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Research Article

Estimation of Permanence Time, Exit Time, Dilution Factor, and Steady-State Volume of Distribution

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General solutions for exit time, permanence time, dilution factor, and volume of distribution at steady state are derived for compartmental and noncompartmental systems. These derivations require that the systems are linear and state-determined. Unique values for these parameters cannot be determined when the site of elimination is not known; in this case the parameters can be defined by a range. Interpretation of this range and its significance and use in clinical situations are illustrated with two examples.

KEY WORDS: allometric scaling; compartmental and noncompartmental pharmacokinetics; dilution factor; exit time; permanence time; protein therapeutics; recombinant human CD4 immunoglobulin G (rCD4-IgG); steady-state volume; tracers.

INTRODUCTION

Many recent papers in the pharmacokinetic literature have dealt with the concepts of transfer time, permanence time, residence time, and steady-state volume of distribution (1–13). Unfortunately, the different authors do not always agree on the definitions of those quantities and frequently use different terms and symbols for the same concepts. Here we show the relationship among them and introduce another quantity, *dilution factor,* defined as the ratio between the steady-state volume of distribution and the initial volume of distribution. Another term that was introduced a while ago, *the exit time* (14), has not been used frequently; in our opinion, the latter two terms help considerably in the description of the pharmacokinetic properties of a drug.

In this paper, we present a general approach to estimating the permanence time, exit time, dilution factor, and volume of distribution at steady state using compartmental and noncompartmental hypotheses. The compartmental approach utilizes either micro- or macroparameters. Explicit solutions for two- and three-compartmental models are presented, as well as the general solution for an n-compartmental model.

The use of the compartmental approach is illustrated with two numerical examples. With only serum concentration-versus-time data, the dilution factor and, consequently, the steady-state volume of distribution cannot be estimated uniquely; rather, they are defined by a discrete range of values. When supplementary data are available, the dilution factor, volume of distribution at steady state, and exit time for the body can be estimated more accurately.

A noncompartmental approach is also provided. The outcome of this approach is highly dependent on the homogeneity of drug concentrations within the system.

Based on the conclusions presented in this paper, it is recommended that exit time, dilution factor, and volume of distribution at steady state be reported as a range, rather than as a discrete number, when a unique solution cannot be ascertained because vital auxiliary data are lacking. This is particularly important for therapeutic agents, such as proteins, which are not amenable to typical mass balance methodology, due to reutilization of the peptides and amino acids that are formed following proteolysis of the parent compound. Furthermore, the general solution provided in this paper makes it possible to provide values for these parameters without the imposed constraint of assuming elimination only from the sampling compartment.

TURNOVER TIME AND PERMANENCE TIME

The *turnover time* t_i of compartment i is defined as the expected interval of time spent by the drug in one passage through it. The general equation of a compartment can be written

$$\frac{dx_i}{dt} = -K_i x_i + r(t)$$

where $x_i(t)$ is the amount of drug present in the compartment, K_i its fractional turnover rate, and $r(t)$ the rate of entry due to external feeding or internal recycling, or both.

The turnover time is the inverse of the fractional turnover rate,

$$t_i = \frac{1}{K_i}$$

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in fact, at any moment the amount of the drug present in the compartment is $x_i(t)$, and its rate of exit is $K_i x_i$; therefore, the ratio

$$\frac{x_i}{K_i x_i} = \frac{1}{K_i}$$

is the time spent by the drug, on the average, in that compartment.

The turnover time of a pool formed by a number of compartments is still defined as the expected interval of time spent by the drug in one passage through it; its determination, though, is possible only if the detailed fate of the drug in all components of that pool is known.

The *permanence time* T_i of a compartment is defined as the expected interval of time spent by the drug in all its passages through it.

If $x_i(t)$ is the amount of drug present in compartment i at time t, and K_i its fractional turnover rate, then

$$K_i x_i(t)dt$$

is the amount of drug leaving that compartment in the interval of time from t to $t + dt$, and

$$\int_0^\infty K_i x_i(t)dt$$

is the total amount of drug leaving that compartment. If the drug was initially administered to that same compartment at time $t = 0$, and if it will eventually leave it totally, then the ratio

$$\nu_i = \frac{\int_0^\infty K_i x_i(t)dt}{x_i(0)}$$

is equal to the expected number of times the drug will go through that compartment; this quantity is called the *turnover number*.

If K_i is constant, it can be exported from the integral above, and we can write

$$\frac{1}{K_i} \cdot \nu_i = \frac{\int_0^\infty x_i(t)dt}{x_i(0)}$$

but the product of the turnover time by the turnover number is equal to the permanence time; therefore, we can write

$$T_i = \frac{\int_0^\infty x_i(t)dt}{x_i(0)}$$

which is valid only if the drug was administered as a bolus at time $t = 0$. If the volume of that compartment is constant, dividing numerator and denominator by it, we get

$$T_i = \frac{\int_0^\infty c_i(t)dt}{c_i(0)}$$

The above expression can be used to compute the permanence time at a specific point of sampling, provided the drug is administered at time $t = 0$ at that same point. If the sampling point is representative of the uniform concentration over a whole compartment, then the fraction above will be equal to the permanence time of that compartment.

With any other mode of administration, i.e., if the drug does not enter compartment i at time $t = 0$, the permanence time is not equal to the fractions

$$\frac{\int_0^\infty x_i(t)dt}{x_i(0)}, \qquad \frac{\int_0^\infty c_i(t)dt}{c_i(0)}$$

but the above integrals have an important role in the description of the properties of a biological system, as shown elsewhere (14).

EXIT TIME

The *first relative moment* of function $x_i(t)$ is defined as the ratio

$$\frac{\int_0^\infty t \cdot x_i(t)dt}{\int_0^\infty x_i(t)dt}$$

With the hypothesis that the system is linear and state-determined, it was shown by Rescigno and Gùrpide (15), and later rediscovered by Yamaoka *et al.* (1), that if $c_i(t)$ is the concentration of a drug that was injected at the same point of sampling as a bolus at time $t = 0$, the first relative moment of $c_i(t)$ is equal to the expected time of exit of the drug from the site of sampling (16).

In general, with the hypothesis that the fractional turnover rate is constant, but with administration of the drug at any time or in any mode, we can write

$$\frac{\int_0^\infty t \cdot x_i(t)dt}{\int_0^\infty x_i(t)dt} = \frac{\int_0^\infty t \cdot K_i x_i(t)dt}{\int_0^\infty K_i x_i(t)dt}$$

In the last fraction, the product $K_i x_i(t)dt$ is the amount of drug leaving the compartment in the interval of time from t to $t + dt$, and t is the time of this event; therefore, that fraction is the expected time of exit of the drug from the compartment, irrespective of when and how the drug entered the compartment. We call this expected time the *exit time*, Ω_i; this quantity is called, by some authors, *resident time*, but we prefer to use this term for a different quantity (16).

Dividing, again, numerator and denominator by the volume of the compartment V_i,

$$\Omega_i = \frac{\int_0^\infty t \cdot x_i(t)dt}{\int_0^\infty x_i(t)dt} = \frac{\int_0^\infty t \cdot c_i(t)dt}{\int_0^\infty c_i(t)dt}$$

where $c_i(t)$ is the concentration in the compartment.

The exit time for a pool of compartments is not necessarily equal to the first relative moment of the function mea-

suring the amount of drug in that pool (17). This fact becomes more evident with a simple example. Suppose that the pool is formed by just two compartments, say i and j; calling $x_i(t)$ and $x_j(t)$ the amount of drug in those two compartments, with

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

we call *apparent* exit time $\Omega^*_{i,j}$ the first relative moment of $x_i(t) + x_j(t)$,

$$\Omega^*_{i,j} = \frac{\int_0^\infty t \cdot [x_i(t) + x_j(t)]dt}{\int_0^\infty [x_i(t) + x_j(t)]dt}$$

while the *real* exit time, according to the definition, must be computed with the ratio

$$\Omega_{i,j} = \frac{\int_0^\infty t \cdot [k_{io}x_i(t) + k_{jo}x_j(t)]dt}{\int_0^\infty [k_{io}x_i(t) + k_{jo}x_j(t)]dt}$$

where k_{io} and k_{jo} are the respective fractional rates of exit of the drug from the two compartments out of the pool. From this fraction, the constants k_{io} and k_{jo} cannot be eliminated, but we can write

$$\Omega_i = \frac{\int_0^\infty t \cdot k_{io}x_i(t)dt}{\int_0^\infty k_{io}x_i(t)dt} = \frac{\int_0^\infty t \cdot x_i(t)dt}{\int_0^\infty x_i(t)dt}$$

$$\Omega_j = \frac{\int_0^\infty t \cdot k_{jo}x_j(t)dt}{\int_0^\infty k_{jo}x_j(t)dt} = \frac{\int_0^\infty t \cdot x_j(t)dt}{\int_0^\infty x_j(t)dt}$$

By simple arithmetic manipulation we can show that

$$\text{Min}(\Omega_i,\Omega_j) \le \Omega_{i,j} \le \text{Max}(\Omega_i,\Omega_j)$$
$$\text{Min}(\Omega_i,\Omega_j) \le \Omega^*_{i,j} \le \text{Max}(\Omega_i,\Omega_j)$$

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

In the same way we can show that the difference

$$\Omega_{ij} - \Omega^*_{i,j}$$

has the sign of the product

$$(\Omega_i - \Omega_j) \cdot (k_{io} - k_{jo})$$

It follows that 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 if the compartment with the larger exit time also has the larger rate of exit, and vice versa.

In conclusion, without any hypothesis on the compartmentalization of a system, we can say only that the first relative moment is an approximation of the exit time, and the approximation depends on the disuniformity of the concentration of the drug inside the system.

A number of properties of the exit time were discussed by Rescigno (14) and by Rescigno and Gùrpide (15).

DILUTION FACTOR AND STEADY-STATE VOLUME OF DISTRIBUTION

Two Compartments

With a system of two compartments and a bolus injection in compartment 1, we have the differential equations

$$\frac{dx_1}{dt} = -K_1x_1 + k_{21}x_2 \tag{1}$$

$$\frac{dx_2}{dt} = +k_{12}x_1 - K_2x_2 \tag{2}$$

with initial conditions

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

In these equations, 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. Of course the following inequalities must hold:

$$0 \le k_{12} \le K_1, \qquad 0 \le k_{21} \le K_2 \tag{3}$$

The constants K_1, K_2, k_{12}, and k_{21} are called the *microparameters* of the system.

The solutions of Eqs. (1) and (2) are

$$x_1(t) = a_{11}e^{-\lambda_1 t} + a_{12}e^{-\lambda_2 t} \tag{4}$$
$$x_2(t) = a_{21}e^{-\lambda_1 t} + a_{22}e^{-\lambda_2 t} \tag{5}$$

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

$$\begin{cases} \lambda_1 + \lambda_2 = K_1 + K_2 \\ \lambda_1 \cdot \lambda_2 = K_1 \cdot K_2 - k_{12} \cdot k_{21} \\ a_{11} + a_{12} = D \\ a_{21} + a_{22} = 0 \\ a_{11} \cdot \lambda_2 + a_{12} \cdot \lambda_1 = D \cdot K_2 \\ a_{21} \cdot \lambda_2 + a_{22} \cdot \lambda_1 = D \cdot k_{12} \end{cases} \tag{6}$$

If only compartment 1 has been sampled, i.e., if $x_1(t)$ is known but not $x_2(t)$, then 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 the above equations we can therefore compute

$$\begin{cases} K_1 = \dfrac{a_{11}\lambda_1 + a_{12}\lambda_2}{a_{11} + a_{12}} \\ K_2 = \dfrac{a_{11}\lambda_2 + a_{12}\lambda_1}{a_{11} + a_{12}} \\ k_{12}k_{21} = \dfrac{a_{11}a_{12}(\lambda_1 - \lambda_2)^2}{(a_{11} + a_{12})^2} \end{cases} \tag{7}$$

and using inequalities (3),

$$\frac{k_{12}k_{21}}{K_2} \le k_{12} \le K_1$$

$$\frac{k_{12}k_{21}}{K_1} \le k_{21} \le K_2$$

thence

$$\frac{a_{11}a_{12}(\lambda_1 - \lambda_2)^2}{(a_{11} + a_{12}) \cdot (a_{11}\lambda_2 + a_{12}\lambda_1)} \le k_{12} \le \frac{a_{11}\lambda_1 + a_{12}\lambda_2}{a_{11} + a_{12}}$$

$$\frac{a_{11}a_{12}(\lambda_1 - \lambda_2)^2}{(a_{11} + a_{12}) \cdot (a_{11}\lambda_1 + a_{12}\lambda_2)} \le k_{21} \le \frac{a_{11}\lambda_2 + a_{12}\lambda_1}{a_{11} + a_{12}} \quad (8)$$

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

$$V_1 = \frac{D}{c_1(0)} \quad (9)$$

Now suppose that the drug is fed continuously into compartment 1 at a constant rate r; when a steady state is reached, Eqs. (1) and (2) become

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

and their solution is

$$x_1 = \frac{K_2 r}{K_1K_2 - k_{12}k_{21}}$$

$$x_2 = \frac{k_{12} r}{K_1K_2 - k_{12}k_{21}}$$

Thus at steady state we have

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

By analogy to definition (9), we can define the steady-state volume of distribution V_{SS} as the ratio between the total amount of drug in the body and its concentration in the sampling compartment at steady state; therefore

$$V_{SS} = \frac{x_1 + x_2}{x_1/V_1} = \frac{K_2 + k_{12}}{K_2} V_1$$

The fraction

$$\theta = \frac{V_{SS}}{V_1} = \frac{K_2 + k_{12}}{K_2}$$

is called the *dilution factor*.

Using inequality (8) we can now write

$$\frac{(a_{11} + a_{12})(a_{11}\lambda_2^2 + a_{12}\lambda_1^2)}{(a_{11}\lambda_2 + a_{12}\lambda_1)^2} \le \theta \le \frac{(a_{11} + a_{12})(\lambda_1 + \lambda_2)}{a_{11}\lambda_2 + a_{12}\lambda_1}$$

The above inequalities can also be written in the form

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

but

$$a_{11} + a_{12} = x_1(0)$$

$$\frac{a_{11}}{\lambda_1} + \frac{a_{12}}{\lambda_2} = \int_0^\infty x_1(t)dt$$

$$\frac{a_{11}}{\lambda_1^2} + \frac{a_{12}}{\lambda_2^2} = \int_0^\infty t \cdot x_1(t)dt$$

therefore, calling θ_{min} and θ_{max} the extreme values of θ,

$$\theta_{min} = \frac{\int_0^\infty t x_1(t)dt \Big/ \int_0^\infty x_1(t)dt}{\int_0^\infty x_1(t)dt / x_1(0)}$$

$$\theta_{max} = \frac{\frac{1}{\lambda_1} + \frac{1}{\lambda_2}}{\int_0^\infty x_1(t)dt / x_1(0)}$$

Thus θ_{min} is the time of exit from compartment 1 divided by the permanence time of the same compartment; θ_{max} is the sum of the time constants divided by the permanence time of compartment 1.

The ratio $\theta_{max}/\theta_{min}$ is a measure of the uncertainty of our knowledge of the behavior of the subject under investigation when the drug will be administered by continuous infusion or by repeated doses. The closer that ratio is to one, the better we can estimate how much drug is present in the body for a particular steady-state systemic concentration.

These results can easily be generalized to systems of three or more compartments and to noncompartmental systems.

Three Compartments

With three compartments connected in all possible ways, we have the differential equations

$$\frac{dx_1}{dt} = -K_1x_1 + k_{21}x_2 + k_{31}x_3$$

$$\frac{dx_2}{dt} = +k_{12}x_1 - K_2x_2 + k_{32}x_3$$

$$\frac{dx_3}{dt} = +k_{13}x_1 + k_{23}x_2 - K_3x_3$$

With continuous infusion in compartment 1 at rate r, at steady state those equations become

$$-K_1x_1 + k_{21}x_2 + k_{31}x_3 + r = 0$$
$$+k_{12}x_1 - K_2x_2 + k_{32}x_3 = 0$$
$$+k_{13}x_1 + k_{23}x_2 - K_3x_3 = 0$$

thence

$$\frac{x_1 + x_2 + x_3}{x_1} = \frac{K_2K_3 - k_{23}k_{32} + k_{12}K_3 + k_{13}k_{32} + k_{13}K_2 + k_{12}k_{23}}{K_2K_3 - k_{23}k_{32}} = \frac{t_1 \cdot (1 - \delta_{23}) + t_2 \cdot (\gamma_{12} + \gamma_{132}) + t_3 \cdot (\gamma_{13} + \gamma_{123})}{t_1 \cdot (1 - \delta_{23})} \tag{10}$$

where

$$t_i = \frac{1}{K_i}$$

is the turnover time of compartment i,

$$\delta_{ij} = \frac{k_{ij}}{K_i} \cdot \frac{k_{ji}}{K_j}$$

is the fraction of drug recirculated from compartment i to compartment j and back, and γ_{ij}, γ_{ijl}, . . . are the fractions transported along the path indicated by the subscripts, i.e.,

$$\gamma_{ij} = \frac{k_{ij}}{K_i}, \qquad \gamma_{ijl} = \frac{k_{ij}}{K_i} \cdot \frac{k_{jl}}{K_j}$$

The fraction in Eq. (10) is, of course, equal to the dilution factor θ, i.e.,

$$\theta = \frac{x_1 + x_2 + x_3}{x_1}$$

We can reach the same conclusion in a different way. The dilution factor can be written in the form

$$\theta = \frac{x_1 + x_2 + x_3}{x_1} = \frac{P_1 + P_2 + P_3}{P_1}$$

where P_1, P_2, and P_3 are the probabilities that a molecule of the drug present in the system is in compartment 1, 2, or 3, respectively. Now once a molecule enters compartment 1, 2, or 3, it spends there, on the average, a time t_1, t_2, or t_3, respectively; the probability of entering compartment 1 is equal to the probability of leaving one of the other two compartments, i.e., $1 - \delta_{23}$; the probability of entering compartment 2 or 3 after leaving compartment 1 is $\gamma_{12} + \gamma_{132}$ or $\gamma_{13} + \gamma_{123}$, respectively. In other words, we can write the proportions,

$$\frac{P_1}{t_1 \cdot (1 - \delta_{23})} = \frac{P_2}{t_2 \cdot (\gamma_{12} + \gamma_{132})} = \frac{P_3}{t_3 \cdot (\gamma_{13} + \gamma_{123})}$$

thence Eq. (10) follows immediately.

Of course the fraction in Eq. (10) cannot be computed if only compartment 1 has been sampled, but we can determine some boundary values for it.

An upper boundary for θ is given by

$$\theta_{max} = \frac{t_1(1 - \delta_{23}) + t_2(1 - \delta_{13}) + t_3(1 - \delta_{12})}{t_1(1 - \delta_{23})}$$

in fact, it is easy to verify that

$$1 - \delta_{13} \geq \gamma_{12} + \gamma_{132}$$
$$1 - \delta_{12} \geq \gamma_{13} + \gamma_{123}$$

the equal signs being valid when

$$K_1 = k_{12} + k_{13}$$
$$K_2 = k_{21} + k_{23}$$
$$K_3 = k_{31} + k_{32}$$

i.e., when the system is closed.

A lower boundary for θ is given by

$$\theta_{min} = \left(\frac{t_1(1 - \delta_{23}) + t_2(1 - \delta_{13}) + t_3(1 - \delta_{12})}{1 - \delta_{12} - \delta_{13} - \delta_{23} - \delta_{123} - \delta_{132}} - \frac{t_2 + t_3}{1 - \delta_{23}}\right) \cdot \frac{1 - \delta_{12} - \delta_{13} - \delta_{23} - \delta_{123} - \delta_{132}}{t_1(1 - \delta_{23})}$$

we should first prove that

$$\left(\frac{t_1(1 - \delta_{23}) + t_2(1 - \delta_{13}) + t_3(1 - \delta_{12})}{1 - \delta_{12} - \delta_{13} - \delta_{23} - \delta_{123} - \delta_{132}} - \frac{t_2 + t_3}{1 - \delta_{23}}\right) \cdot \frac{1 - \delta_{12} - \delta_{13} - \delta_{23} - \delta_{123} - \delta_{132}}{t_1(1 - \delta_{23})} \leq \frac{t_1 \cdot (1 - \delta_{23}) + t_2 \cdot (\gamma_{12} + \gamma_{132}) + t_3 \cdot (\gamma_{13} + \gamma_{123})}{t_1(1 - \delta_{23})}$$

In fact the above inequality is equivalent to the following inequalities:

$$[[t_1(1 - \delta_{23}) + t_2(1 - \delta_{13}) + t_3(1 - \delta_{12})] - \frac{t_2 + t_3}{1 - \delta_{23}} (1 - \delta_{12} - \delta_{13} - \delta_{23} - \delta_{123} - \delta_{132}) \leq t_1 \cdot (1 - \delta_{23}) + t_2 \cdot (\gamma_{12} + \gamma_{132}) + t_3 \cdot (\gamma_{13} + \gamma_{123})]$$

$$[t_2(1 - \delta_{13} - \gamma_{12} - \gamma_{132}) + t_3(1 - \delta_{12} - \gamma_{13} - \gamma_{123}) \leq \frac{t_2 + t_3}{1 - \delta_{23}} (1 - \delta_{12} - \delta_{13} - \delta_{23} - \delta_{123} - \delta_{132})]$$

$$(1 - \delta_{23}) \cdot [t_2(\delta_{13} + \gamma_{12} + \gamma_{132}) + t_3(\delta_{12} + \gamma_{13} + \gamma_{123}) \geq (t_2 + t_3) \cdot (\delta_{12} + \delta_{13} + \delta_{123} + \delta_{132})$$

and, finally, to the two inequalities

$$\gamma_{12} + \gamma_{132} \geq \delta_{12} + \delta_{123} + \delta_{132} + \delta_{23} \cdot (\delta_{13} + \gamma_{12} + \gamma_{132})$$
$$\gamma_{13} + \gamma_{123} \geq \delta_{13} + \delta_{123} + \delta_{132} + \delta_{23} \cdot (\delta_{12} + \gamma_{13} + \gamma_{123})$$

These two inequalities are obviously true, and they become strict equalities when

$$K_2 = k_{21} + k_{23}$$
$$K_3 = k_{31} + k_{32}$$

i.e., when the drug is eliminated only from compartment 1.

Many Compartments

Suppose that the drug is distributed among n compartments, but only one of them can be sampled, and that its

concentration $c_1(t)$, after a bolus administration at time $t = 0$, can be approximated reasonably well by a sum of exponential functions, then

$$c_1(t) = a_1e^{-\lambda_1 t} + a_2e^{-\lambda_2 t} + \cdots + a_ne^{-\lambda_n t}$$

and in operational form (18)

$$\{c_1\} = \frac{a_1}{s + \lambda_1} + \frac{a_2}{s + \lambda_2} + \cdots + \frac{a_n}{s + \lambda_n} = \frac{p_0s^{n-1} + p_1s^{n-2} + \cdots + p_{n-1}}{s^n + q_1s^{n-1} + q_2s^{n-2} + \cdots + q_n} \quad (11)$$

In general, i.e., with elimination from any compartment, we can write

$$\theta = \frac{V_{SS}}{V_1} = \left[\frac{\text{(time of exit from the organism)} - \text{(time of entry into the sampling compartment)}}{\text{(permanence time in the sampling compartment)}}\right]$$

The permanence time T_1 of the sampling compartment is given by

$$T_1 = \frac{\int_0^\infty c_1(t)dt}{c_1(0)} = \frac{p_{n-1}}{p_0q_n} \quad (12)$$

The time of exit Ω_{system} from the organism in general cannot be calculated, but we can establish some boundaries to it. We shall prove in general the following proposition:

$$\frac{p_0q_n}{p_{n-1}} \cdot \left(\frac{q_{n-1}}{q_n} - \frac{p_{n-2}}{p_{n-1}}\right) \le \theta \le \frac{p_0q_{n-1}}{p_{n-1}} \quad (13)$$

The first part of the above inequalities is true because

$$\Omega_1 = \frac{\int_0^\infty t \cdot c_1(t)dt}{\int_0^\infty c_1(t)dt} = \frac{q_{n-1}}{q_n} - \frac{p_{n-2}}{p_{n-1}} \quad (14)$$

is the exit time from compartment 1, therefore

$$\Omega_1 \le \Omega_{system}$$

in general, with the equal sign holding only when the drug leaves the system exclusively from compartment 1.

To prove the second part of the proposition, observe that the maximum possible value of the dilution factor is reached when the drug does not leave the system from the sampling compartment, but from some of the other compartments. If this is the case, then suppose that the drug is administered as a bolus in compartment 1, then infused into that same compartment with a rate exactly equal to the rate of elimination from the rest of the system. A steady state will eventually be reached, and at that point such a system is undistinguishable from a closed system fed with a single bolus. In this system, of course,

$$q_n = 0$$

after a bolus dose D given at time $t = 0$, the concentration in compartment 1 will be

$$\{c_1\} = \frac{p_0s^{n-1} + p_1s^{n-2} + \cdots + p_{n-1}}{s^n + q_1s^{n-1} + q_2{}^{n-2} + \cdots + q_{n-1}s}$$

with

$$p_0 = \frac{D}{V_1}$$

therefore

$$\lim_{t\to 0} c_1(t) = p_0$$

$$\lim_{t\to\infty} c_1(t) = \frac{p_{n-1}}{q_{n-1}}$$

thence the dilution factor is p_0q_{n-1}/p_{n-1}, and it does not matter from which compartment the drug is leaving, as long as this is not the compartment where the drug is initially fed, q.e.d.

Using Eq. (11) it is easy to show that inequalities (13) are equivalent to

$$\frac{\sum_{i=1}^n a_i \cdot \sum_{i=1}^n \frac{a_i}{\lambda_i^2}}{\left(\sum_{i=1}^n \frac{a_i}{\lambda_i}\right)^2} \le \phi \le \frac{\sum_{i=1}^n a_i \cdot \sum_{i=1}^n \frac{1}{\lambda_i}}{\sum_{i=1}^n \frac{a_i}{\lambda_i}}$$

We have shown that

$$\Omega_1 \le \Omega_{system} \le \Omega_{\neq 1}$$

where the last term means the exit time from all compartments excluding the first; from inequalities (13), multiplying each term by T_1, we get

$$\Omega_1 = \frac{q_{n-1}}{q_n} - \frac{p_{n-2}}{p_{n-1}}, \qquad \Omega_{\neq 1} = \frac{q_{n-1}}{q_n}$$

the term

$$\frac{p_{n-2}}{p_{n-1}} = \Omega_{\neq 1} - \Omega_1$$

appearing in Eq. (14), called the *short circuit term* (19,20), is equal to the expected time spent by the drug in the system after leaving the sampling compartment.

Noncompartmental Systems

Nakashima and Benet (8) showed how to compute the exact value of the quantity that we call the dilution factor when the fractional rates of exit from each of the compartments in a linear mammillary model are known; they called their formula a "noncompartmental equation," even though their method depends strictly on strong compartmental hypotheses.

We have shown above that, if $x(t)$ is the amount of drug present in the whole organism at time t, the ratio

$$\frac{\int_0^\infty t \cdot x(t)dt}{\int_0^\infty x(t)dt}$$

is an approximation of the time of exit from the system. Without a detailed knowledge of the compartmentalization of 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; in that case, a lower bound for the dilution factor is

$$\theta \geq \frac{\Omega_1}{T_1} = \frac{c_1(0) \cdot \int_0^\infty t c_1(t)dt}{\left(\int_0^\infty c_1(t)dt\right)^2} \tag{15}$$

where $c_1(t)$ is the concentration of the drug at the sampling site after a bolus administration in the same location.

If we measure the apparent exit time from the whole system, we can also compute an alternate approximation of the dilution factor,

$$\theta \cong \frac{\Omega^*_{\text{system}}}{T_1} = \frac{c_1(0) \cdot \int_0^\infty t \cdot x(t)dt}{\int_0^\infty c_1(t)dt \cdot \int_0^\infty x(t)dt}$$

where $x(t)$ is the total amount of drug in the system, but we do not know whether this approximation is in excess or in deficit.

EXAMPLES

As an example consider a pharmacokinetic study conducted in four different species with recombinant human CD4 immunoglobulin G (rCD4-IgG), a protein under development as an AIDS therapeutic (21,22). Following an intravenous bolus injection of rCD4-IgG, the concentration of the protein in the serum was measured at different times, and the experimental values were fitted to a sum of exponentials,

$$c(t) = \Sigma_i c_i e^{-\lambda_i t}$$

The experimental results are summarized in Table I.

In Table II are listed the coefficients of $\{c(t)\}$ for the four species, computed using Eq. (11). Now we can use Eqs. (12) and (13) to compute T_1 and the lower and upper bound of Ω_1 and θ. These values are shown in Table III, along with V_1 and the lower and upper bound of V_{SS}. It is interesting to note that allometric scaling techniques (23) can be used to predict T_1, V_1, and the lower bound for Ω_1, V_{SS}, and θ in human from the preclinical animal data.

The ratio $\theta_{max}/\theta_{min}$ is approximately 2.6 for the rat, 2.4 for the rabbit, 4.9 for the monkey, and 2.2 for the human. Since this ratio in human is smaller than or equal to the ratio in the other species, the uncertainty in the overall accumulation of drug in the body following chronic administration may be less in humans than in the other species, an important consideration in safety assessment programs. Whether this uncertainty in the determination of the amount of drug in the body at steady state is acceptable or not depends on other considerations. For rCD4-IgG, a compound with a rather innocuous preclinical profile, the small uncertainty was acceptable; for compounds with a narrow therapeutic window or that exhibit unexpected toxicities in chronic dosing situations, excessive accumulation may be potentially harmful. When the behavior of the drug at steady state must be determined with more precision than obtainable from sampling only one compartment after a single bolus injection, other measurements are necessary.

A possible alternative was provided by Berman and Schoenfeld (24) with the following results from an experimental study. After a bolus intravenous injection of labeled 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,

$$\frac{c_1}{c_0} = \frac{3}{8}e^{-3t} + \frac{1}{4}e^{-2t} + \frac{3}{8}e^{-t}$$

$$\frac{c_t}{c_0} = \frac{1}{4}e^{-2t} + \frac{3}{4}e^{-t}$$

where c_0 is the amount of radioactivity injected, c_1 the amount measured in the blood, and c_t the total activity in the body. For the purpose of this discussion the time scale in these two equations is arbitrary. In operational form they become

$$\frac{\{c_1\}}{c_0} = \frac{s^2 + 4s + {}^{15}/_4}{s^3 + 6s^2 + 11s + 6}$$

$$\frac{\{c_t\}}{c_0} = \frac{s + {}^{7}/_4}{s^2 + 3x + 2} \tag{16}$$

Table I. Pharmacokinetic Data of rCD4-IgG in Four Species

Species	Weight (kg)	Dose (mg/kg)	c_1 (μg/ml)	c_2 (μg/ml)	c_3 (μg/ml)	λ_1 (hr^{-1})	λ_2 (hr^{-1})	λ_3 (hr^{-1})
Rat	0.333	0.14	1.21	2.6	0.3	6.15	0.21	0.048
Rabbit	3.3	0.04	0.35	0.23	0.037	0.825	0.0788	0.0172
Monkey	5.6	0.14	4.5	0.076	—	0.098	0.0133	—
Human	82.0	1.00	17.5	3.1	—	0.059	0.014	—

Table II. Coefficients of $\{c(t)\}$ from Table I

Species	n	p_0	p_1	p_2	q_1	q_2	q_3
Rat	3	4.11	18.33	1.167	6.408	1.597	0.06199
Rabbit	3	0.617	0.2607	0.006143	0.921	0.08056	0.001118
Monkey	2	4.576	0.0673	—	0.1113	0.001303	—
Human	2	20.6	0.428	—	0.073	0.000826	—

The permanence time in the sampling compartment is

$$T_1 = \frac{p_{n-1}}{p_0 q_n} = \frac{15/4}{6} = \frac{5}{8}$$

The time of exit from the sampling compartment is

$$\Omega_1 = \frac{q_{n-1}}{q_n} - \frac{p_{n-2}}{p_{n-1}} = \frac{11}{6} - \frac{16}{15} = \frac{23}{30}$$

Without considering the data on c_t, we can compute

$$\frac{p_0 q_n}{p_{n-1}}\left(\frac{q_{n-1}}{q_n} - \frac{p_{n-2}}{p_{n-1}}\right) \le \theta \le \frac{p_0 q_{n-1}}{p_{n-1}}$$

$$\frac{276}{225} \le \theta \le \frac{44}{15}$$

$$1.226 < \theta < 2.934$$

a rather large interval.

Using the additional data for c_t, we can compute an approximate value of θ; in fact, the apparent exit time from the system, Ω_t^*, can be computed from Eq. (16),

$$\Omega_t^* = \frac{3}{2} - \frac{4}{7} = \frac{13}{14}$$

thence

$$\phi \cong \frac{13}{14} \cdot \frac{8}{5} = 1.49$$

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

As shown in the original paper (24), 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

$$k_{10} = \frac{5}{4}$$

$$k_{20} = \frac{5}{4} + \frac{3}{16\eta} - \frac{\epsilon}{2\eta}$$

$$k_{30} = \frac{5}{4} - \frac{\epsilon}{2\eta}$$

Similarly the disposition functions of the three compartments are

$$\frac{c_1(t)}{c_1(0)} = \frac{3}{8} \cdot e^{-3t} + \frac{1}{4} \cdot e^{-2t} + \frac{3}{8} \cdot e^{-t}$$

$$\frac{c_2(t)}{c_1(0)} = -\epsilon \cdot e^{-3t} + \eta \cdot e^{-2t} + (\epsilon - \eta) \cdot e^{-t}$$

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

and in operational form,

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

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

$$\frac{\{c_3\}}{c_1(0)} = \frac{(3/4 - 3\epsilon + \eta)s + 3/2 - 4\epsilon + 3\eta}{s^3 + 6 \cdot s^2 + 11 \cdot s + 6}$$

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,

$$\Omega_t = \frac{k_{10}\Omega_1 + k_{20}\Omega_2 + k_{30}\Omega_3}{k_{10} + k_{20} + k_{30}}$$

Table III. Permanence Time (T_1), Exit Time (Ω_1), Initial Volume of Distribution (V_1), Steady-State Volume of Distribution (V_{ss}), and Dilution Factor (θ) of rCD4-IgG in the Four Species in Table I

		Ω_1 (hr)			V_{ss} (ml)		θ	
Species	T_1 (hr)	Min.	Max.	V_1 (ml)	Min.	Max.	Min.	Max.
Rat	4.58	10.0	25.8	11.3	24.7	63.5	2.19	5.62
Rabbit	8.90	29.6	72.0	214	710	1730	3.32	8.09
Monkey	11.2	17.4	85.4	171	263	1290	1.54	7.57
Human	25.2	40.2	88.4	3,980	6,370	14,000	1.60	3.51

Table IV. Extreme Values of Some of the Parameters of the Compartmental System Examined by Berman and Schoenfeld (24)

ϵ	η	k_{10}	k_{20}	k_{30}	Ω_t	θ
−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

Table IV 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}, and k_{30}, and the resulting values of Ω_t and θ.

Note that this range is much smaller than the one determined from the measurement in the first compartment alone.

SYMBOLS AND DEFINITIONS

Compartment = a homogeneous set of particles with the same, constant probability of being removed or transferred

Dilution factor (θ) = the ratio V_{SS}/V_1, steady-state volume of distribution divided by initial volume of distribution

Exit time of compartment i (Ω_i) = the ratio $\int_0^\infty t \cdot c_i(t)dt / \int_0^\infty c_i(t)dt$

Fractional turnover rate of compartment $i(K_i)$ = fraction of drug in compartment i that is removed or transformed per unit time

Initial volume of distribution (V_1) = amount of drug in the sampling compartment divided by concentration there

Linear system = a system where the principle of superposition holds

Permanence time of compartment i (T_i) = expected interval of time spent by the drug in all its passages through compartment i

Pool = a nonhomogeneous set of particles defined by specific boundaries and composition

State-determined system = a system whose present state determines all future states; also called "time-invariant system"

Steady-state volume of distribution (V_{SS}) = amount of drug in the whole system divided by concentration in the sampling compartment

Turnover number of compartment i (v_{ii}) = the ratio T_i/t_i, or the expected number of passages of a drug through the same compartment

Turnover time of compartment i (t_i) = expected interval of time spent by the drug in each passage through compartment i

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