A Mathematical Model for HIV Apheresis

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Abstract**—**In this paper, the continuous filtering and impulsive filtering policies are incorporated in a mathematical model for the interaction between HIV particles and CD4+T cells. In the case in which a continuous virus filtering is used, we derive sufficient conditions on the system parameters which guarantee that the equilibrium points of the system are either locally asymptotically stable or globally asymptotically stable. In the case in which an impulsive virus filtering is used, we investigate the dynamical behaviors of HIV and CD4+T cell in response to the impulsive treatment and point out that there exists a viral free solution which is globally asymptotically stable. Our results indicate that the period and apheresis rate effect the eradication of the virus. Numerical simulations are carried out to confirm our theoretical results.

Keywords**—**HIV-1 dynamics, CTLs immune response, impulsive filtering model, stability.

I. Introduction

In recent years, the biological meanings, dynamical properties of HIV-1 infection models with or without time delays and general theories on such dynamical systems have been studied by many authors [1]-[12]. Viruses are intracellular parasites that depend on the host cell to survive and duplicate. The host cell can be damaged by the virus or by antibodies, cytokines, natural killer cells, and T cells which are essential components of a normal immune response to the virus. The effective antiviral immune response depends on the amount of virus present, the tissues infected and the chronicity of the infection [13].

To explore the relation among antiviral immune response which includes the appearance of HIV-specific Cytotoxic T lymphocytes (CTLs) and antibodies, virus load and virus diversity, many models include an intracellular delay [4]-[12] which is introduced to account for the time between infection of a CD4+T-cell and production of new virus particles. Furthermore, by a similar theoretical analysis on population dynamical systems and epidemic models [14]-[16], it is shown that time delays play an important role in the dynamical properties of the HIV-1 infection models. The Holling type II function [14] is one of the response functions which is useful in the dynamical systems and epidemic models. It is characterized by a decelerating intake rate which follows from the assumption that the consumer is limited by its capacity to process food. This functional response is often modeled by a rectangular hyperbola, for instance which assumes that processing of food and searching for food are mutually exclusive behaviors.

The filtering policy or apheresis is a medical technology in which the blood of a donor or patient is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation. Apheresis has for some time been used effectively in the treatment of hepatitis C infection [17]-[18]. Apheresis is an extracorporreal blood purification technique designed for the removal of HIV from the plasma of patients.

In 2007, a model developed by T. Dumrongpokaphan et al. [7] was adapted to consider the interaction between HIV infection, CTLs cells and CD4+T cells when the virus particles are filtered. In other words, we modeled the continuous filtering policy as an effect of drug therapy [1], [4] in the same manner as the continuous harvesting in predator-prey models [19]-[22].

Apheresis in a medical term which can be refer to the filtering action to control virus infection. In this work, we have modified the model proposed by T. Dumrongpokaphan et al. [7] to consider the interactions of HIV and CD4+T cells. Motivated by recent works [21] and [23], where impulsive harvesting policy was the effective method in the predator-prey system, we consider continuous filtering and impulsive filtering treatment on an HIV patient by studying two model systems.

The paper is organized as follows. In the next section, the main biological assumptions are formulated by using the qualitative theory of ordinary differential equations. In Section III, we investigate the behavior of the system which models the process of continuous virus filtering. In Section IV, we construct an impulsive system which models the process of periodic filtering at fixed moments. By using comparison techniques, we investigate the global asymptotic stability of the viral free periodic solution and the conditions for the persistence of the system. Finally, numerical results and a brief discussion are provided.

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II. Model Formulation

We denote the population densities of CD4$^+$ T cells, free HIV, and CTLs cells at time t, by $x(t), v(t)$, and $c(t)$, respectively. The effect of the delay between the time a CD4$^+$ T cell is infected and the time it starts producing virus is incorporated into our model.

We make use of the fraction $\dfrac{\beta x(t)v(t)}{1+ax(t)}$ as the virus functional response [14], [19], and $e^{-\mu_1\tau}$ as the term to take into account the probability of cell production having survived from the time $t-\tau$ to t. Then, the fraction $\beta e^{-\mu_1\tau}\dfrac{x(t-\tau)v(t-\tau)}{1+ax(t-\tau)}$ is used to represent the production rate of the virus particles in our model. These assumptions lead us to the following system of differential equations :

$$\begin{aligned} x'(t) &= A-\mu_1 x(t)-\beta\frac{x(t)v(t)}{1+ax(t)}, \\ v'(t) &= \beta e^{-\mu_1\tau}\frac{x(t-\tau)v(t-\tau)}{1+ax(t-\tau)} \\ &\quad -dv(t)c(t)-\mu_2 v(t), \\ c'(t) &= rv(t)c(t)-\mu_3 c(t), \end{aligned} \tag{1}$$

where, the initial conditions $x(\theta)=\phi_1(\theta), v(\theta)=\phi_2(\theta), c(\theta)=\phi_3(\theta), \phi_i(\theta)\geq 0$ are continuous on $[-\tau,0)$, $\phi_i(0)>0, i=1,2,3,$ while A denotes the production rate of CD4$^+$ T cells, β is the rate constant characterizing infection of cells, d is the death rate constant of virus due to CTLs, r is the rate constant of stimulation of CTLs by infective virus, a is the saturation constant and μ_1,μ_2 and μ_3 denote the natural death rate constants of CD4$^+$ T cell, free virus and CTLs, respectively.

We investigate the behavior of the system which models the process of continuous virus filtering as a medical treatment by using the following system

$$\begin{aligned} x'(t) &= A-\mu_1 x(t)-\beta\frac{x(t)v(t)}{1+ax(t)}, \\ v'(t) &= \beta e^{-\mu_1\tau}\frac{x(t-\tau)v(t-\tau)}{1+ax(t-\tau)} \\ &\quad -dv(t)c(t)-\mu_2 v(t)-\eta v(t), \\ c'(t) &= rv(t)c(t)-\mu_3 c(t), \end{aligned} \tag{2}$$

with initial conditions

$(x(t),v(t),c(t))=(\varphi_1(t),\varphi_2(t),\varphi_3(t))\in C_3^+$,
$\varphi_i(0)>0, i=1,2,3,$

where $C_3^+=C([-\tau,0],R_3^+)$. The parameter η represents the virus filtering coefficient.

For the discrete dynamics due to the impulsive virus filtering as in the case of apheresis treatment, we construct an impulsive system which models the process of periodic filtering at fixed moments as follows.

$$\left.\begin{aligned} x'(t) &= A-\mu_1 x(t)-\beta\frac{x(t)v(t)}{1+ax(t)}, \\ v'(t) &= \beta e^{-\mu_1\tau}\frac{x(t-\tau)v(t-\tau)}{1+ax(t-\tau)} \\ &\quad -dv(t)c(t)-\mu_2 v(t), \\ c'(t) &= rv(t)c(t)-\mu_3 c(t), \end{aligned}\right\} t\neq nT$$
$$\left.\begin{aligned} x(t^+) &= x(t), \\ v(t^+) &= (1-\mu)v(t), \\ c(t^+) &= c(t), \end{aligned}\right\} t=nT, n=1,2,... \tag{3}$$

with initial conditions

$$\begin{aligned} &(x(t),v(t),c(t))=(\varphi_1(t),\varphi_2(t),\varphi_3(t))\in C_3^+, \\ &\varphi_i(0)>0, i=1,2,3 \end{aligned} \tag{4}$$

where $C_3^+=C([-\tau,0],R_3^+)$ and $x(t^+), v(t^+)$, and $c(t^+)$ are the right limits of $x(t), v(t)$ and $c(t)$ at time t, respectively. Here n is the set of all non-negative integers. T is the filtering period and $\mu(0<\mu<1)$ represents the filtering effort.

III. Continuous Virus Filtering

In this section, we discuss the existence of three equilibria and prove that all solutions are positive and bounded. Clearly, (2) always has a viral free equilibrium $E_0(A/\mu_1,0,0)$.

Let $\mu_4=\mu_2+\eta$, $z=\dfrac{\beta\mu_3}{r}+\mu_1-aA$, and

$$\mathfrak{R}_0=\frac{A\beta e^{-\mu_1\tau}}{\mu_4(\mu_1+aA)}$$

Here, $\mathfrak{R}_0$ is called the basic reproduction ratio of the model (2). If $\mathfrak{R}_0>1$ and $c=0$ then (2) has an infected equilibrium $E_1(\bar{x}_1,\bar{v}_1,0)$, where $\bar{x}_1=\dfrac{\mu_4}{\beta e^{-\mu_1\tau}-a\mu_4}$ and $\bar{v}_1=\dfrac{e^{-\mu_1\tau}}{\mu_4}(A-\mu_1\bar{x}_1)$.

If $\mathfrak{R}_0>1, c\neq 0$, and $-z+\sqrt{z^2+4aA\mu_1}>\dfrac{2a\mu_1\mu_4}{\beta e^{-\mu_1\tau}-a\mu_4}$ are satisfied, then (2) also has another infected equilibrium $E_2(\bar{x}_2,\bar{v}_2,\bar{c}_2)$, where
$\bar{x}_2=(-z+\sqrt{z^2+4aA\mu_1})/2a\mu_1$, $\bar{v}_2=\dfrac{\mu_3}{r}$, and $\bar{c}_2=(\beta e^{-\mu_1\tau}\frac{\bar{x}_2}{1+a\bar{x}_2}-\mu_4)/d$.

By the continuity of the initial functions the following can be easily shown.

Proposition 1. *Let the initial conditions $x(\theta),v(\theta),c(\theta)\geq 0$ be continuous on $[-\tau,0)$ and $x(0),v(0),c(0)>0$. Then, the solution of (2) satisfies $x(t),v(t),c(t)>0$ for all $t>0$.*

Next, we will carry out a stability analysis, in which the following lemma will be used.

Lemma 2. *[19] Consider the following equation:*

$$\frac{du}{dt}=au(t-\tau)-bu(t),$$

where $a,b,\tau>0$ and $u(t)>0$ for $t\in[-\tau,0]$.

(i) *If* $a<b$, *then* $\lim_{t\to\infty}u(t)=0.$

(ii) *If* $a>b$, *then* $\lim_{t\to\infty}u(t)=+\infty.$

Theorem 3. *If* $\Re_0 < 1$ *then, the viral free equilibrium* $E_0(A/\mu_1, 0, 0)$ *is globally asymptotically stable for any* $\tau \geq 0$.

Proof: See [12]. □

Letting
$$\Re_1 = \frac{Are^{-\mu_1\tau}(aA+\mu_1)(\Re_0 - 1)}{\mu_3\mu_4(aA(\Re_0-1)+\mu_1\Re_0)}$$
we can prove the following result.

Theorem 4. *If* $\Re_0 > 1$ *and* $\Re_1 < 1$, *then the infected equilibrium* $E_1(\bar{x}_1, \bar{v}_1, 0)$, *where* $\bar{x}_1 = \dfrac{\mu_4}{\beta e^{-\mu_1\tau} - a\mu_4}$ *and* $\bar{v}_1 = \dfrac{e^{-\mu_1\tau}}{\mu_4}(A - \mu_1\bar{x}_1)$ *is locally asymptotically stable for* $\tau \geq 0$.

Proof: See [12].

Next, we will state the conditions under which the system (2) possesses a locally asymptotically stable E_2.

Theorem 5. *If* $\Re_0 > 1$ *and*
$$-z + \sqrt{z^2 + 4aA\mu_1} > \frac{2a\mu_1\mu_4}{\beta e^{-\mu_1\tau} - a\mu_4},$$
the infected equilibrium $E_2(\bar{x}_2, \bar{v}_2, \bar{c}_2)$, *where* $\bar{x}_2 = (-z + \sqrt{z^2+4aA\mu_1})/2a\mu_1$, $\bar{v}_2 = \dfrac{\mu_3}{r}$, *and* $\bar{c}_2 = (\beta e^{-\mu_1\tau}\frac{\bar{x}_2}{1+a\bar{x}_2} - \mu_4)/d$ *is locally asymptotically stable for* $\tau = 0$.

Proof: The associated characteristic equation of (2) at E_2 is
$$\begin{aligned}\lambda^3 + (B_1+B_2)\lambda^2 + (B_1B_2+B_3)\lambda + B_1B_3 \\ -(\lambda^2+\mu_1\lambda)B_2e^{-\lambda\tau} = 0,\end{aligned} \tag{5}$$
where $B_1 = \mu_1 + \dfrac{\beta\bar{v}_2}{(1+a\bar{x}_2)^2}, B_2 = \dfrac{\beta e^{-\mu_1\tau}\bar{x}_2}{1+a\bar{x}_2}$, and $B_3 = \mu_3 d\bar{c}_2$. For $\tau = 0$, the equation (5) becomes
$$\lambda^3 + B_1\lambda^2 + ((B_1-\mu_1)B_2 + B_3)\lambda + B_1B_3 = 0 \tag{6}$$
By the Routh-Hurwitz criteria, E_2 is locally asymptotically stable for $\tau = 0$. □

When $\tau > 0$, we assume $\lambda(\tau) = \phi(\tau) + i\omega(\tau)$, where $\phi(\tau), \omega(\tau) \in R$. Since $Re(\lambda(0)) < 0$, by continuity of $Re(\lambda(\tau))$, $Re(\lambda(\tau)) < 0$ for values of τ such that $0 \leq \tau < \tau_c$ for some $\tau_c > 0$. Therefore, E_2 remains stable for these values of τ.

Suppose $Re(\lambda(\tau_c)) = 0$ for some $\tau_c > 0$, and $Re(\lambda(\tau_c)) < 0$ for $0 \leq \tau < \tau_c$, then the equilibrium E_2 may lose stability at $\tau = \tau_c$ or $\lambda = i\omega(\tau_c)$.

Substituting $\lambda = i\omega(\tau_c)$ in (5) and equating real parts and imaginary parts of the right hand side to zero, then we get
$$B_1B_3 - (B_1+B_2)\omega^2 = B_2(\mu_1\omega\sin\omega\tau - \omega^2\cos\omega\tau)$$
$$(B_1B_2+B_3)\omega - \omega^3 = B_2(\mu_1\omega\cos\omega\tau + \omega^2\sin\omega\tau)$$
Squaring and adding above equations, we have that
$$\omega^6 + D_1\omega^4 + D_2\omega^2 + B_1^2B_3^2 = 0, \tag{7}$$
where,
$$\begin{aligned} D_1 &= B_1^2 - 2B_3 \quad \text{and} \\ D_2 &= B_1^2B_2^2 + B_3^2 - \mu_1^2B_2^2 - 2B_1^2B_3. \end{aligned}$$
To simplify equation (7), we set $\kappa = \omega^2$, then (7) reduces to
$$P(\kappa) = \kappa^3 + D_1\kappa^2 + D_2\kappa + B_1^2B_3^2 = 0. \tag{8}$$

Here, we are interested in determining whether there exists a critical delay $\tau_c > 0$ so that $Re(\lambda) > 0$ for $\tau > \tau_c$. Now, we will determine the conditions on the parameters to ensure that E_2 is still stable by considering (5) as a complex variable mapping problem.

Lemma 6. *Let* $\tau > 0$. *Suppose that the equation (8) has no positive roots. Then, all roots of the equation (5) have negative real parts.*

Proof: Since (8) has no positive roots, any real number ω is not a root of (7). Hence, for any real number ω, the value $i\omega$ is not a root of (5), which implies that there is no τ_c such that
$$\lambda(\tau_c) = i\omega(\tau_c),$$
From Theorem 5, we have that all roots of (5) have negative real parts for $\tau = 0$. Since $Re(\lambda(\tau))$ is a continuous function of τ, we conclude that all roots of (5) have negative real parts for $\tau > 0$. □

We next present the conditions under which (8) has a positive root or has no positive roots. To this end, we differentiate (8) to obtain
$$P'(\kappa) = 3\kappa^2 + 2D_1\kappa + D_2, \tag{9}$$
and observe that equation $3\kappa^2 + 2D_1\kappa + D_2 = 0$, has the roots K_1 and K_2 :
$$\begin{aligned} K_1 &= (-D_1 + \sqrt{D_1^2 - 3D_2})/3 \quad \text{and} \\ K_2 &= (-D_1 - \sqrt{D_1^2 - 3D_2})/3. \end{aligned}$$
We are led to the following lemma.

Lemma 7. $i)$ *If a)* $D_1 < 0, D_1^2 - 3D_2 > 0$ *and* $P(K_1) < 0$, *or b)* $D_2 < 0$ *and* $P(K_1) < 0$, *are satisfied then, the equation (8) has a positive root.*
$ii)$ *If* $D_1^2 - 3D_2 < 0$ *are satisfied then, the equation (8) has no positive root.*

Proof: $i)$ If a) is true, we can see that K_1 is real and $K_1 > 0$. From (8), for $\kappa = 0$, we have that $P(0) > 0$. Since $P(K_1) < 0$, by the intermediate value theorem, (8) must have a positive root K^*. If b) is true, then we have $\sqrt{D_1^2 - 3D_2} > |D_1|$. It is easy to see that K_1 is real and $K_1 > 0$. Similarly to the case a), we then have a positive root K^*.
$ii)$ Since $D_2 > \dfrac{D_1^2}{3}$, $P'(\kappa) = 0$ has no real root and
$$P'(0) = D_2 > \frac{D_1^2}{3} > 0.$$
This implies that P is increasing on the set of real numbers. Moreover, we observe that $P(\kappa)$ does not vanish for $\kappa > 0$ and thus, (8) has no positive roots. □

Thus, we can write down the following theorem.

Theorem 8. *Suppose that* $D_1^2 - 3D_2 < 0, \Re_0 > 1$, *and* $-z + \sqrt{z^2+4aA\mu_1} > \dfrac{2a\mu_1\mu_4}{\beta e^{-\mu_1\tau} - a\mu_4}$, *are satisfied. Then, the equilibrium point* $E_2(\bar{x}_2, \bar{v}_2, \bar{c}_2)$ *is locally asymptotically stable for* $\tau \geq 0$.

Proof: By Theorem 5, all real parts of eigenvalues of (5) are negative for $\tau = 0$. By part (ii) of Lemma 7, (8) has no positive roots. Lemma 6 ensures that all roots of (5) have negative real parts for $\tau > 0$. So, E_2 is locally asymptotically stable for $\tau \geq 0$. □

Next, we will provide the conditions on the parameters to ensure that a Hopf bifurcation occurs. We denote, without loss of generality, the positive roots of (8) by κ_0, κ_1, and κ_2. Equation (7), therefore, has six roots, $\omega_j = \pm\sqrt{\kappa_j},\ j = 0, 1, 2$.

For each ω_j, we can write τ in form

$$\tau_j^{(n)} = \frac{1}{\omega_j} \arccos \Theta + \frac{2k\pi}{\omega_j}, \qquad (10)$$

where $\Theta = \frac{\mu_1(B_1B_2+B_3)-B_1B_3+\omega_j^2(B_1+B_2-\mu_1)}{B_2(\omega_j^2+\mu_1^2)}$, $j = 0, 1, 2$, and $n = 0, 1, 2, 3, ...$

Now, let $\tau_c > 0$ be the smallest of such $\tau_j^{(n)}$ for which $\phi(\tau_c) = 0$. Thus,

$$\tau_c = \min\{\tau_j^{(n)} > 0, 0 < j < 2, n \geq 1\}, \qquad (11)$$

Letting
$$\begin{aligned} h_1 &= \omega_c B_2(\mu_1\tau_c - 2), h_2 = B_2(\tau_c\omega_c^2 + \mu_1), \\ H_1 &= B_1B_2 + B_3 - 3\omega_c^2 \\ &\quad + h_1 \sin\omega_c\tau_c - h_2\cos\omega_c\tau_c, \\ H_2 &= 2(B_1 + B_2)\omega_c \\ &\quad + h_1\cos\omega_c\tau_c + h_2\sin\omega_c\tau_c, \end{aligned}$$
we can prove the following theorem.

Theorem 9. *For the time lag τ, let the critical time lag τ_c and ω_c be defined as in (11), and suppose that the conditions*
$i)$ $\frac{H_1}{H_2} \neq \frac{2\mu_1\omega_c}{\omega_c^2 - \mu_1^2}$ and $\frac{H_1}{H_2} \neq \frac{\omega_c(B_1 + \mu_3)}{\omega_c^2 - \mu_3 B_1}$,
$ii)$ $\frac{\omega_c(\omega_c + \mu_1)^2}{\omega_c^2 - \mu_1^2} \neq \frac{(B_1 + B_2)\omega_c^2 - B_1B_3}{\omega_c^2 - (B_1B_2 + B_3)}$
$iii)$ $\omega_c^2 \neq \mu_3 B_1 \neq B_1B_2 + B_3$ and $\omega_c^2 - \mu_1^2 \neq 0$,
are true. Then the system of delay differential equations (1) exhibits a Hopf bifurcation at E_2.

Proof: From (5), we have that
$$\begin{aligned} \frac{d\phi}{d\tau}|_{\tau=\tau_c} = \ & \frac{((\mu_1^2 - \omega_c^2)H_1 + 2\mu_1\omega_c H_2)}{\omega_c^2(1 + \mu_1^2)(H_1^2 + H_2^2)}[\\ & (\omega_c^2 + \mu_1\omega_c)(\omega_c^2 - (B_1B_2 + B_3) + \\ & ((B_1 + B_2)\omega_c^2 - B_1B_3)(\mu_1 - \omega_c)] \\ & -\frac{B_2\mu_1}{(H_1^2 + H_2^2)}[H_1(\omega_c^2 - \mu_3B_1) - \\ & H_2\omega_c(B_1 + \mu_3)] \end{aligned}$$
By the conditions $i), ii)$ and $iii)$, we have that

$$\frac{d\phi}{d\tau}|_{\tau=\tau_c} \neq 0. \qquad (12)$$

Hence, a Hopf bifurcation occurs when τ passes through the critical value τ_c. □

Finally, from the above arguments, it is possible to state the following theorem.

Theorem 10. *For system (2), with τ_c and ω_c defined as in (11), suppose that $\Re_0 > 1, -z + \sqrt{z^2 + 4aA\mu_1} > \frac{2a\mu_1\mu_4}{\beta e^{-\mu_1\tau} - a\mu_4}$, and the condition (i) of Lemma 9 hold. There exists a τ_c such that the equilibrium point E_2 is stable for $0 < \tau < \tau_c$ and unstable for $\tau > \tau_c$.*

IV. Impulsive Virus Filtering

In this section, we start with giving some definitions, notations and lemmas which will be useful.

The smoothness properties of f guarantee the global existence and uniqueness of solution of system (3). For details, see [24]. The following lemma is obvious.

Lemma 11. *Suppose that $X(t) = (x(t), v(t), c(t))$ is a solution of (3) with $X(0^+) \geq 0$, then $X(t) \geq 0$ for all $t \geq 0$. And further $X(t) > 0$, for all $t \geq 0$ if $X(0^+) > 0$.*

We will use an important comparison theorem on impulsive differential equation [24].

Lemma 12. *[24] Suppose that $w \in PC[R^+, R]$ satisfies*

$$\begin{aligned} w'(t) &\leq (\geq) p(t)w(t) + q(t), t \neq nT, \\ w(t^+) &\leq (\geq) d_n w(t) + b_n, t = nT, n \in N, \end{aligned} \qquad (13)$$

where $p(t), q(t) \in PC[R^+, R], d_n > 0$, and b_n are constants. Then

$$\begin{aligned} w(t) \ \leq (\geq) & w(0) \prod_{0<nT<t} d_n exp(\int_0^t p(s)ds) \\ & + \int_0^t \prod_{s<nT<t} d_n exp(\int_s^t p(\theta)d\theta) q(s)ds \\ & + \sum_{0<nT<t} [\prod_{nT<(n+1)T<t} d_{n+1} exp(\\ & \int_{nT}^t p(s)ds)] b_n, \end{aligned} \qquad (14)$$

Lemma 13. *[24] Suppose $V \in V_0$. Assume that*

$$\begin{aligned} D^+V(t, y) &\leq g(t, V(t, y)), & t \neq nT, \\ V(t, y(t^+)) &\leq \psi_n(V(t, y)), & t = nT, \end{aligned} \qquad (15)$$

where $g : R_+ \times R_+ \mapsto R$ is continuous in $(nT, (n+1)T] \times R_+$ and for $u \in R_+, n \in N$,

$$\lim_{(t,\vartheta)\to(nT^+,u)} g(t, \vartheta) = g(nT^+, u)$$

exists, $\psi_n : R_+ \mapsto R_+$ is non-decreasing. Let $r(t)$ be maximal solution of the scalar impulsive differential equation

$$\begin{aligned} u'(t) &= g(t, u(t)), & t \neq nT, \\ u(t^+) &= \psi_n(u(t)), & t = nT, \\ u(0^+) &= u_0, \end{aligned} \qquad (16)$$

existing on $[0, \infty)$. Then $V(0^+, y_0) \leq u_0$, implies that $V(t, y(t)) \leq r(t), t \geq 0$, where $y(t)$ is any solution of (3).

Next, we will consider the Floquet theory [22] for a linear T*-periodic impulsive equation:

$$\begin{aligned} \frac{dx(t)}{dt} &= A(t)x(t), & t \neq t_k, k = 1, 2, ... \\ x(t^+) &= x(t) + B_k x(t) & t = t_k. \end{aligned} \qquad (17)$$

Then, base on [22] the following conditions are introduced:

$(H1)$ $A(.) \in PC(R, C^{n\times n})$ and $A(t+T^*) = A(t)$, $t \in R$ where $PC(R, C^{n\times n})$ is the set of all piecewise continuous matrix functions which is left continuous at $t = t_k$, and $C^{n\times n}$ is the set of all $n \times n$ matrices.

$(H2)$ $B_k \in C^{n\times n}$, $det(I + B_k) \neq 0$; $t_k < t_{k+1}$ $(k \in N)$,

$(H3)$ There exists a $q \in N$ such that $B_{k+q} = B_k$, $t_{k+q} < t_k$.

Let $\phi(t)$ be a fundamental matrix of (17), then there exists a unique non-singular matrix $M \in C^{n\times n}$ such that [22]

$$\phi(t + T^*) = \phi(t)M, \tag{18}$$

By equality (18) there corresponds to the fundamental matrix $\phi(t)$ the constant matrix M which we call the monodromy matrix of (17) (corresponding to the fundamental matrix of $\phi(t)$). All monodromy matrices of (17) are similar and have the same eigenvalues. The eigenvalues $\gamma_1, \gamma_2, ..., \gamma_n$ of the monodromy matrices are called the Floquet multipliers of (17) [22].

Lemma 14. *(Floquet theory [22]) Let conditions $(H1)-(H3)$ hold. Then the linear T-periodic impulsive equation (17) is*

1. *stable if and only if all multipliers γ_j, $(j = 1, 2, 3, ..., n)$ of (17) satisfy the inequality $|\gamma_j| \leq 1$, and moreover, to those γ_j for which $|\gamma_j| = 1$, there correspond simple elementary divisors;*
2. *asymptotically stable if and only if all multipliers γ_j, $(j = 1, 2, 3, ..., n)$ of (17) satisfy the inequality $|\gamma_j| < 1$;*
3. *unstable if $|\gamma_j| > 1$, for some $j = 1, 2, 3, ..., n$.*

Next, we investigate the global asymptotic stability of the viral free periodic solution and the conditions for the permanence of the system

A. Global Stability

First, we determine the local asymptotically stability of the viral free solution $(\frac{A}{\mu_1}, 0, 0)$ of the system (3). Let

$$\Re^* = \frac{A\beta e^{-\mu_1\tau}}{\mu_2(\mu_1 + aA)}.$$

Theorem 15. *The viral free solution $(\frac{A}{\mu_1}, 0, 0)$ of the system (3) is locally asymptotically stable provided that $\Re^* < 1$ hold.*

Proof: Define $x(t) = y(t) + \frac{A}{\mu_1}, v(t) = z(t), c(t) = w(t)$. Then, the system (3) can be expanded when $t \neq nT$ in a Taylor series about $(\frac{A}{\mu_1}, 0, 0)$. Neglecting higher order terms, the linearized equations read:

$$\left.\begin{aligned} y'(t) &= -\mu_1 y(t) - \frac{\beta A}{\mu_1 + aA} z(t), \\ z'(t) &= (\frac{A\beta e^{-\mu_1\tau}}{\mu_1 + aA}) z(t-\tau) - \mu_2 z(t), \\ w'(t) &= -\mu_3 w(t), \end{aligned}\right\} t \neq nT$$
$$\left.\begin{aligned} y(t^+) &= y(t), \\ z(t^+) &= (1-\mu) z(t), \\ w(t^+) &= w(t), \end{aligned}\right\} t = nT, n = 1, 2, ... \tag{19}$$

Next, we are going to find $\phi(t)$, which is the fundamental solution matrix of (19). For $t \neq nT$, we have that the characteristic equation is given by

$$(\lambda + \mu_1)(\lambda - \frac{A\beta e^{-\mu_1\tau}}{\mu_1 + aA} e^{-\lambda\tau} + \mu_2)(\lambda + \mu_3) = 0. \tag{20}$$

So, the eigenvalues are $\lambda_1 = -\mu_1$ and $\lambda_3 = -\mu_3$. Next, we will consider a solution of the equation

$$\lambda - \frac{A\beta e^{-\mu_1\tau}}{\mu_1 + aA} e^{-\lambda\tau} + \mu_2 = 0. \tag{21}$$

To find the location of the eigenvalue λ_2, we introduce the function

$$S(t) = t - \frac{A\beta e^{-\mu_1\tau}}{\mu_1 + aA} e^{-t\tau} + \mu_2, \ \ t \in R.$$

Clearly, $S(t)$ is a continuous and increasing function. We also observe that

$$\lim_{t\to-\infty} S(t) = -\infty, \ \ \lim_{t\to\infty} S(t) = \infty.$$

Hence, the function S has a unique zero. Since $\Re^* < 1$, then we have

$$S(0) = -\frac{A\beta e^{-\mu_1\tau}}{\mu_1 + aA} + \mu_2 > 0.$$

So, we can conclude that $\lambda_2 < 0$. The eigenvectors corresponding to the eigenvalues λ_1, λ_2 and λ_3 are $(1, 0, 0), (\omega, 1, 0)$ and $(0, 0, 1)$, respectively, where $\omega = \frac{-\beta A}{(\mu_1 + \lambda_2)(\mu_1 + aA)}$. Let,

$$P = \begin{bmatrix} 1 & \omega & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}, L_1(t) = \begin{bmatrix} e^{-\mu_1 t} & 0 & 0 \\ 0 & e^{\lambda_2 t} & 0 \\ 0 & 0 & e^{-\mu_3 t} \end{bmatrix}.$$

Therefore a fundamental solution matrix of (19) is given by

$$\phi(t) = PL_1(t) = \begin{bmatrix} e^{-\mu_1 t} & \omega e^{\lambda_2 t} & 0 \\ 0 & e^{\lambda_2 t} & 0 \\ 0 & 0 & e^{-\mu_3 t} \end{bmatrix}$$

where the exact expression of $\omega e^{\lambda_2 t}$ is omitted.

When $t = nT$, the linearization of the fourth, fifth and sixth equations of (19) becomes

$$\begin{bmatrix} y(t^+) \\ z(t^+) \\ w(t^+) \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & (1-\mu) & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} y(t) \\ z(t) \\ w(t) \end{bmatrix} \tag{22}$$

The stability of the solution $(\frac{A}{\mu_1}, 0, 0)$ is determined by the eigenvalues of

$$L_2 = \begin{bmatrix} 1 & 0 & 0 \\ 0 & (1-\mu) & 0 \\ 0 & 0 & 1 \end{bmatrix} \phi(T)$$
$$= \begin{bmatrix} e^{-\mu_1 T} & \omega e^{\lambda_2 T} & 0 \\ 0 & (1-\mu)e^{\lambda_2 T} & 0 \\ 0 & 0 & e^{-\mu_3 T} \end{bmatrix}.$$

Therefore, the characteristic equation is

$$(e^{-\mu_1 T} - \lambda)((1-\mu)e^{\lambda_2 T} - \lambda)(e^{-\mu_3 T} - \lambda) = 0$$

Then, we have the eigenvalues of L_2 are $e^{-\mu_1 T}$, $e^{-\mu_3 T}$, and $(1-\mu)e^{\lambda_2 T}$. Since $\mu_1 > 0$ and $\mu_3 > 0$, obviously, $|e^{-\mu_1 T}| < 1$ and $|e^{-\mu_3 T}| < 1$. Since $0 < \mu < 1$ and $\lambda_2 < 0$, therefore $|(1-\mu)e^{\lambda_2 T}| < 1$. According to Lemma 14, the Floqent theory of impulsive differential equations, the solution $(\frac{A}{\mu_1}, 0, 0)$ is locally asymptotically stable. □

Next, we need to show that the viral free solution of system (3) is global attractive.

Theorem 16. *If $\Re^* < 1$ then the viral free solution $(\frac{A}{\mu_1}, 0, 0)$ of (3) is global attractive.*

Proof: Since $\Re^* < 1$, we can choose $\epsilon_1 > 0$ sufficiently small such that

$$\beta e^{-\mu_1 \tau}(\frac{A}{\mu_1 + aA} + \epsilon_1) < \mu_2 \tag{23}$$

From the first equation in (3), we have $x'(t) \leq A - \mu_1 x(t)$. Consider the following comparison equation:

$$x_1'(t) = A - \mu_1 x_1(t). \tag{24}$$

It is clear that $\limsup_{t\to\infty} x_1(t) = \frac{A}{\mu_1}$.

Let $(x(t), v(t), c(t))$ be the solution of (3) with initial value $x(\theta) = \varphi_1(\theta) > 0$. For $x_1(t)$ be the solution of (24) with the initial value $x_1(\theta) = \varphi_1(\theta) > 0$. By the comparison theorem,

$$\limsup_{t\to\infty} x(t) \leq \limsup_{t\to\infty} x_1(t) = \frac{A}{\mu_1},$$

Then, we have that there exists an integer $n_1 > 0$ such that

$$x(t) \leq x_1(t) < \frac{A}{\mu_1} + \epsilon_1, \qquad t > n_1 T. \tag{25}$$

From the second equation and the fifth equation in (3) we can see that,

$$\begin{aligned} v'(t) \leq \quad & \beta e^{-\mu_1 \tau}(\frac{A}{\mu_1 + aA} + \epsilon_1)v(t-\tau) \\ & -\mu_2 v(t), t \neq nT \\ v(t^+) = \quad & (1-\mu)v(t), t = nT, n = 1, 2, ... \end{aligned}$$

Consider the comparison system for $t > n_1 T$, :

$$\begin{aligned} v_1'(t) = \quad & \beta e^{-\mu_1 \tau}(\frac{A}{\mu_1 + aA} + \epsilon_1)v_1(t-\tau) \\ & -\mu_2 v_1(t), t \neq nT \\ v_1(t^+) = \quad & (1-\mu)v_1(t), t = nT, n = 1, 2, ... \end{aligned} \tag{26}$$

Since we have (23) and by Lemma 2, then we have $\lim_{t\to\infty} v_1(t) = 0$.

Let $(x(t), v(t), c(t))$ be the solution of (3) with initial value $v(\theta) = \varphi_2(\theta) > 0$, $(\theta \in [-\tau, 0])$, and $v_1(t)$ be the solution of (26) with initial value $v_1(\theta) = \varphi_2(\theta) > 0$, $(\theta \in [-\tau, 0])$. By the comparison theorem, we have

$$\limsup_{t\to\infty} v(t) \leq \limsup_{t\to\infty} v_1(t) = 0.$$

Incorporating into the positivity of $v(t)$, we know that

$$\lim_{t\to\infty} v(t) = 0. \tag{27}$$

Therefore, for any $\epsilon_2 > 0$ (sufficiently small), there exists an integer $n_2 > n_1$ such that $v(t) < \epsilon_2$ for all $t > n_2 T$. For the first equation in the system (3), we have

$$x'(t) \geq A - \frac{\beta\epsilon_2}{a} - \mu_1 x(t), \quad t > n_2 T.$$

Consider the following comparison equation:

$$x_2'(t) = A - \frac{\beta\epsilon_2}{a} - \mu_1 x_2(t). \tag{28}$$

Let $(x(t), v(t), c(t))$ be the solution of (3) with initial value $x(\theta) = \varphi(\theta) > 0$, and $x_2(t)$ be the solution of (40) with the initial value $x_2(\theta) = \varphi(\theta) > 0$. By the comparison theorem, we have that

$$\liminf_{t\to\infty} x(t) \geq \liminf_{t\to\infty} x_2(t) = \frac{Aa - \beta\epsilon_2}{a\mu_1}.$$

Therefore, there exists an integer $n_2 > n_1$ such that

$$x(t) \geq x_2(t) > \frac{Aa - \beta\epsilon_2}{a\mu_1} - \epsilon_3, \qquad t > n_2 T \tag{29}$$

Note that ϵ_2, ϵ_3 are arbitrary small, it follows from (25) and (29) that

$$\lim_{t\to\infty} x(t) = \frac{A}{\mu_1}. \tag{30}$$

It follows from (27) that there exists $n_3 > n_2$ such that $v(t) < \epsilon_2$ for all $t > n_3 T$. For the third equation in (3), we have

$$c'(t) \leq (r\epsilon_2 - \mu_3)c(t), \quad t > n_3 T.$$

Consider the following comparison equation:

$$c_1'(t) = (r\epsilon_2 - \mu_3)c_1(t). \tag{31}$$

It easy to see that $\lim_{t\to\infty} c_1(t) = 0$.

Let $(x(t), v(t), c(t))$ be the solution of the system (3) with initial value $c(\theta) = \varphi_3(\theta) > 0$, and $c_1(t)$ be the solution of the system (31) with initial value $c_1(\theta) = \varphi_3(\theta) > 0$. By the comparison theorem, we have

$$\limsup_{t\to\infty} c(t) \le \limsup_{t\to\infty} c_1(t) = 0.$$

Incorporating into the positivity of $c(t)$, we know that

$$\lim_{t\to\infty} c(t) = 0. \tag{32}$$

Together with equations (27), (30), and (32), we get $x(t) \to \frac{A}{\mu_1}$, $v(t) \to 0$ and $c(t) \to 0$ which proves its global attraction. □

Now, we already have the local asymptotically stability of the viral free solution and its global attraction. Therefore, the global asymptotically stability of the viral free solution of system (3) is proved. We can now state the following theorem.

Theorem 17. *If $\Re^* < 1$ then the viral free solution $(\frac{A}{\mu_1}, 0, 0)$ is globally asymptotically stable for system (3).*

B. Persistence

In this section, we say the virus is not eradicated if the virus population persists above a certain positive level for sufficiently large time. The endemicity of the virus can be well captured and studied through the notion of persistence.

Definition 18. *The system (3) is said to be persistent if every solution $(x(t), v(t), c(t))$ with initial condition (4) of system (3) satisfies*

$$\begin{aligned} 0 < \liminf_{t\to\infty} x(t) &\le \limsup_{t\to\infty} x(t) < \infty \\ 0 < \liminf_{t\to\infty} v(t) &\le \limsup_{t\to\infty} v(t) < \infty \\ 0 < \liminf_{t\to\infty} c(t) &\le \limsup_{t\to\infty} c(t) < \infty \end{aligned}$$

We now prove the uniform ultimate boundedness of the solutions of (3).

Theorem 19. *There is $M > 0$ such that $x(t) \le M$, $v(t) \le M$, $c(t) \le M$ for each solutions $X(t) = (x(t), v(t), c(t))$ of (3), for all large t.*

Proof: Define a function $W(t, X)$ as

$$W(t, X) = e^{-\mu_1\tau} x(t-\tau) + v(t) + \frac{d}{r} c(t). \tag{33}$$

When $t \ne nT$, calculating the right derivative of W it follow that

$$\begin{aligned} D^+W(t, X) = {} & e^{-\mu_1\tau}(A - \mu_1 x(t-\tau)) - \mu_2 v(t) \\ & - \frac{d\mu_3}{r} c(t), \end{aligned}$$

Let $\xi = \min\{\mu_1, \mu_2, \mu_3\}$ and choose $0 < h < \xi$. Let $M_0 > 0$ such that

$$D^+W(t, X) + hW(t, X) \le Ae^{-\mu_1\tau} - (\xi - h)W(t, X)$$

when $t = nT$, we get

$$\begin{aligned} W(t^+, X) &= e^{-\mu_1\tau} x(t-\tau) + (1-\mu)v(t) + \frac{d}{r} c(t) \\ &= W(t, X) - \mu v(t) \le W(t, X) \end{aligned}$$

Now, we have the system

$$\begin{aligned} & D^+W(t, X) \le Ae^{-\mu_1\tau} - \xi W(t, X), t \ne nT \\ & W(t^+, X) \le W(t, X), t = nT. \end{aligned} \tag{34}$$

By Lemma 12 and for $t \ge 0$, we have

$$\begin{aligned} W(t) &\le W(0)exp(\int_0^t -\xi ds) \\ & \quad + \int_0^t (exp(\int_s^t -\xi ds))Ae^{-\mu_1\tau} ds, \\ &= W(0)e^{-\xi t} + \frac{Ae^{-\mu_1\tau}}{\xi}. \end{aligned}$$

So, we can see that

$$W(0)e^{-\xi t} + \frac{Ae^{-\mu_1\tau}}{\xi} \to \frac{Ae^{-\mu_1\tau}}{\xi} \text{ as } t \to \infty.$$

Therefore, $W(t) \le \frac{Ae^{-\mu_1\tau}}{\xi}$. Hence, $W(t)$ is uniformly bounded from above. According to the definition of $W(t)$, it is known that there exists a constant $M > 0$, such that $x(t) \le M, v(t) \le M, c(t) \le M$ for all t large enough. The proof is completed. □

Corollary 20. *Denote*

$$M_1 = \frac{Ae^{-\mu_1\tau}}{\min\{\mu_1, \mu_2, \mu_3\}} \tag{35}$$

then $x(t) \le M_1, v(t) \le M_1$ and $c(t) \le M_1$, for each solution $X(t) = (x(t), v(t), c(t))$ of system (3) for all t large enough.

Denote

$$\Re_* = \frac{r}{\mu_3(\mu_2 + M_1 d)}.$$

Theorem 21. *The system (3) is persistent provided that*

$$\Re^* > 1, \text{ and } \Re_* < 1.$$

Proof: We will prove the theorem by several steps. By Corollary 20, without loss of generality, we suppose that $(x(t), v(t), c(t))$ is any solution of system (3) with initial values $x(0) > 0, v(0) > 0$ and $c(0) > 0$ and suppose that $x(t) \le M_1$, $v(t) \le M_1$, and $c(t) \le M_1$ for all $t \ge 0$. We will show that for any $t_0 > 0$, there exist an $m_x > 0$ such that $x(t) \ge m_x$ for all $t > t_0$. From the first equation of system (3) and $v(t) < M_1$, we have that, $x'(t) > A - \mu_1 x(t) - \frac{\beta M_1}{a}$. Consider the following comparison equation for $t \ge t_0$,

$$x'^*(t) = (A - \frac{\beta M_1}{a}) - \mu_1 x^*(t). \tag{36}$$

It is easy to see that $\lim_{t\to\infty} x^*(t) = \frac{Aa - \beta M_1}{a\mu_1}$.

Since $R^* > 1$, we have that, according to Lemma 13, there exists a $t_1 > 0$ such that for all $t > t_1$,

$$x(t) \ge x^*(t) > \frac{Aa - \beta M_1}{a\mu_1} - \epsilon_1 = m_x > 0, \tag{37}$$

Next, we will show that for any $t_0 > 0$, there exists an $m_v > 0$ such that $v(t) \geq m_v$ for all $t > t_0$. By $x(t) > m_x$ and Corollary 20, $x(t) \leq M_1, c \leq M_1$, then the second equation of system (3) can be rewritten as follows:

$$v'(t) \geq \frac{\beta e^{-\mu_1 \tau} m_x}{1 + aM_1} v(t-\tau) - (\mu_2 + M_1 d)v(t).$$

We have that

$$\begin{array}{rcll} v'(t) & \geq & q(t) - pv(t), & t \neq nT \\ v(t^+) & = & (1-\mu)v(t), & t = nT \end{array} \qquad (38)$$

where $p = \mu_2 + M_1 d > 0$ and

$$q(t) = \frac{\beta e^{-\mu_1 \tau} m_x}{1 + aM_1} v(t-\tau).$$

By Lemma 12, we can see that

$$\begin{aligned} v(t) \geq & \ (1-\mu)v(0)exp(\int_0^t (-p)ds) \\ & + \int_0^t [(1-\mu)exp(\int_s^t (-p)d\theta)q(s)]ds \\ \geq & \ (1-\mu)e^{-pt}[v(0) + \int_0^t e^{ps}q(s)ds]. \end{aligned}$$

Since $q(t) > 0$, there exists a $t_2 > 0$ and an $\varepsilon_2 > 0$, such that

$$0 < \varepsilon_2 < \liminf_{t\to\infty} q(t) \quad \text{for all } t \geq t_2.$$

Therefore,

$$\begin{aligned} v(t) & > (1-\mu)e^{-pt}[v(0) + \int_0^t e^{ps}\varepsilon_2 ds] \\ & > (1-\mu)e^{-pt}[v(0) + \varepsilon_2(\frac{e^{pt}-1}{p})] \\ & > (1-\mu)e^{-pt}[v(0) - \frac{\varepsilon_2}{p}] + (1-\mu)\frac{\varepsilon_2}{p} \end{aligned}$$

which implies that $v(t) > (1-\mu)\frac{\varepsilon_2}{p} > 0$ as $t \to \infty$.

Let $m_v = (1-\mu)\frac{\varepsilon_2}{p} = \frac{(1-\mu)\varepsilon_2}{\mu_2 + M_1 d}$. So, we have $v(t) > m_v$ for all $t > t_2$.

Since $\mathfrak{R}_* < 1$ and $(1-\mu)\varepsilon_2 \leq 1$, for ε_2 is arbitrary small, we can see that

$$m_v = \frac{(1-\mu)\varepsilon_2}{\mu_2 + M_1 d} \leq \frac{1}{(\mu_2 + M_1 d)} < \frac{\mu_3}{r}.$$

Next, we will show that $\liminf_{t\to\infty} c(t) > 0$ Since $m_v < \frac{\mu_3}{r}$ and from the third equation of system (3) we have that $c'(t) > (rm_v - \mu_3)c(t)$. Consider the following comparison equation:

$$c_2'(t) = (rm_v - \mu_3)c_2(t). \qquad (39)$$

It is easy to see that $c_2(t) = c_2(0)e^{(rm_v - \mu_3)t}$. Incorporating the positivity of $c(t)$, we know that

$$\lim_{t\to\infty} c_2(t) = 0. \qquad (40)$$

By the comparison theorem, we have

$$\liminf_{t\to\infty} c(t) > \liminf_{t\to\infty} c_2(t) = 0.$$

Thus, we have proved that $\liminf_{t\to\infty} c(t) > 0$. Hence, the proof is complete. □

V. Numerical Result

In what follows, we present five figures to illustrate the main theoretical results in Section III and two figures to confirm Section IV.

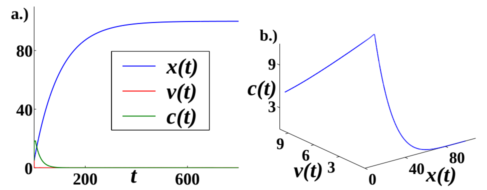

Figure 1: For $A = 1, \beta = 0.015, a = 0.0005, d = 1, r = 1.5, \mu_1 = 0.01, \mu_2 = 0.7, \mu_3 = 0.05, \eta = 0.8, \tau = 5$ and $x(0) = 5, v(0) = 10, c(0) = 5$, $R_0 = 0.9059 < 1$ satisfying the conditions in Theorem 3, and hence, $E_0(100, 0, 0)$ is globally asymptotically stable for $\tau \geq 0$: a) Time series of x, v and c, b) three dimensional phase portrait of x, v and c.

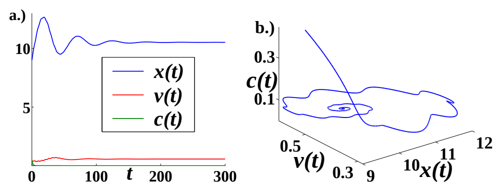

Figure 2: For $A = 1, \beta = 0.15, a = 0.00005, d = 1, r = 0.05, \mu_1 = 0.01, \mu_2 = 0.8, \mu_3 = 0.755, \eta = 0.7, \tau = 5$ and $x(0) = 9, v(0) = 0.5, c(0) = 0.5$, $\mathfrak{R}_0 = 9.4650$ and $\mathfrak{R}_1 = 0.0376$ satisfying the conditions in Theorem 4, $E_1(10.5182, 0.5675, 0)$ is locally asymptotically stable for $\tau \geq 0$: a) Time series of x, v and c, b) three dimensional phase portrait of x, v and c.

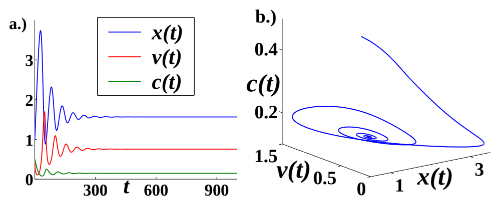

Figure 3: With $A = 0.18, \beta = 0.15, a = 0.05, d = 1, r = 0.1, \mu_1 = 0.01, \mu_2 = 0.01, \mu_3 = 0.0755, \eta = 0.05, \tau = 5$ and $x(0) = 1, v(0) = 0.5, c(0) = 0.5$, $\mathfrak{R}_0 = 4.0552$, $-z + \sqrt{z^2 + 4aA\mu_1} > \frac{2a\mu_1\mu_4}{\beta e^{-\mu_1\tau} - a\mu_4}$, and $D_2^2 - 3D_2 < 0$ satisfying the conditions in Theorem 8, $E_2(1.5648, 0.7550, 0.1471)$ is locally asymptotically stable for $\tau \geq 0$: a) Time series of x, v, and c, b) three dimensional phase portrait of x, v and c.

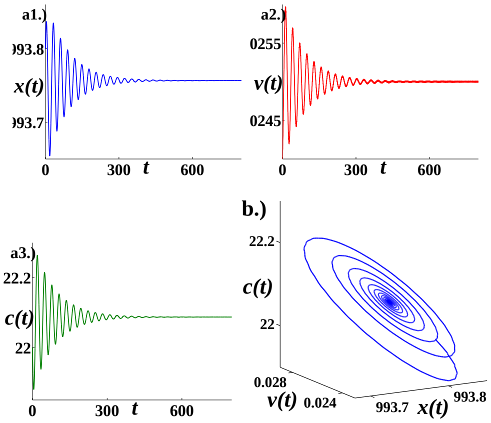

Figure 4: With $A = 100, \beta = 0.15, a = 0.005, d = 1, r = 2, \eta = 0.5, \mu_1 = 0.1, \mu_2 = 0.01, \mu_3 = 0.05, \tau = 1$ and $x(0) = 993.8, v(0) = 0.024, c(0) = 22$, $D_1^2 - 3D_2 = 17.0462, D_2 = -0.6558$ and $P(K_1) = -1.2806$, there exists a τ_c such that $\tau \in (0, \tau_c)$ as predicted in Theorem 10. Hence, $E_2(993.7565, 0.0250, 22.0873)$ is asymptotically stable. a1)- a3) time series of x, v, c, respectively, b) three dimensional phase portrait of x, v and c.

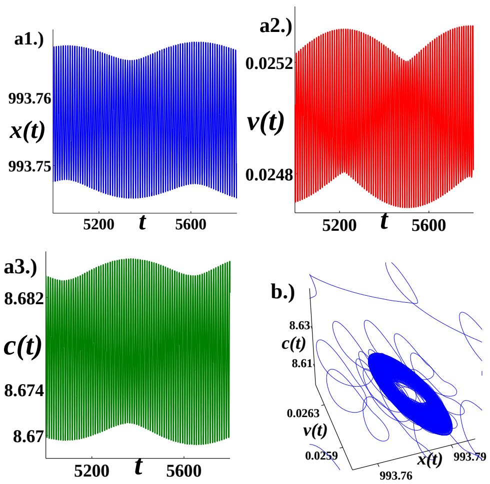

Figure 5: For the same parameters as in Figure 4, except $\tau = 10$ and $x(0) = 993.8, v(0) = 0.024, c(0) = 8.5$, while $D_1^2 - 3D_2 = 2.9275, D_2 = -0.6558$ and $P(K_1) = -0.0872$, there exists a τ_c such that $\tau_c < 10$ as predicted in Theorem 10, and oscillation occurs. a1)-a3) Time series of x, v, c, respectively, b) three dimensional phase portrait of x, v and c.

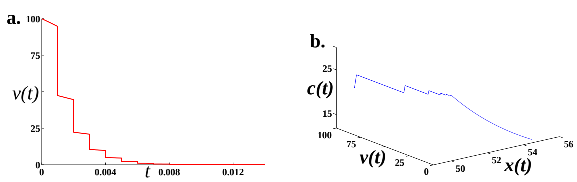

Figure 6: With $A = 5, \beta = 0.0015, a = 0.0001, d = 1, r = 1.5, \mu_1 = 0.01, \mu_2 = 0.7$ and $\mu_3 = 0.755$. For $\tau = 5$ and $\mu = 0.5$ and $x(0) = 50, v(0) = 100, c(0) = 50$, $\mathfrak{R}^* = 0.9706$ as predicted in Theorem 17, $E_0(500, 0, 0)$ is global asymptotically stable. a) Time series of v, b) three dimensional phase portrait of x, v and c.

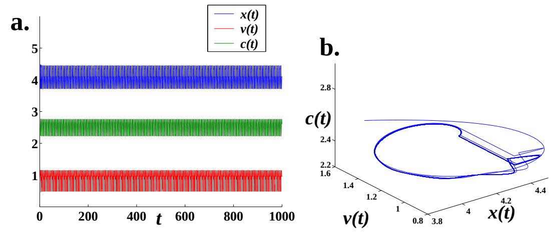

Figure 7: With $A = 10, \beta = 1.5, a = 0.0005, d = 1, r = 1, \mu_1 = 1, \mu_2 = 1$ and $\mu_3 = 1$, $\tau = 0.5$, $\mu = 0.5$ and $x(0) = 3.5, v(0) = 0.9, c(0) = 3$. while, $\mathfrak{R}^* = 9.0527 > 1, \mathfrak{R}_* = 0.1415 < 1$, the system is persist as predicted in Theorem 21. a) Time series of x, v and c, b) three dimensional phase portrait of x, v and c.

VI. Conclusion

In this paper, a more general HIV filtering model (2) with time delay is considered. In the model, a Holling type-II functional response, instead of the mass action response, is used to describe the growth rate of cells, and the delay between the time a cell is infected and the time it starts producing new virus is taken into account. Then, a detailed analysis on the local asymptotic stability of the equilibria of the HIV filtering infection model is carried out. It is shown that, while $\mathfrak{R}_0 < 1$, the viral free equilibrium E_0 is globally asymptotically stable for any time delay so that the virus always dies out. If $\mathfrak{R}_0 > 1$, E_0 becomes unstable while the infected equilibrium point emerges as the unique equilibrium point and becomes locally asymptotically stable for $\tau \geq 0$.

The infected equilibrium point can be determined from given parameters and can be separated into different cases. If $\mathfrak{R}_0 > 1$, and $\bar{c}_1 = 0$, E_1 of (2) exists, and when $\mathfrak{R}_1 < 1$, E_1 is locally asymptotically stable for $\tau \geq 0$ as shown in Theorem 4.

If $\mathfrak{R}_0 > 1, -z + \sqrt{z^2 + 4aA\mu_1} > \dfrac{2a\mu_1\mu_4}{\beta e^{-\mu_1\tau} - a\mu_4}$, and E_2 is locally asymptotically stable for $\tau \geq 0$ if $D_1^2 - 3D_2 < 0$, as proved in Theorem 8. By Theorem 10, there exists a τ_c such that a Hopf bifurcation occurs when τ passes through the critical value τ_c, so that E_2 is stable for $0 < \tau < \tau_c$ and becomes unstable for $\tau > \tau_c$.

Therefore, if the viral free equilibrium point E_0 loses its stability and the infected equilibrium point E_1 or E_2 exists, the virus will start spreading. Either that infected equilibrium point is asymptotically stable or the periodic solution occurs, there will be a balance between the populations of $CD4^+$ T cells, HIV, and the cytotoxic-T-lymphocyte (CTL).

In the impulsive system which models the process of periodic virus filtering at fixed moments, we investigated the global asymptotic stability of the viral free solution and the conditions for the persistence of the system. Threshold $\mathfrak{R}^*$ has been established. Theorem 17 implies that the virus population will vanish and the disease will die out provided that $\mathfrak{R}^* = 0.9706 < 1$. The equilibrium point E_0 of (3) is globally asymptotically stable.

The epidemiological implication of Theorem 21 is that the virus population will persist and the disease will become endemic provided that $\mathfrak{R}^* = 9.0527 > 1$ and $\mathfrak{R}_* = 0.1415 < 1$.

In the real world, complete eradication of HIV population is generally not possible, eventhough it is biologically or economically desirable. A good virus control program should reduce the virus population to acceptable levels .

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