A fractional calculus approach to the dynamic optimization of biological reactive systems. Part I: Fractional models for biological reactions

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HIGHLIGHTS

- The dynamics of reactive systems with atypical behavior are represented by FDE.
- Different fermentation processes were represented by the same fractional model.
- A formal fractionalization approach was used to obtain the model of hydrolysis.
- Results show the capabilities of fractional calculus for modeling dynamic systems.

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ABSTRACT

This series of two papers is concerned with both the modeling and the optimization of systems whose governing equations contain fractional derivative operators. In this first work, we show that the dynamics of some reactive systems displaying atypical behavior can be represented by fractional order differential equations. We consider three different instances of fermentation processes and one case of a thermal hydrolysis process. We propose a fractional fermentation model and, based on experimental data, a non-linear fitting approach that includes fractional integration is used to obtain the fractional orders and kinetics parameters. On the other hand, since the ordinary thermal hydrolysis model used as a reference was derived from fundamental principles, a formal fractionalization approach was used in this work to obtain the corresponding fractional model. Results show the feasibility and capabilities of fractional calculus as a tool for modeling dynamic systems in the area of process systems engineering.

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1. Introduction: fractional calculus and its modeling capabilities

Fractional calculus is a generalization of ordinary calculus which introduces derivatives and integrals of fractional order. Major reviews on the concepts and history of fractional calculus can be found in the books of Samko et al. (1993), Oldham and Spanier (1974), Miller and Ross (1993) and Podlubny (1999). Reports of successful modeling applications of fractional calculus are as old as the works developed by Caputo (1967) and Caputo and Mainardi (1971), related to the modeling of viscoelastic fluids; however, it has not been until the last two decades when the use of fractional order operators and operations has become more popular among many research areas.

Several authors have recently shown that fractional calculus is a powerful modeling tool to represent the behavior of a number of mechanical and electrical dynamic systems (Magin, 2006; Sabatier et al., 2007). In addition, many works describe and/or study the non-locality property and the memory effect of fractional calculus operators (Magin, 2006; Herrmann, 2011; Sun et al., 2011; Constantinescu and Stoicescu, 2011; Du et al., 2013). In particular, Magin (2006) provides a simple but illustrative example of the memory effect of a fractional derivative. It is therefore generally accepted that physical considerations, such as memory and hereditary effects, favor the use of fractional derivative-based models. Theoretical developments are also in progress (Diethelm, 2010; Ortigueira, 2011) in order to consolidate the fundamentals and provide the basis for a more extensive use of this tool in science and engineering.
Of particular interest in this work are the applications of fractional calculus to diffusion and anomalous kinetics. Literature suggests that diffusion processes are accurately represented by fractional differential equations (FDE) (Sokolov et al., 2002; San Jose Martinez et al., 2007). Further, diffusion is one of the main mechanisms of various processes in living organisms and gives rise to kinetics that are referred to as anomalous, to indicate the fact that deviate from the classic description. Anomalous kinetics can also result from reaction-limited processes and long-time trapping. It is thought that anomalous kinetics introduce memory effects in the process that need to be accounted for to correctly describe it (Dokoumetzidis and Macheras, 2009).

In other fields, the applications of fractional calculus are developed as extensions of well established mathematical models that are based upon ordinary differential equations. Therefore, in those cases it is important to understand how to properly fractionalize these classic models (Dokoumetzidis et al., 2010a, 2010b). Dokoumetzidis and Macheras (2009) study the drug release/dissolution processes (pharmaceuticals) as a fractional model. Due to the heterogeneous structure and function of the GI tract, the dissolution or release of drug takes place in a disordered under stirred medium. Since diffusion is the principal transport mechanism, fractional derivatives can be used to describe such anomalous kinetics under the heterogeneous in vivo conditions.

Motivated by the use of fractional calculus in pharmacokinetics, in this work we intend to extend the modeling capabilities of fractional calculus to the areas of chemical and biochemical engineering. In our opinion, it is reasonable to think that the physicochemical nature of biological processes (fermentations, enzymatic reactions, cell growth, etc.) will result in a dynamic behavior with memory. Therefore, we focus on biological reactive systems as the main illustrative cases of our approach. It is interesting that, in spite of the extensive existing literature on fractional calculus applications, literature related to reaction kinetics of chemical and biochemical processes is limited.

Since it can be proved that \( \Gamma(z + 1) = z! \) for all \( z \in \mathbb{R} \). Then, Eq. (2) can be re-written as follows:

\[
D^\alpha x^p = \frac{\Gamma(p + 1)}{\Gamma(p - \alpha + 1)} x^{p - \alpha}
\]

(3)

where \( \alpha \in \mathbb{R}, \alpha \geq 0 \).

Eq. (3) is one of the definitions of the Riemann–Liouville fractional derivative (Oldham and Spanier, 1974; Miller and Ross 1993). A more elegant and general methodology (Magin, 2006) uses Laplace transformation and the definition of the Cauchy integral to obtain expressions for the Riemann–Liouville fractional integration

\[
\mathcal{D}_0^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t \frac{f(\tau)}{(t-\tau)^{\alpha-1}} d\tau \quad 0 < \alpha < 1
\]

(4)

and two alternative definitions of fractional derivative, the Riemann–Liouville definition

\[
f(t) = \alpha \mathcal{D}_t^\alpha Y(t) = \frac{d}{d\alpha} \mathcal{D}_t^{(1-\alpha)} Y(t)
\]

and the Caputo definition

\[
f(t) = \alpha \mathcal{D}_t^\alpha Y(t) = \mathcal{D}_t^{(1-\alpha)} [Y(t)] = \frac{Y(0) \Gamma(\alpha)}{\Gamma(1-\alpha)}
\]

(5)

The fractional derivative definitions differ in the initial condition considered in each case. The order of the derivative can be extended to values of \( \alpha > 1 \). Then, for \( -1 < \alpha < m \), where \( m \) is the smallest positive integer larger than \( \alpha \), the definitions are as follows:

\[
\mathcal{D}_t^\alpha Y(t) = \frac{d^m}{d\alpha^m} \left[ \frac{1}{\Gamma(m-\alpha)} \int_0^t \frac{Y(\tau)}{(t-\tau)^{\alpha+m-1}} d\tau \right]
\]

(6)

and

\[
\mathcal{D}_t^{\alpha} Y(t) = \frac{1}{\Gamma(m-\alpha)} \int_0^t \frac{Y^{(m)}(\tau)}{(t-\tau)^{\alpha+m-1}} d\tau
\]

(7)

Eq. (5) is the Riemann–Liouville fractional derivative definition and Eq. (6) is the Caputo definition, which is generally expressed as \( \mathcal{D}_t^{\alpha} f(x) \). Eqs. (5) and (6) are extensively used in most of the theoretical and practical applications of fractional calculus.

2. Anomalous kinetics and reactive biological systems

Typical simulation and optimization models for reactive biological systems, which exhibit anomalous kinetics that do not necessarily follow the classical mass-action form, include equations involving empirical or semi-empirical expressions. Anticipating a potential memory effect on the dynamics of such systems, one of our goals is to show that, as an alternative, the kinetics of some of the reactive systems, such as fermentation, enzymatic reaction and biomass growth processes, can also be accurately represented by using fractional calculus without the need for empirical considerations.

To illustrate the approach, here we consider three instances of a fermentation process; two of them produce bioethanol with different substrate and microorganisms and the third one is for the production of Tequila. In addition, we also analyze the case of the thermal hydrolysis of Agave salmiana to produce Mezcal under two different temperature conditions.

2.1. Fermentation processes

In general, the models reported in the literature for fermentation are based on empirically driven kinetics. However, many times these models are not the best fit for the experimental data.
In this section, we provide the background information about the current models or data for three fermentation processes used as case-studies.

2.1.1. Fermentation process for tequila production

Tequila is the most important distilled alcoholic beverage in México. It is produced from the fermented juice of cooked Agave tequilana Weber (blue variety). In the tequila fermentation process ethanol and many volatile compounds that may influence the sensory characteristics of the final product are formed. Arellano-Plaza et al. (2007) and Herrera et al. (2009) proposed an unstructured mathematical model for the production of tequila. An unstructured model only consider kinetics of growth, substrate uptake and product formation, and considers that the reaction rates depend only on the conditions presented inside the bioreactor. In their work, the dynamic ordinary model was derived from experimental data. The average or mean values of the duplicate experimental data for the biomass, ethanol (product) and reducing sugars (substrate) were used as the experimental data to validate the model; the Saccharomyces cerevisiae yeast was used in all of their fermentation assays.

The dynamic model for tequila production is given by the following set of ordinary differential equations (Herrera et al., 2009):

\[
\frac{dx_1}{dt} = (\mu - D) x_1 
\]

\[
\frac{dx_2}{dt} = -(Y_{xx} - Y_{ps})\mu x_1 - m_n x_1 - (-S_0 + x_2)D
\]

\[
\frac{dx_3}{dt} = a_0 x_1 - D x_3
\]

\[x_1\] is the biomass, \(x_2\) is the substrate and \(x_3\) is the product and are given in g/l. \(Y_{xx}\) and \(Y_{ps}\) are the dimensionless biomass and product yield coefficients, respectively; \(S_0\) (g/l) is the feed substrate concentration, \(m_n\) (g/l) is the maintenance coefficient, \(\mu\) is a growth associated term and \(D\) (h\(^{-1}\)) is the dilution rate. \(\mu\) (h\(^{-1}\)) is the specific growth rate, which gives the characteristic nonlinear behavior of fermentation processes, and depends on the substrate and the ethanol in the culture. In this model, \(\mu\) is given by the following expression:

\[
\mu = \frac{\mu_{max} x_2}{k_i + x_2 + x_3^2/k_i} (1 - x_3 k_0)
\]

where \(k_0\) (g/l) is a substrate saturation term and \(k_i\) and \(k_p\) are the inhibition parameters for substrate and product, respectively.

2.1.2. Bioethanol production from sugarcane

Pinilla et al. (2011) studied the bioethanol production process by fermentation from sugar cane molasses. Zymomonas mobilis, an anaerobic facultative and Gram negative bacterium, was used as the microorganism for the bioethanol production. Z. mobilis generates a high efficient glucose metabolic flux towards the product, with a low bacterial growth, reaching productivities of ethanol 3–5 times higher than S. cerevisiae, and product yields on substrate about 97%. Further, Z. mobilis tolerates high concentrations of ethanol and has a high yield of product. It also displays high tolerance for changes in pH, so that it guarantees greater time to keep the alcoholic fermentation before being inhibited by acidification of culture medium.

The experimental results obtained by Pinilla et al. (2011) for the kinetics of growth cell (biomass), glucose uptake (substrate) and ethanol production (product) will be used in this paper. No mathematical model was reported in their work.

2.1.3. Bioethanol production from carob pulp fermentation

Carob pulp composition has a high content of sugars, mainly sucrose (more than 30%), fructose, and glucose. This provides economical relevance to carob pulp as an inexpensive and available feedstock for various biological products. Lima-Costa et al. (2012) analyzed the performance of a S. cerevisiae strain for bioethanol production from highly concentrated carob pulp extracts, in an aerated stirred tank reactor; their goal was to identify the factors that limit the efficiency of this fermentation process. In all their runs, 90–95% of the total sugar was consumed and transformed into ethanol with a yield close to the theoretical maximum (0.47–0.50 g/g), and a final ethanol concentration of 100–110 g/l.

The results reported by Lima-Costa et al. (2012) are also used in this work to test the modeling capabilities of fractional calculus. Experimental results provided include the time course of ethanol (product), biomass production and total sugar consumption (substrate). As in the previous case, no mathematical model was proposed in the reference.

2.2. Thermal hydrolysis of A. salmiana for mezcal production

This case-study is taken from the work of García-Soto et al. (2011). Mezcal is an alcoholic beverage of Mexico that is obtained from the fermentation and distillation of the syrup of cooked agaves. Mezcal is manufactured according to a procedure that is similar from the production of tequila. The main difference between the production of mezcal and tequila is that the raw material used in tequila is Agave tequilana Weber, whereas a broad variety of agave species can be used in the production of mezcal; such as Agave angustifolia, Agave esquerrina, Agave potatorum and A. salmiana.

Fructans are the main reserve of polysaccharides in agave plants. In the production process, the agave rich in fructans is cooked in autoclaves to hydrolyze the fructans and release fermentable sugars, principally fructose. After the thermal treatment is complete, agave heads are thus milled to obtain syrup that consists primarily of fructose, glucose, xylose, and maltose. This syrup is fermented with native or selected yeast strains and the fermented syrup is distilled in pot stills to obtain mezcal.

The thermal treatment of fructans is of interest because it is the first step in the production of mezcal and it requires significant amounts of energy. During the cooking step, fructans are hydrolyzed into monomers or oligosaccharides with lower degrees of polymerization. Some of the objectives of the study by García-Soto et al. (2011) were to determine kinetic parameters of the thermal hydrolysis of fructans from A. salmiana and to evaluate the production of reducing sugars and furan compounds during thermal hydrolysis. The kinetic model proposed in the literature (Garcia-Soto et al., 2011) using the following reaction is given below:

\[
\text{Fructans} \xrightarrow{k_1} \text{Reducing sugars}
\]

\[
\text{Furans} \xrightarrow{k_2} \text{other}
\]

Fructans (P) are hydrolyzed into reducing sugars which then might undergo partial degradation to form furans (D). \(k_1\) and \(k_2\) are the rate constants of hydrolysis and degradation, respectively. The dynamic mathematical model is given by the following equations:

\[
\frac{dP}{dt} = -k_1[P]
\]
\[
\frac{d[M]}{dt} = k_b[P] - k_d[M] \\
\frac{d[D]}{dt} = k_d[M]
\]
with initial conditions \((t = 0)\)

\[
[P] = P_0, \quad [M] = M_0, \quad [D] = 0
\]

\[
P_0 = M_f \frac{180n - 18(n - 1)}{180n}
\]

where \(n\) is the degree of polymerization.

3. Non-linear fitting of fractional model parameters

Given either the ordinary dynamic model or the corresponding experimental data, a fractional dynamic model will be proposed for the case-studies described in the previous section. To obtain the model parameters and the fractional order of the differential equations, a non-linear fitting approach must be coupled to a numerical or analytical solution technique for systems of fractional differential equations (FDE). Analytical approaches such as those based on Laplace transformation can be applied to linear models. Non-linear models require the use of numerical techniques.

3.1. Numerical integration of fractional differential equations

Diethelm et al. (2005) provide a review of the numerical solution techniques for systems of FDE. In this work we use the predictor-corrector method proposed by Diethelm et al. (2002). Such a method is a generalization of the Adams–Bashforth–Moulton technique suitable for FDE; the numerical algorithm is based on the Caputo definition for the fractional derivative. The technique can be applied to both linear and non-linear systems of FDE’s with either homogenous or non-homogenous initial conditions.

In summary, the predictor step is calculated through following equation (Diethelm et al., 2002):

\[
y_{k+1}^{\alpha}(t_{n+1}) = \sum_{k=0}^{[\alpha-1]} \frac{t_h^{k+1}}{k!} y_0^k + \frac{\Gamma(\alpha+1)}{\Gamma(\alpha+2)} \sum_{j=0}^{\alpha} b_{j,n+1} f(t_j,y_h(t_j))
\]

where

\[
b_{j,n+1} = \frac{h^n}{\alpha} ((n+1-j)^{\alpha} - (n-j)^{\alpha})
\]

whereas the corrector step is calculated by the following equation:

\[
y_{k+1}^{\alpha}(t_{n+1}) = \sum_{k=0}^{[\alpha-1]} \frac{t_h^{k+1}}{k!} y_0^k + \frac{\Gamma(\alpha+1)}{\Gamma(\alpha+2)} \sum_{j=0}^{\alpha} a_{j,n+1} f(t_j,y_h(t_j))
\]

where

\[
a_{j,n+1} = \begin{cases} 
  \frac{(n-j)^{\alpha}}{\alpha}, & \text{if } j = 0 \\
  \frac{(N-j+2)^{\alpha+1} + (n-j)^{\alpha+1} - 2(n-j+1)^{\alpha+1}}{1}, & \text{if } 1 < j < n \\
  1, & \text{if } j = n+1
end{cases}
\]

Therefore, the basic algorithm, the fractional Adams–Bashforth–Moulton method, is fully described by Eqs. (13) and (15) with the weights defined by Eqs. (14) and (16).

4. Fractional models for reactive biological systems

This section describes the fractional calculus models proposed in this work for the fermentation case-studies as well as for the thermal hydrolysis process.

4.1. Fermentation

Two out of the three instances of fermentation considered in this work provide only experimental data; besides the data, the other case further describes a model based on ordinary differential equations. Literature reports several additional simplified models for fermentation which generally differ in the definition of the specific growth rates for the product and the substrate.

A simple fractional model for fermentation is proposed in this section. The model is based on the classical Lotka–Volterra model for the predator-prey system. The two-species Lotka–Volterra model describes a simple interaction between a prey species, \(y(t)\), and its predator, \(x(t)\), with four parameters: predator mortality rate, \(a\), predator growth rate, \(b\), prey mortality rate, \(c\), and prey growth rate, \(d\). The model is used as a simple representation of the interaction among the species of a biological system. The population dynamics of the two-species are described with two non-linear ordinary first-order differential equations:

\[
\frac{dy}{dt} = -ax + bxy
\]

\[
\frac{dx}{dt} = dx - cxy
\]

A lower prey mortality rate allows the prey population to increase, which also spurs on greater growth of the predator proportional to the product \(bxy > 0\). On the other hand, as prey mortality increases (the prey population decreases) the predator population decreases since it cannot be supported. Similarly, an increase in the predator mortality rate causes a decrease in predator population and a proportional increase in the prey population.

The fractional order fermentation model is proposed as an analogy to the Lotka–Volterra model. Three state variables are considered though, the biomass, the product and the substrate. The Caputo definition of the fractional derivative is assumed since it allows the use of standard initial conditions for the states (as in ordinary calculus).

Assuming that the biomass growth depends only on the substrate, the biomass increase is proportional to the interaction biomass–substrate (product of \(B \times S\), BS). If we further assume a cell mortality rate (equivalent to a term involving inhibition by substrate or product), the biomass concentration will be represented as follows:

\[
\frac{\partial}{\partial t}^{\alpha} B = k_p BS - k_m B
\]

A similar derivation is used for substrate and product differential equations. We assume that substrate concentration decreases proportionally to the interaction biomass–substrate (BS):

\[
\frac{\partial}{\partial t}^{\alpha} S = -k_p BS
\]

and that the product concentration also depends on the same interaction biomass–substrate (BS), so that the following kinetics expression applies:

\[
\frac{\partial}{\partial t}^{\alpha} P = k_p BS
\]

Notice that the resulting equations follow a representation similar to those obtained by the law of mass action in elementary kinetics, so that Michaelis–Menten type of expressions are avoided. The proposed fermentation model involves then
Eqs. (19)–(21). The kinetics constants represent biomass growth \((k_c)\), cell death or inhibition \((k_{ci})\), substrate consumption \((k_p)\) and product formation \((k_p)\). Rate constants and the fractional orders need to be estimated for each of the case-studies. It is important to emphasize that the same formulation will be used to fit the experimental data of the three different instances of fermentation, involving different substrate, microorganisms and process conditions.

In the same way as the Lotka–Volterra model does not explicitly enforce a population balance, this fermentation formulation does not explicitly enforce mass balance constraints to be satisfied. Notice also that the rate constants are independent of each other and that each constant appears only in one differential equation, so there is no dimensional inconsistency. We therefore believe that a fractionalization approach as the one proposed by Dokoumetzidis et al., (2010a, 2010b) is not required in this illustrative example.

4.2. Thermal hydrolysis of agave for mezcal production

This ordinary model presented earlier (Garcia-Soto et al., 2011) is conceptually different from the fermentation formulation used in the first case-study. Observe that the thermal hydrolysis model given by Eqs. (10)–(12) satisfies the mass balance among the participant species and that some of the reactive constants appear in more than one differential equation. As a simple approach, we might attempt to fractionalize the model in a straightforward manner; that is, to generalize the first order derivatives found on the left hand side of ordinary differential equations (ODEs) by replacing them with fractional derivatives. However, this simple change in the order of the derivatives will result in theoretical inconsistencies. First, since the same rate constant would appear in more than one FDE, each of which of different order, the same parameter would have different units in different parts of the system. Moreover, in multi-compartmental models representing the rate of mass transfer from one compartment to another, an outgoing mass flux that is defined as a rate of a fractional order cannot appear as an incoming flux into another compartment as a rate of a different fractional order. This approach produces inconsistent fractional systems and leads to violation of mass balances.

4.2.1. A consistent fraction model for the thermal hydrolysis of agave

There are some alternative techniques to obtain a fractional model from a multi-compartment ordinary model. The trivial case is to consider the same fractional order for all of the differential equations. In that case, the mass balances remain unaffected (as in ordinary models) and the dimensional consistency is achieved just by assigning the appropriate dimensions to the reaction constants.

Diethelm (2013) used a similar but slightly different technique to formulate a fractional model from an ordinary model representing the dynamics of an outbreak of dengue fever; a population balance has to be satisfied on that problem. Starting from an ordinary model, Diethelm (2013) replaced the ordinary operators by Caputo derivatives to get fractional equations; the author then suggested the use of two different fractional orders in five differential equations. As a consequence, terms appearing in the right hand side of the differential equations were dimensionally inconsistent (they remained unchanged at this point). To make the dimensions match, the author did not modify the dimension of the kinetics constants, but they simply raised such constants to the appropriate fractional powers instead.

In this work, we could fractionalize our model either by using the same fractional order in all of the equations or by using the simple but efficient approach described by Diethelm (2013). In both cases, the resulting fractional model would have been similar in nature to the one obtained for the fermentation problem. Then, no special numerical techniques would have been needed when using this model either for non-linear parameter fitting or for optimization purposes. However, we decided to use this example to illustrate the mathematical and numerical complexities added by the use of a formal fractionalization approach.

A formal fractionalization approach to obtain a consistent system of FDE’s from a system of ODE’s has been reported in the works of Dokoumetzidis et al., (2010a, 2010b) and Verotta (2010a; 2010b).

In this work we use that fractionalization strategy reported by Dokoumetzidis et al., (2010a, 2010b) to obtain a fractional version of the dynamic model for the thermal hydrolysis of agave for mezcal production.

The strategy starts with the integration of the ordinary model defined by Eqs. (10)–(12) to obtain a system of integral equations

\[
P(t) = P(0) = -k_h \int_0^t P(\tau) d\tau
\]

\[
M(t) - M(0) = k_h \int_0^t P(\tau) d\tau - k_d \int_0^t M(\tau) d\tau
\]

\[
D(t) - D(0) = k_d \int_0^t M(\tau) d\tau
\]

We now consider that each integral includes a specific kernel \(G_1(t, \tau)\) or \(G_2(t, \tau)\), so that the systems (22)–(24) can be re-written as follow:

\[
P(t) = P(0) = -k_h \int_0^t G_1(t, \tau) P(\tau) d\tau
\]

\[
M(t) - M(0) = k_h \int_0^t G_1(t, \tau) P(\tau) d\tau - k_d \int_0^t G_2(t, \tau) M(\tau) d\tau
\]

\[
D(t) - D(0) = k_d \int_0^t G_2(t, \tau) M(\tau) d\tau
\]

In the ordinary case, this kernel is simply \(G(t, \tau) = \frac{(t-\tau)^{\alpha_1-1}}{\Gamma(\alpha_1)}\). By changing this kernel we can transform the integrals of (25)–(27) to Riemann–Liouville integrals. The appropriate form of the kernel is

\[
G(t, \tau) = \frac{(t-\tau)^{\alpha_1-1}}{\Gamma(\alpha_1)}
\]

where \(0 < \alpha_1 < 1\) is a constant representing the order of the specific process. By substituting Eq. (28), the system of equations becomes

\[
P(t) = P(0) = -k_h \int_0^t \frac{(t-\tau)^{\alpha_1-1}}{\Gamma(\alpha_1)} P(\tau) d\tau
\]

\[
M(t) - M(0) = k_h \int_0^t \frac{(t-\tau)^{\alpha_1-1}}{\Gamma(\alpha_1)} P(\tau) d\tau - k_d \int_0^t \frac{(t-\tau)^{\alpha_2-1}}{\Gamma(\alpha_2)} M(\tau) d\tau
\]

\[
D(t) - D(0) = k_d \int_0^t \frac{(t-\tau)^{\alpha_2-1}}{\Gamma(\alpha_2)} M(\tau) d\tau
\]

Eqs. (29)–(31) can be simplified by using the Riemann–Liouville definition of fractional integration

\[
_0D_{+t}^{\alpha_1} f(t) = \int_0^t \frac{(t-\tau)^{\alpha_1-1}}{\Gamma(\alpha_1)} f(\tau) d\tau
\]
so that the system of equations is now represented by the following equations:

\[ P(t) - P(0) = -k_h \, D_t^{-\alpha_1} P(t) \tag{33} \]

\[ M(t) - M(0) = k_h \, D_t^{-\alpha_1} P(t) - k_d \, D_t^{-\alpha_2} M(t) \tag{34} \]

\[ D(t) - D(0) = k_d \, D_t^{-\alpha_2} M(t) \tag{35} \]

We take now the first derivative of the integral Eqs. (29)–(31):

\[ \frac{dP}{dt} = -k_h \, D_t^{1-\alpha_1} P(t) \tag{36} \]

\[ \frac{dM}{dt} = k_h \, D_t^{1-\alpha_1} P(t) - k_d \, D_t^{1-\alpha_2} M(t) \tag{37} \]

\[ \frac{dD}{dt} = k_d \, D_t^{1-\alpha_2} M(t) \tag{38} \]

The system given by Eqs. (36)–(38) include first order derivatives of fractional integrations. That is, Riemann–Liouville fractional derivatives; then, the system can be re-written as follows:

\[ \frac{dP}{dt} = -k_h \, D_t^{1-\alpha_1} P(t) \tag{39} \]

\[ \frac{dM}{dt} = k_h \, D_t^{1-\alpha_1} P(t) - k_d \, D_t^{1-\alpha_2} M(t) \tag{40} \]

\[ \frac{dD}{dt} = k_d \, D_t^{1-\alpha_2} M(t) \tag{41} \]

In order to use standard initial conditions, the Riemann–Liouville derivatives must be re-defined as Caputo fractional derivatives. The equivalence between these definitions is given by the following equation:

\[ D_t^{\alpha_1} f(t) = \frac{d}{dt} \left( \frac{1}{\Gamma(\alpha_1)} \int_0^t (t - \tau)^{\alpha_1 - 1} f(\tau) d\tau \right) \tag{42} \]

Then, the system of Eqs. (39)–(41) using Caputo derivatives is expressed as follows:

\[ \frac{dP}{dt} = -k_h \left[ \frac{\partial D_t^{1-\alpha_1} P(t) + P(0)\Gamma(\alpha_1)}{\Gamma(\alpha_1)} \right] \tag{43} \]

\[ \frac{dM}{dt} = k_h \left[ \frac{\partial D_t^{1-\alpha_1} P(t) + P(0)\Gamma(\alpha_1)}{\Gamma(\alpha_1)} \right] - k_d \left[ \frac{\partial D_t^{1-\alpha_2} M(t) + M(0)\Gamma(\alpha_2)}{\Gamma(\alpha_2)} \right] \tag{44} \]

\[ \frac{dD}{dt} = k_d \left[ \frac{\partial D_t^{1-\alpha_2} M(t) + M(0)\Gamma(\alpha_2)}{\Gamma(\alpha_2)} \right] \tag{45} \]

The system of Eqs. (43)–(45) is the fractional model for the thermal hydrolysis of agar. Notice that the initial conditions of the ordinary case are used. This model does not follow the mass balance constraints. This system can be used for the non-linear parameter fitting as well as for optimization purposes.

4.2.2. A reformulation of the thermal hydrolysis model through Laplace transformation

Given the linear structure of the system of the Eqs. (43)–(45), Laplace transformation can be used to reformulate the model, so that it can be analyzed in the Laplace domain.

The Laplace transformation needed for the reformulation is (Magin, 2006) as follows:

\[ L[D_t^{\alpha_1} f(t)] = s^\alpha_1 f(s) - s^{\alpha_1 - 1} f(0) \tag{46} \]

where \( f(s) \) is the Laplace transformation of \( f(t) \). If \( \alpha = 1 \), Eq. (46) reduces to the classical expression for the transformation of ordinary derivatives

\[ L[D_t^{1} f(t)] = s f(s) - f(0) \tag{47} \]

In our case, the order is \( 1 - \alpha_1 \), so that Eq. (46) becomes

\[ L[D_t^{1-\alpha_1} f(t)] = s^{\alpha_1 - 1} f(s) - s^{\alpha_1 - 2} f(0) \tag{48} \]

By applying the Laplace transformation to Eq. (43) (fructans), Eq. (49) is obtained

\[ \hat{s}P(s) - P(0) = -k_h \left[ s^{1-\alpha_1} \hat{P}(s) - s^{-\alpha_1} P(0) + P(0) \left( \frac{1}{\Gamma(\alpha_1)} \right) \right] \tag{49} \]

Simplifying

\[ \hat{s}P(s) - P(0) = -k_h [s^{1-\alpha_1} \hat{P}(s)] \tag{50} \]

and re-arranging

\[ \hat{s}P(s) + k_h [s^{1-\alpha_1} \hat{P}(s)] = P(0) \tag{51} \]

\[ \hat{P}(s) \left[ s + k_h s^{1-\alpha_1} \right] = P(0) \tag{52} \]

Eq. (52) can be solved for \( \hat{P}(s) \) to obtain

\[ \hat{P}(s) = \frac{P(0)}{s + k_h s^{1-\alpha_1}} \tag{53} \]

A similar approach is applied to the reducing sugars dynamics to obtain Eq. (54):

\[ \hat{s}M(s) - M(0) = k_h [s^{1-\alpha_1} \hat{P}(s)] - k_d \left[ s^{1-\alpha_2} \hat{M}(s) + M(0) \left( \frac{1}{\Gamma(\alpha_2)} \right) \right] \tag{54} \]

which can be simplified to

\[ \hat{s}M(s) - M(0) = k_h [s^{1-\alpha_1} \hat{P}(s)] - k_d [s^{1-\alpha_2} \hat{M}(s)] \tag{55} \]

and re-arranged as well

\[ \hat{s}M(s) + k_d [s^{1-\alpha_2} \hat{M}(s)] = k_h [s^{1-\alpha_1} \hat{P}(s)] + M(0) \tag{56} \]

\[ \hat{M}(s) [s + k_d s^{1-\alpha_2}] = k_h [s^{1-\alpha_1} \hat{P}(s)] + M(0) \tag{57} \]

Solving for \( \hat{M}(s) \) results in Eq. (58):

\[ \hat{M}(s) = \frac{1}{s + k_d s^{1-\alpha_2}} [k_h [s^{1-\alpha_1} \hat{P}(s)] + M(0)] \tag{58} \]

The same steps are applied to the furans dynamics to obtain the following equations:

\[ \hat{s}D(s) - D(0) = k_d [s^{1-\alpha_2} \hat{M}(s)] \tag{59} \]

\[ \hat{D}(s) = \frac{1}{s} [k_d [s^{1-\alpha_2} \hat{M}(s)] + D(0)] \tag{60} \]

For the purposes of comparison, the ordinary model (10)–(12) is also transformed to the Laplace domain to obtain

\[ \hat{P}(s) = \frac{P(0)}{s + k_h} \tag{61} \]
\[ \dot{M}(s) = \frac{1}{s + \alpha_1} \left( k_d \dot{P}(s) + M(0) \right) \]  
\[ \dot{D}(s) = \frac{1}{s} \left( k_d \dot{M}(s) + D(0) \right) \]  

It can be shown that, if \( \alpha_1 = \alpha_2 = 1 \) in the fractional expressions (Eqs. (53), (58) and (60)), then Eqs. (61)–(63), representing the ordinary case, are obtained. The system defined by Eqs. (53), (58) and (60) does not have an analytical solution. Therefore numerical transformation is needed if the model is used either to fit experimental data or to optimize its dynamic performance; the second alternative is what we used in the second part of this series of papers.

5. Results and discussion: developing fractional models

5.1. Fermentation results

The kinetics parameters for the fractional fermentation model were estimated through non-linear fitting, by using a numerical strategy that combines the Matlab \textit{lsqnonlin} subroutine with the predictor-corrector fractional integration technique described in Section 3 (also coded in Matlab).

5.1.1. Fermentation process for tequila production

Table 1 shows the values of the parameters of the system (19)–(21) which fit experimental data for the tequila production process provided by Arellano-Plaza et al. (2007) and Herrera et al. (2009). All of the fractional orders are bigger than 0.5, and the order of the dynamic equation for the product is very close to 1; this indicates that the tequila production process is better represented by a system involving both ordinary differential equations and fractional differential equations. Notice also that the constant for cell death/inhibition \( \left( k_m \right) \) is almost zero in this case for the time period under consideration.

Fig. 1 displays a comparison among the dynamic profiles obtained for the ordinary and the fractional models; the experimental data is also shown; the advantages of using a fractional model can be observed, mainly in the product time profiles. Table 2 shows the average relative error of the concentrations obtained with the fractional and ordinary models with respect to experimental values. The average relative error is calculated from the following equation:

\[ e = \frac{1}{N} \sum_{i=1}^{N} \left( \frac{|X_{calc,i} - X_{exp,i}|}{X_{exp,i}} \right) \]  

where \( X_{calc} \) is the concentration obtained by the model, \( X_{exp} \) is the experimental value and \( N \) is the number of experimental values available. Results show that the fractional model performs better than the ordinary model with much less number of parameters.

5.1.2. Bioethanol production from sugarcane

Since in this case no ordinary model was reported, the profiles obtained with the fractional model are compared just with the experimental data provided by Lima-Costa et al. (2012). Table 3 shows the fractional orders and the kinetics parameters obtained for the system (19)–(21). The three orders for the derivatives are

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Fitted parameters for the tequila fermentation process.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_1 )</td>
<td>0.7769</td>
</tr>
<tr>
<td>( k_1 )</td>
<td>0.0041 L/g h(^n)</td>
</tr>
<tr>
<td>( k_2 )</td>
<td>0.0156 L/g h(^n)</td>
</tr>
<tr>
<td>( \alpha_2 )</td>
<td>0.8767</td>
</tr>
<tr>
<td>( k_3 )</td>
<td>2.3875 \times 10^{-14} h^{-n}</td>
</tr>
<tr>
<td>( \alpha_3 )</td>
<td>0.998</td>
</tr>
<tr>
<td>( k_4 )</td>
<td>0.0585 L/g h(^n)</td>
</tr>
</tbody>
</table>
fractional and the death/inhibition constant is once again zero. Fig. 2 presents a graphical comparison of the dynamic profiles predicted by the model following the experimental results. Recall that there is no ordinary model proposed for this case.

5.1.3. Bioethanol production from carob pulp

As in the previous case, no ordinary dynamic model was proposed in the literature to fit the experimental data (taken from Pinilla et al. (2011)). Table 4 presents the fitting parameters for the general fractional fermentation model given by (19)–(21). The order for the product dynamics is again close to 1. Fig. 3 shows the dynamic profiles for biomass, ethanol and substrate. In this example, experimental data for the biomass growth display a decay of biomass concentration after about 30 h. That observation is in agreement with the value of \((k_m)\) which is not zero for this case; that would imply that cell death/inhibition has a significant effect here.

5.2. Results for thermal hydrolysis of agave for mezcal production

The kinetics parameters for the system of fractional differential Eqs. (43)–(45) were estimated again through non-linear fitting by using Matlab. However, in this case the fractional predictor-corrector integration technique cannot be used and the non-linear fitting was based on the equivalent modeling Eqs. (61)–(63), derived in the Laplace domain. The numerical algorithm combines then the Matlab **lsqnonlin** subroutine with a Laplace inversion function **invlap** also coded in Matlab. Experimental data for the thermal hydrolysis was provided for two different values of temperature. Results are described as follows.

5.2.1. Results for the thermal hydrolysis at 106 °C

The fitting parameters obtained for the thermal hydrolysis fractional model at 106 °C are provided in Table 5. Fig. 4 compares the values obtained for the fractional and ordinary models against the experimental data. In particular, the results for the reducing sugars time profile show the positive impact of using a fractional model.

5.2.2. Results for the thermal hydrolysis at 96 °C

The non-linear fitting and the simulations were also performed using experimental data obtained at 96 °C. The fitting parameters are provided in Table 6 and the time profiles are presented in Fig. 5. All of the values of the fractional order and the kinetics parameters of Table 6 are similar to those corresponding to the temperature of 106 °C in Table 5. Given that observation, a re-calculation of the parameters at 96 °C is proposed next.
5.2.3. Two-parameter results for the thermal hydrolysis at 96 °C

Experimental data for the thermal hydrolysis provided in Garcia-Soto et al. (2011) depend on the temperature; a standard kinetics model would then capture the variability of the data by proposing the kinetics constants to be functions of temperature, and also assuming that the order of the derivatives is the same even for the different temperature values.

Following this approach (and recalling the numerical similarity of the non-linear fitting results at both values of temperature), the fractional order of the derivatives for the case of 96 °C were fixed as equal to those of the case at 106 °C. In this way, the kinetics parameters for the temperature of 96 °C were recalculated. Table 7 shows the values of the fitted parameters after the recalculation. The fractional orders of the derivatives are of course equal to those of Table 5, and the kinetics constants have been re-estimated accordingly.

Fig. 6 shows the comparison of the time dependent profiles (experimental and fractional) of the states variables for the temperature of 96 °C by using a four-parameter estimation (fractional order and constants) and two-parameter estimation (kinetics constants, fixing fractional orders as equal to those at 106 °C).

Fig. 6 clearly shows that the effect of using the same fractional order in both cases is practically negligible. A significant result is however that now the fractional order derivatives at 96 °C are consistent with the values at 106 °C, achieving physical consistency. Further, the difference in the values of the kinetics constants can be explained in terms of the value of temperature. The recalculation is particularly important for the optimization of the system presented in the second paper of this series.

For this case-study, Table 8 shows the average relative error (Eq. (64)) of the concentrations obtained with the (two-parameter) fractional and the ordinary models with respect to experimental values. Results show that the fractional model performs better than the ordinary model for the reducing sugars (product of interest); the error for furans is quite similar in both of the models.

5.3. Discussion

In general, for the case of the tequila production process, both the ordinary model and the fractional model predict values for the states that are reasonably consistent with the data. However, the fractional model fits the experiments better with a smaller number of parameters and a much simpler numerical expression. Notice also that a further simplification could be done in this case, since one of the terms involved (cell death/inhibition) could be omitted.

The performance of the fractional fermentation model is also reasonable for both cases of the production of bioethanol with respect to the experimental data. We believe then that a significant result is that the same fractional fermentation model was able to fit the three instances of a fermentation process (with different microorganisms and substrate). Classical semi-empirical ordinary models most certainly would have required different terms and physical interpretation of them in order to fit the data of each of the cases. The fractional model was also flexible enough as to represent the biomass growth decay presented in the production of bioethanol from carob pulp; a value of the constant \( k_0 \) different from zero served that purpose. Once again, a reformulation of the fractional model was not needed.

In the example of the thermal hydrolysis of agave, the predictive capabilities of the ordinary and the fractional models are also reasonable in both cases. The fractional model performs...
slightly better to predict the reducing sugars (whose prediction was the goal of the experimental study used as reference) behavior, but the ordinary model performs better for the furans. In general, the ordinary model is simple and accurate enough, so that a fractional approach might not be needed for this case; therefore, it is unclear if memory effects play a significant role in the behavior of this system. However, this case study was selected in this work because it is an example of a set of ordinary differential equations in bioengineering in which the mass balance constraint has been enforced. Therefore, a formal fractionalization approach was required to get a fractional order version of the state equations.

In that sense, this paper shows a simple fractional fermentation model where the modeling capabilities of fractional calculus are clear (a simpler model can be used) and the fitting parameters can be obtained in the straightforward manner. However, through the thermal hydrolysis case-study, we also show a more formal fractionalization approach which does not generate theoretical inconsistencies (i.e. mass balance violations) in multi-compartmental model. The example also allows us to show the theoretical advances and mathematical tools already available in the area of fractional calculus.

Table 5
Fitted parameters for the thermal hydrolysis process at 106 °C.

<table>
<thead>
<tr>
<th>$\alpha_1$</th>
<th>$k_\text{h}$</th>
<th>$k_\text{d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9738</td>
<td>0.1729 h$^{-\alpha_1}$</td>
<td>0.0014 h$^{-\alpha_1}$</td>
</tr>
</tbody>
</table>

Table 6
Fitted parameters for the thermal hydrolysis process at 96 °C (four-parameter fitting).

<table>
<thead>
<tr>
<th>$\alpha_1$</th>
<th>$k_\text{h}$</th>
<th>$k_\text{d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0519 h$^{-\alpha_1}$</td>
<td>4.8592 $\times$ 10$^{-4}$ h$^{-\alpha_1}$</td>
</tr>
</tbody>
</table>

Table 7
Fitted parameters for the thermal hydrolysis process at 96 °C; the fractional orders are fixed as the values obtained at 106 °C (two-parameter fitting).

<table>
<thead>
<tr>
<th>$\alpha_1$</th>
<th>$k_\text{h}$</th>
<th>$k_\text{d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9738</td>
<td>0.0552 h$^{-\alpha_1}$</td>
<td>5.0789 $\times$ 10$^{-4}$ h$^{-\alpha_1}$</td>
</tr>
</tbody>
</table>

Fig. 4. Dynamic profiles in the thermal hydrolysis of agave at 106 °C.

Fig. 5. Dynamic profiles in the thermal hydrolysis of agave at 96 °C.
5.3.1. Beneﬁts and disadvantages of the use of fractional calculus as a modeling tool

Two main disadvantages of the use of fractional calculus as a modeling tool are clearly identiﬁed. The ﬁrst one is related to the complexity involved in the numerical or analytical evaluation of fractional derivatives (or any other related fractional operator, such as fractional integration); this is a direct implication of the non-locality of fractional operators. Then, specialized numerical methods (as the predictor-corrector method of Diethelm et al. (2002)) or special functions (as the Mittag-Leffler function) need to be used to evaluate fractional derivatives. The second disadvantage is the lack of a physical interpretation for the fractional derivative. Despite of some recent attempts to provide a physical meaning for fractional derivative, the task remains as an open question to researchers on this area.

Therefore, clear advantages of the use of ordinary differential equations are their physical and geometric interpretations as well as efﬁcient and relatively simple evaluation mechanisms (numerical or analytical) for ordinary derivatives. Further, ordinary models can directly be derived based on semi-mechanistic reasoning.

We believe that there is no general rule with respect to the potential use of fractional differential equation as a modeling tool. We believe that FDE modeling needs to be evaluated for dynamic systems that, based on physical or phenomenological observation, might potentially possess memory properties. Memory could be represented in terms of time delays; however, a cascade of ordinary differential equations including additional parameters would be needed. That is precisely one of the advantages of fractional calculus as a modeling tool; a single fractional differential equation can be used to model memory effects without the need for a series of ordinary differential equations involving a large number of parameters. Note that these parameters would also lack physical interpretations.

We think that our ﬁrst illustrative example (fermentation case-study) shows exactly what we should expect/require from a fractional calculus based kinetics model. A fractional model, but a simpler one, involving less number of parameters and simpler expressions similar from those derived directly from the law of mass action. Moreover, derivation of a generalized model is also important. The model we proposed was able to ﬁt experimental data from three different instances of a fermentation process (different substrates, conditions and microorganisms).

6. Conclusions

Fractional derivatives are deﬁned by using integrals, so they are non-local operators. Then, calculation of the fractional derivative of a function at a given point in time contains information about all of the values of the function at earlier points; in other words, the expression of fractional order derivative exhibits the memory of considered function’s history. For that reason, when modeling reaction kinetics by using fractional differential equation, we have focused our study on biochemical reactions.

In our opinion, it is reasonable to think that the physicochemical nature of biological processes will result in a dynamic behavior with memory. Biochemical reactions imply the participation of living organisms. Recall that enzymes are catalysts (generally proteins) that help convert other molecules called substrates into products and are particularly efﬁcient at speeding up biological reactions. Furthermore, microorganisms’ activity constitutes the major source for enzymes. So, microorganisms used for enzyme production are growth on fermenters by using a growth medium. The dynamic behavior of living microorganisms will be affected by a number of factors (substrate concentration, medium conditions, etc.) and will adapt to changes on its environment. We believe, therefore, that the dynamic behavior of a living microorganism does not depend only on their conditions at the current point in time, but also on their state at earlier points (at least at some degree). Therefore, it is our opinion that the dynamics of biological reactions can in general involve memory effects.

In fact, in general, enzyme reactions do not follow the law of mass action directly. As the concentration of substrate is increased, the rate of the reaction increases only to a certain extent, reaching a maximal reaction velocity at high substrate concentrations. As a consequence, enzyme kinetics generally includes Michaelis–Menten type of expressions. Our goal, by using fractional calculus based modeling of biological reaction kinetics, was then to avoid the need for complex empirical expressions and to develop (fractional)
dynamic models similar from those obtained by the law of mass action.

Accordingly, in this first paper of a series of two, we intend to demonstrate the suitability of using fractional calculus as a modeling tool in chemical and biochemical engineering. We believe this goal is achieved through the fermentation case-studies. We have proposed however a fairly simple model involving fractional-order derivatives which was able to fit experimental data better in all of the three cases we analyzed. Notice also that the three fermentation cases studied differ in the product, process conditions, substrate and microorganisms used; still, the fractional model proved to be flexible enough to represent the dynamics in all of the cases. The predictive ability of the model was more accurate when compared to ordinary models with a larger number of parameters (production of tequila). In summary, we think that a fractional approach can be useful in this example because memory effects could play a role in fermentation mostly due to the micro-organisms behavior. One can expect the future micro-organisms behavior to be a function not only of their current state, but also of the existing conditions of the system during the whole operation of the process.

The second illustrative case (thermal hydrolysis) describes a model which comes from fundamental principles; the simplified analysis results in a linear ordinary model that reasonably fit the experiments. Therefore, it is difficult to think in developing a simpler fractional model. This case, however, has been used because it is a multi-compartmental model that imposes mass balance constraints and in which some parameters participate in more than one compartment (dimensional consistency is also required). We believe that a case with such type of constraints can be commonly found in the area of process systems engineering. So, the example was used to show the strategy needed to fractionalize a multi-compartmental ordinary model in order to get a fractional model, as well as to show the methodology needed to obtain the model parameters through non-linear fitting in those fractionalized models. Although in this case the fractional model turns out to be more complex that the required for the ordinary model, the model capabilities of fractional calculus were still demonstrated.

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References


