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ORIGINAL PAPER

How to avoid unbounded drug accumulation with fractional pharmacokinetics

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Abstract A number of studies have shown that certain drugs follow an anomalous kinetics that can hardly be represented by classical models. Instead, fractional-order pharmacokinetics models have proved to be better suited to represent the time course of these drugs in the body. Unlike classical models, fractional models can represent memory effects and a power-law terminal phase. They give rise to a more complex kinetics that better reflects the complexity of the human body. By doing so, they also spotlight potential issues that were ignored by classical models. Among those issues is the accumulation of drug that carries on indefinitely when the infusion rate is constant and the elimination flux is fractional. Such an unbounded accumulation could have important clinical implications and thus requires a solution to reach a steady state. We have considered a fractional one-compartment model with a continuous intravenous infusion and studied how the infusion rate influences the total amount of drug in the compartment. By taking an infusion rate that decays like a power law, we have been able to stabilize the amount of drug in the compartment. In the case of multiple dosing administration, we propose recurrence relations for the doses and the dosing times that also prevent drug accumulation. By introducing a numerical discretization of the model equations, we have been able to consider a more realistic two-compartment model with both continuous infusion and multiple dosing administration. That numerical model has been applied to amiodarone, a drug known to have an anomalous kinetics. Numerical results suggest that unbounded drug accumulation can again be prevented by using a drug input function that decays as a power law.

Keywords Fractional kinetics · Compartmental models · Drug accumulation · Amiodarone

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Introduction

Diffusion processes in complex systems are often observed to deviate from standard laws. The discrepancies can occur both for the time relaxation that can deviate from the classical exponential pattern and for the spatial diffusion that can deviate from Fick's second law. The resulting diffusion processes are then no longer Brownian and cannot be represented accurately by classical models. Instead, models based on fractional-order differential equations (FDE's) can provide a more realistic description of the system behavior [24]. Such models have received an increasing attention in recent years and have been used to model a wide range of problems in surface and subsurface hydrology [2, 11, 25], plasma turbulence [9, 10], finance [6, 32], epidemiology [4, 19] and ecology [8, 18].

Fractional-order differential equations have recently been applied in pharmacokinetics (PK) as well. Following the seminal work of Dokoumetzidis and Macheras [12], a number of other studies have followed [13, 14, 26, 28–31, 35, 36]. These studies have been motivated by several examples of drugs PK that do not follow classical laws. These include bone-seeking elements like ^{47}Ca [1],

amiodarone [34], cyclosporin [7], mibefradil [15] and diclofenac [28]. All these datasets depart from the exponential decay predicted by classical models and instead exhibit a power-law time profile. Such a power law is the hallmark of a non-Markovian time dynamics and memory effects. In the long time limit, power laws decay more slowly than exponentials and there is therefore a risk that classical models could underestimate the amount of drug remaining in an organism. Hence, the use of fractional PK models could provide a better estimation of adverse drug reactions by spotlighting issues that were ignored by classical models.

One of those issues is drug accumulation. Dokoumetzidis et al. [14] have shown that a simple one-compartment PK model with constant intraveinous (IV) infusion and fractional elimination predicts an unbounded drug accumulation while classical models predict that the system reaches a steady state. Drug accumulation is obviously necessary to reach the drug concentration required to maximize the therapeutic effectiveness of the medication. However, if the drug concentration does not reach a steady state, it will exceed the therapeutic window and reach toxic levels. That could have serious clinical implications and clearly shows how the behavior of a system can be deeply modified when the kinetics becomes fractional.

The goal of this paper is to propose a way to prevent drug accumulation in fractional PK models. We consider the one-compartment model used by Dokoumetzidis et al. [14] with both continuous IV infusion and multiple IV bolus dosing and show how to modulate the drug input in order to avoid drug accumulation. Analytical results can be derived for a one-compartment model. Further, we present a flexible numerical scheme to solve FDE's. That scheme is used to solve a two-compartment model with continuous infusion and multiple dosing administration. Our model is then applied to a real PK example by considering the kinetics of amiodarone under different multiple-dosing regimens.

Problem statement and analytical results

To illustrate the issue of unbounded drug accumulation for fractional PK and derive an input function that prevents such an accumulation, we shall consider a simple one-compartment system with a time-dependent input and a fractional elimination. This system is schematically represented in Fig. 1. Such a simple system is of course of a rather limited practical interest as it does not even distinguish regions with a well-developed blood supply from the ones with a lower blood flow. However, its inherent simplicity will allow us to gain some insight on the processes at play and derive results that will be applicable in more realistic systems.

The equation governing the time evolution of the amount of drug in the compartment, $A(t)$, can be expressed as follows

$$\frac{\mathrm{dA}}{\mathrm{d}t} = f(t) - k_{10}\,{}_0D_t^{1-\alpha}A, \quad A(0) = 0, \tag{1}$$

where $f(t)$ is an arbitrary input function with units of mass/time, k_{10} is a fractional elimination rate constant with units of time$^{-\alpha}$, $\alpha \in]0, 1]$ is the fractional order of the elimination process and ${}_0D_t^{1-\alpha}$ is a fractional time derivative of order $1 - \alpha$. It should be noted that we have followed the approach of Dokoumetzidis et al. [14] to fractionalize the model equation. That approach does not change the order of the left-hand side derivatives but instead fractionalizes the fluxes in the right-hand side. By doing so, each flux can have a different order without any inconsistencies between incoming and outgoing fluxes in multi-compartment systems. Furthermore, that approach allows us to keep an input function with units of mass/time and not mass/time$^{\alpha}$. The time t is always assumed to be positive.

The fractional time derivative in Eq. (1) is defined in the Riemann-Liouville sense as follows:

$${}_0D_t^{1-\alpha}A(t) = \frac{1}{\Gamma(\alpha)}\frac{\mathrm{d}}{\mathrm{d}t}\int_0^t \frac{A(\tau)}{(t-\tau)^{1-\alpha}}\mathrm{d}\tau,$$

where Γ is Euler's gamma function. Fractional derivatives can also be defined in the Caputo sense as follows:

$${}_0^CD_t^{1-\alpha}A(t) = \frac{1}{\Gamma(\alpha)}\int_0^t \frac{A'(\tau)}{(t-\tau)^{1-\alpha}}\mathrm{d}\tau,$$

where the prime symbol denotes a first-order derivative. Both derivatives are connected through the following relation: ${}_0D_t^{1-\alpha}A(t) = {}_0^CD_t^{1-\alpha}A(t) + \frac{A(0)t^{\alpha-1}}{\Gamma(\alpha)}$ if $\alpha \in]0, 1]$. Caputo derivatives are often preferred to Riemann-Liouville derivatives as they are easier to handle and have a more physical interpretation. In particular, the Caputo fractional derivative of a constant is zero, which is not the case with the Riemann-Liouville derivative. The Laplace transform of the Caputo derivative has the following expression:

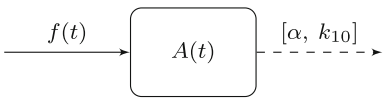

Fig. 1 Schematic representation of a one-compartment model, where $A(t)$ is the amount of drug in the compartment, $f(t)$ is the drug input function and k_{01} is the fractional elimination rate. The *plain arrow* represents a classic kinetics of order 1 while the *dashed arrow* represents a slower fractional kinetics of order $\alpha < 1$

$$\mathcal{L}\left\{{}_0^C D_t^{1-\alpha} A(t), s\right\} = s^{1-\alpha}\hat{A}(s) - s^{-\alpha}A(0),$$

if $\alpha \in]0, 1]$. In our example, we consider an homogeneous initial condition and hence both derivatives are exactly equivalent. That will allow us to use the Laplace transform of a Caputo derivative to derive analytical results. More details on fractional derivatives and their applications can be found, for instance, in [5, 20, 22, 23].

Constant rate input leads to unbounded drug accumulation

To illustrate the potential clinical issues associated with fractional kinetics, we consider the case of a constant rate input in Eq. (1), *i.e.* $f(t) = k_{01}$, where k_{01} has units of mass/time. That case has first been discussed by Dokoumetzidis et al. [14]. In what follows, we reproduce their results in order to build upon them in the following sections. For a constant rate input, the analytical solution can be derived by writing the model equation in the Laplace domain:

$$s\hat{A}(s) - A(0) = \frac{k_{01}}{s} - k_{10}\left(s^{1-\alpha}\hat{A}(s) - s^{-\alpha}A(0)\right).$$

Since $A(0) = 0$, we simply end up with

$$\hat{A}(s) = \frac{k_{01}s^{\alpha-2}}{s^\alpha + k_{10}}.$$

To compute the inverse Laplace transform of that expression, we can use the following result from Podlubny [27]:

$$\mathcal{L}^{-1}\left\{\frac{s^{\alpha-\beta}}{s^\alpha + k}\right\} = t^{\beta-1}E_{\alpha,\beta}(-kt^\alpha),$$

where $E_{\alpha,\beta}$ is the two-parameter Mittag-Leffler function defined as $E_{\alpha,\beta}(z) = \sum_{k=0}^{\infty}\frac{z^k}{\Gamma(\alpha k+\beta)}$. By taking $\beta = 2$ in the above expression, we easily obtain:

$$A(t) = k_{01}tE_{\alpha,2}(-k_{10}t^\alpha). \tag{2}$$

It is then interesting to study the behavior of that solution when $t \to \infty$. To compute that limit, we can use the asymptotic expansion of the Mittag-Leffler function given by Podlubny [27]:

$$E_{\alpha,\beta}(z) = -\sum_{k=1}^{p}\frac{z^{-k}}{\Gamma(\beta-\alpha k)} + \mathcal{O}\left(|z|^{-1-p}\right), \quad \text{for } |z| \to \infty, \tag{3}$$

and an arbitrary integer $p > 1$. By applying that result to Eq. (2) and keeping only the first term in the sum since all the other terms vanish when $t \to \infty$, we can express the limit as follows:

$$\begin{aligned}\lim_{t\to\infty} A(t) &= \lim_{t\to\infty} k_{01}tE_{\alpha,2}(-k_{10}t^\alpha),\\ &= \lim_{t\to\infty}\frac{k_{01}}{k_{10}}\frac{t^{1-\alpha}}{\Gamma(2-\alpha)} = \infty \quad \text{if } \alpha < 1\\ &= \frac{k_{01}}{k_{10}} \quad \text{if } \alpha = 1\end{aligned}$$

This result clearly highlights the clinical issues that can result from a fractional drug kinetics. As soon as the fractional order α is smaller than 1, the drug starts accumulating indefinitely in the compartment and will eventually reach toxic levels if the treatment is not stopped soon enough. It is therefore important to investigate ways of preventing such an unbounded accumulation. This could be done by considering a non-constant input function $f(t)$.

Power-law decaying rate input stabilizes the amount of drug

Since power laws play a central role in fractional kinetics, we now consider a time-dependent drug input function that decays like a power law: $f(t) = k_{01}\, t^{-\xi}$, with $\xi > 0$. It should be noted that k_{01} now has units of mass/time$^{1-\xi}$. In that case, the Laplace transform of Eq. (1) reads

$$\begin{aligned}s\hat{A}(s) - A(0) &= k_{01}\Gamma(1-\xi)s^{\xi-1}\\ &\quad - k_{10}\left(s^{1-\alpha}\hat{A}(s) - s^{-\alpha}A(0)\right),\end{aligned}$$

since $\mathcal{L}\{t^\alpha, s\} = \frac{\Gamma(\alpha+1)}{s^{\alpha+1}}$. The Laplace transform of the solution is then:

$$\hat{A}(s) = k_{01}\Gamma(1-\xi)\frac{s^{\xi-1}}{s + k_{10}s^{1-\alpha}} = k_{01}\Gamma(1-\xi)\frac{s^{\xi+\alpha-2}}{s^\alpha + k_{10}}.$$

To invert that expression, we use the Laplace transform of the two-parameter Mittag-Leffler function given by Podlubny [27]:

$$\mathcal{L}\left\{t^{\alpha k+\beta-1}E_{\alpha,\beta}^{(k)}(\pm at^\alpha), s\right\} = \frac{k!s^{\alpha-\beta}}{(s^\alpha \mp a)^{k+1}}.$$

The model solution can then be expressed as follows:

$$A(t) = k_{01}\Gamma(1-\xi)t^{1-\xi}E_{\alpha,2-\xi}(-k_{10}t^\alpha),$$

where the parameter ξ still has to be adjusted so as to prevent the drug from accumulating indefinitely in the compartment.

By again using Eq. (3), we can compute the asymptotic behavior of the model solution:

$$\begin{aligned}\lim_{t\to\infty} A(t) &= \lim_{t\to\infty} k_{01}\Gamma(1-\xi)t^{1-\xi}\frac{(k_{10}t^\alpha)^{-1}}{\Gamma(2-\xi-\alpha)},\\ &= \frac{k_{01}}{k_{10}}\frac{\Gamma(1-\xi)}{\Gamma(2-\xi-\alpha)}\lim_{t\to\infty} t^{1-\alpha-\xi}.\end{aligned}$$

The drug concentration thus diverges if $\xi < 1 - \alpha$ and vanishes if $\xi > 1 - \alpha$. The only way to reach a non-zero

plateau is to take $\xi = 1 - \alpha$. In that case, the input function is

$$f(t) = k_{01}\ t^{-(1-\alpha)} \tag{4}$$

and the model solution reads:

$$A(t) = k_{01}\Gamma(\alpha)t^{\alpha}E_{\alpha,\alpha+1}(-k_{10}t^{\alpha}). \tag{5}$$

The amount of drug in the compartment then converges towards a plateau whose height is equal to $\frac{k_{01}}{k_{10}}\Gamma(\alpha)$. This steady-state value reduces to the classical result $\frac{k_{01}}{k_{10}}$ when $\alpha = 1$. Among the 3 parameters defining the steady state, only k_{01} can be adjusted through the infusion pump to set the level of the steady state within the therapeutic window. Fig. 2 shows both model solutions obtained with constant and power-law input functions.

Application to multiple IV bolus dosing

So far, we have only considered systems with a continuous drug input. However, many dosage regimens involve discrete dosing events separated by time intervals. This is for instance the case with multiple IV bolus dosing. The input can then be seen as a series of pulses separated in time. It can be represented by a set of doses $\{d_i\}_{i=0,1,\ldots}$ and a set of dosing times $\{T_i\}_{i=0,1,\ldots}$. From a mathematical point of view, the input function is then a sum of Dirac delta functions centered at each dosing time:

$$f(t) = \sum_{i=0}^{M} d_i\delta(t - T_i). \tag{6}$$

The issue is then to find out the set dosing times $\{T_i\}_{i=0,1,\ldots}$ that, for a given set of doses $\{d_i\}_{i=0,1,\ldots}$, stabilizes the amount of drug in the compartment.

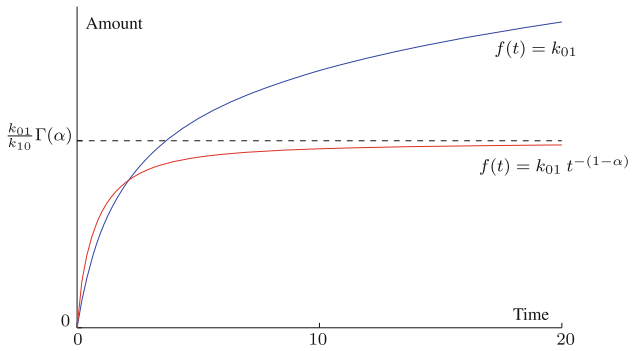

Fig. 2 The model solution (2) obtained with a constant rate input ($f(t) = k_{01}$) does not converge towards a steady state and thus leads to an unbounded drug accumulation. With the power-law input function $\left(f(t) = k_{01}\ t^{-(1-\alpha)}\right)$, the model solution (5) converges towards the steady state $A(t) = \frac{k_{01}}{k_{10}}\Gamma(\alpha)$. In this example, $\alpha = 0.8$ and $k_{01} = k_{10} = 1$. All quantities are dimensionless

In this case, it is more difficult to derive an analytical solution. However, by using a heuristic argument, it is possible to derive a good estimate of the dosing times. We can indeed use the results obtained for a continuous drug input and require that the integral over a dosing interval of the input function (6) be equal to the integral of the continuous power-law input function (4). Mathematically, this can be expressed as follows:

$$\int_{[T_{i-1},T_i[} \sum_{j=0}^{M} d_j\delta(t - T_j)\mathrm{d}t = d_{i-1} = \int_{[T_{i-1},T_i[} k_{01}\ t^{-(1-\alpha)}\mathrm{d}t = \frac{k_{01}}{\alpha}\left(T_i^{\alpha} - T_{i-1}^{\alpha}\right),$$

for $i = 1, 2, \ldots$ In the expression above, the parameter k_{01} does not make much sense in the case of bolus doses. However, by introducing a characteristic dose δ and a characteristic dosing interval $\Delta\tau$, we can express the fractional input rate as follows:

$$k_{01} = \frac{\delta}{\Delta\tau^{\alpha}}$$

since k_{01} has units of mass/time$^{\alpha}$. By doing so, we can derive recursion formulas for the doses and dosing times:

$$d_{i-1} = \frac{\delta}{\alpha\Delta\tau^{\alpha}}\left(T_i^{\alpha} - T_{i-1}^{\alpha}\right), \tag{7}$$

$$T_i = \left(T_{i-1}^{\alpha} + \alpha\frac{d_{i-1}}{\delta}\Delta\tau^{\alpha}\right)^{1/\alpha}, \tag{8}$$

for $i = 1, 2, \ldots$ and where we have assumed that the first dosing time is given, *e.g.* $T_0 = 0$.

In the particular case where all the dosing times are equispaced (*i.e.* $T_i = i\Delta\tau$ for $i = 0, 1, \ldots$), Eq. (7) reduces to

$$d_{i-1} = \frac{\delta}{\alpha}(i^{\alpha} - (i-1)^{\alpha}),$$

and δ can simply be interpreted as the constant dose that would have been used for a non-fractional system. Likewise, when all the doses are the same (*i.e.* $d_i = \delta$ for $i = 0, 1, \ldots$) Eq. (8) reduces to

$$T_i = \left(T_{i-1}^{\alpha} + \alpha\Delta\tau^{\alpha}\right)^{1/\alpha},$$

and $\Delta\tau$ can then be interpreted as the dosing interval that would have been chosen for a non-fractional system.

A high-order numerical scheme to solve FDE's

For models with more than one compartment or when the drug input function is not continuous or too complex, the solution can usually not be computed analytically. For those cases, it is necessary to rely on efficient numerical

schemes to obtain an approximate solution. As mentioned by Verotta [36], numerical schemes to solve fractional differential equations (FDE's) are still in their infancy and flexible algorithms for fractional PK applications are still missing. In this section, we present a novel approach to solve FDE's based on an expansion of the model solution in terms of Chebyshev polynomials. When the model solution is smooth, it yields an exponential rate of convergence.

The proposed numerical scheme first requires to approximate the exact solution $A(t)$ by a discrete solution $\tilde{A}(t)$ defined by the following expansion:

$$A(t) \approx \tilde{A}(t) = \sum_{j=0}^{N} A_j \phi_j(t),$$

in terms of unknown coefficients A_j and high-order basis functions ϕ_j $(0 \le j \le N)$. Since the problem is non-periodic, we are using Chebyshev polynomials as basis functions. In that case, ϕ_j is the Chebyshev polynomial of order j and N represents the polynomial order of the discrete solution. These polynomials have to be defined on the interval $[0,T]$ if the simulation is carried out from $t = 0$ until $t = T$. To compute the unknown coefficients A_j, we use the Galerkin method which amounts to replace $A(t)$ by $\tilde{A}(t)$ in the model equation and then orthogonalize that equation with respect to all the basis functions. The resulting discrete equations then read:

$$\int_0^T \phi_i \frac{\mathrm{d}\tilde{A}}{\mathrm{d}t}\,\mathrm{d}t = \int_0^T \phi_i f\,\mathrm{d}t - k_{10}\int_0^T \phi_i\, {}_0D_t^{1-\alpha}\tilde{A}\,\mathrm{d}t$$
$$\text{for } i = 0,\ldots,N.$$

By replacing $\tilde{A}$ by the expansion in terms of the coefficients A_j, we obtain:

$$\underbrace{\int_0^T \phi_i \frac{\mathrm{d}\phi_j}{\mathrm{d}t}\,\mathrm{d}t}_{\equiv T^1_{ij}} A_j = \underbrace{\int_0^T f\phi_i\,\mathrm{d}t}_{\equiv R_i} - k_{10}\underbrace{\int_0^T \phi_i\, {}_0D_t^{1-\alpha}\phi_j \mathrm{d}t}_{\equiv T^{1-\alpha}_{ij}} A_j,$$

where we have introduced the time derivative matrices T^1 and $T^{1-\alpha}$, and the reaction vector R. The final $(N+1)\times(N+1)$ system of discrete equations can finally be written in matrix form as follows:

$$\left(T^1_{ij} + k_{10}T^{1-\alpha}_{ij}\right)A_j = R_i.$$

It should be noted that by using an integral formulation, we can easily handle the weak singularity of the input function $f(t) = k_{01}\, t^{-(1-\alpha)}$ at $t = 0$. Since the basis functions are Chebyshev polynomials, their fractional derivatives can be computed analytically. All the integrals can also be computed analytically or up to machine precision with a quadrature rule. More details on spectral discretizations of FDE's can be found in [16, 17]. A Matlab implementation of this numerical scheme is available as a Supplemental File.

Thanks to the use of high-order basis functions, this numerical scheme can often achieve the same accuracy as more standard methods, like the finite difference method, with fewer degrees of freedoms. Since the basis functions span over the entire domain, the time derivatives matrices are always full matrices whatever the order of the derivative. Therefore the computational cost of the numerical scheme is not substantially increased when going from a integer-order to a fractional-order model. In each case, we have to handle a small full time-derivative matrix. The main disadvantage of this scheme is that high-order approximations are prone to spurious oscillations when the model solution is not smooth. In that case, a large number of degrees of freedom might be required to obtain a numerical solution close enough to the exact one. For those situations, more standard methods like the finite difference method might perform better.

To highlight the accuracy of the proposed numerical scheme, we have performed a convergence analysis by computing the relative L_2 error defined as

$$\text{error} = \sqrt{\frac{\int_0^T (A(t) - \tilde{A}(t))^2 \mathrm{d}t}{\int_0^T A(t)^2 \mathrm{d}t}}$$

for different values of N, the polynomial order of the discrete solution. We have considered the solution of Eq. (1) with $f(t) = pt^{p-1} + k_{10}\frac{\Gamma(p+1)}{\Gamma(p+\alpha)}t^{p+\alpha-1}$, where $p \in \mathbb{R}^+$, $\alpha = 0.8$ and $k_{10} = 1$. With that input function, the exact solution of Eq. (1) is simply $A(t) = t^p$. When p takes an integer value, the model solution is infinitely smooth over all the domain. However, when p takes a non-integer value, the solution is no longer infinitely smooth as the derivative of order $\lceil p \rceil$ diverges at $t = 0$. This has an impact on the convergence of the numerical scheme.

The convergence of the L_2 error is shown in Fig. 3. As expected, when p is integer, the convergence rate is exponential (left panel of Fig. 3). The numerical solution is equal to the exact one as soon as $N = p$. However, when p takes a non-integer value, the solution contains a singularity at $t = 0$ and convergence is only algebraic (right panel of Fig. 3). According to Darboux's principle, for each type of spectral expansion the rate of convergence is controlled by the strength of the gravest singularity in the complex plane (see [3] for more details). In our example, the exact solution is only $\mathcal{C}^3$ at $t = 0$ when $p = 3.8$. In that particular situation where the branch point is due to a

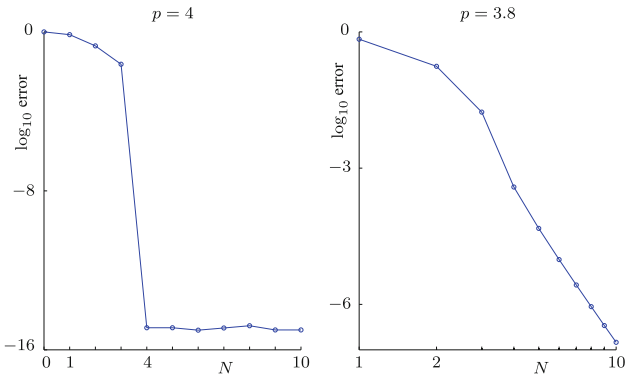

Fig. 3 Relative L_2 error between the numerical solution of Eq. (1) and the exact solution $A(t) = t^p$ with respect to the polynomial order N of the discrete solution. In this example, $\alpha = 0.8$ and $k_{10} = 1$. As expected, the error convergence is exponential when $p = 4$ as the exact solution is smooth (left panel). However, it is only algebraic when $p = 3.8$ as the exact solution has a singularity at $t = 0$ (right panel). According to Darboux's principle, the algebraic rate of convergence is controlled by the order of the singularity. Numerical results are in agreement with a theoretical convergence rate of $2p + 1 = 8.6$

fractional polynomial power and is located at a corner of the computational domain, it is possible to show that the asymptotic convergence rate will be $2\,\psi + 1$, where ψ is the power of the gravest singularity (see [3], Table 2.2). In this case, $\psi = p$ and the algebraic convergence rate should be $2p + 1 = 8.6$. Numerical results are in good agreement with that theoretical rate of convergence. It should be noted that even in that case, only 10 modes are needed for the error to fall well below 10^{-6}. These results do not depend on the value of α, the order of the fractional derivative.

Numerical examples

Thanks to the numerical scheme presented in the previous section, we are now in a position to study systems for which there are no analytical solutions available. The first example consists in the one-compartment system with multiple IV bolus dosing and fractional elimination considered in section 2.3. The second example consists in a two-compartment system with both multiple oral dosing and continuous IV infusion, and fractional transfer from the second compartment to the first one. The third example considers the PK of amiodarone, a drug known to have an anomalous kinetics. For all these examples, we compute the numerical solution and show the impact of the drug input power-law decay.

One-compartment system with multiple IV bolus dosing

In the case of a one-compartment system with multiple IV bolus dosing, the drug input function is given by Eq. (6). In what follows, we shall assume that the doses remain the same, *i.e.* $d_i = \delta$ for $i = 1, 2, \ldots$ and investigate the impact of the dosing times on the drug kinetics within the compartment. In a first case, we assume that the dosing intervals are constant, *i.e.* $T_i = i\Delta\tau$. In order to be able to make comparisons with the continuous-input case, we set $\delta = k_{01}\Delta\tau$ such that the integrals of the constant rate and multiple oral dosing input functions over a dosing interval are equal. In a second case, we apply the recursion (8) to obtain a dosage regimen where administrations are no longer equidistant in time. In order to be able to make comparisons with the previous case and with the continuous IV infusion case, we keep the same value for δ.

Figure 4 shows that indeed a model with multiple IV bolus dosing gives solutions in good agreement with the corresponding continuous IV infusion solutions. In this example, $\alpha = 0.5$ and $k_{01} = k_{10} = 1$. When the dosing interval is kept constant ($\Delta\tau = 2$), we observe a drug accumulation in the compartment similar to the one observed with a constant rate input and hence unbounded drug accumulation. When the time interval between two doses is no longer constant but follows the power-law recursion given by Eq. (8), drug no longer accumulates but reaches a plateau similar to the one reached when using a continuous input function that decays as a power law. It should be noted that the Dirac delta functions have been approximated by a finite support function in order to be able to discretize them with our numerical scheme. The consequence of such an approximation is that the jump in the solution value following a dose administration is not exactly vertical but slightly inclined. That somehow amounts to approximate the IV bolus dosing by an intermittent IV infusion.

Two-compartment system with continuous IV infusion and multiple oral dosing

In this second example, we consider a two-compartment system composed of a central compartment representing the general circulation and well perfused tissues connected to a peripheral compartment representing deeper tissues. This system is schematically represented in Fig. 5. In this example, we assume that the drug input arrives in the central compartment. The following transfer processes are considered: classical elimination from the central compartment at a rate k_{10}, classical transfer from the first compartment to the second at a rate k_{12} and fractional transfer from the second compartment to the first one at a rate k_{21} and fractional order $\alpha < 1$. Initially, both compartments are empty. The model equations can then be expressed as follows:

$$\begin{aligned} \frac{\mathrm{dA}_1}{\mathrm{d}t} &= f(t) - (k_{10} + k_{12})A_1 + k_{21}\,{}_0D_t^{1-\alpha}A_2, \\ \frac{\mathrm{dA}_2}{\mathrm{d}t} &= k_{12}A_1 - k_{21}\,{}_0D_t^{1-\alpha}A_2, \end{aligned} \tag{9}$$

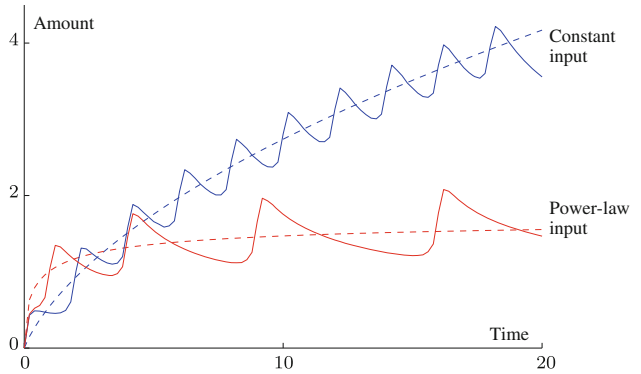

Fig. 4 The one-compartment model solutions obtained for multiple IV bolus dosing (*solid curves*) and for the corresponding continuous infusion (*dashed curves*). For a constant infusion rate or equidistant dosing times, there is a drug accumulation in the compartment. When dosing times are computed according to Eq. (8) or when the infusion rate decays like a power law, drug accumulation is controlled and the solution does not diverge. In this example, $\alpha = 0.5$, $k_{01} = k_{10} = 1$ and $\Delta\tau = 2$. All quantities are dimensionless

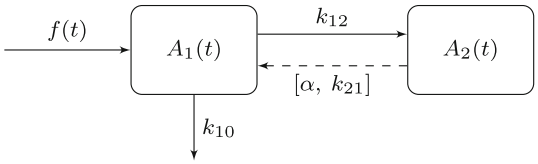

Fig. 5 Schematic representation of a two-compartment PK model, where $A_i(t)$ is the amount of drug in the compartment i, $f(t)$ is the drug input function to compartment 1 and k_{ij} are transfer rate coefficients from compartment i to j. The *plain arrows* represent a classic kinetics of order 1 while the *dashed arrow* represents a slower fractional kinetics of order $\alpha < 1$

where A_1 and A_2 represent the amount of drug in compartments 1 and 2 and $f(t)$ is the drug input function to compartment 1. The initial condition is $A_1(0) = A_2(0) = 0$.

In what follows, we consider four different cases that correspond to the combination of continuous IV infusion and multiple oral dosing with a constant and a power-law time evolution of the drug input. In the case of an IV infusion, the drug arrives in the central compartment in exactly the same way as for the one-compartment model. However, in the case of multiple oral absorption, it is more realistic to assume that the drug arrives in an imaginary compartment corresponding to the gastrointestinal tract and is then transferred to the central compartment. We assume that this transfer from the gastrointestinal tract has a classical kinetics and takes place at a rate k_{01}. For a dose δ absorbed at time T_i, the corresponding drug input in the central compartment can be expressed as:

$$f_i(t) = F\delta k_{01} H(t - T_i) e^{-k_{01}(t-T_i)},$$

where $H(t)$ is Heaviside step function and F is the bioavailable fraction of the absorbed dose. The input functions corresponding to the four cases can be summarized as follows:

	continuous IV infusion	**multiple oral dosing**
constant in time	$f(t) = k_{01}$	$f(t) = \sum_{i=1}^{M^c} F\delta k_{01} H(t - T_i^c) e^{-k_{01}(t-T_i^c)}$
power − law in time	$f(t) = k_{01} t^{-(1-\alpha)}$	$f(t) = \sum_{i=1}^{M^p} F\delta k_{01} H(t - T_i^p) e^{-k_{01}(t-T_i^p)}$

where $T_i^c = i\Delta\tau (i = 0, 1, \ldots), \delta = k_{01}\Delta\tau$ and the dosing times $T_i^p (i = 1, 2, \ldots)$ are given by the recursion (8) with $T_0^p = 0$.

The time evolution of the drug content in the second compartment is shown in Fig. 6 for the following parameter values: $\alpha = 0.5$, $k_{10} = 1$, $k_{12} = 0.8$, $k_{21} = 0.7$, $F = 1$ and $\Delta\tau = 5$. It can be seen that these results are qualitatively similar to the ones obtained for a one-compartment system. Although this system is different, numerical results suggest that drug accumulation can again be prevented by considering a drug input that decays like a power law. The solutions obtained for continuous IV infusion and a multiple oral absorptions show similar trends. By allowing the drug input to decay as a power law or, equivalently, letting the dosing intervals increase like a power law, the drug content in the second compartment no longer increases indefinitely but instead reaches a plateau. The height of the plateau cannot be expressed analytically in terms of k_{01}. However, an optimization procedure could be used to solve the inverse model and hence estimate the value of k_{01} that would yield the desired steady state. Popović et al. [28] have used the Particle Swarm Optimization algorithm for a similar problem.

Evaluation of three multiple dosing regimens of amiodarone

In this final example, we use the two-compartment model described by Eq. (9) to examine the effect of three different dosing regimens of amiodarone, a drug known to have an anomalous kinetics. Amiodarone is an antiarrhythmic agent

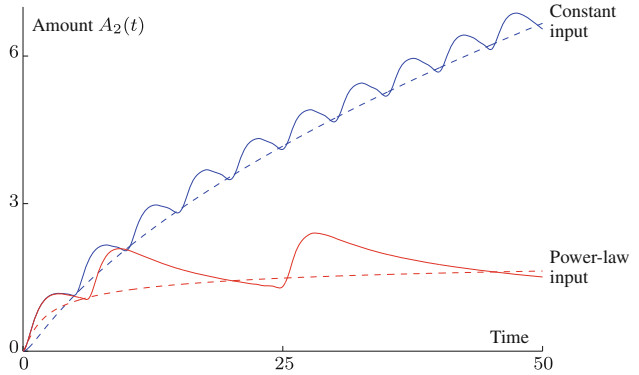

Fig. 6 For the two-compartment model (9), drug accumulation can again be prevented by considering a drug input that decays as a power-law. The model solution in the second compartment, $A_2(t)$, is shown for continuous IV infusion (*dashed curves*) and the multiple oral dosing corresponding to the exponential input from the gastrointestinal tract to the central compartment (*solid lines*). In this example, $\alpha = 0.5$, $k_{10} = 1$, $k_{12} = 0.8$, $k_{21} = 0.7$, $F = 1$ and $\Delta\tau = 5$. All quantities are dimensionless

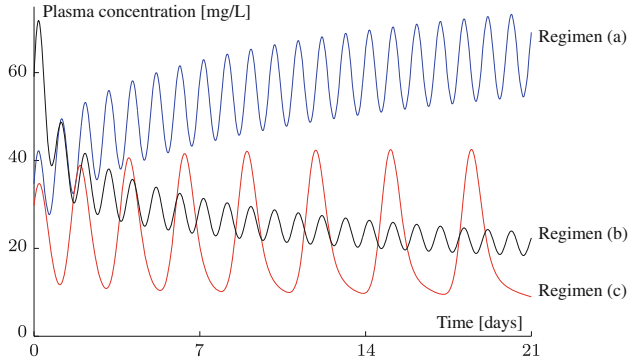

Fig. 7 Amiodarone plasma concentrations resulting from the following multiple IV dosing regimens: (**a**) constant doses δ and constant dosing intervals $\Delta\tau$, (**b**) constant dosing intervals $\Delta\tau$ and doses that decrease according to Eq. (7) and (**c**) constant doses δ and dosing intervals that increase according to Eq. (8). Regimen (**a**) leads to an increasing drug concentration while regimens (**b**) and (**c**) stabilize the drug concentration. In this example, $\delta = 400$ mg and $\Delta\tau = 1$ day

that is used to treat ventricular arrhythmias and atrial fibrillation. It has been known for a long time that amiodarone plasma concentration does not converge towards a steady state following multiple dosing because of its tendency to accumulate in deeper tissues [21]. Classical PK models have proved unable to describe the long-term kinetics of the drug. Those observations lead to the development of non-classical PK models based on fractal kinetics [37] or fractional derivatives [12].

To parametrize the model, we use the parameter estimates computed by Dokoumetzidis et al. [14] from the amiodarone IV database of Holt et al [21]. That database has been obtained during a single-dose study that involved four healthy volunteers who received a 400 mg dose of amiodarone as a 10-min IV infusion. In our example, we look at the amiodarone plasma concentration that would result from the following multiple dosing regimens: (a) constant doses and equispaced dosing times, (b) equispaced dosing times and doses that decrease according to Eq. (7), and (c) constant doses and dosing times that increase according to Eq. (8). The reference values of the dose and dosing interval are $\delta = 400$ mg and $\Delta\tau = 1$ day. This means that with regimen (a), the patient receives an IV bolus dose of 400 mg each day during all the duration of the treatment. The parameters estimates taken from [14] are $k_{10} = 1.4913$ days^{-1}, $k_{12} = 2.9522$ days^{-1}, $k_{21} = 0.4854$ days$^{-\alpha}$ and $\alpha = 0.5870$. We assume that the plasma volume is 3 L and that the treatment takes place during 21 days.

Figure 7 shows the time evolution of the drug plasma concentration for the three dosing regimens. For regimen (a), we observe a steady drug accumulation characteristic of an anomalous PK. It suggests that the drug concentration does not converge towards a steady state and might eventually reach toxic levels if the treatment is not stopped soon enough. For regimen (c), the doses are still constant and all equal to 400 mg but the time interval between 2 doses is no more constant. In that case, the drug concentration converges towards a steady state around which it oscillates. Since the time interval between two doses steadily increases and is of about 3 days after 2 weeks of treatment, the amplitude of the oscillations is quite large. In this example, the difference between the peak and through concentrations reaches 30 mg/L. For regimen (b), a dose is injected every day but the amount of drug injected steadily decreases. The first two doses of the treatment are of about 680 and 340 mg but by the end of the treatment the doses are just slightly larger than 100 mg. For that dosing regimen, the drug concentration also converges towards a steady state around which it oscillates. However, the amplitude of the oscillations is smaller than with regimen (c) and does not exceed 6 mg/L at the end of the treatment.

Conclusions

Among all the complex systems that one can imagine, from financial markets to ecosystems, the human body is certainly one of the most intricate. It is therefore hardly surprising that the time course of some drugs in the body does not always follow the exponential kinetics predicted by classical models. More complex kinetics characterized by power-law terminal phases are indeed observed and require specific tools. Fractional differential equations are one of these tools and provide a much more realistic picture of these drugs kinetics. By providing a better picture of the processes at play, they also shed some light on issues that

were ignored by classical models. One of those issues is the accumulation of drug that can carry on indefinitely when the elimination flux is fractional and the infusion takes place at a constant rate.

In this paper, we have shown that this issue can be avoided by considering a time-dependent rather than a constant-rate drug input. In particular, we have shown that an infusion rate that decays like a power law can stabilize the amount of drug in the compartment. In the case of multiple IV bolus dosing, the analytical results derived for a continuous IV infusion can be used to derive recursion relations for the doses and for the dosing times. These recursions provide a sequence of decreasing doses and increasing dosing intervals. The resulting power-law time dynamics of the drug input counterbalances the slower kinetics of the drug in the body and hence prevents unbounded drug accumulation.

We have only been able to derive analytical results for a one-compartment model. To consider more complex systems, we had to rely on a numerical discretization of the model equations. That has allowed us to study a two-comportment system with both continuous infusion and multiple dosing. Our simulation results suggest that the input functions derived analytically for a one-compartment system are still valid in the case of two-compartment system. In particular, we have been able to propose two multiple dosing regimens of amiodarone that can stabilize the plasma concentration of that drug. We hope that the present study will contribute to the wider use of fractional PK models and to their practical application to tailor dosage regimens that maximize therapeutic effectiveness while minimizing toxicity.

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