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First principles pharmacokinetic modeling: A quantitative study on Cyclosporin

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ABSTRACT

Unknown dose regimes are typically assessed on animals prior to clinical trials. Recent advances in the evaluation of new leads' efficacy have been achieved by pharmacokinetic modeling. Further improvements, including determination of the drug's mechanism of action and organism biodistribution, require an effective methodology for solving parameter estimation challenges. This article solves the problem of rigorously estimating unknown biochemical reaction and transport parameters from *in vivo* datasets and identifying whole-body physiologically based pharmacokinetic (PBPK) models.

A rat blood circulation model was combined with biotransport, biochemical reactions and metabolism of the immunosuppressant Cyclosporin. We demonstrate the proposed methodology on a case study in Sprague-Dawley rats by bolus *iv* injections of 1.2, 6 and 30 mg/kg. Key pharmacokinetic parameters were determined, including renal and hepatic clearances, elimination half-life, and mass transfer coefficients, to establish drug biodistribution dynamics in all organs and tissues. This multi-scale model satisfies first principles and conservation of mass, species and momentum.

Prediction of organ drug bioaccumulation as a function of cardiac output, physiology, pathology or administration route may be possible with the proposed PBPK framework. Successful application of our model-based drug development method may lead to more efficient preclinical trials, accelerated knowledge gain from animal experiments, and shortened time-to-market of new drugs.

1. Introduction

The effect of novel drugs on targeted organs is typically studied in animal drug dosing trials. Pharmacokinetic models establish relationships between drug dosage, bioaccumulation and clearance utilizing dose–response measurements. Classical pharmacokinetic (PK) models relate anatomy and physiology parametrically to dose–response data while fitting exponential functions with multiple adjustable constants or exponential coefficients (Buss & Stepanek, 1993; Legg & Rowland, 1987; Ursino, Avanzolini, & Barbini, 1992). The resulting black-box formulae permit the computation of the area under the curve (AUC), the plasma half-life of elimination ($t_{1/2}$) or the intrinsic clearance rates. Limitations are observed when fitted relations are used to extrapolate drug concentration profiles for different doses (Ring et al., 2011).

Non-mechanistic, classical PK methods derive very little information about reaction kinetics and biotransport phenomena. It is reportedly difficult to scale or extrapolate information among laboratory animals or to predict drug fate for different dosing regimes (Nestorov, Hadjitodorov, Petrov, & Rowland, 1999). Hence, large sets of dose–response data have to be acquired in extensive animal trials in rats, then dogs and monkeys, until finally arriving at reasonably safe specifications for human trials. Prediction accuracy in PK models could be greatly improved by the incorporation of conservation laws, and fundamental transport and biochemical reaction mechanisms, which is beyond the scope of black-box approaches.

The efficacy of novel drugs can be studied more systematically with mechanistic biochemical models. Several authors have proposed whole body physiologically based pharmacokinetic (PBPK) prediction and modeling techniques (Gueorguieva, Nestorov, & Rowland, 2006; Kawai et al., 1994; Kawai, Mathew, Tanaka, & Rowland, 1998; Tanaka, Kawai, & Rowland, 2000). A thorough review of whole body physiologically based pharmacokinetic models (Edginton, Theil, Schmitt, & Willmann, 2008) recognizes the need for methods linking modeling, simulation, drug approval and rigorous experimental data analysis. Previous work commonly deployed compartments, typically encompassing several biological subsystems such as blood, plasma, red blood cells, interstitial fluid, the lymphatic system, the central nervous system, tissues and organs (De Buck et al., 2007).

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One possible scenario for drug fate modeling in the whole body is to determine the drug transport parameters by *in vitro* measurements, for instance with tissue-to-plasma partitioning coefficients (Haritova & Fink-Gremmels, 2010; Schmitt, 2008). However, these compartmental models typically do not account for the physiologically consistent blood perfusion or lymphatic fluid exchange patterns.

Several authors have recently used first principles modeling to elucidate the biochemical reaction mechanisms of new drugs *in vivo* (Espié, Tytgat, Sargentini-Maier, Poggesi, & Watelet, 2009; Garg & Balthasar, 2007; Lüpfert & Reichel, 2005; Laplanche, Meno-Tetang, & Kawai, 2007; Peters & Hultin, 2008; von Kleist & Huisinga, 2007, 2009; Yates, 2006). Although mechanistic, the underlying algorithms commonly infer systemic circulation with a set of continuity and conservation differential equations. Every part of the whole body flow network has to be entered manually. This soon leads to infeasibility if multiple animal models need to be tested.

In contrast, our improved workflow ensures that for arbitrarily complex PBPK networks with hundreds of biological "compartments", corresponding differential equations are automatically generated and validated. This allows for testing various circulatory system configurations with greater detail as more data become available on the drug–organ interactions. Given solid data describing individual pharmacokinetic processes, the selection of an accurate but general mechanistic model still remains a scientific challenge.

In this article a rigorous engineering approach based on first principles of mass, species and momentum conservation is proposed to build upon the advances in classical PK modeling. The presented work aims at determining drug reaction kinetics and transport phenomena from actual experimental dose–response measurements. To scientifically examine drug fate in living organisms, we emphasize the need for a closed loop iterative methodological approach: (i) obtaining experimental data, (ii) constructing first principle models, (iii) estimating parameters and (iv) gaining insights from comparing working hypotheses with experimental sets.

We will demonstrate the advantages of our methodology with a case study on the immunosuppressant Cyclosporin. Our advanced mechanistic model results in a rigorous analysis of biodistribution after a bolus *iv* injection into a rat. The model will also be used to assess different administration regimes, which in the case of Cyclosporin have been shown to enormously affect interactions with physiology, cardiovascular dynamics and pharmacology (Kawai et al., 1994; Kimura et al., 2010; Kovarik et al., 2008; Omar & El-Mas, 2004). We hope to contribute an improved level of understanding in such a complex topic.

This paper is organized as follows. Section 2 lays out the conceptual foundation: (i) steady state systemic blood circulation model, (ii) mechanistic transport, mass transfer and biochemical reaction parameters, and (iii) a parameter estimation technique for determining the unknown model parameters from actual animal experiments. The application of this concept is demonstrated with a case study on Cyclosporin in Section 3. Results are discussed in section four.

2. Mathematical Formulation of Whole Body Pharmacokinetics

This section introduces our PBPK model with inherent first principles intraspecies scaling, an overview of which is shown in Fig. 1. We present a living system model which predicts the drug biodistribution among individual subjects of the same species, in an organism, organs, tissues and cells.

1. *Intraspecies scaling* is accomplished by application of physiological and morphological differences onto the underlying first principles PBPK model.
2. *Whole body drug dynamics* results from application of initial and boundary conditions onto the underlying system, for instance dose regime or weight of subject.
3. *Biodistribution in organs* is given by physiology, blood circulation, fat and muscle content. These parameters are obtained experimentally.
4. Drug transiency in tissues is characterized by biotransport through capillary walls into the interstitium. Biotransport is a function of the size of mass transfer area while the specific mass transfer rate of blood–organ interface may be constant. By solving for unknown specific mass transfer rates, tissue:plasma partition coefficients can be calculated.
5. Drug fate on the cellular level is determined by selected biochemical reactions. Metabolism will be scaled according to chemical principles. Metabolic action has to be studied independently and is usually observed in renal cells, hepatocytes or on cytochromes.

We will introduce a *rigorous parameter estimation technique* for deriving the unknown rate parameters from actual drug dose–response experiments in animals. A mathematical programming technique for solving the transport and kinetic inversion problem will be discussed.

Nomenclature

See Table 1 for list of symbols.

2.1. Steady state model

Rapid systemic drug distribution is mainly due to the convection of blood, lymph or cerebrospinal fluid. The fluid circulation can be mathematically modeled as directed, cyclic graphs (Linninger et al., 2009). To introduce the principle, the first layer of our multiscale pharmacokinetic model elaborates only a systemic blood circulation network disregarding the lymph or cerebrospinal fluid flow for which the same algorithm would be applied. The network graph holds blood pressures at the vertices and computed blood flow rates at the edges, as described by fluid momentum equations. The solution of the steady state equations gives the volumetric blood perfusion rates and blood pressures.

The *blood circulation network* has given pressure boundaries for the heart represented by two atria and two ventricles. The large vessels of the vascular system are composed of simple cylindrical segments, with known radii, lengths and flow resistances. The organs' blood supply is maintained by segments with calculated equivalent hydraulic properties from Eq. (1), so that physiologically consistent perfusion rates (Brown, Delp, Lindstedt, Rhomberg, & Beliles, 1997) and pressure drops are ensured. Each organ's blood supply is further divided into arterial, capillary and venous sections. The distribution of blood flow resistances to these three parts is estimated according to known physiological data (Brown et al., 1997; Delp, Evans, & Duan, 1998).

2.1.1. Blood flow

The blood flow in large arteries and veins may be approximated by the Hagen–Poiseuille equation, as a function of radius (r), length (L) and flow resistance (α) as in Eq. (1). We assume this model for all blood vessels in the body.

$$\Delta P = \alpha F = \frac{8\mu L}{\pi r^4} F \tag{1}$$