Compartmental Models and Their Application

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2 The Dynamics of Linear, Time-invariant Systems

Before considering the dynamics of compartmental systems in particular in Section 2.4, we will review the input–output relationships for systems with linear, time-invariant dynamics in general in Sections 2.1 to 2.3.

2.1 Single-input, single-output (SISO) systems

Consider a dynamic system with input $u(t)$ and response to that input $x(t)$, as shown in Fig. 2.1. Assume the following:

(i). The system is lumped, rather than distributed; that is, its behaviour can be described over a finite number of points in space. The differential equations describing the behaviour are ordinary rather than partial.
(ii). The system is linear so that the principle of superposition applies; that is, the response to an input $u_1(t) + u_2(t)$ is the sum of responses to $u_1(t)$ and $u_2(t)$ applied separately.
(iii). The system is in steady state prior to the application of the input at time $t = 0$. The quantities referred to in the remainder of this chapter are deviations from the (steady) values $u(0^-)$ and $x(0^-)$ immediately prior to the input perturbation. Higher-order derivatives are zero at $t = 0^-$. '

The input and output are then related by the *convolution integral*:

$$x(t) = \int_0^t g(t - \lambda)u(\lambda)\, d\lambda \tag{2.1}$$

where λ is a time variable ranging over the interval up to the present time t during which the input has been applied and $g(t)$ is the *weighting function* of the system, which weights *past* values of the input to give the *present* value of the output.
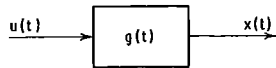

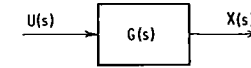**Figure 2.1** Dynamic system with weighting function $g(t)$.

Figure 2.2 Dynamic system with transfer function $G(s)$.

We have further assumed that the system is time-invariant, that is, its dynamics do not change with time. The weighting function is then the same as the response of the system to a unit impulse.

Except for simple forms of input, the convolution integral of eqn (2.1) is difficult to evaluate analytically and use is then made of the corresponding Laplace transform relationship:

$$X(s) = G(s)U(s) \tag{2.2}$$

where $X(s)$ and $U(s)$ are the Laplace transforms of $x(t)$ and $u(t)$ respectively and $G(s)$, the Laplace transform of $g(t)$, is called the (Laplace) *transfer function* of the system (Fig. 2.2).

See Appendix 1 for an exposition of Laplace transforms.

2.1.1 First-order systems

For a first-order, linear, time-invariant system, the input and output are related by the ordinary differential equation:

$$T \cdot \dot{x}(t) + x(t) = K \cdot u(t) \tag{2.3}$$

where K is the *steady-state gain* of the system (i.e. the proportional factor between x and u in the steady state), T is the *time constant* of the system and $\dot{x}(t) \equiv \dfrac{dx}{dt}$. The general solution of eqn (2.3) is given by the sum of the complementary function and particular integral:

$$x(t) = e^{-t/T}x(0^-) + \int_0^t e^{-(t-\lambda)/T}\frac{K}{T}u(\lambda)\, d\lambda. \tag{2.4}$$

The Laplace transform of eqn (2.3) is

$$(sT + 1)X(s) - T \cdot x(0^-) = K \cdot U(s) \tag{2.5}$$

which, on rearrangement, gives

$$X(s) = \frac{T \cdot x(0^-)}{sT + 1} + \frac{K \cdot U(s)}{sT + 1}. \tag{2.6}$$

Assuming that $x(0^-)$ is zero, or has been subtracted from all subsequent values of $x(t)$, eqns (2.4) and (2.6) become

$$x(t) = \int_0^t \frac{K}{T} e^{-(t-\lambda)/T} u(\lambda) \, d\lambda \tag{2.7}$$

$$X(s) = \frac{K \cdot U(s)}{sT + 1}. \tag{2.8}$$

Comparing these with eqns (2.1) and (2.3), it may be seen that the weighting function is given by

$$g(t) = \frac{K}{T} e^{-t/T} \tag{2.9}$$

and that the transfer function is given by

$$G(s) = \frac{X(s)}{U(s)} = \frac{K}{sT + 1}. \tag{2.10}$$

If a unit impulse is applied to the system at $t = 0$, then $U(s) = 1$, $X(s) = G(s)$ and $x(t) = g(t)$. The unit impulse response of a first-order system is shown in Fig. 2.3. At time $t = T$, the value of the response has fallen to

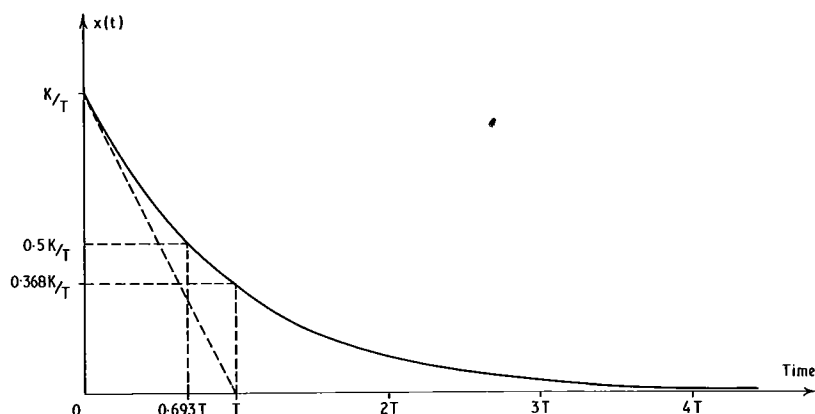$$x(T) = \frac{K}{T} e^{-1} \simeq 0.368 \frac{K}{T} \tag{2.11}$$

Figure 2.3 Unit impulse response of first-order system described by eqn (2.3).

so that, in one time constant, the response has fallen to 36.8% of its maximum value (at $t = 0$). The response falls to 1% of its maximum value when

$$0.01 = e^{-t/T}$$

i.e.
$$t_{0.01} = T \log_e 100 \simeq 4.605T. \tag{2.12}$$

In the medical and biological literature, the half-life, $t_{1/2}$, is more often quoted than the time constant. The half-life is the time taken for the response to fall to 50% of its maximum value and so is related to the time constant by

$$0.5 = e^{-t_{1/2}/T}$$

whence
$$t_{1/2} = T \cdot \log_e 2 \simeq 0.693T. \tag{2.13}$$

The unit step is the integral of the unit impulse and the unit-step response may be found by integrating the unit-impulse response of eqn (2.9):

$$x(t) = \int_0^t \frac{K}{T} e^{-t/T} \, dt = K(1 - e^{-t/T}) \tag{2.14}$$

which is illustrated in Fig. 2.4. The unit-step response may also be found from the transfer function using eqn (2.10). For a unit step, $U(s) = \frac{1}{s}$ so that

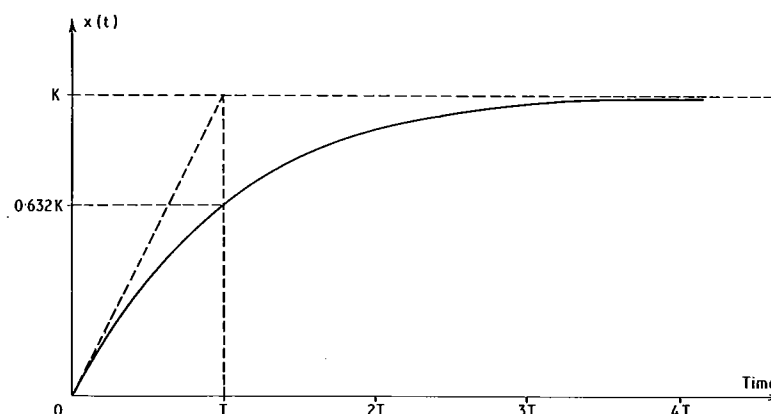$$X(s) = G(s)U(s) = \frac{K}{s(sT + 1)}. \tag{2.15}$$

Figure 2.4 Unit step response of first-order system described by eqn (2.3).

Taking partial fractions (see Appendix 1),

$$X(s) = \frac{K}{s} - \frac{KT}{sT+1} \qquad (2.16)$$

and using the Table of Laplace transforms in Appendix 1,

$$x(t) = K - K e^{-t/T}, \qquad t \geqslant 0 \qquad (2.17)$$

which is the same as eqn (2.14).

Example 2.1. *A resistor R and inductor L are connected in series as shown in Fig. 2.5. The current is zero when, at time $t = 0$, the switch is closed. Find the current $i(t)$ for $t \geqslant 0$.*

Solution. The voltage drops v_R and v_L across the resistor and inductor are:

$$v_R = i \cdot R \quad \text{and} \quad v_L = L\frac{di}{dt}.$$

Applying Kirchhoff's Voltage Law (that the sum of voltage drops around a circuit equals the applied voltage),

$$L\frac{di}{dt} + iR = e(t) = E, \qquad t \geqslant 0.$$

Comparing this with eqn (2.3), it may be seen that $T = \frac{L}{R}$ and $K = \frac{1}{R}$ so that substituting into eqn (2.14),

$$i(t) = \frac{E}{R}(1 - e^{-Rt/L}).$$

Alternatively, Laplace transformation of the differential equation above gives

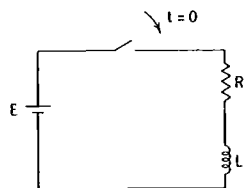$$(sL + R)I(s) = \frac{E}{s} \quad \text{so that} \quad I(s) = \frac{E}{s(sL + R)}.$$

Figure 2.5   Series RL circuit of Example 2.1.

Taking partial fractions (see Appendix 1),

$$I(s) = \frac{E}{R} \cdot \frac{1}{s} - \frac{EL}{R} \cdot \frac{1}{sL + R}$$

giving $i(t) = \frac{E}{R}(1 - e^{-Rt/L})$, on inverse Laplace transformation.

The question of units for an impulsive input sometimes gives rise to confusion. The Dirac delta function is defined by

$$\delta(t) = 0 \qquad t \neq 0 \qquad (2.18a)$$

$$\int_{-\infty}^{\infty} \delta(t)\,dt = 1. \qquad (2.18b)$$

Consider the pulse function $f(t)$ shown in Fig. 2.6, of height $\frac{1}{\varepsilon}$, width ε and unit area. The delta function is given by

$$\delta(t) = \lim_{\varepsilon \to 0} f(t) \qquad (2.19)$$

so that the delta function is a function of infinitely large height acting for an infinitely short time. Such an idealized function cannot be realized in practice, but its shape is approximated in a number of practical instances. For example, an impulsive blow of magnitude P can be regarded as a *force* of $P \cdot \delta(t)$ while a rapidly-administered dose of size D can be regarded as an input *rate* of $D \cdot \delta(t)$. Note the use of "rate", because $\delta(t)$ has units of $(\text{time})^{-1}$. The delta function is clearly the derivative of the unit step function $H(t)$, i.e.

$$\delta(t) = \frac{d}{dt}H(t). \qquad (2.20)$$

To complete the discussion of the use of the delta function, let us return to the circuit of Fig. 2.5, but suppose that, instead of a step E being applied at
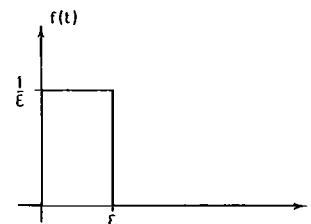

Figure 2.6   A pulse function of unit area.

$t = 0$, an impulsive voltage $E_0 \delta(t)$ is applied. The impulsive voltage is one whose time integral is E_0 and since the units of $E_0 \delta(t)$ are volts and those of $\delta(t)$ are (time)$^{-1}$, the units of E_0 are (volts) × (time). The differential equation is thus

$$L \frac{di}{dt} + iR = E_0 \delta(t).$$

With $i(0^-)$ zero,

$$(sL + R) \cdot I(s) = E_0$$

$$I(s) = \frac{E_0}{sL + R}$$

giving, on inverse Laplace transformation,

$$i(t) = \frac{E_0}{L} e^{-Rt/L}, \qquad t \geqslant 0.$$

2.1.2 Second-order systems

The dynamics of a second-order, linear, time-invariant system may be described by the differential equation

$$\frac{1}{\omega_0^2} \ddot{x} + \frac{2\zeta}{\omega_0} \dot{x} + x = u \tag{2.21}$$

where ζ, the *damping ratio* defines the degree of damping in the system, being a measure of the presence and extent of oscillation in the system response and ω_0, the *undamped natural frequency* is the frequency of oscillation (radians per second) of the system in the absence of damping, i.e. with $\zeta = 0$.

The transfer function of the system is

$$G(s) \triangleq \frac{X(s)}{U(s)} = \frac{\omega_0^2}{s^2 + 2\zeta\omega_0 s + \omega_0^2}. \tag{2.22}$$

Unit step responses for various values of ζ are shown in Fig. 2.7; corresponding impulse responses may be found by differentiation. The unit step responses are given by

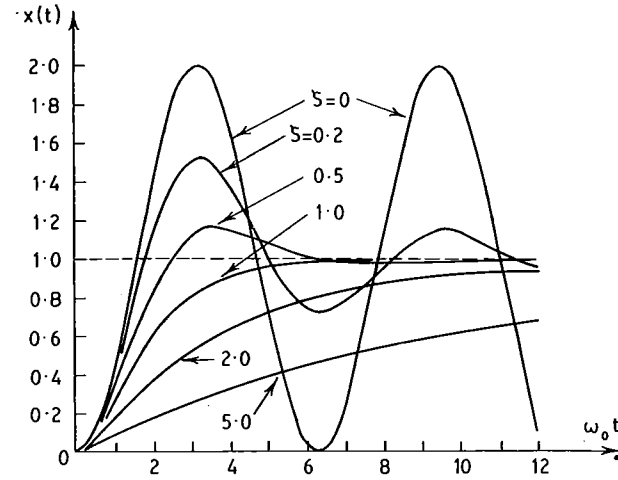$$x(t) = \mathscr{L}^{-1} \left(\frac{G(s)}{s} \right)$$

Figure 2.7 Unit step responses (for various values of ζ) of second-order system described by eqn (2.21).

and to find the inverse Laplace transform using the table given in Appendix 1, it is necessary to complete the square in the denominator of $G(s)$, by writing

$$s^2 + 2\zeta\omega_0 s + \omega_0^2 \equiv (s + \zeta\omega_0)^2 + \omega_0^2(1 - \zeta^2). \tag{2.23}$$

The shape of the response depends on whether $\omega_d^2 \triangleq \omega_0^2(1 - \zeta^2)$ is positive, zero or negative, and we will consider these three cases in turn.

(a) $0 \leqslant \zeta < 1$. Since ω_0 is real, $\omega_0^2(1 - \zeta^2)$ is positive and the system is said to be *underdamped*. The unit step response is the inverse transform of

$$X(s) = \frac{1}{s} - \frac{s + \zeta\omega_0}{(s + \zeta\omega_0)^2 + (1 - \zeta^2)\omega_0^2} - \frac{\zeta\omega_0}{(s + \zeta\omega_0)^2 + (1 - \zeta^2)\omega_0^2}$$

i.e. $\quad x(t) = 1 - e^{-\zeta\omega_0 t} \left(\cos \omega_d t + \frac{\zeta}{(1 - \zeta^2)^{1/2}} \sin \omega_d t \right). \tag{2.24}$

If $\zeta = 0$, the oscillations are undamped, but if $\zeta > 0$, the oscillations are damped by the $e^{-\zeta\omega_0 t}$ factor (damped because ζ and ω_0 are non-negative). The roots of eqn (2.23) are a complex conjugate pair:

$$s = -\alpha \pm j\beta \tag{2.25}$$

where $\alpha = \zeta\omega_0$ is real and non-negative and $\beta = \omega_d = \omega_0(1 - \zeta^2)^{1/2}$ is real.

(b) $\zeta = 1$. The term $\omega_0^2(1 - \zeta^2)$ is zero and the system is said to be *critically damped*. The unit step response is the inverse transform of

$$X(s) = \frac{\omega_0^2}{s(s + \omega_0)^2} = \frac{1}{s} - \frac{s + 2\omega_0}{(s + \omega_0)^2}$$

i.e.
$$x(t) = 1 - e^{-\omega_0 t}(1 + \omega_0 t). \qquad (2.26)$$

The denominator of eqn (2.22) consists of a repeated real root ($s = -\omega_0$). The step response is no longer oscillatory (see Fig. 2.7).

(c) $\zeta > 1$. The term $\omega_0^2(1 - \zeta^2)$ is negative and the system is said to be *overdamped*. The unit step response is the inverse transform of:

$$X(s) = \frac{\omega_0^2}{s(s + \zeta\omega_0 + \omega_0(\zeta^2 - 1)^{1/2})(s + \zeta\omega_0 - \omega_0(\zeta^2 - 1)^{1/2})}$$

i.e. $x(t) = 1 + \dfrac{\omega_0}{2(\zeta^2 - 1)^{1/2}}$

$$\times \left\{ \frac{\exp[-(\zeta + (\zeta^2 - 1)^{1/2})\omega_0 t]}{\zeta + (\zeta^2 - 1)^{1/2}} - \frac{\exp[-(\zeta - (\zeta^2 - 1)^{1/2}\omega_0 t]}{\zeta - (\zeta^2 - 1)^{1/2}} \right\}. \qquad (2.27)$$

The roots of eqn (2.22) are real and distinct and it may be seen from Fig. 2.7 that the unit step response is again non-oscillatory, and gets progressively slower as ζ gets larger.

Example 2.2. *A resistor R, inductor L and capacitor C are connected in series as shown in Fig. 2.8. The current i and capacitor charge q are zero when, at $t = 0$, the switch is closed. Find the current $i(t)$ for $t \geqslant 0$.*
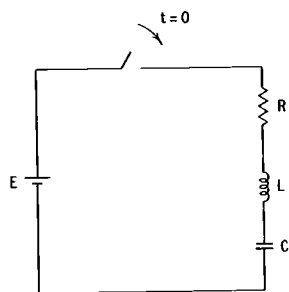

Figure 2.8 Series RLC circuit of Example 2.2.

Solution. There are two storage elements (the inductor and the capacitor) so a second-order differential equation is expected. The voltage drops across the elements of the circuit are:

$$v_L = L\frac{di}{dt} = L\frac{d^2q}{dt^2}$$

$$v_R = Ri = R\frac{dq}{dt}$$

$$v_C = \frac{1}{C}\int_{0^-}^{t} i\,dt = \frac{q}{C}$$

so that, applying Kirchhoff's Voltage Law,

$$L\frac{d^2q}{dt^2} + R\frac{dq}{dt} + \frac{q}{C} = E, \qquad t \geqslant 0.$$

Comparing this with eqn (2.21), it may be seen that

$$\frac{1}{\omega_0^2} = LC \quad \text{so} \quad \omega_0 = \frac{1}{(LC)^{1/2}}$$

$$\frac{2\zeta}{\omega_0} = RC \quad \text{so} \quad \zeta = \frac{R}{2}\left(\frac{C}{L}\right)^{1/2}.$$

Laplace transformation of the differential equation gives, with $i(0^-) = q(0^-) = 0$,

$$(s^2 + (R/L)s + 1/LC)Q(s) = \frac{E/L}{s}$$

whence
$$Q(s) = \frac{E}{L}\frac{1}{s(s^2 + (R/L)s + 1/LC)}.$$

But $i = \dfrac{dq}{dt}$ so that, with $q(0^-) = 0$, $I(s) = s \cdot Q(s)$, giving

$$I(s) = \frac{E}{L} \cdot \frac{1}{s^2 + (R/L)s + 1/LC}.$$

Let us consider one case only, with circuit values so that $\dfrac{R}{2}\left(\dfrac{C}{L}\right)^{1/2} < 1$,

which, from the foregoing, will yield an underdamped system, since

$0 \leqslant \zeta < 1$. From eqns (2.22) and (2.24),

$$i(t) = \frac{E}{\omega_0^2 L} \frac{\omega_0}{(1 - \zeta^2)^{1/2}} e^{-\zeta\omega_0 t} \sin(\omega_0(1 - \zeta^2)^{1/2}t)$$

$$= \frac{E}{L} e^{-\zeta\omega_0 t} \frac{\sin(\omega_0(1 - \zeta^2)^{1/2}t)}{\omega_0(1 - \zeta^2)^{1/2}}$$

$$= \frac{E}{L} e^{-\alpha t} \frac{\sin \omega t}{\omega}$$

where
$$\alpha = \zeta\omega_0 = \frac{R}{2L}$$

and
$$\omega^2 = \omega_0^2(1 - \zeta^2) = \frac{1}{LC}\left(1 - \frac{R^2 C}{4L}\right) = \frac{1}{LC} - \frac{R^2}{4L^2}.$$

2.2 The state variables of a dynamic system

Much of the recent literature on time-domain analysis of a system utilizes the concept of the *state* of a system. The state is a set of numbers such that the knowledge of these numbers and the input functions will, together with the equations describing the dynamics, give the future state and output of the system. The *state variable* representation of a multi-input, multi-output system is:

$$\dot{\mathbf{x}} = \mathbf{A}\mathbf{x} + \mathbf{B}\mathbf{u}. \qquad (2.28)$$

In this *state equation*, the vector **x** represents the state of the system. In some applications, it is difficult to choose variables of direct physical significance (and the state variable set is not necessarily unique) but in compartmental modelling this problem does not exist because all the differential equations are first-order and the state variables are compartmental quantities or concentrations.

Equation (2.28) indicates that the first derivative of state variable x_i is a linear function of the p state variables and m inputs:

$$\dot{x}_i = a_{i1}x_1 + a_{i2}x_2 + \ldots + a_{ip}x_p + b_{i1}u_1 + b_{i2}u_2 + \ldots + b_{im}u_m \quad (2.29)$$

where the a's and b's are constants for a time-invariant system. Equations of the form of (2.29) may be written for all the states:

$$\begin{bmatrix} \dot{x}_1 \\ \vdots \\ \dot{x}_p \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} & \cdots & a_{1p} \\ \vdots & & & \\ a_{p1} & a_{p2} & \cdots & a_{pp} \end{bmatrix} \begin{bmatrix} x_1 \\ \vdots \\ x_p \end{bmatrix} + \begin{bmatrix} b_{11} & b_{12} & \cdots & b_{1m} \\ \vdots & & & \\ b_{p1} & b_{p2} & \cdots & b_{pm} \end{bmatrix} \begin{bmatrix} u_1 \\ \vdots \\ u_m \end{bmatrix}$$

$$(2.30)$$

as in eqn (2.28). The outputs (or observations) are not necessarily the state variables themselves, but may be linear combinations of them:

$$y_i = c_{i1}x_1 + c_{i2}x_2 + \ldots + c_{ip}x_p \qquad (2.31)$$

that is
$$\mathbf{y} = \mathbf{C}\mathbf{x}. \qquad (2.32)$$

Note that the *observation equation* (2.32) is a non-dynamic relationship, being an algebraic, rather than differential, equation.

If there are p states, m inputs and n outputs (observations), **A** is a $p \times p$ matrix, **B** is a $p \times m$ matrix and **C** is a $n \times p$ matrix.

Before proceeding further, let us see how the first-order and second-order SISO systems considered earlier can be formulated in state variable form. For the first-order system, eqn (2.3) can be rearranged as

$$\dot{x}(t) = -\frac{1}{T}x(t) + \frac{K}{T}u(t) \qquad (2.33)$$

which is to be compared with the state variable form

$$\dot{x}(t) = Ax(t) + Bu(t). \qquad (2.34)$$

Direct comparison shows that $A = -\frac{1}{T}$ and $B = \frac{K}{T}$.

The second-order differential eqn (2.21) can be expressed as two simultaneous first-order differential equations. Define $x_1 \triangleq x$, $x_2 \triangleq \dot{x}$ so that $\dot{x} \equiv \dot{x}_1 \equiv x_2$. Then from eqn (2.21),

$$\ddot{x} \equiv \dot{x}_2 = -2\zeta\omega_0\dot{x}_1 - \omega_0^2 x_1 + \omega_0^2 u$$

$$= -2\zeta\omega_0 x_2 - \omega_0^2 x_1 + \omega_0^2 u$$

which may be rearranged to give

$$\dot{x}_1 = x_2$$
$$\dot{x}_2 = -\omega_0^2 x_1 - 2\zeta\omega_0 x_2 + \omega_0^2 u.$$

In vector-matrix form,

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -\omega_0^2 & -2\zeta\omega_0 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} 0 \\ \omega_0^2 \end{bmatrix} u$$

i.e.
$$\dot{\mathbf{x}} = \mathbf{A}\mathbf{x} + \mathbf{b}\mathbf{u}. \qquad (2.35)$$

The approach is readily extended to higher-order equations.

2.3　The dynamics of multivariable systems

2.3.1　The transfer function matrix

The transfer function matrix $\mathbf{G}(s)$ relates all the inputs making up $\mathbf{U}(s)$ to the outputs $\mathbf{Y}(s)$. Taking Laplace transforms of eqns (2.28) and (2.32), with $\mathbf{x}(0^-)$ assumed zero,

$$s \cdot \mathbf{X}(s) = \mathbf{A}\mathbf{X}(s) + \mathbf{B}\mathbf{U}(s) \tag{2.36}$$

$$\mathbf{Y}(s) = \mathbf{C}\mathbf{X}(s). \tag{2.37}$$

Rearranging eqn (2.36),

$$(s\mathbf{I} - \mathbf{A})\mathbf{X}(s) = \mathbf{B}\mathbf{U}(s)$$

whence
$$\mathbf{X}(s) = (s\mathbf{I} - \mathbf{A})^{-1}\mathbf{B}\mathbf{U}(s). \tag{2.38}$$

Substituting into eqn (2.37),

$$\mathbf{Y}(s) = \mathbf{C}(s\mathbf{I} - \mathbf{A})^{-1}\mathbf{B}\mathbf{U}(s) \tag{2.39}$$

so that the transfer function matrix $\mathbf{G}(s)$ is given by

$$\mathbf{G}(s) = \mathbf{C}(s\mathbf{I} - \mathbf{A})^{-1}\mathbf{B}. \tag{2.40}$$

Example 2.3. *Establish the transfer function matrix for the system whose state equations are:*

$$\dot{x}_1 = -2x_1 + x_2 + u_1$$
$$\dot{x}_2 = 2x_1 - 3x_2 + u_2$$
$$y_1 = x_1 \quad \text{and} \quad y_2 = x_2.$$

Solution. For this system,

$$\mathbf{C} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} = \mathbf{I}, \quad \mathbf{B} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} = \mathbf{I} \quad \text{and} \quad \mathbf{A} = \begin{bmatrix} -2 & 1 \\ 2 & -3 \end{bmatrix}$$

$$s\mathbf{I} - \mathbf{A} = \begin{bmatrix} s+2 & -1 \\ -2 & s+3 \end{bmatrix}$$

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

where
$$\Delta(s) = \begin{vmatrix} s+2 & -1 \\ -2 & s+3 \end{vmatrix} = s^2 + 5s + 4 = (s+4)(s+1).$$

Thus
$$\mathbf{G}(s) = \begin{bmatrix} \dfrac{s+3}{(s+4)(s+1)} & \dfrac{1}{(s+4)(s+1)} \\ \dfrac{2}{(s+4)(s+1)} & \dfrac{s+2}{(s+4)(s+1)} \end{bmatrix}$$

and
$$\mathbf{Y}(s) = \mathbf{G}(s)\mathbf{U}(s).$$

If there are m inputs and n outputs, $\mathbf{G}(s)$ is an $n \times m$ matrix. Term $G_{ij}(s)$ within the matrix is the transfer function between the jth input and the ith output.

If only a few of the $G_{ij}(s)$ terms are required, for example because only a few of the states may be perturbed and only a few observed, it is usually easier to use Cramer's rule rather than inverting $(s\mathbf{I} - \mathbf{A})$—see Appendix 2. Thus, in Example 2.3, if it were possible only to perturb x_1 and only to observe x_1 (i.e. $u_2 = 0$, $y_2 = 0$), and it were required to find only $G_{11}(s)$, this could be more easily done as follows:

Transforming the two scalar-state equations,

$$(s+2)X_1(s) - X_2(s) = U_1(s)$$
$$-2X_1(s) + (s+3)X_2(s) = 0$$

so
$$X_1(s) = \frac{\begin{vmatrix} U_1(s) & -1 \\ 0 & s+3 \end{vmatrix}}{\begin{vmatrix} s+2 & -1 \\ -2 & s+3 \end{vmatrix}}$$

$$= \frac{(s+3)U_1(s)}{(s+4)(s+1)}$$

and since $Y_1(s) = X_1(s)$,

$$G_{11}(s) = \frac{Y_1(s)}{U_1(s)} = \frac{s+3}{(s+4)(s+1)}.$$

2.3.2　The transition matrix

The solution of eqn (2.28) is given by

$$\mathbf{x}(t) = e^{\mathbf{A}t}\mathbf{x}(0^-) + \int_{0^-}^{t} e^{\mathbf{A}(t-\lambda)}\mathbf{B}\mathbf{u}(\lambda)\,d\lambda \tag{2.41}$$

(cf. the solution of eqn (2.4) for the first-order system described by eqn (2.3)).

The matrix e^{At} is called the *transition matrix* and is sometimes written as $\Phi(t)$. It is the sum of the infinite series

$$e^{At} = I + At + A^2\frac{t^2}{2!} + A^3\frac{t^3}{3!} + \ldots \qquad (2.42)$$

which is usually an inconvenient expression to evaluate in practice because of the uncertainty as to how many terms must be computed for acceptable accuracy and the need to compute the powers of A. It is often easier to use Laplace transforms. Transforming eqn (2.28),

$$s \cdot X(s) - x(0^-) = AX(s) + BU(s) \qquad (2.43)$$

whence $(sI - A)X(s) = x(0^-) + BU(s)$

giving $X(s) = (sI - A)^{-1}x(0^-) + (sI - A)^{-1}BU(s). \qquad (2.44)$

Inverse transformation gives

$$x(t) = \mathscr{L}^{-1}[(sI - A)^{-1}x(0^-)] + \mathscr{L}^{-1}[(sI - A)^{-1}BU(s)]. \qquad (2.45)$$

Comparing eqns (2.41) and (2.45), it may be seen that

$$e^{At} = \mathscr{L}^{-1}[(sI - A)^{-1}]. \qquad (2.46)$$

For a system with zero initial conditions, we have, from eqns (2.32) and (2.45),

$$y(t) = Cx(t) = C\mathscr{L}^{-1}[(sI - A)^{-1}BU(s)] = \mathscr{L}^{-1}[G(s)U(s)],$$

as expected.

Example 2.4. *Find the transition matrix for the system of Example 2.3.*

Solution. For that system,

$$(sI - A)^{-1} = \begin{bmatrix} \dfrac{s+3}{(s+4)(s+1)} & \dfrac{1}{(s+4)(s+1)} \\[2ex] \dfrac{2}{(s+4)(s+1)} & \dfrac{s+2}{(s+4)(s+1)} \end{bmatrix}$$

$$= \begin{bmatrix} \dfrac{1/3}{s+4} + \dfrac{2/3}{s+1} & \dfrac{-1/3}{s+4} + \dfrac{1/3}{s+1} \\[2ex] \dfrac{-2/3}{s+4} + \dfrac{2/3}{s+1} & \dfrac{2/3}{s+4} + \dfrac{1/3}{s+1} \end{bmatrix}$$

so the transition matrix $= \mathscr{L}^{-1}[(sI - A)^{-1}]$ is given by

$$e^{At} = \Phi(t) = \begin{bmatrix} \frac{1}{3}e^{-4t} + \frac{2}{3}e^{-t} & -\frac{1}{3}e^{-4t} + \frac{1}{3}e^{-t} \\[1ex] -\frac{2}{3}e^{-4t} + \frac{2}{3}e^{-t} & \frac{2}{3}e^{-4t} + \frac{1}{3}e^{-t} \end{bmatrix}.$$

2.3.3   Eigenvalues and eigenvectors

The *eigenvalues* λ_i of a $p \times p$ matrix A are the solutions of the equation:

$$|\lambda I - A| = 0. \qquad (2.47)$$

As we have seen in Section 2.3.2, the transition matrix e^{At} is given by

$$e^{At} = \mathscr{L}^{-1}[(sI - A)^{-1}]$$

$$= \mathscr{L}^{-1}\left[\frac{\text{adj }(sI - A)}{|sI - A|}\right]$$

(see the material on matrix inversion in Appendix 2). Writing the individual elements of the transformed matrix as $\alpha_{ij}(s)$, so that

$$e^{At} = \mathscr{L}^{-1}\begin{bmatrix} \alpha_{11}(s) & \alpha_{12}(s) & \ldots & \alpha_{1p}(s) \\ \vdots & & & \\ \alpha_{p1}(s) & \alpha_{p2}(s) & \ldots & \alpha_{pp}(s) \end{bmatrix} \qquad (2.48)$$

we note that $|sI - A|$ appears in the denominator of all the elements $\alpha_{ij}(s)$.

From the definition of the eigenvalues, $|sI - A|$ has factors $s - \lambda_k$, $k = 1, 2, \ldots, p$ corresponding to the roots λ_k of eqn (2.47). Thus

$$\alpha_{ij}(s) = \frac{a_{ij}(s)}{(s - \lambda_1)(s - \lambda_2) \ldots (s - \lambda_p)}$$

where $a_{ij}(s)$ is a polynomial in s of degree $(p - 1)$ or less. By taking partial fractions, assuming the eigenvalues are all different,

$$\alpha_{ij}(s) = \frac{\beta_1}{s - \lambda_1} + \frac{\beta_2}{s - \lambda_2} + \ldots + \frac{\beta_p}{s - \lambda_p} \qquad (2.49)$$

where $\beta_1 \ldots \beta_p$ are constants. Thus each element of the transition matrix e^{At} will have the form $\beta_1 e^{\lambda_1 t} + \beta_2 e^{\lambda_2 t} + \ldots + \beta_p e^{\lambda_p t}$.

If we consider solution of the homogeneous equation $\dot{x} = Ax$, the foregoing suggests that we can find solutions of the form $x = e^{\lambda t}m$, where m is a non-zero constant vector. From the system equation,

$$\dot{x} = \lambda e^{\lambda t} m = A e^{\lambda t} m$$

whence
$$\lambda\mathbf{m} = \mathbf{A}\mathbf{m}$$

i.e.
$$(\lambda\mathbf{I} - \mathbf{A})\mathbf{m} = \mathbf{0}. \tag{2.50}$$

The vector $\mathbf{m}$ is called an *eigenvector* (of $\mathbf{A}$), and there is an eigenvector associated with each eigenvalue. The p eigenvectors are linearly independent, and the general solution of $\dot{\mathbf{x}} = \mathbf{A}\mathbf{x}$ may be written as

$$\mathbf{x} = c_1 e^{\lambda_1 t}\mathbf{m}_1 + c_2 e^{\lambda_2 t}\mathbf{m}_2 + \ldots + c_p e^{\lambda_p t}\mathbf{m}_p \tag{2.51}$$

where c_1, c_2, ..., c_p are arbitrary constants which depend on the initial conditions. The eigenvectors form the columns of the *modal matrix* $\mathbf{M}$, which is used in a number of approaches to the identifiability problem (see Chapter 5). For the purposes of this book, the above discussion of eigenvectors is sufficient, and for a more detailed description of the use of the modal matrix in system dynamic analysis, the reader is referred to Chapter 2 of Power and Simpson (1978) or Chapter 1 of Owens (1981).

Example 2.5. *For the system of Example 2.3, find the eigenvalues of $\mathbf{A}$ and find the responses $y_1(t)$ and $y_2(t)$ to perturbation $u_1(t) = \delta(t)$, $u_2(t) = 0$. Determine the eigenvectors of $\mathbf{A}$.*

Solution. The eigenvalues are given by:

$$\begin{vmatrix} \lambda + 2 & -1 \\ -2 & \lambda + 3 \end{vmatrix} = 0$$

giving $\lambda^2 + 5\lambda + 4 = 0$ whence $\lambda_1 = -4$, $\lambda_2 = -1$.

$$\mathbf{Y}(s) = \mathbf{C}(s\mathbf{I} - \mathbf{A})^{-1}\mathbf{B}\mathbf{U}(s)$$

$$= \begin{bmatrix} \dfrac{s+3}{(s+4)(s+1)} & \dfrac{1}{(s+4)(s+1)} \\ \dfrac{2}{(s+4)(s+1)} & \dfrac{s+2}{(s+4)(s+1)} \end{bmatrix} \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

$$= \begin{bmatrix} \dfrac{s+3}{(s+4)(s+1)} \\ \dfrac{2}{(s+4)(s+1)} \end{bmatrix}$$

whence
$$y_1(t) = \tfrac{1}{3}e^{-4t} + \tfrac{2}{3}e^{-t}$$

$$y_2(t) = -\tfrac{2}{3}e^{-4t} + \tfrac{2}{3}e^{-t}.$$

Taking the first eigenvalue ($\lambda_1 = -4$), eqn (2.50) gives

$$\begin{bmatrix} -4+2 & -1 \\ -2 & -4+3 \end{bmatrix} \begin{bmatrix} m_{11} \\ m_{21} \end{bmatrix} = 0 \qquad (\lambda I - A)m = 0$$

whence
$$-2m_{11} - m_{21} = 0$$

and
$$-2m_{11} - m_{21} = 0.$$

Note that the same equation is obtained twice, so that only the ratio between m_{11} and m_{21} is available. This is evident from eqn (2.51) because if any $\mathbf{m}_1$ satisfies the equation, so does any scalar multiple of $\mathbf{m}_1$.

Thus
$$\mathbf{m}_1 = m_{11}\begin{bmatrix} 1 \\ -2 \end{bmatrix}.$$

Taking the second eigenvalue, eqn (2.50) gives

$$\begin{bmatrix} -1+2 & -1 \\ -2 & -1+3 \end{bmatrix} \begin{bmatrix} m_{12} \\ m_{22} \end{bmatrix} = 0$$

whence
$$m_{12} - m_{22} = 0$$

$$-2m_{12} + 2m_{22} = 0$$

so that
$$\mathbf{m}_2 = m_{12}\begin{bmatrix} 1 \\ 1 \end{bmatrix}.$$

Thus for this example, the modal matrix $\mathbf{M}$ is given by

$$\mathbf{M} = \begin{bmatrix} m_{11} & m_{12} \\ -2m_{11} & m_{12} \end{bmatrix}.$$

2.4 Dynamics of compartmental systems

As noted previously in this chapter, the state variable description is particularly appropriate for compartmental systems since these consist of sets of first-order differential equations (one per compartment) and the states are the compartmental quantities or concentrations. For a linear, time-invariant compartmental system with p compartments, $\mathbf{A}$ is $p \times p$ and has elements

$$a_{ij} = k_{ij}, \qquad i \neq j \tag{2.52}$$

$$a_{jj} = -\left[\sum_{\substack{i=1 \\ i \neq j}}^{p} k_{ij}\right] - k_{0j}. \tag{2.53}$$

Thus the compartmental form constrains all elements on the main diagonal of $\mathbf{A}$ to be non-positive and all other elements to be non-negative. Further

$$|a_{jj}| \geqslant \sum_{\substack{i=1 \\ i \neq j}}^{p} k_{ij} \qquad (2.54)$$

the equality applying only if $k_{0j} = 0$. So, for example, the system

$$\dot{x}_1 = -x_1 + x_2 + u_1 \qquad (2.55a)$$

$$\dot{x}_2 = x_1 + x_2 + u_2 \qquad (2.55b)$$

is non-compartmental because a_{22} is positive, while the system

$$\dot{x}_1 = -x_1 + 2x_2 + u_1 \qquad (2.56a)$$

$$\dot{x}_2 = 2x_1 - 2x_2 + u_2 \qquad (2.56b)$$

is non-compartmental because $|a_{11}|$ is less than a_{21}. On the other hand, the model considered in Examples 2.3 to 2.5 is compartmental, as it satisfies both of the above requirements. For this system,

$$a_{11} = -2, \quad a_{21} = k_{21} = 2 \quad \text{so} \quad k_{01} = -a_{21} - a_{11} = 0$$

and $\qquad a_{22} = -3, \quad a_{12} = k_{12} = 1 \quad \text{so} \quad k_{02} = -a_{12} - a_{22} = 2.$

The form of $\mathbf{A}$ for a compartmental system imposes some restrictions on the form of the dynamic responses. Firstly, the transition matrix $e^{\mathbf{A}t}$ is non-negative for all t (Bellman, 1960, p. 172). The essence of the proof is to take the largest-magnitude element on the main diagonal, $\hat{a}_{jj}$, and to express $\mathbf{A}$ as

$$\mathbf{A} = \hat{a}_{jj}\mathbf{I} + \mathbf{R} \qquad (2.57)$$

where $\mathbf{R}$ contains only non-negative terms, by definition. Then

$$e^{\mathbf{A}t} = e^{(\hat{a}_{jj}\mathbf{I} + \mathbf{R})t}$$

$$= e^{\hat{a}_{jj}\mathbf{I}t} \cdot e^{\mathbf{R}t} \qquad (2.58)$$

the latter manipulation being possible because $\mathbf{I}$ commutes with any other matrix so that $\mathbf{IR} = \mathbf{RI}$. Although $\hat{a}_{jj}$ is negative, $e^{\hat{a}_{jj}\mathbf{I}t}$ is non-negative, being a diagonal matrix with all its principal diagonal terms non-negative. Since $\mathbf{R}$ has only non-negative elements, $e^{\mathbf{R}t}$ is also non-negative because there are only non-negative terms in the infinite series for $e^{\mathbf{R}t}$ (see eqn (2.42)). Thus, from eqn (2.58), $e^{\mathbf{A}t}$ is non-negative. For a compartmental system, all elements of $\mathbf{B}$ are non-negative, so that for a positive input vector $\mathbf{u}(t)$ and non-negative initial state $\mathbf{x}(0^-)$, *all the states of a compartmental system are non-negative*, from eqn (2.41).

Secondly, the eigenvalues of a compartmental system are real if, for all

cycles of r compartments within a system, a cycle being a series of interconnected compartments $\alpha \to \beta \to \gamma \to \ldots \to \rho \to \alpha$

$$k_{\alpha\beta}k_{\beta\gamma} \ldots k_{\rho\alpha} = k_{\beta\alpha}k_{\gamma\beta} \ldots k_{\alpha\rho} \qquad (2.59)$$

(Goldberg, 1956). This is a sufficient, rather than a necessary, condition for real eigenvalues so that if it does not hold, the eigenvalues may be real or complex.

One of the main implications of this result is that *for a two-compartment system, the eigenvalues must be real*, since $k_{12}k_{21} = k_{21}k_{12}$. This is also evident from the definition of the eigenvalues $|\lambda\mathbf{I} - \mathbf{A}| = 0$ giving

$$(\lambda - a_{11})(\lambda - a_{22}) - a_{12}a_{21} = 0 \qquad (2.60)$$

whence $\quad \lambda_1, \lambda_2 = \frac{1}{2}\{(a_{11} + a_{22}) \pm [(a_{11} - a_{22})^2 + 4a_{12}a_{21}]^{1/2}\} \qquad (2.61)$

Now, $(a_{11} - a_{22})^2 \geqslant 0$ and since $a_{12} = k_{12}$ and $a_{21} = k_{21}$, the product $a_{12}a_{21} \geqslant 0$ so the part under the square root sign in eqn (2.61) cannot be negative and the eigenvalues must be real.

The other main implication concerns two types of compartmental system of considerable practical interest—mammillary systems and catenary-connected systems (Sheppard and Householder, 1951). A mammillary system (Fig. 2.9) is one in which a central compartment (no. 1) is surrounded by $(p - 1)$ peripheral compartments which exchange material only with the central compartment and not with each other. A catenary-connected system (Fig. 2.10) is one in which the compartments are arranged in a chain, each
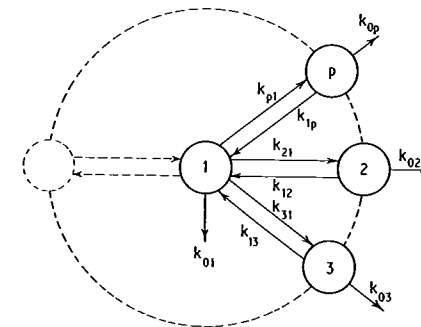

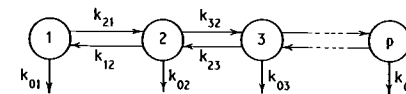**Figure 2.9** A mammillary compartmental system.

Figure 2.10 A catenary-connected compartmental system.

compartment exchanging material only with the immediately preceding and following compartments; in some applications, exchange is unidirectional. For both mammillary and catenary systems, the eigenvalues must be real because at least one pair of rate constants k_{ij} and k_{ji} must be zero, so that both sides of eqn (2.59) are zero. Hearon (1979) has shown that, for compartmental systems with real eigenvalues, in which $x(0^-) = 0$ and an impulsive input is introduced to compartment r at $t = 0$, the subsequent decay of $x_r(t)$ is monotonic, i.e.

$$\frac{dx_r}{dt} \leqslant 0, \qquad t > 0. \tag{2.62}$$

This result does not necessarily hold for systems with complex eigenvalues.

For systems in which three or more compartments are connected in a cycle for which eqn (2.59) does not hold, complex eigenvalues are possible. Because A is real, all complex eigenvalues must occur as complex conjugate pairs:

$$\lambda_m, \lambda_n = -\alpha \pm j\beta$$

where $j = \sqrt{-1}$, α is real and positive and β is real. These give rise to terms of the form $E e^{-\alpha t} \sin(\beta t + \phi)$ in the state responses $x(t)$. (Here, E and ϕ are constants.) However, such oscillatory terms are in practice heavily damped by the $e^{-\alpha t}$ term, and as we have seen above, no state response (compartmental quantity) may cross zero. A particular form of compartmental system giving rise to complex eigenvalues, the unilateral circulation system, will be considered in more detail in Chapter 4.

An experiment of practical interest in physiological applications is the washout test, in which a continuous infusion is made for a long time into one compartment until the system is in a steady state. The infusion is then withdrawn at $t = 0$, and the washout curves are the plots of $x(t)$ for $t > 0$. From eqn (2.41), the washout curves are given by

$$x(t) = e^{At} x(0^-) \tag{2.63}$$

where $x(0^-)$ are the compartmental quantities just before the infusion is withdrawn. Hearon (1968) has shown that for any compartmental system, including those with complex eigenvalues, all the washout curves decay monotonically to zero, i.e.

$$\frac{dx(t)}{dt} \leqslant 0, \qquad t > 0. \tag{2.64}$$

The most general form of B:

$$B = \begin{bmatrix} b_{11} & b_{12} & \dots & b_{1m} \\ \vdots & & & \\ b_{p1} & b_{p2} & \dots & b_{pm} \end{bmatrix}$$

allows for proportions of the same input to be introduced to more than one compartment. In almost all compartmental applications, each input is introduced to one compartment only, so that the off-diagonal elements of B are zero. The vector u in the general system eqn (2.30) is, for compartmental systems, a vector of input rates to the p compartments:

$$u = [u_1 \quad u_2 \dots u_p]^T.$$

For an impulsive input of magnitude D, for example, the input rate would be $D \cdot \delta(t)$, where $\delta(t)$ is the Dirac delta function, while for a step (constant continuous infusion) of magnitude k_i per unit time, the input rate would be k_i, $t > 0$.

For the diagonal form of B, which will be assumed in the remainder of this book, the product Bu is the vector

$$Bu = [b_1 u_1 \, b_2 u_2 \dots b_p u_p]^T \tag{2.65}$$

where $u_1 \dots u_p$ are the input rates to compartments 1 to p and $b_1 \dots b_p$ are the input gains, i.e. those fractions of the inputs administered which appear in the compartmental system. For most experimental situations, $b_1 = b_2 = \dots = b_p = 1$, but an important exception occurs in metabolic systems and pharmacokinetics when a substance is administered via an extravascular route. Then, some of the dose administered does not at any stage appear in the compartmental system; the fraction which does is called the bioavailability fraction and is often not known beforehand.

Similarly, the most general form of C:

$$C = \begin{bmatrix} c_{11} & c_{12} & \dots & c_{1p} \\ \vdots & & & \\ c_{n1} & c_{n2} & \dots & c_{np} \end{bmatrix}$$

allows for proportions of different states to be included in any one measurement. In most compartmental applications, each observation (measurement) is of one state only, so that Cx is a vector:

$$Cx = [c_1 x_1 \, c_2 x_2 \dots c_p x_p]^T. \tag{2.66}$$

An exception to this may occur when external scanning is being used; then,

the measurement of radioactivity may include a portion from more than one compartment. In the remainder of this book though $\mathbf{Cx}$ 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

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

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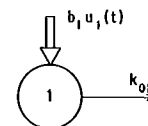
$$c_1 = \frac{1}{V_1} \tag{3.4}$$

Figure 3.1   One-compartment model.