The Design of the New Fractional Block Method in the Solution of the Three-Compartment Pharmacokinetics Model

Nursyazwani Mohamad Noor, Siti Ainor Mohd Yatim and Iskandar Shah Mohd Zawawi

***Abstract*—In this paper, the derivation of the 2-point Fractional Block Backward Differentiation Formula is studied and used to solve the fractional Pharmacokinetics model. The method is developed using the fractional linear multistep method connected to the linear difference operator. The analysis of the method's stability properties confirms that the stability regions appear to be *A*-stable for various values of fractional order α. Numerical results obtained using the proposed method are investigated. Additionally, the impact of fractional order on the quantity of the drug within the human body is examined.**

***Index Terms*—Block Backward Differentiation Formula (BBDF); Fractional order; stability; Pharmacokinetics Model;**

I. Introduction

FRACTIONAL differential equations (FDEs) have recently attracted significant attention among researchers, particularly due to their demonstrated applications in various disciplines of science and engineering. The utilization of fractional order differential equations has emerged as a significant approach in the modelling of several physical processes in recent times [1]. The accurate representation of a physical phenomena relies not only on the current moment in time but also on the preceding temporal history. Fractional calculus provides a viable approach to effectively include this historical information into realistic models [2]. Most fractional equations lack exact analytic solutions, necessitating the use of approximation and numerical techniques [3]. In this article, we consider the following system of fractional initial value problems (FIVPs).

$$\begin{aligned} {}^{C}D_{t_0}^{\alpha_i} &= f_i\left(t, y_1, y_2, \ldots, y_m\right), \\ y_i(t_0) &= y_{0,i}, \qquad i = 1, 2, \ldots, m, \end{aligned} \tag{1}$$

where $0 < \alpha_i < 1$ represents the fractional order and ${}^{C}D_{t_0}^{\alpha_i}$ is denoted as the Caputo α derivative operator. One benefit of employing the Caputo derivative is that it guarantees the same beginning states for FDEs as it does for integer order differential equations. This eliminates concerns related to solvability and optimizes the practical application of the Caputo derivative [4]. Thus, the Caputo fractional derivative of $y(t)$ of order α with $t_0 > 0$ is defined as [5]:

$${}^{C}D_{t_0}^{\alpha_i} y(t) = \frac{1}{\Gamma\left(1-\alpha\right)} \int_{t_0}^{t} \frac{y'(\tau)}{(t-\tau)^{\alpha}} d\tau. \tag{2}$$

In modelling an application problem, FDEs are found to be more plausible than integer orders because the former provides a tool for describing memory effects [4]. Among the mathematical models employing FDEs are the SIR Model, the Prey-Predator Model, the Disease Model, and the Pharmacokinetics Model. The pharmacokinetics model is one of the branches of chemical kinetics that studies the process by which a drug is assimilated, distributed, bioavailable, metabolized, and eliminated via the body's biological systems [6]. To explain the diffusion behavior of pharmaceuticals in biological systems, FDEs were included in the pharmacokinetics model. According to studies, FDEs are more applicable and accurate than integral differential equations [7]. For instance, Qiao et al. [7] applied a pharmacokinetics model with the compartment to calculate drug concentration in the body. Numerous mathematical models for the transport of drugs within the body have been intensively explored [8], [9], [10], [11], [12], [13], [14]. In this paper, the fractional mathematical model of drug diffusion presented in [15] will be solved numerically using the proposed method.

The Fractional Linear Multistep Method (FLMM), which is based on Fractional Backward Differentiation Formulas (FBDFs), is one of the most powerful methods for solving FDEs, which were initially described by Lubich [16] for fractional order in $(0, 1)$. Galeone and Garrappa [17] studied the Fractional Backward Differentiation Formula (FBDF) in explicit and implicit ways to solve FDEs. Biala and Jator [18], [19] extended the ideas by developing the k-step continuous FBDF and k-step implicit Adams Methods (IAMs) to approximate the solution of (1). The FBDF will be studied in the block method first proposed by Ibrahim et al. [20], named Block Backward Differentiation Formulas (BBDF). The advantage of the block method is that the numerical solutions will be approximated concurrently at selected points in the block. Most of the BBDF methods were used to solve stiff Ordinary Differential Equations (ODEs) [21], [22], [23], [24], [25], [26], [27]. Since the BBDF method is widely used and has been demonstrated to be effective for solving ODEs, we are motivated to extend the concepts by adapting the method to solve the fractional model.

In this paper, the Fractional Block Backward Differentiation Formula (FBBDF) will be described in Section II. In Section III, we investigate the convergence and stability

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properties of the derived method. Next, the fractional three-compartment of the pharmacokinetics model is presented, and there will be a discussion of the numerical simulations in Section IV. Section V is devoted to the conclusion of this paper.

II. Derivation of the method

This section details the construction of a 2-point Fractional Block Backward Differentiation Formula (2FBBDF). The method is constructed using the general formula of fractional Linear Multistep Method (LMM) by Galeone and Garrappa [17] and Block Backward Differential Formula (BBDF) by Ijam et al. [28], and presented as

$$\sum_{j=0}^{4}\gamma_{j,i}y_{n+j-2}=h^{\alpha}\beta_i f_{n+i}, \tag{3}$$

where $\gamma_{j,i}$ and β_i are the real parameters, h^{α} is the step length, and $i=1,2$ for y_{n+1} and y_{n+2}, respectively. Then, we associated the linear difference operator L_h in the case of LMM (3), which is defined by,

$$\begin{aligned}L_h\left[y(t),t,\alpha\right]=&\sum_{j=0}^{4}\gamma_{j,i}y_{n+j-2}-h^{\alpha}\beta_i f_{n+i}\\=&\sum_{j=0}^{4}\gamma_{j,i}y_{n+j-2}-h^{\alpha}\beta_i^{C}D_{t_0}^{\alpha}y_{n+i}\\=&\gamma_{0,i}y_{n-2}+\gamma_{1,i}y_{n-1}+\gamma_{2,i}y_n\\&+\gamma_{3,i}y_{n+1}+\gamma_{4,i}y_{n+2}\\&-h^{\alpha}\beta_i^{C}D_{t_0}^{\alpha}y_{n+i}.\end{aligned} \tag{4}$$

Expanding y_{n+j-2} and ${}^{C}D_{t_0}^{\alpha}y_{n+i}$ using Taylor's series expansion about t, we have

$$\begin{aligned}y_{n+j-2}=&y(t_n)+\sum_{k=1}^{m}\frac{(j-2)^k h^k}{k!}y^{(k)}(t_n)+\\&\frac{h^{m+1}}{m!}\\&\int_0^{n-j}(n-s)^m\,y^{(m+1)}\left(t_n+sh\right)ds,\\{}^{C}D_{t_0}^{\alpha}y_{n+i}=&\sum_{k=1}^{m}\frac{(i)^{k-\alpha}h^{k-\alpha}}{\Gamma\left(k+1-\alpha\right)}y^{(k)}(t_n)+\\&\frac{h^{m+1-\alpha}}{\Gamma\left(m+1-\alpha\right)}\\&\int_0^{n-j}(n-s)^m\,y^{(m+1)}\left(t_n+sh\right)ds,\end{aligned} \tag{5}$$

and collecting terms in (5) gives

$$\begin{aligned}L_h\left[y(t),t,\alpha\right]=&C_{0,i}\left(n,\alpha\right)y(t_0)+\\&\sum_{k=1}^{m}h^k C_{k,i}\left(n,\alpha\right)y^{(k)}(t_0)+\\&h^{m+1}R_{m+1},\end{aligned} \tag{6}$$

where the constant $C_{k,i}(n,\alpha)$ is defined as

$$\begin{aligned}C_{0,i}&=\sum_{j=0}^{4}\gamma_{j,i},\\C_{1,i}&=\sum_{j=0}^{4}j\gamma_{j,i}-\frac{1}{\Gamma\left(1+1-\alpha\right)}j^{(1-\alpha)}\beta_i,\\&\vdots\\C_{k,i}&=\sum_{j=0}^{4}\frac{j^k}{k!}\gamma_{j,i}-\frac{1}{\Gamma\left(k+1-\alpha\right)}j^{(k-\alpha)}\beta_i\end{aligned} \tag{7}$$

where $k=2,3,\ldots,m$, $i=1,2$ in (7) are denoted as the first and second points, respectively. The systems of (7) are solved simultaneously to obtain the coefficient values of $\gamma_{j,i}$ and β_i. Therefore, the general corrector formula of the 2FBBDF method is obtained as follows:

$$\begin{aligned}y_{n+1}=&-\frac{\alpha\left(\alpha^2-8\alpha+13\right)}{4\left(2\alpha^3-22\alpha^2+77\alpha-72\right)}y_{n-2}\\&+\frac{\alpha\left(2\alpha^2-14\alpha+21\right)}{2\alpha^3-22\alpha^2+77\alpha-72}y_{n-1}\\&-\frac{3\left(5\alpha^2-35\alpha+48\right)}{2\left(2\alpha^3-22\alpha^2+77\alpha-72\right)}y_n\\&+\frac{\alpha\left(\alpha^2-10\alpha+27\right)}{4\left(2\alpha^3-22\alpha^2+77\alpha-72\right)}y_{n+2}\\&-\frac{3\Gamma\left(5-\alpha\right)}{2\alpha^3-22\alpha^2+77\alpha-72}h^{\alpha}f_{n+1},\\y_{n+2}=&\frac{\alpha\left(\alpha^2-7\alpha-12\right)}{\alpha^3-11\alpha^2+16\alpha+144}y_{n-2}\\&-\frac{8\alpha\left(\alpha^2-5\alpha-8\right)}{\alpha^3-11\alpha^2+16\alpha+144}y_{n-1}\\&+\frac{12\left(5\alpha^2-35\alpha+12\right)}{\alpha^3-11\alpha^2+16\alpha+144}y_n\\&+\frac{8\alpha\left(\alpha^2-13\alpha+48\right)}{\alpha^3-11\alpha^2+16\alpha+144}y_{n+1}\\&+\frac{12(2^{\alpha-1})\Gamma\left(5-\alpha\right)}{\alpha^3-11\alpha^2+16\alpha+144}h^{\alpha}f_{n+2}.\end{aligned} \tag{8}$$

III. Analysis of the method

In this section, the method will be analyzed by determining the order and error constants, the convergence, and the stability properties of the proposed method. We begin with the determination of the order and error constant of the method in the following subsection.

A. Order and Error Constant

By considering the following definition from Zabidi et al. [29], as adapted from Galeone and Garappa [17], the order and error constant of the proposed method are determined.

Definition 1: FLMM is said to be of order p if, $C_0=C_1=\cdots=C_p=0$ and $C_{p+1}\neq 0$. The constant C_p is calculated using the following formula:

$$\begin{aligned}C_p=&\sum_{j=0}^{4}\frac{(j-2)^p}{p!}\gamma_j-\\&\frac{1}{\Gamma\left(p+1-\alpha\right)}\sum_{j=0}^{4}(j-2)^{(p-\alpha)}\,\beta_j,\end{aligned} \tag{9}$$

TABLE I
THE ERROR CONSTANTS OBTAINED FOR EACH VALUE OF α

Error	$\alpha = 0.7$	$\alpha = 0.8$	$\alpha = 0.9$
e_1	$\frac{113323}{4041140}$	$\frac{3679}{102620}$	$\frac{39961}{868380}$
e_2	$-\frac{644854}{10760965}$	$-\frac{1462}{20545}$	$-\frac{284578}{3421655}$

where $p = 0, 1, 2, \ldots$, γ_j and β_j are the coefficients obtained from the proposed method, while $C_{p+1} \neq 0$ is the error constant of the method.

By substituting $\alpha = 0.7$, 0.8 and 0.9 into equation (8), we determined the order and the error constant of the method using equation (9) and obtained the following solutions:

$$\begin{aligned}
C_0 &:= \sum_{j=0}^{4} \gamma_j = \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \\
C_1 &:= \sum_{j=0}^{4} \frac{(j-2)}{1!}\gamma_j - \frac{1}{\Gamma(2-\alpha)} \sum_{j=0}^{4} (j-2)^{(1-\alpha)} \beta_j \\
&= \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \\
C_2 &:= \sum_{j=0}^{4} \frac{(j-2)^2}{2!}\gamma_j - \frac{1}{\Gamma(3-\alpha)} \sum_{j=0}^{4} (j-2)^{(2-\alpha)} \beta_j \\
&= \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \\
C_3 &:= \sum_{j=0}^{4} \frac{(j-2)^3}{3!}\gamma_j - \frac{1}{\Gamma(4-\alpha)} \sum_{j=0}^{4} (j-2)^{(3-\alpha)} \beta_j \\
&= \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \\
C_4 &:= \sum_{j=0}^{4} \frac{(j-2)^4}{4!}\gamma_j - \frac{1}{\Gamma(5-\alpha)} \sum_{j=0}^{4} (j-2)^{(4-\alpha)} \beta_j \\
&= \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \\
C_5 &:= \sum_{j=0}^{4} \frac{(j-2)^5}{5!}\gamma_j - \frac{1}{\Gamma(6-\alpha)} \sum_{j=0}^{4} (j-2)^{(5-\alpha)} \beta_j \\
&= \begin{bmatrix} e_1 \\ e_2 \end{bmatrix} \neq \begin{bmatrix} 0 \\ 0 \end{bmatrix},
\end{aligned} \tag{10}$$

where e_1 and e_2 represent the error constants for y_{n+1} and y_{n+2} respectively. Table I presents the error constants obtained from the solutions in equation (10).

Therefore, we conclude that the method is an order 4 with the error constants at C_5 as presented in Table I.

B. Convergence of the Method

Theorem 1: Let there be a constant L where the coordinates (t, y, y^*) and (t, y^*) for every t, y, y^* are both in R such that

$$|f(t, y) - f(t, y^*)| \leq L\,|y - y^*|\,. \tag{11}$$

By letting $f(t, y)$ be Lipschitz continuous at all points (t, y) in the region R, given by

$$a \leq t \leq b, \qquad -\infty < y < \infty, \tag{12}$$

such that a and b are finite.

Theorem 2: If all IVPs subject to Theorem 1 as $t \in [a, b]$ and $\alpha \in (0, 1)$, then equation (8) is said to be convergent, such that

$$|y - y^*| \leq K.t^{\alpha-1}h^p, \tag{13}$$

where K is a constant that is solely dependent on α and p as $p \in (0, 1)$, and

$$\lim_{h \to 0} y_i = y^*(t_i). \tag{14}$$

Proof: Recalling the proposed method (8), we have

$$\begin{aligned}
y_{n+1} =& -\frac{\alpha\left(\alpha^2 - 8\alpha + 13\right)}{4\left(2\alpha^3 - 22\alpha^2 + 77\alpha - 72\right)} y_{n-2} + \\
& \frac{\alpha\left(2\alpha^2 - 14\alpha + 21\right)}{2\alpha^3 - 22\alpha^2 + 77\alpha - 72} y_{n-1} - \\
& \frac{3\left(5\alpha^2 - 35\alpha + 48\right)}{2\left(2\alpha^3 - 22\alpha^2 + 77\alpha - 72\right)} y_n + \\
& \frac{\alpha\left(\alpha^2 - 10\alpha + 27\right)}{4\left(2\alpha^3 - 22\alpha^2 + 77\alpha - 72\right)} y_{n+2} - \\
& \frac{3\Gamma(5-\alpha)}{2\alpha^3 - 22\alpha^2 + 77\alpha - 72} h^\alpha f_{n+1}, \\
y_{n+2} =& \frac{\alpha\left(\alpha^2 - 7\alpha - 12\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144} y_{n-2} - \\
& \frac{8\alpha\left(\alpha^2 - 5\alpha - 8\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144} y_{n-1} + \\
& \frac{12\left(5\alpha^2 - 35\alpha + 12\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144} y_n + \\
& \frac{8\alpha\left(\alpha^2 - 13\alpha + 48\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144} y_{n+1} + \\
& \frac{12(2^{\alpha-1})\Gamma(5-\alpha)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144} h^\alpha f_{n+2}.
\end{aligned} \tag{15}$$

Referring to equation (15), we let

$$\begin{aligned}
A_1 &= -\frac{\alpha\left(\alpha^2 - 8\alpha + 13\right)}{4\left(2\alpha^3 - 22\alpha^2 + 77\alpha - 72\right)}, \\
A_2 &= \frac{\alpha\left(2\alpha^2 - 14\alpha + 21\right)}{2\alpha^3 - 22\alpha^2 + 77\alpha - 72}, \\
A_3 &= -\frac{3\left(5\alpha^2 - 35\alpha + 48\right)}{2\left(2\alpha^3 - 22\alpha^2 + 77\alpha - 72\right)}, \\
A_4 &= \frac{\alpha\left(\alpha^2 - 10\alpha + 27\right)}{4\left(2\alpha^3 - 22\alpha^2 + 77\alpha - 72\right)}, \\
A_5 &= -\frac{3\Gamma(5-\alpha)}{2\alpha^3 - 22\alpha^2 + 77\alpha - 72}, \\
B_1 &= \frac{\alpha\left(\alpha^2 - 7\alpha - 12\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144}, \\
B_2 &= -\frac{8\alpha\left(\alpha^2 - 5\alpha - 8\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144}, \\
B_3 &= \frac{12\left(5\alpha^2 - 35\alpha + 12\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144}, \\
B_4 &= \frac{8\alpha\left(\alpha^2 - 13\alpha + 48\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144}, \\
B_5 &= \frac{12(2^{\alpha-1})\Gamma(5-\alpha)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144}.
\end{aligned} \tag{16}$$

1) For the exact form of the system, we have

$$\begin{aligned} y_{n+1} =& A_1 y_{n-2} + A_2 y_{n-1} + A_3 y_n + A_4 y_{n+2} \\ &+ A_5 h^\alpha f(t_{n+1}, y_{n+1}) + e_1 h^5 y^{(5)}(\xi), \\ y_{n+2} =& B_1 y_{n-2} + B_2 y_{n-1} + B_3 y_n + B_4 y_{n+1} \\ &+ B_5 h^\alpha f(t_{n+2}, y_{n+2}) + e_2 h^5 y^{(5)}(\xi). \end{aligned} \tag{17}$$

2) For the approximate form of the system, we have

$$\begin{aligned} y^*_{n+1} =& A_1 y^*_{n-2} + A_2 y^*_{n-1} + A_3 y^*_n + A_4 y^*_{n+2} \\ &+ A_5 h^\alpha f(t_{n+1}, y^*_{n+1}), \\ y^*_{n+2} =& B_1 y^*_{n-2} + B_2 y^*_{n-1} + B_3 y^*_n + B_4 y^*_{n+1} \\ &+ B_5 h^\alpha f(t_{n+2}, y^*_{n+2}). \end{aligned} \tag{18}$$

Considering

$$\lim_{h\to 0} y_{n+1} = y^*_{n+1} \quad \text{and} \quad \lim_{h\to 0} y_{n+2} = y^*_{n+2}, \tag{19}$$

as the convergent criteria for the approximate solutions, the result obtained by subtracting equation (17) from equation (18) is

$$\begin{aligned} y_{n+1} - y^*_{n+1} =& A_1 \left[y_{n-2} - y^*_{n-2}\right] + A_2 \left[y_{n-1} - y^*_{n-1}\right] \\ &+ A_3 \left[y_n - y^*_n\right] + A_4 \left[y_{n+2} - y^*_{n+2}\right] + \\ &A_5 h^\alpha \left[f(t_{n+1}, y_{n+1}) - f(t_{n+1}, y^*_{n+1})\right] \\ &+ e_1 h^5 y^{(5)}(\xi), \\ y_{n+2} - y^*_{n+2} =& B_1 \left[y_{n-2} - y^*_{n-2}\right] + B_2 \left[y_{n-1} - y^*_{n-1}\right] \\ &+ B_3 \left[y_n - y^*_n\right] + B_4 \left[y_{n+1} - y^*_{n+1}\right] + \\ &B_5 h^\alpha \left[f(t_{n+2}, y_{n+2}) - f(t_{n+2}, y^*_{n+2})\right] \\ &+ e_2 h^5 y^{(5)}(\xi). \end{aligned} \tag{20}$$

Denoting that $|y_{n+j} - y^*_{n+j}| = |d_{n+j}|$ where $j = -2, -1, 0, 1, 2$, Theorem 1 is applied in equation (20), which yields:

1) For the first point:

$$\begin{aligned} |d_{n+1}| \leq& A_1 |d_{n-2}| + A_2 |d_{n-1}| + \\ &A_3 |d_n| + A_4 |d_{n+2}| + \\ &A_5 h^\alpha L |d_{n+1}| + \\ &e_1 h^5 R, \\ (1 - A_5 h^\alpha L) |d_{n+1}| \leq& A_1 |d_{n-2}| + A_2 |d_{n-1}| + \\ &A_3 |d_n| + A_4 |d_{n+2}| + \\ &e_1 h^5 R. \end{aligned} \tag{21}$$

2) For the second point:

$$\begin{aligned} |d_{n+2}| \leq& B_1 |d_{n-2}| + B_2 |d_{n-1}| + \\ &B_3 |d_n| + B_4 |d_{n+1}| + \\ &B_5 h^\alpha L |d_{n+2}| + \\ &e_2 h^5 R, \\ (1 - B_5 h^\alpha L) |d_{n+2}| \leq& B_1 |d_{n-2}| + B_2 |d_{n-1}| + \\ &B_3 |d_n| + B_4 |d_{n+1}| + \\ &e_2 h^5 R, \end{aligned} \tag{22}$$

where $R = \max_{a\leq t\leq b} |y^{(5)}(t)|$. Rewriting equations (21) and (22) based on Theorem 2 will give

$$\begin{aligned} (1 - Kh^\alpha) |d_{n+1}| \leq& A_1 |d_{n-2}| + A_2 |d_{n-1}| + \\ &A_3 |d_n| + A_4 |d_{n+2}| + \\ &e_1 h^5 R, \\ (1 - Kh^\alpha) |d_{n+2}| \leq& B_1 |d_{n-2}| + B_2 |d_{n-1}| + \\ &B_3 |d_n| + B_4 |d_{n+1}| + \\ &e_2 h^5 R. \end{aligned} \tag{23}$$

Based on the above calculation, $|d_{n+j}| \leq |d_n|$ when h is approaching zero, it implies that $y^*_{n+j} - y^*_n \leq y_{n+j} - y_n$ for $j = 1, 2$. Therefore, we can conclude that the proposed method converges since the conditions in equation (19) are satisfied. ■

C. Stability of the Method

In this subsection, we will examine the stability of the 2FBBDF method (8) for $\alpha \in (0, 1)$ by analyzing the following linear test problem.

$$\begin{aligned} D^\alpha y(t) &= \lambda y(t), \quad \lambda \in \mathbb{C}, \quad 0 < \alpha < 1, \\ y(t_0) &= y_0, \end{aligned} \tag{24}$$

where $y(t) = E_\alpha\left(\lambda (t - t_0)^\alpha\right) y_0$ represents the precise solution and which can be mathematically represented using the Mittag-Leffler function:

$$E_\alpha(t) = \sum_{k=0}^{\infty} \left(\frac{t^k}{\Gamma(\alpha k + 1)}\right). \tag{25}$$

Equation (24) is then substituted into the corrector formula (8), which resulted in the stability polynomial of

$$\begin{aligned} y_{n+1} =& -\frac{\alpha\left(\alpha^2 - 8\alpha + 13\right)}{4\left(2\alpha^3 - 22\alpha^2 + 77\alpha - 72\right)} y_{n-2} \\ &+ \frac{\alpha\left(2\alpha^2 - 14\alpha + 21\right)}{2\alpha^3 - 22\alpha^2 + 77\alpha - 72} y_{n-1} \\ &- \frac{3\left(5\alpha^2 - 35\alpha + 48\right)}{2\left(2\alpha^3 - 22\alpha^2 + 77\alpha - 72\right)} y_n \\ &+ \frac{\alpha\left(\alpha^2 - 10\alpha + 27\right)}{4\left(2\alpha^3 - 22\alpha^2 + 77\alpha - 72\right)} y_{n+2} \\ &- \frac{3\Gamma(5 - \alpha)}{2\alpha^3 - 22\alpha^2 + 77\alpha - 72} \bar{h} f_{n+1}, \\ y_{n+2} =& \frac{\alpha\left(\alpha^2 - 7\alpha - 12\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144} y_{n-2} \\ &- \frac{8\alpha\left(\alpha^2 - 5\alpha - 8\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144} y_{n-1} \\ &+ \frac{12\left(5\alpha^2 - 35\alpha + 12\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144} y_n \\ &+ \frac{8\alpha\left(\alpha^2 - 13\alpha + 48\right)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144} y_{n+1} \\ &+ \frac{12(2^{\alpha-1})\Gamma(5 - \alpha)}{\alpha^3 - 11\alpha^2 + 16\alpha + 144} \bar{h} f_{n+2}, \end{aligned} \tag{26}$$

where $\bar{h} = h^\alpha \lambda$. Rearranging equation (26) into a matrix

form yields

$$\begin{bmatrix} 1+\frac{3\Gamma(5-\alpha)}{2\alpha^3-22\alpha^2+77\alpha-72}\bar{h} & -\frac{\alpha(\alpha^2-10\alpha+27)}{4(2\alpha^3-22\alpha^2+77\alpha-72)} \\ -\frac{8\alpha(\alpha^2-13\alpha+48)}{\alpha^3-11\alpha^2+16\alpha+144} & 1-\frac{12(2^{\alpha-1})\Gamma(5-\alpha)}{\alpha^3-11\alpha^2+16\alpha+144}\bar{h} \end{bmatrix} \begin{bmatrix} y_{n+1} \\ y_{n+2} \end{bmatrix}$$
$$= \begin{bmatrix} \frac{\alpha(2\alpha^2-14\alpha+21)}{2\alpha^3-22\alpha^2+77\alpha-72} & -\frac{3(5\alpha^2-35\alpha+48)}{2(2\alpha^3-22\alpha^2+77\alpha-72)} \\ -\frac{8\alpha(\alpha^2-5\alpha-8)}{\alpha^3-11\alpha^2+16\alpha+144}y_{n-1} & \frac{12(5\alpha^2-35\alpha+12)}{\alpha^3-11\alpha^2+16\alpha+144} \end{bmatrix} \begin{bmatrix} y_{n-1} \\ y_n \end{bmatrix}$$
$$+ \begin{bmatrix} 0 & -\frac{\alpha(\alpha^2-8\alpha+13)}{4(2\alpha^3-22\alpha^2+77\alpha-72)} \\ 0 & \frac{\alpha(\alpha^2-7\alpha-12)}{\alpha^3-11\alpha^2+16\alpha+144} \end{bmatrix} \begin{bmatrix} y_{n-3} \\ y_{n-2} \end{bmatrix}, \tag{27}$$

which is equivalent to

$$AY_m = BY_{m-1} + CYm - 2, \tag{28}$$

where

$$A = \begin{bmatrix} 1+\frac{3\Gamma(5-\alpha)}{2\alpha^3-22\alpha^2+77\alpha-72}\bar{h} & -\frac{\alpha(\alpha^2-10\alpha+27)}{4(2\alpha^3-22\alpha^2+77\alpha-72)} \\ -\frac{8\alpha(\alpha^2-13\alpha+48)}{\alpha^3-11\alpha^2+16\alpha+144} & 1-\frac{12(2^{\alpha-1})\Gamma(5-\alpha)}{\alpha^3-11\alpha^2+16\alpha+144}\bar{h} \end{bmatrix},$$
$$B = \begin{bmatrix} \frac{\alpha(2\alpha^2-14\alpha+21)}{2\alpha^3-22\alpha^2+77\alpha-72} & -\frac{3(5\alpha^2-35\alpha+48)}{2(2\alpha^3-22\alpha^2+77\alpha-72)} \\ -\frac{8\alpha(\alpha^2-5\alpha-8)}{\alpha^3-11\alpha^2+16\alpha+144}y_{n-1} & \frac{12(5\alpha^2-35\alpha+12)}{\alpha^3-11\alpha^2+16\alpha+144} \end{bmatrix},$$
$$C = \begin{bmatrix} 0 & -\frac{\alpha(\alpha^2-8\alpha+13)}{4(2\alpha^3-22\alpha^2+77\alpha-72)} \\ 0 & \frac{\alpha(\alpha^2-7\alpha-12)}{\alpha^3-11\alpha^2+16\alpha+144} \end{bmatrix}, \quad Y_{m-2} = \begin{bmatrix} y_{n-3} \\ y_{n-2} \end{bmatrix},$$
$$Y_m = \begin{bmatrix} y_{n+1} \\ y_{n+2} \end{bmatrix}, \quad Y_{m-1} = \begin{bmatrix} y_{n-1} \\ y_n \end{bmatrix}. \tag{29}$$

From equation (29), we calculate the stability polynomial of the method by using the formula

$$\pi(t;\bar{h}) = \det(At^2 - Bt - C), \tag{30}$$

where t denotes the root of equation (30), yielding

$$\pi(t;\bar{h}) = \det(At^2 - Bt - C)$$
$$= \det\left(\begin{bmatrix} 1+\frac{3\Gamma(5-\alpha)}{2\alpha^3-22\alpha^2+77\alpha-72}\bar{h} & -\frac{\alpha(\alpha^2-10\alpha+27)}{4(2\alpha^3-22\alpha^2+77\alpha-72)} \\ -\frac{8\alpha(\alpha^2-13\alpha+48)}{\alpha^3-11\alpha^2+16\alpha+144} & 1-\frac{12(2^{\alpha-1})\Gamma(5-\alpha)}{\alpha^3-11\alpha^2+16\alpha+144}\bar{h} \end{bmatrix} t^2 - \begin{bmatrix} \frac{\alpha(2\alpha^2-14\alpha+21)}{2\alpha^3-22\alpha^2+77\alpha-72} & -\frac{3(5\alpha^2-35\alpha+48)}{2(2\alpha^3-22\alpha^2+77\alpha-72)} \\ -\frac{8\alpha(\alpha^2-5\alpha-8)}{\alpha^3-11\alpha^2+16\alpha+144}y_{n-1} & \frac{12(5\alpha^2-35\alpha+12)}{\alpha^3-11\alpha^2+16\alpha+144} \end{bmatrix} t - \begin{bmatrix} 0 & -\frac{\alpha(\alpha^2-8\alpha+13)}{4(2\alpha^3-22\alpha^2+77\alpha-72)} \\ 0 & \frac{\alpha(\alpha^2-7\alpha-12)}{\alpha^3-11\alpha^2+16\alpha+144} \end{bmatrix} \right). \tag{31}$$

From equation (31), we plotted the stability regions of the method for different values of α by using Maple software, presenting it as Figure 1. Referring to the definitions from Lambert [30], we investigated the stability region of the method.

Based on Figure 1, the unstable regions are presented inside the circles, while the regions outside the circles represent the stable regions of the method. Next, we ran a few numerical tests to verify the stability region of the graphs in Figure 1. We found that method (8) with $\alpha = 0.7, 0.8$ and 0.9 are the A-stable and $\alpha = 1.0$ is the $A(\mu)$-stable for μ at 0° (see [30]).

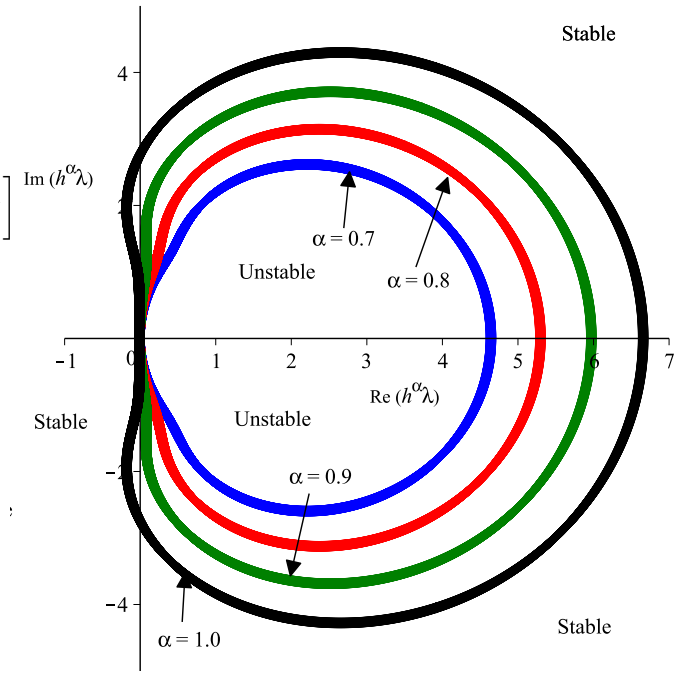

Fig. 1. Stability regions for 2FBBDF with different fractional order, α

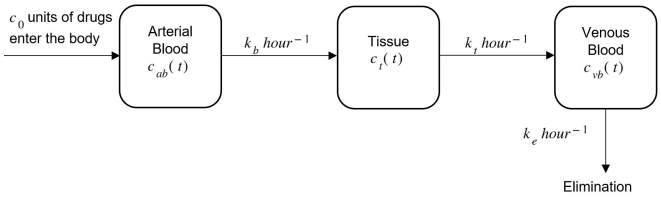

Fig. 2. Mechanism of intravenous drug administration in the three-compartment pharmacokinetics model

IV. Mathematical Model

This section describes the fractional three-compartment pharmacokinetics model depicted in Figure 2 [13]. The concentration of drugs is denoted as c_{ab} in Compartment 1 (arterial blood), c_t in Compartment 2 (tissue), and c_{vb} in Compartment 3 (venous blood).

According to Khanday et al. [13], medication delivery via venous blood follows the pattern shown in Figure 2 because blood flow in the cardiovascular system is unidirectional. Therefore, the fractional mathematical formulation based on Figure 2 is presented as

$$\begin{aligned} {}^{C}D^{\alpha_1}c_{ab} &= -k_b c_{ab}(t), \\ {}^{C}D^{\alpha_2}c_t &= k_b c_{ab}(t) - k_t c_t(t), \\ {}^{C}D^{\alpha_3}c_{vb} &= k_t c_t(t) - k_e c_{vb}(t), \end{aligned} \tag{32}$$

where the flow rate of the drug from Compartment 1 to Compartment 2 is represented by k_b and from Compartment 2 to Compartment 3 by k_t, while the elimination rate is denoted by k_e with the given starting conditions

$$c_{ab,0} = c_0 \geq 0, \qquad c_{t,0} = 0, \qquad c_{vb,0} = 0. \tag{33}$$

As presented in [28], the exact solution of the model (32) is

TABLE II
PARAMETER VALUE IN THE FRACTIONAL PHARMACOKINETICS MODEL

Parameter	Description	Case 1	Case 2
$c_{ab,0}$	The beginning state of the drug's concentration in the arterial blood	500	500
$c_{t,0}$	The beginning state of the drug's concentration in the tissue	0	0
$c_{vb,0}$	The beginning state of the drug's concentration in the venous blood	0	0
k_b	The amount of drug transferred from Compartment 1 to Compartment 2	0.9776	0.5000
k_t	The amount of drug consume between Compartment 2 and Compartment 3	0.3293	0.2500
k_e	Drugs elimination rates from the blood	0.2213	0.0500

obtained as follows:

$$\begin{aligned} c_{ab}(t) =& c_0 e^{-k_b t}, \\ c_t(t) =& \frac{c_0 k_b}{k_b - k_t}\left(e^{-k_t t} - e^{-k_b t}\right), \\ c_{vb}(t) =& c_0 k_b k_t \left(\frac{e^{-k_t t}}{(k_b - k_t)(k_e - k_t)}\right) - \\ & c_0 k_b k_t \left(\frac{e^{-k_b t}}{(k_b - k_t)(k_e - k_b)}\right) + \\ & c_0 k_b k_t \left(\frac{e^{-k_e t}}{(k_e - k_t)(k_e - k_b)}\right). \end{aligned} \tag{34}$$

Then, we solved the model (32) by using the proposed method (8) and the numerical simulations were demonstrated. There is a limitation in method comparison, and the results obtained will be compared with the method in MATLAB solver fde12.m (FDE12) that was established by Garrappa [31] for a significant numerical comparison. The numerical simulations will be plotted together to be compared. The behavior of drug concentration is studied by considering the rate constant as presented in [13] and noting that the value of $k_e < k_t < k_b$. The two cases of rate constants are considered in this study and presented in Table II.

We examine the behavior of the drug concentration in the model with various constant rates based on Table II. As presented in Figure 3, the dashed line represents Case 1 while the solid line represents Case 2. According to the graph, the constant rate with $k \in [0.2213, 0.9776]$ results in quicker drug absorption in the blood vessel than $k \in [0.0500, 0.500]$.

In the subsequent numerical simulations, Case 1 is considered because the rate of drug absorption in the three compartments is speedier than in Case 2. Using the data in Table II, the model (32) was computed using C programming, and the error was calculated using the following formula.

$$error_i = |y_i(t) - y_i(t_n)|, \tag{35}$$

where $y_i(t)$ and $y_i(t_n)$ are the exact solution and the approximate solution, respectively. Then, the maximum error,

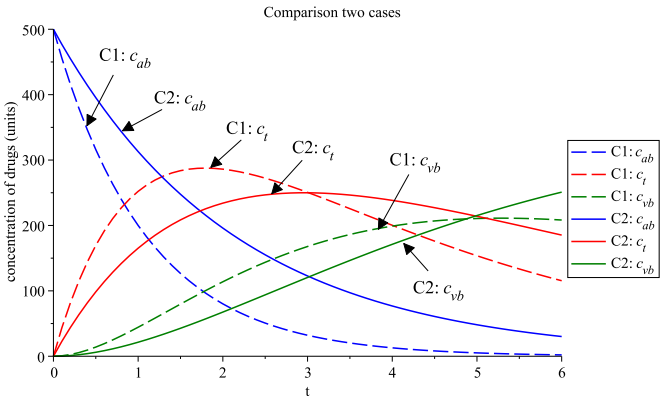

Fig. 3. Drug concentration rate in the three compartments solved using the 2FBBDF method with $\alpha = 0.9$

MAXE, is calculated as

$$MAXE = \max_{0 \le i \le NS} (error_i), \tag{36}$$

where NS is the step number and the average error, AVE, is determined by

$$AVE = \frac{\sum_{i=0}^{NS} (error_i)}{NS}, \tag{37}$$

In order to validate the proposed numerical method, subsequent simulations were plotted using the MAPLE software. We set the step size, $h = 0.01$, and time, $t \in [0, 6]$ hours to generate data for the surveillance of drug behavior in the body within six hours. Then, we analyzed the influence of the fractional order α on the drug concentration in each of the three compartments. Within six hours, the drug concentration in arterial blood decreases from 500 units to zero units, as depicted in Figure 4. As shown in Figure 4, the approximate value of c_{ab} approaches 0 units fastest at $\alpha = 0.9$, followed by $\alpha = 0.8$ and 0.7. Figure 5 depicts the concentration of the drug in the tissue when absorbed from the arterial blood. As demonstrated in the figure, the concentration of the drug in the tissue begins to rise between 0 to 2 hours and then gradually decreases to 0 units after two hours. Thus, the targeted tissue reacted to the drug positively. In Figure 6, we plotted the concentration of the drug in the venous blood and analyzed the pattern of the graphs. As shown in Figure 6, c_{vb} reaches the peak at $t \in (4, 5)$ hours. This demonstrates that the compartments responded favorably to the drug within six hours, which is the timeframe doctors advise. After six hours, the concentrations of the drug in the three compartments would gradually be cleared from the blood via the liver and kidneys.

Next, a comparison is made between the 2FBBDF method and FDE12 by Garrappa [31] in terms of the approximation values for the three compartments. The model (32) is solved using the methods of comparison with $\alpha = 0.7$, 0.8, and 0.9, and its numerical simulations are presented in Figures 7-9. As shown in the figures, we discovered that the amount of drugs in the body is absorbed and excreted more rapidly with the 2FBBDF method than with FDE12.

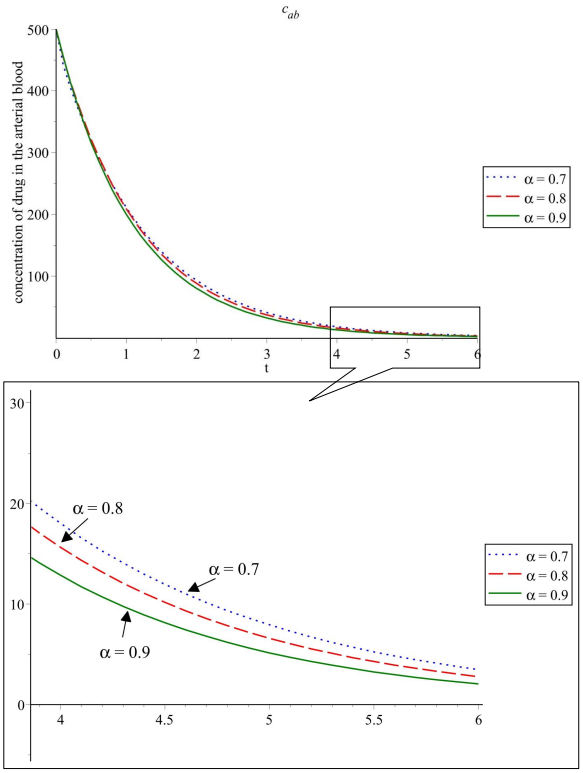

Fig. 4. The amount of drugs in the arterial blood with varying values of α solved using the 2FBBDF method

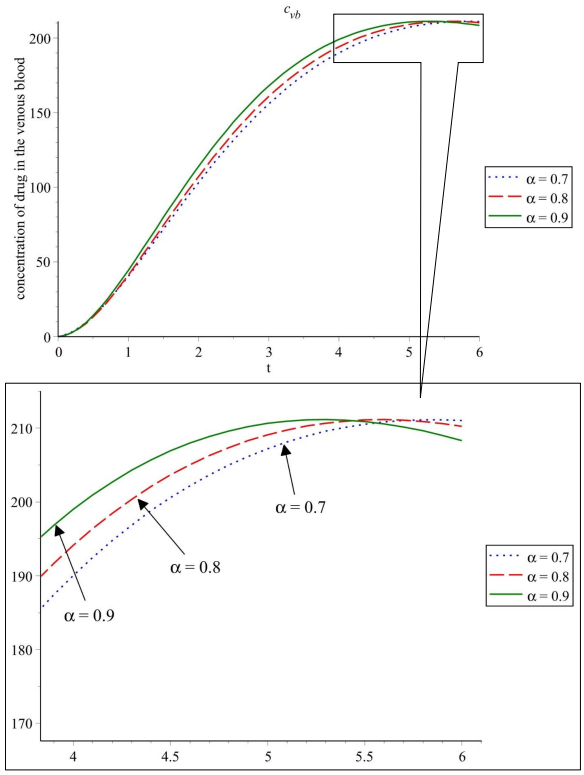

Fig. 6. The amount of drugs in the venous blood with varying values of α solved using the 2FBBDF method.

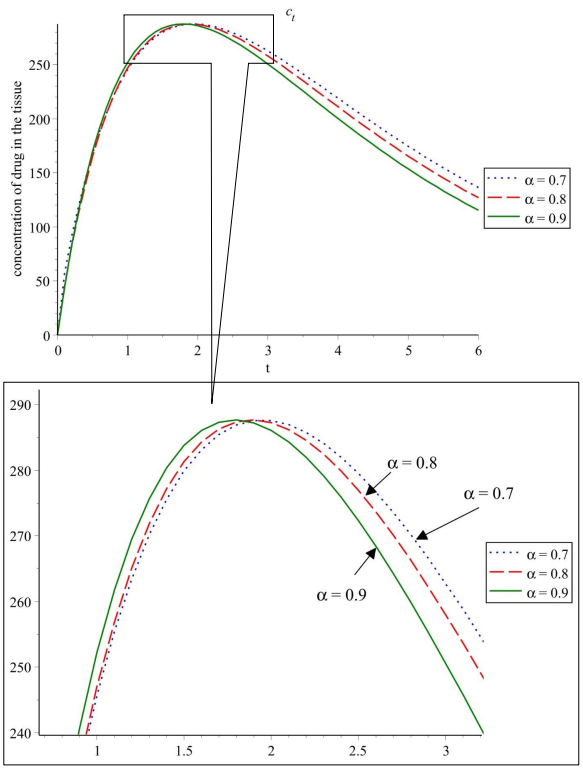

Fig. 5. The amount of drugs in the tissue with varying values of α solved using the 2FBBDF method.

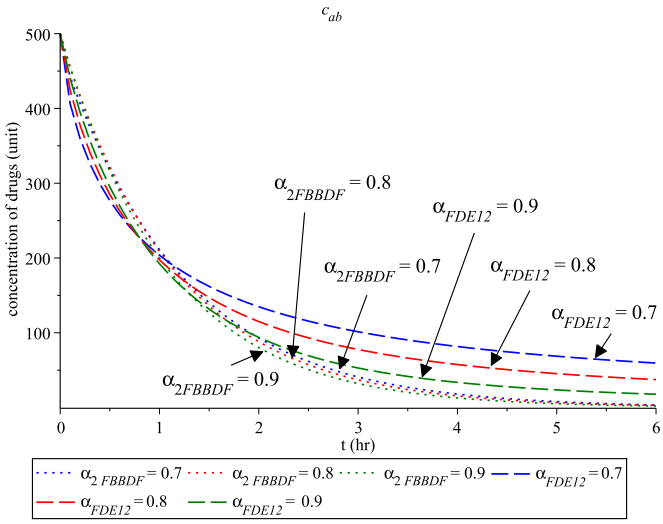

Fig. 7. The amount of drugs in the arterial blood with varying values of α solved using the 2FBBDF method and FDE12

The fractional model (32) is solved using the 2FBBDF method with $\alpha_1 = \alpha_2 = \alpha_3 = 1$, and the numerical results obtained are presented in Table III, which consist of the step size (h), MAXE, AVE, and the computational time (TIME). Based on the table, the MAXE and AVE decreases as the step size, h decreases, except for the AVE at h = 1E-06, where the tolerance error of E-07 indicates that the maximum improvement limit has been reached at that h. However, as the error falls within the tolerance, the outcome is still acceptable. In terms of the computational time, TIME, the process becomes slower as the step size, h gets smaller, because the number of iterations, i, increases as the value of h decreases. Subsequently, the approximation values generated from the 2FBBDF and FDE12 methods are compared with the precise solution and displayed in Table IV. It is evident that the 2FBBDF technique exhibits a high degree of similarity to the exact answer, in comparison

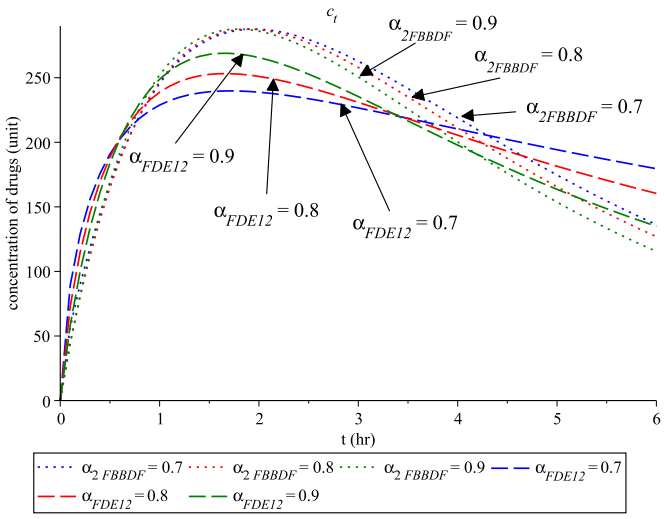

Fig. 8. The amount of drugs in the tissue with varying values of α solved using the 2FBBDF method and FDE12

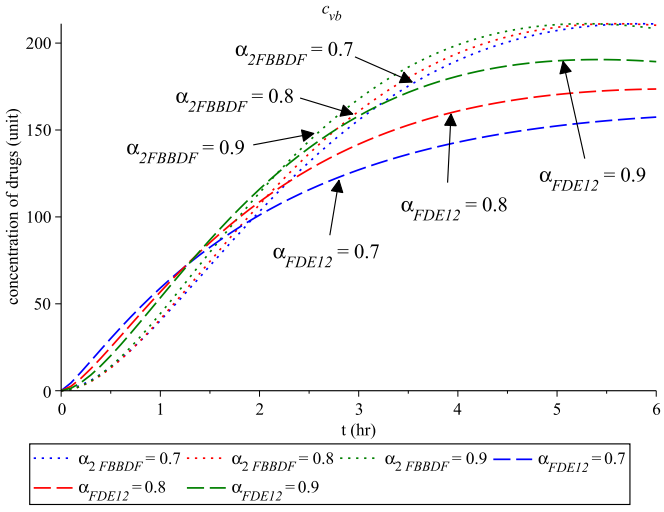

Fig. 9. The amount of drugs in the venous blood with varying values of α solved using the 2FBBDF method and FDE12

TABLE III
NUMERICAL RESULTS FOR THE FRACTIONAL MODEL (32) SOLVED USING 2FBBDF AS $\alpha_1 = \alpha_2 = \alpha_3 = 1$

h	MAXE	AVE	TIME
1E-02	1.32154E-01	4.08596E-02	5.72897E-04
1E-03	1.37676E-03	4.23639E-04	1.09864E-03
1E-04	1.38239E-05	4.25766E-06	2.40807E-03
1E-05	1.38295E-07	4.46724E-08	5.54929E-03
1E-06	1.06907E-07	1.06170E-07	3.52063E-02

to the FDE12 method. The behavior of the exact solution, the 2FBBDF method, and the FDE12 are illustrated in Figures 10-12. The curves are plotted with the value of $\alpha_1 = \alpha_2 = \alpha_3 = 1$ and with the value of $h = 0.1$. From the analysis, the approximate solution of the 2FBBDF method is plotted closely to the exact solution as $\alpha_1 = \alpha_2 = \alpha_3 = 1$ compared to the FDE12. Therefore, the 2FBBDF method is the most appropriate method for solving the model (32).

TABLE IV
METHOD OF COMPARISON FOR THE FRACTIONAL MODEL (32) AS $\alpha_1 = \alpha_2 = \alpha_3 = 1$

t	Method	c_{ab}	c_t	c_{vb}
0	FDE12	500.000	0.000	0.000
	2FBBDF	500.000	0.000	0.000
	Exact	500.000	0.000	0.000
1	FDE12	188.422	258.331	49.151
	2FBBDF	306.297	170.100	23.199
	Exact	303.265	172.270	24.037
2	FDE12	71.006	283.212	122.521
	2FBBDF	185.779	238.006	73.455
	Exact	183.940	238.651	74.574
3	FDE12	26.758	240.449	176.007
	2FBBDF	112.680	249.367	130.102
	Exact	111.565	249.236	131.217
4	FDE12	10.084	186.821	203.831
	2FBBDF	68.344	233.030	182.921
	Exact	67.668	232.544	183.900
5	FDE12	3.800	139.622	211.081
	2FBBDF	41.040	204.420	228.308
	Exact	41.047	204.426	228.298
6	FDE12	1.432	102.417	204.470
	2FBBDF	24.892	173.343	263.206
	Exact	24.896	173.349	263.198

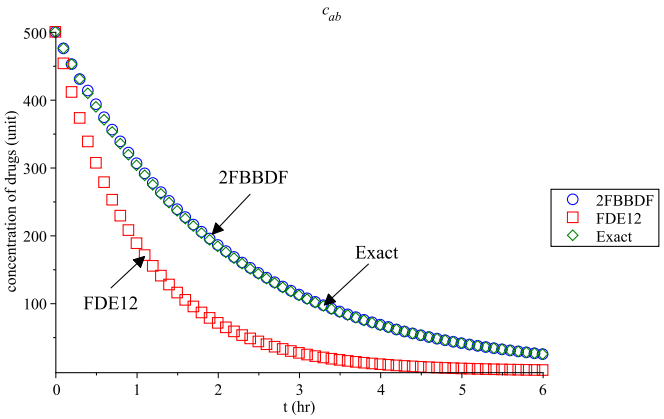

Fig. 10. The behavior of the amount of drugs in the arterial blood as $\alpha_1 = 1$ and $h = 0.1$.

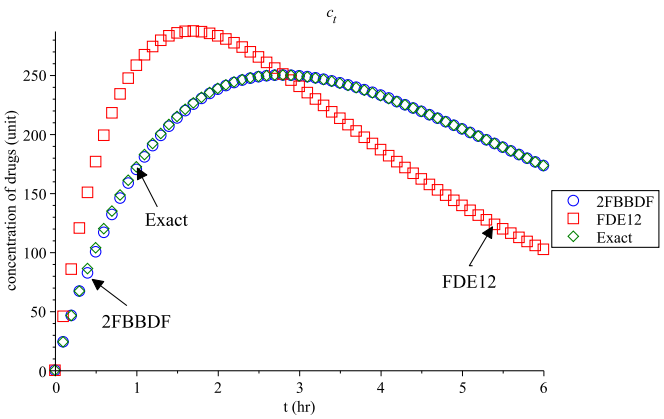

Fig. 11. The behavior of the amount of drugs in the tissue as $\alpha_2 = 1$ and $h = 0.1$.

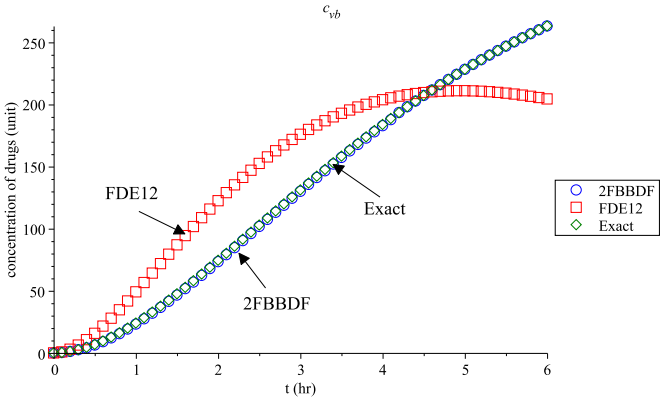

Fig. 12. The behavior of the amount of drugs in the venous blood as $\alpha_3 = 1$ and $h = 0.1$.

V. Conclusion

In this paper, the 2-point Fractional Block Backward Differentiation Formula (2FBBDF) is introduced as a new numerical method that can be used to solve both fractional-order and integer order problems. The stability analysis verifies that the derived method (8) for the fractional order α is convergent and A-stable. Using the 2FBBDF method, the fractional pharmacokinetics model with three compartments (32) was solved. Using the 2FBBDF method, the drug concentration in the three compartments will be excreted from the kidney (approaching zero units) faster when the fractional order, α is greater. Furthermore, the 2FBBDF approach is superior to the FDE12 method proposed by Garrappa [31] for solving model (32). In addition, when $\alpha = 1.0$, the 2FBBDF method returns defects (MAXE and AVE) within the tolerance h. Due to the memory effects of the models, the fractional order is recommended for solving the dynamical system rather than the integer order, even though the behavior of numerical simulations for all fractional orders is almost identical to that of the integer order. All numerical solutions (Figures 10-12) are validated against theoretic outcomes. Consequently, the proposed method can serve as an alternative solver for other application problems, such as the SIR model and the prey-predator model.

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