2\pi x/\lambda). \]

Therefore,

\[ \frac{dy(t)}{dt} \cos(2\pi x/\lambda) = -Dy(t) \left( \frac{2\pi}{\lambda} \right)^2 \cos(2\pi x/\lambda). \]

This equation can be simplified to give

\[ \frac{dy(t)}{dt} + D \left( \frac{2\pi}{\lambda} \right)^2 y(t) = 0, \]
whose solution is
\[ y(t) = C_1 e^{-t/\tau}, \]
where
\[ \tau = \frac{1}{D} \left( \frac{\lambda}{2\pi} \right)^2. \]

Therefore, the total solution has the form
\[ c(x, t) = C_0 + C_1 e^{-t/\tau} \cos(2\pi x/\lambda). \]

Substitution of \( t = 0 \) indicates that the initial boundary condition is
\[ c(x, 0) = C_0 + C_1 \cos(2\pi x/\lambda). \]

Thus, the total solution satisfies the diffusion equation and matches the initial concentration.

The time constant \( \tau \) is a measure of the time it takes for the initial sinusoidal spatial distribution of concentration to reach diffusive equilibrium. This time constant varies inversely with the diffusion coefficient \( D \). That is, for solute particles that diffuse more rapidly, i.e., have a larger diffusion coefficient, the initial spatial concentration will equilibrate more rapidly. The time constant also varies directly as the square of the wavelength of the concentration \( \lambda \). Thus, the time constant increases as the wavelength increases. This makes intuitive sense since we expect that rapid variations of concentration in space, which have small wavelengths, will be smoothed out more rapidly than slow variations in concentration. Thus, high-frequency periodic initial concentrations decay more rapidly than do low-frequency initial concentrations.

c. In part a it was shown that the diffusion equation is a linear partial differential equation and the solution for an initial sinusoidal spatial distribution of concentration was found in part b. These results can be combined with the use of the Fourier series to determine the concentration that results from an arbitrary, periodic initial spatial distribution.

A periodic function of \( x \), such as \( c(x, 0) \), can be expanded in a Fourier series of the form
\[ c(x, 0) = c_0 + \sum_{n=1}^{\infty} c_n \cos(2\pi nx/\lambda) + \sum_{n=1}^{\infty} d_n \sin(2\pi nx/\lambda). \]

The initial rectangular wave of concentration is an even function of \( x \). Hence, the coefficients of the sine terms in the Fourier series must be zero. Furthermore, the constant component is \( C_0 \) so that the Fourier series has the form
\[ c(x, 0) = C_0 + \sum_{n=1}^{\infty} c_n \cos(2\pi nx/\lambda). \]

However \( c_n \) needs to be determined. These coefficients can be found by multiplying both sides by \( \cos(2\pi nx/\lambda) \) and integrating the product over one wavelength.
Therefore,
\[
\frac{1}{\lambda} \int_{-\lambda/2}^{\lambda/2} c(x, 0) \cos(2\pi nx/\lambda) \, dx = \frac{1}{\lambda} \int_{-\lambda/2}^{\lambda/2} C_0 \cos(2\pi nx/\lambda) \, dx \\
+ \sum_{m=1}^{\infty} c_m \frac{1}{\lambda} \int_{-\lambda/2}^{\lambda/2} \cos(2\pi mx/\lambda) \cos(2\pi nx/\lambda) \, dx.
\]

The first term on the right-hand side of the equation is the integral over an integer number of wavelengths of a cosine wave and is zero. The second term can be written as two cosinusoids, one at the sum of the spatial frequencies and the other at the difference of the spatial frequencies. The second term is also zero except when \(m = n\). Under this condition, the integrand is \(\cos^2(2\pi mx/\lambda) = (1/2)(1 + \cos(4\pi mx/\lambda))\). Therefore, the second integral equals \(1/2\) and
\[
c_n = \frac{2}{\lambda} \int_{-\lambda/2}^{\lambda/2} c(x, 0) \cos(2\pi nx/\lambda) \, dx.
\]

The integral can be evaluated over any period of the cosine wave. Because of the symmetry of the rectangular wave,
\[
c_n = \frac{4}{\lambda} \int_{-\lambda/4}^{\lambda/4} c(x, 0) \cos(2\pi nx/\lambda) \, dx.
\]

Therefore,
\[
c_n = \left( \frac{4C_1}{\lambda} \right) \left( \frac{\lambda}{2\pi n} \right) \sin(2\pi nx/\lambda) \bigg|_{-\lambda/4}^{\lambda/4} = 2C_1 \left( \frac{\sin(n\pi/2)}{n\pi/2} \right).
\]

Note that \(\sin(n\pi/2) = 0\) if \(n\) is even. Hence, only the odd terms are non-zero. The concentration as a function of time for an initial sinusoidal concentration profile was found in part b. Now it has been shown that the initial concentration, a rectangular wave, can be expressed as a sum of sinusoidal profiles. Since, the diffusion equation is linear the concentration for each sinusoidal component of the initial rectangular wave can be determined and the components then summed. The result is
\[
c(x, t) = C_0 + \sum_{n=1}^{\infty} 2C_1 \left( \frac{\sin(n\pi/2)}{n\pi/2} \right) e^{-t/\tau_n} \cos(2\pi nx/\lambda).
\]

where
\[
\tau_n = \frac{1}{D} \left( \frac{\lambda}{2\pi n} \right)^2.
\]

The dependence of the fundamental frequency component \((n = 1)\) on \(x\) and \(t\) is shown in Figure 3.8. The graph shows a plot of
\[
\left( \frac{4}{\pi} \right) e^{-t/\tau_1} \cos(2\pi x/\lambda)
\]
as a function of the normalized space and time variables, \(x/\lambda\) and \((D/\lambda^2)t\). The initial sinusoidal spatial distribution of concentration remains sinusoidal but its
CHAPTER 3. DIFFUSION

Figure 3.8: A plot of the fundamental component of the solution for an initial rectangular wave of concentration (Problem 3.12).

Figure 3.9: A plot of the third harmonic component of the solution for an initial rectangular wave of concentration (Problem 3.12).
amplitude decays as time elapses. Figure 3.9 shows a similar plot for the third harmonic of the solution \( n = 3 \). The graph shows a plot of

\[
-\left(\frac{4}{3\pi}\right) e^{-t/\tau_3} \cos(2\pi 3x/\lambda)
\]

as a function of the normalized space and time variables, \( x/\lambda \) and \( (D/\lambda^2)t \). Note that the third harmonic has an amplitude of 1/3 of the fundamental at \( t = 0 \) and decays more rapidly than the fundamental. Figure 3.10 shows a plot of the partial sum of the Fourier series. The graph shows a plot of

\[
\sum_{n=1}^{15} 2 \left(\frac{\sin(n\pi/2)}{n\pi/2}\right) e^{-t/\tau_n} \cos(2\pi nx/\lambda)
\]

as a function of the normalized space and time variables, \( x/\lambda \) and \( (D/\lambda^2)t \). This is the first 15 terms in the solution for a square wave. At \( t = 0 \), the 15-term approximation to the square wave shows the characteristic Gibbs’ phenomenon. As \( t \) increases the high-frequency components decay more rapidly than do the low-frequency components.

**Problem 3.13**

a. Consider the cell as one compartment and a vial as the other compartment. Then conservation of \( X \) implies

\[
-\frac{1}{A} \frac{dn_X^i(t)}{dt} = P_X \left( c_X^i(t) - c_X^o \right).
\]

Because the volume of the cell is much smaller than the volume of the vial, it is reasonable to assume that the vial concentration is negligible compared to the cell concentration, i.e., \( c_X^o \approx 0 \), so that

\[
\frac{dn_X^i(t)}{dt} + \frac{P_X A}{V} n_X^i(t) = 0,
\]
where $V$ and $A$ are the volume and surface area of the cell. The solution to this differential equation with initial value of $n_X^i(0) = N_X$ is

$$n_X^i(t) = N_X e^{-t/\tau},$$

where $\tau = V/(P_X A)$.

b. In the interval $((k-1)T, kT)$ the number of moles leaving the cell must equal the number of moles in the $k$th vial.

$$n_X(k) = N_X \left( e^{-\frac{(k-1)T}{\tau}} - e^{-kT/\tau} \right) = N_X \left( e^{T/\tau} - 1 \right) e^{-kT/\tau}.$$  

c. To estimate the parameters from the data, take the logarithm of $n_X(k)$ to obtain

$$\ln n_X(k) = \ln \left( N_X (e^{T/\tau} - 1) \right) - \frac{kT}{\tau}.$$  

The data indicate that the slope of the line of $\ln n_X(k)$ plotted versus $k$ is $-1/2$ so that $T/\tau = 1/2$. Since $T = 10$ minutes, $\tau = 20$ minutes. But

$$P_X = \frac{V}{A\tau} = \frac{(4/3)\pi r^3}{4\pi r^2 \tau} = \frac{r}{3\tau} = \frac{72 \times 10^{-4}}{3 \cdot 20 \cdot 60} = 2 \times 10^{-6} \text{ cm/s}.$$  

The intercept of the line is $-23.5$ so that

$$\ln \left( N_X (e^{T/\tau} - 1) \right) = -23.5$$  

which implies that

$$N_X = \frac{e^{-23.5}}{e^{0.5} - 1} = \frac{6.2 \times 10^{-11}}{0.65} = 96 \text{ pmol}.$$  

**Problem 3.14**

a. Assume that steady state occurs in the membrane and that diffusion between the inside and outside of the cell can be modeled as two-compartment diffusion. Then the concentration has the form

$$c^i(t) = c^i(\infty) + (c^i(0) - c^i(\infty)) e^{-t/\tau_{eq}} \text{ for } t \geq 0.$$  

The initial concentration of urea in the cell $c^i(0) = 0$. Since $V_o \gg V_i$, the final concentration in the cell will equal that in the bath, $c^i(\infty) = C$. Therefore, the solution will have the form

$$c^i(t) = C (1 - e^{-t/\tau_{eq}}).$$  

The time it takes for the concentration to reach 63% of its final value is the time constant

$$\tau_{eq} = \frac{V_e}{A P}.$$
where 
\[ V_e = \frac{V_i V_o}{V_t + V_o}, \]
and since since \( V_o \gg V_i \)
\[ V_e \approx V_i. \]
Therefore,
\[ \tau_{eq} = \frac{4}{3} \pi a^3 P = \frac{4}{3} \pi a^2 a \]
For a spherical cell with a radius of \( a = 10 \mu m \)
\[ \tau_{eq} = \frac{10^{-3} \text{ cm}}{(3)(3 \times 10^{-4} \text{ cm/s})} \approx 1.1 \text{ s.} \]

b. The time constant for equilibration of a spherical volume in a solution can be obtained from Figure 3.18 (Weiss, 1996a). For the concentration to reach 63% of its final value, the unequilibrated fraction is \( e(t) = 0.37 \). This value of \( e(t) \) for a sphere corresponds to
\[ \frac{D \tau_d}{a^2} \approx 0.05. \]
Therefore,
\[ \tau_d = \frac{0.05 a^2}{D} = \frac{0.05(10^{-3} \text{ cm})^2}{1.4 \times 10^{-5} \text{ cm}^2/\text{s}} \approx 3.6 \text{ ms.} \]

c. The ratio of time constants is
\[ \frac{\tau_d}{\tau_{eq}} \approx \frac{0.05 a^2 / D}{a/3P} = 0.15 \frac{P}{D a}. \]
Therefore, \( \tau_d / \tau_{eq} \approx a \).

d. The following conclusions result
- For \( a \ll 6.7(D/P) \), \( \tau_d \ll \tau_{eq} \) and diffusion across the plasma membrane limits the rate of urea transport into the cell.
- For \( a \gg 6.7(D/P) \), \( \tau_d \gg \tau_{eq} \) and diffusion through the cytoplasm limits the rate of urea transport into the cell.
- For \( a = 10 \mu m \) and the parameters given in the problem, diffusion across the plasma membrane is rate limiting.

**Problem 3.15**

a. If the concentration of sugar in the membrane has reached steady state at time \( t = 0 \), the flux of sugar through the membrane must be a constant and the concentration of sugar must be a linear function of \( x \). Since the partition coefficient \( k = 1 \), \( c(0,0) = c_1(0) \), and \( c(W,0) = c_2(0) \). Therefore
\[ c(x,0) = c_1(0) + \frac{c_2(0) - c_1(0)}{W} x \text{ for } 0 < x < W. \]
From this equation and Fick’s first law, the flux is
\[
\phi(x,0) = -D \frac{\partial c(x,t)}{\partial x} \bigg|_{t=0} = -\frac{D}{W} \frac{c_2(0) - c_1(0)}{L}
\]
\[
= \frac{10^{-5} \text{ cm}^2/\text{s}}{10^{-4} \text{ cm}} \times \frac{1}{L} \times \frac{L}{10^3 \text{ cm}^2} = 10^{-4} \frac{\text{ mol}}{\text{ cm}^2 \cdot \text{s}} \text{ for } 0 < x < W.
\]

b. Because no sugar can enter or exit the two-compartment system, the total amount of sugar in the two compartments must remain constant with time. In particular, the amount at time \(t = 0\), which is equal to \(c_1(0)AL_1 + c_2(0)AL_2\) must equal the amount at \(t \to \infty\), which is \(c_1(\infty)AL_1 + c_2(\infty)AL_2\). As \(t \to \infty\), the concentrations in the two sides will equilibrate, and \(c_1(\infty)\) will equal \(c_2(\infty)\). Therefore,

\[
c_1(\infty)AL_1 + c_1(\infty)AL_2 = c_1(0)AL_1 + c_2(0)AL_2.
\]

Solving for \(c_1(\infty)\) yields

\[
c_1(\infty) = \frac{c_1(0)L_1 + c_2(0)L_2}{L_1 + L_2} = \frac{1 \text{ mol/L} \times 50 \text{ cm} + 0 \text{ mol/L} \times 10 \text{ cm}}{60 \text{ cm}} = \frac{5}{6} \text{ mol/L}.
\]

c. Doubling \(D_{sugar}\) should half \(\tau_{eq}\). The idea is that equilibration occurs because differences between \(c_1(t)\) and \(c_2(t)\) cause a flux of sugar through the membrane. By Fick’s first law, the flux is proportional to \(D_{sugar}\), so doubling \(D_{sugar}\) will double the flux. Doubling the flux, doubles the time rate of change of \(c_1(t)\) and \(c_2(t)\), and thus halves the time to reach any criterion concentration (e.g., \(\tau_{eq}\), the time for \(c_1(t)\) to come to within a factor of \(e\) of its final value).

**Problem 3.16**

a. The steady-state time constant is

\[
\tau_{ss} = \frac{d^2}{2D}.
\]

Therefore, the steady-state time constant for the thin membrane is

\[
\tau_{ss} = \frac{(10^{-4})^2}{2 \cdot 10^{-5}} = 0.0005 \text{ s},
\]

and for the thick membrane is

\[
\tau_{ss} = \frac{1}{2 \cdot 10^{-5}} = 50,000 \text{ s}.
\]

b. The equilibrium time constant is

\[
\tau_{eq} = \frac{\gamma_e}{AP}.
\]

Since the two volumes are identical, \(\gamma_e = \gamma/2\) and since \(P = Dk/d\)

\[
\tau_{eq} = \frac{\gamma d}{2ADk}.
\]
Therefore, the equilibrium time constant for the thin membrane is

\[ \tau_{eq} = \frac{1 \cdot 10^{-4}}{2 \cdot 1 \cdot 10^{-5} \cdot 2} = 2.5 \text{ s.} \]

Therefore, the equilibrium time constant for the thick membrane is

\[ \tau_{eq} = \frac{1 \cdot 1}{2 \cdot 1 \cdot 10^{-5} \cdot 2} = 25,000 \text{ s.} \]

c. Note that for the thin membrane \( \tau_{ss} \ll \tau_{eq} \), i.e., the time it takes for the membrane concentration profile to reach steady state is much less than the time it takes the two volumes to equilibrate. This is the just what is required for Fick’s first law to be valid at each instant in time in the membrane. For the thick membrane, \( \tau_{ss} \approx \tau_{eq} \) and the membrane concentration profile is not in steady state. Therefore, Fick’s law for membranes does not apply at each instant in time.

Problem 3.17 In parts a through f and in part j, \( \phi_1 = \phi_2 = 0 \) implies that in steady state the flux through the membrane is zero. Therefore, the concentration in the membrane must be constant for all these parts. In parts g and h, \( \phi_1 > \phi_2 \) implies that no steady state is possible since there is a net flux into the system consisting of \( V_1 \), membrane, and \( V_2 \). In part i, \( \phi_1 = \phi_2 \) is the flux through the membrane in steady state. Hence, the concentration profile in the membrane is linear.

a. \( D = 0 \) implies that \( P = 0 \) which implies that the flux through the membrane is zero which implies that the concentration is constant. The answer is 9.

b. \( k = 0 \) implies that \( P = 0 \) which implies that the flux through the membrane is zero which implies that the concentration is constant. The answer is 9.

c. \( D > 0, k > 1 \) implies there will be a flux of particles through the membrane until \( V_1 \) and \( V_2 \) equilibrate. The final value of the concentration is \( (20V_1 + 10V_2)/(V_1 + V_2) \) which is between 20 and 10 mM/l. The answer is 4 and 5 (if \( V_1 \gg V_2 \)).

d. This situation is the same as for part c except that \( k < 1 \) which implies that the answer is 6 or 7. If \( k = 0 \), the answer is 9.

e. This is similar to the case considered in part c except that \( V_1 \gg V_2 \). The answer is 5.

f. This is similar to the case considered in part c except that \( V_1 \gg V_2 \) and \( k = 1 \). The answer is 2.

g. From the discussion given above, the answer is NONE.

h. From the discussion given above, the answer is NONE.

i. With constant flux through the membrane, the concentration in the membrane in steady state must be linear with position. Since \( k > 1 \), the answer is 12.

j. There is no flux through the membrane, so there is no change in concentration of \( V_1 \) and \( V_2 \). If \( k < 1 \), the answer is 7. If \( k = 0 \), the answer is 2.
Problem 3.18 An important caveat in this problem is that, where it is so stated, the parameters are to be estimated from the measurements presented in the Figures.

a. Since the membrane:solution partition coefficient is 1, at equilibrium the concentration in the two compartments and in the membrane will be the same. Thus, the total quantity of solute at $t = 0$ can be found and then distributed uniformly over the total volume of the system. The initial quantity of solute is $100 \text{ mmol/cm}^3 \cdot 10 \cdot A$. This is distributed over the total volume of the system which is $(10 + 1 + 0.1) \cdot A \text{ cm}^3$. Therefore, the final concentration is

$$\frac{1000A}{11.1A} = 90.09 \text{ mmol/cm}^3,$$

which is shown in Figure 3.11.

b. This section applies for $t = 100$ seconds.

i. The concentration profile in the membrane is not a linear function of position nor is the flux constant. Hence, diffusion in the membrane is not in steady state.

ii. Because the diffusion regime is not in steady state in the membrane, it is not valid to use results that depend upon steady-state conditions, such as Fick’s law for membranes. However, the diffusion coefficient for the solute in the membrane can be obtained from more fundamental considerations by using Fick’s first law evaluated at $t = 100$

$$\phi(x, 100) = -D \frac{\partial c(x, 100)}{\partial x}.$$
Figure 3.12: The concentration of solute in the two compartments and the membrane (solid line) are shown at $t = 100$ (Problem 3.18). The figure illustrates the concentration in the membrane and in a portion of each compartment only. The concentrations in the compartments are uniform in space. The flux of solute is shown (dashed line) in the membrane only. A line tangent to $c(x, 100)$ at $x = 0$ is also shown (dotted).

As indicated in Figure 3.12, a convenient place to measure the slope of $c(x, 100)$ is at $x = 0^+$, i.e., just inside the membrane. From the figure,

$$
\left(\frac{\partial c(x, 100)}{\partial x}\right)_{x=0^+} \approx -\frac{100 \times 10^{-3}}{0.04} = -2.5 \text{ mol/cm}^4.
$$

At $x = 0^+$, $\phi(0^+, 100) \approx 12.8 \times 10^{-6} \text{ mol/(cm}^2 \cdot \text{s})$. Therefore,

$$
D \approx -\frac{12.8 \times 10^{-6}}{-2.5} = 5.1 \times 10^{-6} \text{ cm}^2/\text{s}.
$$

c. This section applies for $t = 1000$ seconds.

i. The concentration profile in the membrane is linear. Hence, the concentration in the membrane is in steady state.

ii. Note that $c^2(t)$ shows a delay and then a portion that has a linear increase in concentration over a time duration when $c(0.04, t)$ has saturated. Thus, during this time interval, the concentration in the membrane has reached steady state and, therefore, the thin-membrane approximation is a good approximation. Hence, during this time interval, $c^2(t)$ rises exponentially and has the form $C(1 - e^{-t/\tau_{eq}})$. But the time is clearly much less than the equilibrium time, i.e., $t \ll \tau_{eq}$. Therefore, $C(1 - e^{-t/\tau_{eq}}) \approx C(1 - (1 - t/\tau_{eq})) = C t/\tau_{eq}$ where $C$ is the final value or equilibrium value of the concentration which equals 90.09 mmol/cm$^3$. Thus, slope of the concentration must be found from Figure 3.13 during a time interval when steady state has been reached.
Figure 3.13: The dependence of concentration on time is shown for the time interval (0, 1000) for a location in the membrane, $c(0.04, t)$ and in compartment 2, $c^2(t)$ (Problem 3.18). The slope of the line tangent to $c^2(t)$ is shown with a dotted line. A line tangent to $c(0.04, t)$ beginning at $t = 500$ s is also shown.

in the membrane and after the initial transient, i.e., $t > 500$ ms. The slope is approximately $3.1 \times 10^{-3}/700 = 4.4 \times 10^{-6}$ mol/cm$^3$ s. Therefore, $\tau_{eq} = 90.09 \times 10^{-3}/(4.4 \times 10^{-6}) = 2.1 \times 10^4$ s.

iii. The time course for establishing steady state in the membrane consists of a sum of exponentials the slowest of which is the steady-state time constant $\tau_{ss}$. In fact, $c(0.04, t)$ does have a fast transition at the onset and then a slower tail in the response. It is the time constant of the slow tail of the response that needs to be estimated. A line starting at $t = 500$ and tangent to $c(0.04, t)$ crosses the maximum value about 240 s later. Hence, $\tau_{ss} \approx 240$ s.

iv. Method #1. At $t = 1000$, the concentration in the membrane is approximately at steady state and $\partial c(x, 1000)/\partial x \approx -100/0.1 = -1000$ mmol/cm$^3$. Thus, $\phi(x, 1000) = -D \partial c(x, 1000)/\partial x \approx 1000D$. But by continuity, the flux into compartment 2 must equal the rate of increase of solute in compartment 2. Therefore, $\phi(x, 1000) = 1000D = (dc^2(t)/dt)_{t=1000} \cdot 1$. The derivative can be evaluated directly from the lower figure as follows

$$(dc^2(t)/dt)_{t=1000} \approx 3.1/0.7 \times 10^{-3} \text{ mmol/cm}^3 \cdot \text{s}.$$_combining these relations yields $D \approx 4.5 \times 10^{-6}$ cm$^2$/s.

Method #2. A second method involves estimating $D$ from the equilibrium time constant. The equilibrium time constant can be estimated fairly accurately because the thin-membrane approximation holds for times much larger than the steady-state time constant. Therefore, $\tau_{eq} = V_e/(PA)$ for the equilibrium time constant for two-component diffusion through a thin membrane. In this equation, $V_e$ is the equivalent volume of the two compartments, $A$ is the surface area of the membrane, $P = D/d$ is the permeability of the membrane.
Figure 3.14: The dependence of concentration on time is shown for the time interval 
(0, 1000) for a location in the membrane, \( c(0.04, t) \) and in compartment 2, \( c^2(t) \) (Problem 3.18). The 
slope of the line tangent to \( c^2(t) \) is shown with a dotted line. A dashed line tangent to \( c(0.04, t) \) 
beginning at \( t = 500 \) s is also shown.

where \( d \) is the membrane thickness and \( D \) is the diffusion coefficient in the 
membrane. Therefore,

\[
\tau_{eq} = \frac{V_1V_2d}{(V_1 + V_2)DA} = \frac{L_1AL_2Ad}{(L_1A + L_2A)DA} = \frac{L_1L_2d}{(L_1 + L_2)D}
\]

\[
= \frac{10 \cdot 1 \cdot 0.1}{11D} = \frac{0.09}{D} \text{ s},
\]

so that \( D = 0.09/2.1 \times 10^4 = 4.3 \times 10^{-6} \text{ cm}^2/\text{s} \). Note that this estimate is 
within 16% of the estimated value of \( D \) found in part b.

v. The integral is simply the total number of moles of solute that flow through 
the plane at \( x = 0.1 \) per unit area in the time interval (0, 1000). Thus, since 
the number of moles of solutes in compartment 2 is 0 at \( t = 0 \), the number 
of moles of solute in this compartment at \( t = 1000 \) must equal the quantity 
transported into the compartment. Therefore, \( \int_0^{1000} \phi(0.1, t) \, dt = 1 \cdot A \cdot 
\]

\[ c^2(1000) \] \( \frac{\phi(0.1, t)}{D} \text{ s}. \)

From Figure 3.13 it is apparent that \( c^2(1000) = 3.2 \text{ mmol/cm}^3 \). Therefore, 
\( \int_0^{1000} \phi(0.1, t) \, dt = 3.2 \text{ mmol/cm}^2 \).

vi. In a time interval from \( t = 0 \) to \( t = 5\tau_{eq} \), both the concentration in 
the membrane and in both compartments will be close to equilibrium. There-
fore, both will approach a concentration of 90.09 mmol/cm\(^3\) with the equi-
librium time constant which is \( 2.1 \times 10^4 \) s as shown in Figure 3.14. Note that 
in Figure 3.13 \( c(0.04, t) \) \( \text{appears to saturate} \) at a steady-state value which is 
about 60 mmol/cm\(^3\) in under 1000 seconds which represents about \( 4 \times \tau_{ss} \). 
However, this time is short compared to \( \tau_{eq} \). Thus, the steady-state value is 
not really saturated but changes slowly as the two volumes equilibrate. Fig-
ure 3.14 shows that the apparent saturation of \( c(0.04, t) \) shown in Figure 3.13 
is a mirage.
**Problem 3.19** The problem states that the total flux in the positive-\(x\) direction (a direction opposite to that of the force of gravity) is \(\Phi = \Phi_D + \Phi_G\) where \(\Phi_D\) is the flux due to diffusion and \(\Phi_G\) is the flux due to gravity. These fluxes are

\[
\Phi_D = -D \frac{\partial c(x,t)}{\partial x} \quad \text{and} \quad \Phi_G = -\frac{D}{\lambda} c(x,t).
\]

a. The flux due to diffusion is Fick’s law. The flux due to gravity requires some comment. Flux due to a body force on the particles has the form \(\Phi_G = u_p c f_p\) where the particle mobility \(u_p = D/kT\), and the gravitation force on a particle in water is \(f_p = -m_{\text{eff}} g\). Combination of these terms yields

\[
\Phi_G = u_p c f_p = -\frac{D m_{\text{eff}} g}{kT} c(x,t)
\]

from which \(\lambda = kT/(m_{\text{eff}} g)\).

b. At equilibrium \(\Phi = 0\) and \(c(x,t)\) is a function of \(x\) only so that

\[
-D \frac{dc(x)}{dx} - \frac{D}{\lambda} c(x) = 0
\]

which, after canceling some common factors, yields

\[
\frac{dc(x)}{dx} + \frac{c(x)}{\lambda} = 0
\]

which has the solution

\[
c(x) = c(0)e^{-x/\lambda}.
\]

c. The space constant \(\lambda = kT/(m_{\text{eff}} g)\) where \(m_{\text{eff}} = (4/3)\pi r^3 (\rho_p - \rho_w)\). Therefore,

\[
\lambda = \frac{(kT/g)}{(4/3)\pi r^3 (\rho_p - \rho_w)}.
\]

Which has the value

\[
\lambda = \frac{4.2 \times 10^{-17}}{(4/3)\pi r^3 (1)} = \frac{10^{-17}}{r^3} \text{ cm}.
\]

For \(r = 1 \text{ mm}\), \(\lambda = 10^{-17}/10^{-3} = 10^{-14} \text{ cm}\) and for \(r = 1 \text{ nm}\), \(\lambda = 10^{-17}/10^{-21} = 10^4 \text{ cm}\). A 50 ml = 50 cm³ beaker will have a height of a few cm (see Figure 3.15). On the scale of the beaker dimensions, the 1 mm particles will all lie on the bottom of the beaker (within a layer whose dimensions are about \(10^{-14} \text{ cm}\) which equals \(10^{-4} \text{ pm}\)), while the 1 nm particles will be uniformly dispersed in the beaker (with a space constant of \(10^4 \text{ cm}\) which is \(10^2 \text{ m}\)).
In the method used by Perrin (Perrin, 1909), both the particles and the spatial distribution of particle concentration must be resolved with a light microscope whose limit of resolution is the wavelength of light, ca. 0.2 μm. This resolution limit places both an upper and a lower bound on the particle dimensions that are practical. For particles with a radius of 1 mm, the spatial distribution of concentration changes very rapidly, i.e., $\lambda = 10^{-14} \text{ cm} = 10^{-10} \mu\text{m}$ which is more than 9 orders of magnitude below the limits of resolution of a light microscope. For 1 nm radius particles the spatial distribution is very broad and the difference would have to be measured over $10^4 \text{ cm} = 10^2 \text{ m}$ which is impractical with a light microscope. In addition, these particles are too small to be resolved with a light microscope. So the strategy is to pick the smallest particles that can be seen. Particles with $r \geq 0.2 \mu\text{m}$ are close to the smallest that can be resolved in a light microscope. These give $\lambda = 10^{-17}/(0.2 \times 10^{-4})^3 \text{ cm} = 12.5 \mu\text{m}$. Thus, the particles can be counted at different depths and the depths needed are in the range of a few to 10’s of μm which can be easily obtained with a light microscope with the arrangement shown in Figure 3.16. Note that with 1 μm particles, $\lambda = 10^{-17}/(10^{-4})^3 = 10^{-5} \text{ cm} = 0.1 \mu\text{m}$ so the spatial distribution changes appreciable in a few tenths of a μm making measurements versus depth very difficult. Thus, there is a rather narrow range of particles that can be used. Perrin used $r = 0.14 \mu\text{m}$ to $r = 0.52 \mu\text{m}$. Most measurements were obtained for $r = 0.212 \mu\text{m}$.

**Problem 3.20** As shown in the Figure 3.41 (Weiss, 1996a), a regression fit to Collander’s measurements in *Nitella* has the following expression

$$\log(P_nM^{0.2}) = 1.20 \log k_n - 0.96.$$  

Thus, the logarithm of the permeability is given by

$$\log P_n = 1.20 \log k_n - 0.96 - 2.2 \log M.$$  

Therefore, an estimate of the permeability $P_n$ can be computed from this relation to obtain the results shown in Table 3.1. Both a large partition coefficient and a small...
molecular weight are important to achieve a high permeability. For example, although solute D partitions best in the organic solvent, it has a large molecular weight, and hence, a low permeability in Nitella membrane.

**Problem 3.21** Table 3.6 (Weiss, 1996a) indicates that the permeability of membranes of several types of cells for ethanol is at least one order of magnitude larger than for formamide. From Figure 3.36 (Weiss, 1996a) it is apparent that the permeability of erythrocyte membranes for methanol is larger than for ethanol. Furthermore, Figure 3.37 (Weiss, 1996a) indicates that the permeability of the plant *Chara ceratophylla* is very high. In general, the permeability of cellular membranes to alcohols is relatively high. Therefore, the permeability of the membrane for methanol should be much higher than for formamide. This difference is probably due to the large difference in the solubility of these two substances in organic solvents: methanol is highly soluble in organic substances while formamide is not. The difference in solubility is due to the chemical groups that these molecules contain. Methanol contains the nonpolar methyl group and the polar hydroxyl group whereas formamide contains two polar (aldehyde and amino) groups.
Chapter 4

SOLVENT TRANSPORT

Exercises

Exercise 4.1 In a hypertonic extracellular solution, water flows out of the cell through both the cell wall and the cell membrane. As water leaves the cell, the cell volume decreases and the cell membrane shrinks away from the relatively rigid cell wall. This leaves a compartment between the cell wall and cell membrane. Because the cell membrane is highly selectively permeable and the cell wall is less so, the composition of this compartment resembles extracellular rather than intracellular solution.

Exercise 4.2 A property of a solution that depends only on the number of particles in solution and not on their chemical nature is called a colligative property. Colligative properties of solutions include: osmotic pressure, vapor pressure, freezing point depression, and boiling point elevation.

Exercise 4.3 Two solutions are isosmotic if they have the same osmotic pressure.

Exercise 4.4 Two solutions that are isosmotic have the same osmotic pressure. Two extracellular solutions that are isotonic produce the same cell tonicity. That is, if one isotonic solution is replaced by another then the cell volume does not change. Often the two terms are used interchangeably, but they are distinct in that isosmoticity can be determined by physical chemical means, i.e. with an osmometer. However, establishing isotonicity requires measurements on cells.

Exercise 4.5 The ideal gas law is

\[ pV = RTn \text{ or } p = RTc, \]

where \( p \) is the pressure that the gas exerts on the walls of a container of volume \( V \), \( n \) is the number of moles of gas in the container, and \( c = n/V \) is the molar concentration of the gas in the container. Van’t Hoff’s law is

\[ \pi = RTC_S, \]

where \( \pi \) is osmotic pressure and \( C_S \) is the total concentration of solutes in solution, where the ionization of salts into multiple solutes is taken into account. The pressure
that the gas exerts on the walls is measurable directly. The osmotic pressure of a solution is measured with a semi-permeable membrane that allows the solvent but not the solute to permeate. Alternatively, the osmotic pressure can be estimated with an osmometer under the assumption that it is valid to compute the osmotic pressure from the measurement of some other colligative property, e.g., the vapor pressure.

**Exercise 4.6** The osmotic pressure of a solution is given by van’t Hoff’s law as \( \pi = RTC_\Sigma \) where \( C_\Sigma \) is the osmolarity. The osmolarity is the total number of moles of solute in solution divided by the volume of the solution. The osmolarity is usually expressed in mol/L.

**Exercise 4.7** The osmotic coefficient \( \chi \) reflects the deviation of the osmotic pressure of a real solution \( \pi \) from that predicted by van’t Hoff’s law, i.e.,

\[
\chi = \frac{\pi}{RTC_\Sigma}.
\]

**Exercise 4.8** In the left-hand system, osmotic flow of water is from the left to the right chamber and hydraulic flow of water is from the right to the left chamber. Hence, osmotic equilibrium is possible when the two flows are equal and opposite. In the right-hand system, both osmotic and hydraulic flow of water are from the right to the left chamber and no osmotic equilibrium is possible.

**Exercise 4.9** In the absence of a hydraulic pressure difference across a membrane, the flux of volume is

\[
\Phi_V = L_V RT \left( C_\Sigma^2 - C_\Sigma^1 \right).
\]

When the volume flux is carried entirely by water, the volume flux is proportional to the molar flux of water, i.e., \( \Phi_V = \phi_w \overline{V_w} \) where \( \phi_w \) is the number of moles of water flowing through a unit area of membrane per unit time and \( \overline{V_w} \) is the partial molar volume of water which is the volume of a mole of water. The osmotic molar flux of water can be expressed as

\[
\phi_w = P_w \left( C_\Sigma^2 - C_\Sigma^1 \right),
\]

where

\[
P_w = \frac{RTL_V}{\overline{V_w}}.
\]

\( P_w \) is called the **osmotic permeability coefficient** and is a measure of the flow of water in response to a difference in osmotic pressure across a membrane. By using a radioactive tracer for water, the diffusion of water through membranes can be measured in the absence of an osmotic pressure difference across the membrane. The diffusive flux of water can be expressed by Fick’s law for membranes

\[
\phi_w = P \left( c_w^1 - c_w^2 \right),
\]

where \( P \) is the **diffusive permeability** (or simply the **permeability**) of the membrane for water.
**Exercise 4.10** The formal resemblance between the solute flux due to diffusion through a membrane and the osmotic transport of solvent through a membrane is apparent from the two flow equations,

\[
\begin{align*}
\phi_n &= P_n \left( c_n^1 - c_n^2 \right), \\
\Phi_V &= L_V RT \left( C_v^2 - C_v^1 \right).
\end{align*}
\]

\(\phi_n\) has units of mol/(cm\(^2\) · s); is the flux of solute \(n\) through the membrane; depends on the difference in concentration across the membrane of solute \(n\) only. \(\Phi_V\) has units of cm/s; is the flux of volume (predominantly water) through the membrane; depends on the difference in total concentration of all solutes across the membrane. In addition, note the difference in the sign that relates the flux to the difference of concentration across the membrane.

**Exercise 4.11**

a. Water transport through a homogeneous, hydrophobic membrane is by the dissolve-diffuse mechanism. Water first dissolves in the hydrophobic membrane and then diffuses through it. According to this mechanism, water acts as a solute in the membrane. Water transport through a porous membrane is via convection. A difference in osmotic pressure between bath solutions is equivalent to a hydraulic pressure difference across the membrane that acts on the water.

b. A simple criterion is based on estimating \(P_w\), from measurements of water transport due to an osmotic pressure difference, and \(P_w\), from measurements of the diffusion of tracer water in the absence of an osmotic pressure difference. For water transport through a homogeneous, hydrophobic membrane \(P_w/P_w = 1\), while simple theories of water transport through porous membranes predict that \(P_w/P_w > 1\).

**Exercise 4.12** The *solute bombardment* theory gives a reasonable explanation for how an additional pressure can develop on the side containing the solute but does not suggest a mechanism by which this additional pressure can cause a flux of *solvent* into the side that has the larger pressure. Furthermore, the solute bombardment theory ignores the presence of the solvent to which the momentum incurred by solute bombardment must be transferred.

**Exercise 4.13**

a. At osmotic equilibrium

\[
p_1 - p_2 = \pi_1 - \pi_2 = RT \left( C_v^1 - C_v^2 \right).
\]

b. The total volume of water is \(V_1 + V_2 = 2\ L\). Since \(p_1 = p_2\), at osmotic equilibrium \(C_v^1(\infty) = C_v^2(\infty)\). Initially, \(C_v^1(0) = 0.01\ mol/L\) and \(C_v^2(0) = 0.02\ mol/L\) because NaCl dissociates so that a 0.01 mol/L liter solution has an osmolarity of 0.02 mol/L.
The number of moles of glucose is 0.01 mol and of Na\(^+\) plus Cl\(^-\) is 0.02 mol. Therefore at osmotic equilibrium

\[
\frac{0.01}{V_1} = \frac{0.02}{V_2} \quad \text{and} \quad V_1 + V_2 = 2.
\]

These two equations are solved by taking the reciprocal of the equation on the left and substituting the equation on the right to obtain,

\[
100V_1 = 50V_2 = 50(2 - cV_1).
\]

Solving these equations yields \(V_1 = 2/3\) L and \(V_2 = 4/3\) L. The volume can be found as a function of time from the relation

\[
-\frac{1}{A} \frac{dV_1(t)}{dt} = LVRT(C_S^2 - C_S^1).
\]

Note that \(V_1(t) + V_2(t) = 2\) L, \(N_1^1 = 0.01\) mol/L and \(N_2^2 = 0.02\) mol/L so that

\[
\frac{dV_1(t)}{dt} = \frac{1}{\tau} \left( \frac{1}{V_1(t)} - \frac{2}{2 - V_1(t)} \right),
\]

where \(\tau = 100/(LVRTA)\). \(V_2(t) = 2 - V_2(T)\). This differential equation can be integrated numerically to yield the solution shown in Figure 4.1. The differential equation for the volume is nonlinear and the solution shows monotonic, but non-exponential changes in volume.

**Exercise 4.14** The isotonic volume is the volume of a cell in an isotonic solution. Thus, the isotonic volume is the volume of the cell in its normal environment in the body.

**Exercise 4.15**

a. The isotonic volume of these cells is the value of the volume when \(C_S^0 = C_S^{on}\) which is when the abscissa equals 1. The isotonic volume is about \(2.1 \times 10^5\) \(\mu\)m\(^3\).

b. The fraction of the isotonic volume not due to water is obtained when the solute concentration is arbitrarily large. In principle, for such a large solute concentration, the cell shrinks so that no water remains intracellularly and the cell volume equals that not due to water. The regression analysis in the caption of Figure 4.21 (Weiss, 1996a) suggests that when \(C_S^0 \to \infty\), \(V_c \to 2.03 \times 10^4\) \(\mu\)m\(^3\). Thus, about 10% of the volume of the cell is not due to osmotically active water.
**Exercise 4.16** A cell whose shape differs from a sphere can in principle change its volume without changing its surface area. For example, an erythrocyte has the shape of a biconcave disc. The cell can show a large increase in volume without changing its shape simply by becoming more spherical.

**Exercise 4.17** Equation 4.68 (Weiss, 1996a) expresses conservation of water volume between the cell interior and the bath solution. The left-hand side of the equation is the rate of decrease in the volume of the cell water which equals the right-hand side of the equation which is the flux of water volume that leaves the cell.

**Exercise 4.18**

a. At equilibrium,

\[ V_c = \frac{N^i_v}{C^0_v} + V'_c, \]

where \( V'_c \) is the osmotically inactive portion of the total cell volume \( V_c \), and where it is assumed that \( V'_c \ll V_c \). Therefore, the initial and final values of the volume are

\[ V_c(0) = \frac{N^i_v}{C^0_v(0)} \quad \text{and} \quad V_c(\infty) = \frac{N^i_v}{C^0_v(\infty)}, \]

where \( N^i_v \) is constant because the solute is assumed impermeant. Division of these two equations yields

\[ \frac{V_c(0)}{V_c(\infty)} = \frac{C^0_v(\infty)}{C^0_v(0)} = 2. \]

Normalizing the concentration yields

\[ \tilde{c}(\infty) = 2\tilde{c}(0). \]

Therefore, the answer is waveform v.

b. The flux of water is related to the change in volume by the conservation relation

\[ -\frac{1}{A(t)} \frac{dV_1(t)}{dt} = \Phi_V = L_VRT \left( C^0_v(t) - C^i_v(t) \right). \]

If the temperature is decreased, the magnitude of the flux will decrease, and the magnitude of the rate of change of volume will decrease. Hence, the time course of volume change will be slower. The equilibrium condition that \( C^i_v = C^0_v \) does not depend upon temperature. Therefore, the equilibrium volume will be unchanged.

**Exercise 4.19** The time course for equilibration of the volume of a cell with a semipermeable membrane is given in normalized coordinates by Equation 4.69 (Weiss, 1996a). The time course is controlled by the term \( \alpha t a(t) \) which is proportional to the ratio of surface area to volume of the cell. Hence, for two cells with the same volume, the cell with the larger surface area will show a larger rate of change of volume and will equilibrate faster. This makes intuitive sense since a larger area of contact between compartments will allow a greater flow of volume. Therefore, the cylindrical cell with microvilli will equilibrate faster.
Exercise 4.20 An experimental test of a theory often involves plotting a measured variable against another measured variable and comparing this measured relation to that predicted by the theory. When the relation is a straight line, the eye is a good instrument for qualitatively checking whether the measured relation and the theoretical relation agree. More quantitative statistical techniques (e.g., linear regression) exist for assessing the extent to which a set of data are fit by a straight line. For these two reasons, one commonly used method for analyzing data, is to first find a transformation that linearizes the expected relation between variables. Then linear regression techniques are used to assess goodness of fit.

Exercise 4.21

a. The isotonic volume of a cell is its volume in situ, i.e., its volume in its natural environment. If the concentration $C^o$ of an impermeant non-ionic solute is equal to $C^{on}_o$, the isotonic concentration, then we expect the cell volume $V_c$ to equilibrate to the cell’s isotonic volume $V^{in}_c$. Thus, if $C^{on}_o/C^o = 1$, then $V_c = V^{in}_c$ and the value of $V^{in}_c$ can be read from the plot.

\[
V^{in}_c \approx 0.002 \text{ mm}^3
\]

b. Since $V^i$ is osmotically active (by assumption), it should shrink as $C^o$ increases. In the limit $C^o \rightarrow \infty$, $V^i \rightarrow 0$, and $V_c \rightarrow V^i_c$. As $C^o \rightarrow \infty$, $C^{on}_o/C^o \rightarrow 0$. From the plot, $V_c$ is about 0.0006 mm$^3$ when $C^{on}_o/C^o = 0$. Therefore $V^{i}_c \approx 0.0006 \text{ mm}^3$.

c. If the solution of 200 mmol/L NaCl completely dissociates, then its osmolarity will be 400 mosm/L. If $C^{on}_o$ is 200 mosm/L, then $C^{on}_o/C^o$ will be 1/2. From the plot, $V_c$ will be approximately 0.0013 mm$^3$.

d. If the cell volume is at equilibrium just before $t = 0$, then the cell volume will decrease from an initial value of 0.002 mm$^3$ (part a) to a final value of 0.0013 mm$^3$ (part c). Because the equation for volume change is nonlinear, the time course of cell volume is not exponential. Figure 4.2 summarizes these facts. The time course of equilibration will depend on the rate at which water enters the cell. The rate of water entry is given by the product of the water flux $\Phi_v(t)$ and the surface area of the cell membrane. Assuming that the cell membrane supports no hydraulic pressure difference between the intracellular and extracellular spaces (typical of animal cells), the flux of water is equal to the product of the hydraulic conductivity of the cell membrane and the osmotic pressure difference between the intracellular

![Figure 4.2: Time course of cell volume (Exercise 4.21).](image)
and extracellular spaces. This osmotic pressure difference is equal to $RT$ times the difference in osmolarity between the inside and outside of the cell. Combining all of these effects, it is apparent that the rate of water entry, and therefore the rate at which the cell volume is changing, depends on: the area of the cell membrane, the hydraulic conductivity of the cell membrane, and the temperature of the cell. This behavior is expressed mathematically as follows

$$\frac{dV(t)}{dt} = A(t) \ell y RT \left( C^i_y(t) - C^o_y(t) \right)$$

which can be expressed in normalized coordinates for cylindrical cells as

$$\frac{dv(t)}{dt} = \alpha_v \left( v(t) \right)^{1/2} \left( \frac{1}{v(t)} - \tilde{c}(t) \right).$$

The results in Figure 4.2 were obtained by numerically integrating this equation with $\tilde{c}(t) = 2$ for $t > 0$ with the cell volume expressed as

$$V_c(t) = v(t)(0.002 - 0.0006) + 0.0006 (\text{mm}^3).$$

**Exercise 4.22** Water transport in lipid bilayers is not blocked by mercurial compounds, has a ratio of osmotic to diffusive permeability that is near 1, and has a relatively large dependence on temperature. In contrast, water transport through water channels in cell membranes is blocked by mercurial compounds, has a ratio of osmotic to diffusive permeability that exceeds 1, and has a relatively small dependence on temperature. Of course, water transport through a cell membrane that contains water channels is a mixture of transport through the lipid bilayer and through the water channels. When one or the other of these routes predominates the distinction between the two modes of transport is clearly defined.

**Exercise 4.23** These results show that the control oocytes, into which no CHIP RNA was injected, show a relatively small osmotically-induced volume increase that is relatively insensitive to application of a mercury compound. Thus, these results are consistent with water transport by diffusion through the lipid bilayer but not through water channels. Addition of CHIP RNA results in a large increase in osmotically-induced water transport that is reduced by the application of a mercury compound. This latter result is consistent with water transport via water channels. The experiment demonstrates that incorporation of CHIP RNA results in the apparent appearance of water channels suggesting that CHIP RNA codes for the water channel protein.

**Exercise 4.24** Vasopressin binds to vasopressin receptors located on the membranes of target cells. Via a second messenger, vasopressin binding results in the recruitment of cytoplasmic water channels and the incorporation of these channels into the membrane. This incorporation increases the osmotic permeability of the cell.
CHAPTER 4. SOLVENT TRANSPORT

Problems

Problem 4.1 The measurements shown express the pressure and concentration in units that are convenient for making chemical measurements. However, the osmotic pressure is proportional to the molar concentration, i.e., \( \pi = RT C \) where \( R = 8.3 \) J/(mol·K) and \( T = 298K \). Therefore, the molar concentration must be expressed in the units used for the measurements. The data show that a concentration of albumin of 36 g of albumin per kg of water yields an osmotic pressure of 20 cm of water. This pressure can be expressed in pascals by noting that a column of liquid 20 cm high is equivalent to a pressure \( p = \rho gh \) where \( \rho \) is the density of water, \( g \) is the acceleration of gravity, and \( h \) is the height of the column of water. Therefore,

\[
p = (1 \text{ g/cm}^3) \cdot (980 \text{ dyne/g}) \cdot (20 \text{ cm}) = 19600 \text{ dynes/cm}^2 = 1960 \text{ Pa}.
\]

Note that the concentration is given as the number of grams of albumin per kilogram of water. The number of moles of albumin can be obtained from its weight by dividing by the molecular weight of albumin, \( M \). Dividing the given concentration by the molecular weight of albumin yields the molal concentration of the albumin solution. Assume that the concentration is low enough that the molal and molar concentrations are the same. Therefore the molar concentration is \( \frac{36}{M} \times 10^3 \text{ moles/m}^3 \). Van’t Hoff’s law yields

\[
1960 \text{ Pa} = \frac{8.3 \text{ J/(mol·K)} \times 298K \times (36/(1000 \cdot M)) \times 10^3 \text{ moles/m}^3}{1000 \text{ mol/L}}.
\]

Solving this equation yields a molecular weight of \( M = 45 \text{ kg/mol} = 45 \times 10^3 \text{ g/mol} \).

Problem 4.2 Assume that all the sucrose dissolves but that only a fraction of the NaCl, \( \alpha \), ionizes. When a salt dissociates each ion contributes to the osmotic pressure

\[
\text{NaCl} \rightarrow \text{Na}^+ + \text{Cl}^-.
\]

If \( \alpha \) is the fraction of NaCl that is dissociated then \( 1 - \alpha \) is the fraction that is not dissociated. Since each dissociated NaCl molecule contributes 2 ions and each undissociated molecule contributes 1 molecule, the osmolarity of the NaCl solution is \( C_{\Sigma}^{NaCl} = (2\alpha + 1 - \alpha)C_{NaCl} \) whereas the osmolarity of the sucrose solution is \( C_{\Sigma}^{sucrose} = C_{sucrose} \). Therefore,

\[
\frac{\pi_{NaCl}}{\pi_{sucrose}} = \frac{RT C_{\Sigma}^{NaCl}}{RT C_{\Sigma}^{sucrose}} = \frac{(2\alpha + 1 - \alpha)C_{NaCl}}{C_{sucrose}} = \frac{8.75}{4.76} = 1.84.
\]

Therefore, \( \alpha \approx 0.84 \).

Problem 4.3 Sucrose and raffinose have equal osmolarity when they have equal molar concentrations. Therefore, 59.4 grams per liter of raffinose should have an osmolarity of 0.1 mol/L. Hence, 1 mole of raffinose has a weight of 594 grams which is the molecular weight. Hence, computation of the molecular weight will reveal if one of the sugars has a molecular weight of 594. The atomic weights are: C, 12; H, 1; O, 16. Therefore, the molecular weights of the sugars are
Molecular formula | Molecular weight | Notation
--- | --- | ---
C₁₂H₂₂O₁₁ + 3H₂O | 396 | not raffinose,
C₁₈H₃₂O₁₆ + 5H₂O | 594 | raffinose,
C₃₆H₆₄O₃₂ + 10H₂O | 1188 | not raffinose .

Problem 4.4

a. First, check charge neutrality. Bicarbonate and chloride are the principal anions and have an osmolarity of 156 mosm/L; sodium and potassium are the principal cations and have an osmolarity of 160 mosm/L. Thus, the cations and anions are approximately electroneutral and account for an osmolarity of 316 mosm/L. Addition of the osmolarities of the other substances, under the assumption that all substances are fully dissolved, yields an osmolarity of 324 for the inorganic substances and another 157 mosm/L of organic substance to yield 481 mosm/L.

b. Clearly, the sum of the concentrations of all solutes exceeds the measured osmolarity of tears. Presumably, many of the organic substances are parts of macromolecules so that it is not valid to simply add the concentrations of individual moles of nitrogen, for example. Furthermore, some of the salts in tears may not be fully ionized.

c. If the temperature is 27° then the osmotic pressure in pascals is

\[ \pi = RTC_\Sigma = \frac{8.314 \text{ J/(mol-K)}}{300 \text{ K}} \times \frac{320 \text{ mol/m}^3}{300 \text{ K}} \approx 8 \times 10^5 \text{ Pa}, \]

where the measured osmolarity was used to compute the osmotic pressure.

Problem 4.5

a. From the van’t Hoff Law of osmotic pressure, the osmotic pressure difference must equal the hydraulic pressure difference.

\[ p_{fw} - p_{sw} = \pi_{fw} - \pi_{sw} = RT(C_{fw}^{\Sigma} - C_{sw}^{\Sigma}), \]

where \( f \) refers to freshwater and \( s \) refers to seawater. The salt concentration is greater in the salt water so the osmotic pressure will make \( \Phi_V \) flow from the fresh water to the salt water. To determine \( p_{sw} \), determine the osmolarities of the two solutions as follows.

\[
C_{fw}^{\Sigma} = 2 \left( \frac{500 \text{ g of NaCl}}{10^6 \text{ g of water}} \right) \left( \frac{1 \text{ g of water}}{\text{cm}^3} \right) \left( \frac{1 \text{ mole}}{58 \text{ g of NaCl}} \right), \\
C_{fw}^{\Sigma} = 1.72 \times 10^{-5} \text{ moles/cm}^3, \\
C_{sw}^{\Sigma} = 2 \left( \frac{40,000 \text{ g of NaCl}}{10^6 \text{ g of water}} \right) \left( \frac{1 \text{ g of water}}{\text{cm}^3} \right) \left( \frac{1 \text{ mole}}{58 \text{ g of NaCl}} \right), \\
C_{sw}^{\Sigma} = 1.38 \times 10^{-3} \text{ moles/cm}^3.
\]

Therefore,

\[ p_{fw} - p_{sw} = RT(C_{fw}^{\Sigma} - C_{sw}^{\Sigma}). \]
Since $p_{fw} = 0$,

$$p_{sw} = RT(C_{sw}^s - C_{fw}^s).$$

At a temperature of 25°C,

$$p_{sw} = \left(8.314 \times 10^6 \frac{\text{Pa}}{\text{K} \cdot \text{moles/cm}^3}\right)(300\text{K})\left(1.36 \times 10^{-3}\text{moles/cm}^3\right),$$

$$p_{sw} = 3.39 \times 10^9 \text{Pa} = 34 \text{ atmospheres}$$

The pump must apply a hydraulic pressure of at least 34 atm to convert 40,000 ppm salt water to 500 ppm salt water.

b. The pressure can also be produced by raising the height of the salt water tank. One atmosphere of pressure is produced for each 33.5 feet that the water is raised. So to produce 34 atmospheres the salt water tank must be raised 1,139 feet with respect to the fresh water tank.

c. Because you float in the Great Salt Lake and sink at Laguna beach, you realize that the density of the salt water is larger in the lake. This means that the concentration of salt is larger in the lake. The larger salt concentration produces a larger osmotic pressure. Therefore, Utah will need a larger hydraulic pressure to enable reverse osmosis.

**Problem 4.6**

a. If the beach balls are treated as solutes in a solution, then the side of the pool with beach balls has a higher osmotic pressure than the side without beach balls. Therefore, water will flow from the side of the pool without beach balls into the side with beach balls.

b. Let the side of the pool with beach balls be denoted by a $b$ subscript and that without by an $n$ subscript. At osmotic equilibrium $p_b - p_n = \pi_b - \pi_n$, but $\pi_n = 0$. Thus, the difference in hydraulic pressure on the two sides is due to the osmotic pressure of the beach balls. If the difference in hydraulic pressure on the two sides is assumed to be due to the increment in the height of the water on the side with the beach balls, then

$$p_b - p_n = \rho gh = RT C_b^b,$$

where $h$ is the increment in the height of the water in the pool on the side with beach balls above that on the other side. The molar concentration of beach balls is

$$C_b^b = \frac{100}{N_A \cdot \mathcal{V}} = \frac{100}{6.022 \times 10^{23} \cdot 3 \cdot 6 \cdot 10} = 9.23 \times 10^{-25} \text{mol/m}^3.$$

where $N_A$ is Avogadro’s number and $\mathcal{V}$ is the volume of the side of the pool with the beach balls. Therefore,

$$h = \frac{RT C_b^b}{\rho g} = \frac{(8.314 \text{ J/(mol} \cdot \text{K}) (300\text{K}) (9.23 \times 10^{-25} \text{ mol/m}^3)}{(10^3 \text{ kg/m}^3)(9.8 \text{ N/kg})} = 2.3 \times 10^{-25} \text{ m}.$$

Thus, the height of the water on the side with the beach balls is higher than that on the side without beach balls by $2.3 \times 10^{-25} \text{ m}$. 
Table 4.1: Table of solute concentrations and partition positions (Problem 4.7).

c. The problem is that the height difference that needs to be measured is very small, i.e., $2.3 \times 10^{-15}$ Å. This outcome results because the osmotic pressure of 100 beach balls in a pool is very small.

Problem 4.7 At osmotic equilibrium, the difference of hydraulic and osmotic pressure on the two sides of the partition must be the same. Since the partition is free to move, it can sustain no difference of hydraulic pressure. Thus, if osmotic equilibrium is achieved, then the osmotic pressure must be the same on the two sides of the partition which implies that the total solute concentration must be the same.

To solve the problem, the final concentrations and partition positions need to be determined. The final concentration on side 1 is
\[
c_1(\infty) = \frac{c_1(0) V_1(0)}{V_1(\infty)} = \frac{c_1(0) x(0) A}{x(\infty) A} = \frac{c_1(0) x(0)}{x(\infty)},
\]
and on side 2
\[
c_2(\infty) = \frac{c_2(0) V_2(0)}{V_2(\infty)} = \frac{c_2(0) \left(10 - x(0)\right) A}{\left(10 - x(\infty)\right) A} = \frac{c_2(0) \left(10 - x(0)\right)}{10 - x(\infty)},
\]
where $A$ is the cross-sectional area of the compartment. If the concentrations on the two sides are equal at equilibrium, then the final concentrations will be the same,
\[
\frac{c_1(0) x(0)}{x(\infty)} = \frac{c_2(0) \left(10 - x(0)\right)}{10 - x(\infty)}
\]
which can be solved for $x(\infty)$ to yield
\[
x(\infty) = \frac{10 c_1(0) x(0)}{c_2(0) \left(10 - x(0)\right) + c_1(0) x(0)}
\]
Once $x(\infty)$ is determined, then the final concentrations can be computed from the above formulas. The answers are shown in Table 4.1. The following are comments on the different parts:

<table>
<thead>
<tr>
<th>Solutes</th>
<th>Initial Values</th>
<th>Final Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$c_1(0)$ mmol/L</td>
<td>$c_2(0)$ mmol/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Glucose</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Glucose</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Glucose</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Glucose</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>NaCl</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>
Figure 4.3: Photographs of the General Sherman giant sequoia and a mangrove tree (reproduced from Encarta96 Encyclopedia) (Problem 4.8).

Figure 4.4: Variables involved in water transport in a tree root (Problem 4.8).

- When \( c_1(0) = 0 \) water will flow into side 2 pushing the partition to the left. However, osmotic equilibrium cannot be achieved so the partition will move all the way to the left until \( x(\infty) = 0 \). The concentrations in side 1, which is now infinitesimally thin, remains at zero since the solute does not go through the partition. The concentration of side 2 is obtained from the formulas.

- When the initial glucose concentration is the same on both sides, the system is already in osmotic equilibrium. Hence, nothing changes.

- With a different initial concentration of glucose on the two sides of the membrane, straightforward application of the formulas yields the results. Clearly, with the initial concentration of glucose on side 1 greater than on side 2, water will flow into side 1 which will move the partition to the right.

- In the 3 parts that involve NaCl it is important to realize that the total concentration of solutes is twice the concentration of the salt under the assumption that the salt is fully ionized. Thus, case 4 is already at osmotic equilibrium so there are no changes in concentration or partition position. Cases 5 and 6 involve using the derived formulas taking total solute concentration into account.

**Problem 4.8** Figure 4.3 shows a picture of the General Sherman giant sequoia as well as a mangrove tree growing with its roots in salt water. Figure 4.4 shows the variables involved in water transport in a tree root.
Table 4.2: Summary of osmotic and mechanical factors involved in the rising of sap in the giant sequoia and the red mangrove. The height of the trees is expressed in meters; there are 0.3048 meters per foot.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sequoia</th>
<th>Mangrove</th>
</tr>
</thead>
<tbody>
<tr>
<td>$h$ (m)</td>
<td>82.9</td>
<td>24.4</td>
</tr>
<tr>
<td>$p_g$ (Pa)</td>
<td>$8.1 \times 10^3$</td>
<td>$2.4 \times 10^3$</td>
</tr>
<tr>
<td>$C_s^t$ (mol/m³)</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>$C_s^s$ (mol/m³)</td>
<td>51</td>
<td>1050</td>
</tr>
<tr>
<td>$\pi^t$ (Pa)</td>
<td>$1.1 \times 10^3$</td>
<td>$1.1 \times 10^3$</td>
</tr>
<tr>
<td>$\pi^s$ (Pa)</td>
<td>$1.3 \times 10^3$</td>
<td>$2.6 \times 10^6$</td>
</tr>
<tr>
<td>$\pi^t - \pi^s - p_g$ (Pa)</td>
<td>$-8.3 \times 10^3$</td>
<td>$-2.7 \times 10^6$</td>
</tr>
<tr>
<td>$p_o$ (Pa)</td>
<td>$&lt; -8.3 \times 10^3$</td>
<td>$&lt; -2.7 \times 10^6$</td>
</tr>
</tbody>
</table>

(a) At the junction between the roots and the soil/seawater, the flux of water from the soil/seawater into the tree root is

$$\Phi_V = RTL_V((p_g^s - \pi^s) - (p_o + p_g^t - \pi^t)),$$

where the superscript $t$ is used to denote the tree root and the superscript $s$ to denote either soil or seawater. Let $p_g = p_g^t - p_g^s$. Therefore, for the sap to rise in the tree $\pi^t - \pi^s - p_o - p_g + > 0$ which implies that $p_o < \pi^t - \pi^s - p_g$.

(b) The pressure due to gravity is $p_g = \rho gh$ where $\rho$ is the density of water, $g$ is the acceleration of gravity, and $h$ is the height of the tree. This can be expressed as follows

$$p_g = (10^3 \text{ kg/m}^3)(9.8 \text{ N/kg})h = 9.8 \times 10^3 h \text{ Pa}.$$

The osmotic pressure at $27^\circ C$ is

$$\pi = RTC_s = (8.314 \text{ J/(mol} \cdot \text{K)}(300\text{K})C_s = 2.49 \times 10^3 C_s,$$

where $C_s$ is expressed in mol/m³. Note that concentration in mol/L is the same as in mol/m³. Table 4.2 summarizes the relevant factors. There are number of interesting factors involved in the rising of sap that are illustrated in this problem. To interpret results intuitively, recall that atmospheric pressure (which results from the weight of the atmosphere on the surface of the earth) corresponds to $10^5$ pascals also called an atmosphere. Thus, the gravitational pressure due to the height of the tree must be much larger in the giant sequoia, which is a taller tree, than in the red mangrove. Both pressures correspond to several atmospheres. Both of these pressures tend to make the water flow out of the tree root into the soil/seawater. Because, the osmolarity of the soil/seawater exceeds that of sap for both trees, this difference in osmotic pressure also causes water to flow out of the tree. However, this effect is much larger in the red mangrove than in the giant sequoia because the osmolarity of seawater greatly exceeds that of the soil. Thus, the capillary forces that make sap rise must be much greater in the red mangrove than in the giant sequoia.
Problem 4.9 The flux through both membranes is the same

\[ \Phi_V = RT L_1 (C_X - C_{X1}) = RT L_2 (C_X - C_{X2}). \]

\( C_X \) can be determined as follows

\[ L_1 (C_X - C_{X1}) = L_2 (C_X - C_{X2}), \]
\[ (L_1 + L_2) C_X = L_1 C_{X1} + L_2 C_{X2}. \]

Therefore,

\[ C_X = \frac{L_1}{L_1 + L_2} C_{X1} + \frac{L_2}{L_1 + L_2} C_{X2}. \]

Therefore,

\[ \Phi_V = RT L_1 (C_X - C_{X1}), \]
\[ = RT L_1 \left( \frac{L_1}{L_1 + L_2} C_{X1} + \frac{L_2}{L_1 + L_2} (C_X - C_{X1}) \right), \]
\[ = RT \left( \frac{L_1 L_2}{L_1 + L_2} \right) (C_X - C_{X1}). \]

Therefore,

\[ L_V = \frac{L_1 L_2}{L_1 + L_2}. \]

Problem 4.10 The flux through the composite membrane is the total flow of volume through the membrane divided by the membrane area which is

\[ \Phi_V = \frac{\Phi_1 A_1 + \Phi_2 A_2}{A_1 + A_2}, \]

where \( \Phi_1 \) and \( \Phi_2 \) are the fluxes through patch 1 and 2, respectively,

\[ \Phi_1 = RT L_1 \left( C_X - C_{X1} \right) \] and \( \Phi_2 = RT L_2 \left( C_X - C_{X2} \right). \]

Combining these two equations yields

\[ \Phi_V = RT \frac{L_1 A_1 + L_2 A_2}{A_1 + A_2} \left( C_X - C_{X1} \right), \]

from which it is clear that

\[ L_V = \frac{L_1 A_1 + L_2 A_2}{A_1 + A_2}. \]

Problem 4.11

a. Let \( i \) and \( o \) represent the inside and outside of the tube, respectively. Let \( \Phi_V \) represent the flux of water through the membrane with outward flow being taken as positive. The tube contains a volume of solution

\[ V(t) = Ah(t), \]
where \( h(t) \) is the total height of the solution in the glass tube. Conservation of water requires that

\[
\frac{dV(t)}{dt} = -A\Phi_V.
\]

A combination of these equations yields

\[
\frac{dh(t)}{dt} = -\Phi_V.
\]

The volume flux is related to osmotic pressure as follows

\[
\Phi_V = -L_V RT (C_{S1} - C_{S2}),
\]

where the hydraulic pressure is assumed negligible, \( C_{S1} = C_s(t) \), the concentration of sucrose, and \( C_{S2} = 0 \). As water flows into the tube, the concentration of sucrose decreases. However, the total quantity of sucrose remains constant,

\[
C_s(t)V(t) = C_s(0)V(0),
\]

so that

\[
C_s(t) = \frac{C_s(0)V(0)}{V(t)} = \frac{C_s(0)h(0)}{h(t)}.
\]

A combination of these relations results in the differential equation for \( h(t) \),

\[
\frac{dh(t)}{dt} = L_V R T C_s(0) \frac{h(0)}{h(t)}.
\]

b. The differential equation for \( h(t) \) is separable and can be written as

\[
\int_{h(0)}^{h(t)} \frac{h'(t)}{h(0)}\,dh' = \int_0^t R T L_V C_s(0) \,dt',
\]

which upon integration yields

\[
\frac{h^2(t) - h^2(0)}{2h(0)} = R T L_V C_s(0)t.
\]

Therefore,

\[
h(t) = \sqrt{h^2(0) + 2 L_V R T C_s(0) h(0)t}.
\]

We evaluate the constants as follows

\[
h(0) = \frac{V(0)}{A} = \frac{2}{0.5} = 4 \text{ cm} = 0.04 \text{ m},
\]

and

\[
2 L_V R T C_s(0) h(0) = 2 \cdot L_V \cdot 8.314 \text{ J/(mol·K)} \cdot 300 \text{ K} \cdot 10^2 \text{ mol/m}^3 \cdot 0.04 \text{ m} \\
\approx 2 \times 10^4 L_V \text{ m}^2/\text{s}.
\]

Therefore,

\[
h(t) = \sqrt{0.04^2 + 2 \times 10^4 L_V t},
\]

whose form is shown plotted in Figure 4.5.
c. If \( h(t) \approx h(0) + 0.02t \) cm initially, then the derivative of height with respect to time is 0.02 cm/s at \( t = 0 \). The results from part a show that

\[
\frac{dh(t)}{dt}\bigg|_{t=0} = L_V R T C_s(0),
\]

so that

\[
L_V = \frac{dh(t)/dt|_{t=0}}{R T C_s(0)}.
\]

The denominator is

\[
R T C_s(0) = 8.3 \text{ N} \cdot \text{ m/(mol} \cdot \text{ K)} \times 300 \text{ K} \times 100 \text{ mol/m}^3 = 2.49 \times 10^5 \text{ Pa}.
\]

Therefore,

\[
L_V \approx \frac{2 \times 10^{-4} \text{ m/s}}{2.49 \times 10^5 \text{ Pa}} \approx 8 \times 10^{-10} \text{ m/(Pa} \cdot \text{s)}.
\]

Alternatively, the initial slope can be obtained from the solution found in part b, and the value of \( L_V \) determined. For this purpose,

\[
h(t) = h(0) \sqrt{1 + \frac{2L_V R T C_s(0)t}{h(0)}},
\]

\[
h(t) \approx h(0) \left(1 + \frac{1}{2} L_V R T C_s(0)t\right),
\]

\[
h(t) \approx h(0) + L_V R T C_s(0)t.
\]

Hence, the initial slope is \( L_V R T C_s(0) \) which is consistent with the earlier finding.

It is of interest to see if hydraulic pressure due to gravity, which has been ignored in this problem, makes an appreciable contribution. At an initial height \( H \) above the water level in the vessel, the hydraulic pressure is

\[
\rho g H \approx 1000 \text{ kg/m}^3 \times 9.8 \text{ m/s}^2 \times H \text{ m} \approx 10^4 H \text{ Pa}.
\]

Therefore, for a glass tube with water level of a few centimeters, the hydraulic pressure is negligible compared to the osmotic pressure.

Problem 4.12
a. The flux of volume is

\[ \Phi_V = \mathcal{L}_V \left( (p_s - p_o) - (\pi_s - \pi_o) \right). \]

The hydraulic pressure is due to the head of water and the osmotic pressure difference. The osmotic pressure of the fresh water in the pipe is zero. Therefore,

\[ \Phi_V = \mathcal{L}_V \left( (p_s g h_s - p_o g h_o) - (RTC^\Sigma - 0) \right), \]

\[ = \mathcal{L}_V \left( g(p_s h_s - p_o h_o) - RTC^\Sigma \right). \]

Note that the difference in hydraulic pressure must overcome the osmotic pressure of seawater in order for the volume flux to be positive.

b. The derivative of the height is obtained as follows

\[ \frac{d(A h_o(t))}{dt} = A \frac{d h_o(t)}{dt} = A \Phi_V. \]

Substitution for the flux yields

\[ \left( \frac{d h_o(t)}{dt} \right)_{t=0} = \mathcal{L}_V \left( p_s g h_s - p_o g h_o(0) - RTC^\Sigma \right). \]

All the constants are expressed in ISI units. The difference of hydraulic pressure is

\[ p_s g h_s - p_o g h_o(0) = 9.8 \, \text{m/s}^2 \left( 1.03 \times 10^3 \, \frac{\text{kg}}{\text{m}^3} \times 10^2 \, \text{m} - 1 \times 10^3 \, \frac{\text{kg}}{\text{m}^3} \times 1 \, \text{m} \right), \]

\[ = 10^6 \, \text{Pa}. \]

The difference in osmotic pressure is

\[ RTC^\Sigma = 8.314 \, \frac{\text{J}}{\text{mol} \cdot \text{K}} \times 300 \, \text{K} \times 10^3 \, \frac{\text{mol}}{\text{m}^3}, \]

\[ = 2.49 \times 10^6 \, \text{Pa}. \]

Therefore,

\[ \left( \frac{d h_o(t)}{dt} \right)_{t=0} = 3 \times 10^{-12} \, \frac{\text{m}}{\text{Pa} \cdot \text{s}} (1 - 2.49) \times 10^6 \, \text{Pa} = 4.47 \, \text{Pa/s}. \]

c. At equilibrium, \( \Phi_V = 0 \). Therefore,

\[ g \left( p_s h_s - p_o h_o(\infty) \right) - RTC^\Sigma = 0, \]

and

\[ h_o(\infty) = \frac{p_s}{p_o} h_s - \frac{RTC^\Sigma}{g p_o}. \]

The critical height is one for which \( h_o(\infty) > h_s \) so that

\[ \frac{p_s}{p_o} h_s - \frac{RTC^\Sigma}{g p_o} > h_s, \]
and

\[
\left( \frac{\rho_s - \rho_o}{\rho_o} \right) h_s > \frac{RTC_s}{g\rho_o}.
\]

Therefore,

\[
h_s > h_c = \frac{RTC_s}{g(\rho_s - \rho_o)}.
\]

d. The critical assumption is that the ocean’s composition (osmolarity) is constant with depth, i.e., that the ocean is well-mixed. If it were then there would be no intrinsic reason that fresh water and energy could not be extracted. On the other hand, if the ocean were modeled as in equilibrium then the osmolarity would vary exponentially with depth as indicated in Problem 3.19. Thus, as the pipe is lowered deeper into the ocean, the osmotic pressure would rise exponentially with depth. This increase in osmotic pressure with depth would tend to drive fresh water out of the pipe into the ocean. We investigate the effect of the assumed equilibrium distribution of concentration. Diffusive equilibrium in the presence of the force of gravity results in a solute concentration that is an exponential function of depth (see the solution to Problem 3.19), so that

\[
C_s(h_s) = C_s(0)e^{h_s/\lambda},
\]

where

\[
\lambda = \frac{kT}{m_{eff}g}.
\]

Combining this result with the earlier inequality, which is required if useful fresh water is to be obtained, yields

\[
h_s > \frac{RTC_s(0)}{g(\rho_s - \rho_o)}e^{h_s/\lambda}.
\]

The depth variable can be normalized so that \( \gamma = h_s/\lambda \) to give

\[
a \gamma > e^\gamma,
\]

where

\[
a = \lambda \frac{g(\rho_s - \rho_o)}{RTC_s(0)},
\]

\[
= \left( \frac{kT}{m_{eff}g} \right) \left( \frac{g(\rho_s - \rho_o)}{RTC_s(0)} \right),
\]

\[
= \frac{\rho_s - \rho_o}{N_A m_{eff} C_s(0)}.
\]

Note that \( N_A m_{eff} \) is the effective mass of a mole of salt particles and can be expressed as a molar volume times the effective density. The molar volume times the molar concentration is about 1. Thus, \( a \approx 1 \). As shown in Figure 4.6, \( a \gamma > e^\gamma \) for values of \( a > e \) only. Therefore, this argument suggests that the inequality is not satisfied and \( h_s > h_o(\infty) \) so that no fresh water can be extracted from the ocean by this mechanism. The model used here has ignored the change in density of salt water with depth.
Figure 4.6: A plot of the functions $e^y$ and $ay$ versus $y$ for different values of $a$ (Problem 4.12). The functions do not intersect for $a < e$, are tangent for $a = e$ at $y = 1$, and intersect for $a > e$.

Figure 4.7: The hydraulic and osmotic pressure in a porous membrane (Problem 4.13). The solid line is $p(x) - RTC_\Sigma(x)$; the dashed line is $p(x)$; the dotted line is $RTC_\Sigma(x)$.

**Problem 4.13** The key to this problem is the observation that $p - RTC_\Sigma$ is continuous at the membrane solution interface. This can be understood as follows. Since the solvent is incompressible, all of the water that enters the membrane must also flow out of the membrane. Therefore, the flux of water is continuous through the membrane solution interface. It follows from Equation 4.12 (Weiss, 1996a),

$$\Phi_V = -\kappa \frac{\partial(p - \pi)}{\partial x} = 0$$

that $p - \pi$ must also be continuous through the membrane solution interface.

a. To solve this problem, it is easiest to proceed graphically. Make a scale drawing of the membrane pressure variables. $RTC_\Sigma^1$ is the smallest quantity and all variables are scaled to this quantity. $RTC_\Sigma^2 = 3RTC_\Sigma^1$. Inside the membrane $RTC_\Sigma = 0$ since no solute can enter the membrane. Hence, $RTC_\Sigma$ can be sketched in the baths and in the membrane as shown in Figure 4.7. Next sketch $p_1$ and $p_2$ in the baths as given in the problem. With this accomplished, sketch $p - RTC_\Sigma$ in the baths and, since it must be continuous, sketch it in the membrane. A sketch of both $RTC_\Sigma$ and $p - RTC_\Sigma$ in the bath and membrane makes it easy to sketch $p$.

b. In the membrane, there is no osmotic pressure gradient so the volume flux is

$$\Phi_V = -\kappa \frac{dp(x)}{dx}.$$  

Since the slope of $p(x)$ is negative in the membrane, $\Phi_V > 0$ as is shown.

c. With convection in the positive $x$-direction, we expect the concentration profile in the membrane to resemble the curves such as the ones for $y \gamma d$ of 0, 2, or 10 in the figure. The exact shape depends on the exact parameters.
Problem 4.14 This problem also depends for its solution on understand the continuity of $p - \pi$ at a membrane solution interface as described in the solution to Problem 4.13.

a. Since there is a discontinuity in the osmotic pressure at each interface, there must be an equal discontinuity of hydraulic pressure at each interface as shown in Figure 4.8.

b. Once $p$ is obtained, $p - RTc$ can be sketched as indicated in Figure 4.8.

c. The osmotic pressure on side 1 is $RTC_\Sigma^1 = 2$ atmospheres. An atmosphere is $10^5$ Pa, so that

$$C_\Sigma^1 = \frac{2 \times 10^5}{(8.314 \times 10^6)(300)} \text{ mol/cm}^3 = 80 \mu\text{mol/cm}^3$$

c. The volume flux is from side 2 to side 1 for both cases, but is larger for case (2) since the difference in $p - RTC_\Sigma$ between side 2 and side 1 is 1 for case (1) and 2 for case (2). Since the membrane is the same in both cases, the flux is determined by the difference in $p - RTC_\Sigma$ on the two sides of the membrane only.

Problem 4.15 NaCl solution is an isotonic solution. Assume that NaCl is fully ionized into $\text{Na}^+$ and $\text{Cl}^-$. Therefore, the extracellular osmolarity is $C_\Sigma^0 = 0.3$ osmoles/L. Since the cell neither shrinks nor swells in this solution, the intracellular osmolarity must also be $C_\Sigma^i = 0.3$ osmoles/L.

a. The extracellular osmolarity for the 150 mmol/L glucose solution is $C_\Sigma^0 = 0.15$ osmoles/L so that the extracellular osmolarity is less than the intracellular osmolarity and water is transported into the cell to achieve osmotic equilibrium. Therefore, the cell swells.
b. The extracellular osmolarity for the 300 mmol/L glucose solution is \( C^e_x = 0.3 \) osmoles/L so that the extracellular osmolarity equals the intracellular osmolarity. Hence, there is no water transport across the membrane and the cell volume remains the same.

### Problem 4.16

a. i. Because the concentration of solute in Chamber 1 is much larger than the total solute concentration in the body fluids, the osmotic pressure \( \pi = RT C^1_x \) is larger than the external osmotic pressure. Because of the properties of the piston and drug-delivery orifice, no hydraulic pressure differences exist. Flux of water into Chamber 1 is \( \Phi_V = L_V RT (C^1_x - C^{bf}_x) \approx L_V RT C^1_x \). As water flows into Chamber 1, the piston moves to the right and the drug solution is forced out of the orifice at the same volume flow rate.

ii. Chemical energy is stored in the high solute concentration in Chamber 1. This store of energy is dissipated as water flows in and dilutes the solution.

iii. If it is assumed that all the solute in Chamber 1 is in solution initially, then the concentration will decrease as water flows in. The concentration will not change much if \( \Phi_V \cdot A \cdot T \ll V_1 \). Thus, for a given volume flow \( \Phi_V A, T \ll V_1 \left( \Phi_V A \right) \). Alternatively, if enough undissolved solute is in Chamber 1 to keep the solution saturated until all the drug is delivered, then the pump could operate at a constant rate throughout its life.

b. The volume flux is \( L_V RT C^1_x \), and \( \Phi_V A = 1 \) \( \mu \)L/h. Therefore,

\[
L_V = \frac{\Phi_V A}{RT C^1_x A} = \frac{1 \ \mu\text{L/h} \cdot 10^{-9} \text{m}^3/\mu\text{L} \cdot 1/3600 \text{h/s}}{\pi \cdot (0.007/2)^2 \text{m}^2 \cdot 8.314 \text{N} \cdot \text{m/(K}\cdot\text{mol}) \cdot 300 \text{ K} \cdot 10 \text{ mol/L} \cdot 10^3 \text{ L/m}^3} = 2.9 \times 10^{-16} \text{ m}^3/(\text{N}\cdot\text{s})
\]

The principle of the osmotic pump is the basis of commercially available systems for drug delivery (e.g., Figure 4.9).

### Problem 4.17

a. The equation of water volume conservation is

\[
-\frac{1}{A(t)} \frac{dV_c(t)}{dt} = L_V RT \left( C^o_x - \frac{N^i_x}{V_c(t)} \right).
\]

If the surface areas of the circular ends of the cell are ignored, then the surface area of the cell is \( A(t) = 2\pi r(t)l \) and its volume is \( V_c(t) = \pi r^2(t)l \). Substitution of these relations into the conservation relation yields

\[
-\frac{1}{2\pi r(t)l} \frac{d(\pi r^2(t)l)}{dt} = L_V RT \left( C^o_x - \frac{N^i_x}{\pi r^2(t)l} \right),
\]
Figure 4.9: Dimensions (left panel) and schematic diagram (right panel) of commercially available osmotic pumps (Problem 4.16). These Alzet osmotic pumps are made by ALZA Corporation. The osmotic agent causes osmotic water transport into the pump through the semipermeable membrane. Water entry compresses the impermeable reservoir wall thus forcing drug out of the reservoir through the delivery portal.

\[
- \frac{dr(t)}{dt} = L_V RT \left( C_S^0 - \frac{N_i^i}{\pi r^2(t) l} \right),
\]

\[
\frac{dr(t)}{dt} = \frac{L_V R T N_i^i}{r^2(t)} \left( \frac{\pi l}{(\pi l)} \right) = -L_V R T C_S^0.
\]

The last equation has the form

\[
\frac{dr(t)}{dt} + \frac{A}{r^2(t)} = B.
\]

b. The constants are

\[
A = -\frac{L_V R T N_i^i}{\pi l},
\]

\[
B = -L_V R T C_S^0.
\]

**Problem 4.18** As shown in Section 4.7 (Weiss, 1996a), the volume of water in a cell satisfies the differential equation

\[
\frac{dv(t)}{dt} = \alpha_v A(t) \left( \frac{1}{v(t)} - \tilde{c}(t) \right),
\]

where all the variables are normalized. The shape of the cell is expressed by the shape factor \( A(t) \) which is the cell surface area. To solve the differential equation, \( A(t) \) must
be expressed in terms of the volume \( v(t) \). This relation depends upon the shape of the cell. For a constant surface area \( A(t) = 1 \), for a spherical cell \( A(t) = v^{2/3}(t) \), and for a long cylindrical cell (for which the end caps provide negligible area) \( A(t) = v^{1/2}(t) \).

a. The response to halving the osmolarity is an increase in the cell water volume, but the rate of increase in \( v(t) \) is proportional to \( A(t) \). For a constant cell area \( A(t) = 1 \) and for a spherical cell \( A(t) = v^{2/3}(t) \) which is greater than 1 when the cell swells as it does when the osmolarity is reduced. Therefore, the rate of change is larger for the spherical cell than for the cell with constant surface area. This result is shown in Figure 4.51 (Weiss, 1996a).

b. For a cylindrical cell, \( A(t) = v^{1/2}(t) \) which for \( v(t) > 1 \) lies between the value for a constant surface area cell and a spherical cell. Therefore, the rate of change of volume should be larger in a cylindrical cell than in a cell with constant surface area and should be smaller than in a spherical cell. This is born out in the solutions to the three sets of equations shown in Figure 4.10.

**Problem 4.19**

a. If the salts are assumed to dissociate completely so that each mole of NaCl gives rise to 2 moles of ions and that each mole of CaCl2 gives rise to 3 moles of ions, then the osmolarities of the 4 solutions are: NaCl, 300 mosm/L; CaCl2, 600 mosm/L; sucrose, 800 mosm/L; xylose, 150 mosm/L. The order of increasing radius is in the order of decreasing osmolarity. Therefore, solution 1 must be sucrose, solution 2 must be CaCl2, solution 3 must be NaCl, and solution 4 must be xylose. It follows
that the isotonic radius is 80 μm, so that solution 3 must be an isotonic solution which shows that isotonic concentration is 300 mosm/L.

b. At equilibrium,
\[ V_c = \frac{4}{3} \pi r_c^3 = \frac{N_i^t}{C_S^t} + V'_c, \]
where \( r_c \) is the radius of the cell. Thus, this equation is solved for two of the solutions as follows,
\[ \frac{4}{3} \pi (99.1 \times 10^{-4})^3 = \frac{N_i^t}{150 \times 10^{-6}} + V'_c, \]
\[ \frac{4}{3} \pi (60.7 \times 10^{-4})^3 = \frac{N_i^t}{800 \times 10^{-6}} + V'_c. \]
To find \( N_i^t \), subtract these two equations and solve to obtain \( N_i^t = 5.8 \times 10^{-10} \) mol.

c. For an isotonic solution
\[ V_c^n = \frac{N_i^t}{C_S^n} + V'_c, \]
which can be expressed as follows
\[ \frac{V'_c}{V_c^n} = 1 - \frac{N_i^t}{C_S^n V_c^n} = 1 - \frac{5.8 \times 10^{-10}}{(300 \times 10^{-6})(4/3) \pi (80 \times 10^{-4})^3} \approx \frac{1}{10}. \]

Problem 4.20

a. The total solute concentration is
\[ C_S^i(t) = \frac{N_i^t}{V_c(t) - V_c'.} \]
Since, \( N_i^t \) is constant
\[ C_S^i(0) = \frac{N_i^t}{V_c(0) - V_c'.} \]
Dividing these two equations yields
\[ \frac{C_S^i(t)}{C_S^i(0)} = \frac{V_c(0) - V_c'}{V_c(t) - V_c'}. \]
Since the initial extracellular concentration is isotonic, \( C_S^i(0) = C_S^o(0-) \).

b. The efflux of water from the cell is
\[ \Phi_V = L_V RT (C_S^o(t) - C_S^i(t)) \]
From conservation of water volume,
\[ -\frac{1}{A(t)} \frac{dV^i(t)}{dt} = \Phi_V(t) = L_V RT \left( C_S^o(t) - C_S^i(t) \right). \]
PROBLEMS

But \(d \frac{V^i}{dt} = d \frac{V_c}{dt}\) and for a sphere \(A = (36\pi)^{1/3} V_c^{2/3}\). These equations are combined and rearranged to yield

\[
\frac{dV_c(t)}{dt} = (36\pi)^{1/3} V_c^{2/3}(t) \frac{L_V RT}{V_w} \left( C_S^q(0) \frac{V_c(0) - V_c'}{V_c(t) - V_c} - C_S^q(t) \right).
\]

This is a nonlinear equation for the cell volume \(V_c(t)\) given the extracellular solute concentration \(C_S^q(t)\) and the constants \(L_V\) and \(V_c'\).

c. At \(t = 0^+\)

\[
\frac{dV_c(t)}{dt} \bigg|_{t=0^+} = (36\pi)^{1/3} V_c^{2/3}(0^+) \frac{L_V RT}{V_w} \left( C_S^q(0^-) - C_S^q(0^+) \right).
\]

Therefore, \(L_V\) can be computed from the initial rate of change of cell volume, given the temperature, and the change in osmolarity of the extracellular solution (Figure 4.11). As \(t \to \infty\), \(d \frac{V_c(t)}{dt} \to 0\) and

\[
C_S^q(0^-) \frac{V_c(0) - V_c'}{V_c(\infty) - V_c} - C_S^q(0^+) = 0.
\]

Therefore, \(V_c'\) can be computed by knowing the initial and final volume of the cell and the initial and final value of the extracellular concentration.

**Problem 4.21** The particular measurements given in the problem are used to estimate the pore radii using the theoretical results summarized in Figure 4.11 (Weiss, 1996a). All of the parts of the problem involve estimation of the quantity \(P_w/P_w\).

a. First, estimate \(P_w = RT L_V / \bar{V}_w\) as follows

\[
P_w = \frac{RT L_V}{\bar{V}_w} = \frac{\left(8.314 \times 10^6 \frac{\text{Pa}}{\text{K} \cdot (\text{mol/cm}^3)}\right) \cdot (300 \text{ K}) \cdot \left(1.4 \times 10^{-6} \mu\text{m/s}\right)}{18 \text{ mol/cm}^3},
\]

\[
= 194 \mu\text{m/s}.
\]

Therefore, the ratio \(P_w/P_w = 194/24 = 8.1\). Using the theory without hindrance, the pore radius can be estimated from Figure 4.11 (Weiss, 1996a) as \(r = 1.0 \text{ nm}\).
b. Using the theory with hindrance, the pore radius can be estimated from Figure 4.11 (Weiss, 1996a) as $r = 0.8 \text{ nm}$.

c. Measurements in erythrocytes suggest that water permeates the membrane by dissolving and then diffusing through the lipid bilayer and via water channels. If mercury compound are assumed to block only the water channels, then both the osmotic and the diffusive permeabilities through the water channels can be estimated more accurately so that

$$\frac{P_w}{P_w} = \frac{194 - 12}{24 - 12} = 15.2,$$

which gives a pore radius of $r = 1.2 \text{ nm}$.

d. If the results of this problem are assumed to be applicable to erythrocytes, then it follows that the pore radius is of the order of 1 nm, i.e., of molecular dimensions. Therefore, this radius is clearly large enough to admit water molecules whose diameters are of the order of 0.2 nm. However, there are caveats to be made for estimates of pore radius that rely on measurements of $P_w/P_w$ as well as on theories of hindered transport in porous membranes. First, estimates of $P_w/P_w$ based on measurements vary appreciably across different studies as is made clear by comparing the results cited in this problem with those given in Table 4.2. In addition, a variety of theories of hindered transport have been proposed so that estimating pore radii involves choosing among a number of competing theories most of which are derived from continuum hydrodynamic models whose validity at molecular dimensions is not known for certain. These types of estimates can be put on a firm foundation only if measurements are available for porous membranes with nm radii pores of known dimensions.
Chapter 5

CONCURRENT SOLUTE AND SOLVENT TRANSPORT

Exercises

**Exercise 5.1** For thermodynamic equilibrium, both the solute and water must be in equilibrium. Since the solute is permeant, diffusive equilibrium requires that $c_j^1 = c_j^2$. Therefore, if $c_j^1 \neq c_j^2$ then thermodynamic equilibrium is not possible.

**Exercise 5.2** Since the solute is impermeant, the quantity of intracellular solute remains constant at its isotonic value. Therefore, the normalized intracellular quantity $\hat{n}(t) = 1$. Since the extracellular concentration of solute is doubled during the pulse, the volume of water in the cell is halved. Therefore, the volume normalized to its isotonic value $\nu(t) = 0.5$.

**Exercise 5.3** A small value of $\alpha$ corresponds to solute that is relatively impermeant. That is why there is a relatively small change in $n(t)$ and a relatively large change in $\nu(t)$. If the solute were impermeant then doubling the extracellular concentration would halve the volume of water in the cell. The case for a solute with $\alpha = 0.1$ approaches that of an impermeant solute.

**Exercise 5.4** Note that for both $\nu(t)$ and $n(t)$, the time course of the onset of the response differs from the offset. This is most easily seen in $\nu(t)$ in which reduction in volume in response to the onset of the change in osmolarity is faster than the increase in volume at the offset of the change in osmolarity. These differences in time course do not occur for linear differential equations with constant coefficients.

**Exercise 5.5** Since the solute is impermeant, the quantity of impermeant solute does not change. Therefore, as the volume of the cell decreases, the intracellular concentration of solute increases. At equilibrium, doubling the extracellular osmolarity halves the volume and, therefore, doubles the concentration. These trends are apparent in the results shown in Figure 5.1.

**Exercise 5.6** The membrane is more permeable to solute A than to solute B. Therefore, there is a larger transfer of solute A than B and a smaller transfer of volume for solute
Figure 5.1: Volume, intracellular solute content, and intracellular solute concentration in response to doubling the extracellular osmolarity (Exercise 5.5).
Exercise 5.7 Figures 4.21 and 4.27 (Weiss, 1996a) show that changing solution osmolality for the sea water that is extracellular to these invertebrate egg cells results in a change in cell volume that is maintained for a matter of several minutes. Thus, these egg cells are relatively impermeant to the solutes in sea water. However, the volume changes shown in Figure 5.6 (Weiss, 1996a), which result from a change in osmolarity caused by the addition of ethylene glycol to isotonic sea water, show a transient response that takes several hundred ms. Putting these two measurements together suggests that the membrane of these eggs cells are much more permeant to ethylene glycol than to the solutes in sea water.

Exercise 5.8 To *convect* means to *carry*. Hence, in solute convection, the solute is carried by the solvent. Motion of the solvent carries solute along and results in solute transport. In solute diffusion, solute is transported relative to the solvent due to a solute concentration gradient.

Exercise 5.9

a. The reference direction for $\Phi_V$ must be positive from side 1 to side 2. This direction ensures that when the $\Delta p > 0$, $\Phi_V > 0$ (Figure 5.2). The solute flux is positive when $\Delta c_j > 0$. Therefore, the reference direction for $\phi_j$ is the same as for $\Phi_V$.

b. To obtain no solute flux requires $P_j = 0$ and $\sigma_j = 1$. To obtain a non-zero osmotic transport requires $LVT > 0$.

c. Combining equations results in

$$\phi_j = -C_j(1-\sigma_j)\sigma_jLVRT\Delta c_j + P_j\Delta c_j = (P_j - C_j(1-\sigma_j)\sigma_jLVRT)\Delta c_j.$$ 

Therefore, a negative slope to the relation between $\phi_j$ and $\Delta c_j$ can occur if $P_j < C_j(1-\sigma_j)\sigma_jLVRT$. Thus, the result is not inconsistent with the Kedem-Katchalsky equations.
CHAPTER 5. CONCURRENT SOLUTE AND SOLVENT TRANSPORT

Problems

Problem 5.1 The normalized equations of solute and solvent transport of a permeant solute in the presence of an impermeant solute are

\[
\frac{dn(t)}{dt} = \alpha_n A(t) \left( c(t) - \frac{n(t)}{\nu(t)} \right),
\]

\[
\frac{d\nu(t)}{dt} = \alpha_v A(t) \left( \frac{n(t) + \tilde{n}(t)}{\nu(t)} - \left( c(t) + \tilde{c}(t) \right) \right).
\]

a. In the presence of solute A only, the cell is in diffusive and osmotic equilibrium. With the substitution of solute B, the cell is initially at osmotic equilibrium, but not at diffusive equilibrium because there is a difference in the concentration of the permeant solute B across the membrane. Therefore, B diffuses into the cell and increases the intracellular osmolarity so that water enters and the cell swells. This can be seen from the normalized equations. During the interval \(0 < \alpha_v t < 25\), \(c(t) = \tilde{c}(t) = 1/2\). Because the cell was in an isotonic impermeant solution A for \(t < 0\), the quantity of impermeant intracellular solute is the isotonic quantity. That is, \(\tilde{n}(t) = 1\) for \(t < 0\). Since this solute is impermeant, \(\tilde{n}(t) = 1\) for \(t > 0\). Therefore, the equations become

\[
\frac{dn(t)}{dt} = \alpha_n A(t) \left( \frac{1}{2} - \frac{n(t)}{\nu(t)} \right),
\]

\[
\frac{d\nu(t)}{dt} = \alpha_v A(t) \left( \frac{n(t) + 1}{\nu(t)} - 1 \right),
\]

with initial values of \(n(0) = 0\) and \(\nu(0) = 1\). Therefore, initially \(dn(t)/dt > 0\) and solute B enters the cell. Furthermore, as \(n(t)\) increases \(d\nu(t)/dt\) also increases so that water enters and the cell swells.

b. & c. At diffusive equilibrium, the concentration of permeant solute must be the same on the two sides of the membrane. Therefore, since the permeant, normalized extracellular concentration is \(1/2\) that means the permeant, normalized intracellular concentration must also be \(1/2\). At osmotic equilibrium, the total solute concentrations in the cell must equal that of the extracellular concentration. The total, normalized extracellular concentration is \(1\) which guarantees that the total intracellular concentration is also \(1\). Thus, the impermeant and permeant intracellular solutes have concentration \(1/2\). Since the concentrations are equal, the quantities must be equal. Therefore, since the impermeant quantity is \(1\), the permeant quantity must be \(1\). Thus, the total normalized quantity of intracellular solute is \(2\) and the normalized concentration is \(1\). Therefore, the normalized volume is \(2\). This result can also be gotten directly from the equations. At diffusive and osmotic equilibrium, \(dn(t)/dt = 0\) and \(d\nu(t)/dt = 0\). Therefore, substitution of these values into the normalized equations at equilibrium yields

\[
0 = \frac{1}{2} - \frac{n(\infty)}{\nu(\infty)},
\]

\[
0 = \frac{n(\infty) + 1}{\nu(\infty)} - 1,
\]

from which \(n(\infty) = 1\) and \(\nu(\infty) = 2\).
Problem 5.2 The normalized equations of solute and solvent transport of a permeant solute in the presence of an impermeant solute are

\[
\frac{dn(t)}{dt} = \alpha_n a(t) \left( c(t) - \frac{n(t)}{v(t)} \right),
\]

\[
\frac{dv(t)}{dt} = \alpha_v a(t) \left( \frac{n(t) + \hat{n}(t)}{v(t)} - \left( c(t) + \hat{c}(t) \right) \right).
\]

a. If osmotic equilibrium is assumed for each instant in time then \(dv(t)/dt = 0\), and the solution to the second equation is

\[
v(t) = \frac{n(t) + \hat{n}(t)}{c(t) + \hat{c}(t)}.
\]

b. Substitution of the solution for \(v(t)\) (from part a) into the first of the coupled-flow equations yields, after some rearrangement of terms,

\[
\frac{dn(t)}{dt} = \alpha_n a(t) \left( \frac{c(t)\hat{n}(t) - \hat{c}(t)n(t)}{n(t) + \hat{n}(t)} \right).
\]

c. Since the cell has constant surface area, \(a(t) = 1\). Thus, the solute diffusion equation becomes

\[
\frac{dn(t)}{dt} = \alpha_n \left( \frac{c(t)\hat{N} - \hat{c}n(t)}{n(t) + \hat{N}} \right),
\]

where \(c(t) = \hat{C}u(t)\), and where \(u(t)\) is the unit step function. Since \(\hat{C}\) is the isotonic extracellular concentration, \(\hat{N}/\hat{C} = 1\).

i. At \(t = 0+, n(0+) = 0\). Therefore,

\[
\frac{dn(t)}{dt} \bigg|_{0+} = \alpha_n \left( \frac{\hat{C}\hat{N} - \hat{C} \cdot 0}{0 + \hat{N}} \right) = \alpha_n \hat{C},
\]

ii. As \(t \to \infty\), \(dn(t)/dt \to 0\), and the equation derived in part b applies which for the conditions of part c yields

\[
0 = \left( \frac{\hat{C}\hat{N} - \hat{C}n(\infty)}{n(\infty) + \hat{N}} \right),
\]

so that \(n(\infty) = \hat{N}\).

iii. For \(t < 0\), \(n(t) = 0\) and \(v(t) = 1\). For \(t > 0\)

\[
\frac{dn(t)}{dt} = \alpha_n \hat{C} \left( \frac{\hat{N} - n(t)}{\hat{N} + n(t)} \right),
\]

and

\[
v(t) = \frac{n(t) + \hat{N}}{2\hat{C}}.
\]

These equations can be rearranged to yield

\[
\frac{dn(t)/\hat{N}}{dt} = \alpha_n \left( 1 - \frac{n(t)/\hat{N}}{1 + (n(t)/\hat{N})} \right),
\]
and
\[
\nu(t) = \frac{1 + (n(t)/\bar{N})}{2}.
\]
The solutions can be obtained by noting that the differential equations for \(dn(t)/dt\) is separable,
\[
\int \left( \frac{1 + (n(t)/\bar{N})}{1 - (n(t)/\bar{N})} \right) dn(t)/\bar{N} = \int \alpha_n dt.
\]
This equation can be integrated to yield
\[
-(n(t)/\bar{N}) - 2 \ln \left( 1 - (n(t)/\bar{N}) \right) = \alpha_n t.
\]
The arbitrary constant of integration is clearly zero since this equation is satisfied by the initial condition that \(n(0) = 0\). The solutions for both \(n(t)/\bar{N}\) and \(\nu(t)\) are shown plotted versus \(\alpha_n t\) in Figure 5.3. The solutions show that doubling the extracellular osmolarity reduces the cell water volume to 1/2 its value. Because the osmolarity was increased with a permeant solute, the solute diffuses into the cell. An increase in intracellular solute concentration raises the intracellular osmolarity so that water enters the cell to increase its volume. The volume increases until sufficient solute has entered the cell to achieve both diffusive and osmotic equilibrium. The time course of entry of permeant solute is the same as the time course of water entry. This is the basis of the method for estimating the solute permeability from measurements of volume changes.

d. Using the results of part c.iii, the normalized volume of the cell is
\[
-(2\nu(t) - 1) - 2 \ln \left( 1 - (2\nu(t) - 1) \right) = \alpha_n t.
\]
This solution shows that the time course of the volume is not exponential, but does depend upon \(\alpha_n\). Thus, \(\alpha_n\) can be estimated by the following procedure.
- Measure the volume of the cell as a function of time in response to the change in osmolarity caused by the permeant solute.
- Estimate the volume of the cell that is not water and subtract that from the cell volume to give the water volume. The non-water volume of the cell can be obtained from measurements of the relation between the equilibrium volume of the cell as a function of the concentration of an impermeant solute.
- Divide the water volume by the isotonic water volume to obtain the normalized water volume.
- Compute the quantity \[-(2\nu(t) - 1) - 2 \ln \left(1 - (2\nu(t) - 1)\right)\] from the normalized volume.
- Plot this quantity versus time.
- Estimate the slope of the line, e.g., by means of linear regression analysis. The slope of the line equals \(\alpha_n\).
- Since \(\alpha_n = P_j A^n / V^{in}\), in order to estimate the permeability of the solute, \(P_j\), from these measurements, the isotonic surface area, \(A^n\), and the isotonic volume, \(V^{in}\), need to be measured as well.

**Problem 5.3**

a. The system is not in diffusive equilibrium, because at \(t = 0\), there is a concentration difference of solute \(a\) across the membrane separating compartments 1 and 2 and that membrane is permeable to \(a\).

b. The only membrane permeable to water is between compartments 2 and 3. The osmolarities of the solutions in these two compartments are equal (10 mosm/L) at \(t = 0\). Hence, the system is initially in osmotic equilibrium.

c. Because compartment 1 is so much larger than compartment 2, the composition of compartment 1 does not change. Therefore, \(c^1_a(\infty) = 10\) mmol/L and \(c^2_b(\infty) = 0\). Since the membrane separating compartment 1 and 2 is permeable to \(a\) and since \(a\) is not in equilibrium at \(t = 0\), \(a\) will diffuse into compartment 2 until its concentration is the same as that of compartment 1, i.e., \(c^2_a(\infty) = 10\) mmol/L. However, this raises the osmolarity of compartment 2 with respect to compartments 1 and 3. No water flows between compartment 1 and 2, but water does flow from compartment 3 to compartment 2 to establish osmotic equilibrium. Osmotic equilibrium occurs when the osmolarity is the same on the two sides of the membrane that separates compartments 2 and 3. The final osmolarity satisfies the equation

\[
10 + \frac{(10)(100)}{V^2(\infty)} = \frac{(10)(100)}{V^3(\infty)},
\]

where the first term on the left-hand side is the concentration of \(a\) in compartment 2 at equilibrium and the second term is the concentration of \(b\) in compartment 2. The right-hand term is the concentration of \(b\) in compartment 3. In addition, since water is transported only between compartments 2 and 3, water volumes of
those compartments are linked by the equation $V_2(\infty) + V_3(\infty) = 200$. Combining these equations to eliminate $V_3(\infty)$ yields

$$10 + \frac{1000}{V_2(\infty)} = \frac{1000}{200 - V_2(\infty)}.$$ 

Combining these terms and cross-multiply yields the quadratic equation

$$(V_2(\infty))^2 - 2000 = 0,$$

which has one positive solution that equals $V_2(\infty) = 141$ cm$^3$. Therefore, $V_3(\infty) = 59$ cm$^3$. The concentrations in compartments 2 and 3 can now be computed from the volumes. $c_2^b(\infty) = \frac{1000}{V_2(\infty)} = 7.1$ mmol/L. $c_3^b(\infty) = \frac{1000}{V_3(\infty)} = 17.1$ mmol/L. Since the membrane between compartments 2 and 3 is impermeable to $a$, $c_3^a(\infty) = 0$. Now check if these concentrations are in osmotic equilibrium. The total concentrations in compartments 2 and 3 are: $c_2^a(\infty) + c_2^b(\infty) = 10 + 7.1 = 17.1$ mmol/L and $c_3^a(\infty) + c_3^b(\infty) = 0 + 17.1 = 17.1$ mmol/L. Compartments 2 and 3 are in osmotic equilibrium.

**Problem 5.4**

a. Answer: C. For an impermeant test solute the cell acts as a perfect osmometer and shrinks in response to an increase in osmolarity of the extracellular solution. Since the solute is impermeant it cannot enter the cell to allow water to flow back in. That is, the volume change is maintained as long as the increase in osmolarity is maintained.

b. Answer: A. This solute equilibrates so rapidly that there is no water flow at all.

c. It is impossible to determine the concentration for A, and difficult for B, but easy for C. Since the concentration is the same for all three, it is sufficient to compute the concentration for solute C. Since the water volume was halved in response to the pulse of test solute, $c_x/C = 1$.

d. Answer: The permeability of test solute F is larger than the permeability of test solute B. Because the volume change is smaller for F than B, less water was exchanged to achieve equilibrium in F than in B. Hence, more solute must have been exchanged to achieve equilibrium. Therefore, a smaller volume change for the same concentration change implies a larger permeability.

e. Answer: E. The larger volume change implies a larger change in osmolarity, and therefore, a larger value of $C_x$.

f. The time course of the onset is due to the flow of water through the membrane and is determined by cell geometric factors as well as the hydraulic conductivity of the membrane to water $L_V$ which is not varied in this experiment.

**Problem 5.5**
PROBLEMS

73

a. The total solute flux consists of solute flux by convection and by diffusion,

\[ \Phi_j = c_j(x) \Phi_V - D \frac{dc_j(x)}{dx}. \]

b. Since \( \Phi_j \) and \( \Phi_V \) are constant, the equation for \( c_j(t) \) is a first-order, ordinary, linear, differential equations with constant coefficients which can be written as

\[ \frac{dc_j(x)}{dx} - \frac{\Phi_V}{D} c_j(x) = - \frac{\Phi_j}{D}. \]

The solution can be found from a particular solution plus the homogeneous solution

\[ c_j(x) = \frac{\Phi_j}{\Phi_V} + Ae^{\left(\frac{\Phi_V}{D}\right)x}. \]

The boundary conditions are

\[
\begin{align*}
    c_j(-\infty) &= C_1 = \frac{\Phi_j}{\Phi_V} \\
    c_j(0) &= C_0 = C_1 + A.
\end{align*}
\]

Therefore, \( A = C_0 - C_1 \) and the total solution is

\[ c_j(x) = C_1 + (C_0 - C_1)e^{\left(\frac{\Phi_V}{D}\right)x}. \]

Solute convection and diffusion can be computed from the solute concentration,

\[
\begin{align*}
    c_j(x) \Phi_V &= \Phi_V \left(C_1 + (C_0 - C_1)e^{\left(\frac{\Phi_V}{D}\right)x}\right) \\
    -D \frac{dc_j(x)}{dx} &= -\Phi_V (C_0 - C_1)e^{\left(\frac{\Phi_V}{D}\right)x}.
\end{align*}
\]

The results are plotted in Figure 5.4. In the presence of convection, the steady-state spatial distribution of concentration is exponential in space. Note also that while \( \Phi_j \) and \( \Phi_V \) are constant, both convection of solute \( c_j(x) \Phi_V \) and the diffusion of solute \(-Ddc_j(x)/dx\) are exponential functions of \( x \).

Problem 5.6

a. The right-hand side of Equation 5.43 (Weiss, 1996a) shows that the outward flux of D\(_2\)O (considered as the solute) is \( \Phi_j = P_j (c_j^i - c_j^o) \). The concentration of D\(_2\)O outside the cell exceeds that inside, \( c_j^i - c_j^o < 0 \), and \( P_j > 0 \), which implies that \( \Phi_j < 0 \). That is, Equation 5.43 (Weiss, 1996a) predicts that there will be influx of D\(_2\)O. Since, in addition the experiment shows that the cell volume is constant, the left-hand side of Equation 5.43 (Weiss, 1996a) yields

\[
- \frac{1}{A} \frac{d}{dt} \left( c_j(t) V^i \right) = - \frac{V^i}{A} \frac{dc_j(t)}{dt} < 0.
\]
Therefore, $c_j(t)$ will increase with time.

The right-hand side of Equation 5.44 (Weiss, 1996a) implies that since $L_V$, $R$, $T$ and $c_j^0 - c_j^i$ are all positive quantities that $\Phi_V > 0$, i.e., there is a flow of water out of the cell as a result of the higher osmotic pressure outside the cell due to D$_2$O. But the left-hand side of Equation 5.44 implies that

$$\frac{-1}{A} \frac{dV^i(t)}{dt} = \Phi_V > 0.$$

Therefore, $V^i(t)$ decreases with time as water flows out of the cell. This conclusion, derived from these uncoupled equations, is inconsistent with the experimental findings.

b. & c. The Kedem-Katchalsky equations incorporate a modification of Equation 5.44 (Weiss, 1996a) as follows,

$$\frac{-1}{A} \frac{dV^i(t)}{dt} = \Phi_V = \sigma L_V RT (c_j^0 - c_j^i).$$

Therefore, $\Phi_V$ and consequently $dV^i(t)/dt$ can be zero even if $c_j^0 - c_j^i$ is non-zero provided $\sigma = 0$. The reflection coefficient $\sigma$ is a measure of the ability of the membrane to distinguish solute from solvent. If the solute is indistinguishable from the solvent — a reasonable assumption for D$_2$O and H$_2$O — then $\sigma = 0$ and no osmotic flow occurs. Since there is no volume flow, $\Phi_V = 0$ and the convective term of the Kedem-Katchalsky solute transport equation does not differ from Equation 5.43 (Weiss, 1996a).

Problem 5.7
a. Substitute the equation for volume flux into the solute flux equations to yield
\[ \phi_j = P_j \Delta c_j - \bar{C}_j (1 - \sigma_j) \sigma_j \Delta c_j. \]

Therefore,
\[ \frac{\phi_j}{\Delta c_j} = P_{eff} = P_j - L V R T \bar{C}_j (1 - \sigma_j) \sigma_j. \]

b. Since \( L, V, R, T \), and \( \bar{C}_j \) are all non-negative quantities and since \( 0 \leq \sigma_j \leq 1 \), the term \( L V R T \bar{C}_j (1 - \sigma_j) \sigma_j \) is non-negative. Therefore, \( P_{eff} \leq P_j \). The mechanism for the difference between the permeability and the effective permeability results because the transport of solute is due to convection and diffusion. Note that if \( \Delta c_j > 0, \Phi_V < 0 \). Therefore, the diffusive term in the solute transport produces a solute flux that is positive whereas the convective solute flow is negative. The effective permeability is the ratio of solute flux to concentration difference and the solute flux is less than the diffusive solute flux alone.

**Problem 5.8** In this problem it is assumed that the solute added extracellularly is distinct from the intracellular solute(s). In addition, it is assumed that the volume of the cell that is not cell water is negligible. Note that solutes 1 and 2 cause a maintained change in the volume of the cell. Therefore, these solutes are impermeant (at least on the time scale shown). Solute 3 causes no change in volume which could occur either if it were highly permeant or indistinguishable from water. Solutes 4-6 cause transient changes in volume as would be the case if these solutes were permeant.

a. The addition of solute 2 results in a decrease in volume of 20% from the isotonic volume. Therefore, the external concentration solute 2 was increased. At equilibrium
\[ \bar{V}^i = \frac{N_i^2}{C_i}, \]

which can be written in normalized form as
\[ \bar{V} = \frac{1}{c}, \]

where \( \bar{V} = \bar{V}^i / \bar{V}^{in} \) and \( c = (C_i^2 \bar{V}^{in}) / N_i^{in} \). Therefore, \( 0.8c = 1 \) so that \( c = 1.25 \).

The concentration went from 200 mmol/L to 250 mmol/L which implies that 50 mmol/L of solute 2 were added. The solution volume was 10 mL. If the addition of solute 2 is assumed not to change the volume appreciably then the number of moles of solute 2 added is 50 mmol/L \( \times 10^{-2} \) L = 0.5 mmol.

b. **False.** When solute 3 is added, there is no change in the volume. This means that osmotic equilibrium is maintained even though there is an increase in external osmolarity. There are two possibilities for this to occur. Either solute 3 is highly permeant and/or solute 3 is indistinguishable from water, i.e., \( \sigma_3 = 0 \).

c. **False.** The return to equilibrium following the initial change in volume is due to the influx of the permeant solute into the cell. The more permeant solute will enter the cell more rapidly than the less permeant solute. Since the "time constant" for equilibration is shorter for solute 6 than for solute 4, the membrane is more permeable to solute 6 than to solute 4 as shown in Figure 5.5.
d. **True.** The same reasoning as given in part c. The time constant for solute 5 is shorter than for solute 4 as shown in Figure 5.5, so the membrane is more permeable to solute 5.

e. **True — sort of.** Solute 3 causes no osmotic effect. Therefore, there are two possibilities. Either there is no osmotic effect at all and the solute is indistinguishable from water as far as the membrane is concerned. This occurs if $\sigma_3 = 0$. Another possibility is that the solute is highly permeant and causes a small osmotic effect which is too small to be seen on the scale of the figure.

f. **True.** The initial change in the cell volume is caused by the transport of water out of the cell in response to the change in osmotic pressure. The membrane is impermeable to solute 2 because there is no reswelling. The time course of transport of solute 5, as can be seen by the return of the volume to its isotonic value, is slow enough that it is reasonable to assume that the initial reduction in volume occurs before appreciable amounts of solute 5 have entered the cell. Therefore, the initial change in volume is caused predominantly by water flow without solute flow. Since the initial change in volume in response to the two solutes is the same, the same change in osmolarity must have caused the responses.

g. **True.** Since the solute is impermeant no solute is transported across the membrane. Therefore, $\sigma_1 = 1$.

h. **True.** Solute 4 is transported across the membrane because a change in osmolarity due to this solute is not maintained. Therefore, $P_4 \neq 0$.

**Problem 5.9**

a. Since solute $j$ is impermeant in membrane $X$ and indistinguishable from water in membrane $Y$, $\sigma_x = 1$ and $\sigma_y = 0$. Therefore, the volume flux equations for the
two types of membrane are
\[
\Phi_{Vx} = L_x(\Delta p - RT\Delta c_j) \text{ since } \sigma_x = 1,
\]
\[
\Phi_{Vy} = L_y\Delta p \text{ since } \sigma_y = 0.
\]

The total rate of volume transport is
\[
2A\Phi_V = A\Phi_{Vx} + A\Phi_{Vy},
\]
where \( A \) is the surface area of each type of membrane, so that
\[
\Phi_V = \frac{\Phi_{Vx} + \Phi_{Vy}}{2},
\]
\[
\Phi_V = \frac{1}{2}(L_x(\Delta p - RT\Delta c_j) + L_y\Delta p),
\]
\[
\Phi_V = \frac{1}{2}(L_x + L_y)\Delta p - \frac{1}{2}L_xRT\Delta c_j,
\]
\[
\Phi_V = \frac{L_x + L_y}{2} \left( \Delta p - \frac{L_x}{L_x + L_y}RT\Delta c_j \right).
\]

Therefore,
\[
L_m = \frac{L_x + L_y}{2},
\]
\[
\sigma_m = \frac{L_x}{L_x + L_y}.
\]

b. The solute flux equation for the two types of membrane are
\[
\phi_{jx} = 0 \text{ since } \sigma_x = 1, \text{ and } P_j = 0,
\]
\[
\phi_{jy} = \overline{C_j}\Phi_V + P_y\Delta c_j \text{ since } \sigma_y = 1.
\]

As in part a, the total flux is the average of the two fluxes so that
\[
\phi_j = \frac{\overline{C_j}\Phi_V}{2} + \frac{P_y}{2}\Delta c_j.
\]
Thus, \( P_m = P_y/2 \).

**Problem 5.10**

a. Because the dialysate and blood are at the same osmotic pressure under the test conditions, \( \Phi_V = L_V(p_b - p_d) \). Therefore, the slope of Figure 5.24 (Weiss, 1996a) equals \( L_V \) which is
\[
L_V = \frac{6 \times 10^{-4} \text{ cm/s}}{15 \times 10^3 \text{ Pa}} = 4 \times 10^{-8} \text{ cm/(s-Pa)}.
\]

The flux of creatinine is given by the Kedem-Katchalsky equation as
\[
\phi_c = \overline{C}(1 - \sigma)\Phi_V + P_c(c_b - c_d),
\]
where $\bar{C}$ is the average concentration of creatinine across the membrane. When $\Delta p = p_b - p_d = 0$, $\Phi_V = 0$ and $\phi_c = P_c (c_b - c_d)$. The molar concentrations of creatinine are
\[
c_b = \frac{0.1 \text{ mg/cm}^3}{10^5 \text{ mg/mol}} = 10^{-6} \text{ mol/cm}^3 \quad \text{and} \quad c_d = 4 \times 10^{-6} \text{ mol/cm}^3.
\]
Examination of Figure 5.24 (Weiss, 1996a) reveals
\[
P_c = \left. \frac{\phi_c}{c_b - c_d} \right|_{\Phi_V = 0} = \frac{-1 \times 10^{-10} \text{ mol/cm}^2 \cdot \text{s}}{(1 - 4) \times 10^{-6} \text{ mol/cm}^3} = 0.33 \times 10^{-4} \text{ cm/s}.
\]
Note that the slope of the relation of $\phi_c$ to $\Delta p = p_b - p_d$ is simply $\bar{C}(1 - \sigma)\bar{L}_V$ which can be solved for $\sigma$ to obtain
\[
\sigma = 1 - \frac{\text{slope} \bar{C}\bar{L}_V}{\Delta p}.
\]
The slope can be estimated from Figure 5.24 as
\[
\text{slope} = \frac{10 \times 10^{-10} + 1 \times 10^{-10} \text{ mol/(cm}^2 \cdot \text{s})}{14 \times 10^3 \text{ Pa}} = 7.9 \times 10^{-14} \text{ mol/(cm}^2 \cdot \text{s} \cdot \text{Pa}).
\]
Therefore,
\[
\sigma = 1 - \frac{7.9 \times 10^{-14} \text{ mol/(cm}^2 \cdot \text{s} \cdot \text{Pa})}{(2.5 \times 10^{-6} \text{ mol/cm}^3)(4 \times 10^{-8} \text{ cm}/(\text{s} \cdot \text{Pa}))} = 0.21.
\]
b. Assume that the same conditions apply as under test condition, then the volume flux is
\[
\Phi_V = \bar{L}_V (p_b - p_d) = (4 \times 10^{-8} \text{ cm}/(\text{s} \cdot \text{Pa}))(1.24 \times 10^4 \text{ Pa}) = 4.96 \times 10^{-4} \text{ cm/s},
\]
Thus, the total volume flowing through a 100 cm$^2$ membrane in 6 hours is $(4.96 \times 10^{-4})(100)(60 \times 60 \times 6 \text{ s}) = 1071 \text{ cm}^3 = 1.071 \text{ L}$. The flux of creatinine contains both a convective and a diffusive term and can be estimated as follows
\[
\phi_c = (0.25 \times 10^{-5} \text{ mol/cm}^3)(1 - 0.21)(4.96 \times 10^{-4} \text{ cm/s}) \\
+ (0.33 \times 10^{-4} \text{ cm/s})(10^{-6} - 4 \times 10^{-6}) \text{ (mol/cm}^3) \\
= 0.98 \times 10^{-9} - 0.1 \times 10^{-9} = 0.88 \times 10^{-9} \text{ mol/(cm}^2 \cdot \text{s}).
\]
Thus, in 6 hours the amount of creatinine removed from the blood is $(0.88 \times 10^{-9} \text{ mol/(cm}^2 \cdot \text{s}) (100 \text{ cm}^2) (100 \text{ g/mol}) (60 \times 60 \times 6 \text{ s}) = 0.19 \text{ grams}.$
c. The dialysis machine removes the requisite amount of daily water in 6 hours but not enough creatinine. A number of changes could be made to improve the performance. $P_c$ could be reduced to increase the removal of creatinine but only by about 10%. $\sigma$ could be reduced, but this would only increase the solute flux by about 20%. Increasing either the area of the dialysis membrane or $L_v$ by a factor of ~5 would increase the water flow by a factor of 5 and also increase the creatinine flow by about the same factor.
Chapter 6

CARRIER-MEDIATED TRANSPORT

Exercises

Exercise 6.1 Properties of carrier-mediated transport mechanisms that are distinct from transport by diffusion include:

- flux is facilitated,
- flux is highly structure specific,
- relation between flux and concentration saturates at high concentration,
- flux is inhibited by other solutes,
- flux is regulated by hormones.

Exercise 6.2 The rate of change of extracellular galactose at an initial intracellular galactose concentration of 100 mmol/L is the slope of the line for that concentration which equals (34 mmol/L)/(17 s) = 2 mmol/(L·s). Therefore, the efflux through the membrane of one erythrocyte is

\[
\phi_G = \frac{2 \times 10^{-3} \text{ mol/(L·s)}}{(1.4 \times 10^{13} \text{ erythrocytes/L}) \cdot (1.37 \times 10^{-6} \text{ cm}^2/\text{erythrocyte})} = 0.104 \text{ nmol/cm}^2\cdot\text{s}.
\]

Exercise 6.3 If there is a fixed density of carriers in the membrane and each carrier has a flux that saturates at high solute concentration, then the total flux of solute from a population of such carriers will saturate at high solute concentration. The saturated value of the flux will equal the maximum flux per carrier times the number of carriers. However, one can imagine hypothetical mechanisms that would yield saturation of the flux from a population of carriers where the individual carriers did not show saturation of flux. Suppose the number of carriers is not fixed but depends upon solute concentration. For example, imagine carriers whose flux/concentration relation follows Fick’s law for membranes. However, the number of carriers is related inversely to the solute
concentration so that the total flux saturates. In this scheme, the number of carriers is variable, none of the carriers saturates, but the total flux saturates. To be specific, let \( P(c_i^S - c_i^C) \) be the flux relation for a single carrier and let the number of carriers be \( N/(K + (c_i^S - c_i^C)) \). With this scheme, the maximum flux is \( PN/K \).

**Exercise 6.4** This is a simple application of the equilibrium binding of an enzyme and substrate. The quantity of bound enzyme is given by

\[
c_{ES}(\infty) = \left( \frac{c_S(\infty)}{K + c_S(\infty)} \right) C_{ET}.
\]

Therefore,

\[
c_{ES}(\infty) = \left( \frac{9}{5 + 9} \right)^2 = 1.29 \text{ mmol/L}.
\]

Therefore, the concentration of unbound enzyme is \( 2 - 1.29 = 0.71 \text{ mmol/L} \).

**Exercise 6.5** In a second-order binding reaction, an enzyme \((E)\) binds to its substrate to form the bound complex \((ES)\)

\[
S + E \rightleftharpoons ES.
\]

The dissociation constant for this reaction is

\[
K = \frac{c_S(\infty)c_E(\infty)}{c_{ES}(\infty)},
\]

where all the concentrations are at their equilibrium values. For a high affinity ligand, more of the enzyme is found bound to substrate which corresponds to a lower dissociation constant (i.e., less of the enzyme is dissociated). Therefore, if \( K_A > K_B \), then the enzyme has a higher affinity for ligand \( B \).

**Exercise 6.6**

a. According to Equation 6.37 (Weiss, 1996a), the temperature factor for reaction rates at two different temperatures yields the rate at 20°C as

\[
\kappa T \alpha = 3^{(20-5)/10} \alpha = 5.2 \alpha,
\]

where \( \alpha \) is the rate at 5°C. Thus, an increase in temperature from 5°C to 20°C increases the reaction rate by a factor of 5.2.

b. The factor \( A \) is proportional to the absolute temperature which changes from 278K to 293K, a change of 5.4%. Hence, for a small change in temperature, such as 15°C, the factor \( A \) has a much smaller effect on the rate of reaction than does the exponential factor.

**Exercise 6.7** In steady state, there is a flux of bound solute across the membrane but the density of carrier in each of the four states is constant. To see how this can occur, consider the density of bound carrier at the inside surface of the membrane. In steady state, the rate at which carrier binds to solute equals the rate at which bound carrier...
Figure 6.1: Steady state in a hydraulic system (Exercise 6.7).

facing the inside surface of the membrane translocates to bound carrier that faces the outside surface of the membrane. Thus, there is no net change in the density of bound carrier at the inside of the membrane even though net solute passes through this state. Similar arguments hold for the carrier in each of its four states.

The notion of a steady state is illustrated with a simple hydraulic analogy in Figure 6.1. If the rate of water flow into the tank equals the rate at which water flows out of the tank then the water level in the tank will remain constant. Thus, net water flows through the tank in steady state and the level of water in the tank is constant.

Exercise 6.8

a. Since $\alpha$ is zero, none of the enzyme can translocate to face the extracellular solution. Therefore the densities of outward facing enzymes $\mathcal{N}_{ES}^o$ and $\mathcal{N}_E^o$ are zero. The inward facing densities partition in proportion to the intracellular concentration of solute and the dissociation constant for the binding reaction. Therefore,

$$\mathcal{N}_{ES}^i = \frac{c_i^i}{c_i^i + K}\mathcal{N}_{ET} \text{ and } \mathcal{N}_E^i = \frac{K}{c_i^i + K}\mathcal{N}_{ET}.$$ 

Since the enzyme cannot translocate, the flux of solute $\phi_S$ is also zero.

b. The case $\beta = 0$ is similar to the case $\alpha = 0$ except that the enzyme can not face the intracellular solution. Therefore the densities of inward facing enzymes $\mathcal{N}_{ES}^i$ and $\mathcal{N}_E^i$ are zero. The outward facing densities partition in proportion to the extracellular concentration of solute and the dissociation constant for the binding reaction. Therefore,

$$\mathcal{N}_{ES}^o = \frac{c_o^o}{c_o^o + K}\mathcal{N}_{ET} \text{ and } \mathcal{N}_E^o = \frac{K}{c_o^o + K}\mathcal{N}_{ET}.$$ 

Since the enzyme cannot translocate, the flux of solute $\phi_S$ is also zero.

c. If $K = 0$, the enzyme cannot dissociate. Therefore, if there is any extracellular or intracellular solute, it will bind to the enzyme and never unbind. Therefore the unbound densities $\mathcal{N}_E^i$ and $\mathcal{N}_E^o$ will be zero. The bound densities will partition by the forward and reverse translocation rate constants, so that

$$\mathcal{N}_{ES}^i = \frac{\beta}{\alpha + \beta}\mathcal{N}_{ET} \text{ and } \mathcal{N}_{ES}^o = \frac{\alpha}{\alpha + \beta}\mathcal{N}_{ET}.$$ 

Since the solute cannot unbind, there will be no transport, $\phi_S$ will be zero.
Exercise 6.9 For $c_S^i = c_S^o = 0$ there is no carrier bound to enzyme. Therefore, on this basis and by inspection of Equations 6.55 and 6.57 (Weiss, 1996a) $N_{ES}^i = N_{ES}^o = 0$. However, from Equations 6.56 and 6.58 (Weiss, 1996a) it follows that

\[
N_E^i = \frac{\beta}{\alpha + \beta} N_{ET} = \frac{1}{(\alpha/\beta) + 1} N_{ET},
\]

\[
N_E^o = \frac{\alpha}{\alpha + \beta} N_{ET} = \frac{(\alpha/\beta)}{(\alpha/\beta) + 1} N_{ET}.
\]

These relations are plotted in Figure 6.2. If $\alpha/\beta = 1$ then half the carrier is in the inside configuration and the other half is in the outside configuration. As $\alpha/\beta$ is increased, more of the carrier is found in the outside configuration, whereas as $\alpha/\beta$ is decreased, more of the carrier is found in the inside configuration.

Exercise 6.10 For the simple, symmetric, four-state carrier model, the plot of influx of sugar versus the extracellular concentration of sugar is identical to the plot of efflux of sugar versus the intracellular concentration of sugar (Figure 6.3).

Exercise 6.11 As can be seen from Equation 6.111 (Weiss, 1996a) for the zero-trans protocol, the relation between $\Phi_S$ and $c_S^i$ is a rectangular hyperbola that is a straight line when plotted in double reciprocal coordinates.
Exercise 6.12 The relation between flux and concentration given by the simple, symmetric, four-state carrier model is characterized by two macroscopic constants, $K$, and $(\phi_S)_{max}$. Hence, measurements of this relation alone can estimate these two parameters only. These two parameters are estimated most easily from the intercepts of plots of flux versus concentration in double reciprocal coordinates. The macroscopic parameter $(\phi_S)_{max}$ can be expressed in terms of the microscopic parameters as follows,

$$(\phi_S)_{max} = \frac{\alpha \beta}{\alpha + \beta} \mathcal{N}_{ET},$$

but none of the microscopic parameters can be determined uniquely. Unique determination of the other parameters requires different types of experiments. For example, estimates of the density of carriers in the membrane, $\mathcal{N}_{ET}$, can be obtained by binding radioactive blockers that bind to the carrier and estimating the number of such blockers required. The individual rate constants must be obtained from experiments in which the state of the carrier can be determined, e.g., photometrically.

Exercise 6.13 Each of the graphs shows the reciprocal of flux plotted versus the reciprocal of concentration.

a. A competitive inhibitor acts to increase the effective dissociation constant without changing the maximum flux. Thus, the only possibility is Graph 1 where the ordinate intercept for both lines is the same which implies that the maximum flux is the same. However, the intercept on the abscissa, which is the reciprocal of the dissociation constant, is larger for curve 2 than for curve 1. This implies that the dissociation constant is smaller in the presence of the competitive inhibitor. This is false. Thus, the answer for this part is NONE.

b. A non-competitive inhibitor acts to decrease the effective maximum flux without changing the dissociation constant. Thus, the only possibilities are Graphs 4 and 5. Since the ordinate intercept is the reciprocal of the maximum flux, the answer is Graph 4.

c. The simple, symmetric four-state carrier model predicts that the zero-trans efflux as a function of the intracellular concentration is the same as the zero-trans influx as a function of the extracellular concentration. Therefore, Graph 2 is the answer.

d. The general, four-state carrier model predicts that both the effective maximum flux and dissociation constant differ for influx and efflux, but the slope of the relation in reciprocal coordinates is the same. Therefore, Graph 3 is the answer.

Exercise 6.14

a. FALSE. Insulin receptors regulate glucose intake in hepatocytes, adipocytes and muscle cells only.

b. TRUE. See part a.
c. **TRUE.** During fasting, the level of glucose in the blood drops and the secretion of insulin by $\beta$ cells in the pancreas is decreased, while the level of glucagon released by the $\alpha$ cells in the pancreas is increased. These effects stimulate glycogenolysis in the liver which releases glucose into the circulatory system.

d. **FALSE.** Muscle cells do not secrete glucose but do secrete other products of glycolysis, lactate and pyruvate, which can be recycled into glucose by hepatocytes.

e. **FALSE.** Insulin acts to recruit individual glucose transporters.

f. **TRUE.** The $\beta$ cells respond to an increase in blood glucose by releasing insulin.

**Exercise 6.15**

a. **Ans. (2).** At equilibrium, a cell that transports the solute by diffusion will have an intracellular concentration of solute that is the same as the extracellular concentration.

b. **Ans. (2).** At equilibrium, a cell that transports the solute by a simple, symmetric four-state carrier will have an intracellular concentration of solute that is the same as the extracellular concentration.

c. **Ans. (3).** A cell that transports the solute by an active transport mechanism can concentrate the solute intracellularly at a concentration that exceeds the extracellular concentration. Thus, (3) is only possible for an active transport system. However, without further specification of the system all three responses (1)-(3) are, in principle, possible for an active transport system.

**Exercise 6.16**

a. The flux of xylose can be computed directly from

\[
\phi_S = (\phi_S)_{max} \left( \frac{c_i^S}{c_i^S + K} - \frac{c_o^S}{c_o^S + K} \right),
\]

\[
= \frac{\alpha \beta}{\alpha + \beta} M_{ET} \left( \frac{c_i^S}{c_i^S + K} - \frac{c_o^S}{c_o^S + K} \right).
\]

Since, $c_i^S = 0$

\[
\phi_S = \frac{10^5/s \times 10^5/s}{10^5/s + 10^5/s} \times 10^{-10} \text{ mol/m}^2 \times \left( - \frac{1 \text{ mmol/L}}{1 \text{ mmol/L} + 10 \text{ mmol/L}} \right)
\]

\[
= -\frac{1}{22} \times 10^{-5} \text{ mol/m}^2 \cdot \text{s}.
\]

The rate of change of intracellular xylose can be computed from the flux of xylose across the cell membrane by use of the continuity equation,

\[
\frac{dc_S(t)}{dt} = -\frac{A \phi_S}{V} = -\frac{4\pi r^2}{\frac{4}{3}\pi r^3} \phi_S = -\frac{3}{r} \phi_S,
\]
where $A$ represents the area of the membrane, $V$ represents the volume of the cell, and $r$ represents the radius of the cell. Therefore

$$\frac{dc_S(t)}{dt} = -\frac{3}{10 \times 10^{-6}} m \times \frac{1}{22} \times 10^{-5} \text{ mol m}^{-2} \cdot \text{s} = -0.14 \text{ mol m}^{-3} \cdot \text{s} = -0.14 \text{ mmol L}^{-1} \cdot \text{s}.$$ 

b. No.

i. Substituting $K = 0$ into the general expression for flux of xylose shows that

$$\phi_S = \frac{\alpha \beta}{\alpha + \beta} \mu_{ET} \left( \frac{c_S^i}{c_S^i + K} - \frac{c_S^o}{c_S^o + K} \right)$$

$$= \frac{\alpha \beta}{\alpha + \beta} \mu_{ET} \left( \frac{c_S^i}{c_S^i} - \frac{c_S^o}{c_S^o} \right)$$

$$= \frac{\alpha \beta}{\alpha + \beta} \mu_{ET}(1 - 1) = 0.$$  

Thus $K = 0$ implies no flux of xylose.

ii. The only path for solute transport is to bind enzyme, translocate, and then unbind on the other side. If the dissociation constant is zero, then the bound enzyme can never unbind. That is, solute will not be released by the bound complex. Therefore, if there is no unbinding there can be no transport.

Exercise 6.17

a. The plot shows the flux versus the concentration in double reciprocal coordinates. Thus, small values of concentration $c_S^o$ occur for large values of $1/c_S^o$. Maximum influx $\tilde{\phi}$ occurs when $1/\tilde{\phi}$ is a minimum. It follows that the largest influx occurs for condition 1.

b. Large values of concentration $c_S^o$ occur for small values of $1/c_S^o$. Therefore, for high concentration the flux is a maximum for condition 2.

c. No. Addition of substance A increases the flux of sucrose when the bath contains high concentrations of sucrose (i.e. when $c_S^o > (1/0.015) \text{ mmol/L}$). Inhibitors (competitive or noncompetitive) always reduce flux. Thus, substance A cannot be a competitive inhibitor.

d. Yes. Addition of a non-competitive inhibitor decreases the equivalent maximum flux without changing the equivalent dissociation constant. Adding substance B decreases the maximum flux from $(1/0.02) \mu \text{mol/cm}^2 \cdot \text{s}$ to $(1/0.05) \mu \text{mol/cm}^2 \cdot \text{s}$ and does not change $K$, which is equal to $(1/0.05) \text{ mmol/L}$ for both conditions 1 and 3. Thus, substance B acts as a non-competitive inhibitor.

Exercise 6.18 GLUT-1, GLUT-2, GLUT-3, etc. refer to distinct glucose transporter proteins that have been isolated from cellular membranes and then sequenced. These transporters have distinct amino-acid sequences.
Exercise 6.19 Regions labeled 1-12 in Figure 6.41 (Weiss, 1996a) are all segments of the amino acid sequence of the glucose transporter GLUT-1 that are hydrophobic because they have a large hydrophobicity. Each of these segments is 21 amino acids long. Twenty-one amino acids in the form of an α helix have the right length to span the cellular membrane. This argument suggests that these segments are the intramembrane portions of this glucose transporter.

Exercise 6.20 Insulin binds to insulin receptors on the surface of the muscle membrane. This binding results, through second messengers, in the recruitment of glucose transporters that are inserted into the membrane to increase transmembrane glucose transport.

Exercise 6.21 When the blood glucose concentration rises, glucose enters pancreatic β-cells, and results in the secretion of insulin in the circulatory system. Insulin acts on insulin receptors of cells and results in the increase in transport of glucose into those cells thus lowering the blood glucose concentration.

Problems

Problem 6.1

a. The total concentration of binding sites in the membrane is $C$, so that $c_b(x, t) + c_{ab}(x, t) = C$. The dissociation constant is $K = c_a(x, t) c_b(x, t) / c_{ab}(x, t)$, so that $(K + c_a(x, t)) c_{ab}(x, t) = c_a(x, t) C$ and

$$c_{ab}(x, t) = \frac{c_a(x, t)}{c_a(x, t) + K} C$$

b. When $K \gg c_a(x, t)$, this equation in part a becomes $c_{ab}(x, t) \approx (C/K) c_a(x, t)$, so that $\alpha = C/K$. The concentration of binding sites is inversely proportional to the dissociation constant. Therefore, most of the binding sites will be unbound when the dissociation constant is large.

c. Conservation of solute $a$ can be expressed in terms of a continuity relation that relates the local rate of change of concentration of $a$ to the flux divergence of $a$ as follows,

$$\frac{\partial (c_a(x, t) + c_{ab}(x, t))}{\partial t} = -\frac{\partial \phi_a(x, t)}{\partial x}.$$

The mobile solute obey’s Fick’s first law, so that

$$\phi_a(x, t) = -D \frac{\partial c_a(x, t)}{\partial x}.$$

Combining the two equations yields

$$\frac{\partial (c_a(x, t) + c_{ab}(x, t))}{\partial t} = D \frac{\partial^2 c_a(x, t)}{\partial x^2}.$$
PROBLEMS

Figure 6.4: Plot of $\tau_{eq}$ and $\tau_{ss}$ versus $C$. It has been assumed arbitrarily that at $C = 0$, $\tau_{eq} \gg \tau_{ss}$ (Problem 6.1).

Using the assumption that $c_a \ll K$, allows substitution of $c_{ab}(x, t) = (C/K)c_a(x, t)$ which results in

$$\frac{\partial c_a(x, t)}{\partial t} \left(1 + \frac{C}{K}\right) = D \frac{\partial^2 c_a(x, t)}{\partial x^2}.$$ 

Therefore,

$$D_{eff} = \frac{D}{1 + (C/K)}$$

The diffusion coefficient is reduced by the presence of binding sites because the bound solute does not diffuse.

d. The concentration in the membrane is assumed to be in the steady state. Therefore, the dependence of concentration on position in the membrane is linear, i.e.,

$$c_a(x, t) = -\frac{\phi_a(x, t)}{D} x + c_a(0, t),$$

and

$$\phi_a(x, t) = -\frac{D}{d} (c_a(0, t) - c_a(d, t))$$

With a membrane:solution partition coefficient of $\kappa_a$, the permeability is

$$p_a = \frac{D\kappa_a}{d}.$$ 

$D$ appears in the expression for the permeability rather than $D_{eff}$ because the membrane is in steady-state, and therefore, the rate of change in the number of sites bound to solute is zero. Under these conditions, this problem becomes identical to the problem for a thin membrane with two compartments that was solved in Section 3.7 (Weiss, 1996a). Equation 3.59 (Weiss, 1996a) shows that $\tau_{eq} = V_e/(AP_a)$ so that

$$\tau_{eq} = \left(\frac{V_1V_2}{V_1 + V_2}\right) \left(\frac{d}{AD\kappa_a}\right)$$

The equilibrium time constant is independent of $C$ as shown in Figure 6.4.

e. $\tau_{ss}$ is the time constant for the spatial distribution inside the membrane to reach steady state. This time constant can be determined from the solution to the diffusion equation for the mobile solute in the membrane. As was found in part c, this diffusion equation contains an effective diffusion coefficient that is less than the diffusion coefficient in the absence of binding sites. With $D_{eff}$ as the diffusion.
coefficient, this problem is similar to finding the time constant $\tau_{ss}$ in Section 3.7 (Weiss, 1996a). Therefore,

$$\tau_{ss} = \frac{d^2}{\pi^2 D_{\text{eff}}} = \frac{d^2}{\pi^2 D/(1 + C/K)} = \frac{d^2(K + C)}{\pi^2 DK}$$

So $\tau_{ss}$ is linearly related to $C$, and as $C$ increases so does $\tau_{ss}$ as shown in Figure 6.4.

f. If $\tau_{eq} \gg \tau_{ss}$, then the assumption that the concentration in the membrane is in steady state is valid for computing the time course of equilibration across the membrane. Since $\tau_{ss} \propto C$, as $C$ increases, so does $\tau_{ss}$. Therefore, for given bath dimensions, as $C$ increases the assumption that $\tau_{eq} \gg \tau_{ss}$ gets poorer and poorer (Figure 6.4).

The conceptually difficult part of this problem is that there are two diffusion coefficients that apply: one is $D$, the diffusion coefficient of the mobile (unbound) solute which appears in Fick’s first law; the other is $D_{\text{eff}}$, the effective diffusion coefficient that occurs in Fick’s second law. $D$ applies when the concentration of bound solute is not changing, i.e., in steady state. $D_{\text{eff}}$ applies when there is a time rate of change in the concentration of bound solute. Therefore, $D$ determines the equilibration time $\tau_{eq}$ under the assumption that $\tau_{eq} \gg \tau_{ss}$ which validates the steady-state assumption. However, during the time the concentration in the membrane is reaching steady state, there is a time rate of change of concentration of solute $a$ governed by $D_{\text{eff}}$.

**Problem 6.2** The fluxes across the two barriers are $\phi_1$ and $\phi_2$,

$$\phi_1 = \alpha_1 N_1 - \beta_1 N_m,$$
$$\phi_2 = \alpha_2 N_m - \beta_2 N_2.$$

a. Under steady-state condition $\phi_1 = \phi_2 = \phi$ so that

$$\alpha_1 N_1 - \beta_1 N_m = \alpha_2 N_m - \beta_2 N_2.$$

With the relations $N_1 = c_1 d$ and $N_2 = c_2 d$, the solution for $N_m$ is

$$N_m = \frac{\alpha_1 N_1 + \beta_2 N_2}{\alpha_2 + \beta_1} = d \left( \frac{\alpha_1 c_1 + \beta_2 c_2}{\alpha_2 + \beta_1} \right).$$

The flux is

$$\phi = \alpha_1 N_1 - \beta_1 N_m,$$
$$\phi = \alpha_1 d c_1 - \beta_1 d \left( \frac{\alpha_1 c_1 + \beta_2 c_2}{\alpha_2 + \beta_1} \right),$$
$$\phi = d \left( \frac{\alpha_1 \alpha_2 c_1 - \beta_1 \beta_2 c_2}{\alpha_2 + \beta_1} \right).$$

b. If the flux must be zero when the concentration is the same on the two sides of the membrane then $\alpha_1 \alpha_2 = \beta_1 \beta_2$. If this condition is satisfied then the flux satisfies Fick’s first law, and

$$P = d \frac{\alpha_1 \alpha_2}{\alpha_2 + \beta_1} = d \frac{\beta_1 \beta_2}{\alpha_2 + \beta_1}.$$
c. According to the theory of absolute reaction rates

\[
\begin{align*}
\alpha_1 &= Ae^{(0-E_1)/kT}, \\
\alpha_2 &= Ae^{(E_m-E_2)/kT}, \\
\beta_1 &= Ae^{(E_m-E_1)/kT}, \\
\beta_2 &= Ae^{(0-E_2)/kT}.
\end{align*}
\]

The constant \(A\) is the same for all rates since all rates are the same when the energies are all zero. Therefore,

\[
P = d \frac{Ae^{(E_m-E_1)/kT}Ae^{(0-E_2)/kT}}{Ae^{(E_m-E_2)/kT} + Ae^{(E_m-E_1)/kT}}.
\]

This expression can be simplified to

\[
P = d \frac{1}{e^{E_1/kT} + e^{E_2/kT}}.
\]

Therefore, the permeability depends only on \(E_1\) and \(E_2\) and not on \(E_m\). As the barrier energies \(E_1\) and \(E_2\) are increased, the permeability is decreased.

**Problem 6.3** For a simple, symmetric, four-state carrier mechanism

\[
\frac{1}{\phi_s} = \frac{1}{(\phi_s)_{\text{max}}} \left(1 + \frac{K}{c^o}\right).
\]

The intercept at \(1/c^o = 0\) is \(1/(\phi_s)_{\text{max}}\); the intercept for \(1/\phi_s\) is \(-1/K\). The parameters determined from the graph are given in Table 6.1.

**Problem 6.4** Conservation of solute \(M\), under the assumption that the cell volume does not change appreciably, yields

\[
\phi_s = -\frac{\gamma V}{A} \frac{dc^i(t)}{dt}.
\]

For the conditions that both \(c^o \ll K\) and \(c^i(t) \ll K\) (the latter follows from the former), the flux is given by

\[
\phi_s \approx (\phi_s)_{\text{max}} \left(\frac{c^i(t)}{K} - \frac{c^o}{K}\right).
\]

These two equations can be combined to yield

\[
\left(\frac{\gamma K}{A(\phi_s)_{\text{max}}}\right) \frac{dc^i(t)}{dt} + c^i(t) = c^o.
\]
The solution to this first-order, ordinary differential equation with constant coefficients is
\[ c^i(t) = c^o \left( 1 - e^{-t/\tau} \right), \]
since \( c^i(0) = 0 \) and where
\[ \tau = \frac{\gamma K}{A(\phi_s)_{\text{max}}} \]
Therefore,
\[ (\phi_s)_{\text{max}} = \frac{\gamma K}{A\tau} = \frac{(10^{-10} \text{ cm}^3) \cdot (10^{-4} \text{ mol/cm}^3)}{(10^{-6} \text{ cm}^2) \cdot (10^2 \text{ s})} = 10^{-10} \text{ mol/(cm}^2 \cdot \text{s}). \]

**Problem 6.5**

a. Both \( E \) and \( ES \) diffuse across the membrane with the same diffusion coefficient \( D \). As shown in Section 3.5 (Weiss, 1996a), under steady-state conditions the spatial dependence of concentration is linear. Hence,
\[ c_E(x) = \frac{c^o_E - c^i_E}{d} x + c^i_E, \]
\[ c_{ES}(x) = \frac{c^o_{ES} - c^i_{ES}}{d} x + c^i_{ES}, \]
where \( x = 0 \) is the location of the inside and \( x = d \) is the location of the outside interface of the membrane and solution. These equation are linear in \( x \) and have the correct boundary values. For example, for \( x = 0 \), \( c_E(0) = c^i_E \) and \( x = d \), \( c_E(d) = c^o_E \). In addition, the flux is gotten by Fick’s law and is
\[ \phi_E = -D \frac{dc_E(x)}{dx} = -D \frac{c^o_E - c^i_E}{d}, \]
\[ \phi_{ES} = -D \frac{dc_{ES}(x)}{dx} = -D \frac{c^o_{ES} - c^i_{ES}}{d}. \]
Since, \( \phi_E + \phi_{ES} = 0 \)
\[ \frac{c^o_E - c^i_E}{d} = -\frac{c^o_{ES} - c^i_{ES}}{d}, \]
so that the slopes of the linear concentration dependencies have the same magnitude but opposite signs.
Since \( \mathcal{N} = cd \), the equations can be expressed in terms of densities \( (\mathcal{N}) \) instead of concentrations,
\[ \mathcal{N}_E(x) = \frac{\mathcal{N}^o_E - \mathcal{N}^i_E}{d} x + \mathcal{N}^i_E, \]
\[ \mathcal{N}_{ES}(x) = \frac{\mathcal{N}^o_{ES} - \mathcal{N}^i_{ES}}{d} x + \mathcal{N}^i_{ES}, \]
\[ \frac{\mathcal{N}^o_E - \mathcal{N}^i_E}{d} = -\frac{\mathcal{N}^o_{ES} - \mathcal{N}^i_{ES}}{d}. \]
The spatial dependencies of the carrier densities are shown in Figure 6.5.
b. The total carrier densities are

\[
\overline{N}_E = \frac{1}{d} \int_0^d \overline{N}_E(x) \, dx \quad \text{and} \quad \overline{N}_{ES} = \frac{1}{d} \int_0^d \overline{N}_{ES}(x) \, dx,
\]

and are most easily obtained graphically from Figure 6.5.

\[
\overline{N}_E = \frac{N_{E0}^i d + (1/2)(N_{Ei}^i - N_{E0}^i) d}{d} = \frac{N_{Ei}^i + N_{E0}^i}{2},
\]

Similarly,

\[
\overline{N}_{ES} = \frac{N_{ES0}^i d + (1/2)(N_{ESi}^i - N_{ES0}^i) d}{d} = \frac{N_{ESi}^i + N_{ES0}^i}{2}.
\]

c. The flux of S is easily derived

\[
\phi_S = \phi_{ES} = -D \frac{c_{ES}^0 - c_{ES}^i}{d} = \frac{D}{d^2} (N_{ESi}^i - N_{ES0}^i) = \alpha(N_{ESi}^i - N_{ES0}^i).
\]

To proceed further, expressions for \( N_{Ei}^i \) and \( N_{ESi}^i \) are required. But the total density of carrier is

\[
N_{ET} = N_E + N_{ES} = \frac{N_{Ei}^i + N_{E0}^i}{2} + \frac{N_{ESi}^i + N_{ES0}^i}{2}.
\]

In addition, since the carrier remains in the membrane

\[
\phi_E + \phi_{ES} = 0 = \alpha(N_{Ei}^i - N_{E0}^i) + \alpha(N_{ESi}^i - N_{ES0}^i),
\]

which implies that

\[
N_{Ei}^i - N_{E0}^i + N_{ESi}^i - N_{ES0}^i = 0,
\]

and

\[
N_{Ei}^i + N_{ESi}^i = N_{E0}^i + N_{ES0}^i.
\]

These equations are solved for \( N_{ESi}^i \) first. A combination of the two relations derived thus far yields

\[
N_{ET} = \frac{N_{Ei}^i + N_{E0}^i + N_{ESi}^i + N_{ES0}^i}{2} = N_E + N_{ESi}^i.
\]
The interfacial reactions yield
\[ c_S^o \mathcal{N}_E^o = K \mathcal{N}_ES^o \quad \text{and} \quad c_S^i \mathcal{N}_E^i = K \mathcal{N}_ES^i. \]

A combination of these equations yields
\[ \mathcal{N}_{ET} = \frac{K}{c_S} \mathcal{N}_{ES}^i + \mathcal{N}_{ES}^i = \left( \frac{K}{c_S} + 1 \right) \mathcal{N}_{ES}^i, \]
from which
\[ \mathcal{N}_{ES}^i = \left( \frac{c_S^i}{c_S + K} \right). \]

By a similar argument
\[ \mathcal{N}_{ES}^o = \left( \frac{c_S^o}{c_S + K} \right). \]

Therefore,
\[ \phi_S = (\phi_S)_{max} \left( \frac{c_S^i}{c_S + K} - \frac{c_S^o}{c_S + K} \right), \]
where
\[ (\phi_S)_{max} = \alpha \mathcal{N}_{ET} = \frac{D}{d^2} \mathcal{N}_{ET}. \]

d. For \( c_S^i \ll K \) and \( c_S^o \ll K \),
\[ \phi_S \approx P_S (c_S^i - c_S^o), \]
where
\[ P_S = \frac{\alpha \mathcal{N}_{ET}}{K}. \]

**Problem 6.6**

a. Since \( \phi_E + \phi_{ES} = 0 \), \( \alpha(\mathcal{N}_{ES}^i - \mathcal{N}_{ES}^o) + \alpha(\mathcal{N}_{ES}^o - \mathcal{N}_{ES}^i) = 0. \) Hence, \( \mathcal{N}_{ES}^o + \mathcal{N}_{ES}^i = \mathcal{N}_{ES}^i + \mathcal{N}_{ES}^i \).

Therefore,
\[ \mathcal{N}_{ET} = \mathcal{N}_{EI}^o + \frac{\mathcal{N}_{E}^i + \mathcal{N}_{E}^o}{2} + \frac{\mathcal{N}_{ES}^i + \mathcal{N}_{ES}^o}{2} = \mathcal{N}_{EI}^o + \mathcal{N}_{E}^o + \mathcal{N}_{ES}^o. \]

Substituting for the equilibrium reactions at the interfaces yields
\[ \mathcal{N}_{ET} = \frac{c_I^o \mathcal{N}_E^o}{K_i} + \mathcal{N}_E^o + \mathcal{N}_{ES}^o, \]
\[ = \left( 1 + \frac{c_I^o}{K_i} \right) \mathcal{N}_E^o + \mathcal{N}_{ES}^o, \]
\[ = \left( 1 + \frac{c_I^o}{K_i} \right) \frac{\mathcal{N}_{ES}^o K_S}{c_S^o} + \mathcal{N}_{ES}^o, \]
\[ = \left( 1 + \frac{c_I^o}{K_i} \right) \frac{K_S}{c_S^o} + 1 \mathcal{N}_{ES}^o. \]
Therefore,

\[ \mathcal{Y}_{ES} = \frac{c_S^0}{c_S^0 + K \left( \frac{c_I^0}{K_I} \right)} \mathcal{Y}_{ET}. \]

Since \( c_I^0 = 0 \), \( \mathcal{Y}_{ES} = 0 \) and

\[ \phi_S = -\alpha \mathcal{Y}_{ES} = -\alpha \mathcal{Y}_{ET} \frac{c_S^0}{c_S^0 + K \left( \frac{c_I^0}{K_I} \right)}, \]

so that \( (\phi_S)_{max} = \alpha \mathcal{Y}_{ET} \). Hence,

\[ \tilde{\phi}_S = (\phi_S)_{max} \frac{c_S^0}{c_S^0 + K \left( \frac{c_I^0}{K_I} \right)}. \]

b. A plot of \( \tilde{\phi}_S /(\phi_S)_{max} \) versus \( c_S^0/K_S \) for several values of \( c_I^0/K_I \) is shown in Figure 6.6.

c. An increase in \( c_I^0 \) decreases \( \phi_S \) because \( I \) combines with carrier \( E \) and thereby makes \( E \) unavailable to bind with \( S \) and carry it across the membrane. That is, \( I \) competes with \( S \) for \( E \).

**Problem 6.7** From conservation of glucose

\[ -\frac{1}{A} \frac{d(VCG(t))}{dt} = \phi_G(t), \]

where \( \phi_G(t) \) is the outward flux of glucose, \( A \) is the surface area of the cell, and \( V \) is the volume of the cell. Assume that the

- volume does not change;
- transport through the membrane is via a simple, symmetric, four-state carrier mechanism; and
- the extracellular concentration of glucose is zero.
Therefore, 
\[
\frac{dc_G(t)}{dt} = -\frac{A}{V} \phi_M \left( \frac{c_G(t)}{c_G(t) + K} \right).
\]

Because the cell is spherical, \( A/V = 4\pi r^2/((4/3)\pi r^3) = 3/r \). Hence, 
\[
\frac{dc_G(t)}{dt} = -\frac{3\phi_M}{r} \left( \frac{c_G(t)}{c_G(t) + K} \right).
\]

- **Experiment #1** — For \( c_G \ll K \), 
  \[
  \frac{dc_G(t)}{dt} \approx -\frac{3\phi_M}{r} c_G(t),
  \]
  or 
  \[
  \frac{dc_G(t)}{dt} + \frac{3\phi_M}{r} c_G(t) = 0.
  \]
  Therefore, \( \tau = rK/(3\phi_M) = 10 \cdot 60 = 600 \text{s} \).

- **Experiment #2** — For \( c_G \gg K \), 
  \[
  \frac{dc_G(t)}{dt} \approx -\frac{3\phi_M}{r} = -10^{-8} \text{mol}/(\text{cm}^3 \cdot \text{s}),
  \]
  Therefore, 
  \[
  \phi_M = \frac{r}{3} \times 10^{-8} = \frac{30 \times 10^{-4}}{3} \times 10^{-8} = 10^{-11} \text{mol}/(\text{cm}^2 \cdot \text{s}),
  \]
  \[
  K = \frac{600 \cdot 3 \cdot \phi_M}{r} = \frac{600 \cdot 3 \cdot \phi_M}{30 \times 10^{-4}} = 6 \times 10^{-6} \text{mol/cm}^3.
  \]

**Problem 6.8** Assume that the simple, four-state carrier model applies to this cell. Therefore, the efflux of sugar in the presence of no extracellular sugar is

\[
\bar{\phi}_S = (\phi_S)_{\text{max}} \frac{c_S^i}{c_S + K_i},
\]

which for \( c_S^i \ll K_i \) gives

\[
\bar{\phi}_S = (\phi_S)_{\text{max}} \frac{c_S^i}{K_i}.
\]

This is similar to Fick’s law for membranes with a permeability \( P_S = (\phi_S)_{\text{max}}/K_i \). From Chapter 3 (Weiss, 1996a), the equilibration time \( \tau_{eq} = V_e/(A\phi_S) \). Therefore,

\[
\tau_{eq} = \frac{V_e K_i}{A(\phi_S)_{\text{max}}}.
\]

Hence, for larger \( K_i/(\phi_S)_{\text{max}}, \tau_{eq} \) will be larger. From the plot it is apparent that the values of \( K_i \) and \( (\phi_S)_{\text{max}} \) are: for Sugar 1, 20 mmol/L and 20 \( \mu \text{mol/cm}^2 \cdot \text{s} \), with a ratio of 1; for Sugar 2, 100 mmol/L and 50 \( \mu \text{mol/cm}^2 \cdot \text{s} \) with a ratio of 2; for Sugar 3, 20 mmol/L and 50 \( \mu \text{mol/cm}^2 \cdot \text{s} \), with a ratio of 0.4. Thus, since D-glucose equilibrates most rapidly it must be Sugar 3. Since D-xylose equilibrates most slowly, it must be Sugar 2. The results are summarized in Table 6.2.
### PROBLEMS

<table>
<thead>
<tr>
<th>Solute</th>
<th>Sugar #</th>
<th>$K_i$ (mmol/L)</th>
<th>$(\dot{\phi}<em>s)</em>{max}$ (μmol/cm² · s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-glucose</td>
<td>3</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>D-galactose</td>
<td>1</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>D-xylose</td>
<td>2</td>
<td>100</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 6.2: Transport parameters and identification of Sugars 1, 2, and 3 (Problem 6.8).

#### Problem 6.9

a. Conservation of glucose yields

$$-\frac{1}{A(t)} \frac{d}{dt} (V(t)c_G(t)) = \phi_G = \phi_m \left( \frac{c_G(t)}{c_G(t) + K} \right),$$

where it is assumed that the external glucose concentration is zero. Because the cell is spherical

$$-\frac{1}{4\pi r^2(t)} \frac{d}{dt} ((4/3)r^3(t)c_G(t)) = \phi_m \left( \frac{c_G(t)}{c_G(t) + K} \right).$$

If the change in osmolarity due to the change in glucose concentration in the cell is small, then the cell radius does not change and the differential equation becomes

$$-\frac{r}{3} \frac{d c_G(t)}{dt} = \phi_m \left( \frac{c_G(t)}{c_G(t) + K} \right).$$

b. Rearrangement of this differential equation yields

$$\frac{d c_G(t)}{dt} = -\frac{3\phi_m}{r} \left( \frac{c_G(t)}{c_G(t) + K} \right).$$

Cross multiplication and integration yields

$$\int_{c_G(0)}^{c_G(t)} \left( 1 + \frac{K}{c_G(t)} \right) d c_G'(t) = -\frac{3\phi_m}{r} \int_0^t dt',$$

which results in

$$c_G(t) - c_G(0) + K \ln \left( \frac{c_G(t)}{c_G(0)} \right) = -\frac{3\phi_m}{r} t.$$

c. If $K \gg c_G(t)$ then

$$K \ln \left( \frac{c_G(t)}{c_G(0)} \right) \approx -\frac{3\phi_m}{r} t,$$

or

$$c_G(t) \approx c_G(0)e^{-\left(\frac{3\phi_m}{rK}\right)t}.$$

Note that for this condition, the relation between flux and concentration is linear, and therefore, the differential equation is linear with constant coefficients and gives rise to an exponentially decaying glucose concentration. Intuitively, if the rate of efflux of glucose is proportional to the intracellular concentration of glucose then exponential kinetics result.
d. If $K \ll c_G(t)$ then

$$c_G(t) - c_G(0) \approx -\frac{3\phi_m}{r}t,$$

or

$$c_G(t) \approx c_G(0) - \frac{3\phi_m}{r}t.$$

In this limit, the relation between flux and concentration is a constant, the flux is simply the maximum glucose flux possible for the carrier. Hence, the intracellular glucose concentration drops linearly as a constant quantity of glucose flows out of the cell.

**Problem 6.10** From the simple, symmetric, four-state carrier model

$$\frac{(\phi_S)_{\text{max}}}{\phi_S} = 1 + \frac{K_S}{c_G^i} \left(1 + \frac{c_G^i}{K_R}\right),$$

$$\frac{(\phi_S)_{\text{max}}}{\phi_S} = 1 + \frac{K_S}{c_G^o} \left(1 + \frac{c_G^o}{K_R}\right).$$

The parameters estimated from the graphs are shown in Table 6.3. We determine if these results are consistent with a set of parameters for the simple, symmetric, four-state carrier model. First, examine the implications of the slopes.

$$\frac{K_S/(c_G^i K_R)}{K_S/(c_G^o K_R)} = \frac{c_G^o}{c_G^i} = \frac{1/10}{1/20} = 2.$$

Then examine the implications of the intercepts,

$$1 + \frac{K_S}{c_G^i} = 3 \Rightarrow \frac{K_S}{c_G^i} = 2,$$

$$1 + \frac{K_S}{c_G^o} = 2 \Rightarrow \frac{K_S}{c_G^o} = 1.$$

Therefore, the slopes and intercepts are both consistent with $c_G^o/c_G^i = 2$. The above equations also show that $K_S = 2c_G^i$ and $K_R = 20$. Thus, there is a consistent set of parameters that fit the measurements using a simple, symmetric, four-state carrier model.

**Problem 6.11**
Table 6.4: Transport parameters (Problem 6.12).

<table>
<thead>
<tr>
<th>$r$ (μm)</th>
<th>$(\phi_G)_{max}$ (μmol/(cm² · s))</th>
<th>$K$ (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>16 2/3</td>
</tr>
<tr>
<td>27</td>
<td>50</td>
<td>16 2/3</td>
</tr>
</tbody>
</table>

a. For steady-state conditions $\phi_E + \phi_{ES} = 0$. But, $\phi_E = 0$ which implies that $\phi_{ES} = 0$. But since the only way the solute crosses the membrane is in a complex with the carrier, $\phi_S = 0$.

b. In the steady-state $\phi_S = 0$. Hence, there is no net flux of $S$ across the membrane and the internal concentration cannot change. There is one caveat. If the concentration is changed transiently then there will be a transient change in state of the carrier until a new steady state is achieved. During this interval a small amount of solute can be transported but this transport ceases as a new steady state is established.

c. Although the net flux in steady state is zero, the unidirectional fluxes are not zero although they are equal in magnitude. Therefore, there will be a net flux of radioactively labeled $S$. Therefore, while the concentration of total $S$ in the cell does not change, the proportion of radioactive $S$ will increase until the ratio of radioactive to non-radioactive $S$ is the same inside and outside the membrane.

d. Because solute can exchange across the membrane without a change in concentration, this transport mechanism is called *exchange diffusion*.

**Problem 6.12**

a. At equilibrium $c_G^i = c_G^o = 0.01$ mmol/L for all three types of cells.

b. The parameters of the simple, symmetric, four-state carrier mechanism can be estimated directly from the data given. The intercepts for the abscissa and ordinate are $-1/K$ and $1/(\phi_G)_{max}$, respectively. The results are given in Table 6.4. The flux of glucose is

$$
\phi_G(t) = (\phi_G)_{max} \left( \frac{c_G^i(t)}{c_G^i(t) + K} - \frac{c_G^o(t)}{c_G^o(t) + K} \right).
$$

But, for $c_G^o = 0.01$ mmol/L which is much less than $K$ for all three cell types,

$$
\phi_G \approx \frac{(\phi_G)_{max}}{K} (c_G^i(t) - c_G^o(t)).
$$

Conservation of glucose, and the assumption that the change in volume of the cells is small, results in

$$
- \frac{\gamma_A}{A} \frac{dc_G^i(t)}{dt} \approx \frac{(\phi_G)_{max}}{K} (c_G^i(t) - c_G^o(t)),
$$

where $\gamma_A$ is the membrane conductance for glucose transport.
which can be written as
\[
\frac{\gamma^i K}{A(\phi_G)_{max}} \frac{dc^i_G(t)}{dt} + c^i_G(t) = c^i_b(t).
\]

The solution is
\[
c^i_G(t) = C \left(1 - e^{-t/\tau}\right) \quad \text{for } t \geq 0,
\]
where \(C\) is the bath concentration of glucose, and
\[
\tau = \frac{\gamma^i K}{A(\phi_G)_{max}} = \frac{rK}{3(\phi_G)_{max}}.
\]

The time constants are
\[
\tau_6 = \frac{(6 \times 10^{-4} \text{ cm}) \cdot (0.05 \text{ mmol/cm}^3)}{3(2.5 \times \text{mmol/cm}^2 \cdot \text{s})} = 0.4 \text{ ms}
\]
\[
\tau_9 = \frac{(9 \times 10^{-4} \text{ cm}) \cdot (0.0167 \text{ mmol/cm}^3)}{3(2.5 \times \text{mmol/cm}^2 \cdot \text{s})} = 0.2 \text{ ms}
\]
\[
\tau_{27} = \frac{(27 \times 10^{-4} \text{ cm}) \cdot (0.0167 \text{ mmol/cm}^3)}{3(5 \times \text{mmol/cm}^2 \cdot \text{s})} = 0.3 \text{ ms}
\]

c. The cell with radius 9 \(\mu\)m equilibrates most rapidly and the cell with radius 6 \(\mu\)m equilibrates least rapidly.

Problem 6.13

a. The equivalent flux is the maximum flux of glucose and is obtained from the ordinate intercept which is \(1/\phi_{eq} \approx 0.018 \text{ L} \cdot \text{min/mmol}\) from which \(\phi_{eq} \approx 55 \text{ mmol/L} \cdot \text{min}\). The slope of the line fit to the points in the absence of cytochalasin is approximately \((0.042 - 0.018)/(0.05 - 0) = 0.48 \text{ min}\). Since the slope is \(K_{eq}/\phi_{eq}\), \(K_{eq} = 26.4 \text{ mmol/L}\).

b. A similar calculation is used in part b as in part a. The ordinate intercept is the same as in part a. Therefore, \(\phi_{eq} \approx 55 \text{ mmol/L} \cdot \text{min}\). Since the slope of the line fit to the points is approximately \((0.15 - 0.018)/(0.042 - 0) = 3.1 \text{ min}\), \(K_{eq} = 170 \text{ mmol/L}\).

c. The effect of the cytochalasin B is to increase \(K_{eq}\) while \(\phi_{eq}\) is the same with and without cytochalasin B. Thus, cytochalasin B, when applied extracellularly, acts as a competitive inhibitor to glucose efflux.

Problem 6.14

a. If the concentration of glucose in the enterocyte is constant then the net rate of influx of glucose must be zero. Therefore, \(A_a \phi_a = A_b \phi_b\).
b. Since the transport of glucose through the basolateral membrane can be represented by a simple, symmetric, four-state carrier model, the relation of efflux to concentration is

\[ \phi_b = \phi_{\text{max}} \left( \frac{c_{is}^l}{c_{is}^l + K} - \frac{c_{co}^o}{c_{co}^o + K} \right). \]

c. For \( c_{co}^o = 0 \), combining expressions yields

\[ A_a \phi_a = A_b \phi_{\text{max}} \left( \frac{c_{is}^l}{c_{is}^l + K} \right). \]

To solve for \( c_{is}^l \), it is easiest to divide both sides of the equation by \( A_b \phi_{\text{max}} \), invert both sides of the equation and solve for \( 1/c_{is}^l \) and then take the reciprocal to obtain

\[ c_{is}^l = K \frac{(A_a \phi_a/A_b \phi_{\text{max}})}{1 - (A_a \phi_a/A_b \phi_{\text{max}})}. \]

d. i. Note when \( \phi_a = 0 \), \( c_{is}^l(\infty) = 0 \). This is apparent from the results of part c and is consistent with the plot shown in the problem. The physical explanation is that when the apical flux is zero, the basolateral flux is zero. Hence, for zero glucose flux through the basolateral membrane, the intracellular concentration must equal the extracellular concentration of glucose which is zero.

ii. In steady state, as the total rate of influx of glucose in the apical region \( A_a \phi_a \) increases, the efflux through the basolateral region increases to equal the influx. A higher efflux in the basolateral membrane occurs at higher intracellular concentrations of glucose. As the efflux is driven toward saturation, a small increment in efflux requires a large increment in intracellular glucose concentration. A steady-state solution exists provided the influx through the apical membrane is less than the maximum efflux through the basolateral membrane \( A_b \phi_{\text{max}} \).

iii. When the influx exceeds the maximum efflux, i.e., when \( A_a \phi_a > A_b \phi_{\text{max}} \), the enterocyte can no longer transport glucose out of the basolateral membrane fast enough to match the rate of influx through the apical membrane. Hence, no steady state is possible for \( \phi_a/\phi_{\text{max}} > A_b/A_a = 1/24 \). This accounts for the unphysical result in this region, which is that the equations are satisfied only for negative values of the intracellular concentration.

**Problem 6.15**

a. The flux of the tracer is

\[ \phi_S^*(t) = (\phi_S)_{\text{max}} \left( \frac{C + c_S^{i*}(t)}{C + c_S^{i*}(t) + K} - \frac{C + c_S^{o*}(t)}{C + c_S^{o*}(t) + K} \right). \]

Evaluation of the first term on the right-hand side under the assumption that \( c_S^{i*}(t) \ll C \) yields

\[ \frac{C + c_S^{i*}(t)}{C + c_S^{i*}(t) + K} = \frac{C}{C + K} \left( \frac{1 + c_S^{i*}(t)}{C + K} \right). \]
The second term in the flux equation has a similar form as the first,

\[
\frac{C + c_S^0(t)}{C + c_S^0(t) + K} \approx \frac{C}{C + K} \left(1 + \frac{K}{C(C + K)} c_S^0(t)\right).
\]

A combination of these expressions yields

\[
\phi_S^*(t) \approx (\phi_S)_{max} \left(\frac{C}{C + K}\right) \left(1 + \frac{K}{C(C + K)} c_S^0(t) - 1 - \frac{K}{C(C + K)} c_S^0(t)\right),
\]

\[
\phi_S^*(t) \approx (\phi_S)_{max} \left(\frac{K}{(C + K)^2}\right) (c_S^i(t) - c_S^0(t)).
\]

Therefore,

\[
\gamma = (\phi_S)_{max} \left(\frac{K}{(C + K)^2}\right).
\]

b. Conservation of labeled solute yields

\[
-\frac{\gamma_i}{A} \frac{dc_S^i(t)}{dt} = \gamma(c_S^i(t) - c_S^0(t)).
\]

The total quantity of labeled solute is \(c_S^0(0)V^o = N_S^*\) so that conservation of labeled solute also requires \(c_S^i(t)V^i + c_S^0(t)V^o = N_S^*\) so that

\[
\frac{dc_S^i(t)}{dt} + \gamma_i \frac{A}{V^i} \left(1 + \frac{\gamma_i}{V^o}\right) c_S^i(t) = \gamma AN_S^* \frac{1}{V^i V^o}.
\]

Therefore,

\[
\alpha = (\phi_S)_{max} A \frac{\gamma_i}{V^i} \left(1 + \frac{\gamma_i}{V^o}\right) \left(\frac{K}{(C + K)^2}\right) \text{ and } \beta = (\phi_S)_{max} A \frac{K}{V^i V^o} \left(\frac{K}{(C + K)^2}\right) N_S^*.
\]

c. The differential equation for \(c_S^i(t)\) is linear, ordinary, and has constant coefficients. Hence, the solution has the form

\[
c_S^i(t) = c_S^i(\infty) \left(1 - e^{-\alpha t}\right),
\]

where

\[
c_S^i(\infty) = \frac{\beta N_S^*}{\alpha} = \frac{N_S^*}{V^i + V^o}.
\]

Hence, the steady-state value of the concentration is just the total quantity of radioactive sugar divided by the total volume of the system.
d. The steady-state value of the concentration of tracer gives no information about the kinetic parameters but the rate constant $\alpha$ does. If all the parameters aside from $K$ and $(\phi_S)_{max}$ are known or can be determined independently, then measurements of $\alpha$ for different values of $C$ allows estimation of the kinetic parameters.

e. One major advantage of the equilibrium exchange method is that there are no osmotic pressure differences created. Hence, there is no transport of water and the volume of the cell does not change. In addition, the time dependence of concentration is an exponential time function making estimation of parameters simple. In contrast, the zero-trans integrated flux method requires much more complex analysis methods with the possibilities of errors. One disadvantage of the equilibrium exchange method is that a series of measurements have to made at different values of $C$ in order to estimate the kinetic parameters.

Problem 6.16

a. Transport of solute by diffusion satisfies the differential equation

$$-\frac{1}{A} \frac{d(\gamma^i c^i_S(t))}{dt} = \phi_S = P_S(c^i_S - C).$$

Since the volume of the cell is constant,

$$\frac{\gamma^i}{AP_S} \frac{d(c^i_S(t))}{dt} + c^i_S(t) = C.$$ 

If the initial concentration $c^i_S(0) = 0$, then the solution to the differential equation is

$$c^i_S(t) = C_1 (1 - e^{-\tau_1 / \tau}) \text{ for } t \geq 0,$$

where $C_1 = C$ and $\tau_1 = \gamma^i / AP_S = (4/3) \pi r^3 / (4\pi r^2 P_S) = r / (3P_S)$.

b. From the binding reaction

$$K = \frac{c^i_M}{c^i_{SM}},$$

and from conservation of $M$, $c^i_M + c^i_{SM} = C_T$. Combining these two equations yields $Kc^i_{SM} = c^i_S(C_T - c^i_M)$ which can be solved to give

$$c^i_{SM} = \frac{c^i_S}{K + c^i_S} C_T.$$

For $K \gg C$ it follows that $K \gg c^i_S$ since $c^i_S \leq C$. Therefore,

$$c^i_{SM} \approx \frac{C_T}{K} c^i_S.$$

Conservation of $S$ yields

$$-\frac{\gamma^i}{A} \frac{d(c^i_S(t) + c^i_{SM}(t))}{dt} = \phi_S = P_S(c^i_S - C),$$
Table 6.5: The equilibrium value of intracellular solute concentration and the time constant of equilibration are given for the system without and with binding (Problem 6.16).

\[
\begin{array}{|c|c|c|}
\hline
\text{System} & \text{Solute concentration} & \text{Time constant} \\
& \text{Unbound} & \text{Total} \\
\hline
\text{No binding} & C & C \\
\hline
\text{With binding} & C & C \left( \frac{K + C_T}{K} \right) \\
\hline
\end{array}
\]

where \( c_S^i(t) + c_{SM}^i(t) \) is the total concentration of \( S \) in the cell both unbound and bound to \( M \). But, \( c_S^i(t) + c_{SM}^i(t) = (1 + (C_T/K))c_S^i(t) \) Combining these equations yields

\[
\frac{\gamma^i(1 + (C_T/K))}{APS} \frac{d(c_S^i(t))}{dt} + c_S^i(t) = C.
\]

If the initial concentration \( c_S^i(0) = 0 \), then the solution to the differential equation is

\[
c_S^i(t) = C_2(1 - e^{-t/\tau_2}) \text{ for } t \geq 0,
\]

where \( C_2 = C \) and \( \tau_2 = \gamma^i(1 + (C_T/K))/APS = = r(1 + (C_T/K))/(3P_S) \).

c. The final value of the (unbound) intracellular solute concentration and the time constant for equilibration can be estimated directly from measurements solute transport for a cell. If only these quantities are obtained for a single known value of \( C \) and if \( r \) is determined, it is still not possible to determine which of the mechanisms described in parts a and b occur in the cell. For a single value of \( C \), the results in part b could have been obtained by pure diffusion with no binding, if the permeability of the cell membrane had the value \( PS/(1 + (C_T/K)) \). Since \( P_S \) is not know a priori, there is no way to tell from a single measurement which mechanism applies. However, the mechanism could be determined by performing additional experiments. Table 6.5 summarizes the results for the two mechanisms. These two mechanisms can be distinguished by the following methods.

- **Determine the effect of \( C_T \) on \( \tau \).** When there is no binding of solute to \( M \), the time constant is independent of the concentration of \( M \) in the cell. Conversely, if there is binding to \( M \), the time constant increases as the concentration of \( M \) increases because some of the solute that enters the cell by diffusion binds to \( M \) and is not available to equilibrate the intracellular solute concentration.

- **Measure the total concentration of \( S \) in the cell.** In the absence of binding the total quantity of \( S \) in the cell is

\[
c_S^i(t) = C(1 - e^{-t/\tau_1}) \text{ for } t \geq 0.
\]

At equilibrium, \( c_S^i(\infty) = C \). In contrast, in the presence of binding the total quantity of \( S \) in the cell is the sum of the unbound and bound \( S \)

\[
c_S^i(t) + c_{SM}^i(t) = \left( 1 + \frac{C_T}{K} \right) c_S^i(t) = C \left( 1 + \frac{C_T}{K} \right) (1 - e^{-t/\tau_2}) \text{ for } t \geq 0.
\]
Therefore, at equilibrium, the total concentration of $S$ in the cell is $C(1 + (C_T/K))$ which exceeds that in the bath. The total concentration of $S$ in the cell can be measured with a variety of methods, e.g., radioactive tracers, flame photometry or electronprobe analysis.

**Problem 6.17**

a. **True**. This is a basic assumption of the simple, symmetric four-state carrier model and guarantees that the carrier does not leave the membrane.

b. **Ans. ii**. Note $K = c_S^i n_E^i / n_{ES}^i$. With $n_E^i = n_{ES}^i$ (as shown) $K = c_S^i$.

c. **True**. States $E^0$ and $ES^0$ do not change. The change from state (1) to state (3) could have been achieved by changing $c_S^i$ from $c_S^K$ as in (1) to $c_S^0 = 0$ as in (3).

d. **False**. Note that $n_{ES}^i < n_{ES}^0$ which implies that $n_E^i / n_{ES}^i > 1$ which implies that $K / c_S^K > 1$ which implies that $c_S^K < K$. Also $n_{ES}^0 > n_{ES}^i$, so that $c_S^0 > K$ which implies that $c_S^K > c_S^0$ which implies that $\phi_S < 0$.

e. **True**. $n_E^i = n_{ES}^i$ which implies that $c_S^i = K$. $n_E^o = n_{ES}^0$ which implies that $c_S^K = K$. Therefore, $c_S^K = c_S^0$ and $\phi_S = 0$.

f. **True**. $n_{ES}^i = 0$ and $n_E^i > 0$ implies that $c_S^i n_E^i / K = 0$ which implies that for $K$ bounded $c_A^i = 0$.

g. **False**. Changing $K$ changes both $c_S^i n_E^i / n_{ES}^i$ and $c_S^0 n_E^o / n_{ES}^o$. But $n_E^o / n_{ES}^o$ doesn’t change.

h. **Ans. (4)**. $n_E^i = 0$ implies that $c_S^K > K$, and $n_{ES}^0 = 0$ implies that $c_S^K = 0$. In general,

\[
\phi_S = (\phi_S)_{max} \left( \frac{c_S^i}{c_S^i + K} - \frac{c_S^K}{c_S^K + K} \right).
\]

The first term is maximized when $c_S^K > K$ and the second term is minimized when $c_S^K = 0$. For these conditions, $\phi_S = (\phi_S)_{max}$.

**Problem 6.18** The influxes of glucose into $\beta$-cells and erythrocytes are

\[
\phi_\beta = (\phi_G)_{max} \frac{c_G}{c_G + 20} \quad \text{and} \quad \phi_e = (\phi_G)_{max} \frac{c_G}{c_G + 0.5},
\]

where $\phi_\beta$ is the influx of glucose into $\beta$-cells, $\phi_e$ is the influx of glucose into erythrocytes, $(\phi_G)_{max}$ is the maximum flux of the carrier, and $c_G$ is the glucose concentration in the blood in mmol/L.

a. At $c_G = 5 \text{ mmol/L}$,

\[
\phi_\beta = \frac{5}{25} (\phi_G)_{max} \quad \text{and} \quad \phi_e = \frac{5}{5.5} (\phi_G)_{max}.
\]
Hence,
\[
\frac{\phi_\beta}{\phi_e} = \frac{5/25}{5/5.5} = 0.22.
\]

At this concentration of glucose, the relation of flux to concentration is near saturation for the erythrocyte but well below saturation for the \(\beta\)-cell. Hence, the ratio is much less than 1.

b. For the \(\beta\)-cell the percentage increase in flux is
\[
\left(\frac{(\phi_\beta)_{10} - (\phi_\beta)_5}{(\phi_\beta)_5}\right) \times 100 = \frac{10/30 - 5/25}{5/25} \times 100 = 66.7\%,
\]
whereas for the erythrocyte
\[
\left(\frac{(\phi_e)_{10} - (\phi_e)_5}{(\phi_e)_5}\right) \times 100 = \frac{10/10.5 - 5/5.5}{5/5.5} \times 100 = 4.7\%.
\]

Because the flux relation is near saturation for the erythrocyte, doubling the blood glucose concentration does not change the influx of glucose much for this cell. However, the same change in concentration causes a large change in the influx of glucose into the \(\beta\)-cell because the flux relation is well below saturation for this cell.

c. For the normal range of blood glucose, the erythrocyte glucose transporter is near saturation so that the influx of glucose into the cell is maximal. The erythrocyte incorporates as much glucose as is possible until glucose accumulates in the cell to reduce the influx. The erythrocyte is an example of cell that utilizes glucose for its metabolic needs. The \(\beta\)-cell glucose transporter is well below saturation at the normal blood glucose concentration. Hence, a change in blood glucose leads to a relatively large change in glucose influx. This is important for proper functioning of the \(\beta\)-cell as a controller of blood glucose level. The \(\beta\)-cell releases insulin in the blood stream, by a complex mechanism described elsewhere (Weiss, 1996a), in response to an increase in intracellular glucose. Thus, the sensitivity of the \(\beta\)-cell system depends upon the slope of the relation of glucose influx to blood glucose concentration which is a small when the transport system is near saturation.

Problem 6.19

a. First, consider \(c_S^1 / \phi_S\) plotted versus \(c_S^1\).

i. To find the relation, form the ratio
\[
\frac{c_S^1}{\phi_S} = \frac{c_S^1}{(\phi_S)_{max}} \frac{c_S^1}{c_S^{i,K} + K} = \frac{1}{(\phi_S)_{max}} \frac{c_S^1}{c_S^{i,K} + K}
\]

Therefore a plot of \(c_S^1 / \phi_S\) versus \(c_S^1\) is a straight line with slope \(1/(\phi_S)_{max}\) and intercepts at \(-K\) and \(K/(\phi_S)_{max}\) as shown in Figure 6.7.
Figure 6.7: $c_i S / \bar{\phi}_S$ plotted versus $c_i S$ (Problem 6.19).

Figure 6.8: Effect of increasing the concentration of an inhibitor is indicated by a dashed line (Problem 6.19).
ii. As the concentration of a noncompetitive inhibitor is increased, \((\phi_S)_{\text{max}}\) decreases (Table 6.2 (Weiss, 1996a)). In these coordinates, a change in concentration of a noncompetitive inhibitor corresponds to an increase in the slope of the lines while the intercept on the abscissa remains fixed (Figure 6.8).

iii. As the concentration of a competitive inhibitor is increased, \(K\) increases (Table 6.2 (Weiss, 1996a)). In these coordinates, a change in concentration of a competitive inhibitor corresponds to a decrease in the ordinate intercept with the slope fixed (Figure 6.8).

b. Next, consider \(\phi_S\) plotted versus \(\phi_S/c_S^i\).

i. To find the relation, form the ratio

\[ \frac{\phi_S}{(\phi_S)_{\text{max}}} = \frac{c_S^i}{c_S^i + K}, \]

\[ \frac{\phi_S}{(\phi_S)_{\text{max}}} = \frac{1}{c_S^i + K}. \]

A combination of these two relation yields

\[ \frac{\phi_S}{(\phi_S)_{\text{max}}} = c_S^i \left( \frac{\phi_S}{(\phi_S)_{\text{max}}} \right). \]

Next express \(c_S^i\) in terms of \(\phi_S / ((\phi_S)_{\text{max}}c_S^i)\), which is

\[ c_S^i = \frac{1}{\phi_S / ((\phi_S)_{\text{max}}c_S^i)} - K, \]

which yields

\[ \frac{\phi_S}{(\phi_S)_{\text{max}}} = \left( \frac{1}{\phi_S / ((\phi_S)_{\text{max}}c_S^i)} - K \right) \left( \frac{\phi_S}{(\phi_S)_{\text{max}}} \right). \]

Simplifying this result yields

\[ \phi_S = (\phi_S)_{\text{max}} - K \left( \frac{\phi_S}{c_S^i} \right). \]

Hence, this transformation results in a straight line whose slope is \(-K\) and whose ordinate intercept is \((\phi_S)_{\text{max}}\) as shown in Figure 6.9.

ii. As the concentration of a noncompetitive inhibitor is increased, \((\phi_S)_{\text{max}}\) decreases (Table 6.2 (Weiss, 1996a)). In these coordinates, a change in concentration of a noncompetitive inhibitor corresponds to a decrease in the ordinate intercept with the slope fixed (Figure 6.10).

iii. As the concentration of a competitive inhibitor is increased, \(K\) increases (Table 6.2 (Weiss, 1996a)). In these coordinates, a change in concentration of a competitive inhibitor corresponds to an increase in the magnitude of the slope without changing the ordinate intercept (Figure 6.8).
Figure 6.9: $\phi_S$ plotted versus $\phi_S/c_S$ (Problem 6.19).

Figure 6.10: Effect of increasing the concentration of an inhibitor is indicated by a dashed line (Problem 6.19).
Problem 6.20

a. The total flux of solute is \( \phi_S = \Phi_S - \Phi_S \) where Equations 6.111 and 6.113 (Weiss, 1996a) give expressions for the unidirectional fluxes for the general, four-state carrier model. At arbitrarily low concentrations, these two equations reduce to

\[
\begin{align*}
\Phi_S &\approx \frac{c_S^i K_g}{K_g^2 / \phi_z} = \Phi_S^i c_S^i \quad \text{and} \quad \Phi_S \approx \frac{c_S^0 K_g}{K_g^2 / \phi_z} = \Phi_S^0 c_S^0.
\end{align*}
\]

Hence, at arbitrarily low concentrations,

\[ \phi_S \approx \frac{\Phi_S^i}{\phi_z} (c_S^i - c_S^0), \]

and the permeability is

\[
P_S = \frac{\phi_z}{K_g} = \frac{a_i a_o}{a_i + a_o} \left( \frac{b_i h_i h_o}{a_i b_i h_o + a_i g_i h_o + a_o b_i h_i} \right) \eta_{ET}.
\]

This expression can be simplified by making use of the relation \( a_o b_i g_o h_i = a_i b_o g_i h_o \) to yield

\[
P_S = \frac{a_o b_i g_o h_i}{(a_i + a_o)(b_i g_o + g_i g_o + b_o g_i)} \eta_{ET}.
\]

b. Symmetry of the rate constants implies that \( a_i = b_i = \alpha \), \( a_o = b_o = \beta \), \( g_o = g_i \), and \( h_o = h_i \) which results in

\[
P_S = \frac{\beta \alpha g_i h_i}{(\alpha + \beta)(\alpha g_i + g_i^2 + \beta g_i)} \eta_{ET},
\]

\[
= \frac{\alpha \beta h_i}{(\alpha + \beta)(\alpha + \beta + g_i)} \eta_{ET}.
\]

If the interfacial reactions are assumed more rapid than the translocation reaction then \( g_i \gg \alpha + \beta \) and

\[
P_S = \frac{\alpha \beta h_i}{g_i(\alpha + \beta)} \eta_{ET}.
\]

If the interfacial binding reactions are so fast that they are assumed to be at equilibrium, then \( K = g_i / h_i \) and

\[
P_S = \frac{(\phi_S)_{max}}{K},
\]

where

\[
(\phi_S)_{max} = \frac{\alpha \beta}{\alpha + \beta} \eta_{ET}.
\]

Thus, the permeability of the general, four-state carrier model reduces to that for the simple, symmetric, four-state carrier model when the rate constants are symmetric and the interfacial reactions are assumed to be fast compared to the translocation reactions.

Problem 6.21
a. In the steady state the rate of change of state density is zero and the following equations arise. The first two equations represent the rate equations for $N_i E$ and $N_o E$. The third equation represents conservation of carrier.

\[
\begin{bmatrix}
-(a_i + h_i c_S^i) & a_o & g_i \\
 a_i & -(a_o + h_o c_S^o) & g_o \\
 1 & 1 & 1
\end{bmatrix} \begin{bmatrix}
N_i^i \\
N_o^o \\
N_{ES}
\end{bmatrix} = \begin{bmatrix}
0 \\
0 \\
N_{ET}
\end{bmatrix}.
\]

The solutions are ratios of sums of products of rate constants

\[
\frac{N_i^i}{N_{ET}} = \frac{M_i^i}{D}, \quad \frac{N_o^o}{N_{ET}} = \frac{M_o^o}{D}, \quad \frac{N_{ES}}{N_{ET}} = \frac{M_{ES}}{D},
\]

where

\[
\begin{aligned}
M_i^i &= a_o g_o + a_o g_i + g_i h_o c_S^o, \\
M_o^o &= a_i g_i + a_i g_o + g_o h_i c_S^i, \\
M_{ES} &= a_i h_o c_S^o + a_o h_i c_S^i + h_i h_o c_S^i c_S^o, \\
D &= M_i^i + M_o^o + M_{ES}.
\end{aligned}
\]

b. Using the same method as used in the text (Weiss, 1996a), assume that some of the solute on the inside bath is marked $S^*$. Then the efflux can be written as

\[
\tilde{\phi}_S = g_o N_{ES^*} \frac{c_S^i}{c_S^*}.
\]

In the steady state

\[
\frac{dN_{ES^*}}{dt} = 0 = h_i c_S^i N_E^i - (g_i + g_o) N_{ES^*},
\]

which has included the explicit assumption that no $S^*$ binds to $E^o$. This leads to the relation

\[
N_{ES^*} = \frac{h_i c_S^i}{g_i + g_o} N_E^i.
\]

The efflux of solute is obtained by combining these expressions to give

\[
\tilde{\phi}_S = \frac{g_o h_i}{g_i + g_o} c_S^i N_E^i.
\]

The influx is found by the replacement $i \rightarrow o$ to obtain

\[
\tilde{\phi}_S = \frac{g_i h_o}{g_o + g_i} c_S^o N_E^o.
\]

c. Examination of the equation for $\tilde{\phi}_S$ reveals that the numerator can be written as a sum of two terms, one proportional to $c_S^i$ and another proportional to $c_S^i c_S^o$. The denominator can be written as a sum of four terms, one constant, another
proportional to $c_i^1$, another proportional to $c_o^0$, and another proportional to $c_i^1 c_o^0$. Hence, the flux can be written in the form

$$\bar{\Phi}_S = \frac{c_i^1 (K_g + c_o^0)}{(K_g^2 / \phi_z) + (K_g / \phi_{io}) c_i^1 + (K_g / \phi_{oi}) c_i^1 c_o^0 + (1 / \phi_{\infty}) c_i^1 c_o^0}.$$ 

The form of the relation between the flux and the concentrations for the three-state carrier mechanism is identical to that for the four-state carrier mechanism. Therefore, one cannot distinguish between the three-state and four-state carrier mechanisms from measurements of flux versus concentration alone.

d. The macroscopic parameters can be written in terms of the microscopic parameters as follows.

$$K_g = \frac{a_0 g_0}{g_i h_o + h_o} + 1,$$

$$\phi_z = \frac{g_0 h_i (a_0 g_0 + g_0 g_i + g_i h_o)^2}{g_i h_o (g_i + g_o)^2 (a_i + a_o)} \eta_{ET},$$

$$\phi_{io} = \frac{g_0 (a_0 g_0 + g_0 g_i + g_i h_o)}{(a_o + g_o) (g_i + g_o)} \eta_{ET},$$

$$\phi_{oi} = \frac{g_0 h_i (a_0 g_0 + g_0 g_i + g_i h_o)}{h_o (a_i + g_i) (g_i + g_o)} \eta_{ET},$$

$$\phi_{\infty} = \frac{g_i g_o}{g_i + g_o} \eta_{ET}.$$

**Problem 6.22**

a. Because the zero-trans efflux and influx have different parameters, these results are inconsistent with the simple, symmetric, four-state carrier model.

b. The rest of the problem deals with the general, four-state carrier model. Table 6.9 (Weiss, 1996a) shows $\phi_{eq}$ and $K_{eq}$ for the different protocols in this problem.

i. By definition $\phi_{io} = 1.98 \pm 0.31$ and $\phi_{oi} = 0.53 \pm 0.038 \text{ mmol/(L\cdot min)}$.

ii. By definition $\phi_{\infty} = 7.54 \pm 0.45 \text{ mmol/(L\cdot min)}$.

iii. The relation

$$\frac{1}{\phi_z} + \frac{1}{\phi_{\infty}} = \frac{1}{\phi_{io}} + \frac{1}{\phi_{oi}},$$

yields

$$\phi_z = \frac{1}{(1 / \phi_{io}) + (1 / \phi_{oi}) - (1 / \phi_{\infty})}.$$ 

Substitution of the mean values for the parameters yields

$$\phi_z = 0.44 \text{ mmol/(L\cdot min)}.$$

iv. The value of $K_g$ can be computed as shown in Table 6.6. The standard error in $K_g$ is computed from the standard error in $K_{eq}$ only. Hence, this estimate of the standard error in $K_g$ is a lower bound because it does not include the uncertainties in the values of other parameters.
PROBLEMS

Table 6.6: Estimated dissociation constant for different protocols (Problem 6.22).

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Value of $K_g$ (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero-trans efflux</td>
<td>$K_g = K_{eq} \phi_z / \phi_{lo} = (0.4 \pm 0.12) \cdot 0.44 / 1.98 = 0.089 \pm 0.027$</td>
</tr>
<tr>
<td>Zero-trans influx</td>
<td>$K_g = K_{eq} \phi_z / \phi_{oi} = (0.073 \pm 0.069) \cdot 0.44 / 0.53 = 0.061 \pm 0.057$</td>
</tr>
<tr>
<td>Infinite-cis efflux</td>
<td>$K_g = K_{eq} \phi_{1o} / \phi_{so} = (0.252 \pm 0.096) \cdot 1.98 / 7.54 = 0.066 \pm 0.025$</td>
</tr>
<tr>
<td>Infinite-cis influx</td>
<td>$K_g = K_{eq} \phi_{oi} / \phi_{so} = (0.937 \pm 0.226) \cdot 0.53 / 7.54 = 0.066 \pm 0.016$</td>
</tr>
<tr>
<td>Equilibrium exchange</td>
<td>$K_g = K_{eq} \phi_z / \phi_{so} = (1.29 \pm 0.11) \cdot 0.44 / 7.54 = 0.075 \pm 0.006$</td>
</tr>
</tbody>
</table>

v. Note that all the estimates of $K_g$ are consistent in that their mean values do not differ from one another by more than one standard error. Thus, these comparisons reveal no inconsistency with the predictions of the general, four-state carrier model.
Chapter 7

ION TRANSPORT AND RESTING POTENTIAL

Exercises

Exercise 7.1  a. I; b. H; c. X (mol/(cm·s·V)); d. C; e. G; f. E; g. J.

Exercise 7.2

a. Since only potassium permeates the membrane at equilibrium, the membrane potential must equal the potassium equilibrium potential. Assuming normal room temperature of 25°C,

\[ V_m = V_K = 59 \log_{10} \left( \frac{c_2^K}{c_1^K} \right) = 59 \log_{10} (1/10) = -59 \text{ mV}. \]

At equilibrium, the flux due to diffusion (which is from volume 1 to volume 2) is balanced by drift of potassium ions (which must be from volume 2 to volume 1). The drift is in this direction if the potential in volume 1 is less than the potential in volume 2 so that the positive potassium ions flow from a higher to a lower electric potential.

c. Application of a battery to the two volumes completes an electric circuit consisting of the battery and the membrane as shown in Figure 7.1. The membrane is represented by an equivalent conductance and a battery in series.

![Figure 7.1: Electric network model of membrane and source (Exercise 7.2).](image-url)
b. The network shows that \( I_m = G_k (V_m - V_K) \). When \( V_m > V_K \), \( I_m > 0 \), i.e., the current flows from the left to the right compartment. But, \( V_m = -30 \text{ mV} \) and \( V_K = -59 \text{ mV} \), so that \( V_m - V_K = -30 + 59 = 29 \text{ mV} \) and \( I_m > 0 \).

**Exercise 7.3** An ionic solution obeys electroneutrality if its constituent ions contain no net charge so that \( \sum_n z_n F c_n = 0 \). Electroneutrality results from the strong electrostatic forces between charges. A net charge in a solution will tend to be neutralized over a time scale greater than the relaxation time and over a distance scale greater than the Debye length.

**Exercise 7.4** The Nernst equilibrium potential defines the condition for equilibrium of an ion across a membrane permeable to that ion. The condition is

\[
V_n = \frac{RT}{z_n F} \ln \left( \frac{c_n^o}{c_n^i} \right),
\]

where \( V_n \) is the Nernst equilibrium potential defined as the inside minus the outside potential across the membrane, \( R \) is the molar gas constant, \( T \) is the absolute temperature, \( z_n \) is the valence of ion \( n \), \( F \) is Faraday’s constant, and \( c_n^o \) and \( c_n^i \) are the concentrations of ion \( n \) on the outside and inside of the membrane, respectively. When the potential across the membrane equals the Nernst equilibrium potential, the passive flux of that ion is zero. The physical bases of the equilibrium arises because ions are transported by diffusion resulting from a difference of concentration and by drift due to the presence of an electric field across the membrane. When the fluxes due to drift and diffusion are equal and oppositely directed, the net flux is zero and equilibrium occurs.

**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.
Exercise 7.7

a. The answer is iii. There must be cations in the solution to satisfy electroneutrality.

b. Yes, the sodium and chloride concentrations must be equal.

Exercise 7.8

a. At electrodiffusive equilibrium the tendency of the cation to diffuse from right to left must be balanced by a tendency to drift from left to right. Thus, if $V_m > 0$ the cations will tend to drift from left to right. At electrodiffusive equilibrium the drift and diffusion just cancel and there is no net flux of the cation.

b. Both solutions must be electrically neutral. If both the anion and the cation are univalent, then there must be the same number of cations as anions on each side of the membrane as shown in Figure 7.2.

c. Near the membrane, in a layer of solution whose thickness is of the order of the Debye length, there is net charge on each side of the membrane — net cations on the side with positive potential and net anions on the side with negative potential as is shown in Figure 7.3.

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.

Exercise 7.10

a. True or false questions

i. True. By definition the total current flowing out of a cell is zero at rest.

ii. True. In this region, the slope of the line relating the resting membrane potential to the logarithm of the extracellular potassium concentration approaches that for a potassium electrode. Therefore, \( V_m^0 \approx V_K \).

iii. False. Since the pump is nonelectrogenic,

$$V_m^0 = \frac{G_K}{G_K + G_Na} V_K + \frac{G_Na}{G_K + G_Na} V_{Na}.$$  

But since \( V_m^0 \approx V_K, \frac{G_K}{G_Na + G_K} \approx 1 \) which implies that \( G_Na \approx G_K \).

iv. True. \( V_{Na} = 59 \log_{10}(150/15) = 59 \) mV. \( V_m^0 = V_K < 0 \) for the range of concentrations shown. Therefore, \( V_{Na} > V_K \).

v. True. Note that for \( c_K^0 \approx 100 \) mmol/L, \( V_m^0 = V_K = 0 \). Therefore, since \( V_K = 59 \log_{10}(c_K^0/c_K^l) \), then \( c_K^l = 100 \) mmol/L.

vi. True. Since the pump is nonelectrogenic, no net current is carried by the pump so that \( I_K^0 + I_{Na}^a = 0 \).

vii. False. At rest, \( I_m^0 = 0 \) and since the pump is nonelectrogenic, \( I_K^a + I_{Na}^a = 0 \). Therefore, \( I_K^p + I_{Na}^p = 0 \), and \( I_K^p = -I_{Na}^p \).

viii. True. If the pump maintains constant sodium concentration in the cell then \( I_{Na}^a + I_{Na}^p = 0 \). Therefore, \( I_{Na}^a = -I_{Na}^p = -G_Na(V_m^0 - V_{Na}) \).

b. For the nonelectrogenic pump, the equation in part a.iii holds. Note that as \( G_{Na}/G_K \) increases the second term in the equation increases and the first term decreases. In particular, the first term determines the slope of the relation of \( V_m^0 \) to \( c_K^r \). Thus, a reduction of this term will reduce this slope. This theoretical prediction could be the basis of the measured change in slope. According to this argument, \( G_K/G_{Na} \) should be larger at \(-100 \) mV than at \(-125 \) mV.
Exercise 7.11

a. The Nernst equilibrium potentials are

\[ V_K = 60 \log_{10} \left( \frac{15}{150} \right) = -60 \text{ mV}, \]
\[ V_{Na} = 60 \log_{10} \left( \frac{150}{15} \right) = +60 \text{ mV}. \]

b. Note that when \( I_m = 0, V_m = V_m^o = -40 \text{ mV}. \)

c. When \( V_m = V_K, I_K = 0. \) Therefore, \( I_m = I_{Na} \) or \( I_{Na}/I_m = 1. \)

d. The slope of the curve that relates \( V_m \) to \( I_m \) equals the total resistance of the membrane. Hence, the reciprocal is the membrane conductance.

\[ G_m = \frac{0.4 \times 10^{-9}}{40 \times 10^{-3}} = 10 \text{ nS}. \]

e. The resting potential of the cell is related to the ion conductances and Nernst equilibrium potentials by the relation

\[ V_m^0 = \frac{G_K}{G_K + G_{Na}} V_K + \frac{G_{Na}}{G_K + G_{Na}} V_{Na}, \]
\[ -40 = -\frac{G_K}{10} 60 + \frac{G_{Na}}{10} 60. \]

In addition, \( G_K + G_{Na} = 10 \text{ nS}. \) Combining these two equations yields

\[ -\frac{40}{6} = -(10 - G_{Na}) + G_{Na}. \]

Hence, \( G_{Na} = 5/3 \text{ nS} \) and \( G_K = 25/3 \text{ nS}. \) These results fit with the fact that the resting potential is much closer to the potassium than to the sodium equilibrium potential. Hence, we expect the potassium conductance to greatly exceed the sodium conductance.

Exercise 7.12 We explore Sharp Wan’s contention by assuming that puncturing the membrane leads to a leakage resistance \( R_l \) in parallel with the membrane which can be represented by the network shown in Figure 7.4. Note that the resting potential is

\[ V_m^o = \frac{R_l}{R_l + R_m} V_K = \frac{R_l}{R_l + R_m} 59 \log_{10} \left( \frac{c_K^o}{c_K} \right). \]

Thus, the slope of \( V_m^o \) versus \( \log_{10} c_K^o \) is \( 59 R_l/(R_l + R_m) \). Therefore, a slope of \( 59/2 = 29.5 \text{ mV/decade} \) is obtained if \( R_l = R_m. \)

Exercise 7.13 The direct effect of active transport on the membrane potential of a cell results when the active transport mechanism transports a net current across the membrane. This contributes a component of the membrane potential that is directly attributable to active transport in the sense that if the current source is eliminated (e.g.,
by a specific blocker substance), the contribution of the active transport mechanism to the membrane potential goes rapidly to zero. The indirect effect results because if the active transport mechanism is blocked, then ions will flow down their electrochemical potential gradients to reduce these gradients. Hence, ion concentrations will change which will result in changes in the Nernst equilibrium potentials of the permeable ions. The changes in Nernst equilibrium potentials will result in a change in the resting value of the membrane potential. Because, it takes time for the ion concentrations to change appreciably, the change in potential that results from the indirect effect takes longer to be manifested than that caused by the direct effect.

**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.

**Exercise 7.15**

a. Potassium. When $V = 0$, current flow is due to diffusion alone. If $K^+$ were permeant, diffusion of $K^+$ would be upward because the concentration of $K^+$ is greater in compartment 2 than in compartment 1. Thus, if $K^+$ were permeant, current would flow upward through the membrane and then through the wire in the direction opposite to the reference direction — i.e., $I$ would be negative. If $Na^+$ were permeant, diffusion of $Na^+$ would be downward because the concentration of $Na^+$ is greater in compartment 1 than in compartment 2. Thus, if $Na^+$ were permeant, current would flow downward through the membrane and through the wire in the reference direction — i.e., $I$ would be positive. Because the concentration of $Cl^-$ is the same in each compartment, there would be no net diffusion of $Cl^-$ even if
it were permeant, so $I$ would be zero. Thus if $I = -1$ mA when $V = 0$, then the permeant ion must be potassium.

b. The circuit is shown in Figure 7.5. The Nernst equilibrium potential for potassium is

$$V_K = \frac{RT}{F} \ln \frac{c_K^2}{c_K} = 59 \text{ mV} \times \log \left( \frac{1 \text{ mmol/L}}{0.1 \text{ mmol/L}} \right) = +59 \text{ mV}.$$ 

The conductance $G$ can be computed from the condition that $I = -1$ mA when $V = 0$. Therefore

$$G = \frac{I}{V - V_K} = \frac{-1 \text{ mA}}{-59 \text{ mV}} = \frac{1}{59} \text{ S}.$$ 

c. The current $I$ can be determined directly from the model in part b.

$$I = G(V - V_K) = \frac{1}{59} (1 - 0.059) = 15.9 \text{ mA}.$$ 

**Exercise 7.16**

a. The solution is

<table>
<thead>
<tr>
<th>$\phi_N'$</th>
<th>$\phi_K'$</th>
<th>$\phi_{Na}'$</th>
<th>$\phi_K'$</th>
<th>$V_m'$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

where “D” implies decreases, “I” implies increases. When the cell equilibrates in the control solution, there is active transport of sodium out of the cell ($\phi_{Na}' > 0$) and active transport of potassium into the cell ($\phi_K' < 0$). The ouabain in the test solution will slow the pump so that $\phi_{Na}' \rightarrow 0$ and $\phi_K' \rightarrow 0$. Therefore $\phi_{Na}'$ decreases and $\phi_K'$ increases. Since the pump is electrogenic and produces positive outward current, slowing the pump will cause $V_m'$ to increase. Increasing $V_m'$ will tend to increase both $\phi_{Na}'$ and $\phi_K'$.

b. The solution is

<table>
<thead>
<tr>
<th>$\phi_N'$</th>
<th>$\phi_K'$</th>
<th>$\phi_{Na}'$</th>
<th>$\phi_K'$</th>
<th>$V_m'$</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>D</td>
<td>I</td>
<td>D</td>
<td>D</td>
</tr>
</tbody>
</table>

where “D” implies decreases, “I” implies increases. When the cell equilibrates in the control solution, the pumps are disabled because their action depends on intracellular ATP. Therefore $\phi_{Na}' = \phi_K' = 0$. Adding intracellular ATP during the test interval will start the pumps, making $\phi_{Na}' > 0$ and $\phi_K' < 0$, i.e. $\phi_{Na}'$ increases and $\phi_K'$ decreases. Starting the pump causes $V_m'$ to decrease, and thereby causes $\phi_{Na}'$ and $\phi_K'$ to decrease.
Problems

Problem 7.1

a. The conductivity of an electrolyte is related to its composition as follows

\[
\sigma_e = \sum_n u_n z_n^2 F^2 c_n = \sum_n \frac{z_n^2 F^2}{RT} D_n c_n.
\]

We shall compute the conductivity using SI units. Note that concentrations expressed in mmol/L are numerically equal to concentrations expressed in mol/m^3, and that the diffusion coefficient needs to be expressed in m^2/s. For axoplasm,

\[
\sigma_{ax} = \frac{F^2}{RT} (D_{Na} c_{Na} + D_{K} c_{K} + D_{Cl} c_{Cl}),
\]

\[
\sigma_{ax} = \frac{(9.65 \times 10^4)^2}{(8.314)(291)} (1.33 \times 10^{-9} \cdot 50 + 1.96 \times 10^{-9} \cdot 400 + 2.03 \times 10^{-9} \cdot 100),
\]

\[
\sigma_{ax} = 4.06 \text{ S/m}.
\]

Therefore, the resistivity is \(\rho_{ax} = 1/\sigma_{ax} = 1/4.06 = 0.2466 \Omega \cdot \text{m} \) which equals 24.6 \(\Omega \cdot \text{cm}\). Therefore, the estimated resistivity is smaller than the measured resistivity; the ratio is 24.6/30 = 0.82. A number of factors are likely to contribute to a difference between the estimated and measured resistivity. In computing the theoretical estimate it was assumed that the concentration equaled the activity of each ion. Typically, the activity coefficients are less than one. Hence, the estimated conductivity should overestimate the measured conductivity, and the estimated resistivity should underestimate the measured resistivity. Thus, this factor could account for some of the difference. In addition, the composition of axoplasm that is given is clearly incomplete — it is not electroneutral. Hence, some other ions must be present. Taking these additional ions into account would increase the conductivity and decrease the resistivity. This factor would make the difference between the estimated and measured resistivities larger.

b. The conductivity of the external solution is estimated to be

\[
\sigma_e = \frac{(9.65 \times 10^4)^2}{(8.314)(291)} (1.33 \times 10^{-9} \cdot 460 + 1.96 \times 10^{-9} \cdot 10 + 2.03 \times 10^{-9} \cdot 540),
\]

\[
\sigma_e = 6.65 \text{ S/m},
\]

so that the resistivity is 15.0 \(\Omega \cdot \text{cm}\). Hence, the theoretical estimate of the resistivity is smaller than the measured value; the ratio of estimated to measured resistivity is 15/22 = 0.68. Some of the same factors discussed in connection with the resistivity of axoplasm may affect the difference between the measured and estimated resistivity of the external solution. Thus, without further analysis we cannot really account for the difference in resistivity of axoplasm and the external solution. Factors such as those suggested by Katz may make a contribution to the difference.
c. The Stokes-Einstein relation can be solved for the radius to yield

\[
a = \frac{kT}{6\pi D \eta} = \frac{(1.381 \times 10^{-23} \text{ J/K})(291 \text{ K})}{6\pi D(0.9 \times 10^{-3} \text{ Pa \cdot s})} = \frac{2.37 \times 10^{-19}}{D}.
\]

Therefore,

\[
a_{Na} = \frac{2.37 \times 10^{-19}}{1.33 \times 10^{-9}} = 1.78 \times 10^{-10} \text{ m} = 1.78 \text{ Å},
\]
\[
a_K = \frac{2.37 \times 10^{-19}}{1.96 \times 10^{-9}} = 1.21 \times 10^{-10} \text{ m} = 1.21 \text{ Å},
\]
\[
a_{Cl} = \frac{2.37 \times 10^{-19}}{2.03 \times 10^{-9}} = 1.17 \times 10^{-10} \text{ m} = 1.17 \text{ Å}.
\]

Thus, the estimates of the radius of the ions are within a factor of 2 of the crystal radii. A number of factors could account for the differences. First, the diffusion coefficients used for the entire problem are those for infinite dilution. The diffusion coefficient at the concentrations in axoplasm and in the external solution will differ from those at infinite dilution. Furthermore, the diffusion coefficient given in the problem were for a temperature of 25°C and the temperature assumed in the problem was 18°C. In addition, ions in solution bind to water molecules to give a hydrated ion whose radius is larger than the crystal radius of the ion. Finally, the Stokes-Einstein relation is most accurate for large spherical particles in water and its validity for small ions may be questionable.

Problem 7.2

a. The relation between the potential and the concentration is obtained from three relations: steady state yields

\[
J = J_+ + J_- = 0,
\]
electroneutrality yields

\[
c_+(x) = c_-(x) = c(x),
\]
and the Nernst-Planck equation for current density of each ion yields

\[
J_n = -z_n F \left( u_n RT \frac{dc_n(x)}{dx} + u_n z_n F c_n(x) \frac{d\psi(x)}{dx} \right).
\]

Combination of these 3 relations yields

\[
-F \left( u_+ RT \frac{dc(x)}{dx} + u_+ F c(x) \frac{d\psi(x)}{dx} \right) + F \left( u_- RT \frac{dc(x)}{dx} - u_- F c(x) \frac{d\psi(x)}{dx} \right) = 0,
\]
which can be simplified to

\[
(u_+ + u_-) F c(x) \frac{d\psi(x)}{dx} = (u_- - u_+) R T \frac{dc(x)}{dx}.
\]

Rearranging terms yields

\[
\frac{d\psi(x)}{dx} = -\left( \frac{u_+ - u_-}{u_+ + u_-} \right) \frac{RT}{F} \frac{dc(x)}{dx} = -\left( \frac{u_+ - u_-}{u_+ + u_-} \right) \frac{RT}{F} \frac{d \ln c(x)}{dx}.
\]
b. The potential difference across the membrane can be determined by integrating the potential across the membrane

\[ V_j = \int_{0}^{d} d\psi(x) = -\int_{0}^{d} \left( \frac{u_+ - u_-}{u_+ + u_-} \right) \frac{RT}{F} \ln(c(x)) \frac{dc}{dx} dx, \]

\[ = -\left( \frac{u_+ - u_-}{u_+ + u_-} \right) \frac{RT}{F} \ln(c(0)) \bigg|_{0}^{d} \]

\[ = \left( \frac{u_+ - u_-}{u_+ + u_-} \right) \frac{RT}{F} \ln \left( \frac{c(d)}{c(0)} \right). \]

Because, the concentrations are assumed to be continuous at the interfaces,

\[ V_j = \left( \frac{u_+ - u_-}{u_+ + u_-} \right) \frac{RT}{F} \ln \left( \frac{c^2}{c_1} \right). \]

c. The relation between flux and current density is \( J_n = z_n F \phi_n \) so that

\[ \phi_+ = -u_+ RT \frac{dc(x)}{dx} - u_+ F c(x) \frac{d\psi(x)}{dx}, \]

\[ \phi_- = -u_- RT \frac{dc(x)}{dx} + u_- F c(x) \frac{d\psi(x)}{dx}. \]

Therefore,

\[ \phi = \phi_+ + \phi_- = -(u_+ + u_-)RT \frac{dc(x)}{dx} - (u_+ - u_-) F c(x) \frac{d\psi(x)}{dx}, \]

and after substitution for \( d\psi(x)/dx \)

\[ \phi = -(u_+ + u_-)RT \frac{dc(x)}{dx} + \left( \frac{u_+ - u_-}{u_+ + u_-} \right) \frac{RT}{F} \frac{dc(x)}{dx}, \]

which after rearrangement of terms yields

\[ \phi = -u_i RT \frac{dc(x)}{dx}, \]

where

\[ u_i = \frac{4u_+ u_-}{u_+ + u_-}. \]

d. Plots of \( u_i/u_+ \) and \( V_j/((RT/F) \ln(c^2/c_1)) \) are shown in Figure 7.6. The liquid junction potential is zero when the mobilities of the anion and cation are the same. The normalized potential is positive if the cation mobility exceeds the anion mobility and is negative when the anion mobility exceeds the cation mobility.

e. i. The system is not in equilibrium because there is net flux of both the cation and the anion. At equilibrium, \( \phi_+ = \phi_- = 0. \) In contrast, in the liquid junction

\[ \phi_+ = \phi_- = \phi = \frac{u_i RT}{d} (c^2 - c_1), \]

so that \( \phi \neq 0 \) if \( c^2 \neq c_1. \)
ii. Further analysis allows the questions to be answered precisely. The equation that links the flux to the concentration gradient can be integrated since the flux is constant to yield

\[ \int_0^d \phi \, dx = -\int_{c(0)}^{c(d)} u_1 RT \, dc(x), \]
\[ \phi d = -u_1 RT \, (c(d) - c(0)), \]
\[ \phi = \frac{u_1 RT}{d} (c^2 - c^1), \]

where it is assumed that the concentration is continuous through the interface between the liquid junction and the bath solutions. Since the concentration gradient is constant, the concentration profile in the membrane must be linear and can be expressed as

\[ c(x) = c^1 - (c^1 - c^2) \frac{x}{d}, \]

which satisfies the requisite boundary conditions at \( x = 0 \) and \( x = d \). The potential in the liquid junction can be found from the relation between the concentration and potential gradient found in part a,

\[ \psi(x) - \psi(0) = \frac{-RT}{F} \left( \frac{u_+ - u_-}{u_+ + u_-} \right) \ln \left( \frac{c(x)}{c(0)} \right), \]
\[ \psi(x) - \psi(0) = \frac{-RT}{F} \left( \frac{u_+ - u_-}{u_+ + u_-} \right) \ln \left( \frac{c^1 - (c^1 - c^2) \frac{x}{d}}{c^1} \right). \]

The expressions for both the concentration and potential in the liquid junction can be used to compute the diffusive and drift components of the flux which for the cation are

\[ (\phi_+)_{\text{diffusion}} = +\frac{u_+ RT}{d} (c^1 - c^2), \]
\[ (\phi_+)_{\text{drift}} = -\frac{u_+ RT}{d} \left( \frac{u_+ - u_-}{u_+ + u_-} \right) (c^1 - c^2). \]

The sum of the fluxes due to diffusion and to drift is

\[ \phi_+ = (\phi_+)_{\text{diffusion}} + (\phi_+)_{\text{drift}} = \frac{2 u_+ u_-}{u_+ + u_-} RT (c^1 - c^2). \]
The anion fluxes are

\[ \phi_-(\text{diffusion}) = u_+ RT \frac{d}{c^1 - c^2}, \]
\[ \phi_-(\text{drift}) = u_+ RT \frac{d}{u_+ + u_-} \left( \frac{u_+ - u_-}{u_+ + u_-} \right) \left( c^1 - c^2 \right), \]

and

\[ \phi_- = \phi_-(\text{diffusion}) + \phi_-(\text{drift}) = \frac{2u_+ u_-}{u_+ + u_-} RT (c^1 - c^2). \]

The physical basis of these results can now be explored. Consider the results for the condition \( c^1 > c^2 \). The concentration and potential in liquid junction are shown for such a condition in Figure 7.7. For the condition \( c^1 > c^2 \), the net flux of both cations and anions is \( \phi > 0 \). Now suppose the mobility of the cation exceeds that of the anion, i.e., \( u_+ / u_- > 1 \), then the potential gradient is positive. Under these conditions the cation flux due to diffusion is positive and the cation flux due to drift is negative. Thus, the magnitude of the cation flux is reduced below that attributed to diffusion alone. In contrast, the diffusive flux and the drift add for the anion. Thus, the potential gradient that arises in the liquid junction decreases the magnitude of the flux of the more rapidly mobile cations and increases the magnitude of the flux of the slower anions. Thus, the net flux of each ion is the same and electroneutrality is maintained in the liquid junction. If the anions are more mobile, then the sign of the potential gradient is reversed and once again the flux of the faster ion, now the anion, is decreased and that of the slower ion increased. The resultant cation and anion fluxes are equal so that the net current density through the junction is zero.

f. The arrangement for recording the membrane potential with an intracellular micropipette and the resulting junction potentials are shown in Figure 7.8. The measured potential \( V_{meas} \) is related to the resting potential across the membrane \( V_m^0 \).
as follows

\[ V_{\text{meas}} = V_{j1} + V_{o}^m - V_{j2}. \]

Thus, the net junction potential is

\[ V_j = V_{j1} - V_{j2} \]

which can be estimate as

\[
V_{j1} = \left( \frac{u_+ - u_-}{u_+ + u_-} \right) \frac{RT}{F} \ln \left( \frac{0.15}{2} \right) - \left( \frac{u_+ - u_-}{u_+ + u_-} \right) \frac{RT}{F} \ln \left( \frac{0.005}{2} \right)
\]

This can be evaluated using the mobilities from Table 7.2 (Weiss, 1996a),

\[
V_{j1} = \left( \frac{7.89 - 8.21}{7.89 + 8.21} \right) \frac{RT}{F} \ln 30 = \left( \frac{7.89 - 8.21}{7.89 + 8.21} \right) 59 \ln_{10} 30 = -1.7 \text{ mV}.
\]

g. One important criterion for choosing a binary electrolyte to fill the micropipettes is minimization of the junction potential between the electrolyte in the pipette and intracellular solution. Junction potentials are minimized when the mobilities of the cation and anion are the same. According to Table 7.2 (Weiss, 1996a) the best combination for minimization of the junction potential is CsI. However, filling the micropipette with CsI would yield a junction with CsI on the micropipette side and KCl on the intracellular side. The mobilities of potassium and chloride are also quite close. Since intracellular solutions resemble KCl in ion composition, KCl is the best choice.

**Problem 7.3**

a. Using Kirchhoff’s voltage law

\[
V_i = V_{Ag/AgCl-p} + V_{AgCl/KCl-p} + V_{KCl/cyt} + V_{o}^m - V_{KCl/bath} - V_{AgCl/KCl-r} - V_{Ag/AgCl-r}.
\]

b. If the potential across the junction between the silver and silver chloride is constant and the same at both electrodes, that term will drop out of the equation to yield

\[
V_i = V_{AgCl/KCl-p} + V_{KCl/cyt} + V_{o}^m - V_{KCl/bath} - V_{AgCl/KCl-r}.
\]

c. Note that

\[
V_{AgCl/KCl} = V_{AgCl/KCl}^o - \left( \frac{RT}{F} \right) \ln c_{Cl} \quad \text{where} \quad V_{AgCl/KCl} \approx 222 \text{ mV for a 1 mol/L solution of KCl at 25°C.}
\]
i. Since the chloride concentrations is 2 mol/L in both the micropipette and in the salt bridge, the potentials at the AgCl/KCl boundary is the same for both electrodes. Therefore, these two terms cancel to yield

\[ V_i = V_{KCl/cyt} + V_{m}^0 - V_{KCl/bath}. \]

ii. If the salt bridge at the reference electrode is removed then the contribution from the two AgCl/KCl is

\[ (222 - (RT/F) \ln c_{cyl}^b) - (222 - (RT/F) \ln c_{cyt}^b) = (RT/F) \ln \left( \frac{c_{cyl}^b}{c_{cyt}^b} \right). \]

where \( c_{cyl}^b \) and \( c_{cyt}^b \) are the concentrations in the micropipette and bath, respectively. Without the salt bridge, the junction potentials at the AgCl/KCl boundaries make a net contribution to the measured potential that depends upon the chloride concentration. This argument emphasizes the importance of using salt bridges to measure cellular potentials.

**Problem 7.4** The derivation given here is based on one given elsewhere (Patlak, 1960).

a. As stated in the problem, \( \phi_n^i = \frac{p_i^c c_i^c}{n} \) and \( \phi_n^o = \frac{p_o^c c_o^c}{n} \) where \( \frac{p_i^c}{n} \) and \( \frac{p_o^c}{n} \) are independent of concentration. Therefore,

\[ \frac{\phi_n^i}{\phi_n^o} = \frac{p_i^c c_i^c}{p_o^c c_o^c}. \]

Let \( \hat{c}_n^o \) be the outside concentration of ion \( n \) when it is in electrodiffusive equilibrium across the membrane in the presence of a membrane potential \( V_m \). Because the efflux and influx of ion \( n \) are equal at electrodiffusive equilibrium,

\[ 1 = \frac{p_i^c c_i^c}{p_o^c c_o^c}. \]

Therefore, since \( V_m \) equals the Nernst potential when the external concentration is \( \hat{c}_n^o \),

\[ \frac{p_i^c}{p_o^c} = \frac{\hat{c}_n^o}{c_n^c} = e^{(z_n F/RT)V_m}. \]

Substitution of this result into the ratio of unidirectional fluxes yields

\[ \frac{\phi_n^i}{\phi_n^o} = \frac{c_i^c}{c_o^c} e^{(z_n F/RT)V_m} = e^{(-z_n F/RT)V_m} e^{(z_n F/RT)V_m} = e^{(z_n F/RT)(V_m - V_n)}. \]

b. The outward current density due to ion \( n \) is \( J_n = z_n F (\phi_n^i - \phi_n^o) \). Under resting conditions, \( \sum_n J_n = 0 \) and \( V_m = V_m^0 \). Since the ions are all univalent, the valence can be dropped and the summation separated into two summations: one for the cations alone and the other for the anions,

\[ \sum_{+n} J_n + \sum_{-n} J_n = 0, \]
where the lower limit of the summation is used in a non-standard manner; $+n$ means a summation on all cations, and $-n$ means a summation on all anions. The fluxes can be substituted for the current densities and Faraday’s constant can be factored out to yield

$$\sum_{+n}(\phi_n - \phi_n) - \sum_{-n}(\phi_n - \phi_n) = 0.$$ 

This relation can be rewritten as

$$\sum_{+n} \phi_n \left( \frac{\phi_n}{\phi_n} - 1 \right) + \sum_{-n} \phi_n \left( \frac{\phi_n}{\phi_n} - 1 \right) = 0,$$

$$\sum_{+n} P_n^o c_n^o \left( \frac{c_n^i}{c_n^o} e^{(F/RT)\nu_m} - 1 \right) + \sum_{-n} P_n^i c_n^i \left( \frac{c_n^o}{c_n^i} e^{(F/RT)\nu_m} - 1 \right) = 0,$$

$$e^{F/(RT)\nu_m} \left( \sum_{+n} P_n^o c_n^o + \sum_{-n} P_n^i c_n^i \right) - \left( \sum_{+n} P_n^o c_n^o + \sum_{-n} P_n^i c_n^i \right) = 0.$$ 

Therefore,

$$e^{F/(RT)\nu_m} = \frac{\sum_{+n} P_n^o c_n^o + \sum_{-n} P_n^i c_n^i}{\sum_{+n} P_n^o c_n^o + \sum_{-n} P_n^i c_n^i},$$

from which

$$\nu_m^o = \frac{RT}{F} \ln \left( \frac{\sum_{+n} P_n^o c_n^o + \sum_{-n} P_n^i c_n^i}{\sum_{+n} P_n^o c_n^o + \sum_{-n} P_n^i c_n^i} \right).$$

Note that for the special case $P_n^i = P_n^o = P_n$, the expression becomes

$$\nu_m^o = \frac{RT}{F} \ln \left( \frac{\sum_{+n} P_n c_n^o + \sum_{-n} P_n c_n^i}{\sum_{+n} P_n c_n^o + \sum_{-n} P_n c_n^i} \right),$$

which is the same as the potential derived from the Goldman theory.

**Problem 7.5**

a. Because, the membrane is thin compared to the radius of the cell, the capacitance can be approximated by that of a parallel plate capacitance,

$$C = \frac{\kappa_m \epsilon_o A}{d},$$

where $C$ is the capacitance, $\kappa_m$ is the dielectric constant, $\epsilon_o$ is the permittivity of free space, $A$ is the area of each plate, and $d$ is the distance between the plates. Hence,

$$\kappa_m = \frac{C \cdot d}{A \cdot \epsilon_o} = C_m \frac{d}{\epsilon_o} = (10^{-2} \text{ F/m}^2) \times \frac{70 \times 10^{-10} \text{ m}}{8.854 \times 10^{-12} \text{ F/m}} = 7.9$$

Dielectric constants of oils and waxes are typically in the range 2-5 and those of glasses are in the range 3-10. Water has a dielectric constant of 81. Thus, the dielectric constant estimated above is closer to that of glasses than of oils and waxes. However, there is some uncertainty in our estimate. For example, the
CHAPTER 7. ION TRANSPORT AND RESTING POTENTIAL

thickness of the membrane was chosen as 70 Å. The hydrophobic region of the lipid bilayer may be somewhat smaller than that. If the hydrophobic portion of the membrane is taken to have a thickness of 50 Å, then the estimate of the dielectric constant is 5.6 which is near the range of oils and waxes.

b. The magnitude of the electric field in the membrane is \( |V_m^0|/d = 70 \times 10^{-3}/70 \times 10^{-10} = 10^7 \text{ V/m} \). This is two orders of magnitude greater than the dielectric strength of air. Oils have dielectric strengths of about \( 10^7 \text{ V/m} \) and glasses have dielectric strengths of about \( 10^8 \text{ V/m} \).

c. The surface charge per unit area on the inside of the membrane is

\[
Q = C_m V_m^0 = -10^{-6} \text{ F/cm}^2 \times 70 \times 10^{-3} \text{ V} = -70 \text{ nC/cm}^2.
\]

Therefore, the total charge on the inside surface of the membrane is

\[
q_s = QA = -70 \text{ nC/cm}^2 \times 4\pi (25 \times 10^{-4})^2 \text{ cm}^2 = -5.5 \text{ pC}.
\]

This surface charge can be compared to the total quantity of charge due to potassium ions in the cell.

\[
q_i^K = \rho_i^K V = F c_i^K V = (9.65 \times 10^4 \text{ C/mol})(0.2 \times 10^{-3} \text{ mol/cm}^3)((4/3)\pi (25 \times 10^{-4})^3 \text{ cm}^3)
\]

\[
= 1.26 \mu\text{C}.
\]

Therefore, the ratio \( q_s/q_i^K = 5.5 \times 10^{-12}/1.26 \times 10^{-6} = 4.4 \times 10^{-6} \), i.e., the surface charge is a very small fraction of the total charge available in the cell.

d. The resistance of the membrane is

\[
R_m = \frac{\rho_m d}{A} \quad \text{so that} \quad \rho_m = \frac{R_m A}{d} = \frac{R_m d}{A}.
\]

Hence,

\[
\rho_m = (10^3 \text{ } \Omega \cdot \text{cm}^2)/(70 \times 10^{-8} \text{ cm}) = 1.4 \times 10^9 \text{ } \Omega \cdot \text{cm}.
\]

The resistivity in \( \Omega \cdot \text{cm} \) is about \( 10^{-6} \) for copper, \( >10^{13} \) for insulators and about \( 10^3-10^5 \) for semi-conductors.

e. The Nernst equilibrium potential for potassium is

\[
V_K = 59 \log_{10} \left( \frac{c_K^0}{c_K^i} \right) = 59 \log_{10} \left( \frac{0.002}{0.2} \right) = -118 \text{ mV}.
\]

f. At rest \( J_C = C_m (dV_m(t)/dt) = 0 \). Therefore, \( J_K^p + J_K^a = 0 \). Hence,

\[
J_K^a = -J_K^p = -G_K (V_m - V_K) = -10^{-3}(-70 + 118) \times 10^{-3} = -48 \mu\text{A/cm}^2.
\]
g. If $J_K^d = 0$ then the membrane potential changes from $-70$ mV to the potassium equilibrium potential $-118$ mV. This change in potential accompanies a change in the surface charge on the membrane from $-5.5$ pC to $-5.5(-118/-70) = -9.3$ pC. Since the membrane is permeable to potassium only, a net amount of potassium of $9.3 - (5.5) = 3.8$ pC must have crossed the membrane from the inside to the outside to account for the change in potential. This represents a fractional change of potassium charges of $-3.8 \times 10^{-12}/1.26 \times 10^{-6} = -3 \times 10^{-6}$. Therefore, the percentage change in potassium concentration is $-0.003\%$.

Problem 7.6

a. The drift velocity is $\nu = u_K z_K F E$. Hence, when $\nu > 0$, $E > 0$ as shown in Figure 7.9.

b. Equation 7.58 (Weiss, 1996a) shows that at any time, the concentration has a maximum at $x - \nu t = 0$ and the amplitude is reduced by $1/e$ for $(x_w - \nu t)^2 = 4D_K t$. Call $x_w - \nu t = \Delta x_w(t)$. Therefore, $x_w$ is the position at which the concentration is $1/e$ of its maximum value, and $\Delta x_w(t)$ is the width of the concentration from the location of the maximum to the location $x_w$ at time $t$. Since $(\Delta x_w(t))^2 = 4D_K t$, the change in width between two times $t_0$ and $t_1$ is $(\Delta x_w(t_1))^2 = (\Delta x_w(t_0))^2 + 4D_K (t_1 - t_0)$. The data in Figure 7.10 shows the count rate versus position (data points) and a Gaussian curve fit to the data points. Because the curve averages over the data points, the diffusion coefficient will be estimated from the curve. As indicated in Figure 7.10, the widths can be estimated for the two times so that

$$D_K = \frac{(\Delta x_w(t_1))^2 - (\Delta x_w(t_0))^2}{4(t_1 - t_0)} = \frac{(1.43 \times 10^{-2})^2 - (0.87 \times 10^{-2})^2}{4 \cdot 445 \cdot 60} = 1.2 \times 10^{-9} \text{ m}^2/\text{s}.$$

c. Both the diffusion coefficient and the mobility can be estimated from the measurements in the presence of an electric field. The diffusion coefficient can be estimated as in part b, although because these measurements are taken over a shorter time, the estimate based on the figure alone will be quite inaccurate. The inaccuracy occurs because the difference of the squares of the widths of the concentrations must be determined and these widths are difficult to read accurately
from the figure. The estimate of the diffusion coefficient is

\[ D_K = \frac{(\Delta x_W(t_1))^2 - (\Delta x_W(t_0))^2}{4(t_1 - t_0)} \]

\[ = \frac{(1.0 \times 10^{-2})^2 - (0.84 \times 10^{-2})^2}{4 \cdot 37 \cdot 60} = 3.3 \times 10^{-9} \text{ m}^2/\text{s}. \]

The mobility can be estimated from the change in location of the peak value of the concentration. As shown in Figure 7.11, the peak moves from near 1.9 cm to near 2.6 cm, a distance estimated to be about 0.66 cm, in 37 minutes. Therefore, the drift velocity is

\[ \nu = \frac{0.66 \times 10^{-2}}{37 \times 60} = 3.0 \times 10^{-6} \text{ m/s}. \]

From the relation that \( \nu = u_K z_K F \mathcal{E} \), the mobility is estimated as

\[ u_K = \frac{\nu}{F \mathcal{E}} = \frac{3.0 \times 10^{-6} \text{ m/s}}{(9.65 \times 10^4 \text{ C/mol}) \cdot (54.8 \text{ V/m})} = 5.7 \times 10^{-13} \text{ (m/s)/(N/mol)} \]
d. The diffusion coefficient is related to the mobility by the Einstein relation. Therefore, the diffusion coefficient can be calculated from the estimated mobility as follows

\[ D = uRT = (5.7 \times 10^{-13})(8.314)(300) = 1.4 \times 10^{-9} \text{ m}^2/\text{s}. \]

This value agrees within 15% with the estimate of the diffusion coefficient in part b but differs appreciably from the more inaccurate estimate of the diffusion coefficient obtained in part c.

Problem 7.7

a. The network with passive transport only consists of the capacitance in parallel with the two conductances. The time course of the response of this network is given by the passive time constant

\[ \tau_p = \frac{C}{G_{Na} + G_K} = \frac{10^{-9} \text{ F}}{(5 \times 10^{-9} + 5 \times 10^{-7}) \text{ S}} \approx 2 \text{ ms}. \]

This time constant is much faster than the time course of the response to the injection which has a time constant of 5 minutes. Hence, for the measured membrane potential shown, the rate of change of membrane potential is so small that the current through the capacitance is negligible compared to that through the other branches. Hence, the membrane capacitance can be ignored for the remainder of this problem. The measured time constant cannot be accounted for by the passive network.

Can we account for the magnitude of the change in membrane potential by passive transport alone? The membrane potential is

\[ V_m = \left( \frac{G_{Na}}{G_{Na} + G_K} \right) V_{Na} + \left( \frac{G_K}{G_{Na} + G_K} \right) V_K - \frac{I_{Na}^a + I_K^a}{G_{Na} + G_K}. \]

Since \( I_{Na}^a, I_K^a, \) and \( V_K \) are constant during the injection of sodium,

\[ V_m(t) - V_m(0) = \Delta V_m(t) = \left( \frac{G_{Na}}{G_{Na} + G_K} \right) \Delta V_{Na}(t) \approx 10^{-2} \Delta V_{Na}(t). \]

Therefore, the change in the sodium equilibrium potential is 100 times larger than the change in membrane potential. Since the change in membrane potential is 16 mV, the sodium equilibrium potential would have to change by 1.6 V! Is this consistent with the experiment?

\[
\Delta V_{Na}(t) = \frac{RT}{F} \ln \left( \frac{c_{Na}^0}{c_{Na}(t)} \right) - \frac{RT}{F} \ln \left( \frac{c_{Na}^0}{c_{Na}(0)} \right) = - \frac{RT}{F} \ln \left( \frac{c_{Na}^i(t)}{c_{Na}^i(0)} \right),
\]

\[
= - \frac{RT}{F} \ln \left( \frac{\Delta c_{Na}(t) + c_{Na}^i(0)}{c_{Na}(0)} \right) = - \frac{RT}{F} \ln \left( \frac{\Delta c_{Na}(t)}{c_{Na}^i(0) + 1} \right),
\]

\[
\approx -60 \log_{10} \left( \frac{\Delta c_{Na}(t)}{c_{Na}^i(0) + 1} \right) \text{ mV}.
\]
The quantity $\Delta c_{Na}^i(t)/c_{Na}^i(0)$ can be computed for $t = 0.5 \text{ min} = 30 \text{ s}$ from the data given. $c_{Na}^i(0) = 6 \times 10^{-6} \text{ mol/cm}^3$ and

$$\Delta c_{Na}^i(30) = \frac{(48 \times 10^{-12} \text{ mol/min})(0.5 \text{ min})}{4 \times 10^{-6} \text{ cm}^3} = 6 \times 10^{-6} \text{ mol/cm}^3 = c_{Na}^i(0).$$

Therefore,

$$\Delta V_{Na}(30) \approx -60 \log_{10} \left( \frac{6 \times 10^{-6}}{6 \times 10^{-6} + 1} \right) = -60 \log_{10} 2 \approx -18 \text{ mV}.$$

Hence, the change in $V_{Na}$ is much too small to account for the measured change in membrane potential. Therefore, passive transport alone cannot account for either the time constant or the magnitude of the response to the injection of sodium.

b. In part a it was shown that

$$V_m = \frac{1}{G_{Na} + G_K} \left( G_{Na} V_{Na} + G_K V_K - (I_{Na}^a + I_{K}^a) \right),$$

but that a change in $V_{Na}$ cannot account for the change in $V_m$. The point of this part is to determine whether a change in $I_{Na}^a$ can account for the change in $V_m$. Conservation of sodium requires that a change in sodium concentration must be due to a change in sodium current

$$\gamma_c \frac{d\Delta c_{Na}^i(t)}{dt} = -\frac{\Delta I_{Na}^a(t)}{F} = -\frac{\gamma_c}{\tau_a} \Delta c_{Na}^i(t).$$

This equation reduces to

$$\frac{d\Delta c_{Na}^i(t)}{dt} + \frac{\Delta c_{Na}^i(t)}{\tau_a} = 0,$$

which is a first-order, linear, ordinary differential equation whose homogeneous solution is exponential with time constant $\tau_a$,

$$\Delta c_{Na}^i(t) = c_{Na}^i(30)e^{(t-30)/\tau_a} \text{ for } t > 30 \text{ s}.$$

The change in active sodium current can be found from the change in concentration,

$$\Delta I_{Na}^a(t) = \frac{F \gamma_c}{\tau_a} \Delta c_{Na}^i(t) = \frac{F \gamma_c}{\tau_a} c_{Na}^i(30)e^{(t-30)/\tau_a} \text{ for } t > 30 \text{ s}.$$

The membrane potential change is related to the change in active sodium current so that

$$\Delta V_m = -\frac{\Delta I_{Na}^a(t)}{G_{Na} + G_K} = \frac{F \gamma_c}{\tau_a(G_{Na} + G_K)} c_{Na}^i(30)e^{(t-30)/\tau_a} \text{ for } t > 30 \text{ s}.$$

If we choose $\tau_a = 5 \cdot 60 \text{ s}$,

$$\Delta V_m \approx -\frac{(10^5 \text{ C/mol})(4 \times 10^{-6} \text{ cm}^3)(6 \times 10^{-6} \text{ mol/cm}^3)}{(5 \cdot 60 \text{ s})(0.5 \times 10^{-6} \text{ S})} \approx -16e^{(t-30)/300} \text{ mV, for } t > 30 \text{ s},$$

Thus, the model with active sodium transport can account for the measurements.
Problem 7.8

a. Patch 1 contains two conductances each of value \( G \) and each equilibrium potential is zero because solution A has the same composition as intracellular solution. Patch 2 contains a potassium conductance whose value is \( G \) and an equilibrium potential that has the value 

\[
V_K = 59 \log_{10} \left( \frac{c_B^{K}}{c_K^0} \right) \text{ mV} = 59 \log_{10} \left( \frac{15}{150} \right) = -59 \text{ mV}.
\]

The circuit is shown in Figure 7.12.

b. Thus, the resting potential is the potassium equilibrium potential divided by the resistive divider network,

\[
V_m^o = \frac{1/(2G)}{1/(2G) + 1/G} V_K = \frac{V_K}{3} = -19.7 \text{ mV}.
\]

Problem 7.9

a. The cell has passive and active transport of both sodium and potassium. Hence, an appropriate model for the resting potential of the cell is the one given in Figure 7.13. The resting potential can be derived by superposition of the contributions of each source with the other sources set to zero which yields

\[
V_m^o = \frac{G_{Na}}{G_{Na} + G_K} V_{Na} + \frac{G_K}{G_{Na} + G_K} V_K - \frac{1}{G_{Na} + G_K} (I_{Na}^a + I_{K}^a),
\]

with the direct contribution of active transport to the resting membrane potential identified. The active transport currents are

\[
I_{Na}^a = z_{Na} F \phi_{Na} = 1 \cdot (9.65 \times 10^4) \cdot (3 \times 10^{-17}) \approx 3 \text{ pA},
\]

\[
I_{K}^a = z_K F \phi_K = 1 \cdot (9.65 \times 10^4) \cdot (-2 \times 10^{-17}) \approx -2 \text{ pA}.
\]
Therefore, the active component of the membrane potential is

\[ V_{ma}^o = -\frac{(3 - 2) \times 10^{-12}}{10^{-10}} = -10 \text{ mV}. \]

b. Because the cell is at equilibrium, \( I_{Na}^p + I_{Na}^a = 0 \) and \( I_K^p + I_K^a = 0 \). Therefore,

\[
\begin{align*}
I_{Na}^p &= -3 \times 10^{-12} = G_{Na}(V_m^o - V_{Na}), \\
I_K^p &= 2 \times 10^{-12} = G_K(V_m^o - V_K).
\end{align*}
\]

The Nernst equilibrium potentials can be computed

\[
\begin{align*}
V_{Na} &= 59 \log_{10} \frac{106}{15} \approx 50 \text{ mV}, \\
V_K &= 59 \log_{10} \frac{3}{150} \approx -100 \text{ mV}.
\end{align*}
\]

Combining these results yields

\[
\begin{align*}
G_{Na} &= \frac{-3 \times 10^{-12}}{(V_m^o - 50) \times 10^{-3}}, \\
G_K &= \frac{2 \times 10^{-12}}{(V_m^o + 100) \times 10^{-3}},
\end{align*}
\]

where \( V_m^o \) is expressed in mV. In addition,

\[ G_{Na} + G_K = 10^{-10} \text{ S}. \]

Combining these equations to eliminate \( G_{Na} \) and \( G_K \) yields

\[
\frac{-3 \times 10^{-12}}{(V_m^o - 50) \times 10^{-3}} + \frac{2 \times 10^{-12}}{(V_m^o + 100) \times 10^{-3}} = 10^{-10},
\]

which can be manipulated to give

\[
(V_m^o)^2 + 60V_m^o - 1000 = 0,
\]

and has two solutions \( V_m^o = -30(1 \pm 1.45) \) mV. The two values are \(-73.5 \) and \(+13.5 \) mV. Since \( G_K > G_{Na} \), the resting potential must be nearer to \( V_K \) than to \( V_{Na} \) so that the resting potential must be \( V_m^o = -73.5 \) mV.
c. The conductances can be computed as follows

\[ G_{Na} = \frac{-3 \times 10^{-12}}{(-73.5 - 50) \times 10^{-3}} = 24.3 \text{ pS}, \]
\[ G_{K} = \frac{2 \times 10^{-12}}{(-73.5 + 100) \times 10^{-3}} = 75.5 \text{ pS}. \]

**Problem 7.10** The direction of passive transport of each ion can be determined using the relations

\[ J_n = G_n(V_m^o - V_n) \]

where \( V_n = \frac{RT}{z_n F} \ln \left( \frac{c_n^o}{c_n^i} \right) \).

The Nernst equilibrium potential for each ion is

\[ V_{Na} = 59 \log_{10} \frac{0.1}{15} = -128 \text{ mV}, \]
\[ V_{K} = 59 \log_{10} \frac{1}{28.7} = -86 \text{ mV}, \]
\[ V_{Cl} = 59 \log_{10} \frac{1.3}{38} = 86 \text{ mV}. \]

Hence,

\[ J_{Na} = G_{Na}(-86 + 128) \times 10^{-3} = G_{Na}(42 \times 10^{-3}), \]
\[ J_{K} = G_{K}(-86 + 86) \times 10^{-3} = 0, \]
\[ J_{Cl} = G_{Cl}(-86 - 86) \times 10^{-3} = -G_{Cl}(172 \times 10^{-3}). \]

Therefore, the passive current density carried by sodium is outward, which implies that the passive flux of current is outward. Hence, to maintain sodium concentration in sap, sodium must be transported inward by active transport mechanisms. The passive current density carried by potassium is zero. Hence, no active transport of potassium is needed. The passive current density carried by chloride is inward. The inward current carried by a negative ion implies an outward flux of chloride. Hence, chloride must be transported inward by an active transport mechanism to maintain chloride concentration in the sap.

**Problem 7.11**

The results from the two cells are analyzed separately for parts a and b.

**Cell 1** From the graphs it is apparent that Cell 1 acts as a perfect potassium electrode, i.e., the resting potential equals the potassium equilibrium potential and is independent of external sodium concentration. Therefore, \( G_{Na} = 0 \) and \( G_{K} = G_{m} = 10 \text{ nS}. \) Also, when \( V_m^o = -60 \text{ mV} \) (the normal resting potential), \( c_{K}^o = 20 \text{ mmol/L}. \) The value of \( c_{K}^i \) can be computed either by noting that \( V_m^o = V_K = 0 \) when \( c_{K}^o = c_{K}^i \) or by computing \( -60 = 60 \log_{10}(20/c_{K}^i). \) Either way, \( c_{K}^i = 200 \text{ mmol/L}. \) Since \( V_m^o \) is independent of \( c_{Na}^o, c_{Na}^i \) cannot be computed from these results. The results are shown in Table 7.1.
Cell 2 Since the resting potential depends on both $c_{Na}^0$ and $c_{K}^0$, the membrane is permeable to both ions. Since the pumps are non-electrogenic, the direct effect on the membrane potential can be ignored. Therefore,

\[ V_m^o = \frac{G_K}{G_K + G_{Na}} V_K + \frac{G_{Na}}{G_K + G_{Na}} V_{Na}, \]

which can be written as

\[ V_m^o \approx \frac{G_K}{G_K + G_{Na}} 60 \log_{10} \left( \frac{c_{K}^0}{c_{K}^i} \right) + \frac{G_{Na}}{G_K + G_{Na}} 60 \log_{10} \left( \frac{c_{Na}^0}{c_{Na}^i} \right). \]

From the graphs

\[ \frac{G_K}{G_K + G_{Na}} 60 = 48 \text{ mV/dec and } \frac{G_{Na}}{G_K + G_{Na}} 60 = 12 \text{ mV/dec}, \]

which can be solved to yield

\[ \frac{G_K}{G_K + G_{Na}} = \frac{48}{60} = 0.8 \text{ and } \frac{G_{Na}}{G_K + G_{Na}} = \frac{12}{60} = 0.2. \]

Therefore, $G_K/G_{Na} = 4$ satisfies both equations (which are not independent). Since $G_K + G_{Na} = 10 \text{ nS}$, $4G_{Na} + G_{Na} = 5G_{Na} = 10 \text{ nS and } G_{Na} = 2 \text{ nS and } G_K = 8 \text{ nS. Using these values}$

\[ V_m^o = 48 \log_{10} \left( \frac{c_{K}^0}{c_{K}^i} \right) + 12 \log_{10} \left( \frac{c_{Na}^0}{c_{Na}^i} \right). \]

But $c_{Na}^i = 20 \text{ mmol/L. Also from the graphs at } -60 \text{ mV, } c_{K}^{on} = 10 \text{ mmol/L, } c_{Na}^{on} = 200 \text{ mmol/L. Thus, only } c_{K}^i \text{ must be determined, and it can be determined from results at any membrane potential, i.e.,}$

\[ 0 = 48 \log_{10} \left( \frac{200}{c_{K}^0} \right) + 12 \log_{10} \left( \frac{200}{20} \right), \]

from which

\[ \log_{10} \left( \frac{200}{c_{K}^0} \right) = -\frac{12}{48} = -\frac{1}{4}, \]

which implies that $c_{K}^i = 356 \text{ mmol/L. The parameters are given in Table 7.1.}$
c. The networks are shown in Figure 7.14.

**Problem 7.12**

a. Because the cell membrane acts as a perfect potassium electrode, the resting potential of the cell must equal the potassium equilibrium potential,

\[ V_m^o = V_K = \frac{RT}{F} \ln \left( \frac{c_K^o}{c_K^i} \right) \approx 59 \log_{10} \left( \frac{15}{150} \right) = -59 \text{ mV}. \]

b. The membrane and the leakage path are in parallel as shown in Figure 7.4.

c. The membrane resistance is \( R_m = \frac{1}{(G_m A)} \) where \( G_m \) is the specific resistance of the membrane and \( A \) is the surface area of the cell. The membrane resistance is

\[ R_m = \frac{1}{(10^{-3} \text{ S/cm}^2)(4\pi(15 \times 10^{-4})^2 \text{ cm}^2} = 35.4 \text{ M\Omega}. \]

Since \( R_l = 100 \text{ M\Omega} \), the resting potential of the cell with the shunt resistance caused by the leakage path is

\[ V_m = \frac{100}{100 + 35.4} (-60) = -44.3 \text{ mV}. \]

d. The relation of the membrane potential to the Nernst equilibrium potential is

\[ V_m = \frac{100}{100 + 35.4} V_K = 0.74 \times 59 \log_{10} \left( \frac{c_K^o}{150} \right) = 43.6 \log_{10} c_K^o - 94.8 \text{ mV}, \]

where \( c_K^o \) is in mmol/L.

e. The effect of the shunt resistance is to reduce the slope of the relation of membrane potential to the logarithm of the external potassium concentration from 59 to 43.6 mV/decade of concentration. The exact value of this reduction depends upon the resistance of the leakage path. Note that the data for the frog skeletal muscle for concentration above 3 mmol/L shows a linear dependence of resting
potential on the logarithm of the external concentration of potassium with a slope less than that of a potassium electrode. This raises the question of whether the leakage path caused by the penetrating micropipette is in part responsible for these results.

Problem 7.13

a. The following apply to Adrian’s measurements.

i. For large values of \( c_k^o \) the measurements approach that of a perfect potassium electrode which implies that the membrane is permeant to potassium only. Therefore, the conductances for all other ions is zero. Thus, \( G_k = G_m = 2 \times 10^{-6} \, \text{S} \).

ii. Since, the membrane potential acts as a perfect potassium electrode at high extracellular concentration,

\[
V_m^o = V_k = \frac{RT}{F} \ln \left( \frac{c_k^o}{c_k^i} \right),
\]

so that \( V_m^o = 0 \) when the inside and outside concentrations are the same. Therefore, reading the extrapolation of the measurements to a potential of 0 mV yields \( c_k^i \approx 120 \, \text{mmol/L} \).

b. The following apply to Ling and Gerard’s measurements.

i. Clearly the data of Ling and Gerard do not conform to the predictions of a perfect potassium electrode even at high potassium concentration. Thus, ions in addition to potassium must flow between the inside and the outside of the cell. The additional flow of ions is represented by the network shown in Figure 7.15. In the absence of the micropipette, the measurements of Adrian suggest that for large values of \( c_k^o \) only potassium ions permeate the membrane. This pathway is represented by the potassium conductance in series with the Nernst equilibrium potential for potassium. It is hypothesized that insertion of the micropipette caused another pathway, a leakage pathway, for current to flow between the inside and the outside of the cell. Therefore, the
two currents, one due to potassium flowing through the membrane and the other due to ions flowing through the leak, are in parallel. An equivalent circuit for the leakage path consists of a conductance in series with a battery — a Thévenin’s equivalent network.

ii. The resting potential for the network model in Figure 7.15 is found by writing Kirchhoff’s current law, setting the total membrane current to zero, and solving for the membrane potential to obtain

$$V_m^o = \frac{G_K}{G_K + G_L} V_K + \frac{G_L}{G_K + G_L} V_L.$$  

This can be expressed in terms of the potassium concentration

$$V_m^o = \frac{G_K}{G_K + G_L} 58 \log_{10} \left( \frac{c_K^o}{c_K} \right) + \frac{G_L}{G_K + G_L} V_L \text{ mV}.$$  

Because the slope of $V_m^o$ versus $c_K^o$ is 44 mV/dec,

$$\frac{G_K}{G_K + G_L} = \frac{44}{58} = 0.76,$$

which can be solved to determine that $G_L/G_K = 0.32$. The total membrane conductance of the frog sartorius muscle fiber is given, and in part a it was determined that the total conductance of the muscle fiber is due to potassium. Thus, $G_K = 2 \times 10^{-6}$ and $G_L = 0.64 \times 10^{-6}$ s. Note that the value of $c_K^o$ for which $V_m^o = 0$ is approximately the same for both sets of measurements. At this concentration, the measurements of Adrian show that $V_K = 0$. Therefore, $V_L = 0$. This is a satisfying result, since the model for the hole caused by the puncture of the membrane is simply that of a shunt resistance with $V_L = 0$. Finally, $V_K = 58\log_{10}(c_K^o/c_K^i)$.

iii. Clearly the calculations support the hypothesis that the Ling and Gerard measurements at high potassium concentration behave as if they are compromised by the shunt resistance caused by the insertion of the micropipette. Although consistent with this hypothesis, the results do not prove the hypothesis.

iv. The model shown in Figure 7.15 cannot account for the saturation of the resting potential at low extracellular potassium concentration.

**Problem 7.14**

a. If the model involves only the passive transport of sodium and potassium then the network diagram is as shown in Figure 7.16. The circuit can be solved to yield

$$V_{EP} = \left( \frac{G_{Na}}{G_{Na} + G_K} \right) V_{Na} + \left( \frac{G_K}{G_{Na} + G_K} \right) V_K.$$  

This shows that $V_{EP}$ will be closest to the Nernst equilibrium potential of the more permeant ion. The Nernst equilibrium potential for each ion is required for a
quantitative analysis. At 38°C,

\[
V_{Na} = \frac{RT}{F} \ln \left( \frac{c_{Na}^p}{c_{Na}^e} \right) = 61 \log \left( \frac{140}{2} \right) = 113 \text{ mV},
\]

\[
V_{K} = \frac{RT}{F} \ln \left( \frac{c_{K}^p}{c_{K}^e} \right) = 61 \log \left( \frac{5}{150} \right) = -90 \text{ mV}.
\]

Thus, \( V_{EP} = 100 \text{ mV} \) is close to \( V_{Na} = 113 \text{ mV} \), which implies that \( G_{Na} \gg G_{K} \). A quantitative estimate of \( \gamma = G_{Na}/G_{K} \) can be obtained from the equation for \( V_{EP} \) which can be rewritten as

\[
100 = \left( \frac{\gamma}{\gamma + 1} \right) 113 - \left( \frac{1}{\gamma + 1} \right) 90 \text{ mV},
\]

which can be solved for \( \gamma = 14.6 \). Thus, the passive model can account for the value of \( V_{EP} \) provided that the conductance for sodium is 14.6 times that for potassium.

b. If passive transport of sodium and potassium accounts for \( V_{EP} \) with \( G_{Na}/G_{K} = 14.6 \) then

\[
V_{EP} = \left( \frac{14.6}{14.6 + 1} \right) V_{Na} + \left( \frac{1}{14.6 + 1} \right) V_{K} \text{ mV},
\]

\[
= \left( \frac{14.6}{14.6 + 1} \right) 61 \log \left( \frac{c_{Na}^p}{c_{Na}^e} \right) + \left( \frac{1}{14.6 + 1} \right) 61 \log \left( \frac{c_{K}^p}{c_{K}^e} \right) \text{ mV},
\]

\[
= 57 \log \left( \frac{c_{Na}^p}{c_{Na}^e} \right) + 3.9 \log \left( \frac{c_{K}^p}{c_{K}^e} \right) \text{ mV}.
\]

Therefore, the model predicts that a change in concentration of sodium in perilymph from 140 to 40 mmol/L should result in a change in \( V_{EP} \) of

\[
\Delta V_{EP} = 57 \log \left( \frac{40}{2} \right) - 57 \log \left( \frac{140}{2} \right) = 57 \log \left( \frac{40}{140} \right) = -31 \text{ mV}.
\]

Also a change in concentration of potassium from 5 to 1 mmol/L should result in a change in \( V_{EP} \) of

\[
\Delta V_{EP} = 3.9 \log \left( \frac{1}{150} \right) - 3.9 \log \left( \frac{5}{150} \right) = 3.9 \log \left( \frac{1}{5} \right) = -2.7 \text{ mV}.
\]
These predictions of the passive model are not consistent with the results shown. Hence, the passive model does not account for the effect of a change in ion concentration on $V_{EP}$.

c. Part b shows that a model with purely passive transport does not account for the results. Furthermore, since a change in the sodium concentration results in only a small change in $V_{EP}$, and a change in potassium concentration results in a large change in $V_{EP}$, a model that includes potassium transport is required. The simplest model that involves both active and passive potassium transport is shown in Figure 7.17. According to this model, at rest $I_P^P + I_a^a = 0$ so that $G_K(V_{EP} - V_K) + I_a^a = 0$ which can be solved for $V_{EP} = V_K - I_a^a / G_K$. Therefore, according to this model

$$V_{EP} = 61 \log \left( \frac{c_K^p}{c_K^e} \right) - \frac{I_a^a}{G_K} \text{ mV.}$$

Now how does this model compare with the measurements? Note that for $c_K^p = 5$ mmol/L, $V_K = 61 \log(5/150) = -90 \text{ mV}$. This implies that for $V_{EP} = 100 \text{ mV}$, $I_a^a / G_K = V_K - V_{EP} = -90 - 100 = -190 \text{ mV}$. Then, when the solution is changed so that $c_K^p = 1$ mmol/L, $V_K = 61 \log(1/150) = -133 \text{ mV}$, $V_{EP} = -133 + 190 = 57 \text{ mV}$. This prediction of the model with both active and passive potassium transport fits approximately with the experiments that are given.

**Problem 7.15**

a. Because the pump transports 3 sodium molecules out and 2 potassium molecules into the cell for each molecule of ATP split, the pump transfers net charge. Hence, this is inherently an electrogenic pump. However, the pump does not necessarily make a large contribution to the normal resting potential of the cell.

b. An electric network model for the cell is shown in Figure 7.18. The resting potential of the cell is obtained from the relation

$$V_m^o = \frac{G_K}{G_K + G_{Na}} V_K + \frac{G_{Na}}{G_K + G_{Na}} V_{Na} - \frac{J_{K}^{g} + J_{Na}^{a}}{G_{K} + G_{Na}}.$$

Figure 7.17: Model for the endolymphatic potential including active potassium transport (Problem 7.14).
Note that because \( G_K \gg G_{Na} \), the contribution of the sodium equilibrium potential to the resting potential is small. The contribution of the potassium equilibrium potential to the resting potential is easily computed. Because, \( G_K \gg G_{Na} \), \( G_K / (G_K + G_{Na}) \approx 1 \) and

\[
V_K = 59 \log_{10} \left( \frac{c_K^o}{c_K^i} \right) = 59 \log_{10} \left( \frac{15}{156} \right) = -60 \text{ mV}.
\]

Therefore, \( V_m^o \approx V_K \), and the pump makes no contribution to the normal resting potential.

c. The results are interpreted as follows: injection of sodium stimulates the pump and this causes a contribution of \(-20 \text{ mV}\) to the resting potential. Hence, if \( \alpha \) is the utilization of ATP by the pump in a unit area of membrane per second,

\[
\Delta V_m^o = - \frac{J_K^a + J_{Na}^a}{G_K + G_{Na}}
\]

\[
= - \frac{F \phi_K^a + \phi_{Na}^a}{G_K + G_{Na}}
\]

\[
= - \frac{-2\alpha + 3\alpha}{G_K + G_{Na}} = - \frac{2\alpha}{G_K + G_{Na}} \approx - \frac{\alpha F}{G_K}
\]

Therefore,

\[
\alpha \approx - \frac{\Delta V_m^o G_K}{F} = \frac{(20 \times 10^{-3})(1 \times 10^{-3})}{9.65 \times 10^4} = 2.1 \times 10^{-10} \text{ mol/(cm}^2 \cdot \text{s}).
\]

**Problem 7.16**

a. If there is no net hydrogen ion transport at rest, the hydrogen ion concentration ratio must have a Nernst equilibrium potential of \(-70 \text{ mV}\),

\[
-70 = 59 \log_{10} \frac{c_H^o}{c_H^i} = 59 \log_{10} c_H^o - 59 \log_{10} c_H^i.
\]

The pH of the extracellular and intracellular solutions are expressed in terms of the concentrations as

\[
\text{pH}_o = 7.3 = - \log_{10} c_H^o \text{ and pH}_i = - \log_{10} c_H^i
\]
where the concentration are expressed in mol/L. A combination of these equations yields

\[-\frac{70}{59} = -1.19 = \text{pH}_i - \text{pH}_o.\]

Therefore, \(\text{pH}_i = -1.19 + 7.3 = 6.11\). Thus, the intracellular pH is acidic under these conditions.

b. Since hydrogen is not at equilibrium at rest and since the pH of cells is constant, there must be additional hydrogen transporting mechanisms in cellular membranes.

**Problem 7.17** To determine the validity of the suggestion, the work required to move sodium out of the cell against the electrical and chemical gradients must be computed. Equation 7.92 (Weiss, 1996a) gives a formula for the free energy required.

\[
\Delta \mathcal{G}_{Na} = -\nu_{Na} F V_m^o + \nu_{Na} R T \ln \left( \frac{c_{Na}^o}{c_{Na}} \right),
\]

\[
= -4 \times (9.65 \times 10^4) (-70 \times 10^{-3}) + 4 \times (8.314) (300) \ln 8,
\]

\[
= 2.7 \times 10^4 + 2.1 \times 10^4 \text{ J/mol} = 48 \text{ kJ/mol}.
\]

Hence, the energy per mole required to pump out sodium exceeds that available from hydrolysis of ATP. Dr. Tropsnart’s model is not energetically feasible.

**Problem 7.18**

a. As indicated in the solution to Problem 7.6, the mobility can be determined from the drift velocity.

i. Figure 7.19 shows that the center of the count rate distribution has moved slightly to the left of the center of the initial injection region. The displacement is at most 0.3 mm.

ii. Therefore, an upper bound on the drift velocity is

\[\nu = \frac{3 \times 10^{-4}}{(159 \times 60)} \text{ m/s} = 3.1 \times 10^{-8} \text{ m/s},\]
and an upper bound on the molar mechanical mobility is

\[ u_{Ca} = \frac{\nu}{FE} = \frac{3.1 \times 10^{-8}}{(9.65 \times 10^4 \text{ C/mol}) \cdot (51 \text{ V/m})} = 6.3 \times 10^{-15} \text{ (m/s)/(N/mol)}. \]

iii. According to Table 7.2, the molar mechanical mobility for calcium in water (at infinite dilution and at 25°C) is \( 1.60 \times 10^{-13} \text{ (m/s)/(N/mol)} \). Therefore, the estimate based on the data in Figure 7.19 shows that the mobility of calcium in axoplasm is less than 4% that in water. More extensive measurements (Hodgkin and Keynes, 1957) suggest that the mobility of calcium in axoplasm is less than 2% of that in water.

b. The diffusion coefficient can be obtained from the width of the count rate distribution. At time 159 minutes after injection, the curve that fits the measurements has the parameter \( 2\sqrt{Dt} = 0.262 \text{ cm} \). Therefore,

\[ D = \frac{(0.131 \times 10^{-2})^2}{159 \cdot 60} = 1.8 \times 10^{-10} \text{ m}^2/\text{s}. \]

According to Table 7.2, the diffusion coefficient for calcium in water (at infinite dilution and at 25°C) is \( 0.4 \times 10^{-9} \text{ m}^2/\text{s} \). Therefore, the estimate based on the data in Figure 7.19 shows that the diffusion coefficient of calcium in axoplasm is less than 45% that in water. More extensive measurements (Hodgkin and Keynes, 1957) suggest that the diffusion coefficient of calcium in axoplasm is about 10% of that in water.

c. Both the diffusion coefficient and the mobility of calcium in axoplasm are lower than in water. This likely results because calcium binds to a number of different intracellular components and is not free to diffuse.

Problem 7.19

a. The answer is vi. Since the concentration of chloride in the cell is constant, there is no flux of chloride across the cell membrane. Since there is no flux of chloride, there is no chloride current, and the resting potential is independent of the chloride conductance \( G_{CI} \) and the Nernst equilibrium potential for chloride, \( V_{Cl} \). The membrane potential is determined entirely by the flow of sodium and potassium ions. If that membrane potential did not equal the Nernst equilibrium potential for chloride, then chloride ions would flow passively across the membrane and alter the internal concentration of chloride until the chloride equilibrium potential equalled the membrane potential.

b. If the concentration of sodium and potassium in the cell are constant, then there can be no net flux of either ion. Therefore,

\[
G_{Na}(V_m^o - V_{Na}) + I_{Na}^a = 0, \\
G_{K}(V_m^o - V_K) + I_{K}^a = 0.
\]
Combining these equations yields
\[ \frac{g_{Na}(V_m^o - V_{Na})}{g_{K}(V_m^o - V_{K})} = \frac{I_{Na}^d}{I_{K}^d}. \]

This equation can be expressed in terms of the dimensionless ratios \( \gamma = \frac{g_{Na}}{g_{K}} \) and \( \alpha = -\frac{I_{Na}^d}{I_{K}^d} \) as
\[ \frac{g_{Na}(V_m^o - V_{Na})}{g_{K}(V_m^o - V_{K})} = -\alpha. \]

Cross multiplying and combining terms yields the solution
\[ V_m^o = \frac{\gamma V_{Na} + \alpha V_{K}}{\gamma + \alpha}. \]

This result demonstrates the validity of the argument given in part a, namely that \( V_m^o \) is independent of \( g_{Cl} \) and \( V_{Cl} \). Using the numerical values provided yields
\[ V_m^o = \frac{0.1 \cdot 68 + 1.5 \cdot (-68)}{0.1 + 1.5} = -59.5 \text{ mV}. \]

c. Reduction of the external concentration of chloride from 150 to 50 mmol/L changes the Nernst equilibrium potential for chloride as follows
\[ \Delta V_{Cl} = \frac{-RT}{F} \ln \left( \frac{50}{c_{Cl}^i(0+)} \right) - \frac{-RT}{F} \ln \left( \frac{150}{c_{Cl}^i(0-)} \right) = \frac{RT}{F} \ln \left( \frac{150}{50} \right), \]

if it is assumed that the intracellular concentration of chloride does not change instantaneously, i.e., \( c_{Cl}^i(0+) = c_{Cl}^i(0-) \). The temperature is not given, but the concentrations and the Nernst equilibrium potentials for sodium and potassium are given. Therefore,
\[ 68 = \frac{RT}{F \log_{10} e} \log \left( \frac{140}{10} \right), \]

which shows that the \( RT/(F \log_{10} e) \approx 59 \text{ mV} \). Therefore,
\[ \Delta V_{Cl} = 59 \log \left( \frac{150}{50} \right) \approx 28 \text{ mV}. \]

i. The change in \( V_m^o \) that results from a sudden change in the chloride equilibrium potential of 28 mV can be determined easily by superposition. The contribution of the chloride equilibrium potential to \( V_m^o \) is simply \( (g_{Cl}/g_m) V_{Cl} \). Therefore, the change in \( V_m^o \) that results from a change in \( V_{Cl} \) is
\[ \Delta V_m^o = \frac{g_{Cl}}{g_m} \Delta V_{Cl} = \frac{1}{1 + 1 + 0.1} \cdot 28 = 13.3 \text{ mV}. \]

Therefore, \( V_m^o(0+) = -59.5 + 13.3 = -46.2 \text{ mV} \).

ii. Since the equilibrium value of the resting potential is independent of chloride concentration, it must be that \( V_m^o(\infty) = -59.5 \text{ mV} \).
iii. After the cell has equilibrated, the chloride equilibrium potential adjusts itself to the resting potential. Therefore,

\[-59.5 = -59 \log \left( \frac{50}{c_{Cl}^l(\infty)} \right),\]

so that \(c_{Cl}^l(\infty) \approx 5\) mmol/L.

iv. The fundamental idea is that since chloride is transported only passively across the membrane, at equilibrium the Nernst equilibrium potential for chloride must equal the resting potential. The resting potential is determined by the passive and active transport of sodium and potassium only. Therefore, any change in chloride concentration causes a transient change in the membrane potential which is restored to its original value by a net flow of sodium and potassium ions. The resulting change in potential drives a flow of chloride ions so that chloride will once again be in equilibrium with the resting potential.

Further discussion of problem

To analyze this problem more completely, let us determine the intracellular chloride concentration when the extracellular concentration is 150 mmol/L which is

\[-59.5 = -59 \log \left( \frac{150}{c_{Cl}^l(0+)} \right),\]

so that \(c_{Cl}^l(0+) \approx 15\) mmol/L. With 150 mmol/L of external chloride the cell is in equilibrium with an intracellular concentration of chloride of 15 mmol/L. With a sudden reduction in extracellular chloride concentration, the system is taken out of equilibrium and the chloride equilibrium potential is increased by 28 mV which results in a change in the potential across the membrane of 13.3 mV. Thus, chloride is now out of equilibrium across the membrane. The direction that chloride ions flow at \(t = 0^+\) can be determined by noting that \(I_{Cl}^P(0+) = G_{Cl}(V_m(0+) - V_{Cl}(0+))\) and that the sign of the current is determined only by the sign of the difference in potential. This difference in potential is \((-59.5 + 13.3) - (-59.5 + 28) = -14.7\) mV. Therefore, the net chloride current is inward and the chloride flux is outward. However, the equilibrium potential is determined by sodium and potassium concentrations and conductances and is independent of the chloride conductance and concentration. Therefore, the equilibrium membrane potential is the same for both values of external chloride concentration. Therefore, chloride moves out of the cell to reduce the chloride equilibrium potential back to \(-59.5\) mV. In the process the intracellular concentration of chloride is reduced from 15 to 5 mmol/L.

The existence of a net chloride transport out of the cell implies that the assumptions made in the problem statement — i.e., that the intracellular concentrations of sodium and potassium and the volume of the cell were constant — cannot be correct. The efflux of chloride ions alone violates intracellular electroneutrality. Thus, if 10 mmol/L of chloride are transported out of the cell, then 10 mmol/L of cation must also be transported out of the cell. Therefore, the intracellular osmolarity decreases by 20 mosm/L and water must be transported out of the cell to reduce the cell volume and to restore osmotic equilibrium.
Chapter 8

CELLULAR HOMEOSTASIS

Exercises

Exercise 8.1

a. The ions are all univalent, and the sum of the cation concentration equals the sum of the anion concentrations for both solutions at $t = 0$. Therefore, both solutions satisfy electroneutrality. The osmolarity of both solutions is 200 mosm/L. Therefore, the solutions are in osmotic equilibrium. Ionic equilibrium can be assessed from the Nernst equilibrium potentials for the permeant ions. In general, $V_n = 59 \log_{10}(c_n^2/c_n^1)$ mV at normal room temperature. Therefore, for the cation, $V_B = 59 \log_{10}(50/100)$, and for the anion, $V_C = -59 \log_{10}(100/50)$. Thus, both Nernst equilibrium potentials have the same value which is $V_m^o = V_B = V_C$. Therefore, the system is also in ionic equilibrium at $t = 0$.

b. From the analysis in part a, $V_m^o = V_B = V_C = 59 \log_{10}(50/100) = -18$ mV. The negative membrane potential produces a drift of ions that just cancels the diffusion of both B and C.

c. The network model displayed in Figure 8.1 shows that $I_B = G_B(V_m - V_B)$ and $I_C = G_C(V_m - V_C)$. Since $V_m = -40$ mV and $V_B = V_C = -18$ mV, $I_B = -22G_B$ and $I_C = -22G_C$ in mA if $G$ has units of siemens. Thus, there will be a net current from side 2 to side 1 for both the cation and the anion. That implies that the cation will flow from side 2 to side 1 to increase $c_1^B$ and decrease $c_2^B$. The anion will flow

![Figure 8.1: Network model for Exercise 8.1.](image)
from side 1 to side 2 to increase \( c_B^2 \) and decrease \( c_A^1 \). The flow will stop when the concentrations have changed sufficiently that the Nernst equilibrium potentials of both \( B \) and \( C \) are \( V_B = V_C = -40 \text{ mV} \).

d. If an uncharged, impermeant protein is added to side 1 to give a concentration of this protein of 10 mmol/L = 10 mol/m³, electroneutrality is unaffected, ionic equilibrium is unaffected. However, side 1 will have an increase of osmotic pressure of 10 mosm/L. Because the membrane and the walls of the volume are rigid, no water can flow. Therefore, a hydraulic pressure will develop so that \( p_1 - p_2 = \pi_1 - \pi_2 \). Therefore, \( p_1 - p_2 = RT \frac{10}{25} \approx 25 \text{ kPa} \) so that volume 1 will be at a higher hydraulic pressure than volume 2.

**Exercise 8.2**  a. 13; b. 12; c. 8; d. 16; e. 6; f. 2; g. 15; h. 3; i. 10; j. 1; k. 7.

**Exercise 8.3**

a. Water.

b. Cells with vasopressin receptors respond to an increase in systemic vasopressin with an increase in water flux in response to a difference in osmotic pressure across the membrane.

c. Glucose.

d. Cells with insulin receptors respond to an increase in systemic insulin with an increase in glucose flux in response to a difference in glucose concentration across the membrane.

e. Both vasopressin and insulin act by binding to their respective receptors on the membrane. Via second messengers, vasopressin and insulin result in the recruitment of cytoplasmic water channels and glucose carriers, respectively, and their incorporation into the membrane.

**Problems**

**Problem 8.1** There are 5 concentrations in this problem and the values of two of them are given. Therefore, 3 independent equations are needed to specify the remaining concentrations. Electro-neutrality of the two solutions provides 2 equations; osmotic equilibrium across the membrane provides the third. Since, the membrane is permeable to chloride, the potential across the membrane at equilibrium must be the chloride equilibrium potential. Electro-neutrality of the two solutions yields

\[
\begin{align*}
c^1_{Cl} + c^1_A &= c^1_K \\
c^2_{Cl} &= c^2_K,
\end{align*}
\]

which becomes

\[
\begin{align*}
c^1_{Cl} + 135 &= c^1_K \\
150 &= c^2_K,
\end{align*}
\]
so that \( c^2_K = 150 \text{ mmol/L} \). Osmotic equilibrium yields
\[
c^1_{Cl} + c^1_A + c^1_K = c^2_{Cl} + c^2_K,
\]
which gives
\[
c^1_{Cl} + 135 + c^1_K = 300.
\]
Substitution of electroneutrality of side 1 into osmotic equilibrium yields
\[
2c^1_{Cl} + 270 = 300,
\]
so that \( c^1_{Cl} = 15 \) and \( c^1_K = 150 \text{ mmol/L} \). For equilibrium of chloride
\[
V_m = V_{Cl} = \frac{RT}{z_{Cl}F} \ln \left( \frac{c^2_{Cl}}{c^1_{Cl}} \right) = -59 \log_{10} \left( \frac{150}{15} \right) = -59 \text{ mV}.
\]

Problem 8.2 At equilibrium several conditions must hold simultaneously.

- The flux of each ion is zero. Since there are only two permeant ions in this problem, the flux of each must be zero, i.e.,
\[
\phi_{Na} = \phi_{Cl} = 0.
\]

If transport is by passive means only, then the potential across the capillary wall must equal the Nernst equilibrium potential of both sodium and chloride. If the reference direction for potential is defined as positive when the inside of the capillary (the plasma) is at a positive potential with respect to the interstitial fluids then \( V^0_m = V_{Na} = V_{Cl} \), which implies that
\[
\frac{RT}{F} \ln \frac{c^i_{Na}}{c^p_{Na}} = -\frac{RT}{F} \ln \frac{c^i_{Cl}}{c^p_{Cl}},
\]
which yields the Donnan ratio
\[
\frac{c^i_{Na}}{c^p_{Na}} = \frac{c^p_{Cl}}{c^i_{Cl}},
\]
where the superscripts \( i \) and \( p \) refer to interstitial fluids and plasma, respectively.

- The flux of volume is zero at equilibrium. Therefore, the difference in hydraulic pressure across the capillary wall must equal the difference of osmotic pressure, i.e., \( p_p - p_i = \pi_p - \pi_i \).

- Both the plasma and the interstitial fluids obey electroneutrality. The interstitial fluids are defined as 155 mmol/L NaCl. Hence, \( c^i_{Na} = c^i_{Cl} \), which obeys electroneutrality. For electroneutrality of plasma, \( \sum z_n c^p_n = 0 \). Therefore, \( c^p_{Na} - c^p_{Cl} + z_p c^p_p = 0 \), where \( z_p \) and \( c^p_p \) are the valence and the concentration of protein in plasma.

a. For this part \( z_p = 0 \).
i. Electroneutrality implies that since $z_P = 0$, $c_{Na}^P = c_{Cl}^P$. The Donnan ratio together with electroneutrality of the interstitial fluids and plasma implies that $(c_{Na}^i)^2 = (c_{Na}^P)^2$. Therefore, $c_{Na}^i = c_{Na}^P$. Therefore, $c_{Na}^P = c_{Cl}^P = 155$ mmol/L.

ii. Since all the concentrations are the same on both sides of the capillary wall, the Nernst equilibrium potentials for sodium and chloride are zero and the potential across the membrane is zero.

iii. Because of the presence of the uncharged protein in plasma, the plasma is at higher osmotic pressure than the interstitial fluids, so that 27°C

$$\pi_p - \pi_i = RT(311 - 310) \times 10^{-6}$$

$$= \left(8.314 \times 10^6 \frac{\text{Pa}}{\text{K} \cdot \text{mol/cm}^3}\right)(300 \text{ K})(10^{-6} \text{ mol/cm}^3)$$

$$= 2.5 \text{ kPa}.$$ 

iv. Therefore, $p_p - p_i = 2.5 \text{ kPa}$. The plasma is at a higher hydraulic pressure than the interstitial fluids.

b. For this part $z_P = -50$.

i. Electroneutrality of plasma requires that $c_{Na}^P = c_{Cl}^P + 50 c_P$. It is convenient to express all concentration in mmol/L in this problem. With these units $c_{P} = 1$. The Donnan ratio shows that since $c_{i}^i = c_{i}^P$, therefore,

$$\frac{155}{c_{Na}^P} = \frac{c_{Na}^P - 50}{155},$$

which results in the following quadratic equation

$$(c_{Na}^P)^2 - 50c_{Na}^P - (155)^2 = 0.$$ 

A similar quadratic equation is satisfied by chloride

$$(c_{Cl}^P)^2 + 50c_{Cl}^P - (155)^2 = 0.$$ 

Solutions for positive concentrations are $c_{Na}^P = 182$ and $c_{Cl}^P = 132$ mmol/L.

ii. The potential across the membrane is simply the Nernst equilibrium potential for the ions which must be the same.

$$V_m^o = 59 \log \frac{155}{182} = -59 \log \frac{155}{132} = -4 \text{ mV}.$$ 

iii. The osmotic pressure difference is

$$\pi_p - \pi_i = RT(182 + 132 + 1 - 310) \times 10^{-6}$$

$$= \left(8.314 \times 10^6 \frac{\text{Pa}}{\text{K} \cdot \text{mol/cm}^3}\right)(300 \text{ K})(5 \times 10^{-6} \text{ mol/cm}^3)$$

$$= 12.5 \text{ kPa}.$$
iv. Therefore, \( p_p - p_i = 12.5 \) kPa. The plasma is at a higher hydraulic pressure than the interstitial fluids.

Note that the presence of a small concentration of highly-charged impermeant solute has a large effect on the equilibrium values of the concentrations, causes a potential to exist across the capillary wall, and greatly increases the hydraulic pressure difference across the wall.

**Problem 8.3** At \( t = 0 \) the osmolarity of the extracellular solution is increased from 300 mosm/L to 360 mosm/L. Therefore, water will leave the cell to establish osmotic equilibrium, the cell will shrink, and the concentrations of impermeant solutes in the cell will increase.

a. At equilibrium

\[
C^o_i = \frac{N_i}{V^o_i}.
\]

Therefore, if there are two different extracellular osmolarities then

\[
C_{i}^{o1} = \frac{N_i}{V^o_{1i}} \quad \text{and} \quad C_{i}^{o2} = \frac{N_i}{V^o_{2i}}.
\]

The quantity of intracellular solute does not change since the solutes are all impermeant. The ratio of equations yields

\[
\frac{C_{i}^{o1}}{C_{i}^{o2}} = \frac{V^o_{2i}}{V^o_{1i}}.
\]

Therefore,

\[
V^o_{2i} = \frac{C_{i}^{o1}}{C_{i}^{o2}} V^o_{1i} = 300 \times \frac{100}{360} = 83.3 \mu m^3.
\]

b. The intracellular concentration of any component is the ratio of the quantity to the volume. Therefore,

\[
\frac{n_i}{V^i_{1i}} = c_{i}^{1i} \quad \text{and} \quad \frac{n_i}{V^i_{2i}} = c_{i}^{2i}.
\]

Taking the ratio of these equations yields

\[
c_{i}^{2i} = \frac{V^i_{1i}}{V^i_{2i}} c_{i}^{1i}.
\]

This result can be used to find the concentrations of intracellular solutes at equilibrium as follows,

\[
c_1^i = \frac{100}{83.3} \times 180 = 216 \mu m^3,
\]

\[
c_5^i = \frac{100}{83.3} \times 120 = 144 \mu m^3.
\]

The concentrations of all other intracellular solutes is zero.
Problem 8.4  

a. Electroneutrality of the intracellular and extracellular solutions implies that 
\[ z^+_i c^+_i + z^-_i c^-_i = 0 \] and 
\[ z^+_o c^+_o + z^-_o c^-_o = 0. \]

b. At osmotic equilibrium, the osmolarity of the solutions on the two sides of the membrane are equal 
\[ c^+_i + c^-_i = c^+_o + c^-_o. \]

c. The independent variables are iii, iv, vi, vii, and viii. The dependent variables are i, ii, v, ix, and x.

d. The equations for electroneutrality yield 
\[ c^-_o = -\frac{Z^+}{Z^-} c^+_o \text{ and } c^-_i = -\frac{Z^+}{Z^-} c^+_i. \]

Substitution into the equation of osmotic equilibrium yields 
\[ c^+_i \left(1 - \frac{Z^+}{Z^-}\right) = c^+_o \left(1 - \frac{Z^+}{Z^-}\right), \]

which implies that 
\[ c^+_i = c^+_o \text{ and } c^-_i = c^-_o. \]

e. From the relation 
\[ c^-_i = c^+_o \]

\[ \frac{n^-_i}{V} = c^+_o \text{ so that } V = \frac{n^-_i}{c^+_o}. \]

f. The resting membrane potential is 
\[ V_m^o = V_+ = \frac{RT}{z_F} \ln \left(\frac{c^+_o}{c^+_i}\right) = \frac{RT}{z_F} \ln(1) = 0. \]

g. The results for the binary and \( z^+_z, z^-_z \) electrolytes are very similar. In both cases, both the cation and the anion have the same intracellular and extracellular concentrations, and the potential across the membrane is zero. In each case, the cell act as a perfect osmometer. The only differences are due to electroneutrality. In the binary electrolyte 
\[ c^-_i = c^+_i, \]
in the \( z^+_z, z^-_z \) electrolyte 
\[ c^-_i = -(z^+_z / z^-_z) c^+_i. \]

Problem 8.5  

a. Electroneutrality of the intracellular solution implies that 
\[ c^+_i + z^-_i c^-_i = 0. \]

b. At osmotic equilibrium, the osmolarity of the solutions on the two sides of the membrane are equal 
\[ c^+_i + c^-_i = 2C. \]
c. The independent variables are iii, iv, vi, vii, and viii. The dependent variables are i, ii, v, ix, and x.

d. The equation for electroneutrality yields

\[ c^i_- = -\frac{1}{z_\pm}c^i_+. \]

Substitution into the equation of osmotic equilibrium yields

\[ c^i_+ \left( 1 - \frac{1}{z_\pm} \right) = 2C, \]

which implies that

\[ c^i_+ = \left( \frac{z_\pm}{z_\pm - 1} \right) 2C \quad \text{and} \quad c^i_- = \left( \frac{1}{1 - z_\pm} \right) 2C. \]

The dependence of the concentrations on the valence of the anion is shown in Figure 8.2. To satisfy electroneutrality, \( z_- < 0 \). Hence, we plot the concentrations only over this range. Although a single anion has a valence that is an integer, a mixture of anions could have an equivalent non-integer valence. Hence, it is valid to plot the concentrations as a function of negative, real values of the valence. As a consequence of electroneutrality of the intracellular solution, as the valence of the anion is made more negative, the cation concentration increases and the anion concentration decreases. At a valence of \( z_- = -1 \), the concentrations of the cation and the anion are equal, and equal their extracellular concentrations.

e. From the relation

\[ c^i_+ = \frac{n^i_+}{V} = \left( \frac{1}{1 - z_-} \right) 2C, \]

it follows that

\[ V = \frac{n^i_+ (1 - z_-)}{2C}. \]

The volume is plotted versus the anion valence in Figure 8.3. As the valence becomes more negative, the volume increases because electroneutrality requires a larger concentration of cation to neutralize the anion. Hence, the osmotic pressure increases intracellularly and water enters to increase the cell volume and establish osmotic equilibrium.
f. The resting membrane potential is

\[ V_m^o = \frac{RT}{z_+ F} \ln \left( \frac{c_+^0}{c_+^i} \right) \]

\[ = \frac{RT}{F} \ln \left( \frac{C}{\left( \frac{z_-}{z_- - 1} \right) 2C} \right) \]

\[ = \frac{RT}{F} \ln \left( \frac{z_- - 1}{2z_-} \right). \]

The dependence of the resting potential on the valence of the anion is shown in Figure 8.4. When the valence has a small magnitude \((-1 < z_i < 0)\), the concentration of the cation required to satisfy electroneutrality is small which makes the resting potential positive (to prevent influx of cation). At a valence of \(z_- = -1\), the concentrations of anion and cation are the same and each equal \(C\), the extracellular concentrations of cation and anion. Hence, the resting potential is zero. As the valence is further decreased, the intracellular concentration of cation increases above its extracellular concentration and the resting potential becomes negative (to prevent efflux of cation).

g. In contrast to the binary electrolyte, the concentrations of both the anion and cation are not equal for the electrolyte in this problem. Furthermore, there is a potential across the membrane for this electrolyte. However, the cell acts as an osmometer in both cases although the osmotic behavior for the electrolyte in this problem depends on the intracellular anion valence.

**Problem 8.6**

a. Electroneutrality implies that

\[ c_+^i - c_-^i + z_i c_i^i = 0. \]
b. At electrodiffusive equilibrium the potential across the membrane must equal the Nernst equilibrium potential of both the cation and the anion, i.e.,

\[ V_m^{o} = V_+ = V_- = \frac{RT}{F} \ln \left( \frac{C}{c_i^+} \right) = -\frac{RT}{F} \ln \left( \frac{C}{c_i^-} \right), \]

which implies that

\[ \frac{C}{c_i^+} = \frac{c_i^-}{C}, \]

and that \( c_i^+ c_i^- = C^2 \).

c. A combination of the two equations yields

\[ c_i^+ - \frac{C^2}{c_i^+} + z_i c_i^+ = 0, \]

which yields

\[ (c_i^+)^2 + (z_i c_i^+) c_i^+ - C^2 = 0. \]

This quadratic equation can be factored to yield

\[ c_i^+ = \frac{-z_i c_i^+ \pm \sqrt{(z_i c_i^+)^2 + 4C^2}}{2}. \]

Since the concentration must be a positive quantity, the positive root is chosen on physical grounds,

\[ c_i^+ = \frac{\sqrt{(z_i c_i^+)^2 + 4C^2} - z_i c_i^+}{2}. \]

But \( c_i^+ = C^2 / c_i^+ \). Rationalization to remove the radical in the denominator yields

\[ c_i^+ = \frac{\sqrt{(z_i c_i^+)^2 + 4C^2} + z_i c_i^+}{2}. \]

The concentrations can be expressed more conveniently as

\[ \frac{c_i^+}{C} = \sqrt{\left( \frac{z_i c_i^+}{2C} \right)^2 + 1 - \frac{z_i c_i^+}{2C}}, \]

\[ \frac{c_i^-}{C} = \sqrt{\left( \frac{z_i c_i^+}{2C} \right)^2 + 1 + \frac{z_i c_i^+}{2C}}. \]

These normalized concentrations are plotted in Figure 8.5. When \( z_i c_i^+ / (2C) = 0 \), which occurs if \( z_i = 0 \) and/or if \( c_i^+ = 0 \), the intracellular concentrations of cations and anions are equal to their extracellular concentrations. The total concentration of cations and anions, or the osmolarity, is twice that value. If \( z_i > 0 \), the concentration of cations decreases and the concentration of anions increases in order to satisfy electroneutrality. With a positively charged impermeant ion, the concentration of intracellular anion concentration exceeds the extracellular anion concentration. If \( z_i < 0 \), the concentration of cations increases and the concentration of anions decreases in order to satisfy electroneutrality.
Figure 8.5: Dependence of concentrations of cation and anion on the concentration of impermeant solute (Problem 8.6).

![Graph showing the dependence of concentrations of cation and anion on the concentration of impermeant solute.](image)

Figure 8.6: Dependence of the osmotic pressure difference on the concentration of impermeant solute (Problem 8.6). The parameter with each trace is the value of $|z_i|$.

![Graph showing the dependence of the osmotic pressure difference on the concentration of impermeant solute.](image)

d. The osmotic pressure difference is

$$
\pi^i - \pi^o = RT (c^i_+ + c^i - c^i_+ - 2C),
$$

$$
= RT \left( \frac{\sqrt{(z_i c^i_+)^2 + 4C^2} - z_i c^i_+}{2} + \frac{\sqrt{(z_i c^i)^2 + 4C^2} + z_i c^i}{2} + c^i - 2C \right),
$$

$$
= RT \left( \sqrt{(z_i c^i_+)^2 + 4C^2} + c^i - 2C \right).
$$

Let $\Delta\pi = \pi^i - \pi^o$, then

$$
\frac{\Delta\pi}{2RTC} = \sqrt\left(\frac{(z_i c^i_+)^2}{2C}\right) + 1 + \frac{c^i}{2C} - 1,
$$

which is plotted in Figure 8.6. The osmotic pressure is an even function of $z_i$. Hence, we consider plots of the dependence of the osmotic pressure difference on the concentration of impermeant ion for different values of $|z_i|$. When the concentration of impermeant ion is zero, the osmotic pressure intracellularly equals that extracellularly. Increasing the concentration of impermeant ion, for either an anion or a cation, increases the osmotic pressure difference above the osmotic pressure of the extracellular solution.

e. The osmotic pressure difference is zero when

$$
\sqrt{(z_i c^i_+)^2 + 4C^2} = 2C - c^i_+.
$$

Notice that

$$
\sqrt{(z_i c^i_+)^2 + 4C^2} \geq \sqrt{4C^2} = 2C \geq 2C - c^i_+.
$$
Therefore osmotic pressure will be zero only if the two “≥” are in fact “=”. The second “≥” is satisfied with equality only if $c^i = 0$, which also guarantees that the first “≥” is satisfied with equality. Therefore the osmotic pressure is zero if and only if $c^i = 0$.

**Problem 8.7**

a. Figure 8.8 (Weiss, 1996a) deals with a cell model in which there is a binary electrolyte on both sides of the membrane and an additional impermeant intracellular ion of valence $z_i$. The membrane is permeant only to the cation. The results in Figure 8.23 (Weiss, 1996a) are for $z_i = 1$, and indicate that $\hat{c}_- = 1$, $\hat{c}_+ = 1 - \hat{n}_i$, and $\hat{c}_i = \hat{n}_i$. Therefore, the intracellular osmolarity is

$$\hat{c}_- + \hat{c}_+ + \hat{c}_i = 1 - (1 - \hat{n}_i) + \hat{n}_i = 2,$$

which equals the normalized extracellular osmolarity.

b. The concentrations of all intracellular charges are added as follows

$$\hat{c}_+ - \hat{c}_- + \hat{c}_i = 1 - \hat{n}_i - 1 + \hat{n}_i = 0.$$

Therefore, the intracellular solution satisfies electroneutrality.

c. Physically plausible solutions occur only if $\hat{n}_i z_i \leq 1$. Since $z_i = 1$ in this case, physically plausible solutions occur only if $\hat{n}_i \leq 1$. In this range, all concentrations and quantities are non-negative and the volume is a non-negative quantity.

**Problem 8.8**

a.  
i. Electroneutrality of the outside solution is $\sum_n z_n c^0_n = 0$ which yields

$$c^0_{Na} = c^0_{Cl}.$$  

ii. Electroneutrality of the inside solution is $\sum_n z_n c^i_n = 0$ which yields

$$c^i_{Na} = c^i_{Cl}.$$  

iii. Since there is no hydraulic pressure difference across the tubule, osmotic equilibrium across the membrane implies that $C^0_S = C^i_S$ which yields

$$c^0_{Na} + c^0_{Cl} = c^i_{Na} + c^i_{Cl} + \frac{nM}{V}.$$  

iv. For electrodiffusive equilibrium of chloride ions

$$V_m^o = V_{Cl} = -\frac{RT}{F} \ln \left( \frac{c^0_{Cl}}{c^i_{Cl}} \right).$$
v. For quasi-equilibrium of sodium, the net flux of sodium is zero. Therefore, the current density carried by sodium must be zero

\[ J_{Na}^a + G_{Na} \left( V_m^o - \frac{RT}{F} \ln \left( \frac{c_{Na}^0}{c_{Na}^i} \right) \right) = 0. \]

b. Current between the inside and outside of the tubule consists of a passive chloride current and both a passive and an active sodium current as indicated in Figure 8.7.

c. A combination of quasi-equilibrium of sodium and electrodiffusive equilibrium of chloride yields

\[ V_m^o = -\frac{RT}{F} \ln \left( \frac{c_{Cl}^0}{c_{Cl}^i} \right) = -\frac{J_{Na}^a}{G_{Na}} + \frac{RT}{F} \ln \left( \frac{c_{Na}^0}{c_{Na}^i} \right), \]

which results in

\[ \frac{J_{Na}^a}{G_{Na}} = \frac{RT}{F} \ln \left( \frac{c_{Cl}^0}{c_{Cl}^i} \right) + \frac{RT}{F} \ln \left( \frac{c_{Na}^0}{c_{Na}^i} \right), \]

\[ \frac{J_{Na}^a}{G_{Na}} = \frac{RT}{F} \ln \left( \frac{c_{Cl}^0 c_{Na}^0}{c_{Cl}^i c_{Na}^i} \right). \]

Since, \( c_{Cl}^i = c_{Na}^i \) and \( c_{Cl}^0 = c_{Na}^0 \)

\[ \frac{J_{Na}^a}{G_{Na}} = \frac{2RT}{F} \ln \left( \frac{c_{Na}^0}{c_{Na}^i} \right). \]

Therefore,

\[ c_{Na}^i = c_{Na}^0 e^{-\frac{FJ_{Na}^a}{2RTG_{Na}}}, \]
\[ c_{Cl}^i = c_{Cl}^0 e^{-\frac{FJ_{Na}^a}{2RTG_{Na}}}. \]

The equations for \( V_m^o \) and \( c_{Cl}^i \) can be combined to yield

\[ V_m^o = -\frac{J_{Na}^a}{2G_{Na}}. \]

From osmotic equilibrium

\[ \gamma = \frac{n_M}{c_{Na}^0 + c_{Cl}^0 - (c_{Na}^i + c_{Cl}^i)} = \frac{n_M}{2c_{Na}^0 - 2c_{Cl}^i} = \frac{n_M}{2c_{Na}^0 \left( 1 - e^{-\frac{FJ_{Na}^a}{2RTG_{Na}}} \right)}. \]
Figure 8.8: Normalized volume of the tubule as a function of the normalized current density due to active sodium transport (Problem 8.8).

d. Examination of the expressions derived in part c reveals that as $J_{Na}^a \to 0$, $c_{Na}^i \to c_{Na}^o$, $c_{Cl}^i \to c_{Cl}^o$, $V_m^o \to 0$, and $V \to \infty$ (Figure 8.8). That is, if active transport of sodium is reduced to zero then the concentrations of sodium and chloride in the tubule approach the concentrations outside the tubule, the potential between the inside and the outside of the tubule approaches zero, and the tubule swells without bound. Only an infinite volume can satisfy osmotic equilibrium when the concentrations of sodium and potassium inside and outside are the same and there is a fixed quantity of impermeant solute inside. An infinite volume makes the osmolarity of this component zero. Examination of the expressions derived in part c also reveals that as $J_{Na}^a \to \infty$, $c_{Na}^i \to 0$, $c_{Cl}^i \to 0$, $V_m^o \to -\infty$, and $V \to n_M/(c_{Na}^o)$. That is, if the active transport of sodium is increased without limit, then the concentrations of sodium and chloride in the tubule approach zero. Sodium concentration approaches zero because sodium is pumped out faster than it leaks into the tubule. Chloride must follow sodium out to maintain electroneutrality. Therefore, the internal osmotic pressure is due only to $M$ and the osmolarity is $n_M/V$ which must equal the outside osmolarity which is $2c_{Na}^o$. For an arbitrarily large active sodium current, the potential between the inside and outside of the tubule gets arbitrarily negative. That is, the tubule is hyperpolarized by the active sodium current as can be seen from Figure 8.7.

Problem 8.9

a. i. Solute A is impermeant so that the number of moles of A on the two sides of the partition remains the same. Water flows from side 2 to side 1 to equilibrate the concentration. The initial values of variables are as follows,

$$n_A^1(0) = c_A^1(0) \frac{AL}{2} \text{ and } n_A^2(0) = c_A^2(0) \frac{AL}{2}.$$ 

Therefore, the total number of moles of A are

$$N_A = (c_A^1(0) + c_A^2(0)) \frac{AL}{2}.$$ 

Therefore, the final concentrations are

$$c_A^1(\infty) = c_A^2(\infty) = \frac{(c_A^1(0) + c_A^2(0)) \frac{AL}{2}}{AL},$$
\[ c_A^1(\infty) = c_A^2(\infty) = \frac{c_A^1(0) + c_A^2(0)}{2} = \frac{10 + 5}{2} = 7.5 \text{ mmol/L}. \]

To find the location of the partition, note that the final concentration of A on side 1 is

\[ c_A^1(\infty) = \frac{c_A^1(0)(AL/2)}{Ax(\infty)}, \quad 7.5 = \frac{10(L/2)}{x(\infty)}. \]

Therefore, \( x(\infty) = 2L/3 \). This result can be checked by considering \( c_A^2 \),

\[ c_A^2(\infty) = \frac{c_A^2(0)(AL/2)}{A(L - x(\infty))}, \quad 7.5 = \frac{10(L/2)}{x(\infty)}. \]

Solving this equation also yields \( x(\infty) = 2L/3 \).

ii. The equilibrium in concentration will be the same as for solute A discussed in part a.i. \( c_B^1(\infty) = c_B^2(\infty) = 7.5 \text{ mmol/L} \), except that now both water and solute B will flow through the partition.

iii. Several conditions must hold for the two solutions, the position of the partition, and the potential across the partition. The solutions must obey electroneutrality, the two baths must be in osmotic equilibrium, and the two baths must be in electrodiffusive equilibrium. These relations are checked in turn.

- Electroneutrality is checked first. Both side 1 and side 2 contain 10 mmol/L of cation and 10 mmol/L of anion. Hence, both solutions satisfy electroneutrality.
- The osmolarity is 20 mmol/L on both sides of the partition. Hence, there is osmotic equilibrium at \( t = 0 \) and there is no transport of water across the partition.
- Electrodiffusive equilibrium needs to be checked for ions E and F only since only these are permeant. At equilibrium, the potential across the membrane must equal the Nernst equilibrium potentials of both ions. Thus, both of these equilibrium potentials needs to be checked.

\[
V_E = \frac{RT}{F} \ln \left( \frac{c_E^2(0)}{c_E^1(0)} \right) = 26 \ln \left( \frac{5}{10} \right) = -18 \text{ mV},
\]
\[
V_F = \frac{RT}{F} \ln \left( \frac{c_F^2(0)}{c_F^1(0)} \right) = -26 \ln \left( \frac{10}{5} \right) = -18 \text{ mV},
\]

Therefore, \( V(\infty) = -18 \text{ mV} \) and there is no net transport of solutes E and F. The system is at equilibrium at \( t = 0 \) and remains at equilibrium.
b. Conservation of solute B requires that

\[
- \frac{1}{A} \frac{dn_B(t)}{dt} = \phi_B = P_B(c_B^1(t) - c_B^2(t)),
\]

\[
- \frac{1}{A} \frac{dn_B(t)}{dt} = P_B \left( \frac{n_B(t)}{Ax(t)} - \frac{N_B - n_B(t)}{A(L - x(t))} \right),
\]

\[
\frac{dn_B(t)}{dt} = -P_B \left( \frac{Ln_B(t) - N_Bx(t)}{x(t)(L - x(t))} \right).
\]

Therefore, \( \alpha_n = -P_B, \beta_n = L, \) and \( \gamma_n = N_B. \)

c. Conservation of water volume requires that

\[
- \frac{1}{A} \frac{d(Ax(t))}{dt} = \Phi_V = LVRT(c_B^2(t) - c_B^1(t)),
\]

\[
\frac{dx(t)}{dt} = LVRT(c_B^1(t) - c_B^2(t)),
\]

\[
\frac{dx(t)}{dt} = LVRT \left( \frac{n_B(t)}{Ax(t)} - \frac{N_B - n_B(t)}{A(L - x(t))} \right),
\]

\[
\frac{dx(t)}{dt} = LVRT \left( \frac{Ln_B(t) - N_Bx(t)}{x(t)(L - x(t))} \right).
\]

Therefore, \( \alpha_x = \frac{LVRT}{A}, \beta_x = L, \) and \( \gamma_x = N_B. \)

d. The partition is permeable to solute B so that both solute B and water will flow across the partition in response to a solute concentration difference. The parameter \( \delta \) is a measure of the relative permeability of the partition to solute and to water. Intuitively, if \( \delta \) were arbitrarily large then solute B would cross the partition to equilibrate the compartment concentrations before any water was transported. Thus, \( n \) would change a great deal and \( y \) would not change much. Therefore, the correct answers are \( n_3 \) and \( y_3 \). Alternatively, for arbitrarily small values of \( \delta \), very little solute would be transported before the water transport had established osmotic equilibrium across the partition. Thus, for small values of \( \delta \), \( n \) would not change much and \( y \) would change appreciably. This case corresponds to \( n_1 \) and \( y_1 \).

The following addendum explains how the results shown in Figure 8.26 (Weiss, 1996a) were obtained. From parts b and c

\[
\frac{dn_B(t)}{dt} = -P_B \left( \frac{Ln_B(t) - N_Bx(t)}{x(t)(L - x(t))} \right),
\]

\[
\frac{dx(t)}{dt} = LVRT \left( \frac{Ln_B(t) - N_Bx(t)}{x(t)(L - x(t))} \right).
\]

These equation are normalized by dividing by \( N_B \) and \( L \) as follows

\[
\frac{dn_B(t)/N_B}{dt} = -P_B \left( \frac{n_B(t)/N_B - x(t)/L}{(x(t)/L)(1 - x(t)/L)} \right),
\]

\[
\frac{dx(t)/L}{dt} = LVRTN_B \left( \frac{n_B(t)/N_B - x(t)/L}{(x(t)/L)(1 - x(t)/L)} \right).
\]
The normalized variables are defined as \( n = n_B^1(t)/N_B \), \( y = x/L \), and normalized time as 

\[ \tau = \left( \frac{L_v R T N_B}{A L^2} \right) t, \]

to obtain

\[ \frac{dn(\tau)}{d\tau} = -\delta \left( \frac{n(\tau) - y(\tau)}{y(\tau)(1 - y(\tau))} \right), \]
\[ \frac{dy(\tau)}{d\tau} = \left( \frac{n(\tau) - y(\tau)}{y(\tau)(1 - y(\tau))} \right). \]

where

\[ \delta = \frac{A L P_B}{N_B R T L_v}. \]

The two normalized coupled equations have similar right-hand sides. Hence,

\[ \frac{dn(\tau)}{d\tau} = -\delta \frac{dy(\tau)}{d\tau}, \]

which can be integrated to yield

\[ n(\tau) = n_o - \delta y(\tau). \]

Therefore, both \( n \) and \( y \) have the same time dependence. The solutions were obtained by numerical integration of the coupled differential equations.

**Problem 8.10** Since the intracellular solutions are the same for all the cell models, certain relations are common to all the cell models. Electroneutrality of the intracellular solution requires

\[ c_{Na}^i + c_K^i - c_{Cl}^i + z_A c_A^i = 0, \]

where \( z_A \) is the valence of anion \( A \). Electroneutrality of the extracellular solution requires that

\[ c_{Na}^o + c_K^o - c_{Cl}^o = 0. \]

Osmotic equilibrium across the membrane requires that

\[ c_{Na}^i + c_K^i + c_{Cl}^i + c_A^i = c_{Na}^o + c_K^o + c_{Cl}^o. \]

a. For Model 1, electrodiffusive equilibrium for potassium requires that the flux of potassium is zero,

\[ \phi_K = \frac{G_K}{F} (V_m^o - V_K) = 0. \]

Therefore, \( V_m^o = V_K \).

i. False. The membrane is impermeable to chloride. Hence, there is no flux of chloride no matter what the values of the chloride concentrations or the membrane potential.

ii. True.
iii. False. Suppose the membrane were impermeant to all ions. Then a change in composition of the extracellular solution would result in a change in cell volume to satisfy osmotic equilibrium. If the membrane is permeable to potassium, then an infinitesimal flow of potassium across the membrane establishes electrodiffusive equilibrium so that the potential across the membrane is the Nernst equilibrium potential for potassium. Thus, potassium is in equilibrium. Since the quantity of charge required to establish the potential is so small, no appreciable change in concentration occurs and there is not further change in cell volume.

iv. False. Since the cell water volume is bounded, there is no necessity that $c_{Na}^i = 0$.

b. For Model 2, electrodiffusive equilibrium requires that both $\phi_K = 0$ and $\phi_{Cl} = 0$. Therefore,

$$\phi_K = \frac{G_K}{F}(V_m^0 - V_K) = 0,$$

and

$$\phi_{Cl} = \frac{G_{Cl}}{F}(V_m^0 - V_{Cl}) = 0.$$  

Therefore, $V_m^0 = V_K = V_{Cl}$.

i. True.

ii. True.

iii. False. There is no sodium-potassium pump in this model.

c. For Model 3, at quasi-equilibrium for chloride, the net chloride flux must be zero,

$$\phi_{Cl} = -\frac{G_{Cl}}{F}(V_m^0 - V_{Cl}) + 2\alpha_c = 0.$$  

At quasi-equilibrium for potassium, the net potassium flux must be zero,

$$\phi_K = \frac{G_K}{F}(V_m^0 - V_K) + \alpha_c - \nu_K\alpha_{ATP} = 0.$$  

At quasi-equilibrium for sodium, the net sodium flux must be zero,

$$\phi_{Na} = \alpha_c - \nu_{Na}\alpha_{ATP} = 0.$$  

In addition, at rest the total current through the membrane must be zero,

$$J_m = G_K(V_m^0 - V_K) + G_{Cl}(V_m^0 - V_{Cl}) + (\nu_{Na} - \nu_K)F^2\alpha_{ATP} = 0.$$  

The cotransporter makes no direct contribution to the resting potential because it passes no net current. The solution for $V_m^0$ in terms of the other variables is

$$V_m^0 = \left(\frac{G_K}{G_K + G_{Cl}}\right)V_K + \left(\frac{G_{Cl}}{G_K + G_{Cl}}\right)V_{Cl} - \left(\frac{(\nu_{Na} - \nu_K)F}{G_K + G_{Cl}}\right)\alpha_{ATP}.$$  

i. False. It can be seen from above that the resting potential does not equal the chloride equilibrium potential in general.
ii. False. It can be seen from above that the resting potential does not equal the potassium equilibrium potential in general.

iii. False. As can be seen from the equation for quasi-equilibrium of sodium, the two rates $\alpha_{co}$ and $\alpha_{ATP}$ are linked but neither is constrained to be zero.

iv. False. A change in $\alpha_{ATP}$ results in a direct change in $V_m^o$ which changes the potential $(V_m^o - V_{Cl})$ that drives chloride through the membrane.

d. For Model 4, at electrodiffusive equilibrium for chloride, the net chloride flux must be zero,

$$\phi_{Cl} = -\frac{G_{Cl}}{F} (V_m^o - V_{Cl}) = 0.$$ 

Therefore, $V_m^o = V_{Cl}$. At quasi-equilibrium for potassium, the net potassium flux must be zero,

$$\phi_K = \frac{G_K}{F} (V_m^o - V_K) - \nu_K \alpha_{ATP} = 0.$$ 

At equilibrium for sodium, the net sodium flux must be zero,

$$\phi_{Na} = \nu_{Na} \alpha_{ATP} = 0.$$ 

Therefore, $\alpha_{ATP} = 0$ which implies that $(G_K/F)(V_m^o - V_K) = 0$ so that $V_m^o = V_K$.

i. True.

ii. True.

iii. True.

e. For Model 5, at electrodiffusive equilibrium for chloride, the net chloride flux must be zero,

$$\phi_{Cl} = -\frac{G_{Cl}}{F} (V_m^o - V_{Cl}) = 0.$$ 

Therefore, $V_m^o = V_{Cl}$. At quasi-equilibrium for potassium, the net potassium flux must be zero,

$$\phi_K = \frac{G_K}{F} (V_m^o - V_K) - \nu_K \alpha_{ATP} = 0.$$ 

At quasi-equilibrium for sodium, the net sodium flux must be zero,

$$\phi_{Na} = \frac{G_{Na}}{F} (V_m^o - V_{Na}) + \nu_{Na} \alpha_{ATP} = 0.$$ 

Elimination of $\alpha_{ATP}$ between the last two equations yields

$$\alpha_{ATP} = \frac{\phi_K^p}{\nu_K} = -\frac{\phi_{Na}^p}{\nu_{Na}},$$

where

$$\phi_K^p = \frac{G_K}{F} (V_m^o - V_K)$$

and

$$\phi_{Na}^p = \frac{G_{Na}}{F} (V_m^o - V_{Na}).$$

Therefore,

$$\frac{\phi_K^p}{\nu_K} + \frac{\phi_{Na}^p}{\nu_{Na}} = 0.$$
In addition, at rest the total current through the membrane must be zero,

\[ J_m = G_K(V_m^o - V_K) + G_{Na}(V_m^o - V_{Na}) + (V_{Na} - V_K)F\alpha_{ATP} = 0, \]

where the chloride current is zero and has been omitted.

i. True.
ii. False. This is true only if \( \alpha_{ATP} = 0 \) which is not required in general.
iii. False. This is true only if \( \phi_K^P = \phi_{Na}^P = 0 \) which is not required in general.
iv. True.

f. For Model 6, at quasi-equilibrium for potassium, the net potassium flux must be zero,

\[ \phi_K = \frac{G_K}{F}(V_m^o - V_K) - \nu_K\alpha_{ATP} = 0. \]

At quasi-equilibrium for sodium, the net sodium flux must be zero,

\[ \phi_{Na} = \frac{G_{Na}}{F}(V_m^o - V_{Na}) + \nu_{Na}\alpha_{ATP} = 0. \]

In addition, at rest the total current through the membrane must be zero,

\[ J_m = G_K(V_m^o - V_K) + G_{Na}(V_m^o - V_{Na}) + (V_{Na} - V_K)F\alpha_{ATP} = 0. \]

A solution for \( \alpha_{ATP} \) is obtained from one of the flux relations, e.g.,

\[ \alpha_{ATP} = \frac{G_K}{F\nu_K}(V_m^o - V_K), \]

which is substituted into the resting condition equation to yield

\[ G_K(V_m^o - V_K) + G_{Na}(V_m^o - V_{Na}) + (V_{Na} - V_K)\frac{G_K}{\nu_K}(V_m^o - V_K) = 0. \]

Rearranging terms yields

\[ (G_K + G_{Na} + G_K\left(\frac{V_{Na} - V_K}{\nu_K}\right))V_m^o = G_KV_K + G_{Na}V_{Na} + (V_{Na} - V_K)\frac{G_K}{\nu_K}V_K, \]

which, after collecting terms yields

\[ V_m^o = \left(\frac{G_K/\nu_K}{G_K/\nu_K + G_{Na}/\nu_{Na}}\right)V_K + \left(\frac{G_{Na}/\nu_{Na}}{G_K/\nu_K + G_{Na}/\nu_{Na}}\right)V_{Na} \]

i. False. Chloride is not permeant.
ii. False. This is true only if \( \alpha_{ATP} = 0 \) which is not required in general.
iii. True.
CHAPTER 8. CELLULAR HOMEOSTASIS
Bibliography


