



Fractional Kinetics in Multi-Compartmental Systems

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Fractional kinetics

Fractional differential equations (1) include derivatives of fractional order (e.g. a half- derivative) and have been used to describe physical phenomena of anomalous diffusion among other applications. They have been recently used in pharmacokinetics too (2). There is more than one kinds of fractional derivatives. Here, we use the so-called Caputo derivative. A Caputo derivative of order $\alpha < 0$ of the function $f(t)$ is defined as follows (1):

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

One-compartment model

The amount $A(t)$ in a one-compartment model is defined by a simple ODE

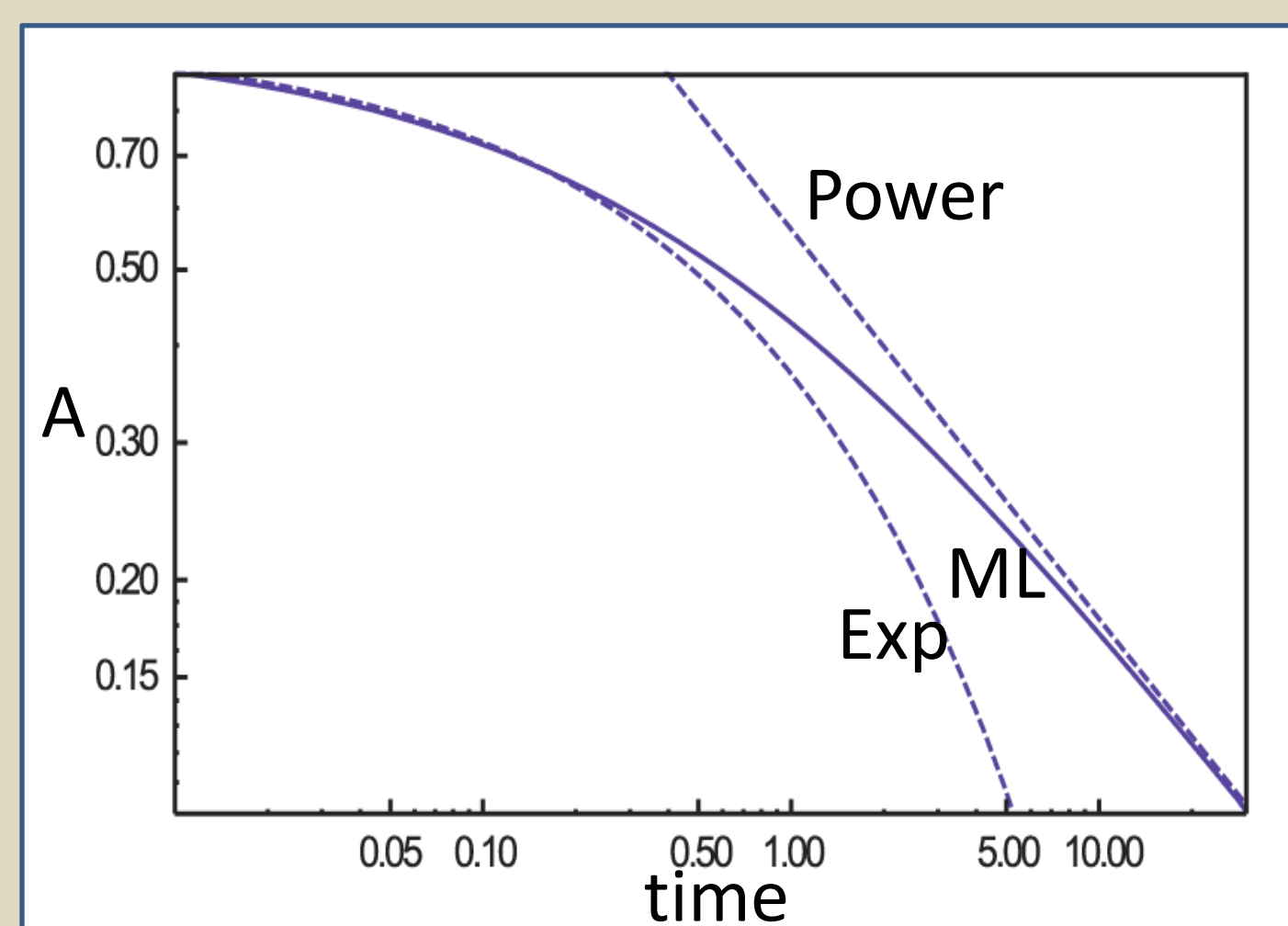
$$\frac{dA(t)}{dt} = -k_{10}A(t)$$

with $A(0)=\text{Dose}$, which has as solution the function $A(t)=\text{Dose}\cdot\exp(-k_{10}\cdot t)$.

We can easily write a fractional equivalent of that replacing the ordinary derivative of order 1 by a Caputo derivative of order $\alpha < 1$, as (2):

$${}_0^C D_t^\alpha A(t) = -k_{10}A(t)$$

The solution of that is the function $A(t)=\text{Dose}\cdot E_\alpha(-k_{10}\cdot t^\alpha)$, where $E_\alpha(\cdot)$ is the Mittag-Leffler (ML) function, which is the fractional equivalent of the exponential function. It has the good property of following the (stretched)



exponential function for small times and the power function for long times, as shown in the log-log plot on the left. This makes it appropriate for describing power-law PK data for both short and long time scales, since it does not explode for $t=0$ as the power-law does (2).

Two-compartment model

A general two-compartment model is formulated as follows

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

It is tempting to attempt fractionalizing the two-compartment model by simply changing the order of the left hand side derivatives

$$\begin{aligned} {}_0^C D_t^\alpha A_1(t) &= -k_{12} \cdot A_1(t) + k_{21} \cdot A_2(t) - k_{10} \cdot A_1(t) \\ {}_0^C D_t^\beta A_2(t) &= k_{12} \cdot A_1(t) - k_{21} \cdot A_2(t) - k_{20} \cdot A_2(t) \end{aligned}$$



But this approach **produces inconsistent models that violate mass balance**. That can be obvious even by looking at the units of the rate constants which are different in each equation for the same constant (3).

A general fractional two-compartment model can be written, correctly, as follows

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

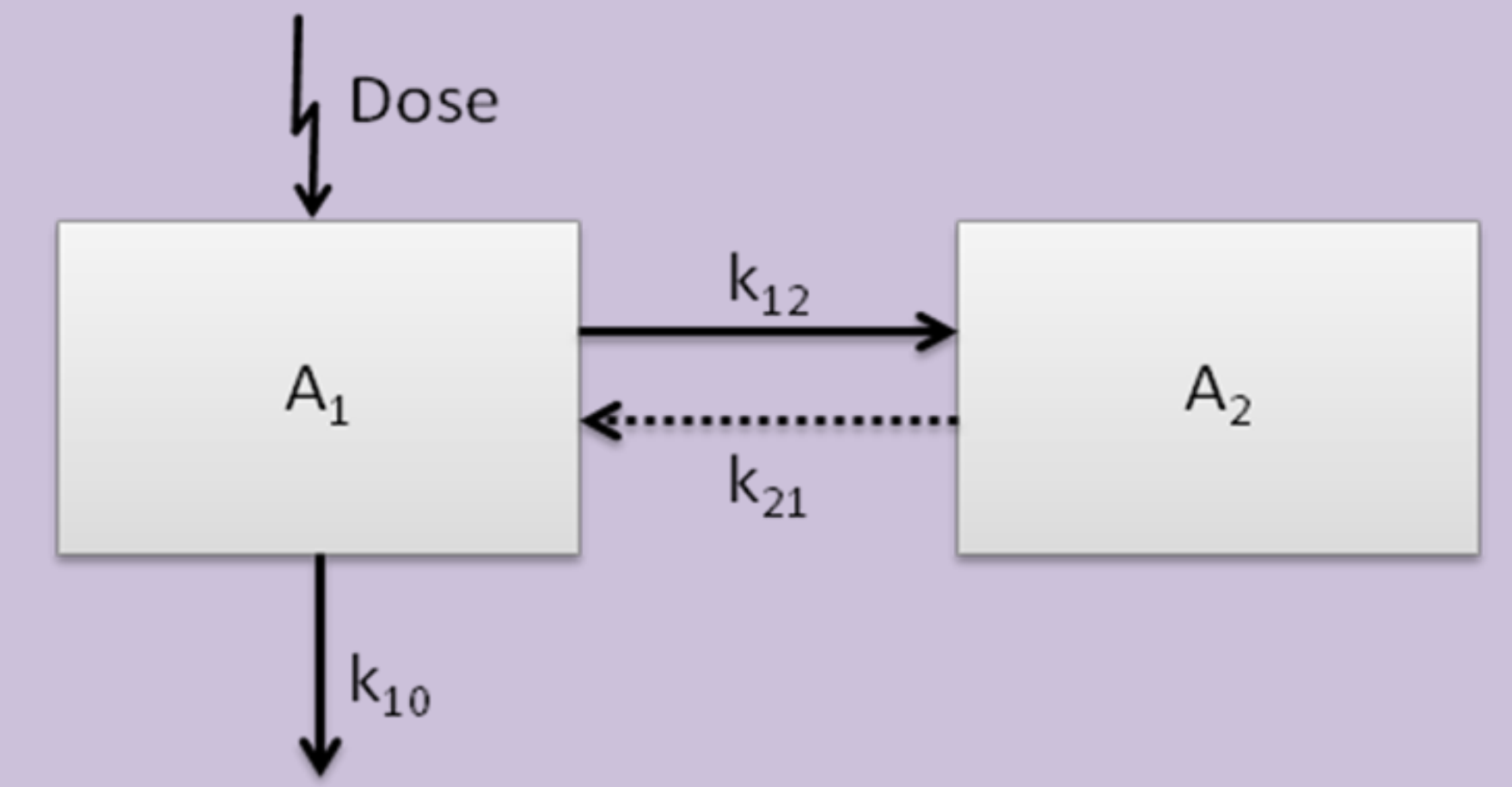


Note that fractionalization of each term is possible separately, which allows mixing different fractional orders in the same system but the same process should keep the same order throughout the system, e.g. terms associated to flux 1-2 are of order α in both equations, but the ones related to flux 2-1 can be of a different order β and so on.

Extending the above approach to **an arbitrary number of n compartments** is straightforward

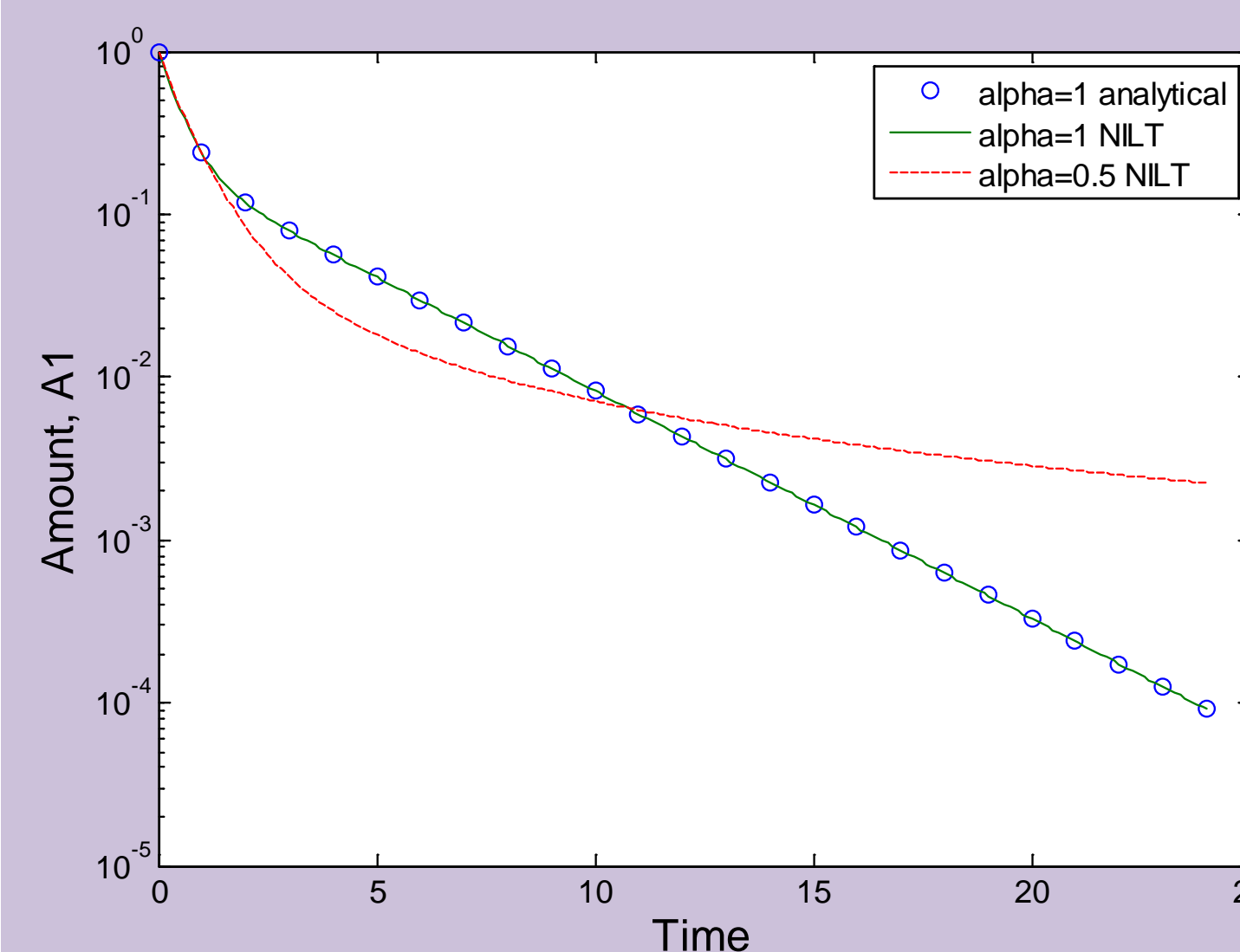
A two-compartment PK model

Elimination and 1-2 flux is considered classical (order 1) but flux 2-1 (dashed arrow) is considered fractional with $\alpha < 1$, accounting for deep tissue trapping of the drug. The following model occurs:



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

Transforming the above equations in the Laplace domain and solving for $A_1(s)$ which we are mostly interested in, gives an expression from which **we can simulate $A_1(t)$ values, in the time domain by using a numerical inverse Laplace transform (NILT) algorithm**. We used "invlap.m" programme written in MATLAB.



$$\hat{A}_1(s) = \frac{\text{dose} \cdot (s^\alpha + k_{21})}{(s + k_{12} + k_{10})(s^\alpha + k_{21}) - k_{12} \cdot k_{21}}$$

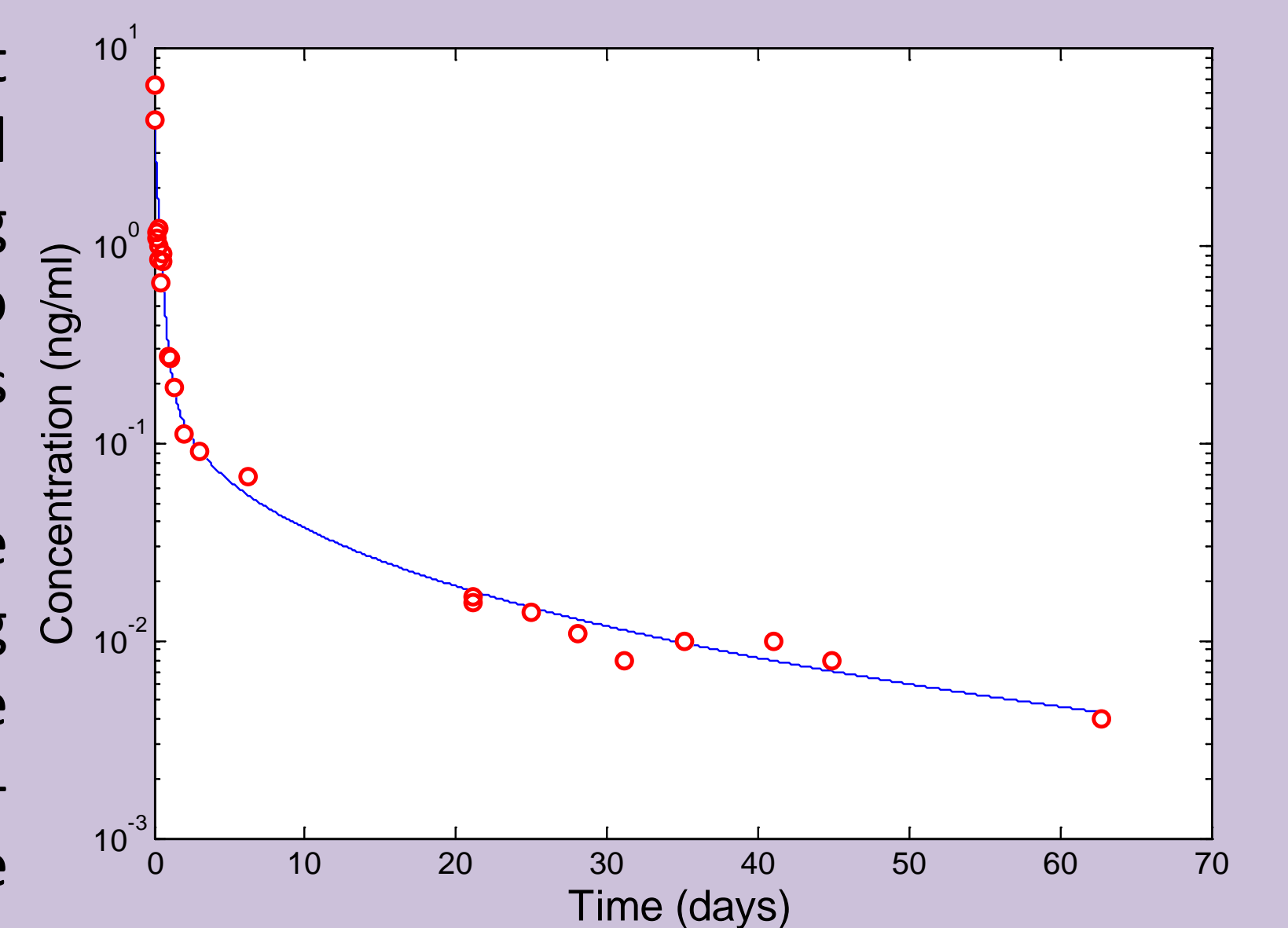
In the plot on the left 3 simulated profiles of $A_1(t)$ of the two-compartment are shown. For the case of $\alpha=1$, which corresponds to the classic PK model, using (i) the analytical solution and (ii) the NILT method. These are shown to be overlapping, therefore providing evidence

That the NILT method works well. The other profile corresponds to the fractional case of $\alpha=0.5$. One may notice that it is non-exponential and eventually slower than the classic case.

Using the NILT algorithm that simulates values of $A_1(t)$, the model may be fitted to PK data of drug concentration $C=A_1(t)/V_1$, in order to estimate the model PK parameters including fractional order α .

As an example we report a fit of the model to amiodarone data coming from literature (4). Amiodarone kinetics is known for its non-exponential character. The fit of the model to the data is shown in the plot on the right, while the parameter estimates are shown in the table.

Note, that the present approach allows in a straight forward manner, the formulation of PK models with oral administration, multiple dosing using superposition, etc.



Parameter	Estimate	St. error (CV)
k_{10} (days ⁻¹)	1.4913	0.1655
k_{12} (days ⁻¹)	2.9522	0.3536
k_{21} (days ^{-α)}	0.4854	0.4943
α	0.5870	0.2457
dose/ V (ng/ml)	4.7268	0.1826

Conclusions

- We introduce a methodology that allows the formulation of fractional multi-compartmental models with mixed fractional orders
- We also introduce a way to solve numerically such systems based on a NILT approach
- We present a pharmacokinetic example where a two compartment model is fitted to amiodarone PK data and the model parameters are estimated
- Our approach allows the formulation of compartmental models of arbitrary structure which may include multiple doses and alternative routes of administration

References

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