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# Analysis of the model of HIV-1 infection of $CD4^+$ T-cell with a new approach of fractional derivative

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## Abstract

By using the fractional Caputo–Fabrizio derivative, we investigate a new version for the mathematical model of HIV. In this way, we review the existence and uniqueness of the solution for the model by using fixed point theory. We solve the equation by a combination of the Laplace transform and homotopy analysis method. Finally, we provide some numerical analytics and comparisons of the results.

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**Keywords:** Fixed point; Homotopy analysis method; Mathematical model; Numerical simulation; The Caputo–Fabrizio derivation

## 1 Introduction

The HIV infection target is  $CD4^+$  T cells which are the largest white blood cells of the immune system [1, 2]. HIV infection infects most cells but has the most destructive effect on  $CD4^+$  T cells and weakens the immune system by destroying them [3]. When the number of  $CD4^+$  T-cell drops below a certain number, the cell-mediated immune system disappears, the immune system becomes weaker, and the body becomes susceptible to any infection [3].

A simple mathematical model for HIV infection was presented by Pearson [4]. This model has been an inspiration for many mathematicians in the modeling of HIV (see, for example, [4–6]). The mathematical models presented for HIV are very useful in understanding the dynamics of HIV infection [7–10]. Many mathematicians and scientists have shown that using fractional order instead of the correct order in modeling natural phenomena yields better results [10–13]. In recent years, Caputo and Fabrizio proposed a new definition of fractional derivative having exponential kernel [14]. Losada and Nieto investigated the properties of the new fractional derivative [15]. The Caputo and Riemann fractional derivatives cannot adequately describe physical phenomena because of their singularity. Recently, many works related to the fractional Caputo–Fabrizio derivative have been published (see, for example, [16–39]). In this paper, we use the Caputo and Fabrizio fractional derivative [14] to express the model of HIV and solve the equations by a method that combines the homotopy and Laplace transforms [14, 40–42].

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Now, we recall some fundamental notions. The Caputo fractional derivative of order  $\nu$  for a function  $f$  via integrable differentiations is defined by

$${}^C D^\nu f(t) = \frac{1}{\Gamma(n-\nu)} \int_0^t \frac{f^{(n)}(s)}{(t-s)^{\nu-n+1}} ds, \quad n = [\nu] + 1.$$

Our second notion is a fractional derivative without singular kernel introduced by Caputo and Fabrizio [14]. Let  $b > a, f \in H^1(a, b)$ , and  $\nu \in (0, 1)$ , the Caputo–Fabrizio derivative of order  $\nu$  for a function  $f$  is defined by

$${}^{CF} D^\nu f(t) = \frac{M(\nu)}{(1-\nu)} \int_a^t \exp\left(\frac{-\nu}{1-\nu}(t-s)\right) f'(s) ds \quad (t \geq 0),$$

where  $M(\nu)$  is a normalization function that depends on  $\nu$  and  $M(0) = M(1) = 1$ . If  $f \notin H^1(a, b)$ , this derivative can be presented for  $f \in L^1(-\infty, b)$  as follows:

$${}^{CF} D^\nu f(t) = \frac{\nu M(\nu)}{(1-\nu)} \int_{-\infty}^b (f(t) - f(s)) \exp\left(\frac{-\nu}{1-\nu}(t-s)\right) ds \quad (0 < \nu < 1).$$

Also, for  $n \geq 1$  and  $\nu \in (0, 1)$ , the fractional derivative  ${}^{CF} D^{\nu+n}$  of order  $\nu + n$  is defined by  ${}^{CF} D^{\nu+n} f(t) := {}^{CF} D^\nu (D^n f(t))$  [43].

The Laplace transform of the Caputo–Fabrizio derivative is defined by [15]

$$L[{}^{CF} D^{(\nu+n)} f(t)](s) = \frac{s^{n+1} L[f(t)] - s^n f(0) - s^{n-1} f'(0) - \dots - f^{(n)}(0)}{s + \nu(1-s)},$$

where  $0 < \nu \leq 1$  and  $M(\nu) = 1$ . The Riemann–Liouville fractional integral of order  $\nu$ ,  $\text{Re}(\nu) > 0$  is defined by  $I^\nu f(t) = \frac{1}{\Gamma(\nu)} \int_0^t (t-s)^{\nu-1} f(s) ds$ . The fractional integral of Caputo–Fabrizio is defined by [15]

$${}^{CF} I^\nu f(t) = \frac{2(1-\nu)}{(2-\nu)M(\nu)} f(t) + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t f(s) ds \quad (0 < \nu < 1).$$

Also, the left and right fractional integrals of  $({}^{CF} D^\nu)$  are defined respectively by [44]:

$$\begin{aligned} ({}^{CF} I_a^\nu f)(t) &= \frac{1-\nu}{B(\nu)} f(t) + \frac{\nu}{B(\nu)} \int_a^t f(s) ds, \\ ({}^{CF} I_b^\nu f)(t) &= \frac{1-\nu}{B(\nu)} f(t) + \frac{\nu}{B(\nu)} \int_t^b f(s) ds. \end{aligned}$$

The Sumudu transform is derived from the classical Fourier integral [45–47]. Consider the set  $A = \{F : \exists \lambda, k_1, k_2 \geq 0, |F(t)| < \lambda \exp(\frac{t}{k_j}), t \in (-1)^j \times [0, \infty)\}$ . The Sumudu transform of a function  $f(t) \in A$  denoted by  $ST[f(t); u] = F(u)$  is defined by

$$F(u) = ST[f(t); u] = \frac{1}{u} \int_0^\infty \exp(-t/u) f(t) dt, \quad u \in (-k_1, k_2),$$

for all  $t \geq 0$ , and the inverse Sumudu transform of  $F(u)$  is denoted by  $f(t) = ST^{-1}[F(u)]$  [46]. The Sumudu transform of the Caputo derivative is given by

$$ST[{}^c D_t^\nu f(t); u] = u^{-\nu} \left[ F(u) - \sum_{i=0}^m u^{\nu-i} [{}^c D_t^{\nu-i} f(t)]_{t=0} \right],$$

where  $(m - 1 < \nu \leq m)$  [45]. Let  $F$  be a function such that its Caputo–Fabrizio fractional derivation exists. The Sumudu transform of  $F$  with Caputo–Fabrizio fractional derivative is defined by [48]

$$ST({}^{CF} D_t^\nu)(F(t)) = \frac{M(\nu)}{1 - \nu + \nu u} [ST(F(t)) - F(0)].$$

Let  $(X, d)$  be a metric space, a map  $g : X \rightarrow X$  is called a Picard operator whenever there exists  $x^* \in X$  such that  $\text{Fix}(g) = \{x^*\}$  and the sequence  $(g^n(x_0))_{n \in \mathbb{N}}$  converges to  $x^*$  for all  $x_0 \in X$  [49].

## 2 Mathematical model of the HIV-1 infection of $CD4^+$ T-cell

The classical order model of HIV-1 infection of  $CD4^+$  T-cell is given by

$$\begin{cases} \frac{dT}{dt} = \beta - kVT - dT + bU, \\ \frac{dU}{dt} = kVT - (b + \delta)U, \\ \frac{dV}{dt} = N\delta U - cV, \end{cases} \tag{1}$$

with initial conditions  $T(0) = T_0, U(0) = U_0, V(0) = V_0$  [1]. Model (1) does not include the internal memory effects of the HIV biological system. To improve the model, we change the first-order time derivative to the Caputo–Fabrizio fractional derivative of order  $\nu$  as follows:

$$\begin{cases} {}^{CF} D_t^\nu T = \beta - kVT - dT + bU, \\ {}^{CF} D_t^\nu U = kVT - (b + \delta)U, \\ {}^{CF} D_t^\nu V = N\delta U - cV, \end{cases} \tag{2}$$

where  $0 < \nu_i \leq 1$  and the initial conditions  $T(0) = T_0, U(0) = U_0$ , and  $V(0) = V_0$ . In this model,  $T$  represents the concentration of uninfected  $CD4^+$  T cells,  $U$  represents the concentration of infected  $CD4^+$  T cells, and  $V$  represents the free HIV infection particles in the blood. The parameters  $\beta, d, k, \delta, b, c$ , and  $N$  denote the new T-cells supply rate, the rate of natural death, the rate of infection T-cells, the death rate of infected T-cells, the rate of return of infected cells to uninfected class, the death rate of virus, and the average number of particles infected by an infected cell, respectively.

In system (2), the right-hand sides of the equations have dimension  $(\text{time})^{-1}$ . When we change the order of the equations to  $\nu$ , the dimension of the left-hand side would be  $(\text{time})^{(-\nu)}$ . To have the dimensions match, we should change the dimensions of the param-

eters  $d, k, \delta, b, c$  and the system we obtain eventually is

$$\begin{cases} {}_0^{\text{CF}}D_t^\nu T = \beta - k^\nu VT - d^\nu T + b^\nu U, \\ {}_0^{\text{CF}}D_t^\nu U = k^\nu VT - (b^\nu + \delta^\nu)U, \\ {}_0^{\text{CF}}D_t^\nu V = N\delta^\nu U - c^\nu V. \end{cases} \tag{3}$$

Numerical solutions of model (3) are presented by using the homotopy analysis transform method (HATM). We transform the fractional differential equation into the algebraic equation by using Laplace transform and solve the resulting algebraic equation by the homotopy analysis method.

### 3 Existence of solution

Consider the following model employing the Caputo–Fabrizio fractional derivative:

$$\begin{cases} {}_0^{\text{CF}}D_t^\nu T = \beta - k^\nu VT - d^\nu T + b^\nu U, \\ {}_0^{\text{CF}}D_t^\nu U = k^\nu VT - (b^\nu + \delta^\nu)U, \\ {}_0^{\text{CF}}D_t^\nu V = N\delta^\nu U - c^\nu V. \end{cases} \tag{4}$$

We get the Losada and Nieto integral operator [15] on both sides of equations (4), so

$$\begin{aligned} T(t) - g_1(t) &= \frac{2(1-\nu)}{(2-\nu)M(\nu)} \{ \beta - k^\nu V(t)T(t) - d^\nu T(t) + b^\nu U(t) \} \\ &\quad + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t [ \beta - k^\nu V(s)T(s) - d^\nu T(s) + b^\nu U(s) ] ds, \\ U(t) - g_2(t) &= \frac{2(1-\nu)}{(2-\nu)M(\nu)} \{ k^\nu V(t)T(t) - (b^\nu + \delta^\nu)U(t) \} \\ &\quad + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t [ k^\nu V(s)T(s) - (b^\nu + \delta^\nu)U(s) ] ds, \\ V(t) - g_3(t) &= \frac{2(1-\nu)}{(2-\nu)M(\nu)} \{ N\delta^\nu U(t) - c^\nu V(t) \} \\ &\quad + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t [ N\delta^\nu U(s) - c^\nu V(s) ] ds. \end{aligned} \tag{5}$$

We present the differential equations (5) as follows:

$$\begin{aligned} T_0(t) &= g_1(t), \quad U_0(t) = g_2(t), \quad V_0(t) = g_3(t), \\ T_{n+1}(t) &= \frac{2(1-\nu)}{(2-\nu)M(\nu)} \{ \beta - k^\nu V(t)T(t) - d^\nu T(t) + b^\nu U(t) \} \\ &\quad + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t [ \beta - k^\nu V(s)T(s) - d^\nu T(s) + b^\nu U(s) ] ds, \\ U_{n+1}(t) &= \frac{2(1-\nu)}{(2-\nu)M(\nu)} \{ k^\nu V(t)T(t) - (b^\nu + \delta^\nu)U(t) \} \\ &\quad + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t [ k^\nu V(s)T(s) - (b^\nu + \delta^\nu)U(s) ] ds, \end{aligned} \tag{6}$$

$$V_{n+1}(t) = \frac{2(1-\nu)}{(2-\nu)M(\nu)} \{N\delta^\nu U(t) - c^\nu V(t)\} + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t [N\delta^\nu U(s) - c^\nu V(s)] ds.$$

Now if we take limit from Picard’s repetitive series (6) when  $n$  is infinite, the solution of the equation is obtained as follows:

$$\begin{cases} \lim_{n \rightarrow \infty} T_n(t) = T(t), \\ \lim_{n \rightarrow \infty} U_n(t) = U(t), \\ \lim_{n \rightarrow \infty} V_n(t) = V(t). \end{cases} \tag{7}$$

### 3.1 Existence of solution by the Picard–Lindelof approach

We use the Picard–Lindelof approach and the Banach fixed point theorem to prove the existence of the solution. At first, we define the following operators:

$$\begin{cases} g_1(t, T) = \beta - k^\nu V(t)T(t) - d^\nu T(t) + b^\nu U(t), \\ g_2(t, U) = k^\nu V(t)T(t) - (b^\nu + \delta^\nu)U(t), \\ g_3(t, V) = N\delta^\nu U(t) - c^\nu V(t). \end{cases} \tag{8}$$

Let

$$L_1 = \sup_{C[a,c_1]} \|g_1(t, T)\|, \quad L_2 = \sup_{C[a,c_2]} \|g_2(t, U)\|, \quad L_3 = \sup_{C[a,c_3]} \|g_3(t, V)\|, \tag{9}$$

where

$$\begin{cases} C[a, c_1] = |t - a, t + a| \times |T - c_1, T + c_1| = A \times C_1, \\ C[a, c_2] = |t - a, t + a| \times |U - c_2, U + c_2| = A \times C_2, \\ C[a, c_3] = |t - a, t + a| \times |V - c_3, V + c_3| = A \times C_3. \end{cases} \tag{10}$$

Assume a uniform norm on  $C[a, c_i]$  ( $i = 1, 2, 3$ ) as follows:

$$\|Y(t)\|_\infty = \sup_{t \in [t-a, t+a]} |Y(t)|. \tag{11}$$

Consider the Picard operator

$$O : C(A, C_1, C_2, C_3) \rightarrow C(A, C_1, C_2, C_3) \tag{12}$$

given as follows:

$$O(Y(t)) = Y_0(t) + \frac{2(1-\nu)}{(2-\nu)M(\nu)} G(t, Y(t)) + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t G(s, Y(s)) ds. \tag{13}$$

So that  $Y(t) = \{T(t), U(t), V(t)\}$ ,  $Y_0(t) = \{T(0), U(0), V(0)\}$  and

$$G(t, Y(t)) = \{g_1(t, T), g_2(t, U), g_3(t, V)\}. \tag{14}$$

Let us assume that the solutions to the problem under investigation are bounded within a time period,

$$\|Y(t)\|_\infty \leq \max\{c_1, c_2, c_3\} = C. \tag{15}$$

Let  $L = \max\{L_1, L_2, L_3\}$  and there exists  $t_0$  so that  $t_0 \geq t$ , then

$$\begin{aligned} \|OY(t) - Y_0(t)\| &= \left\| \frac{2(1-\nu)}{(2-\nu)M(\nu)} G(t, Y(t)) + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t G(s, Y(s)) ds \right\| \\ &\leq \frac{2(1-\nu)}{(2-\nu)M(\nu)} \|G(t, Y)\| + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t \|G(s, Y) ds\| ds \\ &\leq \left( \frac{2(1-\nu)}{(2-\nu)M(\nu)} + \frac{2\nu t}{(2-\nu)M(\nu)} \right) L \end{aligned} \tag{16}$$

$$\leq \left( \frac{2(1-\nu)}{(2-\nu)M(\nu)} + \frac{2\nu t_0}{(2-\nu)M(\nu)} \right) L \leq \mu L \leq C, \tag{17}$$

where we demand that

$$\mu < \frac{C}{L}. \tag{18}$$

Also we evaluate the following equality:

$$\|OY_1 - OY_2\| = \sup_{t \in A} |Y_1(t) - Y_2(t)|. \tag{19}$$

Using the definition of our Picard operator, we have

$$\begin{aligned} \|OY_1 - OY_2\| &= \left\| \frac{2(1-\nu)}{(2-\nu)M(\nu)} \{G(t, Y_1(t)) - G(t, Y_2(t))\} \right. \\ &\quad \left. + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t \{G(s, Y_1(s)) - G(s, Y_2(s))\} ds \right\| \\ &\leq \frac{2(1-\nu)}{(2-\nu)M(\nu)} \|G(t, Y_1(t)) - G(t, Y_2(t))\| \\ &\quad + \frac{2\nu}{(2-\nu)M(\nu)} \int_0^t \|G(s, Y_1(s)) - G(s, Y_2(s))\| ds \\ &\leq \frac{2(1-\nu)}{(2-\nu)M(\nu)} \lambda \|Y_1(t) - Y_2(t)\| \\ &\quad + \frac{2\nu\lambda}{(2-\nu)M(\nu)} \int_0^t \|Y_1(s) - Y_2(s)\| ds \\ &\leq \left( \frac{2(1-\nu)\lambda}{(2-\nu)M(\nu)} + \frac{2\nu\lambda t_0}{(2-\nu)M(\nu)} \right) \|Y_1(t) - Y_2(t)\| \\ &\leq \mu\lambda \|Y_1(t) - Y_2(t)\| \end{aligned} \tag{20}$$

with  $\lambda < 1$ . Since  $G$  is a contraction, then  $\mu\lambda < 1$ , so  $O$  is a contraction. The proof is complete.

#### 4 Special solutions via iteration approach

Here, we provide a special solution to the model of HIV-1 infection. Applying the Sumudu transform to system (3), we get

$$\begin{cases} ST({}_0^{CF}D_t^\nu T(t)) = ST[\beta - k^\nu V(t)T(t) - d^\nu T(t) + b^\nu U(t)], \\ ST({}_0^{CF}D_t^\nu U(t)) = ST[k^\nu V(t)T(t) - (b^\nu + \delta^\nu)U(t)], \\ ST({}_0^{CF}D_t^\nu V(t)) = ST[N\delta^\nu U(t) - c^\nu V(t)]. \end{cases} \tag{21}$$

By using the definition of the Sumudu transform of CF-derivative, we obtain

$$\begin{aligned} \frac{M(\nu)}{1 - \nu + \nu u} (ST(T(t)) - T(0)) &= ST[\beta 0 - k^\nu V(t)T(t) - d^\nu T(t) + b^\nu U(t)], \\ \frac{M(\nu)}{1 - \nu + \nu u} (ST(U(t)) - U(0)) &= ST[k^\nu V(t)T(t) - (b^\nu + \delta^\nu)U(t)], \\ \frac{M(\nu)}{1 - \nu + \nu u} (ST(V(t)) - V(0)) &= ST[N\delta^\nu U(t) - c^\nu V(t)]. \end{aligned} \tag{22}$$

Rearranging, we obtain the following inequalities:

$$\begin{aligned} ST(T(t)) &= T(0) + \frac{1 - \nu + \nu u}{M(\nu)} ST[\beta - k^\nu V(t)T(t) - d^\nu T(t) + b^\nu U(t)], \\ ST(U(t)) &= U(0) + \frac{1 - \nu + \nu u}{M(\nu)} ST[k^\nu V(t)T(t) - (b^\nu + \delta^\nu)U(t)], \\ ST(V(t)) &= V(0) + \frac{1 - \nu + \nu u}{M(\nu)} ST[N\delta^\nu U(t) - c^\nu V(t)]. \end{aligned} \tag{23}$$

The following recursive formula is obtained:

$$\begin{aligned} T_{n+1}(t) &= T_n(0) + ST^{-1} \left\{ \frac{1 - \nu + \nu u}{M(\nu)} ST[\beta - k^\nu V_n(t)T_n(t) - d^\nu T_n(t) + b^\nu U_n(t)] \right\}, \\ U_{n+1}(t) &= U_0(t) + ST^{-1} \left\{ \frac{1 - \nu + \nu u}{M(\nu)} ST[k^\nu V(t)T(t) - (b^\nu + \delta^\nu)U(t)] \right\}, \\ V_{n+1}(t) &= V_0(t) + ST^{-1} \left\{ \frac{1 - \nu + \nu u}{M(\nu)} ST[N\delta^\nu U(t) - c^\nu V(t)] \right\}. \end{aligned} \tag{24}$$

Finally, the solution of equation (24) approximates to the following:

$$T(t) = \lim_{n \rightarrow \infty} T_n(t), \quad U(t) = \lim_{n \rightarrow \infty} U_n(t), \quad V(t) = \lim_{n \rightarrow \infty} V_n(t). \tag{25}$$

#### 4.1 Application of fixed point theorem for stability analysis of iteration method

Consider the Banach space  $(Y, \| \cdot \|)$ , a self-map  $F$  on  $Y$ , and recursive method  $P_{n+1} = \phi(F, P_n)$ . Assume that  $\Omega(F)$  is the fixed point set of  $F$  which  $\Omega(F) \neq \emptyset$  and  $\lim_{n \rightarrow \infty} P_n = p \in \Omega(F)$ . Suppose that  $\{f_n\} \subset \Omega$  and  $e_n = \|f_{n+1} - \phi(F, f_n)\|$ , if  $\lim_{n \rightarrow \infty} e_n = 0$  implies that  $\lim_{n \rightarrow \infty} f_n = p$ , then the recursive procedure  $P_{n+1} = \phi(F, P_n)$  is  $F$ -stable. Suppose that our sequence  $\{f_n\}$  has an upper boundary. If Picard's iteration  $P_{n+1} = FP_n$  is satisfied in all these conditions, then  $P_{n+1} = FP_n$  is  $F$ -stable.

**Theorem 1** ([49]) *Let  $(Y, \| \cdot \|)$  be a Banach space and  $F$  be a self-map of  $Y$  satisfying*

$$\|F_x - F_y\| \leq R\|x - F_x\| + r\|x - y\|$$

*for all  $x, y \in Y$ , where  $R \geq 0$  and  $0 \leq r < 1$ . Then  $F$  is Picard  $F$ -stable.*

Suppose that the fractional model of HIV-1 infection of  $CD4^+$  T-cell (3) is connected with the subsequent iterative formula in (24). Consider the following theorem.

**Theorem 2** *Suppose that  $F$  is a self-map defined as follows:*

$$\begin{aligned} F(T_n(t)) &= T_{n+1}(t) \\ &= T_n(t) + ST^{-1} \left\{ \frac{1 - \nu + \nu u}{M(\nu)} ST[\beta - k^\nu V_n(t)T_n(t) - d^\nu T_n(t) + b^\nu U_n(t)] \right\}, \\ F(U_n(t)) &= U_{n+1}(t) \\ &= U_n(t) + ST^{-1} \left\{ \frac{1 - \nu + \nu u}{M(\nu)} ST[k^\nu V(t)T(t) - (b^\nu + \delta^\nu)U(t)] \right\}, \\ F(V_n(t)) &= V_{n+1}(t) \\ &= V_n(t) + ST^{-1} \left\{ \frac{1 - \nu + \nu u}{M(\nu)} ST[N\delta^\nu U(t) - c^\nu V(t)] \right\}. \end{aligned} \tag{26}$$

*Then (26) is  $F$ -stable in  $L^1(a, b)$  if the following conditions are achieved:*

$$\begin{cases} (1 - d^\nu f_1(\eta) - k^\nu M_3 f_2(\eta) - k^\nu M_1 f_3(\eta) + b^\nu f_4(\eta)) < 1, \\ (1 + (b^\nu + \delta^\nu) f_5(\eta) + k^\nu M_3 f_6(\eta) + k^\nu M_1 f_7(\eta)) < 1, \\ (1 + N\delta^\nu f_8(\eta) - c^\nu f_9(\eta)) < 1. \end{cases} \tag{27}$$

*Proof* At first, we compute the following inequalities for  $(n, m) \in N \times N$  to prove that  $F$  has a fixed point:

$$\begin{aligned} &F(T_n(t)) - F(T_m(t)) \\ &= T_n(t) - T_m(t) + ST^{-1} \left\{ \frac{1 - \nu + \nu u}{M(\nu)} ST[\beta - k^\nu V_n(t)T_n(t) - d^\nu T_n(t) + b^\nu U_n(t)] \right\} \\ &\quad - ST^{-1} \left\{ \frac{1 - \nu + \nu u}{M(\nu)} ST[\beta - k^\nu V_m(t)T_m(t) - d^\nu T_m(t) + b^\nu U_m(t)] \right\}. \end{aligned} \tag{28}$$

Now, we apply norm on both sides of equation (28)

$$\begin{aligned} &\|F(T_n - F(T_m))\| \\ &= \left\| T_n - T_m + ST^{-1} \left\{ \frac{1 - \nu + \nu u}{M(\nu)} ST[-k^\nu (V_n T_n - V_m T_m) \right. \right. \\ &\quad \left. \left. - d^\nu (T_n - T_m) + b^\nu (U_n - U_m)] \right\} \right\| \end{aligned}$$

$$\begin{aligned} &\leq \|T_n - T_m\| + ST^{-1} \left\{ \frac{1 - \nu + \nu u}{M(\nu)} ST \left[ \|-k^\nu V_n(T_n - T_m)\| \right. \right. \\ &\quad \left. \left. + \|-k^\nu T_m(V_n - V_m)\| + \|-d^\nu(T_n - T_m)\| + \|b^\nu(U_n - U_m)\|\right] \right\}. \end{aligned} \tag{29}$$

Because of the same role of both solutions, we shall consider

$$\|T_n(t) - T_m(t)\| \cong \|U_n(t) - U_m(t)\| \cong \|V_n(t) - V_m(t)\|. \tag{30}$$

From equations (29) and (30), we obtain

$$\begin{aligned} \|F(T_n(t) - F(T_m(t)))\| &\leq \|T_n(t) - T_m(t)\| \\ &\quad + ST^{-1} \left\{ \frac{1 - \nu + \nu u}{M(\nu)} ST \left[ \|-k^\nu V_n(t)(T_n(t) - T_m(t))\| \right. \right. \\ &\quad + \|-k^\nu T_m(t)(T_n(t) - T_m(t))\| \\ &\quad \left. \left. + \|-d^\nu(T_n(t) - T_m(t))\| + \|b^\nu(T_n(t) - T_m(t))\|\right] \right\}. \end{aligned} \tag{31}$$

Since  $V_n, T_m, U_n$  are convergent sequences, then they are bounded, so there exist  $M_1, M_2, M_3$  for all  $t$  such that

$$\|V_n\| < M_3, \quad \|T_m\| < M_1, \quad \|U_n\| < M_2, \quad (m, n) \in N \times N. \tag{32}$$

From equations (31) and (32), we obtain the following:

$$\begin{aligned} \|F(T_n(t) - F(T_m(t)))\| &\leq \{1 - d^\nu f_1(\eta) - k^\nu M_3 f_2(\eta) - k^\nu M_1 f_3(\eta) + b^\nu f_4(\eta)\} \\ &\quad \times \|T_n(t) - T_m(t)\|, \end{aligned} \tag{33}$$

where  $f_i$  are functions from  $ST^{-1}[\frac{1-\nu+\nu u}{M(\nu)}ST[*]]$ . In the same way, we get

$$\begin{aligned} \|F(U_n(t) - F(U_m(t)))\| &\leq \{1 + (b^\nu + \delta^\nu) f_5(\eta) + k^\nu M_3 f_6(\eta) + k^\nu M_1 f_7(\eta)\} \\ &\quad \times \|U_n(t) - U_m(t)\|, \end{aligned} \tag{34}$$

$$\|F(V_n(t) - F(V_m(t)))\| \leq \{1 + N\delta^\nu f_8(\eta) - c^\nu f_9(\eta)\} \|V_n(t) - V_m(t)\|, \tag{35}$$

where

$$\begin{cases} \{1 - d^\nu f_1(\eta) - k^\nu M_3 f_2(\eta) - k^\nu M_1 f_3(\eta) + b^\nu f_4(\eta)\} < 1, \\ \{1 + (b^\nu + \delta^\nu) f_5(\eta) + k^\nu M_3 f_6(\eta) + k^\nu M_1 f_7(\eta)\} < 1, \\ \{1 + N\delta^\nu f_8(\eta) - c^\nu f_9(\eta)\} < 1. \end{cases} \tag{36}$$

Then the  $F$  self-mapping has a fixed point. In addition, we show that  $F$  satisfies the conditions in Theorem 1. Let (33), (34), and (35) hold, so we assume

$$R = (0, 0, 0), \quad r = \begin{cases} (1 - d^\nu f_1(\eta) - k^\nu M_3 f_2(\eta) - k^\nu M_1 f_3(\eta) + b^\nu f_4(\eta)), \\ (1 + (b^\nu + \delta^\nu) f_5(\eta) + k^\nu M_3 f_6(\eta) + k^\nu M_1 f_7(\eta)), \\ (1 + N\delta^\nu f_8(\eta) - c^\nu f_9(\eta)). \end{cases} \tag{37}$$

Then all conditions of Theorem 1 are fulfilled and the proof is complete. □

### 5 Solution of equations by HATM method

To solve equations (3), we apply the Laplace transform on the both sides of equations:

$$\begin{cases} L[{}_0^{CF}D_t^\nu T(t)](s) = L[\beta - k^\nu V(t)T(t) - d^\nu T(t) + b^\nu U(t)], \\ L[{}_0^{CF}D_t^\nu U(t)](s) = L[k^\nu V(t)T(t) - (b^\nu + \delta^\nu)U(t)], \\ L[{}_0^{CF}D_t^\nu V(t)](s) = L[N\delta^\nu U(t) - c^\nu V(t)]. \end{cases} \tag{38}$$

So

$$\begin{cases} \frac{sL(T)-T(0)}{s+\nu(1-s)} = L(\beta - k^\nu VT - d^\nu T + b^\nu U), \\ \frac{sL(U)-U(0)}{s+\nu(1-s)} = L(k^\nu VT - (b^\nu + \delta^\nu)U), \\ \frac{sL(V)-V(0)}{s+\nu(1-s)} = L(N\delta^\nu U - c^\nu V). \end{cases} \tag{39}$$

We get

$$\begin{cases} L(T) - \frac{T_0}{s} - \frac{s+\nu(1-s)}{s}L(\beta - k^\nu VT - d^\nu T + b^\nu U) = 0, \\ L(U) - \frac{U_0}{s} - \frac{s+\nu(1-s)}{s}L(k^\nu VT - (b^\nu + \delta^\nu)U) = 0, \\ L(V) - \frac{V_0}{s} - \frac{s+\nu(1-s)}{s}L(N\delta^\nu U - c^\nu V) = 0. \end{cases} \tag{40}$$

Using the homotopy method, the nonlinear operator is defined as follows:

$$\begin{aligned} N_1(\varphi_1(t;p), \varphi_2(t;p), \varphi_3(t;p)) &= L(\varphi_1(t;p)) - \frac{T_0}{s} - \frac{s+\nu(1-s)}{s} \\ &\quad \times L[\beta - k^\nu \varphi_3(t;p)\varphi_1(t;p) - d^\nu \varphi_1(t;p) + b^\nu \varphi_2(t;p)], \\ N_2(\varphi_1(t;p), \varphi_2(t;p), \varphi_3(t;p)) &= L(\varphi_2(t;p)) - \frac{U_0}{s} - \frac{s+\nu(1-s)}{s} \\ &\quad \times L[k^\nu \varphi_3(t;p)\varphi_1(t;p) - (b^\nu + \delta^\nu)\varphi_2(t;p)], \\ N_3(\varphi_1(t;p), \varphi_2(t;p), \varphi_3(t;p)) &= L(\varphi_3(t;p)) - \frac{V_0}{s} - \frac{s+\nu(1-s)}{s} \\ &\quad \times L[N\delta^\nu \varphi_2(t;p) - c^\nu \varphi_3(t;p)]. \end{aligned} \tag{41}$$

The so-called zero-order deformation equations of the Laplace transform equation (41) have been shown by Liao [41] to have the form

$$\begin{aligned} (1-p)L[\varphi_1(t;p) - T_0(t)] &= phH(t)N_1(\varphi_1(t;p), \varphi_2(t;p), \varphi_3(t;p)), \\ (1-p)L[\varphi_2(t;p) - U_0(t)] &= phH(t)N_2(\varphi_1(t;p), \varphi_2(t;p), \varphi_3(t;p)), \\ (1-p)L[\varphi_3(t;p) - V_0(t)] &= phH(t)N_3(\varphi_1(t;p), \varphi_2(t;p), \varphi_3(t;p)), \end{aligned} \tag{42}$$

where  $p \in [0, 1]$  is the embedding parameter,  $h \neq 0$  is a nonzero auxiliary parameter,  $H(t) \neq 0$  is an auxiliary function,  $L$  is an auxiliary linear operator,  $T_0(t)$ ,  $U_0(t)$ , and  $V_0(t)$  are initial

guesses of  $T(t)$ ,  $U(t)$ , and  $V(t)$ , and  $\varphi_i(t;p), i = 1, 2, 3$ , are unknown functions respectively. It is important that one has great freedom to choose auxiliary things in HAM. Obviously, when  $p = 0$  and  $p = 1$ ,

$$\begin{cases} \varphi_1(t;0) = T_0(t), & \varphi_1(t;1) = T(t), \\ \varphi_2(t;0) = U_0(t), & \varphi_2(t;1) = U(t), \\ \varphi_3(t;0) = V_0(t), & \varphi_3(t;1) = V(t). \end{cases} \tag{43}$$

Then as  $p$  increases from 0 to 1, the solution  $(\varphi_1(t;p), \varphi_2(t;p), \varphi_3(t;p))$  varies from the initial guess  $(T_0(t), U_0(t), V_0(t))$  to the solution  $(T(t), U(t), V(t))$ . Expanding  $\varphi_1(t;p)$ ,  $\varphi_2(t;p)$ , and  $\varphi_3(t;p)$  in Taylor series with respect to  $p$ , we have

$$\begin{aligned} \varphi_1(t;p) &= T_0 + \sum_{m=1}^{\infty} T_m(t)p^m, \\ \varphi_2(t;p) &= U_0 + \sum_{m=1}^{\infty} U_m(t)p^m, \\ \varphi_3(t;p) &= V_0 + \sum_{m=1}^{\infty} V_m(t)p^m, \end{aligned} \tag{44}$$

where  $T_m(t) = \frac{1}{m!} \frac{\partial^m \varphi_1(t;p)}{\partial p^m} |_{p=0}$  and  $U_m(t) = \frac{1}{m!} \frac{\partial^m \varphi_2(t;p)}{\partial p^m} |_{p=0}$  and  $V_m(t) = \frac{1}{m!} \frac{\partial^m \varphi_3(t;p)}{\partial p^m} |_{p=0}$ . If the auxiliary linear operator, the initial guess, the auxiliary parameter  $h$ , and the auxiliary function  $H(t)$  are properly chosen, then series (44) converges at  $p = 1$  as proved by Liao [41] (and see [4, 5]), we have

$$\begin{aligned} X(t) &= X_0 + \sum_{m=1}^{\infty} X_m(t), \\ Y(t) &= Y_0 + \sum_{m=1}^{\infty} y_m(t). \end{aligned} \tag{45}$$

The  $m$ th-order deformation equation is presented by

$$\begin{cases} L[T_m(t) - \chi_m T_{m-1}(t)] = hHR_{1,m}(T_{m-1}), \\ L[U_m(t) - \chi_m U_{m-1}(t)] = hHR_{2,m}(U_{m-1}), \\ L[V_m(t) - \chi_m V_{m-1}(t)] = hHR_{3,m}(V_{m-1}). \end{cases} \tag{46}$$

So that

$$\begin{aligned} &R_{1,m}(\vec{T}_{m-1}(t), \vec{U}_{m-1}(t), \vec{V}_{m-1}(t)) \\ &= L[T_{m-1}(t)] - \frac{T_0}{s}(1 - \chi_m) \\ &\quad - \frac{s + v(1 - s)}{s} \times L[\beta - k^v V_{m-1} T_{m-1} - d^v T_{m-1} + b^v U_{m-1}], \end{aligned}$$

$$\begin{aligned}
 &R_{2,m}(\vec{T}_{m-1}(t), \vec{U}_{m-1}(t), \vec{V}_{m-1}(t)) \\
 &= L[U_{m-1}(t)] - \frac{U_0}{s}(1 - \chi_m) \\
 &\quad - \frac{s + \nu(1 - s)}{s} \times L[k^\nu V_{m-1} T_{m-1} - (b^\nu + \delta^\nu) U_{m-1}],
 \end{aligned}$$

and

$$\begin{aligned}
 &R_{3,m}(\vec{T}_{m-1}(t), \vec{U}_{m-1}(t), \vec{V}_{m-1}(t)) \\
 &= L[V_{m-1}(t)] - \frac{V_0}{s}(1 - \chi_m) - \frac{s + \nu(1 - s)}{s} \times L[N\delta^\nu U_{m-1} - c^\nu V_{m-1}]. \tag{47}
 \end{aligned}$$

Using the inverse Laplace transform, we obtain

$$\begin{cases}
 T_m(t) = \chi_m T_{m-1}(t) + hHL^{-1}[R_{1,m}(T_{m-1})], \\
 U_m(t) = \chi_m U_{m-1}(t) + hHL^{-1}[R_{2,m}(U_{m-1})], \\
 V_m(t) = \chi_m V_{m-1}(t) + hHL^{-1}[R_{3,m}(V_{m-1})].
 \end{cases} \tag{48}$$

On solving the above equations for  $m = 1, 2, 3, \dots$ , we get

$$\begin{cases}
 T_1(t) = -hH(1 + \nu(t - 1))(\beta - k^\nu V_0 T_0 - d^\nu T_0 + b^\nu U_0) \\
 \quad = -hH(1 + \nu(t - 1))M_1, \\
 U_1(t) = -hH(1 + \nu(t - 1))(k^\nu V_0 T_0 - (b^\nu + \delta^\nu)U_0) \\
 \quad = -hH(1 + \nu(t - 1))M_2, \\
 V_1(t) = -hH(1 + \nu(t - 1))(N\delta^\nu U_0 - c^\nu V_0) \\
 \quad = -hH(1 + \nu(t - 1))M_3,
 \end{cases} \tag{49}$$

where  $M_1 = \beta - k^\nu V_0 T_0 - d^\nu T_0 + b^\nu U_0$ ,  $M_2 = k^\nu V_0 T_0 - (b^\nu + \delta^\nu)U_0$ , and  $M_3 = N\delta^\nu U_0 - c^\nu V_0$ . Consequently, the solutions of equations (3) are given as follows:

$$\begin{aligned}
 T(t) &= T_0 + T_1 + T_2 + \dots = T_0 - hH(1 + \nu(t - 1))M_1 + \dots, \\
 U(t) &= U_0 + U_1 + U_2 + \dots = U_0 - hH(1 + \nu(t - 1))M_2 + \dots, \\
 V(t) &= V_0 + V_1 + V_2 + \dots = V_0 - hH(1 + \nu(t - 1))M_3 + \dots,
 \end{aligned} \tag{50}$$

where  $M_1 = \beta - k^\nu V_0 T_0 - d^\nu T_0 + b^\nu U_0$  and  $M_2 = k^\nu V_0 T_0 - (b^\nu + \delta^\nu)U_0$  and  $M_3 = N\delta^\nu U_0 - c^\nu V_0$ .

### 5.1 Convergency of HATM for FDEs

We prove the convergence of the HATM method for equation (40) as our next result.

**Theorem 3** *Let the series  $\sum_{m=0}^\infty T_m(t)$  and  $\sum_{m=0}^\infty U_m(t)$  and  $\sum_{m=0}^\infty V_m(t)$  converge uniformly to  $T(t)$ ,  $U(t)$ , and  $V(t)$  respectively, where  $T_m(t)$ ,  $U_m(t)$ ,  $V_m(t) \in L(R^+)$  are produced by the  $m$ th-order deformation (46), and besides  $\sum_{m=0}^\infty D^\nu T_m(t)$  and  $\sum_{m=0}^\infty D^\nu U_m(t)$  and  $\sum_{m=0}^\infty D^\nu V_m(t)$  also converge. Then  $T(t)$ ,  $U(t)$ ,  $V(t)$  is the solution of (40).*

*Proof* Suppose that  $\sum_{m=0}^{\infty} T_m(t)$  converges uniformly to  $T(t)$ , then clearly  $\lim_{m \rightarrow \infty} T_m(t) = 0$  for all  $t \in R^+$ . Since Laplace is a linear operator, we have

$$\begin{aligned} & \sum_{m=1}^n L[T_m(t) - \chi_m T_{m-1}(t)] \\ &= \sum_{m=1}^n [LT_m(t) - \chi_m LT_{m-1}(t)] \\ &= LT_1(t) + (LT_2(t) - LT_1(t)) + \dots + (LT_n(t) - LT_{n-1}(t)) = LT_n(t). \end{aligned} \tag{51}$$

Thus, from (51) we derive

$$\sum_{m=1}^{\infty} L[T_m(t) - \chi_m T_{m-1}(t)] = \lim_{n \rightarrow \infty} LT_n(t) = L\left(\lim_{n \rightarrow \infty} T_n(t)\right) = 0. \tag{52}$$

Hence  $hH \sum_{m=1}^{\infty} R_{1,m}(\vec{T}_{m-1}(t)) = \sum_{m=1}^{\infty} L[T_m(t) - \chi_m T_{m-1}(t)] = 0$ .

Since  $h \neq 0, H \neq 0$ , this yields  $\sum_{m=1}^{\infty} R_{1,m}(\vec{T}_{m-1}(t)) = 0$ . Similarly, we can prove

$$\sum_{m=1}^{\infty} R_{2,m}(\vec{U}_{m-1}(t)) = 0, \quad \sum_{m=1}^{\infty} R_{3,m}(\vec{V}_{m-1}(t)) = 0. \tag{53}$$

Now from (47) we have

$$\begin{aligned} 0 &= \sum_{m=1}^{\infty} \left\{ L[T_{m-1}(t)] - \frac{T_0}{s}(1 - \chi_m) - \frac{s + \nu(1 - s)}{s} \right. \\ &\quad \left. \times L[\beta - k^\nu V_{m-1} T_{m-1} - d^\nu T_{m-1} + b^\nu U_{m-1}] \right\} \\ &= L\left[ \sum_{m=1}^{\infty} T_{m-1}(t) \right] - \frac{T_0}{s} \sum_{m=1}^{\infty} (1 - \chi_m) - \frac{s + \nu(1 - s)}{s} \\ &\quad \times L\left[ \beta - k^\nu \sum_{m=1}^{\infty} V_{m-1}(t) T_{m-1}(t) - d^\nu \sum_{m=1}^{\infty} T_{m-1}(t) + b^\nu \sum_{m=1}^{\infty} U_{m-1}(t) \right] \\ &= L[T(t)] - \frac{T_0}{s} - \frac{s + \nu(1 - s)}{s} L[\beta - k^\nu V(t)T(t) - d^\nu T(t) + b^\nu U(t)]. \end{aligned} \tag{54}$$

Similarly,

$$\begin{aligned} 0 &= \sum_{m=1}^{\infty} \left\{ L[U_{m-1}(t)] - \frac{U_0}{s}(1 - \chi_m) - \frac{s + \nu(1 - s)}{s} L[U_{m-1}(t)] - \frac{U_0}{s}(1 - \chi_m) \right. \\ &\quad \left. - \frac{s + \nu(1 - s)}{s} L[k^\nu V_{m-1} T_{m-1} - (b^\nu + \delta^\nu) U_{m-1}] \right\} \\ &= L\left[ \sum_{m=1}^{\infty} U_{m-1}(t) \right] - \frac{U_0}{s} \sum_{m=1}^{\infty} (1 - \chi_m) \end{aligned}$$

$$\begin{aligned}
 & -\frac{s + \nu(1-s)}{s} L \left[ k^\nu \sum_{m=1}^\infty V_{m-1} T_{m-1} - (b^\nu + \delta^\nu) \sum_{m=1}^\infty U_{m-1} \right] \\
 = & L[U(t)] - \frac{U_0}{s} - \frac{s + \nu(1-s)}{s} L[k^\nu V(t)T(t) - (b^\nu + \delta^\nu)U(t)], \tag{55}
 \end{aligned}$$

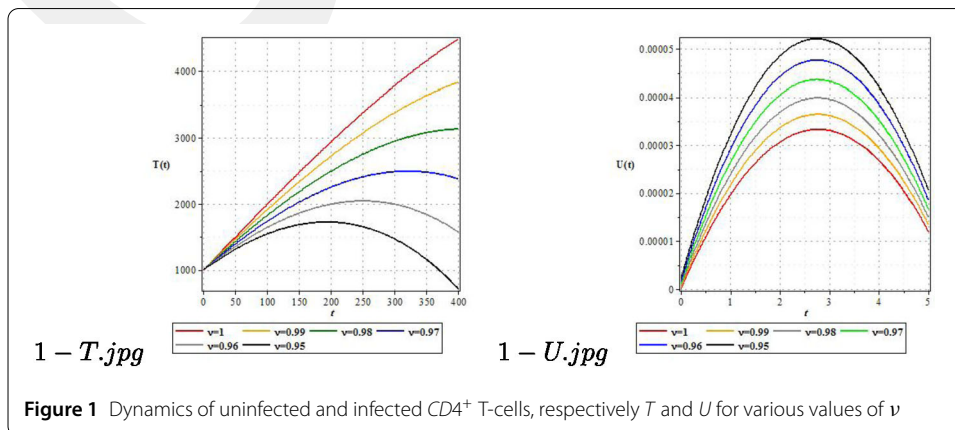
and

$$\begin{aligned}
 0 = & \sum_{m=1}^\infty \left\{ L[V_{m-1}(t)] - \frac{V_0}{s}(1 - \chi_m) - \frac{s + \nu(1-s)}{s} L[V_{m-1}(t)] \right. \\
 & \left. - \frac{V_0}{s}(1 - \chi_m) - \frac{s + \nu(1-s)}{s} L[N\delta^\nu U_{m-1}, -c^\nu V_{m-1}] \right\} \\
 = & L \left[ \sum_{m=1}^\infty V_{m-1}(t) \right] - \frac{V_0}{s} \sum_{m=1}^\infty (1 - \chi_m) \\
 & - \frac{s + \nu(1-s)}{s} L \left[ N\delta^\nu \sum_{m=1}^\infty U_{m-1} - c^\nu \sum_{m=1}^\infty V_{m-1} \right] \\
 = & L[V(t)] - \frac{V_0}{s} - \frac{s + \nu(1-s)}{s} L[N\delta^\nu U(t) - c^\nu V(t)]. \tag{56}
 \end{aligned}$$

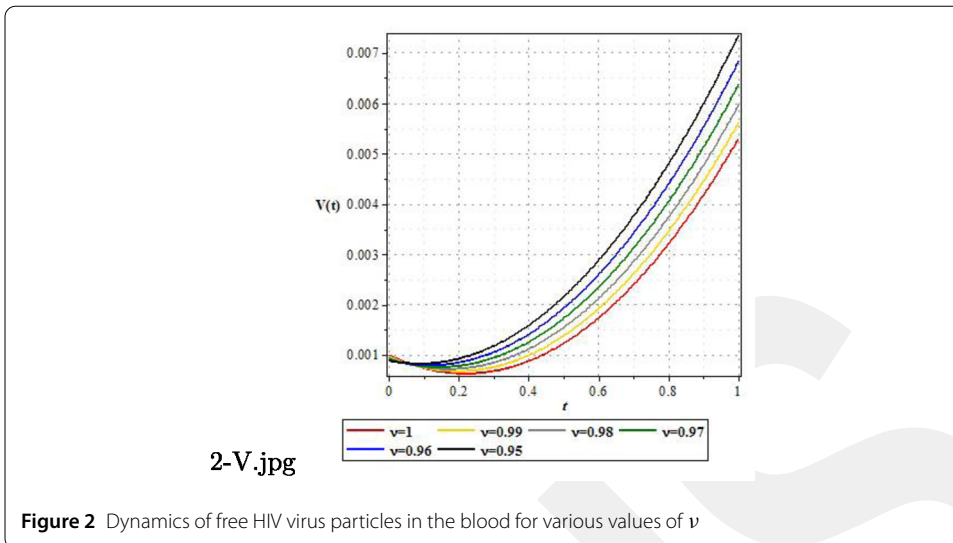
Therefore  $T(t)$ ,  $U(t)$ , and  $V(t)$  are the solutions of equation (40) and the proof is complete.  $\square$

### 6 Numerical results

In this section, we present a numerical simulation of the results of the HIV-1 infection T-cells system (3). The values of the parameters are also selected as  $N = 1000$ ,  $\delta = 0.16$ ,  $k = 0.000024$ ,  $b = 0.2$ ,  $c = 3.4$ ,  $\beta = 10$ ,  $d = 0.01$  and the initial conditions are given by  $V_0 = 0.001$ ,  $U_0 = 0$ ,  $T_0 = 1000$  (see [9]). Next, we compute the HATM solutions for different values of  $\nu = 0.95, 0.96, 0.97, 0.98, 0.99, 1$ ,  $h = -1$ , and  $H = 1$ . Figures 1, 2 show the results and indicate that as  $\nu \rightarrow 1$ , the approximate solutions tend to the classic integer solution with  $\nu = 1$ . A comparison between the noninteger order model with  $\nu = 0.95$  and the integer order  $\nu = 1$  is also given in Tables 1–3. The results verify the efficacy and accuracy of the new fractional model.



**Figure 1** Dynamics of uninfected and infected  $CD4^+$  T-cells, respectively  $T$  and  $U$  for various values of  $\nu$



**Table 1** Results of three types of derivative: ordinary derivative  $D^\nu$ , Caputo fractional derivative  ${}^cD^\nu$ , and Caputo–Fabrizio fractional derivative  ${}^{CF}D^\nu$  for  $T(t)$

$t$	0	1	2	3	4	5
$D^\nu (\nu = 1)$	1000	1010	1020	1030	1040	1050
${}^cD^\nu (\nu = 0.95)$	1000	1007.6	1014.5	1021.4	1028	1034.5
${}^{CF}D^\nu (\nu = 0.95)$	1000.49999	1009.9999	1019.4998	1028.9996	1038.49909	1047.9983

**Table 2** Results of three types of derivative: ordinary derivative  $D^\nu$ , Caputo fractional derivative  ${}^cD^\nu$ , and Caputo–Fabrizio fractional derivative  ${}^{CF}D^\nu$  for  $U(t)$

$t$	0	1	2	3	4	5
$D^\nu (\nu = 1)$	0	0.00001934	0.0000281	0.00002802	0.00001968	0.0000034
${}^cD^\nu (\nu = 0.95)$	0	0.00004318	0.0001218	0.0002826	0.0005667	0.0010129
${}^{CF}D^\nu (\nu = 0.95)$	0.000002	0.0000322	0.0000486	0.0000517	0.0000421	0.0000205

**Table 3** Results of three types of derivative: ordinary derivative  $D^\nu$ , Caputo fractional derivative  ${}^cD^\nu$ , and Caputo–Fabrizio fractional derivative  ${}^{CF}D^\nu$  for  $V(t)$

$t$	0	1	2	3	4	5
$D^\nu (\nu = 1)$	0.001	0.003572	0.018088	0.04455	0.08295	0.1333
${}^cD^\nu (\nu = 0.95)$	0.001	0.0037256	0.017048	0.040028	0.072244	0.11341
${}^{CF}D^\nu (\nu = 0.95)$	0.0008677	0.0058764	0.0244969	0.0567293	0.1026	0.1620

### 7 Conclusion

In this work, we extend the model of HIV-1 infection of  $CD4^+$  T-cell to the concept of Caputo–Fabrizio fractional derivative. We solve the related fractional differential equations by using the HATM method. The existence and uniqueness of the solutions are studied with a fixed point theorem. We present the special solution by using the Sumudu transform of the Caputo–Fabrizio derivation. Also, some numerical results are presented for different values of  $\nu$  to show the effect of the fractional order. Finally, we compare the results of the ordinary, Caputo, and Caputo–Fabrizio derivatives.

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### Competing interests

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### Consent for publication

Not applicable.

### Authors' contributions

The authors declare that the study was realized in collaboration with equal responsibility. All authors read and approved the final manuscript.

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