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2004 Phys. Med. Biol. 49 4657

(http://iopscience.iop.org/0031-9155/49/19/014)

INSTITUTE OF PHYSICS PUBLISHING PHYSICS IN MEDICINE AND BIOLOGY

Phys. Med. Biol. **49** (2004) 4657–4676 PII: S0031-9155(04)73687-8

On the use of pharmacokinetic models

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Received 16 December 2003
Published 20 September 2004
Online at stacks.iop.org/PMB/49/4657
doi:10.1088/0031-9155/49/19/014

Abstract

Extensive use of models in pharmacology, in physiology and in radiotherapy raises some questions on the nature and utility of models in general and of compartmental models in particular. In this paper I will define in a simple and logical way a set of useful pharmacokinetic parameters and show how their estimation depends on the assumed model. A special problem arises when some parameters are not identifiable; in that case I will show how it is possible to determine a range for them. Two examples are used to illustrate how to compute the value of the identifiable parameters and the range of the non-identifiable ones, when the available experimental data are not sufficient to identify a model.

1. Introduction

Pharmacokinetics is the study of the adsorption, distribution, metabolism and elimination of exogenous substances. These processes are described by means of a number of parameters, among which are clearance, turnover time and volume of distribution. Other parameters, such as permanence time and exit time, are not frequently used, and some of the used parameters, such as volume of distribution at steady state, are often presented with strict limitations as to model specification, for instance with the assumption of elimination only from the central compartment. It is not surprising to find confusion surrounding the use of these parameters, given the lack of agreement on how to calculate them and how to interpret the outcome of those calculations (Hearon 1963, Bergner 1966, Rescigno and Segre 1966, Berman 1971, Jacquez 1972, Gùrpide 1975, Rescigno 2003).

In this paper I will show how to define in a simple and logical way a set of useful pharmacokinetic parameters, and how their estimation depends upon the assumed model. The approach will be through a compartmental model, with one or two compartments, as well as with a general n-compartmental model.

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A non-compartmental approach is also possible, but the outcome of this last approach is of course highly dependent on some other hypotheses regarding the system under observation. I will also show with two examples how the experimental data can be used to get the maximum possible information compatible with the chosen model.

2. Compartments

2.1. Definition of compartment

The first author to use the term *compartment* was probably Sheppard (1948): "There are numerous instances in biological and chemical research where multiple compartment systems are encountered. This is undoubtedly true in other fields as well. In such a system, real compartments may exist whose contents are homogeneous and which are separated from one another by real boundaries. However, the concept may be generalized so that a substance, such as a chemical element, can be considered to be in a different compartment when it is in a different state of chemical combination."

Sheppard and Householder (1951) later made this concept more precise: "In isotope studies compartments may be regions of space in which the absolute specific activity . . . is uniform."

Gùrpide (1975) suggested the use of the term *pool* instead of compartment, "to avoid the purely spatial implication that might be assigned to the latter term"; despite its evident merits, this suggestion has not generally been followed.

For a more detailed introduction to the concepts of compartmental analysis see the paper 'The rise and fall of compartmental analysis' (Rescigno 2001).

For all practical purposes, it is convenient to use the operational definition (Rescigno and Beck 1972): "A variable $x(t)$ of a system is called a compartment if it is governed by a differential equation of the type

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -Kx(t) + r(t), \tag{1}$$

with K constant." The constant K may be the rate of radioactive disintegration, or the rate of elimination of a drug, or the probability of a particle passing from its present state to other possible states. In some cases that equation may be arrived at by observing the behaviour of an experimental system, in other cases by induction, but always it must be accepted only if the hypotheses incorporated into the model equations are eventually confirmed by the experimental observations (Bergner 1962, Zierler 1981, Rescigno and Beck 1987).

Of course other definitions are possible, and have been used; sometimes one talks about a 'nonlinear compartment', or its special case 'Michaelis-Menten compartment', meaning a variable $x(t)$ governed by a nonlinear differential equation. Since nonlinear differential equations are not easily tractable and there are no general solutions for them, I will limit the discussion to compartments as defined operationally by equation (1).

2.2. Solution of the compartmental equation

Observe that equation (1) is simply a conservation equation, i.e., it states that the variation $\mathrm{d}x/\mathrm{d}t$ of the quantity $x(t)$ present in the compartment is the difference between its rate of entry $r(t)$ and its rate of exit. Furthermore a fundamental hypothesis is declared by equation (1), that the rate of exit of the substance from the compartment is proportional to the amount present; this implies that the process causing this exit is a process of order one.

Usually we cannot measure the amount of substance in an organ, but only its concentration, therefore sometimes it may be convenient to transform equation (1) by dividing both sides by V, the volume of the compartment, to get

$$\frac{\mathrm{d}c}{\mathrm{d}t} = -Kc(t) + \frac{r(t)}{V}, \tag{2}$$

where $c(t) = x(t)/V$ is the concentration of the substance in the compartment. From a physical point of view, there is an important difference between equations (1) and (2); in fact this last one cannot be viewed as a conservation equation, because the concentration is not a conserved quantity; besides, $r(t)/V$ has the somewhat unusual dimension $[L^{-3}MT^{-1}]$, not a flow rate. Nevertheless from a mathematical point of view equations (1) and (2) are formally identical, and any solution of equation (1) can become a solution of equation (2) by substituting $c(t)$ for $x(t)$ and $r(t)/V$ for $r(t)$.

If we multiply and divide the first term of the right-hand side of equation (1) by V we get

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -VKc(t) + r(t). \tag{3}$$

This form of the one-compartment equation may seem awkward, because it mixes amount and concentration in the same equation, but it is interesting from two points of view; first, it shows that the quantity $x(t)$ is conserved, second it shows that the quantity eliminated per unit time is the product of two quantities, one intensive, $c(t)$, the other extensive, VK, as in all fundamental equations of physics. Now this last quantity is *clearance*, *Cl*, and equation (3) leads to a very interesting conclusion, as I will show later.

The integral of equation (1) is

$$x(t) = \mathrm{e}^{-Kt}\left(x(0) + \int_0^t \mathrm{e}^{K\tau} r(\tau)\,\mathrm{d}\tau\right), \tag{4}$$

where $x(0)$ is the amount of substance present in the compartment at the initial time. Expression (4) is useful only when $r(t)$ has a very simple form, as shown in the first two cases described below.

2.2.1. No recirculation, single-bolus administration. If the substance is administered as a single bolus at time $t = 0$ and there is no recirculation, then $r(t) \equiv 0$ and the integral of equation (1) becomes

$$x(t) = x(0)\,\mathrm{e}^{-Kt}, \tag{5}$$

where $x(0)$ is the amount of substance administered as a bolus. Expression (5) can be transformed logarithmically into

$$\log(x(t)) = \log(x(0)) - Kt,$$

showing that $\log(x(t))$ is a linear functions of t.

From a plot of $\log(x(t))$ versus t we can determine the value of K.

2.2.2. No recirculation, constant infusion. If the substance is administered by constant infusion and there is no recirculation, then $r(t) \equiv r \equiv$ constant, and the integral of equation (1) becomes

$$x(t) = r\,\mathrm{e}^{-Kt}\int_0^t \mathrm{e}^{K\tau}\,\mathrm{d}\tau = \frac{r}{K}(1 - \mathrm{e}^{-Kt}).$$

Observe that

$$\lim_{t\to\infty} x(t) = \frac{r}{K},$$

therefore

$$\lim_{t\to\infty} x(t) - x(t) = \frac{r}{K}\,\mathrm{e}^{-Kt},$$

and again a logarithmic transformation shows that $\log(\lim_{t\to\infty} x(t) - x(t))$ is a linear function of t.

In this case, too, we can determine the value of K from a plot of $\log(x(\infty) - x(t))$ versus t.

2.2.3. Single-bolus administration, recirculation possible. This is an important case where we cannot use expression (4) because function $r(t)$ is generally unknown, but we can get some information using directly equation (1).

Let us perform a thought experiment. We feed the compartment with an infusion at a constant flow rate; after a sufficiently long time, a steady state x_{ss} is reached when the rate of infusion plus the rate of recirculation is equal to the rate of elimination Kx_{ss}; we can write

$$\frac{\text{amount of drug present}}{\text{rate of elimination}} = \frac{x_{ss}}{Kx_{ss}} = \frac{1}{K},$$

but the ratio between the amount present and its rate of elimination is the time elapsed for eliminating an amount of substance equal to the amount present; this time does not depend on r, and it is called the *turnover time* of the compartment; its inverse K is the *turnover rate*.

In an actual experiment, we can measure $x(t)$ and $\mathrm{d}x/\mathrm{d}t$ at a number of time intervals after a bolus administration; even if function $r(t)$ is unknown, we can certainly say that $\lim_{t\to 0} r(t) = 0$, therefore from equation (1) we get

$$\lim_{t\to 0} \frac{-\mathrm{d}x/\mathrm{d}t}{x(t)} = K$$

and from a number of experimental values of $-\mathrm{d}x/\mathrm{d}t$ divided by $x(t)$ we can extrapolate the value of K, the turnover rate.

2.3. Initial volume of distribution

If the concentration of a compartment is uniform, the volume of that compartment is the ratio between the amount of substance present and its concentration.

Consider a simple pharmacokinetic experiment. If a substance is injected as a bolus in a compartment at time $t = 0$, call D the amount of substance administered and $c(t)$ its concentration there at time t. If we ignore the short interval of time necessary for the substance to distribute uniformly in the compartment, then by extrapolation for $t \to 0$ we get an approximate value of the concentration in the compartment if the mixing were instantaneous. Call $c^*(0)$ this extrapolated value; the ratio $D/c^*(0)$ is called *initial volume of distribution* (see figure 1).

Several observations are necessary at this point. The ratio

$$V = \frac{D}{c^*(0)} \tag{6}$$

is not necessarily the physical volume of the compartment, even though it has the dimension of a volume. There may be several reasons for this discrepancy; for instance, the substance may be bound to some other organs before being distributed in the sampled organ, or the mixing may never be complete. The initial volume of distribution, as defined by expression (6), cannot be considered an absolute pharmacokinetic parameter (Rescigno 1997) because its value depends on the hypotheses of rapid and complete mixing, only rarely satisfied, and upon the site of sampling. Nevertheless if, when repeating the experiment with a different

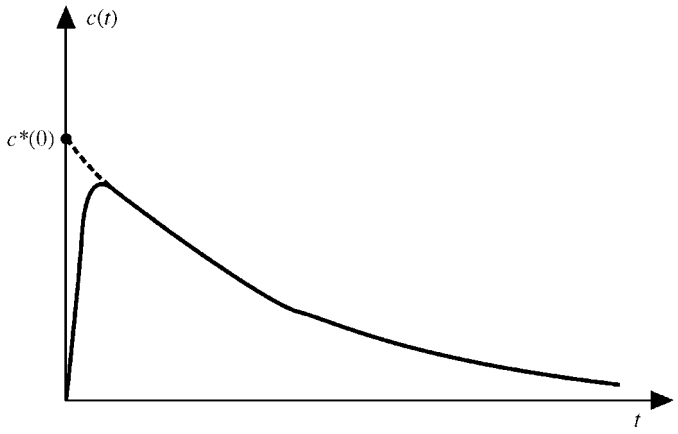

Figure 1. Determination of the initial volume of distribution.

dose D, the concentration $c(t)$ changes in the same proportion, then the ratio in (6) does not change, and we can say that the quantity V is an *invariant*, i.e., it is constant under some changes of the defining quantities D and $c^*(t)$ within certain limits. It can thus be used to predict the values of function $c(t)$ under different administration regimens.

2.4. Two-compartment model

For simplicity we consider two compartments with a single-bolus administration in compartment one only. The equations are

$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = -K_1x_1 + k_{21}x_2, \qquad \frac{\mathrm{d}x_2}{\mathrm{d}t} = +k_{12}x_1 - K_2x_2 \tag{7}$$

with the initial conditions

$$x_1(0) = D, \qquad x_2(0) = 0.$$

In those equations K_1 and K_2 are the turnover rates of compartments 1 and 2, respectively, while k_{12} and k_{21} are the *fractional transfer rates* from compartment 1 to compartment 2, and vice versa, respectively. For the conservation of matter, they must necessarily be

$$0 \leqslant k_{12} \leqslant K_1, \qquad 0 \leqslant k_{21} \leqslant K_2. \tag{8}$$

The integrals of the above differential equations are

$$x_1(t) = \frac{x_0}{\beta - \alpha}[(K_2 - \alpha)\,\mathrm{e}^{-\alpha t} + (\beta - K_2)\,\mathrm{e}^{-\beta t}], \qquad x_2(t) = \frac{x_0 k_{12}}{\beta - \alpha}[\mathrm{e}^{-\alpha t} - \mathrm{e}^{-\beta t}]$$

where α and β are the roots of the ordinary equation

$$x^2 + (K_1 + K_2)x + K_1K_2 - k_{12}k_{21} = 0,$$

provided $\alpha \neq \beta$, which is always true if both k_{12} and k_{21} are not zero.

In the special case $k_{12} = 0$, the substance cannot reach the second compartment, therefore

$$x_1(t) = D\,\mathrm{e}^{-K_1t}, \qquad x_2(t) \equiv 0.$$

In the other special case $k_{21} = 0$, the substance cannot return from compartment 2 to compartment 1 and the differential equations become

$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = -K_1x_1, \qquad \frac{\mathrm{d}x_2}{\mathrm{d}t} = +k_{12}x_1 - K_2x_2$$

whose integrals are

$$x_1(t) = D\,\mathrm{e}^{-K_1 t}, \qquad x_2(t) = \frac{Dk_{12}}{K_2 - K_1}[\mathrm{e}^{-K_1 t} - \mathrm{e}^{-K_2 t}]$$

provided $K_1 \neq K_2$. In the special sub-case $K_1 = K_2$, the integrals are

$$x_1(t) = D\,\mathrm{e}^{-K_1 t}, \qquad x_2(t) = Dk_{12} t\,\mathrm{e}^{-K_1 t}.$$

Returning to the general case, instead of solving the differential equations (7) we integrate all their terms from zero to infinity;

$$x_1(\infty) - x_1(0) = -\int_0^\infty K_1 x_1(t)\,\mathrm{d}t + \int_0^\infty k_{21} x_2(t)\,\mathrm{d}t$$

$$x_2(\infty) - x_2(0) = +\int_0^\infty k_{12} x_1(t)\,\mathrm{d}t - \int_0^\infty K_2 x_2(t)\,\mathrm{d}t.$$

If the system is open, i.e., if no substance will remain in the compartments after a sufficiently long time, then $x_1(\infty) = x_2(\infty) = 0$; using the initial conditions and exporting the constants from the integrals,

$$K_1 \int_0^\infty x_1(t)\,\mathrm{d}t - k_{21} \int_0^\infty x_2(t)\,\mathrm{d}t = D, \qquad k_{12} \int_0^\infty x_1(t)\,\mathrm{d}t - K_2 \int_0^\infty x_2(t)\,\mathrm{d}t = 0.$$

Those are ordinary linear equations in the two quantities $\int_0^\infty x_1(t)\,\mathrm{d}t$ and $\int_0^\infty x_2(t)\,\mathrm{d}t$; the solution is

$$\int_0^\infty x_1(t)\,\mathrm{d}t = \frac{DK_2}{K_1K_2 - k_{12}k_{21}}, \qquad \int_0^\infty x_2(t)\,\mathrm{d}t = \frac{Dk_{12}}{K_1K_2 - k_{12}k_{21}}$$

or, with some elementary transformations,

$$\frac{1}{D}\int_0^\infty x_1(t)\,\mathrm{d}t = \frac{1}{K_1}\frac{1}{1-\gamma}, \qquad \frac{1}{D}\int_0^\infty x_2(t)\,\mathrm{d}t = \frac{k_{12}}{K_1}\frac{1}{K_2}\frac{1}{1-\gamma} \tag{9}$$

where

$$\gamma = \frac{k_{12}k_{21}}{K_1K_2}.$$

Observe that k_{12}/K_1 is the fraction of substance leaving compartment 1 that enters compartment 2, while k_{21}/K_2 is the fraction of substance leaving compartment 2 that enters compartment 1, therefore γ is the fraction of substance recirculated. If there is no recirculation, γ is zero, and in that case

$$\frac{1}{D}\int_0^\infty x_1(t)\,\mathrm{d}t = \frac{1}{K_1},$$

where $1/K_1$ is the time spent by the substance in compartment 1, i.e., its turnover time. If there is recirculation, we can write

$$\frac{1}{1-\gamma} = 1 + \gamma + \gamma^2 + \gamma^3 + \cdots,$$

i.e., one plus the fraction of substance going a second time through the compartment, plus the fraction going through it a third time, and so forth; this expression is equal to the average number of times the substance goes through the compartment; we shall call it the *turnover number*. By multiplying the turnover time $1/K_1$ by the turnover number we get the time spent by the substance in all its passages through the compartment; we will call it the *permanence time*.

Thus the first of expressions (9) can be written as

$$\frac{1}{D}\int_0^\infty x_1\,\mathrm{d}t = \text{turnover number} \times \text{turnover time} = \text{permanence time}.$$

The second of expressions (9) is the permanence time of the second compartment multiplied by the term k_{12}/K_1, i.e., the fraction of the amount of substance D that actually reaches the second compartment. If we call this last quantity the *yield from compartment* 1 *to compartment* 2 we can write

$$\frac{1}{D}\int_0^\infty x_2\,\mathrm{d}t = \text{yield} \times \text{turnover number} \times \text{turnover time} = \text{residence time}.$$

2.5. Multi-compartment models

The results of this last section can be generalized to a system of an unspecified number of compartments.

Observe that $K_i x_i(t)$ is the amount of substance leaving compartment i per unit time, while $K_i x_i(t)\,\mathrm{d}t$ is the amount of substance leaving compartment i in the interval from t to $t + \mathrm{d}t$, therefore the integral from 0 to ∞ of this last quantity is the total amount of substance leaving compartment i at any time. If we divide this integral by the amount of substance D initially given to this compartment we have the average number of times the substance goes through the compartment, i.e., its turnover number,

$$\frac{\int_0^\infty K_i x_i(t)\,\mathrm{d}t}{D} = \nu_i.$$

The numerator of the above expression cannot be computed, but by exporting the turnover rate K_i we get

$$\frac{1}{D}\int_0^\infty x_i(t)\,\mathrm{d}t = \frac{\nu_i}{K_i} = T_i,$$

i.e., the permanence time, interval of time spent by the substance in all its passages through the compartment.

3. Exit time

Consider now the ratio

$$\frac{\int_0^\infty t\,K_i x_i(t)\,\mathrm{d}t}{\int_0^\infty K_i x_i(t)\,\mathrm{d}t}.$$

In the integral at the numerator there is the amount of substance leaving compartment i in the interval from t to $t + \mathrm{d}t$ times the instant t of this event; the ratio of the two integrals is therefore the average time when the substance leaves the compartment; we call it *exit time* from compartment i, Ω_i. Dividing numerator and denominator by the turnover rate and by the volume of the compartment V_i (Rescigno and Gùrpide 1973)

$$\Omega_i = \frac{\int_0^\infty t\,x_i(t)\,\mathrm{d}t}{\int_0^\infty x_i(t)\,\mathrm{d}t} = \frac{\int_0^\infty t\,c_i(t)\,\mathrm{d}t}{\int_0^\infty c_i(t)\,\mathrm{d}t}. \tag{10}$$

Observe that Ω_i is not the interval of time spent by the substance in the system, as stated by some authors, except in the very restrictive case when the measured substance is eliminated only from the sampled compartment; it is rather the time when the measured substance leaves

the sampled compartment for the last time. Furthermore it is very important to remember that when making the simplification

$$\frac{\int_0^\infty t K_i x_i(t)\,\mathrm{d}t}{\int_0^\infty K_i x_i(t)\,\mathrm{d}t} = \frac{\int_0^\infty t x_i(t)\,\mathrm{d}t}{\int_0^\infty x_i(t)\,\mathrm{d}t} \tag{11}$$

we assume that K_i is a constant, i.e., that it does not depend upon $x_i(t)$ and t. If this is not the case, equality (11) ceases to be valid.

3.1. Consequences of non-homogeneity

If a system is not homogeneous it cannot be described as a compartment; in equation (1) the coefficient K is not a constant and the simplification shown in identity (11) is not valid any more; in that case the ratio (10) cannot be called 'exit time'.

This fact becomes more apparent with a simple example. Consider a pool formed by just two compartments, say i and j and call $x_i(t)$ and $x_j(t)$ the amount of substance in those two compartments, with

$$x_i(t) + x_j(t) = x(t).$$

The correct exit time from the two separate compartments is given by

$$\Omega_i = \frac{\int_0^\infty t k_{io} x_i(t)\,\mathrm{d}t}{\int_0^\infty k_{io} x_i(t)\,\mathrm{d}t} = \frac{\int_0^\infty t x_i(t)\,\mathrm{d}t}{\int_0^\infty x_i(t)\,\mathrm{d}t}, \qquad \Omega_j = \frac{\int_0^\infty t k_{jo} x_j(t)\,\mathrm{d}t}{\int_0^\infty k_{jo} x_j(t)\,\mathrm{d}t} = \frac{\int_0^\infty t x_j(t)\,\mathrm{d}t}{\int_0^\infty x_j(t)\,\mathrm{d}t}$$

and from the pool of the two compartments by

$$\Omega_{i,j} = \frac{\int_0^\infty t\,(k_{io} x_i(t) + k_{jo} x_j(t))\,\mathrm{d}t}{\int_0^\infty (k_{io} x_i(t) + k_{jo} x_j(t))\,\mathrm{d}t},$$

where k_{io} and k_{jo} are the respective fractional rates of exit of the substance from the two compartments out of the pool. The rates k_{io} and k_{jo} are generally unknown, together with the separate values of $x_i(t)$ and $x_j(t)$, therefore we cannot compute any of the three quantities $\Omega_{i,j}$, Ω_i, Ω_j; we can only compute the quantity

$$\Omega^*_{i,j} = \frac{\int_0^\infty t x(t)\,\mathrm{d}t}{\int_0^\infty x(t)\,\mathrm{d}t} = \frac{\int_0^\infty t\,(x_i(t) + x_j(t))\,\mathrm{d}t}{\int_0^\infty (x_i(t) + x_j(t))\,\mathrm{d}t}$$

and call it the *apparent* exit time from the pool of compartments i and j.

By simple arithmetic manipulation we can show that

$$\mathrm{Min}(\Omega_i, \Omega_j) \leqslant \Omega_{i,j} \leqslant \mathrm{Max}(\Omega_i, \Omega_j), \qquad \mathrm{Min}(\Omega_i, \Omega_j) \leqslant \Omega^*_{i,j} \leqslant \mathrm{Max}(\Omega_i, \Omega_j)$$

where $\mathrm{Min}(\Omega_i, \Omega_j)$ and $\mathrm{Max}(\Omega_i, \Omega_j)$ mean the smaller and the larger of the quantities in parenthesis, respectively.

If we now compute the difference between the true and the apparent exit time from the pool, after some simplifications we find

$$\Omega_{i,j} - \Omega^*_{i.j} = (k_{io} - k_{jo}) \left(\int_0^\infty t x_j(t)\,\mathrm{d}t \int_0^\infty x_i(t)\,\mathrm{d}t - \int_0^\infty t x_i(t)\,\mathrm{d}t \int_0^\infty x_j(t)\,\mathrm{d}t \right)$$

therefore the apparent exit time and the true exit time coincide when the two compartments have the same exit time or the same fractional rate of exit. When this is not the case, the true exit time will be larger than the apparent one when the compartment with the larger exit time has the smaller fractional rate of exit, and vice versa.

In conclusion, without any hypothesis on the compartmentalization of a system, we can only say that the ratio in (10) is an approximation of the exit time, and the approximation depends on the disuniformity of the concentration of the substance inside the system.

4. Steady-state volume of distribution

The *steady-state volume of distribution*, V_{ss}, is defined as the ratio between the total amount of observed substance inside the system, Q_{ss}, and its concentration, c_{ss}, in the sampling compartment,

$$V_{ss} = Q_{ss}/c_{ss}.$$

The ratio between the steady-state volume and the initial volume of distribution is called the *dilution factor*, δ_i (Mordenti and Rescigno 1992)

$$\delta_i = V_{ss}/V_i.$$

The importance of the dilution factor is that it allows one to determine, albeit approximately, the amount of a substance present in an organism when only its concentration in a particular organ is measurable.

If only one compartment is present, obviously the steady-state volume coincides with the initial volume, and the dilution factor is 1. We shall examine separately the case of two compartments, of many compartments, and of a non-compartmentalized system.

4.1. Two compartments

We return now to the two-compartment model of section 2.4. In equations (7) K_1 and K_2 are the turnover rates of the two compartments, while k_{12} and k_{21} are the transfer rates from 1 to 2 and from 2 to 1, respectively. Those constants are called the *microparameters* of the system. We write the integral of those equations in the form

$$x_1(t) = a_{11}\,\mathrm{e}^{-\lambda_1 t} + a_{12}\,\mathrm{e}^{-\lambda_2 t}, \qquad x_2(t) = a_{21}\,\mathrm{e}^{-\lambda_1 t} + a_{22}\,\mathrm{e}^{-\lambda_2 t} \tag{12}$$

where the parameters λ_1, λ_2, a_{11}, a_{12}, a_{21}, a_{22} are called the *macroparameters* of the system. They are determined by the following equations:

$$\begin{aligned} &\lambda_1+\lambda_2 = K_1+K_2, && \lambda_1\lambda_2 = K_1K_2 - k_{12}k_{21}, && a_{11}+a_{12} = D,\\ &a_{11}\lambda_1 + a_{12}\lambda_2 = DK_1, && a_{21}+a_{22} = 0, && a_{21}\lambda_1 + a_{22}\lambda_2 = -Dk_{12}. \end{aligned} \tag{13}$$

If only compartment 1 has been sampled, i.e., if $x_1(t)$ is known but not $x_2(t)$, then we can determine the macroparameters λ_1, λ_2, a_{11}, a_{12}, and using the first four of equations (13) we can compute the microparameters K_1 and K_2 and the product $k_{12}k_{21}$, but not k_{12} and k_{21} separately. From those four equations we get

$$K_1 = \frac{a_{11}\lambda_1 + a_{12}\lambda_2}{a_{11}+a_{12}}, \qquad K_2 = \frac{a_{11}\lambda_2 + a_{12}\lambda_1}{a_{11}+a_{12}}, \qquad k_{12}k_{21} = \frac{a_{11}a_{12}(\lambda_1-\lambda_2)^2}{(a_{11}+a_{12})^2},$$

and using inequalities (8),

$$\frac{k_{12}k_{21}}{K_2} \leqslant k_{12} \leqslant K_1, \qquad \frac{k_{12}k_{21}}{K_1} \leqslant k_{21} \leqslant K_2,$$

thence

$$\begin{aligned} \frac{a_{11}a_{12}(\lambda_1-\lambda_2)^2}{(a_{11}+a_{12})\cdot(a_{11}\lambda_2+a_{12}\lambda_1)} &\leqslant k_{12} \leqslant \frac{a_{11}\lambda_1+a_{12}\lambda_2}{a_{11}+a_{12}},\\ \frac{a_{11}a_{12}(\lambda_1-\lambda_2)^2}{(a_{11}+a_{12})\cdot(a_{11}\lambda_1+a_{12}\lambda_2)} &\leqslant k_{21} \leqslant \frac{a_{11}\lambda_2+a_{12}\lambda_1}{a_{11}+a_{12}}. \end{aligned} \tag{14}$$

If the initial concentration, $c_1(0)$, of the substance in compartment 1 has been measured, then we can compute the volume, V_1 of that compartment,

$$V_1 = D/c_1(0).$$

Now suppose that the substance is fed continuously into compartment 1 at a constant rate r; when a steady state is reached, the differential equations become

$$-K_1x_1 + k_{21}x_2 = -r, \qquad +k_{12}x_1 - K_2x_2 = 0$$

and their solution is

$$x_1 = \frac{K_2 r}{K_1K_2 - k_{12}k_{21}}, \qquad x_2 = \frac{k_{12}r}{K_1K_2 - k_{12}k_{21}}.$$

Thus, at steady state we have

$$\frac{x_1 + x_2}{x_1} = \frac{K_2 + k_{12}}{K_2}$$

therefore

$$V_{ss} = \frac{x_1 + x_2}{x_1/V_1}, \qquad \delta = \frac{V_{ss}}{V_1} = \frac{K_2 + k_{12}}{K_2}.$$

Using inequalities (14) we can now write

$$\frac{(a_{11} + a_{12})\left(a_{11}\lambda_2^2 + a_{12}\lambda_1^2\right)}{(a_{11}\lambda_2 + a_{12}\lambda_1)^2} \leqslant \delta \leqslant \frac{(a_{11} + a_{12})(\lambda_1 + \lambda_2)}{a_{11}\lambda_2 + a_{12}\lambda_1}.$$

The above inequalities can also be written in the form

$$\frac{(a_{11} + a_{12})\left(\frac{a_{11}}{\lambda_1^2} + \frac{a_{12}}{\lambda_2^2}\right)}{\left(\frac{a_{11}}{\lambda_1} + \frac{a_{12}}{\lambda_2}\right)^2} \leqslant \delta \leqslant \frac{(a_{11} + a_{12})\left(\frac{1}{\lambda_1} + \frac{1}{\lambda_2}\right)}{\frac{a_{11}}{\lambda_1} + \frac{a_{12}}{\lambda_2}}$$

but,

$$a_{11} + a_{12} = x_1(0), \qquad \frac{a_{11}}{\lambda_1} + \frac{a_{12}}{\lambda_2} = \int_0^\infty x_1(t)\,\mathrm{d}t, \qquad \frac{a_{11}}{\lambda_1^2} + \frac{a_{12}}{\lambda_2^2} = \int_0^\infty t x_1(t)\,\mathrm{d}t$$

therefore,

$$\frac{\int_0^\infty t x_1(t)\,\mathrm{d}t \Big/ \int_0^\infty x_1(t)\,\mathrm{d}t}{\int_0^\infty x_1(t)\,\mathrm{d}t / x_1(0)} \leqslant \delta \leqslant \frac{1/\lambda_1 + 1/\lambda_2}{\int_0^\infty x_1(t)\,\mathrm{d}t / x_1(0)}.$$

Thus the minimum value of δ is the time of exit from compartment 1 divided by the permanence time in the same compartment; the maximum value of δ is the sum of the two time constants of the system divided by the permanence time in the first compartment.

The ratio of those two values is a measure of the uncertainty of our knowledge of the behaviour of the subject under investigation when the substance or tracer will be administered by continuous infusion or by repeated doses. The closer that ratio is to 1, the better we can estimate how much substance or tracer is present in the body for a particular steady-state systemic concentration.

4.2. Many compartments

Suppose that the substance or tracer is distributed among n compartments, but only one of them can be sampled, and that its concentration $c_1(t)$, after a bolus administration there at time $t = 0$, can be approximated reasonably well by a sum of exponential functions; then

$$\begin{aligned} c_1(t) &= A_1\,\mathrm{e}^{-\lambda_1 t} + A_2\,\mathrm{e}^{-\lambda_2 t} + \cdots + A_n\,\mathrm{e}^{-\lambda_n t} \\ &= \sum_{i=1}^{n} A_i\,\mathrm{e}^{-\lambda_i t}. \end{aligned}$$

In general, i.e., with elimination from any compartment, we can write (Mordenti and Rescigno 1992)

$$\delta = \frac{V_{ss}}{V_1} = \frac{\text{time spent in the organism}}{\text{time spent in the sampling compartment}}$$

or

$$\delta = \frac{V_{ss}}{V_1} = \frac{\text{time of exit from the organism}}{\text{permanence time in the sampling compartment}}.$$

The time spent in the sampling compartment is its permanence time, T_1; it is given by

$$T_1 = \frac{\int_0^\infty c_1(t)\,dt}{c_1(0)} = \frac{\sum_{i=1}^n \frac{A_i}{\lambda_i}}{\sum_{i=1}^n A_i}. \tag{15}$$

The time of exit from the sampling compartment is given by

$$\Omega_1 = \frac{\int_0^\infty t c_1(t)\,dt}{\int_0^\infty c_1(t)\,dt} = \frac{\sum_{i=1}^n \frac{A_i}{\lambda_i^2}}{\sum_{i=1}^n \frac{A_i}{\lambda_i}}. \tag{16}$$

The time spent in the organism is the time of exit, Ω_{system}; in general it cannot be calculated, but we can establish some boundaries to it. Its minimum value is obtained when the elimination happens only from the central compartment; therefore

$$\Omega_{system} \geqslant \Omega_1 = \frac{\sum_{i=1}^n \frac{A_i}{\lambda_i^2}}{\sum_{i=1}^n \frac{A_i}{\lambda_i}}. \tag{17}$$

Its maximum value is attained when the substance goes through all compartments once without recycling and is eliminated by the last one of them; in this case the time spent in each compartment is $1/\lambda_i$, therefore

$$\Omega_{system} \leqslant \sum_{i=1}^n \frac{1}{\lambda_i}. \tag{18}$$

By dividing the extreme values of the exit time by the permanence time,

$$\frac{\sum_{i=1}^n A_i \sum_{i=1}^n \frac{A_i}{\lambda_i^2}}{\left(\sum_{i=1}^n \frac{A_i}{\lambda_i}\right)^2} \leqslant \delta \leqslant \frac{\sum_{i=1}^n A_i \sum_{i=1}^n \frac{1}{\lambda_i}}{\sum_{i=1}^n \frac{A_i}{\lambda_i}}.$$

4.3. Non-compartmental systems

Without a detailed knowledge of the distribution of the substance inside the system under observation, we can only determine the permanence time and the exit time at the sampling site, provided the system is linear and state-determined; therefore, we can compute a lower bound for the dilution factor,

$$\delta \geqslant \frac{\Omega_1}{T_1} = \frac{c_1(0)\int_0^\infty t c_1(t)\,dt}{\left(\int_0^\infty c_1(t)\,dt\right)^2}.$$

A better approximation of δ is obtained by using the apparent exit time from the system instead of the exit time from the sampling compartment,

$$\delta \approx \frac{\Omega^*_{system}}{T_1} = \frac{c_1(0)\int_0^\infty t c_1(t)\,dt}{\int_0^\infty c_1(t)\,dt \int_0^\infty x(t)\,dt},$$

where $x(t)$ is the total amount of substance or tracer in the system.

5. Example of non-identifiable system

The following data are taken from a paper by Berman and Schoenfeld (1956) and elaborated by Mordenti and Rescigno (1992).

After a bolus intravenous injection of labelled material, the quantity of radioactivity in the blood was determined as a function of time; excreted radioactivity was also collected, and the accumulated amount of tracer in the excreta was obtained as a function of time. Since the tracer accumulated approached 100% of the amount of radioactivity initially injected, it was assumed that the initial quantity injected minus that in the measured compartment and in the collected excreta was equal to the amount of tracer in the remaining compartments of the system. The experimental curves were fitted to a sum of exponentials,

$$\frac{c_1(t)}{c_0} = \frac{3}{8}\,\mathrm{e}^{-3t} + \frac{1}{4}\,\mathrm{e}^{-2t} + \frac{3}{8}\,\mathrm{e}^{-t}, \qquad \frac{c_{\text{total}}(t)}{c_0} = \frac{1}{4}\,\mathrm{e}^{-2t} + \frac{3}{4}\,\mathrm{e}^{-t} \tag{19}$$

where c_0 is the amount of radioactivity injected, $c_1(t)$ is the amount measured in the blood at time t, and $c_{\text{total}}(t)$ the total activity in the body. For the purpose of this example the data have been rounded to make the following derivations more apparent; the timescale in these equations is arbitrary.

It is clear that the two functions (19) describe a three-compartment system. To such a system correspond three linear first-order differential equations containing nine microparameters (see section 4.1), but the experimental macroparameters contained in functions (19) are only seven, therefore this system is not completely identifiable.

The permanence time in the blood, though, can be computed exactly from (15),

$$T_1 = \frac{\frac{3/8}{3} + \frac{1/4}{2} + \frac{3/8}{1}}{3/8 + 1/4 + 3/8} = \frac{5}{8}.$$

The time of exit from the sampling compartment too can be computed exactly from (16),

$$\Omega_1 = \frac{\frac{3/8}{9} + \frac{1/4}{4} + \frac{3/8}{1}}{\frac{3/8}{3} + \frac{1/4}{2} + \frac{3/8}{1}} = \frac{23}{30}.$$

Without considering the data on c_t, we can compute a lower and an upper bound for the exit time, using (17) and (18),

$$\frac{\frac{3/8}{9} + \frac{1/4}{4} + \frac{3/8}{1}}{\frac{3/8}{3} + \frac{1/4}{2} + \frac{3/8}{1}} \leqslant \Omega_{\text{system}} \leqslant \frac{1}{3} + \frac{1}{2} + \frac{1}{1}, \qquad \frac{23}{30} \leqslant \Omega_{\text{system}} \leqslant \frac{11}{6},$$

then, dividing by the permanence time on the sampling compartment, we get, for the dilution factor,

$$\frac{92}{75} \leqslant \delta \leqslant \frac{44}{15}, \qquad 1.227 \leqslant \delta \leqslant 2.933,$$

a rather large interval.

Using the additional data for $c_{\text{total}}(t)$, we can compute a better approximation of δ; in fact, the apparent exit time from the system, Ω^*_{total}, can be computed from the given equations using (17),

$$\Omega^*_{\text{total}} = \frac{\frac{1/4}{4} + \frac{3/4}{1}}{\frac{1/4}{2} + \frac{3/4}{1}} = \frac{13}{14}$$

thence

$$\delta \approx \frac{13}{14} \cdot \frac{8}{5} = 1.49.$$

Table 1. Extreme values of some parameters of the compartmental system.

ε	η	k_{10}	k_{20}	k_{30}	Ω_{total}	δ
−0.09	−0.1875	1.25	0	1	2.149	1.536
0.5625	0.375	1.25	1	0.5	3.792	2.208

An even better approximation is obtained by using the separate values of Ω_1, Ω_2 and Ω_3 of the exit time from the three compartments of the system, as can be estimated from the data available.

From the experimental data shown, the transfer rates of this system can be determined with two degrees of freedom. Calling ε and η two arbitrary parameters, the rates of exit from the three compartments are

$$k_{10} = \frac{5}{4}, \qquad k_{20} = \frac{5}{4} + \frac{3}{16\eta} - \frac{\varepsilon}{2\eta}, \qquad k_{30} = \frac{5}{4} - \frac{\varepsilon}{2\eta}.$$

Similarly the disposition functions of the three compartments are

$$\frac{c_1(t)}{c_1(0)} = \frac{3}{8}\,\mathrm{e}^{-3t} + \frac{1}{4}\,\mathrm{e}^{-2t} + \frac{3}{8}\,\mathrm{e}^{-t} \qquad \frac{c_2(t)}{c_1(0)} = -\varepsilon\,\mathrm{e}^{-3t} + \eta\,\mathrm{e}^{-2t} + (\varepsilon - \eta)\,\mathrm{e}^{-t},$$

$$\frac{c_3(t)}{c_1(0)} = \left(\varepsilon - \frac{3}{8}\right)\mathrm{e}^{-3t} - \eta\,\mathrm{e}^{-2t} + \left(\frac{3}{8} - \varepsilon + \eta\right)\mathrm{e}^{-t}$$

and in operational form (Rescigno 2003)

$$\frac{\{c_1\}}{c_1(0)} = \frac{s^2 + 4s + \frac{15}{4}}{s^3 + 6s^2 + 11s + 6}$$

$$\frac{\{c_2\}}{c_1(0)} = \frac{(2\varepsilon - \eta)s + 4\varepsilon - 3\eta}{s^3 + 6s^2 + 11s + 6}$$

$$\frac{\{c_3\}}{c_1(0)} = \frac{\left(\frac{3}{4} - 3\varepsilon + \eta\right)s + \frac{3}{2} - 4\varepsilon + 3\eta}{s^3 + 6s^2 + 11s + 6}.$$

The permanence time of compartment 1 does not depend upon ε and η, as seen before.

The actual exit time Ω_t from the system will be the weighted average of the exit times from the three compartments, the weights being their respective rates of exit; therefore,

$$\Omega_{\text{total}} = \frac{k_{10}\Omega_1 + k_{20}\Omega_2 + k_{30}\Omega_3}{k_{10} + k_{20} + k_{30}}.$$

Table 1 shows the range of values of ε and η that give physically realizable solutions to this compartmental system, the corresponding extreme values of the parameters k_{10}, k_{20}, k_{30}, and the resulting values of Ω_{total} and δ.

6. The systems theoretical approach

6.1. Matrix equation

The compartmental equations can be written in the form

$$\frac{\mathrm{d}\mathbf{X}(t)}{\mathrm{d}t} = -\mathbf{X}(t) \cdot \mathbf{K} + \mathbf{R}(t) \tag{20}$$

where

$$\mathbf{X}(t) = (x_1(t) \quad x_2(t) \quad \cdots \quad x_n(t))$$

is the vector of the state variables $x_i(t)$ of the n compartments,

$$\mathbf{R}(t) = (r_1(t) \quad r_2(t) \quad \cdots \quad r_n(t))$$

is the vector of the feeding functions $r_i(t)$ of the compartments, and

$$\mathbf{K} = \begin{pmatrix} K_1 & -k_{12} & \cdots & -k_{1n} \\ -k_{21} & K_2 & \cdots & -k_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ -k_{n1} & -k_{n2} & \cdots & K_n \end{pmatrix}$$

is the matrix formed by the turnover rates K_i and by the transfer rates k_{ij}.

6.2. Integration of the matrix equation

The integral of this equation is

$$\mathbf{X}(t) = \left[\mathbf{X}(0) + \int_0^t \mathbf{R}(\tau)\exp(\tau\mathbf{K})\,\mathrm{d}\tau\right]\exp(-t\mathbf{K}), \tag{21}$$

where $\mathbf{X}(0)$ is the value of vector $\mathbf{X}(t)$ at time 0, and by definition,

$$\exp(-t\mathbf{K}) = \sum_{l=0}^{\infty} \frac{(-t\mathbf{K})^l}{l!}.$$

Without any loss of generality we can put

$$\mathbf{X}(0) = \mathbf{0}$$

by redefining the state variables and the feeding functions; equation (21) becomes

$$\mathbf{X}(t) = \int_0^t \mathbf{R}(\tau)\exp(-[t-\tau]\mathbf{K})\,\mathrm{d}\tau,$$

or, with a more concise notation,

$$\mathbf{X}(t) = \mathbf{R}(t) \otimes \exp(-t\,\mathbf{K}), \tag{22}$$

where the symbol $\otimes$ means 'convolution'.

In a typical pharmacokinetic experiment we can usually control only a limited number of the n state variables, and only a few of them can be observed. Let us call $\mathbf{F}$ the vector of the p input variables and $\mathbf{G}$ the vector of the q output variables. We define matrix $\mathbf{A}$ with the product

$$\mathbf{F} \cdot \mathbf{A} = \mathbf{R} \tag{23}$$

where the element of row i and column j of $\mathbf{A}$ is the weight of the input variable i on the state variable j; we define $\mathbf{B}$ with the product

$$\mathbf{X} \cdot \mathbf{B} = \mathbf{G} \tag{24}$$

where the element of row i and column j of $\mathbf{B}$ is the weight of the state variable i on the output variable j.

We multiply on the right both sides of (22) by $\mathbf{B}$ and use (23) and (24) to get

$$\mathbf{G} = \mathbf{F} \cdot \mathbf{A} \otimes \exp(-t\,\mathbf{K}) \cdot \mathbf{B}.$$

This expression shows that

$$\mathbf{A} \otimes \exp(-t\,\mathbf{K}) \cdot \mathbf{B}$$

is the transfer function of the system with input $\mathbf{F}$ and output $\mathbf{G}$.

This notation is more general than the one more current in pharmacokinetics; instead of a single input function and a single output function we shall use p input functions and q output functions, as currently done in systems theory (Willems 1974).

6.3. Generalization of the solution

The transfer function of this system does not change with the transformation

$$(\mathbf{A}, \mathbf{B}, \mathbf{K}) \to (\mathbf{AS}^{-1}, \mathbf{SB}, \mathbf{SKS}^{-1}) \tag{25}$$

where $\mathbf{S}$ is any $n \times n$ non-singular matrix. In fact,

$$\begin{aligned}\mathbf{A} \otimes \exp(-t\mathbf{K}) \cdot \mathbf{B} &= \mathbf{AS}^{-1}\mathbf{S} \otimes \exp(-t\mathbf{K})\mathbf{S}^{-1}\mathbf{S} \cdot \mathbf{B} \\ &= A\mathbf{S}^{-1} \otimes \exp(-t\,\mathbf{SKS}^{-1}) \cdot \mathbf{SB};\end{aligned}$$

in other words the transformation (25), if it exists, defines a class of models consistent with equation (20) but with a different matrix $\mathbf{K}$.

6.4. Conditions for the existence of transformation (25)

Transformation (25) exists under the following conditions:

(a) Matrix $\mathbf{S}$ can be inverted,
(b) $\mathbf{A} \cdot \mathbf{S}^{-1} = \mathbf{A}$,
(c) $\mathbf{S} \cdot \mathbf{B} = \mathbf{B}$,
(d) $\mathbf{S} \cdot \mathbf{K} \cdot \mathbf{S}^{-1}$ is physically realizable.

Observe that

$$\begin{aligned}&\mathbf{A} \cdot \mathbf{S}^{-1} = \mathbf{A} \Rightarrow \mathbf{A} \cdot \mathbf{S}^{-1} \cdot \mathbf{S} = \mathbf{A} \cdot \mathbf{S} \Rightarrow \mathbf{A} = \mathbf{A} \cdot \mathbf{S}, \\ &\mathbf{S} \cdot \mathbf{B} = \mathbf{B} \Rightarrow \mathbf{S}^{-1} \cdot \mathbf{S} \cdot \mathbf{B} = \mathbf{S}^{-1} \cdot \mathbf{B} \Rightarrow \mathbf{B} = \mathbf{S}^{-1} \cdot \mathbf{B};\end{aligned}$$

matrix $\mathbf{S} \cdot \mathbf{K} \cdot \mathbf{S}^{-1}$ is physically realizable if all its non-diagonal elements are non-positive and the sum of all elements of each line is non-negative.

6.5. Example

In a hypothetical experiment a substance has been administered as a unit bolus to the first compartment; its amount has been measured as a function of time in the first compartment and in the whole body. The results were given by the functions

$$x_1(t) = -\mathrm{e}^{-2t} + 2(t+1)\,\mathrm{e}^{-3t}, \qquad x_{\text{total}}(t) = (3t+1)\,\mathrm{e}^{-3t}. \tag{26}$$

Three compartments are present ($n = 3$), one variable is controllable ($p = 1$), i.e., the first compartment, and two variables are observable ($q = 2$), i.e., the first compartment and the sum of the three compartments.

The input vector is

$$\mathbf{F} = (\delta),$$

where δ is the Dirac delta function, the state variable vector is

$$\mathbf{X} = (x_1(t) \quad x_2(t) \quad x_3(t)),$$

and the output vector is

$$\mathbf{G} = (x_1(t) \quad x_1(t) + x_2(t) + x_3(t)).$$

Matrices $\mathbf{A}$ and $\mathbf{B}$ are

$$\mathbf{A} = (1 \quad 0 \quad 0), \qquad \mathbf{B} = \begin{pmatrix} 1 & 1 \\ 0 & 1 \\ 0 & 1 \end{pmatrix}.$$

Condition (b) requires that

$$(1 \quad 0 \quad 0) \cdot \mathbf{S} = (1 \quad 0 \quad 0),$$

therefore

$$\mathbf{S} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & s_{22} & s_{23} \\ 0 & s_{32} & s_{33} \end{pmatrix};$$

condition (c) requires that

$$\mathbf{S} \cdot \begin{pmatrix} 1 & 1 \\ 0 & 1 \\ 0 & 1 \end{pmatrix} = \begin{pmatrix} 1 & 1 \\ 0 & 1 \\ 0 & 1 \end{pmatrix},$$

therefore

$$\mathbf{S} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \alpha & 1-\alpha \\ 0 & \beta & 1-\beta \end{pmatrix},$$

where α and β are arbitrary real numbers; condition (a) requires that $\alpha \neq \beta$.

A possible solution of equations (26) can be obtained with conventional methods and leads to matrix

$$\mathbf{K} = \begin{pmatrix} 2 & -1 & 0 \\ -1 & 3 & -1 \\ -1 & -2 & 3 \end{pmatrix}.$$

The general solution is

$$\mathbf{SKS}^{-1} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \alpha & 1-\alpha \\ 0 & \beta & 1-\beta \end{pmatrix} \cdot \begin{pmatrix} 2 & -1 & 0 \\ -1 & 3 & -1 \\ -1 & -2 & 3 \end{pmatrix} \cdot \begin{pmatrix} 1 & 0 & 0 \\ 0 & \frac{1-\beta}{\alpha-\beta} & \frac{\alpha-1}{\alpha-\beta} \\ 0 & \frac{-\beta}{\alpha-\beta} & \frac{\alpha}{\alpha-\beta} \end{pmatrix},$$

thence

$$\mathbf{SKS}^{-1} = \begin{pmatrix} 2 & \frac{\beta-1}{\alpha-\beta} & \frac{-\alpha+1}{\alpha-\beta} \\ -1 & \frac{-\alpha\beta+5\alpha-\beta-2}{\alpha-\beta} & \frac{\alpha^2-4\alpha+2}{\alpha-\beta} \\ -1 & \frac{-\beta^2+4\beta-2}{\alpha-\beta} & \frac{\alpha\beta+\alpha-5\beta+2}{\alpha-\beta} \end{pmatrix}. \tag{27}$$

To satisfy condition (d) in the first row it must be that

$$\frac{\beta-1}{\alpha-\beta} \leqslant 0, \tag{i}$$

$$\frac{-\alpha+1}{\alpha-\beta} \leqslant 0; \tag{ii}$$

in the second row,

$$\frac{\alpha^2-4\alpha+2}{\alpha-\beta} \leqslant 0, \tag{iii}$$

$$\frac{\alpha^2-\alpha\beta}{\alpha-\beta} \geqslant 0; \tag{iv}$$

Table 2. Coordinates of the rectangle ABCD.

	α	β
A	1	$2-\sqrt{2}$
B	$2+\sqrt{2}$	$2-\sqrt{2}$
C	$2+\sqrt{2}$	0
D	1	0

in the third row,

$$\frac{-\beta^2+4\beta-2}{\alpha-\beta}\leqslant 0, \tag{v}$$

$$\frac{-\beta^2+\alpha\beta}{\alpha-\beta}\geqslant 0. \tag{vi}$$

Observe that substituting α for β and β for α in matrix (27) is equivalent to switching second and third columns and second and third rows in the same matrix; therefore the solution for $\alpha<\beta$ will be the same for $\alpha>\beta$, but with compartments 2 and 3 switched.

Consider the case

$$\alpha>\beta.$$

Inequalities (i) and (ii) imply

$$\beta\leqslant 1, \qquad \alpha\geqslant 1;$$

inequality (iii) implies

$$2-\sqrt{2}\leqslant\alpha\leqslant 2+\sqrt{2};$$

inequality (iv) implies

$$\alpha\geqslant 0;$$

inequality (v) implies

$$\beta\leqslant 2-\sqrt{2} \quad \text{or} \quad \beta\geqslant 2+\sqrt{2};$$

inequality (vi) implies

$$\beta\geqslant 0.$$

We can conclude that the acceptable values of α and β are included by the rectangle ABCD whose coordinates are given in table 2.

To point A corresponds matrix

$$\mathbf{SKS}^{-1}=\begin{pmatrix}2 & -1 & 0\\ -1 & 3+\sqrt{2} & -1-\sqrt{2}\\ -1 & 0 & 3-\sqrt{2}\end{pmatrix};$$

to point B corresponds matrix

$$\mathbf{SKS}^{-1}=\begin{pmatrix}2 & \frac{-2+\sqrt{2}}{4} & \frac{-2-\sqrt{2}}{4}\\ -1 & 3+\sqrt{2} & 0\\ -1 & 0 & 3-\sqrt{2}\end{pmatrix};$$

to point C corresponds matrix

$$\mathbf{SKS}^{-1} = \begin{pmatrix} 2 & \frac{-2+\sqrt{2}}{2} & \frac{-\sqrt{2}}{2} \\ -1 & 3+\sqrt{2} & 0 \\ -1 & -2+\sqrt{2} & 3-\sqrt{2} \end{pmatrix};$$

to point D corresponds matrix

$$\mathbf{SKS}^{-1} = \begin{pmatrix} 2 & -1 & 0 \\ -1 & 3 & -1 \\ -1 & -2 & 3 \end{pmatrix} = \mathbf{K}.$$

All points included by rectangle ABCD are solutions of our problem; in other words the experimental data do not allow one to distinguish among all those solutions.

6.6. Inversion of matrix K

If we integrate equation (20) from 0 to ∞ we get

$$\mathbf{X}(\infty) - \mathbf{X}(0) = -\int_0^\infty \mathbf{X}(t)\,\mathrm{d}t \cdot \mathbf{K} + \int_0^\infty \mathbf{R}(t)\,\mathrm{d}t;$$

if the system is open the first term vanishes, therefore

$$\int_0^\infty \mathbf{X}(t)\,\mathrm{d}t \cdot \mathbf{K} = \mathbf{X}(0) + \int_0^\infty \mathbf{R}(t)\,\mathrm{d}t.$$

Now call **T** the inverse of matrix **K** and multiply to the right both sides of this identity by **T**:

$$\int_0^\infty \mathbf{X}(t)\,\mathrm{d}t = \left[\mathbf{X}(0) + \int_0^\infty \mathbf{R}(t)\,\mathrm{d}t\right] \cdot \mathbf{T}.$$

The vector in square brackets represents the total amount of substance entering the system at the beginning and during the whole experiment; if we think of an experiment where we feed only compartment i with an amount D_i of substance, the product on the right-hand side becomes the product of D_i by row i of matrix **T**, i.e.,

$$\left[\int_0^\infty x_1(t)\,\mathrm{d}t \quad \int_0^\infty x_2(t)\,\mathrm{d}t \quad \cdots \quad \int_0^\infty x_n(t)\,\mathrm{d}t\right] = D_i \cdot [t_{i1} \quad t_{i2} \quad \cdots \quad t_{in}],$$

where t_{ij} is the element of row i and column j of matrix **T**.

We can thus conclude that the inverse of matrix **K** is matrix **T** of the permanence and residence times; in particular, the diagonal elements of **T** are the permanence times of the different compartments, while the element of row i and column j is the fraction of substance fed in i that reaches j multiplied by the permanence time in j.

6.7. Computation of the **T** *matrices*

We go back now to the last example. It is easy to compute matrix **T** at the different points; at point A,

$$\mathbf{T}_\mathrm{A} = \begin{pmatrix} 2 & -1 & 0 \\ -1 & 3+\sqrt{2} & -1-\sqrt{2} \\ -1 & 0 & 3-\sqrt{2} \end{pmatrix}^{-1} \approx \begin{pmatrix} 0.70 & 0.16 & 0.24 \\ 0.40 & 0.32 & 0.48 \\ 0.44 & 0.10 & 0.78 \end{pmatrix};$$

at point B,

$$\mathbf{T}_{\mathrm{B}} = \begin{pmatrix} 2 & \frac{-2+\sqrt{2}}{4} & \frac{-2-\sqrt{2}}{4} \\ -1 & 3+\sqrt{2} & 0 \\ -1 & 0 & 3-\sqrt{2} \end{pmatrix}^{-1} \approx \begin{pmatrix} 0.70 & 0.02 & 0.38 \\ 0.16 & 0.23 & 0.09 \\ 0.44 & 0.01 & 0.87 \end{pmatrix};$$

at point C,

$$\mathbf{T}_{\mathrm{C}} = \begin{pmatrix} 2 & \frac{-2+\sqrt{2}}{2} & \frac{-\sqrt{2}}{2} \\ -1 & 3+\sqrt{2} & 0 \\ -1 & -2+\sqrt{2} & 3-\sqrt{2} \end{pmatrix}^{-1} \approx \begin{pmatrix} 0.70 & 0.09 & 0.31 \\ 0.16 & 0.25 & 0.07 \\ 0.50 & 0.15 & 0.85 \end{pmatrix};$$

at point D,

$$\mathbf{T}_{\mathrm{D}} = \begin{pmatrix} 2 & -1 & 0 \\ -1 & 3 & -1 \\ -1 & -2 & 3 \end{pmatrix}^{-1} \approx \begin{pmatrix} 0.70 & 0.30 & 0.10 \\ 0.40 & 0.60 & 0.20 \\ 0.50 & 0.50 & 0.50 \end{pmatrix}.$$

Observe that the permanence time of the first compartment is 0.70 at all four points, while the permanence time of the second compartment varies from 0.23 to 0.60, of the third compartment from 0.50 to 0.87. Of course the permanence time in the whole system, given by the sum of the permanence times in all compartments, is always 1.80 at all points, because our data were based on measures taken on the whole body.

Other quantities have even larger fluctuations from one point to another; for instance the yield from the first to the second compartment, given by the ratio t_{12}/t_{22}, varies from 8.7% at point B to 50% at points A and D.

7. Conclusion

A statement one frequently reads in the pharmacokinetic literature is that from all possible models one should chose the 'identifiable' one and ignore the 'non-identifiable' ones, even if consistent with the experimental data. This statement is valid only with reference to phenomenological models, i.e., for models that describe the data but whose parameters do not have any physical or physiological meaning; but in this case fitting the data with splines is simpler, faster, and very efficient. When we want the parameters of the model to have some physical or physiological meaning, ignoring the 'non-identifiable' models is self-defeating and anti-scientific. The fact is that, even if a model is not completely identifiable, it is in general possible to determine a range for the parameters of interest. It is also true that, if the degrees of freedom are more than two, the computations are not simple, but this is a price we must pay if we want our results to have a scientific meaning.

In this paper I have tried to show how to deal in general with this kind of model. I am now actively working to develop an efficient algorithm to solve this kind of problem in a faster way.

Acknowledgments

I am grateful to Doctor Aaron B Brill and Doctor Michael G Stabin of the Department of Radiology and Radiological Sciences, Vanderbilt University, Nashville, for suggesting the subject of this paper and for their invaluable help in writing it.

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