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A4S: A user-friendly graphical tool for pharmacokinetic and pharmacodynamic (PK/PD) simulation

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ABSTRACT

Effective communication of PK/PD principles and results in a biomedical research environment remains a significant challenge which can result in lack of buy-in and engagement from scientists outside the modeling and simulation communities. In our view, one of the barriers in this area is a lack of user-friendly tools which allow "non experts" to use PK/PD models without the need to develop technical skills and expertise in advanced mathematical principles and specialist software. The costs of commercial software may also prevent large-scale distribution. One attempt to address this issue internally in our research organizations has resulted in the development of the A4S ("Accelera for Sandwich") software, which is a simple-to-use, menu-drive Matlab-based PK/PD simulator targeted at biomedical researchers with little PK/PD experience.

1. Introduction

Modeling and simulation play an important role in the decision making process within pharmaceutical research & development [1–14]. A better understanding of the inter-relationship between pharmacokinetics and pharmacodynamic (integrative pharmacology or PK/PD) of a compound can provide predictions of the effects of new, untested scenarios (for example different dose levels and/or regimens) via simulation, allowing the optimization of its probability of technical success [15]. Therefore, the assessment and evaluation of drug-concentration–time or drug-effect–concentration data is of pivotal importance in quantitative pharmacological research. Various software packages are available to perform such analyses (e.g., WinNonlin, Pharsight; NONMEM, ICON; SAAMII, University of Washington and Kinetica, Adept Scientific), however these packages are typically expensive and/or require the development of various degrees of technical expertise. In addition, in many cases, the graphical and data management tools are not sufficient for an effective communication of the results obtained to a wider audience. Therefore, it is worthwhile exploring the possibility of cost-effective and easy-to-use alternatives for PK/PD analysis and visualization. Several templates and add-in programs for PK/PD data analysis have already been developed using Microsoft Excel [16–20]. However, typically these programs have limitations in providing a wide range of PK/PD models integrated with a flexible dosing-regimen module and seamless data-input/output management to allow for efficient trial simulations.

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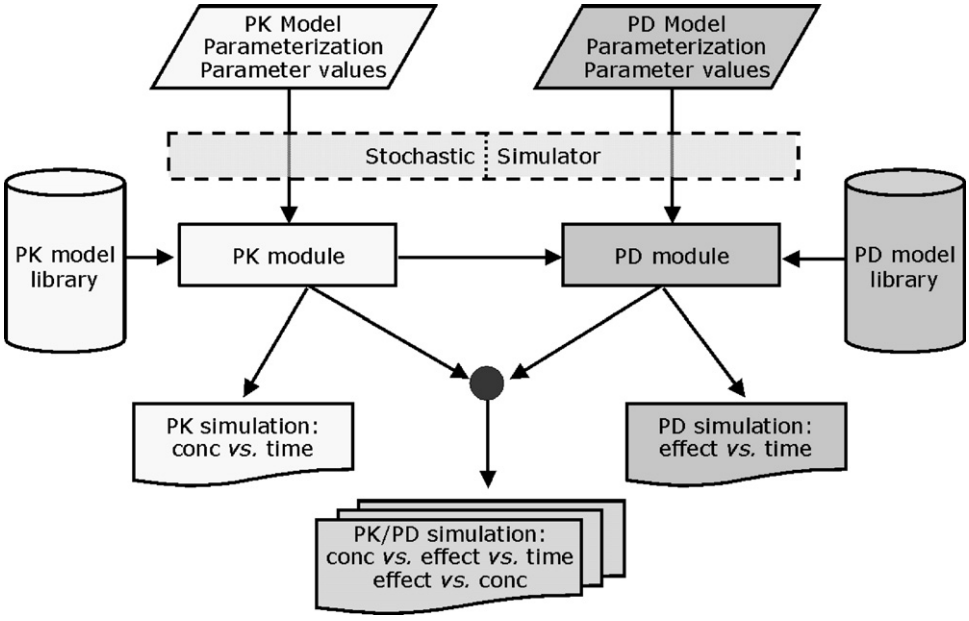

Fig. 1 – A4S Simulator software structure. Stochastic simulation can be addressed considering uncertainty either in PK or in PD model parameters or in both.

In this paper, a program, named A4S Simulator, is proposed. The program is written using the high-level programming language, MatLab, and is provided in its compiled form so that it can be used as a stand-alone application. It comprises a range of different PK and PD models which can all be combined for PK/PD simulations of IV bolus, IV infusion or extra-vascular administrations. A4S allows for stochastic (Monte-Carlo) simulations to explore the impact of PK and/or PD model-parameter uncertainty/variability.

All the features mentioned above can run in batches and the results can be subsequently saved in MS Excel spreadsheets or in standard JPEG files in case of graphs. A4S Simulator was crossvalidated with WinNonlin using data reported in the literature [21].

2. Program description

2.1. *Program interface and flowchart*

The entire simulation process implemented within A4S is schematically shown in Fig. 1. Users may select the module of interest, PK or PD, from the main window and then set simulation options interactively. The A4S Simulator provides many customizable options for PK, PD and PK/PD modeling, including a broad library of models, alternative parameterizations, different treatment schedules, stochastic simulations and chart outputs.

The program guides the user through a stepwise input of the model parameters, data, dosing schedule and other simulation options through a collection of dedicated windows.

The PK and PD modules can work in an integrated manner or independently. In particular, the PD module can be used for exploring an exposure-response profile providing concentrations in a specified range or for performing an integrated PK/PD simulation linking a time–concentration profile previously generated using the PK module.

2.2. *Model libraries and features*

2.2.1. *PK models*

Ten PK models were included in the A4S library (Fig. 2) following the ADVAN and TRANS nomenclature and parameterization implemented in the widely used NONMEM software [22]. In addition, the target-mediated drug-disposition (TMDD) model [23], which is commonly used in the area of biologics, was included in the model library. The non-linear ADVAN 10 and TMDD models were described using systems of ordinary differential equations (see later), solved using the Matlab ordinary differential equation (ODE) suite [24,25]. The Matlab ODE suite is a collection of functions implementing several algorithms for solving systems of ordinary differential equations and plotting their numerical solutions. In particular, the ode15s function was chosen for addressing both stiff and non-stiff problems. All other PK models were described using their standard closed form solutions [21].

The model is chosen by the user through an interactive window, which allows the input of the relevant model parameters. A second window allows the definition of the compound dosing regimen and the range of times for the simulation. Once all the necessary information is available, the A4S Simulator generates the profile of plasma drug concentration versus time data for the selected model, it provides a graph and computes some descriptive parameters (e.g., AUC, C_{max} and half life).

2.2.2. *PD models*

Twelve PD models were included in A4S Simulator (Fig. 3). The software allows to link the drug effect to the concentrations either via direct models (linear, log linear, E_{max},