the measurement of radioactivity may include a portion from more than one compartment. In the remainder of this book though **Cx** will be taken as the vector form of eqn (2.66).

2.5 Frequency-domain characterization of system dynamics

In this chapter, emphasis has deliberately been placed on the time-domain characterization of system dynamics, and the corresponding expressions in the Laplace operator s. There is also a considerable body of theory concerning frequency-domain characterization which gives no additional information, but which presents the same information in a different manner. This is sometimes more appropriate, particularly when sinusoidal input functions are feasible. Such functions are not feasible for most compartmental system applications, for which the inputs are more usually impulse and/or step functions. Details of frequency-domain characterizations will therefore not be given in this book, and the interested reader is instead referred to a standard text, for example Richards (1979).

3 Analysis of Systems with One and Two Compartments

In this chapter, the dynamic response of linear, time-invariant compartmental systems with one and two compartments will be considered.

3.1 One-compartment system

In some practical situations, the system being modelled can be approximated by a model with only one compartment. In physiological systems, for example, the compartment would contain the systemic blood and well perfused tissue, and the effect on the kinetics of less well perfused tissue would be negligible.

The one-compartment system is shown in Fig. 3.1. The differential equation for the quantity x_1 in the compartment is

$$\dot{x}_1(t) = -k_{01}x_1(t) + b_1u_1(t) \tag{3.1}$$

so that

$$\frac{X_1(s)}{U_1(s)} = \frac{b_1}{s + k_{01}}. \tag{3.2}$$

The observation is

$$y_1(t) = c_1x_1(t) \tag{3.3}$$

where c_1 is the observation gain. If the observation (i.e. measurement) is of concentration, for example, and $x_1(t)$ is a quantity,

$$c_1 = \frac{1}{V_1} \tag{3.4}$$

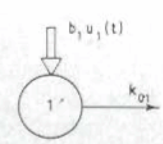

Figure 3.1 One-compartment model.

where V_1 is the *apparent volume of distribution* of the compartment. The overall transfer function $G(s)$ is thus

$$G(s) = \frac{Y_1(s)}{U_1(s)} = \frac{c_1 b_1}{s + k_{01}}. \tag{3.5}$$

3.1.1 *Impulsive input*

If a quantity D_1 is rapidly administered,

$$u_1(t) = D_1\,\delta(t) \tag{3.6}$$

where $\delta(t)$ is the unit delta function (see eqn (2.18)). Thus

$$U_1(s) = D_1 \tag{3.7}$$

and, by inverse Laplace transformation (assuming $x_1(0^-) = 0$),

$$y_1(t) = c_1 b_1 D_1\,\mathrm{e}^{-k_{01}t}, \qquad t \geqslant 0 \tag{3.8}$$

as shown in Fig. 3.2 (cf. Fig. 2.3). The zero-time intercept $y_1(0)$ is $c_1 b_1 D_1$, the time constant is $\frac{1}{k_{01}}$ and, from eqn (2.13), the half-life is $\frac{0.693}{k_{01}}$.

3.1.2 *Step input (constant continuous infusion)*

If, instead of being impulsive, the input is administered at a steady rate k_i per unit time, starting at $t = 0$, i.e.

$$u_1(t) = k_i, \qquad t \geqslant 0 \tag{3.9}$$

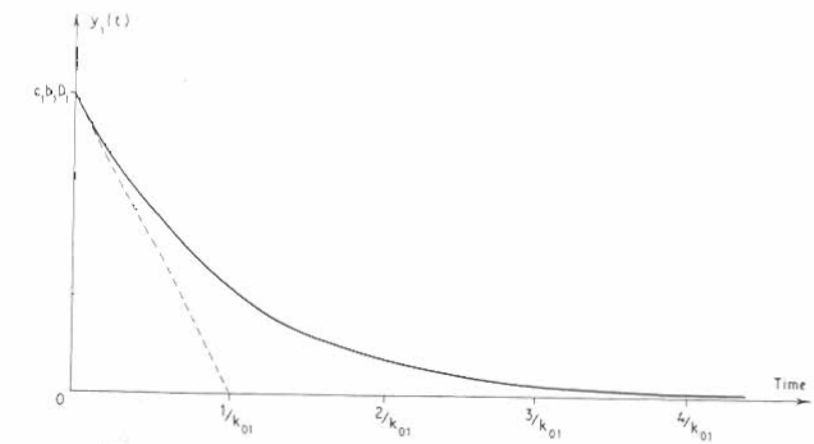

Figure 3.2 Observed impulse response of the one-compartment model.

then

$$U_1(s) = \frac{k_i}{s} \tag{3.10}$$

so that, from eqn (3.2) and eqn (3.3),

$$Y_1(s) = \frac{c_1 b_1 k_i}{s(s + k_{01})} = \frac{c_1 b_1 k_i}{k_{01}}\left(\frac{1}{s} - \frac{1}{s + k_{01}}\right). \tag{3.11}$$

Inverse Laplace transformation gives

$$y_1(t) = \frac{c_1 b_1 k_i}{k_{01}}\,(1 - \mathrm{e}^{-k_{01}t}), \qquad t \geqslant 0 \tag{3.12}$$

as shown in Fig. 3.3 (cf. Fig. 2.4).

Note the general result here (for a linear system) that the unit step response (with $k_i = 1$) is the integral of the unit impulse response (with $D_1 = 1$); this is confirmed by integrating eqn (3.8) to give the unit step response

$$y_1(t) = \int_0^t c_1 b_1\,\mathrm{e}^{-k_{01}t}\,\mathrm{d}t = \frac{c_1 b_1}{k_{01}}\,(1 - \mathrm{e}^{-k_{01}t}), \qquad t \geqslant 0. \tag{3.13}$$

In a number of medical applications, it is preferable to administer a dose D_1 as a constant infusion over a time T_i, so that

$$u_1(t) = \frac{D_1}{T_i}, \qquad 0 \leqslant t < T_i \tag{3.14}$$

$$= 0, \qquad \text{otherwise}. \tag{3.15}$$

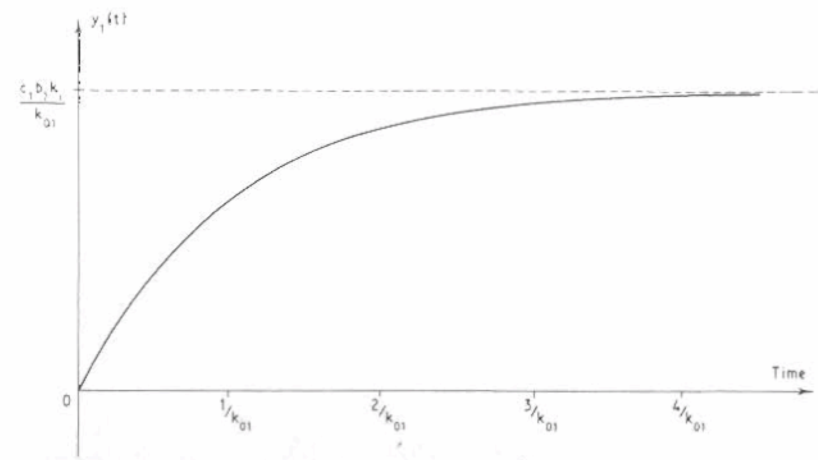

Figure 3.3 Observed step response of the one-compartment model.

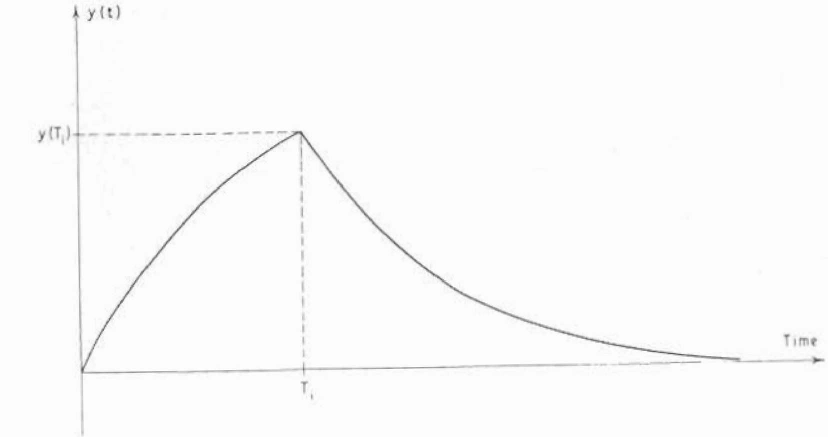

Figure 3.4 Observed response of the one-compartment model to a constant infusion over the time range $0 \leqslant t \leqslant T_i$.

From eqn (3.12), the measured quantity during the infusion is

$$y_1(t) = \frac{c_1 b_1}{k_{01}} \frac{D_1}{T_i} (1 - e^{-k_{01}t}), \qquad 0 \leqslant t < T_i \tag{3.16}$$

reaching a value at the end of the infusion of

$$y_1(T_i) = \frac{c_1 b_1}{k_{01}} \frac{D_1}{T_i} (1 - e^{-k_{01}T_i}). \tag{3.17}$$

After the infusion has stopped,

$$y_1(t) = y_1(T_i)\, e^{-k_{01}(t - T_i)}, \qquad t \geqslant T_i. \tag{3.18}$$

A plot of $y_1(t)$, as given by eqns (3.16) and (3.18), is shown in Fig. 3.4.

3.1.3 *The washout curve*

As noted in Section 2.4, a washout experiment is one in which a continuous infusion is made for a very long time until the system is in a steady state and is then stopped, the subsequent decay curves being the washout. If the input rate is k_i and $b_1 = 1$, then the steady-state value of x_1 is, from eqn (3.12),

$$x_{1ss} = \frac{k_i}{k_{01}} \tag{3.19}$$

so that the washout curve, with the input stopped at $t = 0$, is

$$x_1(t) = \frac{k_i}{k_{01}} e^{-k_{01}t}. \tag{3.20}$$

Comparing eqns (3.8) and (3.20), we see that the form is the same as that of the washout curve; this is applies only to a one-compartment system.

This does not hold for MI studies → system is NOT linear.

3.1.4 *Repeated impulsive input*

In pharmacokinetics applications, doses are often repeated at intervals. Assume that the doses are impulsive, of magnitude D_1 and the constant interval between doses is T_0; let the input fraction b_1 be unity. If the first dose is administered at $t = 0$ and $x_1(0^-) = 0$, then the quantity in the compartment between doses 1 and 2 is

$$x_1(t) = D_1 e^{-k_{01}t}, \qquad 0 \leqslant t < T_0. \tag{3.21}$$

The maximum value in this interval (at $t = 0^+$) is D_1 and the minimum value, just before the administration of the second dose, is $D_1 e^{-k_{01}T_0}$. After the second dose, but before the third dose,

$$x_1(t) = D_1 e^{-k_{01}t} + D_1 e^{-k_{01}(t - T_0)}, \qquad T_0 \leqslant t < 2T_0. \tag{3.22}$$

(The model is linear, so the principle of superposition applies.) The maximum value in this interval is $D_1(1 + e^{-k_{01}T_0})$ and the minimum value is $D_1 e^{-k_{01}T_0}(1 + e^{-k_{01}T_0})$.

By similar argument, in the interval between administration of doses n and $(n + 1)$, the maximum value of the compartmental quantity is

$$\begin{aligned} x_{1\max} &= D_1(1 + e^{-k_{01}T_0} + e^{-2k_{01}T_0} + \ldots + e^{-(n-1)k_{01}T_0}) \\ &= D_1 \frac{1 - e^{-nk_{01}T_0}}{1 - e^{-k_{01}T_0}}. \end{aligned} \tag{3.23}$$

In the same interval, the minimum quantity is

$$x_{1\min} = e^{-k_{01}T_0} \cdot x_{1\max} \tag{3.24}$$

As the number of doses becomes very large, the values of the maxima rise from D_1 towards $\dfrac{D_1}{1 - e^{-k_{01}T_0}}$ while the values of the minima rise from $D_1 e^{-k_{01}T_0}$ towards $\dfrac{D_1 e^{-k_{01}T_0}}{1 - e^{-k_{01}T_0}}$ (see Fig. 3.5).

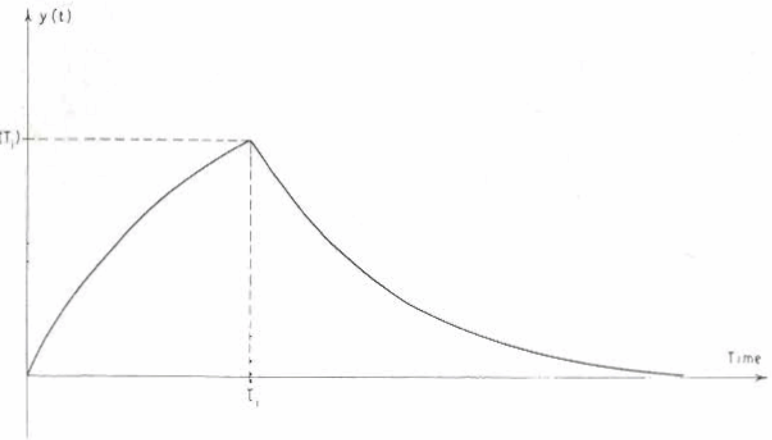

Figure 3.4 Observed response of the one-compartment model to a constant infusion over the time range $0 \leqslant t \leqslant T_i$.

From eqn (3.12), the measured quantity during the infusion is

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Comparing eqns (3.8) and (3.20), we see that the form of the impulse response is the same as that of the washout curve; this is not a general result and applies only to a one-compartment system.

3.1.4 *Repeated impulsive input*

In pharmacokinetics applications, doses are often repeated at regular intervals. Assume that the doses are impulsive, of magnitude D_1 and that the constant interval between doses is T_0; let the input fraction b_1 be unity. If the first dose is administered at $t = 0$ and $x_1(0^-) = 0$, then the quantity in the compartment between doses 1 and 2 is

$$x_1(t) = D_1\, e^{-k_{01}t}, \qquad 0 \leqslant t < T_0. \tag{3.21}$$

The maximum value in this interval (at $t = 0^+$) is D_1 and the minimum value, just before the administration of the second dose, is $D_1\, e^{-k_{01}T_0}$. After the second dose, but before the third dose,

$$x_1(t) = D_1\, e^{-k_{01}t} + D_1\, e^{-k_{01}(t - T_0)}, \qquad T_0 \leqslant t < 2T_0. \tag{3.22}$$

(The model is linear, so the principle of superposition applies.) The maximum value in this interval is $D_1(1 + e^{-k_{01}T_0})$ and the minimum value is $D_1\, e^{-k_{01}T_0}(1 + e^{-k_{01}T_0})$.

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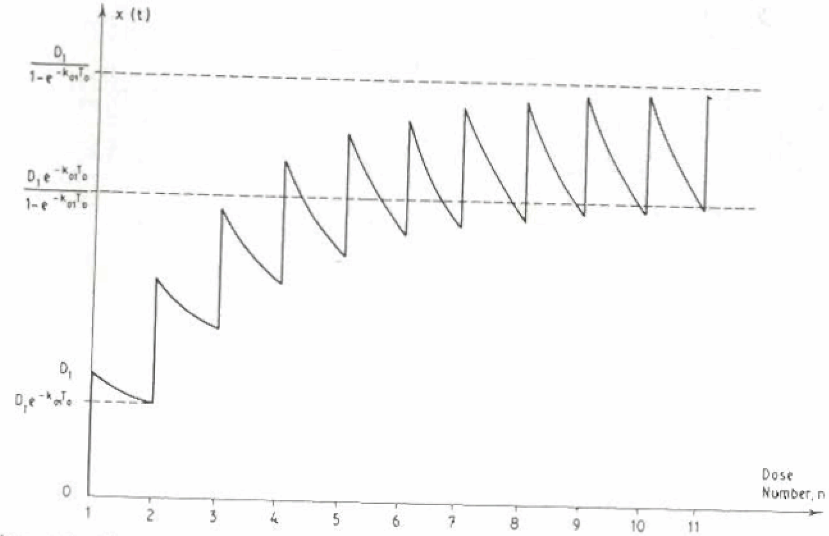

Figure 3.5 Compartmental quantity for a one-compartment model with impulsive inputs of magnitude D_1 repeated at regular intervals T_0.

3.2 Two-compartment systems

3.2.1 *The general two-compartment system*

The most general form of two-compartment system is shown in Fig. 3.6. For this system,

$$\mathbf{A} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$$

where
$$a_{11} = -(k_{01} + k_{21}), \qquad a_{12} = k_{12},$$
$$a_{21} = k_{21}, \qquad a_{22} = -(k_{02} + k_{12}).$$

The eigenvalues are given by eqn (2.61):

$$\lambda_1, \lambda_2 = \tfrac{1}{2}\{(a_{11} + a_{22}) \pm [(a_{11} - a_{22})^2 + 4a_{12}a_{21}]^{1/2}\}$$

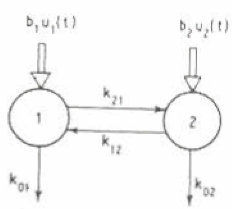

Figure 3.6 General two-compartment model.

and, from Section 2.4, are real. Further, unless

$$(a_{11} - a_{22})^2 + 4a_{12}a_{21} = 0,$$

the eigenvalues are distinct. Thus for repeated eigenvalues, a_{11} and a_{22} must be equal and $a_{12}a_{21}$ must be zero; the latter implies that either a_{12} or a_{21} must be zero (if they were both zero, the compartments would not be connected).

In this section, the most general case will be considered first and we will then proceed to special cases with one or more of the rate constants zero. As before, we are assuming that each input is applied to one compartment only so that $\mathbf{BU}(s) = [b_1 U_1(s) \quad b_2 U_2(s)]^T$, and that observations are of individual compartments only so that $y_1(t) = c_1 x_1(t)$ and $y_2(t) = c_2 x_2(t)$.

From the form of $\mathbf{A}$,

$$(s\mathbf{I} - \mathbf{A}) = \begin{bmatrix} s - a_{11} & -a_{12} \\ -a_{21} & s - a_{22} \end{bmatrix}$$

$$\therefore \quad (s\mathbf{I} - \mathbf{A})^{-1} = \frac{1}{(s - \lambda_1)(s - \lambda_2)} \begin{bmatrix} s - a_{22} & a_{12} \\ a_{21} & s - a_{11} \end{bmatrix}. \tag{3.25}$$

The transfer function matrix is

$$\mathbf{G}(s) = \begin{bmatrix} G_{11}(s) & G_{12}(s) \\ G_{21}(s) & G_{22}(s) \end{bmatrix} = \begin{bmatrix} \dfrac{Y_1(s)}{U_1(s)} & \dfrac{Y_1(s)}{U_2(s)} \\ \dfrac{Y_2(s)}{U_1(s)} & \dfrac{Y_2(s)}{U_2(s)} \end{bmatrix}$$

$$= \begin{bmatrix} \dfrac{c_1 b_1 (s - a_{22})}{(s - \lambda_1)(s - \lambda_2)} & \dfrac{c_1 b_2 a_{12}}{(s - \lambda_1)(s - \lambda_2)} \\ \dfrac{c_2 b_1 a_{21}}{(s - \lambda_1)(s - \lambda_2)} & \dfrac{c_2 b_2 (s - a_{11})}{(s - \lambda_1)(s - \lambda_2)} \end{bmatrix}. \tag{3.26}$$

The Laplace transform of the observations is $\mathbf{Y}(s) = \mathbf{G}(s)\mathbf{U}(s)$ and the time response is given by $\mathbf{y}(t) = \mathscr{L}^{-1}[\mathbf{G}(s)\mathbf{U}(s)]$, assuming that $\mathbf{y}(0^-) = 0$.

Suppose, for example, that an impulsive input $D_1\,\delta(t)$ is introduced into compartment 1 and that there is no perturbation of compartment 2. Then $\mathbf{U}(s) = [D_1 \quad 0]^T$ and

$$\mathbf{Y}(s) = \begin{bmatrix} \dfrac{c_1 b_1 (s - a_{22}) \cdot D_1}{(s - \lambda_1)(s - \lambda_2)} \\ \dfrac{c_2 b_1 a_{21} D_1}{(s - \lambda_1)(s - \lambda_2)} \end{bmatrix}.$$

Taking partial fractions (see Appendix 1),

$$\mathbf{Y}(s) = \begin{bmatrix} c_1 b_1 D_1 \left(\dfrac{\lambda_1 - a_{22}}{\lambda_1 - \lambda_2} \cdot \dfrac{1}{s - \lambda_1} + \dfrac{\lambda_2 - a_{22}}{\lambda_2 - \lambda_1} \cdot \dfrac{1}{s - \lambda_2} \right) \\ \dfrac{c_2 b_1 a_{21} D_1}{\lambda_1 - \lambda_2} \left(\dfrac{1}{s - \lambda_1} - \dfrac{1}{s - \lambda_2} \right) \end{bmatrix}.$$

Inverse Laplace transformation (see Appendix 1) gives:

$$y_1(t) = c_1 b_1 D_1 \left(\frac{\lambda_1 - a_{22}}{\lambda_1 - \lambda_2} e^{\lambda_1 t} + \frac{\lambda_2 - a_{22}}{\lambda_2 - \lambda_1} e^{\lambda_2 t} \right), \qquad t \geqslant 0 \quad (3.27a)$$

$$y_2(t) = \frac{c_2 b_1 a_{21} D_1}{\lambda_1 - \lambda_2} (e^{\lambda_1 t} - e^{\lambda_2 t}), \qquad t \geqslant 0. \quad (3.27b)$$

If, instead, a constant continuous infusion (step function) of rate k_i per unit time is introduced into compartment 1 with no (external) input to compartment 2, so that

$$\mathbf{U}(s) = \begin{bmatrix} \dfrac{k_i}{s} & 0 \end{bmatrix}^T,$$

$$\mathbf{Y}(s) = \begin{bmatrix} \dfrac{c_1 b_1 (s - a_{22}) k_i}{s(s - \lambda_1)(s - \lambda_2)} \\ \dfrac{c_2 b_1 a_{21} k_i}{s(s - \lambda_1)(s - \lambda_2)} \end{bmatrix}$$

$$= \begin{bmatrix} c_1 b_1 k_i \left(-\dfrac{a_{22}}{\lambda_1 \lambda_2} \dfrac{1}{s} + \dfrac{\lambda_1 - a_{22}}{\lambda_1(\lambda_1 - \lambda_2)} \dfrac{1}{s - \lambda_1} + \dfrac{\lambda_2 - a_{22}}{\lambda_2(\lambda_2 - \lambda_1)} \dfrac{1}{s - \lambda_2} \right) \\ c_2 b_1 a_{21} k_i \left(\dfrac{1}{\lambda_1 \lambda_2} \dfrac{1}{s} + \dfrac{1}{\lambda_1(\lambda_1 - \lambda_2)} \dfrac{1}{s - \lambda_1} + \dfrac{1}{\lambda_2(\lambda_2 - \lambda_1)} \dfrac{1}{s - \lambda_2} \right) \end{bmatrix}.$$

Inverse Laplace transformation gives, for $t \geqslant 0$,

$$y_1(t) = c_1 b_1 k_i \left(\frac{-a_{22}}{\lambda_1 \lambda_2} + \frac{\lambda_1 - a_{22}}{\lambda_1(\lambda_1 - \lambda_2)} e^{\lambda_1 t} + \frac{\lambda_2 - a_{22}}{\lambda_2(\lambda_2 - \lambda_1)} e^{\lambda_2 t} \right) \quad (3.28a)$$

$$y_2(t) = c_2 b_1 a_{21} k_i \left(\frac{1}{\lambda_1 \lambda_2} + \frac{1}{\lambda_1(\lambda_1 - \lambda_2)} e^{\lambda_1 t} + \frac{1}{\lambda_2(\lambda_2 - \lambda_1)} e^{\lambda_2 t} \right). \quad (3.28b)$$

The reader is invited to confirm that the unit step responses ($k_i = 1$ in eqns (3.28)) are the same as the integrals of the unit impulse responses ($D_1 = 1$ in eqns (3.27)).

For a third experiment with an impulsive input $D_2\,\delta(t)$ introduced to compartment 2 and no (external) input to compartment 1, so that $\mathbf{U}(s) = [0 \quad D_2]^T$,

$$\mathbf{Y}(s) = \begin{bmatrix} \dfrac{c_1 b_2 a_{12} D_2}{(s - \lambda_1)(s - \lambda_2)} \\ \dfrac{c_2 b_2 D_2 (s - a_{11})}{(s - \lambda_1)(s - \lambda_2)} \end{bmatrix}$$

so that

$$y_1(t) = \frac{c_1 b_2 a_{12} D_2}{\lambda_1 - \lambda_2} (e^{\lambda_1 t} - e^{\lambda_2 t}), \qquad t \geqslant 0 \quad (3.29a)$$

$$y_2(t) = c_2 b_2 D_2 \left(\frac{\lambda_1 - a_{11}}{\lambda_1 - \lambda_2} e^{\lambda_1 t} + \frac{\lambda_2 - a_{11}}{\lambda_2 - \lambda_1} e^{\lambda_2 t} \right), \qquad t \geqslant 0 \quad (3.29b)$$

while for a step input to compartment 2 $\left(\mathbf{U}(s) = \begin{bmatrix} 0 & \dfrac{k_i}{s} \end{bmatrix}^T \right)$,

$$y_1(t) = c_1 b_2 a_{12} k_i \left(\frac{1}{\lambda_1 \lambda_2} + \frac{1}{\lambda_1(\lambda_1 - \lambda_2)} e^{\lambda_1 t} + \frac{1}{\lambda_2(\lambda_2 - \lambda_1)} e^{\lambda_2 t} \right), \qquad t \geqslant 0 \quad (3.30a)$$

$$y_2(t) = c_2 b_2 k_i \left(-\frac{a_{11}}{\lambda_1 \lambda_2} + \frac{\lambda_1 - a_{11}}{\lambda_1(\lambda_1 - \lambda_2)} e^{\lambda_1 t} + \frac{\lambda_2 - a_{11}}{\lambda_2(\lambda_2 - \lambda_1)} e^{\lambda_2 t} \right), \qquad t \geqslant 0. \quad (3.30b)$$

Example 3.1. *Consider a linear, time-invariant two-compartment system with* $k_{12} = k_{21} = k_{01} = k_{02} = 1$. *Determine the states* $x_1(t)$ *and* $x_2(t)$, $t \geqslant 0$, *for the following cases:*

(i). $u_1(t) = D_1\,\delta(t);\ u_2(t) = 0$
(ii). $u_1(t) = k_i,\ t \geqslant 0;\ u_2(t) = 0$
(iii). $u_1(t) = D_1\,\delta(t);\ u_2(t) = D_2\,\delta(t)$
(iv). $u_1(t) = k_i,\ t \geqslant 0;\ u_2(t) = D_2\,\delta(t)$
(v). $u_1(t) = D_1\,\delta(t);\ u_2(t) = k_i,\ t \geqslant 0.$

Both input fractions, b_1 *and* b_2, *may be taken as* 1.

Solution. The state equations are:

$$\dot{x}_1 = -2x_1 + x_2 + u_1(t)$$
$$\dot{x}_2 = x_1 - 2x_2 + u_2(t).$$

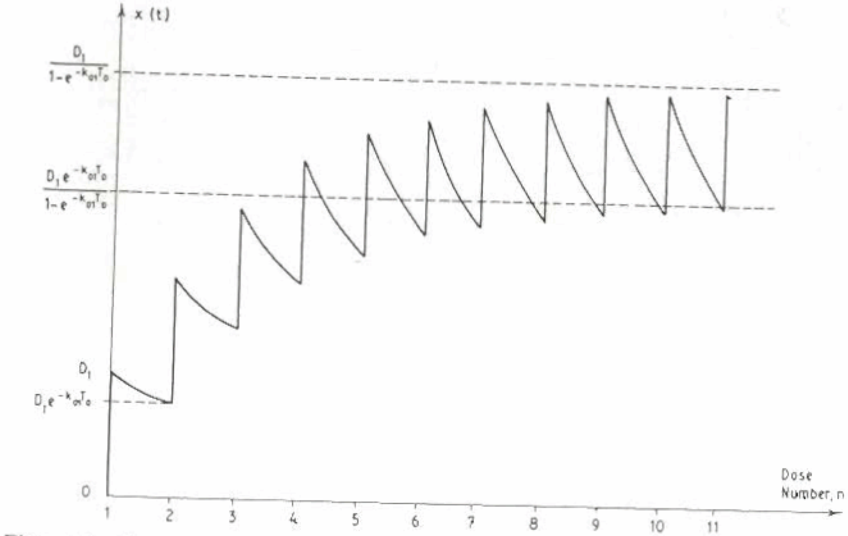

Figure 3.5 Compartmental quantity for a one-compartment model with impulsive inputs of magnitude D_1 repeated at regular intervals T_0.

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$$\mathbf{A} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$$

where

$$a_{11} = -(k_{01} + k_{21}), \qquad a_{12} = k_{12},$$

$$a_{21} = k_{21}, \qquad a_{22} = -(k_{02} + k_{12}).$$

The eigenvalues are given by eqn (2.61):

$$\lambda_1, \lambda_2 = \tfrac{1}{2}\{(a_{11} + a_{22}) \pm [(a_{11} - a_{22})^2 + 4a_{12}a_{21}]^{1/2}\}$$

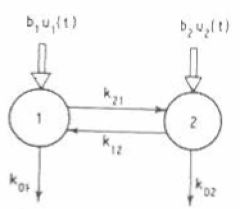

Figure 3.6 General two-compartment model.

and, from Section 2.4, are real. Further, unless

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the eigenvalues are distinct. Thus for repeated eigenvalues, a_{11} and a_{22} must be equal and $a_{12}a_{21}$ must be zero; the latter implies that either a_{12} or a_{21} must be zero (if they were both zero, the compartments would not be connected).

In this section, the most general case will be considered first and we will then proceed to special cases with one or more of the rate constants zero. As before, we are assuming that each input is applied to one compartment only so that $\mathbf{BU}(s) = [b_1U_1(s) \quad b_2U_2(s)]^T$, and that observations are of individual compartments only so that $y_1(t) = c_1x_1(t)$ and $y_2(t) = c_2x_2(t)$.

From the form of **A**,

$$(s\mathbf{I} - \mathbf{A}) = \begin{bmatrix} s - a_{11} & -a_{12} \\ -a_{21} & s - a_{22} \end{bmatrix}$$

$$\therefore \quad (s\mathbf{I} - \mathbf{A})^{-1} = \frac{1}{(s - \lambda_1)(s - \lambda_2)} \begin{bmatrix} s - a_{22} & a_{12} \\ a_{21} & s - a_{11} \end{bmatrix}. \qquad (3.25)$$

The transfer function matrix is

$$\mathbf{G}(s) = \begin{bmatrix} G_{11}(s) & G_{12}(s) \\ G_{21}(s) & G_{22}(s) \end{bmatrix} = \begin{bmatrix} \dfrac{Y_1(s)}{U_1(s)} & \dfrac{Y_1(s)}{U_2(s)} \\[2ex] \dfrac{Y_2(s)}{U_1(s)} & \dfrac{Y_2(s)}{U_2(s)} \end{bmatrix}$$

$$= \begin{bmatrix} \dfrac{c_1b_1(s - a_{22})}{(s - \lambda_1)(s - \lambda_2)} & \dfrac{c_1b_2a_{12}}{(s - \lambda_1)(s - \lambda_2)} \\[2ex] \dfrac{c_2b_1a_{21}}{(s - \lambda_1)(s - \lambda_2)} & \dfrac{c_2b_2(s - a_{11})}{(s - \lambda_1)(s - \lambda_2)} \end{bmatrix}. \qquad (3.26)$$

The Laplace transform of the observations is $\mathbf{Y}(s) = \mathbf{G}(s)\mathbf{U}(s)$ and the time response is given by $\mathbf{y}(t) = \mathscr{L}^{-1}[\mathbf{G}(s)\mathbf{U}(s)]$, assuming that $\mathbf{y}(0^-) = 0$.

Suppose, for example, that an impulsive input $D_1\,\delta(t)$ is introduced into compartment 1 and that there is no perturbation of compartment 2. Then $\mathbf{U}(s) = [D_1 \quad 0]^T$ and

$$\mathbf{Y}(s) = \begin{bmatrix} \dfrac{c_1b_1(s - a_{22})\cdot D_1}{(s - \lambda_1)(s - \lambda_2)} \\[2ex] \dfrac{c_2b_1a_{21}D_1}{(s - \lambda_1)(s - \lambda_2)} \end{bmatrix}.$$

Taking partial fractions (see Appendix 1),

$$\mathbf{Y}(s)=\begin{bmatrix} c_1b_1D_1\left(\dfrac{\lambda_1-a_{22}}{\lambda_1-\lambda_2}\cdot\dfrac{1}{s-\lambda_1}+\dfrac{\lambda_2-a_{22}}{\lambda_2-\lambda_1}\cdot\dfrac{1}{s-\lambda_2}\right)\\ \dfrac{c_2b_1a_{21}D_1}{\lambda_1-\lambda_2}\left(\dfrac{1}{s-\lambda_1}-\dfrac{1}{s-\lambda_2}\right)\end{bmatrix}.$$

Inverse Laplace transformation (see Appendix 1) gives:

$$y_1(t)=c_1b_1D_1\left(\frac{\lambda_1-a_{22}}{\lambda_1-\lambda_2}\,e^{\lambda_1 t}+\frac{\lambda_2-a_{22}}{\lambda_2-\lambda_1}\,e^{\lambda_2 t}\right),\qquad t\geqslant 0 \quad (3.27a)$$

$$y_2(t)=\frac{c_2b_1a_{21}D_1}{\lambda_1-\lambda_2}\,(e^{\lambda_1 t}-e^{\lambda_2 t}),\qquad t\geqslant 0. \quad (3.27b)$$

If, instead, a constant continuous infusion (step function) of rate k_i per unit time is introduced into compartment 1 with no (external) input to compartment 2, so that

$$\mathbf{U}(s)=\begin{bmatrix}\dfrac{k_i}{s} & 0\end{bmatrix}^T,$$

$$\mathbf{Y}(s)=\begin{bmatrix}\dfrac{c_1b_1(s-a_{22})k_i}{s(s-\lambda_1)(s-\lambda_2)}\\ \dfrac{c_2b_1a_{21}k_i}{s(s-\lambda_1)(s-\lambda_2)}\end{bmatrix}$$

$$=\begin{bmatrix} c_1b_1k_i\left(-\dfrac{a_{22}}{\lambda_1\lambda_2}\dfrac{1}{s}+\dfrac{\lambda_1-a_{22}}{\lambda_1(\lambda_1-\lambda_2)}\dfrac{1}{s-\lambda_1}+\dfrac{\lambda_2-a_{22}}{\lambda_2(\lambda_2-\lambda_1)}\dfrac{1}{s-\lambda_2}\right)\\ c_2b_1a_{21}k_i\left(\dfrac{1}{\lambda_1\lambda_2}\dfrac{1}{s}+\dfrac{1}{\lambda_1(\lambda_1-\lambda_2)}\dfrac{1}{s-\lambda_1}+\dfrac{1}{\lambda_2(\lambda_2-\lambda_1)}\dfrac{1}{s-\lambda_2}\right)\end{bmatrix}.$$

Inverse Laplace transformation gives, for $t\geqslant 0$,

$$y_1(t)=c_1b_1k_i\left(\frac{-a_{22}}{\lambda_1\lambda_2}+\frac{\lambda_1-a_{22}}{\lambda_1(\lambda_1-\lambda_2)}\,e^{\lambda_1 t}+\frac{\lambda_2-a_{22}}{\lambda_2(\lambda_2-\lambda_1)}\,e^{\lambda_2 t}\right) \quad (3.28a)$$

$$y_2(t)=c_2b_1a_{21}k_i\left(\frac{1}{\lambda_1\lambda_2}+\frac{1}{\lambda_1(\lambda_1-\lambda_2)}\,e^{\lambda_1 t}+\frac{1}{\lambda_2(\lambda_2-\lambda_1)}\,e^{\lambda_2 t}\right). \quad (3.28b)$$

The reader is invited to confirm that the unit step responses ($k_i = 1$ in eqns (3.28)) are the same as the integrals of the unit impulse responses ($D_1 = 1$ in eqns (3.27)).

For a third experiment with an impulsive input $D_2\,\delta(t)$ introduced to compartment 2 and no (external) input to compartment 1, so that $\mathbf{U}(s)=[0\quad D_2]^T$,

$$\mathbf{Y}(s)=\begin{bmatrix}\dfrac{c_1b_2a_{12}D_2}{(s-\lambda_1)(s-\lambda_2)}\\ \dfrac{c_2b_2D_2(s-a_{11})}{(s-\lambda_1)(s-\lambda_2)}\end{bmatrix}$$

so that

$$y_1(t)=\frac{c_1b_2a_{12}D_2}{\lambda_1-\lambda_2}\,(e^{\lambda_1 t}-e^{\lambda_2 t}),\qquad t\geqslant 0 \quad (3.29a)$$

$$y_2(t)=c_2b_2D_2\left(\frac{\lambda_1-a_{11}}{\lambda_1-\lambda_2}\,e^{\lambda_1 t}+\frac{\lambda_2-a_{11}}{\lambda_2-\lambda_1}\,e^{\lambda_2 t}\right),\qquad t\geqslant 0 \quad (3.29b)$$

while for a step input to compartment 2 $\left(\mathbf{U}(s)=\begin{bmatrix}0 & \dfrac{k_i}{s}\end{bmatrix}^T\right)$,

$$y_1(t)=c_1b_2a_{12}k_i\left(\frac{1}{\lambda_1\lambda_2}+\frac{1}{\lambda_1(\lambda_1-\lambda_2)}\,e^{\lambda_1 t}+\frac{1}{\lambda_2(\lambda_2-\lambda_1)}\,e^{\lambda_2 t}\right),\qquad t\geqslant 0 \quad (3.30a)$$

$$y_2(t)=c_2b_2k_i\left(-\frac{a_{11}}{\lambda_1\lambda_2}+\frac{\lambda_1-a_{11}}{\lambda_1(\lambda_1-\lambda_2)}\,e^{\lambda_1 t}+\frac{\lambda_2-a_{11}}{\lambda_2(\lambda_2-\lambda_1)}\,e^{\lambda_2 t}\right),\qquad t\geqslant 0. \quad (3.30b)$$

Example 3.1. *Consider a linear, time-invariant two-compartment system with $k_{12}=k_{21}=k_{01}=k_{02}=1$. Determine the states $x_1(t)$ and $x_2(t)$, $t\geqslant 0$, for the following cases:*

(i). $u_1(t)=D_1\,\delta(t);\ u_2(t)=0$
(ii). $u_1(t)=k_i,\ t\geqslant 0;\ u_2(t)=0$
(iii). $u_1(t)=D_1\,\delta(t);\ u_2(t)=D_2\,\delta(t)$
(iv). $u_1(t)=k_i,\ t\geqslant 0;\ u_2(t)=D_2\,\delta(t)$
(v). $u_1(t)=D_1\,\delta(t);\ u_2(t)=k_i,\ t\geqslant 0.$

Both input fractions, b_1 and b_2, may be taken as 1.

Solution. The state equations are:

$$\dot{x}_1=-2x_1+x_2+u_1(t)$$
$$\dot{x}_2=x_1-2x_2+u_2(t).$$

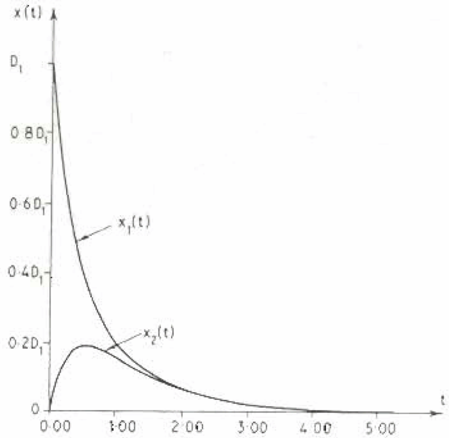

Figure 3.7 Responses of model of Example 3.1 to impulsive perturbation of compartment 1.

The eigenvalues are, from eqn (2.61),

$$\lambda_1, \lambda_2 = \tfrac{1}{2}(-4 \pm (4)^{1/2}) = -3, -1$$

so that

$$(s\mathbf{I} - \mathbf{A})^{-1} = \begin{bmatrix} \dfrac{s+2}{(s+3)(s+1)} & \dfrac{1}{(s+3)(s+1)} \\ \dfrac{1}{(s+3)(s+1)} & \dfrac{s+2}{(s+3)(s+1)} \end{bmatrix}.$$

Case (*i*). $\mathbf{U}(s) = [D_1 \quad 0]^T$.

Recalling that $x_1(t) = \dfrac{y_1(t)}{c_1}$ and $x_2(t) = \dfrac{y_2(t)}{c_2}$, we have, from eqns (3.27),

$$x_1(t) = \tfrac{1}{2}D_1(e^{-3t} + e^{-t})$$
$$x_2(t) = \tfrac{1}{2}D_1(-e^{-3t} + e^{-t})$$

which are shown in Fig. 3.7.

Case (*ii*). $\mathbf{U}(s) = \begin{bmatrix} \dfrac{k_i}{s} & 0 \end{bmatrix}^T$ so that from eqns (3.28),

$$x_1(t) = k_i(\tfrac{2}{3} - \tfrac{1}{6}e^{-3t} - \tfrac{1}{2}e^{-t})$$
$$x_2(t) = k_i(\tfrac{1}{3} + \tfrac{1}{6}e^{-3t} - \tfrac{1}{2}e^{-t})$$

which are shown in Fig. 3.8.

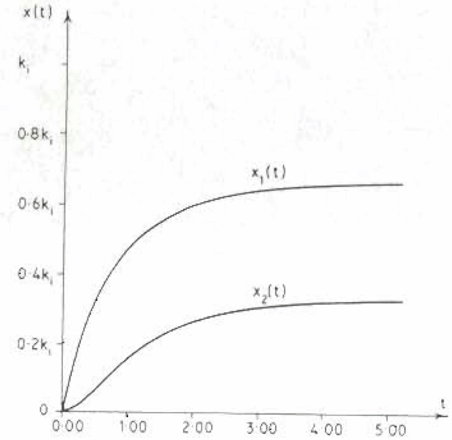

Figure 3.8 Responses of model of Example 3.1 to step perturbation of compartment 1.

Case (*iii*). $\mathbf{U}(s) = [D_1 \quad D_2]^T$ so that

$$\mathbf{X}(s) = \begin{bmatrix} \dfrac{D_1(s+2) + D_2}{(s+3)(s+1)} \\ \dfrac{D_1 + D_2(s+2)}{(s+3)(s+1)} \end{bmatrix}.$$

Inverse Laplace transformation gives

$$x_1(t) = \tfrac{1}{2}[(D_1 - D_2)e^{-3t} + (D_1 + D_2)e^{-t}]$$
$$x_2(t) = \tfrac{1}{2}[(D_2 - D_1)e^{-3t} + (D_1 + D_2)e^{-t}].$$

Note that if $D_1 = D_2$, only one of the exponentials appears in the states; this is not a general result and arises in this case from the symmetry of the model and inputs. With other values for the rate constants, particular sizes of perturbations can usually be found which result in only one exponential appearing in the states.

Case (*iv*). $\mathbf{U}(s) = \begin{bmatrix} \dfrac{k_i}{s} & D_2 \end{bmatrix}^T$ so that

$$\mathbf{X}(s) = \begin{bmatrix} \dfrac{k_i(s+2)}{s(s+3)(s+1)} + \dfrac{D_2}{(s+3)(s+1)} \\ \dfrac{k_i}{s(s+3)(s+1)} + \dfrac{D_2(s+2)}{(s+3)(s+1)} \end{bmatrix}$$

whence $x_1(t) = \frac{2}{3}k_i - (\frac{1}{6}k_i + \frac{1}{2}D_2)\,e^{-3t} - (\frac{1}{2}k_i - \frac{1}{2}D_2)\,e^{-t}$

$$x_2(t) = \frac{1}{3}k_i + (\frac{1}{6}k_i + \frac{1}{2}D_2)\,e^{-3t} - (\frac{1}{2}k_i - \frac{1}{2}D_2)\,e^{-t}.$$

Note that if k_i is numerically equal to D_2, the e^{-t} will not appear in the states. As for case (iii) this is not a general result but may occur with other values of rate constants for particular sizes of perturbations.

Case (v). $\mathbf{U}(s) = \begin{bmatrix} D_1 & \dfrac{k_i}{s} \end{bmatrix}^T$ so that

$$\mathbf{X}(s) = \begin{bmatrix} \dfrac{D_1(s+2)}{(s+3)(s+1)} + \dfrac{k_i}{s(s+3)(s+1)} \\[2ex] \dfrac{D_1}{(s+3)(s+1)} + \dfrac{k_i(s+2)}{s(s+3)(s+1)} \end{bmatrix}$$

whence $x_1(t) = \frac{1}{3}k_i + (\frac{1}{2}D_1 + \frac{1}{6}k_i)\,e^{-3t} + (\frac{1}{2}D_1 - \frac{1}{2}k_i)\,e^{-t}$

$$x_2(t) = \frac{2}{3}k_i - (\frac{1}{2}D_1 + \frac{1}{6}k_i)\,e^{-3t} + (\frac{1}{2}D_1 - \frac{1}{2}k_i)\,e^{-t}.$$

Expressions for $x_1(t)$ in a two-compartment system with impulsive inputs repeated at regular intervals to one of the compartments will be found in Gibaldi and Perrier (1975), p. 119.

3.2.2 *Repeated eigenvalues*

As we have seen above, a_{11} must equal a_{22} and $a_{12}a_{21}$ must be zero for repeated eigenvalues in a two-compartment system. Consider a system in which $a_{12} = 0$ and $a_{11} = a_{22}$, for which $a_{11} = -(k_{01} + k_{21}) = a_{22} = -k_{02}$.

From eqn (2.61), the eigenvalues are

$$\lambda_1, \lambda_2 = \tfrac{1}{2}(a_{11} + a_{22}) = -k_{02}. \tag{3.31}$$

For this system, $\mathbf{A} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} -k_{02} & 0 \\ k_{21} & -k_{02} \end{bmatrix}$

and

$$(s\mathbf{I} - \mathbf{A})^{-1} = \frac{1}{(s+k_{02})^2}\begin{bmatrix} s+k_{02} & 0 \\ k_{21} & s+k_{02} \end{bmatrix} = \begin{bmatrix} \dfrac{1}{s+k_{02}} & 0 \\[2ex] \dfrac{k_{21}}{(s+k_{02})^2} & \dfrac{1}{s+k_{02}} \end{bmatrix}. \tag{3.32}$$

If an impulsive input $D_1\,\delta(t)$ is applied to compartment 1 (with no external input to compartment 2), then

$$y_1(t) = c_1 b_1 D_1\,e^{-k_{02}t}, \qquad t \geqslant 0 \tag{3.33a}$$

$$y_2(t) = c_2 b_1 D_1 k_{21} t\,e^{-k_{02}t}, \qquad t \geqslant 0 \tag{3.33b}$$

while the responses to an impulsive input $D_2\,\delta(t)$ applied to compartment 2 are:

$$y_1(t) = 0 \tag{3.34a}$$

$$y_2(t) = c_2 b_2 D_2\,e^{-k_{02}t}, \qquad t \geqslant 0 \tag{3.34b}$$

($y_1(t)$ is obviously zero in this case because there is no link from compartment 2 to compartment 1).

If, instead, a constant continuous infusion, of rate k_i per unit time, is introduced into compartment 1, with no external input to compartment 2, $\mathbf{U}(s) = \begin{bmatrix} \dfrac{k_i}{s} & 0 \end{bmatrix}^T$, and

$$Y_1(s) = \frac{c_1 b_1 k_i}{s(s+k_{02})}$$

whence

$$y_1(t) = \frac{c_1 b_1 k_i}{k_{02}}(1 - e^{-k_{02}t}), \qquad t \geqslant 0 \tag{3.35a}$$

while

$$Y_2(s) = \frac{c_2 b_1 k_i k_{21}}{s(s+k_{02})^2}$$

whence

$$y_2(t) = \frac{c_2 b_1 k_i k_{21}}{k_{02}^2}(1 - e^{-k_{02}t}) - \frac{c_2 b_1 k_i k_{21}}{k_{02}}\,t\,e^{-k_{02}t}, \qquad t \geqslant 0 \tag{3.35b}$$

(see Appendix 1).

Example 3.2. *For the two-compartment system with $k_{12} = 0$, $k_{21} = k_{01} = 1$ and $k_{02} = 2$, find $x_1(t)$ and $x_2(t)$ for $t \geqslant 0$ for the following cases:*

(i). $u_1(t) = D_1\,\delta(t);\ u_2(t) = 0$

(ii). $u_1(t) = k_i,\ t \geqslant 0;\ u_2(t) = 0.$

The input fraction $b_1 = 1$ in both cases.

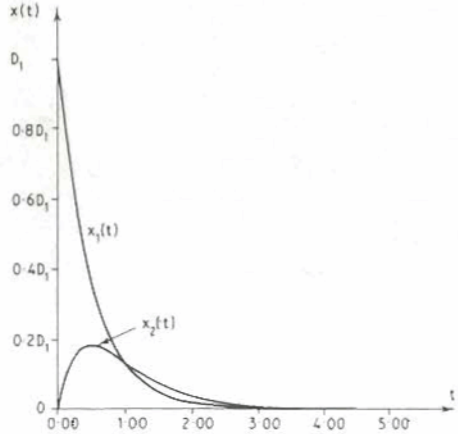

Figure 3.9 Responses of model of Example 3.2 to impulsive perturbation of compartment 1.

Solution. *Case* (*i*). From eqns (3.33),

$$x_1(t) = D_1\,e^{-2t}$$

$$x_2(t) = D_1 t\,e^{-2t}$$

(see Fig. 3.9).

Case (*ii*). From eqns (3.35),

$$x_1(t) = \tfrac{1}{2}k_i(1 - e^{-2t})$$

$$x_2(t) = k_i[\tfrac{1}{4}(1 - e^{-2t}) - \tfrac{1}{2}t\,e^{-2t}]$$

(see Fig. 3.10).

3.2.3 *Source compartments*

A source compartment is one which does not receive material from any other compartment; it may or may not excrete material to the environment. All source compartments respond as a one-compartment system, no matter how many compartments there are in the rest of the system, so that only one of the modes (single-exponential decays) appears in the response of a source compartment to a perturbation.

In a two-compartment system, compartment 1 is a source compartment if $k_{12} = 0$. Although the presence of a source compartment is the only way in which a two-compartment system can have repeated eigenvalues (as in Example 3.2) repeated eigenvalues can only occur if, in addition, $a_{11} = a_{22}$. Let us consider an example with distinct eigenvalues.

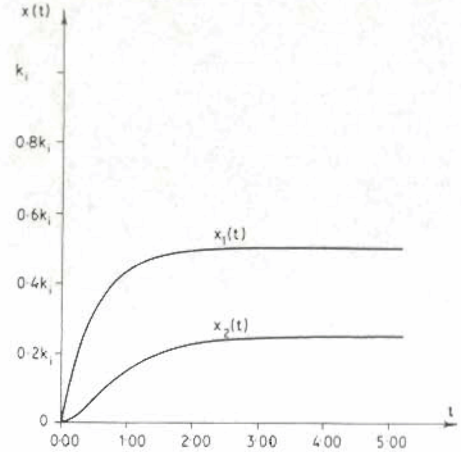

Figure 3.10 Responses of model of Example 3.2 to step perturbation of compartment 1.

Example 3.3. *Let $k_{12} = 0$, $k_{21} = k_{01} = k_{02} = 1$. Determine $x_1(t)$ and $x_2(t)$ for $t \geqslant 0$ if $u_1(t) = D_1\,\delta(t)$, $u_2(t) = 0$ and $b_1 = 1$.*

Solution. For this system,

$$\mathbf{A} = \begin{bmatrix} -2 & 0 \\ 1 & -1 \end{bmatrix},$$

which has eigenvalues $\lambda_1, \lambda_2 = \tfrac{1}{2}(-3 \pm 1) = -2, -1$. Substituting in eqns (3.27),

$$x_1(t) = D_1\,e^{-2t}$$

$$x_2(t) = D_1(e^{-t} - e^{-2t})$$

(see Fig. 3.11).

In many applications, the source compartment does not excrete material to the environment. We will now evaluate a further example with $k_{01} = 0$.

Example 3.4. *For the two-compartment system with $k_{12} = k_{01} = 0$, $k_{21} = 1$ and $k_{02} = 2$, determine $x_1(t)$ and $x_2(t)$ for $t \geqslant 0$ if $u_1(t) = D_1\,\delta(t)$, $u_2(t) = 0$ and $b_1 = 1$.*

Solution. For this system,

$$\mathbf{A} = \begin{bmatrix} -1 & 0 \\ 1 & -2 \end{bmatrix}.$$

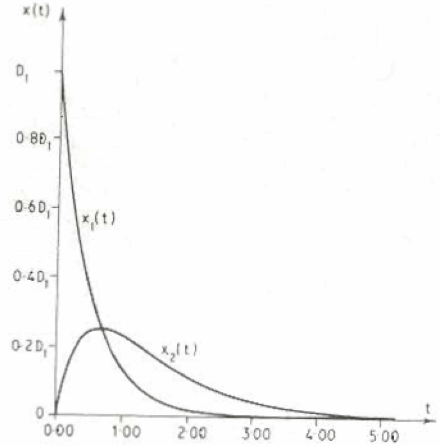

Figure 3.11 Responses of model of Example 3.3 to impulsive perturbation of compartment 1.

with eigenvalues $\lambda_1, \lambda_2 = -2, -1$. Substituting in eqns (3.27),

$$x_1(t) = D_1\,\mathrm{e}^{-t}$$

$$x_2(t) = D_1(\mathrm{e}^{-t} - \mathrm{e}^{-2t})$$

(see Fig. 3.12).

If, instead, k_{02} had been 1, there would have been repeated eigenvalues with $\lambda_1 = \lambda_2 = -1$. For the same input, $x_1(t)$ would still have been the same, but from eqn (3.33b), $x_2(t)$ would have been $D_1 t\,\mathrm{e}^{-t}$.

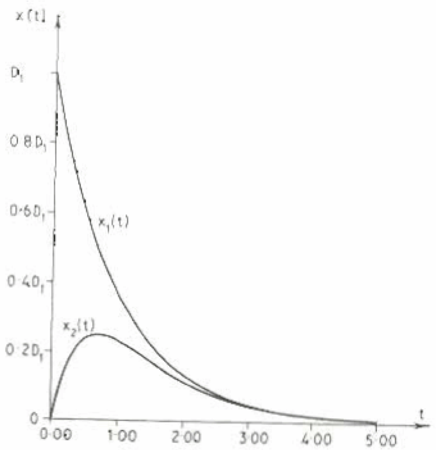

Figure 3.12 Responses of model of Example 3.4 to impulsive perturbation of compartment 1.

3.2.4 *Sink compartments*

A sink (or trap) compartment is one which does not excrete material either to the environment or to any other compartment. It results in a zero on the principal diagonal of **A** and a zero eigenvalue. Physically, a sink compartment acts as a pure integrator of the flows into it.

Consider a two-compartment system in which compartment 2 is a sink, i.e. $k_{12} = k_{02} = 0$ so that $a_{22} = 0$. For this system,

$$\mathbf{A} = \begin{bmatrix} a_{11} & 0 \\ a_{12} & 0 \end{bmatrix}$$

is singular. From $|\lambda\mathbf{I} - \mathbf{A}| = 0$, the eigenvalues are

$$\lambda_1, \lambda_2 = a_{11}, 0$$

and

$$(s\mathbf{I} - \mathbf{A})^{-1} = \frac{1}{s(s - a_{11})}\begin{bmatrix} s & 0 \\ a_{21} & s - a_{11} \end{bmatrix}. \tag{3.36}$$

If $\qquad \mathbf{U}(s) = [D_1 \quad 0]^T,$

$$Y_1(s) = \frac{c_1 b_1 D_1}{s - a_{11}}$$

whence $\qquad y_1(t) = c_1 b_1 D_1\,\mathrm{e}^{-(k_{01}+k_{21})t}, \qquad t \geqslant 0 \qquad (3.37a)$

and $\qquad Y_2(s) = \dfrac{c_2 b_1 D_1 a_{21}}{s(s - a_{11})}$

whence $\qquad y_2(t) = \dfrac{c_2 b_1 D_1 k_{21}}{k_{01} + k_{21}}(1 - \mathrm{e}^{-(k_{01}+k_{21})t}), \qquad t \geqslant 0. \qquad (3.37b)$

If, on the other hand, $\mathbf{U}(s) = [0 \quad D_2]^T$, then

$$Y_2(s) = \frac{c_2 b_2 D_2}{s}$$

whence $\qquad y_2(t) = c_2 b_2 D_2, \qquad t \geqslant 0$

as expected since the dose remains in compartment 2.

Example 3.5. *For the two-compartment system with* $k_{12} = k_{02} = 0$, $k_{21} = k_{01} = 1$, *determine* $x_1(t)$ *and* $x_2(t)$ *for* $t \geqslant 0$ *if* $u_1(t) = D_1\,\delta(t)$, $u_2(t) = 0$ *and* $b_1 = 1$.

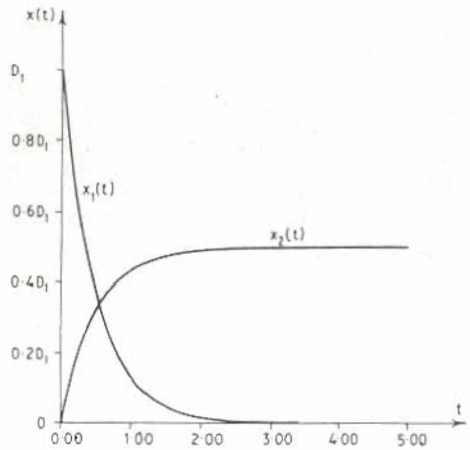

Figure 3.13 Responses of model of Example 3.5 to impulsive perturbation of compartment 1.

Solution. For this system,

$$\mathbf{A} = \begin{bmatrix} -2 & 0 \\ 1 & 0 \end{bmatrix}$$

and $\lambda_1, \lambda_2 = -2, 0$.

Thus, from eqns (3.37),

$$x_1(t) = D_1 \, e^{-2t}$$

$$x_2(t) = \tfrac{1}{2} D_1 (1 - e^{-2t})$$

(which are shown in Fig. 3.13).

3.2.5 *Closed systems*

A closed system is one in which no compartment excretes material to the environment; it may or may not contain sink compartments. All closed systems have a zero eigenvalue.

A two-compartment closed system has $k_{01} = k_{02} = 0$, so that $a_{11} = -k_{21}$ and $a_{22} = -k_{12}$. For this system,

$$\mathbf{A} = \begin{bmatrix} -k_{21} & k_{12} \\ k_{21} & -k_{12} \end{bmatrix}.$$

From $|\lambda \mathbf{I} - \mathbf{A}| = 0$, the eigenvalues are

$$\lambda_1, \lambda_2 = -(k_{12} + k_{21}), 0$$

and
$$(s\mathbf{I} - \mathbf{A})^{-1} = \frac{1}{s(s + k_{12} + k_{21})} \begin{bmatrix} s + k_{12} & k_{12} \\ k_{21} & s + k_{21} \end{bmatrix}. \tag{3.38}$$

If
$$u_1(t) = D_1 \, \delta(t) \quad \text{and} \quad u_2(t) = 0,$$

$$Y_1(s) = \frac{c_1 b_1 D_1 (s + k_{12})}{s(s + k_{12} + k_{21})}$$

whence
$$y_1(t) = \frac{c_1 b_1 D_1}{k_{12} + k_{21}} (k_{12} + k_{21} \, e^{-(k_{12} + k_{21})t}), \qquad t \geqslant 0 \tag{3.39a}$$

and
$$Y_2(s) = \frac{c_2 b_1 D_1 k_{21}}{s(s + k_{12} + k_{21})}$$

whence
$$y_2(t) = \frac{c_2 b_1 D_1 k_{21}}{k_{12} + k_{21}} (1 - e^{-(k_{12} + k_{21})t}), \qquad t \geqslant 0. \tag{3.39b}$$

Note that in the steady state, the quantity administered to the system is shared between the compartments in the ratio $\dfrac{k_{12}}{k_{21}}$.

If, in addition, compartment 2 is a sink compartment, with $k_{12} = 0$, then the responses to the same form of perturbation are

$$y_1(t) = c_1 b_1 D_1 \, e^{-k_{21}t}, \qquad t \geqslant 0 \tag{3.40a}$$

$$y_2(t) = c_2 b_1 D_1 (1 - e^{-k_{21}t}), \qquad t \geqslant 0. \tag{3.40b}$$

Example 3.6. *For the two-compartment system with* $k_{01} = k_{02} = 0$, $k_{12} = k_{21} = 1$, *determine* $x_1(t)$ *and* $x_2(t)$ *for* $t \geqslant 0$ *if* $u_1(t) = D_1 \, \delta(t)$, $u_2(t) = 0$, $b_1 = 1$.

Solution. From eqns (3.39),

$$x_1(t) = \tfrac{1}{2} D_1 (1 + e^{-2t})$$

$$x_2(t) = \tfrac{1}{2} D_1 (1 - e^{-2t})$$

which are shown in Fig. 3.14.

3.2.6 *The washout curves*

Consider the general two-compartment system with distinct eigenvalues and suppose that a constant continuous infusion of rate k_i per unit time has been made into compartment 1 (no external input to compartment 2), until the

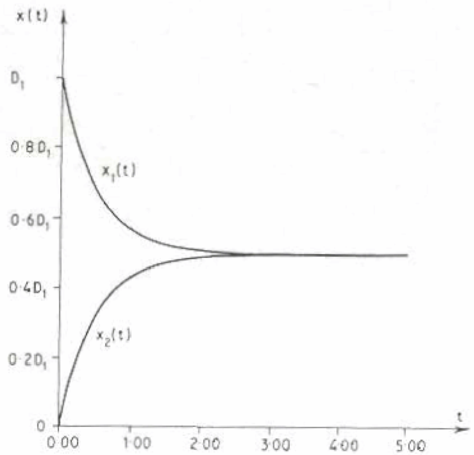

Figure 3.14 Responses of model of Example 3.6 to impulsive perturbation of compartment 1.

system is in a steady state. From eqns (3.28), the steady-state compartmental quantities are

$$x_{1ss} = -\frac{b_1 k_i a_{22}}{\lambda_1 \lambda_2} \qquad (3.41a)$$

$$x_{2ss} = \frac{b_1 k_i a_{21}}{\lambda_1 \lambda_2}. \qquad (3.41b)$$

The washout curves are the compartmental quantities after the infusion has stopped (at $t = 0$), and from eqn (2.63) are given by

$$\mathbf{x}(t) = e^{\mathbf{A}t}\mathbf{x}(0^-)$$

where

$$e^{\mathbf{A}t} = \mathscr{L}^{-1}(s\mathbf{I} - \mathbf{A})^{-1}$$

and $\mathbf{x}(0^-)$ is the vector consisting of x_{1ss} and x_{2ss}, given by eqns (3.41).

From eqn (3.25),

$$(s\mathbf{I} - \mathbf{A})^{-1} = \frac{1}{(s-\lambda_1)(s-\lambda_2)}\begin{bmatrix} s - a_{22} & a_{12} \\ a_{21} & s - a_{11} \end{bmatrix}$$

so that

$$x_1(t) = \frac{b_1 k_i}{\lambda_1 \lambda_2}\mathscr{L}^{-1}\left[\frac{-a_{22}(s - a_{22}) + a_{12}a_{21}}{(s-\lambda_1)(s-\lambda_2)}\right], \qquad t \geqslant 0 \qquad (3.42a)$$

and

$$x_2(t) = \frac{b_1 k_i}{\lambda_1 \lambda_2}\mathscr{L}^{-1}\left[\frac{-a_{21}a_{22} + (s - a_{11})a_{21}}{(s-\lambda_1)(s-\lambda_2)}\right], \qquad t \geqslant 0. \qquad (3.42b)$$

Taking partial fractions and inverse Laplace transforming,

$$x_1(t) = \frac{b_1 k_i}{\lambda_1\lambda_2(\lambda_1 - \lambda_2)}[(-a_{22}(\lambda_1 - a_{22}) + a_{12}a_{21})e^{\lambda_1 t}$$
$$- (-a_{22}(\lambda_2 - a_{22}) + a_{12}a_{21})e^{\lambda_2 t}], \qquad t \geqslant 0 \qquad (3.43a)$$

$$x_2(t) = \frac{b_1 k_i}{\lambda_1\lambda_2(\lambda_1 - \lambda_2)}[(-a_{21}a_{22} + (\lambda_1 - a_{11})a_{21})e^{\lambda_1 t}$$
$$- (-a_{21}a_{22} + (\lambda_2 - a_{11})a_{21})e^{\lambda_2 t}], \qquad t \geqslant 0. \qquad (3.43b)$$

Example 3.7. *Find the washout curves for the compartmental system of Example 3.1 (with $k_{12} = k_{21} = k_{01} = k_{02} = 1$), assuming that, prior to $t = 0$, a constant continuous infusion of 1 unit per unit time had been made to compartment 1, with $b_1 = 1$.*

Solution. For this system, $a_{11} = -2$, $a_{22} = -2$, $\lambda_1 = -3$ and $\lambda_2 = -1$. The initial conditions are, from eqns (3.41), $x_1(0^-) = \frac{2}{3}$, $x_2(0^-) = \frac{1}{3}$. Substituting in eqns (3.43),

$$x_1(t) = \frac{1}{(3)(-2)}[(2(-1) + 1)e^{-3t} - (2(1) + 1)e^{-t}]$$
$$= \tfrac{1}{6}e^{-3t} + \tfrac{1}{2}e^{-t}, \qquad t \geqslant 0$$

$$x_2(t) = \frac{1}{(3)(-2)}[(2 + (-1)(1))e^{-3t} - (2 + (1)(1))e^{-t}]$$
$$= -\tfrac{1}{6}e^{-3t} + \tfrac{1}{2}e^{-t}, \qquad t \geqslant 0$$

which are shown in Fig. 3.15.

3.2.7 *Summary of relationships for two-compartment systems*

For a two-compartment system with

$$\mathbf{A} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$$

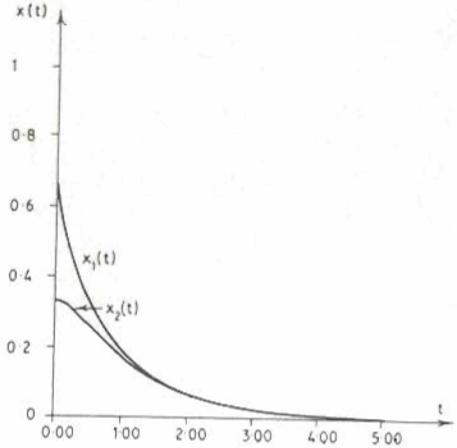

Figure 3.15 Washout curves for the two-compartment model of Example 3.7.

where $a_{11} = -(k_{01} + k_{21})$, $a_{12} = k_{12}$, $a_{21} = k_{21}$, $a_{22} = -(k_{02} + k_{12})$, the eigenvalues must be real. They are also distinct unless $a_{11} = a_{22}$ and $a_{12}a_{21} = 0$. For the system,

$$(s\mathbf{I} - \mathbf{A})^{-1} = \frac{1}{(s-\lambda_1)(s-\lambda_2)} \begin{bmatrix} s - a_{22} & a_{12} \\ a_{21} & s - a_{11} \end{bmatrix}$$

where the eigenvalues are given by

$$\lambda_1, \lambda_2 = \tfrac{1}{2}\{(a_{11} + a_{22}) \pm [(a_{11} - a_{22})^2 + 4a_{12}a_{21}]^{1/2}\}.$$

The responses of the states to $u_1(t) = \delta(t)$, $u_2(t) = 0$, $b_1 = 1$ are

$$x_1(t) = \frac{\lambda_1 - a_{22}}{\lambda_1 - \lambda_2} e^{\lambda_1 t} + \frac{\lambda_2 - a_{22}}{\lambda_2 - \lambda_1} e^{\lambda_2 t}, \qquad t \geqslant 0$$

$$x_2(t) = \frac{a_{21}}{\lambda_1 - \lambda_2}(e^{\lambda_1 t} - e^{\lambda_2 t}), \qquad t \geqslant 0.$$

If a_{12} $(= k_{12}) = 0$ and $(k_{01} + k_{21}) = k_{02}$, the repeated eigenvalue is $\lambda = -k_{02}$ and the corresponding state impulse responses are

$$x_1(t) = e^{\lambda t} \qquad t \geqslant 0$$

$$x_2(t) = a_{21} t\, e^{\lambda t}, \qquad t \geqslant 0.$$

Responses to a unit step input applied to compartment 1 may be found by integration of the unit impulse responses, so that for distinct eigenvalues,

$$x_1(t) = -\frac{a_{22}}{\lambda_1\lambda_2} + \frac{\lambda_1 - a_{22}}{\lambda_1(\lambda_1 - \lambda_2)} e^{\lambda_1 t} + \frac{\lambda_2 - a_{22}}{\lambda_2(\lambda_2 - \lambda_1)} e^{\lambda_2 t}, \qquad t \geqslant 0$$

$$x_2(t) = a_{21}\left(\frac{1}{\lambda_1\lambda_2} + \frac{1}{\lambda_1(\lambda_1 - \lambda_2)} e^{\lambda_1 t} + \frac{1}{\lambda_2(\lambda_2 - \lambda_1)} e^{\lambda_2 t}\right), \qquad t \geqslant 0.$$

while for repeated eigenvalues,

$$x_1(t) = \frac{1}{\lambda}(1 - e^{\lambda t}), \qquad t \geqslant 0$$

$$x_2(t) = a_{21}\left(\frac{1}{\lambda^2} + \frac{1}{\lambda} t\, e^{\lambda t} - \frac{1}{\lambda^2} e^{\lambda t}\right), \qquad t \geqslant 0.$$

If compartment 1 is a source compartment, i.e. $k_{12} = 0$, then $\lambda_1, \lambda_2 = a_{11}$, a_{22} and the unit impulse responses are

$$x_1(t) = e^{a_{11} t}, \qquad t \geqslant 0$$

$$x_2(t) = \frac{a_{21}}{a_{11} - a_{22}}(e^{a_{11} t} - e^{a_{22} t}), \qquad t \geqslant 0.$$

If compartment 2 is a sink compartment, i.e. $k_{02} = k_{12} = 0$, then one of the eigenvalues is zero and the unit impulse responses are

$$x_1(t) = e^{a_{11} t}, \qquad t \geqslant 0$$

$$x_2(t) = \frac{a_{21}}{a_{11}}(e^{a_{11} t} - 1), \qquad t \geqslant 0.$$

For a closed system (k_{01} and k_{02} both zero), one of the eigenvalues is zero and the other is $-(k_{12} + k_{21})$. Since $a_{22} = -k_{12}$, the unit impulse responses are

$$x_1(t) = \frac{k_{12}}{k_{12} + k_{21}} + \frac{k_{21}}{k_{12} + k_{21}} e^{-(k_{12} + k_{21})t}, \qquad t \geqslant 0$$

$$x_2(t) = \frac{k_{21}}{k_{12} + k_{21}} - \frac{k_{21}}{k_{12} + k_{21}} e^{-(k_{12} + k_{21})t}, \qquad t \geqslant 0.$$

Results which carry over to compartmental systems with any number of compartments are:

(i). a source compartment behaves as a first-order system;
(ii). a sink compartment results in a zero eigenvalue;
(iii). a closed system has a zero eigenvalue.