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Discretization and Stability Analysis for a Generalized Type Nonlinear Pharmacokinetic Models

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Highlights

- We found the numerical solutions of the distributed order Pharmacokinetic models.
- Nonstandard finite difference method is applied for the solution of this system.
- The numerical results show that the use of distributed order equations is beneficial.

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Abstract

Estimating the effects of drugs at different stages is directly proportional to the duration of recovery and the duration of pulling through with the disease. It is very important to estimate the effects of drugs at different stages. For this reason, solving Pharmacokinetic models which investigate these effects are very important. In this study, numerical solutions of one, two, and three-compartment nonlinear Pharmacokinetic models have been studied. Distributed order differential equations have been used for the solution. Numerical solutions have been found with the density function contained in distributed order differential equations and different values of this function. A nonstandard finite difference scheme has been used for numerical solutions. Finally, stability analyses of equilibrium points of the obtained discretized system have also been researched with the help of the Matignon criterion.

1. INTRODUCTION

Pharmacokinetics is a field of science that studies the effects and behavior of drugs on the human body. Therefore, mathematical modeling of this effect is very important. Thanks to this modeling, effects of drugs at different stages can be predicted in advance. Pharmacokinetic models can be categorized into three different types. These types are compartment, non-compartment, and physiological Pharmacokinetic models [1]. The compartment model is more useful and beneficial in determining the effects of drugs. Because of that, solutions of one, two, and three-compartment Pharmacokinetic models are examined in this study.

The first study that constituted the basics in this field was developed by Michaelis and Menten [2]. In this study, the Michealis-Menten equation was defined and information about the effects of drugs was obtained with the help of such equations. In completion of these studies and developments, Widmark and Tandberg defined a one-compartment Bolus Infusion and Injection model [3]. Holford and Sheiner defined Pharmacokinetics as an area, where the effects of drugs can be measured using mathematical models, and they conducted studies in this direction [4]. After such studies, Pharmacokinetic stood out as an important area and became the subject of different fields of study. One of these fields of study is the numerical solutions of distributed order differential equations, which will be mentioned in this article. For further detailed information about numerical solutions, source numbers [5-9] can be examined.

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But as can be seen from these studies, solutions are usually limited to differential equations modeling from ordinary or fractional orders. This is the reason why the idea of using differential equations from distributed order derivatives stood out in this article. It is the main intended idea to obtain solutions and data regarding effects of drugs determined by using solutions not only by ordinary or fractional differential equations but also in different cases. For these reasons, by using distributed order derivatives in this type of modeling, it is possible to comment on more than one type of equation by considering a single equation as a ground because distributed order differential equations are the general form of ordinary and fractional order differential equations due to their density functions. For this reason, thanks to the use of distributed order differential equations and choice of the density function, solutions of Pharmacokinetic models in different situations can be easily obtained. In addition, it is possible to show the suitability of using such equations on nonlinear differential equation models in similar forms.

In other words, the main purpose of this article is to predict the effects of drugs under different situations as soon as possible and proceed with the treatment accordingly. For this process, distributed order differential equations will be used, as they can easily explain different situations.

The definition of distributed order derivatives was first given by Caputo [10]. Caputo used the concept of distributed order derivatives in different areas, such as induction and diffusion equations, and caused them to gain significance [11-13]. Studies related to the existence and solutions of distributed order differential equations, which gained importance with Caputo's definition and studies, were published by Bagley and Torvik [14,15]. Diethelm and Ford, and Katsikadelis conducted studies on obtaining numerical solutions of distributed order differential equations [16,17]. In both of these studies, authors turned distributed order differential equations into multi-term equations; and, then they obtained numerical solutions. Li and Wu obtained numerical solutions of distributed order diffusion equations by using reproducing kernel methods [18]. Studies regarding stability analysis of distributed order differential equations were conducted by Najafi et al., and Aminikhah et al. [19,20]. For further detailed information and studies in this area please refer to studies numbered [21-24].

We will use finite difference approaches for the discretization of Pharmacokinetic systems, which we will generalize as distributed order. Numerical methods such as Runge-Kutta, Adams methods, and Theta methods based on these approaches are frequently used to study the dynamics of interacting and communicating populations. However, the disadvantages of such finite difference approaches are that their stability and accuracy depend on the time step. The Nonstandard Finite Difference (NSFD) method guarantees a positive discrete solution due to positive initial conditions. The disadvantage of the method is that a slight delay may occur in the traveling wave for very large step sizes.

So far, there are quite a number of studies on the NSFD scheme in the literature. However, these studies are mostly about ordinary, fractional, and partial-order differential equations. In this study, the general solution of such equations will be obtained with distributed order differential equations. Thus, solutions from a different point of view will be entered into the literature.

Citations must be given in brackets [1]. If there are two citations, use comma to separate [2,3]. If citations are more than two and in consecutive order, give the starting number and the last number [4-8]. For multiple citations with/without consequence, use the combination of the rules above [9,15,17-20].

In this article, nonlinear and distributed order systems of one, two, and three-compartment Pharmacokinetic models are created and examined. This manuscript consists of 6 sections. Basic definitions and concepts are presented in the Preliminaries section. In Section 3, ordinary nonlinear Pharmacokinetic models are presented. In Section 4, the expressions of nonlinear Pharmacokinetic models are defined with distributed order differential equations, later, discretizations of these created models are obtained with the NSFD scheme. In Section 5, stability analyses of discretized two and three-compartment Pharmacokinetic models are performed and numerical simulations of the solutions are included. Section 6 is the conclusion section of the article, where obtained information is assessed.

2. PRELIMINARIES

This section contains some basic concepts of Distributed order differential equations and NSFD method [10-40].

Definition 2.1. [24] Let the function $g(t)$ is integrable in the range of $[\alpha, k]$. Let *n* be a positive integer and α satisfy *n-1* < $\alpha \leq n$. Then, Riemann-Liouville fractional derivatives of order α is defined by

$$D_{RL}^{\alpha} g(t) = \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{dt^n} \int_{\alpha}^{t} \frac{g^{(n)}(k)}{(t-k)^{\alpha-n+1}} dk.$$

Definition 2.2. [24] Let the function $g(t)$ is integrable in the range of $[\alpha, k]$. Let *n* be a positive integer and α satisfy *n-1* < $\alpha \leq n$. Then, Caputo fractional derivatives of order α is defined by

$$D_{C}^{\alpha} g(t) = \frac{1}{\Gamma(n-\alpha)} \int_{\alpha}^{t} \frac{g^{(n)}(k)}{(t-k)^{\alpha-n+1}} dk.$$

Definition 2.3. [10] Let the function $D_t^{\alpha} g(t)$ is a fractional derivative operator which can be determined as Riemann-Liouville, Caputo or Grünwald-Letnikov for $\alpha \epsilon (\tau_1, \tau_2)$ and $\int_{\tau_1}^{\tau_2} u(\alpha) = d > 0$. Distributed order differential equations are defined as;

$$D_t^{u(\alpha)} g(t) = \sum_{i=1}^{n} \alpha^i \int_{\tau_1}^{\tau_2} u_i(\alpha)\, D_t^{i-\alpha} g(t) d\alpha + \sum_{j=0}^{n} b_j g^i(t).$$

The most important factor here is $u(\alpha)$ density function. Distributed order differential equations can evolve into ordinary or fractional order differential equations with density function. For example, by determining $u(\alpha) = 1$, distributed order differential equations evolve into fractional order differential equations; and by doing so solutions for fractional order can be obtained. Thanks to these differential equations, the need for different modeling and equation systems is eliminated in order to be able to model the effects of drugs [11-13]. Another important expression to the study of numerical solution is the approximate Grünwald-Letnikov derivative formula.

Definition 2.4. [25] Grünwald-Letnikov derivative formula is as follows:

$$D_{G-L}^{\alpha} g(t) = \lim_{v \to 0} v^{-\alpha} \sum_{i=0}^{n} (-1)^i \binom{\alpha}{i} g(t - iv).$$

If necessary modifications are applied on this formula, then it turns into:

$$D_t^{\alpha} g(t) = \sum_{i=0}^{n} p_i^{\alpha} g(t_{n-i}), \quad n = 1,2,3, \dots, \frac{t-\alpha}{h},$$

where $p_i^{\alpha} = \left(1 - \frac{1+\alpha}{i}\right) p_{i-1}^{\alpha}$, $p_0^{\alpha} = h^{-\alpha}$ is for , $i = 0,1,2,3, \dots, n$ and h: step size is given a quite small value [26].

In this study, a Nonstandard Finite Difference scheme defined by Mickens will be used for obtaining a numerical solution of distributed order model [27]. In this scheme, instabilities in solutions can be easily eliminated by choosing appropriate denominator functions.

Definition 2.5. [28] If we consider $\varphi(h)$ as a parameter, and $\frac{dg}{dt} = H(\varphi, g)$ as an ordinary differential equation, NSFD scheme shall be as follows:

$$t \to t_n, \qquad R(g) \to R(g_n), \quad g(t) \to g(t_n), \quad \frac{dg}{dt} \to \frac{g_{n+1} - g_n}{\phi}.$$

In this definition, ϕ: $Denominator\ Function$ and $\frac{1-e^{-dh}}{d}$ is related to h step size and d variable which can be obtained with the help of equilibrium point. This scheme can be defined in the same way in fractional order differential equations with the help of the approximate Grünwald-Letnikov derivative formula [27-36]. Resource suggestions for different numerical methods and approaches are as follows [37-40]. Hammouch et al. applied a new numerical method to solve fractional variable order differential equations in the Caputo sense to investigate the dynamics of a circulating Halvorsen system [37]. The Grünwald-Letnikov nonstandard weighted average finite difference method (GL-NWAFDM) is developed for solving the proposed optimal control system by Haq et al. [38]. Sene examined an epidemic model defined by the Caputo fractional derivative. The local stability and global asymptotic stability of the equilibrium points of the SEIR model are presented by the Matignon criterion and the Lyapunov direct method [39].

In this article, the Matignon criterion will be used for the stability analyses of the equilibrium points. Basic information about this criterion will be given in the Numerical simulation section. For more detailed information, see [41,42] resources.

3. NONLINEAR PHARMACOKINETIC MODELS

In this section of the manuscript, ordinary differential equations of one, two, and three-compartment Pharmacokinetic models are expressed. Distributed order Pharmacokinetic equations shall be defined in Section 4 with the help of these definitions and their discretizations shall be provided.

One Compartment I.V. Bolus Injection Nonlinear Pharmacokinetic Model

$$\frac{dC}{dt} = -\frac{V_{max}}{(K_m + C)} C. \tag{1}$$

One Compartment I.V. Bolus Infusion Model Nonlinear Pharmacokinetic Model

$$\frac{dC}{dt} = \frac{R_1}{V_1} - \frac{V_{max}}{(K_m + C)}\ C \tag{2}$$

where C: Concentration of drug in central compartment, V_{max}: Maximal velocity of the metabolism, K_m: Michaelis constant, R_1: Infusion rate per unit time and V_1: Apparent volume of distribution [8].

Two Compartment I.V. Bolus Injection and Infusion Nonlinear Pharmacokinetic Model

$$\frac{dC}{dt} = k_{21} P_1 - \ (k_{12} + \frac{V_{max}}{(K_m + C)}) C + I_0,$$

$$\frac{dP_1}{dt} = k_{12} C - \ k_{21} P_1, \tag{3}$$

here if we consider $I(t)$: $Infusion\ rate$ and $I(t) = I_0 = 0$, then Equation (3) turns into a I.V. Bolus Injection model. If we consider $I_0 \neq 0$, then Equation (3) is called I.V. Bolus Injection model. The values in Equation (3) are as follows [9]: P_1: Concentration of drug in peripheral compartment 1, k_{12}: Transfer rate of drug from central to peripheral compartment 1, k_{21}: Degradation rate of drug in peripheral compartment 1.

Three Compartment I.V. Bolus Injection and Infusion Nonlinear Pharmacokinetic Model

$$\frac{dC}{dt} = k_{21}P_1 + k_{31}P_2 - \ (k_{12} + k_{13} + \frac{V_{max}}{(K_m+C)})C + I_0,$$

$$\frac{dP_1}{dt} = k_{12}C - \ k_{21}P_1,$$

$$\frac{dP_2}{dt} = k_{13}C - \ k_{31}P_2 \qquad (4)$$

where P_2 : Concentration of drug in peripheral compartment 2, k_{13} :Transfer rate of drug from central to peripheral compartment 2, and k_{31}: Degradation rate of drug in peripheral compartment 2 [5]. Here if we consider $I_0 = 0$, then Equation (4) is called I.V. Bolus Injection model; on the other hand, if we consider $I_0 \neq 0$, then this equation is called I.V. Bolus Infusion model [5].

4. DISCRETIZATION OF DISTRIBUTED ORDER NONLINEAR PHARMACOKINETIC MODELS

In this section, nonstandard finite difference scheme, approximate Grünwald-Letnikov formula and classical quadrature formula shall be used for discretizations of distributed order Pharmacokinetic models. First of all, definitions of distributed order differential equations for one, two, and three-compartment Pharmacokinetic models are given respectively.

One compartment:

$$D_t^{u(\alpha)}C = -\frac{V_{max}}{(K_m+C)}C, \qquad (5)$$

$$D_t^{u(\alpha)}C = \frac{R_1}{V_1} - \frac{V_{max}}{(K_m+C)}\ C. \qquad (6)$$

Two compartments:

$$D_t^{u(\alpha)}C = k_{21}P_1 - \ (k_{12} + \frac{V_{max}}{(K_m + C)})C + I_0,$$

$$D_t^{u(\alpha)}P_1 = k_{12}C - \ k_{21}P_1. \qquad (7)$$

Three compartments:

$$D_t^{u(\alpha)}C = k_{21}P_1 + k_{31}P_2 - \ (k_{12} + k_{13} + \frac{V_{max}}{(K_m+C)})C + I_0,$$

$$D_t^{u(\alpha)}P_1 = k_{12}C - \ k_{21}P_1,$$

$$D_t^{u(\alpha)}P_2 = k_{13}C - \ k_{31}P_2. \qquad (8)$$

Discretizations of the distributed order Pharmacokinetic models are presented below.

4.1. Discretization of One Compartment Injection and Infusion Model

If quadrature formula is used together with approximate Grünwald-Letnikov formula, and NSFD scheme, discretizations for Injection and Infusion models become:

$$\sum_{k=1}^{T} \frac{q(\alpha_k)}{T} \sum_{i=0}^{n+1} p_i^{\alpha_k} C_{n+1-i} = -\frac{V_{max}}{(K_m + C_n)} C_{n+1}, \tag{9}$$

$$\sum_{k=1}^{T} \frac{q(\alpha_k)}{T} \sum_{i=0}^{n+1} p_i^{\alpha_k} C_{n+1-i} = \frac{R_1}{V_1} - \frac{V_{max}}{(K_m + C_n)} C_{n+1}, \tag{10}$$

where $p_0^{\alpha_k} = (\phi(h))^{-\alpha_k}$ for $0 < \alpha_k < 1$ and $T = \frac{1}{h}$, $\phi(h) = \frac{1-e^{\frac{V_{max}}{K_m}h}}{\frac{V_{max}}{K_m}}$.

If a term is opened on the left side of Equations (9) and (10), the discretized expressions of the C_{n+1} terms are obtained as shown below:

$$C_{n+1} = \frac{-K\ (\sum_{i=1}^{n+1} p_i^{\alpha_k} C_{n+1-i})}{((L)^{-\alpha_k} + \frac{V_{max}}{(K_m + C_n)})}, \tag{11}$$

$$C_{n+1} = \frac{\frac{R_1}{V_1} - K\ (\sum_{i=1}^{n+1} p_i^{\alpha_k} C_{n+1-i})}{((L)^{-\alpha_k} + \frac{V_{max}}{(K_m + C_n)})} \tag{12}$$

where $\sum_{k=1}^{T} \frac{u(\alpha_k)}{T} = K$ and $\sum_{k=1}^{T} \frac{u(\alpha_k)}{T}\ \phi(h) = L$.

4.2. Discretization of Two Compartment Injection and Infusion Model

In the same way, if discretization is performed for Equation (7):

$$\sum_{k=1}^{T} \frac{q(\alpha_k)}{T} \sum_{i=0}^{n+1} p_i^{\alpha_k} C_{n+1} = k_{21} P_n^1 - \ (k_{12} + \frac{V_{max}}{(K_m + C_n)}) C_{n+1} + I_{0,}$$

$$\sum_{k=1}^{T} \frac{q(\alpha_k)}{T} \sum_{i=0}^{n+1} p_i^{\alpha_k} P_{n+1}^1 = k_{12} C_n - \ k_{21} P_{n+1}^1 \tag{13}$$

where $p_0^{\alpha_k} = (\phi_i(h))^{-\alpha_k}$ for $0 < \alpha_k < 1$, $i = 1,2$ and $T = \frac{1}{h}$, $\phi_1(h) = \frac{1-e^{k_{12}h}}{k_{12}}$, $\phi_2(h) = \frac{1-e^{k_{21}h}}{k_{21}}$. In order to ensure ease of calculations, after placing $\sum_{k=1}^{T} \frac{u(\alpha_k)}{T} = K$ and $\sum_{k=1}^{T} \frac{u(\alpha_k)}{T}\ (\phi_i(h)) = L_i$ for $i = 1,2$ expressions in Equation (13):

$$C_{n+1} = \frac{k_{21} P_n^1 + I_0 - K\ (\sum_{i=1}^{n+1} p_i^{\alpha_k} C_{n+1-i})}{((L_1)^{-\alpha_k} + k_{12} + \frac{V_{max}}{(K_m + C_n)})},$$

$$P_{n+1}^1 = \frac{k_{12} C_n - K \left(\sum_{i=1}^{n+1} p_i^{\alpha_k} P_{n+1-i}^1\right)}{((L_2)^{-\alpha_k} + k_{21})}, \tag{14}$$

a discretized version of Equation (7) is obtained. For equilibrium point of System (14), solutions of the following equations are required

$$C_n = \frac{k_{21} P_n^1 + I_0 - K\ v\ C_n}{((L_1)^{-\alpha_k} + k_{12} + \frac{V_{max}}{(K_m + C_n)})},$$

$$P_n^1 = \frac{k_{12}C_n - K\ v\ P_n^1}{((L_2)^{-\alpha_k} + k_{21})}$$

where $v = \sum_{i=1}^{n+1} p_i^{\alpha_k}$. By solving these two equations, equilibrium point of the system is determined as $D_1 = (C_n, P_n^1)$. Because of complexity of the operations, equilibrium point analysis shall be performed in Section 5 by writing numeric values in their places. Jacobian matrix to be used for equilibrium point analysis is:

$$J(C_n, P_n^1)$$
$$\begin{pmatrix} \frac{-K\ v}{((L_1)^{-\alpha_k} + k_{12} + \frac{V_{max}}{(K_m + C_n)})} + \frac{(k_{21}P_n^1 + I_0 - C\ K\ v\ )V_{max}}{((L_1)^{-\alpha_k} + k_{12} + \frac{V_{max}}{(K_m + C_n)})^2 (K_m + C_n)^2} & \frac{k_{21}}{((L_1)^{-\alpha_k} + k_{12} + \frac{V_{max}}{(K_m + C_n)})} \\ \frac{k_{12}}{((L_2)^{-\alpha_k} + k_{21})} & \frac{-K\ v}{((L_2)^{-\alpha_k} + k_{21})} \end{pmatrix}.$$

4.3. Discretization of Three Compartment Injection and Infusion Model

If we conduct same operations respectively for Equation (8), firstly we obtain:

$$\sum_{k=1}^{T} \frac{q(\alpha_k)}{T} \sum_{i=0}^{n+1} p_i^{\alpha_k} C_{n+1} = k_{21}P_n^1 + k_{31}P_n^2 - (k_{12} + k_{13} + \frac{V_{max}}{(K_m + C_n)})C_{n+1} + I_0,$$

$$\sum_{k=1}^{T} \frac{q(\alpha_k)}{T} \sum_{i=0}^{n+1} p_i^{\alpha_k} P_{n+1}^1 = k_{12}C_n - k_{21}P_{n+1}^1,$$

$$\sum_{k=1}^{T} \frac{q(\alpha_k)}{T} \sum_{i=0}^{n+1} p_i^{\alpha_k} P_{n+1}^2 = k_{13}C_n - k_{31}P_{n+1}^2 \qquad (15)$$

where $p_0^{\alpha_k} = (\phi_i(h))^{-\alpha_k}$ for $0 < \alpha_k < 1$, $i = 1,2,3$ and $T = \frac{1}{h}$, $\phi_1(h) = \frac{1-e^{(k_{12}+k_{13})h}}{(k_{12}+k_{13})}$, $\phi_2(h) = \frac{1-e^{k_{21}h}}{k_{21}}$, $\phi_3(h) = \frac{1-e^{k_{31}h}}{k_{31}}$. With necessary modifications and $\sum_{k=1}^{T} \frac{u(\alpha_k)}{T} = K$ and $\sum_{k=1}^{T} \frac{u(\alpha_k)}{T} (\phi_i(h)) = L_i$ abbreviations for $i = 1,2$ and 3, discretized equations system is obtained as:

$$C_{n+1} = \frac{k_{21}P_n^1 + k_{31}P_n^2 + I_0 - K\ (\sum_{i=1}^{n+1} p_i^{\alpha_k} C_{n+1-i})}{((L_1)^{-\alpha_k} + k_{12} + k_{13} + \frac{V_{max}}{(K_m + C_n)})},$$

$$P_{n+1}^1 = \frac{k_{12}C_n - K\ \left(\sum_{i=1}^{n+1} p_i^{\alpha_k} P_{n+1-i}^1\right)}{((L_2)^{-\alpha_k} + k_{21})},$$

$$P_{n+1}^2 = \frac{k_{13}C_n - K\ (\sum_{i=1}^{n+1} p_i^{\alpha_k} P_{n+1-i}^2)}{((L_3)^{-\alpha_k} + k_{31})} \qquad (16)$$

For equilibrium point of System (16), solutions of the following equations are required.

$$C_n = \frac{k_{21}P_n^1 + k_{31}P_n^2 + I_0 - K\ v\ C_n}{((L_1)^{-\alpha_k} + k_{12} + k_{13} + \frac{V_{max}}{(K_m + C_n)})},$$

$$P_n^1 = \frac{k_{12}C_n - K\,v\,P_n^1}{((L_2)^{-\alpha_k} + k_{21})},$$
$$P_n^2 = \frac{k_{13}C_n - K\,v\,P_n^2}{((L_3)^{-\alpha_k} + k_{31})}$$

where $v = \sum_{i=1}^{n+1} p_i^{\alpha_k}$. By solving these three equations, equilibrium point of the system is found as $D_2 = (C_n, P_n^1, P_n^2)$. Again, just like in two compartment models, equilibrium point analysis shall be performed in the Section 5 with given numeric values. Jacobian matrix to be used for equilibrium point analysis:

$$J(C_n, P_n^1, P_n^2)$$
$$\begin{pmatrix} \frac{-K\,v}{((L_1)^{-\alpha_k} + k_{12} + k_{13} + \frac{V_{max}}{(K_m + C_n)})} + \frac{(k_{21}P_n^1 + k_{31}P_n^2 + I_0 - C\,K\,v)V_{max}}{((L_1)^{-\alpha_k} + k_{12} + k_{13} + \frac{V_{max}}{(K_m + C_n)})^2 (K_m + C_n)^2} & \frac{k_{21}}{((L_1)^{-\alpha_k} + k_{12} + k_{13} + \frac{V_{max}}{(K_m + C_n)})} & \frac{k_{31}}{((L_1)^{-\alpha_k} + k_{12} + k_{13} + \frac{V_{max}}{(K_m + C_n)})} \\ \frac{k_{12}}{((L_2)^{-\alpha_k} + k_{21})}, & \frac{-K\,v}{((L_2)^{-\alpha_k} + k_{21})}, & 0 \\ \frac{k_{13}}{((L_3)^{-\alpha_k} + k_{31})} & 0 & \frac{-K\,v}{((L_3)^{-\alpha_k} + k_{31})} \end{pmatrix}.$$

5. NUMERICAL STABILITY ANALYSIS AND SIMULATIONS

In this section, stability analyses and simulations are investigated. There are some important articles about stability analyses [43-50]. Stability analyses of distributed order differential equations are found by the choice of density function. These analyses are found for the obtained equilibrium points. Two methods can be used for stability analysis. The first is the Laplace transform, and the second is the Matignon criterion. In this study, the Matignon criterion is used. The Matignon criterion is a method that deals with local stability in the context of fractional derivatives [41,42]. First, for the stability of equilibrium points, the information about stability in numerical schemes is expressed by the following Remark.

Remark 5.1. [42] For the Matignon criterion, let J be the Jacobian matrix obtained by the classical method and $\lambda(J)$ be expressed as the set of eigenvalues of the J Jacobian matrix. So, the equilibrium point is locally asymptotically stable if the following condition satisfied:

$$|\arg(\lambda(J))| > \alpha\pi/2.$$

The classical Jacobian matrix is used in the Matignon criterion. For local stability, the difference between the integer ordinal version and the fractional version is that in the fractional version, all matrix eigenvalues must satisfy condition. In other words, in the integer version, local stability of equilibrium points is achieved when the eigenvalues of the Jacobian matrix accept negative real parts. However, in the fractional version, the previous condition is more general [41,42].

For the analysis of resulting solutions, constants are considered as $V_{max} = 3.33$, $K_m = 5.56$, $k_{12} = 0.0187$, $k_{21} = 0.0157$, $k_{13} = 0.0415$ and $k_{31} = 0.0285$. Initial conditions are selected as $C(0) = 1$, $P_1 = 0$ and $P_2 = 0$. The constants here are determined by clinical trials of the drug Sisomycin [9]. Thus, with the data of this drug, it is aimed to find the effect of this drug, which is generally used in infectious diseases in different situations.

First, stability analysis for the two-compartment model is examined. For this purpose, numeric values which mentioned above are first used and considered as $u(\alpha) = \alpha - 0.8$, $h = 0.01$, $I_0 = 1$. According to these numeric values, Equilibrium point is determined as $D_1 = (C_n, P_n^1) = (0.00993, 0.18579.10^{-5})$. $P(\lambda) = \lambda^2 - 0.02403\lambda - 0.00005$ characteristic polynomial is obtained after placing equilibrium point in its place in the Jacobian matrix. In this case, with given numeric values, $D_1 = (C_n, P_n^1)$ equilibrium point is not stable. After solution of characteristic equations, it is seen that $\lambda_1 = 0.02625$ and $\lambda_2 = -0.00221$. If the Matignon criterion is checked with the eigenvalues obtained, we found that the second eigenvalue satisfies Matignon criterion because $|\arg(\lambda_2)| = \pi > \frac{\alpha\pi}{2}$. On the other hand, since it is $|\arg(\lambda_1)| = 0 < \frac{\alpha\pi}{2}$, it was seen that the first eigenvalue does not satisfy Matignon criterion. So, the equilibrium point D_1 is not stable under these conditions.

After then, for three compartment model, equilibrium point is found as $D_2 = (C_n, P_n^1, P_n^2) = (0.00412, 0.30875.10^{-7}, 0.68503.10^{-7})$ with $u(\alpha) = \alpha,\ h = 0.02, I_0 = 1$ and numeric values. Characteristic polynomial is found as $P(\lambda) = \lambda^3 + 0.00002\,\lambda^2 - 0.23579.10^{-8}\ \lambda - 47792.10^{-14}$ by writing equilibrium point in its place in resulting Jacobian matrix. In these conditions, $D_2 = (C_n, P_n^1, P_n^2)$ equilibrium point is not stable with the help of Matignon criterion. By solving characteristic polynomial, eigenvalues are determined as $\lambda_1 = 0.00003$, $\lambda_2 = -0.19992.10^{-5}$ and $\lambda_3 = -0.00006$. We can notice that second and third eigenvalues satisfy Matignon criterion but first eigenvalue doesn't satisfy because of $|\arg(\lambda_1)| = 0 < \frac{\alpha\pi}{2}$. Therefore, equilibrium point D_2 is not stable under the given conditions.

The relationship between simple mathematical modeling and physical or biological system, integer order differential equations express the dynamics of systems. Integer order differential equations unify the relationship between complex system parameters in mathematical modeling, as well as describe the variation in structure, nonlinearity, and multiscale behavior within them.

On the other hand, fractional analysis has attracted great attention by researchers and different aspects of the subject have been examined in recent years. This is because the fractional derivative is an important tool to explain the dynamic behavior of various physical systems. The strength of these differential operators is their nonlocal property which cannot be found in integer ordinal differential operators. The distinguishing features of fractional differential equations are that they summarize the memory and transmitted properties of a large number of mathematical models. Fractional ordinal models are more realistic and practical than traditional integer ordinal models. Arbitrary ordinal derivatives are powerful tools for evaluating the dynamic behavior of various biomaterials and systems.

The most recurring features of these models are their global feature, which are not present in classical layout models. Since Pharmacokinetic models are also models of the above-mentioned styles, it is important to determine the dynamics and reach more realistic values. Therefore, distributed order differential equations are used in this article.

When all graphs are considered, the behavior of all subgroups can be measured biologically by the choice of density function. Thus, the behavior of the populations of the model under variable conditions can be predicted and necessity measures can be taken against various situations according to these predictions [48,49].

Simulations and tables are presented below for both two, and three-compartment models. At the same time, there are different graphs of infusion and injection models in these simulations. In Table 1, CPU times compare for numerical methods. As seen in Table 1, we can say numerical methods evaluated among themselves are not extremely different. In Tables 2 and 3, qualitative results are given for different time step sizes. In Figure 1, fractional differential equation's solution of two compartment model is given with $u(\alpha) = \alpha$ and $\alpha = 1$. As can be seen in Figure 1, solution of different types of differential equations can be obtained with the selection of $u(\alpha)$. In Figure 2, unlike the Figure 1, it is determined as $I_0 = 1$. A graph is obtained for the solution of fractional ordinary I.V. Bolus Infusion model. In between Figures 3-5, some graphs are included to show the effects of different $u(\alpha)$ and h values on solutions. In between Figures 6-9, graphs are included based on the different $u(\alpha)$ and h values of the three-compartment model. In this manuscript, numerical calculations and graphics are obtained with the help of mathematical programs.

Table 1. *CPU Times (seconds) for* $u(\alpha) = \alpha, \alpha = 1\ \ h = 0.01$ *and* $I_0 = 1$

α	Theta Method	Runge Kutta 4th order	NSFD
0.2	0.6427	1.0223	0.6356
0.5	0.6397	0.9881	0.6134
1	0.7341	0.9796	0.5810

Table 2. *Qualitative results for different time step sizes h in two compartment Pharmacokinetic models with $u(\alpha) = \alpha - 0.8$, $\alpha = 1$ and $I_0 = 1$)*

h	Theta Method	Runge Kutta	NSFD
0.002	Convergence	Convergence	Convergence
0.001	Convergence	Convergence	Convergence
0.1	Convergence	Convergence	Convergence
1	Convergence	Convergence	Convergence
1.5	Convergence	Convergence	Convergence
1.9	Convergence	Convergence	Convergence
2.5	Divergence	Divergence	Convergence
5	Divergence	Divergence	Convergence

Table 3. *Qualitative results for different time step sizes h in three compartment Pharmacokinetic models with $u(\alpha) = \alpha$, $\alpha = 1$ and $I_0 = 1$)*

h	Theta Method	Runge Kutta	NSFD
0.002	Convergence	Convergence	Convergence
0.001	Convergence	Convergence	Convergence
0.1	Convergence	Convergence	Convergence
1	Convergence	Convergence	Convergence
1.5	Convergence	Convergence	Convergence
1.9	Divergence	Convergence	Convergence
2.5	Divergence	Divergence	Convergence
5	Divergence	Divergence	Convergence

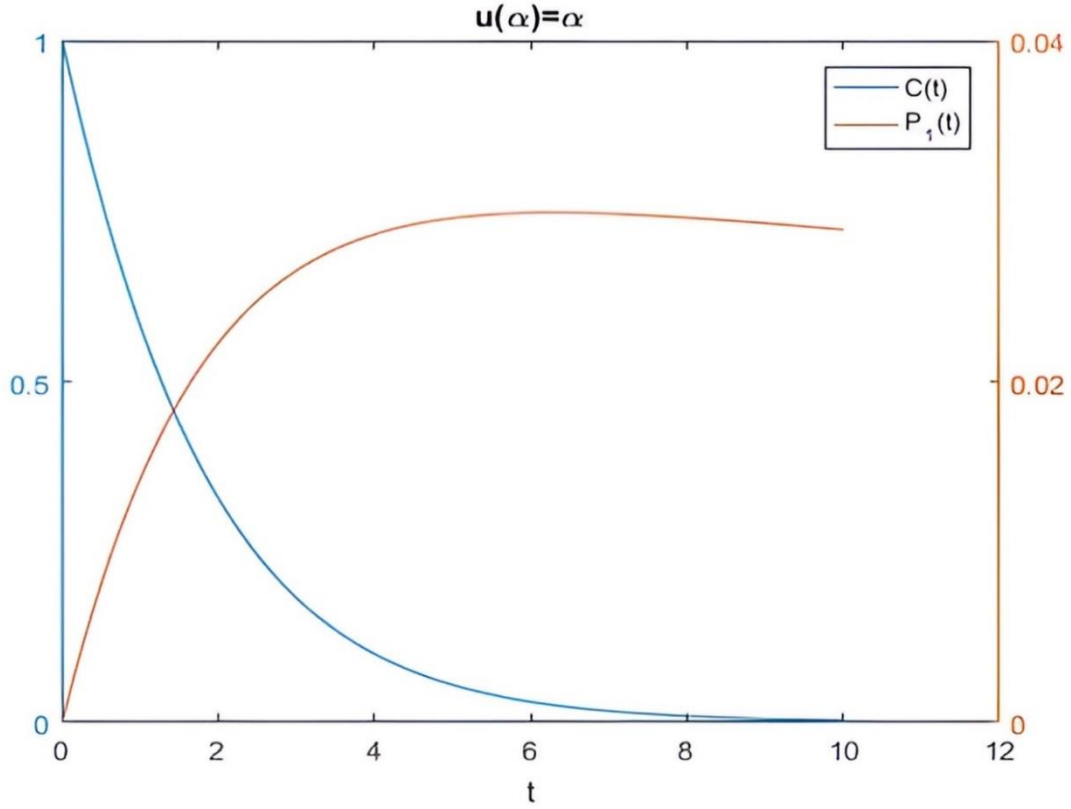

Figure 1. *The concentration of drug in the central compartment and peripheral compartment1 for $u(\alpha) = \alpha$ where $h = 0.01$ $\alpha = 1$ and $I_0 = 0$ (I.V. Bolus Injection)*

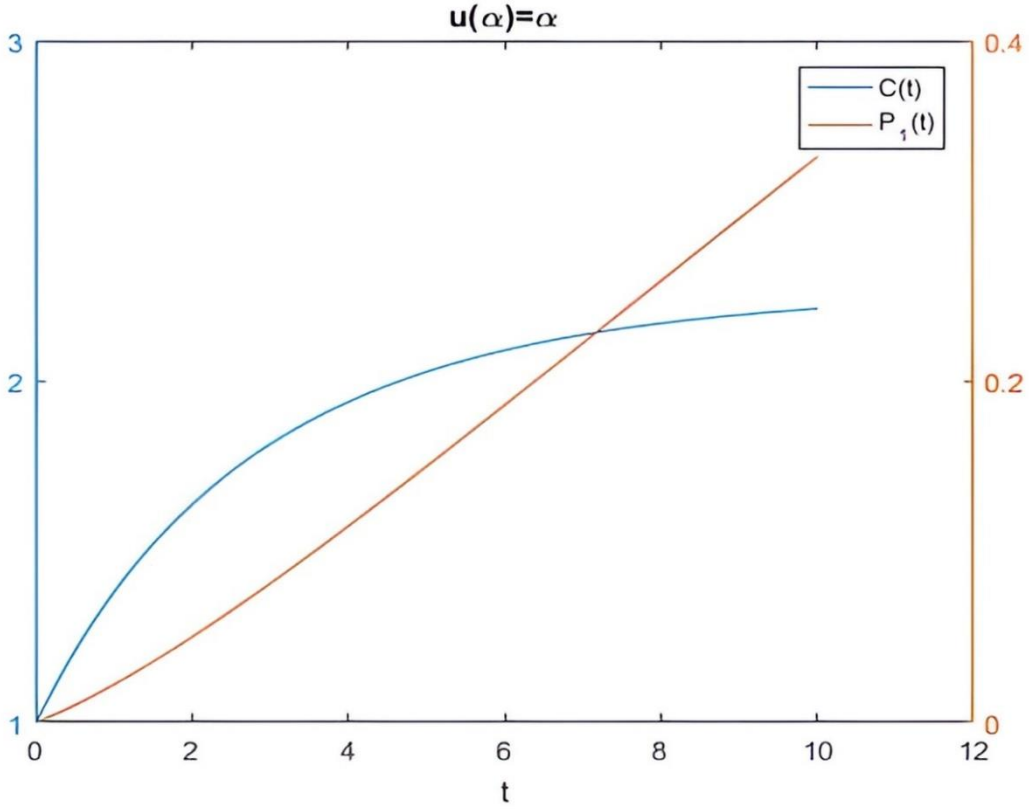

Figure 2. *The concentration of drug in the central compartment and peripheral compartment1 for* $u(\alpha) = 1$ *where* $h = 0.01$ $\alpha = 1$ *and* $I_0 = 1$ *(I.V. Bolus Infusion)*

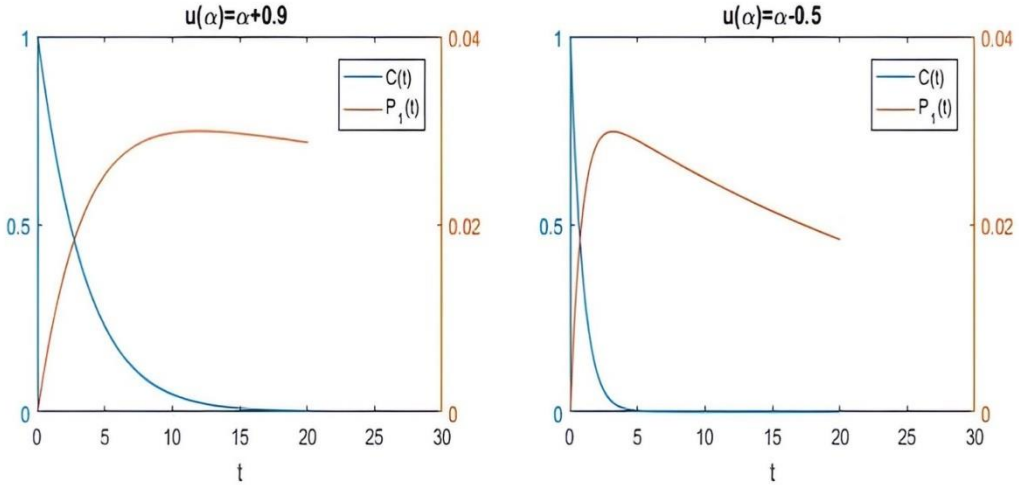

Figure 3. *The concentration of drug in the central compartment and peripheral compartment1 for different* $u(\alpha)$ *values where* $h = 0.02,\ \alpha = 1$ *and* $I_0 = 0$ *(I.V. Bolus Injection)*

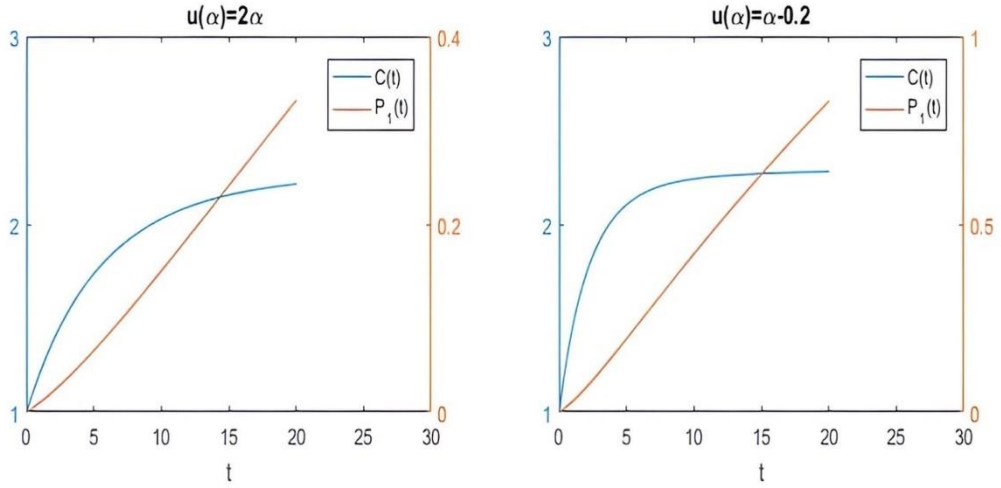

Figure 4. *The concentration of drug in the central compartment and peripheral compartment1 for different* $u(\alpha)$ *values where* $h = 0.02,\ \alpha = 1$ *and* $I_0 = 1$ *(I.V. Bolus Infusion)*

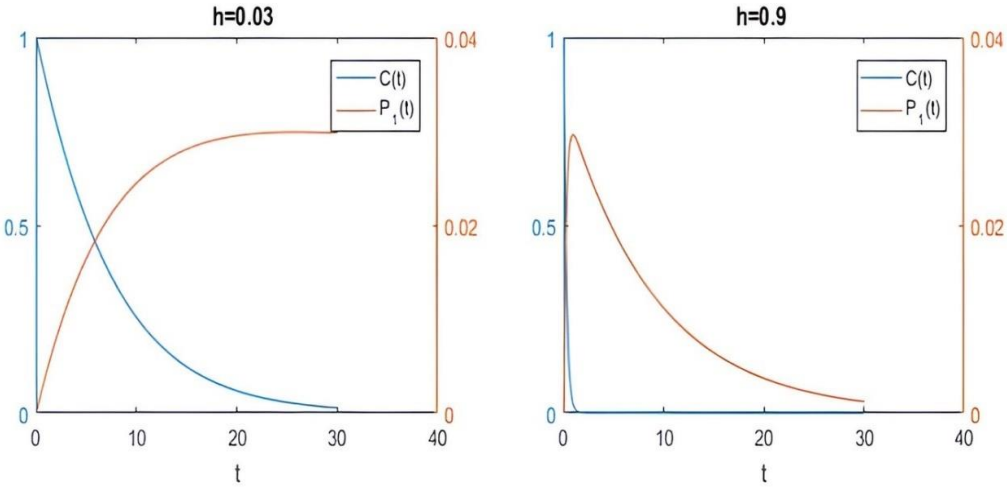

Figure 5. *The concentration of drug in the central compartment and peripheral compartment1 for different h values where* $u(\alpha) = 2\alpha + 1,\ \alpha = 2$ *and* $I_0 = 0$ *(I.V. Bolus Injection)*

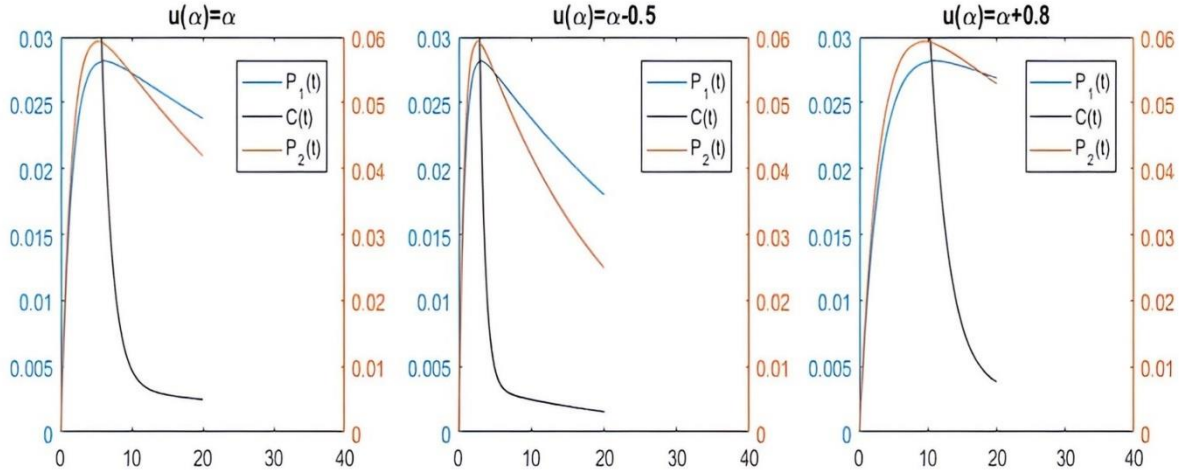

Figure 6. *Comparative for of concentration of drug in the central compartment, peripheral compartment 1 and peripheral compartment 2 for different* $u(\alpha)$ *values where* $h = 0.01,$ $\alpha = 1$ *and* $I_0 = 0$ *(I.V. Bolus Injection)*

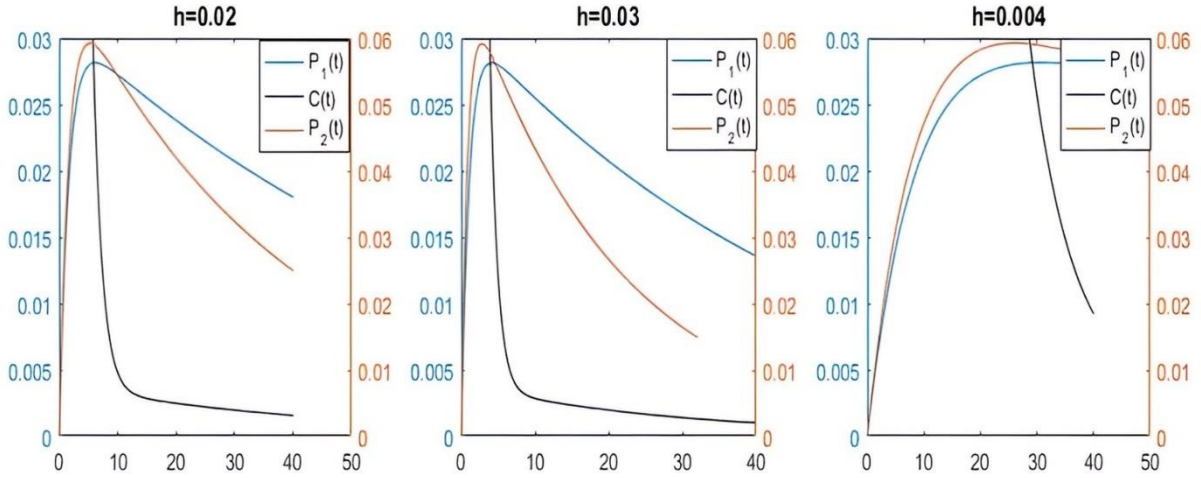

Figure 7. *Comparative for of concentration of drug in the central compartment, peripheral compartment 1 and peripheral compartment 2 for different h values where* $u(\alpha) = \alpha$, $\alpha = 1$ *and* $I_0 = 0$ *(I.V. Bolus Injection)*

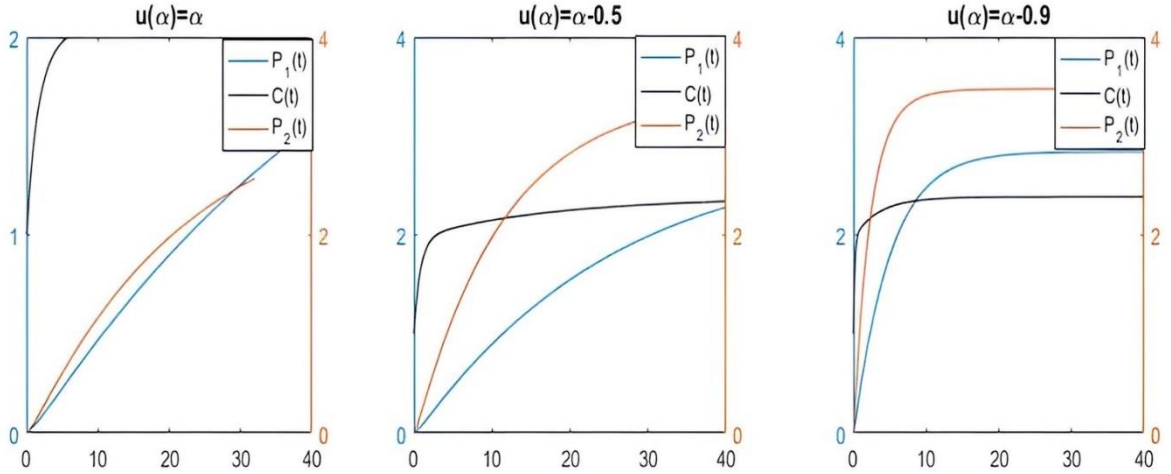

Figure 8. *Comparative for of concentration of drug in the central compartment, peripheral compartment 1 and peripheral compartment 2 for different* $u(\alpha)$ *values where* $h = 0.03$, $\alpha = 1$ *and* $I_0 = 1$ *(I.V. Bolus Infusion)*

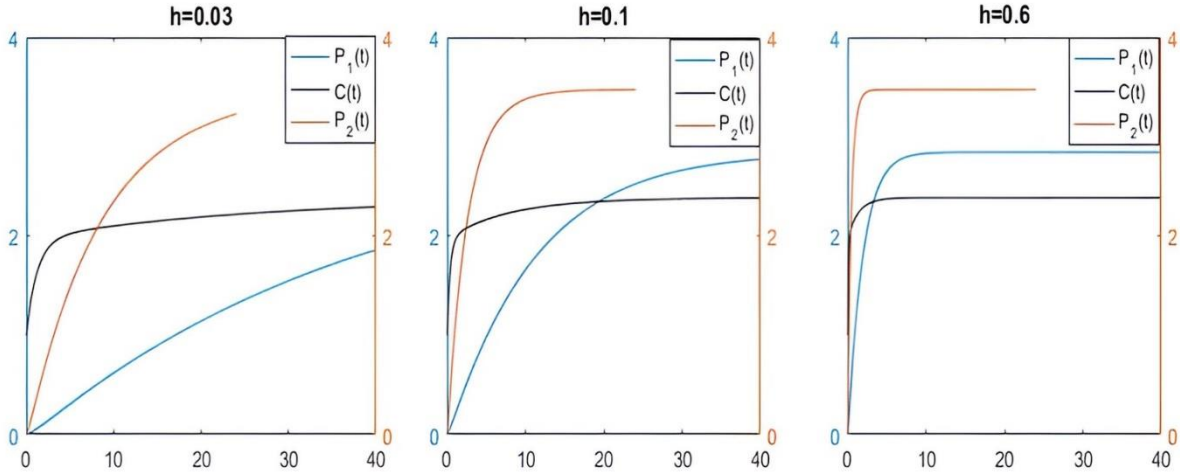

Figure 9. *Comparative for of concentration of drug in the central compartment, peripheral compartment 1 and peripheral compartment 2 for different h values where* $u(\alpha) = \alpha - 0.5$, $\alpha = 1$ *and* $I_0 = 1$ *(I.V. Bolus Infusion)*

The results appear to be consistent when the graphs are compared with the fractional models for $u(\alpha) = 1$. Thus, it has been showed that fractional order differential equation's solutions are found with the help of density function. The analyses show the solutions which obtained by the NSFD method, approach the right endemic equilibrium point. According to these analyses, the dynamics of situations which may occur because of different external factors can be understood with the obtained solutions.

6. CONCLUSION

One, two, and three-compartment of Pharmacokinetic models examined the effects of drugs used on human body. In this article, solutions of these models are researched. Distributed order differential equations used for these solutions. In this way, solutions are found for ordinary, fractional, and different cases with the help of density function. Discretizations are showed by using the NSFD scheme for numerical solution purposes. Equilibrium points are found after discretization. Analyses of these equilibrium points are presented under scope of Matignon criteria.

It is seen that the use of distributed order differential equations in this type of nonlinear modelling is very useful and functional in achieving solutions. At the same time, solutions of models in fractional differential equations are achieved by selecting the density function. It is also seen that results and graphs are consistent with those shown in original articles.

Positivity solutions under positive initial conditions are preserved with the NSFD discretization method. NSFD schemes can retain all the properties of continuous models for any discretization parameter. For this reason, the method is successful in dynamic consistency.

The effects of drug use on the human body are found by using these solutions. In order to change these effects against different factors, the density function can be used. Thus, the main purpose of this article has been achieved. In other words, it is possible to predict the effects of drugs in different situations, and start treatment accordingly, by solving the determined equations.

CONFLICTS OF INTEREST

No conflict of interest was declared by the authors.

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