CHAPTER

7

Compartmental Modeling

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OUTLINE

AT THE CONCLUSION OF THIS CHAPTER, STUDENTS WILL BE ABLE TO:

- Explain the concept of a compartment.
- Quantitatively describe the transfer of substances separated by a membrane.
- Describe how osmosis affects cell volume.
- Analyze a physiological system using a one-compartment model.
- Describe and calculate the half-life of a substance in a one-compartment model.
- Use the washout curve to estimate parameters.
- Describe a pharmacokinetic model and its use.
- Describe how to maintain the concentration of a drug in the body by repeat dosages.
- Use a two-compartment model with sources and sinks.
- Use a three-compartment model with sources and sinks in a general, mammillary, and unilateral configuration.
- Use a multicompartment model with sources and sinks in a general, mammillary, unilateral, and catenary configuration.

7.1 INTRODUCTION

Compartmental modeling describes the movement of a substance from one compartment to another. Its origins are based on the metabolism of tracer-labeled compound studies in the 1920s. As we will see, compartmental modeling is a special case of physiological modeling, which is covered elsewhere in this book. Primarily, it is concerned with maintaining correct chemical levels in the body and their correct fluid volumes. A compartment can be a volume (or space) or the amount of a substance in a volume. Both representations are commonly used. Here we use the amount of substance in a volume as a compartment, with each compartment assumed to be homogeneous, as described later in the chapter. The process of transfer of substance from one compartment to another is based on diffusion and mass conservation. As shown, compartmental analysis provides a uniform theory that can be systematically applied to many linear and nonlinear systems. While interest in compartmental analysis here is focused on the human body, other engineers and scientists use this technique in studying evolution, carcinogenesis, chemical reactions, infectious disease models, and even semiconductor design and fabrication.

Before investigating compartmental modeling, Fick's Law of diffusion and osmosis is presented first from basic principles. Next, the volume of a cell and capillary diffusion are discussed. The basics of compartmental modeling are described from simple to more complex models that are increasingly more realistic. Much of the material in this chapter is based on the book by Godfrey.

7.2 SOLUTES, COMPARTMENTS, AND VOLUMES

When analyzing systems of the body characterized by a transfer of a solution from one compartment to another, such as the respiratory and circulatory systems, it is convenient to describe the system as a finite series of interconnected compartments. A *solution* is defined as a homogeneous mixture of two or more substances in any of the three states of matter: gas, liquid, or solid. Within a solution, we may have a mixture of matter—for instance, solid within a liquid, gas within a liquid, and so on. A solution is described by a component called a solute and another called the solvent. While there are no absolute rules regarding which component is the solute and which is the solvent, we typically call the component in the lesser amount the solute and the other the solvent. For instance, blood is a fluid that consists of 90 percent water with suspended cells such as red blood cells (erythrocytes), white blood cells (leukocytes), platelets, small molecules (i.e., glucose and carbon dioxide), large proteins, and electrolytes (i.e., sodium, calcium, magnesium, potassium). The solute could be a particular protein, and the solvent is the blood minus the protein.

The following are some of the readily identifiable compartments in the human body:

- Cell nucleus that is separated from the cytoplasm of the cell
- Internal organelle volumes, such as the mitochondria, endoplasmic reticulum, and so on that are separated from the cytoplasm
- Cell volume that is separated from the extracellular space by the cell membrane

- Interstitium or interstitial volume[1] that is separated from the plasma[2] by the capillary walls
- Plasma that is separated from the blood

Variables tracked in compartmental analysis are typically quantity or concentration of a solute, temperature, and pressure. Substances of interest are exogenous, such as a drug or tracer, or endogenous, such as glucose or an enzyme or hormone like insulin. Radioactive and stable isotopes[3] are used to track the dispersion in a compartmental system and are easily measured. Often a tracer dose of a radioactive isotope is used so the radiation emitted is small and does not interfere with the system. Typically, a tracer dose is less than 1 percent of the total amount of solute in the compartment. High-performance liquid chromatography (HPLC) is used to measure proteins and other macromolecules. Radioimmunoassay is used to measure hormones or proteins, a method based on the immune response of the body to an antigen, which is then bound to an antibody. Other modes of tracking involve injecting a dye (e.g., Evans blue) at one site in the cardiovascular system and measuring the concentration at one or more sites as a function of time.

Fluid in the body is separated into intracellular and extracellular fluid. A typical 70 kg adult contains 42 L of fluid, which is approximately 60 percent of the total body weight. Fluid in the body is tightly regulated so a relatively constant fluid volume is maintained. Intracellular fluid consists of the fluid inside the approximately 75 trillion cells in the body, totaling about 28 L and 40 percent of total body weight. Extracellular fluid consists of two major compartments, the interstitial fluid compartment and the plasma, and two minor compartments, the transcellular fluid and the lymph. The interstitial fluid is 11 L and the plasma is 3 L. The transcellular fluid includes fluids from the synovial, peritoneal, pericardial, intraocular spaces, and the cerebrospinal fluid. These compartments contain approximately 1 to 2 L of fluid. Lymph is the fluid that originates in the interstitial fluid that diffuses into the lymphatic system through lymph capillaries. It returns to the venous plasma after passing through the lymph nodes and has a volume of approximately 1 L. The blood in the circulatory system is a mixture of intracellular and extracellular fluid totaling 5 L of fluid and is 7 percent of total body weight. It consists of the plasma (3 L) and the fluid in the red blood cells (2 L). Table 7.1 summarizes various volumes in the body.

Typically, we work with the plasma compartment rather than the blood compartment, except when dealing with the cardiovascular system. Fluids in the body continually flow from one compartment to another without much change in fluid volume. As will be described more thoroughly in Section 7.3.5, fluid moves from the plasma to the interstitial fluid through the arterial side of the capillary bed and returns from the interstitial fluid to the plasma from the venous side of the capillary bed. Approximately 10 percent of the interstitial fluid does not immediately return to the plasma but moves into the lymphatic system through lymph capillaries by diffusion. The lymphatic system acts like a second parallel circulatory system, with the lymph returning to the plasma after traveling through

[1]Interstitial volume is the fluid that bathes the cells and is separated from the blood by capillaries.

[2]Plasma is the noncellular part of the blood. The plasma volume bathes the blood cells.

[3]Isotopes of an atom have the same atomic number but differ in mass. Radioactive isotopes disintegrate with time and emit ionizing radiation.

TABLE 7.1 Fluid Volumes in a 70 Kg Adult

Compartments	Volume in L
Total Fluid (60% of total body weight)	42
Intracellular	28
Extracellular	14
Interstitial	11
Blood	5
Plasma	3
Transcellular	1–2
Lymph	1

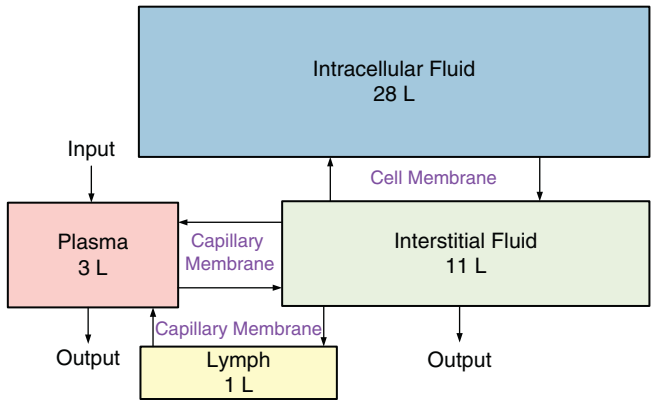

FIGURE 7.1 The compartment volumes of the body. A box depicts the volume. These volumes are tightly controlled by the body through mechanisms that will be described in this chapter. The arrows indicate a flow from one compartment into another (next to the arrows are the types of membranes the fluid must pass through). The rate of flow through a membrane depends on the properties of the membrane. The input includes the fluid ingested. Output is fluid lost from the kidneys, lungs, skin, and sweat, with a small amount lost in the feces. Not shown is the transcellular fluid.

the lymph nodes. The white blood cells in the lymph nodes monitor the lymph and destroy foreign substances to protect the body from disease. Figure 7.1 illustrates the relationships among the compartments.

7.3 TRANSFER OF SUBSTANCES BETWEEN TWO COMPARTMENTS SEPARATED BY A MEMBRANE

7.3.1 Diffusion and Membranes

Molecules and atoms randomly move due to thermal energy. They are never at rest even though the medium in which they are present is still. The speed of the molecules depends

on the temperature—the higher the temperature, the greater the speed of the molecules. The motion of a molecule is completely random and equally likely to move in any direction. If the motion is restricted to one axis, the probability of the molecule moving left or right is equal—that is, $p = 0.5$. This motion is often referred to as a *random walk*. As the molecule is moving, it collides with other molecules or the compartment wall, and then changes direction. The collision of one molecule into another molecule involves a transfer of kinetic energy. Sometimes collisions between molecules cause chemical reactions to occur, as will be described in a later chapter.

Consider a tube with a thin permeable membrane separating molecules from the right and left side at $t = 0$, as illustrated in Figure 7.2. As shown, the number of molecules on the left side is greater than the right side at $t = 0$. After a period of time, half the molecules on the left side move to the right and half of those on the right side move to the left. Thus, there is a net movement of molecules from the left to the right side, since there are more molecules on the left at $t = 0$. The number of molecules on each side are equal at $t = \infty$. We call this process simple diffusion. The rate of simple diffusion is impacted by the velocity of the molecules (temperature) and the number of channels in the membrane. A second type of diffusion is called facilitated diffusion or carrier-mediated diffusion. This requires the binding of carrier proteins to the molecule to move through the membrane and may involve the movement of molecules at rates greater than predicted by simple diffusion.

One typically works with concentrations rather than the number or quantity of molecules or ions, since measurements are made in concentration rather than quantity. The following relationship is used in moving between quantity and concentration:

$$\text{Concentration} = \frac{\text{Quantity}}{\text{Volume}}$$

The flow of particles due to diffusion is along the concentration gradient, with particles moving from high concentration areas to low ones. Physiological compartments are surrounded by membranes. Membranes provide structure, filter molecules and ions entering and leaving the cell, and control the cell volume. A cell membrane readily allows water, oxygen, and carbon dioxide to move across it, but prohibits other molecules and ions from passing through, except through protein channels. For example, a neuron's cell membrane consists of a lipid bilayer made of phospholipids, cholesterol, and proteins, which separates ions from the inside and outside of the cell, as shown in Figure 7.3. Cell membranes are selective, allowing some ions to pass through and not others. Figure 7.3 illustrates the use of a passive channel that allows only a particular ion to pass through by diffusion and

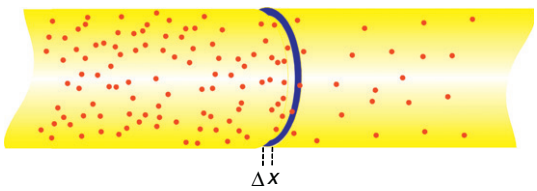

FIGURE 7.2 A tube filled with molecules and separated into two compartments by a thin membrane of width Δx at $t = 0$. The membrane has a number of channels that allow the molecules to pass through it. Assume that the left and right sides of the compartments are of equal volume.

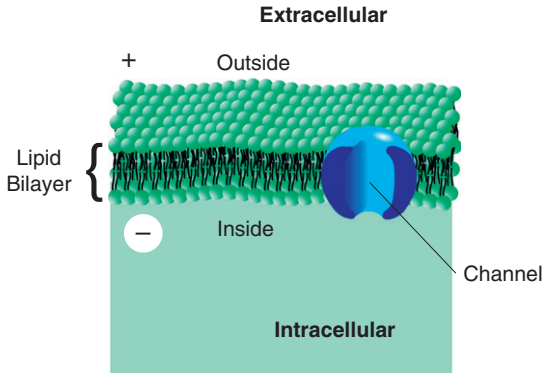

FIGURE 7.3 A typical cell membrane.

prevents other ions from passing through this channel. Passive channels are always open and driven by the concentration gradient.[4] Another type of channel is an active channel that uses energy from adenosine triphosphate (ATP) to move ions across the membrane against a concentration gradient. An active channel may be open all the time, or it may be open or closed based on the voltage across the membrane.

A third type of channel is called a pump, which exchanges ions from the inside to the outside using ATP. The neuron cell membrane uses an $Na^+ - K^+$ pump to remove Na^+ from inside the cell and replaces it with K^+ from the outside, as discussed in Sections 7.3.4 and 8.4.4. One of the most important functions of the pump is to control cell volume. If cell volume is not controlled, the cell will swell and burst. Approximately 60 percent of a neuron's energy requirements are used to maintain the $Na^+ - K^+$ pump.

The use of passive and active channels allows the concentration of ions to be different inside and outside the cell. Table 7.2 gives approximate concentrations across a mammalian cell membrane for some important positively charged ions (cations) and negatively charged ions (anions) in moles/liter.[5] The intracellular space (cytoplasm) has organelles with different ionic compositions. We will return to diffusion across the cell membrane in Section 7.3.4.

Another example of a membrane is the capillary wall. A capillary wall consists of endothelial cells that separate the interstitial volume from the blood volume. The typical length of a capillary is approximately 1 mm, with a diameter of 7 μm. Since the diameter of a

[4]Or an electric gradient as described in Chapter 12.

[5]A mole equals 6.02×10^{23} (Avogadro's number) particles and is defined as a unit in SI. The unit for the mole is M. For any ion or molecule, a mole's weight equals its atomic weight. So one mole of H_2O molecules weighs 18 g. Assuming a cell's volume is 1 nL with concentration of $Cl^- = 4\frac{\text{mM}}{\text{L}}$, the number of Cl^- ions inside the cell equals

$$0.004\ \frac{\text{M}}{\text{L}} \times 6.02 \times 10^{23}\ \frac{\text{molecules}}{\text{M}} \times 1 \times 10^{-9}\text{L} = 2.408 \times 10^{12}\ \text{molecules}$$

TABLE 7.2 Approximate Intracellular (Cytoplasm) and Extracellular Concentrations of the Important Ions across a Mammalian Cell Membrane

Ion	Intracellular (mM/L)	Extracellular (mM/L)
K^+	140	4
Na^+	10	142
Cl^-	4	103
Ca^{++}	0.0001	2.4

capillary is about the same size as a red blood cell, red blood cell movement through the capillary involves significant contact with the wall.

Pores in the capillary wall between cells allow movement between the interstitial volume and blood volume. Water freely moves through the capillary membrane. In fact, all other components of the plasma easily move through the capillary membrane except for some proteins such as albumin. While the interstitial fluid is similar to the plasma except for some proteins, movement of fluid through the interstitial volume is much slower than through the plasma. This is due to the structure of the interstitium that is maintained by collagen fiber bundles and proteoglycan filaments. Fluid flow through the network of filaments is mostly driven by diffusion. We will return to diffusion in capillaries in Section 7.3.5.

In this section we presented the cell as a static structure. In actuality, the cell is dynamic, and rapid changes in ionic concentrations are possible. The amount of water that moves in and out of the cell each second is 100 times the volume of the cell; this process is balanced so there is no net movement of water. Chapter 12 describes the neuron, which, when signaling, involves the rapid movement of sodium and potassium across the membrane. Chapter 4 describes the muscle and muscle contraction involving the rapid movement of calcium across the membrane.

7.3.2 Fick's Law of Diffusion

Fick's Law of diffusion describes the time course of the transfer of a solute between two compartments that are separated by a thin membrane, given by

$$\frac{dq}{dt} = -DA\frac{dc}{dx} \tag{7.1}$$

where

q = quantity of solute
A = membrane surface area
c = concentration
D = diffusion coefficient
dx = membrane thickness
$\frac{dc}{dx}$ = concentration gradient

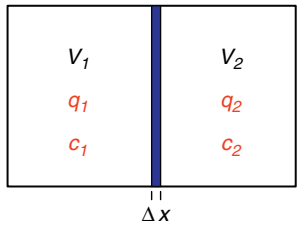

FIGURE 7.4 Two-compartment model with a membrane of width $\Delta x = dx$.

Consider the system of two compartments shown in Figure 7.4, where

V_1 and V_2 are the volumes of compartments 1 and 2
q_1 and q_2 are the quantities of solute in compartments 1 and 2
c_1 and c_2 are the concentrations of solute in compartments 1 and 2

and an initial amount of solute, Q_{10}, is dumped into compartment 1. After approximating the derivative $\frac{dc}{dx}$ as $\frac{c_1 - c_2}{\Delta x}$, the rate of change of solute in compartment 1 is given by

$$\dot{q}_1 = -DA\frac{dc}{dx} = -DA\frac{(c_1 - c_2)}{\Delta x} \tag{7.2}$$

Next, the quantity is converted into a concentration by

$$q_1 = V_1 c_1 \tag{7.3}$$

and after differentiating Eq. (7.3), gives

$$\dot{q}_1 = V_1 \dot{c}_1 \tag{7.4}$$

Substituting Eq. (7.4) into Eq. (7.2) yields

$$V_1 \dot{c}_1 = \frac{-DA}{\Delta x}(c_1 - c_2) \tag{7.5}$$

With the transfer rate K defined as

$$K = \frac{DA}{\Delta x}$$

when substituted into Eq. (7.5) yields

$$\dot{c}_1 = -\frac{K}{V_1}(c_1 - c_2) \tag{7.6}$$

From conservation of mass, we have

$$Q_{10} = q_1 + q_2$$

which after converting to a concentration gives

$$V_1 C_{10} = V_1 c_1 + V_2 c_2 \tag{7.7}$$

where $C_{10} = \frac{Q_{10}}{V_1}$ is the initial concentration in compartment 1 due to the initial amount of solute dumped into the compartment.

The concentration in compartment 2 is found from Eq. (7.7) as

$$c_2 = \frac{C_{10}V_1 - V_1c_1}{V_2} \tag{7.8}$$

which when substituted into Eq. (7.6) gives

$$\dot{c}_1 = \frac{-K}{V_1V_2}(V_2c_1 - V_1C_{10} + V_1c_1) = \frac{KC_{10}}{V_2} - \frac{Kc_1}{V_1V_2}(V_1 + V_2)$$

or

$$\dot{c}_1 + K\left(\frac{V_1 + V_2}{V_1V_2}\right)c_1 = \frac{KC_{10}}{V_2} \tag{7.9}$$

This is a first-order linear differential equation with forcing function

$$f(t) = \frac{KC_{10}}{V_2} \tag{7.10}$$

and initial condition $c_1(0) = C_{10}$.

Assume for simplicity that $V_1 = V_2$. Then Eq. (7.9) becomes

$$\dot{c}_1 + \frac{2K}{V_1}c_1 = \frac{KC_{10}}{V_1} \tag{7.11}$$

To solve Eq. (7.11), note that the root is $-\frac{2K}{V_1}$ and the natural solution is

$$c_{1_n} = B_1e^{\frac{-2Kt}{V_1}} \tag{7.12}$$

where B_1 is a constant to be determined from the initial condition. The forced response has the same form as the forcing function in Eq. (7.9), $c_{1_f} = B_2$, which when substituted into Eq. (7.11) yields

$$\frac{2K}{V_1}B_2 = \frac{KC_{10}}{V_1}$$

or

$$B_2 = \frac{C_{10}}{2}$$

Thus, the complete response is

$$c_1 = c_{1_n} + c_{1_f} = B_1e^{-\frac{2Kt}{V_1}} + \frac{C_{10}}{2}$$

To find B_1, the initial condition is used

$$c_1(0) = C_{10} = B_1e^{-\frac{2Kt}{V_1}}\Big|_{t=0} + \frac{C_{10}}{2} = B_1 + \frac{C_{10}}{2}$$

or

$$B_1 = \frac{C_{10}}{2}$$

The complete solution is

$$c_1 = \frac{C_{10}}{2}\left(e^{-\frac{2Kt}{V_1}} + 1\right)$$

for $t \geq 0$. Note that the concentration in compartment 2 is found using Eq. (7.8) as

$$c_2 = \frac{V_1 C_{10} - V_1 c_1}{V_2} = \frac{C_{10}}{2}\left(1 - e^{-\frac{2Kt}{V_1}}\right)$$

If $V_1 \neq V_2$, then

$$c_1 = \frac{C_{10}}{(V_1 + V_2)}\left(V_2 e^{-K\frac{(V_1+V_2)}{V_1 V_2}t} + V_1\right)u(t)$$

and

$$c_2 = \frac{V_1 C_{10}}{(V_1 + V_2)}\left(1 - e^{-K\frac{(V_1+V_2)}{V_1 V_2}t}\right)u(t)$$

At steady state, the concentrations on either side of the membrane are equal. In fact, if the volumes of the compartments are not equal, the concentrations at steady state are still equal. This should also be clear using Eq. (7.6); setting the derivative term equal to zero gives $c_1(\infty) = c_2(\infty)$. Note, however, that the number of moles of solute will be greater in the larger compartment.

7.3.3 Osmosis

Solutes and fluids must be maintained within a rigid tolerance in the body, both inside and outside the cell. Of all substances that move through the cell membrane, the most plentiful is water. Each second, the amount of water moving in and out of a cell is about 100 times the volume of the cell, with no net movement of water. Osmosis is the process that drives water across the membrane to maintain a zero water concentration gradient across the membrane. If the concentration gradient of water is not zero, then osmosis occurs to force it to zero. Obviously, any net movement of water through a cell membrane causes the cell to swell or shrink.

The distribution of water and solutes among the body's compartments is regulated by chemical and physical forces. The chemical potential is a function of concentration, pressure, and temperature. With regard to water concentration, pure water has a higher concentration than water mixed with a solute. Consider two compartments that are initially filled with water and different solute concentrations on either side of the membrane. Further assume that the membrane is not permeable to the solute. Osmosis causes a net movement of water along the concentration gradient, from the high concentration side to the low concentration side until the gradient is zero.

Pressure, defined as a force per unit area, is observed throughout the body for gases and liquids. The term *pressure* is reserved for gases and liquids, with *stress* used to describe the force per unit area for solids. When discussing pressure, we talk about a pressure difference

between two locations, measured in units of mm Hg.[6] Zero pressure is that observed in a vacuum, and a pressure relative to 0 pressure is called absolute pressure. Unless stated otherwise, pressure is given relative to standard atmospheric pressure. Systolic or peak blood pressure is typically around 120 mm Hg relative to standard atmospheric pressure, or 880 mm Hg in terms of absolute pressure. With regard to inspiration, the pressure within the lungs is -4 mm Hg, a negative pressure (with respect to standard atmospheric pressure) that allows air to move into the lungs.

Within the body, we identify relative pressures that drive solutes in or out of a compartment. For example, the pressure inside a capillary on the arterial end is approximately 30 mm Hg and inside a capillary on the venous end is approximately 10 mm Hg. Thus, a relative pressure difference of 20 mm Hg drives the blood from the arterial to the venous end of the capillary. On the arterial end of the capillary, the pressure in the interstitial fluid is approximately 17 mm Hg, with a relative pressure difference of 13 mm Hg that drives the plasma through the capillary walls into the interstitial fluid. On the venous end of the capillary, the pressure in the interstitial fluid is still approximately 17 mm Hg. Thus, a relative pressure of 7 mm Hg drives the interstitial fluid through the capillary walls into the plasma.

For the cell, the pressure difference between inside and outside is zero. Any pressure difference across the cell membrane causes a flow of water from high pressure to low pressure to equilibrate the pressure gradient.

As given by the ideal gas law, pressure is a function of temperature, volume, and the number of atoms and molecules. The ideal gas law assumes that there is no energy between atoms or molecules, such as attractive forces, and the only energy is kinetic. The motion of atoms and molecules create pressure as they collide with each other and the walls of the compartment—the faster the motion, the larger the pressure. Changes in temperature affect the motion of the particles. Increasing the temperature increases the speed of the atoms and molecules, which in turn, increases the pressure. Increasing the number of particles increases the pressure, since more collisions are possible. Pressure is inversely proportional to volume. Increasing the volume reduces the pressure, since there is more space for the particles to move, which reduces the number of collisions. Since temperature is highly regulated in the body, the affects of temperature changes are not a major consideration in osmosis for the body. To more fully appreciate osmosis, we first present two situations that are analyzed qualitatively. Following this, we quantitatively analyze osmosis.

Consider Figure 7.5, with water on both sides of the membrane. The two pistons allow pressures p_1 and p_2 to be applied to each compartment. If $p_1 > p_2$, Piston 1 drives water through the membrane from the left side to the right side. Suppose $p_1 = p_2$, and water is mixed with a small amount of solute on the left side and water is mixed with a large amount of solute on the right side. Osmosis causes water to move from the left side to the right side until the water concentrations are the same on both sides of the membrane.

[6]In physiology and medicine, the unit for measuring pressure is mm Hg. This unit is defined as the height of a column of mercury that can be supported for a given pressure. The pressure of atmosphere at sea level, called the standard atmospheric pressure, is a commonly used reference for pressure measurements and equals 760 mm Hg. The SI unit of pressure is the *Pascal* (Pa), where $1\text{Pa} = 1\frac{\text{N}}{\text{m}}$, and the U.S. common unit of pressure is $\frac{\text{lb}}{\text{in}^2}$(psi). At sea level, standard atmospheric pressure is 760 mm Hg $= 101.325$ k Pa $= 14.696\,\frac{\text{lb}}{\text{in}^2}$.

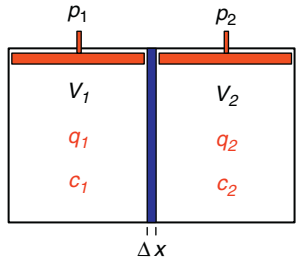

FIGURE 7.5 Two-compartment model with pistons and a membrane. Water can freely move through the membrane, but the solute cannot. The pistons create pressures on either side of the membrane. V_i is the volume, q_i is the quantity of solute, and c_i is the concentration of solute in compartment i. Δx is the width of the membrane.

Next, consider placing pure water into the left side and water mixed with a small amount of solute into the right side, initially with $p_1 = p_2$, and assume no change in volume is possible. Osmosis causes water to flow from the left to the right side. However, osmosis by itself does not allow the system to equalize water concentration, since there is no solute on the left side. As water moves across the membrane, it increases the number of water molecules on the right-hand side, which creates a higher pressure. As the pressure differential between right and left side increases, water is driven from the right to the left side. The pressure-driven water flow continues to increase until it is balanced by the osmosis-driven water flow. The pressure necessary to achieve this balance is called the osmotic pressure.

At this time, we wish to consider these situations from a quantitative point of view. Suppose each compartment in Figure 7.5 is filled with water. The relationship between flow of water through the membrane, Q, and the pressure difference is given by

$$p_1 - p_2 = R_m Q \tag{7.13}$$

where R_m is the resistance of the membrane to water.[7] If $p_1 > p_2$, then water flow is from left to right and equals $Q = \dfrac{p_1 - p_2}{R_m}$. It should be clear that if $p_1 = p_2$, then no net movement of water occurs through the membrane.

Next, consider that a small amount of solute is placed into the water on the left side and pure water is placed in the right side. The flow of water is now given by

$$(p_1 - p_2) - RTc_1 = R_m Q \tag{7.14}$$

where c_1 is the solute concentration, R is the ideal gas constant $\left(R = 62.3637 \ \dfrac{\text{L·mmHg}}{^\circ\text{K·mol}}\right)$, and T is the absolute temperature in degrees Kelvin (273° + centigrade°). Note that normal body temperature is 37°C or 310°K. The flow of water is now given by $Q = \dfrac{(p_1 - p_2) - RTc_1}{R_m}$. To have $Q = 0$ in Eq. (7.14) requires that

$$(p_1 - p_2) - RTc_1 = 0 \tag{7.15}$$

[7]This equation is similar to Ohm's law, where pressure is equivalent to voltage, flow is equivalent to current, and membrane resistance is equivalent to resistor resistance.

that is, a pressure difference is necessary to prevent a net flow of water from traveling to the left side. The pressure difference that causes $Q = 0$ is called the osmotic pressure, with $P_{osmotic} = (p_1 - p_2) = RTc_1$. The traditional symbol used to denote osmotic pressure is π, where $\pi = RTc_1$. If there is no pressure difference, then water is driven from the right side to the left side at a rate $Q = \dfrac{RTc_1}{R_m}$.

If there is solute on both sides of the membrane, then the osmotic pressure equals

$$\pi = RT(c_1 - c_2) \tag{7.16}$$

where c_1 and c_2 are the solute concentration on either side of the membrane. Equation (7.16) is called the van't Hoff law. If there are a number of different impermeable particles on either side of the membrane, then

$$(p_1 - p_2) - RT((c_{A_1} - c_{A_2}) + (c_{B_1} - c_{B_2}) + \cdots + (c_{Z_1} - c_{Z_2})) = R_m Q \tag{7.17}$$

and the total osmotic pressure equals the sum of the concentration differences for each particle (ion or molecule) on either side of the membrane

$$\pi = RT((c_{A_1} - c_{A_2}) + (c_{B_1} - c_{B_2}) + \cdots + (c_{Z_1} - c_{Z_2}))$$

EXAMPLE PROBLEM 7.1

Find the initial osmotic pressure at room temperature for a cell if the only ions present are $NaCl$ on either side of the membrane. Assume the concentrations for Na^+ and Cl^- from Table 7.2 and that the ions cannot cross the membrane, and the cell volume is $V_i = 2$ nL.

Solution

Note first that the cell cannot withstand a pressure gradient across the membrane, so $p_i = p_o$. Therefore, we use Eq. (7.17) to find the initial osmotic pressure at room temperature as

$$\pi = RT\left([Na^+]_i - [Na^+]_o + [Cl^-]_i - [Cl^-]_o\right)$$

where $[Na^+]$ and $[Cl^-]$ are the concentrations of sodium and chlorine on the inside and outside of the membrane.[8] From Table 7.2, we substitute the concentrations into this equation, giving

$$\pi = 62.3637 \times 310((10 - 142) + (4 - 103)) = -4466 \text{ mmHg}$$

The osmotic pressure initially drives water out of the cell to equalize water concentration, which reduces the cell volume. This continues until the inside water concentration equals the outside water concentration. To compute the final cell volume size, note that the number of moles of Na^+ and Cl^- inside the cell remains constant, since it cannot pass through the membrane, and is

$$q_i = \left([Na^+]_i + [Cl^-]_i\right) \times V_i = (10 + 4) \times 2 \times 10^{-9} = 28 \times 10^{-9} \text{ M}$$

To have a zero osmotic pressure at steady state, we require that the inside steady state concentration, $c_{i_{ss}}$, equal the outside concentration, $c_{o_{ss}}$,

Continued

[8]We use the symbol $[I]$ to denote the concentration of ion "I." In this case, $[Na^+]$ and $[Cl^-]$.

$$c_{i_{ss}} = \left([Na^+]_o + [Cl^-]_o\right) = (142 + 103)\,\frac{\mathrm{M}}{\mathrm{L}} = c_{0_{ss}} = 245\,\frac{\mathrm{M}}{\mathrm{L}},$$

giving a new cell volume of $V_i = \frac{q_i}{c_{i_{ss}}} = \frac{28 \times 10^{-9}\mathrm{M}}{245\,\frac{\mathrm{M}}{\mathrm{L}}} = 0.114\,\mathrm{nL}$. Realistically, the cell cannot shrink to this degree, and there are other ions inside and outside the cell that move to maintain osmotic pressure at zero.

Osmotic pressure depends on the total number of particles per unit volume and not the size of the particle or its atomic weight. On average, all particles in the solution exert the same amount of pressure on the membrane; smaller particles move at higher velocities and larger particles move at lower velocities, providing about the same energy.

Since osmotic pressure does not depend on the weight of the particles and only the number of particles, the unit *osmole* (osm) is used. One osmole equals one mole of solute particles. If a molecule dissociates into two ions, then it contributes two osmoles; if a molecule dissociates into three ions, then it contributes three osmoles, and so on. For instance, one mole of glucose contributes 1 osm, since glucose does not dissociate into multiple ions; one mole of sodium chloride ($NaCl$) contributes 2 osm, since it dissociates into 2 ions; one mole of sodium sulfate (Na_2SO_4) contributes 3 osm, since it dissociates into 3 ions. Glucose and sucrose do not dissociate into ions, so their osmolarity equals the number of moles. Body fluids typically are observed in milliosmoles, so these units are expressed in mOsm.

Because concentrations are used in calculating osmotic pressures, we use the term *osmolarity* instead of osmoles. Osmolarity equals the number of osmoles per liter of solution. The osmolarity (in mOsm/L) inside a mammalian cell is approximately 301.2, plasma is 301.8, and the interstitial fluid is 300.8. The plasma has a slightly higher osmolarity than the interstitial fluid because of the proteins that do not diffuse through the capillary wall. For plasma and the interstitial fluid, 80 percent of the total osmolarity is due to $NaCl$. Within the cell, 50 percent of the total osmolarity is due to KCl. A solution containing one osmolarity contains one mole of undissociated particles per liter of solution. If a solute dissociates into more than one particle, then the osmolarity is given by

$$\text{Osmolarity} = \frac{\text{Moles} \times \text{Number of Dissociated Particles}}{\text{1L Solution}}$$

and osmotic pressure in terms of osmolarity is

$$\pi = c\left(\frac{\mathrm{osm}}{\mathrm{L}}\right) \times R\left(\frac{\mathrm{L \cdot mmHg}}{^\circ\mathrm{K \cdot mol}}\right) \times T(^\circ\mathrm{K}) = 62.3637 \times cT\ \mathrm{mmHg} \tag{7.18}$$

EXAMPLE PROBLEM 7.2

Find the osmolarity of 5 mM $NaCl$ in 1 L of solution.

Solution

Since $NaCl$ dissociates into Na^+ and Cl^- in solution, the osmolarity is equal to 2 times the moles of $NaCl$. Thus, a solution of $5\frac{\mathrm{mM}}{\mathrm{L}}$ $NaCl$ forms a $10\,\frac{\mathrm{mOsm}}{\mathrm{L}}$ solution.

EXAMPLE PROBLEM 7.3

Find the osmolarity and osmotic pressure of a 0.5% by weight solution of glucose at room temperature.

Solution

A 0.5% solution of glucose equals $\left(\frac{0.5}{100}\right)\frac{\text{g}}{\text{mL}} = 5\frac{\text{g}}{\text{L}}$. Since the molecular weight of glucose is $180\frac{\text{g}}{\text{mol}}$, we have a molarity of $\frac{5\frac{\text{g}}{\text{L}}}{180\frac{\text{g}}{\text{M}}} = 0.0278\,\frac{\text{M}}{\text{L}}$. Since glucose does not dissociate into separate ions in solution, the osmolarity is equal to the molarity of glucose, giving $27.8\,\frac{\text{mOsm}}{\text{L}}$. The osmotic pressure is therefore

$$\pi = cRT = 0.0278 \times 62.367 \times 310 = 537.5 \text{ mmHg}.$$

EXAMPLE PROBLEM 7.4

Consider a cell with an internal osmolarity of $300\,\frac{\text{mOsm}}{\text{L}}$ and volume of 2 nL, in a 30 nL solution of $300\,\frac{\text{mOsm}}{\text{L}}$. A 5 nL, 2% *NaCl* by weight solution is added to the extracellular space. Assuming that *NaCl* is impermeable and that the moles inside the cell do not change, describe the events that take place until steady state is achieved. What is the volume of the cell at steady state?

Solution

The first step in the solution is to determine the number of osmoles inside and outside the cell at $t = 0^-$. Inside the cell, we have $300\,\frac{\text{mOsm}}{\text{L}} \times 2\text{ nL} = 600 \times 10^{-9}\text{mOsm}$. Outside the cell, we have $300\,\frac{\text{mOsm}}{\text{L}} \times 30\text{ nL} = 9{,}000 \times 10^{-9}\text{mOsm}$.

Next, determine the number of osmoles outside the cell at $t = 0^+$. The 5 nL, 2% solution of *NaCl* added to the solution outside the cell has $\frac{2}{100}\,\frac{\text{g}}{\text{mL}} = 20\frac{\text{g}}{\text{L}}$, and with a molecular weight of $58.5\,\frac{\text{g}}{\text{M}}$, has a molarity of $\frac{20\frac{\text{g}}{\text{L}}}{58.5\frac{\text{g}}{\text{M}}} = 0.342\,\frac{\text{M}}{\text{L}}$. In 5 nL, there are $0.342{\times}5{\times}10^{-9} = 1.71{\times}10^{-9}$ moles of *NaCl*. Since *NaCl* separates into two ions, 3,420 $\times 10^{-9}$ mOsm are added to the solution outside the cell, giving a total of 12,420 mOsm. The outside osmolarity is then $\frac{12420}{35} = 355\,\frac{\text{mOsm}}{\text{L}}$. This difference in osmolarity causes an osmotic pressure of $\pi = \Delta cRT = (355 - 300) \times 62.367 \times 310 = 1{,}063$ mmHg, driving water out of the cell at room temperature.

At steady state, the total inside and outside cell volume is 37 nL, and total inside and outside osmoles equal $13{,}420{\times}10^{-9}$ mOsm. The total osmolarity then is $\frac{13420}{37} = 352\,\frac{\text{mOsm}}{\text{L}}$, which is the osmolarity inside and outside the cell. The final volume of the cell is therefore $\frac{600}{352} = 1.7$ nL.

7.3.4 Cell Volume and Osmosis

The cell regulates its volume by controlling the internal osmolarity through primary active transport mechanisms using ATP-driven pumps for sodium, potassium, calcium, chlorine, hydrogen, and other ions. The most important ATP-driven pump is the *Na-K* pump. Sixty to 70 percent of a cell's energy consumption is devoted to ATP pumps. Within the cell are anions (such as chlorine, proteins, nucleic acids, sulfate ions, and phosphate ions) and cations (such as potassium, calcium, and sodium). As we will see, some of these ions move freely through the membrane, some appear impermeable, and others are impermeable. The ATP pumps move ions through the membrane to maintain nonzero concentration gradients for many ions at steady-state.[9] Transport of ions is achieved using carrier proteins, which differs from diffusion. These pumps are used to keep the intracellular osmolarity of the cell equal to extracellular osmolarity and to maintain cell volume. A secondary active transport of ions not involved in ATP-driven pumps is a by-product of ion concentration gradients created through the primary active transport.

Any change in the steady-state ion concentrations causes water to be drawn into or be withdrawn from the cell by osmosis. Most mammalian cells have an osmolarity equal to plasma, approximately 300 mOsm. Because of its frailty, the cell membrane cannot survive even minimal pressure differences between the intracellular and extracellular fluids. The ATP pumps keep the pressure difference equal to zero and control the cell volume.

Two solutions with the same osmolarity are called isotonic. A solution that has a lower osmolarity to another is called hypotonic, and a solution that has a higher osmolarity to another is called hypertonic. If the osmolarities are not equal, water moves from the lower osmolarity side to the higher osmolarity side until the osmolarities are equal. Water will leave a cell that is hypotonic to the extracellular solution, which decreases the volume until an isotonic condition is achieved. Water will enter a cell if it is hypertonic to the extracellular solution, which increases the volume until an isotonic condition is achieved. ATP pumps also restore the cell volume to its original state.

Cell volume is typically maintained during extracellular osmolarity changes by adjusting the intracellular osmolarity. When the extracellular osmolarity is hypotonic with respect to the intracellular osmolarity, the following occur:

1. Cell volume immediately increases due to osmosis.
2. The ATP pumps drive ions out of the cell to restore cell volume while maintaining the osmotic balance.

When the extracellular osmolarity is hypertonic with respect to the intracellular osmolarity, the following occur:

1. Cell volume immediately decreases due to osmosis.
2. The ATP pumps drive ions into the cell to restore cell volume while maintaining the osmotic balance.

At steady-state, the ionic concentrations across the cell membrane are maintained by ATP pumps that create electrical and concentration gradients. The electrical gradient will be

[9]Note that the system is not in equilibrium, since the pump uses energy to maintain the concentrations. We refer to this situation as steady-state.

discussed in Chapter 12, and here we focus on the concentration gradient. For a typical mammalian cell, the ions of interest are K^+ and Na^+, with Table 7.2 listing the typical ion concentrations inside and outside the cell. To maintain ion concentrations at steady-state, the flow of each ion into the cell must be balanced by the flow of that ion out of the cell. First consider Na^+. The concentration gradient drives Na^+ into the cell. For K^+, the concentration gradient drives K^+ out of the cell. Osmotically, as long as the K^+ loss is balanced by the Na^+ gain, the cell remains isotropic. However, if the loss/gain were allowed to happen, the ionic concentrations across the cell membrane could not be maintained. To maintain the ionic concentrations of K^+ and Na^+, the cell membrane uses the ATP *Na-K* pump, driving Na^+ out of the cell and K^+ into the cell. Due to the action of the *Na-K* pump, Na^+ behaves as if it is impermeable to the membrane.

The *Na-K* pump also controls the volume of the cell. The cell contains a large number of impermeable proteins and molecules that have a negative charge, which attracts positively charged K^+ and Na^+, and water driven into the cell by osmosis. Without the *Na-K* pump, the cell would swell and eventually burst. The *Na-K* pump removes 3 Na^+ ions for every 2 K^+ ions pumped into the cell, thus creating a hypotonic condition that drives water from the cell by osmosis. If the cell changes volume, the *Na-K* pump operates to restore it by fine-tuning the flow of water into or out of the cell.

Consider the membrane illustrated in Figure 7.6, with two passive channels for K^+ and Na^+, an *Na-K* pump and an impermeable anion A^-. Assume that there is no pressure difference between the inside and outside, which is required for a mammalian cell. Thus, the flow equation using Eq. (7.17) is given by

$$-RT\left([K^+]_i - [K^+]_o + [Na^+]_i - [Na^+]_o + [A^-]\right) = R_m Q \tag{7.19}$$

In addition to the flow equation, the flux[10] equation for each of the permeable ions is given as

$$\begin{aligned} \vec{J}_K &= P_K\left([K^+]_i - [K^+]_o\right) - \vec{J}_p \\ \vec{J}_{Na} &= P_{Na}\left([Na^+]_i - [Na^+]_o\right) + \vec{J}_p \end{aligned} \tag{7.20}$$

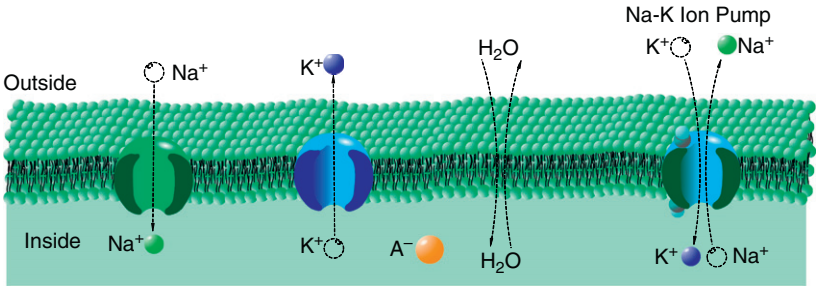

FIGURE 7.6 Cell membrane with two passive channels and a pump. Ions K^+ and Na^+ diffuse through the membrane, while anion A^- is impermeable. As indicated, water easily moves through the cell membrane.

[10]Flux is the number of particles (ions or molecules) that flow through a unit area per unit time. Flux is a vector that is given by the symbol $\vec{J}$.

where P_K and P_{Na} are permeabilities for K^+ and Na^+, and $\vec{J}_p$ is the pump flow rate. Permeability is a function of the membrane that describes the ease with which a particle moves through the cell membrane and is discussed more fully in Chapter 12. Potassium has a high permeability and sodium has a low permeability. To determine the cell volume, we replace $[A^-]$ in Eq. (7.19) with $\frac{a}{V}$, where a is the number of anions and V is the volume of the cell, giving

$$-RT\left([K^+]_i - [K^+]_o + [Na^+]_i - [Na^+]_o + \frac{a}{V}\right) = R_m Q \tag{7.21}$$

At steady state, the net flow of ions, Q, and water is zero, so Eqs. (7.20) and (7.21) reduce to

$$\begin{aligned} 0 &= P_K\left([K^+]_i - [K^+]_o\right) - \vec{J}_p \\ 0 &= P_{Na}\left([Na^+]_i - [Na^+]_o\right) + \vec{J}_p \end{aligned} \tag{7.22}$$

and

$$[K^+]_i - [K^+]_o + [Na^+]_i - [Na^+]_o + \frac{a}{V} = 0 \tag{7.23}$$

Equation (7.22) is solved for the concentrations, $[K^+]_i - [K^+]_o = \frac{\vec{J}_p}{P_K}$ and $[Na^+]_i - [Na^+]_o = -\frac{\vec{J}_p}{P_{Na}}$, and then substituted into Eq. (7.23), giving

$$\frac{\vec{J}_p}{P_K} - \frac{\vec{J}_p}{P_{Na}} + \frac{a}{V} = \vec{J}_p\left(\frac{P_{Na} - P_K}{P_{Na}P_K}\right) + \frac{a}{V} = 0 \tag{7.24}$$

Equation (7.24) is easily solved for V, yielding

$$V = \frac{aP_{Na}P_K}{\vec{J}_p(P_K - P_{Na})} \tag{7.25}$$

Positive cell volumes are possible in Eq. (7.25) when $P_K > P_{Na}$, which is the case for the mammalian cell membrane. Notice that the cell volume is inversely related to the pump rate, so as the pump rate increases, cell volume decreases. The cell carefully controls the pump rate so cell volume is maintained. Also, note that as the cell grows, evidenced by increasing the number of impermeable proteins and molecules (a in Eq. (7.25)), the volume of the cell increases according to Eq. (7.25). Finally, note that when the pump rate goes to zero (death), the cell volume heads to infinity, but before getting there, the cell membrane bursts.

7.3.5 Capillary Diffusion

The movement of water, nutrients, electrolytes, and other particles through the capillary wall is driven by osmotic and hydrostatic pressure. As we will see, these pressures cause fluid to flow out of the capillary at the arterial end and flow into the capillaries at the venous end.

Figure 7.7 illustrates a capillary network. To reach the capillaries, blood first flows from the heart to the aorta under high pressure. The blood leaves the aorta and flows into other arteries until it reaches the arterioles, the smallest branch of the arterial system. From the arterioles, blood flows through the capillaries, where diffusion into the interstitial volume occurs in the lower portion of Figure 7.7. In the upper portion of Figure 7.7, diffusion from the interstitial volume into the capillaries occurs, with the plasma then flowing into the venules, the smallest branch of the venous system. From the venules, blood flows through

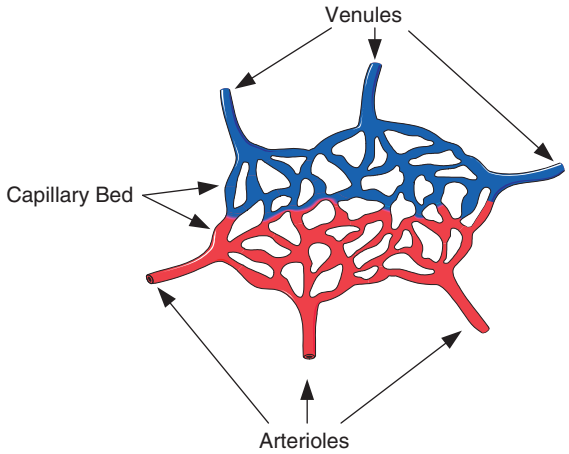

FIGURE 7.7 A capillary network. A sphincter is usually located at the arteriole's entry to the capillary bed that restricts the blood flow. Not all capillaries carry blood all the time, and blood flow is based on the needs of the tissue. For instance, less than 10 percent of the capillaries in muscle carry blood during rest.

TABLE 7.3 Percentage of Plasma Volumes in the Circulatory System

Volume	Percentage
Heart	7%
Pulmonary System	9%
Arteries	13%
Arterioles and Capillaries	7%
Veins and Venules	64%

larger and larger veins until it reaches the heart. Table 7.3 provides the volume percentages in each of the circulatory system compartments. Total plasma volume is approximately 3 L, and total interstitial volume is 11 L.

Plasma proteins are the only substances that are impermeable[11] to the capillary wall, which creates an osmotic pressure. The osmotic pressure created by plasma proteins is called the colloid osmotic pressure, named to differentiate it from the osmotic pressure across the cell membrane. The concentration of proteins in the plasma is 7.5 gm/dl and in the interstitial volume is 3 gm/dl. By far, the protein with the greatest contribution to the colloid osmotic pressure in the plasma/capillary space is albumin (21.8 mm Hg), followed by globulins (6 mm Hg), and then fibrinogen (0.2 mm Hg), giving a total colloid pressure of 28 mm Hg to move fluids inward. The interstitial colloid osmotic pressure due to all proteins within this space is 8 mm Hg. Thus, the total colloid osmotic pressure (difference between plasma/capillary and interstitial volume) is 20 mm Hg, a resultant force that moves fluid inward.

[11]Actually, some plasma proteins slowly leak through the capillary wall into the interstitial compartment, which are then returned to the plasma from lymphatic circulation.

Unlike the cell membrane, hydrostatic pressure exists across the capillary wall that changes as we move from the arteriole to the venule ends. The hydrostatic pressure at the arteriole end is 30 mm Hg and at the venule end is 10 mm Hg. The pressure drop occurs approximately linearly from the arteriole to the venule end of the capillary.

Summing all the pressures at the arteriole end gives the following:

Filtration Pressure	mm Hg
Hydrostatic Pressure	+30
Interstitial Colloid Osmotic Pressure	+ 8
Plasma Colloid Osmotic Pressure	−28
Net Outward Pressure	***+10***

Thus, a net outward pressure of 10 mm Hg exists that moves fluids out of the capillaries into the interstitial volume. Some refer to this pressure as the filtration pressure. The amount of fluid moved is approximately 5 percent of the total plasma.

Summing all the pressures at the venule end gives the following:

Reabsorption Pressure	mm Hg
Hydrostatic Pressure	+10
Interstitial Colloid Osmotic Pressure	+ 8
Plasma Colloid Osmotic Pressure	−28
Net Outward Pressure	***−10***

Thus, a net inward pressure of 10 mm Hg exists that moves fluids out of the interstitial volume into the capillaries. Some refer to this pressure as the reabsorption pressure. Almost all of the fluid that flows into the interstitial volume from the capillaries flows back into the capillaries from the interstitial volume. The remainder left in the interstitial volume flows into the lymphatic fluid, from which it returns to the plasma.

Mathematically, at either end of the capillary, the flow rate of fluid is given by

$$Q_A = \frac{\Delta p_A - RTc_C + RTc_I}{R_m} \tag{7.26}$$

$$Q_V = \frac{\Delta p_V - RTc_C + RTc_I}{R_m} \tag{7.27}$$

where Q_A is the flow rate at the arteriole end into the interstitial fluid, Q_V is the flow rate at the venule end into the capillary, Δp_A is the hydrostatic pressure at the arteriole end, Δp_V is the hydrostatic pressure at the venule end, c_C is the concentration of proteins in the plasma/capillary, and c_I is the concentration of proteins in the interstitial fluid.

With the rate of plasma protein leakage into the interstitial volume given by $\dot{V}_P$, and the rate of fluid that moves from the interstitial volume into lymphatic volume given by $\dot{V}_L$, the change in interstitial volume, denoted $\dot{V}_I$, is given by

$$\begin{aligned}\dot{V}_I &= Q_A - Q_V + \dot{V}_P - \dot{V}_L \\ &= \frac{\Delta p_A - RTc_C + RTc_I}{R_m} - \frac{\Delta p_V - RTc_C + RTc_I}{R_m} + \dot{V}_P - \dot{V}_L\end{aligned} \tag{7.28}$$

Equation (7.28) is useful in studying the effects of pathological conditions. In some types of trauma, Δp_A increases, causing an interstitial volume increase (swelling). If plasma protein concentration, c_C, increases, then the flow rate into the interstitial volume decreases.

7.4 COMPARTMENTAL MODELING BASICS

In the previous section, we worked from basic principles to examine diffusion and osmosis. Here we use a systematic approach called compartmental modeling to describe the movement of a solute through a system. Compartmental modeling involves describing a system with a finite number of compartments, each connected by a flow of solute from one compartment to another. Movement of the solute can be any of the following:

1. Among organelles in a cell
2. A cell and the extracellular space
3. An organ and the interstitial space
4. Among organs through the circulatory system

In modeling a system with compartments in this chapter, we consider a lumped parameter system rather than a distributed system. Therefore, we work with ordinary differential equations. More accurate distributed system models have solutions that involve partial differential equations. In many cases, however, we will find that the more complex distributed system models are quite accurately described by compartmental models using a large number of compartments.

Compartmental modeling applied to the human body is usually a gross simplification of the inherent underlying processes, and there may be a limited anatomical relationship between the true system and the model. For example, we may define the compartments of the body as the plasma compartment (that includes all noncellular fluids in all the blood vessels), tissue compartment (that includes the fluid in 75 trillion cells), interstitial compartment, and the lymph compartment, as illustrated in Figure 7.1. Naturally, the tissue compartment can be further divided into organs and so forth, and the plasma compartment can be further divided into arteries, veins, and progressively smaller vessels. Nevertheless, we will see that compartmental modeling is very useful in describing the movement of a solute through the body, especially when small perturbations from steady-state are considered. Many important applications of compartmental analysis are found in pharmacokinetics.

The alternative to compartmental modeling involves modeling the system via a fluid model of the blood and lymph systems, and the transport phenomena of the solute in each organ. The problem with this approach is finding a model that is time dependent, 3-D, and distributed. The solute is not homogeneously distributed in the organs, and we do not have detailed information about the parameters that describe the model.

As usual in physiological modeling, identifying the number of compartments and the connections between compartments is the most difficult challenge, along with collecting appropriate data. Regardless of the simplicity of the model, there should be some relationship between the model and the system being modeled based on a priori knowledge. Furthermore, it should be possible to test the model after collecting data and compare its performance to the real system. After testing, the model is usually modified, typically

making it more complex. By adding complexity, we add additional parameters, which must be estimated based on the data collected using parameter estimation techniques.

Given a system described by a group of compartments, some exchange of solute (i.e., a radioactive tracer, a molecule like glucose or insulin, a gas like oxygen or carbon dioxide) is expected between compartments by diffusion. Compartmental analysis predicts the quantity or concentration of solutes under consideration in each compartment as a function of time using conservation of mass—that is, accumulation equals input minus output. The model may be linear, nonlinear, continuous, or discrete, and may even have time-varying or stochastic parameters. If the model is continuous and linear, then the change in solute concentration is described as a sum of exponential and sinusoidal terms.

The following assumptions are made when describing the transfer of a solute by diffusion between any two compartments:

1. The volume of each compartment remains constant.
2. Any solute q entering a compartment is instantaneously mixed throughout the entire compartment.
3. The rate of loss of a solute from a compartment is proportional to the amount of solute in the compartment times the transfer rate, K, given by Kq. The transfer rate typically has units of liters per minute.

If two solutes are being tracked in a system, the overall model can be described using two parallel models. For instance, if each solute flows in and out of the plasma, each model can have its own plasma compartment separate from the other. It follows that we can track n solutes, with each solute having its own model, all separately sharing the plasma. This concept follows with additional tissues and blood vessels.

From a modeling perspective, identifying compartments and the number of compartments to describe a system is a difficult step. Acquiring measurement data for model facilitation is another difficult step because some compartments are inaccessible. Both of these steps are beyond the scope of this book; interested readers can examine books listed at the end of this chapter for more information.

7.4.1 Inputs to a Compartmental System

The inputs to a compartmental system are discussed following.

Bolus Injection

A bolus injection is an immediate injection of a solute into a compartment. It is assumed that the injected solute instantaneously mixes with the solution in the compartment. Mathematically, a bolus is approximated as either a change in initial conditions or as an impulse function, $\delta(t)$.

Constant Continuous Infusion

A constant continuous infusion input is delivered by an infusion pump or an intravenous drip into a compartment. It is assumed that the injected solute instantaneously mixes with the solution in the compartment. Mathematically, a constant continuous infusion input is approximated as a unit step function, $u(t)$.

Encapsulated Pill or Hypodermic Needle Injection

An encapsulated pill or hypodermic needle injection provides a constant continuous input over a period of time. It is assumed that the diffused or injected solute instantaneously mixes with the solution in the compartment. Mathematically, an encapsulated pill or hypodermic needle injection is approximated by a pulse function, $u(t)-u(t-t_1)$, where t_1 is the duration of the pulse.

Depending on the type of input, the solute moves through the body via the circulatory system. We assume instantaneous mixing as the solute enters the system by action of the heart. In some situations, the solute enters the body through the digestive system and then through the plasma. The solute diffuses out of the circulatory system into the other compartments of the body. In general, the elimination of a solute from the body occurs through the kidneys; intestines; lungs, skin, and sweat; biotransformation (converted to another form) in the liver and other organs; and metabolized in tissues.

7.5 ONE-COMPARTMENT MODELING

The simplest compartment model consists of only one compartment. A one-compartment model is shown in Figure 7.8, where a box is used to define the compartment, and the flow of solute is defined by arrows. The input to the compartment can be any of those described in Section 7.4.1 or other types of functions. The output transfer rate, K_{10}, depicts the flow of solute from compartment 1 to the environment space, 0. The convention used in writing the transfer rate, K_{ij}, describes the flow of solute leaving compartment i, and entering compartment j. All transfer rates are given by $K_{ij} \geq 0$. While only one output is shown in Figure 7.8, there can be multiple outputs to different spaces, such as the urine, liver, and so on, and multiple inputs. As we will see, all of the outputs in this case can be combined into a single output by summing the transfer rates into a single transfer rate if convenient. There can be more than one input to the compartment, and if so, each input can be solved for separately using superposition, with zero initial conditions, and the natural response to the initial conditions.

To analyze the system in Figure 7.8, we use conservation of mass to write the differential equation describing the rate of change of the quantity of solute in the compartment, given as accumulation = input – output, where

$$\text{Accumulation} = \dot{q}_1$$
$$\text{Input} = f(t)$$
$$\text{Output} = K_{10}q_1$$

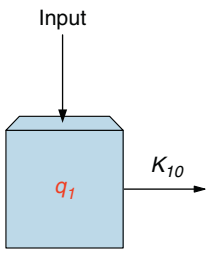

FIGURE 7.8 A one-compartment model. Assume the volume of the compartment is V_1. The input is $f(t)$.

Thus,

$$\dot{q}_1 = f(t) - K_{10}q_1 \tag{7.29}$$

The solution of Eq. (7.29) consists of the natural and forced responses. The natural response has the form $q_{1_n} = B_1 e^{-K_{10}t}$, where the root is $-K_{10}$. The forced response takes the form of the input. For instance, if the input is a constant continuous infusion, $u(t)$, the forced response is $q_{1_f} = \dfrac{1}{K_{10}}$. Thus, the complete unit step response is $q_{1_u} = q_{1_n} + q_{1_f} = \left(B_1 e^{-K_{10}t} + \dfrac{1}{K_{10}}\right)u(t)$, where B_1 is determined from the initial condition of the system. If the initial condition is zero, then $q_{1_u} = \dfrac{1}{K_{10}}\left(1 - e^{-K_{10}t}\right)u(t)$. If the initial condition is not zero, then $B_1 = q_1(0) - \dfrac{1}{K_{10}}$. If the magnitude of the unit step input is ζ, then the response with zero initial conditions is $q_{1_u} = \dfrac{\zeta}{K_{10}}\left(1 - e^{-K_{10}t}\right)u(t)$, and with initial condition $q_1(0)$ is $q_{1_u} = \left(\dfrac{\zeta}{K_{10}} - \left(\dfrac{\zeta}{K_{10}} - q_1(0)\right)e^{-K_{10}t}\right)u(t)$.

If the input is a bolus injection, $\delta(t)$, the solution method begins the same as the unit step response with zero initial conditions, and then the bolus response is $q_{1_\delta} = \dfrac{dq_{1_u}}{dt} = e^{-K_{10}t}u(t)$. If the input is $\zeta\delta(t)$, then the response is $q_{1_\delta} = \zeta e^{-K_{10}t}u(t)$.

If the input is hypodermic needle injection, $u(t)-u(t-t_1)$ with zero initial conditions, then the response based on superposition is $q_{1_p} = \dfrac{1}{K_{10}}\left(1 - e^{-K_{10}t}\right)u(t) - \dfrac{1}{K_{10}}\left(1 - e^{-K_{10}(t-t_1)}\right)u(t-t_1)$. If the input is $\zeta(u(t)-u(t-t_1))$, then the response is

$$q_{1_p} = \frac{\zeta}{K_{10}}\left(1 - e^{-K_{10}t}\right)u(t) - \frac{\zeta}{K_{10}}\left(1 - e^{-K_{10}(t-t_1)}\right)u(t-t_1).$$

7.5.1 Half-Life

When tracking a solute in the body, the half-life of the concentration is an important metric, where the half-life is the time required to reduce the concentration by 50 percent from maximum. Consider the case in which a bolus of $\zeta\delta(t)$ is injected into the system in Figure 7.8, with solution $q_{1_\delta} = \zeta e^{-K_{10}t}u(t)$. To find the half-life, $t_{\frac{1}{2}}$, we convert to concentration by letting $c_1 = \dfrac{q_{1_\delta}}{V_1} = \dfrac{\zeta}{V_1}e^{-K_{10}t}u(t)$, then set $c_1\left(t_{\frac{1}{2}}\right) = \dfrac{\zeta}{2V_1}$, and solve for $t_{\frac{1}{2}}$. Thus, we have

$$\frac{\zeta}{2V_1} = \frac{\zeta}{V_1}e^{-K_{10}t_{\frac{1}{2}}}$$

Taking the natural logarithm gives

$$\ln\left(\frac{1}{2}\right) = -K_{10}t_{\frac{1}{2}}$$

or

$$t_{\frac{1}{2}} = \frac{\ln(2)}{K_{10}} = \frac{.693}{K_{10}} \tag{7.30}$$

7.5.2 Washout Curve

A washout curve is a useful experimental technique for parameter estimation. The experiment begins with a continuous infusion of solute until the concentration reaches steady state. After reaching steady state, the input is stopped; the subsequent decay of solute from its maximum back to zero is called the washout curve. In essence, the input is a pulse input, $\zeta(u(t)-u(t-t_1))$, with a sufficiently large t_1 $\left(\text{much larger than } \frac{5}{K_{10}}\right)$, which has the solution

$$c_1 = \frac{q_{1_p}}{V_1} = \frac{\zeta}{V_1 K_{10}}\left(1 - e^{-K_{10}t}\right)u(t) - \frac{\zeta}{V_1 K_{10}}\left(1 - e^{-K_{10}(t-t_1)}\right)u(t-t_1). \tag{7.31}$$

The washout curve is the portion of the response from t_1 to ∞, which is essentially an impulse response beginning at t_1; ignoring the solution from 0 to t_1, and resetting time t_1 to 0, the washout curve is rewritten as

$$c_{1_{wo}} = \frac{\zeta}{V_1 K_{10}} e^{-K_{10}t} u(t) \tag{7.32}$$

From the experimental data and using Eq. (7.32), the time constant from the data gives K_{10}, and the initial value and time constant gives V_1. Note that the washout curve technique described here only works for one-compartment models.

The following example considers the uptake of radioactive iodine (I^{131}) by the thyroid gland in a very simplified model as depicted in Figure 7.9. We will return to modeling the thyroid system in Section 7.7.4. The compartment represents the plasma. The thyroid gland, located in the neck, absorbs iodine from blood and uses it to produce an iodine-containing hormone, primarily thyroxine, which is then secreted into the blood. Thyroxine increases the chemical reaction rate in the cell and overall metabolic rate of the body. The level of thyroxine is closely regulated by the hypothalamus and the pituitary gland. The hypothalamus releases thyroid releasing hormone (TRH) in reaction to thyroid levels in the blood. TRH stimulates the pituitary gland to release of thyroid-stimulating hormone (TSH), which causes a reaction in the thyroid. Thus, the thyroid gland is used to regulate the body's

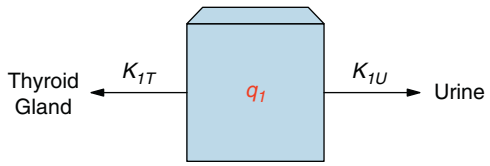

FIGURE 7.9 Illustration for Example Problem 7.5, where q_1 equals quantity of I^{131} in the plasma compartment.

metabolism. If the level of thyroxine is too low, TSH is released by the pituitary gland, which increases the release of thyroxine by the thyroid gland. If the level of thyroxine is too high, then less TSH is released, which reduces the production of thyroxine by the thyroid gland. To examine thyroid disorders, radioactive iodine (I^{131}) is given to the patient, and its uptake by the thyroid gland is measured. Simply put, too much iodine uptake is indicative of hyperthyroidism (too much thyroxine is produced) or too little uptake is indicative of hypothyroidism (too little thyroxine is produced). Removal of I^{131} from the plasma is via the urine by the kidneys or taken up by the thyroid gland.

EXAMPLE PROBLEM 7.5

Consider the removal of I^{131} for the plasma compartment shown in Figure 7.9. Assume that a bolus of I^{131} is injected into the plasma. I^{131} then moves from the plasma into the thyroid gland or is excreted into the urine. Assume the injected quantity of I^{131} in the plasma is $q_1(0)$. Find the response $q_1(t)$.

Solution

Our solution is easily considered by modeling the bolus as a change in initial condition at $t = 0$, and a zero input. Using conservation of mass, the differential equation describing the rate of change of the quantity of I^{131} in the plasma compartment is

$$\dot{q}_1 = -(K_{1T} + K_{1U})q_1$$

The solution is

$$q_1 = q_1(0)e^{-(K_{1T}+K_{1U})t}u(t)$$

Notice that the effect of the removal of I^{131} from the plasma is easily carried out with a single transfer rate, $K_{10} = K_{1T} + K_{1U}$, with no change in the outcome. However, if we are interested in tracking the uptake of I^{131} in the thyroid gland, separating the removals with two different transfer rates allow us to track it.

This example is also solved by applying an input of $q_1(0)\delta(t)$ with a zero initial condition. We start by solving for the response to $u(t)$, $q_{1_u}(t)$, differentiating the unit step response to yield the $\delta(t)$ response, $q_{1_\delta}(t)$, and scale by $q_1(0)$ to give $q_1(t)$.

Conservation of mass yields the following differential equation,

$$\dot{q}_1 = u(t) - (K_{1T} + K_{1U})q_1$$

which has the solution

$$q_{1_u} = \left(\frac{1 - e^{-(K_{1T}+K_{1U})t}}{K_{1T} + K_{1U}}\right)u(t)$$

The impulse response is

$$q_{1_\delta} = \dot{q}_{1_u} = e^{-(K_{1T}+K_{1U})t}u(t)$$

and scaled by $q_1(0)$, gives the response $q_1 = q_1(0)e^{-(K_{1T}+K_{1U})t}u(t)$. Note that treating a bolus as a change in initial conditions yields a much easier solution.

7.5.3 Pharmacokinetic Models

A pharmacokinetic model describes the movement of a drug or anesthetic agent to sites throughout the body, as shown in Figure 7.10. Much of the model focuses on drug absorption, distribution, metabolism, and excretion. Pharmacokinetic models usually have three or fewer compartments. Metabolic models have many more compartments than pharmacokinetic models, typically six or more compartments. Pharmacokinetic models usually are linear, whereas metabolic models are nonlinear in order to capture an adequate representation of the system. Pharmaceutical drugs do not appear naturally in the body and can be traced easily. Since metabolic solutes occur naturally in the body, following the movement of the solute is possible only with the use of isotopes.

Assume that the drug absorption site is the GI tract, where the drug passes to the blood via the liver. Since drugs are relatively small, they easily move through the capillary walls and into the interstitial fluid. From there, the drug then moves into the targeted organs and other tissues. As shown, the drug is removed via the kidneys, GI tract, and biotransformation in the liver and other sites. Transfer from compartment to compartment is through diffusion. The rate of movement from each compartment depends on the transfer rate. Typically, the removal of the drug from the body occurs more slowly than movement among the plasma, body fluids, and tissues. For example, tissues and organs that are highly perfused, such as the thyroid gland, liver, and kidney, have a large transfer rate, and tissues with low perfusion have a small transfer rate. If the removal transfer rates

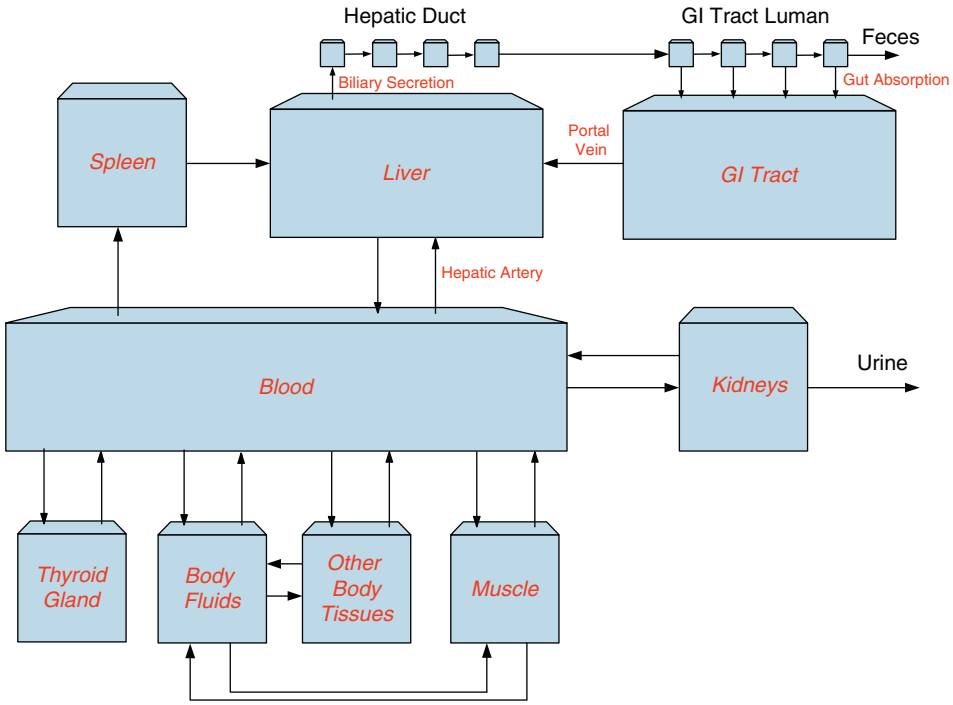

FIGURE 7.10 A pharmacokinetic model describing the movement of a solute in the body.

are considerably smaller than those associated with plasma, body fluids, and tissues, then the removal sites can be eliminated.

By eliminating the removal sites and combining the other compartments in Figure 7.10, we can reduce the model to a one-compartment model, as shown in Figure 7.8, with the drug absorption site as the input to the system. The removal rates can be combined into a single removal rate. While simplistic, this model allows one to judge the therapeutic and toxicological effects of a drug, persistence of the drug in the body, and under- and overdosing of the drug.

To represent the output from the absorption site, an exponential function is used as the input of the one-compartment model, $f(t) = q_2(0)e^{-\gamma t}u(t)$. For $t \geq 0$, the model is described as

$$\dot{q}_1 = q_2(0)e^{-\gamma t} - K_{10}q_1 \tag{7.33}$$

The natural response is the same as before, $q_{1_n} = B_1 e^{-K_{10}t}$. The forced response takes the form of the input, with $q_{1_f} = B_2 e^{-\gamma t}$. Substituting q_{1_f} and $\dot{q}_{1_f} = -\gamma B_2 e^{-\gamma t}$ into Eq. (7.33) gives $B_2 = \dfrac{q_2(0)}{K_{10} - \gamma}$, and $q_{1_f} = \dfrac{q_2(0)}{K_{10} - \gamma} e^{-\gamma t}$. The complete solution is

$$q_1 = q_{1_n} + q_{1_f} = \left(B_1 e^{-K_{10}t} + \frac{q_2(0)}{K_{10} - \gamma} e^{-\gamma t} \right) u(t),$$

where B_1 is determined from the initial condition of the system. With an initial condition of zero, then

$$B_1 = -\frac{q_2(0)}{K_{10} - \gamma},$$

and

$$q_1 = \frac{q_2(0)}{K_{10} - \gamma} \left(e^{-\gamma t} - e^{-K_{10}t} \right) u(t) \tag{7.34}$$

The time course for an exponentially drug administered is illustrated in Figure 7.11.

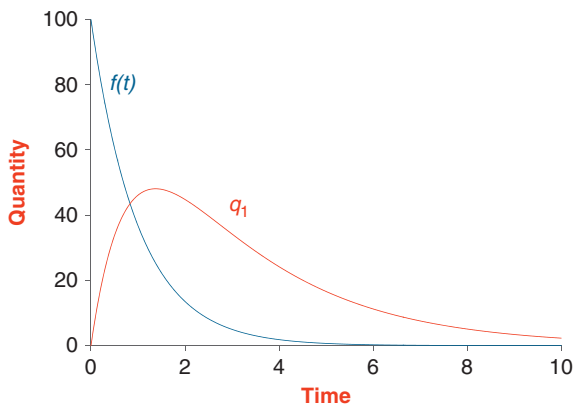

FIGURE 7.11 The time course for an exponentially administered drug. Values used: $q_2(0) = 100$, $K_{10} = 0.4$, and $\gamma = 1.2$.

To determine the time when the maximum drug is in the compartment, Eq. (7.34) is differentiated with respect to t, set equal to zero, and solved as follows:

$$\begin{aligned}\dot{q}_1 &= \frac{d}{dt}\left(\frac{q_2(0)}{K_{10}-\gamma}\left(e^{-\gamma t}-e^{-K_{10}t}\right)\right)\\ &= \frac{q_2(0)}{K_{10}-\gamma}\left(-\gamma e^{-\gamma t}+K_{10}e^{-K_{10}t}\right)\end{aligned} \tag{7.35}$$

Setting Eq. (7.35) equal to zero and $t = t_{\max}$ gives

$$\frac{q_2(0)}{K_{10}-\gamma}\left(-\gamma e^{-\gamma t_{\max}}+K_{10}e^{-K_{10}t_{\max}}\right)=0$$

or

$$\gamma e^{-\gamma t_{\max}} = K_{10}e^{-K_{10}t_{\max}} \tag{7.36}$$

Multiplying both sides of Eq. (7.36) by $e^{K_{10}t_{\max}}$ and dividing by γ yields

$$e^{K_{10}t_{\max}}e^{-\gamma t_{\max}} = e^{(K_{10}-\gamma)t_{\max}} = \frac{K_{10}}{\gamma} \tag{7.37}$$

Taking the logarithm of both sides of Eq. (7.37), we have

$$(K_{10}-\gamma)t_{\max} = \ln\left(\frac{K_{10}}{\gamma}\right)$$

Solving for $t_{\max}$ yields

$$t_{\max} = \frac{\ln\left(\frac{K_{10}}{\gamma}\right)}{K_{10}-\gamma} \tag{7.38}$$

The maximum quantity of drug in the compartment is

$$q_1(t_{\max}) = \frac{q_2(0)}{K_{10}-\gamma}\left(e^{-\gamma t_{\max}}-e^{-K_{10}t_{\max}}\right)\Bigg|_{t_{\max}=\frac{\ln\left(\frac{K_{10}}{\gamma}\right)}{K_{10}-\gamma}}$$

$$= \frac{q_2(0)}{K_{10}-\gamma}\left(e^{-\frac{\gamma}{K_{10}-\gamma}\ln\left(\frac{K_{10}}{\gamma}\right)}-e^{-\frac{K_{10}}{K_{10}-\gamma}\ln\left(\frac{K_{10}}{\gamma}\right)}\right)$$

$$= \frac{q_2(0)}{K_{10}-\gamma}\left(e^{\ln\left(\left(\frac{K_{10}}{\gamma}\right)^{-\frac{\gamma}{K_{10}-\gamma}}\right)} - e^{\ln\left(\left(\frac{K_{10}}{\gamma}\right)^{-\frac{K_{10}}{K_{10}-\gamma}}\right)} \right) = \frac{q_2(0)}{K_{10}-\gamma}\left(\left(\frac{K_{10}}{\gamma}\right)^{-\frac{\gamma}{K_{10}-\gamma}} - \left(\frac{K_{10}}{\gamma}\right)^{-\frac{K_{10}}{K_{10}-\gamma}} \right)$$

$$= \frac{q_2(0)}{K_{10}-\gamma}\left(\left(\frac{\gamma}{K_{10}}\right)^{\frac{\gamma}{K_{10}-\gamma}} - \left(\frac{\gamma}{K_{10}}\right)^{\frac{K_{10}}{K_{10}-\gamma}} \right) = \frac{q_2(0)}{K_{10}-\gamma}\left(\frac{\gamma}{K_{10}}\right)^{\frac{K_{10}}{K_{10}-\gamma}}\left(\left(\frac{\gamma}{K_{10}}\right)^{\frac{\gamma-K_{10}}{K_{10}-\gamma}} - 1 \right)$$

$$= \frac{q_2(0)}{K_{10}-\gamma}\left(\frac{\gamma}{K_{10}}\right)^{\frac{K_{10}}{K_{10}-\gamma}}\left(\left(\frac{K_{10}}{\gamma}\right) - 1 \right) = \frac{q_2(0)}{K_{10}-\gamma}\left(\frac{\gamma}{K_{10}}\right)^{\frac{K_{10}}{K_{10}-\gamma}}\left(\frac{K_{10}-\gamma}{\gamma}\right)$$

$$= \frac{q_2(0)}{\gamma}\left(\frac{\gamma}{K_{10}}\right)^{\frac{K_{10}}{K_{10}-\gamma}} \tag{7.39}$$

The maximum concentration of the drug is

$$c_1(t_{\max}) = \frac{q_2(0)}{V_1\gamma}\left(\frac{\gamma}{K_{10}}\right)^{\frac{K_{10}}{K_{10}-\gamma}} \tag{7.40}$$

With an exponential input, the maximum drug concentration occurs at time $t_{\max} = \ln\frac{\left(\frac{K_{10}}{\gamma}\right)}{K_{10}-\gamma}$ with value $\frac{q_2(0)}{V_1\gamma}\left(\frac{\gamma}{K_{10}}\right)^{\frac{K_{10}}{K_{10}-\gamma}}$ according to Eqs. (7.38) and (7.40). When giving a bolus injection, the maximum drug concentration occurs at time 0 with value $\frac{q_2(0)}{V_1}$ according to Example Problem 7.5. Thus, a bolus injection achieves a higher concentration of the drug in the plasma and is faster than an exponential input.

When administering a drug in the body, the persistence of the drug is an important parameter to judge the clinical effectiveness and to determine a dose administration schedule. To produce a therapeutic effect, a minimum drug concentration in the plasma is required so the drug can diffuse to its target site. Maximum drug concentration is an important parameter, since a dosage at too high a level can be toxic. The next section describes how to maintain a minimum and maximum dosage.

7.5.4 Repeat Dosages

To maintain the concentration of a drug in the body, the drug must be administered on a regular basis to keep the concentration above a minimum value. For simplicity, assume the model in Figure 7.8 and Eq. (7.29), and that the input is a series of boluses, with magnitude

ζ, and the time between dosages is T. With the first dose administered at $t = 0$ and zero initial conditions, we have

$$q_1(t) = \zeta e^{-K_{10}t}$$

for $0 < t < T$. The maximum quantity in the compartment is at $t = 0$, and the minimum is at $t = T^-$. At $t = T$, the second dose is given, and according to superposition, the quantity is

$$q_1(t) = \zeta e^{-K_{10}t} + \zeta e^{-K_{10}(t-T)}$$

for $T \leq t < 2T$, with a maximum of $\zeta e^{-K_{10}T} + \zeta$ at $t = T$, and a minimum of $\zeta e^{-K_{10}2T^-} + \zeta e^{-K_{10}T^-} = \zeta e^{-K_{10}T^-}\left(1 + \zeta e^{-K_{10}T^-}\right)$ at $t = 2T^-$.

In general, for any interval $(n-1)T \leq t < nT$, we have

$$q_1(t) = \zeta e^{-K_{10}t} + \zeta e^{-K_{10}(t-T)} + \cdots + \zeta e^{-K_{10}(t-(n-2)T)} + \zeta e^{-K_{10}(t-(n-1)T)}$$

with the maximum in the interval at $t = (n-1)T$ of

$$q_{1_{\max}}((n-1)T) = \zeta e^{-K_{10}(n-1)T} + \zeta e^{-K_{10}(n-2)T} + \cdots + \zeta e^{-K_{10}T} + \zeta \tag{7.41}$$

Equation (7.41) is written in closed form as

$$q_{1_{\max}}((n-1)T) = \zeta\left(\frac{1 - e^{-K_{10}nT}}{1 - e^{-K_{10}T}}\right) \tag{7.42}$$

To find the minimum quantity at $t = nT^-$,

$$q_{1_{\min}}(nT^-) = \zeta e^{-K_{10}nT^-} + \zeta e^{-K_{10}(n-1)T^-} + \cdots + \zeta e^{-K_{10}2T^-} + \zeta e^{-K_{10}T^-} \tag{7.43}$$

Next, we write a closed form expression for Eq. (7.43), giving

$$q_{1_{\min}}(nT^-) = \zeta e^{-K_{10}T^-}\left(\frac{1 - e^{-K_{10}nT^-}}{1 - e^{-K_{10}T^-}}\right) \tag{7.44}$$

As $n \to \infty$, Eq. (7.42) approaches

$$q_{1_{\max}} = \frac{\zeta}{1 - e^{-K_{10}T}} \tag{7.45}$$

and Eq. (7.43) approaches

$$q_{1_{\min}} = \frac{\zeta e^{-K_{10}T}}{1 - e^{-K_{10}T}} \tag{7.46}$$

With the parameter values shown in Figure 7.12, the maximum approaches

$$q_{1_{\max}} = \frac{\zeta}{1 - e^{-K_{10}T}} = 3.86$$

and the minimum approaches

$$q_{1_{\min}} = \frac{\zeta e^{-K_{10}T}}{1 - e^{-K_{10}T}} = 2.86$$

To convert the quantities into concentrations, simply divide them by the volume of the compartment.

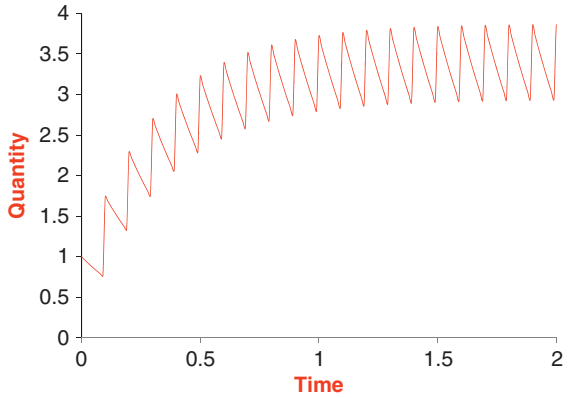

FIGURE 7.12 Illustration of change in quantity due to repeated bolus injections using a one-compartment model. Values used: $\zeta = 1$, $K_{10} = 3$, and $T = 0.1$.

EXAMPLE PROBLEM 7.6

A 3 g bolus of antibiotic is administered to a human with a plasma volume of 3 L. The average impulse response for this drug is shown in Figure 7.13. Assuming a one-compartment model, determine the transfer rate. If the concentration of the drug is not to fall below 30 percent of the initial dosage at steady state, how often does the drug need to be given to maintain this minimum level?

Solution

To determine the transfer rate, K_{10}, the curve in Figure 7.13 is used to determine the half-life, which is approximately $t_{\frac{1}{2}} = 1.4$. Using Eq. (7.4.2), $t_{\frac{1}{2}} = 1.4 = \dfrac{\ln(2)}{K_{10}}$, K_{10} is found as

$$K_{10} = \frac{\ln(2)}{1.4} \simeq 0.5$$

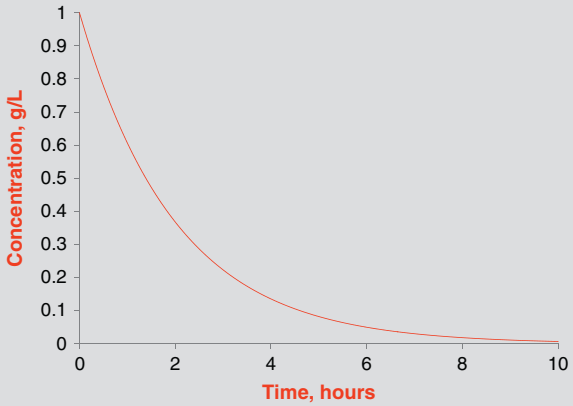

FIGURE 7.13 Illustration for Example Problem 7.6 with 3 g bolus in a 3 L plasma compartment.

In the first interval, $c_1 = \dfrac{q_1(0)e^{-\frac{t}{2}}}{V_1} = e^{-\frac{t}{2}}$, and $c_{1_{\min}}$ equals 30 percent of the initial value, or $c_{1_{\min}} = 0.3$. At steady state, the minimum concentration is determined from Eq. (7.46) as

$$c_{1_{\min}} = 0.3 = \frac{\zeta e^{-K_{10}T}}{V_1(1 - e^{-K_{10}T})} = \frac{e^{-\frac{T}{2}}}{\left(1 - e^{-\frac{T}{2}}\right)}$$

Solving the previous equation for T, we have $T \simeq 3$ hours. Thus, the antibiotic needs to be administered every 3 hours, as shown in Figure 7.14.

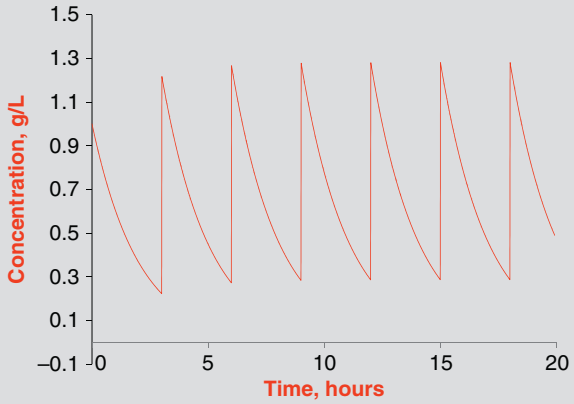

FIGURE 7.14 Change in concentration with a repeat dose of the antibiotic every 3 hours.

7.6 TWO-COMPARTMENT MODELING

The general form of the two-compartment model is shown in Figure 7.15. Here we assume that all transfer rates are constants and $K_{ij} \geq 0$.

We begin with the general form of the two-compartment model and then examine special cases with some of the transfer rates or inputs set equal to zero and other considerations. To analyze the system in Figure 7.15, conservation of mass is used to write a differential equation for each compartment describing the rate of change of the quantity of solute in the compartment, given as accumulation = input – output, where

Compartment 1	Compartment 2
Accumulation $= \dot{q}_1$	Accumulation $= \dot{q}_2$
Input $= f_1(t) + K_{21}q_2$	Input $= f_2(t) + K_{12}q_1$
Ouput $= (K_{10} + K_{12})q_1$	Ouput $= (K_{20} + K_{21})q_2$

Therefore,

$$\begin{aligned} \dot{q}_1 &= f_1(t) + K_{21}q_2 - (K_{10} + K_{12})q_1 \\ \dot{q}_2 &= f_2(t) + K_{12}q_1 - (K_{20} + K_{21})q_2 \end{aligned} \tag{7.47}$$

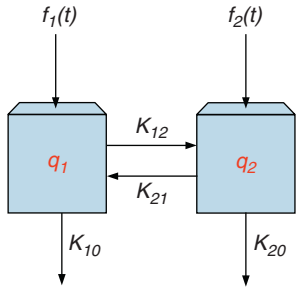

FIGURE 7.15 A general two-compartment model. Compartment 1 has volume V_1 and compartment 2 has volume V_2.

The easiest way to analyze the system in Eq. (7.47) is using the D-Operator or its equivalent, the Laplace variable s, where we represent the system in matrix form as

$$D\mathbf{IQ} = \mathbf{AQ} + \mathbf{F} \tag{7.48}$$

where

$$\mathbf{Q} = \begin{bmatrix} q_1 \\ q_2 \end{bmatrix}, \mathbf{A} = \begin{bmatrix} -(K_{10} + K_{12}) & K_{21} \\ K_{12} & -(K_{20} + K_{21}) \end{bmatrix}, \mathbf{F} = \begin{bmatrix} f_1(t) \\ f_2(t) \end{bmatrix}$$

Equation (7.48) is solved as

$$\mathbf{Q} = (D\mathbf{I} - \mathbf{A})^{-1}\mathbf{F} = \frac{1}{\det(D\mathbf{I} - \mathbf{A})}\text{adj}(D\mathbf{I} - \mathbf{A})\mathbf{F}$$

or

$$\det(D\mathbf{I} - \mathbf{A})\mathbf{Q} = \text{adj}(D\mathbf{I} - \mathbf{A})\mathbf{F} \tag{7.49}$$

and using MATLAB, we have

```
>> syms D q1 q2 K10 K20 K12 K21
>> A=[-(K10+K12) K21;K12 -(K20+K21)]
>> det(D*eye(2)-A)
ans =
  D^2+D*K20+D*K21+K10*D+K10*K20+K10*K21+K12*D+K12*K20
>> adj=det(D*eye(2)-A)*inv(D*eye(2)-A)

  adj =
  [ D+K20+K21,    K21]
  [    K12, D+K10+K12]
```

Substituting these values from MATLAB into Eq. (7.49) gives

$$\begin{aligned}\left(D^2 + D(K_{10} + K_{12} + K_{20} + K_{21}) + (K_{10}K_{20} + K_{10}K_{21} + K_{12}K_{20})\right)\mathbf{Q} \\ = \begin{bmatrix} D + (K_{20} + K_{21}) & K_{21} \\ K_{12} & D + (K_{10} + K_{12}) \end{bmatrix}\mathbf{F}\end{aligned} \tag{7.50}$$

Returning to the time domain, we have the following independent differential equations:

$$\begin{aligned}\ddot{q}_1 + (K_{10} + K_{12} + K_{20} + K_{21})\dot{q}_1 + (K_{10}K_{20} + K_{10}K_{21} + K_{12}K_{20})q_1 \\ = \frac{df_1(t)}{dt} + (K_{20} + K_{21})f_1(t) + K_{21}f_2(t) \\ \ddot{q}_2 + (K_{10} + K_{12} + K_{20} + K_{21})\dot{q}_2 + (K_{10}K_{20} + K_{10}K_{21} + K_{12}K_{20})q_2 \\ = K_{12}\,f_1(t) + \frac{df_2(t)}{dt} + (K_{10} + K_{12})f_2(t)\end{aligned} \tag{7.51}$$

Note that the characteristic equation, $\det(D\mathbf{I} - \mathbf{A})$, is identical for both q_1 and q_2, and the form of the natural response is the same for either variable. Also note that the coefficients in the natural response are not identical for q_1 and q_2, and depend on the input to the compartment and the initial conditions.

The roots of the characteristic equation are determined using MATLAB as

```
>> eig(A)
ans =
-1/2*K10-1/2*K12-1/2*K20-1/2*K21+1/2*(K10^2+2*K10*K12-
2*K10*K20-2*K10*K21+K12^2-2*K12*K20+2*K21*K12+K20^2+
2*K20*K21+K21^2)^(1/2)

-1/2*K10-1/2*K12-1/2*K20-1/2*K21-1/2*(K10^2+2*K10*K12-
2*K10*K20-2*K10*K21+K12^2-2*K12*K20+2*K21*K12+K20^2+
2*K20*K21+K21^2)^(1/2)
```

This expression simplifies to

$$s_{1,2} = -\frac{(K_{10} + K_{12} + K_{20} + K_{21})}{2} \pm \frac{1}{2}\sqrt{(K_{20} + K_{21} - K_{10} - K_{12})^2 + 4K_{21}K_{12}} \tag{7.52}$$

From Eq. (7.52), we note that there can be no positive real roots and no imaginary roots if all $K_{ij} \geq 0$. If $(K_{20} + K_{21} - K_{10} - K_{12})^2 + 4K_{21}K_{12} = 0$, then the roots are repeated and equal to $s_{1,2} = -\dfrac{(K_{10} + K_{12} + K_{20} + K_{21})}{2}$. For repeated roots to happen, $(K_{20} + K_{21})$ must equal $(K_{10} + K_{12})$, and either K_{21} or K_{12} must be zero. If K_{21} and K_{12} are both equal to zero, then there is no movement of solute between the compartments.

In the following example, we revisit Fick's Law of diffusion using compartmental analysis and compute the concentration. The difference in analysis involves the transfer rates as

functions of the volume of each compartment—that is $K_{12} = \frac{K}{V_1}$ and $K_{21} = \frac{K}{V_2}$, where $K = \frac{DA}{\Delta x}$. The system in Example 7.7 is called a *closed compartment* because there is no output to the environment in a closed system.

EXAMPLE PROBLEM 7.7

Consider the two-compartment model in Figure 7.16, with $q_1(0) = \zeta$ and $q_2(0) = 0$. Solve for the concentration in each compartment.

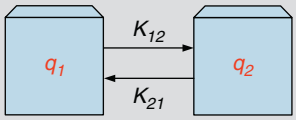

FIGURE 7.16 Illustration for Example Problem 7.7.

Solution

Conservation of mass for each compartment is

$$\dot{q}_1 = K_{21}q_2 - K_{12}q_1$$
$$\dot{q}_2 = K_{12}q_1 - K_{21}q_2$$

Using the D-Operator method gives

$$\ddot{q}_1 + (K_{12} + K_{21})\dot{q}_1 = 0$$
$$\ddot{q}_1 + (K_{12} + K_{21})\dot{q}_2 = 0$$

The roots are $s_{1,2} = 0, -(K_{12} + K_{21})$, which gives

$$q_1(t) = B_1 + B_2 e^{-(K_{12}+K_{21})t}$$
$$q_2(t) = B_3 + B_4 e^{-(K_{12}+K_{21})t}$$

We use the initial conditions to solve for B_i as follows

$$q_1(0) = \zeta = B_1 + B_2 e^{-(K_{12}+K_{21})t}|_{t=0} = B_1 + B_2$$

To find $\dot{q}_1(0)$, we use the conservation of mass equation for $\dot{q}_1$ at time zero

$$\dot{q}_1(0) = K_{21}q_2(0) - K_{12}q_1(0) = -K_{12}\zeta$$

and from the solution,

$$\dot{q}_1 = \frac{d\left(B_1 + B_2 e^{-(K_{12}+K_{21})t}\right)}{dt} = -(K_{12} + K_{21})B_2 e^{-(K_{12}+K_{21})t}$$

$$\dot{q}_1(0) = -K_{12}\zeta = -(K_{12} + K_{21})B_2$$

To solve for B_1 and B_2, we evaluate

$$\begin{bmatrix} 1 & 1 \\ 0 & -(K_{12}+K_{21}) \end{bmatrix} \begin{bmatrix} B_1 \\ B_2 \end{bmatrix} = \begin{bmatrix} \zeta \\ -K_{12}\zeta \end{bmatrix}$$

which gives

$$\begin{bmatrix} B_1 \\ B_2 \end{bmatrix} = \begin{bmatrix} \dfrac{\zeta K_{21}}{(K_{12}+K_{21})} \\ \dfrac{\zeta K_{12}}{(K_{12}+K_{21})} \end{bmatrix}$$

and

$$q_1(t) = \frac{\zeta}{(K_{12}+K_{21})}\left(K_{21} + K_{12}e^{-(K_{12}+K_{21})t}\right)u(t)$$

The concentration is

$$c_1(t) = \frac{\zeta}{V_1(K_{12}+K_{21})}\left(K_{21} + K_{12}e^{-(K_{12}+K_{21})t}\right)u(t)$$

Repeating the same steps for q_2 as before gives

$$q_2(t) = \frac{K_{12}\zeta}{(K_{12}+K_{21})}\left(1 - e^{-(K_{12}+K_{21})t}\right)u(t)$$

and

$$c_2(t) = \frac{K_{12}\zeta}{V_2(K_{12}+K_{21})}\left(1 - e^{-(K_{12}+K_{21})t}\right)u(t)$$

or using $q_2 = \zeta - q_1$ gives the same result.

A more straightforward solution involves substituting $q_2 = \zeta - q_1$ into $\dot{q}_1 = K_{21}q_2 - K_{12}q_1$, and solving $\dot{q}_1 = K_{21}(\zeta - q_1) - K_{12}q_1 = K_{21}\zeta - (K_{21}+K_{12})q_1$.

If $K_{12} = \dfrac{K}{V_1}$ and $K_{21} = \dfrac{K}{V_2}$, and $V_1 = V_2 = V$, then these results are the same as those computed using Fick's Law of diffusion in Section 7.2.2:

$$c_1 = \frac{\zeta}{2}\left(e^{\frac{-Kt}{V}} + 1\right)u(t)$$

and

$$c_2 = \frac{\zeta}{2}\left(1 - e^{\frac{-Kt}{V}}\right)u(t)$$

In a two-compartment model, the half-life is defined using two terms based on the roots of the characteristic equation. The half-life associated with the smaller root is called the elimination half-life, and the distribution half-life is used for the larger root.

7.6.1 Source Compartment

A compartment that only outputs to other compartments, without any inputs from other compartments, is called a source compartment. A source compartment has an input $f(t)$. This type of compartment is simply a one-compartment model that can be solved independently of the other compartments in the system. The output of the source compartment is an exponential decay, as described in Section 7.5. While in many situations, the source compartment does not send the solute to the environment, it is perfectly fine for a source compartment to do so.

Using the model shown in Figure 7.15, a source compartment exists if either K_{12} or K_{21} is zero. For repeated roots in a two-compartment model, a source compartment must be one of the compartments and $(K_{20} + K_{21})$ must equal $(K_{10} + K_{12})$.

In Example Problem 7.8, the digestive system is introduced as a source compartment. By including a digestive system component, the solute is not instantaneously delivered into the plasma but is slowly released from the digestive system into the plasma through a bolus input.

EXAMPLE PROBLEM 7.8

Consider the two-compartment model shown in Figure 7.17 with the ingestion of a bolus solute in the digestive system and removal of the solute via metabolism and excretion in urine. Solve for the plasma concentration.

Solution

This model has a source compartment. Rather than solving the problem with a bolus input, the initial condition is changed to $q_2(0)$ with no input. The conservation of mass for each compartment is

$$\dot{q}_1 = K_{21}q_2 - (K_{1M} + K_{1U})q_1 \tag{7.53}$$

$$\dot{q}_2 = -K_{21}q_2 \tag{7.54}$$

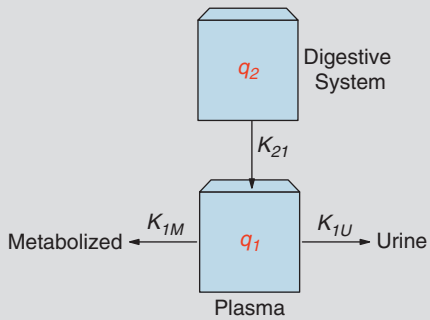

FIGURE 7.17 A two-compartment model with realistic ingestion of solute and removal from the plasma by metabolism and excretion in urine. It normally takes about 30 minutes to pass through the digestive system.

Since Eq. (7.54) involves only q_2, it is easily solved as $q_2 = q_2(0)e^{-K_{21}t}u(t)$. By substituting the solution for q_2 into Eq. (7.53), we now have one equation, giving

$$\dot{q}_1 = q_2(0)K_{21}e^{-K_{21}t} - (K_{1M} + K_{1U})q_1$$

and after rearranging

$$\dot{q}_1 + (K_{1M} + K_{1U})q_1 = q_2(0)K_{21}e^{-K_{21}t} \tag{7.55}$$

This is a first-order differential equation with a forcing function $q_2(0)K_{21}e^{-K_{21}t}$. The natural solution is $q_{1_n} = B_1e^{-(K_{1M}+K_{1U})t}$ and the forced response is $q_{1_f} = B_2e^{-K_{21}t}$. To determine B_2, $q_{1_f} = B_2e^{-K_{21}t}$ is substituted into Eq. (7.55), which gives

$$-K_{21}B_2e^{-K_{21}t} + (K_{1M} + K_{1U})B_2e^{-K_{21}t} = q_2(0)K_{21}e^{-K_{21}t}$$

Solving for B_2 gives

$$B_2 = \frac{q_2(0)K_{21}}{K_{1M} + K_{1U} - K_{21}}$$

The complete response is

$$\begin{aligned} q_1 &= q_{1_n} + q_{1_f} = B_1e^{-(K_{1M}+K_{1U})t} + B_2e^{-K_{21}t} \\ &= B_1e^{-(K_{1M}+K_{1U})t} + \frac{q_2(0)K_{21}}{K_{1M} + K_{1U} - K_{21}}e^{-K_{21}t} \end{aligned} \tag{7.56}$$

B_1 is found using the initial condition $q_1(0) = 0$

$$q_1(0) = 0 = \left[B_1e^{-(K_{1M}+K_{1U})t} + \frac{q_2(0)K_{21}}{K_{1M} + K_{1U} - K_{21}}e^{-K_{21}t}\right]_{t=0} = B_1 + \frac{q_2(0)K_{21}}{K_{1M} + K_{1U} - K_{21}}$$

giving

$$B_1 = -\frac{q_2(0)K_{21}}{K_{1M} + K_{1U} - K_{21}}$$

and

$$q_1 = \frac{q_2(0)K_{21}}{K_{1M} + K_{1U} - K_{21}}\left(e^{-K_{21}t} - e^{-(K_{1M}+K_{1U})t}\right)u(t) \tag{7.57}$$

or in terms of concentration,

$$c_1 = \frac{1}{V_1}\frac{q_2(0)K_{21}}{(K_{1M} + K_{1U} - K_{21})}\left(e^{-K_{21}t} - e^{-(K_{1M}+K_{1U})t}\right)u(t) \tag{7.58}$$

To determine the time when the maximum solute is in compartment 1 in Example Problem 7.8, Eq. (7.57) is differentiated with respect to t, set equal to zero, and solved as follows:

$$\begin{aligned} \dot{q}_1 &= \frac{d}{dt}\left(\frac{q_2(0)K_{21}}{K_{1M} + K_{1U} - K_{21}}\left(e^{-K_{21}t} - e^{-(K_{1M}+K_{1U})t}\right)\right) \\ &= \frac{q_2(0)K_{21}}{K_{1M} + K_{1U} - K_{21}}\left(-K_{21}e^{-K_{21}t} + (K_{1M} + K_{1U})e^{-(K_{1M}+K_{1U})t}\right) \end{aligned} \tag{7.59}$$

Setting Eq. (7.59) equal to zero and $t = t_{\max}$ gives

$$\frac{q_2(0)K_3}{K_{1M}+K_{1U}-K_{21}}\left(-K_{21}e^{-K_{21}t_{\max}}+(K_{1M}+K_{1U})e^{-(K_{1M}+K_{1U})t_{\max}}\right)=0$$

or

$$K_{21}e^{-K_{21}t_{\max}}=(K_{1M}+K_{1U})e^{-(K_{1M}+K_{1U})t_{\max}}$$

Multiplying both sides of the previous equation by $e^{(K_{1M}+K_{1U})t_{\max}}$ and dividing by K_{21} gives

$$e^{(K_{1M}+K_{1U})t}e^{-K_{21}t_{\max}}=e^{(K_{1M}+K_{1U}-K_{21})t}=\frac{K_{1M}+K_{1U}}{K_{21}}$$

Taking the logarithm of both sides gives

$$(K_{1M}+K_{1U}-K_{21})t_{\max}=\ \ln\left(\frac{K_{1M}+K_{1U}}{K_{21}}\right)$$

Solving for $t_{\max}$ yields

$$t_{\max}=\frac{\ln\left(\frac{K_{1M}+K_{1U}}{K_{21}}\right)}{(K_{1M}+K_{1U}-K_{21})} \tag{7.60}$$

It should be clear from Eq. (7.59) that the smaller the term $K_{1M}+K_{1U}$ compared to K_{21}, the more time it takes to reach the maximum concentration or quantity in the plasma.

EXAMPLE PROBLEM 7.9

Suppose 50 g of solute is ingested. Find the maximum amount of solute in the plasma if the compartmental model in Figure 7.17 is used with $K_{1M}+K_{1U}=0.005\ \text{min}^{-1}$ and $K_{21}=0.02\ \text{min}^{-1}$.

Solution

Using Eq. (7.60) gives

$$t_{\max}=\frac{\ln\left(\frac{K_{1M}+K_{1U}}{K_{21}}\right)}{(K_{1M}+K_{1U}-K_{21})}=\frac{\ln\left(\frac{0.005}{0.02}\right)}{0.005-0.02}=\frac{\ln(0.25)}{-0.015}=92.42\ \text{min}$$

The maximum amount of solute in compartment 1 at $t_{\max}$ is therefore

$$q_1(t_{\max})=\frac{q_2(0)K_{21}}{K_{1M}+K_{1U}-K_{21}}\left(e^{-K_{21}t}-e^{-(K_{1M}+K_{1U})t}\right)\Big|_{t=92.42}$$

$$=\frac{50\times0.02}{0.005-0.02}\left(e^{-0.02\times92.42}-e^{-0.005\times92.42}\right)=31.5\ \text{g}$$

The next example introduces an encapsulated pill input that releases a portion immediately and the remainder continuously until the pill completely dissolves. Mathematically this input is approximated as $\zeta\delta(t)+(1-\zeta)(u(t)-u(t-t_0))$. To estimate the gastric transfer

rate and the fraction released immediately experimentally, the pill is dissolved in a solution similar to the stomach, and the concentration is measured. From this data, parameter values can be determined.

EXAMPLE PROBLEM 7.10

Consider the two-compartment model shown in Figure 7.15 with $K_{12} = K_{20} = 0$, $K_{21} = K_{10} = 0.2$, $f_1(t) = 0$, and $f_2(t) = 20\delta(t) + 80(u(t)-u(t-30))$. Assume that the initial conditions are zero (not including that provided by $20\delta(t)$). Solve for the quantity in each compartment.

Solution

Since $K_{12} = 0$, this model has a source compartment. The solution is carried out using superposition, separating the input $f_2(t)$ into $20\delta(t)$, $80u(t)$, and $80u(t-30)$, and then summing the individual responses to get the complete response.

The conservation of mass for each compartment is

$$\dot{q}_1 = 0.2q_2 - 0.2q_1 \tag{7.61}$$

$$\dot{q}_2 = f_2 - 0.2q_2 \tag{7.62}$$

20δ(t) *Input*

First, consider the $20\delta(t)$ input. As in Example Problem 7.8, we treat the impulse input as a change in an initial condition, yielding $q_{2_\delta} = 20e^{-0.2t}u(t)$. Substituting this result into Eq. (7.61) gives

$$\dot{q}_{1_\delta} = 4e^{-0.2t} - 0.2q_{1_\delta} \tag{7.63}$$

The root for Eq. (7.63) is $s = -0.2$, and has a natural solution $q_{1_n} = B_1e^{-0.2t}$. The input in Eq. (7.63) has the same form as the natural solution (expected since $(K_{20} + K_{21})$ equals $(K_{10} + K_{12})$ and $K_{12} = 0$), and so the forced response is $q_{1_f} = B_2te^{-0.2t}$. Substituting q_{1_f} into Eq. (7.63) gives $B_2 = 4$. The complete response is

$$q_{1_\delta} = q_{1_n} + q_{1_f} = B_1e^{-0.2t} + 4te^{-0.2t} \tag{7.64}$$

B_1 is found using the initial condition $q_1(0) = 0$ and

$$q_{1_\delta}(0) = 0 = \left[B_1e^{-0.2t} + 4te^{-0.2t}\right]_{t=0} = B_1$$

Thus,

$$q_{1_\delta} = 4te^{-0.2t}u(t) \tag{7.65}$$

80u(t) *Input*

Next, consider the $80u(t)$ input. The conservation of mass equations are

$$\dot{q}_{1_u} = 0.2q_{2_u} - 0.2q_{1_u} \tag{7.66}$$

$$\dot{q}_{2_u} = 80 - 0.2q_{2_u} \tag{7.67}$$

Continued

Solving Eq. (7.67) gives $q_{2_u} = 400\left(1 - e^{-0.2t}\right)$. Substituting q_{2_u} into Eq. (7.66) gives

$$\dot{q}_{1_u} = 80\left(1 - e^{-0.2t}\right) - 0.2q_{1_u} \tag{7.68}$$

The root for Eq. (7.68) is $s = -0.2$, and has a natural solution $q_{1_n} = B_1 e^{-0.2t}$. The input in Eq. (7.66) has the same term as in the natural solution, and so the forced response is $q_{1_f} = B_3 + B_2 t e^{-0.2t}$. Substituting q_{1_f} into Eq. (7.68) gives $B_2 = -80$ and $B_3 = 400$. The complete response is

$$q_{1_u} = q_{1_n} + q_{1_f} = B_1 e^{-0.2t} + 400 - 80te^{-0.2t} \tag{7.69}$$

B_1 is found using the initial condition $q_1(0) = 0$ and

$$q_{1_u}(0) = 0 = \left[B_1 e^{-0.2t} + 400 - 80te^{-0.2t}\right]_{t=0} = B_1 + 400$$

and $B_1 = -400$. Thus,

$$q_{1_u} = \left(400 - 400e^{-0.2t} - 80te^{-0.2t}\right)u(t) \tag{7.70}$$

$-80u(t-30)$ *Input*

Next, consider the $-80u(t - 30)$ input. By the property of a linear system, then

$$q_{1_{u-30}} = -\left(400 - 400e^{-0.2(t-30)} - 80(t-30)e^{-0.2(t-30)}\right)u(t-30)$$

$$q_{2_{u-30}} = -400\left(1 - e^{-0.2(t-30)}\right)u(t-30)$$

Complete Solution

The complete response is

$$q_1 = q_{1_\delta} + q_{1_u} + q_{1_{u-30}} = 4te^{-0.2t}u(t) + \left(400 - 400e^{-0.2t} - 80te^{-0.2t}\right)u(t) - \left(400 - 400e^{-0.2(t-30)} - 80(t-30)e^{-0.2(t-30)}\right)u(t-30)$$

$$q_2 = q_{2_\delta} + q_{2_u} + q_{2_{u-30}} = 20e^{-0.2t}u(t) + 400\left(1 - e^{-0.2t}\right)u(t) - 400\left(1 - e^{-0.2(t-30)}\right)u(t-30)$$

which is plotted in Figure 7.18.

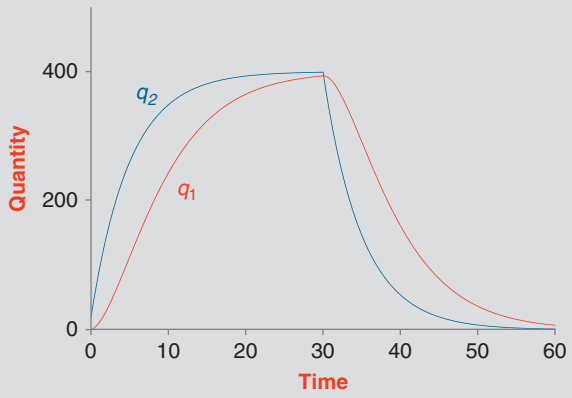

FIGURE 7.18 Plot of the solute quantities for Example Problem 7.10.

When delivering anesthesia, a similar input is used as in Example Problem 7.10—that is, a bolus plus constant infusion. The reason for this type of input is to quickly raise the anesthesia to a desired level (bolus) and then to maintain the level for the operation (step).

7.6.2 Sink Compartment

A sink compartment is one that has only inputs and no output. Similar to the source compartment, a sink acts like an integrator and has a zero root. Moreover, the solution of the nonsink compartment is independent of the sink compartment in the two-compartment case. Once solved, the quantity in the nonsink compartment is used to solve the quantity in the sink compartment. Using the model shown in Figure 7.15, a sink compartment exists if either K_{12} and K_{10}, or K_{21} and K_{20} are zero.

EXAMPLE PROBLEM 7.11

Consider the two-compartment model shown in Figure 7.15 with $K_{12} = K_{10} = 0$, $K_{21} = 0.2$, $K_{20} = 1$, $f_1(t) = 0$, and $f_2(t) = 10\delta(t)$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.

Solution

Since $K_{21} = 0.2$ and $K_{12} = 0$, this compartment model has a sink for compartment 1. As before, rather than solving the problem with a bolus input, the initial condition is changed in compartment 2 to $q_2(0) = 10$, with zero input. The conservation of mass for each compartment is

$$\dot{q}_1 = K_{21}q_2 = 0.2q_2 \tag{7.71}$$

$$\dot{q}_2 = -(K_{21} + K_{20})q_2 = -1.2q_2 \tag{7.72}$$

Since Eq. (7.72) involves only q_2, we solve directly to get $q_2 = 10e^{-1.2t}u(t)$. Next, substitute q_2 into (Eq. 7.71), yielding

$$\dot{q}_1 = 0.2q_2 = 2e^{-1.2t} \tag{7.73}$$

Eq. (7.73) gives a single root at $s = 0$, and $q_{1_n} = B_1$. The forced response is $q_{1_f} = B_2e^{-1.2t}$, which when substituted into Eq. (7.71) gives $B_2 = -1.67$. The complete response is

$$q_1 = q_{1_n} + q_{1_f} = B_1 - 1.667e^{-1.2t} \tag{7.74}$$

With $q_1(0) = 0$, we have $B_1 = 1.667$ from Eq. (7.74), and the complete response is

$$q_1 = 1.667\left(1 - e^{-1.2t}\right)u(t) \tag{7.75}$$

This result indicates that more than 80 percent of the solute has moved from the system into the environment. If $K_{20} = 0$, then $q_2 = 10e^{-0.2t}u(t)$ and $q_1 = 10\left(1 - e^{-0.2t}\right)u(t)$. Here, all the solute exponentially moves from compartment 2 to 1 as expected.

EXAMPLE PROBLEM 7.12

Consider a two-compartment system for the distribution of creatinine in the body illustrated in Figure 7.19. Compartment 1 represents the plasma and compartment 2 the muscle. Creatinine is a waste product of metabolism in the muscle that's cleared from the body through the urine (transfer rate K_{10}). Assume creatinine production in the muscle is $f_2(t)$ and is given by a step input. Find the concentration of creatinine in the plasma compartment.

Solution

The differential equations describing the rate of change of creatinine in the compartments 1 and 2 are written by using the conservation of mass equation as

$$\dot{q}_1 = K_{21}q_2 - (K_{10} + K_{12})q_1 \tag{7.75}$$

$$\dot{q}_2 = K_{12}q_1 - K_{21}q_2 + f_2 = K_{12}q_1 - K_{21}q_2 + 1 \tag{7.76}$$

The D-Operator is used to remove q_2, giving

$$\ddot{q}_1 + (K_{10} + K_{12} + K_{21})\dot{q}_1 + K_{10}K_{21}q_1 = K_{21} \tag{7.77}$$

The roots of the characteristic equation are

$$s_{1,2} = -\frac{(K_{10} + K_{12} + K_{21})}{2} \pm \frac{1}{2}\sqrt{(K_{21} - K_{10} - K_{12})^2 - 4K_{21}K_{10}}$$

The natural response is an overdamped response:

$$q_{1_n} = B_1 e^{s_1 t} + B_2 e^{s_2 t}$$

The forced response is a constant (B_3) and when substituted into the differential equation yields $B_3 = \dfrac{1}{K_{10}}$. The complete response is

$$q_1 = B_1 e^{s_1 t} + B_2 e^{s_2 t} + \frac{1}{K_{10}}$$

and

$$c_1 = \frac{1}{V_1}\left(B_1 e^{s_1 t} + B_2 e^{s_2 t} + \frac{1}{K_{10}}\right)$$

for $t \geq 0$. The constants B_1 and B_2 are determined using the initial conditions.

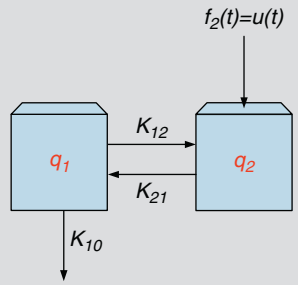

FIGURE 7.19 Illustration for Example Problem 7.12.

7.7 THREE-COMPARTMENT MODELING

The general form of the three-compartment model is shown in Figure 7.20. As before, we begin with the general form of the three-compartment model and then examine special cases. To analyze the system in Figure 7.20, conservation of mass is used to write a differential equation for each compartment describing the rate of change of the quantity of solute in the compartment, given as accumulation = input – output, where

Compartment 1	Compartment 2	Compartment 3
Accumulation $= \dot{q}_1$	Accumulation $= \dot{q}_2$	Accumulation $= \dot{q}_3$
Input $= f_1(t) + K_{21}q_2 + K_{31}q_3$	Input $= f_2(t) + K_{12}q_1 + K_{32}q_3$	Input $= f_3(t) + K_{13}q_1 + K_{23}q_2$
Ouput $= (K_{10} + K_{12} + K_{13})q_1$	Ouput $= (K_{20} + K_{21} + K_{23})q_2$	Ouput $= (K_{30} + K_{31} + K_{32})q_3$

Therefore,

$$\begin{aligned}
\dot{q}_1 &= f_1(t) + K_{21}q_2 + K_{31}q_3 - (K_{10} + K_{12} + K_{13})q_1 \\
\dot{q}_2 &= f_2(t) + K_{12}q_1 + K_{32}q_3 - (K_{20} + K_{21} + K_{23})q_2 \\
\dot{q}_3 &= f_3(t) + K_{13}q_1 + K_{23}q_2 - (K_{30} + K_{31} + K_{32})q_3
\end{aligned} \tag{7.78}$$

The D-Operator is used to simplify the system, where Eq. (7.78) is written in matrix form as

$$D\mathbf{IQ} = \mathbf{AQ} + \mathbf{F} \tag{7.79}$$

where

$$\mathbf{Q} = \begin{bmatrix} q_1 \\ q_2 \\ q_2 \end{bmatrix}, \mathbf{A} = \begin{bmatrix} -(K_{10} + K_{12} + K_{13}) & K_{21} & K_{31} \\ K_{12} & -(K_{20} + K_{21} + K_{23}) & K_{32} \\ K_{13} & K_{23} & -(K_{30} + K_{31} + K_{32}) \end{bmatrix}, \mathbf{F} = \begin{bmatrix} f_1(t) \\ f_2(t) \\ f_2(t) \end{bmatrix}$$

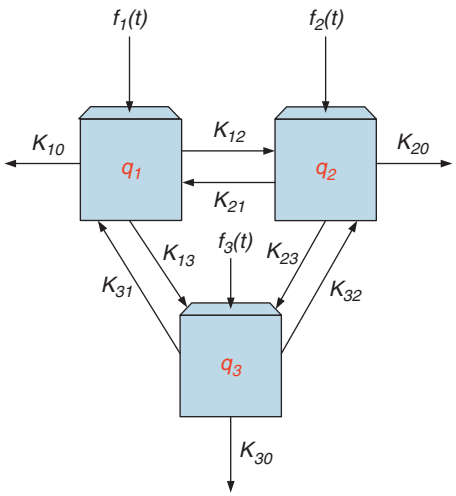

FIGURE 7.20 A general three-compartment model. Compartment 1 has volume V_1, compartment 2 has volume V_2, and compartment 3 has volume V_3.

To make the solution more readable, matrix $\mathbf{A}$ is written as

$$\mathbf{A} = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}$$

Solving Eq. (7.79) gives

$$\mathbf{Q} = (D\mathbf{I} - \mathbf{A})^{-1}\mathbf{F} = \frac{1}{\det(D\mathbf{I} - \mathbf{A})}\text{adj}(D\mathbf{I} - \mathbf{A})\mathbf{F} \tag{7.80}$$

or

$$\det(D\mathbf{I} - \mathbf{A})\mathbf{Q} = \text{adj}(D\mathbf{I} - \mathbf{A})\mathbf{F}$$

and using MATLAB, we have

```
>> syms D q1 q2 q3 a11 a12 a13 a21 a22 a23 a31 a32 a33
>> A=[a11 a12 a13; a21 a22 a23; a31 a32 a33];
>> det(D*eye(3)-A)
ans =
D^3-D^2*a33-a22*D^2+D*a22*a33-D*a23*a32-
a11*D^2+a11*D*a33+a11*a22*D-a11*a22*a33+a11*a23*a32-
a21*a12*D+a21*a12*a33-a21*a13*a32-a31*a12*a23-
a31*a13*D+a31*a13*a22
>> adj=det(D*eye(3)-A)*inv(D*eye(3)-A)
  adj =
[ D^2-D*a33-a22*D+a22*a33-a23*a32, a12*D-a12*a33+a13*a32,
a12*a23+a13*D-a13*a22]
[ a21*D-a21*a33+a23*a31, D^2-D*a33-a11*D+a11*a33-a13*a31,
a23*D-a23*a11+a13*a21]
[ a21*a32+a31*D-a31*a22, a32*D-a32*a11+a12*a31, D^2-a22*D-
a11*D+a11*a22-a12*a21]
```

Substituting the values from MATLAB into Eq. (7.80) gives

$$\begin{pmatrix} D^3 - (a_{11}+a_{22}+a_{33})D^2 + (a_{11}a_{22}+a_{22}a_{33}+a_{33}a_{11}-a_{12}a_{21}-a_{13}a_{31}-a_{23}a_{32})D \\ -a_{11}a_{22}a_{33}+a_{11}a_{23}a_{32}+a_{22}a_{13}a_{31}+a_{33}a_{12}a_{21}-a_{12}a_{23}a_{31}-a_{13}a_{32}a_{21} \end{pmatrix}\mathbf{Q} =$$

$$\begin{bmatrix} D^2-(a_{33}+a_{22})D+a_{22}a_{33}-a_{23}a_{32} & a_{12}D-a_{12}a_{33}+a_{13}a_{32} & a_{13}D+a_{12}a_{23}-a_{13}a_{22} \\ a_{21}D-a_{21}a_{33}+a_{23}a_{31} & D^2-(a_{33}+a_{11})D+a_{11}a_{33}-a_{13}a_{31} & a_{23}D-a_{23}a_{11}+a_{13}a_{21} \\ a_{31}D+a_{21}a_{32}-a_{31}a_{22} & a_{32}D-a_{32}a_{11}+a_{12}a_{31} & D^2-(a_{22}+a_{11})D+a_{11}a_{22}-a_{12}a_{21} \end{bmatrix}\mathbf{F} \tag{7.81}$$

Returning to the time domain gives the following independent differential equations:

$$\begin{aligned} &\dddot{q}_1 - (a_{11}+a_{22}+a_{33})\ddot{q}_1 + (a_{11}a_{22}+a_{22}a_{33}+a_{33}a_{11}-a_{12}a_{21}-a_{13}a_{31}-a_{23}a_{32})\dot{q}_1 \\ &\quad + (a_{11}a_{23}a_{32}-a_{11}a_{22}a_{33}+a_{22}a_{13}a_{31}+a_{33}a_{12}a_{21}-a_{12}a_{23}a_{31}-a_{13}a_{32}a_{21})q_1 \\ &\quad = \ddot{f}_1 - (a_{33}+a_{22})\dot{f}_1 + (a_{22}a_{33}-a_{23}a_{32})f_1 + a_{12}\dot{f}_2 - (a_{12}a_{33}-a_{13}a_{32})f_2 \\ &\quad + a_{13}\dot{f}_3 + (a_{12}a_{23}-a_{13}a_{22})f_3 \end{aligned} \tag{7.82}$$

$$\begin{aligned}&\dddot{q}_2-(a_{11}+a_{22}+a_{33})\ddot{q}_2+(a_{11}a_{22}+a_{22}a_{33}+a_{33}a_{11}-a_{12}a_{21}-a_{13}a_{31}-a_{23}a_{32})\dot{q}_2\\&\quad+(a_{11}a_{23}a_{32}-a_{11}a_{22}a_{33}+a_{22}a_{13}a_{31}+a_{33}a_{12}a_{21}-a_{12}a_{23}a_{31}-a_{13}a_{32}a_{21})q_2\\&\quad=a_{21}\dot{f}_1-(a_{21}a_{33}-a_{23}a_{31})f_1+\ddot{f}_2-(a_{33}+a_{11})\dot{f}_2+(a_{11}a_{33}-a_{13}a_{31})f_2\\&\quad+a_{23}\dot{f}_3-(a_{23}a_{11}-a_{13}a_{21})f_3\end{aligned}\tag{7.83}$$

$$\begin{aligned}&\dddot{q}_3-(a_{11}+a_{22}+a_{33})\ddot{q}_3+(a_{11}a_{22}+a_{22}a_{33}+a_{33}a_{11}-a_{12}a_{21}-a_{13}a_{31}-a_{23}a_{32})\dot{q}_3\\&\quad+(a_{11}a_{23}a_{32}-a_{11}a_{22}a_{33}+a_{22}a_{13}a_{31}+a_{33}a_{12}a_{21}-a_{12}a_{23}a_{31}-a_{13}a_{32}a_{21})q_3\\&\quad=a_{31}\dot{f}_1+(a_{21}a_{32}-a_{31}a_{22})f_1+a_{32}\dot{f}_2-(a_{32}a_{11}-a_{12}a_{31})f_2\\&\quad+\ddot{f}_3-(a_{22}+a_{11})\dot{f}_3+(a_{11}a_{22}-a_{12}a_{21})f_3\end{aligned}\tag{7.84}$$

The characteristic equation, $\det(D\mathbf{I}-\mathbf{A})$, is identical for q_1, q_2, and q_3, as well as the form of the natural response. Note that the coefficients in the natural response are not identical and depend on the input to the compartments and the initial conditions. The characteristic equation is

$$\begin{aligned}&s^3-(a_{11}+a_{22}+a_{33})s^2+(a_{11}a_{22}+a_{22}a_{33}+a_{33}a_{11}-a_{12}a_{21}-a_{13}a_{31}-a_{23}a_{32})s\\&\quad-a_{11}a_{22}a_{33}+a_{11}a_{23}a_{32}+a_{22}a_{13}a_{31}+a_{33}a_{12}a_{21}-a_{12}a_{23}a_{31}-a_{13}a_{32}a_{21}=0\end{aligned}\tag{7.85}$$

The roots of the characteristic equation are determined using the MATLAB command "`eig`" and may be underdamped, overdamped, or critically damped, depending on the transfer rates. The expressions for the roots are far too complex to be usable and will not be written here. With a two-compartment model, there was only one way for repeat roots to occur. With a three-compartment model, there are many more configurations for repeat roots to occur. Complex roots can occur under certain conditions, which are discussed in Section 7.7.2.

In the remainder of this section and the next, we consider special cases of the three-compartment model: mammillary, catenary, and unilateral. Each model may be closed and may have sink and source compartments.

7.7.1 Mammillary Three-Compartment Model

A mammillary three-compartment model is shown in Figure 7.21, which is characterized by a central compartment connected to two peripheral compartments. All exchanges of the solute are through the central compartment, and there is no direct exchange of solute

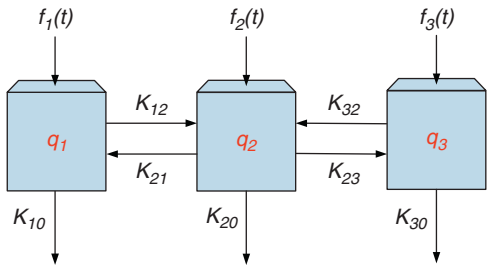

FIGURE 7.21 A mammillary three-compartment model.

between compartments 1 and 3. Each compartment can have an input and an output to the environment.

The mammillary three-compartment model is given by the following set of equations:

$$\begin{aligned}\dot{q}_1 &= f_1(t) + K_{21}q_2 - (K_{10} + K_{12})q_1\\ \dot{q}_2 &= f_2(t) + K_{12}q_1 - (K_{20} + K_{21} + K_{23})q_2 + K_{32}q_3\\ \dot{q}_3 &= f_3(t) + K_{23}q_2 - (K_{30} + K_{32})q_3\end{aligned} \tag{7.86}$$

With

$$\mathbf{A} = \begin{bmatrix} a_{11} & a_{12} & a_{13}\\ a_{21} & a_{22} & a_{23}\\ a_{31} & a_{32} & a_{33}\end{bmatrix} = \begin{bmatrix} -(K_{10} + K_{12}) & K_{21} & 0\\ K_{12} & -(K_{20} + K_{21} + K_{23}) & K_{32}\\ 0 & K_{23} & -(K_{30} + K_{32})\end{bmatrix}$$

and Eq. (7.81), we have

$$\begin{aligned}&\begin{pmatrix} D^3 - (a_{11} + a_{22} + a_{33})D^2 + (a_{11}a_{22} + a_{22}a_{33} + a_{33}a_{11} - a_{12}a_{21} - a_{23}a_{32})D\\ -a_{11}a_{22}a_{33} + a_{11}a_{23}a_{32} + a_{33}a_{12}a_{21} - a_{12}a_{23}a_{31}\end{pmatrix}\mathbf{Q} =\\ &\begin{bmatrix} D^2 - (a_{33} + a_{22})D + a_{22}a_{33} - a_{23}a_{32} & a_{12}D - a_{12}a_{33} & a_{12}a_{23}\\ a_{21}D - a_{21}a_{33} & D^2 - (a_{33} + a_{11})D + a_{11}a_{33} & a_{23}D - a_{23}a_{11}\\ a_{21}a_{32} & a_{32}D - a_{32}a_{11} & D^2 - (a_{22} + a_{11})D + a_{11}a_{22} - a_{12}a_{21}\end{bmatrix}\mathbf{F}\end{aligned} \tag{7.87}$$

Returning to the time domain gives the following independent differential equations:

$$\begin{aligned}&\dddot{q}_1 - (a_{11} + a_{22} + a_{33})\ddot{q}_1 + (a_{11}a_{22} + a_{22}a_{33} + a_{33}a_{11} - a_{12}a_{21} - a_{23}a_{32})\dot{q}_1\\ &\quad + (a_{11}a_{23}a_{32} + a_{33}a_{12}a_{21} - a_{11}a_{22}a_{33})q_1\\ &\quad = \ddot{f}_1 - (a_{33} + a_{22})\dot{f}_1 + (a_{22}a_{33} - a_{23}a_{32})f_1 + a_{12}\dot{f}_2 - a_{12}a_{33}f_2\end{aligned} \tag{7.88}$$

$$\begin{aligned}&\dddot{q}_2 - (a_{11} + a_{22} + a_{33})\ddot{q}_2 + (a_{11}a_{22} + a_{22}a_{33} + a_{33}a_{11} - a_{12}a_{21} - a_{23}a_{32})\dot{q}_2\\ &\quad + (a_{11}a_{23}a_{32} + a_{33}a_{12}a_{21} - a_{11}a_{22}a_{33})q_2\\ &\quad = a_{21}\dot{f}_1 - (a_{21}a_{33} - a_{23}a_{31})f_1 + \ddot{f}_2 - (a_{33} + a_{11})\dot{f}_2 + a_{11}a_{33}f_2 + a_{23}\dot{f}_3 - a_{23}a_{11}f_3\end{aligned} \tag{7.89}$$

$$\begin{aligned}&\dddot{q}_3 - (a_{11} + a_{22} + a_{33})\ddot{q}_3 + (a_{11}a_{22} + a_{22}a_{33} + a_{33}a_{11} - a_{12}a_{21} - a_{23}a_{32})\dot{q}_3\\ &\quad + (a_{11}a_{23}a_{32} + a_{33}a_{12}a_{21} - a_{11}a_{22}a_{33})q_3\\ &\quad = a_{21}a_{32}f_1 + a_{32}\dot{f}_2 - a_{32}a_{11}f_2 + \ddot{f}_3 - (a_{22} + a_{11})\dot{f}_3 + (a_{11}a_{22} - a_{12}a_{21})f_3\end{aligned} \tag{7.90}$$

The roots of a mammillary three-compartment model are all real and determined from the characteristic equation

$$\begin{aligned}&s^3 - (a_{11} + a_{22} + a_{33})s^2 + (a_{11}a_{22} + a_{22}a_{33} + a_{33}a_{11} - a_{12}a_{21} - a_{23}a_{32})s\\ &\quad + a_{11}a_{23}a_{32} + a_{33}a_{12}a_{21} - a_{11}a_{22}a_{33} = 0\end{aligned}$$

EXAMPLE PROBLEM 7.13

Consider the mammillary three-compartment model shown in Figure 7.21, with a loss of solute to the environment only from compartment 1 and input only from compartment 2. Additionally, K_{12}=2, K_{21}=1.5, K_{10}=0.5, K_{23}=1.3, K_{32}=0.4, and $f_2(t)=10\delta(t)$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.

Solution

With the input $f_2(t)=10\delta(t)$ transformed into a change in initial condition for compartment 2 to $q_2(0)$=10 and no input, conservation of mass for each compartment yields

$$\begin{aligned}\dot{q}_1 &= K_{21}q_2 - (K_{10}+K_{12})q_1 = -2.5q_1 + 1.5q_2\\ \dot{q}_2 &= K_{12}q_1 - (K_{21}+K_{23})q_2 + K_{32}q_3 = 2q_1 - 2.8q_2 + 0.4q_3\\ \dot{q}_3 &= K_{23}q_2 - (K_{30}+K_{32})q_3 = 1.3q_2 - 0.4q_3\end{aligned} \tag{7.91}$$

Using the D-Operator method with MATLAB, we get

```
>> syms D
>> A=[-2.5 1.5 0;2 -2.8 0.4;0 1.3 -0.4];
>> det(D*eye(3)-A)
ans =

   D^3+57/10*D^2+28/5*D+3/10
```

and

$$\dddot{q}_1 + 5.7\ddot{q}_1 + \frac{28}{5}\dot{q}_1 + 0.3q_1 = 0$$

$$\dddot{q}_2 + 5.7\ddot{q}_2 + \frac{28}{5}\dot{q}_2 + 0.3q_2 = 0$$

$$\dddot{q}_3 + 5.7\ddot{q}_3 + \frac{28}{5}\dot{q}_3 + 0.3q_3 = 0$$

Using the "`eig(A)`" command gives the roots as −4.46, −1.18, and −0.06. Thus, we have

$$\begin{aligned}q_1 &= B_1e^{-4.46t} + B_2e^{-1.18t} + B_3e^{-0.06t}\\ q_2 &= B_4e^{-4.46t} + B_5e^{-1.18t} + B_6e^{-0.06t}\\ q_3 &= B_7e^{-4.46t} + B_8e^{-1.18t} + B_9e^{-0.06t}\end{aligned}$$

(since the forced response is zero). Note that since there is no input, all we needed to do was define the matrix **A** and then use the "`eig(A)`" command (i.e., no need to use the "`det`" command). However, we shall use the "`det`" command because it gives the intermediate result.

The initial conditions are $q_1(0)$=0, $q_2(0)$=10, and $q_3(0)$=0. To determine the initial conditions for the derivative terms, we use Eq. (7.91) and get

$$\begin{aligned}\dot{q}_1(0) &= -2.5q_1(0) + 1.5q_2(0) = 15\\ \dot{q}_2(0) &= 2q_1(0) - 2.8q_2(0) + 0.4q_3(0) = -28\\ \dot{q}_3(0) &= 1.3q_2(0) - 0.4q_3(0) = 13\end{aligned}$$

Continued

To determine the initial conditions for the second derivative, we take the derivative of Eq. (7.91) and set $t = 0$, giving

$$\ddot{q}_1(0) = -2.5\dot{q}_1(0) + 1.5\dot{q}_2(0) = -79.5$$
$$\ddot{q}_2(0) = 2\dot{q}_1(0) - 2.8\dot{q}_2(0) + 0.4\dot{q}_3(0) = 113.6$$
$$\ddot{q}_3(0) = 1.3\dot{q}_2(0) - 0.4\dot{q}_3(0) = -41.6$$

Solution details are provided for q_1 here, and a final solution for q_2 and q_3. Using the initial conditions, we solve for B_1, B_2 and B_3 from

$$q_1(0) = 0 = B_1 + B_2 + B_3$$
$$\dot{q}_1(0) = 15 = -4.46B_1 - 1.18B_2 - 0.06B_3$$
$$\ddot{q}_1(0) = -79.5 = 19.9B_1 + 1.4B_2 + 0.0036B_3$$

giving

$$B_1 = -4.219,\ B_2 = 3.1818,\ \text{and}\ B_3 = 1.0372.$$

Therefore,

$$q_1 = \left(-4.219e^{-4.46t} + 3.1818e^{-1.18t} + 1.0372e^{-0.06t}\right)u(t)$$

We repeat this process for q_2 and q_3, yielding

$$q_2 = \left(5.51e^{-4.46t} + 2.8179e^{-1.18t} + 1.6721e^{-0.06t}\right)u(t)$$
$$q_3 = \left(-1.762e^{-4.46t} - 4.6849e^{-1.18t} + 6.4469e^{-0.06t}\right)u(t)$$

7.7.2 The Unilateral Three-Compartment Model

A unilateral three-compartment model is shown in Figure 7.22, which is characterized by a closed loop of connected compartments, whereby the solute circulates around the loop in one direction only. Each compartment can have an input and an output to the environment.

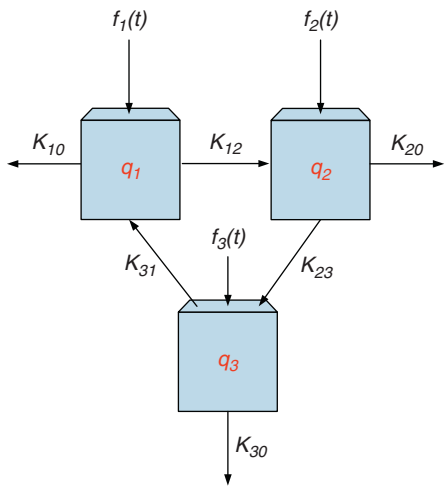

FIGURE 7.22 A unilateral three-compartment model.

In general, the unilateral three-compartment model is given by the following set of equations:

$$\begin{aligned}\dot{q}_1 &= f_1(t) + K_{31}q_3 - (K_{10} + K_{12})q_1 \\ \dot{q}_2 &= f_2(t) + K_{12}q_1 - (K_{20} + K_{23})q_2 \\ \dot{q}_3 &= f_3(t) + K_{23}q_2 - (K_{30} + K_{31})q_3\end{aligned} \tag{7.92}$$

To examine a simple unilateral three-compartment model with complex roots, consider a closed system (i.e., $K_{10} = K_{20} = K_{30} = 0$). From Eq. (7.85), the roots are found from the characteristic equation, given as

$$s^3 + (K_{12} + K_{23} + K_{31})s^2 + (K_{12}K_{23} + K_{23}K_{31} + K_{31}K_{12})s = 0 \tag{7.93}$$

which are $s_1 = 0$, and

$$s_{2,3} = -\frac{(K_{12} + K_{23} + K_{31})}{2} \pm \frac{1}{2}\sqrt{(K_{12} + K_{23} + K_{31})^2 - 4(K_{12}K_{23} + K_{23}K_{31} + K_{31}K_{12})}$$

Complex roots occur when $4(K_{12}K_{23} + K_{23}K_{31} + K_{31}K_{12}) > (K_{12} + K_{23} + K_{31})^2$. Repeated roots occur when $4(K_{12}K_{23} + K_{23}K_{31} + K_{31}K_{12}) = (K_{12} + K_{23} + K_{31})^2$.

Consider the case of complex roots and a zero root, which gives rise to a natural solution of the form

$$q_i = B_1 + e^{-\alpha t}(B_2 \ \cos\omega_d t + B_3 \ \sin\omega_d t) = B_1 + B_4 e^{-\alpha t} \ \cos(\omega_d t + \phi)$$

where α and ω_d are the real and imaginary part of the complex root, and the B_i terms are determined from initial conditions after the forced response is determined. We write the complex roots in standardized format as $s_{2,3} = -\zeta\omega_0 \pm \omega_0\sqrt{\zeta^2 - 1}$, which has a characteristic equation of

$$s^2 + 2\,\zeta\omega_0 s + \omega_0^2 = 0 \tag{7.94}$$

The system is at its most oscillatory when $\zeta = 0$, a pure sinusoid.

To get a better understanding of the system, we determine the extent of its oscillatory behavior by finding the optimal values of the transfer rates to achieve maximum oscillatory behavior (i.e., minimum ζ). To write an expression for ζ, we use the coefficients of the characteristic equation (Eq. (7.93)) and set them equal to the terms in Eq. (7.94):

$$\begin{aligned}2\zeta\omega_0 &= (K_{12} + K_{23} + K_{31}) \\ \omega_0^2 &= (K_{12}K_{23} + K_{23}K_{31} + K_{31}K_{12})\end{aligned}$$

which gives

$$\omega_0 = \sqrt{(K_{12}K_{23} + K_{23}K_{31} + K_{31}K_{12})}$$

and

$$\zeta = \frac{1}{2\omega_0} = \frac{(K_{12} + K_{23} + K_{31})}{2\sqrt{(K_{12}K_{23} + K_{23}K_{31} + K_{31}K_{12})}} \tag{7.95}$$

To find the minimum ζ, we find $\dfrac{\partial\zeta}{\partial K_{12}} = 0$, $\dfrac{\partial\zeta}{\partial K_{23}} = 0$, and $\dfrac{\partial\zeta}{\partial K_{31}} = 0$, which allows us to determine the conditions that allow minimum ζ. First, we use the chain rule to find

$$\frac{\partial \zeta}{\partial K_{12}} = \frac{2(K_{12}K_{23}+K_{23}K_{31}+K_{31}K_{12})^{\frac{1}{2}} - (K_{23}+K_{31})(K_{12}+K_{23}+K_{31})(K_{12}K_{23}+K_{23}K_{31}+K_{31}K_{12})^{-\frac{1}{2}}}{4(K_{12}K_{23}+K_{23}K_{31}+K_{31}K_{12})}$$

$$= \frac{2(K_{12}K_{23}+K_{23}K_{31}+K_{31}K_{12}) - (K_{23}+K_{31})(K_{12}+K_{23}+K_{31})}{4(K_{12}K_{23}+K_{23}K_{31}+K_{31}K_{12})^{\frac{3}{2}}} = 0$$

The minimum occurs when the numerator is zero—that is,

$$\begin{aligned} 2(K_{12}K_{23}+K_{23}K_{31}+K_{31}K_{12}) &= (K_{23}+K_{31})(K_{12}+K_{23}+K_{31}) \\ &= K_{23}K_{12}+K_{23}^2+K_{23}K_{31}+K_{31}K_{12}+K_{31}K_{23}+K_{31}^2 \end{aligned}$$

Simplifying, we have

$$K_{12}(K_{23}+K_{31}) = K_{23}^2 + K_{31}^2$$

or

$$K_{12} = \frac{K_{23}^2+K_{31}^2}{(K_{23}+K_{31})}$$

Repeating for $\frac{\partial \zeta}{\partial K_{23}} = 0$, we get $K_{23} = \frac{K_{12}^2+K_{31}^2}{(K_{12}+K_{31})}$, and for $\frac{\partial \zeta}{\partial K_{31}} = 0$, we get $K_{31} = \frac{K_{12}^2+K_{23}^2}{(K_{12}+K_{23})}$. The only way these relationships are valid is if $K_{12} = K_{23} = K_{31} = K$, and from Eq. (7.95), we find $\zeta = \frac{3}{2\sqrt{3}} = 0.866$, which does not have a very noticeable oscillatory behavior. We will see in the next section that a more noticeable oscillatory response is possible with more than three compartments.

EXAMPLE PROBLEM 7.14

Consider the unilateral three-compartment model shown in Figure 7.22 with no loss of solute to the environment from any compartments and an input for compartment 3 only. Additionally, $K_{12} = K_{23} = K_{31} = 2$, and $f_3(t) = 5\delta(t)$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.

Solution

As before, we transform the input, $f_3(t) = 5\delta(t)$, into a change in initial condition for compartment 3 to $q_3(0)$=5 and no input. The conservation of mass for each compartment yields

$$\begin{aligned} \dot{q}_1 &= K_{31}q_3 - (K_{10}+K_{12})q_1 = -2q_1 + 2q_3 \\ \dot{q}_2 &= K_{12}q_1 - (K_{20}+K_{23})q_2 = 2q_1 - 2q_2 \\ \dot{q}_3 &= K_{23}q_2 - (K_{30}+K_{31})q_3 = 2q_2 - 2q_3 \end{aligned} \tag{7.96}$$

Using the D-Operator method with MATLAB, we get

```
>> syms D
>> A=[-2 0 2;2 -2 0;0 2 -2];
>> det(D*eye(3)-A)
ans =

   D^3+6*D^2+12*D
```

and

$$\dddot{q}_1 + 6\ddot{q}_1 + 12\dot{q}_1 = 0$$
$$\dddot{q}_2 + 6\ddot{q}_2 + 12\dot{q}_2 = 0$$
$$\dddot{q}_3 + 6\ddot{q}_3 + 12\dot{q}_3 = 0$$

The roots from the characteristic equation are $0, -3 \pm j1.7321$. The complete solution is the natural solution, since the forced response is zero, and is given by

$$q_1 = B_1 + e^{-3t}(B_2 \cos 1.7321t + B_3 \sin 1.7321t)$$
$$q_2 = B_4 + e^{-3t}(B_5 \cos 1.7321t + B_6 \sin 1.7321t)$$
$$q_3 = B_7 + e^{-3t}(B_8 \cos 1.7321t + B_9 \sin 1.7321t)$$

The initial conditions are $q_1(0)=0$, $q_2(0)=0$, and $q_3(0)=5$. To determine the initial conditions for the derivative terms, we use Eq. (7.96) and get

$$\dot{q}_1(0) = -2q_1(0) + 2q_3(0) = 10$$
$$\dot{q}_2(0) = 2q_1(0) - 2q_2(0) = 0$$
$$\dot{q}_3(0) = 2q_2(0) - 2q_3(0) = -10$$

To determine the initial conditions for the second derivative, we take the derivative of Eq. (7.96) with $t = 0$, giving

$$\ddot{q}_1(0) = -2\dot{q}_1(0) + 2\dot{q}_3(0) = -40$$
$$\ddot{q}_2(0) = 2\dot{q}_1(0) - 2\dot{q}_2(0) = 20$$
$$\ddot{q}_3(0) = 2\dot{q}_2 - 2\dot{q}_3 = 20$$

For q_1, we have

$$q_1(0) = 0 = B_1 + B_2$$
$$\dot{q}_1(0) = 10 = -3B_2 + 1.7321B_3$$
$$\ddot{q}_1(0) = -40 = 6B_2 - 10.4B_3$$

which gives $B_1 = \frac{5}{3}, B_2 = -\frac{5}{3}$, and $B_3 = 2.9$, and

$$q_1 = \left(\frac{5}{3} - e^{-3t}\left(\frac{5}{3} \cos 1.7321t - 2.9 \sin 1.7321t\right)\right)u(t)$$

Repeating for q_2 and q_3, we have

$$q_2 = \left(\frac{5}{3} - e^{-3t}\left(\frac{5}{3} \cos 1.7321t + 2.9 \sin 1.7321t\right)\right)u(t)$$

$$q_3 = \frac{5}{3}\left(1 + 2e^{-3t} \cos 1.7321t\right)u(t)$$

Continued

Illustrated in Figure 7.23 is a plot of the quantity in each compartment. While it is difficult to see the oscillations, the first peak is evident by the overshoot or undershoot. To determine the time at peak undershoot for q_3, we use the technique of Section 2.9.2 by finding the time that satisfies $\frac{\partial q_3}{\partial t} = 0$, which gives $T_{p_3} = 1.21$. Similarly, $T_p = 1.81$ for both q_1 and q_2.

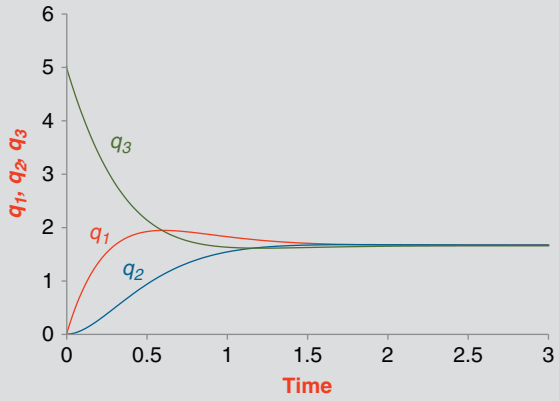

FIGURE 7.23 Illustration of the quantity in each compartment in Example Problem 7.14.

7.7.3 Source Compartment

In Section 7.5.1, a source compartment in a two-compartment model was described as one that only has output to other compartments, without any inputs from other compartments. A source compartment also appears in three-compartment models, whose output is solved independent of the other compartments as before.

The following example involves a three-compartment mammillary model with a source compartment, as illustrated in Figure 7.24. The body is now divided into the digestive system, plasma, and the tissues to more accurately depict their behavior.

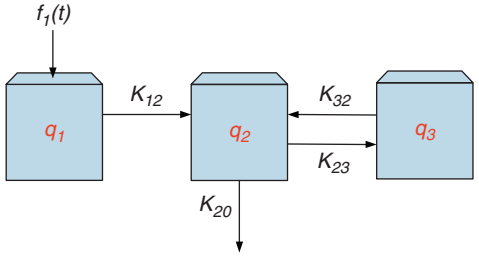

FIGURE 7.24 Illustration for Example Problem 7.15. Compartment 1 is the digestive system, compartment 2 is the plasma, and compartment 3 is the tissues.

EXAMPLE PROBLEM 7.15

Consider the mammillary three-compartment model with the source compartment shown in Figure 7.24. The input is $f_1(t)=\delta(t)$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.

Solution

Once again, the input is transformed into a change in initial condition for compartment 1, $q_1(0)=1$. The equations describing this model are

$$\dot{q}_1 = -K_{12}q_1 \tag{7.97}$$

$$\dot{q}_2 = K_{12}q_1 - (K_{20}+K_{23})q_2 + K_{32}q_3 \tag{7.98}$$

$$\dot{q}_3 = K_{23}q_2 - K_{32}q_3 \tag{7.99}$$

Since Eq. (7.97) involves only q_1, it is easily solved as $q_1 = q_1(0)e^{-K_{12}t}u(t) = e^{-K_{12}t}u(t)$. Substituting the solution for q_1 into Eqs. (7.98) and (7.99), we now have two equations as

$$\dot{q}_2 = K_{12}e^{-K_{12}t}u(t) - (K_{20}+K_{23})q_2 + K_{32}q_3 \tag{7.100}$$

$$\dot{q}_3 = K_{23}q_2 - K_{32}q_3 \tag{7.101}$$

The D-Operator gives the reconstructed differential equations for q_2 and q_3 as

```
>> syms D K20 K23 K32
>> A=[-(K20+K23) K32;K23 -K32];
>> det(D*eye(2)-A)
ans =
  D^2+D*K32+K20*D+K20*K32+K23*D
>> adj=det(D*eye(2)-A)*inv(D*eye(2)-A)
adj =

   [  D+K32, K32       ]
   [  K23,   D+K20+K23]
```

and

$$\ddot{q}_2 + (K_{32}+K_{20}+K_{23})\dot{q}_2 + K_{20}K_{32}q_2 = K_{12}(K_{32}-K_{12})e^{-K_{12}t} \tag{7.102}$$

$$\ddot{q}_3 + (K_{32}+K_{20}+K_{23})\dot{q}_3 + K_{20}K_{32}q_3 = K_{23}K_{12}e^{-K_{12}t} \tag{7.103}$$

The roots are

```
>> eig(A)
ans =

  -1/2*K20-1/2*K23-1/2*K32+1/2*(K20^2+2*K20*K23-
  2*K20*K32+K23^2+2*K32*K23+K32^2)^(1/2)

  -1/2*K20-1/2*K23-1/2*K32-1/2*(K20^2+2*K20*K23-
  2*K20*K32+K23^2+2*K32*K23+K32^2)^(1/2)
```

Continued

which simplifies to

$$s_{1,2} = -\frac{(K_{20} + K_{23} + K_{32})}{2} \pm \frac{1}{2}\sqrt{(K_{32} + K_{20} + K_{23})^2 - 4K_{32}K_{23}} \tag{7.104}$$

Only real roots are possible with $K_{ij} \geq 0$. The natural response for q_2 is

$$q_{2_n} = B_1 e^{s_1 t} + B_2 e^{s_2 t}$$

The forced response is $q_{2_f} = B_3 e^{-K_{12}t}$, which after substituting into Eq. (7.103) gives

$$B_3 = \frac{K_{23}K_{12}}{K_{12}^2 - K_{12}(K_{32} + K_{20} + K_{23}) + K_{20}K_{32}}$$

The complete response is then

$$q_2 = B_1 e^{s_1 t} + B_2 e^{s_2 t} + B_3 e^{-K_{12}t}$$

We use the initial conditions, $q_2(0) = 0$ and $\dot{q}_2(0) = K_{12}q_1(0)$, to solve for B_1 and B_2 as follows:

$$q_2(0) = B_1 + B_2 + B_3 = 0$$

and with

$$\dot{q}_2 = s_1 B_1 e^{s_1 t} + s_2 B_2 e^{s_2 t} - K_{12} B_3 e^{-K_{12}t},$$

we have

$$\dot{q}_2(0) = K_{12} = s_1 B_1 + s_2 B_2 - K_{12} B_3$$

To solve for B_1 and B_2, we evaluate

$$\begin{bmatrix} 1 & 1 \\ s_1 & s_2 \end{bmatrix} \begin{bmatrix} B_1 \\ B_2 \end{bmatrix} = \begin{bmatrix} -B_3 \\ K_{12}(1 + B_3) \end{bmatrix}$$

which gives

$$\begin{bmatrix} B_1 \\ B_2 \end{bmatrix} = \begin{bmatrix} \dfrac{K_{12}B_3 + K_{12} + B_3 s_2}{(s_1 - s_2)} \\ -\dfrac{K_{12}B_3 + K_{12} + B_3 s_1}{(s_1 - s_2)} \end{bmatrix}$$

The final solution is

$$q_2(t) = \left(\begin{array}{l} \dfrac{K_{12}B_3 + K_{12} + B_3 s_2}{(s_1 - s_2)} e^{s_1 t} - \dfrac{K_{12}B_3 + K_{12} + B_3 s_1}{(s_1 - s_2)} e^{s_2 t} \\ + \dfrac{K_{23}K_{12}}{K_{12}^2 - K_{12}(K_{32} + K_{20} + K_{23}) + K_{20}K_{32}} e^{-K_{12}t} \end{array} \right) u(t)$$

Repeating for q_3, we have

$$q_3(t) = \left(\frac{B_3(K_{12} + s_2)}{(s_1 - s_2)} e^{s_1 t} - \frac{B_3(K_{12} + s_1)}{(s_1 - s_2)} e^{s_2 t} + \frac{K_{23}K_{12}}{K_{12}^2 - K_{12}(K_{32} + K_{20} + K_{23}) + K_{20}K_{32}} e^{-K_{12}t} \right) u(t)$$

7.7.4 Sink Compartment

A sink compartment in a three-compartment model gives rise to a zero root and is described as a compartment with only inputs and no output to other compartments except to the environment. The solution for the sink compartment is found as usual using the D-Operator approach from the resulting quantities in the other two compartments.

To illustrate a sink compartment, Example Problem 7.16 involves a three-compartment model describing the transport of a thyroid hormone to the hepatic duct (sink compartment).[12] The thyroid system was first described in Example Problem 7.5 and is extended to this example. We will then extend the model in Section 7.8.4. Before describing the current model, more background material on the thyroid system is presented.

The thyroid hormones thyroxine (T4) and triiodothyronine (T3), which are produced by the thyroid gland, maintain the body temperature, regulate energy metabolism, and are important for growth and development. The thyroid hormones themselves do not exist inside the thyroid cell but are part of a large thyroglobulin molecule that consists of approximately 70 tyrosine amino acids. The metabolic rate falls to approximately 50 percent of normal without these hormones, and too much thyroid hormone can increase the metabolic rate by 100 percent above the normal rate. The pituitary gland controls the discharge of T4 and T3 through its release of the thyroid-stimulating hormone, TSH. As previously described, the pituitary gland is under the control of the hypothalamus through its release of the thyrotropin-releasing-hormone, TRH.

Ingested iodine, in the form of iodide, is an essential element in the formation of thyroid hormones. Blood flow through the thyroid gland is among the highest of any organ in the body, which allows the quick uptake of iodide. Typically after ingestion, 80 percent of the iodide is rapidly excreted by the kidneys, and the other 20 percent is taken up by the thyroid gland.

Once iodide is taken up by the thyroid gland, it is used in a series of enzyme reactions to create the thyroid hormones. Iodide is first transported across the membrane of the thyroid cell by a pump mechanism called the sodium-iodide symporter. The pump allows iodide concentrations in the thyroid cell to be much greater than in the plasma. Once inside the cell, iodide is oxidized by thyroidal peroxidase to iodine, which iodinates the tyrosine component of the thyroglobulin molecule to first form monoiodotyrosine (MIT) and then diiondotryosine (DIT). Thyroperoixidase then catalyzes the joining of two molecules of DIT to form T4 (a two-benzene ringed structure consisting of an inner tyrosyl ring and an outer phenolic ring, within the thyroglobulin-iodine molecule) or to a lesser extent, the joining of one molecule of MIT to DIT to form T3. Reverse T3 is also formed but is excluded from this discussion.

While the process of creating the thyroglobulin-iodine molecule is quick, the thyroid gland keeps approximately a 60-day supply in reserve. Thyroglobulin itself is not released into the plasma when the thyroid is stimulated by TSH, but T4 and T3 are released through a lysosomal protease enzyme action on the thyroglobulin-iodine molecule. Almost all of the output from the thyroid gland is T4 (greater than 90 percent). In addition, MIT and DIT are released from the thyroglobulin-iodine molecule when T4 and T3 are released; however, MIT and DIT do not leave the cell but are deiodinated, allowing the release of iodine.

[12]See Haddad et al., 2003, in references for original problem developement.

The iodine is then reused in the cell, repeating the enzyme reactions to form the thyroid hormones.

Once in the plasma, the thyroid hormones reversibly combine with proteins. The binding to proteins protects T4 and T3 from immediate metabolism and excretion as they are inactive in this mode. T4 binds primarily with thyroid binding globulin (TBG) and, to a lesser extent, to thyroxine-binding prealbumin (TBPA) and albumin. TBG in the plasma is present in low concentrations and has a high affinity for T4; it usually binds about 70 percent of the available T4. TBPA in the plasma is present in high concentrations but has a low affinity for T4. Ten percent of the plasma-bound hormone T4 is used each day, giving it a 7-day half-life. The 7-day half-life for T4 creates a stable pool of thyroid hormone in the plasma. Approximately 0.04 percent of the T4 is not bound to proteins in the plasma during normal conditions, and we call the unbound T4 *free*-T4.

T3 has a lower binding affinity for plasma proteins. Those T3 that are bound are primarily with TBPA and albumin. T3 is rapidly cleared from the plasma with a half-life of 1 day. Approximately 10 percent of T3 is not bound to proteins in the plasma during normal conditions.

While a small amount of T3 is released by the thyroid into the plasma, almost all of the T3 in the plasma is produced by deiodination enzymes in the liver and to a much lesser extent in the kidneys, where an iodine atom is removed from T4 that converts it into T3. T4 is also eliminated within the liver and to a lesser extent in the kidneys, by conjugation of sulfate or glucuronic acid with the phenolic hydroxyl group of the outer phenolic ring, turning T4 into T3. Also within the liver, T4 undergoes deamination and decarboxylase reactions that convert it into T3.

Once in the plasma, free-T3 moves into the interstitial space and easily moves across the cell membranes in the tissues. When transported into the cells, free-T3 moves into the cell nucleus and binds with thyroid hormone receptors, which then synthesize new proteins through gene transcription. These new proteins are connected to energy metabolism, body temperature, body weight, and the control of growth, reproduction, and differentiation. While T4 also moves into the cell and binds with thyroid hormone receptors, it takes about 10 times more T4 than T3 to equal the effect of T3 in gene transcription.

Example Problem 7.16 involves a three-compartment model describing the transport of T4 throughout the body. To model the transport of T4 in the body, a bolus of radioactive iodine-T4 is injected into the plasma. The use of radioactive iodine-T4 allows us to track the transport of T4 in the body apart from the natural T4. The pathways of interest in the following example, as described in Figure 7.25, involve the plasma, liver, and hepatic duct.

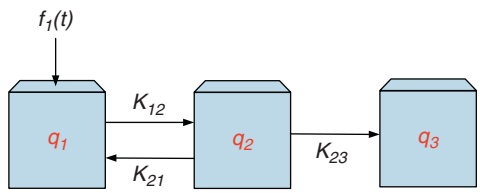

FIGURE 7.25 Illustration for Example Problem 7.16. Compartment 1 is the plasma, compartment 2 is the liver, and compartment 3 is the hepatic duct, simplified to a single compartment. The input $f_1(t)$ is a bolus of radioactive iodine-T4.

Within the liver, some of the T4 is converted into T3 and I^{131}. The I^{131} moves into the hepatic duct, where it is absorbed within the bile. The feedback control by the pituitary gland and the involvement of the kidneys are ignored in this example.

EXAMPLE PROBLEM 7.16

Consider a three-compartment thyroxine transport model as shown in Figure 7.25. The input is $f_1(t) = 0.1 \times 10^{-3}\delta(t)$g of radioactive iodine-T4. Additionally, K_{12}=0.6, K_{21}=0.5, and K_{23}=0.3. Assume that the initial conditions are zero. Solve for the quantity of radioactive iodine-T4 in the plasma compartment.

Solution

Since there is no output to another compartment for compartment 3, this compartment model has a sink for compartment 3. As before, rather than solving the problem with a bolus input, the initial condition is changed for compartment 1 to $q_1(0) = 0.1 \times 10^{-3}$, with zero input. The conservation of mass for each compartment yields

$$\begin{aligned}\dot{q}_1 &= K_{21}q_2 - K_{12}q_1 = -0.6q_1 + 0.5q_2\\ \dot{q}_2 &= K_{12}q_1 - (K_{21} + K_{23})q_2 = 0.6q_1 - 0.8q_2\\ \dot{q}_3 &= K_{23}q_2 = 0.3q_2\end{aligned} \tag{7.105}$$

Using the D-Operator method with MATLAB, we get

```
>> syms D
>> A=[-0.6 0.5 0;0.6 -0.8 0;0 0.3 0];
>> det(D*eye(3)-A)
ans =

   D^3+7/5*D^2+9/50*D
```

and

$$\dddot{q}_1 + \frac{7}{5}\ddot{q}_1 + \frac{9}{50}\dot{q}_1 = 0$$

The "`eig(A)`" command gives the roots as 0, −1.26, and −0.14. Thus, we have

$$q_1 = B_1 + B_2e^{-1.26t} + B_3e^{-0.14t}$$

(since the forced response is zero). The initial conditions are $q_1(0) = 0.1 \times 10^{-3}, q_2(0) = 0$, and $q_3(0)$=0. To determine the initial conditions for the derivative terms, we use Eq. (7.105), which gives

$$\begin{aligned}\dot{q}_1(0) &= -0.6q_1(0) + 0.5q_2(0) = -0.06 \times 10^{-3}\\ \dot{q}_2(0) &= 0.6q_1(0) - 0.8q_2(0) = 0.06 \times 10^{-3}\end{aligned}$$

To determine the initial conditions for the second derivative, we take the derivative of Eq. (7.105) and set t = 0, giving

$$\begin{aligned}\ddot{q}_1(0) &= -0.6\dot{q}_1(0) + 0.5\dot{q}_2(0) = 6.6 \times 10^{-5}\\ \ddot{q}_2(0) &= 0.6\dot{q}_1(0) - 0.8\dot{q}_2(0) = -8.4 \times 10^{-5}\end{aligned}$$

Continued

Using the initial conditions, we solve for B_1, B_2, and B_3 from

$$q_1(0) = 0.1 \times 10^{-3} = B_1 + B_2 + B_3$$
$$\dot{q}_1(0) = -0.06 \times 10^{-3} = -1.26B_2 - 0.14B_3$$
$$\ddot{q}_1(0) = 6.6 \times 10^{-5} = 1.4B_2 + 0.02B_3$$

giving

$$B_1 = 0.48 \times 10^{-4}, B_2 = 0.47 \times 10^{-4}, \text{ and } B_3 = 0.05 \times 10^{-4}, \text{ and}$$
$$q_1 = \left(0.48 + 0.47e^{-1.26t} + 0.05e^{-0.14t}\right) \times 10^{-4} u(t)$$

The model used in Example Problem 7.16 is too simple to capture the real transport dynamics of thyroid hormone. Some investigators have included multiple compartments for the hepatic duct and many other compartments. Some have included chemical reactions in the model. We will investigate these models in a later chapter.

7.8 MULTICOMPARTMENT MODELING

Realistic models of the body typically involve more than three compartments. The concepts described in the previous sections can be applied to a compartment model of any size. Each compartment is characterized by a conservation of mass differential equation describing the rate of change of the solute. Thus, for the case of n compartments, there are n equations of the form

$$\frac{dq_i}{dt} = input - output$$

where q_i is the quantity of solute in compartment i, which can be generalized for the system to

$$D\mathbf{IQ} = \mathbf{AQ} + \mathbf{F} \tag{7.106}$$

where

$$\mathbf{Q} = \begin{bmatrix} q_1 \\ q_2 \\ \vdots \\ q_n \end{bmatrix}, \ \mathbf{A} = \begin{bmatrix} a_{11} & a_{12} & \cdots & a_{1n} \\ a_{21} & a_{22} & \cdots & a_{2n} \\ \vdots & & & \\ a_{n1} & a_{n2} & \cdots & a_{nn} \end{bmatrix}, \ \mathbf{F} = \begin{bmatrix} f_1(t) \\ f_2(t) \\ \vdots \\ f_n(t) \end{bmatrix}$$

and for the first row in $\mathbf{A}$, we have

$$a_{11} = -(K_{10} + K_{12} + K_{13} + \cdots + K_{1n})$$
$$a_{12} = K_{12}$$
$$\vdots$$
$$a_{1n} = K_{1n}$$

and so on for the other rows in $\mathbf{A}$. Equation (7.106) is solved as before from

$$\mathrm{Q} = (D\mathrm{I} - \mathrm{A})^{-1}\mathrm{F} = \frac{1}{\det(D\mathrm{I} - \mathrm{A})}\mathrm{adj}(D\mathrm{I} - \mathrm{A})\mathrm{F} \tag{7.107}$$

or

$$\det(D\mathrm{I} - \mathrm{A})\mathrm{Q} = \mathrm{adj}(D\mathrm{I} - \mathrm{A})\mathrm{F}$$

MATLAB is used to reconstruct the differential equations, as before, in terms of a single variable and the inputs. The characteristic equation, $\det(D\mathbf{I}-\mathbf{A})$, is identical for $q_1, q_2, \ldots q_n$, as well as the form of the natural response. The roots of the characteristic equation are determined using the MATLAB command "`eig(A)`" and may be underdamped, overdamped, or critically damped, depending on the transfer rates. The expression for the roots is far too complex to be usable and will not be written here. Most models will have many elements in $\mathbf{A}$ as zero, which makes the solution much more tractable.

In the remainder of this section, we consider special cases of the multicompartment model: mammillary, catenary, and unilateral. Each model may be closed and may have sink and source compartments.

7.8.1 Mammillary Multicompartment Model

A mammillary n-compartment model is shown in Figure 7.26, which is characterized by a central compartment connected to $n-1$ peripheral compartments. All exchange of solute is through the central compartment, and there is no direct exchange of solute among the other compartments. Each compartment can have an input and an output to the environment.

The matrix $\mathbf{A}$, given in Eq. (7.106), has nonzero elements defined as

$$\begin{aligned} a_{11} &= -(K_{10}+K_{12}+K_{13}+\cdots+K_{1n}) \\ a_{ii} &= -(K_{i1}+K_{i0}), && 2 \le i \le n \\ a_{1i} &= K_{i1}, && 2 \le i \le n \\ a_{i1} &= K_{1i}, && 2 \le i \le n \end{aligned} \tag{7.108}$$

This system only has real roots.

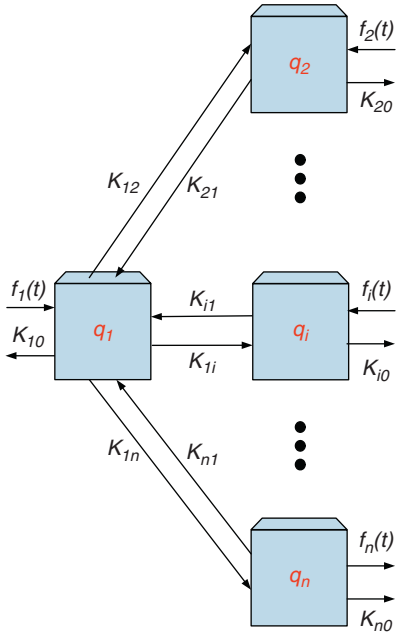

FIGURE 7.26 A mammillary n-compartment model.

7.8.2 Catenary Multicompartment Model

A catenary n-compartment model is shown in Figure 7.27, which is characterized by a chain of compartments, with each compartment exchanging solute with the two adjacent compartments, except for the first and last in the chain. Each compartment can have an input and an output to the environment.

The matrix **A**, given in Eq. (7.106), has nonzero elements defined as

$$\begin{aligned} a_{11} &= -(K_{10} + K_{12}) \\ a_{i,i-1} &= K_{i-1,i}, && 2 \le i \le n \\ a_{ii} &= -\left(K_{i0} + K_{i,(i-1)} + K_{i,(i+1)}\right), && 2 \le i \le n-1 \\ a_{i,i+1} &= K_{i+1,i}, && 2 \le i \le n-1 \\ a_{nn} &= -\left(K_{n0} + K_{n,(n-1)}\right) \end{aligned} \tag{7.109}$$

This system only has real roots.

7.8.3 Unilateral Multicompartment Model

A unilateral n-compartment model is shown in Figure 7.28, which is characterized by a closed loop of connected compartments, whereby solute circulates around the loop in one direction only. Each compartment can have an input and an output to the environment.

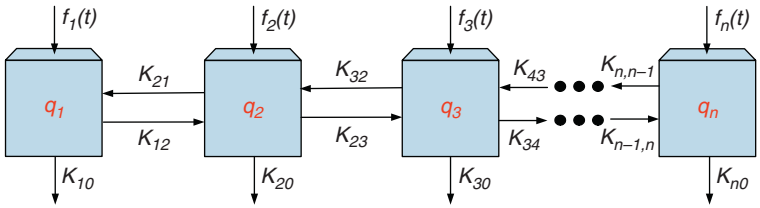

FIGURE 7.27 A catenary n-compartment model.

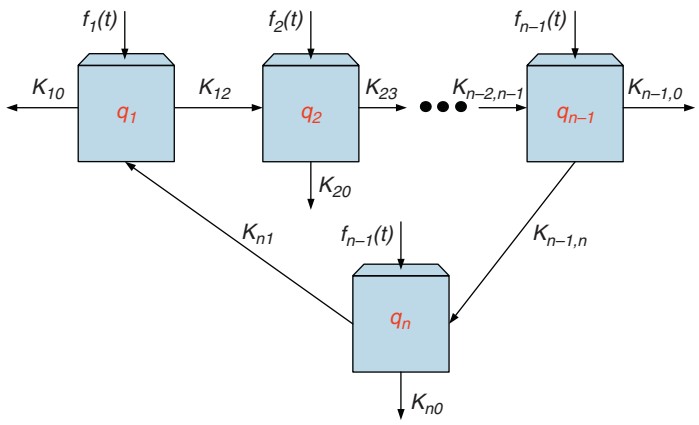

FIGURE 7.28 A unilateral n-compartment model.

The matrix **A**, given in Eq. (7.106), has nonzero elements defined as

$$\begin{aligned} a_{ii} &= -(K_{i0} + K_{i,i+1}), \qquad 1 \le i \le n-1 \\ a_{nn} &= -(K_{n0} + K_{n1}) \\ a_{1n} &= K_{n1} \\ a_{i,i-1} &= K_{i-1,i}, \qquad 2 \le i \le n \end{aligned} \tag{7.110}$$

In Section 7.7.2, we investigated the three-compartment unilateral complex roots case and determined that in the roots with the most oscillatory behavior, all the transfer rates were equal to the same value. We will continue this investigation to explore the oscillatory behavior for a closed system unilateral n-compartment model with equal transfer rates, K, and bolus input. The system matrix **A** is

$$A = \begin{bmatrix} -K & 0 & 0 & \cdots & 0 & K \\ K & -K & 0 & \cdots & 0 & 0 \\ 0 & K & -K & \cdots & 0 & 0 \\ & & \vdots & & & \\ 0 & 0 & 0 & \cdots & K & -K \end{bmatrix}$$

and the determinant of (D**I**-**A**) is

$$\begin{vmatrix} D-K & 0 & 0 & \cdots & 0 & K \\ K & D-K & 0 & \cdots & 0 & 0 \\ 0 & K & D-K & \cdots & 0 & 0 \\ & & \vdots & & & \\ 0 & 0 & 0 & \cdots & K & D-K \end{vmatrix} = (D+K)^n - K^n$$

As Godfrey illustrates, the roots of this system are

$$-K + K\left(\cos\frac{2\pi m}{n} + j\,\sin\frac{2\pi m}{n}\right), \qquad m = 1, 2, \cdots n \tag{7.111}$$

and lie evenly on the unit circle of radius K, centered at (K,0) in the complex plan. For a closed system, one of the roots is 0, and for an even n, there is another root at $-2K$. The remaining roots are complex and given by Eq. (7.111). For $m = 1$ and $m = n-1$, Godfrey shows that the damping ratio is equal to

$$\zeta = \sin\frac{\pi}{n} \tag{7.112}$$

and as n increases to infinity, the damping ratio approaches zero. Since the quantity within a compartment can never be less than zero, as n approaches infinity, the amplitude of the sinusoid approaches 0.

Our approach to solving a unilateral n-compartment model is the same as before, letting MATLAB do the work for us, as shown in the following example.

EXAMPLE PROBLEM 7.17

Consider the unilateral five-compartment model with no loss of solute to the environment from any compartments and an input for compartment 3 only. Additionally, all transfer rates equal 2 and $f_3(t) = 5\delta(t)$. Assume that the initial conditions are zero. Solve for the quantity in compartment 3.

Solution

As before, we transform the input, $f_3(t) = 5\delta(t)$, into a change in initial condition for compartment 3 to $q_3(0) = 5$ and no input. The conservation of mass for each compartment yields

$$\begin{aligned}
\dot{q}_1 &= -2q_1 + 2q_5 \\
\dot{q}_2 &= 2q_1 - 2q_2 \\
\dot{q}_3 &= 2q_2 - 2q_3 \\
\dot{q}_4 &= 2q_3 - 2q_4 \\
\dot{q}_5 &= 2q_4 - 2q_5
\end{aligned}$$

Using MATLAB, we have

```
>> syms D
>> A=[-2 0 0 0 2;2 -2 0 0 0;0 2 -2 0 0;0 0 2 -2 0;0 0 0 2 -2];
>> det(D*eye(5)-A)
ans =

   D^5+10*D^4+40*D^3+80*D^2+80*D
```

and

$$\frac{d^5q_3}{dt^5} + 10\frac{d^4q_3}{dt^4} + 40\frac{d^3q_3}{dt^3} + 80\frac{d^2q_3}{dt^2} + 80\frac{dq_3}{dt} = 0$$

The roots from the characteristic equation (i.e., eig(**A**)) are 0, $-3.6180 \pm j1.1756$, and $-1.3820 \pm j1.9021$. The complete solution for q_3 is the natural solution, since the forced response is zero, and is given by

$$q_3 = B_1 + e^{-3.618t}(B_2\ \cos 1.1756t + B_3\ \sin 1.1756t) + e^{-1.382t}(B_4\ \cos 1.9021t + B_5\ \sin 1.9021t)$$

The initial conditions for q_3 are found using the conservation of mass equations and successive derivatives, giving $q_3(0) = 5$, $\dot{q}_3(0) = -10$, $\ddot{q}_3(0) = 20$, $\dddot{q}_3(0) = -40$, and $\ddddot{q}_3(0) = 80$. Solving for the unknown coefficients using the initial conditions, we have

$$\begin{aligned}
q_3(0) &= 5 = B_1 + B_2 + B_4 \\
\dot{q}_3(0) &= -10 = -3.61B_2 + 1.1756B_3 - 1.382B_4 + 1.9021B_5 \\
\ddot{q}_3(0) &= 20 = 11.72B_2 - 8.51B_3 - 1.71B_4 - 5.26B_5 \\
\dddot{q}_3(0) &= -40 = -32.4B_2 + 44.58B_3 + 7.64B_4 + 4.02B_5 \\
\ddddot{q}_3(0) &= 80 = 64.79B_2 - 199.4B_3 - 18.18B_4 + 9.02B_5
\end{aligned}$$

and using MATLAB yields $B_1 = 1.0$, $B_2 = 2.0$, $B_3 = 0.0$, $B_4 = 2.00$, and $B_5 = 0.0$. Thus, for t$\geq$0, we have

$$q_3 = 1 + 2e^{-3.618t}\ \cos 1.1756t + 2.00e^{-1.382t}\ \cos 1.9021t$$

The same approach can be used to find the quantities in the other compartments, which are plotted in Figure 7.29. Note that the oscillation about the steady state of 1 is more pronounced in q_4 than q_3. In fact, the prominence of oscillation about steady state decreases as we move from q_4 to q_5 to q_1 to q_2 to q_3. In general, we see the most prominent oscillation in the compartment that receives the solute from the compartment stimulated by the bolus. Also note that the steady-state quantity in each compartment equals one.

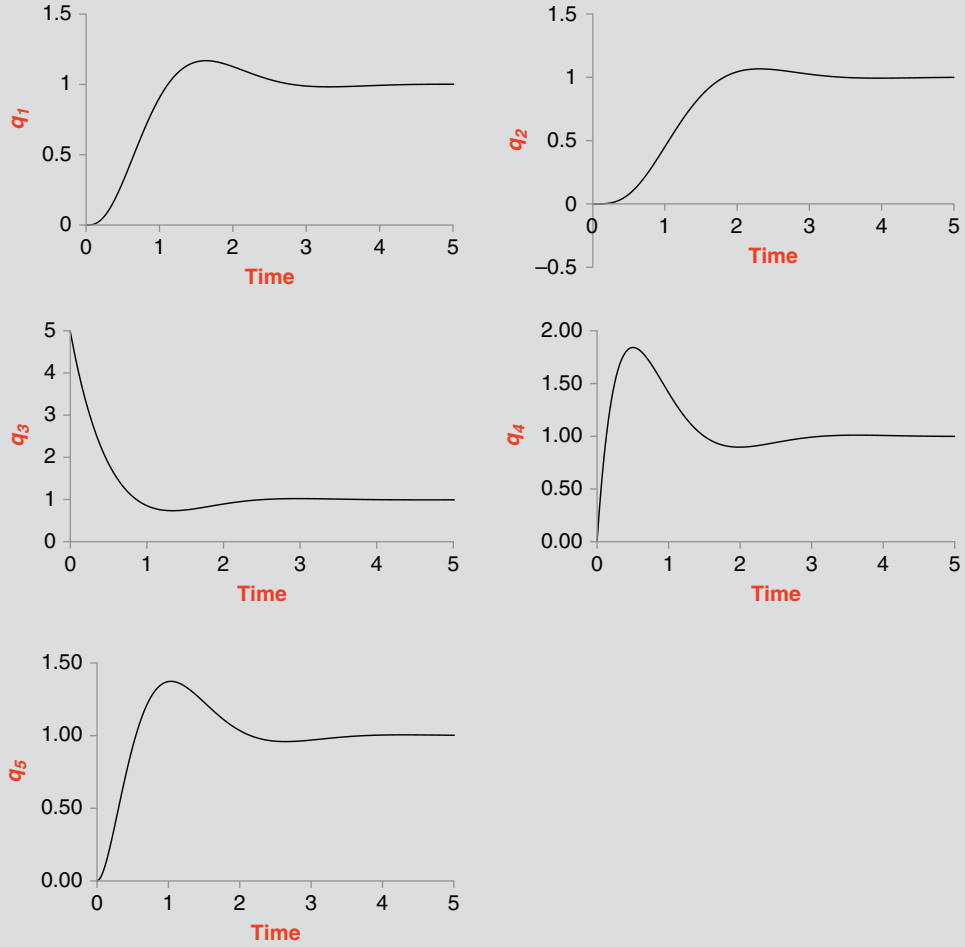

FIGURE 7.29 Plots of the responses for Example Problem 7.17.

As we increase the number of compartments in a closed unilateral system, in general, the more oscillatory the response becomes. In some cases, the oscillatory behavior is prominent but lasts only a very short time. In other cases, the oscillations may be less prominent but last for a longer period of time. Consider the closed system unilateral model shown in

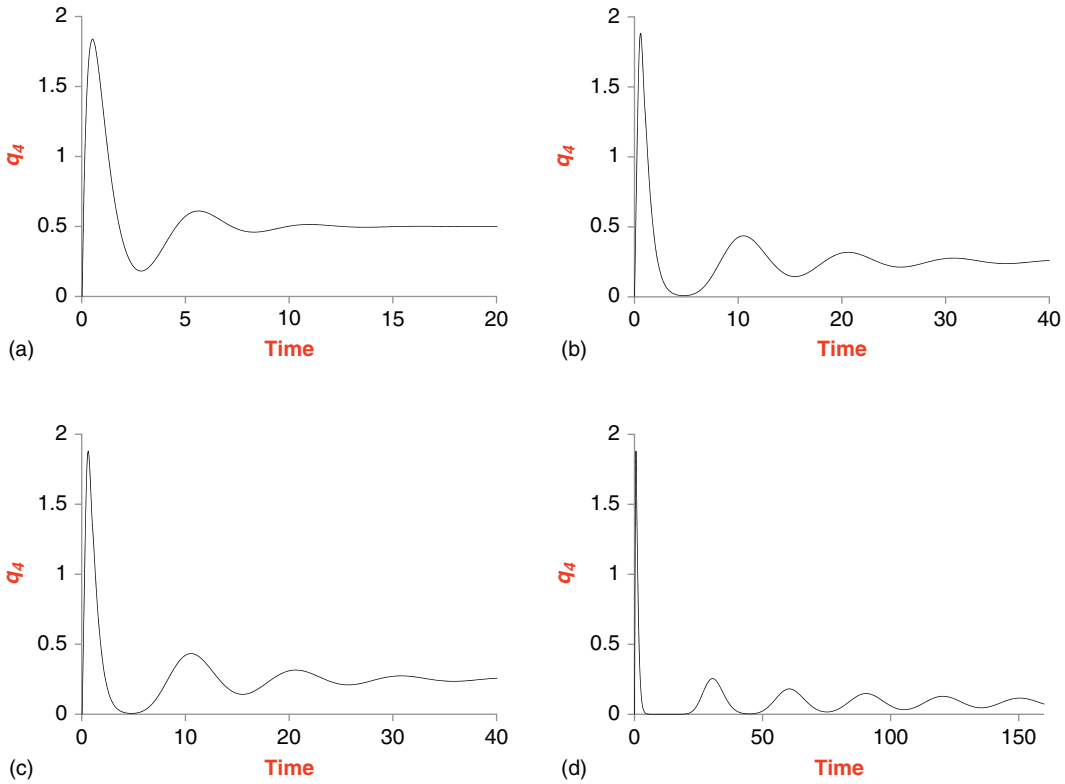

FIGURE 7.30 Plots of the response for q_4 for the closed unilateral system shown in Figure 7.28 for (a) 10, (b) 20, (c) 40, and (d) 80 compartments. A bolus input of 5 to compartment 3 is the only input.

Figure 7.28 (with zero initial conditions and equal transfer rates, $K = 2$) with input $f_3(t) = 5\delta(t)$. The response for a model of 10, 20, 40, and 80 compartments is shown in Figure 7.30 (note the time scale changes for each model). As shown, the number of oscillations increases as the number of compartments increases, and the steady-state value decreases. The time it takes for the solute to move through the system also increases as the number of compartments increases. For 20 compartments and higher, there is essentially no solute left in the compartment after the initial oscillation until the solute flows through the system.

If the system is open and solute is allowed to move into the environment, the oscillatory behavior is reduced. Consider the model used in Figure 7.28, with the exception that solute output to the environment is allowed in compartment 4, with a transfer rate of $K_{40} = 0.2$ (10 percent of the transfer rate among the compartments). Shown in Figure 7.31 is the response for q_4 with 40 and 80 compartments. An oscillatory response is still noted with fewer prominent oscillations as compared with no output to the environment. Also note that the peak oscillation for the first is much smaller than before. Finally, observe that the steady-state value is now zero.

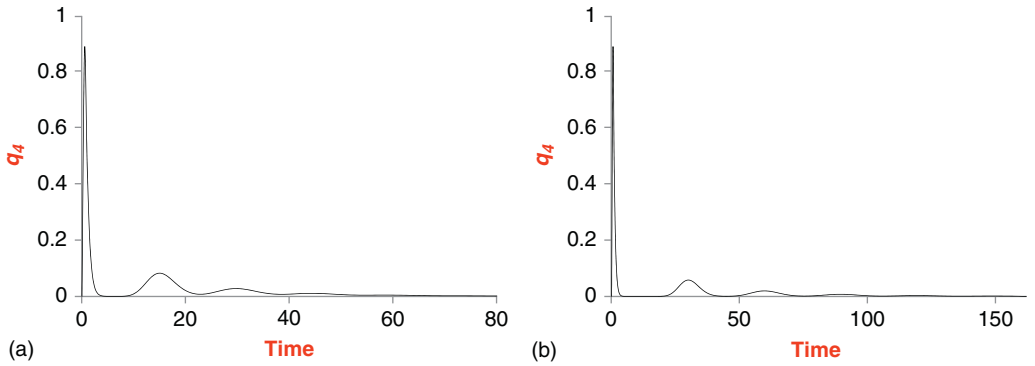

FIGURE 7.31 Plots of the response for q_4 for the open unilateral system shown in Figure 7.27 for (a) 40 and (b) 80 compartments. The model is identical to the one shown in Figure 7.29, except $K_{40} = 0.2$.

7.8.4 General Multicompartment Model

Although the previous models presented in this section are important, many systems are more complex and follow the form of a general multicompartment model. Some systems are composed of subsystems, described in Sections 7.8.1–7.8.3, which are linked together with transference among subunits. For example, a model[13] that describes thyroid hormone distribution and metabolism using two mammillary three-compartment models linked together is shown in Figure 7.32. Mammillary compartments 1–3 describe T3, and mammillary compartments 4–6 describe T4; compartments 1 and 4 are the same space, as are 2 and 5, and 3 and 6. The plasma is represented by compartments 2 and 5, compartments 1 and 4 represent the *fast* tissue (liver, kidneys, lung, heart, and gut), and compartments 3 and 6 represent the *slow* tissue (muscle, skin, and brain). *Fast* and *slow* indicate how quickly the hormones are synthesized via transfer rates K_{i0}. Transfer rates K_{41} and K_{63} are used to

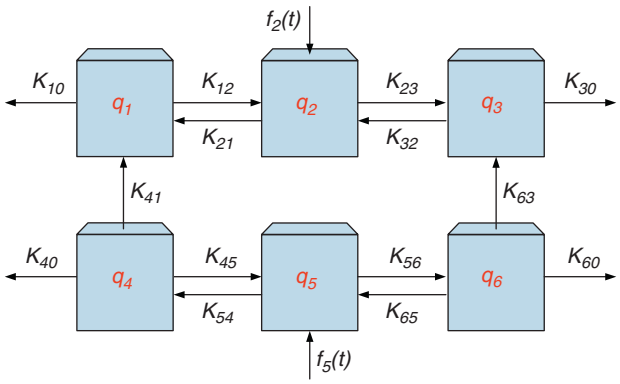

FIGURE 7.32 Six-compartment model that describes thyroid hormone distribution and metabolism.

[13]See DiStefano and Mori, 1977, in references for original problem development.

model the transformation of T4 into T3. Input to the system is through the plasma in either compartment q_2 or q_5.

Consider the movement of a drug in the body with the pharmacokinetic model in Figure 7.10. After ingestion, the drug moves into the blood, where it is distributed in the plasma. Drug distribution in the plasma is among water and proteins. Since drugs are relatively small molecules, they easily move through the capillaries and into most fluids and organs of the body. In addition, drugs move easily into the intracellular fluids of body tissues. Each arrow in Figure 7.10 needs to be defined with a transfer rate. Obtaining values for the transfer rates is usually very difficult or even impossible.

EXAMPLE PROBLEM 7.18

Consider the model[14] illustrated in Figure 7.33 for the oral input of the thyroid hormone replacement therapy in which the body does not produce any thyroid hormone. While the model is appropriate for either T3 or T4, here we track T3 and ignore T4 for simplicity. Assume T3 exists in compartment 1 (gut) in solid form and in compartment 2 (still the gut) in liquid form. Compartment 3 represents the plasma, and compartments 4 and 5 are the slow and fast tissues, respectively. Assume that the input is bolus, $f_1(t) = 25\delta(t)$, and that the initial conditions are zero. Further, $K_{12} = 1.1$, $K_{20} = 0.01$, $K_{23} = 0.9$, $K_{34} = 15$, $K_{43} = 30$, $K_{40} = 1.0$, $K_{35} = 0.5$, $K_{53} = 0.4$, and $K_{50} = 0.05$. Note that K_{40} and K_{50} represent T3 metabolism. Solve for the quantity in compartment 3.

Solution

The input is transformed into a new initial condition, $q_1(0)$. The conservation of mass for each compartment yields

$$\dot{q}_1 = -K_{12}q_1 = -1.1q_1 \tag{7.113}$$

$$\dot{q}_2 = K_{12}q_1 - (K_{20} + K_{23})q_2 = 1.1q_1 - 0.91q_2 \tag{7.114}$$

$$\dot{q}_3 = K_{23}q_2 - (K_{34} + K_{35})q_3 + K_{43}q_4 + K_{53}q_5 = 0.9q_2 - 15.5q_3 + 30q_4 + 0.4q_5 \tag{7.115}$$

$$\dot{q}_4 = K_{34}q_3 - (K_{40} + K_{43})q_4 = 15q_3 - 31q_4 \tag{7.116}$$

$$\dot{q}_5 = K_{35}q_3 - (K_{50} + K_{53})q_5 = 0.5q_3 - 0.45q_5 \tag{7.117}$$

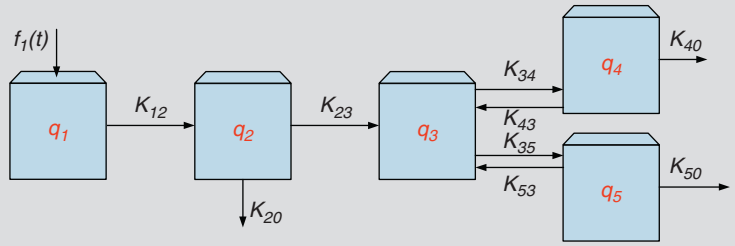

FIGURE 7.33 Illustration for Example Problem 7.18. Compartments 1 and 2 are the digestive system, compartment 3 is the plasma, and compartments 4 and 5 are the fast and slow tissues, respectively.

[14]See DiStefano and Mak, 1979, in references for original problem development.

Since the conservation of mass equation for q_1 involves only q_1, it is easily solved as $q_1 = 25e^{-1.1t}u(t)$. Substituting the solution for q_1 into Eq. (7.114), gives

$$\dot{q}_2 = 27.5e^{-1.1t} - 0.91q_2 \tag{7.118}$$

Equation (7.118) involves an input and only q_2, which is solved independently as

$$q_2 = \frac{K_{12}q_1(0)}{K_{12} - (K_{20} + K_{23})}\left(e^{-(K_{20}+K_{23})t} - e^{-K_{12}t}\right) = 144.74\left(e^{-0.91t} - e^{-1.1t}\right)u(t) \tag{7.119}$$

The solution for q_2 is substituted into Eq. (7.115), yielding

$$\begin{aligned}\dot{q}_3 &= K_{23}\frac{K_{12}q_1(0)}{K_{12} - (K_{20} + K_{23})}\left(e^{-(K_{20}+K_{23})t} - e^{-K_{12}t}\right) - 15.5q_3 + 30q_4 + 0.4q_5 \\ &= 130.27\left(e^{-0.91t} - e^{-1.1t}\right) - 15.5q_3 + 30q_4 + 0.4q_5\end{aligned} \tag{7.120}$$

Equations (7.120), (7.116), and (7.117) are solved using MATLAB and the D-Operator, as follows:

```
>> syms D
>> A=[-15.5 30 0.4;15 -31 0;0.5 0 -0.45];
>> det(D*eye(3)-A)
>> adj=det(D*eye(3)-A)*inv(D*eye(3)-A)
```

which gives the reconstructed differential equations for q_3 as

$$\dddot{q}_3 + 46.95\ddot{q}_3 + 51.225\dot{q}_3 + 7.525q_3 = 2531.8e^{-1.1t} - 1803.12e^{-0.91t} \tag{7.121}$$

with roots -45.84, -0.94, and -0.18. The natural response is

$$q_{3_n} = B_1e^{-45.84t} + B_2e^{-0.94t} + B_3e^{-0.18t}$$

The forced response is $q_{3_f} = B_4e^{-1.1t} + B_5e^{-0.91t}$, which after substituting into Eq. (7.113) gives

$$B_4 = 380.39 \text{ and } B_5 = 1870.41$$

The complete response is then

$$q_3 = B_1e^{-45.84t} + B_2e^{-0.94t} + B_3e^{-0.18t} + 380.39e^{-1.1t} + 1870.41e^{-0.91t}$$

We use the initial conditions, $q_3(0) = 0$, $\dot{q}_3(0) = 0$, and $\ddot{q}_3(0) = 24.75$, to solve for B_1, B_2, and B_3 as follows:

$$q_3(0) = 0 = B_1 + B_2 + B_3 + 380.39 + 1870.41$$

and with $\dot{q}_3 = -45.84B_1e^{-45.84t} - 0.94B_2e^{-0.94t} - 0.18B_3e^{-0.18t} - 418.39e^{-1.1t} - 1701.97e^{-0.91t}$ we have

$$\dot{q}_3(0) = 0 = -45.84B_1 - 0.94B_2 - 0.18B_3 - 418.39 - 1701.97$$

Continued

which with $\ddot{q}_3 = 2101B_1e^{-45.84t} + 0.88B_2e^{-0.94t} + 0.031B_3e^{-0.18t} + 460.23e^{-1.1t} + 1548.80e^{-0.91t}$ gives

$$\ddot{q}_3(0) = 24.75 = 2101B_1 + 0.88B_2 + 0.031B_3 + 460.23 + 1548.80$$

To solve for the unknown constants, we evaluate

$$\begin{bmatrix} 1 & 1 & 1 \\ -45.84 & -0.94 & -0.18 \\ 2101 & 0.88 & 0.031 \end{bmatrix} \begin{bmatrix} B_1 \\ B_2 \\ B_3 \end{bmatrix} = \begin{bmatrix} -2250.7 \\ 2120.3 \\ -1984.3 \end{bmatrix}$$

which gives

$$\begin{bmatrix} B_1 \\ B_2 \\ B_3 \end{bmatrix} = \begin{bmatrix} .004 \\ -2259.51 \\ 8.844 \end{bmatrix}$$

Thus,

$$q_3 = \left(0.004e^{-45.84t} - 2259.51e^{-0.94t} + 8.84e^{-0.18t} + 380.39e^{-1.1t} + 1870.41e^{-0.91t}\right)u(t) \tag{7.122}$$

which is plotted in Figure 7.34. Note that if the oral dose involved T4 instead of T3, the model would need to be changed by adding three more compartments for T4 (lower part of Figure 7.31). We still need the three T3 compartments, since T4 transforms into T3.

Another way to solve for the response is to directly analyze the system using the D-Operator matrix approach on Eqs. (7.113)–(7.117), which appears easier, since the input is 0 and there is no forced response. However, considerable additional work is required to calculate the two extra initial conditions ($\dddot{q}_1(0)$ and $\ddddot{q}_1(0)$) needed to solve for the extra two terms in the natural response, which is not trivial. Thus, we have

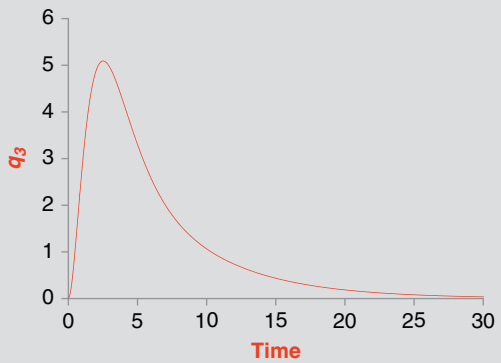

FIGURE 7.34 Illustration of the quantity in compartment 3 in Example Problem 7.18.

```
>> syms D
>> A=[-1.1 0 0 0 0;1.1 -.91 0 0 0;0.9 -15 .5 30 .4;0 0 15 -31 0;0 0 .5 0 -.45];
>> det(D*eye(5)-A)
ans =
  D^5 + (1224*D^4)/25 + (293191*D^3)/2000 + (787421*D^2)/5000 +
  (2656059*D)/40000 + 301301/40000
>> eig(A)
ans =

  -0.1748
  -0.9392
  -45.8360
  -0.9100
  -1.1000
```

The reconstructed differential equation for q_3 is

$$\dddot{\dddot{q}}_3 + 48.92\dddot{\ddot{q}}_3 + 146.6\dddot{\dot{q}}_3 + 157.5\ddot{q}_3 + 66.4\dot{q}_3 + 7.53q_3 = 0$$

From the roots, the response is written as

$$q_3 = B_1e^{-0.18t} + B_2e^{-0.94t} + B_3e^{-45.84t} + B_4e^{-0.91t} + B_5e^{-1.1t} \tag{7.123}$$

which is the same form as Eq. (7.122). To calculate B_1 through B_5, we use the initial conditions, $q_1(0) = 25$, $q_2(0) = 0$, $q_3(0) = 0$, $q_4(0) = 0$, and $q_5(0) = 0$, to find, after considerable effort, that $q_3(0) = 0, \dot{q}_3(0) = 0, \ddot{q}_3(0) = 24.75$, $\dddot{q}_3(0) = -433.3752$, and $\dddot{\dddot{q}}_1(0) = 17,935$.

Using the initial conditions and Eq. (7.123), we have

$$q_3(0) = 0 = B_1 + B_2 + B_3 + B_4 + B_5$$

$$\dot{q}_3(0) = 0 = -0.18B_1 - 0.94B_2 - 45.84B_3 - 0.91B_4 - 1.1B_5$$

$$\ddot{q}_3(0) = 24.75 = (-0.18)^2B_1 + (-0.94)^2B_2 + (-45.84)^2B_3 + (-0.91)^2B_4 + (-1.1)^2B_5$$

$$\dddot{q}_3(0) = -433.3725 = (-0.18)^3B_1 + (-0.94)^3B_2 + (-45.84)^3B_3 + (-0.91)^3B_4 + (-1.1)^3B_5$$

$$\dddot{\ddot{q}}_3(0) = 17,935 = (-0.18)^4B_1 + (-0.94)^4B_2 + (-45.84)^4B_3 + (-0.91)^4B_4 + (-1.1)^4B_5$$

To solve for the unknown constants, we evaluate the unknown coefficients using MatLab:

$$\begin{bmatrix} 1 & 1 & 1 & 1 & 1 \\ -0.18 & -0.94 & -45.84 & -0.91 & -1.1 \\ 0.031 & 0.88 & 2101 & 0.83 & 1.21 \\ -0.005 & -0.83 & -96,298 & -.75 & -1.33 \\ 0.0009 & 0.78 & 4,4139,948 & 0.69 & 1.46 \end{bmatrix} \begin{bmatrix} B_1 \\ B_2 \\ B_3 \\ B_4 \\ B_5 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 24.75 \\ -433.3725 \\ 17,934 \end{bmatrix}$$

Continued

which gives

$$\begin{bmatrix} B_1 \\ B_2 \\ B_3 \\ B_4 \\ B_5 \end{bmatrix} = \begin{bmatrix} 8.84 \\ -2259.15 \\ 0.004 \\ 1870 \\ 380.3 \end{bmatrix}$$

and

$$q_3 = \left(0.004e^{-45.84t} - 2259.15e^{-0.94t} + 8.84e^{-0.18t} + 380.3e^{-1.1t} + 1870e^{-0.91t}\right)u(t)$$

7.9 EXERCISES

1. Determine the number of Na^+ and K^+ ions inside a cell with a volume of 1 nL and concentrations given in Table 7.2.
2. Suppose the concentrations of Na^+, Cl^-, and K^+ are 20, 52, and 158 mM/L, respectively. Determine the number of ions in a cell of 2 nL.
3. A cell with a volume of 1.5 nL contains 2×10^{14} molecules of K^+ and 1.5×10^{13} molecules of Na^+. What is the concentration for each ion?
4. Two compartments, with volumes V_1 and V_2, are separated by a thin membrane, and solute moves from one compartment to the other by diffusion. If an amount ζ of solute is dumped into compartment 1 at $t = 0$, then find the concentration in each compartment.
5. Two compartments, with volumes V_1 and V_2, are separated by a thin membrane, and solute moves from one compartment to the other by diffusion. If an amount ζ of solute is dumped into compartment 2 at $t = 0$, then find the concentration in each compartment.
6. Two compartments, with equal volumes of 0.0572 cm^3, are separated by a thin membrane, and solute moves from one compartment to the other by diffusion. If all of the solute is initially dumped into one compartment, then find the transfer rate if the time constant equals $27 \times 10^3 s^{-1}$.
7. A system is given by two compartments separated by a thin membrane, and solute moves from one compartment to the other by diffusion. The volume of compartment 1 is $0.1 cm^3$ and compartment 2 is 0.3 cm^3. The transfer rate is $2.0 \times 10^{-3} s^{-1}$. Suppose 3 g of solute is dumped into compartment 2. Solve for the concentration in both compartments.
8. A system is given by two compartments separated by a thin membrane, and solute moves from one compartment to the other by diffusion. Suppose the volume of compartment 1 equals 0.0572 cm^3 and is twice as large as compartment 2. If 100 g of solute is dumped into compartment 2, then solve for the concentration in both compartments for an arbitrary transfer rate K (where the solution is expressed in terms of K).
9. A system is given by two compartments separated by a thin membrane, and solute moves from one compartment to the other by diffusion. The volume of compartment 1 is 0.0572 cm^3 and compartment 2 is 0.0286 cm^3. Suppose 100 M of solute is dumped into compartment 2, and the concentration response for compartment 2 is $c_2(t) = \left(1165.67 + 2331.3e^{-0.015t}\right)u(t)\frac{M}{cm^3}$. (a) Find the transfer rate. (b) Solve for the concentration in compartment 1.

10. A system is given by two compartments separated by a thin membrane, and solute moves from one compartment to the other by diffusion. The volume of compartment 1 is 0.03 cm^3 and compartment 2 is 0.01 cm^3. Suppose 50 M of solute is dumped into compartment 2, and the concentration response for compartment 1 is $c_1(t) = 1250\left(1 - e^{-0.01t}\right)u(t)\frac{M}{cm^3}$. (a) Find the transfer rate. (b) Solve for the concentration in compartment 2.
11. Find the initial osmotic pressure at room temperature for a cell if the only ions present are *KCl* on either side of the membrane. Assume the concentrations for K^+ and Cl^- from Table 7.2 and that the ions cannot cross the membrane. The cell volume is 2 nL. Determine the final cell volume.
12. Find the initial osmotic pressure at room temperature for a cell if the only ions present are $CaCl_2$ on either side of the membrane. Assume the concentrations for Ca^{+2} and Cl^- from Table 7.2 and that the ions cannot cross the membrane. The cell volume is 2 nL. Determine the final cell volume.
13. Find the initial osmotic pressure at room temperature for a cell if all the ions present are listed in Table 7.2. Assume that the ions cannot cross the membrane. The cell volume is 2 nL. Determine the final cell volume.
14. Find the initial osmotic pressure at room temperature for a cell if the only ions present are *KCl* and *NaCl* on either side of the membrane. Assume the concentrations for K^+, Na^+, and Cl^- from Table 7.2, and that only K^+ can cross the membrane. The cell volume is 2 nL. Describe what happens to the ions. Determine the final cell volume.
15. Find the initial osmotic pressure at room temperature for a cell if the only ions present are *KCl* and *NaCl* on either side of the membrane, and 0.2×10^{-9} M of a protein inside the cell. Assume the concentrations for K^+, Na^+, and Cl^- from Table 7.2, and that only K^+ can cross the membrane. The cell volume is 2 nL. Describe what happens to the ions. Determine the final cell volume.
16. Find the osmolarity and osmotic pressure of 2 mM Na_2SO_4 at room temperature.
17. Find the osmolarity and osmotic pressure of a 9% solution of *NaCl* at room temperature.
18. Find the osmotic pressure at room temperature for a cell if the ions in Table 7.2 are present.
19. Consider a cell with an internal osmolarity of 300 mOsm and volume of 2 nL in a 30 nL solution of 300 mOsm. A 3 nL, 5% *NaCl* by weight solution is added to the extracellular space. Assuming that *NaCl* is impermeable and that the moles inside the cell do not change, describe the events that take place until steady state is achieved. What is the final osmolarity of the cell? What is the volume of the cell at steady state?
20. Consider a cell with an internal osmolarity of 300 mOsm and volume of 2 nL in a 30 nL solution of 300 mOsm. Three mM of $CaCl_2$ is added to the extracellular space. Assuming that $CaCl_2$ is impermeable and that the moles inside the cell do not change, describe the events that take place until steady state is achieved. What is the final osmolarity of the cell? What is the volume of the cell at steady state?
21. Consider a cell with an internal osmolarity of 300 mOsm and volume of 2 nL in a 30 nL solution of 300 mOsm. Five mM of urea is added to the extracellular space. Assuming that urea is permeable and that the moles originally inside the cell are impermeable, describe the events that take place until steady state is achieved.

Continued

22. Given the cell described in Figure 7.7 with $a = 500$ mM, $P_K = 1.0$, and $P_{Na} = 0.04$, at steady state, plot the relationship between $\vec{J}_p$ and V.
23. Suppose 500 mg of dye was introduced into the plasma compartment. After reaching steady state, the concentration in the blood is $0.0893 \frac{\text{mg}}{\text{cm}^3}$. Find the volume of the plasma compartment.
24. Suppose 1 g bolus of solute is injected into a plasma compartment of 3 L. The transfer rate out of the compartment equals $0.7\ \text{hr}^{-1}$. Solve for the solute concentration. What is the half-life of the solute in the plasma compartment?
25. An unknown quantity of radioactive iodine (I^{131}) is instantaneously passed into the plasma. The time dependence of the quantity of I^{131} in the plasma exhibits an exponential decay from 100 mg with a time constant of 1 day, while the urine shows an exponential rise from zero to 75 mg with a time constant of 1 day. Assuming the compartment model in Example Problem 7.5, determine the transfer rates and the half-life.
26. Suppose a patient ingested a small quantity of radioactive Iodine (I^{131}). A simple model describing the removal of I^{131} from the bloodstream into the urine and thyroid is given in Example Problem 7.5. (a) Sketch the response of the system. (b) Suppose the thyroid is not functioning and does not take up any I^{131}. Sketch the response of the abnormal system and compare to the result from (a).
27. A radioactive bolus of I^{131} is injected into a plasma compartment. The time dependence of the concentration of I^{131} in the plasma is $c_1 = 143e^{-1.6t}\frac{\text{mg}}{100\ \text{mL}}$. The amount of I^{131} is 10 K mg. Assuming the compartmental model in Example Problem 7.5, find (a) the volume of the plasma compartment, (b) $K = K_1 + K_2$, and (c) the half-life.
28. Find the half-life for the model given in Eq. (7.33) and Figure 7.8.
29. Use SIMULINK to simulate the model given in Eq. (7.33) and Figure 7.8. Use the parameters given in Figure 7.11.
30. Demonstrate for the one-compartment pharmacokinetic model given in Section 7.5.3 with Eq. (7.33) and Figure 7.8 that as γ increases, both $t_{\max}$ and $q_1(t_{\max})$ decrease.
31. An antibiotic is exponentially administered into the body, with $f(t) = 75e^{-2t}u(t)$. Assume the model given in Figure 7.8 with $K_{10} = 0.3$. (a) Analytically solve for the quantity of the antibiotic in the plasma. (b) Simulate the quantity of the antibiotic in the plasma using SIMULINK. (c) What is the time to maximum concentration, and what is the quantity in the plasma at that time?
32. For the one-compartment repeat dosage in Section 7.5.4, derive Eq. (7.42) from (7.41) and Eq. (7.44) from (7.33).
33. A 2 g bolus of antibiotic is administered to a person with a plasma volume of 3 L. The average impulse response for this drug is shown in Figure 7.35. Assuming a one-compartment model, determine the transfer rate. If the concentration of the drug is not to fall below 10 percent of the initial dosage at steady state, how often does the drug need to be given to maintain this minimum level?
34. A 4 g bolus of antibiotic is administered to a person with a plasma volume of 3 L. The average washout response for this drug in a plasma volume of 3 L is shown in Figure 7.36. Assuming a one-compartment model, determine the transfer rate. If the concentration of the drug is not to fall below 25 percent of the initial dosage at steady state, how often does the drug need to be given to maintain this minimum level?

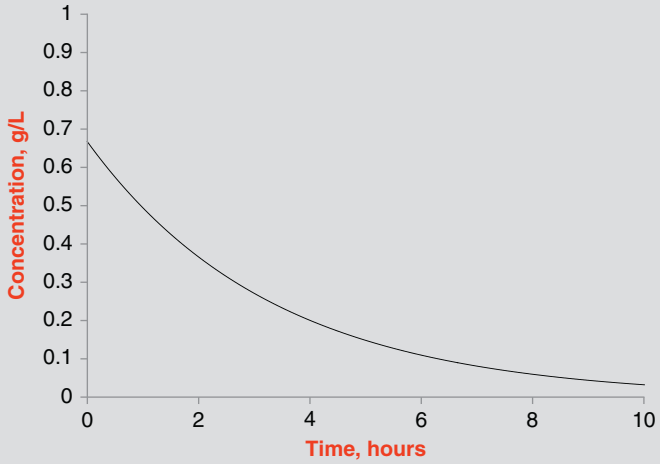

FIGURE 7.35 Illustration for Exercise 33.

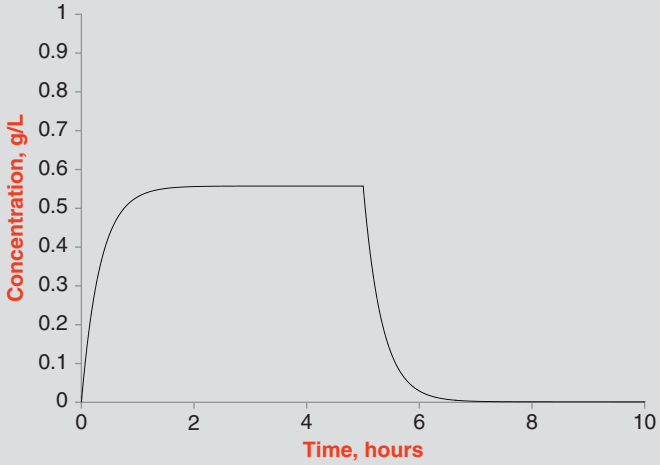

FIGURE 7.36 Illustration for Exercise 34.

35. Given the two-compartment model in Figure 7.16 and $q_1(0) = 0$ and $q_2(0) = \zeta$, solve for the concentration in compartment 2.

36. Given the two-compartment model in Figure 7.16 and $q_1(0) = \alpha$ and $q_2(0) = \zeta$, solve for the concentration in each compartment.

37. Given the two-compartment model shown in Figure 7.17 with a pulse ingestion of solute in the digestive system and removal of solute via metabolism and excretion in urine, solve for the plasma concentration.

Continued

38. Given the two-compartment model shown in Figure 7.17 with a $\zeta\delta(t) + (1-\zeta)(u(t) - u(t-t_0))$ ingestion of solute in the digestive system and removal of solute via metabolism and excretion in urine, solve for the plasma concentration.
39. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0, K_{10} = 0.5,\ K_{21} = 0.3,$ $K_{20} = 0.9,\ f_1(t) = 0,$ and $f_2(t) = 5\delta(t)$. Assume that the initial conditions are zero. (a) Solve for the quantity in each compartment. (b) Find the maximum amount of solute in compartment 1.
40. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0.2, K_{10} = 0.7,$ $K_{21} = 0,\ K_{20} = 1,\ f_1(t) = 2u(t),$ and $f_2(t) = 0$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.
41. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0, K_{10} = 0.6,$ $K_{21} = 0.1,\ K_{20} = 0.8,\ f_1(t) = 0,$ and $f_2(t) = \delta(t) + 5u(t)$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.
42. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0.3, K_{10} = 0.2,$ $K_{21} = 0,\ K_{20} = 0.4,\ f_1(t) = 4u(t),$ and $f_2(t) = 5\delta(t)$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.
43. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0.3, K_{10} = 0.5,$ $K_{21} = 0, K_{20} = 1,\ f_1(t) = 2u(t),$ and $f_2(t) = 3\delta(t)$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.
44. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0, K_{10} = 0.6,$ $K_{21} = 0.1,\ K_{20} = 0.5,\ f_1(t) = 0,$ and $f_2(t) = \delta(t) + 5u(t)$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.
45. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0.3, K_{10} = 0.7,$ $K_{21} = 0, K_{20} = 0.1,\ f_1(t) = 3\delta(t),$ and $f_2(t) = 0$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.
46. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0.4, K_{10} = 1.0,$ $K_{21} = 0, K_{20} = 0.3,\ f_1(t) = 2u(t),$ and $f_2(t) = 0$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.
47. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0.2, K_{10} = 0.8,$ $K_{21} = 0, K_{20} = 0.3,\ f_1(t) = \delta(t) + 2u(t),$ and $f_2(t) = 0$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.
48. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0.3, K_{10} = 0.5,$ $K_{21} = 0.1, K_{20} = 0.4,\ f_1(t) = 2u(t),$ and $f_2(t) = 5\delta(t)$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.
49. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0.3, K_{10} = 0.7,$ $K_{21} = 3, K_{20} = 1,\ f_1(t) = 2\delta(t),$ and $f_2(t) = 5u(t)$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.
50. Consider the two-compartment model shown in Figure 7.15 with $K_{12} = 0.2, K_{10} = 0.6,$ $K_{21} = 0.1, K_{20} = 0.5,\ f_1(t) = 3\delta(t),$ and $f_2(t) = \delta(t) + 5u(t)$. Assume that the initial conditions are zero. Solve for the quantity in each compartment.
51. Suppose 1 g of solute is ingested into the digestive system that has a transfer rate of $1.4\ \text{hr}^{-1}$ into the plasma. The plasma compartment is 3 L and has transfer rate of $0.7\ \text{hr}^{-1}$ into the environment. (a) Solve for the solute concentration in the plasma. (b) When is the maximum solute concentration observed in the plasma compartment? (c) What is the maximum solute in the plasma compartment?

52. Consider the model in Figure 7.37. The time dependence of the concentration of a radioactively labeled solute in the plasma is

$$c_1(t) = 143e^{-1.6t} + 57e^{-2.8t}\,\frac{\text{mg}}{100\text{ mL}}$$

after injecting a bolus of 10 g into the plasma. (a) Find the volume of the plasma compartment. (b) Find the transfer rates K_{12}, K_{21}, and K_{13}. (c) Suppose the input is changed to $5u(t)\,\frac{\text{mg}}{100\text{ mL}}$, and solve for $c_1(t)$ and $c_2(t)$. (d) Suppose the input is changed to $5(u(t) - u(t-2))\,\frac{\text{mg}}{100\text{ mL}}$, and solve for $c_1(t)$ and $c_2(t)$.

53. A unit step input is applied to the compartmental system in Figure 7.38. The transfer rates are $K_{20} = 0.3, K_{21} = 1.0$, and $K_{12} = 0.6$. The initial conditions are $q_1(0) = 2$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

54. A unit step input is applied to the compartmental system in Figure 7.38. The transfer rates are $K_{20} = 0.3, K_{21} = 1.0$, and $K_{12} = 0.6$. The initial conditions are $q_1(0) = 2$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

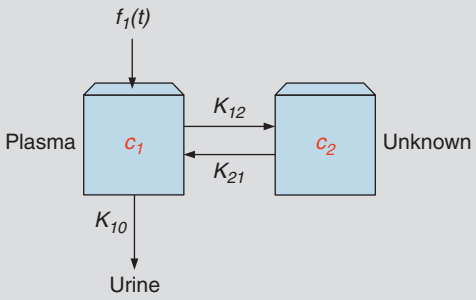

FIGURE 7.37 Illustration for Exercise 52.

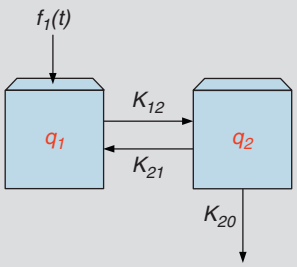

FIGURE 7.38 Illustration for Exercises 53–68.

Continued

55. The input to the compartmental system in Figure 7.38 is $2u(t) - 2u(t-1)$. The transfer rates are $K_{20} = 0.3, K_{21} = 1.0$, and $K_{12} = 0.6$. The initial conditions are $q_1(0) = 2$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

56. The input to the compartmental system in Figure 7.38 is $2u(t-1)$. The transfer rates are $K_{20} = 0.3, K_{21} = 1.0$, and $K_{12} = 0.6$. The initial conditions are $q_1(0) = 0$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

57. The input to the compartmental system in Figure 7.38 is $2e^{-0.5562t}u(t)$. The transfer rates are $K_{20} = 0.2, K_{21} = 0.1$, and $K_{12} = 0.4$. The initial conditions are $q_1(0) = 0$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

58. The input to the compartmental system in Figure 7.38 is $2e^{-0.5562t}u(t)$. The transfer rates are $K_{20} = 0.2, K_{21} = 0.1$, and $K_{12} = 0.4$. The initial conditions are $q_1(0) = 0$ and $q_2(0) = 1$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

59. The input to the compartmental system in Figure 7.38 is $2e^{-0.1438t}u(t)$. The transfer rates are $K_{20} = 0.2, K_{21} = 0.1$, and $K_{12} = 0.4$. The initial conditions are $q_1(0) = 0$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

60. The input to the compartmental system in Figure 7.38 is $2e^{-0.1438t}u(t)$. The transfer rates are $K_{20} = 0.2, K_{21} = 0.1$, and $K_{12} = 0.4$. The initial conditions are $q_1(0) = 2$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

61. The input to the compartmental system in Figure 7.38 is $2e^{-0.1438t}u(t) - 2e^{-0.1438(t-10)t}u(t-10)$. The transfer rates are $K_{20} = 0.2, K_{21} = 0.1$, and $K_{12} = 0.4$. The initial conditions are $q_1(0) = 0$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

62. The input to the compartmental system in Figure 7.38 is $3e^{-t}u(t)$. The transfer rates are $K_{20} = 0.2, K_{21} = 0.1$, and $K_{12} = 0.4$. The initial conditions are $q_1(0) = 2$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

63. The input to the compartmental system in Figure 7.38 is $3e^{-t}u(t) - 3e^{-(t-3)}u(t-3)$. The transfer rates are $K_{20} = 0.2, K_{21} = 0.1$, and $K_{12} = 0.4$. The initial conditions are $q_1(0) = 0$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1;

(b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

64. The input to the compartmental system in Figure 7.38 is $0.5e^{-2t}u(t)$. The transfer rates are $K_{20} = 0.3, K_{21} = 1.0$, and $K_{12} = 0.6$. The initial conditions are $q_1(0) = 0$ and $q_2(0) = 4$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

65. The input to the compartmental system in Figure 7.38 is $0.5e^{-2(t-2)}u(t-2)$. The transfer rates are $K_{20} = 0.3, K_{21} = 1.0$, and $K_{12} = 0.6$. The initial conditions are $q_1(0) = 0$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

66. The input to the compartmental system in Figure 7.38 is $0.5e^{-2t}u(t) - 0.5e^{-2(t-1.5)}u(t-1.5)$. The transfer rates are $K_{20} = 0.3, K_{21} = 1.0$, and $K_{12} = 0.6$. The initial conditions are $q_1(0) = 0$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

67. The input to the compartmental system in Figure 7.38 is $3\cos 4t u(t)$. The transfer rates are $K_{20} = 0.3, K_{21} = 1.0$, and $K_{12} = 0.6$. The initial conditions are $q_1(0) = 0$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

68. The input to the compartmental system in Figure 7.38 is $3\sin 2t u(t)$. The transfer rates are $K_{20} = 3, K_{21} = 5$, and $K_{12} = 7$. The initial conditions are $q_1(0) = 1$ and $q_2(0) = 0$. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2. (e) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1 and q_2.

69. For the compartmental system in Figure 7.39, a bolus of solute $(f_3(t) = \delta(t))$ is ingested into the digestive system (compartment 3). Assume that the initial conditions are zero. Write a single differential equation involving only variable (a) q_1; (b) q_2. For $t > 0$, solve the system for (c) q_1; (d) q_2.

70. Consider the three-compartment model shown in Figure 7.20 with nonzero parameters and inputs $K_{12} = 0.4, K_{10} = 0.5, K_{21} = 0.6, K_{31} = 0.9, K_{32} = 0.7, K_{23} = 0.2, K_{13} = 0.8, f_1(t) = 3u(t)$, and $f_2(t) = 5\delta(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

71. Consider the three-compartment model shown in Figure 7.20 with nonzero parameters and inputs $K_{12} = 0.5, K_{10} = 0.3, K_{21} = 0.6, K_{31} = 0.9, K_{32} = 0.7, K_{23} = 0.2, K_{13} = 0.8$, and $f_3(t) = 3\delta(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

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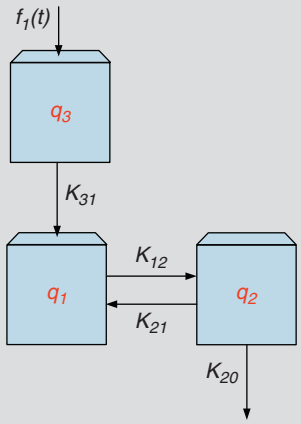

FIGURE 7.39 Illustration for Exercise 69.

72. Consider the three-compartment model shown in Figure 7.20 with nonzero parameters and inputs $K_{12} = 0.4, K_{10} = 0.5,\ K_{21} = 0.6, K_{31} = 0.9,\ K_{32} = 0.7,\ K_{23} = 0.2,\ K_{13} = 0.8,$ and $f_2(t) = 5u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

73. Consider the three-compartment model shown in Figure 7.20 with nonzero parameters and inputs $K_{12} = 0.6, K_{20} = 0.2,\ K_{21} = 0.3, K_{31} = 0.5,\ K_{32} = 0.6,\ K_{23} = 0.4,\ K_{13} = 0.8,$ and $f_1(t) = 2u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

74. Consider the three-compartment model shown in Figure 7.20 with nonzero parameters and inputs $K_{12} = 0.3, K_{20} = 0.4,\ K_{21} = 0.8, K_{31} = 0.5,\ K_{32} = 0.3,\ K_{23} = 0.4,\ K_{13} = 0.8,\ f_1(t) = 3\delta(t),$ and $f_3(t) = 3u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

75. Consider the three-compartment model shown in Figure 7.20 with nonzero parameters and inputs $K_{12} = 0.6, K_{20} = 0.2,\ K_{21} = 0.3, K_{31} = 0.5,\ K_{32} = 0.6,\ K_{23} = 0.4,\ K_{13} = 0.8,$ and $f_2(t) = \delta(t) + 5u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

76. Consider the mammillary three-compartment model shown in Figure 7.21 with nonzero parameters and inputs $K_{12} = 0.3, K_{10} = 0.5, K_{21} = 0.2, K_{23} = 0.4, K_{32} = 0.6,$ and $f_2(t) = 5\delta(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the

input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

77. Consider the mammillary three-compartment model shown in Figure 7.21 with nonzero parameters and inputs $K_{12} = 0.4, K_{30} = 0.5, K_{21} = 0.7, K_{23} = 0.8, K_{32} = 0.2,$ and $f_3(t) = 5\delta(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

78. Consider the mammillary three-compartment model shown in Figure 7.21 with nonzero parameters and inputs $K_{12} = 0.3, K_{20} = 0.2, K_{21} = 0.3, K_{23} = 0.4, K_{32} = 0.6,$ and $f_1(t) = 2u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

79. Consider the mammillary three-compartment model shown in Figure 7.21 with nonzero parameters and inputs $K_{12} = 0.7, K_{10} = 0.3, K_{21} = 0.4, K_{23} = 0.5, K_{32} = 0.6,$ and $f_2(t) = \delta(t) + 5u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

80. Consider the unilateral three-compartment model shown in Figure 7.22 with nonzero parameters and inputs $K_{12} = 0.1, K_{10} = 0.2, K_{23} = 4.0, K_{31} = 0.4,$ and $f_3(t) = 5\delta(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

81. Consider the unilateral three-compartment model shown in Figure 7.22 with nonzero parameters and inputs $K_{12} = 0.3, K_{20} = 0.2, K_{23} = 2.0, K_{31} = 0.6,$ and $f_2(t) = 4\delta(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

82. Consider the unilateral three-compartment model shown in Figure 7.22 with nonzero parameters and inputs $K_{12} = 0.4, K_{10} = 0.2, K_{23} = 5.0, K_{31} = 1.0,$ and $f_3(t) = 2u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

83. Consider the unilateral three-compartment model shown in Figure 7.22 with nonzero parameters and inputs $K_{12} = 0.6, K_{30} = 0.2, K_{23} = 5.0, K_{31} = 1.0,$ and $f_1(t) = u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and

Continued

only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

84. Consider the unilateral three-compartment model shown in Figure 7.22 with nonzero parameters and inputs $K_{12} = 0.3, K_{10} = 0.1, K_{23} = 0.4, K_{31} = 0.6,$ and $f_1(t) = 3\delta(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

85. Consider the unilateral three-compartment model shown in Figure 7.22 with nonzero parameters and inputs $K_{12} = 0.3, K_{20} = 0.1, K_{23} = 0.2, K_{31} = 0.4,$ and $f_2(t) = 4\delta(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

86. Consider the unilateral three-compartment model shown in Figure 7.22 with nonzero parameters and inputs $K_{12} = 0.4, K_{10} = 0.2, K_{23} = 0.5, K_{31} = 1.0,$ and $f_3(t) = 8u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

87. Consider the unilateral three-compartment model shown in Figure 7.22 with nonzero parameters and inputs $K_{12} = 0.6, K_{30} = 0.2, K_{23} = 0.8, K_{31} = 0.3,$ and $f_1(t) = 4u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

88. Consider the mammillary three-compartment model shown in Figure 7.21 with nonzero parameters and inputs $K_{12} = 0.3, K_{10} = 0.5, K_{21} = 0.2, K_{23} = 0.4,$ and $f_2(t) = 5\delta(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

89. Consider the mammillary three-compartment model shown in Figure 7.21 with nonzero parameters and inputs $K_{30} = 0.5, K_{21} = 0.7, K_{23} = 0.8, K_{32} = 0.2,$ and $f_3(t) = 5\delta(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

90. Consider the mammillary three-compartment model shown in Figure 7.21 with nonzero parameters and inputs $K_{12} = 0.3$, $K_{20} = 0.2$, $K_{23} = 0.4$, $K_{32} = 0.6$, and $f_1(t) = 2u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

91. Consider the mammillary three-compartment model shown in Figure 7.21 with nonzero parameters and inputs $K_{12} = 0.7$, $K_{10} = 0.3$, $K_{21} = 0.4$, $K_{32} = 0.6$, and $f_3(t) = 3\delta(t) + 5u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the

input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

92. Consider the three-compartment model shown in Figure 7.20 with nonzero parameters and inputs $K_{12} = 0.4$, $K_{10} = 0.5$, $K_{21} = 0.6$, $K_{31} = 0.9$, $K_{21} = 0.4$, $K_{32} = 0.7$, $K_{23} = 0.2$, $K_{13} = 0.8$, and $f_2(t) = 3e^{-t}\,u(t)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$,solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

93. Consider the three-compartment model shown in Figure 7.20 with nonzero parameters and inputs $K_{12} = 0.4$, $K_{10} = 0.5$, $K_{21} = 0.6$, $K_{31} = 0.9$, $K_{21} = 0.4$, $K_{32} = 0.7$, $K_{23} = 0.2$, $K_{13} = 0.8$, and $f_2(t) = 3e^{-(t-1)}\,u(t–1)$. Assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3. For $t > 0$, solve the system for (d) q_1; (e) q_2; (f) q_3. (g) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, and q_3.

94. Consider the following three-compartment model in Figure 7.40. A 5 g radioactively labeled bolus is injected into compartment 2. The time dependence of solute concentration in compartment 2 is

$$c_2(t) = -6.6271e^{-3.1069t} + 106.6271e^{-0.1931t}\,\frac{\text{mg}}{100\text{ mL}}$$

(a) What is the volume of compartment 2? (b) Determine the transfer rates K_{21}, K_{23}, and K_{32}.

95. Given a mammillary four-compartment model as described in Figure 7.26, with nonzero parameters and inputs $K_{12} = 0.3$, $K_{10} = 0.2$, $K_{21} = 0.4$, $K_{31} = 0.8$, $K_{13} = 0.7$, $K_{14} = 0.2$, $K_{41} = 0.5$, and $f_2(t) = 5\delta(t)$, assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3; (d) q_4. For $t > 0$, solve the system for (e) q_1; (f) q_2; (g) q_3; (h) q_4. (i) Using SIMULINK, simulate the system from the original set of differential equations and graph the quantity in each compartment.

96. Given a mammillary four-compartment model as described in Figure 7.26, with nonzero parameters and inputs $K_{12} = 0.5$, $K_{10} = 0.1$, $K_{21} = 0.3$, $K_{20} = 0.3$, $K_{31} = 0.2$, $K_{13} = 0.5$, $K_{14} = 0.7$, $K_{41} = 0.2$, and $f_1(t) = 5u(t)$, assume that the initial conditions are zero. Write a single differential

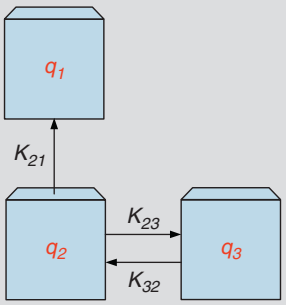

FIGURE 7.40 Illustration for Exercise 94.

Continued

equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3; (d) q_4. For $t > 0$,solve the system for (e) q_1; (f) q_2; (g) q_3; (h) q_4. (i) Using SIMULINK, simulate the system from the original set of differential equations and graph the quantity in each compartment.

97. Given a catenary four-compartment model as described in Figure 7.27, with nonzero parameters and inputs $K_{12} = 0.3$, $K_{10} = 0.1$, $K_{21} = 0.5$, $K_{30} = 0.4$; $K_{32} = 0.6$, $K_{23} = 0.4$, $K_{34} = 0.2$, $K_{43} = 0.7$, and $f_1(t) = 10\delta(t)$, assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3; (d) q_4. For $t > 0$, solve the system for (e) q_1; (f) q_2; (g) q_3; (h) q_4. (i) Using SIMULINK, simulate the system from the original set of differential equations and graph the quantity in each compartment.

98. Given a catenary four-compartment model as described in Figure 7.27, with nonzero parameters and inputs $K_{12} = 0.7$, $K_{10} = 0.2$, $K_{21} = 0.4$, $K_{32} = 0.2$, $K_{23} = 0.7$, $K_{34} = 0.3$, $K_{43} = 0.5$, and $f_3(t) = 20u(t)$, assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3; (d) q_4. For $t > 0$, solve the system for (e) q_1; (f) q_2; (g) q_3; (h) q_4. (i) Using SIMULINK, simulate the system from the original set of differential equations and graph the quantity in each compartment.

99. Given a unilateral four-compartment model as described in Figure 7.28, with nonzero parameters and inputs $K_{12} = 0.4$, $K_{10} = 0.1$, $K_{23} = 0.6$, $K_{34} = 0.7$, $K_{41} = 0.4$, $K_{40} = 0.2$, and $f_3(t) = 20\delta(t)$, assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3; (d) q_4. For $t > 0$, solve the system for (e) q_1; (f) q_2; (g) q_3; (h) q_4. (i) Using SIMULINK, simulate the system from the original set of differential equations and graph the quantity in each compartment.

100. Given a unilateral four-compartment model as described in Figure 7.28, with nonzero parameters and inputs $K_{12} = 0.4$, $K_{10} = 0.1$, $K_{23} = 0.6$, $K_{34} = 0.7$, $K_{41} = 0.4$, $K_{40} = 0.2$, and $f_3(t) = 20\delta(t)$, assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3; (d) q_4. For $t > 0$, solve the system for (e) q_1; (f) q_2; (g) q_3; (h) q_4. (i) Using SIMULINK, simulate the system from the original set of differential equations and graph the quantity in each compartment.

101. Given a unilateral four-compartment model as described in Figure 7.28, with nonzero parameters and inputs $K_{12} = 0.4$, $K_{23} = 0.4$, $K_{34} = 0.4$, $K_{41} = 0.4$, and $f_3(t) = 10\delta(t)$, assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3; (d) q_4. For $t > 0$, solve the system for (e) q_1; (f) q_2; (g) q_3; (h) q_4. (i) Using SIMULINK, simulate the system from the original set of differential equations and graph the quantity in each compartment.

102. Given a unilateral five-compartment model as described in Figure 7.28, with nonzero parameters and inputs $K_{12} = 0.5$, $K_{23} = 0.5$, $K_{34} = 0.5$, $K_{41} = 0.5$, $K_{51} = 0.5$, $K_{40} = 0.1$, and $f_2(t) = 10\delta(t)$, assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3; (d) q_4. For $t > 0$, solve the system for (e) q_1; (f) q_2; (g) q_3; (h) q_4. (i) Using SIMULINK, simulate the system from the original set of differential equations and graph the quantity in each compartment.

103. Given a unilateral five-compartment model as described in Figure 7.28, with nonzero parameters and inputs $K_{12} = 0.5$, $K_{23} = 0.5$, $K_{34} = 0.5$, $K_{41} = 0.5$, $K_{51} = 0.5$, and $f_1(t) = 5\delta(t)$, assume that the initial conditions are zero. Write a single differential equation involving the input and only variable (a) q_1; (b) q_2; (c) q_3; (d) q_4. For $t > 0$, solve the system for (e) q_1; (f) q_2;

(g) q_3; (h) q_4. (i) Using SIMULINK, simulate the system from the original set of differential equations and graph the quantity in each compartment.

104. Suppose 1 g of solute is dumped into compartment 1 as shown in Figure 7.41. The transfer rates are $K_{12} = 0.4$, $K_{23} = 0.6$, $K_{24} = 0.3$, $K_{32} = 1.2$, $K_{34} = 0.8$, and $K_{42} = 0.7$. Write a single differential equation involving only variable (a) q_1; (b) q_2; (c) q_3; (d) q_4. For $t > 0$, solve the system for (e) q_1; (f) q_2; (g) q_3; (h) q_4. (i) Using SIMULINK, simulate the system from the original set of differential equations and each variable.

105. For the compartmental system in Figure 7.42, a radioactively labeled bolus of solute, with magnitude of 1, was injected into compartment 3. Let $K_{21} = 0.2$, $K_{32} = 0.3$, $K_{31} = 0.7$, $K_{13} = 0.4$, $K_{34} = 0.9$, $K_{43} = 0.1$, and $K_{14} = 0.6$. Write a single differential equation involving only variable (a) q_1; (b) q_2; (c) q_3; (d) q_4. For $t > 0$, solve the system for (e) q_1; (f) q_2; (g) q_3; (h) q_4. (i) Using SIMULINK, simulate the system from the original set of differential equations and graph q_1, q_2, q_3, and q_4.

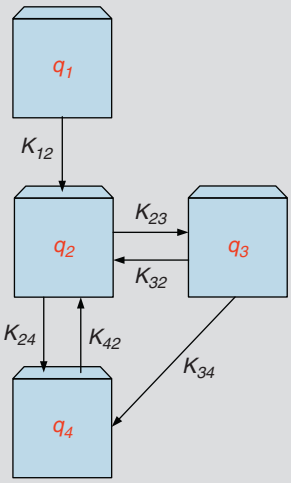

FIGURE 7.41 Illustration for Exercise 104.

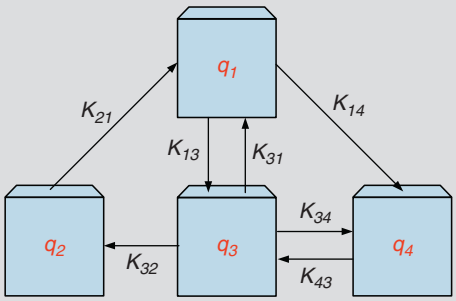

FIGURE 7.42 Illustration for Exercise 105.

Continued

106. Consider the model illustrated in Figure 7.33 for the oral input of T3 thyroid hormone replacement therapy. Assume T3 exists in compartment 1 (gut) in solid form and in compartment 2 (still the gut) in liquid form. Compartment 3 represents the plasma, and compartments 4 and 5 are the fast and slow tissues, respectively. Assume that the input is bolus, $f_1(t) = 5\delta(t)$, and that the initial conditions are zero. Further, assume that $K_{12} = 1.1$, $K_{20} = 0.01$, $K_{23} = 0.9$, $K_{34} = 7.0$, $K_{43} = 30$, $K_{40} = 0.8$, $K_{35} = 2.0$, $K_{53} = 0.3$, and $K_{50} = 0.1$. Note that K_{40} and K_{50} represent T3 metabolism. Solve for the quantity of T3 in compartment 3.

107. Consider the model illustrated in Figure 7.43 for the oral input of thyroid hormone replacement therapy using T4. Assume T4 exists in compartment 7 (gut) in solid form and in compartment 8 (still the gut) in liquid form. Compartments 2 (for T3) and 5 (for T4) represent the plasma, compartments 1 and 4 are the fast tissues, and compartments 3 and 6 are the slow tissues. Assume that the input is bolus, $f_7(t) = 25\delta(t)$, and that the initial conditions are zero. Further, $K_{78} = 1.1$, $K_{80} = 0.01$, $K_{85} = 0.62$, $K_{21} = 15$, $K_{12} = 30$, $K_{10} = 1.0$, $K_{23} = 0.5$, $K_{32} = 0.4$, $K_{30} = 0.05$, $K_{40} = 0.08$, $K_{45} = 0.45$, $K_{54} = 0.28$, $K_{56} = 0.05$, $K_{65} = 0.017$, and $K_{60} = 0.018$. Note that K_{10}, K_{30}, K_{40}, and K_{60} represent T3 and T4 metabolism. Solve for the quantity of T3 in compartment 2.

108. Consider the model illustrated in Figure 7.44 for oral input of T4 thyroid hormone replacement therapy. Assume T4 exists in compartment 7 (gut) in solid form and in compartment 8 (still the gut) in liquid form. Compartments 2 (for T3) and 5 (for T4) represent the plasma, compartments 1 and 4 are the fast tissues, and compartments 3 and 6 are the slow tissues. Assume that the input is bolus, $f_7(t) = 25\delta(t)$, and that the initial conditions are zero. Further, assume that $K_{78} = 1.1$, $K_{80} = 0.01$, $K_{85} = 0.62$, $K_{21} = 7.0$, $K_{12} = 10$, $K_{10} = 0.8$, $K_{23} = 2.0$, $K_{32} = 0.3$, $K_{30} = 0.1$, $K_{40} = 0.06$, $K_{45} = 1.0$, $K_{54} = 0.3$, $K_{56} = 0.0$, $K_{65} = 0.03$, and $K_{60} = 0.02$. Note that K_{10}, K_{30}, K_{40}, and K_{60} represent T3 and T4 metabolism. Solve for the quantity of T3 in compartment 2.

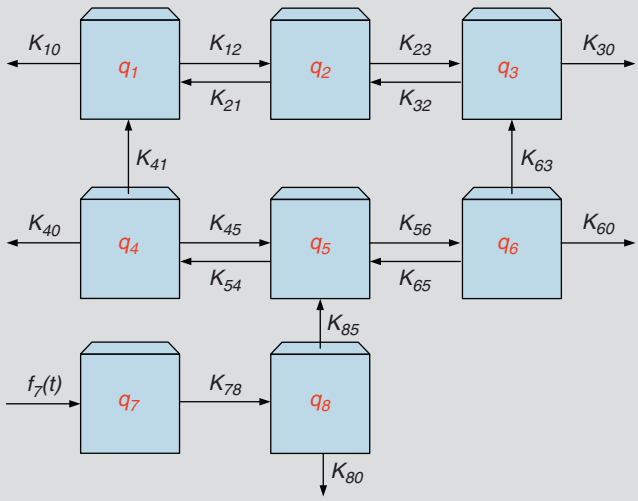

FIGURE 7.43 Illustration for Exercise 107.

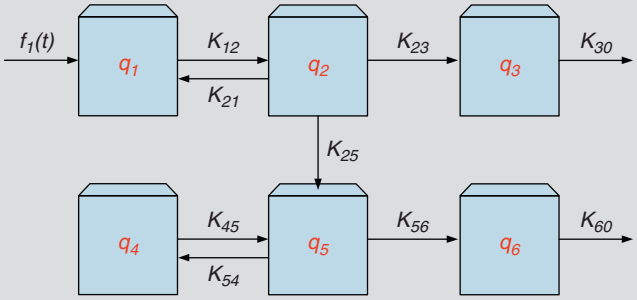

FIGURE 7.44 Illustration for Exercises 108 and 109.

109. Solve for the quantity in each compartment shown in Figure 7.44 given $K_{12} = 1.6$, $K_{21} = 0.5$, $K_{23} = 2.0$, $K_{30} = 0.5$, $K_{25} = 2.5$, $K_{45} = 0.4$, $K_{54} = 1.5$, $K_{60} = 0.5$, $K_{56} = 0.4$, and $f_1(t) = 10\delta(t)$.

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