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Whole body physiologically-based pharmacokinetic (PBPK) modeling attempts to model the uptake and distribution of a drug inside the body. Traditionally, pharmacokinetic models have been developed by simple curve fitting of experimental data without considering the mechanistic and physics of the system. The drawback of such models is their lack of physical insights and the pure extrapolation features to untested conditions, to other drugs as well as to individuals of the same species or different species. Lately, PBPK models, which are based on first principles, have received increasing attention. In this work, a first principles engineering approach to PBPK modeling that is based on conservation equations and advanced scaling laws is proposed. The developed global pharmacokinetic models are based on biochemical, anatomical and physiological data.

The resulting PBPK models are able to extrapolate and scale between species and individuals because they are based on actual occurring physical mechanisms and allow the application of more advanced scaling laws than just considering the differing masses of the individuals. Due to their improved scaling qualities, first principles PBPK models have the potential to reduce the number of undesirable as well as time- and cost-intensive animal experiments during the drug development phase. Further, the development of first principle-based PBPK models leads to a gain of insight in the occurring processes during drug uptake by an organism. Having these models at hand moreover allows the determination of accurate and optimal drug dosage for 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 which are related to identifying the occurring mechanisms inside the body and the appropriate degrees of detail of the models with respect to the modeling goal and the available experimental data:

Firstly, a large number of alternative PBPK models can be generated depending on the degree of detail considered and the assumptions made about the different considered mechanisms in the body. Further, first principle PBPK models are usually complex models which contain a large number of unknown parameters that are not always all identifiable by the limited experimental data accessible. A strategy needs to be found to address the problem of discriminating between the different candidate models and identifying their parameters in order to find the model that is best supported by the experimental data available. In this context, design of experiments for model discrimination and parameter estimation plays an important role. If the models cannot be discriminated based on the available data, or model parameters that are important for the desired model outputs are not identifiable by the available data, methods for optimal design of experiments need to be applied. Design of experiments is especially important in pharmacokinetic modeling because in order to obtain the required datapoints animals need to be sacrificed.

In this work, a systematic methodology for the development, analysis, identification (including sensitivity analysis, identifiability analysis and parameter estimation) and discrimination between different pharmacokinetic candidate models is proposed. The methodology is implemented into a computer-aided modeling framework. The benefit of the proposed systematic approach is an improvement of model quality and an increase of efficiency of the modeler as well as the experimentalist and thereby a reduction of time and resources required for model development, identification, discrimination and application. This is achieved by designing the structure of the computer-aided modeling framework such that it can handle the work-flows and data-flows associated with the different modeling tasks, combining state-of-the-art modeling techniques for the different work-flow steps as well as supporting model-documentation and model reuse.

The proposed modeling framework for PBPK modeling is highlighted through a case study which deals with the development of a

PBPK model for a rat based on available experimental data.

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