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Analytical Solution to the Three-Compartment Pharmacokinetic Model

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Abstract—**Simulations of pharmacokinetic models in software usually rely on discrete approximation of the continuous differential equations describing the system, but this need not be the case. In this communication, the analytical equations describing the temporal behavior of the three-compartment open pharmacokinetic model are derived, and an algorithm for their use in pharmacokinetic simulations is given.**

Introduction

Pharmacokinetic simulations are useful in teaching pharmacokinetic principles, in designing drug dosing schemes, in exploring pharmacokinetic explanations for pharmacodynamic data, and in providing the basis for pharmacokinetic model-driven computer-controlled drug delivery systems. Approaches to simulating the continuous differential equations describing a drug's kinetics in software have typically relied upon discrete numerical approximation techniques, such as the bilinear transform (e.g., [1] and [2]) and Runge–Kutta integration (e.g., [3], [4], and [5]). Presented here is a derivation of the exact analytical time-domain equations describing a common pharmacokinetic model; although computationally somewhat more complex than the approximate solutions, the analytical approach offers increased flexibility and is accurate to within the precision of the particular software implementation.

Mathematical Derivation

In characterizing a drug's pharmacokinetics it is common to conceptualize the body as a system of compartments within the framework of compartmental system analysis. The time course of distribution, metabolism, and excretion of many drugs following intravenous infusion can be schematized by the three-compartment model shown in Fig. 1. In this model, drug is infused into, and eliminated from, the central compartment, which is essentially the blood or plasma. Drug residing in the central compartment may reversibly distribute between two hypothetical peripheral compartments, possibly one of which represents well perfused tissues and the other of which represents poorly perfused tissues. The rate constants and central compartment volume are drug- and population-specific and can be found in the published literature. As is usually the case in pharmacokinetics analysis, the objective of the present derivation is to quantify the temporal relationship between drug administration and central compartment drug concentration.

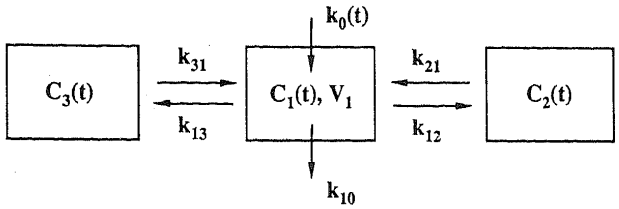

Fig. 1. Schematic representation of the body as a three-compartment model with drug infusion into, and drug elimination from, the central compartment, where k_{ij} (min^{-1}) are rate constants, $C_i(t)$ ($\text{ng} \cdot \text{ml}^{-1}$) is the drug concentration in compartment i at time t, $k_o(t)$ ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) is the drug infusion rate at time t, and V_1 ($\text{l} \cdot \text{kg}^{-1}$) is the apparent volume of the central compartment.

The model given in Fig. 1 is a pictorial abstraction of the following system of linear differential equations:

$$dC_1(t)/dt = k_0(t)/V_1 - [k_{10} + k_{12} + k_{13}]C_1(t) + k_{21}C_2(t) + k_{31}C_3(t) \quad (1)$$

$$dC_2(t)/dt = k_{12}C_1(t) - k_{21}C_2(t) \quad (2)$$

$$dC_3(t)/dt = k_{13}C_1(t) - k_{31}C_3(t). \quad (3)$$

Taking the Laplace transform of (1), (2), and (3) yields (4), (5), and (6), respectively,

$$sC_1(s) - C_1' = k_0(s)/V_1 - [k_{10} + k_{12} + k_{13}]C_1(s) + k_{21}C_2(s) + k_{31}C_3(s) \quad (4)$$

$$sC_2(s) - C_2' = k_{12}C_1(s) - k_{21}C_2(s) \quad (5)$$

$$sC_3(s) - C_3' = k_{13}C_1(s) - k_{31}C_3(s) \quad (6)$$

where s is the Laplace operator and C_i', $i = 1, 2, 3$ are the initial concentrations (initial conditions) in each of the three compartments. These simultaneous equations can be manipulated algebraically to form (7), relating the central compartment drug concentration and

$$C_1(s) = \frac{k_0(s)V_1^{-1}(s + k_{21})(s + k_{31}) + C_1's^2 + [C_1'k_{31} + C_1'k_{21} + C_2'k_{21} + C_3'k_{31}]s + [C_1' + C_2' + C_3']k_{21}k_{31}}{s^3 + s^2(k_{10} + k_{12} + k_{21} + k_{13} + k_{31}) + s(k_{31}k_{21} + k_{10}k_{31} + k_{12}k_{31} + k_{10}k_{21} + k_{13}k_{21}) + k_{10}k_{21}k_{31}} \quad (7)$$

the rate of intravenous drug infusion. The time-domain equation to be used in numerical simulations is obtained through the tedious, but simple, process of using a table of Laplace transform pairs to compute the inverse Laplace transform of (7). To do this, it is first necessary to have an explicit expression for $k_o(s)$. Without loss of generality we can assume the drug infusion rate $k_o(t)$ to be constant at Rate ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) over the period t_o to t, so that $k_o(s)$ = Rate/s. The desired result is then derived as (8), where s_1, s_2, s_3 are the roots of the cubic denominator of (7), which are equal, respectively, to $-\lambda_1$, $-\lambda_2$, and $-\lambda_3$ from the standard pharmacokinetic equation $C_1(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t} + A_3e^{-\lambda_3 t}$ describing the fall in plasma drug concentration following a single bolus injection. (Typically, pharmacokinetic experiments are designed to determine A_1, A_2, A_3, λ_1, λ_2, and λ_3, from which the rate constants

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and V_1 can be derived or vice versa [6]. Alternatively, the cubic roots s_1, s_2, and s_3 can be easily computed using the trigonometric method attributed to Vieta [7].) In (8), t is the current time and t_o is the time at which Rate was begun; the difference $t - t_o$ is expressed in minutes.

Realizing simulations with (8) would be relatively straightforward if not for the requirement to supply new values for C_2' and C_3' whenever Rate changes. It is therefore necessary to also derive expressions describing the time course of drug concentration in the two peripheral compartments. To do this, the inverse Laplace transforms (9) and (10) of (5) and (6), respectively, are formed, after first substituting into them (7) for $C_1(s)$.

Equations (8), (9), and (10) are readily implemented in software and facilitate prediction of drug plasma levels resulting from any intravenous infusion scheme.

$$C_1(t) = -\text{Rate}\,\frac{k_{21}k_{31}}{V_1 s_1 s_2 s_3}$$
$$+\left\{\text{Rate}\left[\frac{k_{21}k_{31}+(k_{21}+k_{31})s_1+s_1^2}{V_1 s_1(s_1-s_2)(s_1-s_3)}\right]+\frac{C_1's_1^2+[C_1'k_{21}+C_1'k_{31}+C_2'k_{21}+C_3'k_{31}]s_1+[C_1'+C_2'+C_3']k_{21}k_{31}}{(s_1-s_2)(s_1-s_3)}\right\}e^{s_1(t-t_o)}$$
$$+\left\{\text{Rate}\left[\frac{k_{21}k_{31}+(k_{21}+k_{31})s_2+s_2^2}{V_1 s_2(s_2-s_1)(s_2-s_3)}\right]+\frac{C_1's_1^2+[C_1'k_{21}+C_1'k_{31}+C_2'k_{21}+C_3'k_{31}]s_1+[C_1'+C_2'+C_3']k_{21}k_{31}}{(s_2-s_1)(s_2-s_3)}\right\}e^{s_2(t-t_o)}$$
$$+\left\{\text{Rate}\left[\frac{k_{21}k_{31}+(k_{21}+k_{31})s_3+s_3^2}{V_1 s_3(s_3-s_1)(s_3-s_2)}\right]+\frac{C_1's_1^2+[C_1'k_{21}+C_1'k_{31}+C_2'k_{21}+C_3'k_{31}]s_1+(C_1'+C_2'+C_3']k_{21}k_{31}}{(s_3-s_1)(s_3-s_2)}\right\}e^{s_3(t-t_o)} \quad (8)$$

$$C_2(t) = -\text{Rate}\,\frac{k_{12}k_{31}}{V_1 s_1 s_2 s_3}$$
$$+\left\{\text{Rate}\left[\frac{k_{12}(s_1+k_{31})}{V_1 s_1(s_1-s_2)(s_1-s_3)}\right]+\frac{C_1's_1^2k_{12}+[C_1'k_{21}+C_1'k_{31}+C_2'k_{21}+C_3'k_{31}]s_1k_{12}+[C_1'+C_2'+C_3']k_{21}k_{31}k_{12}}{(s_1+k_{21})(s_1-s_2)(s_1-s_3)}\right\}e^{s_1(t-t_o)}$$
$$+\left\{\text{Rate}\left[\frac{k_{12}(s_2+k_{31})}{V_1 s_2(s_2-s_1)(s_2-s_3)}\right]+\frac{C_1's_2^2k_{12}+[C_1'k_{21}+C_1'k_{31}+C_2'k_{21}+C_3'k_{31}]s_2k_{12}+[C_1'+C_2'+C_3']k_{21}k_{31}k_{12}}{(s_2+k_{21})(s_2-s_1)(s_2-s_3)}\right\}e^{s_2(t-t_o)}$$
$$+\left\{\text{Rate}\left[\frac{k_{12}(s_3+k_{31})}{V_1 s_3(s_3-s_1)(s_3-s_2)}\right]+\frac{C_1's_3^2k_{12}+[C_1'k_{21}+C_1'k_{31}+C_2'k_{21}+C_3'k_{31}]s_3k_{12}+[C_1'+C_2'+C_3']k_{21}k_{31}k_{12}}{(s_3+k_{21})(s_3-s_1)(s_3-s_2)}\right\}e^{s_3(t-t_o)}$$
$$+\left\{C_2'+\frac{C_1'k_{21}^2k_{12}-[C_1'k_{21}+C_1'k_{31}+C_2'k_{21}+C_3'k_{31}]k_{21}k_{12}+[C_1'+C_2'+C_3']k_{21}k_{31}k_{12}}{(-k_{21}-s_1)(-k_{21}-s_2)(-k_{21}-s_3)}\right\}e^{-k_{21}(t-t_o)} \quad (9)$$

$$C_3(t) = -\text{Rate}\,\frac{k_{13}k_{21}}{V_1 s_1 s_2 s_3}$$
$$+\left\{\text{Rate}\left[\frac{k_{13}(s_1+k_{21})}{V_1 s_1(s_1-s_2)(s_1-s_3)}\right]+\frac{C_1's_1^2k_{13}+[C_1'k_{21}+C_1'k_{31}+C_2'k_{21}+C_3'k_{31}]s_1k_{13}+[C_1'+C_2'+C_3']k_{21}k_{31}k_{13}}{(s_1+k_{31})(s_1-s_2)(s_1-s_3)}\right\}e^{s_1(t-t_o)}$$
$$+\left\{\text{Rate}\left[\frac{k_{13}(s_2+k_{21})}{V_1 s_2(s_2-s_1)(s_2-s_3)}\right]+\frac{C_1's_2^2k_{13}+[C_1'k_{21}+C_1'k_{31}+C_2'k_{21}+C_3'k_{31}]s_2k_{13}+[C_1'+C_2'+C_3']k_{21}k_{31}k_{13}}{(s_2+k_{31})(s_2-s_1)(s_2-s_3)}\right\}e^{s_2(t-t_o)}$$
$$+\left\{\text{Rate}\left[\frac{k_{13}(s_3+k_{21})}{V_1 s_3(s_3-s_1)(s_3-s_2)}\right]+\frac{C_1's_3^2k_{13}+[C_1'k_{21}+C_1'k_{31}+C_2'k_{21}+C_3'k_{31}]s_3k_{13}+[C_1'+C_2'+C_3']k_{21}k_{31}k_{13}}{(s_3+k_{31})(s_3-s_1)(s_3-s_2)}\right\}e^{s_3(t-t_o)}$$
$$+\left\{C_3'+\frac{C_1'k_{31}^2k_{13}-[C_1'k_{21}+C_{31}'+C_2'k_{21}+C_3'k_{31}]k_{31}k_{13}+[C_1'+C_2'+C_3']k_{21}k_{31}k_{13}}{(-k_{31}-s_1)(-k_{31}-s_2)(-k_{31}-s_3)}\right\}e^{-k_{31}(t-t_o)} \quad (10)$$

Since the concentration of drug in the hypothetical peripheral compartments cannot, in general, be measured, it is assumed (at least for pharmacokinetic simulations) that at time $t = 0$, $C_1' = C_2' = C_3' = 0$. As a Rate is specified at time t', $t_o = t'$ and (8) is used to determine the drug plasma level at arbitrarily selected points in real or simulated time. Whenever Rate is changed at time t', the current theoretical drug concentrations in the peripheral compartments are calculated using (9) and (10), (8) is supplied with $C_1' = C_1(t')$, $C_2' = C_2(t')$, and $C_3' = C_3(t')$, $t_o = t'$, and the simulation continues. All computations should be performed using double precision arithmetic.

Discussion

The analytical equations derived in this report obviate the need to use discrete approximation techniques to simulate the continuous differential equations describing the three-compartment open pharmacokinetic model. This particular model was chosen for analysis because of its relative complexity and usefulness; the derivation given here is readily applied to other compartmental structures. Simulations utilizing these analytical equations require more computational effort at each data point than do use of their discrete counterparts, but the analytical approach should not be vulnerable to aliasing, should be less sensitive to round-off error, should not be subject to frequency warping, and solutions need only be calculated at the time points of interest. Where it is desirable or necessary to use one of the discrete techniques, the analytical solution provides a standard by which the integrity of the approximation can be evaluated.

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Correction to "Importance of the Low-Frequency Impedance Data for Reliably Quantifying Parallel Inhomogeneities of Respiratory Mechanics"

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The above paper[1] was improperly listed under *Medical AI and Information Systems*. It should have appeared under the general area of *Respiratory Systems*.

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