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Data-driven modelling of drug tissue trapping using anomalous kinetics

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ABSTRACT

This work revisits the pharmacokinetic models derived from classical differential equations and proposes an extension to fractional differential equations to account for tissue trapping, which modifies the predicted drug concentration profiles. Unlike monotonic decay profiles, an oscillatory behaviour is often observed. The phenomenon may be the result of the recirculation of trapped drug molecules due to the heterogeneity of the tissue combined with the local action of the liver or other organs in depositing part of the drug for later release. The proposed model alleviates this limitation in data fitting profiles, without violating mass balance principles and physiological states. The paper also points to new concepts and techniques in modelling drug pharmacokinetic dynamics to account for short- and long-time recirculation effects. As such, it provides a better characterisation of unexplained secondary effects in patients undergoing treatment. It also establishes a link to unbounded drug accumulation models.

1. Introduction

Selecting appropriate models is a crucial step in capturing complex biological and physiological phenomena. Any choice of a model structure implies a simplified view of the interaction among the various elements that may characterise a dynamical system. In pharmacokinetics, a popular choice is that of compartmental models, due to their implicit simplicity and ease of understanding in relation to the mass balance equations and assumptions for uniform distribution, homogeneous transient times and immediate response to drug bolus administration [1]. Numerous works and decades of research have tailored their applicability for optimal drug delivery assist devices in several domains of medical applications, e.g. diabetes [2], cancer [3,4], anaesthesia [5], immunodeficiency [6] and hormonal treatment [7].

Providing a best fit to data from observed drug concentration profiles implies the existence of some error tolerance intervals. Emerging tools from fractional calculus have proven useful to improve to a great degree the accuracy of dynamical models with respect to classical integer order modelling theory [8,9]. The acceptance of these tools within the engineering community has led perhaps to a significant step forward in terms of data driven modelling and numerical simulation [10–13]. However, their acceptance in clinical practice may require further tailoring for a better characterization of patient variability [14–16].

Compartmental models are a traditional tool for modelling drug pharmacokinetics (PK) in applications of general anaesthesia. The depth of anaesthesia regulatory problem consists of optimal calculation via such patient PK models of the amount of drug necessary to achieve a desired sedation level, irrespective of artefacts and disturbances [17]. Attempts to fractionalise PK compartmental models for anaesthesia have been done with simulated data. A net advantage however has not been shown, since secondary effects due to drug trapping were not accounted for at that time [18,19].

In this work an existing model for drug concentration profile characterisation is revisited in order to capture additional dynamics which otherwise have been overlooked in all previous reports. A complex interaction phenomena between tissue heterogeneity, drug diffusion specificity, molecular binding and recirculation from liver organ dynamics leads to unique drug concentration profiles observed in time. This paper introduces a data fitting algorithm and corresponding model structure to illustrate the added value with respect to the state of the art. Emerging tools from fractional calculus, i.e. fractional order derivatives, are used to mimic heterogeneity among the various compartments in the pharmacokinetic

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models. Data from literature are used to examine the potential of the proposed model for its best linear approximation. The model is nonlinear in the parameters, with coefficients related to drug uptake and clearance rates.

The paper is organized as follows. The next section provides a brief review of existing pharmacokinetic models for capturing dynamic drug concentration profiles. The third section provides the proposed model and explains physiological relevance and further extensions. The fourth section delivers the simulation results for better understanding model parameter effects and finally data from literature is used to indicate its added value. The last section summarizes the main outcome of this work and offers some perspectives.

2. Anomalous kinetics

The PK literature is dominated by compartmental models of drug dynamics in human body, for a wide range of medical application or treatment [20,21]. The mamillary compartmental model with single compartment seems to be the simplest representation of drug uptake and clearance, with the amount of a drug defined by a simple ordinary differential equation (ODE) relation:

$$\frac{dA(t)}{dt} = -k_{10}A(t) \tag{1}$$

with $A(0)$ the dose of bolus intake and K_{10} is the clearance rate constant. The solution, $A(t) = A(0) \cdot \exp -k_{10}t$. However, usually 2-3 compartments are taken into account and as to specify the heterogeneity between the blood, muscle and fat tissue dynamics. It turns out that characterization as a function of time implies a negative power function derived from plasma drug concentration profiles [22]. Nevertheless, triexponentials with power and gamma functions were successfully fitted to power law data and results for several drug pharmacokinetics reported in literature [22]. An important decision at that time was to make observations on log-log plots with y- data and x-time axis. A limitation of the data intervals led to the use of gamma functions, assuming homogeneous distribution of drug into the compartmental volume. The necessity of several exponential terms to fit the data in linear regression algorithms seemed at the time unavoidable.

Later on, the necessity of a recirculation mechanism was to account for observed fluctuations in the time decay of a drug PK [23,24]. The assumption that compartmental models were homogeneous no longer fit the observed data. However, since the tools used to model the dynamical variability were ODEs, augmenting the model with a residence time information was a solution at hand. However, care must be taken when considering transient and residence times, since the two notions are different in PK specifications [23]. As stated in [23], classical compartmental models fail to explain the effect of different sampling sites, due to concentration differences across the various biological tissues. The units of the PK compartmental models are confined to exponentially distributed transit times. By contrast, recirculatory models may be characterized by any parametric or non-parametric class of drug transit time distributions. The choice of the model type is thus important, and it greatly depends on the objective it may serve.

In an effort to circumvent the choice of the model type, non-Markovian compartmental models were proposed [25]. Random particle distribution and transfer based on retention times seem adequate in capturing heterogeneous dynamic effects. The authors provide an adapted view of the models from Weiss in assuming a three compartmental PK model whereas one compartment is seen as a distribution of pseudo-compartments with different retention times. Clearly this is a more realistic approach since it enables phenomenological observations of drug accumulation and/or late recirculation loops. Still, oscillatory behaviour in drug concentration profiles for a single bolus intake are ignored. A conceptual view of such model representation is given in Fig. 1a.

Tissue trapping was addressed by Weiss later in [26], by proposing a non-classical PK model describing well the persistently increasing plasma concentration time curve during long term treatment and the washout curve following terminal therapy. The long tailed tissue residence time distribution is incorporated by means of a recirculatory model. Weiss [26] also acknowledges the anomalous kinetics and the fractal scaling property in characterizing amiodarone drug dynamics. A conceptual schematic of such distribution is given in Fig. 1b.

A decade later, emerging tools from fractional calculus enabled a new wave of PK compartmental modelling theories, indicating some important flaws in the classical PK models. For example, multi-compartmental kinetics with fractional differential equations (FDEs) following consistent physiological mass balance rationale have been reported in [27]. Numerical methods to efficiently compute these equations are largely available to the community and simulations no longer pose tedious implementations. The great revelation of these numerical studies was that the presence of a transfer rate of fractional order produces a non-exponential terminal phase, while multiple dose and constant infusion systems never reach steady-state, resulting in drug accumulation. The latter is a life-threatening issue for the patient and imposes a critical observation on the usefulness of previous PK compartmental model definitions. Deep tissue trapping may account for observed secondary effects days, weeks and months in patients who undergone surgery with general anaesthesia, or following cancer treatment therapies. These new theoretical concepts and PK models may enable a different, novel perspective of drug kinetics. Such models more accurately predict the observed drug profiles and can provide an new basis for optimizing treatment.

Conventional pharmacokinetic concepts fail to describe the long term pharmacokinetcis of the extremely cationic drug amiodarone. Although several clinical data on amiodarone pharmacokinetics have been published the disposition kinetics of this drug is still not well characterized. Drug tissue trapping has been addressed also in [28] using fractional kinetics and data on amiodarone from [26]. Significant differences in linear or logarithmic drug intake profiles have been observed in numerical simulations, suggesting drug accumulation and inherent side effects in patient well-being. The paper from [28] proposes a dosing regime to stabilise the plasma concentration of amiodarone when fractional PK models are used. Applications to cancer treatment using the frud doxorubicine have also been performed with similar conclusions [29]. Still, among all the previous works related to introducing anomalous kinetics and fractional PK compartmental models one cannot but notice the fact that some effects of drug trapping and releasing are yet unaccounted for. Drug accumulation could have important clinical implications and thus requires a solution to reach a steady state. Dokoumetzidis et al. [27] have shown that classical PK models with intravenous drug infusion predicts that steady state will be reached while the compartmental PK model with fractional elimination predicts unbounded drug accumulation. The aim of this paper is propose a revisited fractional order PK model in order to test the hypothesis of preventing drug accumulation.

Continuous random walk have been widely employed in fields such as physics, chemistry, life sciences, etc. Many biological and physical transport processes exhibit anomalous behaviour for which walker mean-squared displacement increases as a fractional power. Anomalous diffusion problems naturally arise in the settings of complex biological environment. Modelling of diffusion in different complex media could provide further understanding in a variety of experimental conditions. Anomalous subdiffusion is

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