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Original article

# ADVAN-style analytical solutions for common pharmacokinetic models

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ABSTRACT

*Introduction:* The analytical solutions to compartmental pharmacokinetic models are well known, but have not been presented in a form that easily allows for complex dosing regimen and changes in covariate/parameter values that may occur at discrete times within and/or between dosing intervals.
*Methods:* Laplace transforms were used to derive ADVAN-style analytical solutions for 1, 2, and 3 compartment pharmacokinetic linear models of intravenous and first-order absorption drug administration. The equations calculate the change in drug amounts in each compartment of the model over a time interval ($t$; $t = t_2 - t_1$) accounting for any dose or covariate events acting in the time interval. The equations were coded in the R language and used to simulate the time-course of drug amounts in each compartment of the systems. The equations were validated against commercial software [NONMEM (Beal, Sheiner, Boeckmann, & Bauer, 2009)] output to assess their capability to handle both complex dosage regimens and the effect of changes in covariate/parameter values that may occur at discrete times within or between dosing intervals.
*Results:* For all tested pharmacokinetic models, the time-course of drug amounts using the ADVAN-style analytical solutions were identical to NONMEM outputs to at least four significant figures, confirming the validity of the presented equations.
*Discussion:* To our knowledge, this paper presents the ADVAN-style equations for common pharmacokinetic models in the literature for the first time. The presented ADVAN-style equations overcome obstacles to implementing the classical analytical solutions in software, and have speed advantages over solutions using differential equation solvers. The equations presented in this paper fill a gap in the pharmacokinetic literature, and it is expected that these equations will facilitate the investigation of useful open-source software for modelling pharmacokinetic data.



## 1. Introduction

The implementation of pharmacokinetic models in modelling software typically uses models expressed as either differential equations or as analytical solutions to compartmental systems. Analytical solutions are often many times faster than differential solutions, and are generally preferred for this reason when a choice is possible. The analytical solutions to 1, 2 and 3 compartment pharmacokinetic models have been known for many decades and are published in a number of sources (Rescigno & Segre, 1966; Wagner, 1975). However, when implementing these equations in programming languages such as R [www.r-project.org] for stochastic simulations or Bayes forecasting (Mould, Upton, & Wojciechowski, 2014) or in hierarchical modelling environments such as rccpbugs [https://github.com/armstrtw/rcppbugs] for population modelling, some limitations of the published forms of the equations are apparent. First, the representation of the effect of discrete changes in covariate/parameter values for different time intervals is not possible, and second the representation of complex dose regimens would require the principle of superposition (Thron, 1974), which is difficult and clumsy to code. Both of these limitations may be a significant obstacle to implementing open-source pharmacokinetic software that is broadly useful in its application.

The proprietary population modelling software NONMEM (Beal, Sheiner, Boeckmann, & Bauer, 2009) implements analytical solutions to common compartment models via its ADVAN routines (e.g. ADVAN1 for a one compartment linear model, ADVAN3 for a two compartment linear model and ADVAN11 for a three compartment linear model). These routines are able to handle both complex dose regimens and the effect of discrete changes in covariate values that may occur at discrete times within or between dosing intervals by "advancing" the kinetic system from one state time point to the next (Beal et al., 2009). The use of this type of "ADVAN" solution requires recasting the analytical equations for common pharmacokinetic models in a form where they can be used to calculate the amount of drug in each compartment of the system at time $t_2$ given the amount in each compartment at time $t_1$ as a starting point, together with any dose or covariate factors acting in the period $t_2 - t_1$. This report presents the analytical solutions to the

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ADVAN-style equations in the public domain for the first time. It is expected that this will facilitate the investigation of useful open-source software for modelling and simulating pharmacokinetic data.

The aims of this paper are:

1 Solve and report the ADVAN-style equations for 1, 2 and 3 compartment pharmacokinetic linear models for intravenous (IV) and first-order absorption drug administration.
2 Compare the output of the equations with the output of NONMEM for the same models.
3 Show example code for the implementation of such equations in the R language.

## 2. Methods

### 2.1. ADVAN-style equations

Solutions of the ADVAN-style equations for 1, 2, and 3 compartment pharmacokinetic linear models were derived using Laplace transforms for finding analytical solutions of compartmental models (Rescigno & Segre, 1966; Wagner, 1975). All state variables were expressed as amounts ($X$) rather than concentrations to ensure mass balance. The solution procedure consisted of the following steps: (1) expressing the mass transfer of a drug for each pharmacokinetic model through a system of differential equations with the initial conditions included as part of the solution process. (2) Taking Laplace transforms of each term in the differential equations (i.e. transform equations from the t-domain into the s-domain). (3) Solving the Laplace of state variable(s) of interest. (4) Finally, taking the inverse of the Laplace of the state variable(s) (i.e. transform equations from the s-domain back into the t-domain). The solution procedure is depicted in Fig. 1. The Laplace transform of a function $F(t)$ is defined by

$$\mathcal{L}\{F(t)\} = f(s) = \int_0^\infty e^{-st} F(t)dt. \quad (1)$$

#### 2.1.1. Intravenous pharmacokinetic models

*2.1.1.1. IV bolus administration.* A one compartment IV bolus is the simplest pharmacokinetic model and is parameterized as presented in (Fig. 2a). The differential equation that describes the model is:

$$\frac{dX_1}{dt} = -k_{10}X_1 \quad (2)$$

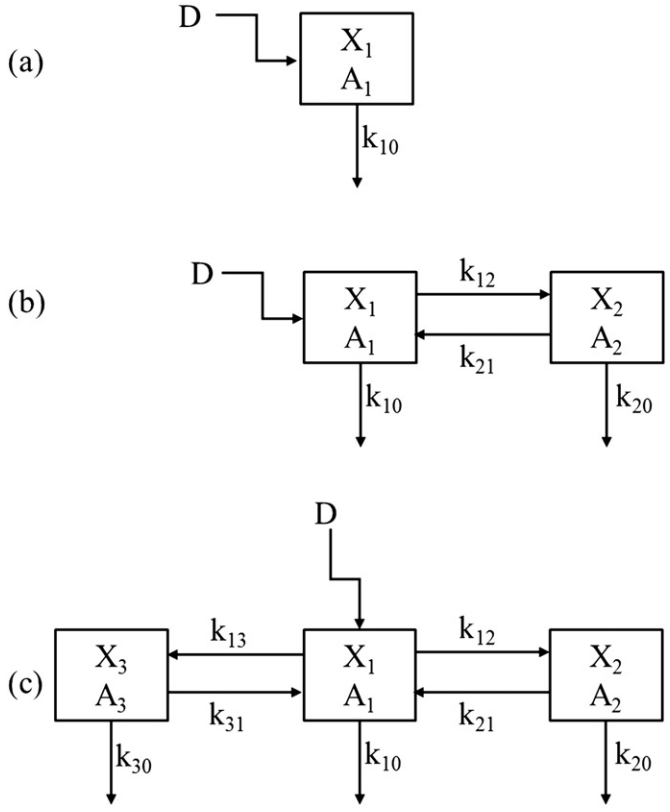


**Fig. 2.** Schematic representations of 1, 2, and 3-compartment pharmacokinetic models with IV bolus administration (Dose = D) expressed in terms of the amount of drug in each compartment. $X_1$, $X_2$, or $X_3$ represents a drug amount in the corresponding compartment at the end of a time period ($t$) where ($t = t_2 - t_1$). $A_1$, $A_2$, or $A_3$ represents the initial drug amount in the corresponding compartment at the beginning of a time interval ($t$). The transfer into and out of the compartments is governed by the micro-rate constants (time$^{-1}$) given the symbol $k$ (e.g. $k_{12}$ between the first and second compartment, $k_{13}$ between the first and third compartment).

where $X_1$ is a drug amount in the central compartment and $k_{10}$ is the first-order elimination rate constant. Laplace transform of the variable of interest ($X_1$) is taken over both sides of the equation:

$$s\mathcal{L}\{X_1\} - X_1(0) = -k_{10}\mathcal{L}\{X_1\}$$

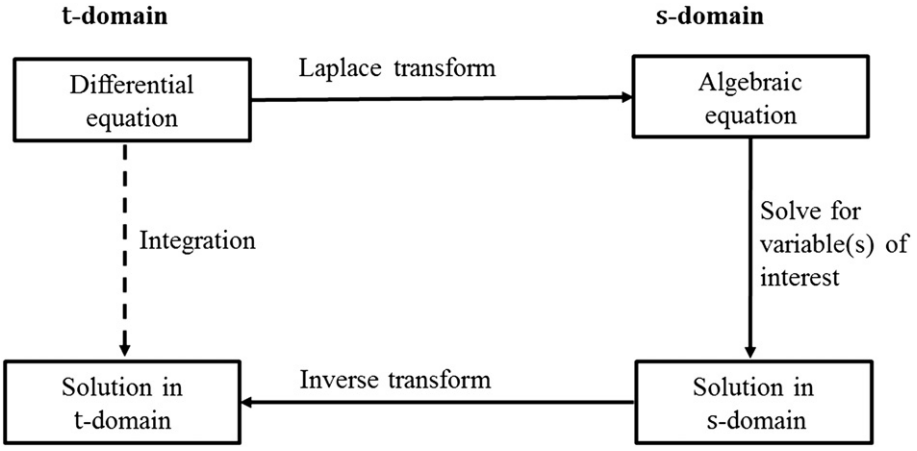


**Fig. 1.** The steps involved in solving differential equations using Laplace transform. The method converts a complex differential equation into a simple algebraic equation that can be solved easily. The dashed line indicates that the differential equation may be solved by integration. However, integration might be difficult for complex models.