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General Treatment of Linear Pharmacokinetics

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Abstract □ A general treatment of linear pharmacokinetics that enables equations to be obtained simply for all linear compartmental models, with input in one or more compartments, is presented. Two approaches are described: one based on a full Laplace transformation and one that avoids transformation of the input functions and the use of convolution integrals. The latter approach is of particular interest when dealing with complex input functions not having a simple Laplace transform. The concept of acceptor and donor subsystems is introduced. It is demonstrated that disposition in certain models may be simplified and analyzed in terms of disposition in subsystems of simpler composition. The treatment presented is illustrated with several examples.

Keyphrases □ Pharmacokinetics—general treatment for derivation of equations for all linear compartmental models □ Models, pharmacokinetic—general treatment for derivation of equations for all linear compartmental models

Mathematical modeling in pharmacokinetics is commonly based on linear models in which it is assumed that the rate of transfer from any compartment is proportional to the amount in that compartment (1–5). Benet (6) presented a general treatment of linear mammillary models that considers elimination from any compartment but allows input into the central compartment only. Other investigators (7, 8) extended Benet's approach to include input into a peripheral compartment, but they only considered mammillary models. This paper presents a general treatment of any linear pharmacokinetic model with input in one or more compartments.

Two approaches are presented: one requires a Laplace transformation of the input functions, and one avoids such a transformation. The concept of subsystems is introduced. It is demonstrated that certain models can be simplified and analyzed in terms of the disposition of the subsystems.

THEORY

Every possible model having n compartments is a subset of the dense n-compartmental system, defined as a system with reversible transfer between all n compartments and elimination and input in every compartment (*e.g.*, Scheme I). A description of the dense system will describe all compartmental models when the domains of the rate constants and input functions are defined as $k_{ij} \geq 0$ and $f_i(t) \geq 0$, $t > 0$, respectively.

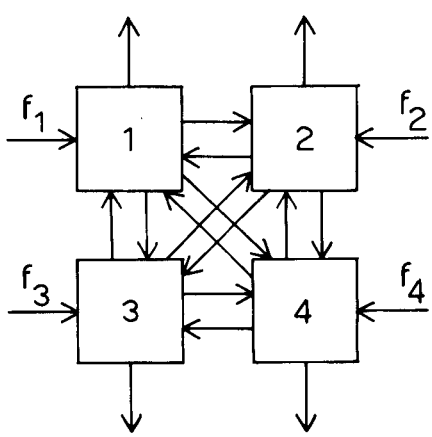
The linear differential equations that describe the kinetics in a dense system are given by[1]:

$$\mathbf{x}' = (\mathbf{K}^T - \mathbf{\Sigma})\mathbf{x} + \mathbf{f} \qquad \text{(Eq. 1)}$$

$$\mathbf{\Sigma} = \text{diag}(E_1, E_2, \ldots, E_n) \qquad \text{(Eq. 2)}$$

$$E_i = \sum_{j=0}^{n} k_{ij} \qquad \text{(Eq. 3)}$$

The ith component of vector $\mathbf{x}$ is the amount in the ith compartment at time t. The ith diagonal element, E_i, of the diagonal matrix, $\mathbf{\Sigma}$, is the sum of the exit rate constants of the ith compartment; $\mathbf{K}^T$ is the transpose of the $n \times n$ matrix, $\mathbf{K} = k_{ij}$, which contains the intercompartmental rate constants. The diagonal elements of $\mathbf{K}$ and $\mathbf{K}^T$ are always zero.



Scheme I—Dense four-compartmental system with reversible transfer between all compartments and elimination and input in every compartment.

[1] Boldface capital letters denote $n \times n$ matrixes, and boldface lower case letters denote vectors of corresponding dimension.

Full Transformation Approach—The Laplace transform of Eq. 1 yields (bars denote transformed quantities):

$$s\bar{\mathbf{x}} - \mathbf{x}(0) = (\mathbf{K}^T - \boldsymbol{\Sigma})\bar{\mathbf{x}} + \bar{\mathbf{f}} \qquad \text{(Eq. 4)}$$

which can be rearranged to:

$$\bar{\mathbf{x}} = [-\mathbf{K}^T + (s\mathbf{I} + \boldsymbol{\Sigma})]^{-1}[\mathbf{x}(0) + \bar{\mathbf{f}}] \qquad \text{(Eq. 5)}$$

where $\mathbf{I}$ is the identity matrix and $\mathbf{x}(0)$ is the vector $\mathbf{x}$ at time $t = 0$.

It is convenient to introduce a matrix, $\mathbf{S}$, defined as:

$$\mathbf{S} = -\mathbf{K} + \text{diag}(s + E_1, s + E_2, \ldots, s + E_n) \qquad \text{(Eq. 6)}$$

Then the solution of Eq. 1 by Eq. 5 simply becomes:

$$\mathbf{x} = L^{-1}(\mathbf{Dv}) \qquad \text{(Eq. 7)}$$

where L^{-1} is the inverse Laplace transform operator. The matrix:

$$\mathbf{D} = (\mathbf{S}^T)^{-1} \qquad \text{(Eq. 8)}$$

will be called the disposition matrix. The vector:

$$\mathbf{v} = \mathbf{x}(0) + \bar{\mathbf{f}} \qquad \text{(Eq. 9)}$$

will be called the input vector.

Equation 7 describes the simultaneous and complete solution of all compartments in any linear pharmacokinetic model. Thus, the solution is simply stated as the inverse transform of the product of the disposition matrix and the input vector.

The ith row of the disposition matrix, $\mathbf{d}_i = (d_{i1}, d_{i2}, \ldots, d_{in})$, will be called the disposition vector for the ith compartment.

It then follows from Eq. 7 that:

$$x_i = L^{-1}(\mathbf{d}_i\mathbf{v}) \qquad \text{(Eq. 10)}$$

i.e., the solution for any compartment is the inverse transform of the scalar product of its disposition vector and the input vector of the system.

The elements of the disposition matrix, $\mathbf{D}$, are simply expressed in terms of $\mathbf{S}$ by:

$$d_{ij} = |\mathbf{S}|_{ij}/|\mathbf{S}| \qquad \text{(Eq. 11)}$$

where $\mathbf{S}$ is the determinant of $\mathbf{S}$ and $\mathbf{S}_{ij}$ is the cofactor corresponding to the ijth element.

Equation 10 can thus be written more specifically as:

$$x_i = L^{-1}\sum_{j=1}^{n}\frac{|\mathbf{S}|_{ij}}{|\mathbf{S}|}[x_j(0) + \bar{f}_j] \qquad \text{(Eq. 12)}$$

or:

$$x_i = L^{-1}\sum_{j=1}^{n}\frac{|-\mathbf{K} + \text{diag}(s + E_1, s + E_2, \ldots, s + E_n)|_{ij}}{|-\mathbf{K} + \text{diag}(s + E_1, s + E_2, \ldots, s + E_n)|} \times [x_j(0) + \bar{f}_j] \qquad \text{(Eq. 13)}$$

Subsystems—A compartmental system can be divided into various subsystems by "pulling it apart," with exit arrows remaining fixed to their respective compartments (*e.g.*, Scheme II).

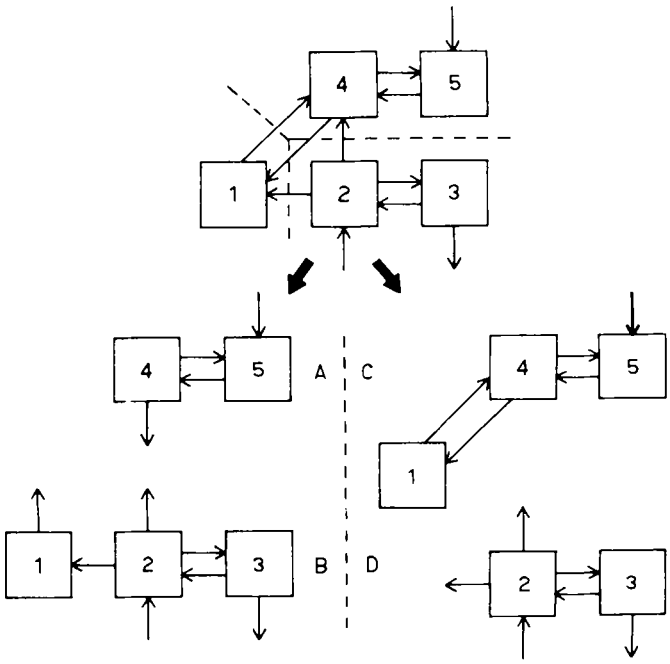
A subsystem not receiving input from other subsystems may be called a donor system and is said to be irreversibly connected (Scheme II, System D). An acceptor system is a subsystem receiving input from other subsystems (Scheme II, Systems A, B, and C).

The usefulness of subsystems arises from the fact that a compartmental system that can be divided into one or more irreversibly connected subsystems can be analyzed in terms of the disposition of subsystems treated as isolated systems. Therefore, the system can be analyzed in a section of simpler composition. For example, consider a system that can be divided into an acceptor and a donor system, denoted [1] and [2], respectively (Scheme III, Systems A and B). Disposition in the donor system is independent of the remainder of the system so that:

$$\mathbf{x}^{[2]} = L^{-1}(\mathbf{D}^{[2]}\mathbf{v}^{[2]}) \qquad \text{(Eq. 14)}$$

where $\mathbf{D}^{[2]}$ and $\mathbf{v}^{[2]}$ are the $n^{[2]} \times n^{[2]}$ disposition matrix and the input vector for the donor system treated as an isolated system, respectively (Scheme III, System B).

Similarly, disposition in the isolated acceptor system (Scheme III, System A) is given by $\mathbf{x}^{[1]} = L^{-1}(\mathbf{D}^{[1]}\mathbf{v}^{[1]})$. In contrast to a donor system, however, this disposition will not be the same as when the system is connected to the other subsystem because it receives input from it. However, the correct disposition is obtained by adding an additional



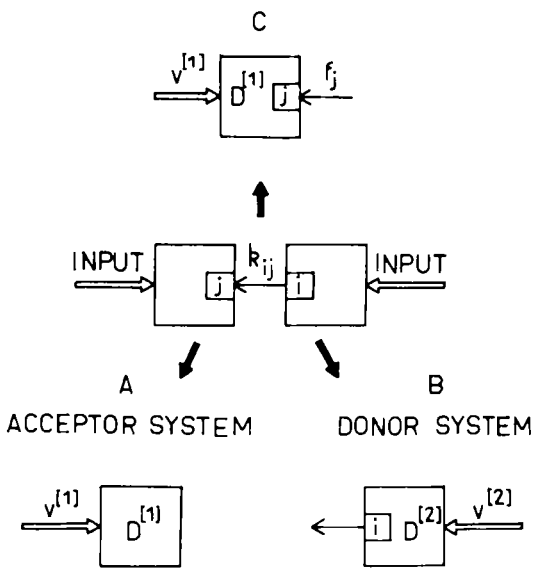
Scheme II—Five compartmental system that can be "pulled apart" to form various subsystems, of which only four are shown. D is a donor system irreversibly connected to the acceptor System C. Partitioning into A and B produces only acceptor systems.

input element, $\bar{f}_j$ (Scheme III, System B), to the jth element of the vector $\mathbf{v}^{[1]}$. This additional element is related to disposition in the donor system and the connector constant, k_{ij}, by:

$$\bar{f}_j = k_{ij}\bar{x}_i^{[2]} = k_{ij}(\mathbf{d}_i^{[2]}\mathbf{v}^{[2]}) \qquad \text{(Eq. 15)}$$

Thus, the general case with N donor systems, each connected to an acceptor system (denoted [1]) by one or more connector constants, is described by:

$$\mathbf{x}^{[1]} = L^{-1}\left(\mathbf{D}^{[1]}\left[\mathbf{v}^{[1]} + \sum_{i=2}^{N}\mathbf{C}^{[i]}\mathbf{D}^{[i]}\mathbf{v}^{[i]}\right]\right) \qquad \text{(Eq. 16)}$$



Scheme III—Simple illustration of the subsystem approach. Disposition in the donor system, B, is unaffected by disposition in the acceptor system, A, so that it can be analyzed separately in terms of the simpler disposition matrix, $\mathbf{D}^{[2]}$, and the input vector, $\mathbf{v}^{[2]}$. The isolated acceptor system, A, can be analyzed similarly; but an additional input element, $\bar{f}_j$, must be added to the input vector, $\mathbf{v}^{[1]}$, to account for the fact that the acceptor system receives input from the donor system (C). The additional input element is simply related to disposition in the donor system via the connector constant, k_{ij} (Eq. 15).

and:

$$\mathbf{x}^{[i]} = L^{-1}(\mathbf{D}^{[i]}\mathbf{v}^{[i]}) \qquad i \neq 1 \qquad \text{(Eq. 17)}$$

where the $n^{[1]} \times n^{[i]}$ matrix $\mathbf{C}^{[i]}$ in Eq. 16 will be called the connector matrix for the ith donor system. The j,kth element of the connector matrix, $C^{[i]}$, contains the connector constant that connects the jth compartment in the acceptor system with the kth compartment in donor system [i].

The ith compartment in a subsystem in this context is defined as the compartment corresponding to the ith row of the disposition matrix of the subsystem. This definition allows arbitrary numbers to be assigned to the compartments so that Eqs. 16 and 17 still apply.

Partial Transformation Approach—The described approach is based on a Laplace transformation of both the disposition and the input kinetics. Its use is convenient in cases where the input functions are simple such that an inverse transformation can be obtained without the use of complex inversion formulas or convolution integrals.

If the input function(s) is not simple, it may be useful to apply the following approach, which does not require transformation of the input functions. According to Eq. 9, Eq. 7 can be written:

$$\mathbf{x} = L^{-1}[\mathbf{D}\mathbf{x}(0) + \mathbf{D}\bar{\mathbf{f}}] \qquad \text{(Eq. 18)}$$

By application of the convolution theorem, this equation becomes:

$$\mathbf{x} = \mathbf{\Phi}(t)\mathbf{x}(0) + \int_0^t \mathbf{\Phi}(t-\tau)\mathbf{f}(\tau)\,d\tau \qquad \text{(Eq. 19)}$$

where the inverse transform of the disposition matrix, given by:

$$\mathbf{\Phi}(t) = L^{-1}\mathbf{D} \qquad \text{(Eq. 20)}$$

is the normalized fundamental matrix of the complementary homogeneous equation $\mathbf{x}' - (\mathbf{K}^T - \mathbf{\Sigma})\mathbf{x} = \mathbf{0}$. The elements of this matrix are readily obtained according to Eq. 11 by:

$$\Phi_{ij}(t) = L^{-1}(d_{ij}) = L^{-1}(|\mathbf{S}|_{ij}/|\mathbf{S}|) \qquad \text{(Eq. 21)}$$

Equation 19 is of little practical interest because it involves a convolution integral. However, the following remarkable property of the fundamental matrix (9):

$$\mathbf{\Phi}(t-\tau) = e^{(\mathbf{K}^T-\mathbf{\Sigma})(t-\tau)} = e^{(\mathbf{K}^T-\mathbf{\Sigma})t}e^{(\mathbf{K}^T-\mathbf{\Sigma})(-\tau)} = \mathbf{\Phi}(t)\mathbf{\Phi}(-\tau) \qquad \text{(Eq. 22)}$$

enables the convolution integral to be converted into an ordinary integral so that Eq. 19 may be written as:

$$\mathbf{x} = \mathbf{\Phi}(t)\left[\mathbf{x}(0) + \int_0^t \mathbf{\Phi}(-t)\mathbf{f}(t)\,dt\right] \qquad \text{(Eq. 23)}$$

RESULTS AND DISCUSSION

Equation 12 describes any compartment of any linear pharmacokinetic model with input in one or more compartments. It is of interest to consider the following commonly applied system.

Special Case: Input in Central Compartment Only—In this case [with $x_{i>1}(0) = 0$], Eq. 12 reduces to:

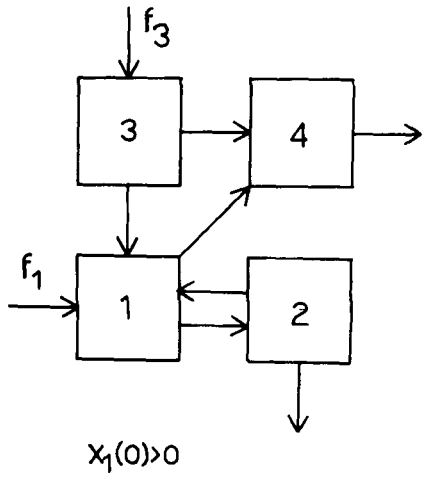
$$x_i = L^{-1}\left[\frac{|\mathbf{S}|_{i1}}{|\mathbf{S}|}[x_1(0) + \bar{f}_1]\right] = L^{-1}(d_{i1}v_1) \qquad \text{(Eq. 24)}$$

More specifically, when $i = 1$, Eq. 24 describes the central compartment. Benet (6) presented a general treatment of mammillary systems with central input that represents a special case within this category. A mammillary model consists specifically of a central compartment connected to a number of peripheral compartments that are themselves unconnected. Benet's approach (6) can be summarized by:

$$x_1 = L^{-1}[(d_{s,1})(in_s)] \qquad \text{(Eq. 25)}$$

where in_s was called the input function and $d_{s,1}$ was called the disposition function for Compartment 1, the central compartment. An elaborate expression (Eq. 1 of Ref. 6) was presented for the disposition function $d_{s,1}$, and examples were given of various input functions, in_s. It is evident from these examples that the vector element, $v_1 = x_1(0) + \bar{f}_1$, in Eq. 24 agrees with the input function, in_s, in Eq. 25.

However, although $d_{s,1}$ as defined by Benet (Eq. 1 of Ref. 6) and the disposition element, $d_{11} = |\mathbf{S}|_{11}/|\mathbf{S}|$ (Eq. 24, $i = 1$), may seem identical from comparison of Eqs. 24 and 25, they are in general not the same. For example, the expression presented (6) for $d_{s,1}$ is not directly applicable to a system if it contains compartments connected in ring arrangement



Scheme IV—Arbitrary linear pharmacokinetic model used to demonstrate the application of Eq. 12.

(*e.g.*, Scheme IV of Ref. 6). Although such systems can sometimes be "broken down" into separate mammillary systems and analyzed in terms of these systems (6), this is not always the case.

Vaughan and coworkers (7, 8) extended Benet's approach to account for cases with input into peripheral compartments. However, their equations (Eqs. 20 and 22 in Ref. 7) are limited to mammillary systems only. In contrast, Eq. 12 describes any linear pharmacokinetic system. Furthermore, this equation is a simpler representation than those presented previously (6–8) and has the additional advantage that the solution for a peripheral compartment can be found as readily as for the central compartment.

Simultaneous Noncentral Input—The applicability of Eq. 12 can be demonstrated using the system in Scheme IV. The **S** matrix (Eq. 6) may be readily assembled so that:

$$|\mathbf{S}| = \begin{vmatrix} (s+E_1) & -k_{12} & 0 & -k_{14} \\ -k_{21} & (s+E_2) & 0 & 0 \\ -k_{31} & 0 & (s+E_3) & -k_{34} \\ 0 & 0 & 0 & (s+E_4) \end{vmatrix}$$
$$= (s+E_3)[(s+E_1)(s+E_2) - k_{12}k_{21}] \qquad \text{(Eq. 26)}$$

where $E_{1-4} = k_{12} + k_{14}, k_{21} + k_{20}, k_{31} + k_{34}$, and k_{40} (Eq. 3). If the solution for Compartment 1 is sought, Eq. 12 gives:

$$x_1 = L^{-1}\left(\frac{|\mathbf{S}|_{11}}{|\mathbf{S}|}[x_1(0) + f_1] + \frac{|\mathbf{S}|_{13}}{|\mathbf{S}|}f_3\right) \qquad \text{(Eq. 27)}$$

where:

$$|\mathbf{S}|_{11} = (-1)^{1+1}\begin{vmatrix} (s+E_2) & 0 & 0 \\ 0 & (s+E_3) & -k_{34} \\ 0 & 0 & (s+E_4) \end{vmatrix}$$
$$= (s+E_4)(s+E_2)(s+E_3) \qquad \text{(Eq. 28)}$$

and:

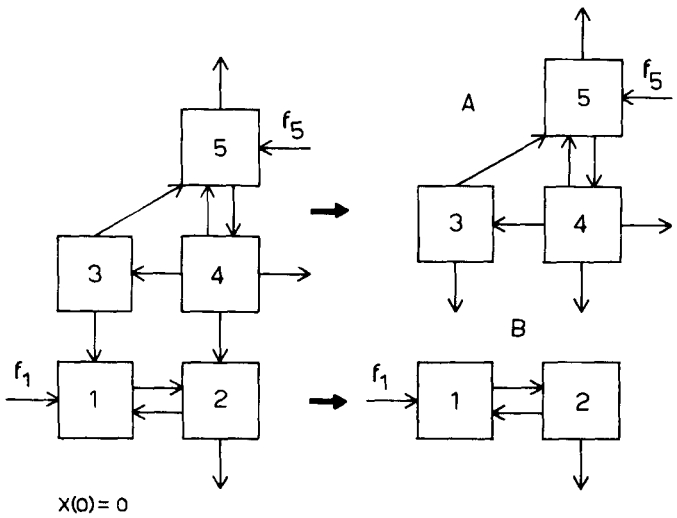
$$|\mathbf{S}|_{13} = (-1)^{1+3}\begin{vmatrix} -k_{21} & (s+E_2) & 0 \\ -k_{31} & 0 & -k_{34} \\ 0 & 0 & (s+E_4) \end{vmatrix}$$
$$= (s+E_4)k_{31}(s+E_2) \qquad \text{(Eq. 29)}$$

It is convenient to write the determinant in "factor form" as $|\mathbf{S}| = (s + \lambda_1)(s + \lambda_2)(s + \lambda_3)(s + \lambda_4)$ where λ_{1-4}, the eigenvalues of the matrix $\mathbf{K} - \mathbf{\Sigma}$, are obtained from Eq. 26. Equation 27 thus becomes:

$$x_1 = L^{-1}\left[\frac{(s+E_2)(s+E_3)(s+E_4)}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)(s+\lambda_4)}[x_1(0) + f_1] + \frac{k_{31}(s+E_2)(s+E_4)}{(s+\lambda_1)(s+\lambda_2)(s+\lambda_3)(s+\lambda_4)}\bar{f}_3\right] \qquad \text{(Eq. 30)}$$

The inverse transform can then be obtained as demonstrated previously when f_1 and f_3 are given (6–8, 10–12).

The input functions f_1 and f_3 may be any continuous or discontinuous



Scheme V—Arbitrary linear pharmacokinetic model used to demonstrate the subsystem approach. A is a donor system and B is an acceptor system.

functions. For example, the input function describing an instantaneous input in Compartment 1 of the amounts m_1, m_2, and m_3 at times t_1, t_2, and t_3, respectively, is:

$$f_1 = m_1\delta(t - t_1) + m_2\delta(t - t_2) + m_3\delta(t - t_3) \qquad \text{(Eq. 31)}$$

where δ is the unit impulse function (12). The Laplace transform of Eq. 31 is then:

$$\bar{f}_1 = m_1e^{-t_1s} + m_2e^{-t_2s} + m_3e^{-t_3s} \qquad \text{(Eq. 32)}$$

Specifically, when $t_1 = 0$, this equation becomes:

$$\bar{f}_1 = x_1(0) + m_2e^{-t_2s} + m_3e^{-t_3s} \qquad \text{(Eq. 33)}$$

Equation 9 shows that the input vector **v** is the sum of the initial condition and the transform of the input. However, the last example demonstrates that the initial conditions can also be considered as the transforms of certain input functions. Therefore, when a full transformation approach is applied, the initial conditions can be included in the input functions, f_i, to give a simpler representation. Therefore, the $x_j(0)$ term in Eqs. 12 and 13 can be omitted, and **v** can be replaced by $\bar{\mathbf{f}}$ in Eqs. 7 and 10 without loss of generality.

A Subsystem Approach—*Solution for Donor System*—The system in Scheme V can be divided into a donor subsystem (Scheme V, System A) and an acceptor subsystem (Scheme V, System B). If the disposition of the donor system is of interest, then Eq. 17 can be used:

$$\begin{bmatrix} x_3 \\ x_4 \\ x_5 \end{bmatrix} = L^{-1}\begin{bmatrix} d_{11} & d_{12} & d_{13} \\ d_{21} & d_{22} & d_{23} \\ d_{31} & d_{32} & d_{33} \end{bmatrix}^{[2]}\begin{bmatrix} 0 \\ 0 \\ \bar{f}_5 \end{bmatrix} \qquad \text{(Eq. 34)}$$

where the superscript, [2], of the disposition elements is placed outside the matrix frame for simplicity. The $d_{ij}^{[2]}$ elements are obtained using Eq. 11 from:

$$|\mathbf{S}|^{[2]} = \begin{array}{c} \\ (3) \\ (4) \\ (5) \end{array}\begin{array}{c} \begin{array}{ccc} (3) & (4) & (5) \end{array} \\ \begin{vmatrix} (s+E_3) & 0 & -k_{35} \\ -k_{43} & (s+E_4) & -k_{45} \\ 0 & -k_{54} & (s+E_5) \end{vmatrix} \end{array} \qquad \text{(Eq. 35)}$$

In applying Eqs. 10–13, it is important to realize that the i and j are independent of the numbers assigned to the compartments. It is completely arbitrary how such a numbering is made. The order in which the elements of the **x** vector are written is also arbitrary as long as the order of the elements of the respective input vector, **v**, corresponds and the **s** matrix is composed accordingly. For example, the **x** vector in Eq. 34 could have been written as $\mathbf{x}^{[2]} = (x_3,x_5,x_4)^T$, which corresponds to $\mathbf{v}^{[2]} = (0,\bar{f}_5,0)^T$ and:

$$|\mathbf{S}|^{[2]} = \begin{array}{c} \\ (3) \\ (5) \\ (4) \end{array}\begin{array}{c} \begin{array}{ccc} (3) & (5) & (4) \end{array} \\ \begin{vmatrix} (s+E_3) & -k_{35} & 0 \\ 0 & (s+E_5) & -k_{54} \\ -k_{43} & -k_{45} & (s+E_4) \end{vmatrix} \end{array} \qquad \text{(Eq. 36)}$$

The solution for Compartment 4 corresponds to element 3 of the $\mathbf{x}^{[2]}$ vector in the latter case. Thus, according to Eq. 12:

$$x_{i=3} = x_4 = L^{-1}\left(\frac{|\mathbf{S}|_{32}^{[2]}}{|\mathbf{S}|^{[2]}}\bar{f}_5\right) \qquad \text{(Eq. 37)}$$

where $|\mathbf{S}|^{[2]}$ is given by Eq. 36. In the other case, one obtains:

$$x_{i=2} = x_4 = L^{-1}\left(\frac{|\mathbf{S}|_{23}^{[2]}}{|\mathbf{S}|^{[2]}}\bar{f}_5\right) \qquad \text{(Eq. 38)}$$

where $|\mathbf{S}|^{[2]}$ is given by Eq. 35, which yields the same solution as Eq. 37.

Solution for Acceptor System—Let the **x** vectors for systems [1] and [2] (Scheme V, Systems B and A) be written arbitrarily as $\mathbf{x}^{[1]} = (x_1,x_2)^T$ and $\mathbf{x}^{[2]} = (x_3,x_4,x_5)^T$, respectively; then Eq. 16 can be written as:

$$\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = L^{-1}\begin{bmatrix} d_{11} & d_{12} \\ d_{21} & d_{22} \end{bmatrix}^{[1]} \times\left(\begin{bmatrix} \bar{f}_1 \\ 0 \end{bmatrix} + \begin{bmatrix} k_{31} & 0 & 0 \\ 0 & k_{42} & 0 \end{bmatrix}\begin{bmatrix} d_{11} & d_{12} & d_{13} \\ d_{21} & d_{22} & d_{23} \\ d_{31} & d_{32} & d_{33} \end{bmatrix}^{[2]}\begin{bmatrix} 0 \\ 0 \\ \bar{f}_3 \end{bmatrix}\right) \qquad \text{(Eq. 39)}$$

The disposition elements $d_{ij}^{[1]}$ and $d_{ij}^{[2]}$ are given by Eq. 11, where **S** is composed as discussed; *i.e.*, $d_{ij}^{[1]}$ is obtained from:

$$|\mathbf{S}|^{[1]} = \begin{vmatrix} (s+E_1) & -k_{12} \\ -k_{21} & (s+E_2) \end{vmatrix} \qquad \text{(Eq. 40)}$$

and $d_{ij}^{[2]}$ is obtained from Eq. 35. The connector constant k_{42} connects the second element of the $\mathbf{x}^{[1]}$ vector with the second element of the $\mathbf{x}^{[2]}$ vector; it is thus placed in the 2,2-position of the connector matrix in Eq. 39. The connector constant k_{31} is placed in the 1,1-position by the same reasoning. The compartments can be numbered arbitrarily as before, but the composition of the **S** and **C** matrices and the input vectors must correspond to the arbitrary order of the elements in the **x** vectors.

For Compartment 1, Eqs. 39 and 11 give:

$$x_1 = L^{-1}\left[\frac{|\mathbf{S}|_{11}^{[1]}}{|\mathbf{S}|^{[1]}}\bar{f}_1 + \frac{k_{31}|\mathbf{S}|_{11}^{[1]}|\mathbf{S}|_{13}^{[2]} + k_{42}|\mathbf{S}|_{12}^{[1]}|\mathbf{S}|_{23}^{[2]}}{|\mathbf{S}|^{[1]}|\mathbf{S}|^{[2]}}\bar{f}_3\right] \qquad \text{(Eq. 41)}$$

from which x_1 can be obtained when f_1 and f_3 are given (6–8, 10–12).

There is always an advantage in using a subsystem approach to solve for a donor system compartment because of the simplification of the system. If the solution for an acceptor system compartment is sought, it will also often be convenient to apply such an approach. The number of algebraic operations required to evaluate a determinant is of the order n^3. With large systems, it should be an advantage to work with the smaller determinants and cofactors of the subsystems.

Partial Transform Approach—Equation 23, which defines the unique time domain solution of Eq. 1, has an advantage over Eq. 12 in that it does not require transformation of the input functions. The elements of the fundamental matrix are always readily found according to Eq. 21 by the method of partial fractions using Heaviside's expansion formula in its extended form (10, 12) because the ratio $|\mathbf{S}|_{ij}/|\mathbf{S}|$ is always of the form $P(s)/Q(s)$, where P and Q are polynomials in s with Q of a higher degree (n) than P. Equation 23, however, has the disadvantage that the input functions, f_i, must be continuous in the time interval of interest. If this is not the case, the approach is still applicable, but the system must be analyzed in sections of time where the input is continuous.

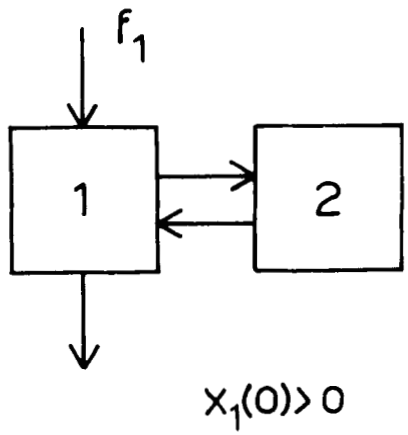
However, in the special case with multiple instantaneous (bolus) inputs into the central compartment, the solution may readily be obtained as:

$$x_j = \sum_{i=1} \Phi_{j1}(t - t_i)m_i \qquad t_i < t \qquad \text{(Eq. 42)}$$

where t_i and m_i are as defined previously (Eq. 31) and the summation is to be taken to the highest integer value of i for which $t_i < t$ is satisfied.

For simplicity, consider the two-compartment system in Scheme VI where the continuous input functions, f_1, is of a form that does not have a simple Laplace transform. For Compartment 1 of this system, Eq. 23 yields directly:

$$x_1 = \Phi_{11}(t)\left[x_1(0) + \int_0^t \Phi_{11}(-t)f_1(t)\,dt\right] + \Phi_{12}(t)\int_0^t \Phi_{21}(-t)f_1(t)\,dt \qquad \text{(Eq. 43)}$$



Scheme VI—Two-compartmental linear pharmacokinetic model used to demonstrate the partial transformation approach that does not require Laplace transformation of the input function f_1.

where, according to Eq. 21:

$$\Phi_{11}(t) = \frac{\alpha - E_2}{\alpha - \beta} e^{-\alpha t} + \frac{E_2 - \beta}{\alpha - \beta} e^{-\beta t} \quad \text{(Eq. 44)}$$

$$\Phi_{12}(t) = \frac{-k_{21}}{\alpha - \beta} e^{-\alpha t} + \frac{k_{21}}{\alpha - \beta} e^{-\beta t} \quad \text{(Eq. 45)}$$

$$\Phi_{21}(t) = \frac{-k_{12}}{\alpha - \beta} e^{-\alpha t} + \frac{k_{12}}{\alpha - \beta} e^{-\beta t} \quad \text{(Eq. 46)}$$

and $\alpha\beta = E_1E_2 - k_{12}k_{21}$ and $\alpha + \beta = E_1 + E_2$.

Equation 43 becomes, after substitution:

$$x_1 = \frac{\alpha - E_2}{\alpha - \beta} e^{-\alpha t} \left[x_1(0) + \int_0^t e^{\alpha t} f_1(t)\, dt \right] + \frac{E_2 - \beta}{\alpha - \beta} e^{-\beta t} \left[x_1(0) + \int_0^t e^{\beta t} f_1(t)\, dt \right] \quad \text{(Eq. 47)}$$

As an example, input f_1 may be in the form of a dissolution rate-limited release from an injected depot of slightly soluble crystalline drug. If it is assumed that *in vivo* dissolution follows the Hixson–Crowell relationship (13), then the input function may be written:

$$f_1(t) = -\frac{d}{dt} m_0(1 - k_d t)^3 = 3k_d m_0(1 - k_d t)^2 \qquad t < 1/k_d \quad \text{(Eq. 48)}$$

where m_0 is the dose injected and k_d is the *in vivo* dissolution constant. Substitution of this equation into Eq. 47 yields, after integration:

$$x_1 = \frac{3k_d m_0(\alpha - E_2)}{\alpha(\alpha - \beta)} \left[k_d{}^2 t^2 - \frac{2k_d{}^2 + 2\alpha k_d}{\alpha} t + \frac{2k_d{}^2 + 2\alpha k_d + \alpha^2}{\alpha^2} \right] + \frac{3k_d m_0(E_2 - \beta)}{\beta(\alpha - \beta)} \left[k_d{}^2 t^2 - \frac{2k_d{}^2 + 2\beta k_d}{\beta} t + \frac{2k_d{}^2 + 2\beta k_d + \beta^2}{\beta^2} \right] + \frac{\alpha - E_2}{\alpha - \beta} \left[x_1(0) - \frac{3k_d m_0(2k_d{}^2 + 2\alpha k_d + \alpha^2)}{\alpha^3} \right] e^{-\alpha t} + \frac{E_2 - \beta}{\alpha - \beta} \times \left[x_1(0) - \frac{3k_d m_0(2k_d{}^2 + 2\beta k_d + \beta^2)}{\beta^3} \right] e^{-\beta t} \qquad t < 1/k_d \quad \text{(Eq. 49)}$$

Equation 49 could have been obtained using a full transformation approach but that would require a somewhat larger derivation. The advantage of using a partial transform approach becomes particularly significant for more complex input functions.

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Physiological Perfusion Model for Cephalosporin Antibiotics I: Model Selection Based on Blood Drug Concentrations

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Abstract □ Various cephalosporins with different degrees of protein binding were administered to human volunteers. Blood samples were collected as a function of time and were assayed for drug content by a microbiological assay. A pharmacokinetic analysis of the data was performed using a two-compartment model with and without protein binding in the central compartment and a perfusion model. Both the two-compartment model without protein binding and the physiological perfusion model adequately described the blood levels of all three cephalosporins.

Keyphrases □ Cephalosporins, various—pharmacokinetic analysis using two-compartment and perfusion models □ Antibiotics, various cephalosporin—pharmacokinetic analysis using two-compartment and perfusion models □ Models, pharmacokinetic—two-compartment and perfusion, for various cephalosporins

Compartmental models are a "black box" approach to predicting blood levels. The model consists of a central compartment, usually considered to be the plasma compartment, and possibly one or more tissue compartments. The compartments and the associated volumes and rate constants have no physiological meaning; *i.e.*, the plasma