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Some Clarifications Regarding Moments of Residence Times with Pharmacokinetic Models

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The stochastic formulation of linear kinetic models is elaborated in order to introduce some new concepts and help clarify the meaning and role of residence time moments. Certain conditional moments are introduced. Multicompartment and steady-state dosing within the stochastic context are considered. A general model-independent formula for steady state volume of distribution and a new concept of steady-state moments are presented. A technique for constructing a model of a given topology from its moments is also given.

KEY WORDS: Stochastic linear kinetic models; residence time moments; method of statistical moments.

INTRODUCTION

Moments of residence times with pharmacokinetic models have received considerable attention since the appearance of a paper by Yomaoka *et al* (1) 9 years ago. They are "model-independent" parameters, i.e., parameters that may be interpreted under somewhat general model assumptions. As such, they also provide an interesting characterization of specific models. A discussion of the latter is given by Matis *et al.* (2), who indicate how moments arise when pharmacokinetic models are given a stochastic formulation. However, it appears that much confusion remains about the interpretability of moments. This paper elaborates the stochastic formulation in order to introduce some new concepts and help clarify further the meaning and role of moments. Certain important conditional moments are introduced. Multicompartment dosing and steady-state dosing within the

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stochastic context are considered. The "model-independent formula" for Vd_{ss} (Ref. 3) is reconsidered and extended. A new concept of steady-state moments is presented. Through the use of the matrix exponential a large degree of generality involving moments can be achieved. A technique for constructing a model of a given topology from its moments is also given.

THE METHOD OF STATISTICAL MOMENTS

A statistical model is a specification of all or part of the joint probability distribution of randomly occurring quantities. A classical method for estimating the parameters of such a distribution, originated near the turn of the century by Karl Pearson (4), is called the *method of moments* (5). It is based on statistically independent replicates of observed values of the random quantities. So-called sample moments are computed from these values and set equal to corresponding theoretical moments derived under the model and expressed in terms of the model parameters. The resulting equations are solved for estimates of the model parameters. These parameters quantify, among other characteristics of the model, the magnitude of the random variability in the observed values.

The *method of statistical moments* described by Yamaoka *et al.* (1) is similar to the method of moments. It is based on observed concentration values. From these concentration values, other values are computed from formulas that we shall call *moments from the data-curve formulas.* These latter values are analogous to (but are not the same as) sample moments and are set equal to corresponding theoretical moments. The theoretical moments may themselves be the pharmacokinetic model parameters of interest, in which case the values from the moments from the data-curve formulas provide estimates of them. Or, if the theoretical moments are expressed in terms of other pharmacokinetic model parameters, which are the parameters of interest, estimates for the latter may be obtained by solving the resulting set of equations. The nature of these theoretical moments is described in detail in the next section. However, the following important points regarding them should be understood at the outset. Though the observed concentration values are subject to assay variability, the moments and other model parameters are *kinetic* and do not quantify the magnitude of this variability. In this respect the method of moments and the method of statistical moments differ. The model parameters quantify the (average) time course of drug amount. Matis *et al.* (2) explain how they also quantify random kinetic molecular variability, another type of variability affecting the concentration values (see also below). However, this source of variability is usually less important than random assay variability.

Since both random assay and random kinetic molecular variability affect the concentration values, errors in the parameter estimates (from the method of statistical moments) occur. Even if the assay had great precision, and the effect of molecular variability on concentrations were negligible, parameter estimation error would still occur due to the numerical error involved in approximating theoretical moments, defined by integrals of continuous functions, by the discrete moments from the data-curve formulas based on a limited number of concentration values. Interestingly, to date quantification of error in parameter estimates from any of these three sources cannot be found in the pharmacokinetic literature. In other words, we have no standard error formulas for parameter estimates produced by the method of statistical moments. On the other hand, in certain cases standard error formulas for parameter estimates produced by the method of moments do exist.

Matis *et al.* (2) give a compartmental model for the kinetics of a particle of drug, which specifies the probabilities that the particle is in various compartments at a given time. The total time the particle resides in a given compartment, or in the body, is called a *residence time* and is a randomly occurring quantity. The statistical moments of the residence time in the body are the theoretical moments involved in the method of statistical moments. Thus, the use of the word "statistical" in the method's name can be rationalized. With Pearson's method of moments the involved theoretical moments are also statistical moments, but they are moments of observable random variables. The residence time of a drug particle is not observable. This is another important difference between the method of moments used by statisticians and the method of statistical moments used by pharmacokineticists. As the reader can plainly see, the terminology currently in use can be confusing, and one needs to be careful. In this spirit we commence our technical presentation.

STOCHASTIC FORMULATION

Notation of Matis *et al.* shall be used. Specifically, let k_{ij}, for $j = 0, 1, \ldots, n$, $i = 1, 2, \ldots, n$, $i \neq j$, be a probability intensity coefficient relating transfer of the particle from compartment i to compartment j. Compartment 0 represents the system exterior. More precisely, let the conditional probability that the particle enters compartment j during the interval $(t, t+u)$, given that at time t it resides in compartment i, be given by $k_{ij}u + \varepsilon_{ij}(u)$, where ε_{ij} is a function of u such that $\varepsilon_{ij}(u)/u \to 0$ as $u \to 0$. In other words, up to a quantity $\varepsilon_{ij}(u)$ that is "of smaller order than u," the probability of interest is proportional to u with proportionality constant k_{ij}. This assumption implies not only a first-order character to the system, but also a homogeneity

insofar as the conditional probability is independent of t itself. This assumption is really all that is needed to compute the conditional probabilities that the particle is in various compartments at time t, given that at time 0 it is in a certain compartment. (Various other assumptions are listed by Matis *et al.*, but they are not needed for this purpose.) Let K be the familiar $n \times n$ matrix whose i, j element is k_{ij}, where $k_{ii} = -\sum_{j=0, j\neq i}^{n} k_{ij}$. Let $w_{ij}(t)$ be the probability that the particle is in compartment j at time t, given that at time 0 it is in compartment i. Then the matrix $W(t) = (w_{ij}(t))$ is simply given by $W(t) = e^{Kt}$, where the involved exponential is the matrix exponential. This follows from standard methods for Markov processes; see, e.g., Ref. 6.

Matis *et al.* discuss the total time τ_{ij} that a particle resides in compartment $j \neq 0$, given that at time 0 it is in compartment i. Its mean, or first moment, is simply $-k^{ij}$, where $K^{-1} = (k^{ij})$. They also give a formula for its variance, or second central moment, and discuss an application of these formulas based on the idea that estimates of the k_{ij} may be obtained directly from concentration data by nonlinear regression and then substituted into these formulas. With the method of statistical moments *per se* one proceeds differently. One estimates the moments of residence times directly from concentration data, and then, in addition, one might invert formulas for these moments to obtain estimates for the k_{ij}. The model of Matis *et al.* must be elaborated in order to discuss the residence time in the body. The moments of this residence time are involved in the method of statistical moments.

Before describing this elaboration, attention should be focused on a second assumption, namely, that the real parts of the eigenvalues of K are negative. This assumption equivalently means that *on the average* the particle cannot reside forever in the body, i.e., that indeed K^{-1} exists. Therefore, a system satisfying this assumption is said to be *nonsingular.* Matis *et al.* describe this assumption by saying that it "insures system stability." It will be useful in the sequel to note now that this assumption is also equivalent to

$$\text{for all} \quad \beta \geq 0, \quad \lim_{t\to\infty} t^{\beta} e^{Kt} = 0 \tag{1}$$

as is shown in Appendix A.

To elaborate the stochastic model we consider the input process. For the moment suppose simply that N_i particles are introduced into compartment i at time 0. Then the expected number $A_j(t)$ of particles in compartment j at time t is given by $\sum_i N_i w_{ij}(t)$, which is just the amount of drug in compartment j at time t given by familiar deterministic linear kinetic theory with given K matrix. (If the eigenvalues of K are distinct, this is a sum of exponentials; however, distinct eigenvalues are not being assumed.) We shall henceforth refer to the expected number of particles as *the amount.*

The probability that a particle chosen at random from the total drug pool ($N_1+N_2+\cdots+N_n$ particles) is in compartment j at time t is given by $\sum_i p_i w_{ij}(t)$, where $p_i = N_i/\sum_j N_j$. This is just a weighted average of the $w_{ij}(t)$ for fixed j. Let p be the column vector of weights $(p_1, p_2, \ldots, p_n)'$, where the prime denotes vector transpose. Let h_j be the column vector of length n consisting of all zeros except in position j, where there is a 1. Then the probability in question may also be written more compactly as $p'e^{Kt}h_j$, and $A_j(t)$ may be written $Np'e^{Kt}h_j$, where $N=\sum_j N_j$. Lastly, the probability that a particle chosen at random from the total drug pool is still in the body at time t is given by $\sum_j p'e^{Kt}h_j = p'e^{Kt}\mathbf{1}$, where $\mathbf{1}$ is the column vector consisting of all ones. The expected number of particles in the body at time t is $\sum_j A_j(t) = Np'e^{Kt}\mathbf{1}$.

The residence time that must now be considered is the time T that a particle chosen at random from the total drug pool resides in the body. This is a well-defined random variable whose cumulative distribution function F must be $F(t)=1-p'e^{Kt}\mathbf{1}$, i.e., the probability that the particle exits from the body before time t. Its density f is obtained by differentiating F with respect to t, i.e., $f(t)=-p'Ke^{Kt}\mathbf{1}$. The statistician would identify T with a survival time variable, the time the particle "survives" in the body. Often the *cumulative hazard function* H of a survival time variable is of interest (7). This is the function

$$H(t)=\int_0^t f(\tau)/[1-F(\tau)]\,d\tau.$$

In the specific situation at hand,

$$H(t)=-\int_0^t p'Ke^{K\tau}\mathbf{1}/p'e^{K\tau}\mathbf{1}\,d\tau \tag{2}$$

(For a one compartment model, all quantities are scalars, and $H(t)=-\int_0^t K\,d\tau=-Kt$.) In general, the relationship $1-F(t)=e^{-H(t)}$ holds (where the involved exponential is now the scaler exponential). So specifically, $p'e^{Kt}\mathbf{1}=e^{-H(t)}$, where $H(t)$ is given by Eq. (2). Therefore, the total amount of drug in the body is always given by an interesting monoexponential $Ne^{-H(t)}$, one whose argument H, however, is not generally linear in time. Of most interest to us, though, are the moments of T.

Define the function Ψ on the set $\alpha>0$ by

$$\Psi(\alpha)=\int_0^\infty t^{\alpha-1}e^{Kt}\,dt.$$

For Ψ to be well-defined, i.e., for the involved integral to exist, (1) must hold. When K is the identity matrix, this is the matrix analogue of the gamma function Γ, and the usual argument establishing the familiar recursive relationship $\Gamma(\alpha+1)=\alpha\Gamma(\alpha)$ also establishes $\Psi(\alpha+1)=-\alpha K^{-1}\Psi(\alpha)$.

In detail:

$$\frac{d}{dt} t^{\alpha} e^{Kt} = \alpha t^{\alpha-1} e^{Kt} + t^{\alpha} K e^{Kt}$$

and then integrating,

$$0 = \alpha \Psi(\alpha) + K\Psi(\alpha+1)$$

Therefore, the rth statistical moment of T, defined by $M_r = \int_0^{\infty} t^r f(t)\, dt$, is

$$M_r = -p'\left(\int_0^{\infty} t^r K e^{Kt}\, dt\right)\mathbf{1} = -p'K\Psi(r+1)\mathbf{1} = r!p'(-K)^{-r}\mathbf{1} \qquad (3)$$

Note that the nonsingularity assumption is sufficient to assure the existence of moments of all orders, not just the first moment. The first moment M_1 may be called the *mean residence time.*

In order to finally relate the M_r to the method of statistical moments one needs to consider a probability distribution on T different from that specified by the density f. One needs to consider the conditional distribution of T, *given* that the particle exits the body from some given compartment. There are in general several such conditional distributions, one for each possible compartment from which exit to the system exterior is possible, i.e., one for each l such that $k_{l0} \neq 0$. Let L be the set of l such that $k_{l0} \neq 0$, and for $l \in L$, let E_l be the event that the particle exits the body from compartment l. Conditional on E_l occurring, the expected value of T will generally be different from M_1, the unconditional expected value of T. Similarly for moments of higher order.

Appendix B sketches an argument for the fact that the conditional probability that a particle chosen at random from the total drug pool is in compartment j at time t, given that E_l occurs, is $p'e^{Kt}h_j h_j' K^{-1}h_l / p'K^{-1}h_l$. (The vectors h_j and h_l are defined above.) Then the conditional probability that a particle chosen at random is in the body at time t, given that E_l occurs, is the sum of these ratios over j, namely $p'K^{-1}e^{Kt}h_l / p'K^{-1}h_l$ (since $\sum_j h_j h_j'$ is the identity matrix and since K^{-1} and e^{Kt} commute.) Therefore, the conditional distribution function of T, given that E_l occurs, is

$$F_l(t) = 1 - (p'K^{-1}e^{Kt}h_l / p'K^{-1}h_l) = p'K^{-1}(I - e^{Kt})h_l / p'K^{-1}h_l \qquad (4)$$

The conditional density of T, given that E_l occurs, is $f_l(t) = -p'e^{Kt}h_l / p'K^{-1}h_l$.

The conditonal rth moment of T, given E_l, may now be computed (similar to the way M_r is computed):

$$M_{lr} = -p'\left(\int_0^{\infty} t^r e^{Kt}\, dt\right)h_l / p'K^{-1}h_l = -p'\Psi(r+1)h_l / p'K^{-1}h_l$$

$$= -r!\, p'(-K)^{-(r+1)} h_l / p' K^{-1} h_l \tag{5}$$

Note that in a similar way

$$\int_0^\infty t^r A_l(t)\, dt = Np' \left(\int_0^\infty t^r e^{Kt}\, dt \right) h_l = Nr!\, p'(-K)^{-(r+1)} h_l \tag{6}$$

Therefore,

$$M_{lr} = \int_0^\infty t^r A_l(t)\, dt \Big/ \int_0^\infty A_l(t)\, dt \tag{7}$$

The quantity on the right side of Eq. (7) can be estimated from a moments from the data-curve formula. Such a formula, then, is estimating a conditional moment of T as defined above. That is, under the homogeneous first-order assumption and assumption (1) only, the right side of Eq. (7) is not only estimable, but physically interpretable as well. This interpretability holds regardless whether elimination to the system exterior takes place from any compartments other than compartment l!

Formula (5) has been derived by Nüesch (8) (readers wishing to follow the recursive-type argument in more detail should see this paper). In that paper moments are discussed. However, they are defined simply by the right side of Eq. (7), rather than in some physically interpretable way. In the special case $p = h_l$, Cobelli and Toffolo (9) give a formula for M_{l1}:

$$M_{l1} = \sum_{j=1}^{n} \frac{k^{jl}}{k^{ll}} k^{lj}$$

which the reader can easily derive from Eq. (5). The ratio k^{jl}/k^{ll} is interpretable as the probability that the particle resides in compartment l at some time point, given that it resides in compartment j at some earlier time point (10).

A basic probabilistic identity gives

$$M_r = \sum_{l \in L} e_l M_{lr} \tag{8}$$

where e_l is the probability that a particle chosen at random from the total drug pool exits the body from compartment l. In Appendix B it is shown that $e_l = -k_{l0} p' K^{-1} h_l$. Clearly, this quantity can be estimated by the total amount of drug eliminated from compartment l to the system exterior, expressed as a fraction of N. This fact, in conjunction with the ability to estimate the M_{lr} with the usual moments from the data-curve formulas, allows M_r to be estimated. Actually, from the point of view of this paper, the moments from the data-curve formulas should be regarded as a general class of formulas that provide estimates of all the terms in Eq. (8), i.e., the

e_l as well as the M_{lr}, and therefore, also provide an estimate of M_r. It must be recognized though, that one's ability to estimate M_r in this way depends on one's ability to identify those compartments from which elimination can occur and to measure concentrations over time in these compartments, as well as the total amounts of drug eliminated from each of them to the system exterior. Often, the additional assumption that for some m, $e_m = 1$ is made. When this is possible, all other $e_l = 0$ (since $\sum_{l \in L} e_l = 0$), $M_r = M_{mr}$, and only concentrations from compartment e_m need be measured. This special case forms the context in which the method of statistical moments has, for the most part, been previously discussed.

A number of authors have previously made the point that when mean residence time is defined by Vd_{ss}/CL, and where the reference compartment is compartment m, then mean residence time is given by the right side of (7) with $r = 1$ and $l = m$, but only under the additional exit assumption $e_m = 1$ (e.g., 11, 12). The definition of mean residence time given in this paper, i.e., M_1, has the advantage that it is defined independently of steady-state considerations and corresponds to a bona fide mean, i.e., the statistical mean of T.

On the other hand, the quantity M_1 depends on p, the fractionalization of the total drug pool into the various compartments at time 0. At time t, fractionalization of the total drug *remaining* in the body into the various compartments is $z = (p'e^{Kt})/(p'e^{Kt}\mathbf{1})$ (in row vector form), and if t is now taken to be time 0, then the mean residence time of a drug particle chosen at random from this smaller pool is $-zK^{-1}\mathbf{1}$. Clearly, Vd_{ss}/CL also suffers from the disadvantage of depending on p. In fact, below we extend the stochastic formulation to the steady-state situation, compute Vd_{ss} and CL, and observe that $M_1 = Vd_{ss}/CL$.

In the special case $r = 1$ and the two-compartment open model with elimination from both compartments, Eq. (8) appears in a paper by Collier (13). The arguments in that paper are not based on stochastic kinetics, and the author describes M_{l1} as "the mean residence time of drug in compartment l," clearly a very inaccurate and misleading description. The mean residence time in compartment l of a particle chosen at random from the drug pool must be $-p'K^{-1}h_l$, which surely is not M_{l1}.

In a later paper by Cobelli and Toffolo (14), where a similar special case is considered and the same basic formula appears, the author's describe M_{l1} as "the expected time a particle will spend in the system before leaving it for the last time from compartment l," a better but still somewhat imprecise description.

STEADY STATE: MULTIPLE BOLUS DOSES

Suppose next that N_i particles are introduced into compartment i at

times $0, \delta, 2\delta, \ldots, l\delta$. Let $s = l\delta$. Then the expected number $A_j(t)$ of particles in compartment j at time $t \geq s$ is given by $\sum_{k=0}^{l} \sum_i Np_i w_{ij}(t - k\delta)$, where N and the p_i are as above. Again, this is the familiar expression for amount of drug. The probability that a particle chosen at random from the total drug pool of $(l+1)N$ particles is in compartment j at time t is given by

$$\frac{1}{l+1} \sum_{k=0}^{l} \sum_i p_i w_{ij}(t - k\delta)$$

This probability may also be written

$$\frac{1}{l+1} \sum_{k=0}^{l} p' e^{K(t-k\delta)} h_j = \frac{1}{l+1} p' e^{Kt} (I - e^{-K(l+1)\delta})(I - e^{-K\delta})^{-1} h_j \qquad (9)$$

using the matrix analogue for the sum of a geometric series. The amount $A_j(t)$ is given by $(l+1)N$ times the expression on the right side of Eq. (9). Let $R = N/\delta$, the "rate" of drug administration over the interval δ. As $l \to \infty$, while N, p, δ, and $\Delta = t - s$ remain constant, $A_j(t)$ tends to

$$A^B_{j,\mathrm{ss}}(\Delta) = -R\,\delta p' e^{K(\Delta-\delta)} (I - e^{-K\delta})^{-1} h_j \qquad (10)$$

[since $e^{Kt} \to 0$ and $t - (l+1)\delta = \Delta - \delta$]. This is the steady-state amount in compartment j, Δ time units into the dosing interval, whence the notation on the left side. (The B is for multiple bolus doses.) If moreover, $t = s$, then using a little algebra, one finds for the steady-state amount at the beginning of the dosing interval

$$A^B_{j,\mathrm{ss}} = R\,\delta p' (I - e^{K\delta})^{-1} h_j \qquad (11)$$

Next, we wish to consider a constant rate infusion. Regarding a constant rate infusion as the limit of multiple (equal) doses, where each dose and the dosing interval decrease in a constant ratio, is commonplace to pharmacokineticists. If this point of view is taken, then, as $\delta \to 0$, while R remains constant, $A^B_{j,\mathrm{ss}} \to -Rp'K^{-1}h_j$. {To see this, observe that, by l'Hospital's rule, for all i, $h_i'(I - e^{K\delta})h_i/\delta \to -h_i' K h_i$, so that $[(I - e^{K\delta})/\delta]^{-1} \to -K^{-1}$.} However, it is physically impossible for N to remain proportional to δ as $\delta \to 0$; after all, $N \geq 1$. So, strictly speaking, a constant rate infusion must be regarded differently.

STEADY STATE: CONSTANT RATE INFUSION

Suppose that the time some given particle enters the body via compartment i can be any time in the interval $(0, s)$ with equal likelihood. That is, suppose that the time this particle enters compartment i is a stochastic variable whose probability density function is given by the constant function $g(\tau) = 1/s$ for all $\tau \in (0, s)$. Then the probability that the particle enters compartment i during any interval of length u is u/s, so that of N_i particles

entering compartment i, each obeying this uniform probability law, $(N_i/s)u$ particles on the average enter during any such interval. The number $R_i = N_i/s$ is the "rate" of infusion and is a constant. However, in contrast to the homogeneous law governing the kinetics in the body, the conditional probability that the particle enters the body via compartment i during the interval $(t, t+u)$, given that at time t it has not yet entered the compartment, is given by $(s-t)^{-1}u$, which is dependent on t.

The probability that the particle is in compartment j $(j = 1, 2, \ldots, n)$ at time $t \geq s$ is

$$x_{ij}(t) = \int_0^s g(\tau) w_{ij}(t-\tau)\, d\tau = s^{-1} h_i' (-K^{-1} e^{K(t-s)} + K^{-1} e^{Kt}) h_j \quad (12)$$

Letting this equation apply to each of N_i particles entering compartment i, we have that the expected number $A_j(t)$ of particles in compartment j at time t is given by $\sum_i N_i x_{ij}(t)$, which can be written $N \sum_i p_i x_{ij}(t)$ with N and the p_i defined as before. Define $R = N/s$, the "global rate of infusion." Also, let $\Delta = t - s$. Then

$$A_j(t) = Rp'(-K^{-1} e^{K\Delta} + K^{-1} e^{Kt}) h_j \quad (13)$$

As the N_i and $s \to \infty$, while the R_i and Δ remain constant, $A_j(t)$ tends to

$$A_{j,\mathrm{ss}}^I(\Delta) = -Rp' K^{-1} e^{K\Delta} h_j \quad (14)$$

This is the steady-state amount in compartment j at Δ time units after steady state is "attained" and the infusion is terminated, whence the notation on the left side. If, moreover, $t = s$, then the steady-state amount is

$$A_{j,\mathrm{ss}}^I = -Rp' K^{-1} h_j \quad (15)$$

Therefore, at steady state, the amount in the body is

$$A_{\mathrm{ss}}^I = \sum_j A_{j,\mathrm{ss}}^I = -Rp' K^{-1} \mathbf{1} = RM_1 \quad (16)$$

The steady-state volume of distribution referenced to compartment j is then

$$Vd_{\mathrm{ss}}^{(j)} = Vd_j RM_1 / A_{j,\mathrm{ss}}^I \quad (17)$$

where Vd_j is the (absolute) volume of compartment j. But the apparent steady-state volume of compartment l referenced to compartment j is $Vd_{l,\mathrm{ss}}^{(j)} = Vd_j \cdot A_{l,\mathrm{ss}}^I / A_{j,\mathrm{ss}}^I$. So, Eq. (17) is equivalent to

$$Vd_{\mathrm{ss}}^{(j)} = Vd_{l,\mathrm{ss}}^{(j)} \cdot RM_1 / A_{l,\mathrm{ss}}^I \quad (18)$$

Clearance, referenced to compartment j, $CL^{(j)}$, may be defined to be the ratio of R to steady-state concentration in compartment j. So, by Eq. (17), the familiar formula $Vd_{\mathrm{ss}}^{(j)} = M_1 CL^{(j)}$ is seen to be derivable from the

principles of stochastic kinetics! Using Eqs. (6)–(8) and (15), one can give the following extension of the Benet-Galeazzi formula:

$$Vd_{ss}^{(j)} = N \sum_{l \in L} e_l \left[\int_0^\infty tC_l(t)\, dt \right] \Big/ \left[\int_0^\infty C_l(t)\, dt \int_0^\infty C_j(t)\, dt \right] \tag{19}$$

where $C_j(t) = A_j(t)/Vd_j$ and $A_j(t)$ is computed as with bolus dosing, and $C_l(t)$ and $A_l(t)$ are similar. When $e_j = 1$, Eq. (19) gives the usual formula.

It is also of interest to consider steady-state amounts and volumes stratified by the events E_l. This allows an interpretation of each individual term in the sum on the right side of Eq. (19) and thereby a decomposition of $Vd_{ss}^{(j)}$ into a sum of (newly defined) steady-state volumes. The probability that a particle is in compartment j at time $t \geq s$ *and* exits the body from compartment l, given that it is in compartment i at time 0, is

$$\begin{aligned} x_{ij(l)}(t) &= -\int_0^s g(\tau) k_{l0} p' e^{K(t-\tau)} h_j h_j' K^{-1} h_l \, d\tau \\ &= s^{-1} k_{l0} h_i' (K^{-1} e^{K(t-s)} - K^{-1} e^{Kt}) h_j h_j' K^{-1} h_l \end{aligned} \tag{20}$$

Then, as above, the expected number of particles at steady state in compartment j that exit the body from compartment l is

$$A_{j(l),ss}^I = R k_{l0} p' K^{-1} h_j h_j' K^{-1} h_l \tag{21a}$$

Therefore, at steady state the amount in the body that exits from compartment l is

$$A_{(l),ss}^I = \sum_j A_{j(l),ss}^I = R k_{l0} p' K^{-2} h_l = e_l R M_{l1} \tag{21b}$$

A new steady-state volume of distribution may be defined by

$$Vd_{(l),ss}^{(j)} = Vd_j \cdot A_{(l),ss}^I / A_{j,ss}^I \tag{22}$$

We have

$$Vd_{(l),ss}^{(j)} = Vd_j \cdot e_l R M_{l1} / A_{j,ss}^I \tag{23}$$

So,

$$Vd_{(l),ss}^{(j)} = e_l M_{l1} CL^{(j)} \tag{24}$$

Therefore, $Vd_{(l),ss}^{(j)}$ is seen to be the "lth term" of the sum in Eq. (19).

STEADY-STATE RESIDENCE TIME MOMENTS

In this section a new class of estimable residence time moments is defined. As mentioned above, the M_r depend on p, the fractionalization of the total drug pool into the various compartments at time 0. What are the

moments of the residence time when p is the fractionalization of the steady-state total body amount into the various compartments? That is, consider the fractionalization given by $\pi_i = A^I_{i,ss}/A^I_{ss}$, $i = 1, 2, \ldots, n$, and the distribution of the time remaining in the body of a particle chosen at random from the steady-state pool with probability π_i of being chosen from compartment i. Then the cumulative distribution function of the time such a particle remains in the body is $1 - \pi' e^{Kt}\mathbf{1}$. From Eq. (3), the moments corresponding to this distribution are $M_{r,ss} = r!\,\pi'(-K)^{-r}\mathbf{1}$. However, from Eqs. (15) and (16), π' itself is $-M_1^{-1}p'K^{-1}$ and depends on the fractionalization of the drug pool at time 0. Therefore,

$$M_{r,ss} = r!\,p'(-K)^{-(r+1)}\mathbf{1}/p'K^{-1}\mathbf{1} \tag{25}$$

In the same way, conditioning on the events E_l,

$$M_{lr,ss} = -r!\,\pi'(-K)^{-(r+1)}h_l/\pi'K^{-1}h_l = r!\,p'(-K)^{-(r+2)}h_l/p'K^{-2}h_l \tag{26}$$

which, using Eq. (6), is

$$M_{lr,ss} = (r+1)^{-1}\int_0^\infty t^{r+1}A_l(t)\,dt \Big/ \int_0^\infty tA_l(t)\,dt \tag{27}$$

We have that $e_{l,ss} = -k_{l0}p'K^{-2}h_l/p'K^{-1}\mathbf{1}$. This probability can be estimated by infusing to steady state, terminating the infusion, measuring the total amount of drug eliminated from the body from compartment l during the subsequent decline, and expressing this amount as a fraction of A^I_{ss}. In this regard A^I_{ss} can itself be estimated via Eqs. (8) and (16). Finally, analogous to Eq. (8),

$$M_{r,ss} = \sum_{l \in L} e_{l,ss}M_{lr,ss} \tag{28}$$

so that $M_{r,ss}$ can be estimated from drug concentrations over time after bolus dosing and from amounts of drug eliminted from the body after bolus dosing and after termination of steady-state infusion.

INVERSION OF THE MOMENTS FORMULAS

In this section we consider the problem of solving the system of equations

$$M_r = r!\,p'(-K)^{-r}\mathbf{1} = c_r, \qquad r = 1, \ldots, m \tag{29}$$

for K, where the c_r are specified constants and m is a number chosen so that the system has a unique solution. The number m is either the number of elements in K or a smaller number when certain constraints are put on K; see below. The ability to solve system (29) is potentially useful in a number of ways. Most importantly, if the method of statistical moments is

used to estimate the moments M_r, and these estimates are given by the c_r, then estimates of the k_{ij} can be obtained by solving system (29) (assuming some specific pharmacokinetic model). In general, the solution to system (29) produces a specific instance of a model of given topology (i.e., a given number of compartments with specified first-order homogeneous connections between them) from its moments, when these moments are known. Note that system (29) is highly nonlinear in the unknowns k_{ij}.

As an example of a solution to system (29), consider two curves shown in Fig. 1. The solid curve is the amount of drug (i.e., mean number of drug particles) in the central compartment of a two-compartment open model, where elimination occurs only from this compartment, after a bolus dose of drug is introduced into a drug depot (a first-order absorption compartment). The governing rate constants are $k_{10} = 0.8$, $k_{12} = 0.05$, $k_{21} = 0.9$, $k_a = 2.5$. These constants determine a set of moments c_r. The dashed curve in the figure is the amount of drug in the central compartment of a one-compartment open model, after a bolus dose of drug is introduced into a drug depot. The two governing rate constants were obtained by solving system (29) for K, subject to constraints deriving from the topology of this special model (see below). (In this case $m = 2$.) Their values are $k_{10} = 0.716$,

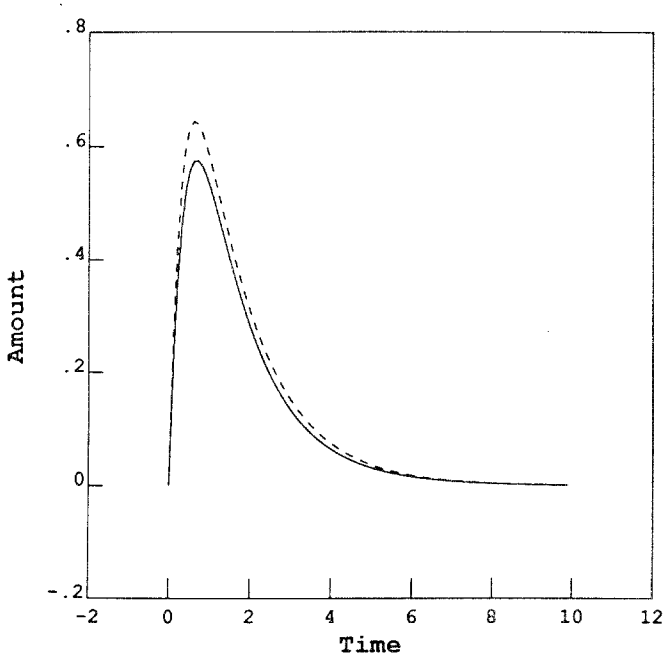

Fig. 1.

$k_a = 3.1$. This is typical of what one would obtain when for the purposes of data analysis a one-compartment model is assumed, but where the true (unknown) model is a two-compartment model, and one estimates the rate constants with the method of statistical moments. The dashed curve lies above the solid curve. This is because the residence time in the peripheral compartment of the true model must be accounted for by a residence time in the central compartment of the assumed model that is longer than the residence time in the central compartment of the true model. (However, see the discussion section.)

One technique for solving system (29) is to proceed directly and, using a good mathematical program for solving nonlinear equations, e.g., ZSPOW from IMSL (15), search through "K space" for the solution. This would involve an inversion of the K matrix each time a value of K is examined, and each such inversion entails both computer time and numerical error (although the latter can be well-controlled using double precision, but at the cost of increased computer time). Alternatively, one can use the program to solve (29) for (the elements of) K^{-1}, and, having this solution in hand, then invert it to obtain K. This is the tack we took to produce the results presented above.

Since we constrained K to be mammillary with exit from the central compartment only, K^{-1} had to be constrained accordingly. Constraints on K can often translate easily into constraints on K^{-1}. The relationships can be determined upon visual inspection, keeping in mind the characterization that $-k^{ij}$ is the mean (total) residence time of a particle in compartment j when it is in compartment i at time 0. For example, when exit is only from compartment 1, then for all i, $k^{i1} = k^{11}$. This is because no matter where a particle begins, it must initially enter compartment 1 at some time, and, once it does, its subsequent path among the compartments is stochastically determined irrespective of where it has been before entering compartment 1. For another example, when, in addition, all compartments are connected only via compartment 1, i.e., the so-called mammillary structure, then for all j, the k^{ij} are equal for all $i \neq j$. In general, constraints can be implemented with ZSPOW in the usual way by defining a transformation between a set of unconstrained variables, numbering (possibly) fewer than n^2, and the variables k^{ij}, and then conducting the search in the unconstrained space. We have found that the computation proceeds faster and more reliably if the additional constraints $-k^{ij} \geq 0$ are also incorporated (using the squaring transformation).

DISCUSSION

It is often asserted that the function $g_l(t) = A_l(t)/\int_0^\infty A_l(\tau)\, d\tau$ has the

mathematical form of a probability density and that its moments can be taken to be meaningful pharmacokinetic parameters (e.g., 8, 17). In no previous paper, though, has it really been made clear how g_l may be physically interpreted, particularly when elimination from the system can occur from several compartments. In this paper we show that $g_l = f_l$, the *conditional* density of the residence time in the body of a particle chosen at random from the total drug pool at time 0, given that this particle exits the body from compartment l [see Eq. (4)]. This fact leads to the conclusion that in general the (unconditional) mean residence time of a particle chosen at random from the drug pool at time 0 can be expressed as a weighted average of the $\int_0^\infty t g_l(t)\, dt$ over all l corresponding to compartments from which drug may leave the system [see Eq. (8)]. In the case that drug can leave the system only from compartment m, then $\int_0^\infty t g_m(t)\, dt$ is the mean residence time. This last fact is emphasized by certain recent authors (e.g., 11, 13), but still not recognized by others (e.g., 8,17). In addition, use of the weighted average, along with the extension of the stochastic formulation to the steady-state context, leads to a generalization of the Benet-Galeazzi formula [see Eq. (19)].

It should also be emphasized that a few items are not discussed in this paper.

Although consideration of the method of statistical moments has motivated certain discussion, this paper is not about the estimation of moments *per se* from concentration data. Formulas for estimating moments from limited concentration data vary and are not given here. Rather, our focus has been on the quantities being estimated, what they mean, and their relationships to the rate constants k_{ij}.

The reader might have noticed that only the means of the *numbers* of particles in compartments have been mentioned, and the variances or other moments of these numbers have not been discussed. These moments are usually thought to be of little interest to pharmacokineticists because it is felt that the numbers of particles are usually quite large and therefore little affected by stochastic behavior. Indeed, in this paper, for expository purposes, the amounts of drug, i.e., the A_j, have been identified with the mean numbers of particles. I feel, on the other hand, that a discussion of the stochastic effect on the (true) amount of drug would be beneficial, and such a discussion is in preparation. This present paper has dealt with the moments of the residence time.

An example of solving for the k_{ij}, given the moments M_r, has also been given. This particular example illustrates "fitting" one model to a second and different model. The fitting is done by equating moments, parameters whose definitions are independent of the topologies of both models. Therefore, the two models need not share any topological features. In fact, strictly

speaking, even the drug input parameters of the first model, i.e., N and p, need bear no relationship to those of the second model.

So this fitting technique is very general. However, whereas values for the k_{ij} of model 1 result, values for volume parameters of model 1 cannot be obtained solely from the moments of model 2. How might such parameters be obtained from volume and other parameters of model 2? One possibility is to compute an "apparent volume" for model 1:

$$vd_j = Vd_j \cdot a^I_{j,ss}/A^I_{j,ss}$$

where Vd_j and $A^I_{j,ss}$ are the volume and steady-sate amount for compartment j of model 2, and $a^I_{j,ss}$ is the steady-state amount for compartment j of model 1. If R is taken to be the same for both models, then by Eqs. (6) and (15),

$$vd_j = \int_0^\infty a_j(t)\,dt \Big/ \int_0^\infty C_j(t)\,dt \tag{30}$$

The integral of a_j can be obtained from p and the k_{ij} of model 1, and the latter results from the moments of model 2. The integral of C_j, however, cannot be obtained from the moments of model 2. More fundamentally, the definition of vd_j requires the identification of the jth compartment of model 1 with some specific compartment of model 2 and so is not independent of the topology of model 2. However, with such an identification, and if concentrations are measured from this compartment, then the integral of C_j can be estimated directly from these measurements. So the definitional dependence on the topology of model 2 is rather weak. Moreover, with this definition

$$vd^{(j)}_{ss} = vd_j \frac{a^I_{ss}}{a^I_{j,ss}} = Vd_j \frac{A^I_{ss}}{A^I_{j,ss}} = Vd^{(j)}_{ss}$$

since by equating moments, the first moments, in particular, are made equal, and so $a^I_{ss} = A^I_{ss}$. That is, as a by-product of this definition, the steady-state volumes of distribution of the two models must be equal.

Lastly, from Eq. (30), $\int_0^\infty c_j(t)\,dt = \int_0^\infty C_j(t)\,dt$, where $c_j(t) = a_j(t)/vd_j$. In other words, vd_j is defined such that the areas under the concentration curves (or, equivalently, the clearances) of the two models must be equal. This by itself does not imply that the two concentration curves are identical. However, for the example depicted in Fig. 1, the two concentration curves are virtually identical, in contrast to what is seen in the figure itself where the two amounts are plotted. Since they are identical, this must, moreover, be independent of the value of Vd_1.

APPENDIX A. NONSINGULARITY ASSUMPTION

In this Appendix a proof that the nonsingularity assumption is equivalent to assumption (1) is outlined. Recall that the nonsingularity assumption states that the real parts of all the eigenvalues of K are negative. Begin with the observation that a nonsingular complex matrix P exists such that $T = P^{-1}KP$ is upper triangular, i.e., all elements below the diagonal are zero (16). The eigenvalues of K, $\lambda_1, \lambda_2, \ldots, \lambda_n$, are identical with those of T. We have $e^{Tt} = P^{-1}e^{Kt}P$ is upper triangular with eigenvalues $e^{\lambda_1 t}, e^{\lambda_2 t}, \ldots, e^{\lambda_n t}$. Under assumption (1), $e^{Tt} \to 0$ as $t \to \infty$, whence the $e^{\lambda_i t} \to 0$, and so the real parts of all the λ_i must be negative. Conversely, if for all i, $\mathrm{Re}(\lambda_i) < 0$, then by repeated use of l'Hospital's rule, for all i, for all $\beta \geq 0$, $t^\beta e^{\lambda_i t} \to 0$ as $t \to \infty$, whence for all $\beta \geq 0$, $t^\beta e^{Tt} \to 0$, and so assumption (1) must hold.

APPENDIX B. A CONDITIONAL PROBABILITY

By dividing the system exterior itself into compartments Q_l, $l \in L$, such that a particle is in Q_l if and only if it exits the body from compartment l, it again may be shown by standard methods for Markov processes (6) that the probability that a particle is in Q_l at time u, given that it is in compartment j at time $t < u$, is $k_{l0}h_j'(K^{-1}e^{K(u-t)} - K^{-1})h_l$. Consequently, the probability e_l that a particle chosen at random from the total drug pool exits the body from compartment l is $-k_{l0}p'K^{-1}h_l$. As a further consequence, the probability that a particle chosen at random from the total drug pool is in compartment j at time t, and thereafter it exits the body from compartment l, is $(p'e^{Kt}h_j)(-k_{l0}h_j'K^{-1}h_l)$. The conditional probability that a particle chosen at random is in compartment j at time t, given that E_l occurs, is the ratio of this product to e_l, namely $p'e^{Kt}h_jh_j'K^{-1}h_l/p'K^{-1}h_l$.

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