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Global dynamics, numerical simulation and drug therapy control of an HIV dynamical model with logistic growth rate and Crowley-Martin incidence rate

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Abstract. Biomathematics is one of the most important interdisciplinary research area which has recently attracted the attention of many researchers and scientists. In this area, population dynamics, biochemical reactions and infectious diseases are modeled with mathematical tools such as differential equations. After modeling, applying nonlinear analysis methods, the dynamical behavior of the model is checked. In this paper, by the theory of dynamical systems, the local and global stability of an HIV viral infection model will be studied. These results will be given using Lyapunov's second method and LaSalle's invariance principle. We will find the equilibrium points of the system and prove the local and global stability of these points based on the values of the basic reproduction number ($\mathbf{R_0}$). It will be proven that if $\mathbf{R_0} \leq 1$, then the virus-free equilibrium $\mathbf{E_0}$ is globally stable and the viruses are cleared. If $\mathbf{R_0} > 1$, then there exists a chronic equilibrium $\mathbf{E_*}$ which is globally stable and the infection becomes chronic. Some numerical examples will be presented to review the theoretical results. Finally, by including the effects of drug therapy on the model, we will introduce a new threshold parameter.

1. Introduction

To understand viral infection dynamics in biology, mathematical modeling has a great important role. These models play a significant role in developing a better understanding of the disease and the various drug therapy strategies. Nowak et al. [11], Nowak and May [12], Perelson and Nelson [13], and Perelson et al. [14] proposed and studied basic models of viral infection. Recently, the authors in [5] have presented the global stability analysis of the viral infection model with logistic growth rate, general incidence function and cellular immunity. They also investigated the stability, Hopf bifurcation and drug therapy control of an HIV viral infection model with a logistic growth rate and two modes of transmission [15] (To see some other works in this area refer to [8], [16] and [17]). In [13], the viral infection model has the form:

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$$\begin{cases} \dfrac{dT}{dt} = s - dT - \beta TV, \\ \dfrac{dI}{dt} = \beta TV - \delta I, \\ \dfrac{dV}{dt} = pI - cV, \end{cases} \tag{1}$$

with the initial conditions $T(0) = T_0$, $I(0) = I_0$ and $V(0) = V_0$.

Here, $T(t)$, $I(t)$ and $V(t)$ denote the number of target cells or uninfected target cells, infected cells that produce virus and HIV particles at time t. This model has been widely used for studying the mathematical analysis of viral infections such as hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In system (1), target cells (T) or CD4$^+$ T helper cells produced at rate s, die at rate dT and are infected by the virus at a rate βTV. Infected cells (I) are generated by a rate βTV and die at rate δI. Free virus (V) is produced by infected cells at a rate pI and die at a rate cV. In system (1), the incidence rate of infection βTV is bilinear. However, the actual incidence rate is probably not linear over the entire range of T. Thus, it is reasonable to assume that the incidence rate is given by some nonlinear functional response.

In this paper, it is assumed that the incidence rate of HIV is given by Crowley-Martin functional response, $\dfrac{\beta TV}{1 + aT + bV + abTV}$, where $a, b > 0$, which was introduced by Crowley and Martin ([1]). If $a > 0$ and $b = 0$, then the Crowley-Martin functional response is reduced to Holling type II functional response ([9]). On the other hand, when $a = 0$, $b > 0$, we have the functional response in Song and Neumann ([18]). The Crowley-Martin functional response is reduced to Holing type I if $a = 0$ and $b = 0$. Also, we assume that the population dynamics of CD4$^+$ cells is as follows:

$$\frac{dT}{dt} = s + rT(1 - \frac{T}{T_{\max}}) - dT - \frac{\beta TV}{1 + aT + bV + abTV},$$

where r is the maximum proliferation rate and $T_{\max}$ is the T cell population density at which proliferation shuts off or is the maximum level of CD4$^+$ cells in the human body.

In this paper the system

$$\begin{cases} \dfrac{dT}{dt} = s + rT(1 - \dfrac{T}{T_{\max}}) - dT - \dfrac{\beta TV}{1 + aT + bV + abTV}, \\ \dfrac{dI}{dt} = \dfrac{\beta TV}{1 + aT + bV + abTV} - \delta I, \\ \dfrac{dV}{dt} = pI - cV, \end{cases} \tag{2}$$

will be studied and some sufficient conditions will be stated about the local and global stability of the rest points. All constants in the system are assumed to be non-negative.

The authors in [21] gave the following theorem for the global stability of positive equilibrium of system (2) with $r = 0$.

Theorem 1.1. *([21]) Suppose that*

$$(i)\ \ \mathbf{R_0} > 1,$$

$$(ii)\ \ c\delta\Big(\frac{\beta V_* + b\beta V_*^2}{(1+aT_*+bV_*+abT_*V_*)^2} + d\Big) > \frac{dp(\beta T_* + b\beta T_*^2)}{(1+aT_*+bV_*+abT_*V_*)^2},$$

$$(iii)\ \ \Big(c+d+\delta+\frac{\beta V_* + b\beta V_*^2}{(1+aT_*+bV_*+abT_*V_*)^2}\Big) \times\Big[cd+d\delta+(c+\delta)\frac{\beta V_* + b\beta V_*^2}{(1+aT_*+bV_*+abT_*V_*)^2}\Big] + (c+\delta)c\delta > p\Big(c+\delta+2dp+\frac{\beta V_* + b\beta V_*^2}{(1+aT_*+bV_*+abT_*V_*)^2}\Big)\times\frac{\beta T_* + b\beta T_*^2}{(1+aT_*+bV_*+abT_*V_*)^2},$$

$$(iv)\ \ d > \frac{ac\delta}{b}.$$

Then, the positive equilibrium (T_*, I_*, V_*) *of* (2) *with* $r = 0$ *is globally asymptotically stable.*

In this paper, without any extra condition, we will prove that if the basic reproduction number is greater than one, then positive equilibrium is always globally asymptotically stable (refer to Theorem 3.2). The organization of this article is as follows. In the next section, we will give some basic properties of the solutions, find the equilibria of (2) and study the local stability of these points. In Section 3, using Lyapunov's second method and LaSalle's invariance principle, some sufficient conditions will be given about the global stability of the equilibria. Numerical analysis will be presented in Section 4 to illustrate our analytical findings. Drug efficacy will be discussed in Section 5. The paper ends with a discussion of the obtained results in the previous sections.

2. Local stability of the model

In this section, the local behavior of system (2) will be studied. Model (2) represents the evolution of a cell population. Hence, the population should remain non-negative and bounded. Therefore, the positivity and boundedness of solutions of (2) will be first established. Next, we will find the equilibria of (2) and finally, the local stability of the rest points of (2) will be proven.

Theorem 2.1. *All solutions of* (2) *starting from non-negative initial points exist for all* $t > 0$ *and remain bounded and non-negative.*

Proof. By Picard-Lindelöf theorem, the existence and uniqueness of solutions of (2) can be given. First, the positivity of solutions will be proven. Define

$$\mathbb{R}^3_+ = \{(T, I, V) \in \mathbb{R}^3 :\ \ T \geq 0, I \geq 0, V \geq 0\}.$$

For any solution $(T(t), I(t), V(t)) \in \mathbb{R}^3_+$, we have

$$\dot{T}\,|_{T=0} = s \geq 0,\ \ \dot{I}\,|_{I=0} = \frac{\beta TV}{1+aT+bV+abTV} \geq 0,\ \ \dot{V}\,|_{V=0} = pI \geq 0.$$

Hence, the positivity of all solutions initiated in $\mathbb{R}^3_+$ is guaranteed due to the well-known theorem given by Nagumo in [10].

Now let $L(t) = T(t) + I(t)$. By computing the derivative of L along the solutions of (2),

$$\dot{L} = s + rT(1-\frac{T}{T_{\max}}) - dT - \delta I = -dT - \delta I + rT - \frac{rT^2}{T_{\max}} + s \leq -hL + M_0,$$

where $M_0 = \dfrac{T_{\max} r^2 + 4rs}{4r}$ and $h = \min\{d, \delta\}$. Thus, there exists $t_1 > 0$ and $M_1 > 0$, depending only on the parameters of (2), such that $L \leq M_1$ for $t > t_1$. Hence, $T(t)$ and $I(t)$ have an ultimately above bound M_1. It follows from the third equation of (2) that $V(t)$ has an ultimately above bound M_2. Let $\hat{M} = \max\{M_1, M_2\}$. Obviously, $T(t) \leq \hat{M}$, $I(t) \leq \hat{M}$ and $V(t) \leq \hat{M}$ for all large t. Therefore, the solutions are bounded and the proof is complete. □

To state our main results, the following definition will be needed.

Definition 2.2. *The basic reproduction number* $\mathbf{R_0}$ *is defined the expected number of secondary infections produced by an index case in a completely susceptible population.*

This number measures the potential for disease spread within a body. If $\mathbf{R_0} < 1$, then a few infected cells introduced into completely susceptible cells will, on average, fail to replace themselves and the disease will not spread. If, on the other hand, $\mathbf{R_0} > 1$, then the number of infected cells will increase with each generation and the disease will spread. For system (2), according to the concept of the next-generation matrix in Diekmann et al. ([2]) and the reproduction number presented in van den Driessche and Watmough ([3]), we can compute the basic reproduction number as

$$\mathbf{R_0} = \frac{p\beta T_0}{c\delta(1 + aT_0)},$$

where $T_0 = \Big(\dfrac{r - d + \sqrt{\Delta}}{2r}\Big) T_{\max}$ and $\Delta = (r - d)^2 + \dfrac{4rs}{T_{\max}}$.

By the values of $\mathbf{R_0}$, the local and global stability of equilibrium points of (2) will be studied. In the following, a theorem about the existence of equilibria of (2) will be presented.

Theorem 2.3. *System* (2) *has a unique virus-free equilibrium of the form* $\mathbf{E_0} = (T_0, 0, 0)$ *if* $\mathbf{R_0} \leq 1$. *Moreover, except* $\mathbf{E_0}$, *it has a unique chronic equilibrium* $\mathbf{E}_* = (T_*, I_*, V_*)$ *for* $T_* \in (0, T_0)$ *if* $d \geq r$ *and* $\mathbf{R_0} > 1$.

Proof. For any equilibrium, the following equations hold.

$$\begin{cases} s + rT(1 - \dfrac{T}{T_{\max}}) - dT - \dfrac{\beta TV}{1 + aT + bV + abTV} = 0, \\ \dfrac{\beta TV}{1 + aT + bV + abTV} - \delta I = 0, \\ pI - cV = 0. \end{cases} \tag{3}$$

Let $f(T, V) = \dfrac{\beta T}{1 + aT + bV + abTV}$. By (3), it can be obtained that:

$$f\Big(T, \frac{p}{c\delta}(s + rT(1 - \frac{T}{T_{\max}}) - dT)\Big) = \frac{\delta c}{p}. \tag{4}$$

Since $V \geq 0$, it can be concluded that $s + rT(1 - \dfrac{T}{T_{\max}}) - dT \geq 0$ which implies $T \leq T_0$. Hence, if $T > T_0$, then there is no equilibrium point. To find the equilibrium points of (2), we have the following steps:
1) If $V = 0$, then by (3), it can be concluded that $I = 0$. In this situation, there always exist virus-free equilibrium $\mathbf{E_0} = (T_0, 0, 0)$ with

$$T_0 = \frac{T_{\max}}{2r}\Big[r - d + \sqrt{(r - d)^2 + \frac{4rs}{T_{\max}}}\Big].$$

The rest point $\mathbf{E_0}$, shows the state that viruses are absent.
2) Suppose that $V \neq 0$. Consider the following function defined on $[0, T_0]$.

$$g(T) = f\Big(T, \frac{p}{c\delta}\Big[s + rT\Big(1 - \frac{T}{T_{\max}}\Big) - dT\Big]\Big) - \frac{\delta c}{p}.$$

We have $g(0) = -\dfrac{\delta c}{p} < 0$ and $g(T_0) = f(T_0, 0) - \dfrac{\delta c}{p} = \dfrac{\delta c}{p}(\mathbf{R_0} - 1) > 0$ and

$$g'(T) = \frac{\partial f}{\partial T} + \frac{p}{c\delta}(r - d)\frac{\partial f}{\partial V} - \frac{p}{c\delta}\Big(\frac{2rT}{T_{\max}}\Big)\frac{\partial f}{\partial V}.$$

Since $\dfrac{\partial f}{\partial T} > 0$ and $\dfrac{\partial f}{\partial V} < 0$, if $r - d \leq 0$, then $g'(T) > 0$. Hence, there exists a unique positive or chronic equilibrium point $\mathbf{E}_* = (T_*, I_*, V_*)$ with $T_* \in (0, T_0)$, $I_* = \dfrac{1}{\delta}\Big[s + rT_*\Big(1 - \dfrac{T_*}{T_M}\Big) - dT_*\Big]$ and $V_* = \dfrac{p}{c}I_*$. □

Remark 2.4. *By attention to the proof of Theorem 2.3, it can be concluded that if* $\mathbf{R_0} < 1$, *then* $g(T_0) < 0$. *Hence, there is no positive equilibrium with* $0 < T < T_0$. *If* $\mathbf{R_0} = 1$, *then* $g(T_0) = 0$ *and* $\mathbf{E}_* = \mathbf{E_0}$

In the following, the local asymptotic stability of these two equilibria will be given.

Theorem 2.5. *If* $\mathbf{R_0} < 1$, *then the disease-free equilibrium* $\mathbf{E_0}$ *is locally asymptotically stable and it is unstable if* $\mathbf{R_0} > 1$.

Proof. The Jacobian matrix of (2) for any rest point $\hat{\mathbf{E}} = (\hat{T}, \hat{I}, \hat{V})$ has the form:

$$J(\hat{\mathbf{E}}) = \begin{bmatrix} r - d - \dfrac{2r\hat{T}}{T_{\max}} - \dfrac{\beta\hat{V} + b\beta\hat{V}^2}{(1 + a\hat{T} + b\hat{V} + ab\hat{T}\hat{V})^2} & 0 & -\dfrac{\beta\hat{T} + a\beta\hat{T}^2}{(1 + a\hat{T} + b\hat{V} + ab\hat{T}\hat{V})^2} \\ \dfrac{\beta\hat{V} + b\beta\hat{V}^2}{(1 + a\hat{T} + b\hat{V} + ab\hat{T}\hat{V})^2} & -\delta & \dfrac{\beta\hat{T} + a\beta\hat{T}^2}{(1 + a\hat{T} + b\hat{V} + ab\hat{T}\hat{V})^2} \\ 0 & p & -c \end{bmatrix}. \tag{5}$$

For $\mathbf{E_0}$ matrix (5) reduces to

$$J(\mathbf{E_0}) = \begin{bmatrix} r - d - \dfrac{2rT_0}{T_{\max}} & 0 & -\dfrac{\beta T_0}{1 + aT_0} \\ 0 & -\delta & \dfrac{\beta T_0}{1 + aT_0} \\ 0 & p & -c \end{bmatrix}. \tag{6}$$

The characteristic polynomial of (6) is

$$\Big(\lambda + d - r + \frac{2rT_0}{T_{\max}}\Big)\Big[\lambda^2 + (c + \delta)\lambda + c\delta - \frac{p\beta T_0}{1 + aT_0}\Big] = 0. \tag{7}$$

The roots of (7) are:

$$\lambda_1 = r - d - \frac{2rT_0}{T_{\max}},$$
$$\lambda_2 = \frac{-(c + \delta) - \sqrt{(c + \delta)^2 - 4c\delta(1 - \mathbf{R_0})}}{2},$$
$$\lambda_3 = \frac{-(c + \delta) + \sqrt{(c + \delta)^2 - 4c\delta(1 - \mathbf{R_0})}}{2}.$$

Hence, $\mathbf{E_0}$ is locally asymptotically stable for $\mathbf{R_0} < 1$ and unstable for $\mathbf{R_0} > 1$. If $\mathbf{R_0} > 1$, then $\mathbf{E_0}$ is saddle with $\dim W^s(\mathbf{E_0}) = 2$ and $\dim W^u(\mathbf{E_0}) = 1$ where $W^s(\mathbf{E_0})$ and $W^u(\mathbf{E_0})$ represent the stable and unstable subspaces of $\mathbf{E_0}$, respectively. □

In the following, we state a theorem about the local stability of the chronic equilibrium of (2), which extends and improves Theorem 1.1 (Theorem 5.1 in [21]) and it is proven with fewer assumptions.

Theorem 2.6. *If $\mathbf{R_0} > 1$ and $d \geq r$, then the chronic equilibrium $\mathbf{E}_*$ is locally asymptotically stable.*

Proof. For equilibrium $\mathbf{E}_* = (T_*, I_*, V_*)$, the characteristic polynomial has the following form:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{8}$$

where

$$\begin{aligned}
a_1 &= c + \delta + d - r + \frac{2rT_*}{T_{\max}} + \frac{1}{1 + aT_*}\Big(\frac{s}{T_*} + \frac{rT_*}{T_{max}} + r - d - \frac{2rT_*}{T_{\max}}\Big) > 0,\\
a_2 &= \frac{bc\delta V_*}{1 + bV_*} + (c + \delta)\Big(d - r + \frac{2rT_*}{T_{max}}\Big) + \frac{c + \delta}{1 + aT_*}\Big(\frac{s}{T_*} + \frac{rT_*}{T_{max}} + r - d - \frac{2rT_*}{T_{\max}}\Big) > 0,\\
a_3 &= \frac{bc\delta V_*}{1 + bV_*}\Big(d - r + \frac{2rT_*}{T_{max}}\Big) + \frac{c\delta}{1 + aT_*}\Big(\frac{s}{T_*} + \frac{rT_*}{T_{max}} + r - d - \frac{2rT_*}{T_{\max}}\Big) > 0.
\end{aligned}$$

These coefficients are all positive since $d \geq r$. According to the equilibrium point conditions, it can be obtained that

$$\frac{\beta T_* V_*}{1 + aT_* + bV_* + abT_*V_*} = s + rT_*(1 - \frac{T_*}{T_{max}}) - dT_*,$$

or

$$\frac{\beta V_*}{1 + aT_* + bV_* + abT_*V_*} = \frac{s}{T_*} + r - \frac{rT_*}{T_{max}} - d = \frac{s}{T_*} + \frac{rT_*}{T_{max}} + r - d - \frac{2rT_*}{T_{max}}.$$

It is easy to conclude that

$$\frac{s}{T_*} + \frac{rT_*}{T_{max}} + r - d - \frac{2rT_*}{T_{max}} > 0.$$

In addition,

$$\begin{aligned}
a_1a_2 - a_3 =& (c + \delta)\frac{bc\delta V_*}{1 + bV_*} + (c + \delta)^2\Big(d - r + \frac{2rT_*}{T_{max}}\Big) + \frac{(c^2 + c\delta + \delta^2)}{1 + aT_*}\Big(\frac{s}{T_*} + \frac{rT_*}{T_{max}} + r - d - \frac{2rT_*}{T_{max}}\Big)\\
&+ (c + \delta)\Big(d - r + \frac{2rT_*}{T_{max}}\Big)^2 + \frac{c + \delta}{1 + aT_*}\Big(d - r + \frac{2rT_*}{T_{max}}\Big)\Big(\frac{s}{T_*} + \frac{rT_*}{T_{max}} + r - d - \frac{2rT_*}{T_{max}}\Big)\\
&+ \frac{bc\delta V_*}{(1 + aT_*)(1 + aV_*)}\Big(\frac{s}{T_*} + \frac{rT_*}{T_{max}} + r - d - \frac{2rT_*}{T_{max}}\Big)\\
&+ (c + \delta)\Big(d - r + \frac{2rT_*}{T_{max}}\Big)\frac{1}{1 + aT_*}\Big(\frac{s}{T_*} + \frac{rT_*}{T_{max}} + r - d - \frac{2rT_*}{T_{max}}\Big)\\
&+ \frac{c + \delta}{(1 + aT_*)^2}\Big(\frac{s}{T_*} + \frac{rT_*}{T_{max}} + r - d - \frac{2rT_*}{T_{max}}\Big)^2 > 0.
\end{aligned}$$

Hence, from Routh-Hurwitz Theorem ([6]), all roots of (8) have negative real parts. Therefore, $\mathbf{E}_*$ is locally asymptotically stable. □

3. Global stability of the model

In the previous section, the local stability of the rest points of (2) was obtained. Now, we study the global behavior of the solutions of (2). In the following, the global stability of $\mathbf{E_0}$ will be proven.

Theorem 3.1. *If $\mathbf{R_0} \leq 1$, then $\mathbf{E_0}$ is globally asymptotically stable.*

Proof. Define the Lyapunov function as

$$L_0(I, V) = I + \frac{\delta}{p}V.$$

Computing the derivative of L_0 along the solutions of (2), it can be obtained that

$$\frac{dL_0}{dt}\,|_{(1.2)} = \dot{I} + \frac{\delta}{p}\dot{V} = \frac{\beta TV}{1 + aT + bV + abTV} - \frac{\delta c}{p}V = \Big(\frac{\beta T}{1 + aT + bV + abTV} - \frac{\delta c}{p}\Big)V = \Big(f(T, V) - \frac{\delta c}{p}\Big)V.$$

Since $\frac{\partial f}{\partial T} > 0$ and $\frac{\partial f}{\partial V} < 0$, it can be concluded that

$$\frac{dL_0}{dt}\,|_{(1.2)} = \Big(f(T, V) - \frac{\delta c}{p}\Big)V \leq \Big(f(T_0, 0) - \frac{\delta c}{p}\Big)V = \Big(\frac{\beta T_0}{1 + aT_0} - \frac{\delta c}{p}\Big)V = \frac{\delta c}{p}(\mathbf{R_0} - 1)V.$$

Therefore, $\frac{dL_0}{dt} \leq 0$ for all $I, V > 0$ if $\mathbf{R_0} \leq 1$. On the other hand, $\frac{dL_0}{dt} = 0$ if and only if $V = 0$. Let Γ be the largest invariant set in

$$D = \{(T, I, V) \mid \dot{L_0}(T, I, V) = 0\} = \{\mathbf{E_0}\}.$$

We have that $\Gamma = \{\mathbf{E_0}\}$. The global stability of $\mathbf{E_0}$ follows from LaSalle's invariance principle ([7]). □

In the sequel, the global stability of chronic equilibrium will be presented. We will prove the following theorem with conditions of Theorem 2.6.

Theorem 3.2. *If $\mathbf{R_0} > 1$ and $d \geq r$, then the chronic equilibrium $\mathbf{E}_*$ is globally asymptotically stable.*

Proof. Define the Lyapunov function as

$$L_*(T, I, V) = T - T_* - \int_{T_*}^{T} \frac{\delta I_*}{\frac{\beta\eta V_*}{1+a\eta+bV_*+ab\eta V_*}} d\eta + I - I_* - I_* \ln \frac{I}{I_*} + \frac{\delta}{p}\Big(V - V_* - V_* \ln \frac{V}{V_*}\Big).$$

Function $L_*(T, I, V)$ is positive definite with respect to $(T - T_*, I - I_*, V - V_*)$. The time derivative of $L_*(T, I, V)$ along the positive solutions of (2) can be written as follows.

$$\begin{aligned}
\frac{dL_*}{dt}\,|_{(1.2)} &= \dot{T} - \delta I_* \frac{1 + aT + bV_* + abTV_*}{\beta TV_*}\dot{T} + \dot{I} - \frac{I_*}{I}\dot{I} + \frac{\delta}{p}\Big(\dot{V} - \frac{V_*}{V}\dot{V}\Big) \\
&= s + rT(1 - \frac{T}{T_{\max}}) - dT - \delta I_* \frac{1 + aT + bV_* + abTV_*}{\beta TV_*} \\
&\quad \times \Big(s + rT(1 - \frac{T}{T_{\max}}) - dT - \frac{\beta TV}{1 + aT + bV + abTV}\Big) \\
&\quad - \frac{I_*}{I}\Big(\frac{\beta TV}{1 + aT + bV + abTV} - \delta I\Big) - \frac{\delta cV}{p} - \frac{\delta V_*}{pV}(pI - cV).
\end{aligned} \tag{9}$$

From the model, we have

$$\begin{aligned}
&s = dT_* + \delta I_* - rT_*(1 - \frac{T_*}{T_{\max}}), \quad \frac{\delta c}{p} = \frac{\delta I_*}{V_*}, \\
&\delta I_* = \frac{\beta T_* V_*}{1 + aT_* + bV_* + abT_*V_*}.
\end{aligned} \tag{10}$$

Thus,

$$s + rT(1 - \frac{T}{T_{\max}}) - dT - \frac{\delta cV}{p} = dT_* + \delta I_* - rT_*(1 - \frac{T_*}{T_{\max}}) + rT(1 - \frac{T}{T_{\max}}) - dT - \frac{\delta I_* V}{V_*}, \tag{11}$$

and

$$\begin{aligned} &-\delta I_* \frac{1 + aT + bV_* + abTV_*}{\beta TV_*}\Big(s + rT(1 - \frac{T}{T_{\max}}) - dT - \frac{\beta TV}{1 + aT + bV + abTV}\Big) \\ &\quad = -\frac{T_*}{T}\frac{1 + aT + bV_* + abTV_*}{1 + aT_* + bV_* + abT_*V_*} \times \Big(dT_* + \delta I_* - rT_*(1 - \frac{T_*}{T_{\max}}) + rT(1 - \frac{T}{T_{\max}}) - dT\Big) \\ &\qquad + \delta I_* \frac{V}{V_*}\frac{1 + aT + bV_* + abTV_*}{1 + aT + bV + abTV}. \end{aligned} \tag{12}$$

Also,

$$-\frac{I_*}{I}\Big(\frac{\beta TV}{1 + aT + bV + abTV} - \delta I\Big) = -\delta I_* \frac{I_* TV}{IT_*V_*}\frac{1 + aT_* + bV_* + abT_*V_*}{1 + aT + bV + abTV} + \delta I_*. \tag{13}$$

From (10)-(13), it can be obtained that

$$\begin{aligned} \frac{dL_*}{dt}\,|_{(1.2)} &= dT_*\Big(1 - \frac{T}{T_*} - \frac{T_*}{T}\frac{1 + aT + bV_* + abTV_*}{1 + aT_* + bV_* + abT_*V_*} + \frac{1 + aT + bV_* + abTV_*}{1 + aT_* + bV_* + abT_*V_*}\Big) \\ &\quad + \Big(rT(1 - \frac{T}{T_{\max}}) - rT_*(1 - \frac{T_*}{T_{\max}})\Big) \times \Big(1 - \frac{T_*}{T}\frac{1 + aT + bV_* + abTV_*}{1 + aT_* + bV_* + abT_*V_*}\Big) \\ &\quad + \delta I_*\Big(1 - \frac{T_*}{T}\frac{1 + aT + bV_* + abTV_*}{1 + aT_* + bV_* + abT_*V_*} + \frac{V}{V_*}\frac{1 + aT + bV_* + abTV_*}{1 + aT + bV + abTV}\Big) \\ &\quad + \delta I_*\Big(1 - \frac{I_*TV}{IT_*V_*}\frac{1 + aT_* + bV_* + abT_*V_*}{1 + aT + bV + abTV}\Big) + \delta I_*\Big(1 - \frac{V}{V_*} - \frac{V_*I}{I_*V}\Big) \\ &= -\Big[d - r + r\Big(\frac{T + T_*}{T_{\max}}\Big)\Big]\frac{(T - T_*)^2(1 + bV_*)}{T(1 + aT_* + bV_* + abT_*V_*)} \\ &\quad + \delta I_*\Big(-1 - \frac{V}{V_*} + \frac{V}{V_*}\frac{1 + aT + bV_* + abTV_*}{1 + aT + bV + abTV} + \frac{1 + aT + bV + abTV}{1 + aT + bV_* + abTV_*}\Big) \\ &\quad + \delta I_*\Big(4 - \frac{T_*}{T}\frac{1 + aT + bV_* + abTV_*}{1 + aT_* + bV_* + abT_*V_*} - \frac{I_*TV}{IT_*V_*}\frac{1 + aT_* + bV_* + abT_*V_*}{1 + aT + bV + abTV} - \frac{V_*I}{I_*V} \\ &\quad - \frac{1 + aT + bV + abTV}{1 + aT + bV_* + abTV_*}\Big). \end{aligned} \tag{14}$$

Since $d \geq r$, we have

$$d - r + r\Big(\frac{T + T_*}{T_{\max}}\Big) > 0.$$

Note that

$$\begin{aligned} &\delta I_*\Big(-1 - \frac{V}{V_*} + \frac{V}{V_*}\frac{1 + aT + bV_* + abTV_*}{1 + aT + bV + abTV} + \frac{1 + aT + bV + abTV}{1 + aT + bV_* + abTV_*}\Big) \\ &\quad = -\frac{b(1 + aT)^2}{V_*(1 + aT + bV + abTV)(1 + aT + bV_* + abTV_*)}(V - V_*)^2. \end{aligned} \tag{15}$$

On the other hand, since the arithmetic mean is greater than or equal to the geometric mean, it is clear that

$$4 - \frac{T_*}{T}\frac{1 + aT + bV_* + abTV_*}{1 + aT_* + bV_* + abT_*V_*} - \frac{I_*TV}{IT_*V_*}\frac{1 + aT_* + bV_* + abT_*V_*}{1 + aT + bV + abTV} - \frac{V_*I}{I_*V} - \frac{1 + aT + bV + abTV}{1 + aT + bV_* + abTV_*} \leq 0. \tag{16}$$

By (15) and (16), it can be concluded that $\frac{dL_*}{dt} \leq 0$ for all $T, I, V > 0$. Hence, the chronic equilibrium $\mathbf{E}_*$ is stable. On the other hand, $\frac{dL_*}{dt} = 0$ if and only if $T = T_*, I = I_*, V = V_*$. Let Λ be the largest invariant set in

$$D = \{(T, I, V) \mid \dot{L_*}(T, I, V) = 0\} = \{\mathbf{E}_*\}.$$

We have that $\Lambda = \{\mathbf{E}_*\}$. The global stability of $\mathbf{E}_*$ follows from LaSalle's invariance principle ([7]). □

4. Numerical Simulations

In the previous sections, the theoretical results of system (2) around the the equilibria $\mathbf{E_0}$ and $\mathbf{E}_*$ were presented. In this section, some light on the solutions around the equilibria of (2) will be shed. To observe the dynamic behavior of system (2), some numerical simulations will be presented by using Python and Runge-Kutta method, with hypothetical values in Table 1 and different values for β (Viral infectivity rate).

Table 1. Parameter Values used for simulation

Parameters	Meaning	Value (Unite)	References
s	Source rate of host cells	10 (cells ml^{-1}day^{-1})	[21]
r	The Logistic growth rate of healthy cells	0.018 (day^{-1})	[19]
d	Decay rate of healthy cells	0.02 (day^{-1})	[19]
$T_{\max}$	Maximum level of host cells in the human body	1200 (Constant)	[20]
a	The positive parameter that describes the effects of capture rate	0.00005	[20]
b	The positive parameter that describes the effects of capture rate	0.000001	[18]
δ	Death rate of infected cells, not killing by CTL	0.8 (day^{-1})	[20]
p	Virion production rate	2.4 (virions cell^{-1}day^{-1})	[18]
c	The clearance rate of virus	2 (day^{-1})	[18]

By using these values and initial values $(60, 10, 2)$, the following dynamic behavior of the system was shown.

In the study of virus dynamics, the infection rate plays a vital role in describing the system's behavior. If we put $\beta = 0.0008$ (ml cell^{-1}day^{-1}), then the infective cells and the free virus will become extinct in the system. By this argument, the virus-free equilibrium $\mathbf{E_0} = (T_0, 0, 0)$ is asymptotically stable with values $T_0 = 752.55$ and $\mathbf{R_0} = 0.8703 < 1$ (Fig. 1).

On the other hand, for $\beta = 0.003$, the chronic equilibrium $\mathbf{E}_*$ is asymptotically stable with values $T_* = 224.7, I_* = 10.99$ and $V_* = 13.19$. In this case, $\mathbf{R_0} = 3.2637 > 1$ and the roots of the characteristic equation are $-0.02 + 0.147i$, $-0.02 - 0.147i$ and -2.801 (Fig. 2). For a range of infection rate, $\beta \leq 0.003367$, the chronic equilibrium $\mathbf{E}_*$ is asymptotically stable with a value $T_* \geq 200$ (Fig. 3). From biology, we know that if $T < 200$ in a microliter of blood, then HIV becomes AIDS ([4]). Thus, we have a pretty level if $\beta \leq 0.00336$. Also, for a range of $\beta \geq 0.00337$, the chronic equilibrium $\mathbf{E}_*$ is asymptotically stable with a value $T_* < 200$ (Fig. 4 and Fig. 5).

5. Drug efficacy

To investigate the effects of the drug on the disease model, consider two parameters η_1 and η_2, that the efficacy of drug treatment in the prevention of new infections and viruses, respectively. Naturally, the effect of the drug varies over time depending on the conditions of the disease. However, like the most mathematical models for ease of calculation, this effect is assumed to be constant. Therefore, system (2) with drug effectiveness becomes

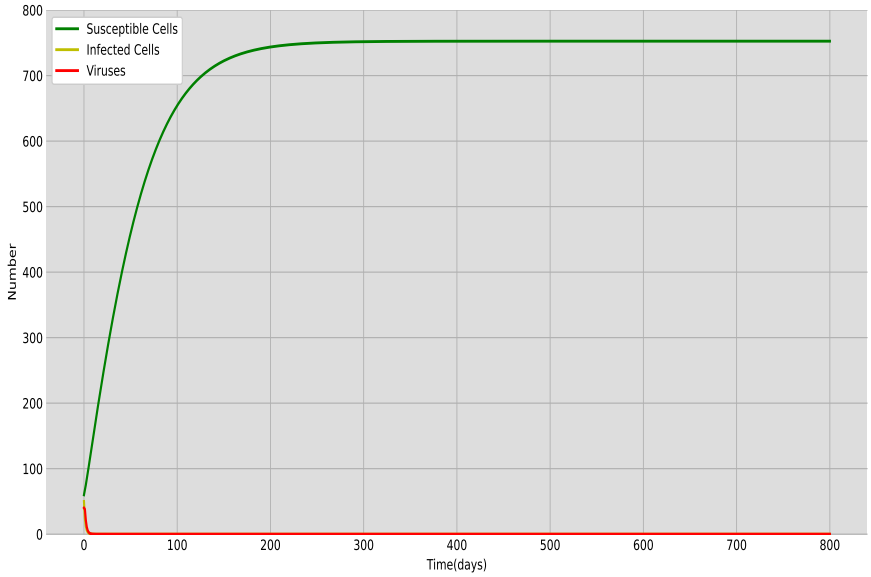

Figure 1: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E_0} = (752.55, 0, 0)$ ($\beta = 0.0008$, $\mathbf{R_0} = 0.8703 < 1$).

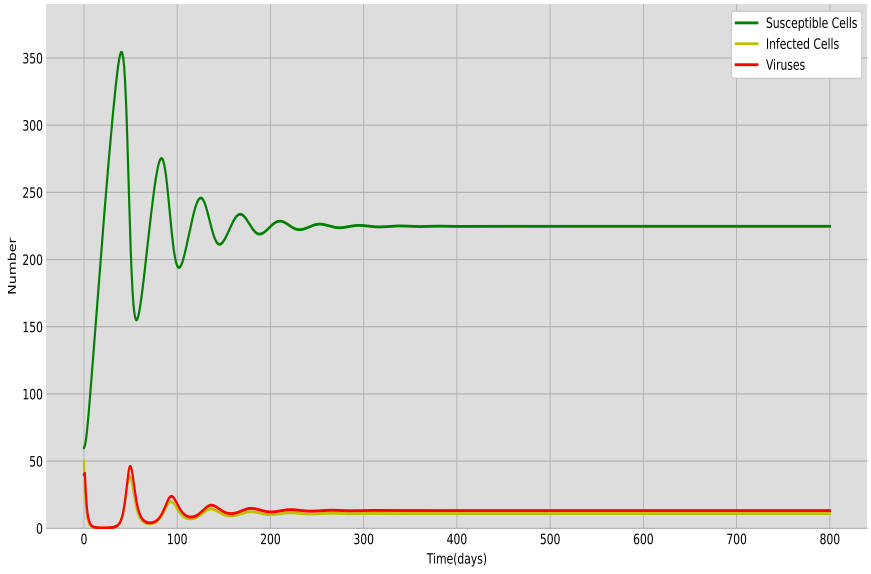

Figure 2: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E}_* = (224.7, 10.99, 13.19)$ ($\beta = 0.003$, $\mathbf{R_0} = 3.2637 > 1$).

$$\begin{cases} \dfrac{dT}{dt} = s + rT(1 - \dfrac{T}{T_{\max}}) - dT - (1 - \eta_1)\dfrac{\beta TV}{1 + aT + bV + abTV}, \\ \dfrac{dI}{dt} = (1 - \eta_1)\dfrac{\beta TV}{1 + aT + bV + abTV} - \delta I, \\ \dfrac{dV}{dt} = (1 - \eta_2)pI - cV. \end{cases} \tag{17}$$

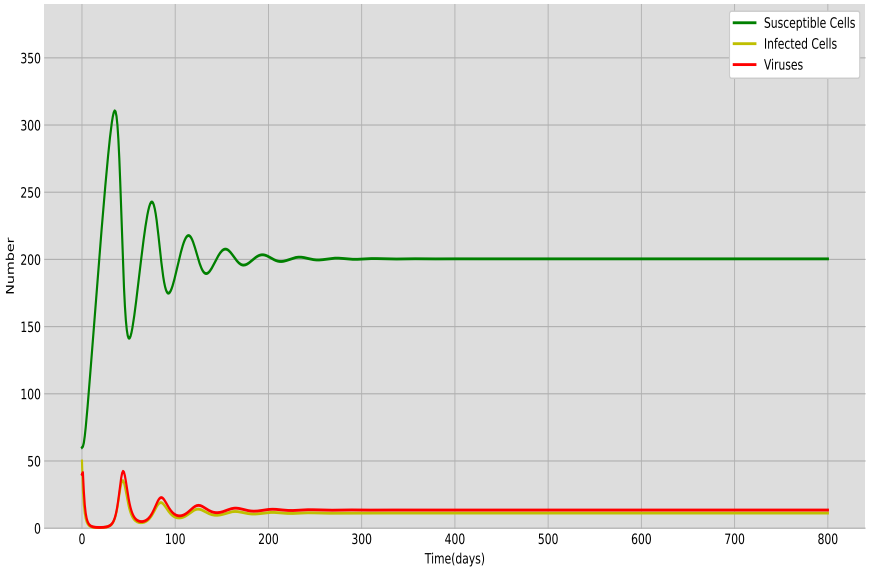

Figure 3: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E}_* = (200.4, 11.25, 13.48)$ ($\beta = 0.00336$, $\mathbf{R_0} = 3.6553 > 1$).

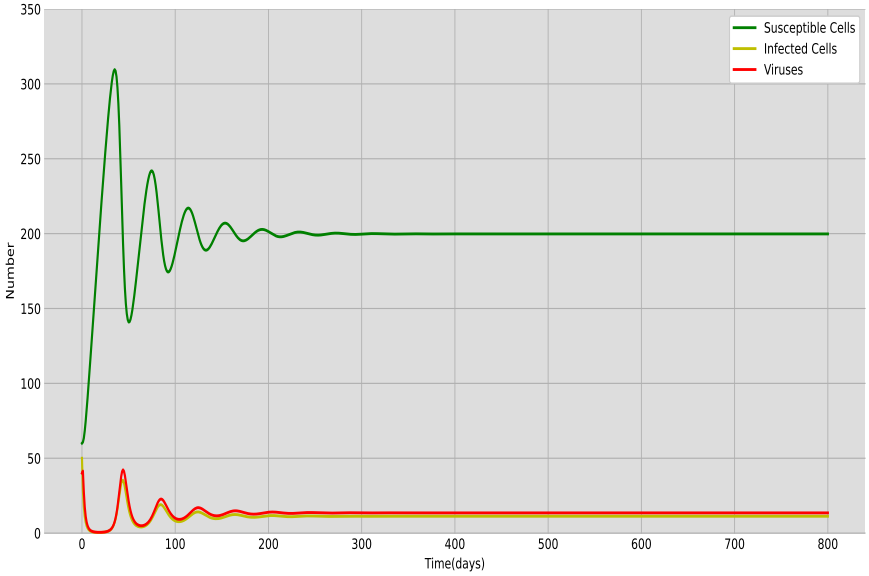

Figure 4: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E}_* = (199.8, 11.25, 13.5)$ ($\beta = 0.00337$, $\mathbf{R_0} = 3.65 > 1$).

Assume that parameters $\eta_i, i = \{1, 2\}$ belong to interval $[0, 1]$. The beginning of the interval is related to the lack of treatment and the end of the interval belongs to the time when drug treatment is one hundred percent successful. For example, if $\eta_2 = 1$, then the drug has been completely effective against viruses. In figures 6, 7 and 8, for the different values of control parameter η_2, the trajectory of susceptible cells, infected cells and viruses are shown. Consequently, with the start of treatment, the $\eta_i, i = \{1, 2\}$, changes between 0 and 1. Clinically, the number of healthy cells and viral load can be measured and displayed

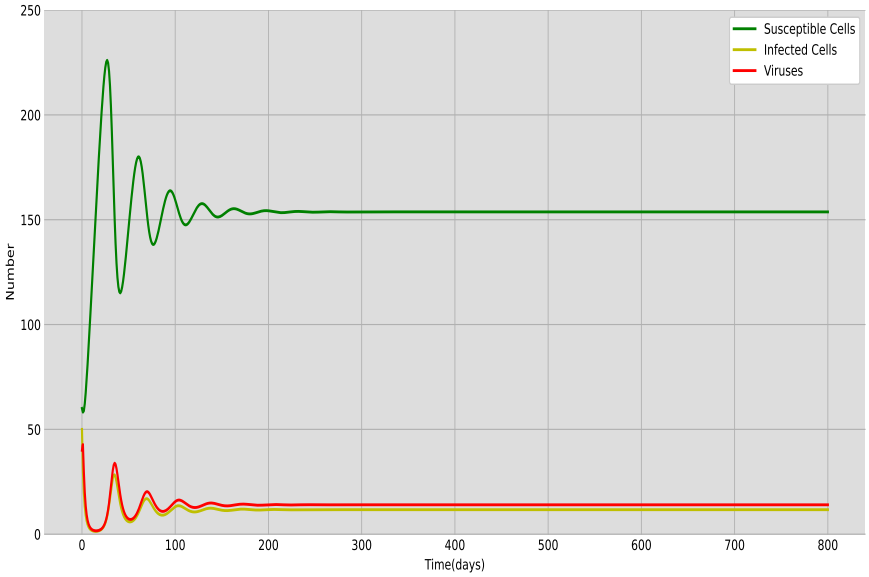

Figure 5: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E}_* = (153.7, 14.01, 11.67)$ ($\beta = 0.00437$, $\mathbf{R_0} = 4.7541 > 1$).

statistically, while the number of infected cells is generally not reported. Follow the attitude of Perelson

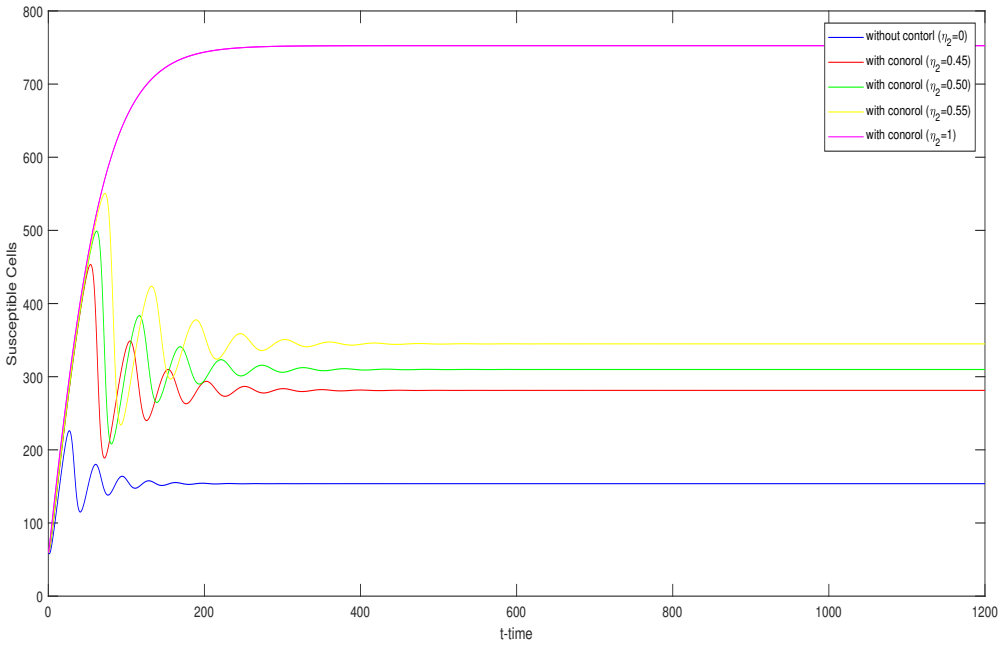

Figure 6: Trajectory of the susceptible cells with different values of control parameter η_2.

and Nelson [13] and suppose $\frac{dV}{dt} = 0$. On the other hand, before therapy virus load changes are almost constant. Consequently, $\frac{dI}{dt} = 0$ at the same time. Therefore, if (T^0, I^0, V^0) corresponds to the pretreatment

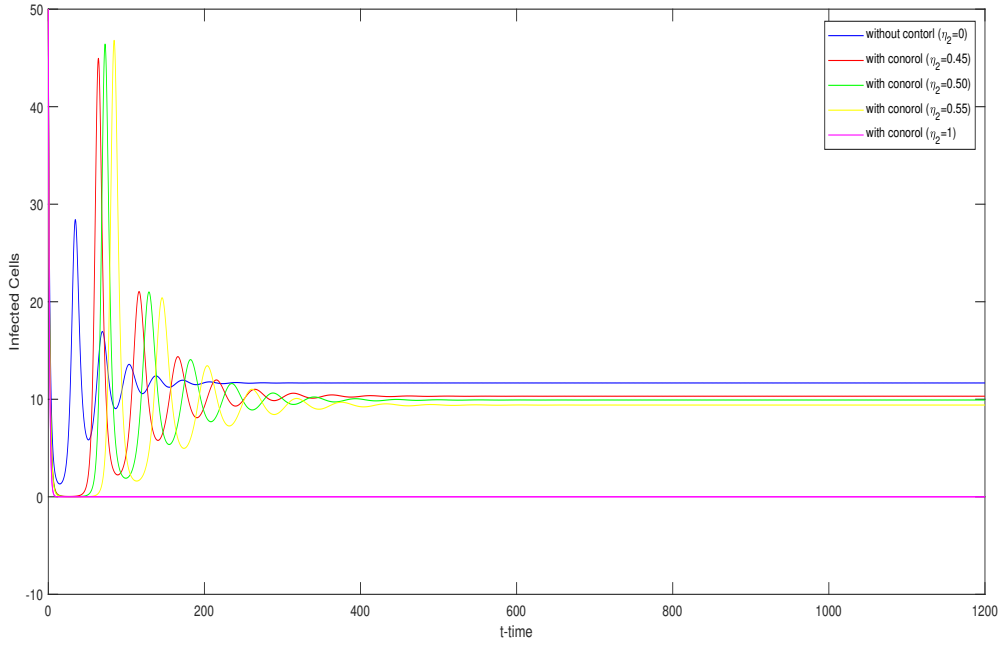

Figure 7: Trajectory of the Infected cells with different values of control parameter η_2.

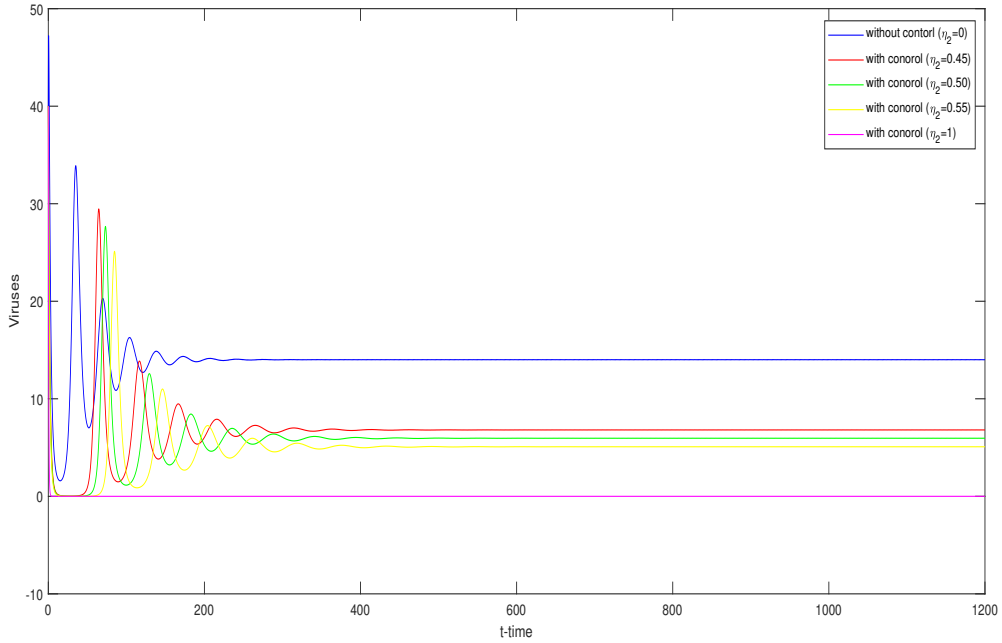

Figure 8: Trajectory of the viruses with different values of control parameter η_2.

mode initial condition for (17), then

$$(1-\eta_2)pI^0 = cV^0. \tag{18}$$

and

$$(1-\eta_1)\frac{\beta T^0 V^0}{1+aT^0+bV^0+abT^0V^0}=\delta I^0. \tag{19}$$

From (17), (18) and (19), for $\eta_1=\eta_2=0$, it can be concluded that

$$I^0=\frac{cV^0}{(1-\eta_2)p},\quad T^0=\frac{c\delta+c\delta bV^0}{(1-\eta_2)p(1-\eta_1)\beta-\delta ac-\delta abV^0c}. \tag{20}$$

With the placement T^0 and I^0 in the first equation of (17), V^0 is also obtained. According to the progress of HIV, suppose that at some point in time, T-cell changes are negligible compared to the changes in infected cells and viruses. Shortly after starting treatment, let $T=T^0$ be constant, one or both of η_i are positive and I and V change according to the last two equations of (17) as follows

$$\begin{cases}\dfrac{dI}{dt}=(1-\eta_1)\dfrac{\beta T^0 V}{1+aT^0+bV+abT^0V}-\delta I,\\[2ex] \dfrac{dV}{dt}=(1-\eta_2)pI-cV.\end{cases} \tag{21}$$

System (21) has two possible equilibria $U_0(0,0)$ and $U_1(I_1,V_1)$ where

$$V_1=\frac{(1-\eta_2)pI_1}{c},\quad I_1=\frac{(1-\eta_2)p(1-\eta_1)\beta T^0-c\delta-ac\delta T^0}{b\delta(1-\eta_2)p(1+aT^0)}.$$

The Jacobian matrix of (21) at an arbitrary point J^* is given by

$$J^*=\begin{bmatrix}-\delta & \dfrac{(1-\eta_1)\beta T^0}{(1+aT^0)(1+bV)^2}\\ p(1-\eta_2) & -c\end{bmatrix}. \tag{22}$$

The characteristic equations associated with $U_0(0,0)$ and $U_1(I_1,V_1)$ are respectively given by

$$\lambda^2+(c+\delta)\lambda+\frac{c\delta(1+aT^0)-(1-\eta_2)p(1-\eta_1)\beta T^0}{(1+aT^0)}=0, \tag{23}$$

and

$$\lambda^2+(c+\delta)\lambda+c\delta\frac{(1-\eta_2)p(1-\eta_1)\beta T^0-c\delta-ac\delta T^0}{(1-\eta_2)p(1-\eta_1)\beta T^0}=0. \tag{24}$$

Let

$$\begin{aligned}F&=c+\delta,\\ E&=c\delta(1+aT^0)-(1-\eta_2)p(1-\eta_1)\beta T^0,\\ E^{'}&=(1-\eta_2)p(1-\eta_1)\beta T^0-c\delta-ac\delta T^0.\end{aligned}$$

Suppose $E\neq 0$. If $E<0$, then $U_0(0,0)$ is a saddle point and if $E>0$, then $U_0(0,0)$ is a stable fixed point. For the existence of equilibrium $U_1(I_1,V_1)$, E' must be positive; in this case, E' is a stable fixed point and all eigenvalues of (23) have negative real parts and the corresponding equilibrium is asymptotically stable. Otherwise for $E'<0$, $U_1(I_1,V_1)$ does not exist.

If $E > 0$, then $U_0(0,0)$ is asymptotically stable. With T constant and for $t > t_0$, it can be concluded that

$$V(t) = V_0[Qe^{-\lambda_1(t-t_0)} + (1-Q)e^{-\lambda_2(t-t_0)}],$$

is the solution of the approximation equation of (21), where

$$\lambda_1, \lambda_2 = \frac{-F \pm \sqrt{F^2 - 4E}}{2} = \frac{(c-\delta) \pm \sqrt{(c+\delta)^2 + 4\dfrac{(1-\eta_1)(1-\eta_2)p\beta T^0}{(1+aT^0)}}}{2}.$$

On the other hand, we have

$$V(t = t_0) = V_0 \qquad \frac{dV}{dt}|_{t=t_0} = -\eta_2 c V_0,$$

and if $T^0 = \dfrac{c\delta}{(1-\eta_2)p\beta} < \dfrac{c\delta}{(1-\eta_2)p(1-\eta_1)\beta}$, then it can be obtained that

$$\lambda_1, \lambda_2 = \frac{(c-\delta) \pm \sqrt{(c+\delta)^2 + 4\dfrac{c\delta}{(1+aT^0)}}}{2}, \qquad Q = \frac{\eta_2 c - \lambda_2}{\lambda_1 - \lambda_2}.$$

According to the above calculations, we introduce the new threshold parameter

$$\mathbf{R_{01}} = \frac{(1-\eta_2)p(1-\eta_1)\beta T^0}{c\delta},$$

which the status of the disease progression depends on. If $\mathbf{R_{01}}$ is more than one, then the disease will worsen and with $\mathbf{R_{01}}$ less than one disease will be removed.

6. Discussion and conclusion

In this work, we analyzed, analytically and numerically, a virus dynamics model with an incidence rate of Crowly-Martin type. By Lyapunov's second method and using LaSalle's invariance principle, we have presented that if one virus produces one or less than one virus during its lifetime ($\mathbf{R_0} \leq 1$), the virus cannot attack and will soon be cleared or equivalently, the virus-free steady state $\mathbf{E_0}$ is globally asymptotically stable. Also, if one virus produces greater than one virus during its lifespan ($\mathbf{R_0} > 1$) and $d \geq r$, the virus can invade and will soon be able to spread in the T cells population or equivalently, the chronic equilibrium $\mathbf{E}_*$ is globally asymptotically stable. It is observed that, when the infection rate $\beta \leq 0.1269$, then the disease does not become to AIDS level. To investigate the effect of the drug on the treatment process of HIV, we defined controls and applied them to system (2). The stability of the equilibria of the new system was investigated. According to the calculations related to drug therapy, we obtained a new threshold parameter $\mathbf{R_{01}}$ such that if $\mathbf{R_{01}}$ is less than one, the disease will improve; otherwise, the disease has not responded well to drug therapy.

We hope that our analytical and numerical results may give a new idea to the experimental biologists and physicians to find a suitable way to control the infection.

Declarations of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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