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Tailored Pharmacokinetic model to predict drug trapping in long-term anesthesia

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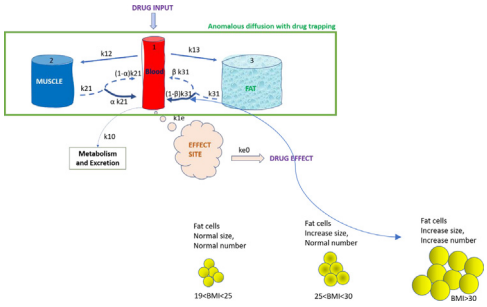
GRAPHICAL ABSTRACT



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ABSTRACT

Introduction: In long-term induced general anesthesia cases such as those uniquely defined by the ongoing Covid-19 pandemic context, the clearance of hypnotic and analgesic drugs from the body follows anomalous diffusion with afferent drug trapping and escape rates in heterogeneous tissues. Evidence exists that drug molecules have a preference to accumulate in slow acting compartments such as muscle and fat mass volumes. Currently used patient dependent pharmacokinetic models do not take into account anomalous diffusion resulted from heterogeneous drug distribution in the body with time varying clearance rates.

Objectives: This paper proposes a mathematical framework for drug trapping estimation in PK models for estimating optimal drug infusion rates to maintain long-term anesthesia in Covid-19 patients. We also propose a protocol for measuring and calibrating PK models, along with a methodology to minimize blood sample collection.

Methods: We propose a framework enabling calibration of the models during the follow up of Covid-19 patients undergoing anesthesia during their treatment and recovery period in ICU. The proposed model can be easily updated with incoming information from clinical protocols on blood plasma drug concentration profiles. Already available pharmacokinetic and pharmacodynamic models can be then calibrated based on blood plasma concentration measurements.

Results: The proposed calibration methodology allow to minimize risk for potential over-dosing as clearance rates are updated based on direct measurements from the patient.

Conclusions: The proposed methodology will reduce the adverse effects related to over-dosing, which allow further increase of the success rate during the recovery period.

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Introduction

Extremely long-term anesthesia, i.e. up to 4 weeks or more, has recently been experienced in Covid-19 patients on life support machines [1,2]. A high risk of drug trapping in slow acting tissue metabolic rates such as muscle, bone and fat has already been observed in moderate long-term anesthesia, i.e. above two hours [3]. There is evidence to suggest that anomalous diffusion is in fact a common environment facilitating drug trapping and molecular conglomerates of drug in sustained drug infusion patterns [4]. An anomalous diffusion pattern modifies the clearance rates in the patient models used by anesthesiologists to determine the required drug infusion rates. Ignoring drug trapping leads to over-dosing and side effects which contribute to longer recovery times and morbidity risk for the patient with possibly longer intervals of anesthesia, i.e. a vicious circle of events.

Nonlinear effects such as volume exclusion (crowding) an adhesion/cohesion of drug molecules in biological tissues has been previously discussed in works on multi-layer diffusion with Langevin dynamics [5–7] and various generalisations proposed [8]. Non-Markovian processes in kinetic uptake and anomalous diffusion have been discussed several decades ago in [9]. Tissue trapping and anomalous diffusion have been also acknowledged in early works of Weiss [10]. However, it is only recently that fractal kinetics have been coined and pharmacological modelling makes use of the powerful tools from fractional calculus [11–16]. New definitions of fractional calculus related to theoretical considerations have been developed and a class of tempered fractional differential equations haven investigated [17]. Recent works have described diffusion of species in steady state conditions [18,19] incorporating chemotaxis as part of nonlinear dynamics in anomalous diffusion. The concept of memory, a unique feature of fractional dynamics, it enables non-specialists to grasp the complexity of the nonlinear physical phenomena of anomalous diffusion in a context which can be readily applied to medicine. New aspects of sophisticated dynamics with memory trace in many physical and biological systems can be taken into account by fractional calculus [20–22]. The use of fractional calculus has been employed to investigate the problem of finding the solution of fractional reaction-diffusion equation [23].

In the last year the world has been affected by COVID-19 pandemic. Since the outbreak of the new virus, researchers worldwide have been focused their attention to several aspects of the COVID-19 epidemic [24]. Clinicians and researchers have been investigated the new virus from several perspectives: virology, infectious disease, microbiology, public health, economics, etc. Some researcher focused on the origins of the COVID-19 virus while others have focused on transmission of the new virus. Recent works have investigated the COVID-19 infection system from the perspective of mathematical modeling [25,26]. In the last decade mathematical modeling of biological systems using fractional calculus methods have become important tools to investigate and understand spread of infectious diseases. The work presented in [27] investigates the use of fractional calculus to describe the transmission of the epidemiological model.

In this paper we provide a mathematical framework for drug trapping occurring in long term drug infusion in human slow uptake dynamics tissue (i.e. fat) governed by multilayered dynamics and anomalous diffusion. This yields added value with respect to current patient pharmacokinetic models which assume homogeneity and linear superposition dynamics. What we aim to achieve is to justify the need for calibration of pharmacokinetic (PK) models used in target controlled infusion for long term anesthesia. In this way, we facilitate to counteract effects in Covid-19 patients as to drug accumulation in fat tissue and lower the risk for over-dosing (which otherwise has undesirable side effects such as prolonged recovery and increased morbidity).

This paper proposes a mathematical framework for drug trapping estimation in PK models for estimating optimal drug infusion rates to maintain long-term anesthesia in Covid-19 patients. We also propose a protocol for measuring and calibrating PK models, along with a methodology to minimize blood sample collection. By means of blood samples, the PK model can be realigned to newly identified coefficients according to a heterogeneous uptake/clearance rates. This is naturally linked to heterogeneus diffusion and fractal kinetics concepts [28,29]. The paper presents simulation results based on curated data from previous trials in our university hospital. The simulations were performed using the comprehensive open source patient simulator presented in [30].

The paper is organized as follows: In Section "Material and methods" the material and methods used in this study are presented. The context of research is presented followed by the introduction of the mathematical models. Also the proposed methodology is also described along with the patient benchmark used to perform the simulations. In Section "Proposed calibration protocol" the proposed calibration protocol is detailed. Section "Results" discussed the obtained results followed by Section "Conclusions" were the conclusions of this study are summarized.

Material and methods

Context

Fractional calculus plays an important role in modeling many phenomena in physics, chemistry, but also in the engineering area [31–33]. This research field promises to serve a whole range of applications with a large impact on the progress of science and welfare. The last decades have shown an increased interest in the research community to employ parametric model structures of fractional-order for analyzing nonlinear biological systems. The concept of fractional-order (FO) systems refers to those dynamical systems whose model structure contains arbitrary order derivatives and/or integrals [31,34]. Recent work suggest that fractional order models can improve the correlation between prediction model and experimental data [35,36]. It has been shown that fractional calculus is an alternative theory that can describe this anomalous behavior [31]. In the past many attempts to model the diffusion process have been made and FO have been shown to well-characterize these diffusion processes. The last decade has shown an increased interest in the research community to employ parametric model structures of FO for analyzing nonlinear biological systems [37,38,35,39].

Anomalous Non-Markovian (NM) sub-diffusive processes have memory properties, e.g. polymers and biological tissues resembling polymer materials. This property is strongly dependent on history and the rate of (sub)diffusion of molecules, involving chemotaxis and chemokinesis to create effects such as adhesion/-cohesion among the commonly encountered nonlinear dynamic effects. In diffusion of drug molecules in human tissue, the inter- and intra-patient variability commonly refers to these effects in terms of pharmacokinetic (PK) and pharmakodynamic (PD) effects in the body.

For long term drug infusion systems to maintain general anesthesia - e.g. trauma induced coma, bariatric surgery, transplant surgery and, the longest hitherto known situation of life support Covid-19 patients - the risk of drug accumulation increases with the period of administration. It has been shown that molecules in slowly acting compartmental volumes (e.g. muscle, fat) tend to

behave as social individuals. The longer they stay, the more they like to remain, forming conglomerates and facilitating crowding effects.

The seminal works of Metzlers (father and son) [40], i.e. the random walk dynamic has been linked to anomalous diffusion and fractional dynamics have propelled in cross-disciplinary applications ever-since. However, it does not capture anomalous NM sub-diffusive dynamics whose mean displacement grows as a function of t^{μ} with $0 < \mu < 1$. Similarly, fractional Brownian motion and continuous time random walk do not consider particle interactions. The latter is very important if for instance cocktails of drug contain synergy effects. In anesthesia related multi-drug infusion systems, there is a strong synergy between hypnotic agent (propofol) and opioid agent (remifentanil).

In the plethora of nonlinear effects in sub-diffusive system dynamics, we focus here on those related to non-uniform concentration distribution and determine a transition probability factor linked to clearance rates between slow acting PK compartmental models for patients undergoing anesthesia. The transition probability from one compartment to another - say, for instance, from fat to blood - is a function of residence time of drug molecules in the fat tissue and the external factor from a time varying, continuous drug infusion in blood.

Fractional sub-diffusion transport

Standard diffusion equation governing the particle density $\rho(\chi, t)$ is given by [40]:

$$\frac{\partial^{\mu}\rho}{\partial t^{\mu}} = D_{\mu}\frac{\partial^2\rho}{\partial\chi^2} \tag{1}$$

for $\rho(\chi, 0) = \rho_0(\chi)$ and D_{μ} is a fractional diffusion constant $(length^2/time^{\mu})$ and the Caputo derivative

$$\frac{\partial^{\mu}}{\partial t^{\mu}}f(t) := \int_0^t f'(t-s)\frac{s^{-\mu}}{\Gamma(1-\mu)}ds \tag{2}$$

The spatial-time dependent drug concentration is governed by the fractional Fokker-Planck equation:

$$\frac{\partial^{\mu}c(\chi,t)}{\partial\chi^2} = \frac{\partial^2}{\partial\chi^2}[D_{\mu}c(\chi,t)] - \frac{\partial}{\partial\chi}[D_{\mu}F(\chi)c(\chi,t)] \tag{3}$$

for $c(\chi, 0) = c_0(\chi)$ and F a constant external signal. However, drug infusion varies in time, hence generalisation to time varying signals $F(\chi, t)$ is

$$\frac{\partial c(\chi,t)}{\partial\chi^2} = \frac{\partial^2}{\partial\chi^2}[D_{\mu}D_t^{1-\mu}c(\chi,t)] - \frac{\partial}{\partial\chi}[D_{\mu}F(\chi,t)D_t^{1-\mu}c(\chi,t)] \tag{4}$$

for $c(\chi, 0) = c_0(\chi)$, and the $1-\mu$ the Riemann-Liouville fractional derivative:

$$D_t^{1-\mu}f(t) = \frac{d}{dt}\int_0^t f(t-s)\frac{s^{-\mu-1}}{\Gamma(\mu)}ds \tag{5}$$

If spatial variations are introduced in (4) replacing $\mu \to \mu(\chi, t)$, then for small spatial volumes h and small time intervals τ, we have in (4) that $D_{\mu}(\chi) \approx \frac{h^2}{2\tau^{\mu(\chi)}}$ [8,41,42]. The rate parameter μ can vary in time as $\mu(\tau) = \frac{\mu_0}{\tau_0+\tau}$, as motivated by NM crowding: the longer the living organisms stay in a particular site, the smaller becomes the escape probability to another medium.

Transport with nonlinear interaction

In this section we limit to the case when the escape rates $e(\chi, \tau)$ of drug molecules from the medium are influenced solely by internal factors. A sub-diffusive drug trapping effect at position χ occurs when $e(\chi, \tau)$ is a decreasing function in t. The escape rate in continuous time random walk framework assumes a waiting time distribution with density $\rho(\chi, \tau)$ for the times between (left,right) jumps of molecules and tail function $\Xi(\chi, \tau) = \int_{\tau}^{\infty}\rho(\chi, \tau')d\tau'$.

Suppose that we use the Mittag-Leffler function E_{μ} to describe the dynamic escape rate term

$$\Xi(\chi, \tau) = E_{\mu}[-(t/\tau_0)^{\mu}] \tag{6}$$

which depends on time, hence memory effect included to described residence time and recall that $0 < \mu < 1$. Alternatives to the Mittag-Leffler distribution function can be found in [41]. The original drug clearance rate will affect the drug concentration according to a sub-diffusive trapping dynamic:

$$\delta(\chi, t) = \tau_0^{-\mu}D_t^{1-\mu}c(\chi, t) \tag{7}$$

which is derived in [8]. A further generalisation to the fractional adhesion-diffusion equation is given in [41], but since we are not interested to model local spatial distribution, it is not used hereafter. In the context of drug infusion in PK compartmental models we can make a gross assumption of space as being bounded volumes of slow acting medium (i.e. muscle and fat compartments).

Assume now that the slow acting PK model compartment behaves as a two-state Markovian random process, where the transition probabilities γ_1 and γ_2 are constant in time. This simplifies the equations but maintains the necessary properties for the purpose of our work. Generic equations for mean density particles in mobile state $\rho_1(x, t)$ (i.e. drug diffuses and clears from medium) and in trapped state $\rho_2(x, t)$ are:

$$\begin{aligned}\tfrac{\partial\rho_1}{\partial t} &= a\rho_1 - \gamma_1\rho_1 + \gamma_2\rho_2\\ \tfrac{\partial\rho_2}{\partial t} &= -r_2(\rho_2)\rho_2 - \gamma_2\rho_2 + \gamma_1\rho_1\end{aligned} \tag{8}$$

where the reaction rate r_2 depends on the density of particles ρ_2, and a is here an input transport rate, for instance the rate at which the drug enters the compartment.

Proposed PK model for anesthesia

Drug absorption in the body is achieved by a complex diffusion process across various cell membranes. Diffusion plays an important role in many processes in living organism, therefore, is a key feature in the course of drug distribution in the human body. It is well known that diffusion processes are (classically) described by Fick's first law [43]. The research performed in the last decades suggest that this is not always the case and diffusion processes can deviate from this law. They can be either faster (super-diffusion) either slower (sub-diffusion) processes. This new approach of diffusion processes is described as anomalous diffusion. In biomedical literature several datasets have been characterized by power-laws, gamma functions or fractal kinetics, and their use has been justified by the presence of the anomalous diffusion [11,28,44].

Pharmacokinetic/pharmacodynamics models represents an important step in the process of drug development and this modeling tool also brought a significant contribution to anesthesia. Such models are a set of mathematical equations used to predict the drug effect in time. In its classical version, compartmental analysis is based on mathematical models, typically in the form of systems of ordinary differential equations that are widely used to characterize the uptake, distribution and elimination of a drug into the body. A schematic representation of a three compartmental model is presented in Fig. 1.

In Fig. 2 a conceptual representation of the fat cells in the human body. Patients with an increase BMI present a larger fat cell size but no increase in total fat cell compared to the lean subjects. However, in the situation of obese patients an increase in the cell

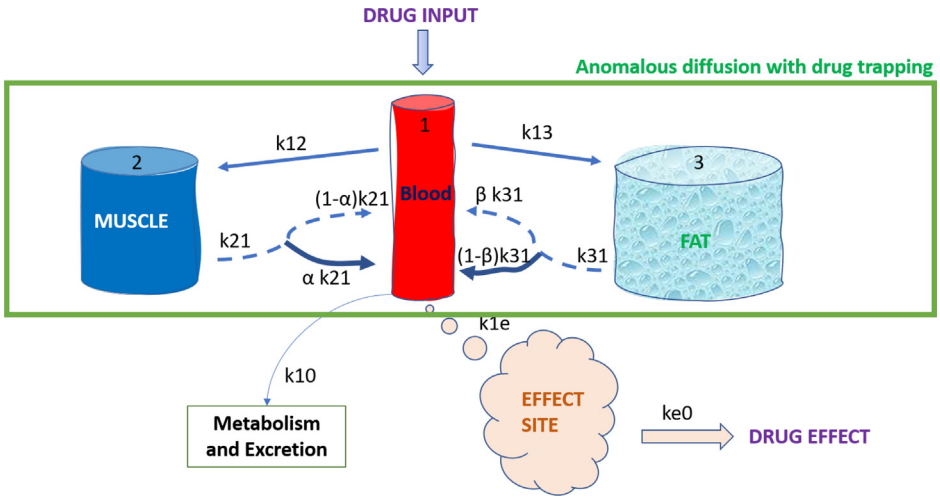

Fig. 1. Illustration of a three-compartment model depicting the drug trapping concept.

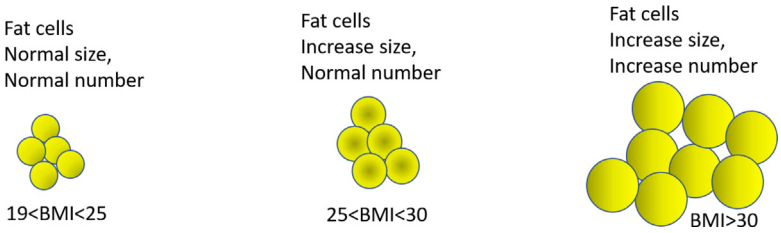

Fig. 2. A conceptual representation of the fat cells in the human body.

number as well as increased size of fat cell is observed when compared to the lean subjects. The larger the number and size of fat cells the slower the drug is eliminated from the tissue and implicitly drug accumulation occurs. In the case of long-term anesthesia patients they represent a high-risk for drug trapping as they have to receive drugs for a very long period of time, increasing the risk for drug overdosing and adverse effects. To overcome this, a new pharmacokinetic model to describe drug diffusion between compartments is presented in this paper. As opposed to classical model, the proposed approach includes two fractional order terms (i.e. α and β) representing the fractal kinetics due to trapping and residence times. Hence, the diffusion rates are no longer constant in time and the compartments are no longer homogeneous.

Fig. 3 illustrates the concept of drug trapping of drug molecules in tissues. Fat tissue drug trapping may account for secondary effects (days, weeks, months) in patients undergoing long term general anesthesia. New approaches, such as the fraction al order pharmacokinetic models may enable a more accurate prediction of drug profiles and can provide a new basis foo optimizing drug administration (e.g. avoiding over dosing).

Here we address the modeling of the PK model taking into account in the model the drug trapping effect. In its classical form (i.e. when α and β are 0) the equations governing the drug transfer from plasma compartment to the peripheral compartments (muscle (slow dynamics) and fat (very slow dynamics)) are given in (9).

$$\begin{aligned}\dot{q}_1(t) &= K_{21}q_2(t) + K_{31}q_3(t) - K_{12}q_1(t) - K_{13}q_1(t) + U(t)\\ \dot{q}_2(t) &= K_{12}q_1(t) - K_{21}q_2(t)\\ \dot{q}_3(t) &= K_{13}q_1(t) - K_{31}q_3(t)\end{aligned} \tag{9}$$

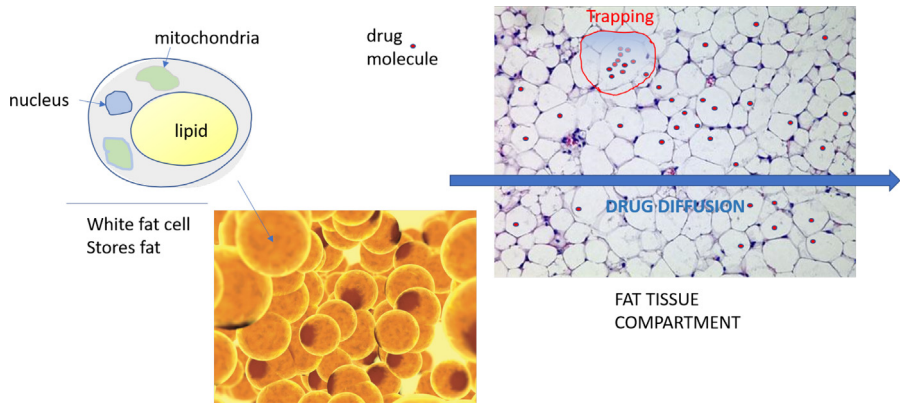

Fig. 3. Conceptual representation of distribution of tissue dynamics with various drug trapping and residence times in the fat compartment.

where: q_1, q_2 and q_3 [mg] denotes the amount of drug in the three compartments. The peripheral compartments 2 (muscle) and 3 (fat) represents the drug exchange of the blood with well and poorly diffused body tissues. The parameters K_{ij} for $i \neq j$, denote the drug transfer frequency from the $i-th$ to the $j-th$ compartment and $U(t)$ [mg/s] is the infusion rate of the analgesic drug into the first compartment.

The parameters of the pharmacokinetic models depend on age, weight, height and gender [45] and can be calculated for Propofol as follows:

$$\begin{aligned} &V_1 = 4.27[l] \quad V_3 = 238[l] \\ &V_2 = 18.9 - 0.391 \cdot (age - 53)[l] \end{aligned} \tag{10}$$

$$\begin{aligned} &C_{l1} = 1.89 + 0.0456(weight - 77) - 0.0681(lbm - 59) \\ &+0.0264(height - 177)[l/min] \\ &C_{l2} = 1.29 - 0.024(age - 53)[l/min] \\ &C_{l3} = 0.836[l/min] \end{aligned} \tag{11}$$

$$k_{10} = \frac{C_{l1}}{V_1}[min^{-1}]; k_{12} = \frac{C_{l2}}{V_1}[min^{-1}]; k_{13} = \frac{C_{l3}}{V_1}[min^{-1}] \tag{12}$$

$$k_{21} = \frac{C_{l2}}{V_2}[min^{-1}]; k_{31} = \frac{C_{l3}}{V_3}[min^{-1}]; k_{e0} = 0.456[min^{-1}] \tag{13}$$

where *lbm* represent the lean body mass, C_{l1} is the rate (called also clearance rate) at which the drug is cleared from the body, C_{l2} and C_{l3} are the rates at which the drug is removed from the central compartment to the other two compartments by distribution.

The *lbm* for man and women is calculated using the following expressions:

$$lbm_m = 1.1 \cdot weight - 128 \cdot \frac{weight^2}{height^2} \tag{14}$$

$$lbm_f = 1.07 \cdot weight - 148 \cdot \frac{weight^2}{height^2} \tag{15}$$

Proposed fractal PK with memory

We address the use of fractional calculus tools to describe the diffusion phenomena in drug molecules. The focus of the paper is on the drug trapping and residence time occuring when a long time drug administration is required. Based on previous studies, we address this problem by means of fractional order PK models [46,38,47,48].

Compartmental models for pharmacokinetics (PK) have been generalized using fractional calculus in order to extend the systems to the form of fractional-order differential equations [36,38,35]. PK can be defined as the study of drug distribution in the body and it focuses on drug plasma (blood) amount changes. The plasma amount of any type of drug depends on three processes: absorption, distribution and elimination. These processes will make the amount of drug molecules to rise and fall according to their rates. Absorption is related to the movement of the drug into the bloodstream. Its rate depends on the physical characteristics of the drug and the drug's chemical formula. Distribution is defined as the process where a drug leaves the bloodstream and goes into neighboring organs and tissues.

Let us consider a three compartmental PK model to simulate and to indicate the benefits of using fractional kinetics in drug trapping problem. Starting from the model in (9) and changing the derivatives on the left hand side of equations with fractional derivatives of order n_1 and n_2 following the rationale proposed in [36] we obtain the following equations:

$$\begin{aligned} &\tau_1^{n_1-1} D_t^{n_1} q_1(t) = K_{21} q_2(t) + K_{31} q_3(t) - K_{12} q_1(t) - K_{13} q_1(t) \\ &\tau_2^{n_2-1} D_t^{n_2} q_2(t) = K_{12} q_1(t) - K_{21} q_2(t) \\ &\tau_3^{n_3-1} D_t^{n_3} q_3(t) = K_{13} q_1(t) - K_{31} q_3(t) \end{aligned} \tag{16}$$

where: τ_1, τ_2 and τ_3 represents the characteristic time for compartment 1, 2 and respectively compartment 3. The units of the parameters K_{ij} are different than the ones in Eq. (9). The introduction of τ leads to the dimensional homogeneity of fractional rate equations. Considering the initial conditions $q_3(0) = d_3 = 0$ $q_2(0) = d_2 = 0$ and $q_1(0) = d_1 = bolusinjection$.

After multiplying (16) with $\tau_1^{-n_1+1}$ and $\tau_2^{-n_2+1}$ respectively and redefining the model coefficients, the model becomes:

$$\begin{aligned} &D_t^{n_1} q_1(t) = k_{21} q_2(t) + k_{31} q_3(t) - k_{12} q_1(t) - k_{13} q_1(t) \\ &D_t^{n_2} q_2(t) = k_{12} q_1(t) - k_{21} q_2(t) \\ &D_t^{n_3} q_3(t) = k_{13} q_1(t) - k_{31} q_3(t) \end{aligned} \tag{17}$$

with: $\tau_1^{n_1-1} = \tau_2^{n_2-1}, k_{12} = K_{12}/\tau^{n_1-1} = K_{12}/\tau^{n_2-1}, k_{02} = K_{02}/\tau^{n_2-1}, k_{21} = K_{21}/\tau^{n_1-1}, k_{01} = K_{01}/\tau^{n_1-1}$. The fractional operator n can be temporary and locally different, however here we consider $n_1 = n_2 = n_3 = n$ for maintaining the mass balance, a generalized representation of (17) is given by:

$$\begin{aligned} &D_t^{n} q_1(t) = k_{21} q_2(t) + k_{31} q_3(t) - k_{12} q_1(t) - k_{13} q_1(t) \\ &D_t^{n} q_2(t) = k_{12} q_1(t) - k_{21} q_2(t) \\ &D_t^{n} q_3(t) = k_{13} q_1(t) - k_{31} q_3(t) \end{aligned} \tag{18}$$

The main characteristic of fractional derivatives, more specifically derivatives of positive real order, is the so called "memory effect" [49,50]. For compartmental models the general numerical solution of the fractional differential equation $D_t^n y(t) = f(y(t), t)$ can be expressed as:

$$y(t_k) = f(y(t_k), t_k) h^n - \sum_{j=1}^{k} c_j^n y(t_{k-j}) \tag{19}$$

where: $t_k = kh$, for $k = 1, 2, 3 \ldots .N$ samples and h is the sampling time. For our case the numerical solution is obtained by applying Eq. (19) on Eqs. (18) and it has the following form:

$$\begin{aligned} &q_1(t_k) = (k_{21} q_2(t_k) + k_{31} q_3(t_k) - k_{12} q_1(t_k) - k_{13} q_1(t_k)) h^n \\ &- \sum_{j=1}^{k} c_j^n q_1(t_{k-j}) \\ &q_2(t_k) = (k_{12} q_1(t_k) - k_{21} q_2(t_k)) \alpha(lmi, bmi, \gamma) h^n - \sum_{j=i}^{k} c_j^n q_2(t_{k-j}) \\ &q_3(t_k) = (k_{13} q_1(t_k) - k_{31} q_2(t_k)) \beta(lmi, bmi, \gamma) h^n - \sum_{j=i}^{k} c_j^n q_2(t_{k-j}) \end{aligned} \tag{20}$$

Relations (20) represent the fractional order compartmental model used further in this paper. The fractional order parameters α and β are as a function of patient parameters such as: lean body mass, body mass index and patient sensitivity to drug. Simulation were performed using the numerical solution from [49].

Open source patient simulator benchmark

The simulations performed in this paper are cut-out from a comprehensive patient simulator for anesthesia and hemodynamic control [30]. Regulating depth of anesthesia using computer control algorithms have been published recently [51,52]. We are at the very beginning of what we call - a new era of personalized medicine - enabled by advances in computer technology and powerful information technology processing tools. In an effort to

provide the cross-disciplinary community with suitable and accessible tools for systematic analysis of pros- and cons- of various control algorithms, a patient simulator has been programmed in Matlab/Simulink from MathWorks(R) software platform [30]. This is an open source patient simulator, where the community can set, add and modify its components as know-how and insight become available. Ensuring clinical relevant progress is a challenging task which requires a systematic comparison of algorithms, thereby demanding availability of adequate simulation tools before transferring results to clinical practice for testing. The novelty is the provision of the patient simulator as to date no such tools has been previously reported in literature for the systems and control community. The originality of the approach is the inclusion of synergy effects, antagonist effects, patient variability, clinical value intervals, nociceptor stimulation disturbance [53,54], drug trapping models and co-simulation of anesthestic and hemodynamic states along with their complex interactions. The aim of developing such a patient simulator is to provide the means and to encourage the research community to work in a systematic and fair-to-compare context while developing computer based control of multi-drug anesthesia regulatory problems.

Proposed calibration protocol

The ultimate goal is to provide a solution which can be easily adapted from blood plasma concentrations of hypnotic or opioid drug measured in patients at regular daily intervals. Calibration should be triggered at the moment that model prediction of plasma concentration differs to the actual measured concentration with more than 15%, this being a limit in robustness of inter-patient variability [55,56]. The proposed calibration protocol is given below.

1. Daily measure plasma concentration in blood for anesthestic drugs (hypnotic drug: propofol, opioid drug: remifentanil) - consistent same hour for measurement e.g. 7am
2. Perform model identification
3. Repeat daily/weekly depending on drug trapping risk level - this risk is proportional with BMI.
4. Evaluate if updated PK model prediction differs with more than 15% and if so, reiterate from step 1.

Results

Given our past expertise and studies in cooperation with Ghent University Hospital Belgium and University Medical Center Groningen The Netherlands, a database of patient profiles has been created to mimic typical patients to include inter-patient variability. The details for the PK models are given in Table 1 [57,58].

In Fig. 4 the simulation results for a classical modeling approach of Propofol diffusion using a three compartmental model (depicted in Fig. 1) are presented. In Fig. 5 the results obtained using the fractional order model from Eqs. (20) is presented. Same value for the fractional order operator has been used (i.e. $n = 0.5$). It can be observed that the in comparison with the classical (integer order) PK model (i.e. $n = 1$) the decrease of the drug in compartment 1 (blood) is faster. This is a very important property of the fractional order modeling approach that can be used to capture inter-patient variability.

Now let us look at compartment 2 and 3 with the proposed PK model to account for drug trapping. Here, we present the results for the very slow compartment (i.e. fat) where the drug diffusion occurs according to Fig. 4. More specifically, to describe the transfer of drug from compartment one to the fat compartment an additional fractional order parameters has been considered (i.e. β). The results for this approach are shown in Fig. 6. In this figure drug trapping and residence times for the fat compartment for the patients database presented in Table 1 are depicted. An analysis on the effect of the β parameter (which is related to the lbm and bmi) has been performed and the results are depicted in Fig. 7.

Discussion

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

Table 1
Patient Database including biometric data and patient sensitivity to drug (i.e. γ).

Index –	Age (yrs)	Height (cm)	Weight (kg)	lbm –	γ –
1	74	164	88	60	3
2	67	161	69	53	2
3	75	176	101	69	1.6
4	69	173	97	67	2.5
5	45	171	64	52	1.78
6	57	182	80	62	2.8
7	74	155	55	44	3.5
8	71	172	78	60	2.9
9	65	176	77	60	1.88
10	72	192	73	62	3.1
11	69	168	84	60	3.1
12	60	190	92	71	2.1
13	61	177	81	63	3
14	54	173	86	62	3
15	71	172	83	63	1.9
16	53	186	114	77	1.6
17	72	162	87	59	2.9
18	61	182	93	69	1.78
19	70	167	77	58	3.1
20	69	168	82	60	1.6
21	69	158	81	55	2.1
22	60	165	85	60	2.51
23	70	173	69	56	3.1
24	56	186	99	73	2.3

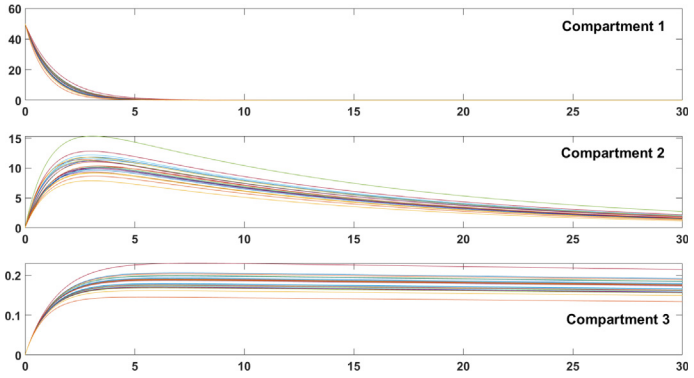

Fig. 4. Propofol amount as a function of time for compartment 1, 2 and respectively 3 for the patients from Table 1 using the model from (9).

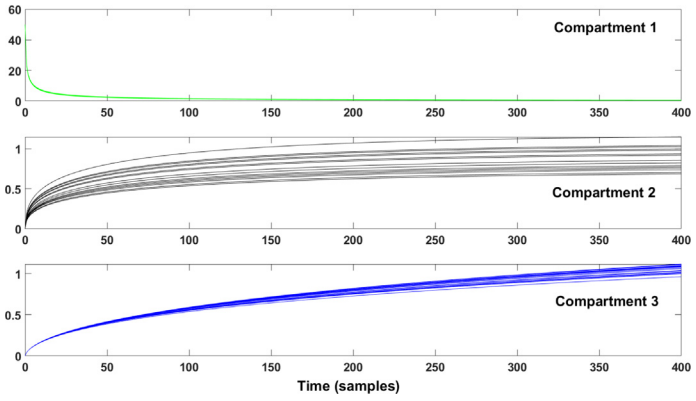

Fig. 5. Propofol ammount as a function of time for compartment 1, 2 and respectively 3 for the patients from Table 1 using the model from (20).

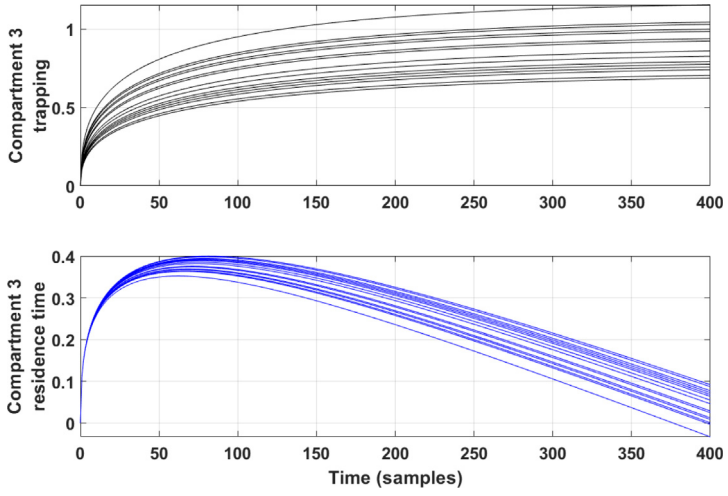

Fig. 6. Trapping and residence time for the slow compartment for the patient database from Table 1 considering the proposed modeling approach.

have been reported in [47]. 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 underwent surgery with general anaesthesia, or following cancer treatment therapies. These new theoretical concepts and PK models may enable a different, novel perspective of drug drug kinetics. Such models more accurately predict the observed drug profiles and can provide an new basis for optimizing treatment.

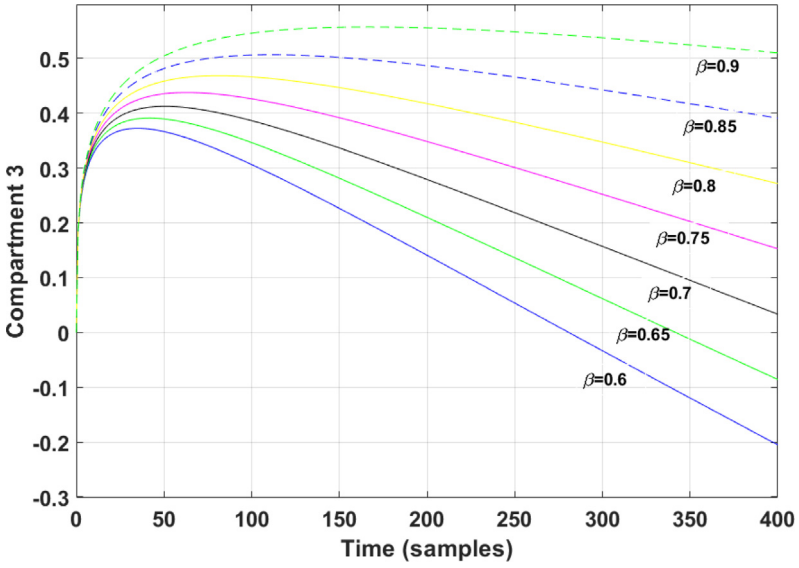

Fig. 7. Effect of varying the fractional order operator (β).

Drug tissue trapping has been addressed also in [59] using fractional kinetics and data on amiodarone from [4]. Significant differences in linear or logarithmic drug intake profiles have been observed in numerical simulations, suggesting drug accumulation and inherent side affects in patient well-being. The paper from [59] proposes a dosing regime to stabilize the plasma concentration of amiodarone when fractional PK models are used. Applications to cancer treatment using the doxorubicine have also been performed with similar conclusions [60].

The nonlinear dynamic effects associated with anomalous diffusion are well described in literature and applications in biology and medicine are prevalent. Recent works abide to the community the acknowledgement of power law functions and time dependent rates for drug absorption and clearance [61,41]. In this work we adapt existing tools readily available from the interdisciplinary community to the purpose of calibrating PK models for general anesthesia.

A rigorous mathematical formalism is not the objective of this paper, as these are already available in literature for specific detailed effects of anomalous diffusion. Instead, a minimal formalism suggesting the link to analytical solutions proposed in literature [41,8,62] is used to provide a basis of conceptual representation in area of applied medicine. The PK model we use to illustrate the results is a broadly used in clinical practice, while the added features capturing effects such as drug trapping and time varying clearance rates are intuitive yet justified with adjacent literature works [46,40,61].

Covid-19 anesthetized patients provide a prolific environment to study the anomalous diffusion as a result of long-term drug infusion management therapy. This induces strong time variability of pharmacokinetic (PK) compartmental model time constants (drug absorption and clearance rates). The changes in the PK balance of uptake/clearance rates affect the pharmacodynamic (PD) part (i.e. drug effect). Since the dosing standard is based on such PK-PD models to indicate a target controlled infusion (TCI) rate of anesthetic drugs, having an accurate model is of life-saving importance [28]. If these models are not calibrated to the actual ongoing intra-patient dynamic variability, then the target controlled infusion management is biased and can have serious over-dosing effects which in turn contribute to increasing the already high Covid-19 mortality risk [29,56]. Our proposed model and protocol allows to get and use information in order to calibrate the PK-PD models and provide a more accurate drug infusion pattern. The solution is a non-invasive detection mechanism to trigger an alarm for calibrating the PK-PD model. We claim that the societal impact of the proposed PK model enables a higher rate of recovery in Covid-19 patients undergoing general anesthesia, while lowering the risk of mortality and increasing potential for faster recovery times. It also resolves potential Propofol drug shortages during pandemic outbreak [63].

Recent works have been also investigated the use of fractional order derivatives for modeling and analysis of COVID-19 epidemics [64,65]. In [64] the transmission dynamics of the new coronavirus have been provided in fractional order derivatives form. The proposed method provides sufficient information to understand the epidemic transmission. Moreover, the use of fractional order equations for epidemiological models has been applied also to other areas, such as diarrhea transmission dynamics based on real data [66]. In the last years the use of fractional order modeling tools have intensively employed in the area of biological systems. Recent works have proposed new differential operators which may open new research directions in the area of dynamical systems [67,68].

The proposers are not aware of any ongoing study of anomalous diffusion effects on drug trapping potential with inherent changes to the PK-PD model variable values in extremely long term anesthesia Covid-19 patients. We speculate the presence of twofold major reasons. Firstly, because prior to Covid-19 pandemic the longest term anesthesia was rather limited in time to several hours, e.g. in bariatric surgery, some transplant surgery. Secondly, because the tools used to model anomalous diffusion in biological tissue uptake are only recently introduced in our interdisciplinary community [28,46]. We confidently expect that the proposed model delivers useful information to support further developments in PK-PD modelling in the cross-disciplinary community.

Conclusions

In this paper we revisited the existing compartmental modelling approaches and extended their usefulness by employing emerging tools from fractional calculus. The latest works have shown that fractional calculus tools can be successfully applied to investigate epidemiological situations [65,?,66,16,27]. Undoubt-

edly, the fractional kinetics approach outperforms the classical ODE models while maintaining the link to physiological phenomena. 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. In this paper the model from (20) has been simulated but other models can be also considered. 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. Long-term anesthetized patients are a prolific environment to dtudy the anomalous diffusion as a result of long-term infusion management therapy, which induces strong time variability of PK model time constants (e.g. drug absorption and clearance rates). Moreover, these changes in the PK model will also have an effect on the PD part (i.e. drug effect). Since standard dosing is based on such PK-PD models to indicate a target controlled infusion (TCI) rate of anesthetic drugs, having an accurate model is of life-saving importance. If these models are not calibrated to the actual ongoing intra-patient dynamic variability, then the TCI management is biased and can have serious over-dosing effects which in turn contribute to increasing the already high mortality risk in patients with the new virus. The proposed calibration protocol allows to get and use information in order to calibrate the PK-PD models and provide a more accurate drug infusion pattern. From societal standpoint a higher rate of recovery in Covid19 patients undergoing general anesthesia might be achiever, lowering the risk of mortality and increasing potential for faster recovery times.

The simulations performed in this study are cut-out from a a comprehensive patient simulator available for download on the following link Patient Simulator. It is to believe that the proposed model and developed patient simulator will open new directions of research in the field of anesthesia modeling and control.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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