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Fractional Kinetics Compartmental Models

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1. Introduction

Dynamic models of many processes in the physical and biological sciences give rise to systems of differential equations called compartmental systems. These assume that state variables are continuous and describe the movement of material from compartment to compartment as continuous flows. Together with the mass balance requirements of compartmental systems, these assumptions lead to highly constrained systems of ordinary differential equations, which satisfy certain physical and/or physiological constraints. In this chapter we deal with equivalent structures represented using systems of differential equations of fractional order, that is fractional compartmental systems. The calculus of fractional integrals and derivatives is almost as old as calculus itself going back as early as 1695, to a correspondence between Gottfried von Leibnitz and Guillaume de l'Hôpital. Until a few decades ago, however, expressions involving fractional derivatives, integrals and differential equations were mostly restricted to the realm of mathematics. The first modern examples of applications can be found in the classic papers by Caputo (Caputo) and Caputo and Mainardi (Caputo and Mainardi) (dealing with the modeling of viscoelastic materials), but it is only in recent years that it has turned out that many phenomena can be described successfully by models using fractional calculus. In physics fractional derivatives and integrals have been applied to fractional modifications of the commonly used diffusion and Fokker–Planck equations, to describe sub-diffusive (slower relaxation) processes as well as super-diffusion (Sokolov, Klafter et al.). Other examples are of applications are in diffusion processes (Oldham and Spanier), signal processing (Marks and Hall), diffusion problems (Olmstead and Handelsman). More recent applications are in mainly in physics: finite element implementation of viscoelastic models (Chern), mechanical systems subject to damping (Gaul, Klein et al.), relaxation and reaction kinetics of polymers (Glockle and Nonnenmacher), so-called ultraslow processes (Gorenflo and Rutman), relaxation in filled polymer networks (Metzler, Schick et al.), viscoelastic materials (Bagley and Torvik), although there are recent applications in splines and wavelets (Unser and Blu ; Forster, Blu et al.), control theory (Podlubny ; Xin and Fawang), and biology (El-Sayed, Rida et al.) (bacterial chemotaxis), pharmacokinetics (Dokoumetzidis and Macheras ; Popovic, Atanackovic et al. ; Verotta), and pharmacodynamics (Verotta). Surveys with collections of applications can also be found in Matignon and Montseny , Nonnenmacher and Metzler (Nonnenmacher and Metzler), and Podlubny (Podlubny). A brief history of the development of fractional calculus can be found in Miller and Ross (Miller and Ross).

In this chapter we discuss and show results related to a number of issues related to the definition and use of fractional differential equations to define compartmental systems, in particular we: (1) review ordinary compartmental systems, (2) review fractional calculus, with particular regard to the mathematical objects needed to deal with fractional differential equations ;(3) define commensurate fractional differential equation (linear kinetics) compartmental models; (4) discuss and describe the conditions that allow the formulation of non-commensurate fractional differential equations to represent compartmental systems; (5) show relatively simple analytical solutions (based on the use of Mittag-Leffler functions) for the input-output response functions corresponding to commensurate and non-commensurate fractional (linear kinetics) compartmental models; (6) demonstrate the use of non-linear regression to estimate the parameters of fractional kinetics compartmental models from data available from (simulated) experiments; (7) describe general formulations for fractional order non-linear kinetics compartmental models.

2. Compartmental models

A compartment is fundamentally an idealized store of a substance. If a substance is present in a biological system in several forms or locations, then all the substance in a particular form or all the substance in a particular location, or all the substance in a particular form and location are said to constitute a compartment. Thus, for instance, erythrocytes, white blood cells, and platelets blood, can each be considered as a compartment. The function of the compartment as a store can be described by mass balance equations. The general form of the mass balance equation for a compartment is as follows. If x_i is the quantity of substance in compartment i that interchanges matter with other compartments constituting its environment, then the mass balance takes the form

$$\sum R_{ij} - \sum R_{ji} \tag{1}$$

where $\sum R_{ij}$ represents the summation of the rates of mass transfer into i from relevant compartments or the external environment, and $-\sum R_{ji}$ the summation of the rates of mass transfer from i to other compartments of the system or into the environment. The transfer of material between compartments takes place either by physical transport from one location to another or by chemical reactions. The treatment of a compartment as a single store is an idealization, since a compartment is a complex entity. For example, the concentration of erythrocytes in blood is generally not uniform and one could devise detailed models to describe their distribution. However, in general a compartment is characterized by the idealized average concentration in a compartment. In the rate of mass transfer to other compartments is thus generally of the form

$$R_{ij} = R_{ij}(x_j) \tag{2}$$

where x_j is the quantity of substance in compartment j. Mathematically, the process of aggregation involved in a lumped representation leads to ordinary differential equations as opposed to the partial differential equations that would be required to describe distributed effects. In the formulation of a model of chemical and material transfer processes in a biological system, the system is first divided into (n) relevant and convenient compartments.

The mathematical model then consists of mass balance equations for each compartment and relations describing the rate of material transfer between compartments. The general form of equation defining the dynamics of the *i*-th compartment is given by

$$. \frac{dx_i}{dt} = R_{io} + \sum_{\substack{j=1 \\ j\neq i}}^{n} R_{ij}(x_j) - \sum_{\substack{j=1 \\ j\neq i}}^{n} R_{ji}(x_i) + R_{oi}(x_i) \tag{3}$$

where now R_{oi} indicates the flux of material from compartment *i* into the external environment, and R_{io} the flux of material into compartment i from external environment. The second stage requires specifying the functional dependences of each flux, which may be linear or nonlinear. Two commonly occurring types of functional dependence are the linear dependence and the threshold/saturation dependence, which includes the Michaelis-Menten form and the Hill equation sigmoid form. The linear and Michaelis-Menten dependences can be described mathematically in the form

$$R_{ij} = k_{ij} x_j \tag{4}$$

where. k_{ij} is a constant defining the fractional rate of transfer of material into compartment *i* from compartment *j*, and

$$R_{ij} = \frac{a_{ij} x_j}{b_{ij} + x_j} \tag{5}$$

where a_{ij} is the saturation value of flux R_{ij} and b_{ij} is the value of x_j at which R_{ij} is equal to half its maximal value. In many instances, the adoption of a linear time- invariant dynamic model for a metabolic system is adequate, at least within certain ranges of exogenous inputs and endogenous production rates. For a linear compartmental linear the state variables, x_j, appear in linear combinations only, and as a consequence the superposition theorem applies: the total response to several inputs is the sum of the responses to the individual inputs. In particular a linear (time-invariant) compartmental model can be written as

$$\begin{gathered} \frac{d}{dt}\begin{pmatrix} x_1(t) \\ \dots \\ x_m(t) \end{pmatrix} = \begin{pmatrix} k_{11} & \dots & k_{1m} \\ \dots & \dots & \dots \\ k_{m1} & \dots & k_{mm} \end{pmatrix} \begin{pmatrix} x_1(t) \\ \dots \\ x_m(t) \end{pmatrix} + \begin{pmatrix} f_1(t) \\ \dots \\ f_m(t) \end{pmatrix} = \mathbf{A}\mathbf{x}(t) + \mathbf{f}(t) \\ \mathbf{Y}(t) = \mathbf{B}\mathbf{x}(t) \end{gathered} \tag{6}$$

with initial conditions $\mathbf{x}(0) = \mathbf{x}_0$, where now $\mathbf{f}(t)$ is the (vector valued) input function to the system, and $\mathbf{Y}(t)$ is the output equation, a linear combination of the variables *x(t)*, where **B** is an appropriately dimensioned matrix. The (rate) constants in equation (6) satisfy:

$$\begin{aligned} & k_{ij} \geq 0, \qquad \mathrm{i} \neq \mathrm{j} \\ & k_{ii} \leq 0 \\ & \left|k_{ii}\right| \geq \sum_{\substack{j=1 \\ j\neq i}}^{m} k_{ji} \end{aligned} \tag{7}$$

where $k_{ii} = -\sum_{\substack{j=0 \\ j\neq i}}^{m} k_{ji}$, which guarantee that all states are non-negative (for non-negative inputs $\mathbf{f}(t)$).

3. Fractional integrals and derivatives

Mathematical modelers dealing with dynamical systems are very familiar with derivatives of integer order, $\frac{d^m y}{dx^m}$, and their inverse operation, integrations, but they are generally much less so with fractional-order derivatives, for example $\frac{d^{\frac{1}{3}} y}{dx^{\frac{1}{3}}}$. One way to formally introduce fractional derivatives proceeds from the repeated differentiation of an integral power:

$$\frac{d^m}{dx^m} x^p = \frac{p!}{(p-m)!} x^{p-m} \tag{8}$$

For an arbitrary power *p*, repeated differentiation gives

$$\frac{d^m}{dx^m} x^\delta = \frac{\Gamma(\delta+1)}{\Gamma(\delta-m+1)!} x^{\delta-m} \tag{9}$$

with gamma functions replacing the factorials. The gamma functions allow for a generalization to an arbitrary order of differentiation α,

$$\frac{d^\alpha}{dx^\alpha} x^\delta = \frac{\Gamma(\delta)}{\Gamma(\delta-\alpha+1)!} x^{\delta-\alpha} \tag{10}$$

The extension defined by equation (10) corresponds to the Riemann–Liouville derivative. (Oldham and Spanier ; Miller and Ross).

A more elegant and general way to introduce fractional derivatives uses the fact that the *m*-th derivative is an operation inverse to *m*-fold repeated integration. Basic to the definition is the integral identity

$$\int_a^x \int_a^{y1} \cdots \int_a^{ym-1} f(y_m)\, dy_m \ldots dy_1 = \frac{1}{(m-1)!} \int_a^x (x-y)^{m-1} f(y) dy \tag{11}$$

Clearly, the equality is satisfied at *x*=*a*, and it is not difficult to see iteratively that the derivatives of both sides of the equality are equal. A generalization of the expression allows the definition of a fractional integral (FI) of arbitrary order via

$$J_a^\alpha f(x) = \frac{1}{\Gamma(\alpha)} \int_a^x (x-y)^{\alpha-1} f(y) dy \,. \tag{12}$$

where again the gamma function is replacing the factorial. In this paper we are concerned with fractional time derivatives, and we take the lower limit in equation (12) to be zero. For

this reason in the following we will drop the subscript *a* in the definition of the operators we consider, and use *t,* instead of *x,* to indicate the independent variable time. Starting from equation (12), one can construct several definitions for fractional differentiation. The fractional differential operator $D_{\blacktriangle}^{\alpha}$ is defined by

$$D_{\blacktriangle}^{\alpha} f(t) \overset{def}{=} J^{m-\alpha} D^m f(t) \tag{13}$$

where m is the smallest integer greater than α, $D^m = \frac{d^m}{dx^m}$ (m integer) is the classical differential operator, and *f(t)* is required to be continuous and α-times differentiable in *t*. The operator $D_{\blacktriangle}^{\alpha}$ is named after Caputo (Caputo), who was among the first to use it in applications and to study some of its properties. It can be shown that the Caputo differential operator is a linear operator, i.e. that for arbitrary constants a and b,

$$D_{\blacktriangle}^{\alpha} \left(af(t) + bg(t) \right) = aD_{\blacktriangle}^{\alpha} f(t) + bD_{\blacktriangle}^{\alpha} g(t) \tag{14}$$

that it commutes:

$$D_{\blacktriangle}^{\alpha} D_{\blacktriangle}^{\beta} f(t) = D_{\blacktriangle}^{\beta} D_{\blacktriangle}^{\alpha} f(t) \tag{15}$$

and that it possesses the desirable property that:

$$D_{\blacktriangle}^{\alpha} c = 0 \tag{16}$$

for any constant *c*.
Having defined $D_{\blacktriangle}^{\alpha}$, we can now turn to fractional differential equations (FDE), and systems of FDE. A FDE of the Caputo type has the form

$$D_{\blacktriangle}^{\alpha} \mathbf{y}(t) = \mathbf{f}(t, \mathbf{y}(t)), \tag{17}$$

where $\mathbf{y}(t)$ is a vector of dependent state variables, and $\mathbf{f}(t,\mathbf{y}(t))$ a, dimensionally conforming, vector valued function, satisfying a set of (possibly inhomogeneous) initial conditions

$$D^k \mathbf{y}(0) = \mathbf{y}_0^{(k)}, \quad \text{k=0,1,…,m-1} \tag{18}$$

It turns out that under some very weak conditions placed on the function **f** of the right-hand side of Eq. (17) , a unique solution to Eqs. (17) and (18) does exist (Diethelm and Ford).
A typical feature of differential equations (both classical and fractional) is the need to specify additional conditions in order to produce a unique solution. For the case of Caputo fractional differential equations, these additional conditions are just the static initial conditions listed in (18) which are similar required by classical ordinary differential equations, and are therefore familiar. In contrast, for Riemann–Liouville fractional differential equations, these additional conditions constitute certain fractional derivatives (and/or integrals) of the unknown solution at the initial point *t=0* (Kilbas and Trujillo), which are functions of *t*. These initial conditions are not physical; furthermore, it is not clear how such quantities are to be measured from experiment, say, so that they can be

appropriately assigned in an analysis (Miller and Ross). If for no other reason, the need to solve fractional differential equations is justification enough for choosing Caputo's definition for fractional differentiation over the more commonly used (at least in mathematical analysis) definition of Liouville and Riemann, and this is the operator that we choose to use in the following.

3.1 Mittag-Leffler functions

Mittag-Leffler functions are generalizations of the exponential function (Erdélyi, Magnus et al.). The solutions of fractional order linear differential equations are often expressed in terms of Mittag-Leffler functions in similar way that the solutions of integer order linear differential equations are expressed in terms of the exponential function. The single parameter Mittag-Leffler function takes the form:

$$E_{\alpha}(z)=\sum_{i=0}^{\infty}\frac{z^{i}}{\Gamma(\alpha i+1)} \tag{19}$$

while the two-parameters Mittag-Leffler function is:

$$E_{\alpha,\beta}(z)=\sum_{i=0}^{\infty}\frac{z^{i}}{\Gamma(\alpha i+\beta)} \tag{20}$$

The relationship with the exponential function is made clear by the relationships:

$$e^{z}=\sum_{i=0}^{\infty}\frac{z^{i}}{i!}=\sum_{i=0}^{\infty}\frac{z^{i}}{\Gamma(i+1)}=E_{1}(z) \tag{21}$$

The Laplace transform of the Mittag-Leffler functions are given by:

$$L\left\{t^{\alpha k+\beta-1}E_{\alpha,\beta}^{(k)}\left(-\lambda t^{\alpha}\right)\right\}=\frac{k!s^{\alpha-\beta}}{\left(s+\lambda\right)^{k+1}} \tag{22}$$

where $E_{\alpha,\beta}^{(k)}(z)=\frac{d^{k}}{dz^{k}}E_{\alpha,\beta}(z)$.

The solutions of fractional order linear differential equations are often expressed in terms of Mittag-Leffler functions in similar way that the solutions of integer order linear differential equations are expressed in terms of the exponential function. As shown in, e.g., (Bonilla, Rivero et al. ; Odibat) sums of Mittag-Leffler acquire a prominent role in the solutions of systems of fractional order differential equations, and, as we will see, compartmental models.

In the following to evaluate the single and two-parameters Mittag-Leffler function we implemented a FORTRAN 90 version the algorithm reported in (Gorenflo, Loutchko et al.).

Contrary to α, which has a strong influence on the overall shape of the curve for the case of the single parameter Mittag-Leffler function, the parameter β for has its most pronounced influence on the value of the function at $t = 0$.

The Mittag-Leffler function of the form $E_{\alpha}(-\lambda t)$ is non-negative and strictly non-increasing for $\lambda>0$, $0<\alpha<1$, t > 0 (Podlubny), while for the function of the form $E_{\alpha,\beta}(-\lambda t^{\beta})$ this is

not the case, as it can be seen in Figure 1 for $\lambda = 1$. However, a remarkable property, especially in view of the following applications to system of fractional order differential equations, is that the function:

$$t^{1-\beta} E_{\alpha,\beta}\left(-\lambda t^{\beta}\right) \tag{23}$$

is non-negative and strictly non-increasing when $\lambda > 0$, $0 < \alpha < 1$, $0 < \alpha \le \beta \le 1$ (Gorenflo and Mainardi).
Figure 1. shows the Mittag-Leffler function corresponding to choice of parameters α and β reported in (Diethelm, Ford et al.):

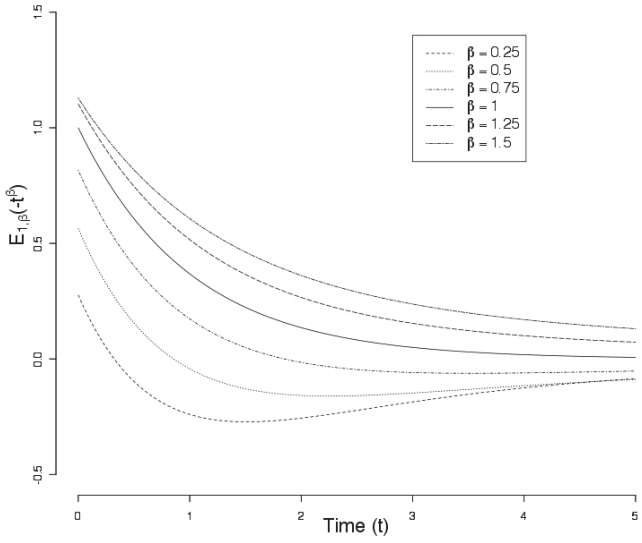

Fig. 1. The Mittag-Leffler function for $\alpha = 1$ and different values of β.

4. Commensurate fractional order linear compartmental models

Commensurate fractional order linear systems are described by a system of linear fractional differential equations (FDE) of the form (Bonilla, Rivero et al.):

$$\begin{aligned} D_{\blacktriangle}^{\alpha}\mathbf{x}(t) &= \begin{pmatrix} D_{\blacktriangle}^{\alpha}x_1(t) \\ \dots \\ D_{\blacktriangle}^{\alpha}x_m(t) \end{pmatrix} = \begin{pmatrix} k_{11} & \dots & k_{1m} \\ \dots & \dots & \dots \\ k_{m1} & \dots & k_{mm} \end{pmatrix} \mathbf{x}(t) \\ \mathbf{x}(0) &= \mathbf{x}_0 \end{aligned} \tag{24}$$

where now $D_{\blacktriangle}^{\alpha}$ indicates the Caputo fractional differential operator in respect to time ($D_{\blacktriangle}^{1}\mathbf{x}(t) = d\mathbf{x}(t)/dt$) (Caputo). These systems are called commensurate because all the differential equations are of the same fractional order, α, obtained, for $0 < \alpha \le 1$, exactly as for a standard (ODE) compartmental system.

To construct the solution of the system (24) (see e.g. (Bonilla, Rivero et al. ; Odibat)), we apply the Laplace transform to both sides of the system, to obtain

$$\begin{pmatrix} s^{\alpha}x_1(s)-s^{\alpha-1}x_1(0) \\ \dots \\ s^{\alpha}x_m(s)-s^{\alpha-1}x_m(0) \end{pmatrix}=\begin{pmatrix} k_{11} & \dots & k_{1m} \\ \dots & \dots & \dots \\ k_{m1} & \dots & k_{mm} \end{pmatrix}\begin{pmatrix} x_1(s) \\ \dots \\ x_m(s) \end{pmatrix} \tag{25}$$

from which it follows that

$$x_j(s)=\frac{\det\left(B_j(s)\right)}{\det\left(B(s)\right)},\ j=1,\dots,m \tag{26}$$

where

$$B(s)=\begin{pmatrix} k_{11}-s^{\alpha} & \dots & k_{1m} \\ \dots & \dots & \dots \\ k_{m1} & \dots & k_{mm}-s^{\alpha} \end{pmatrix} \tag{27}$$

and $B_j(s)$ is the matrix formed by replacing the *j*-th column of $B(s)$ by the column $\left(s^{\alpha-1}x_1(0),\dots,s^{\alpha-1}x_m(0)\right)^T$ $\left(s^{\alpha-1}x_1(0),\dots,s^{\alpha-1}x_m(0)\right)^T$; $\det\left(B(s^{1/\alpha})\right)$ is a polynomial of degree *m*, that can be rewritten as $\det\left(B(s^{1/\alpha})\right)=(s-\lambda_1)^{q1}\dots(s-\lambda_l)^{ql}$; from equation (25) $\det\left(B_j(s^{\alpha})\right)$ can be rewritten as $s^{\alpha-1}\left(P_1^j(s)x_1(0)+\dots P_m^j(s)x_m(0)\right)$ where $P_1^j(s^{1/\alpha})$ is a polynomial of order *m*-1. Thus, we obtain

$$x_j(s)=\frac{s^{\alpha-1}\left(P_1^j(s)x_1(0)+\dots P_m^j(s)x_m(0)\right)}{(s^{\alpha}-\lambda_1)^{q1}\dots(s^{\alpha}-\lambda_l)^{ql}} \tag{28}$$

If we now apply a partial fraction decomposition to the *j*-th term of equation (28), we obtain:

$$\frac{P_1^j(s)}{(s^{\alpha}-\lambda_1)^{q1}\dots(s^{\alpha}-\lambda_l)^{ql}}=\sum_{k=1}^{q1}\frac{M_{i1}^{kj}}{(s^{\alpha}-\lambda_1)^{q1}}+\dots+\sum_{k=1}^{qm}\frac{M_{il}^{kj}}{(s^{\alpha}-\lambda_l)^{ql}} \tag{29}$$

Thus we can write:

$$x_j(s)=\sum_{i=1}^{m}\left(\sum_{k=1}^{q1}\frac{M_{i1}^{kj}}{(s^{\alpha}-\lambda_1)^{q1}}+\dots+\sum_{k=1}^{qm}\frac{M_{il}^{kj}}{(s^{\alpha}-\lambda_l)^{ql}}\right)s^{\alpha-1}x_i(0) \tag{30}$$

Applying the inverse Laplace transform to equation (30) and taking into account the Laplace trasfrom , we obtain the desired solution as a sum of single parameter Mittag-Leffner functions:

$$x_j(t)=\sum_{i=1}^{m}\left(\sum_{k=1}^{q1}M_{i1}^{kj}E_{\alpha}(-\lambda_1 t^{\alpha})+\dots+\sum_{k=1}^{qm}M_{il}^{kj}E_{\alpha}(-\lambda_l t^{\alpha})\right)x_i(0) \tag{31}$$

The solution to the initial value problem given by system of fractional order differential equations (24) represents the entire state of the system at any given time, is unique (as

remarked by (Odibat) for the case of a linear system), and is continuous since it is a sum of continuous functions.

If the solution equation (34) is indicated by $\left(h_1(t),...,h_n(t)\right)^T$, then the initial value problem for the commensurate fractional order compartmental system,

$$\begin{aligned} D_{\blacktriangle}^{\alpha}\mathbf{x}(t) &= \mathbf{A}\mathbf{x}(t)+\mathbf{f}(t) \\ \mathbf{x}(0) &= \mathbf{x}_0 \end{aligned} \tag{32}$$

has the solution:

$$\mathbf{x}(t) = \mathbf{h}(t) + \int_0^t \mathbf{h}(t-\tau)\mathbf{f}(\tau)d\tau \tag{33}$$

Note that direct differentiation of terms of the form $\mathbf{x}(t) = \mathbf{u}E_{\alpha}\left(\lambda t^{\alpha}\right)$, substitution in equation (24), followed by removing the non-zero term $E_{\alpha}\left(\lambda t^{\alpha}\right)$ on both sides of the equation, and rearranging yields, $\mathbf{u}(\lambda\mathbf{I}-\mathbf{A})=0$, where $\mathbf{I}$ is the $m \times m$ identity matrix. Therefore, $\mathbf{x}(t) = \mathbf{u}E_{\alpha}\left(\lambda t^{\alpha}\right)$ is a solution of the system provided that λ is an eigenvalue and $\mathbf{u}$ an associated eigenvector of the characteristic equation associated with the matrix $\mathbf{A}$, that is

$$\mathbf{x}(t) = b_1\mathbf{u}_1^{(1)}E_{\alpha}(\lambda_1 t^{\alpha}) + b_2\mathbf{u}_2^{(2)}E_{\alpha}(\lambda_2 t^{\alpha}) + ... + b_m\mathbf{u}_m^{(m)}E_{\alpha}(\lambda_m t^{\alpha}) \tag{34}$$

where $b_1, b_2, \ldots, b_m$ are arbitrary constants, $\lambda_1, \lambda_2, \ldots, \lambda_m$ and $\mathbf{u}_1^{(1)}, \mathbf{u}_2^{(2)}, ..., \mathbf{u}_m^{(m)}$ are the eigenvalues and eigenvectors of the characteristic equation for (24).

It is interesting, because of its wide range of applications, to consider the case when the eigenvalues of the characteristic equation are real and distinct. When this property holds the solution to equation (32) for a unit impulse input of a substance given in the *j-th* compartment and observations taken in the same compartment, takes the form:

$$h_{jj}(t) = \theta_1 E_{\alpha}(\lambda_1 t^{\alpha}) + \theta_2 E_{\alpha}(\lambda_2 t^{\alpha}) + ... + \theta_m E_{\alpha}(\lambda_m t^{\alpha}) \tag{35}$$

where now $h_{jj}(t)$, with slight abuse of notation, is the unit-input response functions of compartment *j* for input in *j*. Equation (35) establishes a direct connection with the familiar multi-exponential response function corresponding to ordinary multi-compartment linear systems with distinct eigenvalues:

$$h_{jj}(t) = \theta_1 e^{\lambda 1 t} + \theta_2 e^{\lambda 2 t} + ... + \theta_m e^{\lambda m t} \tag{36}$$

In both cases the parameters $\theta_1, \ldots, \theta_m$, $\lambda_1, ..., \lambda_m$ and α can be estimated from available input-output data, therefore effectively identifying the unit-impulse response corresponding to a *m*-order compartmental model that can be used to, e.g., predict the responses to arbitrary inputs making use of relationship (33) (Jacquez).

We now give an example of a possible use of fractional compartmental models to approximate data obtained from a system of unknown structure. To do so we generated error corrupted data using an eight compartments mammillary system based on the drug thiopental distribution in rats (Stanski, Hudson et al. ; Verotta, Sheiner et al.). The rate constants from the central compartment (blood) to the 7 peripheral compartments are: k_{j1} = 1.80, 0.116, 0.126, 0.171, 2.43, 0.275, and $0.348\,(\text{min}^{-1})$, for *j*=2,…,8, respectively; the rate

constants from the peripheral compartment to central are k_{j1} = 0.559, 0.172, 0.117, 0.0975, 4.84, 0.411, and 0.0499 $(\min^{-1})$, for *j*=2,…,8, respectively; the exit rate from the elimination compartment (liver) is k_{02} = 0.0258 $(\min^{-1})$, and the volume of the central compartment (for a 365 grams rat) is 9.89 (ml).

Figure 2 shows the fit of models equation (35) (solid line), and (36) (dashed line) with *m*=2, to the simulated data (open circles) obtained adding a proportional normally distribute error (according to a constant plus proportional error model). The parameters $\theta_1, \theta_2, \lambda_1, \lambda_2, \alpha$ are estimated from the data, with the constraints $\theta_1, \theta_2 > 0$, $\lambda_1, \lambda_2 < 0$, and $0 < \alpha \leq 1$, which guarantee that equation (35) (and (36)) is non-negative and non-increasing (strictly monotone) for $t \geq 0$.

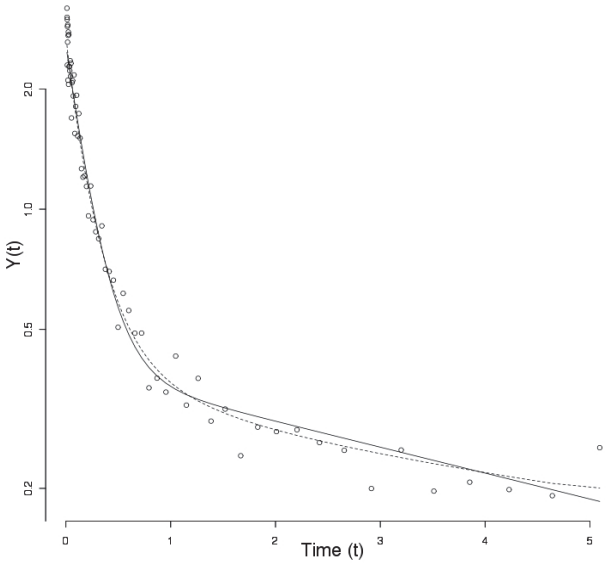

Fig. 2. The fit of the response function corresponding to integer (solid line) and commensurate fractional order (dashed line) two compartments system (dashed line) to simulated data (open circles). The data are generated using an eight compartments integer order mammillary system.

Note the added flexibility introduced by use of a sum Mittag-Leffler functions in respect to exponentials: the values of minus twice log-likelihood for the fit of the simulated data were -668.45, and -731.43, for models (35)-(36), respectively, a drop in the objective function that is highly significant according to, e.g. the Akaike criterion (Akaike). (We remark that this is an example provided to show the added flexibility introduced by the use of fractional differential equations: for this simulation, a sum of exponentials would fit the simulated data perfectly well when the number of exponential terms in the fitted response function is increased.)

5. Non-commensurate fractional order linear compartmental systems

In a non-commensurate fractional order linear system (Bonilla, Rivero et al.), the fractional order for each equation of the system are distinct (real positive) numbers $(\alpha_1, \cdots, \alpha_m)$. To

obtain a non-commensurate compartmental system it would appear that all is required is to allow for a distinct fractional orders of differentiation in equations (24), to obtain the system of fractional differential equations:

$$\begin{pmatrix} D_{\blacktriangle}^{\alpha 1} x_1(t) \\ \dots \\ D_{\blacktriangle}^{\alpha m} x_m(t) \end{pmatrix} = \begin{pmatrix} k_{11} & \dots & k_{1m} \\ \dots & \dots & \dots \\ k_{m1} & \dots & k_{mm} \end{pmatrix} \mathbf{x}(t) \qquad \mathbf{x}(0) = \mathbf{x}_0 \tag{37}$$

where $0 < \alpha_i \le 1, i = 1,...,m$. Note however that now the flux of mass from the *j*-th to the *i*-th compartment, R_{ij} , appears inconsistently, since it is defined as am outgoing flux of fractional order α_j in the *j*-th differential equation, and appears as an incoming flux into compartment *i* as a rate of fractional order $\alpha_i \neq \alpha_j$. (As a consequence the equations in (37) do not necessarily satisfy mass-balance, even if the matrix **A** would guarantee mass balance in equation (24)). (The dimensions of the rate constants are also inconsistent in equation (37), since they change depending on the fractional differential equation they appear in.)
An example will clarify the problem. Consider the following second order model:

$$\begin{pmatrix} D_{\blacktriangle}^{\alpha 1} x_1(t) \\ D_{\blacktriangle}^{\alpha 2} x_2(t) \end{pmatrix} = \begin{pmatrix} -(k_{01} + k_{21}) & k_{12} \\ -k_{21} & -(k_{02} + k_{12}) \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix} \tag{38}$$

in this representation the fluxes from the compartment to the outside of the system pose no problem, but the fluxes between compartments are not balanced: the outgoing flux from compartment 1 to 2 is at rate α_1 , but it appears as incoming flux in compartment 2 at rate α_2, and vice-versa. In addition the rate constants are not expressed consistently in terms of their dimensions. In the first differential equation the units for the rate constant k_{01}, k_{12}, k_{21} are the fractional reciprocal of unit time (*ut*) of order α_1 , while in the second the units for k_{02}, k_{12}, k_{21} are $(ut)^{-\alpha 2}$, which give inconsistent dimensions for the transfer rates between compartments k_{12}, k_{21} . $(ut)^{-1}$. Similarly to the suggestion reported in (Popovic, Atanackovic et al.), the problem of inconsistent units can be solved by normalizing the units of the rate constants in the system (that is left multiply equations (38), i.e. (37), by $diag\left(\tau^{\alpha 1},...,\tau^{\alpha m}\right)$, where $\tau^{\alpha 1},...,\tau^{\alpha m}$ are the characteristic time for each compartment, so that the elements in the matrix **A** have all dimensions $(ut)^{-1}$, see also (Dokoumetzidis, Magin et al.). However, the problem of balancing the fluxes is more fundamental and need to be addressed if one has to provide a general representation that allows a physical interpretation of the system.
We now describe three possible alternatives to represent non-commensurable fractional order compartmental systems.

5.1 Reducible systems

A possibility to solve the problem associated with equations (37) is to consider compartmental structures that include subsystems that do not transfer material to other parts of the system. For example if the matrix **A** in equation (37) can be put in the form:

$$\mathbf{A} = \begin{pmatrix} \mathbf{A}_{11} & \mathbf{0} \\ \mathbf{A}_{21} & \mathbf{A}_{22} \end{pmatrix} \tag{39}$$

where $\mathbf{A}_{11}$ and $\mathbf{A}_{22}$ are square matrices of order m_1 and m_2, respectively ($m_1 + m_2 = m$), that is if the matrix **A** is reducible, the corresponding compartmental topology includes two subsystems, of which the first (of dimension m_1) does not transfer material to the second. We can then consider a representation in which each subsystem is characterized by one fractional rate, α_1 and α_2 respectively, obtaining the representation:

$$\left(D_{\blacktriangle}^{\alpha 1} x_1(t) \quad \ldots \quad D_{\blacktriangle}^{\alpha 1} x_{m1}(t) \quad D_{\blacktriangle}^{\alpha 2} x_{m1+1}(t) \quad \ldots \quad D_{\blacktriangle}^{\alpha 2} x_{m1+m2}(t) \right)^T = \begin{pmatrix} \mathbf{A}_{11} & 0 \\ \mathbf{A}_{21} & \mathbf{A}_{22} \end{pmatrix} \mathbf{x}(t) \tag{40}$$

where T indicates matrix transpose. The physical interpretation is that of two sub-systems that operate at distinct fractional rates, with the first receiving inputs from the second sub-system. A great number of situations can be modeled using reducible compartmental structures, for example cascades of chemical or metabolic reactions with one, or, multiple, irreversible steps; drug absorption, in which the intestine acts as a separated sub-system delivering substance/drug to the circulatory subsystem; administration o drugs using complex using external devices/formulation, e.g. nicotine patches or sustained release formulations (Pitsiu, Sathyan et al.) etc..

5.2 General representation

A second, and more general, alternative is to start from the commensurate system, equation (24), and introduce additional fractional kinetics in the form of departures from a reference fractional rate. Continuing with the second order model example reported above, we write:

$$D_{\blacktriangle}^{\alpha} \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix} = \begin{pmatrix} -(k_{01} + k_{21}) & k_{12} \\ -k_{21} & -(k_{02} + k_{12}) \end{pmatrix} \begin{pmatrix} x_1(t) \\ D_{\blacktriangle}^{\alpha - \alpha 2} x_2(t) \end{pmatrix} \tag{41}$$

where $\alpha = \alpha_1$. In this formulation the fluxes from compartment 1 to 2 ($k_{21} x_1(t)$) and from compartment 2 to 1 ($k_{12} D_{\blacktriangle}^{\alpha - \alpha 2} x_2(t)$) now appear as incoming/outgoing fluxes in fractional differential equations of the same order α, so that mass balance is satisfied. The general case is (a representation for non-commensurate fractional differential equation models that is, to the best of our knowledge, novel) takes the form:

$$\begin{aligned} D_{\blacktriangle}^{\alpha} \mathbf{x}(t) &= \begin{pmatrix} k_{11} & \ldots & k_{1m} \\ \ldots & \ldots & \ldots \\ k_{m1} & \ldots & k_{mm} \end{pmatrix} \begin{pmatrix} D_{\blacktriangle}^{\alpha 1 - \alpha} x_1(t) \\ D_{\blacktriangle}^{\alpha 2 - \alpha} x_2(t) \\ \ldots \\ D_{\blacktriangle}^{\alpha m - \alpha} x_m(t) \end{pmatrix} \\ \mathbf{x}(0) &= \mathbf{x}_0 \end{aligned} \tag{42}$$

where $\alpha = \alpha_1$, $0 < \alpha_i \leq 1$, $i = 1, \ldots, m$, and with no lack of generality, we order the indexes of the compartments so that $\alpha \geq \alpha_2, \ldots, \alpha_m$. The representation is now balanced in term of fluxes, and it is now consistent in terms of the units for the rate constants in **A**, with the rates appearing in each column of the matrix now expressed with consistent dimensions

$\left[k_{ij}\right]=(ut)^{-(\alpha-\alpha j)}$. Equation (42) reduces to the commensurate fractional order differential equation compartmental case equation (24) when $\alpha_2,...,\alpha_m=\alpha$.

The main problem with this representation is that it seems to require a numerical approximation to its solution. That is, no analytical solution for equation (42), of a form similar to, e.g., equation (34), could be found at the time of this writing.

The need to use numerical approximations has been present from the beginning of the modern investigation of fractional calculus, and analytical solutions to fractional differential and integral equations are known only for specific cases (see, e.g., the examples reported in (Magin ; Magin)). Algorithms dealing with fractional differential equations are reported in (Gorenflo ; Podlubny) but focus on solving Riemann–Liouville fractional differential equations and usually restrict the class of fractional differential equations to be linear with homogeneous initial conditions. The more general algorithms reported in (Diethelm, Ford et al. ; Diethelm, Ford et al.), could be adapted to solve the problem of integrating equation (42), and we have already adapted the algorithms to solve certain kinds fractional differential equations related to pharmacodynamics models (Verotta)).

The main modification of the fractional differential equation solver, which is of the Predict-Evaluate-Correct-Evaluate type, is to incorporate a fractional integrator to evaluate the terms of the form $D_{\blacktriangle}^{\alpha_i-\alpha}x_i(t)\quad i=2,...,m$, on the right hand-side of equation (42) (note that, by construction, $-1<\alpha_i-\alpha<0$, so that all terms of the form $D_{\blacktriangle}^{\alpha_i-\alpha}x_i(t)$ corresponds to fractional integrals); an algorithm for fractional integration can also be found in (Diethelm, Ford et al.)).

5.3 Response function representation

We return to the system of fractional differential equations (37) to show how certain analytical solutions can be used as response functions corresponding to compartmental systems.

In general an analytical solution to (37) does not exist, however solutions can be obtained if it is assumed that the fractional orders of the differential equations are rational numbers: $\alpha_i=r_i/q_i$ where p_i, q_i are integers, $i=1,\ldots,m$. (Note that any real number can be approximated arbitrarily closely by a rational number and therefore one can approximate any system of differential equations with multiple fractional derivatives by a system fractional differential equations with orders that are as close as we choose to the original orders, a property that will apply in any case as soon as the orders are stored in a computer.)

The derivation of the solution follow the steps used for the commensurate case equations (25) – (31) (see (Diethelm and Ford ; Lakshmikantham and Vatsala ; Odibat), to arrive at the expression for $x_j(s)$ of the form:

$$x_j(s)=\sum_{i=1}^{m}\left(\sum_{k=1}^{q1}\frac{M_{i1}^{kj}}{(s^\gamma-\lambda_1)^{q1}}+\ldots+\sum_{k=1}^{qm}\frac{M_{il}^{kj}}{(s^\gamma-\lambda_l)^{ql}}\right)s^{\alpha j-1}x_i(0) \tag{43}$$

Applying the inverse Laplace transform to equation (30) and taking into account the Laplace trasfrom (22), we obtain the solution for the non-commensurate fractional order system as a sum of two parameters Mittag-Leffner functions:

$$x_j(t)=\sum_{i=1}^{m}t^{\gamma-\alpha_j}\left(\sum_{k=1}^{q1}M_{i1}^{kj}E_{\gamma,\gamma-\alpha j+1}^{(k)}(-\lambda_1 t^\gamma)+\ldots+\sum_{k=1}^{qm}M_{il}^{kj}E_{\gamma,\gamma-\alpha m+1}^{(k)}(-\lambda_l t^\gamma)\right)x_i(0) \tag{44}$$

where $\gamma = 1/q$, $q = M.C.D(q_1,...,q_m)$ and $E^{(k)}_{\alpha,\beta}(z) = \frac{d^k}{dz^k} E_{\alpha,\beta}(z)$. If the eigenvalues of the characteristic equation for the system are real and distinct the solution simplifies to:

$$x_j(t) = \sum_{i=1}^{m} t^{\gamma-\alpha i} \left(M^j_{i1} E_{\gamma,\gamma-\alpha i+1}(-\lambda_1 t^\gamma) + ... + M^j_{il} E_{\gamma,\gamma-\alpha m+1}(-\lambda_l t^\gamma) \right) x_i(0) \tag{45}$$

and in particular the unit-impulse response function for input/output in compartment *j*, takes the form:

$$h_{jj}(t) = t^{\gamma-\alpha j} \left[\theta_1 E_{\gamma,\gamma-\alpha j+1}(\lambda_1 t^\gamma) + \theta_2 E_{\gamma,\gamma-\alpha j+1}(\lambda_2 t^\gamma) + ... + \theta_m E_{\gamma,\gamma-\alpha j+1}(\lambda_m t^\gamma) \right] \tag{46}$$

which depends on γ, α_j but not on the fractional orders associated to the other compartments.

To show an application of this type of response functions we consider the same mammilary eight compartment model with input/output in compartment *j*. The input is now at a constant rate of 2 (um) for 0.5 (ut). As before we estimate $\theta_1, \theta_2, \lambda_1, \lambda_2, \alpha$ and in addition γ, with the constraints $\theta_1, \theta_2 > 0 =, \lambda_1, \lambda_2 < 0$, and $0 < \gamma, \alpha \leq 1$.

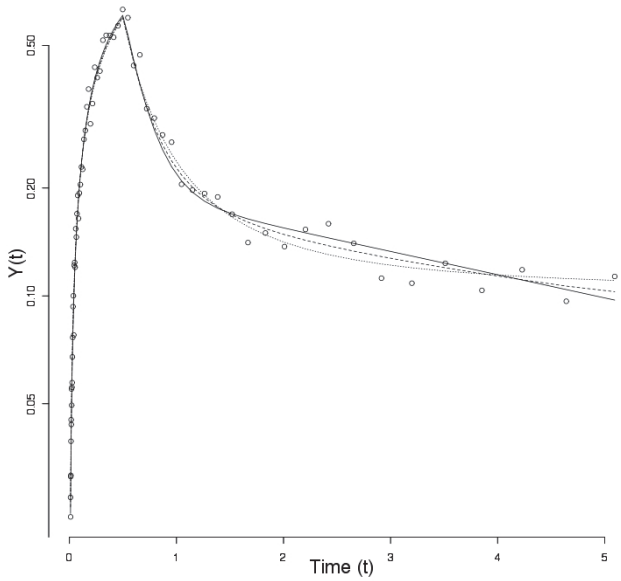

Fig. 3. The fit of the response function corresponding to ODE (solid line), commensurate FDE (dashed line), and non-commensurate FDE (widely dashed line) two compartments system to simulated data (open circles) generated using an eight compartments ODE mammillary model and step function input.

Note again the added flexibility introduced by use of a sum Mittag-Leffler functions in respect to a sum of exponentials: the decreases in objective function values (minus twice log-likelihood) for model (36) (commensurate system response function) and (46) (non-

commensurate system response function) vs. model (35) (ordinary system response function), were -39.3 and -58.22, respectively, values that are again highly significant according to the Akaike criterion (Akaike), and that would select the response function corresponding to the non-commensurate system.

The response functions used above are of course not limited to input-output in the same compartment. The following figure shows the result of the fit to simulated data generated using the same mammillary model used in Figure 2 and 3 but with an added ninth compartment (gut) which receives the and delivers it to the central compartment (at a rate k_{19} =1 (min^{-1})), that is an example of a reducible system. The input consist now of two unit-impulses at time 0 and 2.3 (min) in the gut compartment. The competing models (for the response function in blood to a unit-input in the gut, $h_{19}(t)$) are the convolutions of the same models used in the previous examples with the mono-exponential $\theta_3 e^{\lambda_3 t}$ (that is, the open-loop unit-impulse response function for the gut). We estimate the same parameters as for the previous example, with the addition of λ_3 (constrained to be negative), and θ_3 fixed to one since it is not identifiable from the experiment.

Figure 4 shows the result of the fit of the models to the simulated data.

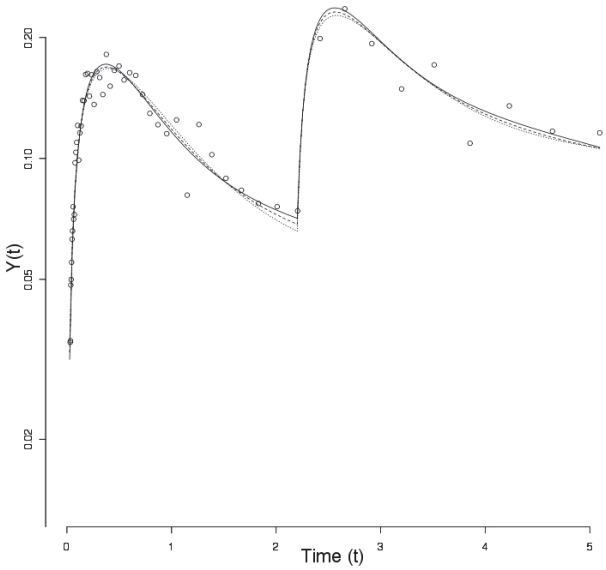

Fig. 4. See legend to Figure 3. Simulated data (open circles) correspond to two unit-impulse inputs in a peripheral compartment (gut).

The decreases in objective function for the commensurate and non-commensurate vs. the ordinary system response functions were -7.2 and -6.9, respectively. These values that are still significant according to the Akaike criterion (Akaike), and select the commensurate response function as "best" model. More importantly the narrowing distance between the likelihood of the models demonstrates how the choice of the input can influence model selection, and how a single unit-impulse input might result in the most informative model

selection test input to discriminate between ordinary and fractional (linear) compartmental models.

6. Fractional order non-linear compartmental models

The generalization of commensurate fractional order linear compartmental systems to non-linear systems can be achieved simply by considering fluxes other than the linear case equation (4). For example a Michaelis-Menten compartmental model includes fluxes given by equations (5), and takes the form:

$$D_{\blacktriangle}^{\alpha}\mathbf{x}(t)=\begin{pmatrix} -\sum\limits_{\substack{j=0\\ j\neq 1}}^{m}\dfrac{a_{j1}}{b_{j1}+x_1} & \cdots & \dfrac{a_{1m}}{b_{1m}+x_m} \\ \cdots & \cdots & \cdots \\ \dfrac{a_{m1}}{b_{m1}+x_1} & \cdots & -\sum\limits_{\substack{j=0\\ j\neq m}}^{m}\dfrac{a_{jm}}{b_{jm}+x_m} \end{pmatrix}\mathbf{x}(t) \qquad \mathbf{x}(0)=\mathbf{x}_0 \tag{47}$$

which is analogous to the ordinary differential compartmental model with Michelis-Menten elimination (Tong and Metzler). The non-commensurate case can be similarly be defined by the following representation:

$$D_{\blacktriangle}^{\alpha}\mathbf{x}(t)=\begin{pmatrix} -\sum\limits_{\substack{j=0\\ j\neq 1}}^{m}\dfrac{a_{j1}}{b_{j1}+x_1} & \cdots & \dfrac{a_{1m}}{b_{1m}+D_{\blacktriangle}^{\alpha m-\alpha}x_m(t)} \\ \cdots & \cdots & \cdots \\ \dfrac{a_{m1}}{b_{m1}+x_1} & \cdots & -\sum\limits_{\substack{j=0\\ j\neq m}}^{m}\dfrac{a_{jm}}{b_{jm}+D_{\blacktriangle}^{\alpha m-\alpha}x_m(t)} \end{pmatrix}\begin{pmatrix} x_1(t) \\ D_{\blacktriangle}^{\alpha 2-\alpha}x_2(t) \\ \cdots \\ D_{\blacktriangle}^{\alpha m-\alpha}x_m(t) \end{pmatrix} \qquad \mathbf{x}(0)=\mathbf{x}_0 \tag{48}$$

where $\alpha_1=\alpha,\ \alpha\geq\alpha_2,...,\alpha_m$. This model is well defined in terms of flux balances, and the dimensions of the constants a_{ij} and b_{ij}. The most general case of non-linear non-commensurate fractional order compartmental structure can be obtained from the general case equation

$$D_{\blacktriangle}^{\alpha}x_i(t)=R_{1o}(t)+\sum_{\substack{j=1\\ j\neq i}}^{n}R_{ij}(D_{\blacktriangle}^{\alpha-\alpha j}x_j)-\sum_{\substack{j=1\\ j\neq i}}^{n}R_{ji}(D_{\blacktriangle}^{\alpha-\alpha i}x_i)+R_{oi}(D_{\blacktriangle}^{\alpha-\alpha i}x_i) \tag{49}$$

where again all the differential equations are of the same fractional order, allowing of mass balance and units consistency across equations.

7. Final remarks

The main purpose of this chapter is to discuss the use of systems of fractional differential equations to represent compartmental models. We first considered commensurate fractional differential equations compartmental systems, and show how they have a direct

relationship with ordinary differential equation compartmental systems. We also showed how non-commensurate systems of fractional differential equations require special formulations to correspond to a compartmental system, and describe alternative way to represent such systems, including a novel general representation (equation (42)).

For both commensurate and non-commensurate compartmental systems we give expressions for response functions that can be used to describe input-output experiments, and satisfy physical constraints (non-negativity in particular). We show how sums of Mittag-Leffler functions with a single parameter, equation (35), are solutions for the response of compartmental system of commensurate fractional differential to impulse-inputs, while sums of two-parameters Mittag-Leffler functions, equation (46), are the corresponding solutions for a system of non-commensurate fractional differential equations. The corresponding unit-impulse response functions (sums of Mittag-Leffler functions, defined for each of the input/output possible combinations, $h_{ij}(t)$, $i, j = 1,...,m$) can be used to represent the response of a fractional order compartmental system to arbitrary inputs by means of the ordinary convolution operator, e.g. equation (33). This is in direct analogy with the use of unit-impulse response functions (consisting of sum of exponentials) used for ordinary compartmental models.

We also describe general formulations for fractional order non-linear kinetics compartmental models, and briefly discuss how such models could be implemented and solved using software algorithms.

In conclusion, while insight into the physiological interpretability of fractional compartmental system remains open to discussion, the technology is becoming available to investigate the application of these models to data sets that might show complex fractional kinetics. The bottleneck to initiate this kind of investigation is the development of appropriate software. In particular, while the evaluation of (sums of) Mittag-Leffler functions can be considered (to some extent) solved, the stable and reliable integration of system of fractional differential equations of the form (37), and even more so of the form of (42) or (49), is not non-trivial task, especially taking into consideration that the corresponding software needs to be interfaced with a non-linear regression program. The author is actively working on a set of routines that will interface with the open source program R and allow the use of multi-term Mittag-Leffler response functions as well as the integration of fractional compartmental models.

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This book provides an example of the successful and rapid expansion of bioengineering within the world of the science. It includes a core of studies on bioengineering technology applications so important that their progress is expected to improve both human health and ecosystem. These studies provide an important update on technology and achievements in molecular and cellular engineering as well as in the relatively new field of environmental bioengineering. The book will hopefully attract the interest of not only the bioengineers, researchers or professionals, but also of everyone who appreciates life and environmental sciences.

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