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Global Stability of a Delayed HIV-1 Model with Saturations Response

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Abstract: In this article, an HIV-1 infection dynamical model with saturation response including two continuous delays is presented. One delay represents the latent period between the time of contact of virus particles with targeted cells and the time of entering into the cells. While the other delay is used for the period of production of new virions that release from the infected cells. The basic reproduction number R_0 is investigated and proved that if $R_0 \leq 1$, the infection-free equilibrium is globally asymptotically stable. However, if $R_0 > 1$, then an infected equilibrium occurs which is globally asymptotically stable. The analytical and numerical results show that time delays have great effect on the global stability of equilibria because the basic reproduction number depends on both the delays.

Keywords: HIV Epidemic model, delay differential equation; stability analysis; numerical simulation

1 Introduction

Mathematical modeling is used in epidemiology, to understand the mechanisms of the spread of any disease and its control strategies. Human immunodeficiency virus (HIV-1) is a lentivirus that causes acquired immunodeficiency syndrome (AIDS). The HIV-1 infection passes through three stages that are: (1) acute HIV infection, (2) clinical latency, and (3) AIDS (acquired immunodeficiency syndrome). During the acute period of infection, large amounts of virus are being produced in your body. The virus uses CD4 count to replicate and destroys them in the process which can fall CD4 cells rapidly. During this infection the immune response will begin to bring the level of virus in human body back down to a level called a viral set point, which is a relatively stable level of virus in human body. After the acute stage of HIV infection, the disease moves into a stage called the clinical latency stage. During the clinical latency stage, the HIV virus continues to reproduce at very low levels, although it is still active. AID is the stage of HIV infection that occurs when your immune system is badly damaged and you become vulnerable to opportunistic infections.

People living with HIV may progress through these stages at different rates, depending on a variety of factors, including their genetic makeup, how healthy they were before they were infected, how soon after infection they are diagnosed and linked to care and treatment. Some mathematical models for controlling the infectious of HIV-1 recombinant virus can be found in [1,2,3]. A following differential equations is used as a classical model for the HIV-1

$$\begin{aligned} \dot{x}(t) &= \lambda - dx(t) - \beta x(t)v(t), \\ \dot{y}(t) &= \beta x(t)v(t) - ay(t), \\ \dot{v}(t) &= ky(t) - pv(t), \end{aligned} \tag{1}$$

where $x(t)$ represents the density of uninfected cells, $y(t)$ stands for infected cells density and $v(t)$ denoted the density of infected virus. λ is the rate of production uninfected cells and d is their death rate. β is the rate of contact of virus with the target cells. It is assumed in the above model that the infected cells, may die at a rate a or each cell creates the virus at a rate k. This model was modified by Revilla and Garcia-Ramos in [3] by adding

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recombinant virus to the model (1) is given by

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - \beta x(t)v(t),\\
\dot{y}(t) &= \beta x(t)v(t) - ay(t) - \alpha w(t)y(t),\\
\dot{z}(t) &= \alpha w(t)y(t) - bz(t),\\
\dot{v}(t) &= ky(t) - pv(t),\\
\dot{w}(t) &= cz(t) - qw(t),
\end{aligned} \tag{2}$$

with initial condition

$$x(0) \geq 0, y(0) \geq 0, z(0) \geq 0, v(0) \geq 0, w(0) \geq 0. \tag{3}$$

Here $w(t)$ represents the density of recombinant virus and $z(t)$ denotes the density of cells which are infected by both viruses. α is the rate of infection of infected cells by recombinant virus. q is the rate of removal of recombinant virus. b is death rate of infected cells z. These infected cells release recombinant at rate cz. Revilla and Garcia-Ramos [3] presented the structure of equilibrium solutions and their simulations of the model (2). Jiang et. al. [4] further modified the model (2) and presented a control strategy by incorporating the constant injection rate of the recombinant virus. It has been shown that increasing the injection rate of recombinant is fruitful for reducing the HIV virus [5,6,7].

We extend the model (2) by considering the Holling type-II functional response and two delays functions. The delay term τ_1 represents the latent period between the time of contact of virus particles with target cells and the time of entering into the cells and while the other delay τ_2 is used for the period of production of new virion that release from the infected cells. The Holling type-II functional response is represented by $\frac{1}{1+\sigma v(t)}$. By incorporating the above modification, our model becomes

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - \frac{\beta x(t)v(t)}{1+\sigma v(t)},\\
\dot{y}(t) &= \frac{\beta e^{-a_1\tau_1} x(t-\tau_1)v(t-\tau_1)}{1+\sigma v(t-\tau_1)} - ay(t) - \alpha w(t)y(t),\\
\dot{z}(t) &= \alpha w(t)y(t) - bz(t),\\
\dot{v}(t) &= ke^{-a_2\tau_2} y(t-\tau_2) - pv(t),\\
\dot{w}(t) &= cz(t) - qw(t).
\end{aligned} \tag{4}$$

First, the positivity and bounded of the proposed model will be presented. Then, the reproduction number R_0 will be investigated to prove the global behavior of the proposed model. We will study global stability of the equilibria at the disease free and endemic equilibria. The analytical and numerical results show that time delays have great effect on the global stability of equilibria because the basic reproduction number depends on both the delays.

In next the section, the positivity and well posdeness of the solutions is proved. In the same section the basic reproduction number R_0 is presented. The analysis of the disease free equilibrium E_0 and single-infection equilibrium E_1, under some conditions on the reproductive numbers, are discussed in Section 3. Numerical examples are presented in Section 4. In the last Section, conclusion and discussion are drawn.

2 Positivity and well-posdeness of the solution

The following theorem gives boundedness and positivity of the solution.

Theorem 2.1. The solutions of the model (4) are non-negative and bounded with the initial condition (3).

Proof. Let $X = C[(-\max(\tau_1,\tau_2),0); R^5]$ be the Banach space of continuous mapping from $[(-\max(\tau_1,\tau_2),0); R^5]$ to R^5 equipped with the sup-norm. We further suppose that $\mathbf{x}(t) = \big(x(t), y(t), z(t), v(t), w(t)\big)$ and $\mathbf{x}_t(\nu) = \mathbf{x}(t+\nu)$ for $\nu \in [(-\max(\tau_1,\tau_2),0]$. By using fundamental theory of FDEs [8], for any initial condition $\varphi \in X$ with $\varphi \geq 0$ we know that there exists a unique solution $x(t,\varphi)$ satisfying $x(\nu,\varphi) = \varphi(\upsilon)$.
Now the system (4) can be written as $\dot{\mathbf{x}}(t) = f(x_t)$, where

$$f(x_t) = \begin{pmatrix}
\lambda - dx(0) - \frac{\beta x(0)v(0)}{1+\sigma v(0)}\\
\frac{\beta e^{-a_1\tau_1} x(-\tau_1)v(-\tau_1)}{1+\sigma v(-\tau_1)} - ay(0) - \alpha w(0)y(0)\\
\alpha w(0)y(0) - bz(0)\\
ky(0) - pv(0)\\
cz(0) - qw(0)
\end{pmatrix}.$$

It can be shown that if any $\varphi \in X$ satisfies $\varphi \geq 0$, $\varphi_i(0) = 0$ for some i, then $f(\varphi_i) \geq 0$. Therefore, by using Theorem 2.1 on page (81) in [9], we know that $\mathbf{x}(t,\varphi) \geq 0$ for all $t \geq 0$ in its maximal interval of existence if $\varphi \geq 0$.

Next we show the boundedness of the solution. To do this let us consider

$$\begin{aligned}
G(t) = {} & cke^{-a_1\tau_1} x(t-\tau_1) + \frac{ac}{2} e^{a_2\tau_2} v(t+\tau_2) + \frac{bk}{2} w(t)\\
& + cky(t) + ckz(t).
\end{aligned}$$

Calculating the derivative, and using the system (4), we have

$$\begin{aligned}
\frac{dG(t)}{dt} = {} & cke^{-a_1\tau_1}\Big(\lambda - dx(t-\tau_1) - \beta x(t-\tau_1)v(t-\tau_1)\Big)\\
& + ck\Big(\beta e^{-a_1\tau_1} x(t-\tau_1)v(t-\tau_1) - (a+\alpha w(t))y(t)\Big)\\
& + ck\Big(\alpha w(t)y(t) - bz(t)\Big) + \frac{ac}{2} e^{a_2\tau_2}\Big(ke^{-a_2\tau_2} y(t)\\
& - pv(t+\tau_2)\Big) + \frac{bk}{2}\Big(cz(t) - qw(t)\Big).
\end{aligned}$$

After some rearrangement, we get

$$\begin{aligned}\frac{dG(t)}{dt} &= ck\lambda e^{-a_1\tau_1} - \Big(cdke^{-a\tau_1}x(t-\tau_1) + \frac{1}{2}acky(t) \\ &\quad + \frac{1}{2}bckz(t) + \frac{bkq}{2}w(t) + \frac{ac}{2}pe^{a_2\tau_2}v(t+\tau_2)\Big) \\ &\leq ck\lambda e^{-a_1\tau_1} - \rho G(t),\end{aligned}$$

where $\rho = \min\{d, \frac{a}{2}, \frac{b}{2}, q, p\}$. Which shows that $G(t)$ is bounded. □

3 Analysis of single and double infections

The system (4) has three equilibria, virus-free equilibrium E_0, recombinant absent equilibrium E_1 and recombinant present equilibrium E_2 as follows:

$$\begin{aligned}E_0 &= (\tfrac{\lambda}{d}, 0, 0, 0, 0), \\ E_1 &= \Big(\tfrac{ape^{a_1\tau_1+a_2\tau_2}+\sigma\lambda k}{k(\sigma d+\beta)}, \tfrac{pe^{-a_1\tau_1}}{ak}(\tfrac{\lambda\beta k - apde^{a_1\tau_1+a_2\tau_2}}{\sigma d+\beta}), 0, \\ &\quad \tfrac{\lambda\beta k - apde^{a_1\tau_1+a_2\tau_2}}{ape^{a_1\tau_1+a_2\tau_2}(\sigma d+\beta)}0\Big), \\ E_2 &= \Big(\tfrac{A}{B}, \tfrac{qb}{\alpha c}, \tfrac{1}{B\alpha c}(\tfrac{\alpha c\beta ke^{-(a_1\tau_1+a_2\tau_2)}A - a(\alpha cp+kqbc\sigma e^{-a_2\tau_2}))B}{(\alpha cp+kqbc\sigma e^{-a_2\tau_2})}), \\ &\quad \tfrac{kqbe^{-a_2\tau_2}}{\alpha cp}, \tfrac{1}{B\alpha}(\tfrac{\alpha c\beta ke^{-(a_1\tau_1+a_2\tau_2)}A - a(\alpha cp+kqbc\sigma e^{-a_2\tau_2})B}{(\alpha cp+kqbc\sigma e^{-a_2\tau_2})})\Big),\end{aligned}$$

where, $A = \alpha cp\lambda + \sigma kqbde^{-a_2\tau_2}\lambda$ and $B = \alpha cpd + \sigma kqbde^{-a_2\tau_2} + \beta kqbe^{-a_2\tau_2}$.

In epidemiological models the threshold quantity R_0 is called the basic reproduction number of the disease which is a key concept [10]. It represents the expected average number of new infections produced directly and indirectly by a single infective, when introduced into a completely susceptible population. The basic reproductive number for our proposed model is

$$R_0 = \frac{\lambda\beta k}{apd}e^{-(a_1\tau_1+a_2\tau_2)}.$$

For the third equilibrium to exist, the density of the recombinant virus must be exist and should be greater than zero, which determine the other reproductive number

$$R_2 = \frac{\alpha cdp}{\beta bkqe^{-a_2\tau_2}}(R_0 - 1).$$

Hence, $R_2 > 1$ if and only if $R_0 > R_1$, where $R_1 = 1 + \frac{\beta bkqe^{-a_2\tau_2}}{\alpha cdp}$.

Theorem 3.1. If $R_0 < 1$, then E_0 is globally asymptotically stable.

Proof. Let us consider

$$\begin{aligned}V_0(t) &= \frac{e^{-a_1\tau_1}}{2}(x(t) - \frac{\lambda}{d})^2 + \frac{\lambda}{d}(y(t)+z(t)) + e^{a_2\tau_2}\frac{a\lambda}{kd}v(t) \\ &\quad + \frac{b\lambda}{cd}w(t) + \frac{\beta\lambda}{d}e^{-a_1\tau_1}\int_{t-\tau 1}^{t}\frac{x(\phi)v(\phi)}{1+\sigma v(\phi)}d(\phi) \\ &\quad + \frac{a\lambda}{d}\int_{t-\tau_2}^{t}y(\phi)d\phi.\end{aligned}$$

By taking derivative, we have

$$\begin{aligned}\frac{d}{dt}(V_0(t)) &= -e^{-a_1\tau_1}(x(t) - \frac{\lambda}{d})\dot{x} + \frac{\lambda}{d}\dot{y} + \frac{\lambda}{d}\dot{z} + e^{a_2\tau_2}\frac{a\lambda}{kd}\dot{v} \\ &\quad + \frac{\beta\lambda}{d}e^{-a_1\tau_1}\Big(\Psi(t-\tau_1) - \frac{x(t)v(t)}{1+\sigma v(t)}\Big) \\ &\quad + \frac{b\lambda}{cd}\dot{w} + \frac{a\lambda}{d}\Big(y(t-\tau_2) - y(t)\Big),\end{aligned}$$

where $\Psi(t-\tau_1) = \frac{x(t-\tau_1)v(t-\tau_1)}{1+\sigma v(t-\tau_1)}$. By using the system (4) and after some rearrangement, we have

$$\begin{aligned}\frac{d}{dt}(V_0(t)) &= -e^{-a_1\tau_1}(x(t) - \frac{\lambda}{d})\Big(\lambda - dx(t) - \frac{\beta x(t)v(t)}{1+\sigma v(t)}\Big) \\ &\quad + \frac{\lambda}{d}\Big(\beta e^{-a_1\tau_1}\Psi(t-\tau_1) - (a+\alpha w(t))y(t)\Big) \\ &\quad + \frac{\lambda}{d}\Big(\alpha w(t)y(t) - bz(t)\Big) + e^{a_2\tau_2}\frac{a\lambda}{kd}\Big(ky(t) - pv(t)\Big) \\ &\quad + \frac{\beta\lambda}{d}e^{-a_1\tau_1}\Big(\Psi(t-\tau_1) - \frac{x(t)v(t)}{1+\sigma v(t)}\Big) \\ &\quad + \frac{b\lambda}{cd}\Big(cz(t) - qw(t)\Big) + \frac{a\lambda}{d}\Big(y(t-\tau_2) - y(t)\Big).\end{aligned}$$

Now using the infection free equilibrium point and some simplification, we get

$$\begin{aligned}\frac{d}{dt}(V_0(t)) &= -e^{-a_1\tau_1}(x(t) - \frac{\lambda}{d})^2 - \frac{ape^{a_2\tau_2}\lambda}{dk}(1-R_0)v(t) \\ &\quad - \frac{qb\lambda}{cd}w(t).\end{aligned}$$

Noting that when $R_0 \leq 1$, we have $\frac{d}{dt}(V_0(t)) \leq 0$. But the equality holds only if $x_0 = \frac{\lambda}{d}$, $y(t) = 0$, $z(t) = 0$, $v(t) = 0$, $w(t) = 0$. Then by LaSalle's invariance principle (see [11, 12]), we conclude that E_0 is globally asymptotically stable when $R_0 < 1$. □

Theorem 3.2. When $1 < R_0 < R_1$, then E_1 is globally asymptotically stable.

Proof. Let us construct the following Lyapunov functional

$$V_1(t) = V_{11}(t) + \beta x_1 v_1 e^{-a_1\tau_1}V_{12}(t) + aV_{13}(t), \quad (5)$$

where

$$\begin{aligned}V_{11}(t) &= e^{-a_1\tau_1}(x(t) - x_1\ln x(t)) + (y(t) - y_1\ln y(t)) + z(t) \\ &\quad + \frac{ae^{a_2\tau_2}}{k}(v(t) - v_1\ln v(t)) + \frac{b}{c}w(t), \\ V_{12}(t) &= \int_{t-\tau_1}^{t}\Big(\frac{x(\xi)v(\xi)}{x_1v_1(1+\sigma v(t))} \\ &\quad - \frac{1}{(1+\sigma v_1)}\ln(\frac{x(\xi)v(\xi)}{x_1v_1(1+\sigma v(t))})\Big)d\xi, \\ V_{13}(t) &= \int_{t-\tau 2}^{t}y(\xi)d\xi.\end{aligned}$$

Now by taking derivative of (5), we have

$$\frac{d}{dt}V_1(t) = e^{-a_1\tau_1}(1-\frac{x_1}{x(t)})x'(t)+(1-\frac{y_1}{y(t)})y'(t)+\frac{b}{c}w'(t)$$
$$+z'(t)+\frac{ae^{a_2\tau_2}}{k}(1-\frac{v_1}{v})v'(t)+\beta x_1v_1e^{-a_1\tau_1}\Big(\frac{\Psi(t)}{x_1v_1}$$
$$-\frac{1}{1+\sigma v_1}\ln\big(\frac{x(t)v(t)}{x_1v_1(1+\sigma v(t))}\big)-\frac{x(t-\tau_1)v(t-\tau_1)}{x_1v_1(1+\sigma v(t-\tau_1))}$$
$$+\frac{1}{1+\sigma v_1}\ln(\frac{x(t-\tau_1)v(t-\tau_1)(1+\sigma v_1)}{x_1v_1(1+\sigma v(t-\tau_1))}\Big)$$
$$+a\big(y(t)-y(t-\tau_2)\big). \tag{6}$$

By using the recombinant absent equilibrium E_1 and the model (4), we get the following identities

$$\lambda = dx_1 - e^{-a_1\tau_1}\frac{\beta x_1v_1}{1+\sigma v_1},$$
$$\frac{\beta e^{-a_1\tau_1}x_1v_1}{1+\sigma v_1} = ay_1,$$
$$e^{-a_2\tau_2}ky_1 = pv_1.$$

Using the above identities in equation (6) and the system (4), we obtain

$$\frac{d}{dt}V_1(t) = e^{-a_1\tau_1}(2-\frac{x_1}{x}-\frac{x}{x_1})+\frac{\beta x_1v_1e^{-a\tau_1}}{1+\sigma v_1}$$
$$\Big(3-\frac{x_1}{x}-\frac{v_1y(t-\tau_2)}{vy_1}-\frac{(1+\sigma v(t))y_1x(t-\tau_1)v(t-\tau_1)}{(1+\sigma v(t-\tau_1))x_1v_1y}$$
$$+\ln(\frac{x(t-\tau_1)v(t-\tau_1)(1+\sigma v(t))}{x(t)v(t)(1+\sigma v(t-\tau_1))})\Big)$$
$$+\frac{\alpha dp}{a\beta ke^{-a_2\tau_2}}(R_0-R_1)w(t). \tag{7}$$

By using the results in [13], the following inequities hold,

$$e^{-a_1\tau_1}(2-\frac{x_1}{x}-\frac{x}{x_1})\le 0,$$

$$\Big(3-\frac{x_1}{x}-\frac{v_1y(t-\tau_2)}{vy_1}-\frac{(1+\sigma v(t))y_1x(t-\tau_1)v(t-\tau_1)}{(1+\sigma v(t-\tau_1))x_1v_1y}$$
$$+\ln\big(\frac{x(t-\tau_1)v(t-\tau_1)(1+\sigma v(t))}{x(t)v(t)(1+\sigma v(t-\tau_1))}\big)-\frac{v_1y(t-\tau_2)}{vy_1}\Big)\le 0.$$

Therefore, from equation (7), we have $\frac{dV_1}{dt}\le 0$, when $R_0\le R_1$ but the equality holds, when $x=x_1$ and $y=y_1$ $v=v_1$ and $w=0$. We conclude that E_1 is globally asymptotically stable (see [11]). □

4 Numerical simulation

In this section, we give some numerical examples to illustrate the above theoretical results. For numerical simulation, we choose the parameters values which are biological feasible from [14,15] with the initial conditions $x(0)=5.0, y(0)=1.0, z(0)=2.0, v(0)=0.5, w(0)=4.0$.

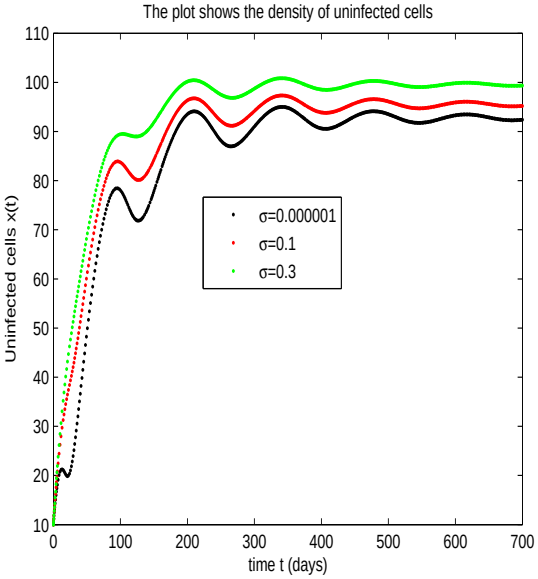

Fig. 1: The plot shows the density of uninfected cells.

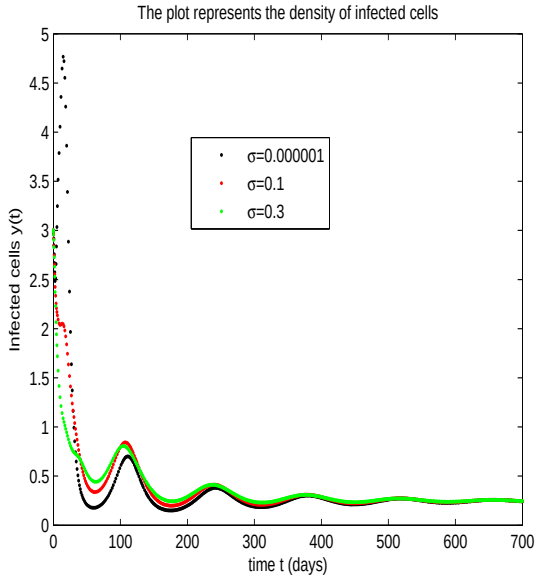

Fig. 2: The plot represents the density of infected cells.

Example 1. In the system (4) we choose the parameters values as $\lambda=4, d=0.21, a=0.33, c=40, b=5.6, p=q=5.6, \tau_1=10, \tau_2=10, k=50, \alpha=\beta=0.004, \sigma=0.000001, a_1=a_2=0.1$. The results of numerical simulation are represented in Figure 1 - 5. It gives that $R_0=0.0272889842985<1$ and the system (4) has disease free equilibrium $E_0(19,0,0,0,0)$. By the

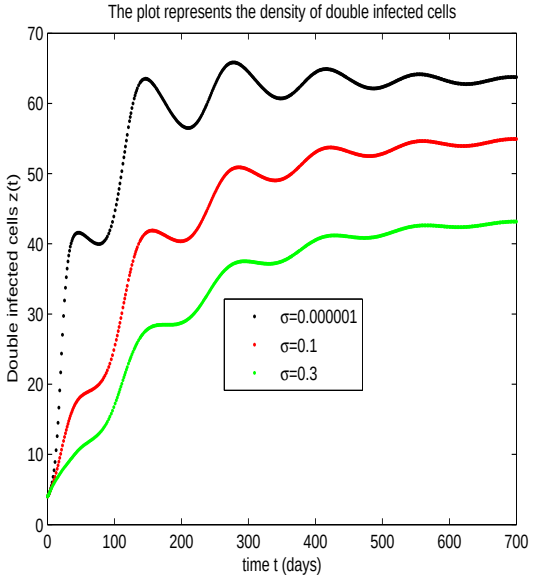

Fig. 3: The plot represents the density of double infected cells.

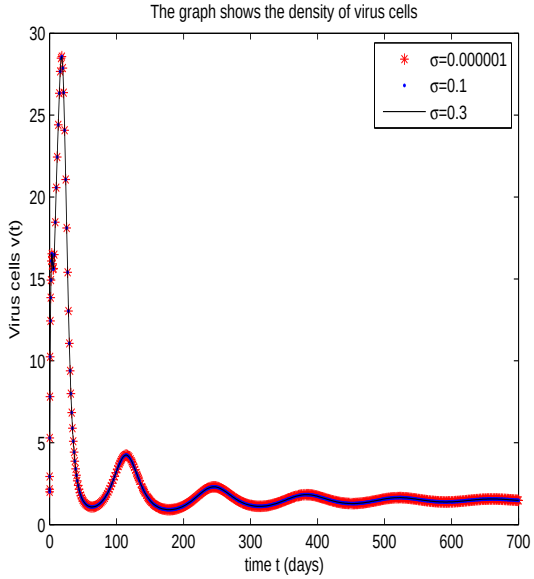

Fig. 4: The graph shows the density of virus cells.

theorem(2.1), we obtain infection-free equilibrium E_0 of the system (4) is globally asymptotically stable. In figure 1 the uninfected cells increasing sharply for all given values of σ at the first few days and then gradually goes to stable state. In figures 2 and 3 sharply decreases and the density of double infected and infected cells are almost similar for all given values of σ. In figures 4 and 5 sharply increases and the density of virus and recombinant cells are different for all given values of σ.

Example 2. In the system (5), we set $\lambda = 2, d = 0.10, a = 0.5, c = 40, b = p = q = 5.6, \sigma = 0.0005, \alpha = \beta = 0.002, a_1 = a_2 = 0.2, \tau_1 = \tau_2 = 5$ with the above initial conditions. It shows that $1 < R_0 = 1.34 < R_1 = 13.84$ and the system (5) has single infection equilibrium $E_0(2.94, 140, 3.696, 170, 0, 0)$. Thus by theorem (2.1) we prove that the system 4) is globally asymptotically stable.

Example 3. In the system (5, we take $\lambda = 2, \alpha = \beta = 0.002, d = 0.10, a = 0.5, c = 40, b = 2, p = q = 5.6, k = 70, a_1 = a_2 = 0.2, \tau_1 = \tau_2 = 5, \sigma = 0.0009$ with the above initial conditions. It shows that $R_1 = 1.34 > 1$ and thus the system (4), is globally asymptotically stable.

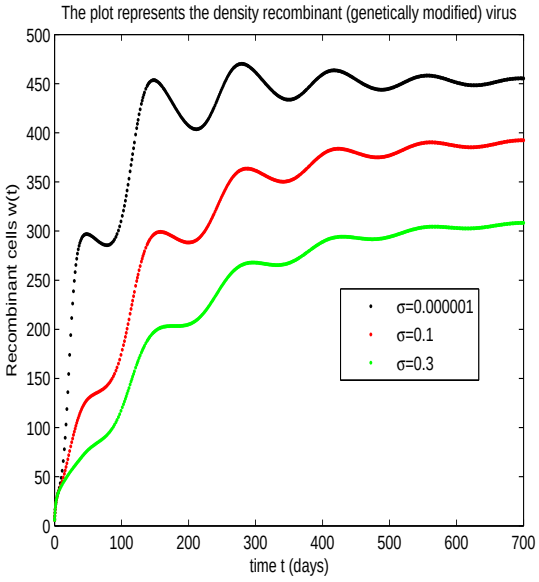

Fig. 5: The plot represents the density recombinant (genetically modified) virus.

5 Conclusion and discussion

We developed HIV-1 therapy delay differential model with saturation rate by including two delays. One delay represented in the latent period for cell infection while the second delay the other delay is used for the period of production of new virion that release from the infected cells. The basic reproduction number R_0 is obtained and two others reproduction numbers R_1 and R_2 are also investigated which are different from the basic reproduction number R_0. We proved that the infection-free equilibrium is globally asymptotically stable if $R_0 < 1$. While if $R_0 > 1$, then the infection-free equilibrium becomes unstable and there occurs a single-infection equilibrium which is globally asymptotically stable if $R_0 < R_1$. Furthermore, if $R_1 < R_2$, then E_1 is unstable and there exists E_2. Our Numerical

results shown that delay can control the viral load to minimum value due to which the rate of infection is reduced and the number of infected cells becomes minimum.

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