Compartmental Models and Their Application

1 Introduction to Compartmental Modelling

1.1 What is a compartmental system?

Compartmental systems consist of a finite number of homogeneous, well-mixed, lumped subsystems, called compartments, which exchange with each other and with the environment so that the quantity or concentration of material within each compartment may be described by a first-order differential equation. A compartmental system may be used to model either the kinetics of one substance, in which case the compartments occupy different spaces and the inter-compartment transfers represent flow of material from one location to another, or the kinetics of two or more substances (such as a drug and its metabolites) in which case different compartments may occupy the same space and some of the inter-compartment transfers represent transformation from one substance to another.

In the literature, the words "compartment" and "pool" have, to a considerable extent, come to be interchangeable, although Atkins (1969) observes that, strictly speaking, there is a distinction between the two. He notes that Sprinson and Rittenberg (1949) defined a metabolic pool of an animal (or organ or cell) as "that mixture of compounds derived either from the diet or from the breakdown of the tissues, which the animal (or organ or cell) employs for the synthesis of tissue constituents." On the other hand, Atkins defines a compartment—a term first used in this context by Sheppard (1948)—as "a quantity of a substance which has a uniform and distinguishable kinetics of transformation or transport." With this distinction, a pool will often be distributed among many compartments, although when referring to plasma, the pool and compartment will usually be the same. In this book, the term compartment will be used, as defined above.

The most general form of compartmental equations (Sandberg, 1978) for a system with p compartments is:

$$\frac{dx_i}{dt} = f_{i0} + \sum_{\substack{j=1 \\ j \neq i}}^{p} f_{ij} - \sum_{\substack{j=1 \\ j \neq i}}^{p} f_{ji} - f_{0i}, \qquad i = 1, 2, \ldots, p \tag{1.1}$$

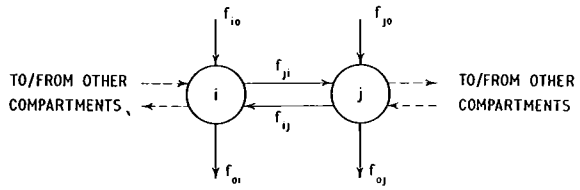

Figure 1.1 Two compartments of a general compartmental model, as described by eqn (1.1). Arrowed quantities are flow rates.

where x_i is the amount of material in compartment i (x_i can also be taken to represent concentration, but in this book it will be used for quantity); f_{ij} is the flow rate *to* compartment i *from* compartment j (note that in the pharmacokinetics literature, the order of the subscripts is reversed); and subscript 0 denotes the environment.

If the flow rates from all compartments to the environment are zero ($f_{0i} = 0, i = 1, 2, \ldots, p$), the system is said to be closed—otherwise it is open. Equation (1.1) is illustrated for two of the p compartments in Fig. 1.1.

We see that compartmental models are simply sets of constrained first-order differential equations, the constraints being the physical requirement that flow rates are non-negative. It is difficult to make progress with equations of as general a form as eqn (1.1) and most of the work reported to date has assumed a more specific form.

By far the biggest body of theory and applications has been concerned with linear, time-invariant compartmental models, for which the flow rates are directly proportional to the quantity in the donor compartment, the constant of proportionality being referred to as a rate constant. Equation (1.1) then simplifies to:

$$\frac{dx_i}{dt} = \sum_{\substack{j=1 \\ j \neq i}}^{p} k_{ij}x_j - \sum_{\substack{j=1 \\ j \neq i}}^{p} k_{ji}x_i - k_{0i}x_i + u_i(t), \qquad i = 1, 2, \ldots, p \tag{1.2}$$

where the input flow rate f_{i0} from the environment has been written as $u_i(t)$ to conform with the usual notation of linear systems theory. Note that in this model, the flow rate to compartment i from compartment j is $k_{ij}x_j$, i.e. directly proportional to the quantity (x_j) in the donor compartment but independent of the quantity (x_i) in the receptor compartment. Equation (1.2) is illustrated for two of the p compartments in Fig. 1.2.

Such a model is a gross simplification of the actual system being modelled, but it does seem to provide a good description of the responses of many systems when a small perturbation is made to a system previously in a steady state, for example to describe the kinetics of a labelled tracer added to a

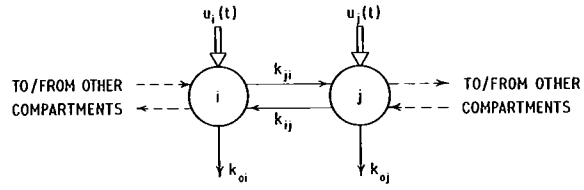

Figure 1.2 Two compartments of a linear, time-invariant compartmental model, as described by eqn (1.2). The k's are rate constants, so that flow rates are $k_{ij}x_j$, etc.; the inputs $u_i(t)$ and $u_j(t)$ are flow rates.

system. We will see in Chapters 3 and 4 that the responses of a linear, time-invariant compartmental system to an impulsive perturbation consist of sums of exponentials (usually with as many exponentials as compartments). It is interesting to note how often tracer response data from human beings and other animals approximate closely to this form, indicating that, over the range of values covered by the responses, a linear-dynamics model is reasonable.

To date, much less work has appeared on nonlinear systems, and it has concentrated on two forms of simplification of eqn (1.1). The first simplification is for systems where inter-compartment transfers, though nonlinear, are still donor-controlled. Such a system is still described by eqn (1.2), but some (or all) of the k_{ij} and k_{ji} are no longer constants, and so are referred to as rate coefficients. One frequently-occurring example describes capacity-limited (Michaelis–Menten) excretion of a drug from a compartment (i, say), when

$$\text{Excretion flow rate } f_{0i} = \frac{V_m}{K_m + x_i(t)}\, x_i(t) \tag{1.3}$$

where V_m is a constant having dimensions of (time)$^{-1}$ and K_m is a constant having the same units as $x_i(t)$. (This is an adaptation of the Michaelis–Menten form of enzyme kinetics; a good introduction will be found in Riggs (1963, Chapter 11).) For small values of $x_i(t)$ such that $K_m \gg x_i(t)$,

$$f_{0i} \simeq \frac{V_m}{K_m}\, x_i(t) \tag{1.4}$$

which is of first-order linear form, with $\frac{V_m}{K_m}$ replacing the rate constant k_{0i} in eqn (1.2). For large values of $x_i(t)$ such that $K_m \ll x_i(t)$,

$$f_{0i} \simeq V_m \tag{1.5}$$

which is constant. The elimination does not now depend on $x_i(t)$ and is usually referred to as zero-order elimination. The model is no longer linear; doubling the input will more than double the responses of the compartmental quantities.

The second form of simplification of eqn (1.1) is for systems where some of the inter-compartmental transfers are functions of two or more states (quantities or concentrations) of the system:

$$k_{ij} = k_{ij}(x_1, x_2, \ldots, x_p). \tag{1.6}$$

Such transfer occurs in chemical reaction kinetics (see Section 1.2). One particular example occurs when the rate coefficient is a function of the state of the receptor compartment, as well as that of the donor compartment:

$$k_{ij} = k_{ij}(x_i, x_j). \tag{1.7}$$

An example is discussed in Application Example 3 in Chapter 11.

Some work has also been reported recently on two further departures from the linear, time-invariant compartmental model of eqn (1.2), the first concerning time-varying models and the second, stochastic models. Most work reported to date on time-varying models has assumed what to the control engineer is a linear, time-varying model, that is, a model where the rate coefficients in eqn (1.2) vary with time, but are not functions of the states:

$$k_{ij} = k_{ij}(t). \tag{1.8}$$

In the biochemistry literature, such a model is often called nonlinear. Of particular interest are systems where some of the rate coefficients are periodic functions of time, for example

$$k_{ij}(t) = k_{ij}(1 + \gamma \sin \omega t) \tag{1.9}$$

where γ is a constant which must be less than one to preserve the non-negativity of the rate coefficient.

Stochastic models by contrast have some feature (or features) which vary *randomly* with time, and a substantial body of theory has been built up over the past few years concerning such systems. The theory may be classified into approaches where the rate coefficients are assumed stochastic and those where the number of particles of interest within a compartment is assumed stochastic (the rate coefficients being constant); some recent work has combined the two approaches. Time-varying models and stochastic models are discussed in Chapter 10.

1.2 Some processes described by first-order differential equations

Many processes can be described by first-order differential equations, and many such equations are compartmental in form, although often not described as such. A familiar example is the equation for radioactive decay:

$$\frac{dN}{dt} = -\lambda N \tag{1.10}$$

where $N(t)$ is the number of radioactive particles at time t and λ is a constant. This is compartmental since N is non-negative and λN is non-negative, $\frac{dN}{dt}$ being non-positive.

The diffusion of material across a membrane according to Fick's Law is also a first-order process. The material transfer takes place from regions of high concentration to those of low concentration along the line of the concentration gradient, and the flow of substance per unit area is proportional to the gradient. If the concentrations in two constant-volume compartments (volumes V_1 and V_2) are C_1 and C_2, then the mass transfer equations according to Fick's Law are:

$$V_1 \frac{dC_1}{dt} = k \cdot \frac{S}{X}(C_2 - C_1) \tag{1.11a}$$

$$V_2 \frac{dC_2}{dt} = k \cdot \frac{S}{X}(C_1 - C_2) \tag{1.11b}$$

where k is the coefficient of diffusion, S is the effective surface area between the compartments, and X is the effective separation between the compartments. If k, S and X are constants, eqns (1.11) are linear and time-invariant.

Another process in which first-order differential equations arise is a simple irreversible, single-stage chemical reaction whereby chemicals A and B react to give products. The change of mass, x_A, of A is described by the equation

$$\frac{dx_A}{dt} = -k_{\alpha+\beta} C_A^{\alpha} C_B^{\beta} \tag{1.12}$$

where C_A is the concentration of A; C_B is the concentration of B; α is the order of the reaction with respect to A; β is the order of the reaction with respect to B; $\alpha + \beta$ is the order of the reaction; $k_{\alpha+\beta}$ is a constant with dimensions dependent on $\alpha + \beta$.

For a first-order reaction ($\alpha + \beta = 1$) with A (only) reacting to give products

$$\frac{dx_A}{dt} = -k_1 C_A, \tag{1.13}$$

and if the reaction takes place in a vessel of constant volume,

$$\frac{dx_A}{dt} = -k x_A. \tag{1.14}$$

For a reversible first-order reaction

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \tag{1.15}$$

$$\frac{dx_A}{dt} = -k_1 x_A + k_2 x_B.$$

For a reaction of the form

$$A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C$$

the forward reaction is at rate $k_1 C_A C_B$ and the backward reaction is at rate $k_2 C_c$, so that

$$\frac{dC_A}{dt} = -k_1 C_A C_B + k_2 C_c \tag{1.16}$$

which is of nonlinear compartmental form, with the first term on the right-hand side dependent on two states. Many equations involving conservation of mass or energy are of compartmental form.

1.3 The origins of compartmental modelling

The fact that many first-order differential equations are compartmental without necessarily being described as such makes tracing the exact origins of compartmental models rather difficult. In the biological area, Atkins (1969) notes that, while radioactive tracers were first applied to biological systems as long ago as 1923, the majority of work on such systems up to the early 1940s was of a qualitative nature. During the 1940s, there was a trend towards treating data in a more quantitative manner, so that the use of differential equations (and, consequently, compartments) to describe the behaviour of tracers became increasingly important. The first good quantitative treatment was probably that of Zilversmit, Entenman and Fishler (1943), but the term

"compartment" was first introduced by Sheppard in 1948. A further significant early paper was that of Sheppard and Householder (1951) discussing the mathematical basis for interpreting tracer experiments.

The origins of pharmacokinetics are usually attributed to Teorell who published a systematic study of the kinetics of drugs introduced into the mammalian body via extravascular routes (1937a) and via intravascular routes (1937b). He gave four differential equations representing the transfer of material from the subcutaneous depot to the blood, elimination of drug from the blood to the urine, the exchange between blood and tissue, and tissue elimination. Teorell derived expressions for the quantity of drug in the subcutaneous depot (for the extravascular administration), in the blood and in the tissue and found that the last two were tri-exponential.

In a review of linear compartmental analysis in ecosystem modelling, O'Neill (1979) notes that linear, time-invariant compartmental modelling has played an important role in the development of systems ecology since its inception in the late 1950s, but models closely resembling compartmental models had appeared much earlier than this—certainly as early as 1935 in the atmospheric sciences.

These, then, seem to be the beginning of compartmental modelling in the three main applications areas. In Section 1.4, the present-day role of compartmental modelling will be assessed.

1.4 The role of compartmental modelling

Compartmental modelling has been and is being used widely in biomedicine (particularly in the modelling of metabolic processes), in pharmacokinetics and in ecosystem modelling.

In modelling metabolic system dynamics, compartmental modelling is the most widely-used approach, although it is not universally applicable. Probably the best guide on when to consider using such a model is to return to the definition given at the beginning of this chapter and for experimenters to ask themselves whether the concept of homogeneous, well-stirred tanks is appropriate to their particular application. Two recent reviews have given guidelines on when it is appropriate to model metabolic systems using compartments (Carson, Cobelli and Finkelstein, 1981; Carson, Godfrey and Reeve, 1982). In some instances, it is appropriate to model only part of a system with compartments; for example, models of the role of insulin in the regulation of blood glucose level (Carson, Godfrey and Reeve, 1982, Section 1.4.3) have equations of compartmental form in the forward path, with a non-compartmental feedback control mechanism incorporated into the overall model. Carson, Cobelli and Finkelstein (1981) note that where a

compartmental structure is not well-defined, or where experimental data are insufficient for its identification, it may be more appropriate to adopt a non-compartmental approach, focusing on overall input–output relationships, especially at the level of the whole organism; several examples are cited.

Compartmental models have also been used elsewhere in biomedicine, for example, to model gas exchange in lungs, where, with modern measuring devices, it is now possible to verify such models by externally scanning radioactivity in the lungs. Examples of such modelling are given by Bajzer and Nosil (1977) and Bache, Gray and Murray-Smith (1981). External scanning has also featured in the modelling of metabolic systems—see Application Example 2 in Chapter 11.

In pharmacokinetics, it is rare for compartments to be assigned a physiological label. For linear modelling, the model is tailored to the observations, the number of compartments of an open model being made equal to the number of observed exponentials. This approach is often referred to as "black-box" modelling. If the drug in plasma concentration-time curve has two exponentials, the two compartments are called the central compartment and the peripheral compartment. If there are three exponentials, a form of model is assumed with a central compartment exchanging with a shallow peripheral compartment and a deep peripheral compartment; the peripheral compartments do not exchange directly with each other. The adjectives "shallow" and "deep" reflect fast and slow exchange with the central compartment and the only physiology in the model is that the central compartment contains the systemic plasma.

With no assumption of physiological significance for the compartments, the purpose of a linear compartmental model describing the time course of drug in plasma (or urine) becomes difficult to define. The lack of relevance of such models has been commented upon by experts in the pharmacokinetics field (see, for example, Wagner, 1975). As noted above, an approach focusing on overall input–output relationships seems preferable (provided, of course, that the resulting model is as economical a description as the compartmental alternative). Such a relationship in this case would be the fitting of exponentials (or the corresponding Laplace transfer function) to the responses of compartmental quantities to impulse or step perturbation. Going further, some pharmacokinetic quantities of interest, such as the area under the curve (AUC) and, following oral administration, peak concentration (C_{max}) and time to peak (T_{max}) do not even require the fitting of exponentials and can be found from a plot of concentration v. time.

Linear compartmental models are useful in pharmacokinetics in the simultaneous description of the kinetics of a drug and its metabolites. A metabolite is a substance formed from a drug by biotransformation (usually mainly in the liver) and is of considerable importance in that, while it may

occasionally have the same therapeutic effect as the drug, it quite often produces side-effects which can limit the quantity of drug administered, particularly orally. A multi-species example, with two compartments each for the drug and its metabolites (Boxenbaum and Riegelman, 1976) is discussed in Application Example 4 in Chapter 11.

In most pharmacokinetics trials, drugs are administered in therapeutic quantities rather than minute (trace) quantities; so that some nonlinear effects might be expected (Wagner, 1973b). Although, as noted above, linear compartmental models do not seem necessary for describing the time course of drugs alone, modelling nonlinear drug kinetics within a compartmental framework proves particularly useful. Much of the work hitherto reported has been on systems with Michaelis–Menten elimination kinetics (Wagner, 1973a). Wagner (1973b) has given examples from the literature to suggest that the elimination pathways (both hepatic and renal) for many drugs are very liable to become saturated. The importance of recognizing capacity-limited elimination cannot be overemphasized. Pharmacokinetics measured following a single administration may appear linear but if a multiple-dosing regimen is then designed on the basis of linear (first-order) elimination, it can lead to a considerable build-up of drug in the body if the elimination pathway becomes saturated at higher drug levels. This has been graphically illustrated in simulation results by Wagner (1978), while Garrettson and Jusko (1975) quote an example of children overdosed with diphenylhydantoin which led these authors to fit Michaelis–Menten kinetics to the subsequent decline in drug concentration in the children.

The first application describing fitting Michaelis–Menten elimination kinetics to a single concentration-time curve seems to be that of Lundquist and Wolthers (1958) concerning alcohol elimination. The recent impetus towards nonlinear modelling in pharmacokinetics has been fostered by the publication of a single journal (*Journal of Pharmacokinetics and Biopharmaceutics*) which contains a high proportion of the good-quality papers on mathematical modelling in pharmacokinetics.

A further recent development involving compartmental models in the pharmacokinetics area concerns the simultaneous measurement of drug concentration in venous plasma (pharmacokinetics) and the pharmacological response (pharmacodynamics). The pharmacodynamics are traditionally modelled as a nonlinear function of the drug concentration at the receptor site, but this gives rise to two problems. Firstly exactly what form of nonlinear function should be used, and secondly, how should the concentration at the receptor site be related to the (measured) concentration in the central compartment and/or the (unmeasured) concentration in the peripheral compartment of the model describing the pharmacokinetics? Recent work in this area will be discussed in Application Example 7 in Chapter 11.