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A commentary on fractionalization of multi-compartmental models

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Fractional calculus, the branch of calculus that deals with derivatives of non-integer order, e.g., a half derivative, allows the formulation of fractional differential equations (FDEs), capable of describing a range of phenomena, most of them related in one way or another to anomalous diffusion processes [1, 2].

FDEs have recently found application in the field of pharmacokinetics (PK), since the presence of non-classical, anomalous kinetics has been established years ago and many articles have appeared in the literature trying to quantify these processes by the use of either empirical power-laws or fractal kinetics [3, 4]. Fractional pharmacokinetics (fPK) was first described by Dokoumetzidis and Macheras in [5] where the concept was introduced for a simple "one-compartment" model that gave rise to a Mittag-Leffler function (MLF). The MLF has very nice properties since it behaves as a power law for large time scales but as an exponential for small times, hence the MLF can describe kinetic data that follows power law terminal kinetics without presenting problems for $t = 0$. However, if we want to write models in more physiological terms then eventually we will need a formulation with more than one compartments. The first attempt to write multi-compartmental fPK models was done by Popovic et al. [6], who basically fractionalized the classic compartmental pharmacokinetics in a straightforward manner, i.e., they generalized the classic first order derivatives found on the left hand side of ordinary differential equations (ODEs) by replacing them with fractional derivatives. But is this change in the order of the derivatives all that is needed to establish correct and consistent fPK models? In this note we will demonstrate that it is not.

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The first hurdle that one encounters when the classic rates defined by the first derivatives are changed to fractional derivatives, is that the units of the rate constants, used in the linear models, change from "per time" to "per time to the power of alpha", where alpha is the order of the derivative found on the left hand side of the FDE. An obvious problem arises when the same rate constant appears in more than one FDE, each of which is of different order, because the same parameter has different units in different parts of the system. This inconsistency means that there is something fundamentally wrong with the system setup. It is tempting to try to correct the problem by removing the units altogether, by normalizing these parameters, as Popovic et al. [6] have done, but this change alone does not solve the problem. The problem is not the units, in fact the units help to reveal the problem, which is simply that a rate of order one, for example, is a different kind of rate than the rate of order one-half, much the same way as the rate of order one, of the distance covered by a moving body, which is its velocity, is different from the corresponding rate of order two, which is its acceleration. And clearly, in this case, to normalize by dividing by a time constant may correct the units, but it will not address the fact that these two rates, velocity and acceleration have a different physical meaning and hence cannot be used interchangeably. In this vein, caution should be exercised when reporting mean values of estimates for rate constants expressed in units "$(\text{time})^{-\alpha}$". When the individual values do not have identical units, as happens to be the case for the values of the rate constants reported in Table 1 of Ref 6, a mean value cannot be defined.

In compartmental kinetics, fluxes are defined, which describe the rate of mass transfer, from one compartment to the other. When a model is being built, typically an outgoing mass flux is by definition an incoming flux to the next compartment. An outgoing mass flux that is defined as a rate of fractional order, cannot appear as an incoming flux into another compartment as a rate of a different fractional order. This has been done in ref. [6] and we believe produces inconsistent fractional systems, with the exception of the special case, when all the FDEs of the system are of the same order. We will now demonstrate, in a simple two-compartment system, that this approach leads to violation of mass balance when the orders of the corresponding FDEs for each of the two compartments are different, α_1 and α_2, respectively. Let the amounts in each of the compartments be q_1 and q_2 and assuming J_{12}, J_{21}, J_{10}, J_{20} to represent the fluxes, with normalized units or not, describing mass transfer between the two compartments and the elimination from each of the compartments, respectively. Note that we prefer to use the standard PK convention where J_{12} corresponds to the transfer from the first to the second compartment and not the other way around as in Popovic et al. [6] where the "engineering" convention is followed. Then, the system is written as follows using ordinary derivatives:

$$\begin{aligned} \frac{dq_1}{dt} &= -J_{12} + J_{21} - J_{10} \\ \frac{dq_2}{dt} &= J_{12} - J_{21} - J_{20} \end{aligned} \tag{1}$$

Changing ordinary derivatives on the left hand side of Eqs. 1 to fractional derivatives of order α_1 and α_2, respectively, following the rationale of Popovic et al. [6], we obtain the following system:

$$\begin{aligned} \tau_1^{\alpha_1-1}\,{}_0^C D_t^{\alpha_1} q_1 &= -J_{12} + J_{21} - J_{10} \\ \tau_2^{\alpha_2-1}\,{}_0^C D_t^{\alpha_2} q_2 &= J_{12} - J_{21} - J_{20} \end{aligned} \tag{2}$$

where τ_1 and τ_2 are time constants used to balance the units, such that fluxes J_{ij} have "mass per time" units; the operator ${}_0^C D_t^{\alpha} f(t)$ denotes the Caputo derivative of order α of the function $f(t)$ with respect to t, defined as follows [5]:

$${}_0^C D_t^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{f'(\tau)}{(t-\tau)^{\alpha}} d\tau \tag{3}$$

where $\Gamma(x)$ is the Gamma function and $f'(\tau) = df/dt$. The exact functional form of the fluxes J_{ij} is typically assumed to be linear of the form $J_{ij} = k_{ij} q_i$ [2], but it can also be non-linear or even constant. To make things simpler, we assume that the system is closed, so we set J_{10} and J_{20} equal to zero and we also assume that J_{21} is zero, such that the transfer is unidirectional and that J_{12} is constant. Then, the system can be written in the following trivial way:

$$\tau_1^{\alpha_1-1}\,{}_0^C D_t^{\alpha_1} q_1 = -J_{12} \tag{4a}$$

$$\tau_2^{\alpha_2-1}\,{}_0^C D_t^{\alpha_2} q_2 = J_{12} \tag{4b}$$

Also, let, $q_1(0) = 1$ and $q_2(0) = 0$, which means that the "dose" is normalized to 1 and appears initially in the first compartment. For as long as compartment 1 has not emptied, i.e., $q_1(t) \geq 0$, the solution of each one of Eqs. 4, independently, yields:

$$\begin{aligned} q_1(t) &= 1 - \frac{J_{12}}{\tau_1^{\alpha_1-1}\Gamma(1+\alpha_1)} t^{\alpha_1} \\ q_2(t) &= \frac{J_{12}}{\tau_2^{\alpha_2-1}\Gamma(1+\alpha_2)} t^{\alpha_2} \end{aligned} \tag{5}$$

which is trivial to verify since the Caputo derivative of order α_1 of the first equation is ($-J_{12}$), while the Caputo derivative of order α_2 of the second equation is J_{12} [2].

Plausibly, the solution of this system should satisfy at any time, the condition

$$q_1(\mathrm{t}) + q_2(\mathrm{t}) = 1 \tag{6}$$

which simply means that since nothing is lost the total amount in the two compartments should be the initial amount available. But one can immediately spot that the condition of Eq. 6, only holds when $\alpha_1 = \alpha_2$, and also $\tau_1 = \tau_2$. In the general case, the principle of mass balance is violated. Note that the normalizing time constants of τ_1 and τ_2 fix the units such that J_{12} has consistent units in both equations, but do not solve the problem of mass balance. The main conclusion here is that the method of fractionalization of the classic models by changing the ordinary derivatives of the left hand side of the ODEs to fractional derivatives, produces inconsistent systems. In our simplified example the constant α_1-rate of the outgoing flux, J_{12}, cannot be defined also as a constant α_2-rate.

As a second example we will use the two compartment system found in page 6 of Popovic et al. [6]:

$$D^{\alpha_1} q_1 = -k_{12} q_1 \tag{7a}$$

$$D^{\alpha_2} q_2 = k_{12} q_1 - k_{20} q_2 \tag{7b}$$

with $q_1(0) = d_1$ and $q_2(0) = d_2$. Note that we have used again the pharmacokinetic notation for the indices of the rate constants. This model clearly has an inconsistency with the units since k_{12} appears in the first equation with units "per time to the power of α_1" and in the second equation with units "per time to the power of α_2". In [6] it is claimed that the rate constants are in fact "dimensionless" since the time factors τ_1 and τ_2 have been incorporated into them such that $k_{12} = K_{12}/\tau_1^{\alpha_1 - 1}$, where K_{12} is the original rate constant. However this suggests multiple definitions of k_{12}, since for Eq. 7b, k_{12} is defined differently as $k_{12} = K_{12}/\tau_2^{\alpha_2 - 1}$. Also, these rate constants are not "dimensionless" and instead have units "per time to the power of α_i". So to overcome these problems we will retain the constants τ_1 and τ_2 explicitly and use the following system:

$$\begin{aligned} \tau_1^{\alpha_1 - 1} D^{\alpha_1} q_1 &= -k_{12} q_1 \\ \tau_2^{\alpha_2 - 1} D^{\alpha_2} q_2 &= k_{12} q_1 - k_{20} q_2 \end{aligned} \tag{8}$$

The solution of the above system in the Laplace domain is

$$\hat{q}_1(s) = \frac{s^{\alpha_1 - 1} d_1}{s^{\alpha_1} + k_{12} \tau_1^{1-\alpha_1}} \tag{9a}$$

$$\hat{q}_2(s) = \frac{k_{12} \tau_2^{1-\alpha_2} s^{\alpha_1 - 1} d_1}{(s^{\alpha_1} + k_{12} \tau_1^{1-\alpha_1})(s^{\alpha_2} + k_{20} \tau_2^{1-\alpha_2})} + \frac{s^{\alpha_2 - 1} d_2}{s^{\alpha_2} + k_{20} \tau_2^{1-\alpha_2}} \tag{9b}$$

which appears on page 7 of [6] without the constants τ_1 and τ_2. Setting the elimination rate constant, k_{20} equal to 0, we obtain a closed system, which allows us to check mass conservation. Then, Eq. 9b becomes:

$$\hat{q}_2(s) = \frac{k_{12} \tau_2^{1-\alpha_2} s^{\alpha_1 - 1} d_1}{(s^{\alpha_1} + k_{12} \tau_1^{1-\alpha_1}) s^{\alpha_2}} + s^{-1} d_2 \tag{10}$$

Adding Eq. 9a and 10 gives

$$\begin{aligned} \hat{q}_1(s) + \hat{q}_2(s) &= \frac{s^{\alpha_1 - 1} d_1}{s^{\alpha_1} + k_{12} \tau_1^{1-\alpha_1}} + \frac{k_{12} \tau_2^{1-\alpha_2} s^{\alpha_1 - 1} d_1}{(s^{\alpha_1} + k_{12} \tau_1^{1-\alpha_1}) s^{\alpha_2}} + s^{-1} d_2 \\ &= \frac{s^{\alpha_1 - 1} (s^{\alpha_2} + k_{12} \tau_2^{1-\alpha_2}) d_1}{(s^{\alpha_1} + k_{12} \tau_1^{1-\alpha_1}) s^{\alpha_2}} + s^{-1} d_2 \end{aligned} \tag{11}$$

For the special case of $\alpha_1 = \alpha_2$ and $\tau_1 = \tau_2$, Eq. 11 collapses to:

$$\hat{q}_1(s) + \hat{q}_2(s) = s^{-1}(d_1 + d_2) \tag{12}$$

This is the expected result, because the system is closed and therefore the sum of the two quantities, $q_1 + q_2$, in the time domain, should be equal to the entire amount, $d_1 + d_2$, which in the Laplace domain is $(d_1 + d_2)/s$. But in the general case of $\alpha_1 \neq \alpha_2$ and/or $\tau_1 \neq \tau_2$, Eq. 11 does not collapse to Eq. 12, which means that the system is not well formulated and there is a violation of mass balance.

In this commentary we take the opportunity from the recently published article of Popovic et al. [6] to argue that an intuitive way of fractionalization of models, by simply changing the order of the derivatives of a system of ODEs, thus obtaining a system of FDEs, leads to inconsistent systems, unless all the FDEs are of the same fractional order. This does not mean that mixing fractional orders in systems of FDEs is not possible. Building more complex, compartmental models is indeed feasible, without violation of mass balance or unit inconsistencies. In a future, full length article, we will present a general approach of how to fractionalize multi-compartmental models.

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