Model-Independent Method of Analyzing Input in Linear Pharmacokinetic Systems Having Polyexponential Impulse Response I: Theoretical Analysis

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Abstract □ A rigorous treatment of linear compartmental systems is presented, which allows the input rate of drugs into the systemic circulation to be evaluated without assuming a specific kinetic model. The method allows the input to be evaluated in the presence or absence of any combination of intravenous bolus input and infusion input. Only data for the blood drug concentration are required; there are no requirements for specific sampling times. Applications of the equations are given in several examples. The input rate is evaluated with data obtained from a disposition experiment involving an intravenous bolus or zero-order infusion input and an experiment involving the input to be evaluated. The two experiments can be merged so that the input can be evaluated without a washout period between the two drug administrations. The equations also enable model-independent calculations of the optimal drug input control that produces any desirable drug concentration profile. The approach is a useful deconvolution method for any linear pharmacokinetic system where the impulse response can be approximated by a polyexponential expression.

Keyphrases □ Pharmacokinetic models, linear—model-independent method of input analysis, derivation of equations for linear compartmental systems, blood drug levels, polyexponential impulse response □ Blood drug levels—model-independent method of input analysis, linear pharmacokinetic model □ Models, pharmacokinetic—derivation of equations for linear compartmental systems, model-independent method of input analysis

The study of drug input plays such a fundamental role in biopharmaceutics that it has been suggested that biopharmaceutics be defined as the science of drug input (1). Numerous methods of evaluating the pharmacokinetics of drug input have been suggested (2–14), and they can be divided into model-dependent and model-independent methods.

The model-dependent methods assume a specific model for drug input (*e.g.*, first-order or zero-order input) and a specific model for drug disposition (*e.g.*, one- or multiple-compartment models). The blood profile of the drug is analyzed according to the model equation and the specific input parameter(s) that are determined graphically or by a regression technique (15). These methods often do not give a reliable estimate of the input kinetics because they are defined too specifically with respect to drug disposition and because the input is considered to be a simple process that can be described in simple mathematical terms (*e.g.*, zero- and first-order input).

With the many variables affecting the input, particularly in oral administration, it seems unlikely that the input can be approximated well in such simple terms. Nevertheless, it is not uncommon to have good agreement between such model equations and drug level data, as judged by goodness-of-fit when the equations are fitted to the data. However, the good fit may be explained by an inherent flexibility of the equations used. The equations are derived based on a model for the input and a model for the drug disposition. If the input model is wrong, the flexibility of the equation used may compensate for this error in that the disposition parameters in the iterative curve-fitting procedure take values that do not reflect the disposition but provide a good fit. Therefore, it is not uncommon when using model-dependent methods to obtain parameter values of unrealistic magnitude, even when the curve fitting is satisfactory.

Certain methods partly eliminate this problem by combining information about the drug's disposition, obtained from separate intravenous bolus or infusion data, with data resulting from the input to be evaluated. Among these methods are the deconvolution methods (9–14), which have the additional advantage of not assuming a model for the input.

This paper presents a novel method of input analysis; it is applicable to systems with central input and to certain systems with noncentral input. The method is model independent in that it does not assume any specific disposition model. The method enables an unknown input to be evaluated quantitatively in the presence or absence of any combination of intravenous bolus and infusion input. The method requires only blood drug level data with no special requirements for sampling times.

BACKGROUND

Drug input in a subject is studied most accurately by following the blood concentration–time profile. The aim of this theoretical analysis is to derive a suitable method for analyzing blood profiles to quantitate an unknown input.

The total input in the sampleable compartment is the sum of two kinds of input: the primary and the secondary. The primary input is the input into the sampleable compartment of those drug molecules that arrive there for the first time. The secondary input is the input into the sampleable compartment of those drug molecules that previously have been present there. The primary input, the object of this analysis, is of interest for bioavailability studies and for the evaluation of drug delivery systems. The secondary input encompasses ordinary back-transfer from reversible distributions between the sampleable compartment and other compartments, as well as previously presented cyclic processes (recycling) (16).

The present method uses two fundamental properties of linear response systems: the superposition property and the convolution integral property. These properties can be verified only for a known input, *i.e.*, an input made directly into the sampleable compartment. However, the primary input to be evaluated is not a direct input, so it is necessary to assume or verify that the primary input is noninteracting. It must not change the basic linear response property of the system that is evaluated from a direct input but is used to calculate an indirect input.

This requirement is basic for any model-independent and most model-dependent approaches. Its importance cannot be emphasized enough since several factors in the first-pass transfer of a drug may cause a significant interaction. Little attention has been given to this issue. The justification of linear pharmacokinetic principles in drug absorption studies often has been limited to verification of the superposition property. However, it is equally important to test for interaction, *e.g.*, by comparing the concentration profiles of a labeled drug introduced directly into the sampleable compartment in the absence and in the presence of absorption of the unlabeled drug.

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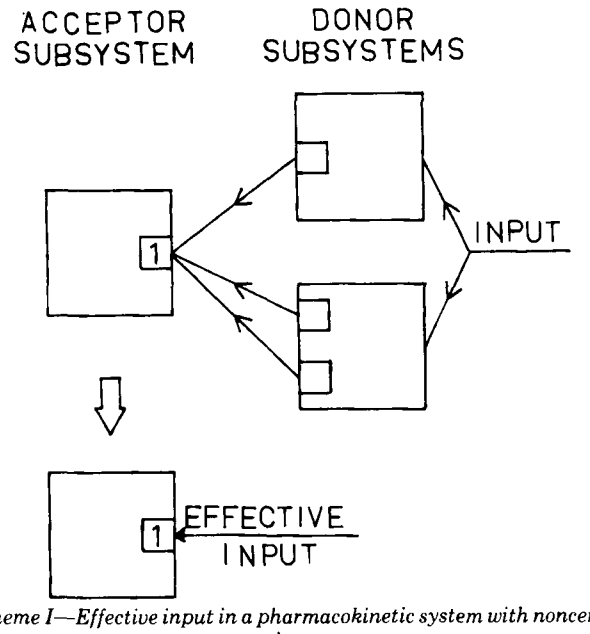

Scheme I—Effective input in a pharmacokinetic system with noncentral input

In the context of the classical linear compartmental systems discussed previously (16), a noninteracting input is either a direct input or an input reaching the sampleable compartment from one or more irreversibly connected donor subsystems (Scheme I).

The following theoretical analysis shows how a noninteracting primary input (subsequently to be referred to as the input) can be rigorously evaluated (blood = sampleable compartment) when blood level data from a known input such as an intravenous bolus or zero-order infusion input are available. The input may be of any linear or nonlinear kinetic form. Although the analysis forms a link to classical linear compartmental pharmacokinetics (16), it is not limited to such systems. The analysis applies to any linear response system where the unit impulse response is appropriately approximated by a polyexponential function with real and/or complex (conjugate) time coefficients.

In the context of compartmental principles (16), the method allows the kinetic processes in irreversibly connected donor subsystems to be of any nonlinear form. In the context of general linear system theory, the method allows individual kinetic processes to be of nonlinear form as long as the total effect of all of the processes results in an approximately linear input–response relationship.

THEORY

In a general treatment of linear compartmental pharmacokinetics, the following matrix–vector equation was presented (16):

$$\mathbf{x} = L^{-1}(\mathbf{Dv}) \qquad \text{(Eq. 1)}$$

where x_i, the ith component of the vector $\mathbf{x}$, is the amount in the ith compartment at time t; and v_i, the ith component of the input vector $\mathbf{v}$, is the sum of the initial amount in the ith compartment and the Laplace transform of the external input rate (*i.e.*, not coming from other compartments) into the ith compartment.

The disposition is defined uniquely by the disposition matrix, **D**. The operator L^{-1} denotes the inverse Laplace transform operator. In the case of central input only, the amount in the central compartment is given by:

$$x_1 = L^{-1}(d_{11}v_1) \qquad \text{(Eq. 2)}$$

where d_{11} is the 1,1 element of the disposition matrix. When a generalized function approach is used in the mathematical analysis, continuous and discontinuous input can be superimposed so that the central input, $v_1(t)$, is written as:

$$v_1(t) = f(t) + f_{bol}(t) + f_{inf}(t) \qquad \text{(Eq. 3)}$$

where $f(t)$ is the unknown input rate to be determined and $f_{bol}(t)$ and $f_{inf}(t)$ are the known bolus input rate and the infusion input rate, respectively. It is most accurate to determine $f(t)$ in the absence of other input. However, this may not always be possible. The following treatment enables $f(t)$ to be determined in the presence or absence of bolus and infusion input.

The bolus input component of Eq. 3 is described in terms of the unit impulse function or Dirac delta function, $\delta(t)$, by:

$$f_{bol}(t) = \sum_{i=1}^{R} q_i\delta(t - \tau_i) \qquad R = 1,2,..,N \qquad \text{(Eq. 4)}$$

where q_i is the quantity of the ith intravenous bolus, τ_i is the time for the ith bolus injection, R is the highest integer for which $\tau_R < t$ is satisfied, and N is the number of bolus inputs. If $\tau_R < t$ cannot be satisfied for any R, then R is defined as zero. Therefore, the right side of Eq. 4 becomes zero by definition. The Laplace transform (bars denote transformed functions) of Eq. 3 is:

$$\bar{v}_1(s) = \bar{f}(s) + \sum_{i=1}^{N} q_i e^{-\tau_i s} + \bar{f}_{inf}(s) \qquad \text{(Eq. 5)}$$

so that Eq. 2 can be written as:

$$c(t) = V^{-1}L^{-1}\left[d_{11}\bar{f}(s) + d_{11}\sum_{i=1}^{N} q_i e^{-\tau_i s} + d_{11}\bar{f}_{inf}(s)\right] \qquad \text{(Eq. 6)}$$

where the conversion from the amount, x_1, to the concentration, $c(t)$, has been done by the central volume term, V. The concentration profile following a single initial intravenous bolus input is:

$$c^*(t) = V^{-1}L^{-1}(d_{11}q^*) \qquad \text{(Eq. 7)}$$

where * distinguishes between the separate intravenous bolus experiment and the input experiment in further derivations. The transforms of Eqs. 6 and 7 are, respectively:

$$\bar{c}(s) = V^{-1}\left[d_{11}\bar{f}(s) + d_{11}\sum_{i=1}^{N} q_i e^{-\tau_i s} + d_{11}\bar{f}_{inf}(s)\right] \qquad \text{(Eq. 8)}$$

$$\bar{c}^*(s) = V^{-1}d_{11}q^* \qquad \text{(Eq. 9)}$$

When $d_{11} = V\bar{c}^*(s)/q^*$ from Eq. 9 is substituted into Eq. 8, Eq. 8 becomes:

$$\bar{c}(s) = \frac{1}{q^*}\left[\bar{c}^*(s)\bar{f}(s) + \bar{c}^*(s)\sum_{i=1}^{N} q_i e^{-\tau_i s} + \bar{c}^*(s)\bar{f}_{inf}(s)\right] \qquad \text{(Eq. 10)}$$

Therefore, the transform of the input rate can be written as:

$$\bar{f}(s) = \frac{\bar{g}(s)}{\bar{c}^*(s)} \qquad \text{(Eq. 11)}$$

where:

$$\bar{g}(s) = q^*\bar{c}(s) - \bar{c}^*(s)\sum_{i=1}^{N} q_i e^{-\tau_i s} - \bar{c}^*(s)\bar{f}_{inf}(s) \qquad \text{(Eq. 12)}$$

To facilitate a suitable solution of Eq. 11, it can be written as:

$$\bar{f}(s) = s\{[s\bar{g}(s)]\bar{h}(s)\} \qquad \text{(Eq. 13)}$$

where:

$$\bar{h}(s) = s^{-2}\bar{c}^*(s)^{-1} \qquad \text{(Eq. 14)}$$

Since $vg(0) = 0$, it follows that:

$$L^{-1}[s\bar{g}(s)] = g'(t) \qquad \text{(Eq. 15)}$$

It will be shown later that $c^*(t)$ has a functional form such that $L^{-1}[s^{-2}\bar{c}^*(s)^{-1}]$ exists. Thus, according to the convolution theorem, Eq. 13 can be transformed to:

$$f(t) = \frac{d}{dt}\int_0^t g'(u)h(t - u)du \qquad \text{(Eq. 16)}$$

According to the Leibnitz rule, Eq. 16 can be written as:

$$f(t) = \int_0^t g'(u)h'(t - u)du + g'(t)h(0) \qquad \text{(Eq. 17)}$$

Integrating by parts and noting that $g(0) = 0$, Eq. 17 becomes:

$$f(t) = h'(0)g(t) + h(0)g'(t) + \int_0^t g(u)h''(t - u)du \qquad \text{(Eq. 18)}$$

Equation 18 forms the basis for further deviations, leading to a final, more specific expression for the input, $f(t)$. The following sections deal with

the problem of deriving specific expressions for $h(0)$, $h'(0)$, $g(0)$, $g'(t)$, and $h''(t)$ in Eq. 18.

If the system has distinct eigenvalues, then the impulse response is given by:

$$c^*(t) = \sum_{i=1}^{n} a_i e^{\lambda_i t} \qquad \text{(Eq. 19)}$$

so that:

$$\bar{c}^*(s) = \sum_{i=1}^{n} \frac{a_i}{s - \lambda_i} \qquad \text{(Eq. 20)}$$

The relationship between the macroparameters in Eq. 19, the coefficient matrix, and the fundamental matrix of the compartmental system is given in the *Appendix*.

According to Eq. 20, Eq. 14 can be written as:

$$\bar{h}(s) = s^{-2}\left[\sum_{i=1}^{n} \frac{a_i}{s - \lambda_i}\right]^{-1} \qquad \text{(Eq. 21)}$$

so that, according to the initial value theorem and L'Hôspital's rule, $h(0)$ in Eq. 18 is:

$$h(0) = \lim_{s \to \infty} s\bar{h}(s) = \left[\sum_{i=1}^{n} a_i\right]^{-1} \qquad \text{(Eq. 22)}$$

Similarly, it can be shown that:

$$h'(0) = \lim_{s \to \infty} s\bar{h'}(s) = \lim_{s \to \infty} [s^2 h(s) - sh(0)] = -\frac{\sum_{i=1}^{n} a_i \lambda_i}{\left[\sum_{i=1}^{n} a_i\right]^2} \qquad \text{(Eq. 23)}$$

The $h(t)$ function can be written, according to Eq. 21, as:

$$h(t) = L^{-1} \frac{\prod_{i=1}^{n} (s - \lambda_i)}{s^2 \sum_{i=1}^{n} a_i \prod_{\substack{j=1 \\ \neq i}}^{n} (s - \lambda_j)} \qquad \text{(Eq. 24)}$$

where the numerator and denominator are polynomials of nth and $(n + 1)$th degree, respectively. Therefore, according to Heaviside's expansion theorem, Eq. 24 can be written as:

$$h(t) = A_1 t + A_2 + \sum_{i=1}^{n-1} E_i e^{\beta_i t} \qquad \text{(Eq. 25)}$$

where A_1 and A_2 are functions of $\{a_i, \lambda_i\}_1^n$ only and the $\{\beta_i\}_1^{n-1}$ are the roots of the $(n - 1)$th degree polynomial:

$$Q(s) = \sum_{i=1}^{n} a_i \prod_{\substack{j=1 \\ \neq i}}^{n} (s - \lambda_j) \qquad \text{(Eq. 26)}$$

The $\{E_i\}_1^{n-1}$ terms in Eq. 25 are given by:

$$E_\nu = \left.\frac{\prod_{i=1}^{n} (s - \lambda_i)}{\frac{d}{ds}\left[s^2 \sum_{i=1}^{n} a_i \prod_{\substack{j=1 \\ \neq i}}^{n} (s - \lambda_j)\right]}\right|_{s = \beta_\nu} \qquad \text{(Eq. 27)}$$

which leads to:

$$E_\nu = \frac{\prod_{i=1}^{n} (\beta_\nu - \lambda_i)}{2\beta_\nu \sum_{i=1}^{n} a_i \prod_{\substack{j=1 \\ \neq i}}^{n} (\beta_\nu - \lambda_j) + \beta_\nu^2 \sum_{i=1}^{n} a_i \sum_{\substack{j=1 \\ \neq i}}^{n} \prod_{\substack{m=1 \\ \neq i \text{and} j}}^{n} (\beta_\nu - \lambda_m)} \qquad \text{(Eq. 28)}$$

The first term in the denominator of Eq. 28 is equal to zero, according to the property of β_ν since $Q(\beta_\nu) = 0$ (Eq. 26). Therefore, after further simplification, Eq. 28 can be written as:

$$E_\nu = \left[\beta_\nu^2 \sum_{i=1}^{n} \frac{a_i}{\beta_\nu - \lambda_i} \sum_{\substack{j=1 \\ \neq i}}^{n} \frac{1}{\beta_\nu - \lambda_j}\right]^{-1} \qquad \text{(Eq. 29)}$$

For further simplification in later derivations, it is convenient to introduce $b_\nu = \beta_\nu^2 E_\nu$ so that:

$$b_\nu = \left[\sum_{i=1}^{n} \frac{a_i}{\beta_\nu - \lambda_i} \sum_{\substack{j=1 \\ \neq i}}^{n} \frac{1}{\beta_\nu - \lambda_j}\right]^{-1} \qquad \text{(Eq. 30)}$$

According to Eq. 25, h'' in Eq. 18 is given by:

$$h''(t - u) = \sum_{i=1}^{n-1} \beta_i^2 E_i e^{\beta_i t} e^{-\beta_i u} = \sum_{i=1}^{n-1} b_i e^{\beta_i t} e^{-\beta_i u} \qquad \text{(Eq. 31)}$$

By substituting $h''(t - u)$, $h'(0)$, and $h(0)$, as given by Eqs. 31, 23, and 21, respectively, into Eq. 18, this equation becomes:

$$f(t) = -\frac{\sum_{i=1}^{n} a_i \lambda_i}{\left[\sum_{i=1}^{n} a_i\right]^2} g(t) + \frac{g'(t)}{\sum_{i=1}^{n} a_i} + \sum_{i=1}^{n-1} b_i e^{\beta_i t} \int_0^t g(u) e^{-\beta_i u}\, du \qquad \text{(Eq. 32)}$$

This equation can also be written:

$$f(t) = -\frac{\sum_{i=1}^{n} a_i \lambda_i}{\left[\sum_{i=1}^{n} a_i\right]^2} g(t) + \frac{g'(t)}{\sum_{i=1}^{n} a_i} + z(t)^* g(t) \qquad \text{(Eq. 33)}$$

where:

$$z(t) = \sum_{i=1}^{n-1} b_i e^{\beta_i t} \qquad \text{(Eq. 34)}$$

and $z(t)^*g(t)$ is the convolution of $z(t)$ and $g(t)$.

The $g(t)$ function remains to be derived and substituted into Eq. 32 to yield the final expression for the input rate, $f(t)$. The $g(t)$ function is obtained as the inverse transform of Eq. 12. It is useful to partition $g(t)$ into a basic component, a bolus component, and an infusion component, according to their origin in Eq. 12, so that it can be written as:

$$g(t) = g_0(t) - g_{bol}(t) - g_{inf}(t) \qquad \text{(Eq. 35)}$$

where:

$$g_0(t) = q^* c(t) \qquad \text{(Eq. 36)}$$

$$g_{bol}(t) = L^{-1}\left[\bar{c}^*(s) \sum_{i=1}^{N} q_i e^{-\tau_i s}\right] \qquad \text{(Eq. 37)}$$

$$g_{inf}(t) = L^{-1}[\bar{c}^*(s)\bar{f}_{inf}(s)] \qquad \text{(Eq. 38)}$$

When each of the three components of $g(t)$ is substituted for $g(t)$ in Eq. 32, this substitution leads to three corresponding components of $f(t)$:

$$f(t) = U_0(t) - U_{bol}(t) - U_{inf}(t) \qquad \text{(Eq. 39)}$$

where $U_0(t)$ is the basic function, and $U_{bol}(t)$ and $U_{inf}(t)$ are the bolus corrector function and the infusion corrector function, respectively, because these functions are subtracted from the basic function if the unknown input rate, $f(t)$, is evaluated in the presence of bolus or infusion input.

The basic function, $U_0(t)$, is obtained by substituting q*c(t) for $g(t)$ in Eq. 32, which yields:

$$U_0(t) = q^*\left[-\frac{\sum_{i=1}^{n} a_i \lambda_i}{\left[\sum_{i=1}^{n} a_i\right]^2} c(t) + \frac{c'(t)}{\sum_{i=1}^{n} a_i} + \sum_{i=1}^{n-1} b_i e^{\beta_i t} \int_0^t c(u) e^{-\beta_i u}\, du\right] \qquad \text{(Eq. 40)}$$

According to Eq. 20, Eq. 37 can be written as:

$$g_{bol}(t) = \sum_{m=1}^{R} q_m \sum_{j=1}^{n} a_j e^{\lambda_j (t - \tau_m)} \qquad \text{(Eq. 41)}$$

which, when substituted for $g(t)$ in Eq. 32, yields:

$$\begin{aligned} U_{bol}(t) = &-\frac{\sum_{i=1}^{n} a_i \lambda_i}{\left[\sum_{i=1}^{n} a_i\right]^2} \sum_{m=1}^{R} q_m \sum_{j=1}^{n} a_j e^{\lambda_j (t - \tau_m)} \\ &+ \frac{\sum_{m=1}^{R} q_m \sum_{j=1}^{n} a_j \lambda_j e^{\lambda_j (t - \tau_m)}}{\sum_{i=1}^{n} a_i} \\ &+ \sum_{m=1}^{R} q_m \sum_{i=1}^{n-1} b_i \sum_{j=1}^{n} \frac{a_j}{\lambda_j - \beta_i} e^{\lambda_j (t - \tau_m)} \\ &- \sum_{m=1}^{R} q_m \sum_{i=1}^{n-1} b_i e^{\beta_i (t - \tau_m)} \sum_{j=1}^{n} \frac{a_j}{\lambda_j - \beta_i} \end{aligned} \qquad \text{(Eq. 42)}$$

The last two terms of Eq. 42 are obtained from:

$$\sum_{i=1}^{n-1} b_i e^{\beta_i t} \int_0^t \left[\sum_{m=1}^{R} q_m \sum_{j=1}^{n} a_j e^{\lambda_j(u-\tau_m)}\right] e^{-\beta_i u}\, du$$

$$= \sum_{m=1}^{R} q_m \sum_{i=1}^{n-1} b_i \sum_{j=1}^{n} \frac{a_j}{\lambda_j - \beta_i} e^{\lambda_j(t-\tau_m)}$$

$$- \sum_{m=1}^{R} q_m \sum_{i=1}^{n-1} b_i e^{\beta_i(t-\tau_m)} \sum_{j=1}^{n} \frac{a_j}{\lambda_j - \beta_i} \quad \text{(Eq. 43)}$$

It can be shown that the sum of the first three terms of Eq. 42 is zero[1]:

$$-\frac{\sum_{i=1}^{n} a_i\lambda_i}{\left[\sum_{i=1}^{n} a_i\right]^2} \sum_{m=1}^{R} q_m \sum_{j=1}^{n} a_j e^{\lambda_j(t-\tau_m)} + \frac{\sum_{m=1}^{R} q_m \sum_{j=1}^{n} a_j\lambda_j e^{\lambda_j(t-\tau_m)}}{\sum_{i=1}^{n} a_i}$$

$$+ \sum_{m=1}^{R} q_m \sum_{i=1}^{n-1} b_i \sum_{j=1}^{n} \frac{a_j}{\lambda_j - \beta_i} e^{\lambda_j(t-\tau_m)} = 0 \quad \text{(Eq. 44)}$$

The fact that the last term of Eq. 42 also equals zero is seen from the innermost summation term, which can be written as:

$$\sum_{j=1}^{n} \frac{a_j}{\lambda_j - \beta_i} = -\frac{\sum_{j=1}^{n} a_j \prod_{\substack{m=1 \\ \neq j}}^{n} (\beta_i - \lambda_m)}{\prod_{j=1}^{n} (\beta_i - \lambda_j)} \quad \text{(Eq. 45)}$$

It is apparent from Eq. 26 and the property of β_i that this term is zero because:

$$\sum_{j=1}^{n} a_j \prod_{\substack{m=1 \\ \neq j}}^{n} (\beta_i - \lambda_m) = Q(\beta_i) = 0 \quad \text{(Eq. 46)}$$

Therefore, the right side of Eq. 42 is zero; *i.e.*, the bolus correction function is zero:

$$U_{bol}(t) = 0 \quad \text{(Eq. 47)}$$

Therefore, the input, $f(t)$ (Eq. 39), can be evaluated in the presence of the bolus input without any correction.

Equation 38 can be written according to Eq. 9 as:

$$g_{inf}(t) = q^* \frac{L^{-1}[d_{11}\bar{f}_{inf}(s)]}{V} \quad \text{(Eq. 48)}$$

According to Eq. 2, the term $L^{-1}[d_{11}\bar{f}_{inf}(s)]/V$ is the blood level, $c_{inf}(t)$, resulting from the infusion input, $f_{inf}(t)$, so Eq. 48 can be written as:

$$g_{inf}(t) = q^* c_{inf}(t) \quad \text{(Eq. 49)}$$

The infusion correction function, $U_{inf}(t)$, is obtained by substituting $g_{inf}(t)$ for $g(t)$ in Eq. 32, which gives:

$$U_{inf}(t) = q^* \times \left[-\frac{\sum_{i=1}^{n} a_i\lambda_i}{\left[\sum_{i=1}^{n} a_i\right]^2} c_{inf}(t) + \frac{c'_{inf}(t)}{\sum_{i=1}^{n} a_i} + \sum_{i=1}^{n-1} b_i e^{\beta_i t} \int_0^t c_{inf}(u) e^{-\beta_i u}\, du\right] \quad \text{(Eq. 50)}$$

If the infusion input, $f_{inf}(t)$, is considered an unknown input to be evaluated in the absence of other inputs, then by substituting $c_{inf}(t)$ for $c(t)$ in Eq. 40, $f_{inf}(t)$ is given by:

$$f(t) = f_{inf}(t) = U_0(t) = q^* \left[-\frac{\sum_{i=1}^{n} a_i\lambda_i}{\left[\sum_{i=1}^{n} a_i\right]^2} c_{inf}(t) + \frac{c'_{inf}(t)}{\sum_{i=1}^{n} a_i} + \sum_{i=1}^{n-1} b_i e^{\beta_i t} \int_0^t c_{inf}(u) e^{-\beta_i u}\, du\right] \quad \text{(Eq. 51)}$$

[1] The derivations that show that Eq. 44 holds for $n \geq 1$ are extensive. They are omitted because they are not crucial for understanding the theoretical approach.

By comparing Eqs. 50 and 51, it follows that:

$$U_{inf}(t) = f_{inf}(t) \quad \text{(Eq. 52)}$$

Thus, the infusion correction function is the rate of infusion input. Analogous to Eqs. 48 and 49, it is seen that $g_{bol}(t) = q^* c_{bol}(t)$, where $c_{bol}(t)$ is the drug level resulting from bolus input only. From Eq. 47, it follows that when $c_{bol}(t)$ is substituted for $c(t)$ in Eq. 40, the basic function becomes zero.

To unify these findings in a simple way, it is useful to define the input-generating function, ψ:

$$\psi[c(t)] = q^* \left[-\frac{\sum_{i=1}^{n} a_i\lambda_i}{\left[\sum_{i=1}^{n} a_i\right]^2} c(t) + \frac{c'(t)}{\sum_{i=1}^{n} a_i} + \sum_{i=1}^{n-1} b_i e^{\beta_i t} \int_0^t c(u) e^{-\beta_i u}\, du\right] \quad \text{(Eq. 53)}$$

This function generates the input from the drug level profile, $c(t)$. It is evident from above that the input-generating function has the following remarkable properties:

$$\psi[c_{bol}(t)] = 0 \qquad t \neq \tau_i \quad \text{(Eq. 54)}$$

$$\psi[c_{inf}(t)] = f_{inf}(t) \quad \text{(Eq. 55)}$$

$$\psi[c(t)] = f(t) + f_{inf}(t) \qquad t \neq \tau_i \quad \text{(Eq. 56)}$$

Equation 54 states that there is no drug input between the bolus input in an experiment only involving bolus input. Equation 56 states that the input-generating function generates the sum of all nonbolus input. Independent of any bolus input, the drug input rate therefore is given by the input-generating function corrected for the rate of superimposed intravenous infusion input that may or may not be present:

$$f(t) = \psi[c(t)] - f_{inf}(t) \qquad t \neq \tau_i \quad \text{(Eq. 57)}$$

which is rewritten as:

$$f(t) = q^* \left[-\frac{\sum_{i=1}^{n} a_i\lambda_i}{\left[\sum_{i=1}^{n} a_i\right]^2} c(t) + \frac{c'(t)}{\sum_{i=1}^{n} a_i} + \sum_{i=1}^{n-1} b_i e^{\beta_i t} \int_0^t c(u) e^{-\beta_i u}\, du\right] - f_{inf}(t) \qquad t \neq \tau_i \quad \text{(Eq. 58)}$$

RESULTS AND DISCUSSION

If the eigenvalues of the A matrix are distinct, then the impulse response function always is given by Eq. 19. Systems with cyclic structures may give rise to complex conjugate eigenvalues. However, the method still can be applied. An eigenvalue is either zero, due to a subsystem being closed, or is functionally related to the dynamic processes. The input analysis deals with the transport and transition dynamics of drug molecules in a fairly random state. Consequently, nonzero eigenvalues show a stochastic behavior; therefore, the statistical probability of two nonzero eigenvalues being equal is zero.

It is evident that the rank of the coefficient matrix for a closed system is full rank minus one and that a lower rank than that contradicts the randomness condition. Therefore, in an applied (*i.e.*, not theoretical) closed system, there is one and only one zero eigenvalue. Open applied systems are of full rank with no zero eigenvalues (17). The eigenvalues for any applied linear compartmental system are distinct and give rise to a unit impulse response as given by Eq. 19. Therefore, the method of analysis is applicable to any applied linear compartmental system. However, the method is not applicable to every theoretical linear compartmental system because of the possibility of nondistinct eigenvalues, which would result in an equation different from Eq. 19.

The method also could have been derived from the linear system theory for linear systems, where the impulse response can be approximated by a polyexponential expression. As such, it represents a new deconvolution approach. The present derivation method is valuable because it forms a link between classical pharmacokinetics and the linear system approach,

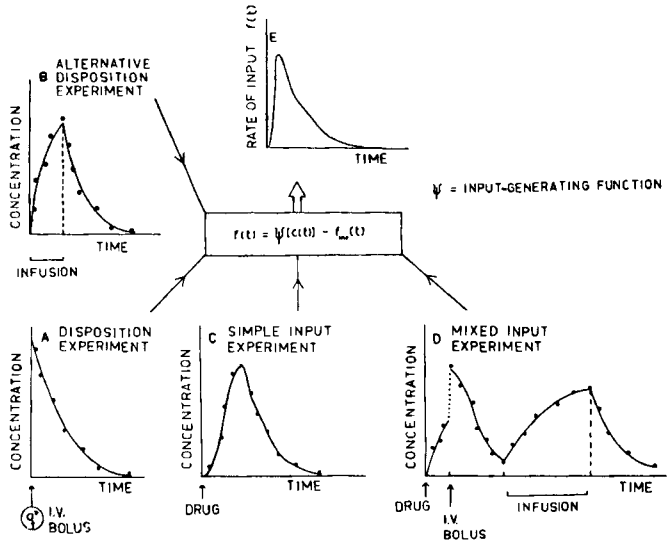

Figure 1—*Summary of model-independent approach of evaluating the drug input rate. The drug is given intravenously either as an initial bolus, q* (A), or alternatively as a zero-order infusion (B) to a subject as a nonprecipitating solution. Equation 19 or Eqs. 75 and 76 are fitted to the respective drug concentration data to give the parameters* $\{a_i, \lambda_i\}_1^n$ *and q* (A and B). The rate of drug input into the blood from a drug delivery system can be evaluated in the same subject in the absence of other input (C) or in the presence of any combination of intravenous bolus and infusion input (D). An appropriate arbitrary function,* c(t) *(e.g., a least-squares spline function), is fitted to the data from the input experiment (C and D). The rate of input is calculated from the parameters* $\{a_i, \lambda_i\}_1^n$, q*, *and the drug level profile,* c(t), *according to the input-generating function and corrected for any superimposed infusion input (E).*

thereby enabling classical pharmacokinetics to be analyzed in a new context.

The input rate can be determined quantitatively in the absence or presence of any combination of intravenous bolus input and infusion input.

The procedure for the evaluation of an input rate is mathematically defined by Eqs. 19, 26, 30, and 58. These equations are used as follows. Equation 19 is fitted to the drug level data from a single intravenous bolus input, q^*, to give $\{a_i, \lambda_i\}_1^n$ (Fig. 1A). If $n > 1$, these parameters are inserted into Eq. 26 to give the auxiliary parameters, $\{\beta_i\}_1^{n-1}$, which when subsequently inserted into Eq. 30 give another set of auxiliary parameters, $\{b_i\}_1^{n-1}$. An arbitrary function is fitted to the drug level data from the input to be evaluated (Fig. 1C). The arbitrary function is denoted briefly as $c(t)$ in the derivations. Since both b and β are functions of $\{a_i, \lambda_i\}_1^n$, only q^*, $\{a_i, \lambda_i\}_1^n$, and $c(t)$ are required to calculate $f(t)$ from Eq. 58. The input-generating function, ψ, is uniquely defined from the disposition experiment by the parameters q^* and $\{a_i, \lambda_i\}_1^n$.

Which arbitrary function, $c(t)$, is chosen to estimate the true drug level profile depends on the accuracy of the data and their general shape as well as any assumptions made about the variation and smoothness of the input process. The method by which a chosen function is fitted to the data should relate to assumptions made about the statistical properties of the errors in the data. For a fairly smooth input process, the best general choice of a function seems to be a weighted or unweighted least-squares spline function. Such a function is particularly suitable because of its smoothness, great flexibility, and optimal properties in estimating the rate of change [the $c'(t)$ term in Eq. 58] and the fact that it readily describes the disturbance(s) caused by bolus input (Fig. 1D). Due to the linear nature of the parameters defining the spline function, it also has desirable computational and statistical properties (18, 19).

If the drug level data are sampled frequently and are not too erratic, then a fitting of an ordinary polynomial may be quite appropriate. To avoid bias in the estimation of the drug level and to avoid an erratic behavior of the first derivative, it has been suggested that the degree of polynomial fitted by least squares should not exceed two times the square root of the number of data points (20). Use of exponential expressions for $c(t)$ can be troublesome because of the problem of getting initial parameter estimates and because of the computational problems associated with nonlinear curve fitting (21). If the drug levels range over several orders of magnitude, it is recommended that a logarithmic transformation or other suitable transformation be applied to the data before the curve fitting (22).

Although Eq. 58 involves an integral, no computational problems should be caused in the evaluation of $f(t)$ since the functions likely to be used for $c(t)$, such as spline functions, ordinary polynomials, and exponential expressions, lead to simple algebraic expressions without an integral that can be evaluated readily and exactly. Although the equations used to calculate $f(t)$ may seem complex, their use is straightforward.

Example 1, $n = 1$—This example represents a drug that behaves in a subject, following a single intravenous bolus, q^*, according to a one-compartment model so the intravenous bolus blood level data are described by:

$$c^*(t) = ae^{\lambda t} \qquad \text{(Eq. 59)}$$

The equation necessary for calculating the input rate of the drug administered to the same subject is simplified in this case with $n = 1$, since the summation term involving a summation to $i = n - 1$ is zero by definition. Thus, in the absence of intravenous infusion input, the input rate is given by:

$$f(t) = \frac{q^*}{a}[c'(t) - \lambda c(t)] \qquad \text{(Eq. 60)}$$

It is of interest to compare this equation with the Wagner–Nelson model-independent method of evaluating the absorption rate in a one-compartment system. The Wagner–Nelson equation is (15):

$$A_t = V\left[c(t) + K\int_0^t c(t)dt\right] \qquad \text{(Eq. 61)}$$

so that:

$$dA_t/dt = V[c'(t) + Kc(t)] \qquad \text{(Eq. 62)}$$

where A_t is the amount absorbed between time zero and time t and K is the first-order elimination rate constant. Since $dA_t/dt = f(t)$, $K = -\lambda$ and $V = q^*/a$, Eq. 62 can be written the same as Eq. 60. Therefore, for $n = 1$, the input-generating function reduces to an expression that is essentially identical to the Wagner–Nelson equation.

Example 2, $n = 2$—In this case, the intravenous bolus data are described by:

$$c^*(t) = a_1e^{\lambda_1 t} + a_2e^{\lambda_2 t} \qquad a_i > 0, \lambda_i < 0 \qquad \text{(Eq. 63)}$$

Equation 26 is used to obtain the auxiliary parameter, β_1:

$$Q(s) = a_1(s - \lambda_2) + a_2(s - \lambda_1) = (a_1 + a_2)s - (a_1\lambda_2 + a_2\lambda_1) \qquad \text{(Eq. 64)}$$

so that:

$$\beta_1 = \frac{a_1\lambda_2 + a_2\lambda_1}{a_1 + a_2} \qquad \text{(Eq. 65)}$$

The other auxiliary parameter, b_1, is obtained from β_1 using Eq. 30:

$$b_1 = \left[\frac{a_1}{(\beta_1 - \lambda_1)}\frac{1}{(\beta_1 - \lambda_2)} + \frac{a_2}{(\beta_1 - \lambda_2)}\frac{1}{(\beta_1 - \lambda_1)}\right]^{-1} = -\frac{a_1a_2(\lambda_1 - \lambda_2)^2}{(a_1 + a_2)^3} \qquad \text{(Eq. 66)}$$

The input-generating function then becomes:

$$\psi[c(t)] = q^*\left\{-\frac{a_1\lambda_1 + a_2\lambda_2}{(a_1 + a_2)^2}c(t) + \frac{c'(t)}{a_1 + a_2} - \frac{a_1a_2(\lambda_1 - \lambda_2)^2}{(a_1 + a_2)^3}\exp\left[\frac{a_1\lambda_2 + a_2\lambda_1}{a_1 + a_2}t\right] \times \int_0^t c(u)\exp\left[-\frac{a_1\lambda_2 + a_2\lambda_1}{a_1 + a_2}u\right]du\right\} \qquad \text{(Eq. 67)}$$

Example 3, $n = 3$— The intravenous bolus data are described by:

$$c^*(t) = a_1e^{\lambda_1 t} + a_2e^{\lambda_2 t} + a_3e^{\lambda_3 t} \qquad a_i > 0, \lambda_i < 0 \qquad \text{(Eq. 68)}$$

The $n - 1 = 2$ auxiliary parameters, β_1 and β_2, are obtained as the two roots of Eq. 26:

$$Q(s) = a_1(s - \lambda_2)(s - \lambda_3) + a_2(s - \lambda_1)(s - \lambda_3) + a_3(s - \lambda_1)(s - \lambda_2) \qquad \text{(Eq. 69)}$$

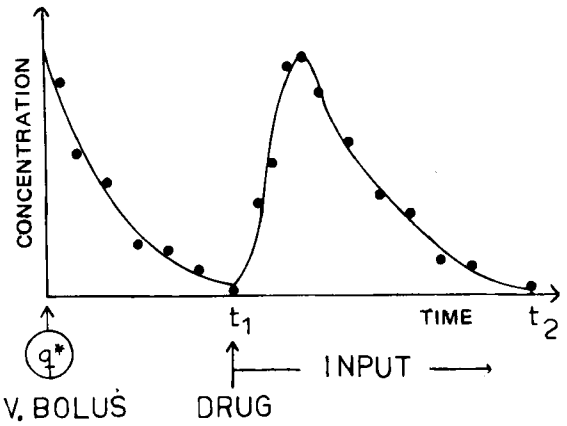

Figure 2—*Summary of input analysis based on a merged bolus and input approach. An initial intravenous bolus solution of the drug is given, and the drug level is followed for a sufficiently long time, t_1, to get proper estimates of $\{a_i, \lambda_i\}_1^n$ by fitting Eq. 19 to the drug level data for $0 < t \leq t_1$. Then, the drug delivery system is administered (t_1) and the drug level is followed for the appropriate length of time (t_2). The input rate is calculated from the input-generating function. The arbitrary function, c(t), fitted to the data must consist of Eq. 19 for the time period $0 < t \leq t_1$ and some other appropriate function (e.g., a least-squares spline function) for $t_1 < t \leq t_2$. This approach of input analysis is powerful because it does not require a washout period between the disposition and the input experiments and because errors arising from changes in the subject's drug disposition with time are reduced to a minimum by bringing the two drug administrations close together.*

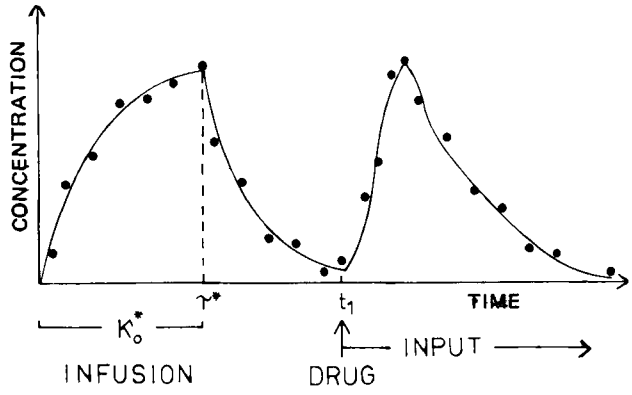

Figure 3—*Summary of input analysis based on a merged infusion and input approach. A zero-order (κ_0^*) infusion is given from $t = 0$ to $t = \tau^*$, and the drug level is allowed to drop to a proper level before the drug delivery system is administered at t_1. Equations 75 and 76 are fitted simultaneously to the data for $0 < t \leq \tau^*$ and $\tau^* < t \leq t_1$, respectively, to give the parameters $\{a_i, \lambda_i\}_1^n$ and q^*. The rate of drug input ($t > t_1$) is calculated from the input-generating function. The arbitrary function, c(t), must consist of Eq. 75 (with the estimated parameters) for $0 < t \leq \tau^*$, of Eq. 76 for $\tau^* < t \leq t_1$, and of some suitable function (e.g., a least-squares spline function) for $t > t_1$.*

so that:

$$Q(s) = [a_1 + a_2 + a_3]s^2 - [a_1(\lambda_2 + \lambda_3) + a_2(\lambda_1 + \lambda_3) + a_3(\lambda_1 + \lambda_2)]s + [a_1\lambda_2\lambda_3 + a_2\lambda_1\lambda_3 + a_3\lambda_1\lambda_2] \quad \text{(Eq. 70)}$$

The two other auxiliary parameters, b_1 and b_2, are obtained from Eq. 30:

$$b_1 = \left[\frac{a_1}{\beta_1 - \lambda_1}\left(\frac{1}{\beta_1 - \lambda_2} + \frac{1}{\beta_1 - \lambda_3}\right) + \frac{a_2}{\beta_1 - \lambda_2}\left(\frac{1}{\beta_1 - \lambda_1} + \frac{1}{\beta_1 - \lambda_3}\right) + \frac{a_3}{\beta_1 - \lambda_3}\left(\frac{1}{\beta_1 - \lambda_1} + \frac{1}{\beta_1 - \lambda_2}\right)\right]^{-1} \quad \text{(Eq. 71)}$$

so that:

$$b_1 = \frac{(\beta_1 - \lambda_1)(\beta_1 - \lambda_2)(\beta_1 - \lambda_3)}{(\beta_1 - \beta_2)(a_1 + a_2 + a_3)} \quad \text{(Eq. 72)}$$

and similarly:

$$b_2 = \frac{(\beta_2 - \lambda_1)(\beta_2 - \lambda_2)(\beta_2 - \lambda_3)}{(\beta_2 - \beta_1)(a_1 + a_2 + a_3)} \quad \text{(Eq. 73)}$$

The input-generating function is:

$$\psi[c(t)] = q^*\left[-\frac{a_1\lambda_1 + a_2\lambda_2 + a_3\lambda_3}{(a_1 + a_2 + a_3)^2}c(t) + \frac{c'(t)}{a_1 + a_2 + a_3} + b_1e^{\beta_1 t}\int_0^t c(u)e^{-\beta_1 u}\,du + b_2e^{\beta_2 t}\int_0^t c(u)e^{-\beta_2 u}\,du\right] \quad \text{(Eq. 74)}$$

where b_1, b_2, β_1, and β_2 are described in terms of $\{a_i, \lambda_i\}_1^2$.

Merged Bolus and Input Approach—The fact that the input-generating function automatically corrects for the disturbance in the drug level profile bolus input makes it particularly suitable for performing an input analysis in a single experiment. For example, it may be of interest to study the input rate from an oral administration. This study can be done by giving an initial intravenous bolus solution of the drug (Fig. 2) and following the drug profile for a sufficiently long time, t_1, to get proper estimates of $\{a_i, \lambda_i\}_1^n$ by fitting Eq. 19. Thereafter, the oral dosage form of the drug is administered and the drug level is followed for the appropriate length of time, t_2.

The input rate ($t > t_1$) is calculated from the input-generating function. The arbitrary function, $c(t)$, representing the data must consist of Eq. 19 for $0 < t \leq t_1$ and of some other appropriate function (*e.g.*, a least-squares spline function) for $t_1 < t \leq t_2$. This input analysis approach is powerful because it does not require a washout period between the disposition and the input experiments and because errors arising from changes in the subject's drug disposition with time are reduced to a minimum by bringing the two drug administrations close together.

Alternative Approach to Intravenous Bolus Input—It is assumed that the intravenous bolus administered to estimate $\{a_i, \lambda_i\}_1^n$ is given in a solution that does not precipitate on dilution with the blood so that it is available immediately to the systemic circulation. Some drugs may be so slightly soluble or so toxic that it is not feasible to administer an intravenous bolus dose to estimate $\{a_i, \lambda_i\}_1^n$. However, this study can be done by an alternative approach. It can be proven that if an intravenous bolus, q^*, produces a concentration profile in a linear pharmacokinetic system as described by Eq. 19, then the profile resulting from a zero-order (κ_0^*) infusion from $t = 0$ to $t = \tau^*$ in the same system is given by:

$$c_0^*(t) = \frac{\kappa_0^*}{q^*}\sum_{i=1}^{n}\frac{a_i}{\lambda_i}[e^{\lambda_i t} - 1] \qquad t \leq \tau^* \quad \text{(Eq. 75)}$$

and:

$$c_0^*(t) = \frac{\kappa_0^*}{q^*}\sum_{i=1}^{n}\frac{a_i e^{\lambda_i t}}{\lambda_i}[1 - e^{-\lambda_i \tau^*}] \qquad t > \tau^* \quad \text{(Eq. 76)}$$

Thus, q^* and $\{a_i, \lambda_i\}_1^n$ required for the calculation of the input rate are obtained by fitting Eqs. 75 and 76 to the infusion data.

Merged Infusion and Input Approach—The infusion disposition experiment can be merged with the input experiment by stopping the infusion after the proper length of time (τ^*, Fig. 3) and then letting the drug level drop to a proper level before the drug delivery system is administered (t_1, Fig. 3). The arbitrary function, $c(t)$, fitted to the data must consist of Eq. 75 (using the estimated parameters) for $0 < t \leq \tau^*$ and Eq. 76 for $\tau^* < t \leq t_1$ and an appropriate arbitrary function for the drug input interval $t > t_1$ (Fig. 3). The rate of drug input, $t > t_1$, is calculated from the input-generating function (without infusion correction). The rate of drug input, $t < t_1$, calculated according to Eq. 58 [with $f_{inf}(t) = \kappa_0^*$ for $0 < t < \tau^*$] is zero if the process has been correctly defined mathematically. This can be used to check the computations when the method is implemented on a computer.

Drug Input Control—Although the presented analysis is directed at a model-independent evaluation of drug input, it is equally applicable to control of drug input. Any desirable drug profile may be produced by a controlled intravenous input according to the equations presented. The application of the theory to model-independent optimized drug input is under investigation.

Although the equations used to calculate the input rate may appear complex, they are presented in a general form that readily allows them to be programmed and implemented on a computer. A general-purpose drug input analysis program can be developed from the equations presented. Ultimately, the investigator will need only to supply the blood level data and information about the experimental design, and the program will automatically compute and plot the drug input rate profile.

The practical application of the drug input analysis presented appears versatile and powerful. It provides some important tools for the evalua-

tion and design of drug delivery systems. In particular, it enables the rate and extent of drug bioavailability to be evaluated in a more intrinsic and accurate way than previous methods for linear systems with a polyexponential impulse response.

APPENDIX

The system of n linear differential equations describing the kinetics after an initial bolus input into a linear pharmacokinetic system is (16):

$$\mathbf{x}' = \mathbf{A}\mathbf{x} \qquad \text{(Eq. A1)}$$

where the square matrix **A** contains the first-order intercompartmental rate constants and the elimination rate constants (16). If the eigenvalues of **A** are distinct, then the solution of Eq. A1 is:

$$\mathbf{x} = \mathbf{P} \exp(t\mathbf{\Lambda})\mathbf{P}^{-1}\mathbf{x}(0) \qquad \text{(Eq. A2)}$$

where $\mathbf{\Lambda}$ is a diagonal matrix of the eigenvalues $\{\lambda_i\}_1^n$ of **A** and the columns of **P** are the corresponding eigenvectors.

From Eq. A2, the following equation is obtained:

$$x_i = \sum_{j=1}^{n} \Omega_{ij} e^{\lambda_j t} \qquad \text{(Eq. A3)}$$

where:

$$\Omega_{ij} = \mathbf{P}_{ij}[\mathbf{P}_{ij}^{-1}\mathbf{x}(0)]_j \qquad \text{(Eq. A4)}$$

An initial bolus input in the central compartment is described by $\mathbf{x}(0)^T = (q^*, 0, 0, \ldots, 0)$, which according to Eqs. A3 and A4 leads to:

$$c^*(t) = \sum_{j=1}^{n} \Omega_{1j} e^{\lambda_j t}/V \qquad \text{(Eq. A5)}$$

Thus, a_i in Eq. 19 is given by:

$$a_i = \Omega_{1i}/V = q^* \mathbf{P}_{1i}\mathbf{P}_{1i}^{-1}/V \qquad \text{(Eq. A6)}$$

Note that:

$$L^{-1}\mathbf{D} = \mathbf{\Phi}(t) = \mathbf{P} \exp(t\mathbf{\Lambda})\mathbf{P}^{-1} \qquad \text{(Eq. A7)}$$

where $\mathbf{\Phi}(t)$, introduced previously (16), is the fundamental matrix of the pharmacokinetic system.

NOTATIONS[2]

a_i = defined by Eq. 19
A_1, A_2 = defined by Eq. 25
A_t = amount absorbed between $t = 0$ and time t
A = coefficient matrix, Eq. A1
b_i = auxiliary parameter defined in terms of $\{a_i, \lambda_i\}_1^n$ by Eq. 30 (see β_i)
β_i = auxiliary parameter defined in terms of $\{a_i, \lambda_i\}_1^n$ by Eq. 26
$c(t)$ = arbitrary function(s) describing the drug concentration
$c^*(t)$ = function (Eq. 19) describing the drug concentration data following an initial intravenous bolus input, q^*
$c_0^*(t)$ = drug concentration resulting from a zero-order infusion starting at $t = 0$
$c_{bol}(t)$ = drug concentration resulting from one or more intravenous bolus input
$c_{inf}(t)$ = drug concentration resulting from continuous or discontinuous intravenous infusion input
d_{ij} = i-, jth element of disposition matrix **D**
D = disposition matrix
$\delta(t)$ = Dirac delta function
e = 2.71828 . . .
E_ν = expression defined by Eq. 27
$f(t)$ = rate of input to be evaluated (amount per unit of time)
$f_{bol}(t)$ = bolus input component
$f_{inf}(t)$ = rate of intravenous infusion input
$g(t)$ = function whose Laplace tranform is defined by Eq. 12
$g_{bol}(t)$ = bolus component of $g(t)$
$g_{inf}(t)$ = infusion component of $g(t)$
$g_0(t)$ = component of $g(t)$ corresponding to $f(t)$
$h(t)$ = function whose Laplace transform is defined by Eq. 16
i = index variable
j = index variable
K = first-order elimination constant in a one-compartment model
κ_0^* = zero-order infusion rate from $t = 0$ to $t = \tau^*$ used in the disposition experiment and in the merged infusion and input approach
λ_i = defined by Eq. 19, ith eigenvalue of matrix **A**
L, L^{-1} = Laplace and inverse Laplace transform operator
$\mathbf{\Lambda}$ = diagonal matrix defined by Eq. A3
m = index variable
n = defined by Eq. 19
N = number of bolus input
ν = index variable
p_{ij} = i-, jth element of the eigenvector matrix
$\mathbf{p}_i$ = ith column vector of the eigenvector matrix
P = eigenvector matrix defined by Eq. A2
π = product operator
q^* = bolus amount injected intravenously initially in the disposition experiment resulting in a drug level described by Eq. 19
q_i = ith bolus injected intravenously
$Q(s)$ = auxiliary function defining β_i (Eq. 26)
R = highest integer for which $\tau_R < t$ is satisfied or defined as zero if inequality cannot be satisfied
s = complex domain variable
t = time
t_1, t_2 = defined in Fig. 2
τ_i = time when the ith intravenous bolus is given
τ^* = time for zero-order infusion stop (Fig. 3)
$U_0(t)$ = basic function
$U_{bol}(t)$ = bolus corrector function
$U_{inf}(t)$ = infusion corrector function
v = input vector
v_1 = first element of input vector
V = constant with dimension of volume
x = vector containing the amounts in the n compartments at time t
x_1 = first element of vector **x**
y = vector defined by Eq. A6
$z(t)$ = auxiliary function defined in terms of $\{a_i, \lambda_i\}_1^n$ by Eq. 34 (see b_i and β_i)
$\Phi(t)$ = fundamental matrix of pharmacokinetic system
$\Psi[c(t)]$ = input-generating function

[2] Bars denote Laplace transforms, bold-faced capital letters denote matrixes, and bold-faced noncapital letters denote vectors.

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Model-Independent Method of Analyzing Input in Linear Pharmacokinetic Systems Having Polyexponential Impulse Response II: Numerical Evaluation

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Received September 22, 1978, from the *Department of Pharmacy, School of Pharmacy, University of California, San Francisco, CA 94143.* Accepted for publication October 11, 1979.

Abstract □ The investigated method is based on an exact mathematical solution to the deconvolution problem of linear pharmacokinetic systems with a polyexponential impulse response. The accuracy of the method is determined only by how well the curves fitted to the intravenous and absorption data represent the true drug level. Consequently, the method enables objective evaluation of the input. It permits the user to assess whether discrepancies in a calculated input are due to an improper data representation, as judged from the fitted curves, to the inherent nature of the data, or to a violation of the pharmacokinetic assumptions. The method is compared to another method using simulated data containing various degrees of random noise. The accuracy of the two methods was not significantly different and was of the same magnitude as the noise level of the data. The theoretical properties of the two methods and their expected performance in various pharmacokinetic situations are discussed. The method is applied to pentobarbital data from oral and intravenous administrations.

Keyphrases □ Pharmacokinetics—linear systems, polyexponential impulse response, analysis of input, model-independent method □ Model-independent analysis—linear pharmacokinetic systems, polyexponential impulse response, analysis of input □ Drug input—linear pharmacokinetic systems, polyexponential impulse response, analysis by model-independent method

A previous article (1) presented the theoretical derivation and analysis of a novel input analysis method. The method allows a drug input to be evaluated in the presence or absence of any combination of intravenous bolus input and infusion input. Three approaches were discussed: evaluation of the input rate based on a separate intravenous bolus experiment and an input (absorption) experiment, evaluation based on a merged intravenous bolus and input experiment, and evaluation based on a merged infusion and input experiment.

The present work is confined to the first approach and is based on an exact mathematical solution to the deconvolution problem of linear pharmacokinetic systems with a polyexponential impulse response. Several methods for deconvolution have been presented (2–5). The Wagner–Nelson method usually is limited to one-compartment systems (6), and the methods investigated by Benet and Chiang (2) were shown to be very sensitive to errors in the data. The numerical deconvolution method presented by Gamel *et al.* (3) did not provide satisfactory results, possibly due to numerical ill conditioning. Cutler (5) improved Gamel's approach by using orthogonal polynomials to avoid the problem of ill conditioning. The improved method seems to be the most accurate method for numerical deconvolution. It appears to be superior to the many model-dependent methods (6–10) because it is based on fewer assumptions and, therefore, is more likely to result in a meaningful evaluation of the drug input.

This work compares the new method with Cutler's approach using Cutler's simulated test data that contain various degrees of random noise (4, 5).

THEORY

Let the concentration of drug in the blood, $c^*(t)$, following an initial intravenous bolus dose, q^*, be described by a multiexponential relationship (1):

$$c^*(t) = \sum_{i=1}^{n} a_i e^{\lambda_i t} \qquad \text{(Eq. 1)}$$

Let $c(t)$ denote the drug level resulting from an unknown input of a drug that, in the same subject with the same linear relationship between input and response, results in the blood level $c^*(t)$ (Eq. 1) when an intravenous bolus dose, q^*, is given. It has been shown (1) that the rate of input of the drug then is given by:

$$f(t) = q^* \left[-\frac{\sum_{i=1}^{n} a_i \lambda_i}{\left[\sum_{i=1}^{n} a_i\right]^2} c(t) + \frac{c'(t)}{\sum_{i=1}^{n} a_i} + \sum_{i=1}^{n-1} b_i e^{\beta_i t} \int_0^t c(u) e^{-\beta_i u}\, du \right] \qquad \text{(Eq. 2)}$$

where β_i, $i = 1, 2, \ldots, n-1$ are the roots of the $(n-1)$th-degree polynomial:

$$Q(x) = \sum_{i=1}^{n} a_i \prod_{\substack{j=1 \\ \neq i}}^{n} (x - \lambda_j) \qquad \text{(Eq. 3)}$$

and b_ν, $\nu = 1, 2, \ldots, n-1$ are obtained from:

$$b_\nu = \left[\sum_{i=1}^{n} \frac{a_i}{\beta_\nu - \lambda_i} \sum_{\substack{j=1 \\ \neq i}}^{n} \frac{1}{\beta_\nu - \lambda_j} \right]^{-1} \qquad \text{(Eq. 4)}$$

Integration of $f(t)$ from time zero to time t yields the cumulative amount of input:

$$A(t) = q^* \left[-\left\{ \frac{\sum_{i=1}^{n} a_i \lambda_i}{\left(\sum_{i=1}^{n} a_i\right)^2} + \sum_{i=1}^{n-1} \frac{b_i}{\beta_i} \right\} \int_0^t c(t)\, dt + \frac{c(t)}{\sum_{i=1}^{n} a_i} + \sum_{i=1}^{n-1} \frac{b_i}{\beta_i} e^{\beta_i t} \int_0^t c(u) e^{-\beta_i u}\, du \right] \qquad \text{(Eq. 5)}$$

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