$\lambda_{01} = 0.10$ $\lambda_{02} = 0.46$ $\lambda_{03} = 0.37$ $\lambda_{04} = 0.20$
$\tau_{21} = 1.15$ $\tau_{32} = 0.74$ $\tau_{43} = 0.27$
$\alpha_{21} = 20.0$ $\alpha_{32} = 15.0$ $\alpha_{43} = 5.0$
$\gamma_{21} = 5.0$ $\gamma_{32} = 2.0$ $\gamma_{43} = 0.50$
$\alpha_{22} = 10.0$ $\alpha_{33} = 5.0$ $\alpha_{44} = 1.0$
$\gamma_{22} = 30.0$ $\gamma_{33} = 20.0$ $\gamma_{44} = 20.0$

Use a constant input for this system of $F_{10} = 20.0$. For initial values of the compartments, use the following:

$N_1 = 10.0$ $N_2 = 2.0$ $N_3 = 5.0$ $N_4 = 1.0$

In this simulation, units of time and units of mass are arbitrary. As output for this simulation, plot values of the compartmental densities N_i against time for 0 to 240 units of time.

Exercise 13-8: Modify the simulation of Exercise 13-7 to show the effect of limiting the maximum density of the top carnivore. This modification might be needed for a simulation with a species that is more territorial, for example. Thus, in your program reduce the constant for maximum top carnivore density, γ_{44}, from 20 to 10 units and then rerun the simulation.

Conclusion

This chapter has introduced you to some of the concepts and techniques of working with models of material and energy flow through large-scale systems. In succeeding chapters you will work with compartmental models of smaller systems, and many of the methods you have learned here will be useful. The direct two-stage Euler approach has been described for implementing these models on the computer. The more elegant matrix approach will be taken up in Chapter 16. The three examples described in this chapter were relatively simple and designed to promote understanding of methodology. However, the same techniques may be applied to more complex, diverse systems. The simulation programs become longer, and the results less intuitively obvious, but the fundamental methods still apply.

CHAPTER 14
DIFFUSION MODELS

In the compartmental ecological systems of the previous chapter, the mechanisms of transport of material and energy between compartments were relatively straightforward. In physiological models, the mechanisms of transport are frequently the subject of interest. These mechanisms usually fall into three general categories: diffusion, active transport, and fluid flow. Each of these presents different problems requiring different modeling approaches. We will consider the first two mechanisms in this chapter. Fluid flow and other transfers among physiological compartments will be discussed in the next chapter.

A solution is made by dissolving some matter (solute) in a fluid (solvent). A solution may be described by its mass concentration, which is the mass of the solute per unit volume of solution. Molecules of solute are dispersed through the solvent by diffusion, a result of the thermal movements of the solvent molecules colliding with the molecules of solute.

14.1 Transport by Simple Diffusion

A simple model of transport of material by diffusion between a single compartment and an unchanging environment was discussed in Section 1.5. Frequently we are interested in diffusion between compartments, for example between two adjacent cells (Figure 14.1). Across a membrane separating the two compartments, net material transfer will proceed from the compartment of higher concentration to the compartment of lower concentration. The rate of transfer will be proportional to the difference in concentrations. For the simple model here, we will assume constant compartmental volumes and uniformity of concentration inside compartments.

The following equation describes forward diffusion from compartment i to j:

$$\left(\frac{dQ_i}{dt}\right)_f = \frac{-kQ_i}{V_i} \tag{14.1}$$

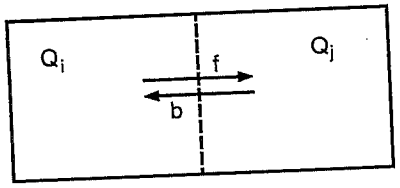

Figure 14.1. Diagram representing simple transport between two cells, with Q representing concentration. The direction of diffusion is indicated with f (forward) and b (back), relative to compartment i.

Q_i is the mass of some diffusing substance in compartment i, V_i is the volume of compartment i, and k is the rate constant for diffusion. Note that concentration is Q_i/V_i, and that k has units of volume (unit time)$^{-1}$. A negative is included to indicate a loss of material from compartment i.

When an amount of material exists in compartment j, there will occur a reverse or back diffusion from j to i. The effect of this on compartment i is described with

$$\left(\frac{dQ_i}{dt}\right)_b = \frac{kQ_j}{V_j} \tag{14.2}$$

The net rate of diffusion of the substance from compartment i is the sum of these two equations:

$$\left(\frac{dQ_i}{dt}\right)_{net} = \left(\frac{dQ_i}{dt}\right)_f + \left(\frac{dQ_i}{dt}\right)_b = k\left(\frac{Q_j}{V_j} - \frac{Q_i}{V_i}\right) \tag{14.3}$$

The change in amount of substance in each compartment may be solved with the usual procedure for two-stage simple Euler numerical integration. The first stage requires two equations:

$$\Delta Q_i = k\left(\frac{Q_j}{V_j} - \frac{Q_i}{V_i}\right)\Delta t \tag{14.4}$$

$$\Delta Q_j = k\left(\frac{Q_i}{V_i} - \frac{Q_j}{V_j}\right)\Delta t \tag{14.5}$$

The second stage involves the usual update procedure:

$$Q_i \leftarrow Q_i + \Delta Q_i \tag{14.6}$$

$$Q_j \leftarrow Q_j + \Delta Q_j \tag{14.7}$$

Exercise 14-1: Write and implement a program to simulate diffusion of a substance between two compartments of a hypothetical system. Initally only one of the compartments will contain a quantity of the diffusing substance. Use the following as constants in your simulation:

$$k = 0.75 \text{ ml min}^{-1} \qquad V_j = 60 \text{ ml} \qquad V_i = 20 \text{ ml}$$

For initial values, set $Q_j = 0$ mg and $Q_i = 100$ mg. Use a Δt value of 0.1 with simple Euler integration. As output, produce a graph which shows the concentration of substance in each compartment, from time 0 to a few minutes past the point at which steady-state occurs.

14.2 Linear Diffusion Gradient

The following simulation is an elaboration of the two-compartment model above. It provides a method for studying the pattern of concentration which results when solutes diffuse across a boundary that is initially quite sharp. Such a boundary might occur, for example, when a lump of sugar is dropped into a cup of tea and allowed to dissolve without stirring.

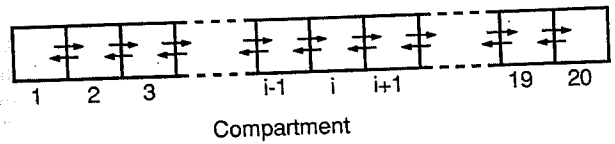

Figure 14.2. Diffusive transport along a linear gradient of 20 compartments.

Assume that the diffusion system is represented by a series of compartments (Figure 14.2). For simplicity in simulation, assume also that the subcompartments are all of the same unit volume, i.e. $V_i = 1$. The net flux from compartment i to adjacent compartment $i+1$ will be described by Equation 14.3, with slightly modified terminology:

$$F_i = k\,(C_i - C_{i+1}) \tag{14.8}$$

where F_i is net flux from compartment i to $i+1$, C_i and C_{i+1} are the concentrations (Q/V) in compartments i and $i+1$, and k is the diffusion rate constant as above.

The diffusion along the gradient of compartments can be found with two-stage Euler numerical integration. In stage one, all flows first are found between all compartments with Equation 14.8. Then as the second part of stage one, the net change is calculated for each compartment with

$$\Delta C_i = (F_{i-1} - F_i)\,\Delta t \tag{14.9}$$

For the second stage of the Euler procedure, concentrations in each compartment are found with the usual Euler equation for up-dating:

$$C_i \leftarrow C_i + \Delta C_i \tag{14.10}$$

Exercise 14-2: Write and implement the simulation of diffusion along a linear gradient of 20 compartments. Set $k = 0.1$. Use a Δt value of 0.1. Begin your simulation with $C_i = 100$ for values of i from 1 to 10, and $C_i = 0$ for $i = 11$ to 20. Output should consist of a graph showing compartment number (distance) on one axis and concentration on the other. Show these plots of concentration after 0, 20, 40, 60, 80 and 100 time units. The equations above are set up to permit easy use of subscripted variables. Set $F_0 = 0$ and $F_{20} = 0$.

14.3 Osmotic Pressure Model

Osmosis is a special case of diffusion in which the solvent, usually water, is the primary diffusing substance. The following model of osmotic pressure is based on the classical osmosis experiment, illustrated in Figure 14.3. The movement of water during osmosis is simply diffusion along a concentration gradient from high concentration of water towards a lower concentration of water. Only water can pass through the membrane; the large molecules of the solute are restricted to the osmometer chamber. Rate of water diffusion into the chamber is described by the equation

$$\text{Flow in } = k_i\,(W_e - W_i) \tag{14.11}$$

The diffusion rate constant k_i is a function of the properties of the membrane, including its thickness and area. W_e is the concentration of water outside the compartment expressed as a mole fraction, usually 1.0, which indicates pure water. W_i is the mole fraction of water inside the membrane. If w is the number of moles of water and s is the number of moles of solute per unit volume inside the compartment, then

$$W_i = \frac{w}{(w+s)} \tag{14.12}$$

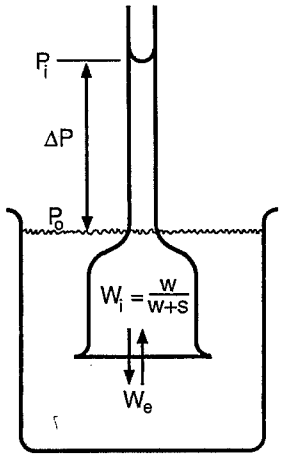

Figure 14.3. Diagram of the apparatus for the classic experiment for determining osmotic pressure. Terminology is defined in the text.

Substituting this into Equation 14.11 gives

$$\text{Flow in } = k_i \left(W_e - \frac{w}{w+s}\right) \tag{14.13}$$

The backflow of water across the membrane is the result of a difference in hydrostatic pressure, and is described by the equation

$$\text{Flow out } = k_h(\Delta P) \tag{14.14}$$

where k_h is a constant relating the flow rate to the difference in hydrostatic pressure across the membrane (ΔP; see Figure 14.3). k_h will vary with the area, thickness, and porosity of the membrane and with the fluid viscosity. Pressure difference ΔP will partly depend on the geometry of the manometer. Equation 14.14 may be simplified by basing the outflow on the amount of water in the chamber relative to the initial amount, which will be adjusted so that $\Delta P = 0$. This will give the following:

$$\text{Flow out } = k_o(w - w_0) \tag{14.15}$$

where w is the amount of water in the chamber at any time t, and w_0 is the initial amount of water when $\Delta P = 0$. k_o is k_h multiplied by a proportionality constant.

Equations 14.13 and 14.15 can be combined to produce an equation for net flow across the membrane as a result of two processes. The equation in words is:

Net flow of water = flow in (by diffusion)
- flow out (due to hydrostatic flow)

With the terms used above the equation is:

$$\frac{dw}{dt} = k_i\left(W_e - \frac{w}{w+s}\right) - K_o(w - w_0) \qquad (14.16)$$

This equation can be solved by the usual two-stage Euler procedure for numerical integration. After the system reaches equilibrium, when net flow is zero (flow in = flow out),

$$k_i\left(W_e - \frac{w}{w+s}\right) = k_o(w - w_0) \qquad (14.17)$$

Exercise 14-3: Write and implement a program to simulate a determination of osmotic pressure using the model above. Use the following constants and initial values:

$$k_i = 20 \qquad k_o = 0.30 \qquad W_e = 1 \qquad w_0 = 55 \qquad s = 1$$

For the Euler integration, let $\Delta t = 0.1$. The backflow from Equation 14.15 may be converted to pressure (atmospheres) with multiplication by a factor of 62.199. This in turn may be converted to inches of water with multiplication by a factor of 414, or to mmHg by a factor of 760.

Run your simulation until the net flow across the membrane is almost zero. At this point, the atmospheric pressure is the osmotic pressure. As output, plot osmotic pressure and net flow from time = 0 to equilibrium.

14.4 Countercurrent Diffusion

Countercurrent diffusion has evolved in a number of species as an efficient mechanism to transport materials or heat from one fluid-carrying vessel to another. One example is the special anatomical relationship

between the loops of Henle in the kidney nephron and the medullary interstitial fluid (Guyton 1971). Another example is the system that whales, seals and birds use to transfer heat between arterial and venous circulation in their feet and flippers. This system, called the *rete mirabile*, is designed for the efficient conservation of heat. Both of these mechanisms have two counter-flowing vessels close together, so that materials or heat may be exchanged through simple diffusion. The countercurrent system maximizes the intensity of the gradient at all points where diffusion is occurring.

An effective model of countercurrent diffusion may be based upon two series of parallel compartments, separated by a membrane which permits transport. The A compartments represent one vessel through which fluid passes and the B compartments represent another vessel parallel to A.

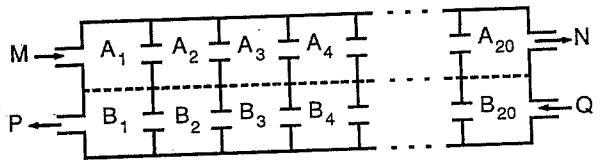

Figure 14.4. Conceptual diagram for a model to simulate countercurrent flow. The terminology is explained in the text.

Figure 14.4 illustrates the model system using terminology that simplifies programming. The diffusion between any pair of compartments A_j and B_j may be described by Fick's Law, which states that the rate of diffusion across a thin membrane is proportional to the area of the membrane, the difference in concentrations, and a constant of permeability:

$$F_{BA} = p\,a\,(A_j - B_j) \qquad (14.18)$$

where F is the flow to compartment B_j from compartment A_j, p is the permeability constant, and a is the membrane area. A_j and B_j designate not only the compartments, but represent the concentrations of the diffusing substance in the compartments. The simplifying assumptions associated with the model are (1) membrane area and permeability constants are the same for all compartments; (2) volume of each compartment is constant and equal to unity, so that concentrations and amounts in each compartment are equivalent.

Movement of fluid in the vessels is assumed to occur by plug flow. This flow is modeled by having the material in each of the A compartments

move one compartment to the right for each time unit. Simultaneously material in each B compartment moves one compartment to the left for countercurrent flow. Simulation of countercurrent flow involves two sets of equations, one set for calculating diffusion flow, and a second set for the plug flow of fluids through the system. Diffusion may be simulated with the usual two-stage Euler procedure. As part of the first stage the diffusion between each pair of compartments is found with Equation 14.18, and then the changes in each compartment are found with

$$\Delta A_j = -F_{BA}\Delta t \tag{14.19}$$

$$\Delta B_j = +F_{BA}\Delta t \tag{14.20}$$

Each compartment is updated as usual with

$$A_j \leftarrow A_j + \Delta A_j \tag{14.21}$$

$$B_j \leftarrow B_j + \Delta B_j \tag{14.22}$$

The procedure for programming plug flow involves the use of the following sequence for the A compartments:

$$N \leftarrow A_n \tag{14.23}$$

$$A_j \leftarrow A_{j-1} \tag{14.24}$$

$$A_1 \leftarrow M \tag{14.25}$$

M represents the concentration of the input to the A compartments, and N the concentration of the output. The countercurrent flow through the B compartments will involve:

$$P \leftarrow B_1 \tag{14.26}$$

$$B_{j-1} \leftarrow B_j \tag{14.27}$$

$$B_n \leftarrow Q \tag{14.28}$$

Q is the input to the low concentration side, and P is the output. The terminology for these procedures is given in Figure 14.4.

In contrast with countercurrent flow, concurrent flow involves the flow of the solution through the B compartments in the same direction as

through the A compartments. In Figure 14.4, concurrent flow through the B compartments would be from left to right. A simulation of concurrent flow would follow the same procedures as above, except that the sequence of Equations 14.26-14.28 would be reversed:

$$Q \leftarrow B_n \tag{14.29}$$

$$B_j \leftarrow B_{j-1} \tag{14.30}$$

$$B_1 \leftarrow P \tag{14.31}$$

Note that with concurrent flow, Q becomes the output and P the input for the B compartments.

Exercise 14-4: Program the model for countercurrent flow using a system of 20 pairs of A and B compartments ($n = 20$). Using subscripted variables will make your program much shorter than otherwise. This will allow you to write one FOR-NEXT loop to solve Equations 14.18-14.20 for all 20 pairs of compartments, and another loop to perform the updates with Equations 14.21-14.22. Then, a loop may be set up for the sequence involved with Equation 14.24, and finally another loop for Equation 14.27. Use constants of $a = 1.0$, and $p = 0.1$. Set $M = 100$ and $Q = 0$. For the Euler procedure let $\Delta t = 1$. Begin your simulation with A_1 through $A_n = 0$, and B_1 through $B_n = 0$. Allow your simulation to proceed for about 40 time intervals, and then plot concentration vs. compartment number for both A and B.

After you have produced the above output, modify your model to simulate concurrent flow, and run the simulation similarly. You can then compare efficiency of two flow types for lowering concentration of material in the A compartments.

14.5 A Model of Active Transport

A simple model for the active transport of some metabolite, B, into a cell may be developed from the following assumptions based on the diagram in Figure 14.5:

(1) Assume there are two compartments separated by a membrane with different permeabilities for substance B and a closely related compound C, with C having a higher permeability than B.

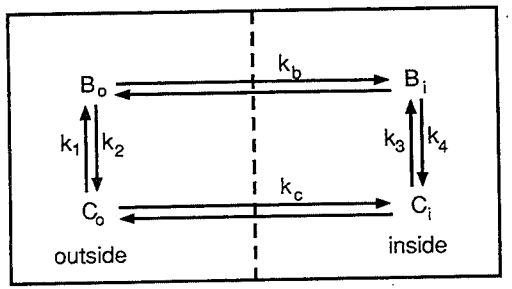

Figure 14.5. Diagram for a simple model of active transport. The terminology is explained in the text.

(2) Assume there is an enzyme on one side of the membrane which catalyzes the conversion of B to C. This might occur by a reaction such as:

$$B + W \rightleftharpoons C + X$$

where W is an activating molecule, such as ATP. In this reaction, the equilibrium lies far to the right, so that the equilibrium constant $K >> 1$ and $\Delta G_o << 0$.

(3) Assume there is another enzyme which catalyzes the conversion of C to B. This might occur as:

$$C + Y \rightleftharpoons B + Z$$

Again, the equilibrium is assumed to lie far to the right, and $\Delta G_o << 0$.

(4) Assume that concentrations of enzymes on each side of the membrane remain constant.

(5) Assume the two compartments have a unit volume and the separating membrane has a unit area. Following Equation 14.4, the rate of transport of B and C from inside the cell to the outside compartment due to diffusion would be described by these equations for the first stage of a two-stage Euler integration:

$$\Delta B_d = k_b (B_i - B_o) \Delta t \tag{14.32}$$

$$\Delta C_d = k_c (C_i - C_o) \Delta t \tag{14.33}$$

where k_b and k_c are diffusion rate constants, and B_i, B_o, C_i and C_o represent concentrations of the two compounds inside and outside of the cell.

(6) Assume that the enzymatic reactions follow first-order kinetics, which will be the case if the reactants other than B and C have constant concentrations, and if the enzymes are well below saturation by substrate. The reactions will alter the concentrations of B and C inside and outside the cell according to the following first-stage Euler equations:

$$\Delta B_i = (k_3 C_i - k_4 B_i) \Delta t \tag{14.34}$$

$$\Delta Ci = (k_4 B_i - k_3 C_i) \Delta t \tag{14.35}$$

$$\Delta B_o = (k_1 C_o - k_2 B_o) \Delta t \tag{24.36}$$

$$\Delta C_o = (k_2 B_o - k_1 C_o) \Delta t \tag{14.37}$$

where k_1, k_2, k_3, and k_4 are the rate constants for the reactions.

In the system based on the above assumptions, the concentration of B and C will be altered by diffusion and by the enzymatic reactions. The update expressions for the Euler integration of the equations will be

$$B_i \leftarrow B_i + \Delta B_i - \Delta B_d \tag{14.38}$$

$$B_o \leftarrow B_o + \Delta B_o + \Delta B_d \tag{14.39}$$

$$C_i \leftarrow C_i + \Delta C_i - \Delta C_d \tag{14.40}$$

$$C_o \leftarrow C_o + \Delta C_o + \Delta C_d \tag{14.41}$$

Exercise 14-5: Using the equations in Section 14.5, write and implement a program to simulate active transport of B against a diffusion gradient. Use the following rate constants, all with units of min^{-1}:

$$k_1 = 0.005 \qquad k_2 = 0.5 \qquad k_3 = 0.5$$
$$k_4 = 0.005 \qquad k_b = 0.001 \qquad k_c = 0.1$$

Begin your simulation with these initial values for concentration (mM l^{-1}):

$$B_o = 50 \qquad B_i = 50 \qquad C_o = 1 \qquad C_i = 1$$

Use a Δt value of 1.0 minute. Your output of the simulation should be a graph of the concentration of B_i and B_o against time. Allow the simulation to proceed to near steady-state.

14.6 Simple Approach to Active Transport

In the previous section we discussed a possible mechanism for active transport of a substance against a diffusion gradient. This resulted in a steady-state concentration gradient across the membrane. This same result could be obtained by simply employing different constants for the diffusion rates in each direction across the membrane.

In this case, rate of diffusion is described by a modification of Equation 14.3:

$$\frac{dQ_j}{dt} = k_1 \frac{Q_j}{V_j} - k_2 \frac{Q_i}{V_i} \tag{14.42}$$

where Q and V are defined as before, and k_1 is greater than k_2 if active transport is toward compartment i. At equilibrium the rates in each direction are equal, so that

$$k_1 \frac{Q_j}{V_j} = k_2 \frac{Q_i}{V_i} \tag{14.43}$$

and

$$\frac{k_1}{k_2} = \frac{Q_i V_j}{Q_j V_i} = \frac{C_i}{C_j} \tag{14.44}$$

Thus, the ratio of the two constants is equal to the equilibrium or steady-state ratio of the two concentrations, C_i and C_j.

Neither of the active transport processes described above account for mediated or facilitated transport processes. These are membrane transport processes, either active or passive, that show saturation-type kinetics because only a limited number of transport sites exist. In addition, they may show specificity for a particular chemical species being transported.

The distinction between simple diffusion and mediated-transport processes is seen in Figure 14.6. This shows graphically that the carrier or transport sites of the mediated-transport system become saturated at high concentrations of the diffusing substance, and that the rate does not exceed $T_{\max}$. This may be represented with a model equation of the Michaelis-Menten type:

$$T_c = T_{\max} \frac{C_i}{K_c + C_i} \tag{14.45}$$

where T_c is the rate of carrier-mediated diffusion, $T_{\max}$ is the maximum rate, C_i is the concentration of diffusing substance, and K_c is the half-saturation constant.

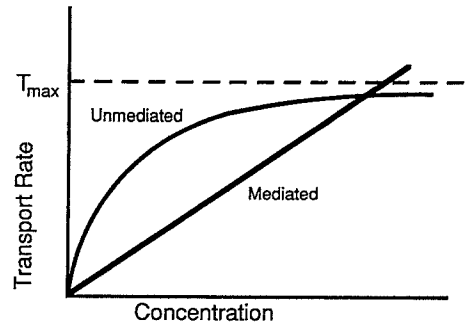

Figure 14.6. Graph showing general relationship between rates of transport and external concentration for mediated and unmediated (passive diffusion) transport processes. Based on a graph in Lehninger (1975).

Conclusion

As part of the coverage of compartmental models in physiology, this chapter has looked at simple models of diffusion. The modeling and simulation of diffusion can become quite complex; see Crank (1956) for example. The next chapter considers some different physiological models of fluid flow among compartments.