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Research paper

Handling of computational in vitro/in vivo correlation problems by Microsoft Excel: IV. Generalized matrix analysis of linear compartment systems

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Abstract

A linear system comprising n compartments is completely defined by the rate constants between any of the compartments and the initial condition in which compartment(s) the drug is present at the beginning. The generalized solution is the time profiles of drug amount in each compartment, described by polyexponential equations. Based on standard matrix operations, an Excel worksheet computes the rate constants and the coefficients, finally the full time profiles for a specified range of time values.

Keywords: IVIVC; Excel; Systems analysis; Pharmacokinetics; Compartmental models

1. Introduction

Continuing the discussion of IVIVC applications of Excel in previous papers [1–3], this last communication of the series is devoted to the analysis of linear pharmacokinetic systems with n compartments. The pharmacokinetic literature, e.g. Refs. [4–9], discusses a manifold of compartment models in terms of the defining microscopic rate constants, the initial conditions, and the resulting polyexponential time profiles expressed in terms of macroscopic rate constants and corresponding coefficients. The claimed number n of compartments in these models is sometimes misleading, since they are defined as 'open', i.e. with input from and/or output to an unspecified environment. For instance, the well-known 'open two-compartment model' specifies only the distribution of a drug between 'plasma' and 'tissue'. A systematic definition must necessarily include at least one 'elimination' compartment; if the drug is not administered as i.v. bolus, also an 'administration' compartment is required.

Papers dealing with more sophisticated pharmacokinetics, e.g. [10–14], prefer the definition of a system as 'closed', where the drug including all metabolites is present in the system from the time of administration up to the final excretion. Such models will have considerably more than two compartments. Even in simple cases, explicit formulas are rather cumbersome, in particular since numbering of compartments and rate constants is arbitrary. The problem increases with each compartment added to the model.

A generalized treatment of closed models with any number of compartments is provided by the theory of linear differential equations which, based on mathematical matrix operations, frees the user from the task to find and remember particular solutions. Various mathematical approaches are found in relevant textbooks, e.g. Ref. [15] or [16].

The present paper presents an Excel solution based on the matrix approach of Ref. [15]. For illustration and verification it uses a simple literature case with $n=3$ compartments: plasma, tissue and elimination. Expansion to any larger number of compartments is obvious. The documentation IVIVC.DOC, available together with associated EXCEL workbooks from the author upon request, provides a worksheet COMPSYST designed for $n=5$. This may be used to augment the present model by an absorption site for

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non-bolus input to the plasma, and/or other distribution or elimination compartments.

2. Conventional analysis (illustration example)

Following closely the presentation in chap. 14 of Welling [4], the further discussion uses an illustration example shown in Fig. 1, which is conventionally known as 'open two-compartment model' with plasma (#1) and tissue (#2) only. The double-bordered circle indicates that all drug is present in #1 at time zero. If defined as closed system, elimination is defined as a distinct compartment (#3), hence the actual number of compartments is $n=3$. Microscopic rate constants are positive values, specified in consistent units, e.g. [1/h]. According to matrix notation, k_{ij} denotes transfer 'to i from j', which differs from pharmacokinetic convention where it denotes transfer 'from i to j'.

Even for this simple model, notation differs considerably in the literature, e.g. numbering of compartments varies with the actual context; rate constants are defined ambiguously as k_+ or k_-. The problem increases when including further compartments. If input into the plasma compartment is by an absorption step rather than i.v. bolus, an additional input compartment (#4) has to be added to the model (note that (#0) is not suitable as subscript for matrix analysis). If elimination is modeled by parallel pathways, e.g. urinary excretion and metabolism, this would require the addition of another compartment. These modest expansions would require new model definitions with differing compartment numbering and a completely new and complicated definition of formulas.

Returning to the illustration case with $n=3$, two macroscopic rate constants, usually denoted α and β, are obtained from these conditions

$$\alpha\beta = k_{31}k_{12} = 0.027; \quad \alpha+\beta = k_{31}+k_{12}+k_{21} = 1.35$$

which gives $\alpha=1.330$ and $\beta=0.020$ as solution of the quadratic equation

$$\frac{\alpha}{\beta} = \left\{(k_{31}+k_{12}+k_{21}) \pm \sqrt{(k_{31}+k_{12}+k_{21})^2 - 4k_{31}k_{12}}\right\} \Big/ 2$$

Since all k_{ij} have positive values by definition, also α and β are positive numbers, with the property that $\alpha>\beta$, i.e α is the faster of both.

Time profiles in the relevant compartments (plasma, tissue, elimination) are described by three polyexponential functions:

$$Y_1(t) = c_{11}\,e^{-0t} + c_{12}\,e^{-\alpha t} + c_{13}\,e^{-\beta t};$$

$$Y_2(t) = c_{21}\,e^{-0t} + c_{22}\,e^{-\alpha t} + c_{23}\,e^{-\beta t};$$

$$Y_3(t) = c_{31}\,e^{-0t} + c_{32}\,e^{-\alpha t} + c_{33}\,e^{-\beta t}$$

Although the analysis uses only two parameters α and β, the systematic treatment suggests inclusion of a third term with rate constant '0'. Coefficients c_{ij} are then defined as follows:

$$c_{11}=0 \quad c_{12} = -\frac{k_{12}-\alpha}{\alpha-\beta} = +0.901 \qquad c_{13} = +\frac{k_{12}-\beta}{\alpha-\beta} = +0.099$$

$$c_{21}=0 \quad c_{22} = -\frac{k_{21}}{\alpha-\beta} = -0.779 \qquad c_{23} = +\frac{k_{21}}{\alpha-\beta} = +0.779$$

$$c_{31}=1 \quad c_{32} = +\frac{(k_{12}-\alpha)k_{31}}{(\alpha-\beta)\alpha} = -0.122 \quad c_{33} = -\frac{(k_{12}-\beta)k_{31}}{(\alpha-\beta)\beta} = -0.878$$

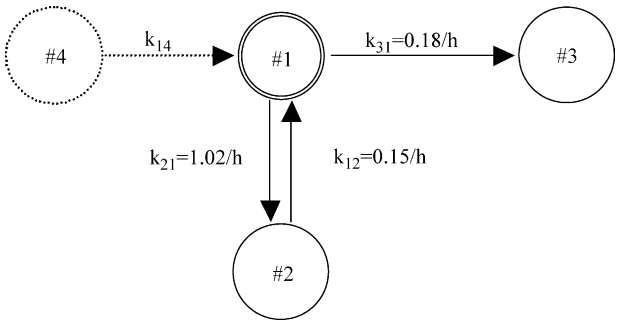

Fig. 1. Illustration example according to digoxin data [9]. Compartments are numbered according to general conventions, rate constants k_{ij} as 'to i from j'.

By substituting the original conditions, the above literature definitions of c_{32} and c_{33} may be altered to $(\alpha-\beta)$ as common denominator for all coefficients:

$$c_{32} = \frac{(k_{12}-\alpha)k_{31}/\alpha}{\alpha-\beta} = \frac{\beta-k_{31}}{\alpha-\beta} = \frac{k_{12}+k_{21}-\alpha}{\alpha-\beta};$$

$$c_{33} = \frac{(k_{12}-\beta)k_{31}/\beta}{\alpha-\beta} = \frac{\alpha-k_{31}}{\alpha-\beta} = \frac{k_{12}+k_{21}-\beta}{\alpha-\beta}$$

The first form is an obvious rearrangement, the second is most convenient for actual computation, the third indicates that $c_{32}=-(c_{12}+c_{22})$ and $c_{33}=-(c_{13}+c_{23})$ are the negative sums of the corresponding coefficients of Y_1 and Y_2. In summary, the model is described by these functions:

- Y_1 is a Bateman function with two positive terms.
- Y_2 is a Bateman function with two identical coefficients with opposite sign.
- $Y_3=1-(Y_1+Y_2)$ is defined according to mass balance.

All coefficients are based on the condition that a dose $D=1$ is administered to the plasma compartment at time zero. A distribution volume V_P, converting amounts into