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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

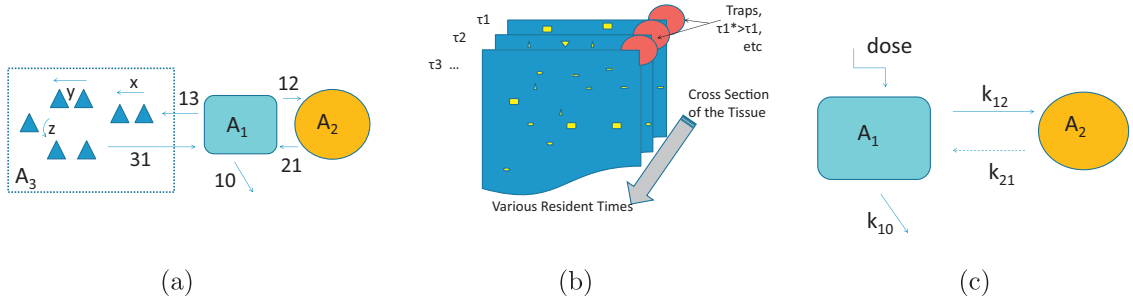

Fig. 1. (a) Distributed compartmental PK models. A three-compartmental scheme is given with classical two compartments on the right side combined with a distributed drug retention times compartment on the left side. Notice that intermediate drug profiles x,y,z may vary locally due to tissue trapping. Note that all drug fluxes denoted by arrows may have different dynamics (FDEs) as opposed to classical ODEs. (b) A conceptual view of distribution of tissue dynamics with various residence times and drug trapping areas. (c) Two-compartmental PK model representation. The continuous arrows denote ODEs, whereas dashed arrows denote FDEs.

represented by:

$$< X^2(t) > \approx t^{\mu} \tag{2}$$

with $0 < \mu < 1$. Subdiffusion could be used to model molecules of drug trapped in deep tissue for long times. The subdiffusive fractional Fokker–Planck equation can be employed as from [30]. Let $p(x, t)$ be the density function for finding the particle in the interval $(x, x + dx)$ at the time instant t; then

$$\frac{\partial p}{\partial t} = -\frac{\partial (v_{\mu}(x) D_t^{1-\mu} p)}{\partial x} + \frac{\partial^2 (D_{\mu}(x) D_t^{1-\mu} p)}{\partial x^2} \tag{3}$$

in which $D_{\mu}(x)$ is the fractional diffusion and $v_{\mu}(x)$ is the drift, with $\mu < 1$, and the Riemann–Liouville derivative is defined as

$$D_t^{1-\mu} p(x,t) = \frac{1}{\Gamma(\mu)} \frac{\partial}{\partial t} \int_0^t \frac{p(x,u)du}{(t-u)^{1-\mu}} \tag{4}$$

where we see the difference between the standard Fokker–Planck equation and the its fractional version by means of the rate of relaxation

$$p(x,t) \longrightarrow p_{st}(x) \tag{5}$$

When using this equation to extract residence times, on the long term, as $t \longrightarrow \infty$ the non-homogeneous variations of the parameter μ as a function of space should be carefully checked. When a cell performs a random walk it waits for a random time in space before making a jump to another point. The most important characteristic of this movement is the transition rate for jumps at point x. For continuous time random walks the following assumption is made: transition rate is dependent on the residence time. The residence time is the time interval between two successive jumps of the cell. Recent studies by [30–32] reported that the diffusion coefficient is a nonlinear function of the nonlinear reaction rate. In this model [32] the escape rate $\mathcal{T}$ of a particle from a position is modelled as a decreasing function of density $\rho(x, t)$:

$$\mathcal{T}(\tau, \rho) = \frac{\mu(\tau)}{1 + A\rho(x,t)} \tag{6}$$

which describes the phenomenon of con-specific attraction: the rate at which individual molecules or particles of drug emigrate from the point x is reduced due to the presence of many other con-specifics. The rate parameter $\mu(\tau)$ is a decreasing function of the residence time:

$$\mu(\tau) = \frac{\mu_0}{\tau_0 + \tau} \tag{7}$$

where μ_0 and τ_0 are positive parameters. This particular choice of the rate has been motivated by non-Markovian crowding: the longer the particles stay in a particular site, the smaller the escape probability to another site (e.g. fat). Although the space dependent order has been introduced in this paper since it can be further employed in order to investigate tissue trapping. Drug is trapped differently depending on the heterogeneity of the tissue. However, this is not the scope of this paper.

3. Revisited FDE PK model

It has been suggested that instead of combining power law and exponential functions to account for anomalous kinetics, it is more efficient to use the Mittag–Leffler function [27]. This function has the capability to follow the stretched exponential for small times and the power function for long times, thus it is appropriate for characterizing both the short and the long time scales of drug concentration profiles.

A classical two-compartmental model is given by the following ODEs:

$$\begin{aligned} \frac{dA_1(t)}{dt} &= -k_{12}A_1(t) + k_{21}A_2(t) - k_{10}A_1(t) \\ \frac{dA_2(t)}{dt} &= k_{12}A_1(t) - k_{21}A_2(t) - k_{20}A_2(t) \end{aligned} \tag{8}$$

The correct fractionalisation of Eq. (8) maintaining mass balance, is given by:

$$\begin{aligned} \frac{dA_1(t)}{dt} &= -k_{12}{}_0^C D_t^{1-\alpha} A_1(t) + k_{21}{}_0^C D_t^{1-\beta} A_2(t) - k_{10}{}_0^C D_t^{1-\gamma} A_1(t) \\ \frac{dA_2(t)}{dt} &= k_{12}{}_0^C D_t^{1-\alpha} A_1(t) - k_{21}{}_0^C D_t^{1-\beta} A_2(t) - k_{20}{}_0^C D_t^{1-\delta} A_2(t) \end{aligned} \tag{9}$$

with k_{ij} rate constants and initial conditions $A_1(0) = dose$, $A_2(0) = 0$ which account for bolus injection and no initial amount in peripheral compartment. Here, the fractional order of the Caputo fractional derivative represents the heterogeneity of the diffusion dynamics [33].

Take for instance the two-compartmental PK model depicted in Fig. 1c. Clearance and diffusion from compartment one to compartment 2 is considered as a classical (ODE) whereas diffusion compartment two to compartment one is fractional (FDE), with $\alpha < 1$ to account for deep tissue trapping of the drug.

The model can be described by the following set of equations:

$$\begin{aligned} \frac{dA_1(t)}{dt} &= -(k_{12} + k_{10})A_1(t) + k_{21}{}_0^C D_t^{1-\alpha} A_2(t) \\ \frac{dA_2(t)}{dt} &= k_{12}A_1(t) - k_{21}{}_0^C D_t^{1-\alpha} A_2(t) \end{aligned} \tag{10}$$

The model has been transformed to the Laplace domain and solved for A_1 using a numerical inverse Laplace transform program in Matlab as described in [27]. The solution is given by:

$$A_1(s) = \frac{dose(s^{\alpha} + k_{21})}{(s + k_{12} + k_{10})(s^{\alpha} + k_{21}) - k_{12}k_{21}} \tag{11}$$

For values $\alpha < 1$ the solution behaves essentially as a first order system, i.e. two poles of which one is cancelled by a zero at

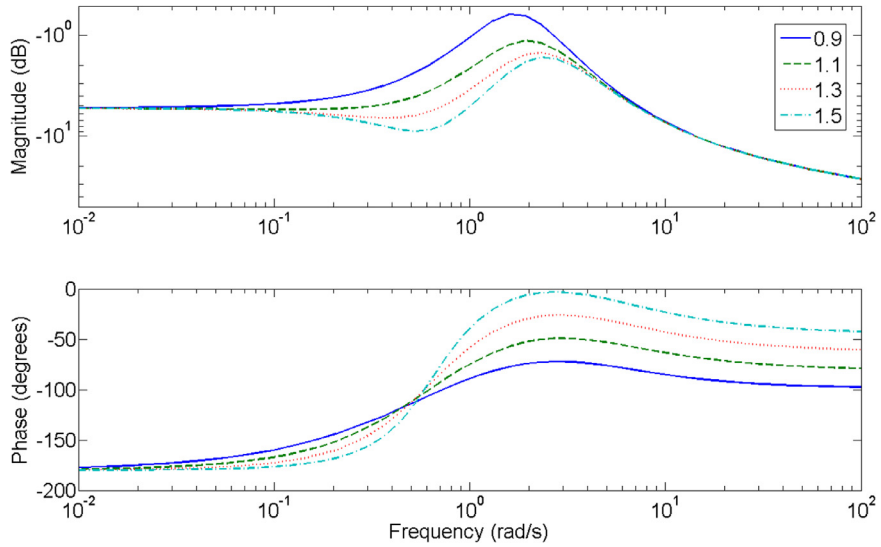

Fig. 2. Frequency response of (11) for various values of α.

Table 1
Estimated model parameters used in simulation, with k the transfer rates between the compartments and clearance rate, and V the volume of the central compartment.

Parameter	Value
k_{10} (days^{-1})	1.49
k_{12} (days^{-1})	2.95
k_{21} (days$^{-\alpha}$)	0.48
α (-)	(0.5,1.5)
dose/V (ng/ml)	4.72

Table 2
Identified model parameters used in simulation from (11) for a fixed dose of 4.7268 (ng/ml).

Parameter	Value
k_{10} (days^{-1})	1.7
k_{12} (days^{-1})	2.5
k_{21} (days$^{-\alpha}$)	0.6
α (-)	1.5

high frequencies. Suppose now that the values of α may increase above 1. The Bode plot of the transfer function is given in Fig. 2 for various values of α, simulated with parameters as in Table 1.

From an engineering point of view, this non-rational transfer function changes dynamic behaviour from a first order to a second order system. In order to verify the time response of these transfer functions, it is necessary to use an inverse Laplace transform for non-rational polynomial representations. A numerical algorithm in Matlab has been proposed in [27], and it is used to simulate the results reported in this paper as well. The time domain simulations are given in Fig. 3.

4. Illustrative example

A dynamic concentration profile (see Fig. 3) for the drug Amiodarone taken from [26] has been mimicked for simulation purposes. The model from (11) has been identified to fit data which poses characteristics observed in real concentration values reported in literature. Of particular importance are the oscillatory dynamics which relate to recirculation effects as discussed above.

It is well known that the amiodarone plasma concentration does not converge towards a steady state following multiple dosing because of its tendency to accumulate in deeper tissues. In Fig. 3 the time evolution of drug concentration for various values of α. It can be noticed that for values of $\alpha > 1$ an oscillatory effect is noticed.

Using the nonlinear least squares algorithm in Matlab provided by the function `lsqnonlin` the parameters have been identified as in Table 2.

The potential of increasing $\alpha > 1$ is observed in capturing possible variations in the concentration profiles, when compared to the result for $\alpha < 1$ sketched in Fig. 4. Of course, the model may be further tuned on real data profiles. It should be also noted that the amount of variability as a function of time differs from one patient to another, hence the model parameters could be fit in an individualised PK model framework.

The model with the solution given in (11) has some limitations in capturing all oscillatory dynamic profiles. This is due to the fact that only two compartments have been used, without recirculation, and without taking into account heterogeneity in the tissue. The distributed parameter compartmental models may potentially be employed to circumvent this limitation.

Higher order transfer functions may also be introduced, resulting in added dynamic complexity. However, stability must be ensured since non-rational transfer functions obey different stability rules that those from classical system theory [34].

To investigate the behaviour noticed in Fig. 3 we have employed a discretization method in order to approximate the high order transfer function with a first order plus dead time (FODT) transfer function. Literature offers several methods for approximating such non-rational continuous time transfer functions, through various steps. The one proposed in this work is based on four steps, leading to a low order, stable, discrete time rational approximation of any general fractional order system. The details have been outlined in [35], with various examples to illustrate the ability of the method.

In short, the steps are as follows.

- Step 1: discretize the FODT using a generating function.

This function has been proposed as an interpolation between Euler and Tustin discretisation rules:

$$s(z^{-1}) = \frac{1+a}{T_s}\frac{1-z^{-1}}{1+az^{-1}} \tag{12}$$

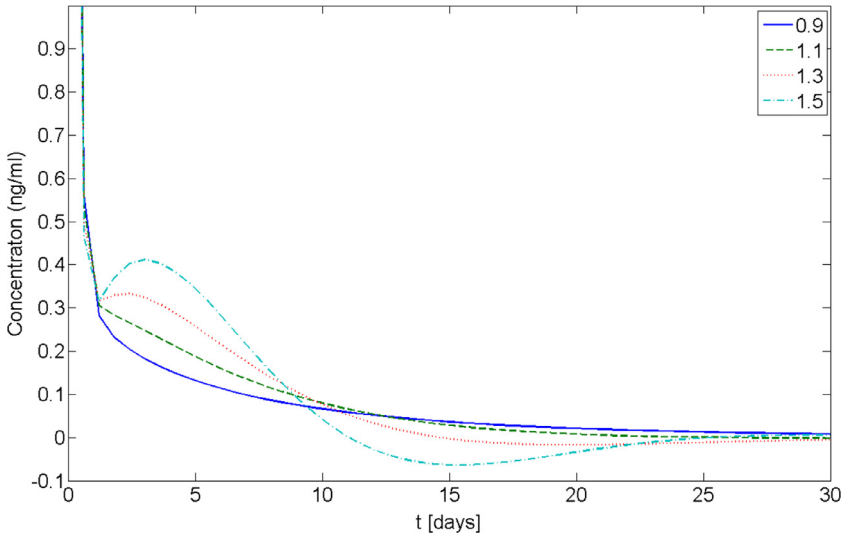

Fig. 3. Time domain behaviour of the transfer function from (11) for various values of α.

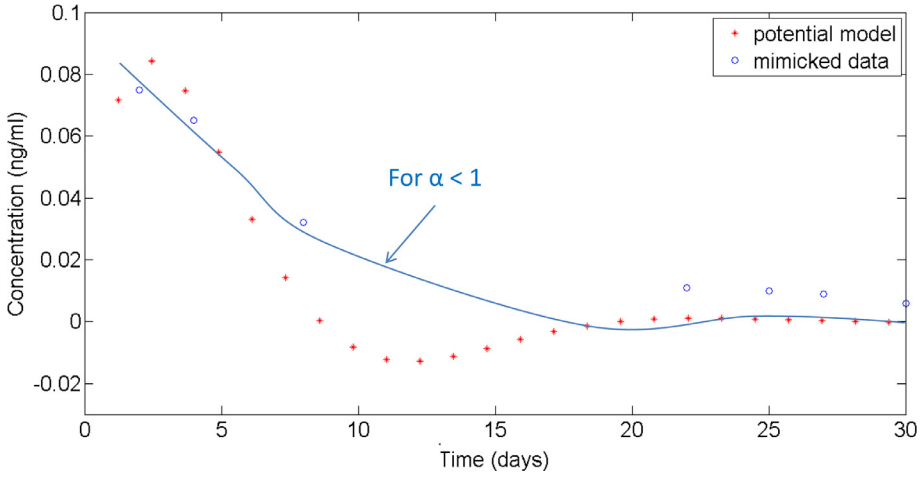

Fig. 4. Variations obtained with sub- and supra- unitary values of α.

with the weighting parameter $a \in [0 \div 1]$ and T_s the sampling period, with special cases for $a = 0$ (Euler discretization) and for $a = 1$ (Tustin discretization).

- Step 2: calculate the frequency response of the discrete-time fractional order system from FODT.

This approximation is done in a pre-determined frequency interval, of equally spaced frequency points, around a predetermined frequency ω, e.g. the critical frequency ω_c. The frequencies below the critical frequency are more important for the prediction quality of the time response of the obtained model than frequencies above ω_c.

- Step 3: calculate the impulse response of the discrete-time fractional order system.

This step employs the inverse Fast Fourier Transform (FFT), which converts the previously computed frequency domain response into a time domain response.

- Step 4: determine a rational discrete time transfer function that produces a similar impulse response as that obtained from the inverse FFT.

The result is the something in the form

$$G(z^{-1}) = \frac{c_0 + c_1 z^{-1} + \ldots + c_N z^{-N}}{d_0 + d_1 z^{-1} + \ldots + d_N z^{-N}} \tag{13}$$

where N is the desired order of approximation. All tuning parameters in these steps are discussed in detail in [35].

The conclusions taken after employing this method is that the "inflexion point" at about t = 2 are due to the zero in the transfer function. This is a property of the Mittag–Leffler function which requires a zero. The effect of this zero can be seen as the clearance rate (which has faster dynamics than the diffusion).

5. Discussion and perspectives

In this paper we revisited the existing compartmental modelling approaches and extended their usefulness by employing emerging tools from fractional calculus. Undoubtedly, the fractional kinetics approach outperforms the classical ODE models while maintaining the link to physiological phenomena. It is worth mentioning that the assumption of a homogeneous compartment representation is no longer limiting in view of modelling objectives. Instead, tissue trapping and heterogeneous resident times may be taken into account by using distributed compartmental models with various diffusion rates. The combination of classical PK models and with fractional PK models is then the natural next step

in the quest to improve their ability to mimic complex observed physiological phenomena.

Naturally, tissue porosity, molecular binding and permeability vary within the organ, within the system and within the assumed compartment. Taking tissue specificity into account when modelling PK dynamic profiles may lead to increased model complexity. A trade off between the usefulness and computational efficiency of such models must be made when evaluating the model objectives. If prediction for treatment optimisation is envisaged, then one may include as many details as possible to account for a personalised healthcare plan. If mere evaluation of dosing profiles and observational studies are involved, tissue specificity may be limited to the strictly necessary number of details (e.g. Occam's Razor approach). Obviously, large population data sets will be necessary to provide some reference baseline values for initial start-up. However, if data is available, data driven modelling/identification may be performed and model parameters tuned to fit the specificity of the case.

Applications of augmented PK models with FDEs are numerous and not limited in the number of turns. One may freely consider their application to modelling any drug PK dynamics. Multiples types of dosing intake may be assumed, either as a single type, or as combinations hereof: single dose, bolus, multiple dose, continuous infusion. When using FDEs in PK models, care must be taken for intake profiles may lead to drug accumulation and possibly over-dosing in some time intervals. Linear or power-law dosing profiles may be investigated to optimally use the dynamic model properties.

As such, time FDEs have been considered hitherto. However, tissue heterogeneity is also structural, geometric, and not only present in dynamic fluctuations. It may be worth considering introducing a time-space mathematical formulation (e.g. by employing fractional order space derivatives) to account for drug intake whereas time and location may be specified. This is of great importance in pathology cases, where changes in tissue structure and morphology affects directly the dynamic profiles of drug diffusion, permeability and molecular binding. Specific structural changes with disease may also reveal various paths of deep tissue trapping of drug and latency nodes which could explain effects observed in long-tailed observations.

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