Nonlinear Models: Analysis of Anomalous Drug Diffusion

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***Abstract*—The present study models the ADME process by a nonlinear compartmental fractional differential system. The existence and uniqueness of the proposed models are discussed. The models are evaluated using the fde12 algorithm on MATLAB, where a code is generated to minimize mean squared error (MSE) and estimate the parameters considered in the models via nonlinear regression (optimization algorithm) PSO. The experimental data-sets of Diclofenac delayed release and the drug concentration based on the stated model, motivated the authors to the present study. A comparative study based on the suggested models is demonstrated in the context of MSE. The comprehensive results and evaluations are demonstrated through statistical analysis.**

***Index Terms*—Drug diffusion, FDE, commensurate, nonlinear model, metabolism.**

I. Introduction

THE authors have employed one-compartment pharmacokinetics with its applications to drug dissolution [1] to establish fractional calculus in PKPD. [2], [3] have proven using multi-compartment linear FDE to create a relationship between model predictions and experimental results. In [4], identifying and examining the differences between commensurate and non-commensurate models helped advance the theory of FDE in PK. As biological processes are modelled appropriately using nonlinear functions over linear models, authors in [5] explored a nonlinear function in the fractional two-compartmental model for improving the fit. Theorems related to the existence, uniqueness, and stability of solutions in linear and nonlinear FDE have been proved in [6],[7] and [8]. In the current study, the authors have extended the concept of nonlinear fractional models to anomalous drug diffusion given in-vivo results of Diclofenac delayed-release drug in six human volunteers contributions [9], [10].

In [11] and [12], the authors have provided an algorithm, namely the predictor-corrector method of Adams-Bashforth-Moulton for the numerical solution of nonlinear FDE which has been extended to multi-term FDE in 2003 for investigating mathematical models. For the said algorithm, [13] addressed an extensive error analysis and its convergence. Author in [14] elaborated linear stability analysis of an algorithm, which was previously presented by researchers in [11] and [12], further [14] developed routine fde12 in MATLAB. In the present context, a modified algorithm is illustrated to solve FDE models for drug diffusion using fde12, which future researchers may utilize to deal with linear and nonlinear compartmental models. Further, the authors have suggested a modified algorithm to estimate the parameters of the models from the existing experimental data [9] to explore regression using PSO MATLAB [15].

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II. Motivation

A modified approach is provided by nonlinear FDEs, which facilitate modelling complex dynamics and memory effects commonly observed in tissue structure and drug interactions. The study suggests using FDE-based nonlinear models to model drug distribution mechanisms more accurately. The solution's existence, uniqueness, and stability in the proposed models are explored to guarantee their reliability. The parameters are further assessed, and their significance is investigated through hypothesis testing to ensure that the investigated models provide meaningful information regarding the consumption of drugs.

The present work aims to create precise and theoretically solid models with strong mathematical characteristics and a good fit for experimental data. As a result, the objective of strengthening pharmacokinetic modelling, which will improve drug efficacy, optimize drug distribution forecasts, and enable safer therapeutic approaches, has been achieved.

III. Pre-requisite

In [16], authors defined Caputo's fractional derivative of any real number α of a continuous function $\phi(t)$ as

$$ {}_a^C D_t^\alpha \phi(t) = \frac{1}{\Gamma(\alpha - m)} \int_a^t \frac{\phi^{(m)}(\eta)}{(t-\eta)^{\alpha-m+1}} d\eta \qquad (1) $$

for $m-1 < \alpha < m$, where $m \in \mathbb{N}$ and a is the lower limit of t.

The linearity property of the Caputo derivative is given as [16]:

$$ {}_a^C D_t^\alpha (p\phi(t) + q\psi(t)) = p\, {}_a^C D_t^\alpha (\phi(t)) + q\, {}_a^C D_t^\alpha (\psi(t)) \qquad (2) $$

where p and q are arbitrary constants, $\phi(t)$ and $\psi(t)$ are continuous functions. Authors of [17] explored corrector (3) and predictor (4) formulae, respectively, for fractional Adams-Bashforth-Moullton method, used

in PSO algorithm to solve FDE.

$$\overrightarrow{y_{k+1}} = \sum_{i=0}^{n-1} y_0{}^{(i)} \frac{t_{k+1}^i}{i!} + \frac{\sum_{i=0}^{k} a_{i,k+1} \overrightarrow{\phi}\left(t_i, \overrightarrow{y_i}\right)}{\Gamma(\alpha)} + \frac{a_{k+1,k+1}}{\Gamma(\alpha)} \overrightarrow{\phi}\left(t_{k+1}, \overrightarrow{y_{k+1}^p}\right) \tag{3}$$

for suitable values of $a_{i,k+1}$.

$$\overrightarrow{y_{k+1}^p} = \sum_{i=0}^{n-1} y_0{}^{(i)} \frac{t_{k+1}^i}{i!} + \frac{1}{\Gamma(\alpha)} \left[\sum_{i=0}^{k} b_{i,k+1} \overrightarrow{\phi}\left(t_i, \overrightarrow{y_i}\right)\right] \tag{4}$$

where

$$b_{i,k+1} = \frac{h^\alpha}{\alpha}\left[(k+1-i)^\alpha - (k-i)^\alpha\right]$$

for $h = \frac{\tau}{N}$; some positive integer N.

Remark 1.

$$|e^{-x} - e^{-y}| \leq |x-y| \ \textit{for } x, y \geq 0. \tag{5}$$

IV. FDE for drug diffusion

Fick's law states that the material transfer rate over the tissue is proportional to the concentration gradient between the two locations [18]. The transfer procedures in drug diffusion processes of complex systems adhere to the power-law trends rather than Fick's law, which can be described through FDE. Fractional Calculus accurately describes such anomalous drug diffusion kinetics with the experimental data-set. FDE system with the initial conditions for drug diffusion is considered for $k = 0, 1, 2, \cdots, [\alpha]$ as follows:

$$D^\alpha\left[\overrightarrow{y}(t)\right] = \phi\left(t, \overrightarrow{y}(t)\right);\ \overrightarrow{y}^{(k)}(t_l) = \overrightarrow{c_k} \tag{6}$$

where $\phi\left(t, \overrightarrow{y}(t)\right) : [t_l, \tau] \times V \to \mathbb{R}^2$.
Considering $V_1 = [y_1(t_l) - r_1, y_1(t_l) + r_1]$ and
$V_2 = [y_2(t_l) - r_2, y_2(t_l) + r_2]$ such that
$V = V_1 \times V_2 \subset \mathbb{R}^2,\ t \in [t_l, \tau]$,
$\tau > t_l > 0,\ r_1, r_2 > 0$ and $0 < \alpha < 1$.
In the present study, the authors have proposed two compartmental models with $\phi\left(t, \overrightarrow{y}(t)\right)$ as:

$$\phi(t, \overrightarrow{y}(t)) = \left(\phi_1(t, \overrightarrow{y}(t)),\ \phi_2(t, \overrightarrow{y}(t))\right). \tag{7}$$

In (7), the function $\phi_1(t, \overrightarrow{y}(t))$ and $\phi_2(t, \overrightarrow{y}(t))$ are defined as

$$\phi_1(t, \overrightarrow{y}(t)) = -k_{21} f_1(y_1(t)). \tag{8}$$

$$\phi_2(t, \overrightarrow{y}(t)) = k_{21} f_1(y_1(t)) - k_{02} y_2(t) - K_{02} f_2(y_2(t)). \tag{9}$$

The nonlinear functions $f_1(y_1(t))$ and $f_2(y_2(t))$ mentioned in equations (8) and (9) are defined as

$$f_1(y_1(t)) = \frac{1 - e^{-\frac{y_1(t)}{l}}}{d} \tag{10}$$

and

$$f_2(y_2(t)) = \frac{y_2(t)}{K_m + y_2(t)} \tag{11}$$

where $\overrightarrow{y}(t) = (y_1(t), y_2(t)) \in \mathbb{R}^2$. Pharmacokinetics (PK) uses compartmental models to anticipate the safe and efficient manner in which medications are provided to a patient by assuring the interval of intake and excretion. The core and the peripheral compartments are thought to exchange the medicament. In the context, $y_1(t)$ and $y_2(t)$ are drug concentration at time t in first and second compartments respectively. $K_{02}, k_{21}, k_{02}, K_m$[19], l and t_l are as mentioned in the Nomenclature APPENDIX A and d be real positive constant. The nonlinear function (10) depicts the whole concentration in the first compartment at time t_l for a suitable value of d and continuous decay towards zero as the drug diffuses to the second compartment.
(6) is analogues to Volterra integral equation in the form of

$$\overrightarrow{y}(t) = \sum_{k=0}^{m-1} y^{(k)}(t_l) \frac{t^k}{k!} + \frac{1}{\Gamma(\alpha)} \int_{t_l}^{t} (t-v)^{\alpha-1} \phi\left(v, \overrightarrow{y}(v)\right) dv. \tag{12}$$

The integration in (12) can be evaluated by using (3) and (4).

V. Model Analysis

In the present section, authors explored the conditions with uniqueness, existence, and stability of the proposed model (6).

Definition 1.

$$\|\overrightarrow{y}\|_1 = |y_1| + |y_2|. \tag{13}$$

Proposition 1. *Let $\phi(t, \overrightarrow{y}(t)) : [t_l, \tau] \times V \to \mathbb{R}^2$ from (7) be the nonlinear function in FDE (6), then $\phi(t, \overrightarrow{y}(t))$ satisfies Lipschitz condition with respect to $\overrightarrow{y}(t) = (y_1(t), y_2(t))$*
i.e. $\|\phi(t, \overrightarrow{y}) - \phi(t, \overrightarrow{z})\| \leq L \|\overrightarrow{y} - \overrightarrow{z}\|$.

Proof: Consider

$$\begin{aligned}
&\|\phi(t, \overrightarrow{y}) - \phi(t, \overrightarrow{z})\| = |k_{21}\{f_1(y_1(t)) - f_1(z_1(t))\}| \\
&+ |-k_{21}\{f_1(y_1(t)) - f_1(z_1(t))\} - k_{02}\{y_2(t) - z_2(t)\} \\
&- K_{02}\{f_2(y_2(t)) - f_2(z_2(t))\}| \ \text{from(13)} \\
&\leq 2d|k_{21}||y_1(t) - z_1(t)| + |-k_{02}||y_2(t) - z_2(t)| \\
&+ |-K_{02}||f_2(y_2(t)) - f_2(z_2(t))| \ \text{from(5)} \\
&\leq 2d|k_{21}||y_1(t) - z_1(t)| + |-k_{02}||y_2(t) - z_2(t)| \\
&+ |-K_{02}||y_2(t) - z_2(t)| \\
&\text{for } y_2, z_2 \geq 0, K_m > 1 \\
&\leq \max\{2d|k_{21}|, |-k_{02}| + |-K_{02}|\} \\
&\{|y_1(t) - z_1(t)| + |y_2(t) - z_2(t)|\} \\
&= L\|y - z\|
\end{aligned}$$

where $L = \max\{2d\,|k_{21}|, |-k_{02}| + |-K_{02}|\}$.
Thus the function $\phi(t, \overrightarrow{y}(t)) : [t_l, \tau] \times V \to \mathbb{R}^2$ is locally Lipchitz continuous. ■

Proposition 2. *The function $\phi\left(t, \overrightarrow{y}(t)\right) : [t_l, \tau] \times V \to \mathbb{R}^2$ defined in Proposition 1 is bounded in $[t_l, \tau]$, $\infty > \tau > t_l > 0$.*

Proof: As $f_1(y_1(t))$ is bounded function between 0 to $\frac{1}{d}$, $y_2(t)$ and $f_2(y_2(t))$ are bounded functions between

0 to $c_{\max}$ for the considered time interval. Thus linear combination of bounded functions is bounded. ■

Proposition 3. *The solution of model with* $\phi(t, \overrightarrow{y}(t)) : [t_l, \tau] \times V \to \mathbb{R}^2$ *as the nonlinear function exists and unique in the interval* $[t_l, \tau]$, $\infty > \tau > t_l > 0$ *with* $y_1(t), y_2(t) > 0 \ \forall \ t \geq 0$.

Proof: As $\phi_1(t, \overrightarrow{y}(t))$ and $\phi_2(t, \overrightarrow{y}(t))$ are bounded, completely continuous and locally Lipchitz continuous on $C^1(\mathbb{R}^2_+)$, the solution $(y_1(t), y_2(t))$ for the model (6) with $\phi(t, \overrightarrow{y}(t))$ as nonlinear function exists and is unique on (t_l, τ), where $0 < t_l < \tau < \infty$ using theorem 1 [8].
Thus for the system (6) we get

$$y_1(t) = y_1(t_l) + I^{\alpha}(\phi(t, y_1(t))) \geq 0$$
$$y_2(t) = y_2(t_l) + I^{\beta}(\phi(t, y_2(t))) \geq 0.$$

■

Proposition 4. *The solution of the model with* $\phi(t, \overrightarrow{y}(t)) : [t_l, \tau] \times V \to \mathbb{R}^2$ *as nonlinear function is Mittag-Leffler stable.*

Proof: To proceed with the proposition we consider norm of $\phi(t, \overrightarrow{y}(t))$ for $t \in [t_l, \tau]$ as

$$\begin{aligned}
&\|\phi(t, \overrightarrow{y}(t))\| = |-k_{12}(f_1(y_1(t)))| \\
&+ |k_{12}(f_1(y_1(t))) - k_{02}y_2(t) - K_{02}(f_2(y_2(t)))| \\
&\qquad \text{from(13)} \\
&\leq 2|k_{12}||f_1(y_1(t))| + |k_{02}||y_2(t)| + |K_{02}||f_2(y_2(t))| \\
&\leq |c_1||y_1(t)| + |c_2||y_2(t)| \\
&\text{where } |c_1| > 2|k_{12}| \text{ and } c_2 = \max\{k_{02}, K_{02}\} \\
&= |c| \, \|\overrightarrow{y}(t))\| \\
&\text{where } c = \max\{c_1, c_2\} \text{ using(13).}
\end{aligned}$$

Here $\|\phi(t, \overrightarrow{y}(t))\| \leq |c| \, \|\overrightarrow{y}(t)\| = g(t, \|\overrightarrow{y}(t)\|)$ where $g \in C([t_l, \tau], \mathbb{R}^+)$ is monotonically increasing with $g(t, 0) = 0$.
Consider FDE

$$D^{\alpha}u(t) = g(t, u), u(t_l) = u_0 \tag{14}$$

where $g(t, u) = c \, u(t)$.
Clearly, the zero solution of (14) is a Mittag-Leffler system. Moreover for $c \leq 0$, (14) is Mittag-Leffler stable [8]. Hence the zero solution $\overrightarrow{y}(t) = (0, 0)$ of the model (6) with $\phi(t, \overrightarrow{y}(t)) : [t_l, \tau] \times V \to \mathbb{R}^2$ is Mittag-Leffler stable for choice of $u_0 > \|\overrightarrow{y}(t_l)\|$ [20]. ■

VI. Bi-compartmental Models

A. Model-1

A bi-compartmental biological system is deliberated in this section by applying a para-vascular drug. For the comparison between model results and the validation of the proposed models, the following linear FDE is represented by

$$D^{\alpha}y_1(t) = -k_{21}y_1(t) \tag{15}$$

$$D^{\beta}y_2(t) = k_{21}y_1(t) - k_{02}y_2(t). \tag{16}$$

After certain time-lag the concentration starts due to the delayed release drug, represented by the initial conditions as

$$y_1(t_l) = l, \ \ y_2(t_l) = 0. \tag{17}$$

The second compartment in the model (15)~(16) is characterized by the kinetics of the drug having movement in the body with the uniformity of plasma. Authors in [21] evaluated FDE using the Homotopy Analysis Method. In [8], authors have evaluated (15)~(16) with initial conditions (17) using the Adomian Decomposition Method (ADM) to estimate the parameters such as rate of transfer of drug, rate of elimination, order of FDE, etc. for the experimental data-set of Diclofenac delayed release concentration-vs-time. The authors have explored the numerical way of evaluating proposed nonlinear FDE models for drug diffusion in the present study.

B. Model-2

Diclofenac is metabolized primarily by cytochrome P450 enzymes, particularly CYP2C9, in the liver, transforming it into various metabolites [22]. Urinary excretion accounts for the majority of drug and metabolite disposal. Only one percent of the unmodified Diclofenac is eliminated through urine, and the residue is metabolized. Thus, Diclofenac is generally released by metabolism [23], [24]. Hence considering the metabolized factor by adapting Michaelis-Menten equation in (16) along with (15), we propose

$$D^{\beta}y_2(t) = k_{21}y_1(t) - K_{02}f_2(y_2(t)) \tag{18}$$

incorporating the conditions mentioned in (17).

C. Model-3

(15) and (18) with (17) assume that the transfer rate across one compartment to the next is proportional to the amount of the initial compartment. In a pharmacokinetic process, the transfer rate is defined as the function of the amount of concentration (various compartments) and time. Moreover, linear fractional compartmental models exhibit linear combinations of Mittag-Leffler functions of time as in [8]. Thus, considering (10) as the function of concentration satisfying necessary conditions of proposition (3) and (4), we write:

$$D^{\alpha}y_1(t) = -k_{21}f_1(y_1(t)) \tag{19}$$

$$D^{\beta}y_2(t) = k_{21}f_1(y_1(t)) - K_{02}f_2(y_2(t)) \tag{20}$$

with (17). A choice of $\phi(t, \overrightarrow{y}(t))$ in (19)~(20) can result in a set of concentration functions which can produce data-fit with lesser MSE than the linear one and hence enhancing the compartmental modelling for ADME.

D. Model-4

Now considering nonlinear FDE along with eliminating factor and metabolism parameter as explained in (18), considering (19) and initial conditions (17), we present:

$$D^{\beta} y_2(t) = k_{21} f_1(y_1(t)) - k_{02} y_2(t) - K_{02} f_2(y_2(t)). \tag{21}$$

Remark 2.

1. *In Model-4 if elimination parameter is dropped, we get Model-3.*
2. *In Model-3 if nonlinearity in distribution parameter is dropped, we get Model-2.*
   Thus, the solutions' existence, uniqueness, and stability for all proposed models are proved using proposition (3) *and* (4)*, respectively.*

VII. Modified algorithm

A code for generating function of mean squared error in MATLAB is designed as:

```
1. function x=fdewp1(x0)
2. clc;
3. alpha=x0(1);
4. b=x0(2);
5. c=x0(3);
6. d=x0(4);
7. e=x0(5);
8. f=x0(6);
9. g=x0(7);
10. param=[b, c, d, e, f, g];
11. f_fun = @(t, y, par)
[-par(1)*((1-exp(-y(1)/par(6)))/par(5));
par(1)*((1-exp(-y(1)/par(6)))/par(5))
-par(2)*y(2)-(par(3)*y(2))/(par(4)+y(2))];
12. t0=0;
13. T=8;
14. y0=[x0(7); 0];
15. h=2^(-5);
16. [t, y] =
fde12(alpha,f_fun,t0,T,y0,h,param);
17. sum=0;
18. t1 = [data];
19. yobs = [data];
20. for k=1:385
21. for j=1:number of observations
22. if (t1(j)==t(k))
23. g(j)=y(2,k);
24. sum=sum+(yobs(j)-y(2,k))^2;
25. end
26. end
27. end
28. matrix = [t', y(2,1:385)'];
29. writematrix(matrix, 'path to store the
matrix');
30. plot(t, y(2,1:385),t1,yobs,'▲')
31. x=sum;
32. end
```

Remark 3.

1. *For Model-3, line 11 in the above code can be modified as f_fun = @(t, y, par) [-par(1)*((1-exp(-y(1)/par(5)))/par(3));*
   par(1)((1-exp(-y(1)/par(5)))/par(3))-(par(2)*y(2))/(par(4)+y(2))];*
2. *For Model-2, f_fun = @(t, y, par) [-par(1)*y(1); par(1)*y(1)-(par(2)*y(2))/(par(3)+y(2))];*
3. *For Model-1, f_fun = @(t, y, par) [-par(1)*y(1); par(1)*y(1)-par(2)*y(2)];*
4. *The lines for defining parameters and displaying estimated parameters are % as per the need of model.*

A code for minimizing the above function and hence estimating parameters using PSO program [15] in MATLAB is proposed as:

```
1. fun = @fdewp1;
2. lb = [];
3. ub = [];
4. nvars = 7;
5. nparticles = 30;
6. maxiter = 150;
7. options = optimoptions('particleswarm',
'Display', 'iter', 'UseParallel', true);
8. [x, fval] = particleswarm(fun, nvars, lb,
ub, options);
9. disp('Optimization results:')
10. disp(['alpha = ', num2str(x(1))])
11. disp(['b = ', num2str(x(2))])
12. disp(['c = ', num2str(x(3))])
13. disp(['d = ', num2str(x(4))])
14. disp(['e = ', num2str(x(5))])
15. disp(['f = ', num2str(x(6))])
16. disp(['g = ', num2str(x(7))])
17. disp(['Minimum value = ', num2str(fval)])
```

VIII. Observation

Utilizing the code presented in section VII, parameters considered in the Model-1 ~Model-4 are estimated and displayed in I ~IV respectively. Table I represents estimated parameters of linear model (15)~(16), with the initial conditions (17) to the experimental data of Diclofenac delayed release time-concentration profile for chosen six subjects. Predicted parameters from the fitting of model (15) and (18), which includes the metabolism parameter with (17) to the same experimental data, are shown in Table II. We observe that $K_m > 1$ for all the subjects, as per the need of proposition 1. MSE with the considered model is less than that of linear. Equipped with model (19)~(20) fitted to the same experimental data, Table III displays estimated parameters, considering nonlinearity in the distributing parameter with (17). MSE generated by the modified algorithm reflects the efficacy of the function (10). After fitting the nonlinear model (19) and (21) with (17), alongside the elimination and metabolism parameter, to the data from the experiment, the estimated parameters are shown in Table IV.

Based on the MSE values, Model-4 has the lowest MSE compared to Model-1~3, which indicates that Model-4's predictions are closer to the actual Diclofenac plasma concentration than other models. Including metabolic parameter and adding nonlinear function in Model-4 likely contributed to its improved performance by

Table I: Parameters estimation for Model-1

Subject	α	k_{21}	k_{02}	$l\,(mg/ltr)$	MSE	t-stats
1	0.9738	5.2108	2.5941	24.99	0.0144	-0.537937
2	0.966	2.8047	4.6108	22.024	0.0015	0.0989256
3	0.98349	6.1867	2.6965	30.01	0.0608	-1.43506
4	0.9780	6.2848	2.5013	24.99	0.0175	-0.966578
5	0.98166	1.609	4.537	16.2183	0.00898	0.418072
6	0.9896	6.1462	2.0753	15.25	0.1525	-1.25759
Mean ± SD	0.9797 ± 0.0093	5.2078 ± 1.4546	2.5545 ± 1.0712	18.8588 ± 7.3528		

Table II: Parameters estimation for Model-2

Subject	α	k_{21}	K_{02}	K_m	$l\,(mg/ltr)$	MSE	t-stats
1	0.8386	15.6006	23.2618	3.2320	21.4395	0.006	-1.07984
2	0.9572	11.3779	26.6082	9.7345	9.8352	0.0014	-0.872885
3	0.7620	15.12	14.99	1.01	18.6132	0.0131	-1.30657
4	0.7599	18.0517	19.9994	1.9539	20.6653	0.0046	-1.02123
5	0.98659	6.7153	18.0283	11.4291	4.9341	0.00895	-0.807238
6	0.694	13.3566	29.9790	2.1329	27.9751	0.0907	-1.13256
Mean ± SD	0.833 ± 0.1172	13.3704 ± 3.955	22.1444 ± 5.57286	4.9154 ± 4.477	17.2437 ± 8.399		

Table III: Parameters estimation for Model-3

Subject	α	k_{21}	K_{02}	K_m	d	$l\,(mg/ltr)$	MSE	t-stats
1	0.8332	20.1938	24.9233	2.6833	0.1914	23.8196	0.0058	-0.728406
2	0.9462	29.7637	24.1054	7.9439	0.4044	9.5402	0.0013	-0.0995952
3	0.8664	21.9630	24.9998	3.8145	0.0683	21.6874	0.0026	-1.38582
4	0.86	27.1314	29.9966	5.0579	0.1046	22.6426	0.0034	-1.00408
5	0.9592	31.4074	26.6165	13.3588	1.0511	5.8296	0.00888	1.10479
6	0.8071	24.3327	22.0482	2.5798	0.0761	20.15	0.0262	-1.07042
Mean ± SD	0.8668 ± 0.0479	22.6333 ± 6.0789	23.9365 ± 4.0807	4.0089 ± 2.2164	0.2074 ± 0.1569	18.7018 ± 5.5754		

Table IV: Parameters estimation for Model-4

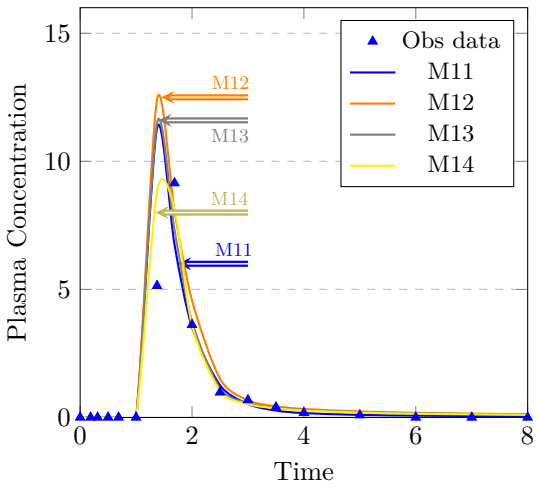
Subject	α	k_{21}	k_{02}	K_{02}	K_m	d	$l\,(mg/ltr)$	MSE	t-stats
1	0.9177	24.9527	2.3153	14.9923	3.5140	0.1102	39.8253	0.0056	-0.887177
2	0.9515	39.6520	5.4214	26	1.7709	0.3848	49.9963	0.0011	0.178827
3	0.9640	16.8393	2.5873	14.829	18.4583	0.0533	37.7992	0.001	-1.63094
4	0.9478	29.99	3.0364	9.3637	13.117	0.0951	39.993	0.0023	-1.00323
5	0.9731	28.6252	8.9212	29.4916	14.6046	0.39164	39.5833	0.008858	0.396875
6	0.8039	29.3124	0.7676	29.3452	2.6895	0.0533	34.7122	0.0166	-1.08458
Mean ± SD	0.9332 ± 0.0406	27.953 ± 10.4287	2.9725 ± 1.8283	18.49185 ± 7.8033	9.7276 ± 8.1536	0.2754 ± 0.3515	33.7871 ± 13.3616		

capturing more variability in the drug concentration. The comparison shows that Model-4 outperforms other model's prediction accuracy, as indicated by the lower MSE. Based on this analysis, Model-4 is recommended for predicting drug concentration due to its superior performance as measured by MSE.

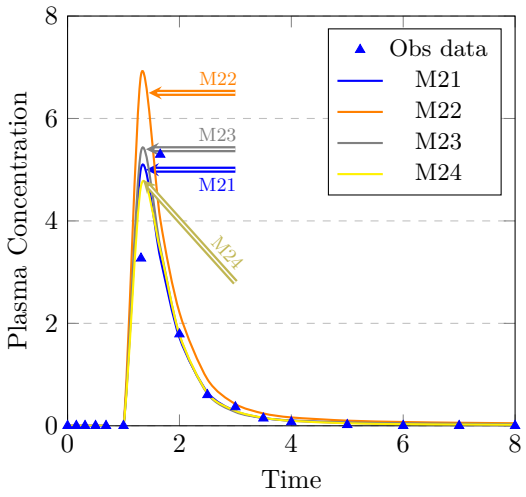
In Figure 1, smooth curves represent the simulated plasma concentration of Diclofenac delayed release by models (15)~(16), (15) and (18), (19)~(20), (19) and (21) with the initial conditions (17) whereas blue triangles reflect experimental data conducted on Subject 1 to 6. M_{ij} represents simulation of j^{th} model on data-set of i^{th} subject.

IX. Discussion

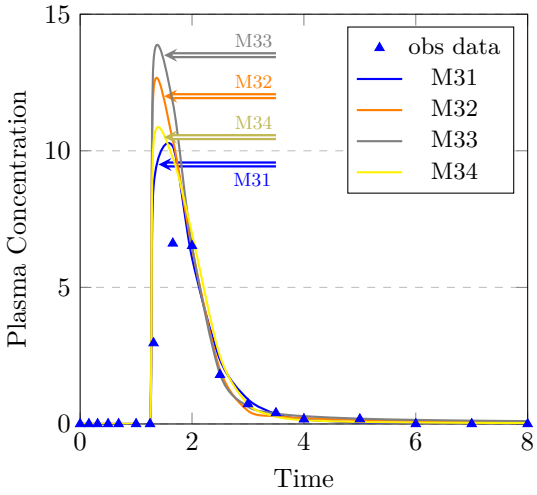
The main objective of the work is to present robust nonlinear fractional order models, including metabolism parameters, that could fit the experimental data set of anomalous drugs. Further, it presents an algorithm that could estimate the parameters while minimizing the mean squared error function after evaluating the presented models by fde12



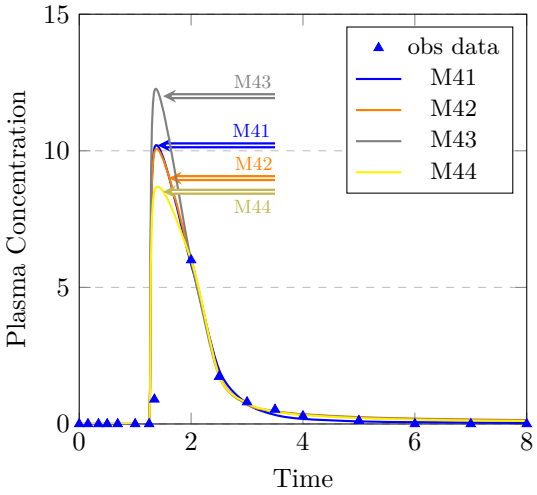
(a) Subject 1



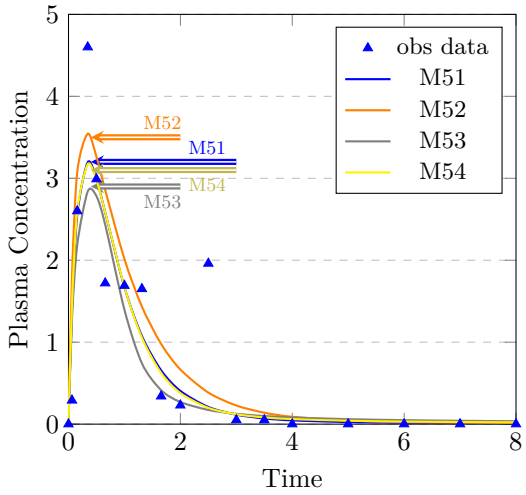
(b) Subject 2



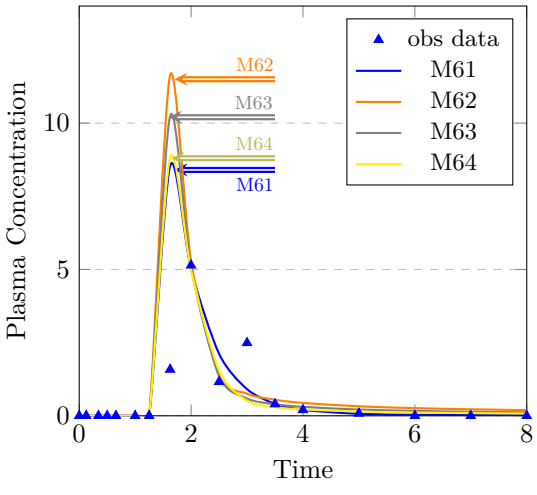
(c) Subject 3



(d) Subject 4



(e) Subject 5



(f) Subject 6

Figure 1: Plots of Diclofenac-concentration-verses time (h) for Subjects 1-6

implementation on MATLAB. FO model is the generalized case of integer order model fitting data-set of all categories of drugs for different values of α. Risk of toxicity or ineffectiveness of the treatment is involved in the process of ADME, where control of drug concentration in plasma is mandatory. In order to forecast the parameters influencing the sequence of events for each individual, one requires a PK model.

A function is created to define mean squared error with the parameters involved in the models, and the related study is further explored. As per the proposed models, the drug absorbed in the first compartment after a certain time-lag is treated as a parameter, because it differs for different subjects as observed in the experimental data. The range for time is specified as 8 hours, depending on the sample taken. The step size, h is considered to be $\left(\frac{1}{2}\right)^5$. The fde12 code is implemented on above discussed factors (`[t, y] = fde12(alpha,f_fun,t0,T,y0,h,param)`).

The regression is done using the particle swarm algorithm, where PSO parameters are set as a number of particles equal to 30, and the maximum number of iterations is 150. The optimization results by the PSO algorithm for concentration data of six subjects are referred from [9] and are displayed in Table I~IV for various models. The authors conducted a study/experiment on six healthy volunteers using a slow-release 100 mg single dose of oral Diclofenac tablet formulation.

Anatomical regions of the body represented by a two-compartmental model in this text include the bloodstream and a tissue compartment. As mentioned in the main results, it is often believed that these compartments' drug distribution and elimination procedures are alike. Therefore, assuming that both compartments have a similar fractional order is biologically logical. Hence, the order is similar in both equations while analyzing them for real data.

Model-1 to Model-4 represented by (15)~(16), (15) and (18), (19)~(20), (19) and (21) respectively with the initial conditions (17) were fitted to the Diclofenac delayed release profile taken from literature for six subjects. The parameter estimates are presented in Table I~IV with respective mean squared errors for the respective models. MSE reveals that the fitting with the nonlinear model with metabolic parameter is proved effective over the domain research done in the recent past. The fractional profile first seems quicker from the first to the second compartment but subsequently slows down. The power-law kinetics of the final state in the fractional case leads to slower kinetics. Considering the null hypothesis with the mean of the residuals as zero, the t-test is performed to validate the proposed models. The mod of t-value is compared with the t-table value at 95% LOS and 'n minus parameters' degree of freedom. The comparison indicates the robustness of the models considered in the study.

X. Comparison and analysis

In the present section, t-stats, p-value, and confidence interval at 95% LOS have been computed for the estimated parameters of all the proposed regression models, using Mathematica 13.0 to process the significance of the parameters. Observation made from table (V), the comparatively narrow confidence ranges for subjects 1, 3, 4, and 6 show that the estimates are precise. The CI for the second parameter for subject 5, which contains 0, indicates that the result for this parameter may not be significant, which can suggest that the estimations for this subject are more variable or imprecise than those for other subjects. Table (VI) shows that the t-stats for subjects 1, 3, 4, and 6 are extremely high, suggesting that the outcomes are not likely to be the result of chance. The variations found in the data are pretty significant. The t-stats for subjects 2 and 5 are slightly lower than the others. Thus, this indicates that the effect might be less than that of the other subjects, even though they are still significant. The dataset's p-values are all exceedingly small, ranging between 10^{-3} and 10^{-53}, substantially lower than the 0.05 cut-off, which suggests that the null hypothesis is firmly rejected for all subjects and parameters. From Table (VII), we see that t-stats for subject 2 in the parameters K_m and d and for subject 4 in d are low, whereas for all other parameters, it is very high. The p-value for all the parameters is far below the threshold of 0.05. Table (VIII) shows that the results from subjects 1, 3, 4, and 6 are consistently robust and reliable. Subject 5 exhibits marginally more significant variability, especially about k_{02} parameter. Subject 2 exhibits the most variability and contains non-significant parameters such as K_{02} and K_m.

Overall, as per the models for the considered subjects, a high t-statistic and a low p-value have been observed for all estimated parameters, which suggests that the parameters are significantly different from zero at 95% LOS. Given that there is a statistically significant association between the related predictor and response variable, it is unlikely that the outcome is an effect of random chance. As a result, the authors state that these predictor variables contribute significantly to the model and need to be considered during the present text's analysis. Comprehending and forecasting a drug's pharmacokinetics requires knowledge about ADME parameter rates. A high transfer/distribution rate seen in Tables V~VIII indicates rapid absorption, which can lead to quicker onset of action. It determines how fast Diclofenac reaches its target sites. The higher metabolism rate indicates how fast the drug is broken down into active or inactive metabolites for the mentioned drug. A lower elimination rate is seen, leading to slower clearance of the drug from the body.

The right amount of drug must be maintained in the body for the intended therapeutic effect. During drug development, the understanding of optimizing the rate of transfer parameters is always intended to ensure safer and more effective drugs.

For the matter of presentation, Subject i depicted in the graphs is the same as Sub i mentioned in the Tables V~VIII, where $i = 1, 2, \cdots, 6$.

Table V: Statistical analysis for Model-1

Model 1	α	k_{21}	k_{02}	$l\,(mg/ltr)$
Sub 1: t-stats	2271.17	354.213	90.3076	47.9479
p-value	$4.32758 * 10^{-53}$	$9.2981 * 10^{-38}$	$1.72627 * 10^{-26}$	$2.74189 * 10^{-21}$
CI	(0.968224, 0.975726)	(5.14496, 5.40605)	(2.46117, 2.99029)	(22.4728, 32.5272)
Sub 2: t-stats	1423.51	8.02476	9.65034	16.5291
p-value	$2.12145 * 10^{-25}$	$2.15948 * 10^{-5}$	$4.80817 * 10^{-6}$	$4.84199 * 10^{-8}$
CI	(0.969829, 0.978311)	(2.56811, 19.9941)	(1.08752, 4.99228)	(10.2599, 22.5703)
Sub 3: t-stats	1321.36	85.6937	40.5473	24.7004
p-value	$1.27514 * 10^{-48}$	$4.66471 * 10^{-26}$	$6.43559 * 10^{-20}$	$6.65454 * 10^{-16}$
CI	(0.980199, 0.993291)	(5.28463, 6.48888)	(1.9085, 2.9612)	(16.451, 34.549)
Sub 4: t-stats	873.697	451.912	73.4919	47.9479
p-value	$3.30411 * 10^{-45}$	$9.0913 * 10^{-40}$	$8.56368 * 10^{-25}$	$2.74189 * 10^{-21}$
CI	(0.963382, 0.982908)	(6.21819, 6.46417)	(2.34249, 2.97693)	(22.4728, 32.5272)
Sub 5: t-stats	393.739	6.12083	7.0751	6.9287
p-value	$2.23819 * 10^{-20}$	0.000174775	$5.82338 * 10^{-5}$	$6.84468 * 10^{-05}$
CI	(0.965509, 0.996391)	(−0.0326401, 5.21402)	(0.436264, 6.60154)	(1.3299, 23.8895)
Sub 6: t-stats	1380.79	118.398	62.1561	39.2301
p-value	$5.52781 * 10^{-49}$	$1.01421 * 10^{-28}$	$2.03957 * 10^{-23}$	$1.19682 * 10^{-19}$
CI	(0.979865, 0.992385)	(5.88627, 6.8275)	(1.9168, 2.54616)	(13.9782, 22.0218)

Table VI: Statistical analysis for Model-2

Model 2	α	k_{21}	K_{02}	K_m	$l\,(mg/ltr)$
Sub 1: t-stats	132.875	20.8626	30.2895	12.5982	65.2736
p-value	$3.93522 * 10^{-16}$	$6.25429 * 10^{-9}$	$2.27982 * 10^{-10}$	$5.08245 * 10^{-7}$	$2.34685 * 10^{-13}$
CI	(0.788863, 0.866057)	(12.3731, 22.8319)	(16.9384, 25.6538)	(1.42942, 4.19792)	(19.0005, 22.9875)
Sub 2: t-stats	207.066	4.36805	16.128	9.02866	7.39883
p-value	$7.26976 * 10^{-18}$	0.0018022	$6.00063 * 10^{-8}$	$8.31879 * 10^{-6}$	$4.10849 * 10^{-5}$
CI	(0.92526, 0.98236)	(-4.20192, 24.2622)	(15.6773, 35.2476)	(2.51747, 13.5417)	(1.83923, 20.8244)
Sub 3: t-stats	92.7185	30.5145	28.8548	9.63593	121.394
p-value	$1.04756 * 10^{-26}$	$1.31833 * 10^{-17}$	$3.73425 * 10^{-17}$	$9.53262 * 10^{-9}$	$6.31296 * 10^{-29}$
CI	(0.723905, 0.875065)	(12.473, 22.5266)	(11.5921, 21.7075)	(0.153874, 3.25194)	(17.9127, 20.7008)
Sub 4: t-stats	421.651	23.2655	65.6799	71.6181	231.905
p-value	$1.20837 * 10^{-20}$	$2.38315 * 10^{-9}$	$2.21962 * 10^{-13}$	$1.01988 * 10^{-13}$	$2.62288 * 10^{-18}$
CI	(0.748996, 0.771344)	(12.9162, 22.297)	(17.8404, 21.5583)	(1.78263, 2.12041)	(20.1295, 21.235)
Sub 5: t-stats	219.836	3.76945	13.0326	14.189	62.879
p-value	$4.24278 * 10^{-18}$	0.0044202	$3.80041 * 10^{-7}$	$1.82634 * 10^{-7}$	$3.28306 * 10^{-13}$
CI	(0.947988, 1.00299)	(-9.39694, 38.5683)	(8.17934, 23.0141)	(5.06332, 12.9176)	(4.69711, 5.72435)
Sub 6: t-stats	44.353	13.884	179.199	16.214	84.44
p-value	$7.52413 * 10^{-12}$	$2.20364 * 10^{-7}$	$2.66901 * 10^{-17}$	$5.72862 * 10^{-8}$	$2.32112 * 10^{-14}$
CI	(0.617648, 0.818312)	(8.22288, 21.4846)	(28.8011, 30.8647)	(1.52917, 3.42169)	(24.6231, 28.5242)

XI. Conclusion

In the present study, authors have explored different linear and nonlinear models considering with and without metabolic parameters to study the release profile of Diclofenac delayed release. The existence and uniqueness of the suggested models have been discussed. The algorithm is presented to evaluate the considered models numerically and estimate the study parameters. Diclofenac concentration-vs-time graphs are plotted for various models, which are further compared w.r.t MSE. The t-test on residuals performed on the models validates the proposed models. The importance of the metabolism parameter is showcased in the continuous curves plotted. The existing linear models are now generalized to the nonlinear models in the present text.

Table VII: Statistical analysis for Model-3

Model 3	α	k_{21}	K_{02}	K_m	d	$l\,(mg/ltr)$
Sub 1: t-stats	130.391	162.704	31.5927	24.4694	15.0092	69.3142
p-value	$4.663 * 10^{-16}$	$6.363 * 10^{-17}$	$1.565 * 10^{-10}$	$1.523 * 10^{-9}$	$1.122 * 10^{-7}$	$1.368 * 10^{-13}$
CI	(0.7835, 0.8617)	(19.348, 20.8805)	(21.8031, 32.4459)	(1.922, 3.226)	(0.0959, 0.2309)	(21.5571, 25.7909)
Sub 2: t-stats	241.795	12.2408	15.4445	5.7108	5.94061	13.3507
p-value	$1.801 * 10^{-18}$	$6.5 * 10^{-7}$	$8.751 * 10^{-8}$	0.00029	0.0002178	$3.088 * 10^{-7}$
CI	(0.927, 0.9757)	(12.2687, 37.436)	(15.4354, 36.128)	(-0.5961, 14.5745)	(-0.0176, 0.8315)	(4.6017, 12.5765)
Sub 3: t-stats	69.9628	41.4767	39.012	12.086	15.5976	61.4025
p-value	$1.258 * 10^{-13}$	$1.372 * 10^{-11}$	$2.374 * 10^{-11}$	$7.245 * 10^{-7}$	$8.031 * 10^{-8}$	$4.064 * 10^{-13}$
CI	(0.7708, 0.9206)	(19.4225, 26.247)	(19.8505, 27.3493)	(-0.5556, 6.943)	(-3.6631, 3.8356)	(19.7737, 24.2137)
Sub 4: t-stats	238.689	9.76035	69.8137	23.6667	5.11001	68.6253
p-value	$2.023 * 10^{-18}$	$4.377 * 10^{-6}$	$1.282 * 10^{-13}$	$2.047 * 10^{-9}$	0.000636	$1.496 * 10^{-13}$
CI	(0.8296, 0.8738)	(8.9226, 39.9705)	(26.6855, 31.8853)	(3.3929, 5.8006)	(-0.02334, 0.2426)	(20.9167, 25.07)
Sub 5: t-stats	139.211	20.3803	12.7685	7.60711	19.2462	6.94707
p-value	$2.588 * 10^{-16}$	$7.689 * 10^{-9}$	$4.53 * 10^{-7}$	0.000033	$1.273 * 10^{-8}$	$6.706 * 10^{-5}$
CI	(0.9096, 0.9944)	(21.4119, 40.1266)	(12.6268, 36.4484)	(1.8279, 17.9077)	(0.669, 1.3046)	(0.834, 14.6365)
Sub 6: t-stats	255.138	20.1333	141.082	42.6483	19.6094	156.004
p-value	$1.11 * 10^{-18}$	$8.562 * 10^{-9}$	$2.295 * 10^{-16}$	$1.069 * 10^{-11}$	$1.08 * 10^{-8}$	$9.289 * 10^{-17}$
CI	(0.7876, 0.8268)	(15.1611, 28.6474)	(20.058, 25.177)	(2.404, 3.222)	(0.04979, 0.0958)	(19.9736, 21.6264)

Table VIII: Statistical analysis for Model-4

Model 4	α	k_{21}	k_{02}	K_{02}	K_m	d	$l\,(mg/ltr)$
Sub 1: t-stats	110.6	47.7627	15.9269	80.0792	5.74398	37.4839	27.545
p-value	$2.05 * 10^{-15}$	$3.873 * 10^{-12}$	$6.694 * 10^{-8}$	$3.738 * 10^{-14}$	0.000278401	$3.395 * 10^{-11}$	$5.315 * 10^{-10}$
CI	(0.861279, 0.963541)	(20.8152, 27.0229)	(1.33829, 3.04343)	(13.6449, 15.9342)	(-0.30278, 7.96476)	(0.0851594, 0.118901)	(29.8828, 47.2354)
Sub 2: t-stats	483.307	19.2581	6.23111	5.66878	3.4361	8.54934	10.5238
p-value	$3.538 * 10^{-21}$	$1.2669 * 10^{-8}$	0.000153051	0.0003062	0.00743619	$1.297 * 10^{-5}$	$2.335 * 10^{-6}$
CI	(0.950246, 0.974934)	(24.3772, 47.5147)	(0.0286753, 10.7479)	(-1.77352, 39.7713)	(-1.56391, 5.45533)	(0.117727, 0.738353)	(16.122, 62.3196)
Sub 3: t-stats	385.891	13.6853	23.7082	9.06127	7.05812	14.0216	55.9173
p-value	$2.682 * 10^{-20}$	$2.495 * 10^{-7}$	$2.016 * 10^{-9}$	$8.076 * 10^{-6}$	0.000059328	$2.023 * 10^{-7}$	$9.415 * 10^{-13}$
CI	(0.944581, 0.975419)	(11.7632, 31.2381)	(2.15673, 3.68353)	(3.78854, 20.1899)	(1.64234, 25.3099)	(0.0433153, 0.111945)	(34.0354, 42.5211)
Sub 4: t-stats	688.285	30.7622	29.0886	5.31164	9.7271	16.0251	123.686
p-value	$1.468 * 10^{-22}$	$1.985 * 10^{-10}$	$3.27 * 10^{-10}$	0.00048632	$4.502 * 10^{-6}$	$6.345 * 10^{-8}$	$7.498 * 10^{-16}$
CI	(0.939741, 0.956819)	(21.1175, 31.774)	(2.42918, 3.74464)	(-1.43053, 18.5769)	(5.01187, 22.6157)	(0.0484579, 0.109582)	(37.3622, 41.3042)
Sub 5: t-stats	180.115	11.5822	5.5844	8.04798	10.7219	7.97626	29.8344
p-value	$2.549 * 10^{-17}$	$1.04 * 10^{-6}$	0.00034102	$2.11 * 10^{-5}$	$1.997 * 10^{-6}$	$2.266 * 10^{-5}$	$2.609 * 10^{-10}$
CI	(0.928597, 0.994783)	(11.8097, 38.9983)	(-0.589582, 11.3218)	(4.39325, 33.8297)	(5.07958, 18.9979)	(0.113417, 0.904003)	(28.6234, 43.6346)
Sub 6: t-stats	86.8778	32.5366	5.38366	16.2776	7.41463	10.8735	40.2908
p-value	$1.797 * 10^{-14}$	$1.203 * 10^{-10}$	0.000442371	$5.536 * 10^{-8}$	$4.04 * 10^{-5}$	$1.774 * 10^{-6}$	$1.779 * 10^{-11}$
CI	(0.779275, 0.899005)	(22.6643, 33.3309)	(-0.142279, 2.02362)	(19.3868, 43.2288)	(0.573825, 6.42014)	(0.0317722, 0.116008)	(31.5271, 42.9901)

Appendix

Nomenclature

Symbol	Quantity
t	time
FDE	Fractional differential equations
α, β	non-integer order
Γ	Gamma function
$\phi^{(n)}$	n^{th} order derivative of the function
$\mathbb{N}$	set of natural numbers
$\sum$	summation
k_{ij}	drug transfer rate from j^{th} compartment to i^{th} compartment
k_{0j}	drug elimination rate from j^{th} compartment
K_{0j}	drug metabolism rate from j^{th} compartment
K_m	Michaelis-Menten parameter
$[\ ]$	greatest integer not greater than
!	factorial
t_l	time-lag
l	initial concentration in the first compartment at time t_l
τ	upper bound of the time domain
MSE	mean squared error
$\mathbb{R}^2$	set of ordered pairs with real elements
$\|\|\|$	norm of the function in a normed space
sup	supremum
$c_{\max}$	maximum drug concentration in the second compartment
CI	Confidence interval

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