A computer-aided framework for development, identification and management of physiologically-based pharmacokinetic models

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ABSTRACT

The objective of this work is the development of a generic computer-aided modelling framework to support the development of physiologically-based pharmacokinetic models thereby increasing the efficiency and quality of the modelling process. In particular, the framework systematizes the modelling process by applying the workflow involved and providing the required methods and tools for model documentation, construction, analysis, identification and discrimination. The application and benefits of the developed framework are demonstrated by a case study related to the whole-body physiologically-based pharmacokinetic modelling of the distribution of the drug cyclosporin A in rats and humans. Four alternative candidate models for rats are derived and discriminated based on experimental data. The model candidate that is best represented by the experimental data is scaled-up to a human being applying physiologically-based scaling laws and identifying model parameters that can be re-fitted by the limited experimental data accessible for humans using sensitivity and identifiability analysis techniques.

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1. Introduction

Computer-aided modelling techniques have gained increasing importance in chemical, biochemical and biomedical engineering due to their many potentials and benefits. For instance, computer-aided model-based techniques are applied to predict, optimize and design product–system behaviour. In biomedical engineering, for example, the system could be the human body whereas the product is a medication and/or delivery device. Alternatively, the system could be a bioreactor and the product could be a certain enzyme. Another example for product–system behaviour is a chemical production process. For all these examples, computer-aided modelling has the potential to deliver truly innovative solutions, to reduce the number of required resource-demanding experiments to a great extend and to gain insight and a better understanding of product–system behaviour.

However, the required models are complex, often of multiple time- and/or length-scales and many times require prediction accuracy to a high degree of detail with only limited accessible experimental data. For these reasons many authors state the need of advanced modelling frameworks that include state-of-the-art methods and tools, increase the efficiency of the modelling process as well as the quality of the developed models (e.g. Foss et al., 1998; Sales-Cruz, 2006; Preisig, 2010; Klatt and Marquardt, 2009).

To address these needs, a computer-aided modelling framework for systematic and efficient model development and application in chemical, biochemical and biomedical engineering has been developed based on a generic work-flow-based modelling methodology. The objectives of the developed framework are to systematize the process of model development and application, identify and connect the required methods and tools for each work-flow step and increase the efficiency of the modeller as well as the quality of developed models. The computer-aided modelling framework has been published previously (Heitzig et al., 2011; Heitzig, 2011) where the emphasis was on model construction and application. In this paper, the focus is on the application of the computer-aided modelling framework customized for the needs of whole-body physiologically-based pharmacokinetic (PBPK) modelling efforts, a topic of high interest to the pharmaceutical therapy development in pharmaceutical industries, with particular emphasis on supporting tools and methods for model documentation, model identification and discrimination. PBPK models are important tools for supporting evaluation of the efficacy of novel drugs prior to

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clinical trials (Mosat et al., 2013). The goal in this study is to develop a dynamic PBPK model based on a systematic engineering approach for the administration and distribution of drugs in the organs and blood of rats considering metabolism. The developed model is then scaled-up to a human body that can serve as a tool to evaluate administration route and drug dosage strategies for humans. Traditionally, the modelling of pharmacokinetics is based on simple curve-fitting of experimental data which has two main drawbacks (Mosat et al., 2013; Espié et al., 2009): (i) lack of physiological insight and (ii) poor extrapolation quality (to different conditions, within individuals of the same species, between different species or for different drugs).

Physiologically based pharmacokinetic (PBPK) models, in contrast, are mechanistic models based on blood flows, tissue volumes, routes of administration, biotransformation pathways, and interactions with the tissue organ (Espié et al., 2009). The engineering approach to pharmacokinetic modelling considers conservation equations including transport and reaction rates and advanced scaling laws (Mosat et al., 2013). The resulting PBPK models are mechanistic, based on the actual phenomena occurring in the body. The main advantages of this approach are:

- Increase of system knowledge: gain of insights in the actual processes occurring during drug uptake and distribution.
- Better extrapolation ability, which has the potential to reduce the required number of undesirable as well as time- and cost-intensive animal experiments during drug development.
- Application of models for designing optimized and personalized drug dosage strategies for patients and desired therapeutic effects.

However, the development of first principles PBPK models, their identification and discrimination between different candidate models is a non-trivial task inherent with a number of challenges that relate to the identification of the occurring phenomena and mechanisms within the body and especially finding the appropriate degree of detail in the models with respect to the modelling goal. The degree of detail is a trade-off between model complexity and model identifiability under a given accessible experimental data. In general PBPK models have a large number of equations and parameters (depending on the degree of detail, e.g. in the order of 100s).

To address these challenges in PBPK modelling, a computer-aided modelling framework for model development, model analysis, model identification/discrimination and model evaluation has been developed with the objective to systematizes the process of model development and application, combine all required methods and tools, increase model quality and thereby making the modeller more efficient. The paper is organized as follows: first, the computer-aided framework and its features is introduced step-by-step in Section 2, then in Section 3 a case study application of the framework is presented and finally concluding remarks are given in Section 4.

2. Computer-aided framework for model development, identification and discrimination

The presented computer-aided modelling framework is based on a generic modelling methodology which decomposes the process of model development and application in a sequence of five phases and provides an in-depth algorithmic work-flow for each phase (see Fig. 1, left). These phases are:

- Phase I: Modeling objective and system information.
- Phase II: Single-scale or multi-scale model construction.
- Phase III: Model identification/discrimination.
- Phase IV: Model validation/evaluation.
- Phase V: Model application for (A) simulation and/or (B) optimization.

The overall computer-aided modelling framework has been implemented into a user-friendly software tool (see Fig. 1, right) by extending the existing modelling software ICAS-MoT ('Modeling Testbed', Russel and Gani, 2000; Sales-Cruz and Gani, 2003; Sales-Cruz, 2006; Heitzig et al., 2011; Heitzig, 2011) and is integrated within the ICAS ('Integrated Computer-Aided System') software (Gani et al., 1997). ICAS combines a number of tools for product-process engineering (e.g. property prediction, solvent design, process simulation, equation generation and thermodynamic databases).

A detailed overview over the generic modelling methodology including the algorithmic work-flows of Phases I and II as well as their computer-aided framework implementation is given in Heitzig (2011). For the computer-aided framework and work-flows of Phases IV and V the reader is referred to Heitzig (2011). In this paper, the computer-aided framework for model identification/discrimination (Phase III) is presented together with its in-depth work-flow as these steps are deemed the most significant for PBPK modelling efforts.


The computer-aided framework for model identification/discrimination (Phase III of generic modelling methodology shown in Fig. 1) has been developed based on a generic in-depth work-flow (see Section 2.2) by identifying the required features, support and the automation potential of a computer-aided modelling framework for each work-flow step. The computer-aided modelling framework for model identification/discrimination is given in Fig. 2. It shows the work-flow steps. Furthermore, the required features and support for each work-flow step are indicated in the brackets on the right hand side. For each step it is indicated how the modeller and the computer interact and which parts of the work-flow can be automated by a modelling tool. Features required for all work-flow steps are provision of theoretical background of applied methods and tools, automated generation of reports containing the provided information and obtained results from the different work-flow steps. Moreover, the computer-aided modelling framework for model identification/discrimination (Phase III) is integrated with the frameworks for the other phases of the modelling process given in Fig. 1.

For Step 1 of the work-flow for model identification/discrimination a computer-aided modelling framework should provide an interface for experimental data which can handle different forms of data as well as computer-aided work-flows for data analysis and design of experiments for parameter estimation and model discrimination. The modeller needs to input (newly) available experimental data while the computer-aided modelling framework allows connection of the measurements to the corresponding model variables and automatically