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MATHEMATICAL ANALYSIS OF HIV VIRAL INFECTION MODEL WITH LOGISTIC GROWTH RATE AND CELL-TO-CELL AND CELL-FREE TRANSMISSIONS

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Abstract. It is well known that dynamical systems are very useful tools to study the viral disease such as HIV, HBV, HCV, Ebola and Influenza. This paper deals with a mathematical model of the cell-to-cell and the cell-free spread of HIV with both linear and nonlinear functional responses and logistic target cell growth. The reproduction number of each mode of transmission has been calculated and their sum has been considered as the basic reproduction number. Based on the values of the reproduction number, the local and global stability of the rest points have been investigated.

1. Introduction

Over decades, human societies have been affected by human immunodeficiency virus (HIV). HIV viruses attack the body's immune system and destroy a type of target cells known as $CD4^+$ T-cells. Studies have shown that HIV infection in humans came from a type of chimpanzee in Africa. Today, HIV infection is a contagious disease that can be transmitted from person to person. If HIV is not treated, it can lead to acquired immunodeficiency syndrome (AIDS). Unfortunately, there is currently no effective

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cure and only with proper medical care patients may have a better quality of life. The stages of HIV infection are as follows: acute HIV infection, chronic HIV infection and AIDS. AIDS is a communicable disease and HIV is the causative agent for AIDS which damages the ability of the body to fight against diseases and leave it open to attack from usual innocuous infections ([2]). In recent years, some mathematical models have been proposed to investigate the distribution of disease and to describe epidemic illnesses related to AIDS ([3]).

Mathematical modeling involves breaking down a problem into its measurable parts and representing those parts in the equations. Mathematical models have been invaluable in the fight against Covid 19. They have been used to determine the length of quarantine and school closures, to predict the shortage of ventilators and to produce vaccines. The models used for each of these problems were ready in 2020 thanks to years of basic research. The most useful mathematical tools used throughout the epidemic, from classical differential equations to newer techniques, were in many cases invented by mathematicians who did not have a specific goal in mind, but ultimately when we came up with Covid 19 encountered, they helped humanity a lot. It is clear that the mathematicians who are doing basic research today are laying the groundwork for combating the spread of future diseases.

Song and Neumann in [15] studied the spread of HIV by model

$$\begin{aligned} \frac{dT(t)}{dt} &= s - dT + aT(1 - \frac{T}{T_M}) - \frac{\beta TV}{1+\alpha V}, \\ \frac{dI(t)}{dt} &= \frac{\beta TV}{1+\alpha V} - \delta I, \\ \frac{dV(t)}{dt} &= pI - cV, \end{aligned} \tag{1.1}$$

where $T(t)$, $I(t)$ and $V(t)$ represent the number of target cells, the number of infected cells and viral load of the virus, respectively. δ is the loss rate constant of infective cells, p is virus production rate for infected cell, c is the clearance rate constant of free viruses, s represents the rate at which new T cells are created from the source within the body, rate of infection is given by βTV, a is the maximum proliferation rate of target cells, T_M is the population density at which proliferation shuts off, d is the death rate of T cells and $\alpha > 0$ is constant for saturated mass action. In model (1.1) the dynamics of HIV with the classical mathematical model with saturation response of the infection rate was studied. Sufficient conditions on the parameters for the global stability of the infection-free and positive equilibria were obtained. Also, they gave an existence result of an orbitally asymptotic stable periodic solution.

Two dominant infection modes of HIV-1 are the cell-free infection, that is the classical one, and cell-to-cell delivery which has been examined in recent years. In the classical mode, infected cells spread viral components which infect the new cell over a distance. In the cell-to-cell mode disease is spread

through direct contact of infected cells with uninfected ones ([10]). Lai and Zou in [11] considered a model containing two modes for HIV-1 infection and spread, classical cell-free infection and direct cell-to-cell transmission.

Motivated by the works of Lai and Zou in [11] and Song and Neumann in [15], in the present work, we shall study the following model of HIV infection with logistic target cell growth and two predominant transmission. Using the same notations as in [15], we investigate the model

$$\begin{aligned}
\frac{dT(t)}{dt} &= s - dT + rT(1 - \frac{T}{T_M}) - \frac{b_1 TV}{1+aV} - b_2 TI, \\
\frac{dI(t)}{dt} &= \frac{b_1 TV}{1+aV} + b_2 TI - \delta I, \\
\frac{dV(t)}{dt} &= hI - lV,
\end{aligned} \qquad . \tag{1.2}$$

The rest of the paper is organized as follows. Section 2 deals with some basic results e.g., boundedness and non-negativity of the solutions, the basic reproduction number and the existence of equilibria. The stability of the equilibria are considered in section 3. Some of the results are illustrated numerically in section 4.

2. Equilibria and basic results

In this section, the basic properties of the solutions of (1.2) will be presented. There exists an infection-free equilibrium $E_1(T_1, 0, 0)$ where

$$T_1 = \frac{T_M}{2r}\left[r - d + \sqrt{(r-d)^2 + \frac{4rs}{T_M}}\right],$$

which represents the state of system (1.2) without viruses. Considering the activity of the virus in the body, it can be proven that there exists a positive equilibrium like $E_2(T_2, I_2, V_2)$. System (1.2) shows the interaction of cell population in the body. Hence, the amount of cells should remain positive and bounded. In the following, the positivity and the boundedness of the solutions of (1.2) will be shown.

Theorem 2.1. *Starting from non-negative initial points, all solutions of* (1.2) *exist for all* $t > 0$ *and remain bounded and non-negative.*

Proof. Since the functions in (1.2) are continuous and smooth, the existence and uniqueness of solutions of (1.2) are established by Picard Theorem. To prove the positivity of solutions, define

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

For any solution in $\mathbb{R}^3_+$, it can be concluded that

$$\dot{T}\mid_{T=0} = s \geq 0, \quad \dot{I}\mid_{I=0} = \frac{b_1 TV}{1+aV} \geq 0, \quad \dot{V}\mid_{V=0} = hI \geq 0.$$

Due to the theorem by Nagumo in [13], the positivity of all solutions is proven.

For the boundedness of solutions, let $L(t) = T(t) + I(t)$. Therefore,

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

where $M_0 = \frac{T_M r^2 + 4rs}{4r}$ and $h = \min\{d, \delta\}$. Hence, there exist $M_1 > 0$ and $t_1 > 0$ such that $L \leq M_1$ for any $t > t_1$. From the third equation of (1.2), with the same way, we can find $M_2 > 0$ as an upper bound for $V(t)$. Now, let $M = \max\{M_1, M_2\}$. Obviously, $T(t) \leq M$, $I(t) \leq M$ and $V(t) \leq M$ 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 as the expected number of secondary infections produced by an index case in a completely susceptible body cells.

According to the concept of next-generation matrix in Diekmann et al. ([5]) and the production number presented in van den Driessche and Watmough ([19]), we can compute the basic reproduction number of (1.2) as

$$\mathbf{R_0} = \mathbf{R_{01}} + \mathbf{R_{02}}, \quad \textit{where} \quad \mathbf{R_{01}} = \frac{b_1 h}{l\delta} T_1, \quad \mathbf{R_{02}} = \frac{b_2}{\delta} T_1,$$

where $T_1 = (\frac{r - d + \sqrt{\Delta}}{2r}) T_M$ and $\Delta = (r-d)^2 + \frac{4rs}{T_M}$.

Actually, to obtain $\mathbf{R_0}$, following the method of [6], first consider the linearization of (1.2) around the infection-free equilibrium E_1 as

$$\begin{pmatrix} \frac{d\gamma_1(t)}{dt} \\ \frac{d\gamma_2(t)}{dt} \end{pmatrix} = \begin{pmatrix} b_2 T_1 & b_1 T_1 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \gamma_1(t) \\ \gamma_2(t) \end{pmatrix} - \begin{pmatrix} \delta & 0 \\ -h & l \end{pmatrix} \begin{pmatrix} \gamma_1(t) \\ \gamma_2(t) \end{pmatrix},$$

where $\gamma_1(t)$ and $\gamma_2(t)$ represent the perturbation of $I(t)$ and $V(t)$ from E_1, respectively. Let $\Gamma(0) = (\gamma_1(0), \gamma_2(0))$ be the initial distribution. Therefore, if there is no new infection, then the cell population will evolve $e^{-Ut}\Gamma(0)$ where $U = \begin{pmatrix} \delta & 0 \\ -h & l \end{pmatrix}$. The total distribution of the new infectious cells occurring at $t = 0$ is

$$L(\Gamma(0)) = \int_0^\infty \begin{pmatrix} \beta_2 T_1 & \beta_1 T_1 \\ 0 & 0 \end{pmatrix} e^{-Yt} \gamma(0) dt = \begin{pmatrix} b_2 T_1 & b_1 T_1 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \delta & 0 \\ -h & l \end{pmatrix}^{-1} \Gamma(0).$$

It follows from [17] that

$$\mathbf{R_0} = \rho(L) = \rho(\begin{pmatrix} b_2 T_1 & b_1 T_1 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{\delta} & 0 \\ \frac{h}{l\delta} & \frac{1}{l} \end{pmatrix}) = \mathbf{R_{01}} + \mathbf{R_{02}},$$

where ρ shows the spectral radius of the matrix.

By the values of $\mathbf{R_0}$, the local and the global stability of the equilibrium points of (1.2) will be studied in the next sections.

Consider the set

$$\Gamma = \left\{ \xi \in [0, T_1] \mid \ (n(T) - n(\xi))(T - \xi) < 0 \ \ for \ \ T \neq \xi, T \in [0, T_1] \right\}, \quad (2.1)$$

where $n(T) = s - dT + rT(1 - \frac{T}{T_M})$. Substituting $n(T)$ in (2.1), Γ can be written as

$$\Gamma = \left\{ \xi \in [0, T_1] \mid \ d - r + r\left(\frac{T + \xi}{T_M}\right) > 0 \ \ for \ \ T \neq \xi, T \in [0, T_1] \right\}.$$

If Γ is nonempty, then there are cell densities at which the net growth rate is lower than the net growth rates at lower densities yet higher than the net growth rates at higher densities.

In the following, a theorem about the existence of the rest points of (1.2) will be presented.

Theorem 2.3. *System (1.2) has a unique infection-free equilibrium $E_1(T_1, 0, 0)$ if $\mathbf{R_0} \leq 1$. Except for E_1, if $\mathbf{R_0} > 1$, then (1.2) has a unique positive (endemic) equilibrium $E_2(T_2, I_2, V_2)$ with $T_2 \in (0, T_1)$ where*

$$I_2 = \frac{l}{h} V_2 \quad \text{and} \quad V_2 = \frac{1}{a} \frac{\mathbf{R_0} T_2 - T_1}{T_1 - \mathbf{R_{02}} T_2}. \quad (2.2)$$

Proof. The following relations hold at any equilibrium point.

$$\begin{aligned} &n(T) - V f_1(T, V) - I f_2(T) = 0, \\ &V f_1(T, V) + I f_2(T) - \delta I = 0, \\ &hI - lV = 0, \end{aligned}$$

where $f_1(T, V) = \dfrac{b_1 T}{1 + aV}$ and $f_2(T) = b_2 T$. Therefore,

$$V = \frac{h}{l} I, \quad I = \frac{1}{\delta} n(T) = \frac{1}{\delta}\left(s - dT + rT(1 - \frac{T}{T_M})\right),$$

which implies that $T \leq T_1$. Consider the following function on $[0, T_1]$:

$$G(T) = n(T)\left(\frac{h}{l\delta} f_1\big(T, \frac{h}{l\delta} n(T)\big) + \frac{1}{\delta} f_2\big(T\big) - 1\right).$$

We have $G(0) = -s < 0$ and $G(T_1) = 0$. On the other hand,

$$G'(T_1) = n'(T_1)\left(\frac{h}{l\delta} f_1\big(T_1, 0\big) + \frac{1}{\delta} f_2\big(T_1\big) - 1\right) = n'(T_1)(\mathbf{R_0} - 1).$$

Therefore, $G'(T_1) < 0$ since $n'(T_1) < 0$ and $\mathbf{R_0} > 1$. By this argument, there exists $T_2 \in (0, T_1)$ such that $G(T_2) = 0$. Thus, there exists positive equilibrium $E_2(T_2, I_2, V_2)$ with $T_2 \in (0, T_1)$, $I_2 > 0$ and $V_2 > 0$.

Suppose that there exists another equilibrium $\bar{E}_2(\bar{T}_2, \bar{I}_2, \bar{V}_2)$. Without loss of generality, we may assume that $\bar{T}_2 < T_2$. Then, $T_2 \in \Gamma$ implies that $n(\bar{T}_2) > n(T_2)$. From equilibrium conditions, we have

$$\begin{aligned} n(T_2) &= V_2 f_1(T_2, V_2) + I_2 f_2(T_2) = \delta I_2 = \frac{l\delta}{h} V_2, \\ n(\bar{T}_2) &= \bar{V}_2 f_1(\bar{T}_2, \bar{V}_2) + \bar{I}_2 f_2(\bar{T}_2) = \delta \bar{I}_2 = \frac{l\delta}{h} \bar{V}_2. \end{aligned} \tag{2.3}$$

Therefore, $\bar{I}_2 > I_2$ and $\bar{V}_2 > V_2$ since $n(\bar{T}_2) > n(T_2)$. Computing the derivatives of f_1 and f_2, we deduce that $\dfrac{\partial f_1}{\partial T} > 0$, $\dfrac{\partial f_1}{\partial V} < 0$ and $f_2'(T) > 0$. Thus,

$$\begin{aligned} &f_1(\bar{T}_2, \bar{V}_2) < f_1(T_2, \bar{V}_2) < f_1(T_2, V_2) \\ &f_2(\bar{T}_2) < f_2(T_2). \end{aligned}$$

On the other hand, it follows from (2.3) that

$$f_1(T_2, V_2) + \frac{l}{h} f_2(T_2) = f_1(\bar{T}_2, \bar{V}_2) + \frac{l}{h} f_2(\bar{T}_2) = \frac{l\delta}{h}.$$

This is a contradiction, and therefore $E_2(T_2, I_2, V_2)$ is the unique endemic equilibrium of (1.2). □

Remark 2.4. By attention to (2.2), it can be concluded that the infected equilibrium $E_2(T_2, I_2, V_2)$ exists if and only if $\mathbf{R_0} T_2 > T_1 > \mathbf{R_{02}} T_2$.

3.

In this section, the local asymptotic stability of equilibria of (1.2) will be considered. Next, under certain conditions, the global asymptotic stability of E_1 will be investigated.

Theorem 3.1. *If $\mathbf{R_0} < 1$, then the infection-free equilibrium E_1 is locally asymptotically stable. If $\mathbf{R_0} > 1$, then E_1 is unstable.*

Proof. The Jacobian matrix of (1.2) at E_1 is given by

$$J_{E_1} = \begin{bmatrix} r - d - \frac{2rT_1}{T_M} & -b_2 T_1 & -b_1 T_1 \\ 0 & b_2 T_1 - \delta & b_1 T_1 \\ 0 & h & -l \end{bmatrix}. \tag{3.1}$$

The characteristic polynomial of (3.1) is as

$$\left(\lambda - r + d + \frac{2rT_1}{T_M}\right)\left[\lambda^2 + (l + \delta(1 - \mathbf{R_{02}}))\lambda + l\delta(1 - \mathbf{R_0})\right] = 0. \tag{3.2}$$

It is clear that equation (3.2) has a root as $\lambda = r - d - \dfrac{2rT_1}{T_M} < 0$. On the other hand, if $\mathbf{R_0} < 1$, then $l + \delta(1 - \mathbf{R_{02}}) > 0$ and $l\delta(1 - \mathbf{R_0}) > 0$. This means that the roots of (3.2) have negative real part if $\mathbf{R_0} < 1$. If $\mathbf{R_0} > 1$, let

$$f(\lambda) = \lambda^2 + (l + \delta(1 - \mathbf{R_{02}}))\lambda + l\delta(1 - \mathbf{R_0}). \tag{3.3}$$

In this case, $f(0) = l\delta(1 - \mathbf{R_0}) < 0$ and $\lim_{\lambda\to+\infty} f(\lambda) = +\infty$. From the continuity of f on $(-\infty, +\infty)$ and using Intermediate Value Theorem, it can be concluded that equation (3.3) has at least one positive root. Hence, E_1 is unstable when $\mathbf{R_0} > 1$. □

Theorem 3.2. *If* $\mathbf{R_0} < 1$, *then* $E_1(T_1, 0, 0)$ *is globally asymptotically stable.*

Proof. From Theorem 3.1, we see that if $\mathbf{R_0} < 1$, then all eigenvalues have negative real parts. We need to show that $\lim_{t\to\infty}(T, I, V) = (T_1, 0, 0)$ where $T_1 = \frac{T_M}{2r}[r - d + \sqrt{(r-d)^2 + \frac{4rs}{T_M}}]$. Define the following linear cooperative system

$$\begin{aligned} \frac{d\bar{I}(t)}{dt} &= b_1 T_M \bar{V}(t) + b_2 T_M \bar{I}(t) - \delta \bar{I}(t), \\ \frac{d\bar{V}(t)}{dt} &= h\bar{I} - l\bar{V}. \end{aligned} \tag{3.4}$$

Suppose that λ_0 be the principal eigenvalue associated with strictly positive eigenvector ϵ_0. It is clear that $\lambda_0 < 0$. For $Z > 0$, let $(\bar{I}(t), \bar{V}(t)) = Ze^{\lambda_0 t}\epsilon_0$ be a solution of (3.4). It is clear that $T(t) \le T_M$ and for $t \ge 0$ we have

$$\frac{dI(t)}{dt} \le \frac{d\bar{I}(t)}{dt} \quad and \quad \frac{dV(t)}{dt} \le \frac{d\bar{V}(t)}{dt}.$$

By choosing the appropriate $Z > 0$ and the comparison principal, it can be concluded that $(I(t), V(t)) \le Ze^{\lambda_0 t}\epsilon_0$, and $\lim_{t\to\infty}(I(t), V(t)) = (0, 0)$. According to the above calculations and first equation of (3.4), the following equation can be obtained.

$$\frac{d\bar{T}}{dt} = s - d\bar{T} + r\bar{T}(1 - \frac{\bar{T}}{T_M}).$$

Finally, we conclude that $\lim_{t\to\infty} \bar{T}(t) = T_1$.

It follows from Corollary 4.3 in [18], as asymptotic autonomous semi flow theory, that $\lim_{t\to\infty} T(t) = T_1$. Therefore, $\lim_{t\to\infty}(T(t), I(t), V(t)) = (T_1, 0, 0)$. □

In the following, the local stability of E_2 will be presented.

Theorem 3.3. *Suppose that*

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

(ii) $b_1hT_2 + b_2lT_2 - \delta l + la^2V_2^2(\delta - b_2T_2) + (1 + aV_2)^2\left(\frac{s}{T_2} + \frac{rT_2}{T_M}\right)\left[\frac{s}{T_2} + \frac{rT_2}{T_M} + \delta + l - b_2T_2\right] + (1 + aV_2)\left[\frac{1}{\delta + l - b_2T_2}\left(\frac{s}{T_2} + \frac{rT_2}{T_M}\right) + 1\right]\left(b_1b_2T_2V_2 + b_2^2T_2I_2(1 + aV_2)\right) > \frac{\delta l}{h}\left[\frac{b_1hV_2 + b_2l(1 + aV_2)^2}{\delta + l - b_2T_2}\right]$.

Then, the positive equilibrium $E_2(T_2, I_2, V_2)$ *is locally asymptotically stable.*

Proof. The Jacobian matrix of (1.2) at E_2 is given by

$$J_{E_2} = \begin{bmatrix} r - d - \dfrac{2rT_2}{T_M} - \dfrac{b_1V_2}{1+aV_2} - b_2I_2 & -b_2T_2 & -\dfrac{b_1T_2}{(1+aV_2)^2} \\ \dfrac{b_1V_2}{1+aV_2} + b_2I_2 & b_2T_2 - \delta & \dfrac{b_1T_2}{(1+aV_2)^2} \\ 0 & h & -l \end{bmatrix}.$$

For E_2, the characteristics polynomial is

$$\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3 = 0, \tag{3.5}$$

where the coefficients p_i, $i = 1, 2, 3$ are:

$$\begin{aligned}
p_1 &= \frac{s}{T_2} + \frac{rT_2}{T_M} + l + \frac{\delta}{T_1}(T_1 - \mathbf{R_{02}}T_2) > 0, \\
p_2 &= \left(l + \frac{\delta}{T_1}(T_1 - \mathbf{R_{02}}T_2)\right)\left(\frac{s}{T_2} + \frac{rT_2}{T_M}\right) + b_2T_2\left(\frac{b_1V_2}{1+aV_2} + b_2I_2\right) \\
&\quad + \frac{\delta l}{T_1(1+aV_2)^2}(\mathbf{R_0}T_2 - T_1 + a^2V_2^2(T_1 - \mathbf{R_{02}}T_2)) > 0, \\
p_3 &= \frac{\delta l}{T_1(1+aV_2)^2}\left(\frac{s}{T_2} + \frac{rT_2}{T_M}\right)(\mathbf{R_0}T_2 - T_1 + a^2V_2^2(T_1 - \mathbf{R_{02}}T_2)) \\
&\quad + \frac{(b_1hT_2 + b_2lT_2(1+aV_2)^2)(b_1V_2 + b_2I_2(1+aV_2))}{(1+aV_2)^3} > 0.
\end{aligned}$$

By Remark 2.4, it is clear that $p_i > 0$ for $i = 1, 2, 3$. On the other hand, we also have

$$p_1p_2 - p_3 = \frac{\delta(T_1 - \mathbf{R_{02}}T_2)}{T_1(1+aV_2)^2}\Gamma,$$

where

$$\begin{aligned}
\Gamma =& b_1hT_2 + b_2lT_2 - \delta l + la^2V_2^2(\delta - b_2T_2) \\
&+ (1+aV_2)^2\left(\frac{s}{T_2} + \frac{rT_2}{T_M}\right)\left[\frac{s}{T_2} + \frac{rT_2}{T_M} + \delta + l - b_2T_2\right] \\
&+ (1+aV_2)\left[\frac{1}{\delta + l - b_2T_2}\left(\frac{s}{T_2} + \frac{rT_2}{T_M}\right) + 1\right](b_1b_2T_2V_2 + b_2^2T_2I_2(1+aV_2)) \\
&- \frac{\delta l}{h}\left[\frac{b_1hV_2 + b_2l(1+aV_2)^2}{\delta + l - b_2T_2}\right].
\end{aligned}$$

By Routh–Hurwitz stability criterion, the proof is complete. □

In the sequel, the global stability of E_2 will be presented.

Theorem 3.4. *Suppose that* $\mathbf{R_0} > 1$. *Then, the endemic equilibrium* E_2 *is globally asymptotically stable.*

Proof. Define a Lyapunov function as

$$L(T,I,V) = T - T_2 - T_2 \ln \frac{T}{T_2} + I - I_2 - I_2 \ln \frac{I}{I_2} + \frac{b_1 T_2 V_2}{hI_2(1+aV_2)}\left(V - V_2 - V_2 \ln \frac{V}{V_2}\right).$$

Computing the derivative of $L(T,I,V)$ along the positive solutions of (1.2), it can be written that

$$\frac{dL}{dt}\,|_{(3)} = \left(1 - \frac{T_2}{T}\right)\dot{T} + \left(1 - \frac{I_2}{I}\right)\dot{I} + \frac{b_1 T_2 V_2}{hI_2(1+aV_2)}\left(1 - \frac{V_2}{V}\right)\dot{V}. \tag{3.6}$$

From model (1.2) we get

$$\begin{aligned} s &= dT_2 - rT_2(1 - \frac{T_2}{T_M}) + \frac{b_1 T_2 V_2}{1+aV_2} + b_2 T_2 I_2, \\ \frac{b_1 T_2 V_2}{1+aV_2} &+ b_2 T_2 I_2 = \delta I_2, \\ V_2 &= \frac{h}{l} I_2. \end{aligned} \tag{3.7}$$

Therefore, from (3.6) and (3.7), it can be obtained that

$$\begin{aligned} \frac{dL}{dt}\,|_{(3)} = & \left(1 - \frac{T_2}{T}\right)\left(s - dT + rT(1 - \frac{T}{T_M}) - \frac{b_1 TV}{1+aV} - b_2 TI\right) \\ & + \left(1 - \frac{I_2}{I}\right)\left(\frac{b_1 TV}{1+aV} + b_2 TI - \delta I\right) \\ & + \frac{b_1 T_2 V_2}{hI_2(1+aV_2)}\left(1 - \frac{V_2}{V}\right)(hI - lV) \\ = & -\left[d - r + r\left(\frac{T+T_2}{T_M}\right)\right]\frac{(T-T_2)^2}{T} \\ & - \frac{b_1 T_2 V_2}{1+aV_2}\left[\frac{a(V-V_2)^2}{(1+aV_2)(1+aV)V_2}\right] \\ & + \frac{b_1 T_2 V_2}{1+aV_2}\left[4 - \frac{T_2}{T} - \frac{IV_2}{I_2 V} - \frac{1+aV}{1+aV_2} - \frac{TV(1+aV_2)I_2}{T_2 V_2(1+aV)I}\right] \\ & + b_2 T_2 I_2\left[2 - \frac{T}{T_2} - \frac{T_2}{T}\right]. \end{aligned} \tag{3.8}$$

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

$$\begin{aligned} 4 - \frac{T_2}{T} - \frac{IV_2}{I_2 V} - \frac{1+aV}{1+aV_2} - \frac{TV(1+aV_2)I_2}{T_2 V_2(1+aV)I} \le 0, \\ 2 - \frac{T}{T_2} - \frac{T_2}{T} \le 0. \end{aligned} \tag{3.9}$$

By (3.8) and (3.9) , it can be concluded that $\frac{dL}{dt} \leq 0$ for all $T, I, V > 0$. Hence, the endemic equilibrium E_2 is stable. On the other hand, $\frac{dL}{dt} = 0$ if and only if $T = T_2$, $I = I_2$ and $V = V_2$. Let Ω be the largest invariant set in

$$\Psi = \{(T, I, V) \mid \dot{L} = 0\} = \{E_2\}.$$

We have that $\Omega = \{E_2\}$. The global asymptotically stability of E_2 follows from LaSalle's invariance principle ([7]). □

4. Numerical simulations

In this section, using the standard *Matlab* differential equations integrator for the Runge–Kutta method (ODE45), the numerical simulation of (1.2) will be studied. The stability of first equilibrium $E_1(1166.8560, 0, 0)$ can be seen in Fig. 1. It is obtained for the parametric values

$$s = 2, \quad r = 0.2, \quad T_M = 1200, \quad d = 0.01, \quad b_1 = 0.0006,$$
$$b_2 = 0.0004, \quad a = 0.00005, \quad \delta = 0.8, \quad h = 0.15, \quad l = 2.4.$$

In this case, $\mathbf{R_0} = 0.6291 < 1$ and the infection free equilibrium E_1 is asymptotically stable. Hereafter, we consider a set of parameters

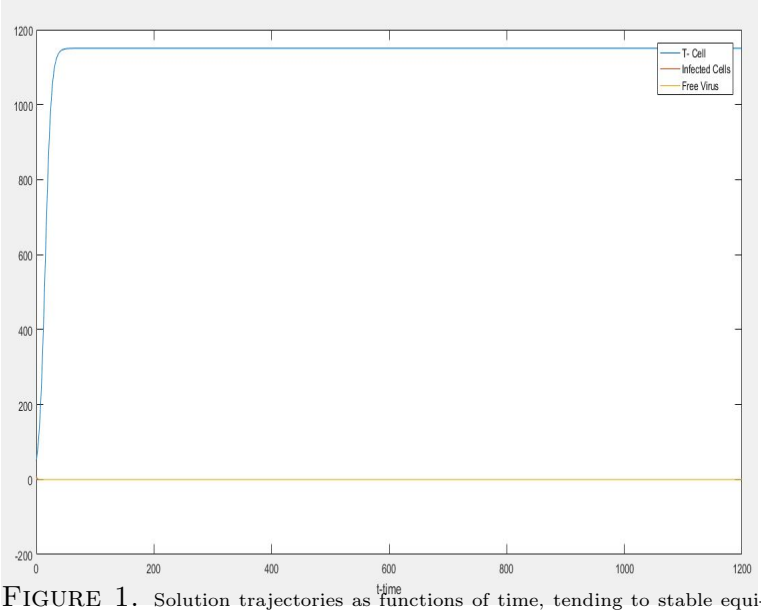

FIGURE 1. Solution trajectories as functions of time, tending to stable equilibrium $E_1(1166.8560, 0, 0)$ ($r = 0.2$, $\mathbf{R_0} = 0.6291 < 1$).

$$s = 2, \quad T_M = 1200, \quad d = 0.01, \quad b_1 = 0.11,$$
$$b_2 = 0.004, \quad a = 0.00005, \quad \delta = 0.8, \quad h = 0.15, \quad l = 2.4$$

and different values of r. Our numerical analysis shows that for $r = 0.3$, the endemic equilibrium $E_2(73.5672, 27.4768, 1.7173)$ is asymptotically stable (See Fig. 2). In this case, $\mathbf{R_0} = 15.8619 > 1$ and eigenvalues of the characteristic equation (3.5) are $\lambda_1 = -0.0026 + 0.3871i$, $\lambda_2 = -0.0026 - 0.3871i$ and $\lambda_3 = -2.9460$.

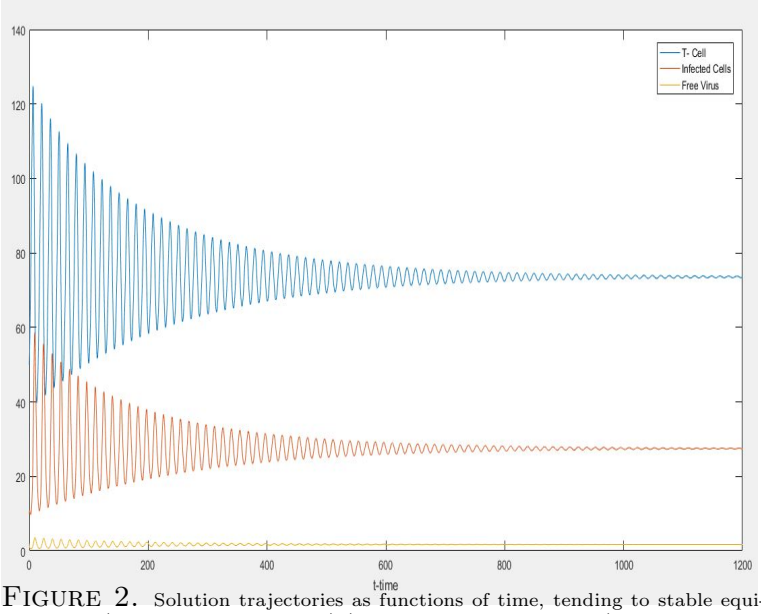

FIGURE 2. Solution trajectories as functions of time, tending to stable equilibrium $E_2(73.5672, 27.4768, 1.7173)$ ($r = 0.3$, $\mathbf{R_0} = 15.8619 > 1$).

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