Multiple dosing for linear fractional pharmacokinetic systems

A. Dokoumetzidis[1], RL Magin[2] and P. Macheras[1]

[1]School of Pharmacy, University of Athens, Greece (email A.D.: adokoum@pharm.uoa.gr)

[2]Department of Bioengineering, University of Illinois at Chicago, IL, USA

Objective

One of the problems of fractional calculus is the initialisation of fractional differential equations because of the time memory effects, which may have consequences in the implementation of multiple dosing systems. We investigate the implementation of a multiple dosing scheme in a one compartment model, with two methods, both valid in the classic, non-fractional case: (i) Piecewise solution and (ii) using the superposition principle. We assess whether each of these techniques works for fractional systems by comparing them to the limit case of a one-compartment fractional model with constant infusion which has an analytical solution.

The one-compartment model

The amount A(t) in a one-compartment fractional PK model after an IV bolus dose is given by

$$ {}_0^C D_t^\alpha A_1(t) = -k_{10} A_1(t) $$

with $A_1(0)$=Dose, where the operator ${}^CD^\alpha$ stands for the Caputo derivative of order α, and has as solution the function**,**

$$ A_1(t) = Dose \cdot E_{\alpha,1}(-k_{10} \cdot t^\alpha) \qquad (1) $$

where $\mathbf{E_{\alpha,\beta}(\cdot)}$ is the Mittalg-Leffler (ML) function.

The fractional one-compartment model with a constant infusion is given by

$$ \frac{dA_1(t)}{dt} = k_{01} - k_{10} \cdot {}_0^C D_t^{1-\alpha} A_1(t) $$

Which can also be solved in terms of a ML function

$$ A_1(t) = k_{01} \cdot t \cdot E_{\alpha,2}(-k_{10} t^\alpha) \qquad (2) $$

Multiple dosing

Multiple dosing, in classic, non-fractional PK can be implemented either by **piecewise solution** of each dosing interval, where the initial value of each dosing interval is the final value of the previous one plus the next dose, as follows:

$$ A^i(t) = A_1(t + T_i, A^{i-1}(T_i) + dose_i) $$

Alternately, linear systems, can be solved by the **superposition** of several, time-lagged, single dose solutions $A^i(t)$ as follows:

$$ A^i(t) = \begin{cases} 0 & \text{for } t < T_i \\ A_1(t + T_i, dose_i) & \text{for } t \geq T_i \end{cases} $$

$$ A(t) = \sum_{i=1}^{N} A^i(t) $$

Both of these approaches give identical results in non-fractional PK, but the question is whether any of these is appropriate for fractional kinetics given the peculiarities of fractional differential equations regarding initial values.

To test whether the methods are applicable for fractional PK we compare the multiple dosing implementations with the constant infusion. Regular multiple dosing and constant infusion should give the same result in the case of very frequent small doses.

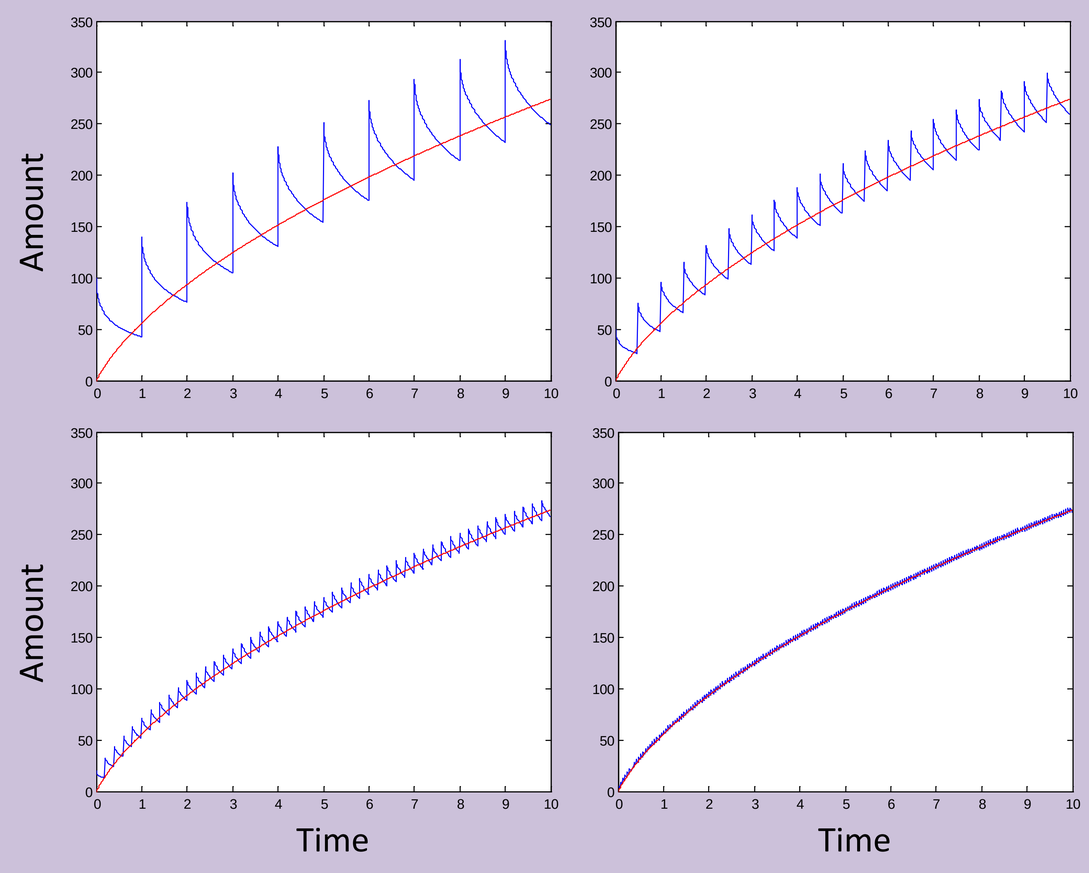
For the constant infusion we set α=0.5, k_{01}=100 and K_{10}=1, while the dose is varied with the dosing frequency to match the infusion rate as follows:

$$ dose = \frac{k_{01}}{freq} $$

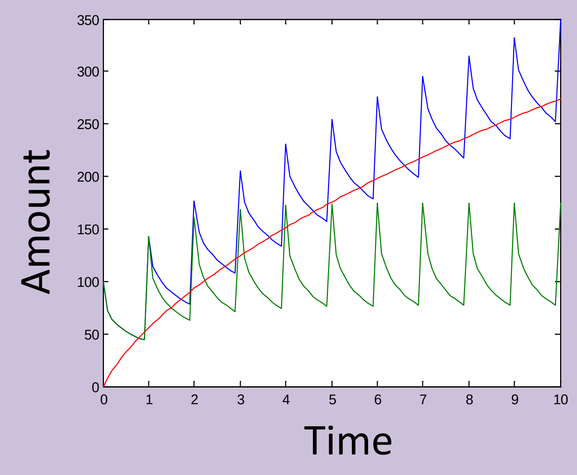
Results

Superposition vs Piecewise solution

a) Multiple dosing profiles implemented by *superposition* (**blue**), are in agreement with the constant infusion model (**red**), for various dosing frequencies, while for the limit of a very frequent dosing interval the two solution practically overlap.



b) A multiple dosing profile implemented by *piecewise solution* (**green line**) is different to the one implemented by superposiition (**blue line**), and of course does not agree with the constant infusion model (**red line**).



So in conclusion, superposition works while piecewise solution does not. The former is not surprising since the models tested are linear and despite their fractional order, superposition principle still holds. The disadvantage of this method is that it is not applicable for nonlinear systems.

Accumulation of drug

As already pictured above the solution of the constant rate infusion does not reach the steady state k_{01}/k_{10}, instead it diverges. We can show analytically by using Eq. 2, that the limit of $A_1(t)$ when t goes to infinity, is also infinite.
Taking the limit as $t \to \infty$, we expand and keep only first term using the formula:

$$ E_{\alpha,\beta}(z) = -\sum_{k=1}^{p} \frac{z^{-k}}{\Gamma(\beta - \alpha)} + O(|z|^{-1-p}) $$

The result is $\lim_{t\to\infty}\{A_1(t)\} = \lim_{t\to\infty}\{k_{01} t \cdot E_{\alpha,2}(-k_{10} t^\alpha)\} \cong \lim_{t\to\infty}\left\{\frac{k_{01}}{k_{10}} \cdot \frac{t^{1-\alpha}}{\Gamma(2-\alpha)}\right\} = \infty$

for α<1, while replacing α=1, gives the usual steady state $\lim_{t\to\infty}\left\{\frac{k_{01}}{k_{10}} \cdot \frac{t^0}{\Gamma(1)}\right\} = \frac{k_{01}}{k_{10}}$

Conclusions

- Multiple dosing in linear pharmacokinetic systems with fractional rates can be implemented using the superposition principle exactly the same way as in ordinary PK systems, while the piecewise solution method fails.
- An important implication of the presence of fractional kinetics is the lack of a steady state and the infinite accumulation of drug, for a system with a constant rate multiple dosing (or infusion).