Fractional Order Model of Human T-cell Lymphotropic Virus I (HTLV-I) Infection of CD4$^+$ T-Cells

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Abstract

In this paper, we introduce fractional-order into a model of (HTLV-I) infection of CD4$^+$ T-cells. Generalized Euler method (GEM) is implemented to give approximate and analytical solutions of the presented problem. The fractional derivatives are described in the Caputo sense.

Keywords: HTLV-I infection, Fractional order models, Generalized Euler method

1 Introduction

Human T-cell lymphotrophic virus type I (HTLV-I) infection is associated with a variety of human diseases. Human T-cell lymphotrophic virus (HTLV) is a
member of the exogeneous human retroviruses that have a tropism for T lymphocytes. HTLV-I belongs to the delta-type retroviruses, which also include bovine leukemia virus; human T-cell leukemia virus type II (HTLV-II), and simian T-cell leukemia virus [12]. Infection with HTLV-I is now a global epidemic, affecting 10 million to 20 million people. This virus has been linked to life-threatening, incurable diseases:

a) Adult T-cell leukemia (ATL).

b) HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP).

These syndromes are important causes of mortality and morbidity in the areas where HTLV-I is endemic, mainly in the tropics and subtropics [13]. There are large endemic areas in southern Japan, the Caribbean, Central and West Africa, the Middle East, Melanesia, and equatorial regions of Africa. In Europe and North America, the virus is found chiefly in immigrants from the endemic areas and in some communities of intravenous drug users. Like HIV, HTLV-I targets CD$^4$ T-cells, the most abundant white cells in the immune system, decreasing the body’s ability to fight infection. Primary infection leads to chronic infection, the proviral load of which can be extremely high, approximately 30–50% [10]. Unlike in the case of HIV infection [4], however, only a small percentage of infected individuals develop the disease and 2–5% percent of HTLV-I carriers develop symptoms of ATL [13]. Also, there is very little cell-free virus in the plasma. Almost all viral genetic material resides, in DNA form, integrated within the host genome of infected cells. HTLV-I infection is achieved primarily through cell-to-cell contact [10]. The activity of which produces a DNA copy of the viral genome that is integrated into the DNA of the host genome. After this takes place, the latency period can persist for a long period of time. Latently infected cells contain the virus, but do not produce DNA and are incapable of contagion. When such cells are stimulated by antigen, they can become active and infect healthy cells. Taking these factors into consideration, Stilianakis and Seydel [12] proposed a model that formulates a system of nonlinear differential equations that divides CD$^4$ T-cells into four compartments: uninfected CD$^4$ T-cells, latently infected cells, actively infected cells, and leukemia cells. Patricia Katri et al [10] modified the classic model for the system of non-linear differential equations to distinguish, in terms of parameters, between contact and infectivity rates. The resulting ODE model is

\[
\begin{align*}
\frac{dT}{dt} &= \lambda - \mu_T T - \kappa VT, \\
\frac{dl}{dt} &= \kappa_1 VT - (\mu_L + \alpha)L, \\
\frac{dv}{dt} &= \alpha I - (\mu_A + \rho)V, \\
\frac{dl}{dt} &= \rho V + \beta L \left(1 - \frac{L}{L_{max}}\right) - \mu_M L.
\end{align*}
\]
That model describes the T-cell dynamics of human T-cell lymphotropic virus I (HTLV-I) infection and the development of adult T-cell leukemia (ATL), where $T(t)$ represents the concentration of healthy CD4$^+$ T-cells at time $t$, $I(t)$ represents the concentration of latently infected CD4$^+$ T-cells, $V(t)$ the concentration of actively infected CD4$^+$ T-cells, and $L(t)$ the concentration of leukemic cells at time $t$. To explain the parameters, we note that $\lambda$ is the source of CD4$^+$ T-cells from precursors $\mu_T$ is the natural death rate of CD4$^+$ T-cells, $\kappa$ is the rate at which uninfected cells are contacted by actively infected cells. The parameter $\kappa_1$ represents the rate of infection of T-cells with virus from actively infected cells. $\mu_L$, $\mu_A$ and $\mu_M$ are blanket death terms for latently infected, actively infected and leukemic cells, to reflect the assumption that we do not initially know whether the cells die naturally or by bursting. In addition, $\alpha$ and $\rho$ represent the rates at which latently infected and actively infected cells become actively infected and leukemic, respectively. The ATL cells grow at a rate $\beta$ of a classical logistic growth function. $L_{max}$ is the maximal population level of leukemic CD4$^+$ T-cells. All parameters are assumed to be positive constants.

The rest of the paper is organized as follows. Section 2 gives an idea about the fractional calculus theory. A discussion about the Generalized Taylor formula and generalized Euler method (GEM) is presented in section 3 and section 4 respectively. In section 5, we introduce fractional-order into the model (1). Section 6 is devoted for the numerical results of the presented problem.

## 2 Fractional calculus

Fractional calculus (FC) has been extensively applied in many fields [1,8]. Many mathematicians and applied researchers have tried to model real processes using the fractional calculus. Petrovic et al developed a fractional-order mathematical model of a human root dentin [11]. In biology, it has been deduced that the membranes of cells of biological organism have fractional-order electrical conductance [3,9] and then are classified in groups of non-integer order models. Fractional derivatives embody essential features of the behavior of the pattern formation in bacterial colonies [5]. Also, it has been shown that modeling the behavior of brainstem vestibule-oculomotor neurons by fractional ordinary differential equations (FODE) has more advantages than classical integer-order modeling [2]. FODE are naturally related to systems with memory which exists in most biological systems [7]. There are several approaches to the generalization of the notion of differentiation to fractional orders. For the concept of fractional derivative, we will adopt Caputo's definition.

**Definition 1.** The fractional integral of order $\alpha > 0$ of a function $f: \mathbb{R}^+ \to \mathbb{R}$ is given by

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

(2)
\[ f^0(x) = f(x). \]

**Definition 2.** Riemann–Liouville and Caputo fractional derivatives of order \( \alpha \) where \( \alpha \in (n - 1, n) \) of a continuous function \( f: \mathbb{R}^+ \to \mathbb{R} \) is given respectively by

\[
D^\alpha f(x) = D^m \left( f^{m-\alpha} f(x) \right), \tag{3}
\]

\[
D^\alpha f(x) = f^{m-\alpha} (D^m f(x)), \tag{4}
\]

Where \( m - 1 < \alpha \leq m, m \in \mathbb{N} \).

### 3 Generalized Euler method (GEM)

Most nonlinear fractional differential equations do not have analytic solutions [15], so approximations and numerical techniques must be used. A few numerical methods for fractional differential equations 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 [15], 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. Consider the initial value problem

\[
D^\alpha y(t) = f \left( t, y(t) \right), y(0) = y_0, 0 < \alpha \leq 1, t > 0 \tag{5}
\]

The formula for generalized Euler’s method (GEM) when \( t_{j+1} = t_j + h \) is

\[
y(t_{j+1}) = y(t_j) + \frac{h^\alpha}{\Gamma(\alpha + 1)} f \left( t_j, y(t_j) \right) \tag{6}
\]

for \( j = 0, 1, \ldots, k - 1 \). It is clear that if \( \alpha = 1 \), then the generalized Euler’s method (6) reduces to the classical Euler’s method.

### 4 Model derivation

Now we introduce fractional-order into the model (1). The new system is described by the following set of FODEs of order \( \alpha_1, \alpha_2, \alpha_3, \alpha_3 > 0 \):

\[
D^{\alpha_1}(T) = \lambda - \mu_T T - \kappa V T,
\]

\[
D^{\alpha_2}(I) = \kappa_1 V I - (\mu_I + \alpha) I,
\]

\[
D^{\alpha_3}(V) = \alpha I - (\mu_A + \rho) V,
\]

\[
D^{\alpha_4}(L) = \rho V + \beta L \left( 1 - \frac{L}{L_{\text{max}}} \right) - \mu_M L. \tag{7}
\]

With initial conditions \( T(0) = 1000, I(0) = 250, V(0) = 1.5, L(0) = 0 \).
Model of human T-cell lymphotropic virus I infection

This paper attempts to find numerical solution for a general class of fractional order model of human T-cell lymphotropic virus I (HTLV-I) infection of CD4+ T-cells. For this purpose the paper summarizes specific techniques for generalized Euler method (GEM), as well as the applications of Caputo fractional calculus. The reason of using fractional order differential equations (FOD) is that FOD are naturally related to systems with memory because 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 \( t = t_1 \). Also they are closely related to fractals which are abundant in biological systems. The results derived of the fractional system (7) are of a more general nature. However, the fundamental solutions of these equations still exhibit useful scaling properties that make them attractive for applications. We would like to put your attention that time fractional derivatives change also the solutions we usually get in standard system (1). The concept of fractional or non-integer order derivation and integration can be traced back to the genesis of integer order calculus itself.

5 Numerical results

We will solve the system (7) by using (GEM). Consider that \( \alpha_1 = \alpha_2 = \alpha_3 = \alpha \). We assumed that all parameters are positive and in \( \text{mm}^3/\text{day} \) as follows:

\[
\begin{align*}
\mu_T &= 0.6, \\ 
\mu_L &= 0.006, \\ 
\mu_A &= 0.05, \\ 
\mu_M &= 0.0005, \\ 
\beta &= 0.0003, \\ 
\gamma &= 0.0004, \\ 
\rho &= 0.00004, \\ 
L_{max} &= 2200, \\ 
\lambda &= 6 \\
\end{align*}
\]

\( \kappa_1, k \) vary.

![Fig.1 Plots of the components of lymphotropic virus I (HTLV) infection of CD4+T-cells Model at \( \kappa_1 = k = 0.1 \): Gray solid line (\( \alpha = 1 \)), Dotted line](image)

\[\text{Fig.1} \text{ Plots of the components of lymphotropic virus I (HTLV) infection of CD4+T-cells Model at } \kappa_1 = k = 0.1: \text{Gray solid line (}\alpha = 1\text{), Dotted line} \]
Conclusion

In this paper we employed the generalized Euler method as a reasonable basis for studying the solution of the fractional model of human T-cell lymphotropic virus I (HTLV-I) infection of CD4+ T-cells. From the obtained results in the presented figures and tables, it is clear that varying the values of $\kappa$ and $\kappa_1$ will alter the number of uninfected CD4+ T-cells, infected cells, and leukemic cells. In [10], a threshold parameter $R_0 = \frac{\gamma \lambda k}{\mu_T (\mu_L + \gamma) (\mu_A + \rho)}$ is derived. $R_0$ is typically called a basic reproduction number. If $R_0 > 1$, the HTLV infection persists in the T-cell population and infected T cells persists but if $R_0 < 1$ always die out. For example, if $k_1 = k = 0.1$, then $R_0 = 1.2$. The numerical results show that increasing the value of $\kappa$ and $\kappa_1$ makes the number of healthy CD4+ T-cells decreases dramatically, while the numbers of latently infected cells and leukemic cells increase substantially (see fig 1). If $k_1 = k = 0.06$, then $R_0 = 0.75$ (fig. 2). It is clear from the definition of $R_0$ that $R_0$ decreases as the parameter, $k$ decreases, hence $R_0$ can be low for a low parametric value of $k$. The results show that the solution continuously depends

Fig. 2 Plots of the components of lymphotropic virus I (HTLV) infection of CD4+ T-cells Model at $\kappa_1 = k = 0.06$: Gray solid line ($\alpha = 1$), Dotted line ($\alpha = 0.99$), Black solid line ($\alpha = 0.95$).
on the time-fractional derivative. When $\alpha \to 1$ the solution of the fractional model (7) $T_\alpha(t)$, $I_\alpha(t)$, $V_\alpha(t)$, $L_\alpha(t)$ reduce to the standard solution $T(t), I(t), V(t), L(t)$ (see fig.1, and fig.2).

References


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