Numerical solution of nonlinear fractional compartmental systems

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Objective

We present a method to formulate and solve numerically, nonlinear pharmacokinetic systems which include fractional rates. As an example we consider the fractional Michaelis – Menten (MM) kinetics.

Nonlinear fractional models

We are interested to solve numerically nonlinear models of the form:

$$\begin{aligned}\frac{dA_1(t)}{dt} &= {}_0^C D_t^{1-\alpha} f_1(A_1(t), A_2(t)) + g_1(A_1(t), A_2(t)) \\ \frac{dA_2(t)}{dt} &= {}_0^C D_t^{1-\beta} f_2(A_1(t), A_2(t)) + g_2(A_1(t), A_2(t))\end{aligned} \quad (1)$$

where f_1, g_1, f_2 and g_2 are non-linear functions (or linear).
This general form that includes derivatives of fractional order "1-α" which appear on the right hand side while an ordinary derivative appears on the left hand side, gives the flexibility to formulate arbitrary non-commensurate compartmental models that respect mass balance.
Note that models of larger dimensions can be treated with the same methodology, and also more fractional derivatives can be considered.

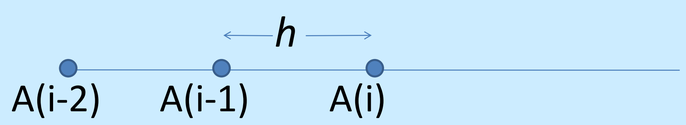
A fractional finite difference scheme

In order to solve nonlinear systems of the form of Eqs. 1, we discretize the differential equations using a finite difference scheme. We use the one found in the book of *Petras I. Fractional-Order Nonlinear Systems. Springer 2011*, which is available in MATLAB code at http://www.mathworks.com/matlabcentral/fileexchange/27336-fractional-order-chaotic-systems.

The finite difference scheme of is Petras appropriate for systems of the form:

$${}_0^C D_t^{\alpha} A(t) = f(A(t))$$

It is an ***explicit scheme*** where the value of A(i) in every next time step, is an explicit function of the value of A(i-1) in the previous time step as follows:



$$A(i) = f(A(i-1)) * h^{\alpha} - memo(...)$$

Where *memo(…)* is a function related to the memory effects, not discussed here.

For equations of the form we are interested in, i.e.:

$$\frac{dA(t)}{dt} = {}_0^C D_t^{1-\alpha} f(A(t)) + g(A(t))$$

the finite difference scheme has to be modified and it is defined ***implicitly*** with respect to the value of A(i) for the next time step:

$$A(i) = (g(A(i-1)) + h^{-(1-\alpha)} * (f(A(i) + memo(...))) * h + A(i-1) \quad (2)$$

So at each time step we need to solve numerically the above scheme in order to obtain the value of A(i). For the implementation of the numerical solution if Eq. 2, the MATLAB function fzero() was used, which works by the bisection algorithm. The initial guess for the value of A(i) needed in the root finding algorithm was set to be A(i-1) which is known from the previous step and is very close to the solution A(i). This is means that the root finding procedure needs very few steps to converge to the solution and it is very fast. This procedure is repeated for the entire integration time interval.

A simple test example

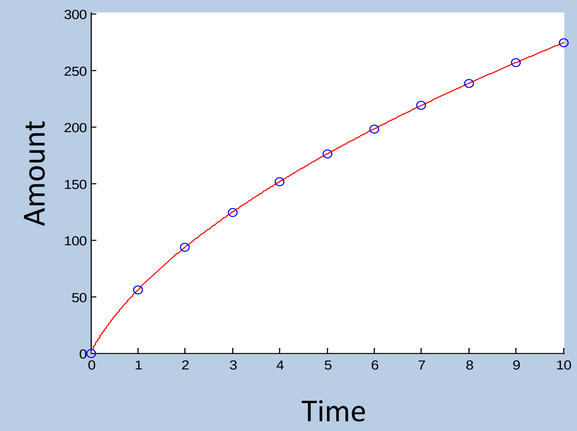
In order to test the algorithm, we use it to solve a system with a known analytical solution, to be able to compare it to the numerical solution. The system we choose is a constant input one-compartment model with fractional elimination.

$$\frac{dA(t)}{dt} = 100 - {}_0^C D_t^{1-\alpha} A(t) \quad \text{For } \alpha=0.5$$

This system has the following analytical solution, where $E_{\alpha,\beta}$ is the Mittag-Leffler function

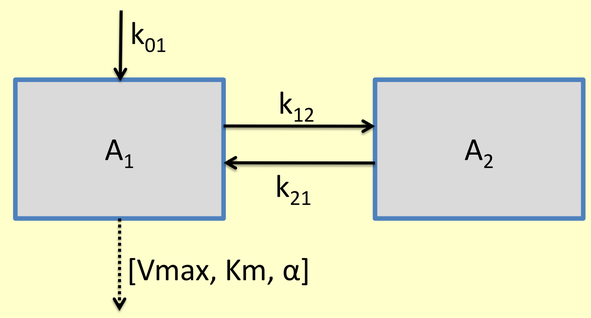
$$A(t) = 100 \cdot t \cdot E_{0.5,2}(-t^{0.5})$$

We observe that the numerical solution of the system (**red line**) is identical to the analytical solution (**blue circles**)



A 2-compartment model with fractional Michaelis – Menten elimination

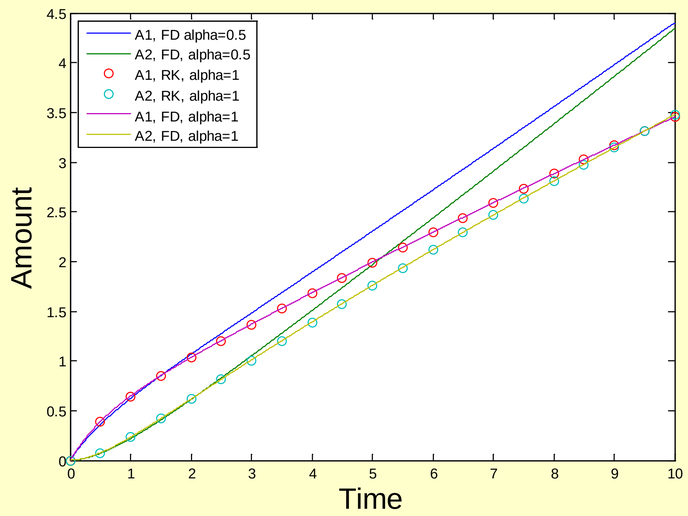
Following the general form of Eqs. 1 we can formulate an example nonlinear, 2-compartment pharmacokinetic model with a constant input rate and fractional Michaelis – Menten elimination.



$$\frac{dA_1(t)}{dt} = k_{01} - k_{12} \cdot A_1(t) + k_{21} \cdot A_2(t) - {}_0^C D_t^{1-\alpha} \frac{V_{\max} A_1(t)}{A_1(t) + K_m}$$

$$\frac{dA_2(t)}{dt} = k_{12} \cdot A_1(t) - k_{21} \cdot A_2(t), \quad A_1(0) = 0, \quad A_2(0) = 0$$

Solving the system numerically for arbitrary values of the parameters using the method presented gives profiles which are identical to the ones produced by a Runge – Kutta method (circles) for the non-fractional case of α=1.
For the fractional case of α=0.5 the profiles clearly deviate from the integer case, however we have no alternative method to compare them to.



The presented method is a general purpose way for solving non-linear fractional models and may be used for linear systems too, alternatively to other methods presented previously, such as the one based on Numerical Inverse Laplace Transform (*PAGE 19 (2010) Abstr 1718 [www.page-meeting.org/?abstract=1718]*)

Conclusions

- An algorithm to solve numerically nonlinear systems of FDEs was shown to perform well.
- This algorithm can be considered as general purpose and may be used for linear systems too.