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A Project work on

Numerical solution of fuzzy fractional pharmacokinetics model arising from drug assimilation into the bloodstream

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CERTIFICATE

This is to be certified that the work content in the project entitled " ***Numerical solution of fuzzy fractional pharmacokinetics model arising from drug assimilation into the bloodstream*** " submitted by ***Avijit Maiti (Roll : MC/PG/S-IV/19, No : 5209)*** of DEPERMENT OF MATHEMATICS of MIDNAPORE COLLEGE(AUTONOMOUS) towards the requirement of the course MTMPG-404 has been carried out under my supervisor and that is not been submitted for word of any degree elsewhere

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CONTENT

(1)

Numerical Solution of Fuzzy Fractional Pharmacokinetics Model Arising from Drug Assimilation into the Bloodstream

1.Introduction

Pharmacokinetics is defined as the study of the time course of drug absorption ,distribution , and excretion. Pharmacokinetics determines bioavailability, volume of distribution, and clearance. Bioavailability is the fraction of a drug absorbed into the systemic circulation, while volume of distribution and clearance are measure of apparent space in the body available to contain the drug and measure of the body's ability to eliminate the drug, respectively. In pharmacokinetics , as a basic hypothesis, always a relationship exists between the pharmacologic or toxic response to a drug and the concentration of the drug in the blood (plasma). However for some drug there is no straightforward relationship between concentration in plasma and pharmacologic effects. Generally, the concentration of drug in the systemic circulation is related to the concentration of drug as its sites of action. Absorption, drug distribution(target tissues), drug concentration in circular system ,rate of elimination /plasma concentration, and elimination(metabolism, excretion) are some parameters that directly modify the pharmacokinetics parameters.

Mathematics is widely used for the quantitative description of drug absorption, distribution, metabolism, and excretion. Some parameters in pharmacokinetics are defined by mathematic equations which can be obtained directly by measurement or through calculation using experimental data based on developed mathematical equations.

In this study of this model, our focus is to find the approximate solution of the fuzzy fractional model of the compartment model for the flow of antihistamine in the blood. To this end, we use the operational matrix of the Caputo fractional derivative of the Jacobi tau approximation based on the Jacobi

polynomials to derive the fuzzy fractional approximate solution under Hukuhara differentiability (H-differentiability).

2.Preliminaries and notations

In this section we are going to state the definition and preliminaries of fuzzy mathematics, fractional calculus, and some properties of shifted Jacobi polynomials.

2.1.The Fuzzy settings Definitions

Definition 1. Let u be a fuzzy set in $\mathbb{R}$. u is called a fuzzy number if :

(i) u is normal: there exists $x_0 \epsilon \mathbb{R}$ such that $u(x_0)=1$;

(ii) u is convex: for all x, y $\epsilon \mathbb{R}$ and $0 \leq \lambda \leq 1$, it holds that

$$u(\lambda x + (1-\lambda)y \geq min\{u(x), u(y)\})$$

(iii) u is upper semi continuous: for any $x_0 \epsilon \mathbb{R}$, it holds that

$$u(x_0) \geq \lim_{x \to x_0^{\pm}} u(x);$$

(iv) $[u]^0 = \overline{supp(u)}$ is a compact subset of $\mathbb{R}$.

In this paper, the set of all fuzzy numbers is denoted by $\mathbb{R}_{\mathcal{F}}$.

Definition 2. Let u $\epsilon \mathbb{R}_{\mathcal{F}}$ and r $\epsilon [0,1]$. The r-cut of u is the crisp set $[u]^r$ that contains all elements with membership degree in u greater than or equal to r; that is

$$[u]^r = \{x \epsilon \mathbb{R} \mid u(x) \geq r\}$$

For a fuzzy number u, its r-cuts are closed intervals in $\mathbb{R}$, and we denote them by

$$[u]^r = [u_1^r, u_2^r]$$

According to Zadeh's extension principle, the operation of addition on $\mathbb{R}_{\mathcal{F}}$ is defined as follows:

$$(u + v)(x) = \sup_{y \epsilon \mathbb{R}} \min \{u(y), v(x-y)\}, \quad x \epsilon \mathbb{R},$$

And scalar multiplication of a fuzzy number is given by

$$(k \odot u)(x) = \begin{cases} u\left(\frac{x}{k}\right), & k > 0 \\ \tilde{0}, & k = 0 \end{cases}$$

Where $\tilde{0} \in \mathbb{R}_{\mathcal{F}}$.

Definition 3. Let f and g be the two fuzzy number-valued functions on the interval [a, b], that is f, g : [a, b] $\rightarrow \mathbb{R}_{\mathcal{F}}$. The uniform distance between fuzzy number-valued functions is defined by

$$D^*(f, g) = \sup_{x \in [a,b]} D(f(x), g(x))$$

Definition 4. Let x, y$\in \mathbb{R}_{\mathcal{F}}$. If there exists z $\in \mathbb{R}_{\mathcal{F}}$ such that

$x = y \oplus z$, then z is called the H-difference of x and y, and it is denoted by $x \ominus y$

In this paper, the sign " $\ominus$ " always stands for H-difference, and note that $x \oplus y \neq x + (-y)$. Also throughout the paper, it is assumed that the Hukuhara difference and generalized Hukuhara differentiability exist.

Theorem 1. Let F : (a, b) $\rightarrow \mathbb{R}_{\mathcal{F}}$ be a function and denoted

$[F(t)]^r = [f_r(t), g_r(t)], for\ each\ r \in [0, 1]$. Then ,

(i) If F is (1)-differentiable, then $f_r(t)$ and $g_r(t)$ are differentiable function and

$$[F'(t)]^r = [f_r'(t), g_r'(t)];$$

(ii) If F is (2)-differentiable, then $f_r(t)$ and $g_r(t)$ are differentiable functions and

$$[F'(t)]^r = [f_r'(t), g_r'(t)];$$

Definition 5: Consider the n × n linear system of the following equations:

$$a_{11}x_1 + a_{12}x_2 + \cdots + a_{1n}x_n = y_1$$
$$a_{21}x_1 + a_{22}x_2 + \cdots + a_{2n}x_n = y_2$$
$$\vdots$$
$$a_{n1}x_1 + a_{n2}x_2 + \cdots + a_{nn}x_n = y_n$$

$$AX=Y,$$

Where the coefficient matrix $A=(a_{ij})$, $1\leq i,j \leq n$ is a crisp $n \times n$ matrix and $y_i \in \mathbb{R}_{\mathcal{F}}, 1\leq i \leq n$. This system is called a fuzzy linear system (FLS).

Definition 6. A fuzzy number vector $(x_1, x_2, \ldots . x_n)^t$ given by $x_i = (x_{i-}^r, x_{i+}^r)$, $1\leq i \leq n, 0 \leq r \leq 1$ is called a solution of the fuzzy linear system if

$$(\sum_{j=1}^n a_{ij}x_j)_-^r = \sum_{j=1}^n (a_{ij}x_j)_-^r = y_{i-}^r ,$$

$$(\sum_{j=1}^n a_{ij}x_j)_+^r = \sum_{j=1}^n (a_{ij}x_j)_+^r = y_{i+}^r$$

If for particular k, $a_{kj} > 0, 1 \leq j \leq n$, we simply get

$$\sum_{j=1}^n a_{kj}x_{j-}^r = y_{k-}^r , \quad \sum_{j=1}^n a_{kj}x_{j+}^r = y_{k+}^r$$

In this part, we firstly give some basic definitions and some properties of fractional calculus.

Let m be the smallest integer that exceeds v, then Caputo's fractional derivative operator of order v > 0 is defined as

$${}^cD^v f(x) = \begin{cases} J^{m-v}D^m f(x), & if\ m-1 < v < m \\ D^m f(x), & if\ v = m,\ m\epsilon\mathbb{N} \end{cases}$$

Where

$$J^v f(x) = \frac{1}{\Gamma(v)}\int_0^x (x-t)^{v-1} f(t)\, dt , \qquad v > 0,\ x > 0.$$

For the Caputo derivative, we have

$${}^cD^v C = 0, \qquad (C\ is\ a\ constant\ )$$

$${}^cD^v x^\beta = \begin{cases} 0, & for\ \beta \epsilon \mathbb{N}_0,\ \beta < [v] \\ \frac{\Gamma(\beta+1)}{\Gamma(\beta+1-v)} x^{\beta-v}, & for\ \beta \epsilon \mathbb{N}_0,\ \beta \geq [v] \end{cases}$$

Caputo fractional differentiation is a linear operation, namely,

$${}^cD^v\big(\lambda f(x) + \mu g(x)\big) = \lambda\, {}^cD^v f(x) + \mu\, {}^cD^v \mathrm{g(x)},$$

Where λ *and* μ are constants.

Theorem 2. (generalized Taylor formula). Suppose that $D_a^{k\alpha} f(t) \in C(a, b]$ for k= 0,1, ….. , n+1. Where $0 < \alpha \leq 1$; then

$$f(t) = \sum_{i=0}^{n} \frac{(t-a)^{i\alpha}}{\Gamma(i\alpha+1)} [\, {}^{c}D_a^{k\alpha} f(t)]_{t=a} + R_n^{\alpha}(t, a),$$

with

$$R_n^{\alpha}(t, a) = \frac{(t-a)^{(n+1)\alpha}}{\Gamma((n+1)\alpha+1)} [\, {}^{c}D_a^{(n+1)\alpha} f(t)]_{t=\xi},$$

$$a \leq \xi \leq t, \; t \in [a, b],$$

where

$${}^{c}D_a^{n\alpha} = \underbrace{{}^{c}D_a^{\alpha} \; {}^{c}D_a^{\alpha} \; \dots\dots\dots \; {}^{c}D_a^{\alpha}}_{n\ times},$$

Here, ${}^{c}D^{\alpha}$ shows fractional derivative operator in the Caputo sense, and

$f_T^{ni}(t) = \sum_{i=0}^{n} \frac{(t-a)^{i\alpha}}{\Gamma(i\alpha+1)} [\, {}^{c}D_a^{k\alpha} f(t)]_{t=a}$ is called fractional Taylor expansion with degree ni of f , and $R_n^{\alpha}(t, a)$ is remainder term in fractional Taylor expansion of f.

Definition 7. Let $f \in C^{\mathbb{R}_{\mathcal{F}}}[a, b] \cap L^{\mathbb{R}_{\mathcal{F}}}[a, b]$. The Riemann-Liouville integral of fuzzy-valued function f is defined as

$$({}^{RL}I_{a+}^{v} f)(x) = \frac{1}{\Gamma(v)} \int_a^x \frac{f(t)}{(x-t)^{1-v}} dt, \qquad x > a, \; 0 < v \leq 1.$$

Theorem 3. (Fuzzy generalized Taylor's formula) Let $f(x) \in AC^{\mathbb{R}_{\mathcal{F}}}[0, b]$, and suppose that ${}^{c}D^{k\alpha} f(x) \in C^{\mathbb{R}_{\mathcal{F}}}[0, b]$ for k = 0,1,…..,n+1 where $0 < \alpha < 1, 0 \leq x_0 \leq x$ and $x \in [0, b]$. Then one has

$$[f(x)]^r = [\underline{f}^r(x), \overline{f^r}(x)],$$

Where $\underline{f}^r(x) = \sum_{i=0}^{n} \frac{x^{i\alpha}}{\Gamma(i\alpha+1)} \, {}^{c}D^{i\alpha} \underline{f}^r(0^+) + \frac{{}^{c}D^{(n+1)\alpha} f^r(x_0)}{\Gamma(n\alpha+\alpha+1)} x^{(n+1)\alpha},$

$\overline{f^r}(x) = \sum_{i=0}^{n} \frac{x^{i\alpha}}{\Gamma(i\alpha+1)} \, {}^{c}D^{i\alpha} \overline{f^r}(0^+) + \frac{{}^{c}D^{(n+1)\alpha} f^r(x_0)}{\Gamma(n\alpha+\alpha+1)} x^{(n+1)\alpha},$

And ${}^{c}D^{\alpha}\underline{f^{r}}(0) = {}^{c}D^{\alpha}\underline{f^{r}}(x)|_{x=0}$, ${}^{c}D^{\alpha}\overline{f^{r}}(0) = {}^{c}D^{\alpha}\overline{f^{r}}(x)|_{x=0}$.

Jacobi's Polynomials. The well-known Jacobi polynomials associated with the parameters $(\alpha > -1, \beta > -1)$, are a sequence of polynomials $P_i^{(\alpha,\beta)}(t)$ (i = 0, 1, ...), each, respectively, of degree i. For using these polynomials by implementing the change of variable t = (2x/L-1). Let the shifted Jacobi polynomials $P_i^{(\alpha,\beta)}(2x/L-1)$ be denoted by $P_{L,i}^{(\alpha,\beta)}(x)$, satisfying the orthogonality relation

$$\int_0^L P_{L,j}^{(\alpha,\beta)}(x) P_{L,k}^{(\alpha,\beta)}(x) w_L^{(\alpha,\beta)}(x)\, dx = h_k,$$

Where $w_L^{(\alpha,\beta)}(x) = x^{\beta}(L-x)^{\alpha}$ and

$$h_k = \begin{cases} \frac{L^{\alpha+\beta+1}\Gamma(k+\alpha+1)\Gamma(k+\beta+1)}{(2k+\alpha+\beta+1)K!\Gamma(k+\alpha+\beta+1)} & i = j \\ 0 & i \neq j \end{cases}$$

The shifted Jacobi polynomial $P_{L,i}^{(\alpha,\beta)}(x)$ of degree i has the form

$$P_{L,i}^{(\alpha,\beta)}(x) = \sum_{k=0}^{i}(-1)^{i-k} \frac{\Gamma(i+\beta+1)\Gamma(i+k+\alpha+\beta+1)}{\Gamma(k+\beta+1)\Gamma(i+\alpha+\beta+1)(i-k)!k!L^k} x^k,$$

Where

$$P_{L,i}^{(\alpha,\beta)}(L) = \frac{\Gamma(i+\alpha+1)}{\Gamma(\alpha+1)i!}$$

Also we can state the shifted Jacobi polynomial by the following recurrence relation :

$$P_{L,i}^{(\alpha,\beta)}(x) = (\alpha+\beta+2i-1\left\{\left(\alpha^2-\beta^2+\left(\frac{2x}{L}-1\right)\right)\times(\alpha+\beta+2)(\alpha+\beta+2i-2)\right\} \times (2i(\alpha+\beta+i)(\alpha+\beta+2i-2))^{-1} \times P_{L,i-1}^{(\alpha,\beta)}(x) - \frac{(\alpha+i+1)(\beta+i-1)(\alpha+\beta+2i)}{i(\alpha+\beta+i)(\alpha+\beta+2i-2)} \times P_{L,i-2}^{(\alpha,\beta)}(x) \qquad i = 2, 3, ...$$

Where $P_{L,0}^{(\alpha,\beta)}(x) = 1$ and $P_{L,i}^{(\alpha,\beta)}(x) = ((\alpha+\beta+2)/2)(2x/L-1)+(\alpha-\beta)/2$.

We notice that a function u(x), square integrable in (0,L), can be expanded in terms of shifted Jacobi polynomials as

$$u(x) = \sum_{j=0}^{+\infty} a_j P_{L,j}^{(\alpha,\beta)}(x),$$

where the coefficients a_j are given by

$$a_j = \frac{1}{h_j}\int_0^L P_{L,i}^{(\alpha,\beta)}(x)u(x)w_L^{(\alpha,\beta)}(x)\,dx, \qquad j = 0, 1, \ldots\ldots$$

For a given particular problem, only the first (N+1)-terms shifted Jacobi polynomials are used. Therefore we have

$$u_N(x) = \sum_{j=0}^{N} a_j P_{L,j}^{(\alpha,\beta)}(x).$$

3.Pharmacokinetics model equation

3.1. Drug assimilation into the Blood.

The drug dissolves in the gastrointestinal tract(GI), and each ingredient is diffused into the bloodstream. They are carried to the locations in which they act and ae removed from the blood by the kidneys and liver. Generally, the problem of drug assimilation into the body can be considered as a two-compartment model: GI- tract and the bloodstream . Different compartments and the input/output of the model are depicted in Figure 1.

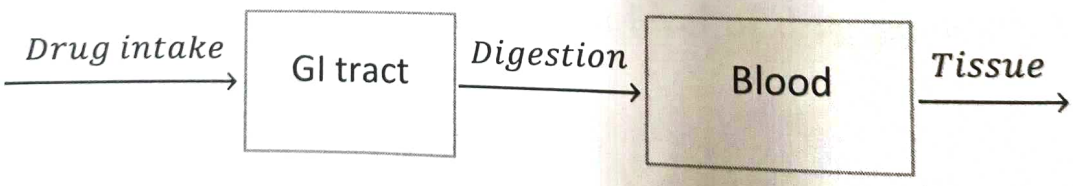

FIGURE 1: Schematic of input/output compartment for drug assimilation.

For each compartment by applying the balance law we can obtain

$$\left\{\begin{array}{c} rate\ of\ change\ of \\ drug\ in\ GI\ tract \end{array}\right\} = \left\{\begin{array}{c} rate\ of\ drug \\ intake \end{array}\right\} - \left\{\begin{array}{c} rate\ drug\ leaves \\ GI\ tract \end{array}\right\}$$

$$\left\{\begin{matrix}\text{rate of change of}\\ \text{drug in blood}\end{matrix}\right\} = \left\{\begin{matrix}\text{rate drug}\\ \text{enters blood}\end{matrix}\right\} - \left\{\begin{matrix}\text{rate drug leaves}\\ \text{blood}\end{matrix}\right\}$$

In this study, we consider a case of a single cold pill. Also, there is no diet of the drug except that which occurs initially.

3.2. **Case of a single cold pill:**

Let us consider x(t) to be the amount of drug in the GI-tract at time t and y(t), the amount in the bloodstream at time t. In the GI-tract we suppose that the pill is to be eaten, and so after this event we have nothing more entering the GI-tract. The pill dissolves and diffuses into the bloodstream from the GI-tract. So, the GI-tract is only the output term. Assume that output rate is proportional to the amount of drug in the bloodstream, which is in fact proportional to the GI-tract drug concentration, then

$$\frac{dy}{dt} = -k_1 x, \qquad x(0) = x_0.$$

Where x_0 is the amount of drug in the pill and k_1 is a positive coefficient. We suppose that y(0)=0, which means that the initial amount of the drug in the bloodstream is zero. As the drug diffuses from the GI-tract, the level increases, and as the kidneys and liver remove it, the level of drug gradually decreases. Thus,

$$\frac{dy}{dt} = k_1 x - k_2 x, \qquad y(0) = 0.$$

with k_2 another positive constant. Decongestant and an antihistamine are the component of the cold pill, and the coefficient of proportionality (k_1 *and* k_2) is different for the different component drugs in the pill.

In order to obtain the growth and decay of antihistamine levels in the GI-tract and

the bloodstream, rearrange the first rate equation, multiply by the integrating factor $e^{k_1 t}$, integrate, and then use the initial data to obtain

$$X = Ae^{-k_1 t},$$

Insert this formula for x(t) into the second rate equation, which becomes

$$\frac{dy}{dt} + k_2 y(t) = k_1 A e^{-k_1 t}, \qquad y(0)=0$$

We start by representing drug concentration in the effect compartment by the (Caputo) fractional differential equation:

$$^{c}D^{\alpha}y(t) + k_2 y(t) = k_1 A e^{-k_1 t} \qquad y(0)=0$$

However to generate a wider class of relationships, we assume that the effect at time t ϵ [0,1] is related to the fuzzy Caputo fractional derivative of y(t). So, we have

$$^{c}D^{\alpha}y(t) + k_2 y(t) = k_1 A e^{-k_1 t} \qquad y(0;r) = [\underline{y_0^r}, \overline{y_0^r}],$$

In which y(x) is a continuous fuzzy valued function and $^{c}D_0^{\alpha}$, denotes the fuzzy Caputo fractional derivatives of order v ϵ [0, 1].

4. Description of the Method

In this study, by developing the Jacobi polynomial approximation with the help of matrix operations, the tau method, and the fuzzy Caputo fractional derivative, we obtain an approximate solution of the problem for different values of k_1 and k_2.

Here we assume that the shifted Jacobi polynomials are defined on (0, 1), so we have

$$u(x) = \sum_{i=0}^{+\infty} a_i \odot P_{1,i}^{(\alpha,\beta)}(x),$$

where the fuzzy coefficient a_i are gained by

$$a_i = = \frac{1}{h_i}\int_0^1 P_{1,i}^{(\alpha,\beta)}(x) \odot u(x) \odot w_1^{(\alpha,\beta)}(x)\, dx , \qquad i = 0,1,.....$$

And $w_1^{(\alpha,\beta)}(x) = (1-x)^{\alpha} \odot x^{\beta}$, $u \in L_p^{\mathbb{R}_{\mathcal{F}}}[0,1] \cap C^{\mathbb{R}_{\mathcal{F}}}[0,1]$, and $P_{1,i}^{(\alpha,\beta)}(x)$ is as the shifted Jacobi polynomials.

5. Numerical Results

In this section, the fuzzy fractional pharmacokinetics-pharmacodynamic (PKPD) model is solved for different values of k_1 and k_2 by using the JT(Jacobi Tau) method presented in above. We can perform all numerical computations with a computer program written in MATLAB. Also, absolute errors between fuzzy approximate solution $[y_N]^r = [\underline{y}_N^r, \overline{y}_N^r]$ and the corresponding exact solutions $y(t;r) = [\underline{y}(t;r), \overline{y}(t;r)]$, that is, $[N_e]^r = [\,|\underline{y}_N^r - \underline{y}^r|, |\overline{y}_N^r - \overline{y}^r|\,]$, are not considered.

Now, we recall the fuzzy fractional differential equation(FFDE) as follows:

$$^{c}D^{\alpha}y(t) + k_2 y(t) = k_1 A e^{-k_1 t}$$

$$y(0;r) = [-1+r, 1-r],$$

in which $y(x) : L^{\mathbb{R}_{\mathcal{F}}}[0,1] \cap C^{\mathbb{R}_{\mathcal{F}}}[0,1]$ is a continuous fuzzy valued function and $^{c}D_{0+}^{\alpha}$ denotes the fuzzy Caputo fractional derivative of order $v \epsilon [0,1]$

let us consider a arbitrary value of k_2=0.0231(say) but let k_1 vary (e.g., 0.6931,0.11, and 0.3) so, with the assumption, namely, k_2=0.0231 and Dose A=1, is as follows:

$$^{c}D^{\alpha}y(t) + 0.0231 y(t) = 0.6931 e^{-0.6931 t}$$

$$y(0;r) = [-1+r, 1-r].$$

By using the fuzzy differentiability, we have the following systems:

$$\begin{aligned} {}^{c}D^{\alpha}\underline{y}(t;r) + 0.0231\underline{y}(t;r) &= 0.6931e^{-0.6931t}, && 0 < v \leq 1, \\ & && 0 < r \leq 1, \\ \underline{y}(0;r) &= -1+r, \end{aligned}$$

$$\begin{aligned} {}^{c}D^{\alpha}\overline{y}(t;r) + 0.0231\,\overline{y}(t;r) &= 0.6931e^{-0.6931t}, && 0 < v \leq 1, \\ & && 0 < r \leq 1, \\ \underline{y}(0;r) &= -1+r, \end{aligned}$$

Solving above to determining the exact solution we get the solution as follows:

$$\begin{aligned} \underline{Y}(t;r) = (-1+r)\,E_{v,1}[-0.0231t^{v}] + \int_0^t (t-x)^{v-1}\,E_{v,v}[-0.0231(t-x)^{v}] \\ \times (0.6931e^{-0.6931x})\,dx, \qquad 0 < v \leq 1, \end{aligned}$$

$$\begin{aligned} \overline{Y}(t;r) = (-1+r)\,E_{v,1}[-0.0231t^{v}] + \int_0^t (t-x)^{v-1}\,E_{v,v}[-0.0231(t-x)^{v}] \\ \times (0.6931e^{-0.6931x})\,dx, \qquad 0 < v \leq 1, \end{aligned}$$

Where $E_{v,v}$ and $E_{v,1}$ are the error function of fuzzy Caputo fractional derivative operator by using the shifted Jacobi polynomials.

6. conclusion

Fuzzy theory provides a suitable way to objectively account for parameter uncertainty in models. Considerable progress has been made in the last few years in the development of computational approaches for prediction of drug absorption, distribution, metabolism, and excretion.

In summary in this research, a tau method based on the Jacobi operational matrix was utilized to numerically solve the PKPD equation arising

from drug assimilation into the bloodstream. The comparison of the results shows that the present method is a powerful mathematical tool for finding the numerical solution of a generalized linear fuzzy fractional PKPD equation.

Although we concentrated on applying our algorithm to solve fuzzy fractional PKPD equation, we show that such algorithm can be applied to solve other types of fractional equations models in science and engineering fields. Our algorithm for the fuzzy fractional PKPD equations is efficient and numerically stable. Numerical results are presented which display the high accuracy of the proposed algorithm. In this model the fuzzy fractional differential equation was converted into a fuzzy algebraic system of equations simplifying the solution procedure. Also this method is computer oriented ;thus, solving fuzzy fractional differential equations of different fractional orders v becomes a matter of changing v only.

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