8th International Conference on
Combinatorics, Cryptography, Computer Science and Computation
November. 15-16, 2023

GLOBAL DYNAMIC AND NUMERICAL SIMULATION OF AN HIV MODEL WITH TWO MODES OF TRANSMISSION AND CELLULAR AND HUMORAL IMMUNITY

Tohid Kasbi Gharahasanlou[1]
Imam Hossein University, Tehran, Iran

Abstract

In this paper, we incorporate immune systems containing Cytotoxic T lymphocyte and humoral immunity into a general human immunodeficiency viruses infection model, which also considers logistic growth for target cells and both modes of spread; cell-to-cell and cell-free represent by linear functions. We derive five threshold parameters which establish to study the existence of equilibria. By considering the characteristic equations, the local stability of disease-free and immune-free equilibria is investigated. Lyapunov functions and LaSalle's invariance are constructed to prove the global stability of all steady states. Global dynamics of the human immunodeficiency viruses model can be accurately expressed by threshold parameters. Furthermore, numerical simulations are confirmed the corresponding theoretical results.

Keywords: HIV-1 infection, Stability, Dynamical systems

AMS Mathematical Subject Classification [2010]: 34D23, 37B25

1 Introduction

Following the recent epidemics, the importance of studying such diseases is becoming increasingly clear. Many mathematical models were developed to study and analyze infectious diseases such as human immunodeficiency viruses (HIV), Human Papillomavirus (HPV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and new efforts have been made to model COVID-19. Modeling and analyzing the mathematical model of an infectious disease such as HIV in detail can also be applied to understand the behavior of other viruses, tumors and epidemic models ([10, 12, 31]). Also, by using fractional derivatives, the modeling of illnesses will be entered at a new level of researchs ([25]). After COVID-19, various aspects of the study of infectious diseases, including vaccine production, statistics, modeling and control have been considered ([1]). The HIV has been threatening human health for many years. Extensive studies have been conducted over the decades to understand the nature of this virus. The main targets of this virus in the human body are macrophages, dendritic cells and helper T cells ([3]). Two important factors in the fight against HIV infection are B and Cytotoxic T Lymphocyte (CTL) cells. The role of CTL cells is to attack infected cells and B cells to produce antibodies to attack HIV components ([6]). Considering both immunities in the

[1]speaker

mathematical model gives us a deeper insight into the functioning of the disease, which ultimately allows us to design treatment strategies and achieve the goal of producing an effective vaccine ([18]). Many authors have investigated the effect of CTL and humoral immunity alone or both on the dynamical behavior of the mathematical model of HIV([2, 7, 8, 9, 13, 14, 18, 19, 20, 28, 29, 24]).

Li and Wang in [15] proposed the following model where the target cells have a logistic term and incorporating two modes of transmission of HIV-1.

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - dT + rT\left(1 - \frac{T}{K}\right) - \beta_1 TV - \beta_2 TT^*,\\
\frac{dT^*}{dt} &= \beta_1 TV + \beta_2 TT^* - \delta T^*,\\
\frac{dV}{dt} &= N\delta T^* - cV,
\end{aligned} \tag{1}$$

where T, T^* and V are concentrates of $CD4^+$, infected cells and viruses, respectively. λ, d and K are the recruitment rate, the natural death rate and the maximum level of $CD4^+$ T cells, respectively. r, β_1 and β_2 are positive constants and the terms $\beta_1 TV$ and $\beta_2 TT^*$ represent the infection rates related to two modes of HIV-1 transmission. Viruses are assumed to be produced by each infected cell at rate N and disappear at rate c. The death rate of infected cells is shown by constant δ. They investigated the local and global asymptotic stability of the equilibria and the occurrence of Hopf bifurcation by identifying two bifurcation parameters.

In this paper, we incorporate cellular immunity and humoral immunity in the model of (1) and introduce the following model

$$\begin{aligned}
\dot{T} &= \lambda - dT + rT\left(1 - \frac{T}{T_M}\right) - \beta_1 TV - \beta_2 TI,\\
\dot{I} &= \beta_1 TV + \beta_2 TI - aI - pIZ,\\
\dot{V} &= kI - uV - qVW,\\
\dot{W} &= gVW - hW,\\
\dot{Z} &= cIZ - bZ,
\end{aligned} \tag{2}$$

where T, I, V, W, and Z represent the numbers of the uninfected host cells, the infected cells, the free virus, antibody response and the CTL response, respectively. λ, β_1, β_2, d and r have the same meaning as those in (1). B cells and CTL cells are activated at rate gVW and cIZ and died at rate hW and bZ, respectively. Virus are produced from infected cells at rate kI, died at rate uV and are disappearing by antibodies at rate qVW. Terms aI and pIZ describe the death rate of infected cells and destruction rate of infected cells by cellular immunity, respectively.

The main aim of this work is to generalize the model (1) that takes into account the role of both modes of immunity. To this end, in the next section, we present the basic details such as the positivity and boundedness of solutions and introduce the five threshold parameters related to our model and identify the existence conditions of the equilibria. The global stability of the equilibria is described in Section 3 and finally the mathematical and biological conclusions are given in Section 4.

2 Equilibria, reproduction number

From a biological point of view and due to the nature of the disease model, only non-negative solutions are acceptable for system (2) and hence, the initial conditions of system (2) are assumed as follows:

$$T(0) > 0, \quad I(0) > 0, \quad V(0) > 0, \quad W(0) > 0, \quad \textit{and} \quad Z(0) > 0. \tag{3}$$

The right hand side functions of (2) are continuous, smooth and Lipschitz on $[0, N]$, $N > 0$. Therefore, from Picard-Lindelöf theorem there is a unique solution to system (2) with the initial conditions (3).

Proposition 2.1. *All solutions of* (2) *with non-negative initial conditions exist for all* $t > 0$ *and remain bounded and non-negative.*

In the following, we consider the equilibria of (2) and introduce the basic reproduction number $\mathbf{R_0}$. In general (2) has five equilibrium points, $\mathbf{E_0}$, $\mathbf{E_1}$, $\mathbf{E_2}$, $\mathbf{E_3}$ and $\mathbf{E_4}$. In the absence of infection and immunity, there always exists an infection-free equilibrium $\mathbf{E_0} = (T_0, 0, 0, 0, 0)$ where

$$T_0 = \frac{T_M}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4r\lambda}{T_M}}\right].$$

The basic reproduction number of system (2) is

$$\mathbf{R_0} = \mathbf{R_{01}} + \mathbf{R_{02}},$$

where $\mathbf{R_{01}} = \dfrac{\beta_1 k T_0}{au}$ and $\mathbf{R_{02}} = \dfrac{\beta_2 T_0}{a}$, which are corresponded to the cell-free virus spread and cell-to-cell transfer, respectively. By attention to quantity of $\mathbf{R_0}$, it can be concluded that by adding the cell-to-cell term in system, $\mathbf{R_{02}}$ be added to $\mathbf{R_0}$ and this value show the effects of cell-to-cell transmission on basic reproduction number.

Regardless of immunity, there exists an immune-free equilibrium $\mathbf{E_1} = (T_1, I_1, V_1, 0, 0)$ provided that $\mathbf{R_0} > 1$, where

$$\begin{aligned}
T_1 &= \frac{au}{\beta_1 k + \beta_2 u} = \frac{T_0}{\mathbf{R_0}},\\
I_1 &= \frac{u}{k} V_1 = \frac{(\lambda + r)(\mathbf{R_0} - 1)}{\mathbf{R_0} a},\\
V_1 &= \frac{(\beta_1 k + \beta_2 u) k (\lambda + r) T_m - k(dT_M + r)au}{auT_M(\beta_1 k + \beta_2 u)} = \frac{k(\lambda + r)(\mathbf{R_0} - 1)}{\mathbf{R_0} au}.
\end{aligned}$$

Actually, $\mathbf{R_0} > 1$ means $(\beta_1 k + \beta_2 u) k (\lambda + r) T_m > k(dT_M + r)au$ which can make $V_1 > 0$ and it yields the existence of the immune-free equilibrium.

Assuming the potential development of immune responses, inequalities $cI_1 > b$ and $gV_1 > h$ must be established. Given these conditions, the CTL immune reproduction number $\mathbf{R_{CTL}}$ and the humoral immune reproductive number $\mathbf{R_{Hum}}$ can be defined as

$$\begin{aligned}
\mathbf{R_{CTL}} &= \frac{cI_1}{b} = \frac{c(\lambda + r)(\mathbf{R_0} - 1)}{ab\mathbf{R_0}},\\
\mathbf{R_{Hum}} &= \frac{gV_1}{h} = \frac{gk(\lambda + r)(\mathbf{R_0} - 1)}{hau\mathbf{R_0}}.
\end{aligned}$$

As a result, by developing the CTL response while $\mathbf{R_{CTL}} > 1$ and $d \geq r$, system (2) has the unique humoral immune-free equilibrium $\mathbf{E_2} = (T_2, I_2, V_2, 0, Z_2)$ where

$$T_2 \in [0, \bar{T}], \quad I_2 = \frac{b}{c}, \quad V_2 = \frac{kb}{cu}, \quad Z_2 = \frac{1}{pI_2}\left[\lambda - dT_2 + rT_2\left(1 - \frac{T_2}{T_M}\right) - aI_2\right].$$

Now, assuming that the only immune system that is stimulated is the humoral immune response, conditions $gV_2 > h$ and $cI_3 > b$ must be established. The humoral immune competitive reproduction number $\mathbf{R_{HumC}}$ and the CTL immune competitive reproduction number $\mathbf{R_{CTLC}}$ can be defined as

$$\mathbf{R_{HumC}} = \frac{gV_2}{h} = \frac{gkb}{hcu},$$
$$\mathbf{R_{CTLC}} = \frac{cI_3}{b} = \frac{csh}{bkg}.$$

CTL immune-free equilibrium $\mathbf{E_3} = (T_3, I_3, V_3, W_3, 0)$ occurs when the only active immunity in the body is humoral immunity. Therefore, if $\mathbf{R_{HumC}R_{CTLC}} > 1$, $\mathbf{R_{Hum}} > 1$, $a \leq \beta_2 \bar{T_3}$ and $d \geq r$, then there exists a unique CTL immune-free equilibrium $\mathbf{E_3}$.

The last equilibrium is related to the case that both humoral immune response and CTL immune response have been stimulated. In this case, W and Z are non-zero. Hence, from the last three equations of (2), it can be concluded that

$$I = \frac{b}{c}, \quad V = \frac{h}{g}, \quad W = \frac{kbg - cuh}{cqh} = \frac{u}{q}(\mathbf{R_{HumC}} - 1).$$

Hence, if $\mathbf{R_{CTLC}} > 1$, $\mathbf{R_{HumC}} > 1$ and $d \geq r$, then $h^{'}(T) > 0$ and there exists a unique positive equilibrium $\mathbf{E_4} = (T_4, I_4, V_4, W_4, Z_4)$ with

$$T_4 \in [0, \bar{T}], \quad I_4 = \frac{b}{c}, \quad V_4 = \frac{h}{g},$$
$$W_4 = \frac{kbg - cuh}{cqh} = \frac{u}{q}(\mathbf{R_{HumC}} - 1),$$
$$Z_4 = \frac{1}{pI_4}\left[\lambda - dT_4 + rT_4\left(1 - \frac{T_4}{T_M}\right) - aI_4\right].$$

3 Global properties

In this section, the global stability of all steady states will be established by constructing some suitable Lyapunov functions and LaSalle's invariance principle. It is clear that the stability of the equilibria depends on the sign of $\mathbf{R_0} - 1$ and conditions on the other reproduction numbers $\mathbf{R_{CTL}}$, $\mathbf{R_{Hum}}$, $\mathbf{R_{HumC}}$ and $\mathbf{R_{CTLC}}$. In this section, to prove the global stability of the equilibrium points, function $F : (0, \infty) \to [0, \infty)$ will be needed which is defined by

$$F(m) = m - 1 - \ln m.$$

Theorem 3.1. *The infection-free equilibrium* $\mathbf{E_0}$ *is globally asymptotically stable if* $\mathbf{R_0} \leq 1$.

Proof. Define a Lyapunov function $\mathbf{L_0}$ as

$$\mathbf{L_0}(T, I, V, W, Z) = T_0 F\left(\frac{T}{T_0}\right) + I + \frac{\beta_1 T_0}{u} V + \frac{\beta_1 q T_0}{gu} W + \frac{p}{c} Z.$$

Therefore,

$$\frac{d\mathbf{L_0}}{dt} = \left(1 - \frac{T_0}{T}\right)\dot{T} + \dot{I} + \frac{\beta_1 T_0}{u}\dot{V} + \frac{\beta_1 q T_0}{gu}\dot{W} + \frac{p}{c}\dot{Z}. \tag{4}$$

Applying the conditions of equilibrium $\mathbf{E_0}$, we have

$$\lambda = dT_0 - rT_0 + \frac{rT_0^2}{T_M}. \tag{5}$$

Hence,

$$\begin{aligned}\frac{d\mathbf{L_0}}{dt} \,|_{(1.3)}= &\left(1-\frac{T_0}{T}\right)\left(\lambda - dT + rT\left(1-\frac{T}{T_M}\right) - \beta_1 TV - \beta_2 TI\right)\\ &+ \beta_1 TV + \beta_2 TI - aI - pIZ + \frac{\beta_1 T_0}{u}\left(kI - uV - qVW\right)\\ &+ \frac{\beta_1 qT_0}{gu}\left(gVW - hW\right) + \frac{p}{c}\left(cIZ - bZ\right)\\ = &-\left[d - r + r\left(\frac{T+T_0}{T_M}\right)\right]\frac{(T-T_0)^2}{T} - \frac{\beta_1 qhT_0}{gu}W - \frac{pb}{c}Z + aI(\mathbf{R_0}-1).\end{aligned} \tag{6}$$

Since $\mathbf{R_0} \leq 1$, by (4)-(6), it can be concluded that $\frac{d\mathbf{L_0}}{dt} \leq 0$ for all $T, I, V, W, Z > 0$. Hence, the infection-free equilibrium $\mathbf{E_0}$ is stable. On the other hand, $\frac{d\mathbf{L_0}}{dt} = 0$ if and only if $T = T_0$, $I = 0$, $W = 0$ and $Z = 0$. By attention to equilibrium conditions and using the third equation of (2), it can be concluded that if $I = W = 0$, then $V = 0$. Let Ω_0 be the largest invariant set in

$$\Psi_0 = \{(T, I, V, W, Z) \mid \dot{\mathbf{L_0}} = 0\} = \{\mathbf{E_0}\}.$$

We have that $\Omega_0 = \{\mathbf{E_0}\}$. The global asymptotic stability of $\mathbf{E_0}$ follows from LaSalle's invariance principle (Theorem 7.2 in [21]). □

By the similar arguments, we can prove the following theorems.

Theorem 3.2. *The immune-free equilibrium* $\mathbf{E_1}$ *is globally asymptotically stable if* $\mathbf{R_0} > 1$, $\mathbf{R_{Hum}} \leq 1$ *and* $\mathbf{R_{CTL}} \leq 1$.

Proof. Define a Lyapunov function $\mathbf{L_1}$ as

$$\mathbf{L_1}(T, I, V, W, Z) = T_1 F\left(\frac{T}{T_1}\right) + I_1 F\left(\frac{I}{I_1}\right) + \frac{\beta_1 T_1 V_1}{u} F\left(\frac{V}{V_1}\right) + \frac{\beta_1 qT_1}{gu}W + \frac{p}{c}Z.$$

Therefore,

$$\frac{d\mathbf{L_1}}{dt} = \left(1-\frac{T_1}{T}\right)\dot{T} + \left(1-\frac{I_1}{I}\right)\dot{I} + \frac{\beta_1 T_1}{u}\left(1-\frac{V_1}{V}\right)\dot{V} + \frac{\beta_1 qT_1}{gu}\dot{W} + \frac{p}{c}\dot{Z}. \tag{7}$$

Using the conditions of equilibrium $\mathbf{E_1}$, we have

$$\begin{aligned}&\lambda = dT_1 - r + \frac{rT_1}{T_M} + \beta_1 T_1 V_1 + \beta_2 T_1 I_1,\\ &\beta_1 T_1 V_1 + \beta_2 T_1 I_1 = aI_1,\\ &kI_1 = uV_1.\end{aligned} \tag{8}$$

Also, we need the equalities

$$\begin{aligned}&\ln(1) = \ln\left(\frac{TIV_1}{T_1 I_1 V}\right) + \ln\left(\frac{I_1 V}{IV_1}\right) + \ln\left(\frac{T_1}{T}\right),\\ &\ln(1) = \ln\left(\frac{T_1}{T}\right) + \ln\left(\frac{T}{T_1}\right).\end{aligned} \tag{9}$$

Hence,

$$\begin{aligned}\frac{d\mathbf{L_1}}{dt}\mid_{(1.3)}=&\left(1-\frac{T_1}{T}\right)\left(\lambda-dT+rT\left(1-\frac{T}{T_M}\right)-\beta_1TV-\beta_2TI\right)\\&+\left(1-\frac{I_1}{I}\right)\left(\beta_1TV+\beta_2TI-aI-pIZ\right)+\frac{\beta_1T_1}{u}\left(1-\frac{V_1}{V}\right)\left(kI-uV-qVW\right)\\&+\frac{\beta_1qT_1}{gu}\left(gVW-hW\right)+\frac{p}{c}\left(cIZ-bZ\right)\\=&-\left[d-r+r\left(\frac{T+T_1}{T_M}\right)\right]\frac{(T-T_1)^2}{T}-(\beta_1T_1V_1+\beta_2T_1I_1)F\left(\frac{T_1}{T}\right)\\&-\beta_1T_1V_1F\left(\frac{TVI_1}{T_1V_1I}\right)-\beta_2T_1I_1F\left(\frac{T}{T_1}\right)-\beta_1T_1V_1F\left(\frac{IV_1}{I_1V}\right)\\&+\frac{\beta_1qT_1}{u}\left(V_1-\frac{h}{g}\right)W+p\left(I_1-\frac{b}{c}\right)Z.\\=&-\left[d-r+r\left(\frac{T+T_1}{T_M}\right)\right]\frac{(T-T_1)^2}{T}+\beta_1T_1V_1\left[3-\frac{T_1}{T}-\frac{IV_1}{I_1V}-\frac{TVI_1}{T_1V_1I}\right]\\&+\beta_2T_1I_1\left[2-\frac{T}{T_1}-\frac{T_1}{T}\right]+\frac{\beta_1qhT_1}{gu}(\mathbf{R_{Hum}}-1)W+\frac{pb}{c}(\mathbf{R_{CTL}}-1)Z.\end{aligned}\tag{10}$$

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

$$\begin{aligned}&3-\frac{T_1}{T}-\frac{IV_1}{I_1V}-\frac{TVI_1}{T_1V_1I}\le 0,\\&2-\frac{T}{T_1}-\frac{T_1}{T}\le 0.\end{aligned}\tag{11}$$

Since $\mathbf{R_{Hum}}\le 1$, $\mathbf{R_{CTL}}\le 1$ and $d\ge r$, by (7)-(11), it can be concluded that $\frac{d\mathbf{L_1}}{dt}\le 0$ for all $T,I,V,W,Z>0$. Hence, the immune-free equilibrium $\mathbf{E_1}$ is stable. On the other hand, $\frac{d\mathbf{L_1}}{dt}=0$ if and only if $T=T_1$, $I=I_1$, $V=V_1$, $W=0$ and $Z=0$. Let Ω_1 be the largest invariant set in

$$\Psi_1=\{(T,I,V,W,Z)\mid \dot{\mathbf{L_1}}=0\}=\{\mathbf{E_1}\}.$$

We have that $\Omega_1=\{\mathbf{E_1}\}$. The global asymptotic stability of $\mathbf{E_1}$ follows from LaSalle's invariance principle (Theorem 7.2 in [21]). □

By the similar arguments, we can prove the following theorems.

Theorem 3.3. *The humoral immune-free equilibrium* $\mathbf{E_2}$ *exists and is globally asymptotically stable if* $\mathbf{R_{CTL}}>1$, $\mathbf{R_{HumC}}\le 1$ *and* $\mathbf{R_{CTLC}}>1$.

Theorem 3.4. *The CTL immune-free equilibrium* $\mathbf{E_3}$ *exists and is globally asymptotically stable if* $\mathbf{R_{Hum}}>1$, $\mathbf{R_{CTLC}}\le 1$ *and* $\mathbf{R_{HumC}}>\frac{1}{\mathbf{R_{CTLC}}}$.

Theorem 3.5. *The endemic equilibrium* $\mathbf{E_4}$ *exists and is globally asymptotically stable if* $\mathbf{R_{CTLC}}>1$ *and* $\mathbf{R_{HumC}}>1$.

4 Examples and Numerical Simulations

In this section, to illustrate the theoretical results, applying Python with Runge–Kutta method, some numerical examples will be presented. Hereafter, we consider a set of parameters

$$\lambda = 10, \quad r = 0.018, \quad d = 0.02, \quad T_M = 1200, \quad a = 0.8,$$
$$p = 0.9, \quad k = 10, \quad u = 3, \quad q = 0.01, \quad h = 2, \quad b = 0.755$$

and different values of β_1, β_2, g and c. For the numerical study of the stability of the infection-free equilibrium $\mathbf{E_0}$, we consider the parameter values from Table 2 and $\beta_1 = 0.00003$, $\beta_2 = 0.00002$, $g = 0.03$ and $c = 0.04$. The basic reproduction number takes the value $\mathbf{R_0} = 0.8215 < 1$. In this case, the solutions of the system converge to infection-free equilibrium $\mathbf{E_0} = (752.5470, 0, 0, 0, 0)$. The stability of the first equilibrium $\mathbf{E_0}$ can be seen in Figure 1.

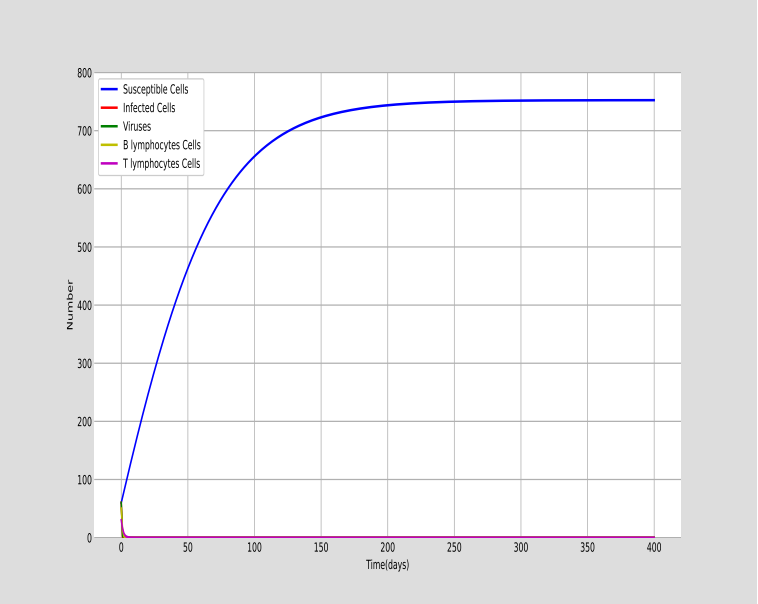

Figure 1: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E_0}$

The immune-free equilibrium $\mathbf{E_1}$ is asymptotically stable with the values of Table 2 and for the parameter values $\beta_1 = 0.003$, $\beta_2 = 0.002$, $g = 0.03$ and $c = 0.04$. It can be seen that the basic reproduction number equals to $\mathbf{R_0} = 11.2882$ and the immune-free equilibrium is given by $\mathbf{E_1} = (T_1, I_1, V_1, 0, 0) = (66.6667, 12.2523, 40.8333, 0, 0)$. In this case, the CTL immune reproduction number $\mathbf{R_{CTL}}$ and humoral immune reproductive number $\mathbf{R_{Hum}}$ are calculated as 0.4868 and 0.8166, respectively which are less than one. Also according to Theorem 3.2, the equilibrium point is expected to be globally asymptotically stable, which is shown in Figure 2.

By Theorem 3.3, the humoral immune-free equilibrium $\mathbf{E_2} = (T_2, I_2, V_2, 0, Z_2)$ is globally asymptotically stable in the absence of humoral immunity with the values of Table 2 and the parameter values $\beta_1 = 0.003$, $\beta_2 = 0.002$, $g = 0.03$ and $c = 0.15$ which is depicted in Figure 3. In this case, the reproduction number is greater than one and equals to $\mathbf{R_0} = 11.2882$ and all solutions converge to $\mathbf{E_2} = (T_2, I_2, V_2, 0, Z_2) = (154.5180, 5.0333, 16.7778, 0, 1.1713)$. Subsequently, it can be concluded that $\mathbf{R_{CTL}} = 2.4342 > 1$, $\mathbf{R_{CTLC}} = 2.4216 > 1$, $\mathbf{R_{Hum}} = 0.8166 < 1$ and $\mathbf{R_{HumC}} = 0.3356 < 1$.

In the study of the stability of CTL immune-free equilibrium $\mathbf{E_3}$, considering the values of Table 2

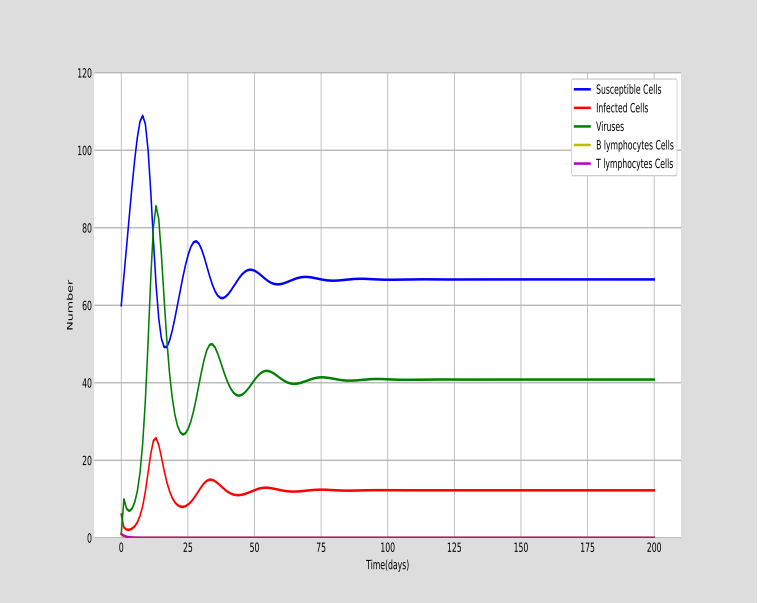

Figure 2: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E_1}$.

and taking $\beta_1 = 0.003$, $\beta_2 = 0.002$, $g = 0.14$ and $c = 0.04$, it can be leads $\mathbf{E_3} = (T_3, I_3, V_3, W_3, 0) = (141.8015, 11.7685, 14.2857, 523.7934, 0)$ and $\mathbf{R_0} = 11.2882$. According to the relations intended for the reproduction numbers in this case, it can be concluded that $\mathbf{R_{CTL}} = 0.9073 < 1$, $\mathbf{R_{CTLC}} = 0.8729 < 1$, $\mathbf{R_{Hum}} = 2.8583 > 1$ and $\mathbf{R_{HumC}} = 1.1744 > 1$. Also, we have $\mathbf{R_{HumC}} > \frac{1}{\mathbf{R_{CTLC}}} = \frac{1}{0.8729} = 1.1456$. Identical to Theorem 3.4, we expect the CTL immune-free equilibrium $\mathbf{E_3}$ to be globally stable, as shown in Figure 4.

Finally, Figure 5 represents the case that both immunities are active in the body. In this case, by using the values in Table 2 and assuming $\beta_1 = 0.003$, $\beta_2 = 0.002$, $g = 0.125$ and $c = 0.15$, the positive equilibrium and the basic reproduction number are $\mathbf{E_4} = (160.0822, 5.0333, 16, 14.5833, 1.1630)$ and $\mathbf{R_0} = 11.2882$, respectively. Alternatively, with the help of related relations, it can be calculated that $\mathbf{R_{CTL}} = 2.4303 > 1$, $\mathbf{R_{CTLC}} = 2.3381 > 1$, $\mathbf{R_{Hum}} = 2.5521 > 1$ and $\mathbf{R_{HumC}} = 1.0486 > 1$. Hence, in this case all the solutions tend to positive equilibrium $\mathbf{E_4} = (160.0822, 5.0333, 16, 14.5833, 1.1630)$. .

References

[1] Abdel-Aty, A., Khater, M.M.A., Dutta, H., Bouslimi, J. & Omri, M. [2020] "Computational solutions of the HIV-1 infection of $CD4^+$ T-cells fractional mathematical model that causes acquired immunodeficiency syndrome (AIDS) with the effect of antiviral drug therapy," *Chaos, Solitons and Fractals* **139**, 110092.

[2] Alshaikh, M. A., AlShamrani, N. H. & Elaiw, A. M. [2021] "Stability of HIV/HTLV co-infection model with effective HIV-specific antibody immune response," *Results in Physics* **27**, 104448.

[3] Cunningham, AL., Donaghy, H., Harman, AN., Kim, M. & Turville, S.G. [2014] "Manipulation of dendritic cell function by viruses," *Current Opinion in Microbiology* **13**(4), pp. 524–529.

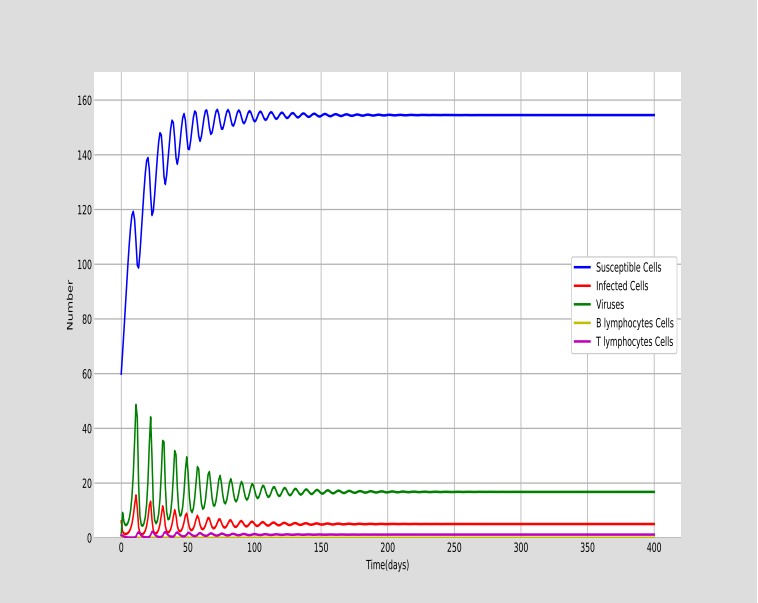

Figure 3: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E_2}$

[4] Diekmann, O., Heesterbeek, J.A.P. & Metz, J.A.J. [1990] "On the definition and the computation of the basic reproduction ratio $\mathbf{R_0}$ in models for infectious diseases in heterogeneous populations," *Journal of Mathematical Biology* **28**(4), pp.365–382.

[5] Elaiw, A.M. [2015] "Global stability analysis of humoral immunity virus dynamics model including latently infected cells," *Journal of Biological Dynamics* **9**(1), pp. 215-228.

[6] Elaiw, A. M., Raezah, A. A. & Alofi, A. S. [2016] "Effect of humoral immunity on HIV-1 dynamics with virus-to-target and infected-to-target infections," *AIP Advances* **6**(8), pp. 1-16.

[7] Elaiw, A. M., AlShamrani, N. H. & Hobiny, A. D. [2020] "Mathematical modeling of HIV/HTLV co-infection with CTL-mediated immunity," *AIMS Mathematics* **6**(2), pp. 1634–1676.

[8] Elaiw, A. M. & Elnaharyb, E. Kh. [2018] "Stability analysis of general humoral immunity HIV dynamics models with discrete delays and HAART," *J. Math. Computer Sci.* **18**, pp. 430-452.

[9] Elaiw, A. M., AlShamrani, N. H., Hobiny, A. D. & Abbas, I. A. [2020] "Global stability of an adaptive immunity HIV dynamics model with silent and active cellto- cell transmissions," *AIP Advances* **10**(8), pp. 1-19.

[10] Elkaranshawy, H. A., Ezzat, H. M. & Ibrahim, N. N. [2021] "Lyapunov function and global asymptotic stability for a new multiscale viral dynamics model incorporating the immune system response: Implemented upon HCV," *International Journal of Bifurcation and Chaos* **31**(9), pp. 1-26.

[11] Gharahasanlou, T. K., Roomi, V. & Hemmatzadeh, Z. [2022] "Global stability analysis of viral infection model with logistic growth rate, general incidence function and cellular immunity," *Mathematics and Computers in Simulation* **194**, pp. 64-79.

[12] GOKGOZ, N. & ÖKTEM, H. [2021] "Modeling of Tumor-Immune System Interaction with Stochastic Hybrid Systems with Memory: A Piecewise Linear Approach," *Advances in the Theory of Nonlinear Analysis and its Application* **5**(1), pp. 25-38.

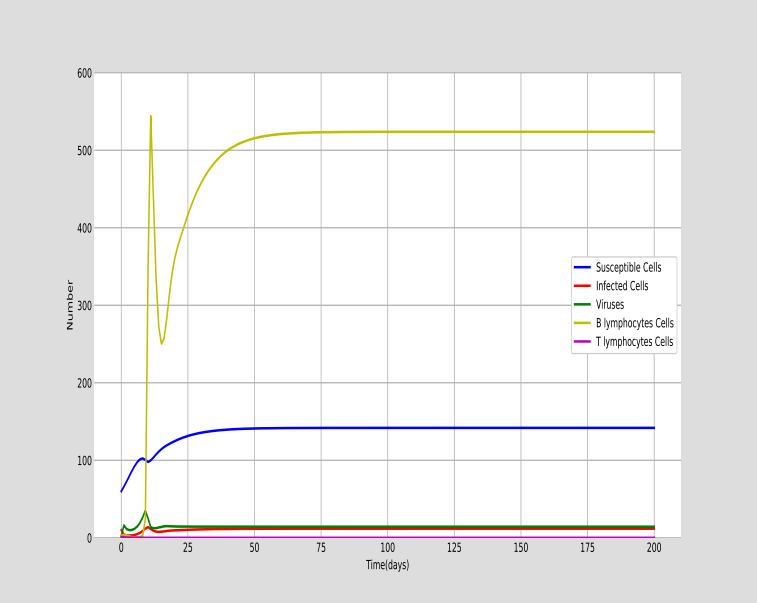

Figure 4: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E_3}$

[13] Hattaf, Kh. & Yousfi, N. [2018] "Modeling the Adaptive Immunity and Both Modes of Transmission in HIV Infection," *Computation* **6**(2), 37.

[14] Jaouad, D & Allali, K. [2019] "Mathematical Analysis and Clinical Implications of an HIV Model with Adaptive Immunity," *Computational and Mathematical Methods in Medicine* **2019**, pp. 1-19.

[15] Li, F. & Wang, J. [2015] "Analysis of an HIV infection model with logistic target cell growth and cell-to-cell transmission," *Chaos, Solitons and Fractals* **81**, pp. 136-145.

[16] Lai, X. & Zou, X. [2015] "Modeling cell-to-cell spread of HIV-1 with logistic target cell growth," *Journal of Mathematical Analysis and Applications* **426**, pp. 563-584.

[17] Liao, M., Liu, Y. & Meyad, A. M. [2021] "Stability analysis of general humoral immunity HIV dynamics models with discrete delays and HAART," *J. Biol. Dynam.*, DOI: 10.1080/17513758.2021.1895334

[18] Lin, J., Xu, R. & Tian, X.[2017] "Threshold dynamics of an HIV-1 virus model with both virus-to-cell and cell-to-cell transmissions, intracellular delay, and humoral immunity," *Applied Mathematics and Computation* **315**, pp. 516–530.

[19] Luo, J. & Zhao, Y. [2019] "Dynamic Behavioral Analysis of an HIV Model Incorporating Immune Responses," *International Journal of Bifurcation and Chaos* **29**(9), pp. 1-22.

[20] Mann Manyombe, M. L., Mbang, J. & Chendjou, G., [2021] "Stability and Hopf bifurcation of a CTL-inclusive HIV-1 infection model with both viral and cellular infections, and three delays," *Chaos, Solitons and Fractals* **144**, 110695.

[21] Martcheva M. [2015] *An introduction to mathematical epidemiology*, (Texts in Applied Mathematics, Springer).

[22] Mercer P. A. [2014] *More Calculus of a Single Variable*, (Texts in Applied Mathematics, Springer).

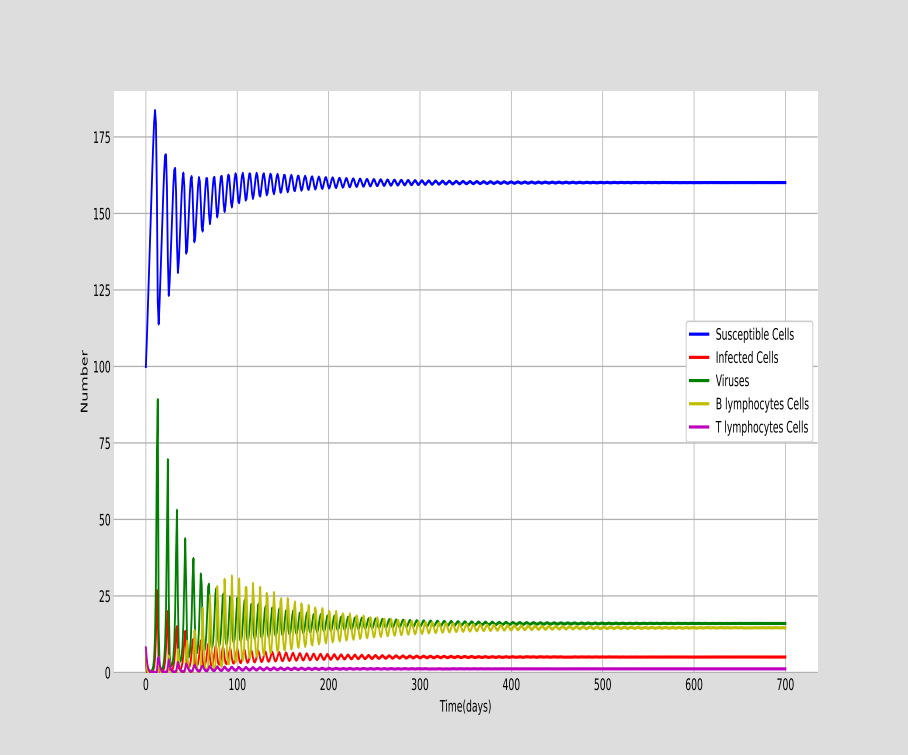

Figure 5: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E_4}$

[23] Nagumo M.[1942] *Uber die Lage der Integralkurven gewohnlicher Differential gleichungen, Proc. Phys. Math. Sot. Japan.* **24**, pp. 551-559.

[24] Roomi, V., Afshari, H. & Gharahasanlou, T. K. [2023] "Global Stability of an HIV Dynamical Model with Crowley-Martin Functional Response," *Letters in Nonlinear Analysis and its Applications* **1**(1), pp. 39-46.

[25] Roomi, V., Afshari, H. & Nosrati, M. [2023] "Existence and uniqueness for a fractional differential equation involving Atangana-Baleanu derivative by using a new contraction ," *Letters in Nonlinear Analysis and its Applications* **1**(2), pp. 52-56.

[26] Roomi, V., Gharahasanlou, T. K. & Hemmatzadeh, Z. [2022] "Stability Analysis, Hopf Bifurcation and Drug Therapy Control of an HIV Viral Infection Model with Logistic Growth Rate and Cell-to-Cell and Cell-Free Transmissions," *International Journal of Bifurcation and Chaos* **32**(10), pp. 1-15.

[27] Su, Y., Sun D. & Zhao, L. [2014] "Global analysis of a humoral and cellular immunity virus dynamics model with the Beddington–DeAngelis incidence rate," *Math. Meth. Appl. Sci.*, 1-20 (2014). DOI:10.1002/mma.3274

[28] Sun, C., Li, L. & Jia, J. [2020] "Hopf bifurcation of an HIV-1 virus model with two delays and logistic growth," *Math. Model. Nat. Phenom.* **15**, pp. 1-20.

[29] Tiab, X. & Xu, R. [2014] "Global stability and Hopf bifurcation of an HIV-1 infection model with saturation incidence and delayed CTL immune response," *Applied Mathematics and Computation* **237**, pp. 146-154.

[30] Van den Driessche, P. & Watmough, J. [2002] "On the definition and the computation of the basic reproduction ratio $\mathbf{R_0}$ in models for infectious diseases in heterogeneous populations," *Mathematical Biosciences* **180**, pp. 29-48.

[31] Wang, L. & Wu, X. [2018] "Stability and Hopf Bifurcation for an SEIR Epidemic Model with Delay," *Advances in the Theory of Nonlinear Analysis and its Application* **2**(3), pp. 113-127.

[32] Wodarz, D. [2003] "Hepatitis C virus dynamics and pathology: the role of CTL and antibody responses," *Journal of General Virology* **84**, pp. 1743-1750.

[33] Yan, Y. & Wang, W. [2012] "Global stability of a five-dimensional model with immune responses and delay," *Discrete and Continuous Dynamical Systems - Series B* **17**(1), pp. 401-416.

[34] Yu, P. [2005] "Closed-form conditions of bifurcation points for general differential equations," *Internat. J. Bifur. Chaos Appl. Sci. Engrg.* **15**(4), pp. 1467–1483.

[35] Yang, Y., Zou, L. & Ruanet, S. [2015] "Global dynamics of a delayed within-host viral infection model with both virus-to-cell and cell-to-cell transmissions," *Mathematical Biosciences* **270**, pp.183-191.

[36] Zhou, X., Shi, X., Zhang, Z. & Song, X. [2009] "Dynamical behavior of a virus dynamics model with CTL immune response," *Applied Mathematics and Computation* **213**(2), pp. 329-347.