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Research article

Fractional numerical simulation of mathematical model of HIV-1 infection with stem cell therapy

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Abstract: This paper introduces fractional-order into a mathematical model of HIV infection of $CD4^+$ T-cells combining with the rate of multiply uninfected $CD4^+$ T-cells through mitosis and stem cell therapy. The paper shows the theoretical studies including positivity and stability of the solution. In addition, the numerical solutions are obtained and illustrated. The results show that the stem cell's therapy increases the quality of a HIV patient's life only for short time. This results are consistent with medical case studies.

Keywords: HIV infection; stem cell therapy; fractional numerical solution
Mathematics Subject Classification: 34K25, 34C27, 34D20, 92D25

1. Introduction

The human immunodeficiency virus (HIV) infection was revealed in early 1980 and affected more than 39.5 million people in the world. Since then the HVI has received attention by researchers and scientists [1]. In period between 2000 to 2016, the death from HIV in the Middle East and North Africa increased about 274% according to World Health Organization. Thus, the scientists have made efforts to find and develop an appropriate treatment for AIDS over the years.

The HIV infection is one of contagious disease and it occurs as a result of attacking the $CD4^+$ T-cells by the virus. Thus, $CD4^+$ T-cells will not be able to engulf a pathogen efficiently which leads to damage an immune system. Many treatments are suggested to improve the quality of HIV patient's life such as antiretroviral therapy [2], aggressive chemotherapy [3] and stem cell therapy. Indeed, the antiretroviral therapy is combination of medicine and the most common treatment for HIV infection, but it causes several side effects [4]. The stem cell therapy is very limited because the difficulty of finding healthy

and matched donors and it is expensive treatment. Therefore, in literature of medical case study, there are only two cases that used stem cell therapy to treat the HIV patient up to our knowledge [5, 6]. To better understand the behavior of the treatment into the HIV infection, the mathematical model is one of optimal way to study the effect of stem cell in quality of life for HIV patients.

The mathematical model of HIV infection of $CD4^+$ T-cells within a single patient of HIV-1 infection was first introduced by Perelson et al. [7]. The model studied the concentration of four components in blood: Infected and uninfected $CD4^+$ T-cells, virus, and latent infected cell. This model have been modified and widely studied by several researchers [8–12]. Perelson's model was developed by eliminating latent infected cell by Duffin and Tullis [8]. The last model was developed to include the stem cell therapy by Alqudah et al. [13] and have been studied theoretically and numerical by Alqudah and Aljahdaly [14]. Wang and Li modified the Duffin model to include the rate of multiply uninfected $CD4^+$ T-cells through mitosis [15].

The novelty of this work is to combine the equation of stem cell therapy with the Wang model and compare the results with the results in [13]. In addition, it will introduce the fractional-order into a mathematical model of HIV infection of $CD4^+$ T-cells with stem cell therapy since the membranes of cells of biological organism have fractional-order electrical conductance.

The paper is arranged as following: (1) presenting the the fractional-order into a mathematical model for aforementioned problem, (2) studding the model in terms of existence, uniqueness and positivity, (3) showing equilibrium points and their stability, (4) plotting the numerical solutions and discussing the results, finally summing up the results and conclusion of the study.

2. Fractional mathematical model

Fractional Calculus (i.e factional derivative and anti-derivative in time or space domain) as a branch of mathematical analysis, represents a simple way to investigate the dynamics of complex systems in many areas of science and engineering [16–23]. The order of the fractional derivative is an additional parameter in the adopted model associated with non-local effects in the space domain or memory effects in the time domain. In recent years, fractional calculus has attracted the interest of many researchers in, e.g., fluid flow, viscoelastic study of soft biological tissues that is useful in medical diagnosis, digital control and signal processing. Membranes of cells of biological are classified in groups of non-integer order models [24, 25].

The HIV mainly attacks $CD4^+$ T-cells (T). The range of T-cell level l is $[800 \;\; 1200] mm^{-3}$. Assume that λ_T is the rate of producing T-cell in bone marrow and thymus. The T cell has also natural death rate at d_T. Therefore, the T dynamic can be described by

$$\frac{d^\alpha T(t)}{dt^\alpha} = \lambda_T - d_T T(t) + r_T T(t)\left(1 - \frac{T(t)}{T_{max}}\right) - k_T T(t) V(t)$$

where r_T is the rate of T mitosis and T_{max} is the maximum population level of T.

We introduced the mathematical model of HIV in [15] as a fractional differential equation (FDE) to examine the effect of the FDE parameter α, $0 < \alpha < 1$ as follows,

$$\frac{d^\alpha T(t)}{dt^\alpha} = \lambda_T - d_T T(t) + r_T T(t)\left(1 - \frac{T(t)}{T_{max}}\right) - k_T T(t) V(t)$$

$$\begin{aligned}\frac{d^{\alpha}T_i(t)}{dt^{\alpha}} &= k_T T(t)V(t) - \beta_{Ti}T_i(t)\\ \frac{d^{\alpha}V(t)}{dt^{\alpha}} &= N\beta_{T_i}T_i(t) - c_v V(t)\end{aligned} \tag{1}$$

where T, T_i and V are concentration of uninfected CD4$^+$ T-cells, infected CD4$^+$ T-cells and HIV-1 virus in the blood, respectively. d_T and β_{Ti} are the death rate of T and T_i respectively. k_T is infection of CD4$^+$ T-cells. c_v is clearance rate of V and N is the number of virus particle produced by each T_i cell. In addition, the stem cell which is denote by S has division rate at k. The probability of the type of stem cell division are: (i) division into two undifferentiated cells at rate α_s, (ii) division into undifferentiated cell and differentiated cell at rate α_D and (iii) division into two differentiated cells at rate α_T such that $\alpha_A + \alpha_s + \alpha_D = 1$. Also, the S cell has natural death at rate δ_s. Therefore, the following is HIV model with the rate of multiply uninfected CD4$^+$ T-cells through mitosis and effect of stem cell therapy,

$$\begin{aligned}\frac{d^{\alpha}S(t)}{dt^{\alpha}} &= (k(\alpha_s - \alpha_D) - \delta_s)\,S(t)\\ \frac{d^{\alpha}T(t)}{dt^{\alpha}} &= \lambda_T - d_T T(t) + (2\alpha_D + \alpha_A)kAS(t) + r_T T(t)\left(1 - \frac{T(t)}{T_{max}}\right) - k_T T(t)V(t)\\ \frac{d^{\alpha}T_i(t)}{dt^{\alpha}} &= k_T T(t)V(t) - \beta_{Ti}T_i(t)\\ \frac{d^{\alpha}V(t)}{dt^{\alpha}} &= N\beta_{T_i}T_i(t) - c_v V(t)\end{aligned} \tag{2}$$

where A is amplification factor [14, 15].

3. Existence, uniqueness and positivity solutions

Following the **Theorem 3.1** and **Remark 3.2** in reference [26] gives that the solutions of the system (2) are existent and unique in $R^+ = (0, \infty)$.

Theorem 1. There exists a unique solution $f(t) = (S, T, T_i, V)$ to Eq (2) on $t \geq 0$ and the solution is positive in $R^4 = \{f \in R | f \geq 0\}$. Moreover, $T(t)$ and $T_i(t)$ are all bounded by $\lambda_T + (2\alpha_D + \alpha_A)kAS_{max}(t)$, where $S_{max}(t)$ denotes stem-cells carrying capacity

Proof. From Eq 2, we find

$$\begin{aligned}\frac{d^{\alpha}S(t)}{dt^{\alpha}}|_{S=0} &= 0 \geq 0,\\ \frac{d^{\alpha}T(t)}{dt^{\alpha}}|_{T=0} &= \lambda_T + (2\alpha_D + \alpha_A)kAS(t) \geq 0\\ \frac{d^{\alpha}T_i(t)}{dt^{\alpha}}|_{T_i=0} &= k_T T(t)V(t) \geq 0,\\ \frac{d^{\alpha}V(t)}{dt^{\alpha}}|_{V=0} &= N\beta_{T_i}T_i(t) \geq 0\end{aligned}$$

by the **Corollary 1** in reference [25], the solution (S, T, T_i, V) is positive in R^4. Moreover from Eq (2),

$$\frac{d^{\alpha}(T + T_i)}{dt^{\alpha}} = \lambda_T + (2\alpha_D + \alpha_A)kAS(t) - \beta_{Ti}T_i(t)$$

$$+ r_T T(t)\left(1 - \frac{T(t)}{T_{max}}\right)$$

$$\begin{aligned}\frac{d^\alpha(T+T_i)}{dt^\alpha} &\leq \lambda_T + (2\alpha_D + \alpha_A)kAS(t) + r_T T(t)\left(1 - \frac{T}{T_{max}}\right)\\ &= \lambda_T + (2\alpha_D + \alpha_A)kAS(t)\end{aligned}$$

where $T_{max} = T + T_i$, the exact solution of S is $S(t) = e^{(k(\alpha_s - \alpha_D) - \delta_s)} > 0$ for all t which mean $S_{max} \geq S(t) > 0$. Therefore,

$$\frac{d^\alpha(T+T_i)}{dt^\alpha}|_{S_{max},T_{max}} \leq \lambda_T + (2\alpha_D + \alpha_A)kAS_{max}(t).$$

Thus, by he **Corollary 1** in reference [25], the T-cell population, $(T + T_i)$ in case of HIV infection with stem cell therapy are bounded by $\lambda_T + (2\alpha_D + \alpha_A)kAS_{max}(t)$. □

4. Equilibrium points and their stability

To obtain the equilibrium points of Eq (2), we solve the system at the steady state (i.e $\frac{d^\alpha S(t)}{dt^\alpha} = \frac{d^\alpha T(t)}{dt^\alpha} = \frac{d^\alpha T_i(t)}{dt^\alpha} = \frac{d^\alpha V(t)}{dt^\alpha} = 0$), hence

$$\begin{aligned}\bar{S} &= 0\\ \bar{T} &= \frac{c_v}{k_T N}\\ \bar{T}_i &= \frac{NT_{max}k_T(\lambda_T N k_T - d_T c_v + r_T c_v) - r_T c_v^2}{k_T^2 N^2 T_{max}\beta_{T_i}}\\ \bar{V} &= \frac{NT_{max}k_T(\lambda_T N k_T - d_T c_v + r_T c_v) - r_T c_v^2}{k_T^2 N T_{max} c_v}\\ b_1 &= \frac{-T_{max}(d_T - r_T) \pm \sqrt{T_{max}^2(d_T - r_T)^2 + 4r_T\lambda_T T_{max}}}{2r_T}\end{aligned} \tag{3}$$

Then, both $E_0 = (0, b_1, 0, 0)$ and $E_1 = (\bar{S}, \bar{T}, \bar{T}_i, \bar{V})$ are the equilibrium points of the system (1). The obtained equilibrium points are consistent with the equilibrium points of the system (1) in case of $\alpha = 1$ and $S(t) \equiv 0$. The stability of these equilibrium points have been studied in reference [25]. The equilibrium point E_0 is asymptotically stable when $N \leq \frac{d_T(c_v + k_T b_1)}{k_T \Pi_{T_i} b_1}$, N is the virus particles produced by $CD4^+$ T. The The equilibrium point E_1 is asymptotically stable under the conditions in Proposition 1 and Proposition 2 in [25].

5. Numerical simulation and discussion

The numerical scheme, Eq (2), can be solved by adopting the following Caputo definition of fractional derivative of order α $(0 < \alpha < 1)$ [27].

Caputo's n^{th} order fractional derivative is defined as,

$$\frac{d^\alpha}{dr^\alpha} f^{(n)}(r) = \frac{1}{\Gamma(n-\alpha)} \int_0^r \frac{1}{(r - r')^{(1-n+\alpha)}} f^{(n)}(r')\, dr';\ n = 1, 2, \ldots. \tag{4}$$

where $\Gamma(x)$ is the Gamma function.

The 1^{st} order derivative S, T, T_i and V term in Eq (2) becomes,

$$\frac{d^\alpha}{d\tau^\alpha} f(\tau) = \frac{1}{\Gamma(1-\alpha)} \int_0^\tau \frac{1}{(\tau - t')^\alpha} \frac{d}{dt'} f(t')\, dt', \tag{5}$$

We use the numerical technique of the Euler's method to solve Eq (2) with the same ICs. as in Table 1 [28, 29]. The system of Eq (2) subjects to the following initial conditions

$$S(0) = S_0, \quad T(0) = T_0, \quad T_i(0) = T_{i_0}, \quad V(0) = V_0.$$

Table 1. The value of the parameters based on the reference [13, 30].

Parameter	Value
k	0.035/day
α_S	0.21/day
α_D	0.16/day
δ_S	0.03/day
λ_T	0.17 cells/ul.day
d_T	0.01/day
α_A	0.6 /day
A	0.5
r_T	3
T_{max}	1500
k_T	6.5×10^{-4} virus/ul.day
β_{T_i}	0.39/day
N	10
c_V	3/day
S_0	18 cells/ul
T_0	900 cells/ul
T_{i_0}	100 cells/ul
V_0	10^{-6} virus/ul

The iterative numerical scheme can be described as follows,

(i) The initial values of $t(0) = 0, S(0) = 18, T(0) = 900, T_i(0) = 100$ and $V(0) = 10^{-6}$ are set.

(ii) Transforming Eq (2) over the interval $t \in [0, a]$ to integral equations by Applying Caputo's formula Eq (5).

(iii) $S(t_j), T(t_j), T_i(t_j)$ *and* $V(t_j)$ are computed with fractional Euler's method approximation scheme,

$$S(t_{j+1}) = S(t_j) + \frac{h^\alpha}{\Gamma(\alpha+1)} f_1(t_j, S(t_j), T(t_j), T_i(t_j), V(t_j))$$
$$T(t_{j+1}) = T(t_j) + \frac{h^\alpha}{\Gamma(\alpha+1)} f_2(t_j, S(t_j), T(t_j), T_i(t_j), V(t_j))$$

$$T_i(t_{j+1}) = T_i(t_j) + \frac{h^\alpha}{\Gamma(\alpha+1)} f_3(t_j, S(t_j), T(t_j), T_i(t_j), V(t_j))$$
$$V(t_{j+1}) = V(t_j) + \frac{h^\alpha}{\Gamma(\alpha+1)} f_4(t_j, S(t_j), T(t_j), T_i(t_j), V(t_j)) \quad (6)$$

The functions $f_{1,2,3,4}(t_j, S(t_j), T(t_j), T_i(t_j), V(t_j))$ are given by,

$$\begin{aligned} f_1(t_j, S(t_j), T(t_j), T_i(t_j), V(t_j)) &= (k(\alpha_s - \alpha_D) - \delta_s) S(t_j) \\ f_2(t_j, S(t_j), T(t_j), T_i(t_j), V(t_j)) &= \lambda_T - d_T T(t_j) + (2\alpha_D + \alpha_A) kAS(t_j) \\ &\quad + r_T T(t_j)\left(1 - \frac{T(t_j)}{T_{max}}\right) - k_T T(t_j) V(t_j) \\ f_3(t_j, S(t_j), T(t_j), T_i(t_j), V(t_j)) &= k_T T(t_j) V(t_j) - \beta_{Ti} T_i(t_j) \\ f_4(t_j, S(t_j), T(t_j), T_i(t_j), V(t_j)) &= N\beta_{T_i} T_i(t_j) - c_v V(t_j) \end{aligned} \quad (7)$$

where, $0 \le j \le n$, $t_{i+1} = t_i + h$ and h is the step size.

(iv) A set of points, $(t_j, S(t_j))$, $(t_j, T(t_j))$, $(t_j, T_i(t_j))$ and $(t_j, V(t_j))$, are produced for different values of α.

The numerical results are shown in Figures 1 and 2. The initial conditions define the case of patient who has infected and uninfected CD4$^+$ T-cells by V virus and has received stem cell transplantation. Concentration of stem cells, $S(t)$, shown in Figure 1a, decays more rapidly as α decreases for all $t \in (0, 120)$.

Figure 1b,c predicts that stem cell transplantation increase the uninfected cell T until T reaches its maximum value at early time around $t \simeq 2$ and decrease infected cell T_i. Figure 1d shows that the virus concentration deceases during short period of time and the same behavior of infected cell T_i is observed. Ultimately the concentration of T cell reaches the peak, Figure 1b. Then, the patient face rebound during very short time which means the patient returned to worst case. This shows that the stem cell can improved the patient quality life during short time and the procedure must to be applied again. These results are matched the reported medical cases [5, 6].

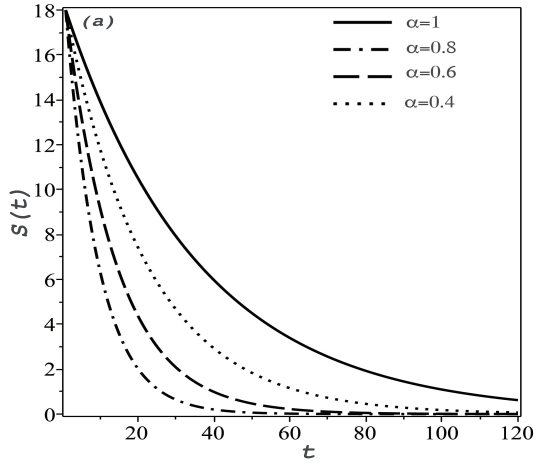

Figure 1a. Plot of $S(t)$ in Eq 2 for different values of α.

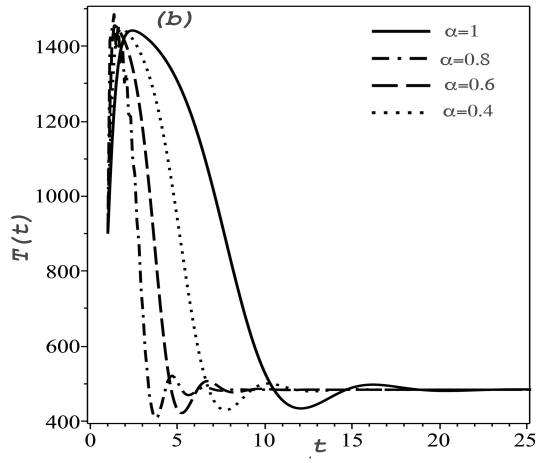

Figure 1b. Plot of $T(t)$ in Eq 2 for different values of α.

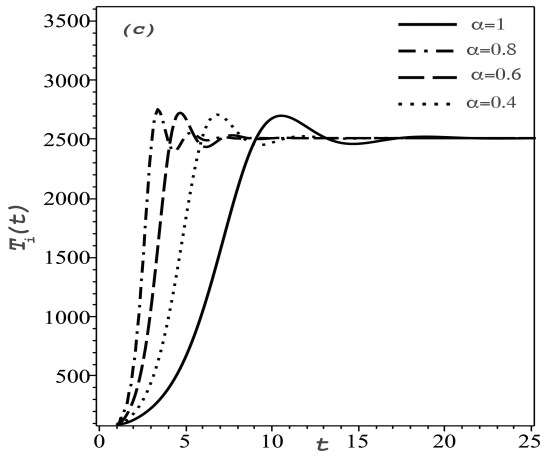

Figure 1c. Plot of $T_i(t)$ in Eq 2 for different values of α.

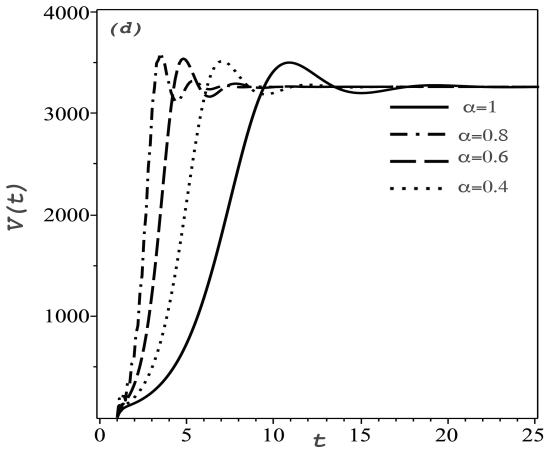

Figure 1d. Plot of $V(t)$ in Eq 2 for different values of α.

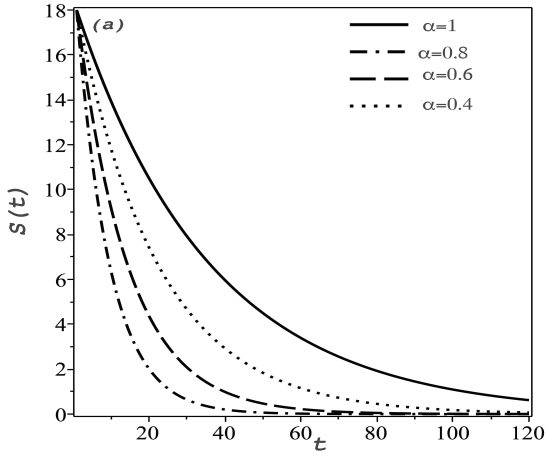

Figure 2a. Plot of $S(t)$ in the fractional model in Ref. [14] for different values of α.

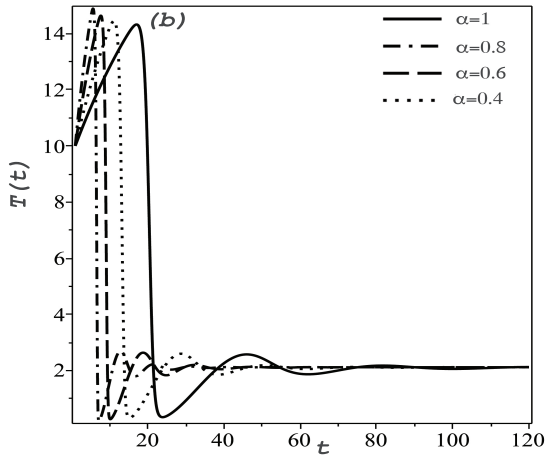

Figure 2b. Plot of T in the fractional model in Ref. [14] for different values of α.

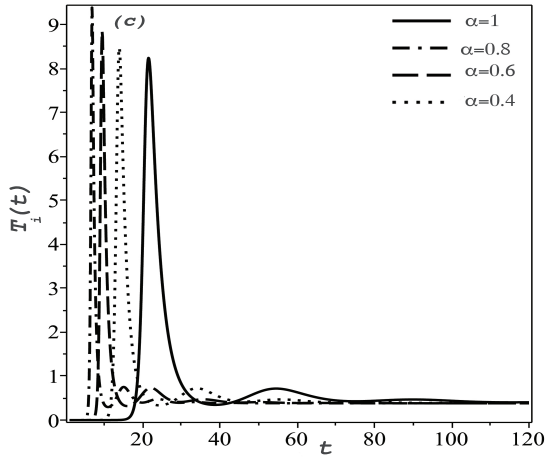

Figure 2c. Plot of $T_i(t)$ in the fractional model in Ref. [14] for different values of α.

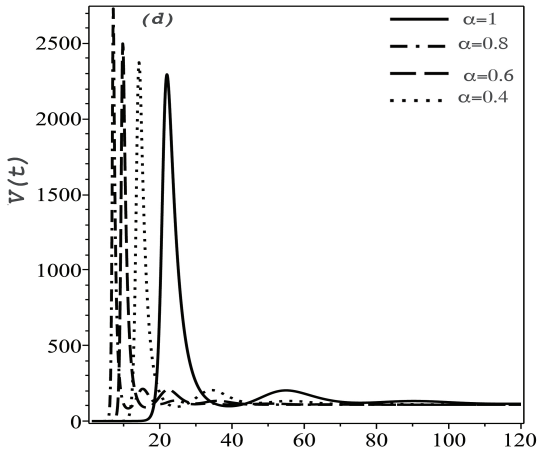

Figure 2d. Plot of $V(t)$ in the fractional model in Ref. [14] for different values of α.

6. Connection with the previous studies

The numerical solutions of a mathematical model for treatment of HIV infection by stem cell therapy with consider the maximum population of cell T_{max} are obtained in this work. The results can be compared with results for fractional mathematical model of HIV infection by stem cell therapy without consider T_{max} [14] as we see in Figure 2a–d . First, in Figure 1b, T increases but does not pass T_{max} and this is more realistic. The behavior of the solutions in both results are consistent with the medical cases results [5, 6].

7. Conclusions

In this work, since the cells of biological organism has fractional order, we modified the ODE model of HIV-1 infection with stem cell therapy into a system of fractional-order. In addition, the level of population T and T_i is controlled by T_{max} which is more realistic. We proved that the solutions are existent, unique, and positive for all $t \geq 0$. Moreover, the fractional model is asymptotically stable. The numerical solutions show that patient quality life can be improved for short time, then the patient will face rebound during short time of period. This results are consist with the medical case that reported in references [5, 6]. We found that the fractional order model reflects the problem successfully.

Data availability

The data supporting this research are from previously reported studies, which have been cited.

Conflicts of interest

The authors declare that there is no conflicts of interest regarding the publication of this paper.

Authors' contributions

Noufe Aljahdaly proposed the Mathematical model of this paper and analyzed the data. R. A. Alharbey implemented the solutions with software. All authors studied the model theoretically, wrote this paper, read, and approved the final manuscript.

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