Evolutionary Intelligence
https://doi.org/10.1007/s12065-023-00840-4

SPECIAL ISSUE

Numerical solution of a new mathematical model for intravenous drug administration

Zahra Alijani[1] · **Babak Shiri**[2] · **Irina Perfilieva**[1] · **Dumitru Baleanu**[3]

Received: 1 September 2022 / Revised: 5 January 2023 / Accepted: 10 February 2023

Abstract

We develop and analyze a new mathematical model for intravenous drug administration and the associated diffusion process. We use interval analysis to obtain a system of weakly singular Volterra integral equations over ordinary functions. We then use the operational method based on Chebyshev polynomials for obtaining an approximate solution of the numerical form. We show that for a certain class of fuzzy number valued functions, their generalized Hukuhara derivatives can be reduced to the derivatives of ordinary real-valued functions. By using our approach, we are able to estimate numerical solutions very accurately.

Keywords Differential equation · Chebyshev polynomials · Fractional-fuzzy differential equations · Dynamic of the Bromsulphthalein · Concentration of drug in the arterial tissue

1 Introduction

In connection with the rapid development of informatics and its hardware and software support, it is now relevant to consider natural and biological processes without the restrictions imposed by classical mathematics. The dynamics of nature-inspired systems are influenced by various latent factors so that the whole process can be described as "dynamic systems with memory". These systems are the focus of fractional calculus. Among its recent advantages, demonstrated in [1], is the ability to reduce the high dimensional of the original model using a properly selected memory kernel.

✉ Zahra Alijani
zahra.alijani@osu.cz

Babak Shiri
shiri@njtc.edu.cn

Irina Perfilieva
irina.perfilieva@osu.cz

Dumitru Baleanu
dumitru@cankaya.edu.tr

1 Institute for Research and Application in fuzzy modeling, University of Ostrava, Ostrava, Czech Republic

2 Data Recovery Key Laboratory of Sichuan Province, College of Mathematics and Information Science, Neijiang, China

3 Cankaya University, Department of Mathematics, Balgat, Ankara, Turkey

Fractional calculus appeared in 1695 and is currently an important tool and concept in many fields of science [2–6], and especially, in the analysis of systems of differential equations [7]. Another important feature of the modern approach to modeling is the emphasis on data and the use of the so-called "data-driven" approach. This implies the inclusion of uncertainty as one of the parameters of the model. In this regard, replacing normal values with fuzzy ones is a common technique that is becoming more and more common when modeling the real world, see, for example, [8–11]. Recently, both of the aforementioned tools have appeared together in modeling with fuzzy fractional differential equations (FFDE) and their systems and have gained attention [12, 13]. In this connection, many attempts have been made to define fuzzy derivatives. The Hukuhara derivative [14, 15], the gH-derivative [16] and the g-derivative [8] are widely accepted concepts, and dynamical systems using these concepts are currently being actively studied, see [14, 17–19].

The relationship between fuzzy analysis and interval analysis has been extensively studied in [17, 19–23]. Many properties of this relationship are used in our study of fuzzy derivatives below. In this manuscript, we develop and analyze a new mathematical model for intravenous drug administration and the associated diffusion process. We propose this model as a natural extension of the well established [24] model based on the linear ODE

Published online: 05 April 2023

system. The latter describes the rate of change in drug concentration over time in each relevant part of the human body. Other theoretical approaches to replacing linear systems of ODEs with complex models based on differential equations of various types appeared in e.g., [25–29].

Since the exact solution of the system of fractional-fuzzy differential equations cannot be easily obtained, numerical methods for solving them are mainly applicable. This is the reason why many works have recently focused on numerical solutions of FFDE, see e.g., [30]. We consider a system of linear fractional-fuzzy differential equations (linear FFDE) of the form

$$\begin{aligned} {}^{C}D^{\beta}\mathbf{y}(t) &= A\mathbf{y}(t) + \mathbf{u}(t), \quad t \in [0, T], \\ \mathbf{y}(0) &= \mathbf{y}_0, \end{aligned} \tag{1}$$

such that ${}^{C}D^{\beta}$ is a Caputo-type fractional-fuzzy derivative of order $0 < \beta \leq 1$, A is a $\nu \times \nu$ matrix of real numbers, $\mathbf{u} = [u_1, \cdots, u_\nu]^T$ is a vector of fuzzy (source) functions, and $\mathbf{y} = [y_1, \cdots, y_\nu]^T$ is an unknown vector of fuzzy functions. Finally, $\mathbf{y}_0 = [y_{01}, \cdots, y_{0\nu}]^T$ is a given vector of fuzzy numbers with ν as a dimension.

Here we consider the dynamic fuzzy control system (1), where y_0 and y_1 are initial values. If $u(t)$ is crisp, then system (1) is a classical crisp control system. In the case that y_0 is a fuzzy initial value and $u(t)$ is the fuzzy input, we have a different system with fuzzy inputs and fuzzy outputs. The deterministic control system with fuzzy inputs can generate a fuzzy control system. Fuzzy control systems have several attractive features based on the fuzzy differential equations aspect such as stability, observeability and controllability. Feng et al. [31] have studied the observability in other forms. As a result, (1) can be considered a system based on the fact given below. If the initial value $y_0 \in \mathbb{R}^\nu$ and the input $u(t) \in \mathbb{R}^\nu$, then (1) is the well known dynamic crisp system, but the initial value y_0 is not known exactly and the input $u(t)$ sometimes needs to be vague. We are motivated to respond to uncertainty by implementing fuzzy set theory.

Our contribution is twofold: (1) we extend the applicability of fuzzy differential calculus to biological systems; (2) we carried out a complete numerical analysis of the proposed model, including issues related to convergence, error estimation, and stability. In the first area, we expanded on current knowledge by showing that:

- Extending (1) to fuzzy-valued functions gives its solution an additional meaning associated with a data-driven approach to problems modeled by the solution. Due to the presence of a fuzzy initial value, the whole problem becomes an instance of an inverse problem, where the model is parameterized by degrees of membership, and the data are the observations of medical experts. The solution in the form of a fuzzy-valued function is matched against the expert knowledge related to the desired dynamics of the analyzed problem.
- The presence of fractionality refers to a parameterized approach to the concept of a derivative. This additional degree of flexibility turns the model (1) to a particular dynamic process whose response-to-time ratio differs from one process to another. This fact is important when the process is associated with the absorption of the drug by the human body. In this analysis, fractionality is used as a parameter that can be easily converted to a numerical value according to additional information about the process.

In the second area, our contribution is summarized as follows:

- We propose to reduce the analysis of equation (1) to the case when we are dealing with ordinary (not fuzzy) functions in order to be able to apply traditional numerical methods. To do this, we first assume that "fuzzy function" means a fuzzy-number-valued function (*fn*-function) that admits a parametric representation. Based on this assumption, we further reduce the problem to a system that includes interval-valued functions.
- We use the interval analysis, and after a number of transformation steps, we obtain a system of weakly singular Volterra integral equations over ordinary functions. We then use the operational method based on Chebyshev polynomials for obtaining an approximate solution to (1) in the numerical form. A new feature of our analysis is that two different parametric models of the considered equation can be processed "in one go" (without numerous branching). This is a significant advantage in the area of *fn*-valued functions and commonly used generalized Hukuhara derivatives. This advantage is achieved using the new proposed parametric form of vector *fn*–functions and the new operation of "flipping" (Section 2).
- Another advantage is the use of an analytical approximation model based on Chebyshev polynomials for all functional components found in the equation (1). This allows for accurate analytical integration of the Caputo-type fractional derivatives and the subsequent application of the method of undetermined coefficients. As a consequence, we achieve a very good error estimation of the numerical solutions.
- We complete the numerical analysis with a stability analysis, which gives an additional degree of confidence in the final selection.

The work consists of nine sections and an appendix; the latter contains the necessary technical details concerning Chebyshev polynomials. In Sect. 2, we give preliminary notions and remind some statements about general facts regarding interval analysis and fuzzy numbers. Section 3 shows how the original problem can be reduced to the ordinary one. Section 4 discusses the numerical method based on Chebyshev polynomials. In Sects. 5 and 6 we give a theoretical basis for the proposed algorithm. Sections 7 and 8 implement the proposed method and discuss numerical solutions related to dynamic processes in the human body associated with the use of medications. We conclude the manuscript with a conclusion and further work.

2 Preliminaries

In this section, we briefly recall the basic notation and some principal claims.

2.1 Interval analysis

The set of all compact (non empty) intervals of the real line is denoted by $\mathcal{K}$. Let λ be a real number, $A, B \in \mathcal{K}$ closed intervals on the real line such that $A = [\underline{a}, \overline{a}]$, $B = [\underline{b}, \overline{b}]$. The operations over intervals in $\mathcal{K}$ are defined as follows [16, 32] :

$$A + B = [\underline{a} + \underline{b}, \overline{a} + \overline{b}],$$

and

$$\lambda A = \begin{cases} [\lambda \underline{a}, \lambda \overline{a}], & \text{if } \lambda > 0, \\ 0, & \text{if } \lambda = 0, \\ [\lambda \overline{a}, \lambda \underline{a}], & \text{if } \lambda < 0, \end{cases}$$

respectively. Furthermore,

$$A \ominus_g B = [\min\{\underline{a} - \underline{b}, \overline{a} - \overline{b}\}, \max\{\underline{a} - \underline{b}, \overline{a} - \overline{b}\}].$$

is the generalized Hukuhara difference.

Proposition 1 [22] *Let $u : [a, b] \longrightarrow \mathcal{K}$ be an interval-valued function where $u(t) = [\underline{u}(t), \overline{u}(t)]$, $t \in [a, b]$. If the functions $\underline{u}(t)$ and $\overline{u}(t)$ are differentiable at $t \in (a, b)$, then u is generalized Hukuhara differentiable (gH-differentiable) at $t \in (a, b)$ and*

$$u'(t) = \left[\min\{\frac{d}{dt}\underline{u}(t), \frac{d}{dt}\overline{u}(t)\}, \max\{\frac{d}{dt}\underline{u}(t), \frac{d}{dt}\overline{u}(t)\}\right].$$

The length of interval $A = [\underline{a}, \overline{a}]$ is denoted as $l(A) = \overline{a} - \underline{a}$. An interval-valued function $u : [a, b] \longrightarrow \mathcal{K}$ is l–increasing (l–decreasing), if $l(u(t))$ is increasing (decreasing) function with respect to t.

In what follows, we refer to case 1 (2) as (gH-) differentiability of type (1) (type (2)).

2.2 Fuzzy numbers and related analysis

In this section, we introduce details of calculus over fuzzy numbers that are necessary for introducing Caputo-type fuzzy fractional derivatives. We are identifying a fuzzy number and a parametric interval family. In order to avoid repetition, we skip the definition of LU-representation of fuzzy numbers [13]. We just recall that $\underline{u}(r)$ and $\overline{u}(r)$ are called the left and right r-cut boundaries, respectively, where $0 \le r \le 1$. The space of fuzzy numbers is denoted $\mathbb{R}_{\mathcal{F}}$, and the assumed parametric representation implies that all important notions related to fuzzy numbers are formulated in terms of their left and right r-cut boundaries.

Definition 1 For arbitrary fuzzy numbers u, v, the distance $D(u, v)$ is given by

$$D(u, v) = \sup_{0 \le r \le 1} \max\{|\overline{u}(r) - \overline{v}(r)|, |\underline{u}(r) - \underline{v}(r)|\}. \tag{2}$$

It is known [15] that $(\mathbb{R}_{\mathcal{F}}, D)$ is a complete metric space. Let $u = (\underline{u}, \overline{u})$ and $v = (\underline{v}, \overline{v})$ be fuzzy numbers and $k \in \mathbb{R}$. Then,

the generalized Hukuhara difference is defined by

$$(u \ominus_g v)(r) = [\min\{\underline{u}(r) - \underline{v}(r), \overline{u}(r) - \overline{v}(r)\}, \max\{\underline{u}(r) - \underline{v}(r), \overline{u}(r) - \overline{v}(r)\}]. \tag{3}$$

It is not difficult to show that $(\mathbb{R}_{\mathcal{F}}, +)$ is a commutative groupoid with the neutral element $0 = (0, 0)$. However, the *group equation*

$$v + x = u, \quad \text{where } u, v, x \text{ are fuzzy numbers,} \tag{4}$$

This leads to other rules that can be applied to (4) to get its solution. Below we offer some of them. We contrapose $\mathbb{R}_{\mathcal{F}}$ to $\mathbb{R}^f_{\mathcal{F}}$ by setting

$$\mathbb{R}^f_{\mathcal{F}} = \{u^f = (\overline{u}, \underline{u}) \mid u = (\underline{u}, \overline{u}) \in \mathbb{R}_{\mathcal{F}}\}, \tag{5}$$

and consider $\mathbb{R}^0_{\mathcal{F}} = \mathbb{R}_{\mathcal{F}} \cup \mathbb{R}^f_{\mathcal{F}}$. In (5), we made use of a new operation $(\cdot)^f$ on $\mathbb{R}^0_{\mathcal{F}}$ called *flipping* that reverse the order of components in a functional pair, i.e. if $(u_1, u_2) \in \mathbb{R}^0_{\mathcal{F}}$, then $(u_1, u_2)^f = (u_2, u_1) \in \mathbb{R}^0_{\mathcal{F}}$. In fact, with the exception of $0 = (0, 0)$, the elements of $\mathbb{R}^f_{\mathcal{F}}$ are not fuzzy numbers, so we use this extension to characterize the (analytic) solution to the group equation (4). Below, we give the corresponding statement.

Proposition 2 *Let the equation* (4) *be given, where fuzzy numbers* $u, v \in \mathbb{R}_{\mathcal{F}}$. *Then, the equation is solvable in* $\mathbb{R}^0_{\mathcal{F}}$, *and*

1. *if* $l(v) \le l(u)$, *the solution* $x = (-1)(v \ominus_g u)$;
2. *if* $l(u) \le l(v)$, *the solution* $x = ((-1)(v \ominus_g u))^f$ *or* $x^f = ((-1)(v \ominus_g u))$.

2.3 Fuzzy vectors and related analysis

In this section, we extend fuzzy number calculus to vectors with fuzzy numbers as components - simply, fuzzy vectors. Similarly to fuzzy numbers, we identify fuzzy vectors with their one-parametric families of vector-intervals.

Let $\mathbf{y} = [y_1, \cdots, y_\nu]^T$, $\nu \ge 1$, be a vector of fuzzy numbers where for $j = 1, \cdots, \nu$, $y_j = (\underline{y}_j, \overline{y}_j) \in \mathbb{R}_{\mathcal{F}}$. Then, $\mathbf{y}$, and $\mathbf{y}^f$ are represented respectively, by

$$\mathbf{y} = [\underline{y_1}, \cdots, \underline{y_\nu}, \overline{y_1}, \cdots, \overline{y_\nu}]^T, \tag{6}$$

$$\mathbf{y}^f = [\overline{y_1}, \cdots, \overline{y_\nu}, \underline{y_1}, \cdots, \underline{y_\nu}]^T. \tag{7}$$

where each component $\underline{y}_j$ or $\overline{y}_j$ is a real function on [0, 1]. We call (6) a *parametric form* of a fuzzy vector. For example, if $\mathbf{y} = [y_1, y_2]^T$, and $y_1(r) = (r, 2-r)$, $y_2(r) = (2r, 4-2r)$, then the parametric form of $\mathbf{y}$ is $\mathbf{y}(r) = [r, 2r, 2-r, 4-2r]^T$, where $0 \le r \le 1$. The set of ν-dimensional fuzzy vectors is denoted by $\mathbb{R}^\nu_{\mathcal{F}}$, and the set of r-cuts related to the corresponding parametric forms belongs to $\mathbb{R}^{2\nu}$. Below, we give more details to the matrix multiplication. Let $A = (a_{ij})$ be a $\nu \times \nu$ real matrix, $\mathbf{y} = [y_1, \cdots, y_\nu]^T$ a fuzzy vector. The product $\mathbf{c} = A\mathbf{y}$ is a fuzzy vector $\mathbf{c} = [c_1, \cdots, c_\nu]^T$, where for $i = 1, \cdots, \nu$, $c_i = \sum_{k=1}^{\nu} a_{ik} y_k$. The next proposition shows how the parametric form of $\mathbf{c}$ and $\mathbf{c}^f$ can be obtained directly from the parametric form of $\mathbf{y}$ and the extended forms of the matrix A (below in (8)).

Proposition 3 *Let* $A = (a_{ij})$ *be a* $\nu \times \nu$ *real matrix,* $\mathbf{y}$ *a* ν*-dimensional fuzzy vector* $\mathbf{y}$ *with the* 2ν*-dimensional parametric form* $\mathbf{y} = [\underline{y_1}, \cdots, \underline{y_\nu}, \overline{y_1}, \cdots, \overline{y_\nu}]^T$. *We use two intermediate* $\nu \times \nu$ *real matrices* A^+ *and* A^- *as those that differ from A in that the negative, respectively, positive components of the matrix A are replaced by zeros. Let us compose two new* $2\nu \times 2\nu$ *real matrices* $A^\pm$ *and* $A^\mp$ *as follows*:

$$A^\pm = \begin{pmatrix} A^+ & A^- \\ A^- & A^+ \end{pmatrix}, \quad A^\mp = \begin{pmatrix} A^- & A^+ \\ A^+ & A^- \end{pmatrix}. \tag{8}$$

Then, the parametric form $\mathbf{c}$ (*respectively* $\mathbf{c}^f$) *of fuzzy vector* $\mathbf{c} = A\mathbf{y}$ *is equal to* $\mathbf{c} = A^\pm \mathbf{y}$ (*respectively* $\mathbf{c}^f = A^\mp \mathbf{y}$). *Moreover,*

$$(A^\pm \mathbf{y})^f = A^\mp \mathbf{y}. \tag{9}$$

Below, we will be working with *fn*-valued functions, defined on the real domain, i.e. functions $F : [a, b] \to \mathbb{R}_{\mathcal{F}}$, such that for each $t \in [a, b]$, $F(t)$ is a fuzzy number $F(t) = (\underline{f}(t), \overline{f}(t))$ where functions $\underline{f}(t), \overline{f}(t) : [0, 1] \to \mathbb{R}$, are $L-U$ representation functions of r. If a level cut $0 \le r \le 1$ is fixed, then the corresponding function $F(t, r)$ is interval-valued.

Proposition 4 *Let* $F : [a, b] \longrightarrow \mathbb{R}_{\mathcal{F}}$ *be an fn-valued function, such that for each fixed* $r \in [0, 1]$, *the corresponding interval-valued functions* $F(t, r)$ *are l-increasing* (*decreasing*) *and gH-differentiable on* $[a, b]$. *Then for every* $r \in (0, 1)$, *and for all* $t \in (a, b)$, $\frac{d}{dr}\underline{f}(t, r)$ *and* $\frac{d}{dr}\overline{f}(t, r)$ *exist, and if* $F(t, r)$ *is* 1- (*or* 2-) *differentiable, then* $F'(t, r) = [\frac{\partial}{\partial r}\underline{f}(t, r), \frac{\partial}{\partial r}\overline{f}(t, r)]$ (*or* $(F')^f(t, r) = [\frac{\partial}{\partial r}\underline{f}(t, r), \frac{\partial}{\partial r}\overline{f}(t, r)]$).

To continue our analysis, we repeat the definition of the definite integral of an *fn*-valued function from [33], based on the concept of the Riemann integral.

Definition 2 Let $f : [a, b] \to \mathbb{R}_{\mathcal{F}}$ be an *fn*-valued function. For every partition $P = \{t_0, \ldots, t_n\}$ of $[a, b]$ and for arbitrary $\xi_i \in [t_{i-1}, t_i]$, $1 \le i \le n$, let us denote

$$R_P = \sum_{i=1}^{n} f(\xi_i)(t_i - t_{i-1}),$$

$$\Delta_P := \max\{|t_i - t_{i-1}|, i = 1, ..., n\}.$$

Assume that there exists a fuzzy number I with the following property: for arbitrary $\varepsilon > 0$, there exists $\delta > 0$, such that for any partition P with $\Delta_P < \delta$, we have $D(I, R_P) < \varepsilon$. We say that I is a definite integral of f over $[a, b]$ and denote it as

$$I = \int_a^b f(t)dt.$$

If an *fn*-valued function f is continuous in the metric D, its definite integral exists and its parametric form with left and right r-cut boundaries is as follows

$$\int_a^b f(t, r)dt = \Big(\int_a^b \underline{f}(t, r)dt, \int_a^b \overline{f}(t, r)dt \Big), \quad 0 \le r \le 1. \tag{10}$$

It should be remarked that fuzzy integral can be also defined using the Lebesgue approach [8].

3 Fuzzy fractional integral and Caputo-type derivatives

Definition 3 [12] If u is a continuous fn-valued function, then the fuzzy Riemann-Liouville integral is defined as follows:

$$J^{\beta}u(t) = \frac{1}{\Gamma(\beta)}\int_0^t \frac{u(x)}{(t-x)^{1-\beta}}dx, \quad 0 < \beta < 1, t > 0,$$

where Γ is the Gamma function.

Definition 4 [12] Suppose that u is a differentiable fn-valued function, and let $u \in AC_{\mathcal{F}}[a,b]$, where $AC_{\mathcal{F}}[a,b]$, denotes the space of absolutely continuous fuzzy functions. The Caputo-type fractional-fuzzy derivative is defined by

$${}^{C}D^{\beta}u(t) = \frac{1}{\Gamma(1-\beta)}\int_0^t \frac{u'(x)}{(t-x)^{\beta}}dx, \quad 0 < \beta < 1, t > 0.$$

for $\beta = 1$, it is defined by classical integer order derivative, i.e.,

$${}^{C}D^{1}u(t) = \frac{du(t)}{dt}.$$

Suppose $0 < \beta < 1$. For a real-valued and continuously differentiable function y, we have

$$J^{\beta}({}^{C}D^{\beta}y)(t) = y(t) - y(0), \tag{11}$$

$$J^{\beta}t^{\alpha} = \frac{\Gamma(\alpha+1)}{\Gamma(\alpha+\beta+1)}t^{\beta+\alpha}, \quad \alpha > -1, \tag{12}$$

and

$$L({}^{C}D^{\beta}y(t)) = s^{\beta}L(y) - s^{\beta-1}y(0). \tag{13}$$

where L is the Laplace transform [3].

4 Reduction of the original problem to the ordinary case

We have shown above (Proposition 4) that for a certain class of fn-valued functions, their generalized Hukuhara derivatives can be reduced to the derivatives of ordinary real-valued functions. This fact will be used in the proposed method for solving the problem (1). Below, we repeat its main equation and initial value:

$$\begin{aligned}{}^{C}D^{\beta}\mathbf{y}(t) &= A\mathbf{y}(t) + \mathbf{u}(t), \quad t \in [0,T],\\ \mathbf{y}(0) &= \mathbf{y}_0,\end{aligned}$$

In this section, we show that the Caputo-type fractional derivatives of fn-valued functions can be reduced to the Caputo-type fractional derivatives of ordinary real-valued functions. Then, we propose to apply the flipping and to reduce the original problem (1) to the two systems of linear fractional differential equations over ordinary functions. The "crossroad" goes through the choice of a set of solutions.

Theorem 5 *Assume that system* (1) *is solvable and its solution* $\mathbf{y}$ *is an fn-valued* ν*-dimensional vector-function on* $t \in [0,T]$, *such that for each* $r \in [0,1]$, *the corresponding interval-valued vector-functions* $\mathbf{y}(\cdot, r)$ *are l-increasing (l-decreasing) and continuously differentiable. Then problem* (1) *has two solutions ((1)-differentiable and the other one (2)-differentiable) on* $[0,T]$.

Proof Let the assumptions of the case (1) be satisfied, and $\mathbf{y} = [y_1, \cdots, y_\nu]^T$ be a solution of (1). Let $1 \le i \le \nu$ and $0 \le r \le 1$ be fixed. By Proposition (4) and the definition of Caputo derivative, we have

$$\begin{aligned}{}^{C}D^{\beta}y_i(t) &= \frac{1}{\Gamma(1-\beta)}\int_0^t \frac{y_i'(x)}{(t-x)^{\beta}}dx\\ &= \frac{1}{\Gamma(1-\beta)}\int_0^t \frac{[\underline{y_i}'(x), \overline{y_i}'(x)]^T}{(t-x)^{\beta}}dx.\end{aligned}$$

By (10), we obtain that ${}^{C}D^{\beta}y_i(t,r)$ is equal to

$$\begin{aligned}&\left[\frac{1}{\Gamma(1-\beta)}\int_0^t \frac{\underline{y_i}'(x)}{(t-x)^{\beta}}dx, \frac{1}{\Gamma(1-\beta)}\int_0^t \frac{\overline{y_i}'(x)}{(t-x)^{\beta}}dx\right]^T\\ &\qquad = \left[{}^{C}D^{\beta}\underline{y_i}(t), {}^{C}D^{\beta}\overline{y_i}(t)\right]^T\end{aligned} \tag{14}$$

or equivalently,

$$\underline{{}^{C}D^{\beta}y_i}(t) = {}^{C}D^{\beta}\underline{y_i}(t)$$

and

$$\overline{{}^{C}D^{\beta}y_i}(t) = {}^{C}D^{\beta}\overline{y_i}(t).$$

Using vector notation, we write

$$\underline{{}^{C}D^{\beta}\mathbf{y}}(t) = {}^{C}D^{\beta}\underline{\mathbf{y}}(t)$$

and

$$\overline{{}^{C}D^{\beta}\mathbf{y}}(t) = {}^{C}D^{\beta}\overline{\mathbf{y}}(t).$$

Finally,

$${}^{C}D^{\beta}\mathbf{y}(t) = ({}^{C}D^{\beta}\underline{\mathbf{y}}(t), {}^{C}D^{\beta}\overline{\mathbf{y}}(t)). \tag{15}$$

The proof of case (2) is similar. □

Corollary 1 *Let the system* (1) *be solvable and its solution* $\mathbf{y}$ *fulfill assumptions given in Theorem* 5. *Then, the equivalent to* (1) *system of ordinary fractional differential equations has the following parametric form*:

$$[\underline{y_1}, \cdots, \underline{y_v}, \overline{y_1}, \cdots, \overline{y_v}]^T = A^{\pm} J^{\beta}\mathbf{y}(t) + \mathbf{y}(0) + J^{\beta}\mathbf{u}(t), \tag{16}$$

$$[\underline{y_1}, \cdots, \underline{y_v}, \overline{y_1}, \cdots, \overline{y_v}]^T = A^{\mp} J^{\beta}\mathbf{y}(t) + \mathbf{y}(0) + J^{\beta}\mathbf{u}^f(t). \tag{17}$$

Proof The proof follows easily from the equivalent transformations of ordinary fractional differential equations discussed above, where we first transform the equation (1), by applying flipping (as in (5)) to both sides of it, and then (9) to matrix multiplication, and after that we transform both equations using the fuzzy Riemann-Liouville integral (11), applied to both sides of each of them. □

Below we will support our theoretical elaboration with an example of a fuzzy fractional equation that admits two different fuzzy solutions: one has l-increasing corresponding interval-valued vector-functions, and the other one has l-decreasing. Both solutions are exact, and their analytic representation is obtained using the Riemann-Liouville integration (see (11)) and its application to polynomials (see (12)).

Example 1 Let the system (1) have the following simple form:

$$\begin{aligned} {}^{C}D^{\beta}y(t,r) &= (t^2(r-1), t^2(-r+1)), \quad t \in [0,T],\\ y(0) &= (r-0.5, -r+1.5), \end{aligned} \tag{18}$$

where $v = 1$, $A = 0$, and the fuzzy source function u in its parametric form is equal to $u(t,r) = (t^2(r-1), t^2(-r+1))$.

1. Assume that this system has l-increasing solution on [0, T]. Then, can be represented using (16). In the parametric form, we have

$$\begin{bmatrix} \underline{y}(t,r) \\ \overline{y}(t,r) \end{bmatrix} = \begin{bmatrix} r-0.5 \\ -r+1.5 \end{bmatrix} + J^{\beta}\begin{bmatrix} t^2(r-1) \\ t^2(-r+1)) \end{bmatrix}.$$

By (12), we obtain

$$\begin{bmatrix} \underline{y}(t,r) \\ \overline{y}(t,r) \end{bmatrix} = \begin{bmatrix} \frac{2}{\Gamma(3+\beta)}t^{2+\beta}(r-1) + r - 0.5 \\ \frac{2}{\Gamma(3+\beta)}t^{2+\beta}(-r+1) - r + 1.5. \end{bmatrix} \tag{19}$$

The length of the corresponding r-cut, where $0 \le r \le 1$, is equal to

$$\overline{y}(t,r) - \underline{y}(t,r) = \frac{4}{\Gamma(3+\beta)}t^{2+\beta}(1-r) + 2(1-r).$$

It is easy to see that this function is increasing with respect to t on every interval [0, T] where $T > 0$. Therefore, a fuzzy solution to the initial system (18) in the set of fn-valued functions with the corresponding l-increasing interval-valued vector-functions exists and is given by (19).

2. On the other hand, suppose that the system (18) has l-decreasing solution on [0, T]. Then, it can be represented using (17). In the parametric form, we have

$$\begin{bmatrix} \underline{y}(t,r) \\ \overline{y}(t,r) \end{bmatrix} = \begin{bmatrix} r-0.5 \\ -r+1.5 \end{bmatrix} + J^{\beta}\begin{bmatrix} t^2(-r+1) \\ t^2(r-1) \end{bmatrix},$$

and after applying (12), we obtain

$$\begin{bmatrix} \underline{y}(t,r) \\ \overline{y}(t,r) \end{bmatrix} = \begin{bmatrix} \frac{2}{\Gamma(3+\beta)}t^{2+\beta}(-r+1) + r - 0.5 \\ \frac{2}{\Gamma(3+\beta)}t^{2+\beta}(r-1) - r + 1.5. \end{bmatrix} \tag{20}$$

$$= \begin{bmatrix} \left(-\frac{2}{\Gamma(3+\beta)}t^{2+\beta} + 1\right)r + \frac{2}{\Gamma(3+\beta)}t^{2+\beta} - 0.5 \\ \left(\frac{2}{\Gamma(3+\beta)}t^{2+\beta} - 1\right)r + 1.5 - \frac{2}{\Gamma(3+\beta)}t^{2+\beta}. \end{bmatrix}$$

The length of the corresponding r-cut, where $0 \le r \le 1$, is equal to

$$\overline{y}(t,r) - \underline{y}(t,r) = \frac{4}{\Gamma(3+\beta)}t^{2+\beta}(r-1) - 2(r-1).$$

It is easy to see that if $t \in [0, T^*]$, where $T^* = \left(\frac{\Gamma(3+\beta)}{2}\right)^{\left(\frac{1}{2+\beta}\right)}$, this length is positive for $0 \le r < 1$, and it is decreasing with respect to t. Therefore, a fuzzy solution to the initial system (18), considered on the interval $[0, \left(\frac{\Gamma(3+\beta)}{2}\right)^{\left(\frac{1}{2+\beta}\right)}]$, in the set of fn-valued functions with the corresponding l-decreasing interval-valued vector-functions exists and is given by (20).

Remark 1 Comments should be made regarding the existence of the two topologically non-equivalent solutions to (1). This effect is known as bifurcation and is caused by a fuzzy initial value and/or a fuzzy source function. Without going into technical details, we note that this phenomenon requires additional analysis beyond the scope of our current research. We refer to [34] where the values of the bifurcation of fuzzy dynamical systems were studied.

As an advantage of our approach, we emphasize that two systems of ordinary fractional differential equations (16) and (17) can be easily unified into the following general form:

$$\mathbf{y}(t) = \mathcal{A}J^{\beta}\mathbf{y}(t) + \mathbf{y}(0) + J^{\beta}\mathbf{u}(t), \quad t \in [0,T], \tag{21}$$

where $\mathcal{A}$ denotes a real matrix, and $\mathfrak{u}$ is a vector of real functions. As the example 1 shows, an analytical solution is possible if (21) contains simple functions (for example, polynomials) for which the application of the

Riemann-Liouville integral has an analytical representation, see (12). Otherwise, the solution of (21) can only be approximate, obtained using suitable numerical methods. In the next section, we will discuss this issue in more detail.

4.1 Fuzzy logic description of input-output relation

As it is mentioned in the Introduction the concept of observability is concerned with the problem of whether the fuzzy inputs $u(t)$ and the fuzzy outputs $y(t)$ of system (1) over a finite interval $[t_0, t_1]$ can uniquely determine the initial fuzzy state y_0. Let $A(t), u(t), t \geq 0$, be the same as in system (1). For the given initial value $y_0 \in \mathbb{R}^\nu_{\mathcal{F}}$ and the given input $u(t) \in \mathbb{R}^\nu_{\mathcal{F}}$, for each $t \geq 0$, in system (1), we can obtain the system state $y(t) \in \mathbb{R}^\nu_{\mathcal{F}}$, for each $t \geq 0$. We quantify the input-output relations by using fuzzy logic together with the system model (1).

$$\begin{aligned} R^i : IF \quad u_{01} \quad \text{is} \quad u^i_{01} \quad \text{and} \cdots u_{0\nu} \quad \text{is} \quad u^i_{0\nu}; t_0 \leq t \leq t_1; \\ THEN \quad y_1(t_1) \quad \text{is} \quad y^i_1(t_1) \quad \text{and} \cdots \quad y_k(t_1) \quad \text{is} \quad y^i_k(t_1), i = 1, ..., \nu \end{aligned} \tag{22}$$

where the relation between input and output is

$$^C D^\beta y(t_1) = Ay(t_1) + u(t_1). \tag{23}$$

In the fuzzy based rule (22), since $u(t) \in u^i(0, t)$ for $t \geq t_0$, then $y(t_1) \in y^i(0, t_1)$.

5 Chebyshev polynomials and analytical representation of the approximate and solution

In this section, we focus on finding approximate solutions for (21), where this equation contains the Riemann-Liouville integral applied to real vector functions. We propose to approximate the integrands that appear in (21) by polynomials close to them and use the fact that the application of the Riemann-Liouville integral to polynomials has an analytical representation. As a result, we obtain an analytical representation of the approximate solution. In this case, the quality of the approximation is controlled by the degree of the approximating polynomial. We propose to use Chebyshev polynomials, which are known for relationshipod approximating ability. In the Appendix, we review some basic definitions and results related to the Chebyshev polynomials [35].

5.1 Operational Chebyshev method in algorithmic form

Below we describe the sequence of steps that leads to an approximate numerical solution $\mathbf{y}_N$ to (21) where $N \geq 2$ corresponds to the maximal degree of Chebyshev polynomials used in the representation of $\mathbf{y}_N$. The following are inputs parameters: A, $\mathbf{u}$, $\mathbf{y}_0$ (parameters of the equation (21), N (maximal degree of Chebyshev polynomials), β (fractional order of the Caputo-type fuzzy derivative), r (level of the cut), all of them must be initialized before the first step. The algorithm runs "in one go" and produces approximate numerical solution (output) $\mathbf{y}_N$ in matrix form. The quality of the approximation is an offline parameter, so that it can be estimated by the norm of the difference between two consecutive solutions $\mathbf{y}_N$ and $\mathbf{y}_{N+1}$. colorblack

1. For the chosen N, represent the approximate solution $\mathbf{y}_N$ by a linear combination of the first $(N+1)$ Chebyshev polynomials, see (A5) in the Appendix. We explicitly write

$$\mathbf{y}_N(t) = Y^T \Psi(t), \tag{24}$$

where $\Psi^T(t) = [T^*_0(t), \dots, T^*_N(t)]$ is the vector of mentioned above Chebyshev polynomials and Y - unknown coefficient matrix with dimension $2\nu \times (N+1)$.

The remaining parameters in (21) are also expanded using the same Chebyshev polynomials in Ψ^T, so that we have

$$\begin{aligned} \mathbf{y}_0 &= Y_0 \Psi(t), \\ \mathbf{u}(t) &\approx U^T \Psi(t), \end{aligned} \tag{25}$$

where $Y_0 = [\mathbf{y}_0, 0, \dots, 0]^T$, and the components of the U are computed as in (A7).

2. Substitute (24 - 25) into equation (21) and rewrite it as follows:

$$\begin{aligned} Y^T \Psi(t) = \mathcal{A} J^\beta (Y^T \Psi(t)) + Y_0 \Psi(t) + \\ J^\beta (Y^T \Psi(t)), \; t \in [0, T]. \end{aligned} \tag{26}$$

3. By Theorem 6, we have

$$\begin{aligned} J^\beta (U^T \Psi(t)) &\approx U^T P_{\beta,M} \Psi(t), \\ J^\beta (Y^T \Psi(t)) &\approx Y^T P_{\beta,M} \Psi(t). \end{aligned} \tag{27}$$

Substitute (27) into (26) and obtain

$$Y^T\Psi(t) = \mathcal{A}Y^T P_{\beta,M}\Psi(t) + Y_0\Psi(t) + U^T P_{\beta,M}\Psi(t). \quad (28)$$

4. Multiplying the left and right sides of (28) by $w^*(t)$ and $\Psi^T(t)$, respectively, and applying the integration in t along $[0, T]$, we obtain

$$Y^T \int_0^T w^*(t)\Psi(t)\Psi^T(t)dt = \left(\mathcal{A}Y^T P_{\beta,M} + Y_0 + U^T P_{\beta,M}\right)\times \int_0^T w^*(t)\Psi(t)\Psi^T(t)dt. \quad (29)$$

5. Note that due to the orthogonality of the Chebyshev polynomials and the estimate (A3) of their norm squares, the integrals on the left and right sides of (29) are equal to

$$\Lambda_N := \int_0^T w^*(t)\Psi(t)\Psi^T(t)dt = diag([\gamma_1, \cdots, \gamma_N]),$$

where $diag([\gamma_1, \cdots, \gamma_N])$ is a diagonal invertible matrix. Therefore, multiplying both sides of (29) by Λ_N^{-1}, we obtain a system of equations independent of t, i.e.,

$$(Y^T - \mathcal{A}Y^T P_{\beta,M}) = H, \quad (30)$$

where

$$H := Y_0 + U^T P_{\beta,M}.$$

6. To solve (30), use the vectorization operator vec [7] to obtain a system of linear algebraic equations in the standard form of a matrix equation. This operator rewrites $m \times n$ matrices in mn-dimensional vectors using concatenation of rows. In particular, the vectorization of a matrix is given below:

$$vec(A) := (a_{1,1} \dots, a_{m,1}, \dots, a_{1,n}, \dots, a_{m,n})^T.$$

The vectorization vec has the property

$$vec(ABC) = (C^T \otimes A)vec(B),$$

where $\otimes$ is the Kronecker product. Thus, the system (30) can be converted to the standard form

$$\left(\mathbf{I} \otimes \mathbf{I} - P_{\beta,M}^T \otimes \mathcal{A}\right)vec(Y^T) = vec(H), \quad (31)$$

where $I_{\nu\times\nu}$ is the identity matrix, and $vec(Y^T)$ is the unknown vector.

7. Solve (31) as a standard system of linear equation[1] and obtain the (exact) solution $vec(Y^T)$.
8. Apply the inverse of vec to $vec(Y^T)$ and get $2\nu \times (N+1)$ vector Y^T; substitute it into analytical form (24) to get the desired approximate solution $\mathbf{y}_N$ of (21).

In the following section, we refer to Theorem 6, which guarantees the convergence of the above algorithm of the Chebyshev operational method. We also prove Theorem 7, which estimates the complexity of this algorithm as $O(N^3)$.

6 Convergence of the operational Chebyshev method and complexity of its algorithmic form

In this section, we prove that the algorithmic form of the Chebyshev operational method proposed in Sect. 5 is correct. We also estimate the complexity of the corresponding algorithm.

The following theorem, proved in [7], gives an approximate value of the Riemann-Liouville integral applied to the vector of Chebyshev polynomials in (A6).

Theorem 6 *Let $0 < \beta < 1$, $\Psi^T(t) = [T_0^*(t), \dots, T_N^*(t)]$, and $N, M \in \mathbb{N}$. Then, there is an $(N+1)\times(N+1)$ (operational) matrix $P_{\beta,M}$, such that*

$$J^\beta\Psi(t) \simeq P_{\beta,M}\Psi(x). \quad (32)$$

Moreover,

$$p_N(J^\beta\Psi) = P_\beta\Psi(x), \quad (33)$$

where $P_\beta = \lim_{M\to\infty} P_{\beta,M}$.

The proof of the following theorem with an estimate of complexity was developed for this article.

Theorem 7 *The total complexity TC of the algorithm described in Sect. 5 is $O(N^3)$.*

Proof We remind that the algorithm is focused on the numerical solution of equation (21) in its reduced form (30) or equivalently (31). The proof consists in the complexity estimation of calculating the parameters $\mathcal{A}$, $P_{\beta,M}$, Y^T included in (31), and estimating the computation complexity of the numerical method for solving the system (31) of linear equations.

1. $\mathcal{A}$ is a matrix of dimension $2\nu \times 2\nu$. It is computed by the concatenation operator of A^+ and A^-, each of which requires ν^2 comparisons. Thus, the computational cost of obtaining $\mathcal{A}$ is $O(\nu^2)$;

[1] We propose to apply LU (Lower-Upper) decomposition to the matrix of coefficients and obtain the (exact) solution $vec(Y^T)$ directly by forward and backward substitution.

2. $P_{\beta,M}$ is a matrix of dimension $(N+1)\times(N+1)$. According to [7], the computational cost of $P_{\beta,M}$, where we use the constant $M=100$, is

$$(1+2+\ldots+N)NM=\frac{MN(N+1)N}{2}\le O(N^3);$$

3. Y^T is a $v\times(N+1)$ matrix. This matrix is computed by applying the inverse of the vectorization operator to vector $vecY^T$. Thus, the computational cost of obtaining Y^T is $2v(N+1)$;
4. $vecY^T$ is obtained by the LU decomposition with the computational cost of $O((2v\times(N+1))^3)$;
5. The summarized complexity of the algorithm is

$$\begin{aligned}&O((2v(N+1))^3)+2v(N+1)+O(v^2)+O(N^3)\\=&O((2v(N+1))^3)+O(N^3)=O(8v^3(N+1)^3).\end{aligned}$$

Therefore, the estimated total complexity of the method is $TC=O(N^3)$. □

7 Numerical examples

In this section, we will illustrate the above proposed numerical method and the entire computational procedure with an example. The notation system used below is the same as in the sections discussed above. In addition, we use generally accepted quality measures and denote them as follows:

$$\underline{E}_i(N,t)=|\underline{\mathbf{y}}_{iN}(t)-\underline{y}_i(t)|$$

and

$$\overline{E}_i(N,t)=|\overline{\mathbf{y}_{iN}}(t)-\overline{y}_i(t)|,$$

where $\mathbf{y}_{iN}$ is the ith component of $\mathbf{y}_N(t)$ for $i=1,\ldots,v$. The corresponding maximal error is

$$\mathcal{E}_i(N,r)=\max_{t\in[0,T]}\{\underline{E}_i(N,t),\overline{E}_i(N,t)\},\quad r\in[0,1]. \tag{34}$$

In Tables 1, 2, we will see a stable decrease in $\mathcal{E}_i(N,r)$ in relation to N, which confirms our theoretical conclusions regarding the convergence of the proposed algorithmic method.

Example 2 Consider the two-dimensional system (1) of FFDEs given by $A=\mathbf{I}$ and

$$\begin{aligned}u_1&=t^2(r^2+r,4-r^3-r),\\u_2&=t^3(r^2+r,4-r^3-r),\end{aligned}$$

where

Table 1 The maximum error for various values of N and r with $\beta=0.5$ in Example 2

N	$\mathcal{E}_1(N,0.5)$	$\mathcal{E}_2(N,0.5)$	$\mathcal{E}_1(N,0.9)$	$\mathcal{E}_2(N,0.9)$
2	1.7184e-01	2.9500e-01	1.2072e-01	2.0724e-01
3	6.8835e-03	2.9774e-02	4.8358e-03	2.0916e-02
4	9.9725e-04	9.9302e-04	7.0058e-04	6.9762e-04
5	1.9769e-04	1.1260e-04	1.3888e-04	7.9103e-05
6	9.0588e-05	1.5185e-05	6.3640e-05	1.0668e-05
7	4.3181e-05	5.8318e-06	3.0335e-05	4.0969e-06
8	2.2807e-05	2.2936e-06	1.6022e-05	1.6113e-06
9	1.2957e-05	1.0190e-06	9.1027e-06	7.1587e-07
10	7.8023e-06	4.9350e-07	5.4813e-06	3.4670e-07
11	4.9255e-06	2.5630e-07	3.4602e-06	1.8005e-07
12	3.2335e-06	1.4096e-07	2.2716e-06	9.9027e-08

$$y_0=\begin{bmatrix}(0,0)\\(0,0)\end{bmatrix}$$

and $t\in[0,1]$.

It is easy to see that since the initial condition is a real (not fuzzy) vector, the system has no l-decreasing solution. Therefore, we assume that the solution is l-increasing. In this case, the equivalent to (1) system of ordinary fractional differential equations has the parametric form (16), where $A^{\pm}=\mathbf{I}_4$ (4-dimensional identity matrix), $\mathbf{y}(0)=[0,0,0,0]^T$ and $\mathbf{y}=[\underline{y}_1,\underline{y}_2,\overline{y_1},\overline{y_2}]^T$. Substituting this data into (16), we get

$$\mathbf{y}=J^{\beta}\mathbf{y}+J^{\beta}\mathbf{u}. \tag{35}$$

The exact solution can be obtained by iterative application of (12):

$$\begin{aligned}y_1(t)&=\sum_{i=1}^{\infty}\frac{\Gamma(3)}{\Gamma(3+i\beta)}t^{2+i\beta}(r^2+r,4-r^3-r),\\y_2(t)&=\sum_{i=1}^{\infty}\frac{\Gamma(4)}{\Gamma(4+i\beta)}t^{3+i\beta}(r^2+r,4-r^3-r).\end{aligned}$$

At the same time, we apply the numerical method proposed in Sect. 5 and obtain a sequence of approximate numerical solutions for $\beta=0.5,09$, and $N=2,\ldots,12$. We compare them with the exact solution and estimate the maximum errors $\mathcal{E}_i(N,r)$, $i=1,2$, according to (34). Table 1 ($\beta=0.5$) and Table 2 ($\beta=0.9$) contain estimates of the maximum error for all considered values of N and three r-cuts, where $r=0.2,0.5,0.9$.

These tables validate the proposed method. Note that somewhat better convergence is observed in the Table 2, where $\beta=0.9$, due to the increase in the regularity of the solution with $\beta\to1$. In particular, and in addition to the

Table 2 The maximum error for various values of N and r with $\beta = 0.9$ in Example 2

N	$\mathcal{E}_1(N, 0.5)$	$\mathcal{E}_2(N, 0.5)$	$\mathcal{E}_1(N, 0.9)$	$\mathcal{E}_2(N, 0.9)$
2	7.8256e-02	1.1755e-01	5.4977e-02	8.2580e-02
3	4.1932e-03	1.3698e-02	2.9458e-03	9.6233e-03
4	2.7444e-04	6.1198e-04	1.9280e-04	4.2992e-04
5	1.2078e-05	3.3096e-05	8.4852e-06	2.3250e-05
6	8.0339e-06	8.1176e-07	5.6440e-06	5.7028e-07
7	3.3286e-06	5.5968e-07	2.3384e-06	3.9319e-07
8	1.6042e-06	1.9087e-07	1.1270e-06	1.3409e-07
9	8.3714e-07	7.8072e-08	5.8811e-07	5.4847e-08
10	4.6671e-07	3.4956e-08	3.2787e-07	2.4557e-08
11	2.7457e-07	1.6903e-08	1.9289e-07	1.1874e-08
12	1.6891e-07	8.7054e-09	1.1866e-07	6.1157e-09

estimates in Tables 1, 2, we got that, up to a computational error, $\mathcal{E}_2(12, 0.9) = 1.1102e - 15$, for $\beta = 0.99999999$.

8 Real world applications

After we have tested our model in Example 1, and proved the correctness of the related algorithm, we move on to two real applications. Both are associated with dynamic processes in the human body associated with the use of medications.

In the following, we consider two dynamic processes in which both extensions mentioned above can be useful: the dynamics of drug distribution in the blood and the evolution of the amount of cholesterol in the human body [24–27]. Two important factors should be analyzed: the memory of dynamic changes (closely related to the specific reaction of the human body) and the robustness to uncertainty (related to the initial prescription of the drug). The first is the result of modeling with a fractional derivative, and the second is due to fuzzy values. In both cases, linear fractional-order differential equations are proposed as suitable models.

Example 3 In this example, an extended fractional fuzzy mathematical model for drug diffusion in the human body through blood and tissue is analyzed, and its solution in the form of a dynamic process is discussed.

Consider k_e, k_b and k_t as the corresponding rates of drug elimination from blood, drug transportation from arterial blood to tissue, and from tissue to venous blood. Let $c_{ab}(t)$, $c_t(t)$ and $c_{vb}(t)$ denote the concentration of drug in the arterial blood, tissue and venous blood at time t, c_0 the initial dose of the drug taken. The conventional mathematical model [24] for the drug concentration based on the ODE system is reproduced below:

$$\begin{cases} \dfrac{dc_{ab}(t)}{dt} = -k_b c_{ab}(t), & c_{ab}(0) = c_0, \\ \dfrac{dc_t(t)}{dt} = k_b c_{ab}(t) - k_t c_t(t), & c_t(0) = 0, \\ \dfrac{dc_{vb}(t)}{dt} = k_t c_t(t) - k_e c_{vb}(t), & c_{vb}(0) = 0. \end{cases} \tag{36}$$

The exact solution of this system can be found in [24]. If we make a reasonable assumption that the rate of absorption varies from recipient to recipient, we can extend (36) to the following fractional model:

$$\begin{cases} {}^C D^\beta c_{ab}(t) = -k_b c_{ab}(t), & c_{ab}(0) = c_0, \\ {}^C D^\beta c_t(t) = k_b c_{ab}(t) - k_t c_t(t), & c_t(0) = 0, \\ {}^C D^\beta c_{vb}(t) = k_t c_t(t) - k_e c_{vb}(t), & c_{vb}(0) = 0, \end{cases} \tag{37}$$

where $0 < \beta \leq 1$ is a fractional order that indicates the human's body reaction. The system (37) is the first extension of (36) that takes into account the specific reaction of the human body. If $\beta \to 1$, then the solution (37) tends to normal (36) dynamics. However, at lower values of β, the response to treatment is slower.

In Fig. 1, we plot numerical solutions of systems (36) and (37) on the interval [0, 15] with parameters $k_b = 0.5, k_e = 0.05$ and $k_t = 0.25$ and various values of β. The initial state of this system with $c_0 = 1$. For $\beta = 1$, we have used the exact solution described in [24]. For other values of β we have used the numerical method described in [7]. Figure 1 illustrates our expectation that the solutions of system (37) approach the solutions of system (36) as $\beta \to 1$. Furthermore, we take into account that the initial values are assigned in accordance with the competence of the doctor. Therefore, we proposed to extend the system in (37) to the space of fn– valued functions with fuzzy numbers as initial conditions. The solution of this extended system shows a variety of patient feedback that can be compared with expert knowledge. In the following, we trace numerical solutions for two types of their l-monotonicity at different evolutionary times. In all the systems considered below, the fractional order is $\beta = 0.95$.

1. At first, we restrict system (37) to the first equation and assume that its fn-valued solution is l-increasing. The corresponding fractional-order system over fn-valued functions is

$$\begin{cases} {}^C D^\beta \underline{c_{ab}}(t) = -k_b \overline{c_{ab}}(t), \\ {}^C D^\beta \overline{c_{ab}}(t) = -k_b \underline{c_{ab}}(t) \end{cases} \tag{38}$$

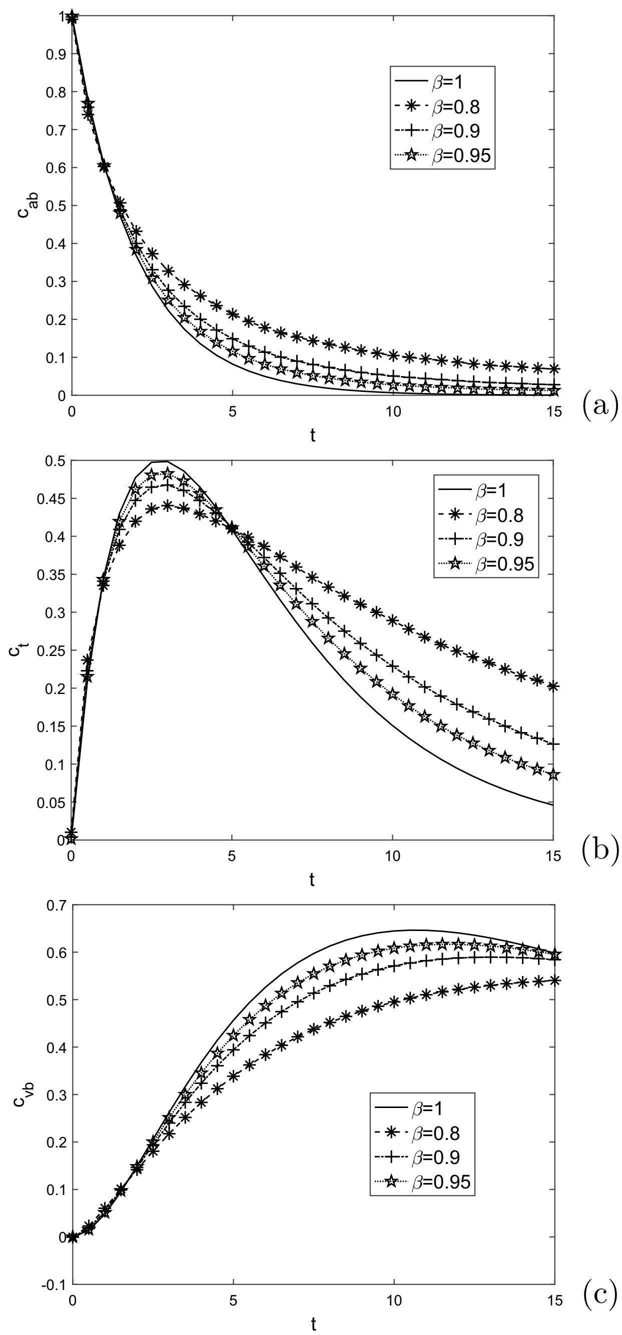


Fig. 1 Numerical and exact (thin solid lines) solutions of systems (37) and (36) considered in the Example 3: **a** First component $c_{ab}(t)$, **b** Second component $c_t(t)$, and **c** Third component $c_{vb}(t)$

with fuzzy initial condition $c_0(r, 2-r)$. For $\beta = 1$ we obtain

$$D^2\underline{c_{ab}}(t) = k_b^2\underline{c_{ab}}(t),$$

and write a solution in the form

$$\underline{c_{ab}}(t) = Ae^{-k_bt} + Be^{k_bt},$$

where A, B are arbitrary complex numbers. Then

$$\overline{c_{ab}}(t) = \frac{-1}{k_b}\,{}^{C}D^{\beta}\underline{c_{ab}}(t) = \frac{-1}{k_b}(Ae^{-k_bt} + Be^{k_bt}) = Ae^{-k_bt} - Be^{k_bt}. \tag{39}$$

Imposing the initial condition, we obtain

$$\begin{cases} A + B &= c_0 r, \\ A - B &= c_0(2-r), \end{cases} \tag{40}$$

which leads to $A = c_0$, $B = c_0 r - c_0$. Therefore, the exact solution is

$$\begin{aligned} \underline{c_{ab}}(t) &= c_0e^{-k_bt} + (c_0 r - c_0)e^{k_bt}, \\ \overline{c_{ab}}(t) &= c_0e^{-k_bt} + (c_0 - c_0 r)e^{k_bt}. \end{aligned} \tag{41}$$

If $r = 1\,(c_0 r - c_0 = 0)$, the corresponding (deterministic) solution

$$\underline{c_{ab}}(t) = c_0e^{-k_bt}, \qquad \overline{c_{ab}}(t) = c_0e^{-k_bt},$$

is asymptotically stable at infinity. However, if $r \in [0, 1)$, then the *fn*-valued $c_{ab}(t)$ tends to ∞ as t tends to ∞. This is because the exponential term e^{k_bt} with positive k_b comes into play. In this case, the extension to *fn*-valuedness changes the asymptotically stable behavior to an unstable one.

2. At second, we continue working with the first equation in system (37) and assume that its *fn*-valued solution is *l*-decreasing. The corresponding parametric form is

$$\begin{cases} {}^{C}D^{\beta}\underline{c_{ab}}(t) = -k_b\underline{c_{ab}}(t), & \underline{c_{ab}}(0) = c_0 r, \\ {}^{C}D^{\beta}\overline{\underline{c_{ab}}}(t) = -k_b\overline{\underline{c_{ab}}}(t), & \overline{\underline{c_{ab}}}(0) = c_0(2-r), \end{cases} \tag{42}$$

and the solution is as follows:

$$\begin{cases} \underline{c_{ab}}(t) = c_0 re^{-k_bt}, \\ \overline{\underline{c_{ab}}}(t) = c_0(2-r)e^{-k_bt}. \end{cases} \tag{43}$$

It is easy to see that this solution is asymptotically stable at any level $r \in [0, 1]$.

Remark 2 The conclusion about the asymptotic stability of the solution calculated in (43) can be confirmed by a theoretically substantiated analysis of stability. This is discussed in more detail in Appendix. On its basis, we check the spectra of the matrices $A^+ - A^-$ and $A^- - A^+$ for the *l*-increasing and *l*-decreasing cases, respectively. With a straightforward computation we have $\sigma(A^+ - A^-) = \{k_b\}$ and $\sigma(A^- - A^+) = \{-k_b\}$. Obviously, $\sigma(A^- - A^+)$ is a subset of

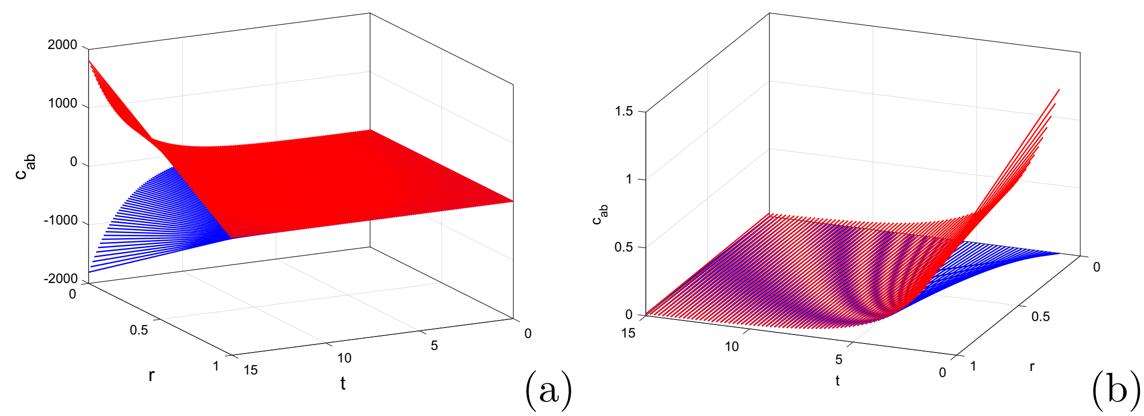


Fig. 2 **a** The unstable *fn*-valued solution to (38) under the assumption of its *l*- increasing behavior; **b** The stable *fn*-valued solution to (42) under the assumption of its *l*- decreasing behavior. In both cases, the blue (red) surface corresponds to the left (right) *r*-cut boundaries

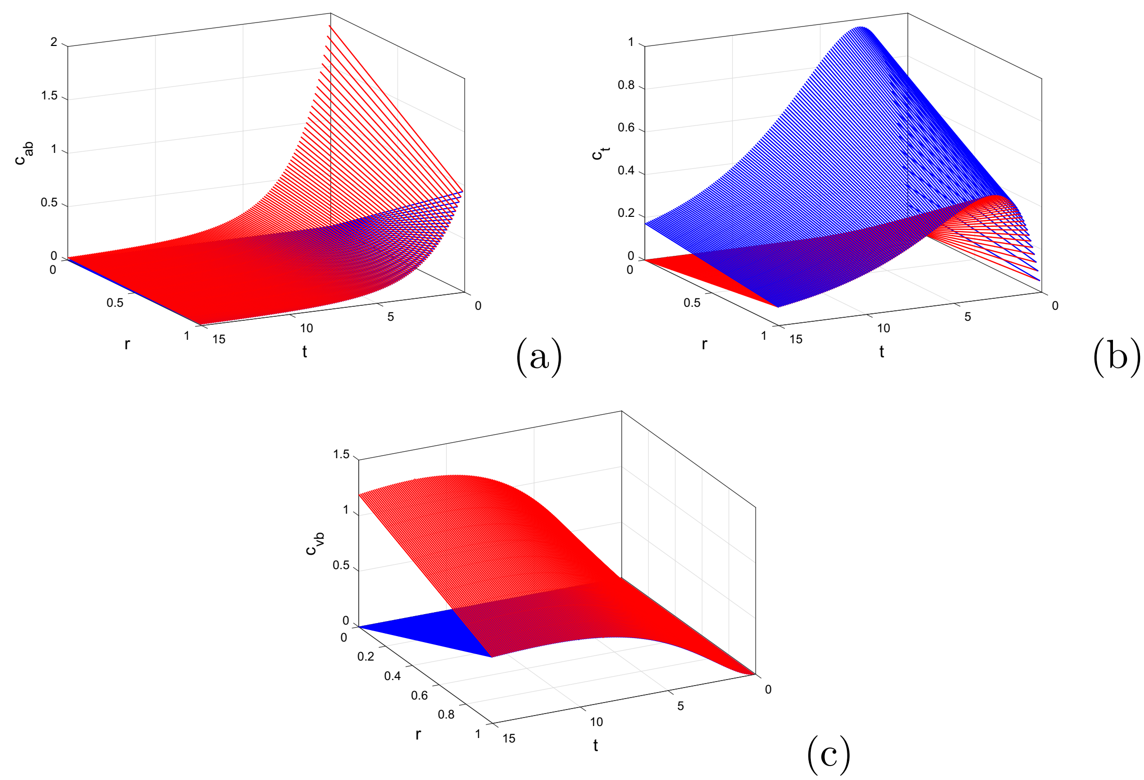


Fig. 3 Three components of the *fn*-valued solution to (37) under the assumption that all of them are *l*-decreasing; **a** c_{ab}, **b** c_t and **c** c_{vb}

$$\left\{ \lambda \in \mathbb{C} \setminus \{0\}; |\arg(\lambda)| > \frac{\beta\pi}{2} \right\},$$

so that by (A11), the *l*-decreasing solution is stable. On the other hand, the $\sigma(A^+ - A^-)$ does not satisfies (A12), and the *l*-increasing case is not stable.

In Fig. 2, we show solutions to (38) and (42) on the interval [0, 15], and illustrate two different behaviors according to selected assumptions about their *l*-monotonicity.

3. Third, we consider the entire system (37) under two opposite assumptions about the *l* -monotonicity of the solution components. Based on our analysis of the stability of the solution (38), we leave the only case

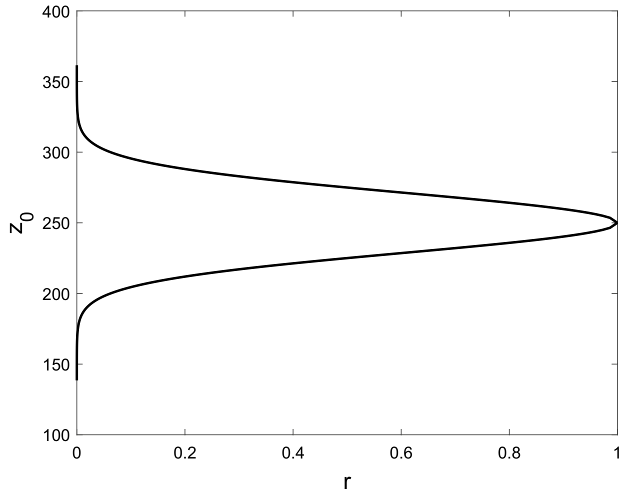


Fig. 4 The initial amount of BSP in the blood with Gaussian fuzzy depiction ($\sigma = 30$)

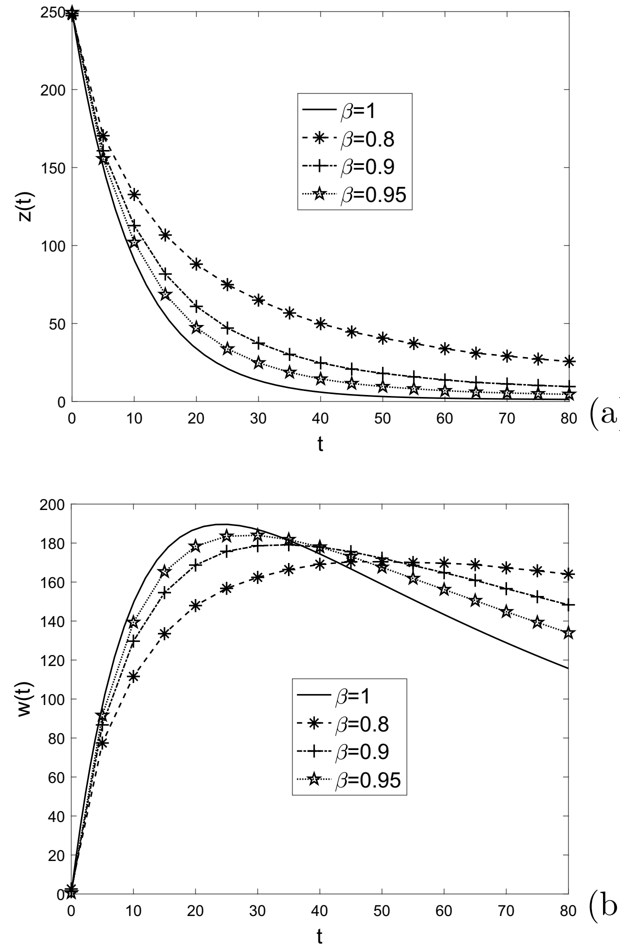


Fig. 5 Solutions of the system (45) with various values of β **a** First component, **b** Second component

when all components of the solution are l -decreasing. In Fig. 3 we have illustrated the three-dimensional evolution of the *fn*-valued solution on the [0, 15] under the assumption that all its components are l -decreasing (Fig. 4).

In conclusion, the extension to *fn*-valued solutions, together with the choice of the type of their l-monotonicity, correlates with our intuition about the dynamic behavior of drug transportation. In particular, if at least one component of the solution is unstable, then it is not feasible for a given model.

Example 4 In this example, we study the dynamics of bromsulfein (BSP) in the human liver. Let $z(t)$, $w(t)$ and $x(t)$ represent the amounts of BSP at time t in blood, liver, and bile, respectively. Suppose that the coefficients a, b, and d characterize the transfer rates of the respective dynamics. The first-order model proposed by Watt is described as [36, 37].

$$\begin{cases} \frac{dz(t)}{dt} = -az(t) + bw(t), \\ \frac{dw(t)}{dt} = az(t) - (b+d)w(t), \\ \frac{dx(t)}{dt} = dw(t), \end{cases} \tag{44}$$

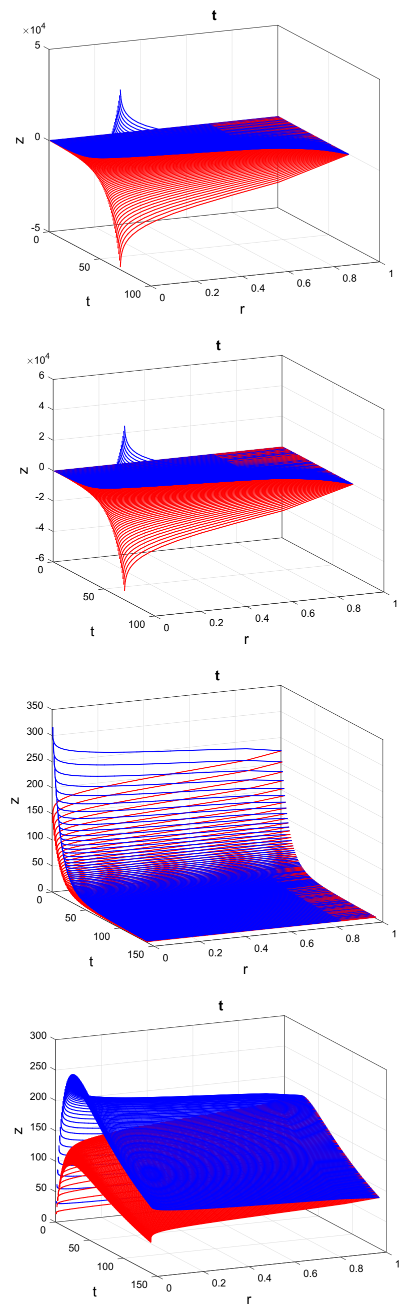
where the initial conditions $(z(0), w(0)) = (z_0, 0)$ such that $(z_0 > 0)$, are known constants. As we can see, the third equation does not affect the first two. Thus, solving the system of the first two equations is sufficient to analyze the dynamics of BSP in the human liver. Therefore, the presence of memory in the BSP dynamics is a natural requirement of the model, which is better reflected in the fractional-order model in the Caputo sense:

$$\begin{cases} {}^{C}D^{\beta} z(t) = -az(t) + bw(t), \\ {}^{C}D^{\beta} w(t) = az(t) - (b+d)w(t). \end{cases} \tag{45}$$

In (45), the fractional order $0 < \beta \leq 1$ corresponds to a certain effect of memory. The third equation from (44) with the dynamics of $x(t)$ is not included in the system (45) and can be solved separately. To avoid dimension mismatch, we consider the dimension unit of coefficients $t^{-\beta}$.

Let us first find the solution of the fractional-order system (45) with real value functions on [0, 80] with$a = 0.102$, $b = 0.001$ and $d = 0.011$. In Fig. 5, we illustrate the solution for various values of $\beta \in \{0.85, 0.9, 0.95\}$. These figures show that as $\beta \to 1$, the solutions tend to the solution of the first-order system (44).

Second, we consider the extension to an *fn*-valued functions as a solution space. Let an expert measure the initial amount of BSP in the human liver several times



(a) l-decreasing

(b) l-decreasing

(c) l-increasing

(d) l-increasing

Fig. 6 Time evolution of solutions of the system (45) with $\beta = 0.95$ **a–c** First component, **b–d** Second component

and obtain the average value $z_0 = 250$ with the standard deviation $\sigma = 30$. Thus, the normal distribution (see Fig. 4) is used for the characterization of the fuzzy initial value:

$$\left[z_0 - \sigma\sqrt{-\ln(r)}, z_0 + \sigma\sqrt{-\ln(r)}\right].$$

Figure 6 illustrates the 3-D evolution of some solutions valued *fn*-of (36) with $\beta = 0.95$ under assumptions about l-monotonicity. The blue surface corresponds to the cut boundaries on the left r, and the red surface corresponds to the right boundaries. In case (a), all components of the solution are functions valued at l decreasing *fn*-, and in case (b), they are all l increasing.

9 Conclusion

The main contribution of the proposed manuscript is a new methodology for studying dynamic processes, which extends the applicability of already existing (and well-established) models to cases that are close enough to the cases with a fixed (crisp) value. The proposed methodology and technical solution make it possible to carry out a reasonable theoretical analysis based on asymptotically stable numerical methods. In detail: 1) we extended the applicability of fractional-fuzzy differential calculus to biological systems (methodology); 2) we carried out a complete numerical analysis of the proposed model, including issues related to convergence, error estimation, and stability (technical solution). We showed that the combination of of fractional and fuzzy extensions captures two types of uncertainty in biological processes: one is related to the variety of human organs and the other is related to treatment. Finally, we discussed in detail our methodology for real-world applications, where we showed how the different types of proposed extensions affect the solution (individually and together).

Appendix A Chebyshev polynomials

In this section, we recall some relevant definitions related to Chebyshev polynomials, with an emphasis on their approximating capabilities [35].

Definition 5 Let $x = \cos(\theta), \theta \in [0, \pi]$. Then the Chebyshev polynomial $T_n(x)$, can be defined either explicitly using

$$T_n(x) = \cos(n \arccos(x)), \tag{A1}$$

or implicitly using the recursive formula;

$$T_{n+1}(x) = 2xT_n(x) - T_{n-1}(x), \; n \in \mathbb{N}, \tag{A2}$$

where $T_0(x) = 1$, and $T_1(x) = x$.

Since the analyzed equation (21) is considered in the interval $[0, T]$, we define the shifted Chebyshev polynomials $T_n^*(x)$ as

$$T_n^*(x) = T_n\left(\frac{2}{T}x - 1\right),\ n \in \mathbb{N}.$$

The corresponding shifted weight function used to prove its orthogonality, see [35], is $w^*(x) = w(\frac{2}{T}x - 1)$. Furthermore, the corresponding square of the L_2 norm for $T_n^*(x)$ is equal to

$$\gamma_n := \|T_n^*(x)\|^2 = \int_0^T w^*(x)(T_n^*)^2(x)dx = \frac{T}{2}\begin{cases} \frac{\pi}{2},\ n > 0, \\ \pi,\ n = 0. \end{cases} \tag{A3}$$

The weighted orthogonality mentioned of the Chebyshev polynomials leads to the Cleanshaw-Curtis formula, which gives a good estimate of the integral.

$$\int_{-1}^{1} w(x)f(x)dx \simeq \frac{\pi}{N+1}\sum_{k=1}^{N+1} f(x_k), \tag{A4}$$

where f is an arbitrary integrable function in $[-1, 1]$, and $x_1, \dots, x_{N+1}$, are zeros of the Chebyshev polynomial $T_{N+1}(x)$. For a function f in $[0, T]$, the Cleanshaw-Curtis estimate is recomputed to

$$\int_0^T w^*(x)f(x)dx = \int_{-1}^{1} w(x)f\left(\frac{T}{2}(x+1)\right)dx \simeq \frac{T\pi}{2(N+1)}\sum_{k=1}^{N+1} f\left(\frac{T}{2}(x_k+1)\right).$$

A function $f(t)$ on $[0, T]$ can be expanded using the first $(N+1)$ Chebyshev polynomials as follows:

$$f(t) \simeq \sum_{m=0}^{N} c_m T_m^*(t) = \mathbf{C}^T\Psi(t),\ N \in \mathbb{N}, \tag{A5}$$

where $\mathbf{C}$ and Ψ are vectors $(N+1)\times 1$

$$\begin{aligned} \mathbf{C}^T &= [c_0, \cdots, c_N], \\ \Psi^T(t) &= [T_0^*(t), \dots, T_N^*(t)], \end{aligned} \tag{A6}$$

and

$$\begin{aligned} c_i &= \frac{1}{\gamma_i}\int_0^T w^*(x)f(x)T_i^*(x)dx \\ &\simeq \frac{T\pi}{2\gamma_i(N+1)}\sum_{k=1}^{N+1} f(\frac{T}{2}(x_k+1))T_i(x_k), \quad i = 0, \dots, N. \end{aligned} \tag{A7}$$

Let π_N be the linear space of polynomials of degree at most N, where $N \in \mathbb{N}$. We define the linear operator (orthogonal projection) $p_N : C[0, T] \mapsto \pi_N$ according to (A5) so that

$$p_N(f) = \sum_{m=0}^{N} c_m T_m^* = \mathbf{C}^T\Psi.$$

Stability analysis

There are different methods for parameter fitting, for instance, Bayesian inference, then one can deal with the system and it is crucial to have knowledge of the stability of the system. In a real evolutionary process, sometimes small uncertainty tends to be unbounded over time. Thus, we need to introduce a concept that shows during the evolution, uncertainty does not increase infinitely. Therefore, we propose an analysis of asymptotic stability for uncertainty.

Let $l(\mathbf{y})(t, r) = \overline{\mathbf{y}}(t, r) - \underline{\mathbf{y}}(t, r)$ be the length of the fn-valued function y, that shows the measure of uncertainty. Let the solution be l-increasing. Taking fractional derivative from $l(t, r)$ with respect to t and applying Theorem 5, we obtain

$$\begin{aligned} {}^{C}D^{\beta}l(\mathbf{y})(t, r) &= {}^{C}D^{\beta}\overline{\mathbf{y}}(t, r) - {}^{C}D^{\beta}\underline{\mathbf{y}}(t, r) = A^-\underline{y}(t, r) \\ &+ A^+\overline{y}(t, r) - (A^+\underline{y}(t, r) + A^-\overline{y})(t, r) \\ &+ l(\mathbf{u})(t, r) = A^+l(\mathbf{y})(t, r) - A^-l(\mathbf{y})(t, r) \\ &+ l(\mathbf{u})(t, r). \end{aligned}$$

Thus, the dynamic of $L(t, r) = l(\mathbf{y})(t, r)$ satisfies the following system of fractional differential equations:

$${}^{C}D^{\beta}L(t, r) = (A^+ - A^-)L(t, r) + l(\mathbf{u})(t, r). \tag{A8}$$

Similarly, if the solution is l-decreasing, applying Theorem 5 leads to the following.

$${}^{C}D^{\beta}L(t, r) = (A^- - A^+)L(t, r) + l(\mathbf{u})(t, r). \tag{A9}$$

Fix r and consider the dynamic of $l(\mathbf{u})(t, r)$. Our interest is in the asymptotic stability of ordinary deterministic systems (A8) and (A9). To eliminate the effect of a constant source function, let L_e be an equilibrium point of the system (A8), i. e., $(A^+ - A^-)L_e + l(\mathbf{u})(t, r) = 0$. Then, $L - L_e$ is satisfied in

$${}^{C}D^{\beta}(L(t, r) - L_e) = (A^+ - A^-)(L(t, r) - L_e). \tag{A10}$$

The system (A10) is known to be asymptotically stable at zero if the spectrum $\sigma(A^+ - A^-)$ (the set of eigenvalues of the matrix $A^+ - A^-$) of the matrix $A^+ - A^- \in R^{\nu\times\nu}$ satisfies the condition.

$$\sigma(A^+ - A^-) \subset \left\{\lambda \in \mathbb{C} \setminus \{0\}; |\arg(\lambda)| > \frac{\beta\pi}{2}\right\}, \tag{A11}$$

where $\mathbb{C}$ stands for the space of complex numbers; see [38]. Similarly, the system (A9) is asymptotically stable at zero if the spectrum $\sigma(A^- - A^+)$ satisfies the condition.

$$\sigma(A^- - A^+) \subset \left\{\lambda \in \mathbb{C} \setminus \{0\}; |\arg(\lambda)| > \frac{\beta\pi}{2}\right\}. \tag{A12}$$

Remark 3 If systems (A8) and (A9) have a zero equilibrium (i.e. $L_e = 0$), uncertainty vanishes and the behavior of the system becomes determined. However, if L_e is a non-zero equilibrium point, then uncertainty does not disappear but is bounded to $|L_e| + \epsilon$. On the other hand, if the system is not stable, the uncertainty becomes unbounded.

Acknowledgements The work of Irina Perfilieva was partially supported by the Czech Republic Grant Agency, Project No.18-06915S.

Funding Open access publishing supported by the National Technical Library in Prague.

References

1. Nigmatullin R, Baleanu D, Fernandez A (2021) Balance equations with generalised memory and the emerging fractional kernels. Nonlinear Dyn 45:1–13
2. Baleanu D, Machado JA, Luo CJ (2012) Fractional dynamics and control. Springer-Verlag, New York
3. C. Li C, M. Cai M (2020) "Theory and numerical approximations of fractional integrals and derivatives," SIAM, Philadelphia,
4. Podlubny I (1999) Fractional differential equations: an introduction to fractional derivatives, fractional differential equations, to methods of their solution and some of their applications, San Diego Academic Press,
5. Qureshi S (2020) Effects of vaccination on measles dynamics under fractional conformable derivative with Liouville-Caputo operator. The European Physical Journal Plus 135(1):63
6. Karamali G, Shiri B, Kashfi M (2017) Convergence analysis of piecewise polynomial collocation methods for a system of weakly singular volterra integral equations of the first kind. Appl Comput Math 7:1–11
7. Baleanu D, Shiri B, Srivastava HM, Al M (2018) Qurashi,"A Chebyshev spectral method based on an operational matrix for fractional differential equations involving nonsingular Mittag-Leffler kernel,''. Adv Diff Eq 353:1–23
8. Bede B, Gal SG (2005) Generalizations of the differentiability of fuzzy number-valued functions with applications to fuzzy differential equations. Fuzzy Sets Syst 151:581–599
9. Bede B (2013) Studies in fuzziness and soft computing. Springer, Cham
10. Shiri B, Perfilieva I, Alijani Z (2021) Classical approximation for fuzzy Fredholm integral equation. Fuzzy Sets Syst 404:159–177
11. Shiri B (2023) A unified generalization for Hukuhara types differences and derivatives: Solid analysis and comparisons. AIMS Math 8:2168–2190
12. Agarwal RP, Lakshmikantham V (2010) On the concept of a solution for fractional differential equations with uncertainty. Nonlinear Anal: Theory Methods Appl 72:2859–2862
13. Kaleva O (1987) Fuzzy differential equations. Fuzzy Sets Syst 24:301–317
14. Hukuhara M (1976) Integration des applications measurables dont la valeur est un compact convex. Funkcial Ekvacioj 10:205–229
15. Puri ML, Ralescu DA (1983) Differentials of fuzzy functions. J Math Anal Appl 91(2):552–558
16. Markov SS (1979) Calculus for interval functions of a real variables. Computing 22:325–337
17. Bede B, Stefanini L (2013) Generalized differentiability of fuzzy-valued functions. Fuzzy Sets Syst 230:119–141
18. Chalco-Cano Y, Rufian-Lizana Y, Roman-Flores H, Jimenez-Gamero MD (2013) Calculus for interval-valued functions using the generalized Hukhara derivative and applications. Fuzzy Sets Syst 219:49–67
19. Stefanini L, Bede B (2009) Generalized Hukuhara differentiability of interval valued functions and interval differential equations. Non Linear Anal 71:1311–1328
20. Alijani Z, Kangro U (2021) On the smoothness of the solution of fuzzy volterra integral equations of the second kind with weakly singular Kernels. Numer Funct Anal Optim 42:819–833
21. Alijani Z, Kangro U (2022) Numerical solution of a linear fuzzy Volterra integral equation of the second kind with weakly singular kernels. Soft Comput 26:12009–12022
22. Stefanini LA (2010) A generalization of Hukuhara difference and division for interval and fuzzy arithmetic. Fuzzy Sets Syst 161:1564–1584
23. Zadeh LA (1965) Fuzzy sets. Inf Control 8:338–353
24. Khandy MA, Rafiq A, Nazir K (2017) Mathematical models for drug diffusion through the compartments of blood and tissue medium. Alexandria J Med 53:245–249
25. Abd-el-Malek MB, Kassem MM, Meky ML (2002) Group theoretic approach for solving the problem of diffusion of a drug through a thin membrane. J Comput Appl Math 140:1–11
26. Hrydziuszko O, Wrona A, Balbus J, Kubica K (2014) Mathematical two-compartment model of human cholestrol transport in application to high-blood cholestrol diagnosis and treatment. Electronic Notes Theor Computer Sci 306:19–30
27. Shojania M, Volk C, Hirschbeck S (2009) "A two-compartment model interacting with dynamic drugs. Appl Math Lett 22:1205–1209
28. Keshavarz M, Allahviranloo T (2022) Fuzzy fractional diffusion processes and drug release,". Fuzzy Sets Syst 436:82–101
29. Chakraverty S, Tapaswini S, Behera D (2016) "Fuzzy arbitrary order system: fuzzy fractional differential equations and applications. Wiley, New Jersey
30. Tomasiello S, Macías-Díaz J (2017) Note on a Picard-like method for Caputo fuzzy fractional differential equations. Appl Math Inf Sci 11(1):281–287
31. Feng Y, Chen M, Hu L (2007) On the observability of continuous-time dynamic fuzzy control systems. Int J Uncertainty Fuzziness Knowledge-Based Syst 15:75–91
32. Mayer O (1970) Algebraische und metrische Strukturen inder Intervall-rechnung und einige Anwendungen. Computing 5:144–162
33. Goetschel R, Vaxman W (1986) Elementary calculus. Fuzzy Sets Syst 18:31–43
34. Hong L, Sun JQ (2006) Bifurcations of fuzzy nonlinear dynamical systems. Commun Nonlinear Sci Numer Simul 11:1–12
35. Mason JC, Handscomb DC (2002) Chebyshev polynomials. CRC Press, Boca Raton
36. Celechovska LLA (2004) A simple mathematical model of the human liver. Appl Math 49:227–246

37. Watt JM, Young A (1962) An attempt to simulate the liver on a computer. Computer J 5(3):221–227
38. Diethelm K (2010) "The analysis of fractional differential equations An application-oriented exposition using differential operators of Caputo type. Springer Science & Business Media, Cham

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.