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The effect of anti-viral drug treatment of human immunodeficiency virus type 1 (HIV-1) described by a fractional order model

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ABSTRACT

In this paper, generalized Euler method (GEM) and homotopy analysis method (HAM) are performed to solve the problem of the population dynamics of the human immunodeficiency type 1 virus (HIV-1). We introduce fractional orders to the model of HIV-1 whose components are plasma densities of uninfected $CD4^+$ T-cells, the infected such cells and the free virus. The effect of the drug treatment of HIV-1 will be discussed in this paper.

1. Introduction

Mathematical models have become important tools in analyzing the spread and control of infectious diseases. Understanding the transmission characteristics of infectious diseases in communities, regions, and countries can lead to better approaches to decreasing the transmission of these diseases [1]. There has been much interest recently in mathematical models of viral population dynamics in host cells with most attention focused on HIV [2–4]. Different methods were investigated to get approximate analytic solution or numerical solutions for the different models of the dynamics of HIV disease [5–7]. In [8], the variational iteration method and modified variational iteration method were applied to obtain approximate solution of HIV infection model. We will consider some models for HIV-1 population dynamics below but first analyze a simplified model introduced by Bonhoeffer et al. in [9]. Here there are two components: x, the number of uninfected $CD4^+$ T-cells and y, the number of infected such cells. Then the following two equations describe the evolution of the system:

$$\frac{dx}{dt} = s - \mu x - \beta xy,$$
$$\frac{dy}{dt} = \beta xy - \nu y,$$

where all parameters and variables are non-negative. Again s is the assumed constant rate of production of $CD4^+$ T-cells, μ is their per capita death rate, βxy is the rate of infection of $CD4^+$ T-cells by virus, and νy is the rate of disappearance of infected cells. The viral variable has been omitted for simplicity as it is here assumed to be linearly related to y. A more complete model of human immunodeficiency virus type 1 (HIV-1) dynamics considers in addition to the uninfected and infected

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$CD4^+$ T-cells, x and y, respectively, the number of virions in plasma, z. The following three equations are a slightly modified version of those in [2]:

$$\frac{dx}{dt} = s - \mu x - \beta xz,$$
$$\frac{dy}{dt} = \beta xz - \nu y,$$
$$\frac{dz}{dt} = cy - \gamma z - \beta xz.$$

A modified model was presented in [2] as follows:

$$\frac{dx}{dt} = s - \mu x - \beta xz,$$
$$\frac{dy}{dt} = \beta xz - \varepsilon y,$$
$$\frac{dz}{dt} = cy - \gamma z,$$

with initial conditions

$$x(0) = M_1, \ \ y(0) = M_2, \ \ z(0) = M_3,$$

where s is the (assumed constant) rate of production of $CD4^+$ T-cells, μ is their per capita death rate, β is the rate of infection of $CD4^+$ T-cells by virus, ε is the per capita rate of disappearance of infected cells, c is the rate of production of virions by infected cells, γ is the death rate of virus particles.

When the therapy drug was given, it affects the rate of death of the infected cells which produce virus particles. But since, drug may not be 100% effective hence only a part of infected cells will revert back to uninfected class and the remaining will progress and become productively infected and then produce virus. Typical parameter values are found in [10,3], with time in days and particle (cell) densities in numbers per cubic millimeter:

$$s = 0.272, \ \ \mu = 0.00136, \ \ \varepsilon = 0.33, \ \ \gamma = 2, \ \ \beta = 0.00027 \ \text{ and } \ c = 50.$$

Now we introduce the generalized model of the viral dynamic model where $\alpha_1, \alpha_2, \alpha_3 > 0$. The system is described by the following system of FODE:

$$\begin{aligned} D^{\alpha_1}(x) &= s - \mu x - \beta xz, \\ D^{\alpha_2}(y) &= \beta xz - \varepsilon y, \\ D^{\alpha_3}(z) &= cy - \gamma z. \end{aligned} \tag{1}$$

Subject to the initial values

$$x(0) = 200, \ \ y(0) = 0, \ \ z(0) = 1.$$

The reason of using fractional order differential equations (FOD) is that FOD are naturally related to systems with memory which exists in most biological systems. Also they are closely related to fractals which are abundant in biological systems. The results derived of the fractional system (1) are of a more general nature.

The rest of the paper is organized as follows. In Section 2, a discussion about the fractional calculus theory is presented. The idea of Generalized Taylor formula and generalized Euler method (GEM) for solving fractional order ordinary differential equations are discussed in Section 3 and Section 4 respectively. The idea of Homotopy analysis (HAM) method is presented in Section 5. Numerical results of GEM and HAM are presented in Section 6 with comparisons with the results other methods. Numerical simulation and discussion is presented in Section 7.

2. Fractional calculus

The field of fractional calculus is almost as old as calculus itself, but over the last decades the usefulness of this mathematical theory in applications as well as its merits in pure mathematics has become more and more evident [11,12]. Fractal differential equations have attracted many researchers due to their important applications in fluid flow, mechanics, biology, physics, epidemiology and engineering, and other applications. This is because of the fact that the realistic modeling of a physical phenomenon does not depend only on the instant time, but also on the history of the previous time which can also be successfully achieved by using fractional calculus. In other words, previous values of the solution and the derivatives in fractional order differential equations are required to obtain a solution at a particular instance. The memory effect of the convolution in the fractional integral gives the equation increased expressive power. There are several definitions of a fractional derivative of order $\alpha > 0$ [13]. The two most commonly used definitions are Riemann–Liouville and Caputo. Each definition uses Riemann–Liouville fractional integration and derivatives of whole order. The difference between the two definitions is in the order of evaluation.

Definition 2.1. Riemann–Liouville fractional integration of order α is defined as:

$$J^{\alpha}f(x) = \frac{1}{\Gamma(\alpha)}\int_0^x (x-t)^{\alpha-1}f(t)dt, \quad \alpha > 0,\ x > 0,$$

$$J^0 f(x) = f(x).$$

Definition 2.2. Riemann–Liouville and Caputo fractional derivatives of order α can be defined respectively as:

$$D^{\alpha}f(x) = D^m(J^{m-\alpha}f(x)),$$
$$D_*^{\alpha}f(x) = J^{m-\alpha}(D^m f(x)),$$

where

$$m-1 < \alpha \leqslant m, \quad m \in N.$$

Properties of the operator J^{α} can be found in [11,12], we mention only the following:

(1) $J^{\alpha}J^{\beta}f(x) = J^{\alpha+\beta}f(x)$,

(2) $J^{\alpha}J^{\beta}f(x) = J^{\beta}J^{\alpha}f(x)$,

(3) $J^{\alpha}t^{\gamma} = \dfrac{\Gamma(\gamma+1)}{\Gamma(\alpha+\gamma+1)}t^{\alpha+\gamma}, \quad \alpha > 0,\ \gamma > -1,\ t > 0.$

The definition of fractional derivative involves an integration which is non local operator (as it is defined on an interval) so fractional derivative is a non local operator. In other word, calculating time-fractional derivative of a function $f(t)$ at some time $t = t_1$ requires all the previous history, i.e., all $f(t)$ from $t = 0$ to $t = t_1$. Many mathematicians have tried to study some models of infectious diseases models using the fractional calculus. A fractional order differential system for modeling human T-cell lymphotropic virus I (HTLV-I) infection of $CD4^+$ T-cells is studied in [14] and its approximate solution is presented using a multi-step generalized differential transform method. An Adams-type predictor–corrector method was applied in [15] to give numerical solutions for fractional-order into a model of HIV infection of $CD4^+$ T-cells. The authors in [16] considered the classical mathematical models with saturation response of the infection rate of some diseases like HCV, HIV, and HBV. They studied the existence of such models and numerical simulations are presented to illustrate the results.

3. Generalized Taylor's formula

In this section we introduce a generalization of Taylor's formula that involves Caputo fractional derivatives. This generalization is presented in [17].

Suppose that $D_*^{k\alpha}f(x) \in C(0,a]$, for $k = 0, 1, \ldots, n+1$, where $0 < \alpha \leqslant 1$. Then we have

$$f(x) = \sum_{i=0}^{n}\frac{x^{i\alpha}}{\Gamma(i\alpha+1)}(D_*^{i\alpha})(0+) + \frac{(D_*^{(n+1)\alpha}f)(\zeta)}{\Gamma((n+1)\alpha+1)}x^{(n+1)\alpha}, \tag{2}$$

with $0 \leqslant \zeta \leqslant x, \forall x \in (0,a]$.

In case of $\alpha = 1$, the generalized Taylor's formula (2) reduces to the classical Taylor's formula.

4. Generalized Euler method (GEM)

Most nonlinear fractional differential equations do not have analytic solutions, so approximations and numerical techniques must be used [18,19]. The decomposition method (ADM), the variational iteration method (VIM), and The homotopy analysis method (HAM) are relatively new approaches to provide an analytical approximate solution to linear and nonlinear problems, and they are particularly valuable as tools for scientists and applied mathematicians, because they provide immediate and visible symbolic terms of analytic solutions, as well as numerical approximate solutions to both linear and nonlinear differential equations [8,11,12]. In recent years, the application of the ADM, VIM, in linear and nonlinear problems has been developed. On the other hand, these methods are effective for small time, i.e., $t \ll 1$, however the such methods cannot solve the problem for larger time and in fact the solution of the chaotic system using HPM is an open problem. Nevertheless by chance, there are cases at which these methods give good approximation for a large range of time (t). A few numerical methods for fractional differential equations models of infectious diseases models have been presented in the literature. However many of these methods are used for very specific types of differential equations, often just linear equations or even smaller classes. In [20], Odibat and Momani derived the generalized Euler's method that we have developed for the numerical solution of initial value problems with Caputo derivatives. The method is a generalization of the classical Euler's

method. Arafa et al. used GEM to obtain numerical solution of fractional order model of HTLV infection [21] while in [22] they apply GEM to study the HIV during the primary infection. Consider the initial value problem

$$(D_*^{\alpha} y(t) = f(t, y(t)), \quad y(0) = y_0, \;\; 0 < \alpha \leqslant 1, \;\; t > 0. \tag{3}$$

Let $[0, a]$ be the interval over which we want to find the solution of the problem (3). In actuality, we will not find a function $y(t)$ that satisfies the initial value problem (6). Instead, a set of points $\{t_j, y(t_j)\}$ is generated, and the points are used for our approximation. For convenience we subdivide the interval $[0, a]$ into k subintervals $[t_j, t_{j+1}]$ of equal width $h = \frac{a}{k}$ by using the nodes $t_j = jh$, for $j = 0, 1, \ldots, k$. Assume that $y(t), D_*^{\alpha} y(t)$ and $D_*^{2\alpha} y(t)$ are continuous on $[0,a]$ and use the generalized Taylor's formula (5) to expand $y(t)$ about $t = t_0 = 0$. For each value t there is a value c_1 so that [20]

$$y(t) = y(t_0) + (D_*^{\alpha} y(t))(t_0)\frac{t^{\alpha}}{\Gamma(\alpha+1)} + ((D_*^{2\alpha} y(t))(c_1)\frac{t^{2\alpha}}{\Gamma(2\alpha+1)}. \tag{4}$$

When $(D_*^{\alpha} y(t))(t_0) = f(t_0, y(t_0))$ and $h = t_1$ are substituted into Eq. (4), the result is an expression for $y(t_1)$:

$$y(t) = y(t_0) + f(t_0, y(t_0))\frac{h^{\alpha}}{\Gamma(\alpha+1)} + ((D_*^{2\alpha} y(t))(c_1)\frac{h^{2\alpha}}{\Gamma(2\alpha+1)}.$$

If the step size h is chosen small enough, then we may neglect the second-order term (involving $h^{2\alpha}$) and get

$$y(t_1) = y(t_0) + \frac{h^{\alpha}}{\Gamma(\alpha+1)} f(t_0, y(t_0)),$$

and so on, we can get $y(t_1), y(t_2), \ldots$, the process is repeated and generates a sequence of points that approximates the solution, then we can get the general formula for generalized Euler's method (GEM) when $t_{j+1} = t_j + h$ as follow [20]

$$y(t_{j+1}) = y(t_j) + \frac{h^{\alpha}}{\Gamma(\alpha+1)} f(t_j, y(t_j)) \tag{5}$$

for $j = 0, 1, \ldots, k-1$. It is clear that if $\alpha = 1$, then the generalized Euler's method (5) reduces to the classical Euler's method. This method discuss in details in [20].

5. Homotopy analysis method

Many of the (FDEs) that arise in physical or biological situations are highly non-linear. As a result, it is often difficult to obtain analytical solutions to these problems. Some of the recent analytic methods for solving nonlinear problems include the Adomian decomposition method (ADM), homotopy-perturbation method (HPM), variational iteration method (VIM). Liao [23,24] gives an example that effectively illustrates the limitations of traditional perturbation methods: the problem of a body falling freely through. He then goes on to give an alternative technique known as the basic idea of the HAM method is to produce a succession of approximate solutions that tend to the exact solution of the problem. The presence of auxiliary parameters and functions in the approximate solution results in the production of a family of approximate HAM provides us with a simple way to adjust and control the convergence region of the series solution by introducing the auxiliary parameter $h \neq 0$, and the auxiliary function $H \neq 0$. One can get accurate approximations by only a few terms with $h = -1$ and $H = 1$. Besides, the so-called "homotopy perturbation method" (proposed in 1998) is exactly the same as the early homotopy analysis method (proposed in 1992) and is a special case of the late homotopy analysis method in case of $h = -1$ Consider the following system of (FDE):

$$D^{\alpha_i}(u_i(t)) = f_i(t, u_1, \ldots, u_n), \quad i = 1, 2, 3, \ldots, n, \;\; 0 \leqslant \alpha_i \leqslant 1. \tag{6}$$

subject to the initial conditions:

$$u_i(0) = \alpha_i, \quad i = 1, 2, \ldots, n. \tag{7}$$

Liao [10] constructed the so-called zeroth-order deformation equation:

$$(1-q)\mathcal{L}_i[\phi_i(t,q) - u_{i0}(t)] = qh_i H_i(t) N_i[\phi_i(t,q)], \quad i = 1, 2, 3, \ldots, n, \tag{8}$$

subject to the initial conditions:

$$\phi_i(0, q) = a_i, \tag{9}$$

where $q \in [0, 1]$ is an embedding parameter, N_i are nonlinear operators, $\mathcal{L}_i$ are auxiliary linear operators satisfy $\mathcal{L}_i(0) = 0$, $u_{i0}(t)$ are initial guesses satisfy the initial conditions (7), $h_i \neq 0$ are auxiliary parameters, $H_i(t) \neq 0$ are auxiliary functions, $\phi_i(t, q)$ are unknown functions. It should be emphasized that one has great freedom to choose, the auxiliary linear operators $\mathcal{L}_i$, the auxiliary parameters h_i and the auxiliary functions H_i. Obviously, when $q \neq 0$, since $u_{i0}(t)$ satisfy the initial conditions (7) and $\mathcal{L}_i(0) = 0$ we have

$$\phi_i(t, 0) = u_{i0}(t), \quad i = 1, 2, 3, \ldots, n, \tag{10}$$

Table 1
The numerical results of $x(t)$.

t	GEM	HPM	HAM	RK4
0	100	100	100	100
0.2	100.023	100.023	100.023	100.023
0.4	100.047	100.047	100.047	100.047
0.6	100.071	100.071	100.071	100.071
0.8	100.097	100.097	100.096	100.097
1	100.122	100.123	100.122	100.122

Table 2
The numerical results of $y(t)$.

t	GEM	HPM	HAM	RK4
0	0	0	0	0
0.2	0.00434	0.00434	0.004336	0.004336
0.4	0.00715	0.00721	0.007141	0.007154
0.6	0.00908	0.00934	0.009094	0.009081
0.8	0.01049	0.01117	0.010631	0.010492
1	0.01161	0.01276	0.011945	0.011610

Table 3
The numerical results of $z(t)$.

t	GEM	HPM	HAM	RK4
0	1	1	1	1
0.2	0.69030	0.69071	0.69059	0.69070
0.4	0.51152	0.51208	0.51237	0.51190
0.6	0.41069	0.41394	0.40994	0.41103
0.8	0.35656	0.37749	0.35148	0.35684
1	0.33053	0.42419	0.32869	0.33073

when $q = 1$, since $h_i \neq 0$ and $H_i(t) \neq 0$, the zeroth-order deformation equation (8) and (9) are equivalent to (6) and (7), hence

$$\phi_i(t,1) = u_{i0}(t), \quad i = 1,2,3,\ldots,n. \tag{11}$$

Thus, as q increasing from 0 to 1, the solutions $\phi_i(t,q)$ various from $u_{i0}(t)$ to $u_i(t)$. Expanding $\phi_i(t,q)$ in Taylor series with respect to the embedding parameter q, one has

$$\phi_i(t,q) = u_{i0}(t) + \sum_{m=1}^{\infty} u_{im}(t) q^m, \quad i = 1,2,3,\ldots,n, \tag{12}$$

where

$$u_{im}(t) = \frac{1}{m!} \left. \frac{\partial^m \phi_i(t,q)}{\partial q^m} \right|_{q=0}, \quad i = 1,2,3,\ldots,n. \tag{13}$$

Assume that the auxiliary parameters h_i, the auxiliary functions H_i(t), the initial approximations $u_{i0}(t)$ and the auxiliary linear operators $\mathcal{L}_i$ are properly chosen so that the series (12) converges at $q = 1$. Then at $q = 1$, and by (11) the series (12) becomes

$$u_i(t) = u_{i0}(t) + \sum_{m=1}^{\infty} u_{im}(t), \quad i = 1,2,3,\ldots,n \tag{14}$$

and now define the vector

$$\vec{u}_i = \{u_{i0}, u_{i1}, u_{i2}, \ldots, u_{ij}\}, \quad i = 1,2,3,\ldots,j. \tag{15}$$

Differentiating equations (8) m times with respect to the embedding parameter q, then setting $q = 0$ and dividing them by $m!$, finally using (13), we have the so-called mth-order deformation equations:

$$\mathcal{L}_i[u_{im} - \chi_m u_{i(m-1)}(t)] = h_i H_i(t) \Re_{im}(\vec{u}_{i(m-1)}(t)), \quad i = 1,2,3,\ldots,n, \tag{16}$$

subject to the conditions:

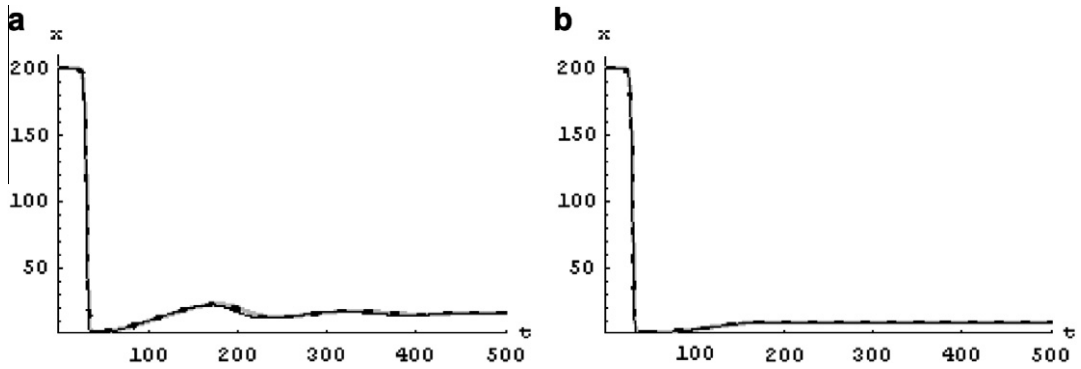

Fig. 1. The densities of the uninfected CD4$^+$ T-cells $\underline{\underline{x}}(t)$, when $\varepsilon = 0.1$ (a), and $\varepsilon = 0.05$ (b): gray solid line ($\alpha = 1$), dotted line ($\alpha = 0.99$), black solid line ($\alpha = 0.95$).

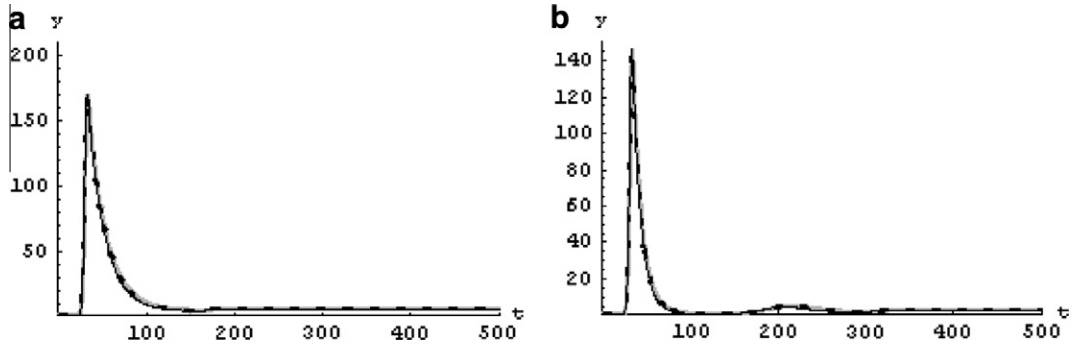

Fig. 2. The densities of the infected CD4$^+$ T-cells $y(t)$, when $\varepsilon = 0.1$ (a), and $\varepsilon = 0.05$ (b): gray solid line ($\alpha = 1$), dotted line ($\alpha = 0.99$), black solid line ($\alpha = 0.95$).

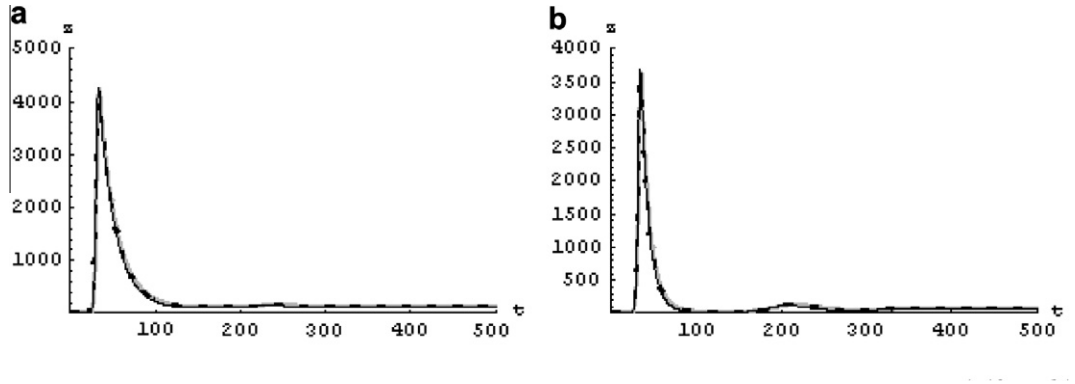

Fig. 3. The densities of the free virus $z(t)$, when $\varepsilon = 0.1$ (a), and $\varepsilon = 0.05$ (b): gray solid line ($\alpha = 1$), dotted line ($\alpha = 0.99$), black solid line ($\alpha = 0.95$).

$$u_{im}(0) = 0, \quad i = 1, 2, \ldots, n, \;\; m = 1, 2, 3, \ldots, n, \tag{17}$$

where

$$\Re_{im}(\vec{u}_{i(m-1)}(t)) = \frac{1}{(m-1)!} \frac{\partial^{m-1} N_i(\phi_i(t,q))}{\partial q^{m-1}}\bigg|_{q=0}, \tag{18}$$

and

$$\chi_m = \begin{cases} 0, & m \leqslant 1, \\ 1, & m > 1. \end{cases} \tag{19}$$

If we choose the linear operator $\mathcal{L}_i = D_i^{\alpha}$ then according to (16), we have

$$J^{\alpha_i} D^{\alpha_i}[u_{im} - \chi_m u_{i(m-1)}(t)] = h_i J^{\alpha_i}[H_i(t)\Re_{im}(\vec{u}_{i(m-1)}(t))]. \tag{20}$$

Finally it seems that, as long as a nonlinear fractional order differential equation has at least one solution, then one can always construct a kind of zeroth-order deformation equation to get convergent homotopy-series solution as

$$u_i m = x_m u_{i(m-1)}(t) + h_i J^{\alpha_i}[H_i(t)\Re_{im}(\vec{u}_{i(m-1)}(t))] \tag{21}$$

and $u_i = u_{i0} + u_{i1} + u_{i2} + u_{i3} + u_{i4} + \cdots$

6. Numerical results

Generalized Euler method (GEM) and homotopy analysis method (HAM) were applied to solve the system (1) by when $\alpha = 1$, then we have compared the results with the results of HPM in [25] and the results of the classical RK4 as shown in Tables 1–3.

From Tables 1–3, we can deduce that the results of GEM have an excellent agreement with the results of HPM in [25].

7. Numerical simulation and discussion

More realistic pharmacological dynamics, such as first-order kinetics for drug absorption in the gut and blood plasma, translate into a gradual increase of the drug concentration in the blood, and consequently, a gradual increase of the drug effectiveness [26]. For the virus dynamics, this leads to an intricate interplay between pharmacological effects, intracellular delays, the decay of infected cells, and the clearance of free virus particles. In general, the dynamical equations can no longer be solved analytically, but numerical simulations show that, as expected, the transient phase becomes smoother. The same is true if one assumes that virus production sets in gradually after the infection. In this section, we assume that $\alpha_1 = \alpha_2 = \alpha_3 = \alpha$. $x(0) = 200$, $y(0) = 0$, $z(0) = 0.000001$.

8. Conclusion

In this paper, (GEM) and (HAM) were implemented to approximate the solution of the presented fractional model. A comparison was made between the results of GEM and the results of HAM, results of HPM [25] and the results of RK4 in the standard integer order form, i.e., when $\alpha = 1$ in (1) to prove the accuracy of GEM. The results show that the solution continuously depends on the time-fractional derivative and on the values of the parameters. Before therapy, the rate of death of the infected cells is $\varepsilon = 0.05$ (see Figs. 1b, 2b and 3b), while during treatment $\varepsilon = 0.1$ (see Figs. 1a, 2b and 3b). The death rate of infected cells increases due to efficacy of drug therapy. As a definition of fractional calculus: $\lim_{\alpha\to 1} D^{\alpha} f(t) = Df(t)$ has been provided. In the presented problem, the number of susceptible individuals $x(t)$, the number of infected individuals $y(t)$, the number of isolated individuals $z(t)$ have been obtained, therefore when $\alpha \to 1$ the solution of the fractional model (1) $x_\alpha(t)$, $y_\alpha(t)$, $z_\alpha(t)$, reduce to the standard solution $x(t)$, $y(t)$, $z(t)$. Finally, the recent appearance of fractional differential equations as models in some fields of applied mathematics makes it necessary to investigate methods of solution for such equations (analytical and numerical) and we hope that this work is a step in this direction.

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