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FRACTIONAL CALCULUS APPROACH TO BIOREACTION MODELING

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Abstract

In this work, the application of fractional calculus to mathematical modeling of bioreactions is analyzed. The proposed models, employing fractional order operators in time, are generalizations of the classical bioreactor model, which consists of a system of nonlinear ODEs. Different ways for introducing time-fractional operators in the classical model are discussed. It is shown that formal "fractionalization" can lead to physically unacceptable models and some solutions to overcome this problem are proposed. To evaluate the ability of the considered fractional order models to correctly reproduce the expected behavior of the system, numerical experiments are performed, based on a generalization of the fractional Adams method.

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1. Introduction

In the past few decades fractional-order generalizations of various classical integer-order models are extensively studied [3, 4]. In many cases they allow to obtain better quantitative agreement with experimental data. The non-local character of fractional derivatives in time makes their use appropriate in the modeling of phenomena, where some hereditary mechanisms are present. In such cases a physical meaning of the order of fractional derivative is an index of memory [12].

Due to the non-locality property of time-fractional derivatives, they appear to be suitable for describing biological reactive systems, where the memory effects are important. Time-fractional models for some biological reactions are proposed and studied in [21], including models of fermentation processes. In general, a bioreaction model is based on a system of nonlinear ordinary differential equations [2, 14, 19]. Therefore, a natural question is how to treat the different equations in the system during the "fractionalization". In [21] the orders of the fractional derivatives in the different equations of the system are considered to be independent. In [1], a fractional order model was proposed for a bioreactor system, considering a fractional differential equation for the biomass evolution and an integer-order differential equation for the substrate dynamics. Starting from the proposed in [21] models, a discussion on the question of proper "fractionalization" of a bioreactor system is initiated in [9] with emphasis on the question whether a fractional model is able to reproduce correctly the naturally expected behavior of the underlying processes.

The present work extends our previous study [5] on the modeling of diffusion-bioreaction systems by employing fractional time-derivatives. Different approaches for "fractionalization" are discussed and the behavior of the corresponding solutions is assessed with the help of computer simulations. The numerical solutions are found by applying the fractional Adams method [10, 11] and its generalization proposed in [6].

The rest of the paper is organized as follows. In Section 2 some basic definitions and properties of fractional calculus operators are summarized. In Section 3 the relaxation equation with the composite fractional derivative is discussed. In Section 4, after describing the classical model of a bioreactor, we present different approaches for its generalization by employing fractional derivatives. For further improvement of the results at the beginning of the process, a fractional model with composite derivatives is considered in Section 5. To examine the qualitative behavior of the solutions to the considered fractional bioreactor models in Sections 4 and 5, numerical experiments are performed for different values of the parameters. Section 6 contains concluding remarks.

2. **Preliminaries in Fractional calculus**

We list first basic definitions and properties of fractional calculus operators and special functions, used throughout this work. For more details we refer e.g. to [16].

The Riemann-Liouville fractional integral J_t^α of order $\alpha > 0$ is defined for locally integrable functions by the identity

$$J_t^\alpha u(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} u(\tau)\, \mathrm{d}\tau, \quad \alpha > 0, \tag{1}$$

where $\Gamma(\cdot)$ denotes the Gamma function. For $\alpha = 0$ we set $J_t^0 = I$, where I is the identity operator. The Caputo fractional derivative ${}^{C}D_t^\alpha$ and the Riemann-Liouville fractional derivative ${}^{RL}D_t^\alpha$ of order $\alpha \in (0,1)$ are defined as follows

$${}^{C}D_t^\alpha = J_t^{1-\alpha} \frac{\mathrm{d}}{\mathrm{d}t}, \quad {}^{RL}D_t^\alpha = \frac{\mathrm{d}}{\mathrm{d}t} J_t^{1-\alpha}, \qquad \alpha \in (0,1). \tag{2}$$

The fractional derivatives of Caputo and Riemann-Liouville types are related via the identities

$${}^{C}D_t^\alpha u(t) = {}^{RL}D_t^\alpha \left(u(t) - u(0)\right) = {}^{RL}D_t^\alpha u(t) - u(0) \frac{t^{-\alpha}}{\Gamma(1-\alpha)}. \tag{3}$$

For $\alpha = 1$ the above definitions give the classical first order differentiation and integration operators. For the first order derivative the notation D_t^1 is also used in the sequel.

The following relations between fractional derivatives and integrals are satisfied (see e.g. [16, 5]):

$${}^{RL}D_t^\alpha J_t^\alpha u(t) = {}^{C}D_t^\alpha J_t^\alpha u(t) = u(t), \tag{4}$$

$$J_t^\alpha \ {}^{RL}D_t^\alpha u(t) = u(t) - \left(J_t^{1-\alpha} u\right)(0^+) \frac{t^{\alpha-1}}{\Gamma(\alpha)} = u(t), \tag{5}$$

$$J_t^\alpha \ {}^{C}D_t^\alpha u(t) = u(t) - u(0). \tag{6}$$

In (5) it is used that $\left(J_t^{1-\alpha} u\right)(0^+) = 0$ for locally integrable functions u. Moreover, the definition of the Caputo derivative in (2) and property (4) yield

$${}^{RL}D_t^{1-\alpha} \ {}^{C}D_t^\alpha u(t) = {}^{RL}D_t^{1-\alpha} \ J_t^{1-\alpha} D_t^1 u(t) = D_t^1 u(t). \tag{7}$$

The classical Mittag-Leffler function $E_{\alpha,\beta}(\cdot)$ is defined by the series

$$E_{\alpha,\beta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k + \beta)}. \qquad z \in \mathbb{C}, \ \alpha > 0, \beta \in \mathbb{R}, \tag{8}$$

If $\beta = 1$ the traditional notation $E_\alpha(z) = E_{\alpha,1}(z)$ is used.

The fractional relaxation equation

$${}^{C}D_t^\alpha u(t) = -\lambda u(t), \quad t > 0, \ \ 0 < \alpha \leq 1, \ \ \lambda > 0, \tag{9}$$

has a unique solution, given by

$$u(t) = u(0)E_\alpha(-\lambda t^\alpha). \tag{10}$$

The relation

$$\frac{\mathrm{d}}{\mathrm{d}t}E_\alpha(-\lambda t^\alpha) = -\lambda t^{\alpha-1}E_{\alpha,\alpha}(-\lambda t^\alpha) \tag{11}$$

together with definition (8) implies

$$\frac{\mathrm{d}}{\mathrm{d}t}E_\alpha(-\lambda t^\alpha) \sim -\lambda\frac{t^{\alpha-1}}{\Gamma(\alpha)}, \quad t \to 0^+, \quad 0 < \alpha < 1. \tag{12}$$

Therefore, the gradient of the solution $u(t)$ to the relaxation equation (9) is infinite as $t \to 0^+$.

Concerning the asymptotic behavior of $E_\alpha(-\lambda t^\alpha)$ for large t, we have [16]

$$E_\alpha(-\lambda t^\alpha) \sim \frac{t^{-\alpha}}{\lambda\Gamma(1-\alpha)}, \quad t \to +\infty, \quad \lambda > 0, \quad 0 < \alpha < 1. \tag{13}$$

The slow algebraic decay (13) of the relaxation function (10) for $0 < \alpha < 1$, compared to the exponential decay when $\alpha = 1$, motivates the use of fractional derivatives in the modeling of anomalous relaxation. However, the infinite rate of change in (12) for small t seems unphysical. A step towards resolving this problem is to consider the so-called composite fractional derivative (this notion is introduced in [16]). Some basic results on the composite fractional relaxation equation are given in the next section.

3. Composite fractional relaxation equation

Let $\alpha \in (0, 1)$ and $c_1, c_\alpha > 0$. Consider the composite fractional relaxation equation

$$\mathbb{D}_t^{1,\alpha}u(t) = -\lambda u(t), \quad t > 0, \quad 0 < \alpha < 1, \quad \lambda > 0, \tag{14}$$

where $\mathbb{D}_t^{1,\alpha}$ is the composite differential operator of Caputo type defined as follows

$$\mathbb{D}_t^{1,\alpha}u(t) = c_1 D_t^1 u(t) + c_\alpha {}^C D_t^\alpha u(t). \tag{15}$$

The solution of equation (14) is given by (see e.g. [7])

$$u(t) = u(0)\left(1 - \frac{\lambda}{c_1}tE_{(1,1-\alpha),2}\left(-\frac{\lambda}{c_1}t, -\frac{c_\alpha}{c_1}t^{1-\alpha}\right)\right), \tag{16}$$

where $E_{(\alpha_1,\alpha_2),\beta}$ denotes the multinomial Mittag-Leffler function

$$E_{(\alpha_1,\alpha_2),\beta}(z_1, z_2) = \sum_{k=0}^{\infty}\sum_{l=0}^{\infty}\frac{(k+l)!}{k!l!}\frac{z_1^k z_2^l}{\Gamma\left(\beta + \alpha_1 k + \alpha_2 l\right)}, \tag{17}$$

introduced in [17], see also [7, 13] where some basic properties are established.

After differentiation in (16) it follows by applying property (2.11) in [7] that the solution of the composite equation (14) satisfies

$$\frac{\mathrm{d}u}{\mathrm{d}t} = -\frac{\lambda}{c_1} E_{(1,1-\alpha),1}\left(-\frac{\lambda}{c_1}t, -\frac{c_\alpha}{c_1}t^{1-\alpha}\right) u(0).$$

Therefore, taking into account definition (17), we deduce that the rate of change of the solution for $t \to 0^+$ is $-\frac{\lambda}{c_1}u(0)$, i.e. it is finite as in the classical case. The asymptotic behavior of the solution for $t \to +\infty$ is similar to that of the solution of (9), i.e. it is proportional to $t^{-\alpha}$, see e.g. [16].

Let us define the convolutional operator

$$\mathbb{J}_t^{1,\alpha} u(t) = (\kappa_\alpha * u)(t) = \int_0^t \kappa_\alpha(t-\tau)u(\tau)\,\mathrm{d}\tau, \tag{18}$$

where

$$\kappa_\alpha(t) = \frac{1}{c_1} E_{1-\alpha}\left(-\frac{c_\alpha}{c_1}t^{1-\alpha}\right). \tag{19}$$

Operator $\mathbb{J}_t^{1,\alpha}$ is a left inverse operator of the composite fractional differential operator (15). More precisely, it is related to the composite derivative (15) via the identities

$$\mathbb{D}_t^{1,\alpha}\mathbb{J}_t^{1,\alpha} u(t) = u(t), \qquad \mathbb{J}_t^{1,\alpha}\mathbb{D}_t^{1,\alpha} u(t) = u(t) - u(0). \tag{20}$$

Indeed, from definitions (15) and (18), and using the commutativity and associativity properties of convolution, and the fact that $(\kappa_\alpha * u)(0) = 0$ implies $J_t^{1-\alpha} D_t^1 (\kappa_\alpha * u) = D_t^1 J_t^{1-\alpha}(\kappa_\alpha * u)$ (see e.g. (3)), we deduce

$$\begin{aligned} \mathbb{D}_t^{1,\alpha}\mathbb{J}_t^{1,\alpha} u(t) &= \left(c_1 D_t^1 + c_\alpha D_t^1 J_t^{1-\alpha}\right)(\kappa_\alpha * u) \\ &= D_t^1\left(\left(c_1\kappa_\alpha + c_\alpha J_t^{1-\alpha}\kappa_\alpha\right) * u\right), \end{aligned} \tag{21}$$

$$\begin{aligned} \mathbb{J}_t^{1,\alpha}\mathbb{D}_t^{1,\alpha} u(t) &= \kappa_\alpha * \left(c_1 D_t^1 u + c_\alpha J_t^{1-\alpha} D_t^1 u\right) \\ &= \left(c_1\kappa_\alpha + c_\alpha J_t^{1-\alpha}\kappa_\alpha\right) * D_t^1 u. \end{aligned} \tag{22}$$

Applying the integration formula

$$J_t^\beta\left(E_\alpha(-\lambda t^\alpha)\right) = t^\beta E_{\alpha,\beta+1}(-\lambda t^\alpha)$$

and the identity

$$E_\alpha(-\lambda t^\alpha) + \lambda t^\alpha E_{\alpha,\alpha+1}(-\lambda t^\alpha) = 1,$$

which follow directly from the definition of the Mittag-Leffler function (8), we obtain

$$c_1\kappa_\alpha(t) + c_\alpha J_t^{1-\alpha}\kappa_\alpha(t) = 1.$$

By plugging the last identity in (21) and (22) we deduce the properties in (20).

4. **Fractional bioreaction models**

4.1. **Classical bioreactor model.** Let us consider first the classical model of a bioreaction. In a continuous bioreactor due to presence of biomass (e.g. bacteria) with concentration $B(t)$ and substrate (nutrient) with concentration $S(t)$ a process takes place. As a result, a product with concentration $P(t)$ is produced. Thus, due to the bioprocess, the concentrations of biomass $B(t)$ and product $P(t)$ increase at the expense of the nutrient concentration $S(t)$. To keep the process, it is fed with fresh nutrient with given concentration S_{in} via inflow at a given rate q.

A classical bioreactor model describes the evolution of the concentrations $S(t)$, $B(t)$ and $P(t)$ via the following system of ordinary differential equations [14, 19, 2]:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -a\ \mu(S)B(t) - q(S(t) - S_{in}), \qquad S(0) = S_0, \tag{23}$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = \mu(S)B(t) - qB(t) - dB(t), \qquad B(0) = B_0, \tag{24}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = b\ \mu(S)B(t) - qP(t), \qquad P(0) = P_0. \tag{25}$$

Here $a > 0$, $b > 0$, $q \geq 0$, $d \geq 0$ are constant parameters: a - growth yield, b - product rate, q - dilution rate, d - mortality rate (of bacteria). S_0, B_0 and P_0 are the initial concentrations of substrate, biomass, and product, respectively, t is time. The specific growth rate $\mu(S) \geq 0$ represents the dynamic behavior of microorganisms. Different types of specific growth rate functions $\mu(\cdot)$ are used in the literature (see [14, 19, 2]). One of the most popular is the Monod function [18]:

$$\mu(S) = \mu^* \frac{S}{k + S}, \tag{26}$$

where μ^* and k are positive parameters. For the numerical simulations presented in this work the Monod function (26) is used.

4.2. **"Fractionalization" of the bioreactor model.** The simplest formal approach to "fractionalize" the classical bioreaction model (23)-(25) is via replacement of the first order derivatives by Caputo fractional derivatives (see e.g. [21, 9, 1]). This leads to the system

$${}^{C}D_t^{\alpha} S(t) = -a\ \mu(S)B(t) - q_{\alpha}(S(t) - S_{in}), \quad S(0) = S_0, \tag{27}$$

$${}^{C}D_t^{\beta} B(t) = \mu(S)B(t) - q_{\beta}B(t) - dB(t), \quad B(0) = B_0, \tag{28}$$

$${}^{C}D_t^{\gamma} P(t) = b\ \mu(S)B(t) - q_{\gamma}P(t), \quad P(0) = P_0, \tag{29}$$

where, in the general case, the three orders of fractional derivatives $\alpha, \beta, \gamma \in (0, 1)$ and the corresponding dilution rates $q_{\alpha}, q_{\beta}, q_{\gamma}$ are considered independent.

It should be emphasized that in the equations (27)-(29) the parameters a, b, and d, as well as μ^* in (26), have dimensions different from these in the classical system (23)-(25). Their dimensions correspond to the dimensions of the fractional derivatives in the left-hand side of the respective equations. For the same reason the fractional dilution rates q_δ ($\delta = \alpha,\ \beta$, or γ) have dimensions $[T^{-\delta}]$, where T is the characteristic time.

In order to analyze how the direct replacement of the first order derivatives with fractional Caputo derivatives affects the different terms in the right-hand side of the equations (27)-(29) they are rewritten in an equivalent form. This is done in a standard way by applying Riemann-Liouville derivative operators ${}^{RL}D_t^{1-\alpha}$, ${}^{RL}D_t^{1-\beta}$ and ${}^{RL}D_t^{1-\gamma}$ to equations (27), (28) and (29), respectively, and by using identity (7). In this way the system (27)-(29) is transformed into the following system of equations:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -a\,{}^{RL}D_t^{1-\alpha}\left(\mu(S)B\right) - q_\alpha\,{}^{RL}D_t^{1-\alpha}\left(S(t) - S_{in}\right), \tag{30}$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = {}^{RL}D_t^{1-\beta}\left(\mu(S)B\right) - q_\beta\,{}^{RL}D_t^{1-\beta}B(t) - d\,{}^{RL}D_t^{1-\beta}B(t), \tag{31}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = b\,{}^{RL}D_t^{1-\gamma}\left(\mu(S)B\right) - q_\gamma\,{}^{RL}D_t^{1-\gamma}P(t), \tag{32}$$

with initial conditions $S(0) = S_0, B(0) = B_0, P(0) = P_0$. Taking into account relations (2) and (5), it is easy to verify that the two systems (27)-(29) and (30)-(32) are equivalent.

Some faults of this way of "fractionalization" are discussed in our previous work [5]. For example, in the right-hand sides of equations (30)-(32) different terms, describing different subprocesses, are present. However, all terms in a given equation have one and same order of fractional evolution (index of memory), which seems unnatural. Another inconsistency of the fractional derivative model (30)-(32) is related to the fact that at different orders of the fractional derivatives the different equations predict different outflow rates, is discussed in [5]. Therefore, a direct replacement of the first time-derivatives in the system (23)-(25) with derivatives of fractional orders is not an appropriate approach for "fractionalization" of a bioreaction model. Let us note that the above problems do not appear in fractional derivative models of batch bioreactors (see, for instance, [9, 21]), where inflow and outflow are not present, i.e. $q_\delta = 0$, $\delta = \alpha, \beta, \gamma$.

To avoid the contradictions encountered above, an alternative approach of "fractionalization" of system (23)-(25) is proposed in [5]. The classical mathematical model (23)-(25) represents mass conservation of the considered substances at already specified rates of their change. Since the first derivatives in the classical model guarantee the mass conservation of the corresponding substances, any change in the left-hand sides of these equations can lead to

violation of the mass conservation, which is demonstrated by an example in [5]. Therefore, alternatively to system (30)-(32), the fractional order derivatives of Riemann-Liouville type are applied to the terms in the right-hand side that correspond to the constitutive relations, depending on the process that they describe:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -a\,{}^{RL}D_t^{1-\alpha}(\mu(S)B) - q(S(t)-S_{in}), \tag{33}$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = {}^{RL}D_t^{1-\beta}(\mu(S)B) - qB(t) - d\,{}^{RL}D_t^{1-\beta_d}B(t), \tag{34}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = b\,{}^{RL}D_t^{1-\gamma}(\mu(S)B) - qP(t), \tag{35}$$

with initial conditions $S(0)=S_0, B(0)=B_0, P(0)=P_0$. The fractional derivative model (33)-(35) is equivalent to the previously described (27)-(29) and (30)-(32)in the case of $q=d=0$. An advantage of this approach is that different sub-processes can be treated separately via the corresponding to the constitutive relations terms in the right-hand sides of the equations. Regarding the in/out flows it is not physically justified that they have fractional evolution and they stay unchanged, as in (23)-(25). Also the possibility is considered that the mortality can have a nonlocal effect on the evolution of the biomass with memory index, β_d, which can be different than that of the bacterial, β, however this needs further clarification.

As pointed out in [9] and [5], another open question is related to the orders α,β,γ of the fractional evolution terms ${}^{RL}D_t^{1-\delta}(\mu(S)B(t))$ in the system (33)-(35), $\delta=\alpha,\beta,\gamma$. Can the orders of fractional derivatives in the different equations be considered different, or they should be equal, i.e. $\alpha=\beta=\gamma$? The arguments given in [5] are in favor of equal fractional orders in the model (33)-(35). However, further investigations are necessary for a definitive answer of this question.

4.3. **Numerical results.** The discussed above fractional order bioreaction models are studied numerically in [5] for different functions μ in the case of absence of inflow/outflow ($q=0$) and (in most of the cases) in the absence of mortality ($d=0$). Let us recall that in this case all fractional models considered above are equivalent and can be rewritten as the following system of (nonlinear) integral equations

$$S(t) = S_0 - a\ J_t^{\alpha}\left(\mu(S)B(t)\right), \tag{36}$$

$$B(t) = B_0 + J_t^{\beta}\left(\mu(S)B(t)\right), \tag{37}$$

$$P(t) = P_0 + b\ J_t^{\gamma}\left(\mu(S)B(t)\right). \tag{38}$$

The system is solved numerically by using the fractional Adams method [10, 11].

In a physically meaningful bioreaction model the functions $B(t)$ and $P(t)$ should be monotonically increasing, while $S(t)$ should be a monotonically decreasing function. To demonstrate how the orders α, β, γ in the model (36-38) can affect the monotonicity of the results, a group of simulations is performed in [5], where the specific growth rate function $\mu(S)$ is the Monod function (26) and for fixed other parameters a, b, μ^* and $q = d = 0$ the fractional orders α, β and γ vary in the interval $(0, 1]$. The numerical results in [5] show that there exists a set of parameters ($\mu^*,\ a,\ b,\ S_0,\ B_0$ and P_0) such that:
- If $\beta < \alpha$ then $B(t)$ is a non-monotone function;
- If $\gamma < \alpha$ then $P(t)$ is a non-monotone function.

Therefore, at some values of the fractional orders $\alpha,\ \beta$ and γ in the interval $(0, 1)$ in the absence of in/outflow and mortality of bacteria the numerical results predict non-monotonic evolution of biomass and product. This indicates that for these values the model is not physically meaningful.

Similar numerical results are obtained also in [20] for different specific growth rate functions $\mu(S)$ and a large set of parameters.

To avoid unphysical non-monotone results, in what follows we consider only models with one and the same fractional operator acting in the three equations of the system.

To illustrate the typical behavior of the functions $S(t)$, $P(t)$, and $B(t)$, in Figure 1 we present some numerical results from [5] in the case when the three fractional orders are equal $\alpha = \beta = \gamma = 0.25;\ 0.5;\ 0.75$. In all simulations presented in this work the specific growth rate function $\mu(S)$ is the Monod function (26) and the values of the parameters are taken from the experimental study [8] : $\mu^* = 0.6[h^{-1}];\ k = 0.81[g/L];\ a = 4.5$ and $b = 3.4$. The initial values are $S_0 = 5[g/L],\ B_0 = 0.1[g/L]$ and $P_0 = 0[g/L]$.

In Figure 1 we observe that the results for the classical case $\alpha = \beta = \gamma = 1$, given by dashed lines, are very close to that of $\alpha = \beta = \gamma = 0.75$. It is seen that at $t \to \infty$ the values for $S(t),\ B(t)$ and $P(t)$ are independent of the values of the fractional orders $\alpha = \beta = \gamma$. Thus the final values of $S(t),\ B(t)$ and $P(t)$ depend only on the parameters ($\mu^*,\ a,\ b,\ S_0,\ B_0$ and P_0). At given other parameters the evolution to these final values is determined by the fractional order $\alpha = \beta = \gamma$: the smaller the fractional order, the slower the process for large t, but faster for small t. Let us note that similar relationship between the rate of change and the fractional order is observed in the behavior of the Mittag-Leffler function, see (12) and (13), which is determining for the behavior of solutions to fractional order equations.

To examine the behavior of the solution at the beginning of the process, in Figure 2 the results for the substrate $S(t)$ and the product $P(t)$ from Figure 1 are shown for small times. It is seen that at $t \to 0^+$ the gradient of the solution is infinite (negative for S and positive for P). This conclusion is confirmed numerically by decreasing of the time step h. A solution to overcome this

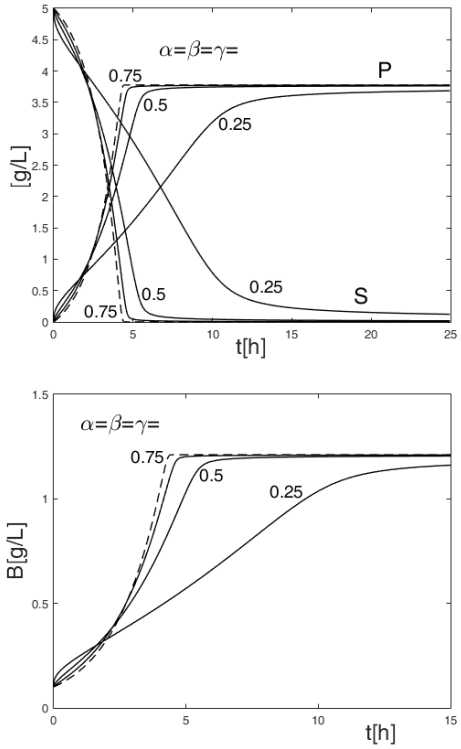

FIGURE 1. Evolution of concentrations $S(t)$ and $P(t)$ (left), and $B(t)$ (right) for $\alpha = \beta = \gamma = 0.25;\ 0.5;\ 0.75$. Dashed lines correspond to the classical model $\alpha = \beta = \gamma = 1$.

nonlogical behavior at the beginning of the process predicted by the fractional order models is proposed in the next section.

5. **A bioreaction model with composite fractional derivatives**

As discussed in the previous section, introduction of time-fractional derivatives in the system implies that the decay of $S(t)$ and the increase of $B(t)$ and $P(t)$ become slower for large times, compared to the classical model, which is a typical behavior for a bioprocess. However, this type of "fractionalization" has also an unwanted effect: the rate of change of these functions becomes infinite for $t \to 0^+$, which does not correspond to the real process. To improve this fault, we next propose a bioreaction model, based on the composite fractional derivative (15) and the corresponding integral operator (18).

Let us start again from the classical bioreaction model (23)-(25) and replace formally the first order time derivatives by the composite fractional

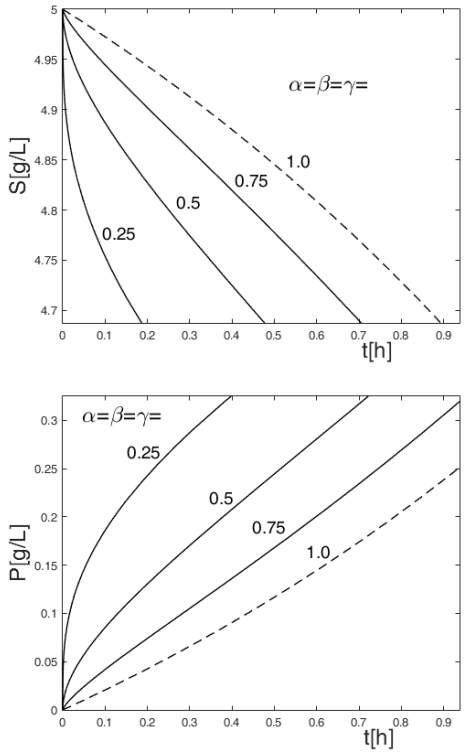

FIGURE 2. Evolution of concentrations $S(t)$ (left), and $P(t)$ (right) from Figure 1 at the beginning of the process (small t).

derivative $\mathbb{D}_t^{1,\alpha}$, defined in (15):

$$\mathbb{D}_t^{1,\alpha}S(t) = -a\ \mu(S)B(t) - q(S(t) - S_{in}), \qquad S(0) = S_0, \tag{39}$$

$$\mathbb{D}_t^{1,\alpha}B(t) = \mu(S)B(t) - qB(t) - dB(t), \qquad B(0) = B_0, \tag{40}$$

$$\mathbb{D}_t^{1,\alpha}P(t) = b\ \mu(S)B(t) - qP(t), \qquad P(0) = P_0, \tag{41}$$

Since our aim is to assess numerically the effect of the composite derivative, we assume further $q = d = 0$. Applying relations (20) for the composite differential operator and the corresponding integral operator we deduce the following system

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -a\ \frac{\mathrm{d}}{\mathrm{d}t}\mathbb{J}_t^{1,\alpha}(\mu(S)B(t)), \quad S(0) = S_0, \tag{42}$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = \frac{\mathrm{d}}{\mathrm{d}t}\mathbb{J}_t^{1,\alpha}(\mu(S)B(t)), \quad B(0) = B_0, \tag{43}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = b\ \frac{\mathrm{d}}{\mathrm{d}t}\mathbb{J}_t^{1,\alpha}(\mu(S)B(t)), \quad P(0) = P_0, \tag{44}$$

where $\mathbb{J}_t^{1,\alpha}$ is the convolution operator with kernel $\kappa_\alpha(t)$, defined in (18). After integration we deduce the following system of Volterra integral equations, equivalent to system (42)-(44)

$$S(t) = S_0 - a\, \mathbb{J}_t^{1,\alpha}\left(\mu(S)B(t)\right), \tag{45}$$

$$B(t) = B_0 + \mathbb{J}_t^{1,\alpha}\left(\mu(S)B(t)\right), \tag{46}$$

$$P(t) = P_0 + b\, \mathbb{J}_t^{1,\alpha}\left(\mu(S)B(t)\right). \tag{47}$$

For the numerical solution of the system (45)-(47) we use the predictor-corrector technique, developed in [6]. The integral equations are solved on a uniform mesh $t_j = jh$, $h = T/N$, $j = 0, 1, ..., N$, in two steps (y_j denotes the approximation for $y(t_j)$):

- Predictor step:

$$y_{n+1}^P = y_0 + \sum_{j=0}^{n} b_{j,n+1}\, F(t_j, y_j) \tag{48}$$

- Corrector step:

$$y_{n+1} = y_0 + \sum_{j=0}^{n} a_{j,n+1}\, F(t_j, y_j) + a_{n+1,n+1}\, F(t_{n+1}, y_{n+1}^P) \tag{49}$$

The coefficients $b_{j,n+1}$ in (48) and $a_{j,n+1}$ in (49) in the case of system (45)-(47) are given by

$$b_{j,n+1} = \kappa_\alpha^1\left(t_{n+1-j}\right) - \kappa_\alpha^1\left(t_{n-j}\right)$$

and

$$a_{j,n+1} = \begin{cases} \dfrac{\kappa_\alpha^2(t_n) - \kappa_\alpha^2(t_{n+1})}{h} + \kappa_\alpha^1(t_{n+1}) & \text{if } j = 0, \\ \dfrac{\kappa_\alpha^2(t_{n+2-j}) - 2\kappa_\alpha^2(t_{n+1-j}) + \kappa_\alpha^2(t_{n-j})}{h} & \text{if } 1 \le j \le n, \\ \dfrac{\kappa_\alpha^2(t_1)}{h} & \text{if } j = n+1. \end{cases}$$

Here

$$\kappa_\alpha^1(t) = \int_0^t \kappa_\alpha(\tau)\, \mathrm{d}\tau, \qquad \kappa_\alpha^2(t) = \int_0^t \kappa_\alpha^1(\tau)\, \mathrm{d}\tau,$$

where $\kappa_\alpha(t)$ is the function defined in (18).

The above representations for the coefficients $b_{j,n+1}$ and $a_{j,n+1}$ are derived applying the technique, developed in [6].

The equations (45)-(47), are solved simultaneously. At any time instant t_j, $j = 1, 2, ..., N$, the predictor step is performed first, for the three equations (36)-(38), then the obtained results are used in the corrector step, which gives the approximate solution at $t = t_j$ and the whole process is repeated.

For the numerical computation of ω_1 and ω_2 on the mesh we use numerical integration and the following formula to evaluate numerically the Mittag-Leffler kernel k_α, defined in (19), (see [16]):

$$E_\alpha(-\lambda t^\alpha) = \int_0^\infty e^{-rt} K_\alpha(r;\lambda)\,\mathrm{d}r, \quad 0 < \alpha < 1, \quad \lambda > 0,$$

where

$$K_\alpha(r;\lambda) = \frac{1}{\pi} \frac{\lambda r^{\alpha-1} \sin \alpha\pi}{r^{2\alpha} + 2\lambda r^\alpha \cos \alpha\pi + \lambda^2}.$$

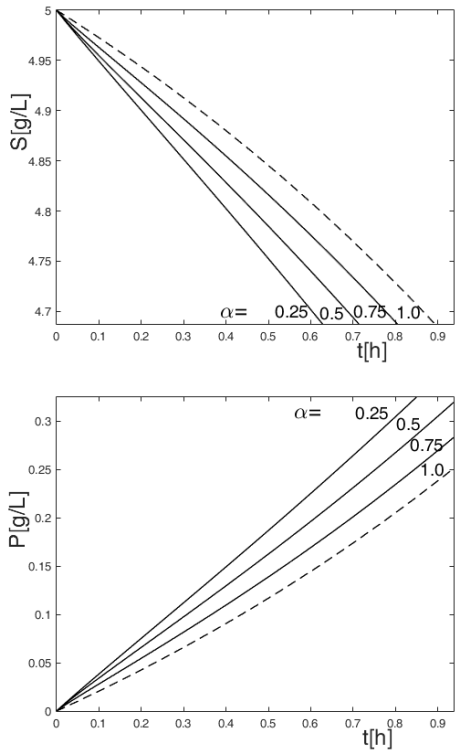

FIGURE 3. Evolution of concentrations $S(t)$ (left), and $P(t)$ (right) at the beginning of the process (small t) for the composite fractional model with different values of α and $c_1 = c_\alpha = 0.5$.

Numerical results for $S(t)$ and $P(t)$ in the case of the composite fractional model are presented in Figure 3 for different values of α, $c_1 = c_\alpha = 0.5$. The other parameters are taken as in the previous numerical experiments.

It is seen from Figure 3 that the gradient of the solution for $\alpha < 1$ is finite at $t \to 0^+$ in contrast to the results in Figure 2. The numerical results are in

agreement with the analytical findings given in Sections 2 and 3, regarding the properties of the solutions, which correspond to single Caputo and composite derivatives, as $t \to 0^+$. This is an argument to consider the model (42)-(44) based on composite fractional derivative as an alternative to that based on single fractional derivative (33)-(35).

Therefore, the question about the choice of a proper fractional derivative for "fractionalization" of the models of a bioreaction is essential and further investigations are necessary.

6. **Concluding remarks**

Fractional derivatives are a useful tool for modeling of different processes. However, an improper "fractionalization" of a classical model can lead to incorrect results. In the present study we analyze different approaches for modeling of a bioprocess, employing fractional derivatives in time.

As a general direction, in a mathematical model time-fractional evolution of a given process has to be introduced via the corresponding constitutive equation. Applying such an approach, different sub-processes, e.g. bioreaction, convection, diffusion, etc., that can have different evolution rates will be treated individually. Sub-processes that are related via a constitutive equation, on the other hand, will stay related after the "fractionalization" of the model.

Such an approach is used extensively in the case of viscoelastic models, where time fractional derivatives are introduced in the constitutive equations, see e.g. [3].

A model with composite time-fractional derivatives is proposed and studied numerically. The obtained results indicate that by the use of composite fractional derivative instead of single fractional Caputo derivative the problem with infinite rate of change of the solutions for small times is resolved.

The discussed approaches can be extended to the modeling of more complex processes such as biosurfactant production, transport and effect in multiphase fluid systems, where convection, diffusion, interface mass transfer, adsorption on the interfaces as well as complex fluid flow have to be considered.

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