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A FRACTIONAL APPROACH TO SOLVE A MATHEMATICAL MODEL OF HIV INFECTION OF $CD4^+T$ CELLS

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Abstract. A mathematical model that calculates susceptible $CD4^+T$ cells, infected $CD4^+T$ cells and virus particles has been examined here using the fractional differential transform method (FDTM) with stability analysis. A stability of the fractional nonlinear model with Hurwitz state matrix is examined using the Lyapunov direct method. A nonlinear mathematical model of differential equations has been put forward and analyzed by applying FDTM. An infinite series solution of the system of differential equation is computed by defining fixed components with different time intervals. Furthermore, the solution calculated through FDTM (integer order) is correlated with the solution calculated using DTM and LADM. The solution is analyzed numerically and graphically by using the software Python.

Keywords: Lyapunov direct method; fractional differential transform method; HIV infection; $CD4^+T$ cells.

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1. INTRODUCTION

Human immunodeficiency virus (HIV) infection is a disease which impacts on the immune system of human being caused by the HIV virus(avert.org). HIV corrupts the white blood cells

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in the immune system when it enters into the body. HIV can not reproduce by its own. The life cycle of HIV goes through the different steps taken by the virus in which it multiplies and make the copies of itself. First, on arriving into the human body the virus gets attached itself to the T - helper cells (also called $CD4^+T$ cells) and gets blended with it. Virus starts regulated the original cells and takes the control of its DNA. The virus starts created copies of itself and discharges more HIV into the blood. This process of multiplying and discharging of virus into the blood never gets stopped and termed as the HIV life cycle.A person can get HIV infection by coming into contact with the bodily fluid like blood, semen,breast milk of someone living with the virus. HIV can also be transmitted during unprotected sex, through sharing surgical equipment,from mother to baby during pregnancy,at the time of birth and breastfeeding, it also enters into human body through contaminated blood transfusion. HIV can not be transmitted through other bodily fluids like saliva, sweat or urine as there is not enough virus present in these fluids.HIV is most infectious in the first few weeks after infection. There is no proper medicine developed for this disease although ART(Antiretroviral treatment) can control this virus. Anti HIV drug targets into different stages in the HIV life cycle. The researcher are looking for a functional cure where HIV is reduced to undetectable and harmless level in the body as well as for the sterilizing cure where HIV is removed from the body. By knowing how HIV infects the body can help one to understand the prevention and treatment. UNAIDS (The joint United Nations program on AIDS/HIV) is the leading global attempt which aims to eradicate the HIV/AIDS by 2030 as the part of Sustainable Development Goals.(unaids.org). The result of the efforts taken by the UNAIDS, the rate of progress of new HIV infections is getting reduced, increasing access to treatment and AIDS related deaths is getting slowed down. Since the first case of HIV were reported more than 35 years ago,the fresh data provided by the UNAIDS, nearly 1.5 million people are newly infected with HIV in 2020, nearly 37.7 million people are living with HIV and 680 thousand people died of AIDS related illness in 2020.

A mathematical model that has been put forward by Perelson et. al.[1] in which the interaction of HIV with $CD4^+T$ cells is considered here for computation of solution using Fractional Differential Transform Method (FDTM). Already numerous mathematical computations have been done on the model using various mathematical methods by different authors.Homotopy

Perturbation Method(HPM) is used by Mehmet MERDAN(2007)[4]. Mehmat Merdan et. al. has solved model using Variational Iterational Method(2011)[5]. M.Y. Ongun worked with the Laplace Adomain Decomposition Method(LADM) in (2011)[6].The Multistep Laplace Adomain Decomposition Method(MLADM) is used by Nurettin Dogan in (2012)[7]. Kolebaje Olusola T. et.al. used the Multistage Differential Transform Method in (2014)[8]. A.S. Malik et.al. solved with a Genetic Algorithm(GA), Interior Point Algorithm(IPA) and Active Set Algorithm(ASA) in (2014)[9].M. Khalid et.al. worked out with the new iteration Algorithm in (2014)[11].Recently Attaullah and Muhammad Sohaib worked out with Continuous Galerkin Petrov Method(cGP2) and Legendre Wavelet Collocation Method(LWCM) in (2020)[12]. All thees mentioned mathematical methods have been compared with the Runge-Kutta method of order four (RK4) and analysed the solutions.

A fractional differentiation in Caputo sense is more applicable to real world problems. Semi analytical numerical technique that is developed to study fractional power series in a same way Differential Transform Method does for Taylor series. A mathematical model of HIV infection of $CD4^+T$ cells given in [1] is reviewed here for finding the solution of it using Fractional Differential Transform Method.The system of differential equation is given as follows;

$$\begin{aligned}
\frac{ds(t)}{dt} &= p - \alpha s(t) + rs(t)\left(1 - \frac{s(t)+i(t)}{s_{max}}\right) - \delta v(t)s(t) \\
\frac{di(t)}{dt} &= \delta v(t)s(t) - \beta i(t) \\
\frac{dv(t)}{dt} &= n\beta i(t) - \gamma v(t)
\end{aligned} \tag{1}$$

With the initial conditions:

$$s(0) = 0.1, \;\; i(0) = 0, \;\; v(0) = 0.1 \tag{2}$$

Where the terms denote

$s(t) \longrightarrow$ Concentration of susceptible $CD4^+T$ cells.

$i(t) \longrightarrow$ Concentration of $CD4^+T$ cells infected by HIV virus.

$v(t) \longrightarrow$ Free HIV virus particles presented in the blood.

$\left(1 - \frac{s(t)+i(t)}{s_{max}}\right) \longrightarrow$ Logistic growth of healthy $CD4^+T$ cells.

$\delta v(t)s(t) \longrightarrow$ Incidence of HIV infection of healthy $CD4^+T$ cells.

TABLE 1. Parameter Description and their Values

Sr. No.	Parameter	Description	Value
1	α	Turnover rate of uninfected T - cells	0.02
2	β	Turnover rate of infected T - cells	0.3
3	γ	Turnover rate of virus particle	2.4
4	δ	Infection rate	0.0027
5	n	Production rate of virus particles	10
6	p	$CD4^+T$ cells constant source	0.1
7	r	$CD4^+T$ cells production rate	3
8	s_{max}	Maximum level of $CD4^+T$ cells in the body	1500

The remaining parameters are described in the table 1. Proposed model has been discussed in different sections. In section 2 the necessary pre-requisites are collected on FDTM. Brief calculations is given in section 3 which is further divided into two subsections, in first subsection stability analysis of the model is discussed and in other subsection methodology using FDTM for different orders of the model is proposed. Result and discussion is given section 4 and finally results are analyzed in conclusion part.

2. PRELIMINARIES

The fractional differential transform method is used in this paper to obtain the solution of mathematical model of HIV Infection of $CD4^+$T cells. This method has been developed in [3] as follows. The fractional differentiation in Riemann-Liouville sense is defined as

$$D^q_{x_0} = \frac{1}{\Gamma(m-q)} \frac{d^m}{dx^m} \int_{x_0}^{x} (x-t)^{m-q-1} f(t) dt \tag{3}$$

where $m-1 \leq q < m$, m is an positive integer and $x > x_0$. The expansion of analytic and continuous function $f(x)$ in terms of fractional power series is given as:

$$f(x) = \sum_{k=0}^{\infty} F(k)(x-x_0)^{\frac{k}{\lambda}} \tag{4}$$

where λ is the order of the fraction and $F(k)$ is the fractional differential transform of $f(x)$. The relation between the Riemann-Liouville operator and Caputo operator is given as follows;

$$D^q_{*x_0} f(x) = D^q_{x_0}\left[f(x) - \sum_{k=0}^{m-1} \frac{1}{k!}(x-x_0)^k f^k(x_0)\right] \tag{5}$$

$*$ is used for the Caputo operator to distinguish between Riemann-Liouville operator and Caputo operator.Denoting $f(x) = f(x) - \sum_{k=0}^{m-1} \frac{1}{k!}(x-x_0)^k f^k(x_0)$ in above equation. We obtain fractional derivative in the Caputo sense as follows;

$$D^q_{*x_0} = \frac{1}{\Gamma(m-q)} \frac{d^m}{dx^m} \int_{x_0}^{x} (x-t)^{m-q-1} \left[f(t) - \sum_{k=0}^{m-1} \frac{1}{k!}(t-x_0)^k f^k(x_0)\right] dt \tag{6}$$

Since the initial conditions are implemented to the integer order differential equation, the transformed initial conditions can be obtained using the below relation;

$$F(k) = \begin{cases} \frac{1}{(k/\lambda)!}\left[\frac{d^{k/\lambda} f(x))}{dx^{k/\lambda}}\right]_{x=x_0}, k/\lambda \in Z^+ \\ 0 \quad , \qquad k/\lambda \notin Z^+ \end{cases} \tag{7}$$

Where $k = 0, 1, 2, ---, q\lambda - 1$ and q is the order of the FDE. λ is to be chosen such that $q\lambda$ is a positive integer. The following theorems can be proved using equations 3 and 4.For more detail refer [3].

Theorem 2.1. If $u(x) = f(x) \pm g(x)$ then $U(k) = F(k) \pm G(k)$

Theorem 2.2. If $u(x) = f(x) \times g(x)$ then $U(k) = \sum_{l=0}^{k} F(l) \times G(k-l)$

Theorem 2.3. If $u(x) = (x-x_0)^p$ then $U(k) = \delta(k - \lambda p)$

$$where\ \delta(k) = \begin{cases} 1, k = 0 \\ 0, k \neq 0 \end{cases}$$

Theorem 2.4. If $f(x) = D^q_{x_0}[u(x)]$ then $F(k) = \frac{\Gamma(q+1+k/\lambda)}{\Gamma(1+k/\lambda)} U(k + \lambda q)$

3. Main Results

3.1. Lyapunov Stability Analysis of Fractional Nonlinear System: The stability analysis of the proposed model is studied using Lypunov function in Caputo sense[13].The main purpose is to discuss asymptotic stability of the model. Before approaching to the methodology we will

consider few statements of the theorems which will be required for the analysis. Consider the system

$$D^{\mu}_{t_0}x(t) = f(t,x(t)) = Ax(t) + a(t,x(t)), \;\; x(t_0) = x_0 \tag{8}$$

where $\mu \in (0,1)$,$x \in \mathbb{R}^n$ represents the state vector of the system, $A \in \mathbb{R}^{n\times n}$ is a constant matrix and $a : \mathbb{R}_+ \times \mathbb{R}^n \longrightarrow \mathbb{R}^n$ is a nonlinear function.

Theorem 3.1.[13] Let $x = 0$ be an equilibrium point of the system $D^{\mu}_{t_0}x(t) = f(t,x(t)) = Ax(t)$. If the state matrix A is Hurwitz then the trivial solution of the fractional linear system is fractional asymptotically stable.

Theorem 3.2.[13] Let $x = 0$ be an equilibrium point of the system $D^{\mu}_{t_0}x(t) = f(t,x(t)) = Ax(t)$. Let that the state matrix A is Hurwitz and the condition $\|a(t,x(t))\| < \rho\|x(t)\|$ holds. If there exists a positive definite matrix P such that the following inequality holds $\rho < \frac{\lambda_{min}(Q)}{2\lambda_{max}(P)}$ where $A^TP + PA = -Q$, then the trivial solution of the fractional linear system is asymptotically stable.

Theorem 3.3.[13] If a function $a(t,x(t))$ is an one - sided Lipschitz and quadratically inner bounded with constants ρ, σ and ω. Assume that there exists two matrices P and Q which verifies:

$$A^TP + PA = -Q$$

$$[(\sigma+1) + \rho(\omega+2)]\lambda_{max}(P) < \lambda_{min}(P) + \lambda_{min}(Q)$$

Then the origin of the system is asymptotically stable.

Theorem 3.4.[13] If the function $a(t,x(t))$ of the system $D^{\alpha}_{t_0}x(t) = f(t,x(t)) = Ax(t) + Bu + a(t,x(t))$ with $x(t_0) = x_0$ is an one - sided Lipschitz and quadratically inner bounded with constants ρ, σ and ω. Assume that there exists a positive symmetric matrix P, a constant matrix $K \in \mathbb{R}^{p\times n}$ and positive constant ε such that;

$$(A+BK)^TP + P(A+BK) = -\varepsilon I$$

$$[(\sigma+1) + \rho(\omega+2)]\lambda_{max}(P) < \lambda_{min}(P) + \varepsilon,$$

Where $B \in \mathbb{R}^{n\times p}$ is a constant matrix and $u \in \mathbb{R}^p$ is the control input to be defined. Then the control law $u(x) = Kx$ render the above system is fractional asymptotically stable.

Writing the proposed model in the form $D^{\alpha}_{t_0}x(t) = f(t,x(t)) = Ax(t)+Bu+a(t,x(t))$, where

$$A=\begin{bmatrix}(r-\alpha) & 0 & 0\\ 0 & -\beta & 0\\ 0 & n\beta & -\gamma\end{bmatrix} B=\begin{bmatrix}p\\0\\0\end{bmatrix} x(t)=\begin{bmatrix}s(t) & i(t) & v(t)\end{bmatrix}$$

$a(t,x(t))$ is nonlinear term of the model. Selecting P as a symmetric and positive definite matrix and K;

$$P=\begin{bmatrix}3 & 0 & 0\\ 0 & 2 & 1\\ 0 & 1 & 2\end{bmatrix} K=\begin{bmatrix}-100 & 0 & 0\end{bmatrix}$$

Taking the parameters $\rho = 0$, $\sigma = -49.899$,$\omega = 99$ and $\varepsilon = 1$, and by theorem (3.4) we get;

$$\begin{aligned}T^{\mu}V(t) &= x^{T}(t)((A+BK)^{T}P+P(A+BK))x(t)+2x^{T}(t)Pf(t,x(t))\\ &\leqslant -[\varepsilon+\lambda_{min}(P)-\lambda_{max}(P)((\sigma+1)+\rho(\omega+2))]\|x(t)\|^{2}\\ &\leqslant -151.697\|x(t)\|^{2}\end{aligned}$$

Hence we can say the proposed model is fractional asymptotically stable with the defined parameters.

3.2. Methodology of the Proposed Model: Rewriting equation (1) taking fractional order μ.

$$\begin{aligned}\frac{d^{\mu}s(t)}{dt} &= p-\alpha s(t)+rs(t)\left(1-\frac{s(t)+i(t)}{s_{max}}\right)-\delta v(t)s(t)\\ \frac{d^{\mu}i(t)}{dt} &= \delta v(t)s(t)-\beta i(t)\\ \frac{d^{\mu}v(t)}{dt} &= n\beta i(t)-\gamma v(t)\end{aligned} \tag{9}$$

Transforming Equation using Theorems 2.1, 2.2, 2.3 and 2.4 as follows;

$$\begin{aligned}S(k+\mu\lambda) &= \frac{\Gamma(1+k/\lambda)}{\Gamma(\mu+1+k/\lambda)}\Big[p\delta(k)-\alpha S(k)+rS(k)-\frac{r}{s_{max}}\sum_{l=0}^{k}S(l)S(k-l)\\ &\quad -\frac{r}{s_{max}}\sum_{l=0}^{k}S(l)I(k-l)-\delta\sum_{l=0}^{k}V(l)S(k-l)\Big]\\ I(k+\mu\lambda) &= \frac{\Gamma(1+k/\lambda)}{\Gamma(\mu+1+k/\lambda)}\left[\delta\sum_{l=0}^{k}V(l)S(k-l)-\beta I(k)\right]\\ V(k+\mu\lambda) &= \frac{\Gamma(1+k/\lambda)}{\Gamma(\mu+1+k/\lambda)}\left[n\beta I(k)-\gamma V(k)\right]\end{aligned} \tag{10}$$

Where λ is the fraction of order μ and $S(k)$, $I(k)$ and $V(k)$ are fractional differential transform of $s(t)$, $i(t)$ and $v(t)$ respectively. The initial conditions in equation 2 is transformed using equation 7 as follows;

$S(k) = 0$ for$k = 1,2,3,---,\mu\lambda - 1.$

$I(k) = 0$ for $k = 0,1,2,3,---,\mu\lambda - 1$

$V(k) = 0$ for $k = 1,2,3,---,\mu\lambda - 1$

$S(0) = 0.1$ *and* $V(0) = 0.1$

$S(k)$,$I(k)$ and $V(k)$ are calculated using equation 10 upto 9 iterations i.e. for $k = 8$ and taking the values $\mu = 1$ and $\lambda = 1$(integer order). Using the equation 4, the solution $s(t)$,$i(t)$ and $v(t)$ are obtained as follows;

$$s(t) = 0.1 + 0.397953t + 0.5928490530450001t^2 + 0.588718771230983t^3 + 0.43829515871882024t^4 + 0.26086329472570297t^5 + 0.12919694443368607t^6 + 0.054687111904082666t^7 + 0.02010958621960049t^8$$

$$i(t) = 0.000027t + 1.7273655000000004e-05t^2 - 8.40515372594998e-06t^3 + 6.147278206097574e-06t^4 - 2.8358618680451083e-06t^5 - 1.153299830876218e-06t^6 - 3.9066623036655364e-07t^7 + 2.6591863951142754e-05t^8$$

$$v(t) = 0.1 - 0.24t + 0.2880405t^2 - 0.23041512634499997t^3 + 0.1382427719417055t^4 - 0.06635284216509499t^5 + 0.02653971893510397t^6 - 0.00909883793496527t^7 + 0.0027295048806531934t^8$$

Solution calculated for the integer order i.e. $\mu = 1$ and $\lambda = 1$ resembles with the solution calculated using Differential Transform Method.Next we check the solution for fractional order.Taking $\mu = 0.5$ and $\lambda = 2$. Using equation 4 we find the solution $s(t)$, $i(t)$ and $v(t)$ as follows;

$$s(t) = 0.1 + 0.44904187468316054t^{1/2} + 1.1856981060900003t + 2.6572241776977754t^{3/2} + 5.260909245707374t^2 + 9.428667740666786t^{5/2} + 15.53871921659617t^3$$

$$i(t) = 3.046623751157884e-05t^{1/2} + 3.454731000000001e-05t + 0.00010304461754158183t^{3/2} +$$
$$0.0001576728974403265t^2 + 0.0002328348946658959 6t^{5/2} + 0.0004417577529442307t^3$$
$$v(t) = 0.1 - 0.2708110001029 23t^{1/2} + 0.576081t - 1.0399825134055134t^{3/2} +$$
$$1.6591943817418235t^2 - 2.3961318156845235t^{5/2} + 3.1856616940270155t^3$$

Next solution is calculated for fractional order $\mu = 0.6$ and $\lambda = 5$ and using equation 4 we again find one more solution $s(t)$, $i(t)$ and $v(t)$ as follows;

$$s(t) = 0.1 + 0.4453790304970674t^{3/5} + 1.0761439694543644t^{6/5} + 2.106989883633 41t^{9/5}$$
$$+ 3.5292581381438075t^{12/5} + 5.221833782679645t^3 + 6.965164687940874t^{18/5}$$
$$i(t) = 3.0217723759893305e-05t^{3/5} + 3.1355265835727414e-05t^{6/5} + 6.527549811859222e-05t^{9/5}$$
$$+ 9.838360418549366e-05t^{12/5} + 8.612663131639861e-05t^3 + 0.0001717816772908717t^{18/5}$$
$$v(t) = 0.1 - 0.26860198897682935t^{3/5} + 0.5228532380064229t^{6/5} - 0.8246336741960394t^{9/5}$$
$$+ 1.113074925251696t^{12/5} - 1.3271757973561693t^3 + 1.4283292312594995t^{18/5}$$

4. Results and Discussion

Stability plays the vital role in discussing the dynamics of the biological model.In the first section of the main result of the paper stability of the proposed model is discussed using the Lyapunov direct method. The nonlinear model is converted into the standard form with initial conditions and by getting satisfied the certain conditions and by defining parameters with positive definite symmetrical matrix, we concluded that the model is asymptotically stable. In the second section of the main result, the solution is specified for the three different orders, one for integer and other two for fractional order. From table 2,3 and 4 we can conclude that as we approach integer order from fractional order we get similar results as of previously done studies. Initially the results overlap but after some time interval the values are different so that we can distinguished the methods.

TABLE 2. Numerical Evaluation of $s(t)$

Sr. No.	t	$\mu = 0.5$	$\mu = 0.6$	$\mu = 1$
1	0	0.1	0.1	0.1
2	0.1	0.54256204	0.33418942	0.14635908
3	0.2	1.27903813	0.67899307	0.20880808
4	0.3	2.49610088	1.2398303	0.29292927
5	0.4	4.32084841	2.10316783	0.40623862
6	0.5	6.87418025	3.36314387	0.55884853
7	0.6	10.27373841	5.12186632	0.76434496
8	0.7	14.63496558	7.48905418	1.04093452
9	0.8	20.07165585	10.58164291	1.41292594
10	0.9	26.69629512	14.52343048	1.91261778
11	1.0	34.62029307	19.44476949	2.58267292

TABLE 3. Numerical Evaluation of $i(t)$

Sr. No.	t	$\mu = 0.5$	$\mu = 0.6$	$\mu = 1$
1	0	$0.00000000e+00$	$0.00000000e+00$	$0.00000000e+00$
2	0.1	$1.91023335e-05$	$1.11242279e-05$	$2.86491915e-06$
3	0.2	$4.37570235e-05$	$2.29319430e-05$	$6.03277003e-06$
4	0.3	$8.15788202e-05$	$3.95893764e-05$	$9.47309162e-06$
5	0.4	$1.36217314e-04$	$6.31922444e-05$	$1.31756972e-05$
6	0.5	$2.11046039e-04$	$9.59026407e-05$	$1.71821964e-05$
7	0.6	$3.09327289e-04$	$1.40039760e-04$	$2.16686866e-05$
8	0.7	$4.34258736e-04$	$1.98092929e-04$	$2.71169410e-05$
9	0.8	$5.88993500e-04$	$2.72720071e-04$	$3.46221469e-05$
10	0.9	$7.76651002e-04$	$3.66742725e-04$	$4.63959665e-05$
11	1.0	$1.00032371e-03$	$4.83140401e-04$	$6.65344152e-05$

TABLE 4. Numerical Evaluation of $v(t)$

Sr. No.	t	$\mu = 0.5$	$\mu = 0.6$	$\mu = 1$
1	0	0.1	0.1	0.1
2	0.1	0.05128338	0.05591331	0.07866318
3	0.2	0.05007673	0.04513601	0.06187984
4	0.3	0.07083141	0.04321698	0.0486785
5	0.4	0.12294137	0.05189535	0.03829506
6	0.5	0.2182849	0.07634455	0.03012914
7	0.6	0.36977915	0.12380671	0.02371095
8	0.7	0.59096253	0.20319608	0.01867802
9	0.8	0.89581047	0.32491914	0.01476211
10	0.9	1.29863333	0.50076804	0.01178788
11	1.0	1.81401175	0.74384593	0.00968569

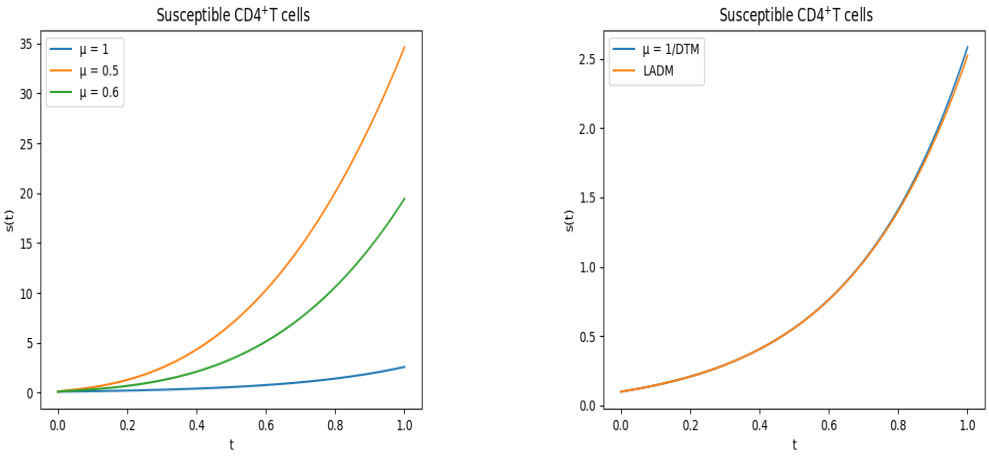

FIGURE 1. Graphical comparison of $s(t)$ for $\mu = 0.5$, $\mu = 0.6$ and $\mu = 1$ with LADM[6]

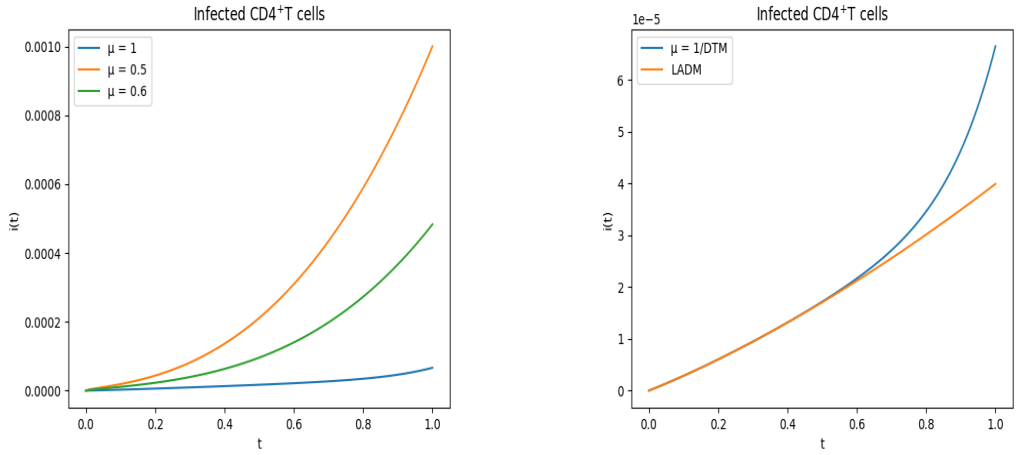

FIGURE 2. Graphical comparison of $i(t)$ for $\mu = 0.5$, $\mu = 0.6$ and $\mu = 1$ with LADM[6]

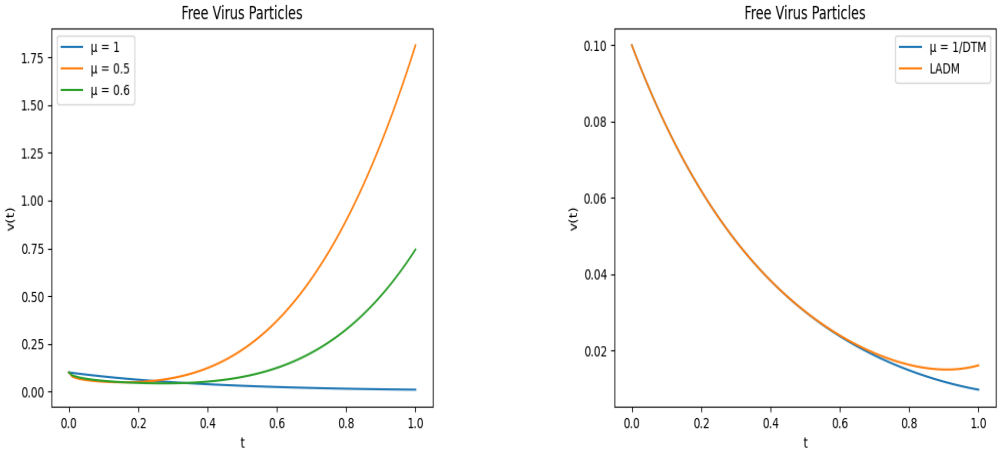

FIGURE 3. Graphical comparison of $v(t)$ for $\mu = 0.5$, $\mu = 0.6$ and $\mu = 1$ with LADM[6]

5. CONCLUSIONS

A stability of the fractional nonlinear model with Hurwitz state matrix is examined using the Lyapunov direct method. This analysis plays a vital role to describe the behavior of physical systems when modeled by means of FDEs. Lyapunov direct method provides a very effective way to analyze stability of nonlinear systems.In this paper, with stabilty a fractional approach is also used to solve the system of ordinary differential equations. A nonlinear mathematical model has been solved by using Fractional Differential Transform Method(FDTM). FDTM provides the solution in terms of a series in a direct way without using linearization or perturbation. The $s(t)$, $i(t)$ and $v(t)$ are calculated for the different order $\mu = 0.5$, $\mu = 0.6$ and for integer order i.e. for $\mu = 1$. The solution calculated for integer order resembles with the solution calculated by DTM. Integer order solution is also compared with the method LADM(Laplace Adomain Decomposition Method) as we found very closed match between them. All the calculated values with fixed parameters are displayed in the Table 2, 3 and 4. Graphical interpretation is given side by side of fractional order, integer order and LADM in figure 1 , 2 and 3.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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