

RESEARCH ARTICLE

Numerical simulation of a two compartmental fractional model in pharmacokinetics and parameters estimation

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Abstract

Compartmental model is the classic and widely used approach in pharmacokinetics. Recently, fractional calculus is introduced to describe the time course of drugs in human body which follow the anomalous diffusion mechanism. To consider the different fractional order transmission process, the two compartmental fractional model has been proposed and studied. And, it will be of great significance to find out a simple and efficient numerical method to solve the model and estimate model parameters. This work investigates two numerical methods of the two compartmental fractional model using finite difference schemes, which are based on the shifted Grünwald-Letnikov approximate formula and $L1$ formula, respectively. The hybrid Nelder-Mead simplex search and particle swarm optimization, denoted as NMSS-PSO, is provided to estimate the fractional model parameters. Comparison between the numerical solution and the solution by the numerical inverse Laplace transform method establishes the validity of the developed numerical algorithms. Then, the influence of the order of fractional derivative on the drug amount in human body is also discussed. Finally, the two compartmental fractional model is applied to fit the amiodarone pharmacokinetics data based on the NMSS-PSO algorithms. This work will be of importance for the development of fractional pharmacokinetics.

KEYWORDS:

Fractional compartmental model; Fractional pharmacokinetics; Finite difference method; Nelder-Mead simplex search method; Particle swarm optimization

1 | INTRODUCTION

Fractional calculus, which introduces integrals and derivatives of fractional order, has almost the same history as classical calculus. However, only in recent decades, fractional calculus becomes popular because of its successful applications in different fields, such as physics, electrochemistry, bioengineering and pharmacology^{1,2,3,4}. Now it is well known that fractional kinetics offers an elegant description of anomalous kinetics owing to its memory effect and the non-local property. So it is natural to adopt the theory of fractional calculus to improve compartmental analysis when modeling the uptake, distribution and elimination of drug in human body⁵.

Compartmental analysis originated from the study of radioactive tracers and was used to simplify complex physiological systems. In recent years, compartmental analysis, which plays an important role in bioengineering and pharmacology, especially in pharmacokinetics, is given series attention. Compartmental models were applied to calculate drug concentration in body^{6,7}.

However, it has found that the classical compartmental analysis is hard to characterize some complicated phenomenon that follows the anomalous diffusion mechanism, such as the distribution process of diclofenac used for the anti-inflammatory and analgesic⁸, the concentration in the blood of amiodarone after administer drug⁹. Hence, fractional calculus has been gradually introduced and used for compartmental analysis. It has been proved that the fractional differential equation is more suitable and accurate than the integral differential equation in describing the anomalous diffusion behavior of drugs in biological systems¹⁰.

Now, fractional compartmental models have been proved to be useful and successfully applied to describing the absorption of drug in a living biological system. Dokoumetzidis and Macheras firstly used the fractional kinetics to model the process of drug dissolution in pharmacokinetics¹¹. Considering a common fractional order in the process of mass transfer of the compartment, Popović et al.^{8,12} proposed a multi-compartmental fractional model with a commensurate order to simulate the distribution and uptake of diclofenac and also gave a non-linear two compartmental fractional model to evaluate the valproic acid pharmacokinetics after oral administration. Then they presented a two compartmental fractional model with the different order in different compartment¹³. Dokoumetzidis et al.¹⁴ built a new method to fractionalize multi-compartmental model with the conservation of mass where they considered the different fractional order transmission process in body and demonstrated the fractional model can well describe the pharmacokinetics of amiodarone in human body. Moreover, Angstmann et al.¹⁵ derived the fractional compartmental model according to the basic physical stochastic process to ensure that the order of the fractional model had physical significance.

But with the development of fractional calculus in pharmacokinetics and other fields, a new problem how to analytically and numerically solve the fractional compartmental model appeared naturally. Unlike the integer differential equations, fractional differential equations with the specified initial conditions are difficult and even impossible to find their analytical solutions. Therefore, it is essential to build efficient numerical algorithms to solve these corresponding problems. The two compartmental fractional model with a commensurate order was investigated in Refs.^{16,17} and solved numerically by using the Grünwald-Letnikov (GL) approximation. Dokoumetzidis et al. applied the numerical inverse Laplace transform (NILT) method to solve the system they proposed¹⁴, but the direct numerical simulation of the two compartmental fractional model was not considered in their studies. Based on the fact, we propose two numerical methods of the two compartmental fractional model by using the shifted GL approximate formula and $L1$ formula respectively and compare the numerical solutions with the semi-analytical solution by the NILT method. In addition, the least-squares method and particle swarm optimization (PSO) algorithm were used to estimate the model parameters of fractional compartmental models^{8,14}. However, the least-squares method requires that we give an appropriate initial value of unknown parameters, otherwise it will fall into local extremum. And we also know PSO is a random global optimization technology moving towards the best goal and the Nelder-Mead simplex search (NMSS) algorithm remove the worst. So we use the NMSS-PSO method to improve the accuracy of the parameter estimation. This method is proposed by Liu et al. and has been proven the effectiveness for the fractional dynamical models^{18,19,20}.

The remainder of this paper is organized as follows: some relevant theories about fractional calculus is briefly introduced in Section 2. In Section 3, we show the two compartmental fractional model with different conditions and the semi-analytical solution of the model in Laplace domain. The finite difference schemes and the NMSS-PSO algorithm of parameters estimation are proposed in Section 4. In Section 5, the numerical results are presented and the influence of the order of fractional derivative on the drug amount in human body is also discussed. And the result of parameter estimation is obtained based on the amiodarone pharmacokinetics data. Finally, some conclusions are presented in Section 6.

2 | FRACTIONAL CALCULUS

The integral of order $\alpha (\alpha > 0)$ of a function f with respect to time variable t can be written as

$${}_a D_t^{-\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_a^t (t - \tau)^{\alpha-1} f(\tau) d\tau, \quad (1)$$

where $\Gamma(\cdot)$ is the Gamma function^{21,22}. Note that, when $\alpha = n, n \in \mathbb{N}$, the above definition will be reduced to the classical n -fold integral. As for the definition of fractional derivatives, Riemann-Liouville derivative, Caputo derivative and GL derivative will be considered in the following^{21,22}.

The Riemann-Liouville fractional derivative of a function f is defined as Eq.(2). It is one of the most popular definition in fractional calculus

$${}_a^R D_t^\alpha f(t) = \frac{d^n}{dt^n} \left[\frac{1}{\Gamma(n-\alpha)} \int_a^t \frac{f(\tau)}{(t-\tau)^{\alpha-n+1}} d\tau \right], \quad n-1 < \alpha \leq n. \quad (2)$$

The Caputo derivative of $\alpha \in [n-1, n]$ of a function f with respect to the time variable t is defined as

$${}_a^C D_t^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \int_a^t \frac{f^{(n)}(\tau)}{(t-\tau)^{\alpha-n+1}} d\tau. \quad (3)$$

From the above formula, we have the Caputo derivative of a constant equals to zero. Thus, this fractional definition is superior for most physical processes as the initial conditions for fractional differential equations with the Caputo derivative have the same form as the integer-order differential equations²¹.

The GL derivative of order α can be written as

$${}_a^{GL} D_t^\alpha f(t) = \lim_{h \rightarrow 0} h^{-\alpha} \sum_{j=0}^{\infty} (-1)^j \binom{\alpha}{j} f(t-jh), \quad \binom{\alpha}{j} = \frac{\alpha(\alpha-1) \cdots (\alpha-j-1)}{j!} \quad (4)$$

For convenience, we introduced a notation,

$$g_j^{(\alpha)} = (-1)^j \binom{\alpha}{j}, \quad g_0^{(\alpha)} = 1, \quad g_j^{(\alpha)} = \left(1 - \frac{\alpha+1}{j}\right) g_{j-1}^{(\alpha)}, \quad j = 1, 2, \dots \quad (5)$$

In this paper, we consider the shifted GL fractional operator:

$${}_a^{GL} D_{t,p}^\alpha f(t) = h^{-\alpha} \sum_{j=0}^{[(t-a)/h+p]} g_j^{(\alpha)} f(t-(j-p)h), \quad (6)$$

where p is a constant. When $p = 0$, Eq. (6) is referred as the standard GL formula. For $p = 1$, Eq. (7) can be regarded as the first order approximation of Riemann-Liouville fractional derivative,

$${}_a^{GL} D_{t,1}^\alpha f(t) = h^{-\alpha} \sum_{j=0}^{[(t-a)/h+1]} g_j^{(\alpha)} f(t-(j-1)h). \quad (7)$$

Considering the relationship between GL fractional derivative, Riemann-Liouville fractional derivative and Caputo fractional derivative, we have the following approximation for $f(a) = 0$,

$${}_a^C D_t^\alpha f(t) = {}_a^{GL} D_t^\alpha f(t) = h^{-\alpha} \sum_{j=0}^{[(t-a)/h+1]} g_j^{(\alpha)} f(t-(j-1)h), \quad 0 < \alpha < 1. \quad (8)$$

The expressions of fractional derivatives in Laplace domain can be easily obtained since each fractional derivatives in time domain can be transformed similarly to the integer derivatives, as follows, for order $\alpha \leq 1$:

$$L \{ {}_0^C D_t^\alpha f(t) \} = s^\alpha \tilde{f}(s) - s^{\alpha-1} f(0), \quad (9)$$

where $\tilde{f}(s)$ is the Laplace transform of the function $f(t)$.

3 | TWO COMPARTMENTAL FRACTIONAL MODEL

A two compartment fractional model shown schematically in Fig. 1 in pharmacokinetics will be considered. Compartment 1 corresponds to general circulation and well perfused tissue while compartment 2 represents the target tissue. The system can be represented mathematically as^{14,5}:

$$\begin{aligned} \frac{dq_1(t)}{dt} &= -k_{10} {}_0^C D_t^{1-\alpha_{10}} q_1(t) - k_{12} {}_0^C D_t^{1-\alpha_{12}} q_1(t) + k_{21} {}_0^C D_t^{1-\alpha_{21}} q_2(t) + u_1(t), \\ \frac{dq_2(t)}{dt} &= -k_{20} {}_0^C D_t^{1-\alpha_{20}} q_2(t) - k_{21} {}_0^C D_t^{1-\alpha_{21}} q_2(t) + k_{12} {}_0^C D_t^{1-\alpha_{12}} q_1(t) + u_2(t), \end{aligned} \quad (10)$$

where $0 < \alpha_{ij} \leq 1$ and $q_i(t)$ is the mass of drug in the compartment i . k_{ij} represents the rate of elimination, distribution and uptake from compartment i to compartment j and has a dimension of $[\text{time}]^{-\alpha_{ij}}$. $u_i(t)$ is the infusion rate in compartment i , which

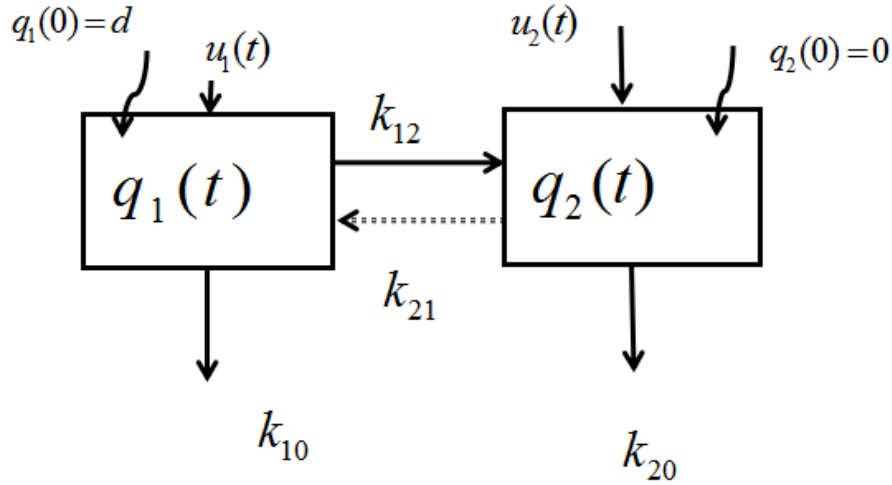


FIGURE 1 Schematic representation of a fractional two compartmental model. k_{ij} are constants that represent the rate of mass transfer from compartment i to compartment j , k_{i0} are elimination rates from compartment i and $u_i(t)$ denote infusion rates.

has a dimension of [mass/time] and may be zero, constants or time dependent. Initial value for $q_1(t)$ and $q_2(t)$ can be considered $q_1(0) = d$, $q_2(0) = 0$, respectively. For this non-zero initial conditions, we can convert it to a zero initial value problem by variable substitution ($q_1^*(t) = q_1(t) - q_1(0)$) and then solve it numerically by means of the relationship of Caputo derivative and GL derivative.

In this paper, we focus mainly on the following model including several processes of drug release in the body. One is the elimination from compartment 1, one is the distribution from compartment 1 to compartment 2 and the rest is the mass flux from compartment 2 to compartment 1. The first two processes are assumed to follow classic kinetics, while the last one is supposed to follow fractional kinetics. The system can be expressed in the following form

$$\begin{aligned} \frac{dq_1(t)}{dt} &= -(k_{12} + k_{10}) q_1(t) + k_{21} {}^C D_t^{1-\alpha} q_2(t) + u_1(t), \\ \frac{dq_2(t)}{dt} &= k_{12} q_1(t) - k_{21} {}^C D_t^{1-\alpha} q_2(t), \end{aligned} \quad (11)$$

where $q_1(0) = d$, $q_2(0) = 0$ are initial conditions of the model. In this paper, we pay attention to the following two important cases of Eq. (11).

1. We first consider the system Eq.(11) with oral absorption ($u_1(t) \neq 0$) and the zero initial conditions ($q_1(0) = q_2(0) = 0$). Unlike the integer-order compartmental model that the amounts of the system approach to a steady state, the amounts will keep rising in the fractional case. In pharmacokinetics, it is common to adapt exponential input or power input to account for the oral absorption in order to avoid drug accumulation in body^{14,25}. Here, without loss of generality, we assume the input function is

$$u_1(t) = R e^{-\lambda t}, \quad (12)$$

where the R and λ are positive numbers. Applying the Laplace transform to the above system: Eqs. (11), (12) and the zero initial conditions, we obtain

$$\tilde{q}_1(s) = \frac{R}{s + \lambda} \frac{s^\alpha + k_{21}}{(s + k_{12} + k_{10})(s^\alpha + k_{21}) - k_{12} k_{21}}, \quad (13)$$

$$\tilde{q}_2(s) = \frac{R}{s + \lambda} \frac{s^{\alpha-1} k_{12}}{(s + k_{12} + k_{10})(s^\alpha + k_{21}) - k_{12} k_{21}}. \quad (14)$$

2. Next, we investigate the following case

$$u_1(t) = 0, \quad q_1(0) = d \neq 0, \quad \text{and} \quad q_2(0) = 0. \quad (15)$$

It corresponds to a bolus dose injection in the compartment 1 and no amount in the compartment 2 at initial moment. By the Laplace transform method to Eqs. (11) and (15), we have

$$\tilde{q}_1(s) = \frac{d(s^\alpha + k_{21})}{(s + k_{12} + k_{10})(s^\alpha + k_{21}) - k_{12}k_{21}}, \quad (16)$$

$$\tilde{q}_2(s) = \frac{d s^{\alpha-1} k_{12}}{(s + k_{12} + k_{10})(s^\alpha + k_{21}) - k_{12}k_{21}}. \quad (17)$$

Using the above results for $\tilde{q}_1(s)$ and $\tilde{q}_2(s)$, we can estimate the values of model parameters in the system. It is important to note that we pay more attention to the value of $q_1(t)$ in the time domain in practical application, **because we only have the experimental data of compartment 1**. The value of $q_1(t)$ from the numerical solution can be combined with the following equation to estimate parameters k_{10} , k_{12} , k_{21} , v_1 and α

$$c_1(t) = q_1(t)/v_1, \quad (18)$$

where $c_1(t)$ is the drug concentration in the blood and v_1 is the apparent volume of distribution of compartment 1.

4 | NUMERICAL ALGORITHMS AND PARAMETERS ESTIMATION

4.1 | Numerical algorithms

In this section, the finite difference methods based on the shifted GL approximate formula and $L1$ formula are proposed to solve Eq. (11) with the initial condition $q_1(0) = d$, $q_2(0) = 0$.

Firstly, let $t_k = k\tau$, $k = 0, 1, 2, \dots, N$, where N is a positive integer, $\tau = T/N$ is the time step and T is the simulation time. We introduce the following approximation using forward-Euler difference method

$$\left. \frac{dq_i(t)}{dt} \right|_{t_k} \approx \tau^{-1}[q_i(t_{k+1}) - q_i(t_k)], \quad i = 1, 2. \quad (19)$$

Secondly, we can obtain the following expression utilizing Eq. (8),

$${}_0^C D_t^{1-\alpha} q_2(t) \Big|_{t_k} \approx \tau^{-(1-\alpha)} \sum_{j=0}^{k+1} g_j^{(1-\alpha)} q_2(t_{k-j+1}). \quad (20)$$

Finally, for Eq. (11), we have the following finite difference scheme using the shifted GL approximate formula

$$\begin{aligned} \frac{q_1(t_{k+1}) - q_1(t_k)}{\tau} &= -(k_{12} + k_{10})q_1(t_k) + k_{21}\tau^{-(1-\alpha)} \sum_{j=0}^{k+1} g_j^{(1-\alpha)} q_2(t_{k-j+1}) + u_1(t_k), \\ \frac{q_2(t_{k+1}) - q_2(t_k)}{\tau} &= k_{12}q_1(t_k) - k_{21}\tau^{-(1-\alpha)} \sum_{j=0}^{k+1} g_j^{(1-\alpha)} q_2(t_{k-j+1}). \end{aligned} \quad (21)$$

Further, we can substitute the shift GL approximate formula with the following $L1$ formula²⁴

$${}_a^C D_t^\alpha q_2(t) \Big|_{t_k} \approx \frac{\tau^{-\alpha}}{\Gamma(2-\alpha)} \left[a_0^{(\alpha)} q_2(t_k) - \sum_{i=1}^{k-1} (a_{k-i-1}^{(\alpha)} - a_{k-i}^{(\alpha)}) q_2(t_i) - a_{k-1}^{(\alpha)} q_2(t_0) \right], \quad (22)$$

where $a_l^{(\alpha)} = (l+1)^{1-\alpha} - l^{1-\alpha}$, $l \geq 0$. Then, we construct another finite difference scheme for this problem

$$\begin{aligned} \frac{q_1(t_{k+1}) - q_1(t_k)}{\tau} &= k_{21} \frac{\tau^{-(1-\alpha)}}{\Gamma(1+\alpha)} \left[a_0^{(1-\alpha)} q_2(t_k) - \sum_{i=1}^{k-1} (a_{k-i-1}^{(1-\alpha)} - a_{k-i}^{(1-\alpha)}) q_2(t_i) - a_{k-1}^{(1-\alpha)} q_2(t_0) \right] \\ &\quad - (k_{12} + k_{10})q_1(t_k) + u_1(t_k), \end{aligned} \quad (23)$$

$$\frac{q_2(t_{k+1}) - q_2(t_k)}{\tau} = -k_{21} \frac{\tau^{-(1-\alpha)}}{\Gamma(1+\alpha)} \left[a_0^{(1-\alpha)} q_2(t_k) - \sum_{i=1}^{k-1} (a_{k-i-1}^{(1-\alpha)} - a_{k-i}^{(1-\alpha)}) q_2(t_i) - a_{k-1}^{(1-\alpha)} q_2(t_0) \right] + k_{12}q_1(t_k). \quad (24)$$

The matrix form of Eqs. (23) and (24) can be written as following

$$Q^k = A Q^{k-1} + k_{21} \frac{\tau^\alpha}{\Gamma(1+\alpha)} \sum_{i=1}^{k-2} B Q^i + C Q^0 + D U^{k-1}, \quad k \geq 3. \quad (25)$$

where $Q^k = (q_1(t_k), q_2(t_k))^T$, $U^k = (u_1(t_k), 0)^T$,

$$A = \begin{pmatrix} 1 - \tau(k_{12} + k_{10}) & k_{21} \frac{\tau^\alpha}{\Gamma(1+\alpha)} \\ \tau k_{12} & 1 - k_{21} \frac{\tau^\alpha}{\Gamma(1+\alpha)} \end{pmatrix}, \quad B = \begin{pmatrix} 0 - (a_{k-i-2}^{(1-\alpha)} - a_{k-i-1}^{(1-\alpha)}) \\ 0 & a_{k-i-2}^{(1-\alpha)} - a_{k-i-1}^{(1-\alpha)} \end{pmatrix},$$

$$C = \begin{pmatrix} 0 & -k_{21} \frac{\tau^\alpha}{\Gamma(1+\alpha)} a_{k-2}^{(1-\alpha)} \\ 0 & k_{21} \frac{\tau^\alpha}{\Gamma(1+\alpha)} a_{k-2}^{(1-\alpha)} \end{pmatrix} \quad \text{and} \quad D = \begin{pmatrix} \tau & 0 \\ 0 & 0 \end{pmatrix}.$$

The initial conditions can be represents as

$$q_1(t_0) = d, \quad q_2(t_0) = 0. \quad (26)$$

4.2 | Parameters estimation

We fit the system of Eq. (11) to the amiodarone dataset in order to estimate five parameters of the two compartment fractional model. For a particular choice of these parameter, the mean-square error (MSE) of the logarithm of the drug concentration $c_1(t)$ is

$$\underline{g}_i = \underline{g}(\lambda^i) = \frac{1}{M} \sum_{j=0}^M [\log(c_1(t_j)) - \log(c_n(t_j))]^2, \quad (27)$$

where λ^i is the approximate estimate of the unknown parameter vector Λ , $c_n(t_j)$ is the measured concentration, $c_1(t_j)$ is the semi-analytical solution by the NILT algorithm, t_j are the times of measurements and M is the number of measurements. It is obviously that MSE is a function of parameters of the fractional system. When the MSE value is minimal, model parameters are the optimal. Here we use the hybrid NMSS-PSO algorithm to estimate parameters in the optimization process. NMSS-PSO algorithm is based on the advantages of the Nelder-Mead simplex search and Particle Swarm Optimization algorithm. And the original population of NMSS-PSO algorithm consists of $3m + 1$ particles where m is the number of the parameters of the two compartmental fractional model. $m + 1$ particles of the population can be regarded as the standard starting point and the $2m$ particles are randomly generated in the PSO part. The NMSS-PSO algorithm can be summarized as follows:

Step 1: Initialization. Generate a population of size $3m + 1$.

Step 2: Repeate until the stopping criterion is met.

Step 2.1: Evaluation the objective function value in Eq. (27) of each particle and rank them.

Step 2.2: Apply the NMSS algorithm to the best $m + 1$ particles.

Step 2.3: Apply the PSO algorithm to update the $2m$ particles with the worst objective function value.

The definition of the stopping criterion is:

$$S_c = \left[\sum_{i=1}^{m+1} \frac{(\bar{g} - \sqrt{g_i})^2}{m+1} \right]^{\frac{1}{2}} < \varepsilon, \quad (28)$$

where $\bar{g} = \sum_{i=1}^{m+1} \frac{\sqrt{g_i}}{m+1}$, $\sqrt{g_i} = \underline{g}_i = \underline{g}(\lambda_{1,i}, \lambda_{2,i}, \dots, \lambda_{m,i})$ and ε is a small error parameter. More details can be found in ^{18,19,20}.

5 | RESULTS AND DISCUSSIONS

In this section, we give a comparison of the numerical solution and the semi-analytical solution with the help of MATLAB software and also discuss the effects of the order α on drug amounts.

The model we considered, Eq. (11), is a common one in pharmacokinetics. It is usually used to keep the concentrations of drugs in the therapeutic range by multiple administrations. Here in order to prove the availability of our numerical methods, we only investigate the variations of drug amount in 48 hours in human body after a single oral administration. And without loss of generality, we also assume the oral absorption of drug following exponential kinetic. Figs. 2 and 3 show the drug amounts

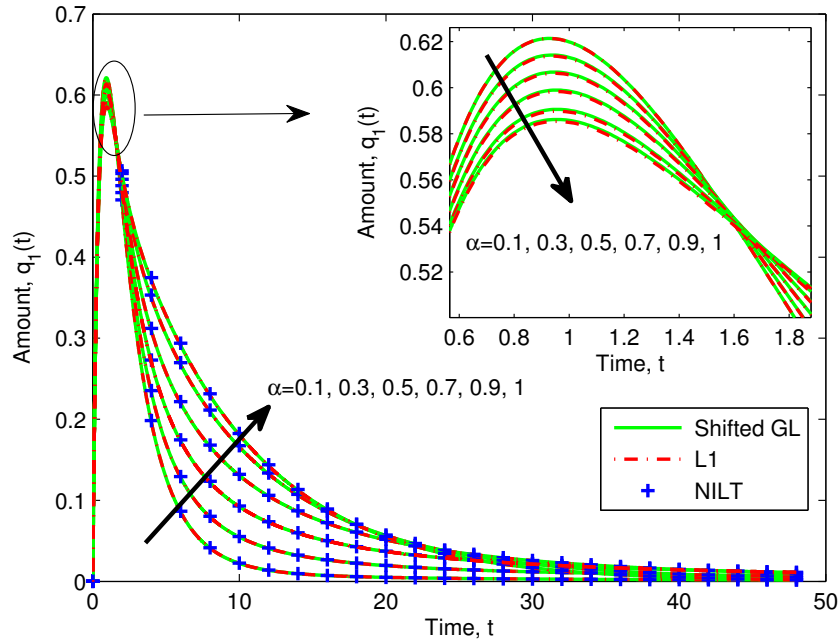


FIGURE 2 Amount-time profile of the compartment 1 in the system of (11) and (12) for different values of α with $k_{10} = 0.2$, $k_{12} = 0.6$, $k_{21} = 1$, $R = 2$ and $\lambda = 2$. The profile (Inset) is an enlargement of the amounts of the compartment 1 around the peak value. The solid lines correspond to the numerical solutions.

of the compartments 1 and 2, respectively. We can see that the numerical solutions and the semi-analytical solutions of the system Eq. (11) with oral absorption Eq. (12) under the zero initial conditions are remarkably agreement, which demonstrates that two numerical methods are effective and they have a similar accuracy. Meanwhile the experimental results show that the computational time of the shifted GL algorithm is essentially in agreement with that of the L1 algorithm.

The effects of the fractional order α on the amounts of the two compartmental fractional model Eq. (11) are also shown in Figs. 2 and 3. The numerical solutions are given together with different order α . We can see from Fig. 2 that the drug amounts of compartment 1 of the system with smaller fractional order α reach larger peak values at the same time and then get equilibrium in less time. This indicates that the profiles initially present exponential characteristics and later follow the power-law distribution showing the long-tailed character. Dokoumetzidis et al.¹⁴ also found this phenomenon. Similarly, Fig. 3 shows that the drug amounts of the compartment 2 also have larger crest values with the fractional order α decreasing and gradually go to different steady states. The fact has very important clinical implication in pharmacokinetics.

In Figs. 4 and 5, we plot the semi-logarithm profiles of the variations of the drug amounts of the system Eqs. (11) and (15) with time in 24 hours. We can see that the excellent agreement between the solutions is obviously which further proves that the two numerical methods are available. Fig. 4 shows that when the other parameters of the system Eq. (11) are fixed, the drug amounts of compartment 1 descend faster at first with the order α decreasing and show long-tailed character. Then we can clearly recognize that the profiles resemble the power-law distribution for $\alpha < 1$ and follow exponential kinetics for $\alpha = 1$. On the contrary, Fig. 5 indicates that when the other parameters of the system Eq. (11) are fixed, the amounts of compartment 2 have a rapid increase up to a maximum and then as the order α is increasing, the drug amount will decrease faster with time. These phenomena reveal the influence of α on drug dosage of the two compartments.

In addition, the two compartmental fractional model Eq. (11) is well fitted with an amiodarone pharmacokinetics dataset. Amiodarone is an antiarrhythmic drug following the anomalous kinetics. It has important clinical significance to study the accumulation pattern of the drug after taking this drug. Holt et al. have studied amiodarone in 1983 and first present the amiodarone dataset in⁹. Here, we use the NMSS-PSO algorithm and the NILT algorithm to estimate parameters of the system Eq. (11) with $\varepsilon = 10^{-2}$. The estimates of the unknown parameters are shown in Table 1 and the stopping criterion is satisfied with $S_c = 9.6918 \times 10^{-3}$. Then the comparison between the numerical solutions, the semi-analytical solution and the amiodarone

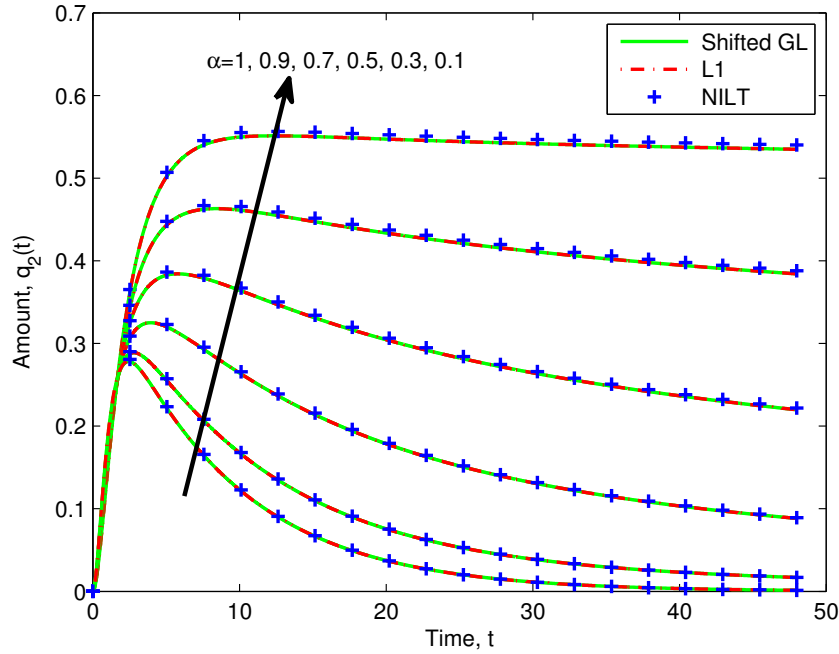


FIGURE 3 Amount-time profile of the compartment 2 in the system of (11) and (12) for different values of α with $k_{10} = 0.2$, $k_{12} = 0.6$, $k_{21} = 1$, $R = 2$ and $\lambda = 2$. The solid lines correspond to the numerical solutions.

dataset is given in Fig. 6 . We can see from the profile that those solutions maintain a highly consistent for 60 hours of this study which also proves the availability of the two numerical methods.

TABLE 1 Parameters estimated by the NMSS-PSO algorithm and the MSE.

Parameter	α	k_{10}	k_{12}	k_{21}	$q_1(0)/v_1$	MSE
Estimate	0.6886	1.4652	4.0370	0.3566	4.4764	3.20×10^{-3}

6 | CONCLUSION

In this work, we investigate two numerical methods and parameters estimation of a two compartmental fractional model with the different transmission processes in pharmacokinetics under different initial conditions. The finite difference schemes based on the shifted GL approximate formula and the $L1$ formula of the Caputo derivative are proposed, respectively. Meanwhile, the NMSS-PSO algorithm is used to achieve the parameters estimation. Then we compare the numerical solutions with the semi-analytical solutions and amiodarone data. These results indicate that the two numerical methods are effective and available. And the influence of the order of fractional derivative on the drug amount in human body is also presented. The results show that the drug amounts of the compartment 1 resemble the power-law distribution and the amounts of compartment 2 decline more quickly with α increasing.

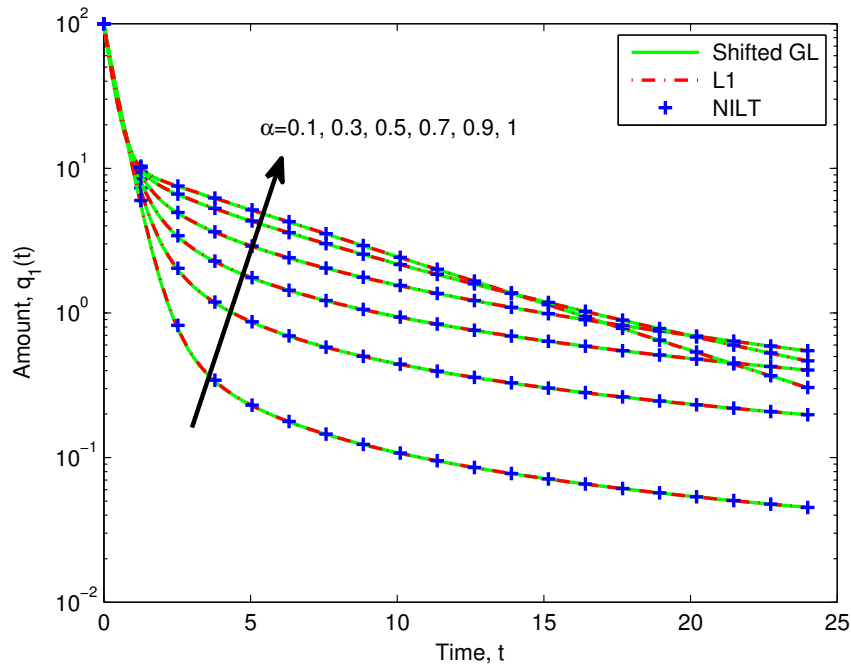


FIGURE 4 Amount-time profile of the compartment 1 in the system of (11) and (15) for different values of the fractional order α with $k_{10} = 1$, $k_{12} = 2$, $k_{21} = 0.5$ and the initial value $d = 100mg$. The solid line and the dotted line represent the numerical solutions and the pluses represent the semi-analytical solutions.

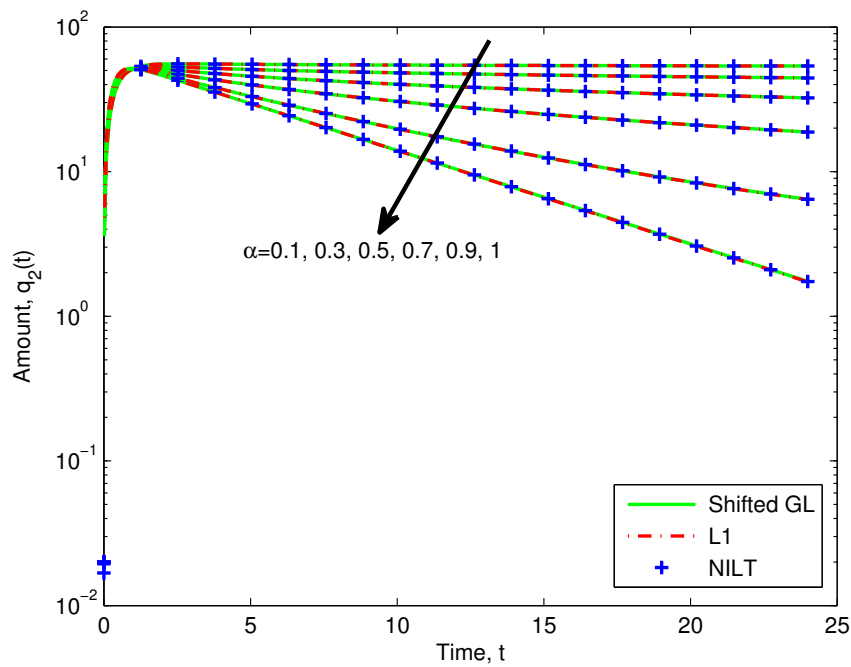


FIGURE 5 Amount-time profile of the compartment 2 in the system of (11) and (15) for different values of the fractional order α with $k_{10} = 1$, $k_{12} = 2$, $k_{21} = 0.5$ and the initial value $d = 100mg$. The solid line and the dotted line represent the numerical solutions and the pluses represent the semi-analytical solutions.

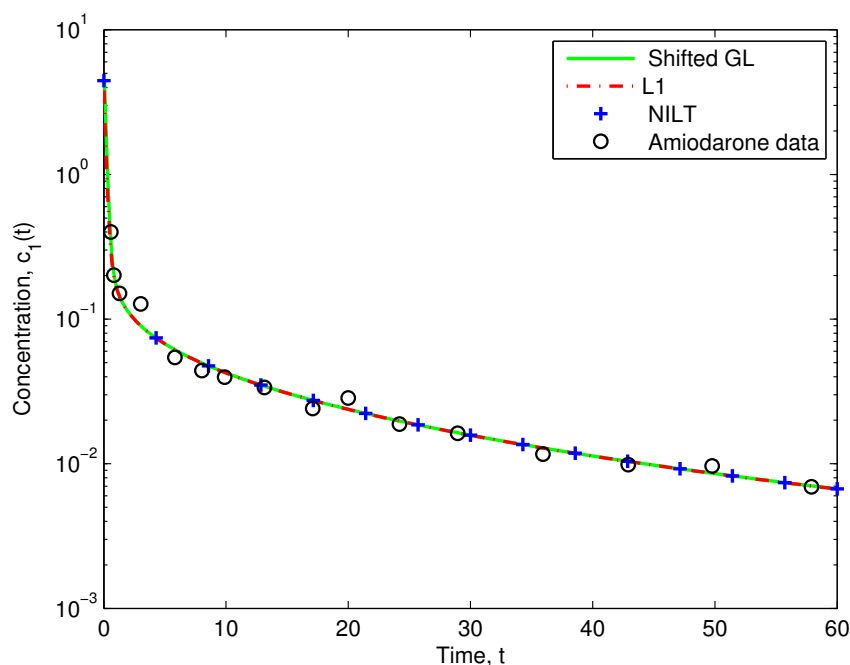


FIGURE 6 Concentration-time profile amiodarone in the compartment 1 of Eq.(11). The solid line and the dotted line correspond to the numerical solutions based on the shifted GL approximate formula and the $L1$ formula, respectively, The circles correspond to the experimental data and the pluses correspond to the semi-analytical solution of Eq.(11).

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CONFLICT OF INTEREST

This work does not have any conflicts of interest.

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