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Fractional Derivative Modeling of Bioreaction-Diffusion Processes

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Abstract. The aim of this work is to analyze the application of fractional derivatives in time for the mathematical modeling of complex processes. As an example, a bioprocess is considered and the related distribution of nutrients, bacteria and bioproduct in multiphase fluid systems. The mathematical model under investigation includes convection, diffusion, bioreaction and boundary conditions at the interfaces: interface mass-transfer and adsorption. Different approaches of time-fractional modeling of a bioprocess are discussed. To evaluate the ability of a fractional order model to correctly reproduce the behavior that the underlying process must exhibit, numerical procedures are developed and computer simulations are performed.

INTRODUCTION

Fractional dynamics has experienced a firm progress during the past few decades [1, 2, 3]. A large number of recent experiments indicate that it is possible to significantly improve the agreement between the measured data and the solutions to the mathematical model equations if fractional order derivatives are used in the equations. One of the advantages of fractional derivatives is that they have a non-local character, in contrast to the integer order ones. In the case of time-fractional derivatives this can be interpreted as memory and a physical meaning of the fractional order is an index of memory [4]. It seems particularly natural to incorporate memory effects in the modeling equations, especially in models from life sciences [2]. Of particular interest is the application of Fractional Calculus to anomalous diffusion (see e.g. [5]). Anomalous diffusion is usually a part of a more complex process, such as reaction-diffusion [6, 7, 8], convection-diffusion [9, 10, 11], convection-reaction-diffusion [12], diffusion with mass absorption [13], diffusion with adsorption/desorption process at the boundary [14, 15, 16], diffusion and emission of volatile organic compounds [17]; or the diffusion character is different in the different space directions as in comb-like models for transport along spiny dendrites [18].

The nonlocality property makes time-fractional derivatives suitable for describing processes related to bioreaction. A time-fractional model describing a fermentation process is proposed in [19]. Based on this model, a discussion is initiated in [20] on the question whether the fractional order model is able to correctly reproduce the behavior that the underlying process must exhibit.

In the present work we discuss the modeling of bioreaction-diffusion processes by the use of fractional derivatives in time. In the case of such complex multi-component processes it is of crucial importance to use a proper "fractionalization" of the classical integer-order models. In a number of studies on time-fractional models the integer order time-derivatives are simply replaced by fractional order ones. While for mathematical modeling of a single process such a direct replacement could lead to correct results, in the case when several sub-processes are involved, each with its own specific evolution, this approach seems inappropriate. In the present analysis, in order to understand the relations between sub-processes, basic physical concepts (conservation laws and constitutive equations) are used. Such are Fick's first law that gives the relation between the diffusive flux and the gradient of the concentration; conservation of mass, microbial kinetics, Reynolds transport theorem, Gauss-Ostrogradsky theorem.

The rest of the paper is organized as follows. In the next section some basic definitions and properties of fractional calculus operators are listed. The classical model of a bioprocess and two approaches for its time-fractional general-

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ization are given in the following two sections. To obtain information about the qualitative behavior of the solutions to the time-fractional model (especially, the monotonicity of the solutions), numerical experiments are performed using the fractional Adams method. Further, the time-fractional modeling of anomalous diffusion is discussed in the case when it is a part of a more complex process and as an application a bioreaction-diffusion model is proposed. The last section contains a summary of our conclusions, conjectures and open questions.

PRELIMINARIES IN FRACTIONAL CALCULUS

In this section some basic definitions and properties of fractional calculus operators are summarized. For more details we refer to [1, 3, 21]. Since in this work we consider fractional order differential operators in Caputo and Riemann-Liouville sense, which orders are between 0 and 1, we present below only relevant definitions and properties, concerning these operators.

The Caputo fractional derivative ${}^{C}D_t^{\alpha}$ of order $\alpha \in (0,1)$ is defined by the identity:

$$ {}^{C}D_t^{\alpha} u(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{u'(\tau)}{(t-\tau)^{\alpha}} \, \mathrm{d}\tau, \quad \alpha \in (0,1), \tag{1} $$

where $\Gamma(\cdot)$ denotes the Gamma function.

The Riemann-Liouville fractional derivative ${}^{RL}D_t^{\alpha}$ of order $\alpha \in (0,1)$ is defined by:

$$ {}^{RL}D_t^{\alpha} u(t) = \frac{1}{\Gamma(1-\alpha)} \frac{\mathrm{d}}{\mathrm{d}t} \int_0^t \frac{u(\tau)}{(t-\tau)^{\alpha}} \, \mathrm{d}\tau, \quad \alpha \in (0,1). \tag{2} $$

The Riemann-Liouville fractional integral J_t^{α} of order $\alpha > 0$ is defined by

$$ J_t^{\alpha} u(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} u(\tau) \, \mathrm{d}\tau, \quad \alpha > 0. \tag{3} $$

Therefore, the fractional derivatives have the following representations

$$ {}^{C}D_t^{\alpha} = J_t^{1-\alpha} \frac{\mathrm{d}}{\mathrm{d}t}, \quad {}^{RL}D_t^{\alpha} = \frac{\mathrm{d}}{\mathrm{d}t} J_t^{1-\alpha}, \qquad \alpha \in (0,1). \tag{4} $$

In the limiting case $\alpha = 1$ the classical differentiation and integration operators are recovered:

$$ {}^{C}D_t^{1} u(t) = {}^{RL}D_t^{1} u(t) = \frac{\mathrm{d}u}{\mathrm{d}t}, \quad J_t^{1} u(t) = \int_0^t u(\tau) \, \mathrm{d}\tau. $$

The two types of fractional derivatives are related by the identity

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

which is often used as an alternative definition for the Caputo derivative (1).

The operators of fractional integration satisfy the semigroup property:

$$ J_t^{\alpha} J_t^{\beta} = J_t^{\alpha+\beta}, \quad \alpha, \beta > 0. \tag{6} $$

The related basic identities hold true

$$ J_t^{\alpha} g_{\beta}(t) = g_{\alpha+\beta}(t), \quad {}^{RL}D_t^{\alpha} g_{\beta}(t) = g_{\beta-\alpha}(t), \tag{7} $$

where

$$ g_{\beta}(t) = \frac{t^{\beta-1}}{\Gamma(\beta)}, \quad \beta > 0, \ t > 0. $$

The semigroup property (6) yields

$$ {}^{RL}D_t^{\alpha} J_t^{\alpha} u(t) = u(t). \tag{8} $$

Indeed, by applying the representation for the Riemann-Liouville derivative in (4) and property (6) it follows

$$ {}^{RL}D_t^{\alpha} J_t^{\alpha} u(t) = D_t^1 J_t^{1-\alpha} J_t^{\alpha} u(t) = D_t^1 J_t^1 u(t) = u(t), $$

where $D_t^1 = \mathrm{d}/\mathrm{d}t$. For an analogous property for the Caputo derivative we use (5) and (8) to obtain

$$ {}^{C}D_t^{\alpha} J_t^{\alpha} u(t) = {}^{RL}D_t^{\alpha} \left(J_t^{\alpha} u(t) - (J_t^{\alpha} u)(0) \right) = {}^{RL}D_t^{\alpha} J_t^{\alpha} u(t) = u(t) \tag{9} $$

for sufficiently well behaved functions u, for which $(J_t^{\alpha} u)(0) = 0$. For example, such are all locally integrable functions.For such functions also holds

$$ J_t^{\alpha} \, {}^{RL}D_t^{\alpha} u(t) = u(t) - \left(J_t^{1-\alpha} u \right)(0) \frac{t^{\alpha-1}}{\Gamma(\alpha)} = u(t), \tag{10} $$

where we have applied consecutively the definitions (2) and (1) to deduce

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

and then have used (9).

Further, applying the definition (1) for the Caputo derivative, the semigroup property (6) and the classical integral formula $J_t^1 D_t^1 u(t) = u(t) - u(0)$ we get $J_t^{\alpha} \, {}^{C}D_t^{\alpha} u(t) = J_t^{\alpha} J_t^{1-\alpha} D_t^1 u(t) = J_t^1 D_t^1 u(t) = u(t) - u(0)$. Therefore

$$ J_t^{\alpha} \, {}^{C}D_t^{\alpha} u(t) = u(t) - u(0). \tag{11} $$

The ordinary differential equation of fractional order

$$ {}^{C}D_t^{\alpha} y(t) = \lambda y(t) + f(t), \quad t > 0, \;\; 0 < \alpha \leq 1, \tag{12} $$

has a unique solution given by

$$ y(t) = y(0) E_{\alpha}(\lambda t^{\alpha}) + \int_0^t \tau^{\alpha-1} E_{\alpha,\alpha}(\lambda \tau^{\alpha}) f(t-\tau) \, \mathrm{d}\tau, \tag{13} $$

where $E_{\alpha}(\cdot)$ and $E_{\alpha,\alpha}(\cdot)$ denote Mittag-Leffler functions.

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

$$ E_{\alpha,\beta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k + \beta)}, \quad E_{\alpha}(z) = E_{\alpha,1}(z), \qquad \alpha, \beta, z \in \mathbb{C}, \;\; \Re\alpha > 0. \tag{14} $$

It is a generalization of the exponential function:

$$ E_{1,1}(z) = E_1(z) = e^z. \tag{15} $$

The relation

$$ \frac{\mathrm{d}}{\mathrm{d}t} E_{\alpha}(\lambda t^{\alpha}) = \lambda t^{\alpha-1} E_{\alpha,\alpha}(\lambda t^{\alpha}), \quad \lambda \in \mathbb{R}, \; 0 < \alpha \leq 1, \tag{16} $$

which can be verified by the use of definition (14), shows that for $0 < \alpha < 1$ the gradient of the Mittag-Leffler function $E_{\alpha}(\lambda t^{\alpha})$, is infinite as $t \to 0^+$, more precisely

$$ \frac{\mathrm{d}}{\mathrm{d}t} E_{\alpha}(\lambda t^{\alpha}) \sim t^{\alpha-1}, \quad t \to 0^+, \quad 0 < \alpha < 1. \tag{17} $$

On the other hand, the asymptotic behavior of the Mittag-Leffler function $E_{\alpha}(-\lambda t^{\alpha})$, $0 < \alpha < 1$, for large t is as follows

$$ E_{\alpha}(-\lambda t^{\alpha}) \sim t^{-\alpha}, \quad t \to +\infty, \quad \lambda > 0, \;\; 0 < \alpha < 1. \tag{18} $$

CLASSICAL MODELS OF A BIOPROCESS

A classical bioreactor is filled with a certain material, the so-called substrate (nutrient, which is usually some kind of sugar like glucose or fructose) and an amount of biomass (a special type of bacteria). Due to the presence of bacteria and nutrient for them there is a process of fermentation. As a result of this process a product (for example biofuel, biosurfactant, etc.) is produced, at the expense of the nutrient. To keep the process, nutrition is continuously supplied via inflow to the reactor, and at the same rate outflow the product is extracted. A few other ingredients are present in the bioreactor, however, they do not take part in the reaction in a substantial way and are not explicitly modeled.

We denote the concentrations of biomass, substrate and product in the reactor at time t by $B(t)$, $S(t)$ and $P(t)$, respectively. Fresh nutrient with concentration S_{in} is fed into the reactor at a rate q (inflow per volume of the reactor). At the same rate, q, outflow with concentrations $S(t)$, $B(t)$ and $P(t)$, respectively, is leaving the reactor.

In the classical model for a bioprocess the evolution of the concentrations $S(t)$ of substrate (nutrient), $B(t)$ of biomass (bacteria), and $P(t)$ of the product of the bioreaction is described by the equations [22, 23, 24, 25]:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -a\,\mu(S(t))B(t) - q(S(t) - S_{in}), \qquad S(0) = S_0, \tag{19}$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = \mu(S(t))B(t) - qB(t) - dB(t), \qquad B(0) = B_0, \tag{20}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = b\,\mu(S(t))B(t) - qP(t), \qquad P(0) = P_0. \tag{21}$$

Here a, b, q, S_{in}, d, are nonnegative constants ($1/a$ is the growth yield, b is the product rate, q is the dilution rate, d is a parameter describing the mortality rate of bacteria); $\mu(S)$ is the specific growth rate function; t is time; S_0, B_0, and P_0 are the initial concentrations of substrate, biomass, and product, respectively.

The specific growth rate $\mu(S)$ is the most important parameter during fermentation as it represents the dynamic behavior of microorganisms. The function $\mu(S) \geq 0$ is defined for $S \geq 0$ and may take various forms (see [22, 23, 24, 25]). Some of them are listed below:

- Monod function [26]:

$$\mu(S) = \mu^* \frac{S}{k + S}, \tag{22}$$

- Andrews function [27]:

$$\mu(S) = \mu^* \frac{S}{k + S + S^2/k_i}, \tag{23}$$

- Webb function [28]:

$$\mu(S) = \mu^* \frac{S(1 + \nu S/k_i)}{k + S + S^2/k_i}. \tag{24}$$

Here μ^*, k, k_i, and ν are positive parameters, which represent different physical or biological quantities.

APPROACHES TOWARDS TIME-FRACTIONAL MODELING OF A BIOPROCESS

First Approach

The simplest approach to introduce fractional derivatives in the model (19)-(21) is to replace the first order time derivatives in the equations by Caputo fractional derivative of orders $\alpha, \beta, \gamma \in (0, 1)$, respectively, which leads to the system

$${}^{C}D_t^{\alpha} S(t) = -a\,\mu(S(t))B(t) - q_{\alpha}(S(t) - S_{in}), \qquad S(0) = S_0, \tag{25}$$

$${}^{C}D_t^{\beta} B(t) = \mu(S(t))B(t) - q_{\beta}B(t) - dB(t), \qquad B(0) = B_0, \tag{26}$$

$${}^{C}D_t^{\gamma} P(t) = b\,\mu(S(t))B(t) - q_{\gamma}P(t), \qquad P(0) = P_0. \tag{27}$$

This approach is also the most frequently used, see for instance [19, 20, 29].

It has to be pointed out that in the above equations the parameters a, b, μ^*, and d, have different dimensions than these in the eqs. (19)-(21), which are consistent with the dimensions of the fractional derivatives in the corresponding

equations. The parameters q_σ (σ stands for α, β, or γ) are fractional dilution rates and have dimensions $[T^{-\sigma}]$, where T is the characteristic time. In this context we want to mention that in [29] the model described in their equations (5) is incorrect - in the first equation the dilution rate D has dimension $T^{-\alpha}$, while in the second equation its dimension is T^{-1}. This discrepancy is discussed at the end of the present section.

Now we represent system (25)-(27) in an equivalent form by the use of Riemann-Liouville derivative operators. To this end we apply the Riemann-Liouville derivative of order $1-\alpha$ to both sides of the first equation (25). By the definition (1) of the Caputo derivative and property (8) we get in the left hand side of equation (25)

$$ {}^{RL}D_t^{1-\alpha}\ {}^{C}D_t^{\alpha} S(t) = {}^{RL}D_t^{1-\alpha}\ J_t^{1-\alpha} D_t^1 S(t) = D_t^1 S(t). \tag{28}$$

By applying operators ${}^{RL}D_t^{1-\beta}$ and ${}^{RL}D_t^{1-\gamma}$ to equations (26) and (27), respectively, and by using the same argument, the system (25)-(27) is transformed into the following system of equations

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -a\ {}^{RL}D_t^{1-\alpha}\left(\mu(S(t))B(t)\right) - q_\alpha\ {}^{RL}D_t^{1-\alpha}\left(S(t)-S_{in}\right), \qquad S(0)=S_0, \tag{29}$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = {}^{RL}D_t^{1-\beta}\left(\mu(S(t))B(t)\right) - q_\beta\ {}^{RL}D_t^{1-\beta}B(t) - d\ {}^{RL}D_t^{1-\beta}B(t), \qquad B(0)=B_0, \tag{30}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = b\ {}^{RL}D_t^{1-\gamma}\left(\mu(S(t))B(t)\right) - q_\gamma\ {}^{RL}D_t^{1-\gamma}P(t), \qquad P(0)=P_0. \tag{31}$$

The two systems (25)-(27) and (29)-(31) are equivalent. Indeed, equation (25) can be obtained by applying the operator $J_t^{1-\alpha}$ to both sides of equation (29) and taking into account relations (4) and (10). In an analogous way equation (30) implies (26) and (31) implies (27) after applying $J_t^{1-\beta}$ and $J_t^{1-\gamma}$, respectively.

Let us have a closer look at system (29)-(31). The right-hand side of any of the three equations is a sum of different parts, corresponding to different sub-processes. Applying a fractional derivative to a specific term in the equation introduces a memory effect to the underlying sub-process. The physical meaning of the order of the fractional derivative is an index of memory [4]. Let us consider for instance the right-hand side of equation (30), where all three terms contain a fractional derivative of one and the same order. Here an open question is whether the mortality rate of bacteria can have the same order of fractional evolution (index of memory) as the bacterial growth rate?

Another weak point of the model based on the systems (25)-(27), respectively (29)-(31), is that at different fractional orders (especially, if $\alpha \neq \gamma$) the terms corresponding to the outflow of the reactor predict different flow rates in the different equations of the system. This can be demonstrated by the following example: consider a situation at absence of bacteria and supply of nutrients, i.e. $B(t)=0$ and $S_{in}=0$ (inflow of pure water). Let us assume that initially the concentrations of substrate and product are equal, $S(0)=P(0)$. Then they have to be equal throughout the whole process, $S(t)\equiv P(t)$, independently of the inflow and outflow rates. In this situation the mathematical model (25)-(27) reduces to the following system of two equations (since $B(t)=0$ the second equation drops out):

$${}^{C}D_t^{\alpha} S(t) = -q_\alpha S(t), \quad S(0)=S_0, \tag{32}$$

$${}^{C}D_t^{\gamma} P(t) = -q_\gamma P(t), \qquad P(0)=S(0). \tag{33}$$

The solutions of equations (32) and (33) are given by (see (13)):

$$S(t) = S(0)E_\alpha(-q_\alpha t^\alpha), \quad P(t) = P(0)E_\gamma(-q_\gamma t^\gamma),$$

where $E_\alpha(\cdot)$ and $E_\gamma(\cdot)$ are Mittag-Leffler functions. Therefore, if $\alpha \neq \gamma$, then $S(t) \neq P(t)$ for $t>0$, independently of the values of the parameters q_α and q_γ. This contradiction is a result of the fact that model (25)-(27) is obtained by a direct replacement of the first time-derivatives in the system (19)-(21) with derivatives of fractional orders. Such an approach implies that in each equation all terms in the right-hand side have one and same index of fractional evolution, as we see in the equivalent form (29)-(31). Thus, if different orders of fractional evolution are used in the different equations, the result will be that the outflow in the different equations is different, i.e. different substances - substrate, bacteria and product leave the reactor at different outflows, which is physically incorrect. Let us note that in [20, 19] there is no inflow/outflow ($q=0$) and such a problem does not appear. However, the model in the above papers can not be extended to describe the processes in bioreactors.

Our conclusion is that even if the models (25)-(27), resp. (29)-(31), are physically correct in the case $q_\sigma = 0$, the approach of simply replacing the classical time-derivatives with fractional ones is not appropriate. An alternative approach of "fractionalization" is considered in the next section.

Second Approach

Next we propose another approach to "fractionalize" system (19)-(21). To avoid the contradictions encountered in the previous subsection we modify system (29)-(31) and apply the fractional order derivatives of Riemann-Liouville type in the right hand side of the equations only on the term $\mu(S(t))B(t)$, and possibly on the mortality term, as follows:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -a\ {}^{RL}D_t^{1-\alpha}(\mu(S(t))B(t)) - q_\alpha(S(t) - S_{in}), \qquad S(0) = S_0, \tag{34}$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = {}^{RL}D_t^{1-\beta}(\mu(S(t))B(t)) - q_\beta B(t) - d\ {}^{RL}D_t^{1-\beta_d}B(t), \qquad B(0) = B_0, \tag{35}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = b\ {}^{RL}D_t^{1-\gamma}(\mu(S(t))B(t)) - q_\gamma P(t), \qquad P(0) = P_0. \tag{36}$$

The obtained in this way fractional derivative model (34)-(36) is equivalent to the previously described (25)-(27) in the case of $q_\sigma = d = 0$, $\sigma = \alpha, \beta, \gamma$. The orders $1-\alpha$, $1-\beta$, $1-\gamma$, of the Riemann-Liouville fractional derivatives are chosen to correspond to these in the first approach.

The main idea behind this approach corresponds to the main laws of modeling of processes (e.g. physical, biological). In general, the mathematical model is designed to satisfy: First, the conservation/balance law, e.g. mass, volume, momentum, energy, etc.; Second, constitutive relations that describe the processes (sub-processes) under consideration, e.g. the first Fick's law in the case of diffusion. In our case as constitutive relation can be considered the specific growth rate given by $\mu(S(t))$ that describes the decrease of the substrate $S(t)$ and the increase of bacteria $B(t)$ and the product $P(t)$ due to the fermentation process, as well as the mortality rate and the dilution rate (inflow and outflow) that correspond to the process. Having the rates of change of the substances (S, B and P) due to growth, death and in/outflows the equations (19)-(21) represent mass conservation of these substances, respectively. Thus, if the first order derivatives in the left-hand side of the equations are altered, as in the first approach, then the question of the conservation of mass appears. The example considered in the previous section shows clearly that problem with conservation of mass is possible. This is discussed further in the study in the context of fractional derivative modeling of the diffusion equation.

In the present approach we consider fractional evolution of the growth of substrate, bacteria and product, respectively. An advantage of this approach is that the different terms in the right-hand side of the equations, that correspond to different sub-processes can be treated separately. For instance, it is not expected that the in/out flows have fractional evolution, that is why they stay as in the classical model (19)-(21). Also there is no proof that the growth and the death of bacteria have fractional evolution of one and the same order. Thus, we consider the possibility that the evolution of the mortality can be of different fractional order (β_d), than the bacterial growth rate fractional order (memory index).

Open question: Can the fractional growth evolution term ${}^{RL}D_t^{1-\sigma}(\mu(S(t))B(t))$ have different orders in the different equations? Should not $\alpha = \beta = \gamma$? In fact, the increase of bacteria (concentration $B(t)$) is the main bioprocess. In the first equation (34) and in the third one (36) the corresponding terms represent the nutrient $S(t)$ that is necessary for this increase, and respectively, how much product $P(t)$ will be produced due to the increase.

NUMERICAL RESULTS

In this section the numerical solution of the fractional-order bioreaction model is discussed. The system of equations (34)-(36) is solved numerically in the case $q_\sigma = d = 0$. Let us recall that in this particular case it is equivalent to (25)-(27).

Numerical solution is obtained using the fractional Adams method ([30, 31]). In this method a fractional order differential equation is rewritten first as a Volterra integral equation

$$y(t) = y_0 + J_t^\alpha F(y(t)). \tag{37}$$

The integral equation (37) is solved on a uniform mesh $t_j = jh$, $h = T/N$; y_j denotes the approximation for $y(t_j)$, $j = 0, 1, ..., N$, in two steps:

Predictor step:

$$y_{k+1}^P = y_0 + \frac{1}{\Gamma(\alpha)}\sum_{j=0}^{k} b_{j,k+1}\, F(y_j), \quad b_{j,k+1} = \frac{h^\alpha}{\alpha}((k+1-j)^\alpha - (k-j)^\alpha). \tag{38}$$

Corrector step:

$$y_{k+1} = y_0 + \frac{1}{\Gamma(\alpha)} \left(\sum_{j=0}^{k} a_{j,k+1} F(y_j) + a_{k+1,k+1} F(y_{k+1}^P) \right), \tag{39}$$

where

$$a_{j,k+1} = \frac{h^\alpha}{\alpha(\alpha+1)} A_{j,k+1} \tag{40}$$

and the coefficients $A_{j,k+1}$ are defined by

$$A_{j,k+1} = \begin{cases} k^{\alpha+1} - (k-\alpha)(k+1)^\alpha \ \text{ if } j = 0, \\ (k-j+2)^{\alpha+1} + (k-j)^{\alpha+1} - 2(k-j+1)^{\alpha+1} \ \text{ if } 1 \le j \le k, \\ 1 \ \text{ if } j = k+1. \end{cases}$$

To apply the fractional Adams method we first rewrite the system (25)-(27) as follows (for $q_\sigma = d = 0$):

$$S(t) = S_0 - a\, J_t^\alpha \left(\mu(S(t))B(t)\right), \tag{41}$$

$$B(t) = B_0 + J_t^\beta \left(\mu(S(t))B(t)\right), \tag{42}$$

$$P(t) = P_0 + b\, J_t^\gamma \left(\mu(S(t))B(t)\right). \tag{43}$$

Here we have applied J_t^σ, $\sigma = \alpha, \beta, \gamma$, to both sides of the equations (25)-(27) and used identity (11).

An important property of the system (25)-(27), respectively (41)-(43), is that the first two equations, for $S(t)$ and $B(t)$, do not depend on $P(t)$. Thus, the first two equations are solved simultaneously by applying the fractional Adams method. At any node t_j, $j = 1, 2, ..., N$, we perform first the predictor steps for both equations (41) and (42) and using the results, we perform then the corrector steps for both equations. In this way the functions $S(t)$ and $B(t)$ are computed on the mesh. The function $P(t)$ is evaluated numerically by plugging the results for $S(t)$ and $B(t)$ in equation (43). From (43) it is seen that the solution $P(t)$ for arbitrary values of P_0 and b can be expressed directly by the solution for $P_0 = 0$ and $b = 1$.

A first group of simulations is performed for comparison with the results of [19]. In these simulations, as in [19], the fractional derivative generalization of Lotka-Volterra model is used, where $\mu(S(t)) = \mu^* S(t)$. Our results are in good agreement with the results of [19]. In two of the discussed results (see Figures 1-3 in [19]) the function of the biomass $B(t)$ is not monotone, i.e. after an initial increase the biomass decreases. This is partially due to the nonzero mortality rate in [19] (their parameter $k_m > 0$). However, our numerical results indicate that even without mortality the biomass $B(t)$ can still be non-monotonic. As it is discussed in [20], it is expected that without in/outflow and without death of bacteria, the substrate $S(t)$ should be strictly decreasing, respectively the biomass $B(t)$ and the product $P(t)$ are strictly increasing. This is a natural property and in the classical case $\alpha = \beta = \gamma = 1$ the analytical proof that $S(t)$, $B(t)$ and $P(t)$ are monotonic functions is straightforward, see [20]. Thus, the non-monotone behavior discussed above is due to the presence of fractional order derivatives in the model.

To get an idea how the "fractionalization" of the bioprocess model can affect the monotonicity of the results, simulations at different fractional orders α, β and γ are performed at fixed other parameters and $q_\sigma = d = 0$. For the specific growth rate function $\mu(S)$ we take the Monod function (22) in our simulations. The values of the parameters are taken from the experimental study [32] for the case of classical Monod model: $\mu^* = 0.6[h^{-1}]$; $k = 0.81[g/L]$; $a = 4.5$ and $b = 3.4$. The initial values in the simulations are fixed at $S_0 = 5[g/L]$; $B_0 = 0.1[g/L]$ and $P_0 = 0[g/L]$.

Let us note that, strictly speaking, in the case of fractional derivative model the dimensions of μ^*, a and b should depend on the fractional orders α, β and γ.

From Figure 1 (left) it is seen that for all considered values of β (0.25, 0.5, 0.75 and 1.) the product $P(t)$ has non-monotonic behavior. This is due to the fact that the fractional order γ in the equation for $P(t)$ is smaller than α ($\alpha = 0.75$, $\gamma = 0.5$). Figure 1 (right) shows that the biomass $B(t)$ is strictly increasing when $\beta \ge \alpha$ ($\beta = 1.$ and 0.75), however when $\beta < \alpha$ ($\beta = 0.25$ and 0.5) $B(t)$ is not monotonic. Based on the results presented in Figure 1, as well as a number of simulations at different values of the parameters, we can formulate the following conjecture.

Conjecture. For the solution of the fractional derivative model (34)-(36) at $d = q_\sigma = 0$ it is true that:
- If $\beta \ge \alpha$ the biomass function $B(t)$ is increasing;
- If $\gamma \ge \alpha$ the product function $P(t)$ is increasing;
There exists a set of parameters (μ^*, a, b, S_0, B_0 and P_0) such that:

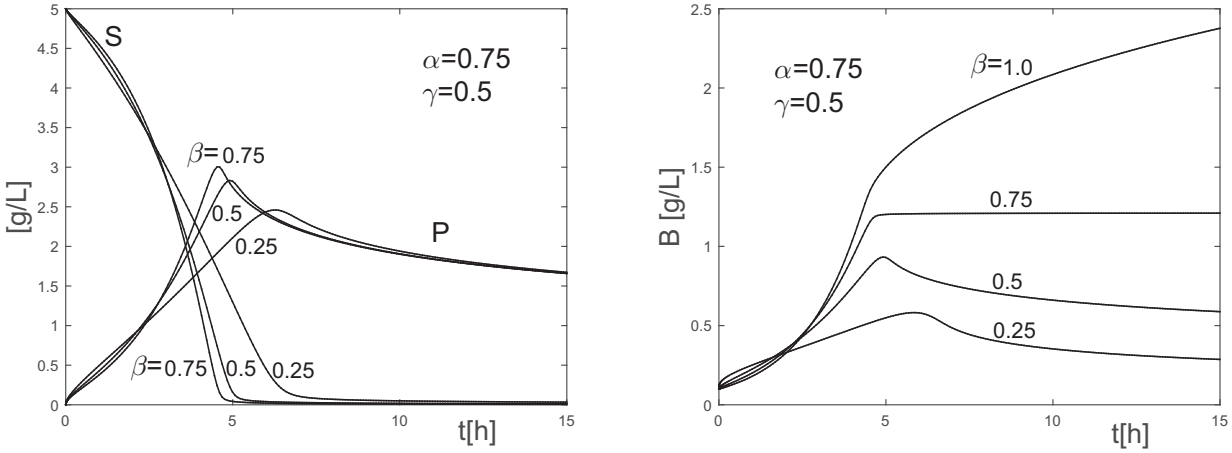

FIGURE 1. The evolution of the substrate $S(t)$ and product $P(t)$ (left), and biomass $B(t)$ (right) at $\alpha = 0.75$, $\gamma = 0.5$ and different values of β (0.25; 0.5; 0.75; 1.). The curves for $S(t)$ and $P(t)$ at $\beta = 1.$ are not presented, because they are very close to those for $\beta = 0.75$.

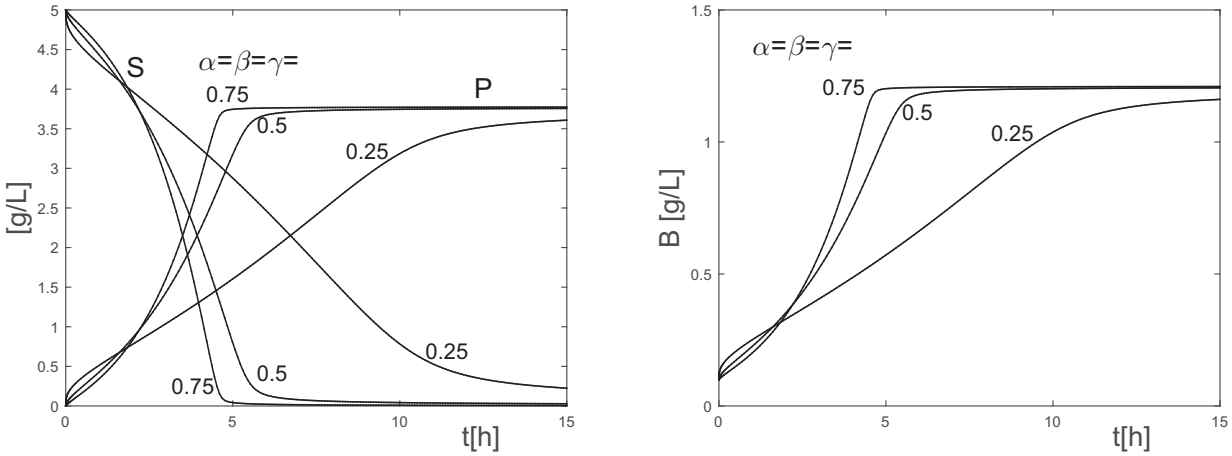

FIGURE 2. The evolution of the substrate $S(t)$ and product $P(t)$ (left), and biomass $B(t)$ (right) in the case when the tree fractional orders are equal, $\alpha = \beta = \gamma = 0.25;\ 0.5;\ 0.75$.

- If $\beta < \alpha$ the function $B(t)$ is not monotonic;
- If $\gamma < \alpha$ the function $P(t)$ is not monotonic.

In Figure 2 the numerical results for $S(t)$, $P(t)$, and $B(t)$, are presented in the case $\alpha = \beta = \gamma = 0.25;\ 0.5;\ 0.75$. The results for the classical case $\alpha = \beta = \gamma = 1$ are very close to that of 0.75 and are not shown in the figure. It is seen that the values for $S(t)$, $B(t)$ and $P(t)$ at $t \to \infty$ are independent of the values of the fractional orders $\alpha = \beta = \gamma$. Thus, in this case, $\alpha = \beta = \gamma$, the final values of $S(t)$, $B(t)$ and $P(t)$ depend on the other parameters (μ^*, a, b, S_0, B_0 and P_0). The value of the fractional order $\alpha = \beta = \gamma$ determines the evolution to these final values ($S(\infty)$, $B(\infty)$, $P(\infty)$): The smaller the fractional order, the faster the process for small t, but slower for large t. Let us note that such a behavior is common in fractional order equations, for instance similar relationship between the rate of change and the fractional order is observed in the behavior of the Mittag-Leffler function, see (17) and (18).

For the numerical solution of system (34)-(36) in the general case ($q_\sigma \neq 0$ and/or $d \neq 0$) we first rewrite the three equations in the form of Volterra integral equations. This is done it by applying the operator J_t^1 to any of the equations of the system and taking into account the identities $J_t^1 D_t^1 u(t) = u(t) - u(0)$ and $J_t^1 \, {}^{RL}D_t^{1-\sigma} u(t) = J_t^1 D_t^1 J_t^\sigma u(t) =$

$J_t^\sigma u(t) - (J_t^\sigma u)(0) = J_t^\sigma u(t)$. In this way we rewrite system (34)-(36) in the form

$$S(t) = S_0 - a\, J_t^\alpha(\mu(S(t))B(t)) - q_\alpha J_t^1(S(t) - S_{in}), \tag{44}$$

$$B(t) = B_0 + J_t^\beta(\mu(S(t))B(t)) - q_\beta J_t^1 B(t) - d\, J_t^{\beta_d} B(t), \tag{45}$$

$$P(t) = P_0 + b\, J_t^\gamma(\mu(S(t))B(t)) - q_\gamma J_t^1 P(t). \tag{46}$$

Then a modification of the above described predictor-corrector method (with different approximations for the terms containing integral operators of different orders) can be applied for the solution of this system.

TIME-FRACTIONAL DIFFUSION-BIOREACTION MODEL

First, the application of fractional time-derivatives in the modeling of anomalous diffusion is discussed briefly. The related processes of reaction or convection/advection, as well as specific boundary conditions are considered. As a starting point the physical laws, on which the diffusion equation is based, are given in the context of its fractionalization in time.

Let $\mathbf{x}$ be the position vector and t - the time. The Fick's first law of diffusion states that the concentration $c(\mathbf{x}, t)$ of a substance and the diffusion flux vector $\mathbf{J}(\mathbf{x}, t)$ are related by the identity

$$\mathbf{J}(\mathbf{x}, t) = -\kappa\, \nabla c(\mathbf{x}, t), \tag{47}$$

where κ is the diffusion coefficient and ∇ denotes the gradient vector.

According to the continuity equation (conservation of mass) in differential form the time derivative of the concentration $c(\mathbf{x}, t)$ is the negative of the divergence of the flux $\mathbf{J}(\mathbf{x}, t)$:

$$\frac{\partial c}{\partial t} = -\nabla \cdot \mathbf{J}(\mathbf{x}, t). \tag{48}$$

Combining (47) and (48) the classical diffusion equation in its simplest form (also called Fick's second law of diffusion) is derived:

$$\frac{\partial c}{\partial t} = \kappa\, \Delta c(\mathbf{x}, t), \tag{49}$$

where Δ denotes the Laplace operator in space. This is a purely macroscopic way of obtaining the classical diffusion equation.

The following two time-fractional generalizations for the classical diffusion equation are most frequently considered in the literature as models for anomalous diffusion:

$${}^C D_t^\sigma c(\mathbf{x}, t) = \kappa\, \Delta c(\mathbf{x}, t), \quad 0 < \sigma < 1, \tag{50}$$

and

$$\frac{\partial c}{\partial t} = \kappa\, {}^{RL}D_t^{1-\sigma} \nabla c(\mathbf{x}, t), \quad 0 < \sigma < 1. \tag{51}$$

In this simplest case, the time-fractional diffusion equations (50) and (51) are equivalent. This can be seen as in the previous section by applying relations (28), (4) and (10). However, in more complex situations, such as in the presence of a source, or, in the case of reaction-diffusion or convection-diffusion equations, the equivalence is lost. The question is how to properly "fractionalize" such a more complex equation.

Similarly to the "fractionalization" of the bioreaction model, we consider two formal approaches in the case of diffusion: the first is leading to equation (50) and the second to equation (51) in the simplest diffusion model. In the literature, the first approach, consisting in replacing the time derivative in the classical diffusion equation by a fractional Caputo derivative, is predominant. It is used in the most of the studies of time-fractional diffusion, see [7, 9, 10, 11, 12, 13, 15]. The second approach, consisting in the application of fractional differential operators in the right-hand side of the diffusion equation, seems to be less popular, see for instance [6, 8, 17, 18].

Let us look how equations (50) and (51) can be formally derived from "fractionalized" versions of (47) or (48). Equation (50) can be formally derived from a modified continuity equation (48), where the time derivative is replaced by a fractional order one:

$${}^C D_t^\sigma c(\mathbf{x}, t) = -\nabla \cdot \mathbf{J}(\mathbf{x}, t), \quad 0 < \sigma < 1, \tag{52}$$

and the standard Fick's first law (47).

On the other hand, equation (51) can be formally derived from the following modification of the Fick's first law

$$\mathbf{J}(\mathbf{x},t) = -\kappa\ {}^{RL}D_t^{1-\sigma}\nabla c(\mathbf{x},t), \quad 0<\sigma<1, \tag{53}$$

and the continuity equation (48).

The above fractional versions of equations (47) and (48) are considered e.g. in [33].

To analyze whether such "fractionalizations" are physically meaningful let us look what the continuity equation (48) and the Fick's first law (47) represent. The continuity equation (48) is in fact a mass/particle conservation law. Indeed, mass conservation of c in volume V is given by the the identity

$$\frac{\partial}{\partial t}\iiint_V c\,\mathrm{d}V = \iiint_V \frac{\partial c}{\partial t}\,\mathrm{d}V = -\oiint_S \mathbf{J}\cdot\mathbf{n}\,\mathrm{d}S, \tag{54}$$

where $S=\partial V$ denotes the boundary of V and $\mathbf{n}$ is an outward unit vector, normal to S. On the other hand, according to Gauss–Ostrogradsky theorem

$$\oiint_S \mathbf{J}\cdot\mathbf{n}\,\mathrm{d}S = \iiint_V \nabla\cdot\mathbf{J}\,\mathrm{d}V \tag{55}$$

Combining (54) and (55) we see that equation (48) represents the law of conservation of mass.

The other underlying equation, the Fick's first law (47) represents the flux in the case of normal (Fickian) diffusion, which corresponds to linear scaling relation between the mean squared displacement $\langle r^2\rangle$ and time t:

$$\langle r^2(t)\rangle \sim t. \tag{56}$$

Cases of deviation from normal diffusion, called anomalous or non-Fickian diffusion, are often related to a power-law form of the mean squared displacement (see e.g. [5])

$$\langle r^2(t)\rangle \sim t^{\sigma}, \quad 0<\sigma<1. \tag{57}$$

The flux that corresponds to the above relation (57) is given by equation (53) (see also [18]), which clearly indicates that the fractional order derivative can be introduced to the diffusion equation via the first Fick's law, as in (53). On the other hand, if it is introduced in the continuity equation, as in (52), then it is not clear whether the resulting model satisfies mass conservation of c.

The next two examples demonstrate that a simple replacement of the first time derivative in the diffusion equation by a fractional one can lead to physically incorrect models.

Example 1. Adsorption-diffusion. Consider a multiphase fluid system, where together with diffusion in a continuous phase there is also a process of adsorption of c on an interface between two continuous phases. Such situation is typical in the case of surfactant transport (diffusion) in a phase Ω and adsorption on its surface $\Theta=\partial\Omega$. In the particular case of the so-called diffusion controlled adsorption (see e.g. [16]) the classical mathematical model includes the diffusion equations in Ω:

$$\frac{\partial c}{\partial t} = -\nabla\cdot\mathbf{J}(\mathbf{x},t), \quad \mathbf{J}(\mathbf{x},t) = -\kappa\nabla c(\mathbf{x},t), \quad \mathbf{x}\in\Omega,\ t>0, \tag{58}$$

with a boundary condition of adsorption on the interface

$$\left.\frac{\partial\Gamma}{\partial t}\right|_{\Theta} = -\mathbf{J}\cdot\mathbf{n} \quad \text{on } \Theta, \tag{59}$$

where Γ is the surfactant concentration on the interface Θ. Equation (59) represents the first Fick's law on the interface. In this case the two different approaches of "fractionalization" will lead to different models. Following the first approach, the boundary condition (59) will stay unchanged, or will possibly have time-fractional derivative of order independent of that in the diffusion equation, as in [15]. Following the second approach, equation (53) gives the following fractional derivative model

$$\frac{\partial c}{\partial t} = \kappa\ {}^{RL}D_t^{1-\sigma}\Delta c(\mathbf{x},t), \qquad \left.\frac{\partial\Gamma}{\partial t}\right|_{\Theta} = \kappa\ {}^{RL}D_t^{1-\sigma}\nabla c\cdot\mathbf{n}. \tag{60}$$

Thus, in the diffusion equation and in the adsorption boundary condition appear time-fractional derivatives of one and the same order. If these derivatives have different orders, as in [15], the mass conservation of c in the vicinity of the interface Θ will not be satisfied. Indeed, if we consider mass conservation (54)-(55) in a vicinity V of the interface, i.e. part of the boundary S of V is on the interface Θ, then the flux $\mathbf{J}$ will be different at the different parts of S: One fractional order of $\mathbf{J}$ on the part of the interface Θ; Another on the rest of S, $S\setminus\Theta$, which comes from the diffusion equation. This, however, lead to contradiction that the diffusion equation and the mass conservation both can not be satisfied in the vicinity of the interface Θ. The only possible way both to be satisfied is to have one and the same order of fractional derivatives, as in (60).

In this context we want to mention that in our previous work [16] the boundary condition on the interface is not correct, because it is not consistent with the fractional order of the diffusion equation.

Let us note that in the case of space-fractional model of diffusion-adsorption the fractional orders of the spatial fractional derivatives have to be also consistent: order σ in the adsorption boundary condition corresponds to $1+\sigma$ in the diffusion equation.

Example 2. Convection-diffusion. Consider diffusion of particles of concentration c in the presence of advection velocity $\mathbf{u}$. Mass conservation of c in volume V, which boundary $S = \partial V$ is moving with velocity $\mathbf{u}$, is given by the Reynolds transport theorem as follows

$$\frac{\partial}{\partial t}\iiint_V c\,\mathrm{d}V = \iiint_V \frac{\partial c}{\partial t}\,\mathrm{d}V + \oiint_S (\mathbf{u}\cdot\mathbf{n})c\,\mathrm{d}S = -\oiint_S \mathbf{J}\cdot\mathbf{n}\,\mathrm{d}S, \tag{61}$$

where $\mathbf{n}$ is the outward unit normal to S vector. Using Gauss-Ostrogradsky theorem we have:

$$\oiint_S (\mathbf{u}\cdot\mathbf{n})c\,\mathrm{d}S = \iiint_V \nabla\cdot(c\mathbf{u})\,\mathrm{d}V, \quad \oiint_S \mathbf{J}\cdot\mathbf{n}\,\mathrm{d}S = \iiint_V \nabla\cdot\mathbf{J}\,\mathrm{d}V. \tag{62}$$

Combining (61) and (62) we deduce the mass conservation equation in differential form

$$\frac{\partial c}{\partial t} + \mathbf{u}\cdot\nabla c = -\nabla\cdot\mathbf{J}, \tag{63}$$

where for simplicity the flow is considered divergence free ($\nabla\mathbf{u} = 0$).

It is obvious that if the first approach is used, i.e. the first time-derivative in (63) is simply replaced by a fractional order one, as in [11, 9, 10], then the mass conservation of c (equation (61)) is not guaranteed.

Summarizing our observations so far we propose a time-fractional model that includes different sub-processes such as convection, diffusion, bioreaction. For example, an equation governing the concentration of bacteria $B(\mathbf{x},t)$ admits the form

$$\frac{\partial B}{\partial t} + \mathbf{u}\cdot\nabla B(\mathbf{x},t) = \kappa\, {}^{RL}D_t^{1-\delta}\Delta B(\mathbf{x},t) + {}^{RL}D_t^{1-\beta}\mu(S,B) - d\, {}^{RL}D_t^{1-\beta_d}B(\mathbf{x},t) - qB(\mathbf{x},t), \qquad \delta,\beta,\beta_d \in (0,1). \tag{64}$$

The equations for the substrate $S(\mathbf{x},t)$ and product $P(\mathbf{x},t)$ can be deduced in a similar way.

In equation (64) the different sub-processes (diffusion, bacterial growth and death) are considered to have fractional evolution of different orders. For the conservation of mass of $B(\mathbf{x},t)$ the convection term, $\mathbf{u}\nabla B$, and dilution term, $-qB$, should be as in the classical model.

Let us note that some authors consider equal fractional orders for the different sub-processes, see e.g. [20] for the case of growth and death of bacteria; [7, 9, 11, 12] for the reaction-diffusion equation. Interesting situation appears when the diffusion is different in different directions. Such a case is considered in [18], where the authors study normal diffusion in x direction and fractional diffusion in y direction, which model is impossible to obtain by using the first approach.

A number of other questions have to be also addressed, such as multicomponent diffusion, chemotaxis, etc. However, they are out of the scope of the present paper.

CONCLUDING REMARKS

Fractional order time-derivatives are a useful tool for modeling of different processes. However, a direct replacement of integer order time-derivatives in the classical models with fractional order ones could be an incorrect approach to

fractional order modeling. This is especially true in the development of evolution models, where different sub-process are involved.

In the present study a number of examples are given when simple replacement of the integer order derivative with a fractional order one leads to a physically incorrect model. Most of the evolution models of processes (e.g. physical, biological, etc.) involve a conservation law combined with a constitutive equation that describes the process. The integer order time derivative in a classical model comes from the corresponding conservation law. a direct replacement of this derivative with a fractional order one can lead to violation of the corresponding conservation law. Therefore, our conclusion is that a correct approach to introduce time fractional evolution in a mathematical model is via the corresponding constitutive equation. This approach guarantees that the different sub-processes, e.g. bioreaction, convection, diffusion, etc., can be treated individually. On the other hand, sub-processes that are related via a constitutive equation stay related after the fractionalization of the model. Such are, for instance, diffusion and adsorption or diffusion and interface mass-transfer, which are both described by the first Fick's law via the diffusive flux in the bulk and on the interface respectively. This is in analogy with the case of viscoelastic models, where the correct way to introduce time fractional derivatives is via the constitutive equations, as in [1, 3]. Let us note that the above conclusion is not restricted only to fractional derivatives in the Caputo and Riemann-Liouville sense, but is applicable for modeling by the use of general integro-differential operators in time.

Numerical simulations for time-fractional bioprocess models are performed, based on Lotka-Volterra and Monod models. The numerical results show that at some values of the fractional parameters in the interval $(0, 1)$ both models predict non-monotonic evolution of biomass and product in the absence of in/outflow and death of bacteria. Therefore, in such cases the models are not physically meaningful. Based on our numerical results at different values of the fractional orders we put forward the following suggestion: For correct behavior of the solution (monotone $S(t)$, $B(t)$ and $P(t)$), the fractional orders α, β and γ have to satisfy $\beta \geq \alpha$ and $\gamma \geq \alpha$. Further in this direction, we present arguments supporting the suggestion that the three fractional orders have to be equal, $\alpha = \beta = \gamma$. These conjectures, however, need to be further studied theoretically and numerically.

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REFERENCES

[1] T. M. Atanacković, S. Pilipović, B. Stanković, and D. Zorica, *Fractional Calculus with Applications in Mechanics: Vibrations and Diffusion Processes* (John Wiley & Sons, London, 2014).

[2] D. Baleanu, K. Diethelm, E. Scalas, and J. Trujillo, *Fractional Calculus: Models and Numerical Methods* (World Scientific, Singapore, 2012).

[3] F. Mainardi, *Fractional Calculus and Waves in Linear Viscoelasticity* (Imperial College Press, London, 2010).

[4] M. Du, Z. Wang, and H. Hu, Sci. Rep. **3**, p. 3431 (2013).

[5] R. Metzler and J. Klafter, J. Phys. A: Math. Gen. **37**, R161–R208 (2004).

[6] B. I. Henry and S. L. Wearne, Physica A: Statistical Mechanics and its Applications **276**, 448–455 (2000).

[7] V. Gafiychuk, B. Datsko, and V. Meleshko, J. Comput. Appl. Math. **220**, 215–225 (2008).

[8] J. Yang and J. D. Rademacher, Reaction-subdiffusion systems and memory: spectra, Turing instability and decay estimates, 2019, arXiv preprint, arXiv:1910.03822 [math.AP].

[9] S. Momani, Communications in Nonlinear Science and Numerical Simulation **12**, 1283–1290 (2007).

[10] Z. Wang and S. Vong, Comput. Math. Appl. **68**, 185–196 (2014).

[11] M. Cui, Applied Mathematics and Computation **246**, 464–473 (2014).

[12] L. Ren and Y.-M. Wang, Applied Mathematics and Computation **312**, 1–22 (2017).

[13] B. Datsko, I. Podlubny, and Y. Povstenko, Mathematics **7**, p. 433 (2019).
[14] E. K. Lenzi, M. A. F. dos Santos, M. K. Lenzi, D. S. Vieira, and L. R. da Silva, Journal of King Saud University - Science **28**, 3–6 (2016).
[15] G. Baumann and F. Stenger, Fract. Calc. Appl. Anal. **16**, 737–764 (2013).
[16] I. Bazhlekov and E. Bazhlekova, AIP Conference Proceedings **2048**, p. 050012 (2018).
[17] Y. Zhang, J. Jiang, Y. Bai, J. Liu, H. Shao, C. Wu, and Z. Guo, Build. Environ. **152**, 182–191 (2019).
[18] V. Méndez and A. Iomin, Chaos, Solitons & Fractals **53**, 46–51 (2013).
[19] R. Toledo-Hernandez, V. Rico-Ramirez, G. A. Iglesias-Silva, and U. M.Diwekar, Chemical Engineering Science **117**, 217–228 (2014).
[20] K. Diethelm, "Properties of the solutions to "fractionalized" ODE systems, with applications to processes arising in the life sciences," in *Proc. Internat. Conf. Fractional Differentiation and its Applications 2016, Vol. 1.*, edited by D. Spasic, N. Grahovac, M. Zigic, M. Rapaic, and T. Atanackovic (Faculty of Technical Sciences, Novi Sad, 2016), pp. 32–44.
[21] E. Bajlekova, "Fractional evolution equations in Banach spaces," Ph.D. thesis, Eindhoven University of Technology, Eindhoven, The Netherlands 2001.
[22] M. Gerber and R. Span, "An analysis of available mathematical models for anaerobic digestion of organic substances for production of biogas," in *Proc. IGRC, Paris* (2008).
[23] C. Sissons, M. Cross, and S. Robertson, Appl. Math. Modelling **10**, 33–40 (1986).
[24] H. Smith and P. Waltman, *The Theory of the Chemostat - Dynamics of Microbial Competition* (Cambridge University Press, 1995).
[25] R. Alt and S. Markov, Comput. Math. Appl. **64**, 350–360 (2012).
[26] J. Monod, Annual Reviews of Microbiology **3**, 371–394 (1949).
[27] J. Andrews, Biotechnology and Bioengineering **10**, 707–723 (1968).
[28] J. Webb, *Enzyme and Metabolic Inhibitors* (Academic Press, 1963).
[29] W. Ahmad and N. Abdel-Jabbar, IFAC Proceedings Volumes **39**, 260–264 (2006).
[30] K. Diethelm, N. Ford, and A. Freed, Numer. Algorithms **36**, 31–52 (2004).
[31] K. Diethelm, N. Ford, and A. Freed, Nonlinear Dynam. **29**, 3–22 (2002).
[32] S. Das, R. K. Calay, and R. Chowdhury, ChemEngineering **4**, p. 41 (2020).
[33] E. Awad and R. Metzler, Fract. Calc. Appl. Anal. **23**, 55–102 (2020).