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Title:
Derivation and presentation of formulas for drug concentrations in two-, three- and four-compartment pharmacokinetic models

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Abstract:
Although compartment models are frequently used in pharmacokinetics, it is difficult to find complete analytical formulas describing the behaviour of drugs in universal simpler compartment models in the accessible literature. The paper presents derivations of formulas for general two- and three-compartment models, including the possibilities of original non-zero quantity in all compartments and elimination from all compartments. Formulas for four-compartment models are also derived with the restriction that original quantity is non-zero in only one compartment. Derivation uses Laplace transformation but does not require prior knowledge of the technique. The derived analytical formulas are verified numerically. These formulas can be easily simplified to less complex cases.

Introduction

To describe and understand the pharmacokinetics of a drug, it is very often useful to set up a model and determine the model parameters best fitting the data. Compartment models are useful tools in this respect; however, it is difficult to find complete analytical formulas describing the behaviour of drugs in universal simpler compartment models. A three-compartment model (3-C) is frequently mentioned in the literature; however, the accessible references are limited for mammillary models and present complete formulas neither for catenary nor for cyclic models [1, 2, 3, 4, 5]. The accessible literature for four-compartment models (4-C) also does not present the final complete equations [6, 7]. Although the formulas for two-compartment models (2-C) are better known, they will be presented here as well for a better demonstration of the derivation method.

The purpose of the paper is to give a derivation of the concentration formulas for 2-C, 3-C, and 4-C models, in a form accessible to readers knowledgeable of compartment models and not scared by math, but without assuming prior knowledge of advanced techniques such as Laplace transformations. In Supplementary Material, the results are presented as computer algorithms to make the formulas easier applicable for the readers. These algorithms are implemented in PHP, but, after minor changes, can be used in other software languages as well.
The treatment will be general, except that it will be assumed that all drug has entered the system at time t=0. While this restriction excludes cases where drugs are introduced gradually, it can be circumvented for cases where further drug is introduced at specific time points t_1, t_2, etc.: First the problem is solved from 0 until t_1, then using the final quantities + newly introduced drug is used to solve from t_1 to t_2, etc.

Briefly on compartment models

In modelling, a compartment is used to specify where (e.g. in the plasma) or in what state (e.g. free or bound) the discussed substance is distributed. As such, pharmacokinetic compartments do not necessarily correspond to structurally delineated anatomic compartments. Compartment modelling assumes uniform distribution within each compartment, i.e. that each compartment can be assigned a concentration. After the drug has entered the system (e.g. by injection), the concentration in a given compartment at time t can be generally described by a multi-exponential function:

$$C_t = \sum_{i=1}^{n} c_i \cdot e^{-b_i \cdot t} \qquad \{\text{eq. 1}\}$$

where n is the number of compartments in the system.

Having the above formula, the area under the time-concentration curve (AUC) in the compartment can be expressed as:

$$AUC = \sum_{i=1}^{n} c_i / b_i. \qquad \{\text{eq. 2}\}$$

In the specific case of a 2-C model, a common notation is to write $A \cdot \exp(-\alpha \cdot t) + B \cdot \exp(-\beta \cdot t)$ rather than $c_1 \cdot \exp(-b_1 \cdot t) + c_2 \cdot \exp(-b_2 \cdot t)$. In this case,

$$AUC = A/\alpha + B/\beta. \qquad \{\text{eq. 3}\}$$

The exponentials describe the overall behaviour of the system. This behaviour arises from the inherent parameters of the model: elimination rate constants, clearances, and compartment volumes. These parameters are sometimes referred to as micro-constants.

In the models considered here, the rate of the transport of a drug (quantity per time) is proportional to its concentration in the respective compartment (linear models, first order processes). The transport rate constants (k) are signed with lower indices describing the direction of the transport, i.e., k_{ij} denotes elimination rate constant from compartment i to j, k_{ji} from j to i, k_{i0} from compartment i to the environment (and, hence, from the entire organism). In passive transport, there is no preferred direction of transport, leading to the following dependence:

$$k_{ij} \cdot V_i = k_{ji} \cdot V_j = Cl_{ij}, \qquad \{\text{eq. 4}\}$$

where Cl_{ij} is the intercompartmental clearance (the same in both directions) and V_i is the volume of the compartment i. Additionally, Q_{ti} and C_{ti} denote the quantity and concentration, respectively, of the drug in compartment i in a given time point t. Similarly, Q_{i0} is its initial amount, and C_{i0} its initial concentration in compartment i.

By definition, a single compartment has only a single concentration, corresponding to assuming instantaneous mixing of the injected drug with the entire volume of the compartment. If that assumption is a problem in a given context, then a different model is needed, e.g. a compartment models where the "problematic" compartment is represented by more than one compartment.

Introduction to Laplace transformation

A compartment model can be described with a system of differential equations in which the behaviour of the drug in each compartment is described with a separate equation.
The Laplace transformation can be used as a powerful tool in finding solutions for such systems by turning the differential equations into normal equations [8]. Overall, the procedure is:

1) Use the Laplace transformation to replace the differential equations by normal (non-differential) equations on the so-called Laplace transforms.
2) Solve these equations to obtain the solutions for the Laplace transforms.
3) Rewrite the solutions into a form that can be inversely transformed without too much difficulty.
4) Perform inverse Laplace transformation to obtain the solution to the original problem, i.e. to solve the differential equations.

Shortly, Laplace transformation is a mathematical operation which changes a t-dependent function into an s-dependent one according to a general rule:

$$F(s) = \mathcal{L}\big(f(t)\big) = \int_0^\infty f(t) \cdot e^{-s \cdot t}\, dt. \qquad \{\text{eq. 5}\}$$

The function $F(s)$ is called a Laplace transform. The variable s is abstract and has no obvious interpretation, but is mathematically needed to avoid loss of information: One function is transformed into another function, allowing inverse transformation (see below). Such inverse transformation would not be possible if only a single value (rather than a full function) was known, e.g. *AUC* can be calculated from the curve, but the curve cannot be calculated from the value of *AUC*.

In the equations, the distinction between letter *t* and letter *s* distinguishes original functions from Laplace transforms.
The Laplace transformation is linear:

$$\mathcal{L}\big(a \cdot f(t) + b \cdot g(t)\big) = a \cdot \mathcal{L}\big(f(t)\big) + b \cdot \mathcal{L}\big(g(t)\big) \qquad \{\text{eq. 6}\}$$

Noteworthy, the Laplace transform of a derivative has a simple relation to the transform of the original function:

$$\mathcal{L}\big(f'(t)\big) = s \cdot \mathcal{L}\big(f(t)\big) - f(0), \qquad \{\text{eq. 7}\}$$

where $f(0)$ is the value of the function for t=0 (initial value).
Thus, Laplace transformations can be used to change a problem of differential equations into a problem of non-differential equations. Solving these equations yields the Laplace transforms $F(s)$.
The last step is inverse transformation to obtain the solutions $f(t)$ to the original problem:

$$\mathcal{L}^{(-1)}\big(F(s)\big) = f(t). \qquad \{\text{eq. 8}\}$$

However, inverse Laplace transformation is in general far from easy, which is the reason for step 3 in the outlined procedure. Tables exist for a number of inverse transformations, so step 3 typically consist of rewriting $F(s)$ into a linear combination of such known results.
In pharmacokinetics of tracers, the involved functions are most often exponentials, allowing us to focus on only the Laplace transform of an exponential:

$$\mathcal{L}(e^{-a \cdot t}) = \frac{1}{s+a} \qquad \{\text{eq. 9}\}$$

with inverse transform:

$$\mathcal{L}^{(-1)}\left(\frac{1}{s+a}\right) = e^{-a \cdot t}. \qquad \{\text{eq. 10}\}$$

The linearity of the Laplace transformation tells us that if the solution for the transforms can be written as a sum of simple fractions $A/(s+a)$ then the solution for the original equations will be a sum of exponentials $A \cdot \exp(-a \cdot t)$.
For simplicity of notation, the independent variable is sometimes written as index, e.g. f_t and F_s, or even the same letter for the original function and transform, e.g. Q_t and Q_s

Two-compartment model

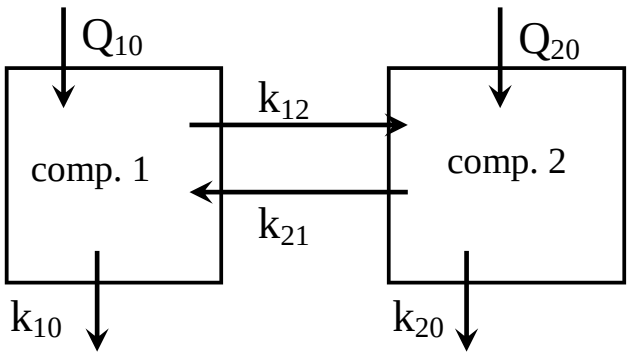


Figure 1: The universal two-compartment model. See the Introduction for the explanations of the symbols used.

Setup of equations
The 2-C model is presented in the Figure 1. Additionally, the following variables are defined:

$$K_1 = k_{10} + k_{12}$$
$$K_2 = k_{20} + k_{21}$$ {eq. 11}

The behaviour of the drug can be described by the initial system of differential equations:

$$\begin{cases} \frac{dQ_1}{dt} = -Q_1 \cdot K_1 + Q_2 \cdot k_{21} \\ \frac{dQ_2}{dt} = +Q_1 \cdot k_{12} - Q_2 \cdot K_2 \end{cases},$$ {eq. 12}

where the dQ_i/dt are the derivatives and the Q_{ti} are the sought variables (quantities of the drug) related to the concentrations with a formula:
$C_{ti} = Q_{ti}/V_i$.

Step 1: Laplace transformations
The Laplace transform of the system is:

$$\begin{cases} sQ_{s1} - Q_{10} = -Q_{s1} \cdot K_1 + Q_{s2} \cdot k_{21} \\ sQ_{s2} - Q_{20} = +Q_{s1} \cdot k_{12} - Q_{s2} \cdot K_2 \end{cases}.$$ {eq. 13}

Rearranging:

$$\begin{cases} -Q_{10} = -Q_{s1}(K_1 + s) + Q_{s2} \cdot k_{21} \\ -Q_{20} = +Q_{s1} \cdot k_{12} - Q_{s2}(K_2 + s) \end{cases}.$$ {eq. 14}

This allows to directly re-write the system in a matrix form:

$$\begin{bmatrix} -Q_{10} \\ -Q_{20} \end{bmatrix} = \begin{bmatrix} -(K_1 + s) & +k_{21} \\ +k_{12} & -(K_2 + s) \end{bmatrix} \cdot \begin{bmatrix} Q_{s1} \\ Q_{s2} \end{bmatrix},$$ {eq. 15}

where the left-side consists of one column matrix ("Q-zero" column) and the main matrix can be named matrix *A*:

$$A = \begin{bmatrix} -(K_1 + s) & +k_{21} \\ +k_{12} & -(K_2 + s) \end{bmatrix}$$ {eq. 16}

in which (according to the rules of multiplying of matrices) the first column is the Q_{s1}-column and the second is Q_{s2}.

Step 2: Solving for Laplace transforms
Linear equations on matrix form can be solved as ratios of determinants (Cramer's formulas). For the 2-C system, the main matrix *A* was given above. The determinant of this 2×2 matrix is a quadratic polynomial:

$$\det A = s^2 + (K_1 + K_2)s + K_1 K_2 - k_{12} k_{21}.$$ {eq. 17}

If the Q_{s1}-column is replaced by the "Q-zero" column, then one receives the A_{Q1}-matrix:

$$A_{Q1} = \begin{bmatrix} -Q_{10} & +k_{21} \\ -Q_{20} & -(K_2 + s) \end{bmatrix}$$ {eq. 18}

whose determinant is:

$$\det A_{Q1} = Q_{10}(K_2 + s) - Q_{20} k_{21}$$ {eq. 19}

The solution of the system for Q_{s1} comes from the division:

$$Q_{s1} = \frac{\det A_{Q1}}{\det A}.$$ {eq. 20}

Analogously, one can obtain the solution of the second compartment:

$$A_{Q2} = \begin{bmatrix} -(K_1 + s) & -Q_{10} \\ +k_{12} & -Q_{20} \end{bmatrix}, \qquad \{\text{eq. 21}\}$$

$$\det A_{Q2} = -Q_{20}(K_1 + s) + Q_{10} k_{12}, \qquad \{\text{eq. 22}\}$$

and

$$Q_{s2} = \frac{\det A_{Q2}}{\det A}. \qquad \{\text{eq. 23}\}$$

The solution of the entire system for Q_{s1} and Q_{s2} is then:

$$\left\{ \begin{array}{l} Q_{s1} = \dfrac{s \cdot Q_{10} + Q_{10} \cdot K_2 + Q_{20} \cdot k_{21}}{s^2 + s \cdot (K_1 + K_2) + K_1 \cdot K_2 - k_{12} \cdot k_{21}} \\ Q_{s2} = \dfrac{s \cdot Q_{20} + Q_{20} \cdot K_1 + Q_{10} \cdot k_{12}}{s^2 + s \cdot (K_1 + K_2) + K_1 \cdot K_2 - k_{12} \cdot k_{21}} \end{array} \right\} \qquad \{\text{eq. 24}\}$$

Step 3: Rewriting of the Laplace transforms

The above expressions are the solutions for the Laplace transforms, but inverse transformation is far from obvious. However, as noted earlier, if Q_s can be rewritten as a sum of terms on the form $A/(s+a)$, then inverse transformation will be simple.

In both Q_{s1} and Q_{s2}, the numerator is a linear expression of s, and the denominator is a quadratic expression of s (namely the common value *det A*). As a first step, the denominator (the polynomial {eq. 17}) can be factorized:

$$\det A = s^2 + s \cdot (K_1 + K_2) + K_1 \cdot K_2 - k_{12} \cdot k_{21} = (s + b_1) \cdot (s + b_2), \qquad \{\text{eq. 25}\}$$

where $-b_1$ and $-b_2$ are the roots of the quadratic function; this non-standard form of the factorized polynomial is chosen so that the resulting formulas better fit the next steps. The roots can be found either by solving of the quadratic equation or by use of the Vieta equations resulting from {eq. 25}:

$$b_1 + b_2 = K_1 + K_2 \qquad \{\text{eq. 26}\}$$

$$b_1 \cdot b_2 = k_{10} \cdot k_{21} + k_{20} \cdot k_{12} + k_{10} \cdot k_{20} \qquad \{\text{eq. 27}\}$$

Either way, the solutions for b_1 and b_2 are:

$$b_1, b_2 = \frac{1}{2} \cdot \left(K_1 + K_2 \mp \sqrt{(K_1 + K_2)^2 - 4 \cdot (k_{21} \cdot k_{10} + k_{12} \cdot k_{20} + k_{20} \cdot k_{10})} \right)$$

{eq. 28}

Which solutions becomes b_1 and which b_2 is a matter of choice. When the minus sign is applied for b_1 and the plus sign for b_2 then the expressions have $b_1 < b_2$, which in the final result will make b_1 part of the most slowly decaying exponential.

The system of transforms becomes:

$$\left\{ \begin{array}{l} Q_{s1} = \dfrac{s \cdot Q_{10} + Q_{10} \cdot K_2 + Q_{20} \cdot k_{21}}{(s + b_1) \cdot (s + b_2)} \\ Q_{s2} = \dfrac{s \cdot Q_{20} + Q_{20} \cdot K_1 + Q_{10} \cdot k_{12}}{(s + b_1) \cdot (s + b_2)} \end{array} \right\}. \qquad \{\text{eq. 29}\}$$

Each of these fractions can be decomposed into a sum of simple fractions according to the method introduced by Oliver Heaviside:

$$Q_{s1} = \frac{s \cdot Q_{10} + Q_{10} \cdot K_2 + Q_{20} \cdot k_{21}}{(s + b_1) \cdot (s + b_2)} = \frac{A_1}{(s + b_1)} + \frac{B_2}{(s + b_2)}, \qquad \{\text{eq. 30}\}$$

where A_1 and B_2 are variables to be found according to an algorithm presented below. This method can be used with only some exceptions which, in turn, are not expected to occur in the compartment models.
Multiplying by the denominator of the left side gives:

$$s \cdot Q_{10} + Q_{10} \cdot K_2 + Q_{20} \cdot k_{21} = A_1 \cdot (s + b_1) + B_2 \cdot (s + b_2); \quad \{\text{eq. 31}\}$$

The equation should be valid for all values of s. Setting $s = -b_2$ yields:

$$Q_{10} \cdot (K_2 - b_2) + Q_{20} \cdot k_{21} = A_1 \cdot (-b_2 + b_1) + B_2 \cdot (-b_2 + b_2) \quad \{\text{eq. 32}\}$$

and hence:

$$Q_{10} \cdot (K_2 - b_2) + Q_{20} \cdot k_{21} = A_1 \cdot (b_1 - b_2), \quad \{\text{eq. 33}\}$$

and further:

$$A_1 = \frac{Q_{10} \cdot (K_2 - b_2) + Q_{20} \cdot k_{21}}{(b_1 - b_2)}. \quad \{\text{eq. 34}\}$$

Similarly, setting $s = -b_1$ yields:

$$-b_1 \cdot Q_{10} + Q_{10} \cdot K_2 + Q_{20} \cdot k_{21} = A_1 \cdot (-b_1 + b_1) + B_2 \cdot (-b_1 + b_2), \quad \{\text{eq. 35}\}$$

after rearrangement:

$$B_2 = \frac{Q_{10} \cdot (K_2 - b_1) + Q_{20} \cdot k_{21}}{(b_2 - b_1)}. \quad \{\text{eq. 36}\}$$

Step 4: Inverse transformation to find the solution for the original problem
The Laplace transform for compartment 1 is now on the form:

$$Q_{s1} = A_1 \cdot \frac{1}{(s + b_2)} + B_2 \cdot \frac{1}{(s + b_1)} \quad \{\text{eq. 37}\}$$

Accordingly, the tracer quantity as a function of time is:

$$Q_{s1} = A_1 \cdot \exp(-b_2 \cdot t) + B_2 \cdot \exp(-b_1 \cdot t) \quad \{\text{eq. 38}\}$$

A similar procedure should be performed for compartment 2.

After division of the formulas by the volume of the respective compartment, one receives the final solution of the concentrations in both compartments as follows:

$$\left\{ \begin{array}{l} C_{1t} = c_1 \cdot \exp(-b_1 \cdot t) + c_2 \cdot \exp(-b_2 \cdot t) \\ C_{2t} = d_1 \cdot \exp(-b_1 \cdot t) + d_2 \cdot \exp(-b_2 \cdot t) \end{array} \right\}, \quad \{\text{eq. 39}\}$$

where:

$$c_1 = \frac{Q_{10} \cdot (K_2 - b_1) + Q_{20} \cdot k_{21}}{V_1 \cdot (b_2 - b_1)}, \quad \{\text{eq. 40}\}$$

$$c_2 = \frac{Q_{10} \cdot (K_2 - b_2) + Q_{20} \cdot k_{21}}{V_1 \cdot (b_1 - b_2)}, \quad \{\text{eq. 41}\}$$

$$d_1 = \frac{Q_{10} \cdot k_{12} + Q_{20} \cdot (K_1 - b_1)}{V_2 \cdot (b_2 - b_1)}, \quad \{\text{eq. 42}\}$$

$$d_2 = \frac{Q_{10} \cdot k_{12} + Q_{20} \cdot (K_1 - b_2)}{V_2 \cdot (b_1 - b_2)}. \quad \{\text{eq. 43}\}$$

Readers preferring a different notation, e.g. plasma concentration on the form $A \cdot \exp(-\alpha \cdot t) + B \cdot \exp(-\beta \cdot t)$, are welcome to rewrite in this notation. The only pitfall could be the choice of – and + in the equations for b_1 and b_2, see {eq. 28} and the comment below the equation.

Numerical verification for 2-C model

Verification of the above derived analytical model followed by the comparison of the concentrations obtained with the analytical and numerical (Runge-Kutta second order, RK2) models within a time window of zero to 300 (in the below presented examples for 2-C and higher models, all the faster decaying components of the time-concentration curve are comparable to the slowest-decaying in the time point zero, but lower by several orders of magnitude in the time point 300). For RK2 (the algorithm – see Table 1), the concentrations were obtained within this time window in consecutive time steps Δt. The error was calculated as the quotient of the concentrations: analytic by numeric; thus, an error-free method would correspond to the quotient of exactly one. Several combinations of micro-constants have been tested and gave comparable results; the set below is an example.

Table 1: The RK2-algorithm used for testing of the formulas in the 2-C model.

Compartment 1; initial condition:	Compartment 2; initial condition:
Q_{10} (given)	Q_{20} (given)
and then:	and then:
$m_{1(1)} = -K_1 \cdot Q_{1A} + k_{21} \cdot Q_{2A}$	$m_{1(2)} = -K_2 \cdot Q_{2A} + k_{12} \cdot Q_{1A}$
$Q_{1*} = Q_{1A} + m_{1(1)} \cdot \frac{\Delta t}{2}$	$Q_{2*} = Q_{2A} + m_{1(2)} \cdot \frac{\Delta t}{2}$
$m_{2(1)} = -K_1 \cdot Q_{1*} + k_{21} \cdot Q_{2*}$	$m_{2(2)} = -K_2 \cdot Q_{2*} + k_{12} \cdot Q_{1*}$
$Q_{1B} = Q_{1A} + m_{2(1)} \cdot \Delta t$	$Q_{2B} = Q_{2A} + m_{2(2)} \cdot \Delta t$

Example

1. Input values:

V_1= 8100, V_2= 5400 (and hence ECV= 13 500), Cl_{12}= 125, Cl_{10}= 100, Cl_{20}= 0, Q_{10}= 20 000 000, Q_{20}= 0.

2. Elimination rate constants:

- with eq. 4 one receives k_{10}= 0.012345679, k_{20}= 0, k_{12}= 0.015432099, k_{21}= 0.023148148;
- with eq. 11 one receives: K_1= 0.027777778, K_2= 0.023148148.

3. Calculation of the macro-constants b_i (eq. 28): b_1= 0.006421354, b_2= 0.044504572.
4. Calculation of the macro-constants c_i and d_i (eqs. 40-43): c_1= 1084.486253, c_2= 1384.649549, d_1= 1500.816479, d_2= -1500.816479.
5. The quotients of concentrations (analytical result over numerical result) for Δt= 0.01:

- compartment 1: maximal 1.000443465 (in t= 300), minimal 1.0000000 (t= 0),
- compartment 2: maximal 1.000118681 (t= 300), minimal 0.999722267 (t= 0.01).

6. The quotients of concentrations for Δt= 0.1:

- compartment 1: maximal 1.00444 (in t= 300), minimal 1.0000000 (t= 0),
- compartment 2: maximal 1.001185 (t= 300), minimal 0.99723 (t= 0.1).

Thus, a very good agreement was found between results of the analytical derivation and results of the numerical calculation, with a quotient deviating less than 1% from the ideal value of 1.

Three-compartment universal model

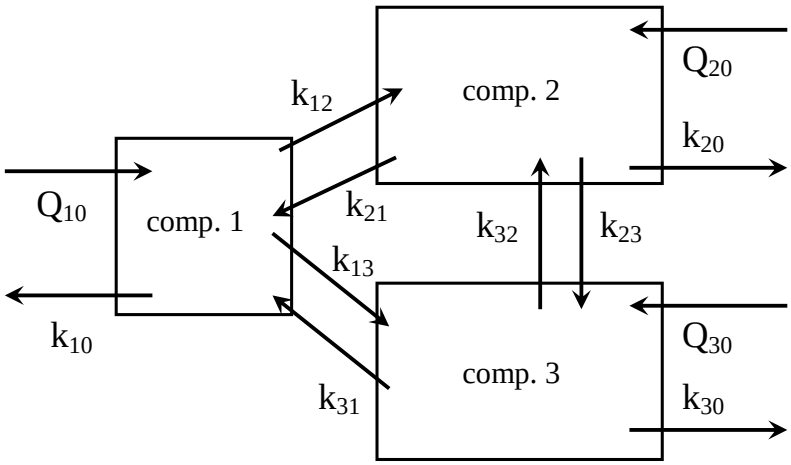


Figure 2: Universal 3-C model discussed in this study. If exchange between all compartments is possible (all *k* are >0), this is a cyclic model. Under assumption that compartment 1 is the central compartment, $k_{23}=k_{32}=0$ for the mammillary model (parallel compartments); for the catenary model (serial compartments), $k_{13}=k_{31}=0$.

Setup of equations
The general 3-C model is shown in Figure 2. To ease notation, we define:

$$\begin{aligned} K_1 &= k_{10}+k_{12}+k_{13} \\ K_2 &= k_{20}+k_{21}+k_{23} \\ K_3 &= k_{30}+k_{31}+k_{32} \end{aligned} \qquad \{\text{eq. 44}\}$$

The initial system of differential equations is:

$$\begin{cases} \dfrac{dQ_1}{dt} = -Q_1 \cdot K_1 + Q_2 \cdot k_{21} + Q_3 \cdot k_{31} \\ \dfrac{dQ_2}{dt} = +Q_1 \cdot k_{12} - Q_2 \cdot K_2 + Q_3 \cdot k_{32} \\ \dfrac{dQ_3}{dt} = +Q_1 \cdot k_{13} + Q_2 \cdot k_{23} - Q_3 \cdot K_3 \end{cases}, \qquad \{\text{eq. 45}\}$$

Step 1: Laplace transformation
The Laplace transform of the system is:

$$\begin{cases} sQ_1(s) - Q_{10} = -Q_1(s) \cdot K_1 + Q_2(s) \cdot k_{21} + Q_3(s) \cdot k_{31} \\ sQ_2(s) - Q_{20} = +Q_1(s) \cdot k_{12} - Q_2(s) \cdot K_2 + Q_3(s) \cdot k_{32} \\ sQ_3(s) - Q_{30} = +Q_1(s) \cdot k_{13} + Q_2(s) \cdot k_{23} - Q_3(s) \cdot K_3 \end{cases} \qquad \{\text{eq. 46}\}$$

Its matrix form is:

$$\begin{bmatrix} -Q_{10} \\ -Q_{20} \\ -Q_{30} \end{bmatrix} = A \cdot \begin{bmatrix} Q_{s1} \\ Q_{s2} \\ Q_{s3} \end{bmatrix}, \text{ where} \qquad \{\text{eq. 47}\}$$

$$A = \begin{bmatrix} -(K_1 + s) & +k_{21} & +k_{31} \\ +k_{12} & -(K_2 + s) & +k_{32} \\ +k_{13} & +k_{23} & -(K_3 + s) \end{bmatrix}. \qquad \{\text{eq. 48}\}$$

Step 2: Solving for Laplace transforms
The main matrix was given above. The other matrices are:

$$A_{Q1} = \begin{bmatrix} -Q_{10} & +k_{21} & +k_{31} \\ -Q_{20} & -(K_2 + s) & +k_{32} \\ -Q_{30} & +k_{23} & -(K_3 + s) \end{bmatrix} \qquad \{\text{eq. 49}\}$$

$$A_{Q2} = \begin{bmatrix} -(K_1 + s) & -Q_{10} & +k_{31} \\ +k_{12} & -Q_{20} & +k_{32} \\ +k_{13} & -Q_{30} & -(K_3 + s) \end{bmatrix} \qquad \{\text{eq. 50}\}$$

$$A_{Q3} = \begin{bmatrix} -(K_1 + s) & +k_{21} & -Q_{10} \\ +k_{12} & -(K_2 + s) & -Q_{20} \\ +k_{13} & +k_{23} & -Q_{30} \end{bmatrix} \qquad \{\text{eq. 51}\}$$

Further solutions proceed according to the schema used for the 2-C model, i.e.:

$$Q_{s1} = \frac{\det A_{Q1}}{\det A} \qquad \{\text{eq. 52}\}$$

$$Q_{s2} = \frac{\det A_{Q2}}{\det A} \qquad \{\text{eq. 53}\}$$

$$Q_{s3} = \frac{\det A_{Q3}}{\det A}. \qquad \{\text{eq. 54}\}$$

In the later factorisation of det *A* there will be a minus sign due to the odd number of rows containing a negatively signed *s* (cf. eq. 48):

$$\det A = -(s + b_1) \cdot (s + b_2) \cdot (s + b_3). \qquad \{\text{eq. 55}\}$$

Instead of keeping this minus sign, we have chosen to calculate –det *A*, as well as –det A_{Qi}. This makes no difference in the fractions eq. 52-54, as the changed signs cancel each other.

The negative determinant of the main matrix is:

$$-\det A = s^3 + s^2 \cdot (K_1 + K_2 + K_3) + s \cdot (K_1 \cdot K_2 + K_2 \cdot K_3 + K_1 \cdot K_3 - k_{12} \cdot k_{21} - k_{13} \cdot k_{31} - k_{23} \cdot k_{32})$$
$$+ K_1 \cdot K_2 \cdot K_3 - K_1 \cdot k_{32} \cdot k_{23} - K_2 \cdot k_{13} \cdot k_{31} - K_3 \cdot k_{12} \cdot k_{21} - k_{21} \cdot k_{13} \cdot k_{32} - k_{31} \cdot k_{12} \cdot k_{23}$$
{eq. 56}

The other negative determinants are:

$$-\det A_{Q1} = s^2 \cdot Q_{10} + s \cdot (Q_{10} \cdot K_2 + Q_{10} \cdot K_3 + Q_{20} \cdot k_{21} + Q_{30} \cdot k_{31})$$
$$+ Q_{10} \cdot (K_2 \cdot K_3 - k_{23} \cdot k_{32}) + Q_{20} \cdot (K_3 \cdot k_{21} + k_{31} \cdot k_{23}) + Q_{30} \cdot (K_2 \cdot k_{31} + k_{32} \cdot k_{21}) \qquad \{\text{eq. 57}\}$$

$$-\det A_{Q2} = s^2 \cdot Q_{20} + s \cdot \left(Q_{20} \cdot K_1 + Q_{20} \cdot K_3 + Q_{10} \cdot k_{12} + Q_{30} \cdot k_{32}\right) + Q_{10} \cdot \left(K_3 \cdot k_{12} + k_{13} \cdot k_{32}\right) + Q_{20} \cdot \left(K_1 \cdot K_3 - k_{13} \cdot k_{31}\right) + Q_{30} \cdot \left(K_1 \cdot k_{32} + k_{31} \cdot k_{12}\right) \quad \{\text{eq. 58}\}$$

$$-\det A_{Q3} = s^2 \cdot Q_{30} + s \cdot \left(Q_{30} \cdot K_1 + Q_{30} \cdot K_2 + Q_{10} \cdot k_{13} + Q_{20} \cdot k_{23}\right) + Q_{10} \cdot \left(K_2 \cdot k_{13} + k_{12} \cdot k_{23}\right) + Q_{20} \cdot \left(K_1 \cdot k_{23} + k_{21} \cdot k_{13}\right) + Q_{30} \cdot \left(K_1 \cdot K_2 - k_{12} \cdot k_{21}\right) \quad \{\text{eq. 59}\}$$

The solution of the entire equation system is then:

$$Q_{s1} = \frac{s^2 \cdot Q_{10} + s \cdot \left(Q_{10} \cdot K_2 + Q_{10} \cdot K_3 + Q_{20} \cdot k_{21} + Q_{30} \cdot k_{31}\right) + Q_{10} \cdot \left(K_2 \cdot K_3 - k_{23} \cdot k_{32}\right) + Q_{20} \cdot \left(K_3 \cdot k_{21} + k_{31} \cdot k_{23}\right) + Q_{30} \cdot \left(K_2 \cdot k_{31} + k_{32} \cdot k_{21}\right)}{\left(s + b_1\right) \cdot \left(s + b_2\right) \cdot \left(s + b_3\right)} \quad \{\text{eq. 60}\}$$

$$Q_{s2} = \frac{s^2 \cdot Q_{20} + s \cdot \left(Q_{20} \cdot K_1 + Q_{20} \cdot K_3 + Q_{10} \cdot k_{12} + Q_{30} \cdot k_{32}\right) + Q_{10} \cdot \left(K_3 \cdot k_{12} + k_{13} \cdot k_{32}\right) + Q_{20} \cdot \left(K_1 \cdot K_3 - k_{13} \cdot k_{31}\right) + Q_{30} \cdot \left(K_1 \cdot k_{32} + k_{31} \cdot k_{12}\right)}{\left(s + b_1\right) \cdot \left(s + b_2\right) \cdot \left(s + b_3\right)} \quad \{\text{eq. 61}\}$$

$$Q_{s3} = \frac{s^2 \cdot Q_{30} + s \cdot \left(Q_{30} \cdot K_1 + Q_{30} \cdot K_2 + Q_{10} \cdot k_{13} + Q_{20} \cdot k_{23}\right) + Q_{10} \cdot \left(K_2 \cdot k_{13} + k_{12} \cdot k_{23}\right) + Q_{20} \cdot \left(K_1 \cdot k_{23} + k_{21} \cdot k_{13}\right) + Q_{30} \cdot \left(K_1 \cdot K_2 - k_{12} \cdot k_{21}\right)}{\left(s + b_1\right) \cdot \left(s + b_2\right) \cdot \left(s + b_3\right)} \quad \{\text{eq. 62}\}$$

Step 3: Rewriting of the Laplace transforms
Again, we should rewrite the transforms Q_s as sums of simple fractions, $1/(s+b_i)$. Basic relationships (derived from the Vieta formulas):

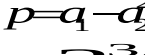
{eqs. 63-65}

The solution of these equations involves finding roots of third-degree polynomial. There are many possible ways to find these solutions [2, 3, 4, 5], an exemplary solution is:

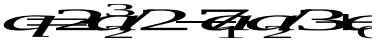
$$b_{1,2,3} = a_2 / 3 - \cos(\phi + \frac{2 \cdot k \cdot \pi}{3}) \cdot r_2 \quad \{\text{eq. 66}\}$$

for k=0,1,2.

A number of the following auxiliary variables have been defined:



{eq. 67}



{eq. 68}

{eq. 69}

$$r_2 = 2 \cdot r_1^{1/3} \quad \{\text{eq. 70}\}$$

{eq. 71}

For brevity, the numerators are stated only in the final results below.

Step 4: Inverse transformation to find the solution for the original problem
The final results for the concentrations (after divisions $C_i = Q_i/V_i$) become:

$$\left\{\begin{array}{l} C_{t1} = c_1 \cdot \exp(-b_1 \cdot t) + c_2 \cdot \exp(-b_2 \cdot t) + c_3 \cdot \exp(-b_3 \cdot t) \\ C_{t2} = d_1 \cdot \exp(-b_1 \cdot t) + d_2 \cdot \exp(-b_2 \cdot t) + d_3 \cdot \exp(-b_3 \cdot t) \\ C_{t3} = e_1 \cdot \exp(-b_1 \cdot t) + e_2 \cdot \exp(-b_2 \cdot t) + e_3 \cdot \exp(-b_3 \cdot t) \end{array}\right\} \quad \{\text{eq. 72}\}$$

where:

$$c_1 = \frac{Q_{10}\left[(k_{12}-b_2)(k_{13}-b_3)-k_{23}k_{32}\right] + Q_{20}(k_{13}k_{21}+k_{23}k_{31}-b_3k_{21}) + Q_{30}(k_{12}k_{31}+k_{32}k_{21}-b_3k_{31})}{V_1(b_2-b_1)(b_3-b_1)} \quad \{\text{eq. 73}\}$$

$$c_2 = \frac{Q_{10}\left[(k_{12}-b_1)(k_{13}-b_3)-k_{23}k_{32}\right] + Q_{20}(k_{13}k_{21}+k_{23}k_{31}-b_3k_{21}) + Q_{30}(k_{12}k_{31}+k_{32}k_{21}-b_3k_{31})}{V_1(b_1-b_2)(b_3-b_2)} \quad \{\text{eq. 74}\}$$

$$c_3 = \frac{Q_{10}\left[(k_{12}-b_1)(k_{13}-b_2)-k_{23}k_{32}\right] + Q_{20}(k_{13}k_{21}+k_{23}k_{31}-b_2k_{21}) + Q_{30}(k_{12}k_{31}+k_{32}k_{21}-b_2k_{31})}{V_1(b_1-b_3)(b_2-b_3)} \quad \{\text{eq. 75}\}$$

$$d_1 = \frac{Q_{10}(k_{13}k_{12}+k_{13}k_{32}-b_1k_{12}) + Q_{20}\left[(k_{11}-b_1)(k_{13}-b_3)-k_{13}k_{31}\right] + Q_{30}(k_{11}k_{32}+k_{31}k_{12}-b_1k_{32})}{V_2(b_2-b_1)(b_3-b_1)} \quad \{\text{eq. 76}\}$$

$$d_2 = \frac{Q_{10}(k_{13}k_{12}+k_{13}k_{32}-b_2k_{12}) + Q_{20}\left[(k_{11}-b_2)(k_{13}-b_3)-k_{13}k_{31}\right] + Q_{30}(k_{11}k_{32}+k_{31}k_{12}-b_2k_{32})}{V_2(b_1-b_2)(b_3-b_2)} \quad \{\text{eq. 77}\}$$

$$d_3 = \frac{Q_{10}(k_{13}k_{12}+k_{13}k_{32}-b_3k_{12}) + Q_{20}\left[(k_{11}-b_3)(k_{13}-b_3)-k_{13}k_{31}\right] + Q_{30}(k_{11}k_{32}+k_{31}k_{12}-b_3k_{32})}{V_2(b_1-b_3)(b_2-b_3)} \quad \{\text{eq. 78}\}$$

$$e_1 = \frac{Q_{10}(k_{21}k_{13} + k_{12}k_{23} + b_2k_{13}) + Q_{20}(k_{12}k_{23} + k_{21}k_{13} + b_1k_{23}) + Q_{30}[(k_{12} + b_2)(k_{21} + b_1) - k_{12}k_{21}]}{V_3(b_2 - b_1)(b_3 - b_1)}$$ {eq. 79}

$$e_2 = \frac{Q_{10}(k_{21}k_{13} + k_{12}k_{23} + b_2k_{13}) + Q_{20}(k_{12}k_{23} + k_{21}k_{13} + b_2k_{23}) + Q_{30}[(k_{12} + b_2)(k_{21} + b_2) - k_{12}k_{21}]}{V_3(b_2 - b_1)(b_3 - b_2)}$$ {eq. 80}

$$e_3 = \frac{Q_{10}(k_{21}k_{13} + k_{12}k_{23} + b_3k_{13}) + Q_{20}(k_{12}k_{23} + k_{21}k_{13} + b_3k_{23}) + Q_{30}[(k_{12} + b_3)(k_{21} + b_3) - k_{12}k_{21}]}{V_3(b_1 - b_3)(b_2 - b_3)}$$ {eq. 81}

Numerical verification of the 3-C results

The verification was performed analogically as for the 2-C model. The numerical algorithm is presented in Table 2.

Table 2: The RK2-algorithm used for testing of the formulas in the 2-C model.

Compartment 1; initial condition: Q_{10} (given) and then: $m_{1(1)} = -K_1 \cdot Q_{1A} + k_{21} \cdot Q_{2A} + k_{31} \cdot Q_{3A}$ $Q_{1^*} = Q_{1A} + m_{1(1)} \cdot \frac{\Delta t}{2}$ $m_{2(1)} = -K_1 \cdot Q_{1^*} + k_{21} \cdot Q_{2^*} + k_{31} \cdot Q_{3^*}$ $Q_{1B} = Q_{1A} + m_{2(1)} \cdot \Delta t$	Compartment 2; initial condition: Q_{20} (given) and then: $m_{1(2)} = -K_2 \cdot Q_{2A} + k_{12} \cdot Q_{1A} + k_{32} \cdot Q_{3A}$ $Q_{2^*} = Q_{2A} + m_{1(2)} \cdot \frac{\Delta t}{2}$ $m_{2(2)} = -K_2 \cdot Q_{2^*} + k_{12} \cdot Q_{1^*} + k_{32} \cdot Q_{3^*}$ $Q_{2B} = Q_{2A} + m_{2(2)} \cdot \Delta t$
Compartment 3; initial condition: Q_{30} (given) and then: $m_{1(3)} = -K_3 \cdot Q_{3A} + k_{23} \cdot Q_{2A} + k_{13} \cdot Q_{1A}$ $Q_{3^*} = Q_{3A} + m_{1(3)} \cdot \frac{\Delta t}{2}$ $m_{2(3)} = -K_3 \cdot Q_{3^*} + k_{23} \cdot Q_{2^*} + k_{13} \cdot Q_{1^*}$ $Q_{3B} = Q_{3A} + m_{2(3)} \cdot \Delta t$	

Example

1. Input values: V_1= 3000, V_2= 2000, V_3= 5000, Q_{10}= 20 000 000, k_{10}= 0.003333, k_{20}= 0.025, k_{30}= 0.012, k_{12}= 0.166667, k_{21}= 0.25, k_{13}= 0.033333, k_{31}= 0.02, k_{23}= 0.2, k_{32}= 0.08.
2. Macro-constants: b_1= 0.011882, b_2= 0.173534, b_3= 0.604917, c_1= 4138.613, c_2= 2602.983, c_3= -74.9293, d_1= 3956.416, d_2= 857.6132, d_3= 185.9709, e_1= 3988.164, e_2= -1961.02, e_3= -27.1427.

3. The error calculation for the respective compartments, Δt= 0.1:
- compartment 1: minimal 0.99999, maximal 1.000000,
- compartment 2: minimal 0.999988, maximal 1.000000,
- compartment 3: minimal 0.999999, maximal 1.000014.

General remarks on the 2-C and 3-C models

The models considered above have no preferred or central compartment, e.g. allowing for the possibility of initial injection into all compartments. Accordingly, a kind of symmetry can be noticed among the formulas for different compartments.
In practice, however, a parallel injection into multiple compartments seems a rare phenomenon. The above formulas could be remarkably simplified if the initial amounts of the drug were set to zero in all except for one compartment. Further simplification will result if some of the *k*-values are assumed to be zero, e.g. reduction of the cyclic model to mammillary or catenary.

Four-compartment models

The above remarks on possible simplification allow reducing the necessary calculations for a universal 4-C model just to injection into the compartment number 1. As the model is otherwise universal, a simple change of numbering will handle the case where e.g. compartment 2 is the only compartment initially containing the drug. However, the algorithm for the 4-C model found in the Supplementary Material can be set up with non-zero starting values for any compartment.

The (simplified) derivation follows according to the schema presented above for the 2-C and 3-C. The most important steps are summarized in the following.

Main matrix and determinant
The matrix form of the Laplace-transformed equation system is:

$$\begin{bmatrix} -Q_{10} \\ 0 \\ 0 \\ 0 \end{bmatrix} = A \cdot \begin{bmatrix} Q_{s1} \\ Q_{s2} \\ Q_{s3} \\ Q_{s4} \end{bmatrix}, \text{ where matrix } A \text{ is:} \qquad \{\text{eq. 82}\}$$

$$A = \begin{bmatrix} -(K_1 + s) & k_{21} & k_{31} & k_{41} \\ k_{12} & -(K_2 + s) & k_{32} & k_{42} \\ k_{13} & k_{23} & -(K_3 + s) & k_{43} \\ k_{14} & k_{24} & k_{34} & -(K_4 + s) \end{bmatrix} \qquad \{\text{eq. 83}\}$$

Its determinant is a quartic pentanomial:

$$d = a_4 s^4 + a_3 s^3 + a_2 s^2 + a_1 s + a_0 \qquad \{\text{eq. 84}\}$$

where:

$a_4 = 1$

$$a_2 = K_1 \cdot K_2 + K_1 \cdot K_3 + K_1 \cdot K_4 + K_2 \cdot K_3 + K_2 \cdot K_4 + K_3 \cdot K_4$$
$$- k_{12} \cdot k_{21} - k_{13} \cdot k_{31} - k_{14} \cdot k_{41} - k_{23} \cdot k_{32} - k_{24} \cdot k_{42} - k_{34} \cdot k_{43}$$

$$a_1 = K_1 \cdot \left(K_2 \cdot K_3 + K_2 \cdot K_4 + K_3 \cdot K_4 - k_{23} \cdot k_{32} - k_{24} \cdot k_{42} - k_{34} \cdot k_{43}\right)$$
$$+ K_2 \cdot \left(K_3 \cdot K_4 - k_{13} \cdot k_{31} - k_{14} \cdot k_{41} - k_{24} \cdot k_{42}\right)$$
$$- K_3 \cdot \left(k_{12} \cdot k_{21} - k_{14} \cdot k_{41} - k_{24} \cdot k_{42}\right)$$
$$- k_{12} \cdot k_{23} \cdot k_{31} - k_{13} \cdot k_{32} \cdot k_{21} - k_{12} \cdot k_{24} \cdot k_{41} - k_{13} \cdot k_{34} \cdot k_{41}$$
$$- k_{14} \cdot k_{42} \cdot k_{21} - k_{23} \cdot k_{34} \cdot k_{42} - k_{14} \cdot k_{43} \cdot k_{31} - k_{24} \cdot k_{43} \cdot k_{32}$$

$$a_0 = K_1 \cdot \left(K_2 \cdot K_3 \cdot K_4 - K_2 \cdot k_{34} \cdot k_{43} - K_3 \cdot k_{24} \cdot k_{42} - K_4 \cdot k_{23} \cdot k_{32} - k_{23} \cdot k_{34} \cdot k_{42} - k_{24} \cdot k_{43} \cdot k_{32}\right)$$
$$- K_2 \cdot \left(K_3 \cdot k_{14} \cdot k_{41} + K_4 \cdot k_{13} \cdot k_{31} + k_{13} \cdot k_{34} \cdot k_{41} + k_{14} \cdot k_{43} \cdot k_{31}\right)$$
$$- K_3 \cdot \left(K_4 \cdot k_{12} \cdot k_{21} + k_{12} \cdot k_{24} \cdot k_{41} + k_{14} \cdot k_{42} \cdot k_{21}\right)$$
$$- k_{13} \cdot k_{32} \cdot k_{24} \cdot k_{41} - k_{12} \cdot k_{23} \cdot k_{34} \cdot k_{41} - k_{14} \cdot k_{42} \cdot k_{23} \cdot k_{31}$$
$$- k_{13} \cdot k_{34} \cdot k_{42} \cdot k_{21} - k_{12} \cdot k_{24} \cdot k_{43} \cdot k_{31} - k_{14} \cdot k_{43} \cdot k_{32} \cdot k_{21}$$
$$+ k_{12} \cdot k_{21} \cdot k_{34} \cdot k_{43} + k_{13} \cdot k_{31} \cdot k_{24} \cdot k_{42} + k_{14} \cdot k_{41} \cdot k_{23} \cdot k_{32}$$

{eqs. 85-89}

Solution of the polynomial allows presenting the determinant as a product:

 {eq. 90}

Other determinants
The determinants of the other matrices are:

{eqs. 91-94}

Solutions
The solutions of the Laplace transforms of the equation systems are:

$$Q_i = \frac{\det A_{Qi}}{\det A}, \qquad \{\text{eq. 95}\}$$

where *i* denotes the number of the respective compartment (from 1 to 4).

The final solution for the four compartments can be presented as:

$$C_1 = \sum_{i=1}^{4} c_i \cdot e^{(-b_i t)} \qquad \{\text{eq. 96}\}$$

$$C_2 = \sum_{i=1}^{4} c_i \cdot e^{(-b_i t)} \qquad \{\text{eq. 97}\}$$

$$C_3 = \sum_{i=1}^{4} c_i \cdot e^{(-b_i t)} \qquad \{\text{eq. 98}\}$$

$$C_4 = \sum_{i=1}^{4} c_i \cdot e^{(-b_i t)} \qquad \{\text{eq. 99}\}$$

where:

$$c_1 = \frac{Q_{10}}{V_1} \cdot \frac{\left(\begin{array}{l}(K_2 - b_1)\cdot(K_3 - b_1)\cdot(K_4 - b_1) + b_1 \cdot (k_{23}\cdot k_{32} + k_{24}\cdot k_{42} + k_{34}\cdot k_{43}) \\ -K_2 \cdot k_{34}\cdot k_{43} - K_3 \cdot k_{24}\cdot k_{42} - K_4 \cdot k_{23}\cdot k_{32} - k_{23}\cdot k_{34}\cdot k_{42} - k_{24}\cdot k_{43}\cdot k_{32}\end{array}\right)}{(b_2 - b_1)\cdot(b_3 - b_1)\cdot(b_4 - b_1)}$$

$$c_2 = \frac{Q_{10}}{V_1} \cdot \frac{\left(\begin{array}{l}(K_2 - b_2)\cdot(K_3 - b_2)\cdot(K_4 - b_2) + b_2 \cdot (k_{23}\cdot k_{32} + k_{24}\cdot k_{42} + k_{34}\cdot k_{43}) \\ -K_2 \cdot k_{34}\cdot k_{43} - K_3 \cdot k_{24}\cdot k_{42} - K_4 \cdot k_{23}\cdot k_{32} - k_{23}\cdot k_{34}\cdot k_{42} - k_{24}\cdot k_{43}\cdot k_{32}\end{array}\right)}{(b_1 - b_2)\cdot(b_3 - b_2)\cdot(b_4 - b_2)}$$

$$c_3 = \frac{Q_{10}}{V_1} \cdot \frac{\left(\begin{array}{l}(K_2 - b_3)\cdot(K_3 - b_3)\cdot(K_4 - b_3) + b_3 \cdot (k_{23}\cdot k_{32} + k_{24}\cdot k_{42} + k_{34}\cdot k_{43}) \\ -K_2 \cdot k_{34}\cdot k_{43} - K_3 \cdot k_{24}\cdot k_{42} - K_4 \cdot k_{23}\cdot k_{32} - k_{23}\cdot k_{34}\cdot k_{42} - k_{24}\cdot k_{43}\cdot k_{32}\end{array}\right)}{(b_1 - b_3)\cdot(b_2 - b_3)\cdot(b_4 - b_3)}$$

$$c_4 = \frac{Q_{10}}{V_1} \cdot \frac{\left(\begin{array}{l}(K_2 - b_4)\cdot(K_3 - b_4)\cdot(K_4 - b_4) + b_4 \cdot (k_{23}\cdot k_{32} + k_{24}\cdot k_{42} + k_{34}\cdot k_{43}) \\ -K_2 \cdot k_{34}\cdot k_{43} - K_3 \cdot k_{24}\cdot k_{42} - K_4 \cdot k_{23}\cdot k_{32} - k_{23}\cdot k_{34}\cdot k_{42} - k_{24}\cdot k_{43}\cdot k_{32}\end{array}\right)}{(b_1 - b_4)\cdot(b_2 - b_4)\cdot(b_3 - b_4)}$$

{eqs. 100-103}

$$d_1 = \frac{Q_{10}}{V_2} \cdot \frac{\begin{pmatrix} b_1^2 \cdot k_{12} - b_1 \cdot \left(K_3 \cdot k_{12} + K_4 \cdot k_{12} + k_{13} \cdot k_{32} + k_{14} \cdot k_{42}\right) \\ + K_3 \cdot K_4 \cdot k_{12} + K_3 \cdot k_{14} \cdot k_{42} + K_4 \cdot k_{13} \cdot k_{32} + k_{13} \cdot k_{34} \cdot k_{42} + k_{14} \cdot k_{43} \cdot k_{32} - k_{12} \cdot k_{34} \cdot k_{43} \end{pmatrix}}{\left(b_2 - b_1\right) \cdot \left(b_3 - b_1\right) \cdot \left(b_4 - b_1\right)}$$

$$d_2 = \frac{Q_{10}}{V_2} \cdot \frac{\begin{pmatrix} b_2^2 \cdot k_{12} - b_2 \cdot \left(K_3 \cdot k_{12} + K_4 \cdot k_{12} + k_{13} \cdot k_{32} + k_{14} \cdot k_{42}\right) \\ + K_3 \cdot K_4 \cdot k_{12} + K_3 \cdot k_{14} \cdot k_{42} + K_4 \cdot k_{13} \cdot k_{32} + k_{13} \cdot k_{34} \cdot k_{42} + k_{14} \cdot k_{43} \cdot k_{32} - k_{12} \cdot k_{34} \cdot k_{43} \end{pmatrix}}{\left(b_1 - b_2\right) \cdot \left(b_3 - b_2\right) \cdot \left(b_4 - b_2\right)}$$

$$d_3 = \frac{Q_{10}}{V_2} \cdot \frac{\begin{pmatrix} b_3^2 \cdot k_{12} - b_3 \cdot \left(K_3 \cdot k_{12} + K_4 \cdot k_{12} + k_{13} \cdot k_{32} + k_{14} \cdot k_{42}\right) \\ + K_3 \cdot K_4 \cdot k_{12} + K_3 \cdot k_{14} \cdot k_{42} + K_4 \cdot k_{13} \cdot k_{32} + k_{13} \cdot k_{34} \cdot k_{42} + k_{14} \cdot k_{43} \cdot k_{32} - k_{12} \cdot k_{34} \cdot k_{43} \end{pmatrix}}{\left(b_1 - b_3\right) \cdot \left(b_2 - b_3\right) \cdot \left(b_4 - b_3\right)}$$

$$d_4 = \frac{Q_{10}}{V_2} \cdot \frac{\begin{pmatrix} b_4^2 \cdot k_{12} - b_4 \cdot \left(K_3 \cdot k_{12} + K_4 \cdot k_{12} + k_{13} \cdot k_{32} + k_{14} \cdot k_{42}\right) \\ + K_3 \cdot K_4 \cdot k_{12} + K_3 \cdot k_{14} \cdot k_{42} + K_4 \cdot k_{13} \cdot k_{32} + k_{13} \cdot k_{34} \cdot k_{42} + k_{14} \cdot k_{43} \cdot k_{32} - k_{12} \cdot k_{34} \cdot k_{43} \end{pmatrix}}{\left(b_1 - b_4\right) \cdot \left(b_2 - b_4\right) \cdot \left(b_3 - b_4\right)}$$

{eqs. 104-107}

$$e_1 = \frac{Q_{10}}{V_3} \cdot \frac{\begin{pmatrix} b_1^2 \cdot k_{13} - b_1 \cdot \left(K_2 \cdot k_{13} + K_4 \cdot k_{13} + k_{12} \cdot k_{23} + k_{14} \cdot k_{43}\right) \\ + K_2 \cdot K_4 \cdot k_{13} + K_2 \cdot k_{14} \cdot k_{43} + K_4 \cdot k_{12} \cdot k_{23} + k_{12} \cdot k_{24} \cdot k_{43} + k_{14} \cdot k_{23} \cdot k_{42} - k_{13} \cdot k_{24} \cdot k_{42} \end{pmatrix}}{\left(b_2 - b_1\right) \cdot \left(b_3 - b_1\right) \cdot \left(b_4 - b_1\right)}$$

$$e_2 = \frac{Q_{10}}{V_3} \cdot \frac{\begin{pmatrix} b_2^2 \cdot k_{13} - b_2 \cdot \left(K_2 \cdot k_{13} + K_4 \cdot k_{13} + k_{12} \cdot k_{23} + k_{14} \cdot k_{43}\right) \\ + K_2 \cdot K_4 \cdot k_{13} + K_2 \cdot k_{14} \cdot k_{43} + K_4 \cdot k_{12} \cdot k_{23} + k_{12} \cdot k_{24} \cdot k_{43} + k_{14} \cdot k_{23} \cdot k_{42} - k_{13} \cdot k_{24} \cdot k_{42} \end{pmatrix}}{\left(b_1 - b_2\right) \cdot \left(b_3 - b_2\right) \cdot \left(b_4 - b_2\right)}$$

$$e_3 = \frac{Q_{10}}{V_3} \cdot \frac{\begin{pmatrix} b_3^2 \cdot k_{13} - b_3 \cdot \left(K_2 \cdot k_{13} + K_4 \cdot k_{13} + k_{12} \cdot k_{23} + k_{14} \cdot k_{43}\right) \\ + K_2 \cdot K_4 \cdot k_{13} + K_2 \cdot k_{14} \cdot k_{43} + K_4 \cdot k_{12} \cdot k_{23} + k_{12} \cdot k_{24} \cdot k_{43} + k_{14} \cdot k_{23} \cdot k_{42} - k_{13} \cdot k_{24} \cdot k_{42} \end{pmatrix}}{\left(b_1 - b_3\right) \cdot \left(b_2 - b_3\right) \cdot \left(b_4 - b_3\right)}$$

$$e_4 = \frac{Q_{10}}{V_3} \cdot \frac{\begin{pmatrix} b_4^2 \cdot k_{13} - b_4 \cdot \left(K_2 \cdot k_{13} + K_4 \cdot k_{13} + k_{12} \cdot k_{23} + k_{14} \cdot k_{43}\right) \\ + K_2 \cdot K_4 \cdot k_{13} + K_2 \cdot k_{14} \cdot k_{43} + K_4 \cdot k_{12} \cdot k_{23} + k_{12} \cdot k_{24} \cdot k_{43} + k_{14} \cdot k_{23} \cdot k_{42} - k_{13} \cdot k_{24} \cdot k_{42} \end{pmatrix}}{\left(b_1 - b_4\right) \cdot \left(b_2 - b_4\right) \cdot \left(b_3 - b_4\right)}$$

{eqs. 108-111}

$$f_1 = \frac{Q_{10}}{V_4} \cdot \frac{\begin{pmatrix} b_1^2 \cdot k_{14} - b_1 \cdot \left(K_2 \cdot k_{14} + K_3 \cdot k_{14} + k_{12} \cdot k_{24} + k_{13} \cdot k_{34}\right) \\ + K_2 \cdot K_3 \cdot k_{14} + K_2 \cdot k_{13} \cdot k_{34} + K_3 \cdot k_{12} \cdot k_{24} + k_{12} \cdot k_{23} \cdot k_{34} + k_{13} \cdot k_{24} \cdot k_{32} - k_{14} \cdot k_{23} \cdot k_{32} \end{pmatrix}}{\left(b_2 - b_1\right) \cdot \left(b_3 - b_1\right) \cdot \left(b_4 - b_1\right)}$$

$$f_2 = \frac{Q_{10}}{V_4} \cdot \frac{\begin{pmatrix} b_2^2 \cdot k_{14} - b_2 \cdot \left(K_2 \cdot k_{14} + K_3 \cdot k_{14} + k_{12} \cdot k_{24} + k_{13} \cdot k_{34}\right) \\ + K_2 \cdot K_3 \cdot k_{14} + K_2 \cdot k_{13} \cdot k_{34} + K_3 \cdot k_{12} \cdot k_{24} + k_{12} \cdot k_{23} \cdot k_{34} + k_{13} \cdot k_{24} \cdot k_{32} - k_{14} \cdot k_{23} \cdot k_{32} \end{pmatrix}}{\left(b_1 - b_2\right) \cdot \left(b_3 - b_2\right) \cdot \left(b_4 - b_2\right)}$$

$$f_3 = \frac{Q_{10}}{V_4} \cdot \frac{\begin{pmatrix} b_3^2 \cdot k_{14} - b_3 \cdot \left(K_2 \cdot k_{14} + K_3 \cdot k_{14} + k_{12} \cdot k_{24} + k_{13} \cdot k_{34}\right) \\ + K_2 \cdot K_3 \cdot k_{14} + K_2 \cdot k_{13} \cdot k_{34} + K_3 \cdot k_{12} \cdot k_{24} + k_{12} \cdot k_{23} \cdot k_{34} + k_{13} \cdot k_{24} \cdot k_{32} - k_{14} \cdot k_{23} \cdot k_{32} \end{pmatrix}}{\left(b_1 - b_3\right) \cdot \left(b_2 - b_3\right) \cdot \left(b_4 - b_3\right)}$$

$$f_4 = \frac{Q_{10}}{V_4} \cdot \frac{\begin{pmatrix} b_4^2 \cdot k_{14} - b_4 \cdot \left(K_2 \cdot k_{14} + K_3 \cdot k_{14} + k_{12} \cdot k_{24} + k_{13} \cdot k_{34}\right) \\ + K_2 \cdot K_3 \cdot k_{14} + K_2 \cdot k_{13} \cdot k_{34} + K_3 \cdot k_{12} \cdot k_{24} + k_{12} \cdot k_{23} \cdot k_{34} + k_{13} \cdot k_{24} \cdot k_{32} - k_{14} \cdot k_{23} \cdot k_{32} \end{pmatrix}}{\left(b_1 - b_4\right) \cdot \left(b_2 - b_4\right) \cdot \left(b_3 - b_4\right)}$$

{eqs. 112-115}

For calculation of the exponentials from the micro-constants – see the Appendix.

Numeric verification
The verification of the derived formulas followed as for the 2- and 3-C models. The numerical algorithm is presented in Table 3.

Table 3: Numeric model (RK2) used for verification of the analytical 4-C model.

Compartment 1; initial condition: Q_{10} (given, >0), and then: $m_{1(1)} = -K_1 \cdot Q_{1A} + k_{21} \cdot Q_{2A} + k_{31} \cdot Q_{3A} + k_{41} \cdot Q_{4A}$ $Q_{1^*} = Q_{1A} + m_{1(1)} \cdot \frac{\Delta t}{2}$ $m_{2(1)} = -K_1 \cdot Q_{1^*} + k_{21} \cdot Q_{2^*} + k_{31} \cdot Q_{3^*} + k_{41} \cdot Q_{4^*}$ $Q_{1B} = Q_{1A} + m_{2(1)} \cdot \Delta t$
Compartment 2; initial condition: $Q_{20} = 0$, and then: $m_{1(2)} = -K_2 \cdot Q_{2A} + k_{12} \cdot Q_{1A} + k_{32} \cdot Q_{3A} + k_{42} \cdot Q_{4A}$ $Q_{2^*} = Q_{2A} + m_{1(2)} \cdot \frac{\Delta t}{2}$ $m_{2(2)} = -K_2 \cdot Q_{2^*} + k_{12} \cdot Q_{1^*} + k_{32} \cdot Q_{3^*} + k_{42} \cdot Q_{4^*}$ $Q_{2B} = Q_{2A} + m_{2(2)} \cdot \Delta t$
Compartment 3; initial condition: $Q_{30} = 0$, and then: $m_{1(3)} = -K_3 \cdot Q_{3A} + k_{23} \cdot Q_{2A} + k_{13} \cdot Q_{1A} + k_{43} \cdot Q_{4A}$ $Q_{3^*} = Q_{3A} + m_{1(3)} \cdot \frac{\Delta t}{2}$ $m_{2(3)} = -K_3 \cdot Q_{3^*} + k_{23} \cdot Q_{2^*} + k_{13} \cdot Q_{1^*} + k_{43} \cdot Q_{4^*}$ $Q_{3B} = Q_{3A} + m_{2(3)} \cdot \Delta t$
Compartment 4; initial condition: $Q_{40} = 0$, and then: $m_{1(4)} = -K_4 \cdot Q_{4A} + k_{14} \cdot Q_{1A} + k_{24} \cdot Q_{2A} + k_{34} \cdot Q_{3A}$

$$Q_{4*} = Q_{4A} + m_{1(4)} \cdot \frac{\Delta t}{2}$$
$$m_{2(4)} = -K_4 \cdot Q_{4*} + k_{14} \cdot Q_{1*} + k_{24} \cdot Q_{2*} + k_{34} \cdot Q_{3*}$$
$$Q_{4B} = Q_{4A} + m_{2(4)} \cdot \Delta t$$

Example

1. Input values: V_1= 3000, V_2= 1000, V_3= 4000, V_4= 5000, Q_{10}= 20 000 000, k_{10}= 0.033333, k_{20}= 0.01, k_{30}= 0.005, k_{40}= 0.006, k_{12}= 0.066667, k_{21}= 0.2, k_{13}= 0.1, k_{31}= 0.075, k_{14}= 0.166667, k_{41}= 0.1, k_{23}= 0.1, k_{32}= 0.025, k_{24}= 0.2, k_{42}= 0.04, k_{34}= 0.025, k_{43}= 0.02.
2. Calculated macro-constants: b_1= 0.011985, b_2= 0.162998, b_3= 0.42268, b_4= 0.575005, c_1= 1388.721, c_2= 62.4713, c_3= 3816.194, c_4= 1399.281, d_1= 1451.115, d_2= 85.5152, d_3= 3158.319, d_4= -4694.95, e_1= 1502.112, e_2= -437.644, e_3= -1085.88, e_4= 21.41068, f_1= 1473.612, f_2= 304.7205, f_3= -1894.33, f_4= 115.9929.
3. Error calculation for the respective compartments for Δt= 0.1:

- compartment 1: minimal 0.999998, maximal 1.000254,
- compartment 2: minimal 0.999165, maximal 1.000011,
- compartment 3: minimal 0.999731, maximal 1.000000,
- compartment 4: minimal 0.999697, maximal 1,000001.

Discussion

When the pharmacokinetics of a drug in the body is to be studied, understood and described, it is often useful to focus on a limited number of organs or states, each of which represented by a "compartment". Typically, the important compartments and possible interactions are theorized (the model), and a concentration curve from e.g. the blood is known from measurements (the input). A solution to the model will then be the strengths of the transfer rates between compartments, possibly along with concentrations curves for drugs in all compartments. These results allow the researcher to evaluate where the drug goes, for how long, and through which interactions.

While solutions can surely be used without full understanding of the mathematics behind, some understanding is generally helpful. Treating the solution as a "black box" not just limits understanding, but can also increase the risk of drawing fragile conclusions. Understanding is not a guarantee against mistakes, but it can be a valuable component in drawing sound and robust conclusions, as well as in spotting pitfalls.

The above examples of universal 2-C, 3-C and 4-C models show that derivation of higher compartment models, as a five-compartment one, although possible, would meet the following problems:
1. Complexity of the intermediate and the final formulas – this could be, however, alleviated, if a proper computer algorithm were used.
2. Necessity of solution of a higher-degree polynomial; according to the Abel-Ruffini theorem, however, an algebraic, analytic solution for quintic hexanomials or higher polynomials cannot be achieved except for some special cases which, in turn, are not expected

to occur in the discussed compartment models. Instead, application of iterative algorithms would be inevitable.

The parallel presented numeric RK2 models can be an alternative for the derived analytic models. In case of typical values of micro-constants and for time step (Δt) of 0.1 second, the relative difference between the analytic and the numeric solution will typically be less than a few per mille; a (reasonable) shortening of the time step and/or applying a more accurate (but also mathematically more complex) numeric model, as Runge-Kutta fourth order, would further reduce the errors. Such a numeric model consists of many (number of time units multiplied by the number of time steps per the unit) systems of equations, but can be built using a common commercially or even free available software and a more modern personal computer.

A more basic problem, however, is that a model with many parameters need data of both high quantity and quality to obtain stable results. A universal model with many compartments is very prone to instability, where calculated parameters depend on small variations in the input data. Thus, even a mathematically correct result may contain very little information about the modelled system. Put another way: A more complex model is not necessarily a better model.

This should be remembered already when going from a 2-C to a 3-C model, or from a 3-C to a 4-C model. On the other hand, it should be remembered that for modelling, the most basic measure of "complexity" (and following risk of instability) is not the number of compartments, but the number of fitted parameters. If some of the *k*-values are restricted to zero, this helps reduce complexity of the model. There may also be cases where a non-zero but fixed *k*-value is used, e.g. an independently known value. For example, if a drug with well-established 3-C model was not injected intravenously but given orally, a gastro-intestinal (fourth) compartment could be defined, with a transfer rate (outgoing *k*-value) set to a physiologically reasonable value. It will of course be wise to verify that the important results are relatively insensitive to small changes in the values chosen for the fixed *k*-parameters.

The quality of data must also be considered when the allowed complexity of the model is decided. For clinical pharmacokinetics, the known inputs are often the initial amount of drug and measurements of drug concentration within one compartment at a series of time points. A first step can then be to determine the macro-constants from {eq. 1}, e.g. by the "peeling-off" or "curve-stripping" procedure [9, 10], where the slowest exponential is determined from late points and subtracted from the earlier concentration data points. The process is then repeated to determine the second-slowest exponential, etc. Dunne [10] pointed out that the determination of the early exponentials can be unstable if the exponential decay rates are not very clearly separated, and provided a more robust algorithm. Still, the quality of the time-concentration curve will depend on the quality of the input data.

In summary, even the best real-world data contain some element of noise, so even with a perfect model (which is in itself unlikely), the result should be critically examined. An in-depth evaluation of model stability is beyond the scope of this paper, but a good starting point can be to critically test the model. If a small change in input can result in a non-ignorable change in the results of modelling, then it is wise to critically evaluate if the model can be simplified.

Conclusion

In this paper we have attempted to provide tools for kinetic modelling with compartment models of up to 4 compartments. Performance of kinetic modelling is partly an art, but even art requires tools and craftsmanship in order to be expressed. The development of craftsmanship is the responsibility of the artist, but understanding of the tools can be a help in this process. We hope that we have not just presented final results, but also presented the tools in a way that allows both understanding and use.

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Appendix

Solution of quartic pentanomials (adopted from Shmakov [11])

The key of this algorithm is to factorize the quartic:

into two quadratics:

$$x^4+ax^3+bx^2+cx+d=(x^2+g_1x+h_1)(x^2+g_2x+h_2)$$

which can be easily solved.

In this factorization:

$$\begin{cases} 1: g_1+g_2=a \\ 2: g_1\cdot g_2+h_1+h_2=b \\ 3: g_1\cdot h_2+g_2\cdot h_1=c \\ 4: h_1\cdot h_2=d \end{cases}.$$

where a, b, c and d are the coefficients in the monic form:

$$x^4+ax^3+bx^2+cx+d$$

1. Calculation of the coefficients of the monic polynomial:

$a=a_3/a_4$

$b=a_2/a_4$

$c=a_1/a_4$

$d=a_0/a_4$

2. Resolvent cubic ($y^3+b_{cub}y^2+c_{cub}y+d_{cub}=0$):

2A: coefficients:

$b_{cub}=-b$

$c_{cub}=ac-4d$

$d_{cub}=4bd-a^2d-c^2$

2B: solution:

$$p=\frac{3c_{cub}-b_{cub}^2}{3}$$

$$q=\frac{2b_{cub}^3-9b_{cub}c_{cub}+27d_{cub}}{27}$$

$r_1=\sqrt{-p^3/27}$

$r_2=-2\sqrt[3]{-p/3}$

$$\Phi=\frac{1}{3}\cdot\arccos\left(\frac{-q}{2r_1}\right)$$

$$y_0=r_2\cdot\cos\left(\Phi+\frac{2k\pi}{3}\right)-\frac{b_{cub}}{3}$$

The other two solutions of the cubic (for *k=1* and *k=2*) lead to the same final solutions.

3. Equations G ($g^2+b_g\cdot g+c_g=0$) and H ($h^2+b_h\cdot h+c_h=0$):

3A: coefficients

$b_g=-a$

$c_g=b-y$

$b_h=-y$

$c_h=d$

3B: solution

$$\Delta_g = b_g^2 - 4 \cdot c_g$$

$$\Delta_h = b_h^2 - 4 \cdot c_h$$

On condition that Δ_g and Δ_h are not negative, the following solutions can be obtained:

$$\begin{Bmatrix} g_1 = 1/2 \cdot \left(-b_g - \sqrt{\Delta_g}\right) \\ g_2 = 1/2 \cdot \left(-b_g + \sqrt{\Delta_g}\right) \\ h_k = 1/2 \cdot \left(-b_h - \sqrt{\Delta_h}\right) \\ h_n = 1/2 \cdot \left(-b_h + \sqrt{\Delta_h}\right) \end{Bmatrix}$$

4. Establishing and solution of the ultimate quadratics:
Checking the third equation of the initial system:
if

$$g_1 \cdot h_1 + g_2 \cdot h_k = c$$

then

$h_1 = h_k$ and $h_2 = h_n$,

else if

$$g_1 \cdot h_k + g_2 \cdot h_1 = c$$

then

$h_1 = h_n$ and $h_2 = h_k$.

Supplementary material

Computer algorithm for calculation of macro-constants from micro-constants in 2-, 3- and 4-compartment models (available and ready to copy in the electronic version).

Dear Lars,
below, there is a project of such a letter. I tried to explain additionally why it had occurred. Is it helpful or better not?

About the order of the terms in the equations: I tried to make it more comprehensible for a reader – in my sense, of course ☺ . Just, if anyone were so patient to read the terms, he/she could perhaps see the "pathway" of the transport between the compartments. Hence, for example, k14*k43*k34 (pathway), instead of k14*k34*k43 (increasing numbers).

In a book on pharmacokinetics, I saw a statement that the terms are the sum of all possible permutations of k minus the "loop-forming" terms. In the 3-C, everything seems obvious, i.e. (eq. 63),
a0= K1*K2*K3 – K1*k23*k32 (example of a short loop k23*k32) – k12*k23*k31 (a long loop) – other loops.

In the 4-C, however, it looks more sophisticated like (eq. 89):
a0= K1*K2*K3*K4 ("main term") - …

There are not only just more loops. Note, that K1 is a sum of k10+…+k14, likewise K2 and other "big Ks". Then, if you subtract from the main term the exemplary two short loops: K2*K3*k14*k41 and K1*K4*k23*k32,
then you subtract the double loop:
k23*k32*k14*k41
two times. Thus, at the end, you have to add this double loop to the equation.

Below, the project of the letter is presented.

Best Regards,

Cyprian

Erratum to "Derivation and presentation of formulas for drug concentrations in two-, three- and four-compartment pharmacokinetic models" Journal of Pharmacological and Toxicological Methods 100 (2019) 106621]

Unfortunately, the paper contained errors in several equations. Fortunately, these errors did not affect the final results, and did not influence the algorithms in the supplementary material. The corresponding corrections are given below. The authors apologize for the errors.

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Errors in the equations (31)-(38), 2-C model:
In the decomposition of the fractions into simple ones needed for the inverse Laplace transformation, the $(s+b_1)$ term was swapped with $(s+b_2)$; thus, the eight equations were written erroneously. However, this did not influence the final results of the model (eqs. 39-43). The text describing equation (31) to equation (38) should be:

Multiplying by the denominator of the left side gives:

$$s \cdot Q_{10} + Q_{10} \cdot K_2 + Q_{20} \cdot k_{21} = A_1 \cdot (s + b_2) + B_2 \cdot (s + b_1); \quad (31)$$

The equation should be valid for all values of s. Setting $s = -b_2$ yields:

$$Q_{10} \cdot (K_2 - b_2) + Q_{20} \cdot k_{21} = A_1 \cdot (-b_2 + b_2) + B_2 \cdot (-b_2 + b_1) \quad (32)$$

and hence:

$$Q_{10} \cdot (K_2 - b_2) + Q_{20} \cdot k_{21} = B_2 \cdot (b_1 - b_2), \quad (33)$$

and further:

$$B_2 = \frac{Q_{10} \cdot (K_2 - b_2) + Q_{20} \cdot k_{21}}{(b_1 - b_2)}. \quad (34)$$

Similarly, setting $s = -b_1$ yields:

$$-b_1 \cdot Q_{10} + Q_{10} \cdot K_2 + Q_{20} \cdot k_{21} = A_1 \cdot (-b_1 + b_2) + B_2 \cdot (-b_1 + b_1), \quad (35)$$

after rearrangement:

$$A_1 = \frac{Q_{10} \cdot (K_2 - b_1) + Q_{20} \cdot k_{21}}{(b_2 - b_1)}. \quad (36)$$

Step 4: Inverse transformation to find the solution for the original problem
The Laplace transform for compartment 1 is now on the form:

$$Q_{s1} = A_1 \cdot \frac{1}{(s+b_1)} + B_2 \cdot \frac{1}{(s+b_2)} \quad (37)$$

Accordingly, the tracer quantity as a function of time is:

$$Q_{t1} = A_1 \cdot exp(-b_1 \cdot t) + B_2 \cdot exp(-b_2 \cdot t) \quad (38)$$

Errors in the 4-C model:

Equation 88 should be:

$$\begin{aligned} a_1 = {} & K_1 \cdot (K_2 \cdot K_3 + K_2 \cdot K_4 + K_3 \cdot K_4 - k_{34} \cdot k_{43} - k_{24} \cdot k_{42} - k_{23} \cdot k_{32}) \\ & + K_2 \cdot (K_3 \cdot K_4 - k_{13} \cdot k_{31} - k_{14} \cdot k_{41} - k_{34} \cdot k_{43}) \\ & - K_3 \cdot (k_{12} \cdot k_{21} + k_{14} \cdot k_{41} + k_{24} \cdot k_{42}) \\ & - K_4 \cdot (k_{12} \cdot k_{21} + k_{13} \cdot k_{31} + k_{23} \cdot k_{32}) \\ & - k_{12} \cdot (k_{23} \cdot k_{31} + k_{24} \cdot k_{41}) \end{aligned}$$

$-k_{13} \cdot (k_{32} \cdot k_{21} + k_{34} \cdot k_{41})$
$-k_{14} \cdot (k_{42} \cdot k_{21} + k_{43} \cdot k_{31})$
$-k_{23} \cdot k_{34} \cdot k_{42} - k_{24} \cdot k_{43} \cdot k_{32}$

Equation 89 should be:
$a_0 = K_1 \cdot \begin{pmatrix} K_2 \cdot K_3 \cdot K_4 - K_2 \cdot k_{34} \cdot k_{43} - K_3 \cdot k_{24} \cdot k_{42} - K_4 \cdot k_{23} \cdot k_{32} \\ -k_{23} \cdot k_{34} \cdot k_{42} - k_{24} \cdot k_{43} \cdot k_{32} \end{pmatrix}$
$-K_2 \cdot (K_3 \cdot k_{14} \cdot k_{41} + K_4 \cdot k_{13} \cdot k_{31} + k_{13} \cdot k_{34} \cdot k_{41} + k_{14} \cdot k_{43} \cdot k_{31})$
$-K_3 \cdot (K_4 \cdot k_{12} \cdot k_{21} + k_{12} \cdot k_{24} \cdot k_{41} + k_{14} \cdot k_{42} \cdot k_{21})$
$-K_4 \cdot (k_{12} \cdot k_{23} \cdot k_{31} + k_{13} \cdot k_{32} \cdot k_{21})$
$-k_{12} \cdot k_{23} \cdot k_{34} \cdot k_{41} - k_{12} \cdot k_{24} \cdot k_{43} \cdot k_{31}$
$-k_{13} \cdot k_{34} \cdot k_{42} \cdot k_{21} - k_{13} \cdot k_{32} \cdot k_{24} \cdot k_{41}$
$-k_{14} \cdot k_{43} \cdot k_{32} \cdot k_{21} - k_{14} \cdot k_{42} \cdot k_{23} \cdot k_{31}$
$+k_{12} \cdot k_{21} \cdot k_{34} \cdot k_{43} + k_{13} \cdot k_{31} \cdot k_{24} \cdot k_{42} + k_{14} \cdot k_{41} \cdot k_{23} \cdot k_{32}$

Equation 93 should be:
$detA_{Q3} = s^2 \cdot Q_{10} \cdot k_{13} + s \cdot Q_{10} \cdot (K_2 \cdot k_{13} + K_4 \cdot k_{13} + k_{12} \cdot k_{23} + k_{14} \cdot k_{43})$
$+Q_{10} \cdot \begin{pmatrix} K_2 \cdot K_4 \cdot k_{13} + K_2 \cdot k_{14} \cdot k_{43} + K_4 \cdot k_{12} \cdot k_{23} + k_{12} \cdot k_{24} \cdot k_{43} + k_{14} \cdot k_{42} \cdot k_{23} \\ -k_{13} \cdot k_{24} \cdot k_{42} \end{pmatrix}$

Sincerely Yours,

Cyprian Świętaszczyk, Lars Jødal