Volterra Integral Equations in an HIV Model

Rujira Ouncharoen, Thongchai Dumrongpokaphan, Yongwimon Lenbury

Abstract**—**We investigate the effects of continuous delay in the viral production in the dynamics of an HIV infection model. We focus on the qualitative behavior of the solutions. This result can be used to explain the complexity of continuous intracellular interaction in the HIV infection process with delay. Numerical simulations are carried out to confirm the main results.

Keywords**—**Delay, Integral equation, Asymptotic behavior, HIV, Gamma Distribution.

I. Introduction

In the last decade, Acquired Immunodeficiency Syndrome (AIDS) has spread widely and become a serious problem in public health around the world. Mathematical modeling and model analysis of the pathogenesis of the HIV infection are important for understanding possible mechanisms and dynamical behaviors of the viral infection process, designing treatment strategies, and guiding development efficient antiviral drug therapies. Clearly, the time from viral infection to viral production is not instantaneous, and it is estimated that the first viral release occurs approximately 24 hours after the initial infection. In vivo, on the order of 10^{10} virions are assembled and cleared everyday [1]-[4]. Former works [5]-[16] have studied the HIV models incorporating the delay between the occurrence of viral infection to the start of viral production. Specifically, Nelson et al. [5] showed that the delay affects the estimated value for the infected T-cell loss rate when we assume that the drug is not completely effective. Also, Grossman et al., [6] showed that including a delay in the model for the death of infected cells leads to different conclusions regarding residual transmission of infection. Therefore, mathematical models for HIV infection that incorporate these delays will provide qualitative insights and lead to more accurate representations of the biological data. Based on these earlierefforts, we formulate here a model which consists of a set of second type Volterra integral equations that can account for the interaction among replicating virus, CD4+ T-cell and the cytotoxic lymphocytes (CTL). However, CTL play a critical role in antiviral defense by eliminating or controlling the infected cells in vivo. It is reasonable to also incorporate the number of CTLs into mathematical models [16]-[18].

In [19]-[20], integro-differential equations (IDEs) were used to represent some key properties of the infection dynamics. Investigation have been carried out on the effect of treatments on the population dynamics.

In this work, we assume that the intracellular delay in the viral production is a continuous random variable having a Gamma probability distribution. We describe the dynamics of the infection in the most natural situation, that is in the absence of drugs and only the CTL plays a role in the immunological process, using the fact that there is no differentiation between infected and non-infected CD4+T-cells when the number of CD4+T-cells is routinely counted in a patient. We employ a delay to mathematically represent the temporal lag between the initial viral infection and the first release of new virions. Thus, greater understanding of HIV viral infection dynamics may be attained.

We consider the following nonlinear mathematical model of three Volterra integral equations.

$$
\begin{aligned}
T(t) &= T_0 e^{-\delta_3 t} + \int_0^t e^{-\delta_3(t-\tau)}[\delta_1 - \delta_2 V(\tau)T(\tau)]d\tau \\
V(t) &= V_0 e^{-\delta_5 t} + \int_0^t e^{-\delta_5(t-\tau)} V(\tau)[\delta_4 F(t-\tau)T(\tau) - \delta_6 C(\tau)]d\tau \qquad (1) \\
C(t) &= \int_0^t e^{-\delta_8(t-\tau)} \delta_7 V(\tau) d\tau, \; t \in [0, t_f]
\end{aligned}
$$

where, $T(t), V(t)$, and $C(t)$ represent the three populations which are present in a volume unit of plasma at time *t*: which are the population of CD4+ T lymphocytes, virus, and Cytotoxic T lymphocytes, $\delta_4 > 0$ is the rate of virus production, $\delta_5 > 0$ is the infectious viral clearance rate, and $\delta_6 > 0$ is the rate of clearance of Lymphocytes. $\delta_1 > 0$ is the constant rate of CD4+ T cell replacement, $\delta_2 > 0$ is the rate of infection, $\delta_3 > 0$ is the rate of clearance by CD4+ T due to CTL, $\delta_7 > 0$ is the rate of CTL stimulation by virus, and $\delta_8 > 0$ is the rate of clearance of CTL.

The function $F(t)$ represents a continuously distributed intracellular delay. It takes into account the temporal lag

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between initial viral infection and the first release of new virions. We assume that the delay is a continuous random variable having a Gamma probability distribution, i.e. the probability density function of the delay is in the form

$$f_{n,b}(t)=\frac{t^{n-1}}{(n-1)!b^n}e^{-\frac{t}{b}} \quad , \; n\in\mathbb{N}, b\in\mathbb{R}^+ \qquad (2)$$

Where n, and b are the parameters of the Gamma distribution whose product represents the expected value, that is

$$E=\int_0^\infty tf(t)dt=nb$$

The Distribution function is then

$$F(t)=\int_0^t f(\tau)d\tau=1-e^{-\frac{t}{b}}\sum_{k=0}^{n-1}\frac{t^k}{k!b^k} \qquad (3)$$

We suppose that the delay between infection and production varies across the population with probability distribution $F(t)$ and corresponding density $f(t)$. To obtain the number of virus at time t that have been produced by infected cells, we must consider the number of each population provided in a particular time subinterval, say Δ_k; repeat the process for all the subintervals of $[0,t_f]$; add the quantities obtained, and pass to the limit as Δ_k goes to zero.

II. Mathematical Properties

From a mathematical point of view, we want to show that the solutions of the system (1) exist. Let

$$Y(t)=X(t)+\int_0^t K(t,\tau,Y(\tau))d\tau$$

where

$Y=[Y_1,Y_2,Y_3]^T$, $X=[X_1,X_2,X_3]^T$,

$K=[K_1,K_2,K_3]^T \in\mathbb{R}^3$

are defined as follows

$$Y(t)=[T(t),V(t),C(t)]^T \quad ,$$

$$X(t)=\left[\frac{\delta_1}{\delta_3},V_0e^{-\delta_5 t},0\right]^T$$

and

$$K(t,\tau,Y)=\begin{bmatrix}-e^{-\delta_3(t-\tau)}\delta_2Y_1(\tau)Y_2(\tau)\\ e^{-\delta_5(t-\tau)}Y_2(\tau)[\delta_4F(t-\tau)Y_1(\tau)-\delta_6Y_3(\tau)]\\ e^{-\delta_8(t-\tau)}\delta_7Y_2(\tau)\end{bmatrix}$$

and $T_0>0$, $V_0>0$, $C_0\ge 0$ are $T(0)$, $V(0)$, $C(0)$, respectively.

Note that $K(t,\tau,Y)$ is continuous with respect to the three variables and satisfies a local Lipchitz condition with respect to Y so that there is a unique solution in some small interval $[0,t_1]$ which in turn can be continued to a larger one. We assume that $[0,t_f]$ is in that interval.

From a biological point of view, we want to show that the solutions of system (1) are positive and bounded since T,V, and C represent populations in a volume unit of plasma.

Note that in the absence of virus, the number of CD4+ T cells should remain constant, because they are provided and removed at a constant rate.

Therefore

$$T_0=\frac{\delta_1}{\delta_3}$$

Substituting this into the first equation of system (1), we obtain

$$T(t)=\frac{\delta_1}{\delta_3}e^{-\delta_3 t}+\delta_1e^{-\delta_3 t}\int_0^t e^{\delta_3\tau}d\tau-\int_0^t e^{-\delta_3(t-\tau)}\delta_2V(\tau)T(\tau)d\tau$$

$$T(t)=\frac{\delta_1}{\delta_3}e^{-\delta_3 t}+\frac{\delta_1}{\delta_3}e^{-\delta_3 t}\left[e^{\delta_3 t}-1\right]-\int_0^t e^{-\delta_3(t-\tau)}\delta_2V(\tau)T(\tau)d\tau$$

and hence (1) becomes

$$T(t)=\frac{\delta_1}{\delta_3}-\int_0^t e^{-\delta_3(t-\tau)}\delta_2V(\tau)T(\tau)d\tau$$

$$V(t)=V_0e^{-\delta_5 t}+\int_0^t e^{-\delta_5(t-\tau)}V(\tau)[\delta_4F(t-\tau)T(\tau)-\delta_6C(\tau)]d\tau \quad (4)$$

$$C(t)=\int_0^t e^{-\delta_8(t-\tau)}\delta_7V(\tau)d\tau \qquad , \qquad t\in[0,t_f]$$

Therefore, the system of the rates of change of T,V, and C is

$$T'(t)=\delta_1-\delta_3T(t)-\delta_2V(t)T(t)$$

$$V'(t)=-\delta_5V(t)-\delta_6V(t)C(t)+\int_0^t e^{-\delta_5(t-\tau)}V(\tau)\delta_4f(t-\tau)T(\tau)d\tau \quad (5)$$

$$C'(t)=\delta_7V(t)-\delta_8C(t).$$

We first state and prove a result on the positivity of the solutions.

Theorem 1. *Solutions $T(t),V(t)$ and $C(t)$ of (4) are always positive for all $t>0$.*

Proof: Notice that $T(0)=\frac{\delta_1}{\delta_3}>0$, $V(0)=V_0>0$ and $C(0)=0$. From the fact that $T(t),V(t)$, and $C(t)$ are continuous, there exists a $t_0>0$ such that $V(t)T(t)C(t)>0$ for $0<t<t_0$. Assume that

$$V(t_0)T(t_0)C(t_0)=0.$$

By the third equation of system (4), $C(t_0)>0$ so that $V(t_0)T(t_0)=0$. By the continuity of $T(t),V(t)$, $C(t)$ and their derivatives, the behavior of $V(t)T(t)$ for $t>t_0$ can be one of the following three cases.

Case 1: There exists a t_1, $t_1 > t_0$, such that $V(t)T(t) < 0$ for $t_0 < t < t_1$.

Since $T'(t_0) = \delta_1 - \delta_3 T(t_0)$, by the first equation of system (5), and $T(t_0) < T(0) = \dfrac{\delta_1}{\delta_3}$, we then have that $T'(t_0) > 0$.

Therefore, $T(t) > 0$, when t is in a small interval which starts from t_0, say $t_0 < t < t_1$.

Hence, $V(t) < 0$ for $t_0 < t < t_1$. Let $g(t) = \int_0^t e^{-\delta_5(t-\tau)} V(\tau)\delta_4 f(t-\tau)T(\tau)d\tau$.

Then, $g(t)$ is a continuous function and $g(t_0) > 0$.

Note that $V(t) > 0$ for $0 < t < t_0$ and $V(t) < 0$ for $t_0 < t < t_1$. We can then find a $t_2 \in (t_0, t_1)$ such that $V'(t_2) < 0$, $C(t_2) > 0$ and $g(t_2) > 0$ by the continuity of $C(t)$ and $g(t)$.

Hence, by the second equation of system (5),

$$V'(t_2) = -\delta_5 V(t_2) - \delta_6 V(t_2) C(t_2) + g(t_2) > 0,$$

which contradicts the assumption that $V'(t_2) < 0$. So, Case 1 is impossible.

Case 2: $V(t)T(t) = 0$ for $t_0 < t < t_1$.

There exists a $t_2 \in (t_0, t_1)$ such that $V(t) \equiv 0$ or $T(t) \equiv 0$ for $t \in (t_0, t_2)$ because of the continuity of $V(t)$ and $T(t)$. If $V(t) \equiv 0$ then $V'(t) \equiv 0$, but for $t_0 < t < t_2$, by the second equation of system (5), we have

$$V'(t) = \int_0^t e^{-\delta_5(t-\tau)} V(\tau)\delta_4 f(t-\tau)T(\tau)d\tau$$
$$= \int_0^{t_0} e^{-\delta_5(t-\tau)} V(\tau)\delta_4 f(t-\tau)T(\tau)d\tau \quad > 0.$$

If $T(t) \equiv 0$, then $T'(t) \equiv 0$, but $T'(t) = \delta_1 > 0$ for $t_0 < t < t_2$. So, Case 2 is impossible.

Case 3: $V(t)T(t) > 0$ for $t_0 < t < t_1$.

$V(t)$ and $T(t)$ can not be negative since $T'(t_0) > 0$ and $T(t_0) \ge 0$. Therefore, $V(t)$ and $T(t)$ are both non-negative for $t_0 < t < t_1$. So, $V(t)T(t) = 0$ only at $t = t_0$. If $T(t_0) = 0$ then t_0 is the local minimum point of $T(t)$. Thus, the derivative of $T(t)$ should be zero at $t = t_0$. However, $T'(t_0) > 0$ which is a contradiction. If $V(t_0) = 0$, similarly the derivative of $V(t)$ should be zero at $t = t_0$. However, $V'(t_0) = g(t_0) > 0$. So, Case 3 is impossible.

Thus, the assumption that $V(t_0)T(t_0) = 0$ is not correct. Hence, $T(t), V(t)$ and $C(t)$ are always positive for $t > 0$.

Next, it is shown that the solutions are bounded under suitable conditions.

Theorem 2. *The solution $T(t)$ is bounded for all $t > 0$. Furthermore, if $\delta_5 + b^{-1} > \delta_3$ then $V(t)$ and $C(t)$ are also bounded for all $t > 0$.*

Proof: (i) By Theorem 1, $V(t)T(t) > 0$ for all t and therefore $T(t) \le \dfrac{\delta_1}{\delta_3}$ for $t \ge 0$.

(ii) Assume $V(t)$ is unbounded. Then, there exists a t_0 such that $V(t_0)$ is large enough and $V'(t_0) > 0$.

Let us consider $g(t)$, as defined in the proof of Theorem 1:

$$g(t) = \int_0^t e^{-\delta_5(t-\tau)} V(\tau)\delta_4 f(t-\tau)T(\tau)d\tau.$$

First, we can show that

$$e^{-(\delta_5-\delta_3)t} f(t) \le M.$$

for some constant M which does not depend on t. Since

$$e^{-(\delta_5-\delta_3)t} f(t) = e^{-(\delta_5+b^{-1}-\delta_3)(t)} \frac{t^{n-1}}{(n-1)!b^n}$$

and

$$\lim_{t\to\infty} e^{-(\delta_5+b^{-1}-\delta_3)(t)} t^{n-1} = 0$$

as $\delta_5 + b^{-1} > \delta_3$, $e^{-(\delta_5-\delta_3)t} f(t)$ is bounded, say

$$e^{-(\delta_5-\delta_3)t} f(t) \le M.$$

On comparing with $T(t)$, we find

$$g(t) = \int_0^t e^{-\delta_5(t-\tau)} V(\tau)\delta_4 f(t-\tau)T(\tau)d\tau$$
$$\le \frac{\delta_4}{\delta_2} M \int_0^t e^{-\delta_3(t-\tau)} \delta_2 V(\tau)T(\tau)d\tau \le \frac{\delta_1\delta_4}{\delta_2\delta_3} M.$$

Choose t_0 such that

$$V(t_0) > \frac{\delta_1\delta_4}{\delta_2\delta_3\delta_5} M$$

and $V'(t_0) < 0$. Note that by Theorem 1, $C(t_0) > 0$, using the second equation of (5). We therefore obtain

$$V'(t_0) \le -\delta_5 V(t) - \delta_6 V(t)C(t) + \frac{\delta_1\delta_4}{\delta_2\delta_3} M$$
$$< -\delta_5 \frac{\delta_1\delta_4}{\delta_2\delta_3\delta_5} M + \frac{\delta_1\delta_4}{\delta_2\delta_3} M < 0.$$

This contradicts the assumption that $V'(t_0) > 0$. Therefore, $V(t)$ is bounded.

(iii) Denote by K the upper bound of $V(t)$. Then

$$C(t) = \int_0^t e^{-\delta_8(t-\tau)} \delta_7 V(\tau)d\tau \le K \int_0^t e^{-\delta_8(t-\tau)} \delta_7 d\tau < \frac{\delta_7}{\delta_8} K.$$

Hence, $C(t)$ is bounded.

III. Asymptotic Properties

Our main interest in this section is on the emission of virus. We study the behavior of $T(t), V(t)$, and $C(t)$ as $t\to\infty$ to provide necessary and sufficient conditions in order to achieve the situation where $\lim_{t\to\infty} T(t)=\frac{\delta_1}{\delta_3}$ and $\lim_{t\to\infty} V(t)=0$.

Observe that, by using the linear chain trick, our model can be transformed into a system of $n+3$ ordinary differential equations. For convenience, we let

$$E_j(t)=\int_0^t f_{j,b}(t-\tau)\delta_4 e^{-\delta_5(t-\tau)}V(\tau)T(\tau)d\tau . \tag{6}$$

where $f_{j,b}(\tau)$ is the probability density function given in (2), and then, with the boundedness of $T(t)$ and $V(t)$, we have that $E_j, j=1,...,n$, are continuous and bounded functions for all $t>0$. Then, system (5) can be transformed into

$$E_1'(t)=-\left(\delta_5+\frac{1}{b}\right)E_1(t)+\frac{\delta_4}{b}V(t)T(t) \tag{7}$$

$$E_j'(t)=-\left(\delta_5+\frac{1}{b}\right)E_j(t)+\frac{1}{b}E_{j-1}(t),\ j=2,...,n \tag{8}$$

$$V'(t)=-\delta_5 V(t)-\delta_6 V(t)C(t)+E_n(t) \tag{9}$$

$$T'(t)=\delta_1-\delta_3 T(t)-\delta_2 V(t)T(t) \tag{10}$$

$$C'(t)=\delta_7 V(t)-\delta_8 C(t) \tag{11}$$

$$E_j(0)=0,\ j=1,...,n,\ C(0)=0,\ V(0)=V_0,\ T(0)=\frac{\delta_1}{\delta_3}.$$

The functions E_j, given in (6), are auxiliary functions related to the probability density in (2) which does not represent any specific biological component.

We need the following Lemmas [12] to prove our main results.

Lemma 3. *Let $\tau:\mathbb{R}^+\to\mathbb{R}$ be any function such that*

i) $\tau'(t)$ exists and is bounded for $t\in\mathbb{R}^+$

ii) $\int_0^\infty \tau(t)dt<\infty$.

Then, $\lim_{t\to\infty}\tau(t)=0$.

Lemma 4. *If $\tau:\mathbb{R}^+\to\mathbb{R}$ is a differentiable function and $\liminf_{t\to\infty}\tau(t)<\limsup_{t\to\infty}\tau(t)$ then there exist two divergent sequences $\{t_j'\}_{j\geq 0}$ and $\{t_j''\}_{j\geq 0}$ such that*

$$\lim_{j\to\infty}\tau(t_j')=\liminf_{t\to\infty}\tau(t),\ \tau'(t_j')=0,\ j\geq 0$$

$$\lim_{j\to\infty}\tau(t_j'')=\limsup_{t\to\infty}\tau(t),\ \tau'(t_j'')=0,\ j\geq 0$$

We can now state and prove our main results in the following theorems.

Theorem 5. *Let*

$$\delta_5+b^{-1}>\delta_3 .$$

If one of the functions $T,V,C,E_1,...,E_n$ converges as $t\to\infty$ then also the remaining functions converge as $t\to\infty$.

Proof: With no loss of generality assume

$$\lim_{t\to\infty}C(t)=l_C\geq 0 \tag{12}$$

Observe that $C(t)$ is bounded on $[0,\infty)$ and $C'(t)$ is continuous and bounded on $[0,\infty)$, thus $C(t)$ is Lipschitz continuous and hence uniformly continuous. Therefore (12) implies

$$\lim_{t\to\infty}C'(t)=0 \tag{13}$$

and from

$$C'(t)=\delta_7 V(t)-\delta_8 C(t),$$

we have

$$\lim_{t\to\infty}V(t)=\frac{\delta_8}{\delta_7}\lim_{t\to\infty}C(t)=l_V\geq 0 \tag{14}$$

Since $V(t)$ is bounded on $[0,\infty)$ and $V'(t)$ is continuous and bounded on $[0,\infty)$, $V(t)$ is therefore Lipschitz continuous and hence uniformly continuous. Thus, (14) implies $\lim_{t\to\infty}V'(t)=0$ and from

$$V'(t)=-\delta_5 V(t)-\delta_6 V(t)C(t)+E_n(t),$$

one has

$$\lim_{t\to\infty}E_n(t)=\delta_5 l_V+\delta_6 l_V l_C=l_{E_n}\geq 0$$

Assume, by contradiction, that $T(t)$ does not converge as $t\to\infty$, that is

$$\liminf_{t\to\infty}T(t)<\limsup_{t\to\infty}T(t) \tag{15}$$

From (10)

$$T'(t)=\delta_1-\delta_3 T(t)-\delta_2 V(t)T(t)$$

Applying Lemma 4,

$$\lim_{j\to\infty}T(t_j')=\liminf_{t\to\infty}T(t),\quad T'(t_j')=0,\ j\geq 0$$

Then, we have

$$0=\delta_1-\delta_3\lim_{j\to\infty}T(t_j')-\delta_2\lim_{j\to\infty}V(t_j')\lim_{j\to\infty}T(t_j')$$

That is,

$$\lim_{j\to\infty}T(t_j')=\frac{\delta_1}{\delta_3+\delta_2\lim_{j\to\infty}V(t_j')}$$

or

$$\liminf_{t\to\infty}T(t)=\frac{\delta_1}{\delta_3+\delta_2\liminf_{t\to\infty}V(t)}=\frac{\delta_1}{\delta_3+\delta_2 l_V}$$

Similarly, by Lemma 4,

$$\limsup_{t\to\infty}T(t)=\frac{\delta_1}{\delta_3+\delta_2 l_V},$$

and therefore,

$$\lim_{t\to\infty}\sup T(t)=\lim_{t\to\infty}\inf T(t)=\frac{\delta_1}{\delta_3+\delta_2 l_V}=l_T$$

which contradicts (15) and hence $T(t)$ converges.

Theorem 6. *Let*

$$\delta_5+b^{-1}>\delta_3 \ ,$$

$$\omega_n=\delta_4/(\delta_5 b+1)^n \ ,$$

and

$$R_n=\delta_5/\omega_n \ ,$$

then

$$R_n\ge\frac{\delta_1}{\delta_3}\leftrightarrow\lim_{t\to\infty}V(t)=0 \ .$$

Proof: $(\to)$ Consider

$$H(t)=V(t)+b\sum_{j=1}^{n}\frac{E_j}{(\delta_5 b+1)^{n+1-j}} \tag{16}$$

so that

$$\begin{aligned}H'(t)&=-\delta_5 V(t)-\delta_6 V(t)C(t)+\frac{\delta_4 V(t)T(t)}{(\delta_5 b+1)^n}\\ &\le-\delta_5 V(t)+\omega_n V(t)T(t)\\ &\le\omega_n V(t)(T(t)-R_n)\end{aligned} \tag{17}$$

Recalling that

$$T(t)\le\frac{\delta_1}{\delta_3} \ ,$$

we therefore have

$$H'(t)\le\omega_n(\frac{\delta_1}{\delta_3}-R_n)V(t)\le 0 \tag{18}$$

We have that.

$$\lim_{t\to\infty}H(t)=l_H\ge 0$$

and since $H(t)$ is uniformly continuous, we therefore have

$$\lim_{t\to\infty}H'(t)=0 \tag{19}$$

Assume $R_n>\frac{\delta_1}{\delta_3}$. By integrating both sides of (18), we obtain

$$\int_0^t H'(x)dx\le\omega_n(\frac{\delta_1}{\delta_3}-R_n)\int_0^t V(x)dx$$

Then,

$$-\omega_n(\frac{\delta_1}{\delta_3}-R_n)\int_0^t V(x)dx\le-\omega_n(\frac{\delta_1}{\delta_3}-R_n)\int_0^t V(x)dx+H(t)$$

$$\le H(0)=V_0 \ .$$

The positivity of $V(t)$ assures that $V(t)$ satisfies the hypotheses of Lemma 3 and therefore

$$\lim_{t\to\infty}V(t)=0 \ .$$

Next assume that $R_n=\frac{\delta_1}{\delta_3}$. Since

$$H'(t)\le\omega_n(T(t)-R_n)V(t)\le 0$$

and

$$\lim_{t\to\infty}H'(t)=0 \ ,$$

we then have

$$\lim_{t\to\infty}\inf V(t)=0$$

or

$$\lim_{t\to\infty}\sup T(t)=\frac{\delta_1}{\delta_3}, \text{ and}$$

$$\lim_{t\to\infty}\inf C(t)=\lim_{t\to\infty}\inf E_j(t)=0,\ j=1,\dots,n \ .$$

This implies

$$\lim_{t\to\infty}\inf H(t)=0 \ ,$$

However, $H(t)$ converges at infinity so that we have

$$\lim_{t\to\infty}H(t)=0 \ .$$

Therefore,

$$\lim_{t\to\infty}V(t)=0 \ .$$

$(\leftarrow)$ From the proof of Theorem 5, we have

$$\lim_{t\to\infty}V(t)=0 \ .$$

Then,

$$\lim_{t\to\infty}C(t)=\lim_{t\to\infty}E_j(t)=0,\ j=1,\dots,n$$

and

$$\lim_{t\to\infty}T(t)=\frac{\delta_1}{\delta_3} \ . \tag{21}$$

Hence,

$$\lim_{t\to\infty}H(t)=0$$

and $H(t)$ is a positive function vanishing at infinity. Thus, there exists a t_i such that

$$\lim_i t_i=+\infty \ ,$$

and $H'(t_i)\le 0$, $i\ge 0$. Therefore,

$$T(t_i)\le R_n$$

By passing to the limit as i goes to infinity and by (21), we therefore have $R_n\ge\frac{\delta_1}{\delta_3}$.

From the above, we can obtain our final results.

Theorem 7. A*ssume that*

$$\delta_5+b^{-1}>\delta_3 \ .$$

If $R_n\ge\frac{\delta_1}{\delta_3}$, *then*

$$\lim_{t\to\infty}T(t)=\frac{\delta_1}{\delta_3} \ ,$$

$$\lim_{t\to\infty}V(t)=0 \ ,\ \lim_{t\to\infty}C(t)=0 \ ,$$

and $\lim_{t\to\infty}E_j(t)=0,\ j=1,\dots,n$.

Moreover, if $R_n<\frac{\delta_1}{\delta_3}$ *then* $V(t)$ *cannot vanish as* $t\to\infty$.

Theorem 8. *Assume that*

$$\delta_5+b^{-1}>\delta_3 \ ,$$

$$R_n < \frac{\delta_1}{\delta_3},$$

and one of the functions $V, T, C, E_1, \ldots, E_n$ *converges at infinity. Then,*

$$\lim_{t\to\infty} T(t) = R_n,$$

$$\lim_{t\to\infty} V(t) = \frac{\delta_4(\delta_1 - \delta_3 R_n)}{\delta_2\delta_5(\delta_5 b + 1)^n},$$

$$\lim_{t\to\infty} C(t) = \frac{\delta_4\delta_7(\delta_1 - \delta_3 R_n)}{\delta_2\delta_5\delta_8(\delta_5 b + 1)^n},$$

$$\lim_{t\to\infty} E_j(t) = \frac{\delta_4(\delta_1 - \delta_3 R_n)}{\delta_2(\delta_5 b + 1)^n} + \frac{\delta_6\delta_7}{\delta_8}\left(\frac{\delta_4(\delta_1 - \delta_3 R_n)}{\delta_2\delta_5(\delta_5 b + 1)^n}\right)^2, \; j = 1, \ldots, n.$$

Proof. By Theorem 5, functions $V, T, C, E_1, \ldots, E_n$ converge at infinity, and thus $\lim_{t\to\infty} H'(t) = 0$. By Theorem 7, we have $\lim_{t\to\infty} V(t) > 0$ and therefore from (17) we obtain $\lim_{t\to\infty} T(t) = R_n$. The rest can be derived from (7)-(11).

IV. Numerical Results

In order to illustrate some of the effects of distributed delays, we numerically solve the system of delay differential equations using MATLAB.

In Figure 1, we show a computer simulation of the system (5) with initial conditions $T(0) = 7.5188$ $V(0) = 10$ $C(0) = 0$ and using the parameters δ_1 = 1, δ_2 = 0.005, δ_3 = 0.133, δ_4 = 0.05, δ_5 = 0.85, δ_6 = 1, δ_7 = 0.2, δ_8 = 1.22, b = 0.01. Therefore,

$$\delta_5 + b^{-1} = 100.88 > \delta_3 = 0.133$$

and $R_n = 17.5854 > \frac{\delta_1}{\delta_3} = 7.5188$ as required in Theorem 7. Hence,

$$\lim_{t\to\infty} T(t) = \frac{\delta_1}{\delta_3} = 7.5188,$$

$$\lim_{t\to\infty} V(t) = 0,$$

and

$$\lim_{t\to\infty} C(t) = 0.$$

In Figure 2, we show a computer simulation of the system (5) with initial conditions $T(0) = 1$, $V(0) = 1.7$, $C(0) = 0.02$ and using the parameters δ_1 = 1, δ_2 = 0.5, δ_3 = 0.133, δ_4 = 0.05, δ_5 = 0.05, δ_6 = 1, δ_7 = 0.02, δ_8 = 1.22, and b = 0.01. Therefore,

$$\delta_5 + b^{-1} = 100.5 > \delta_3 = 0.133$$

and

$$R_n = 1.385 < \frac{\delta_1}{\delta_3} = 7.5188$$

satisfying the conditions in Theorem 8. Hence,

$$\lim_{t\to\infty} T(t) = 1.385,$$

and

$$\lim_{t\to\infty} V(t) > 0.$$

In Figure 3, we show a computer simulation of the system (5) with initial conditions $T(0) = 1$, $V(0) = 2$, $C(0) = 0.02$ and using the parameters δ_1 = 1, δ_2 = 0.5, δ_3 = 0.01, δ_4 = 0.05, δ_5 = 0.05, δ_6 = 1, δ_7 = 0.02, δ_8 = 1.22, and b = 0.01. Therefore,

$$\delta_5 + b^{-1} = 100.5 > \delta_3 = 0.01$$

and

$$R_n = 1.423 << \frac{\delta_1}{\delta_3} = 1000$$

satisfying the conditions in Theorem 8. We also have

$$\lim_{t\to\infty} T(t) = 1.423,$$

$$\lim_{t\to\infty} V(t) > 0.$$

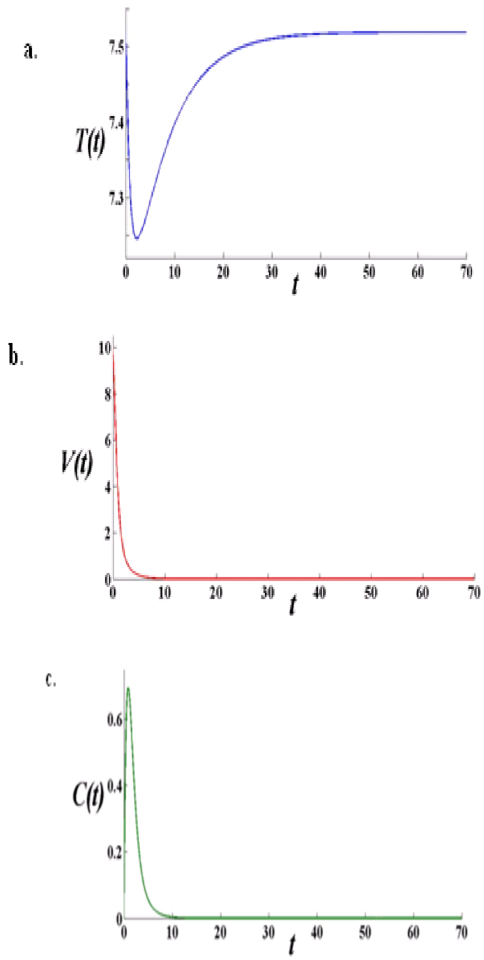

Figure 1. For δ_1 = 1, δ_2 = 0.005, δ_3 = 0.133, δ_4 = 0.05, δ_5 = 0.85, δ_6 = 1, δ_7 = 0.2, δ_8 = 1.22, b = 0.01, with $T(0) = 7.5188$ $V(0) = 10$, and $C(0) = 0$, we have $\delta_5 + b^{-1} = 100.88 > \delta_3 = 0.133$ and $R_n = 17.5854 > \frac{\delta_1}{\delta_3} = 7.5188$ as predicted in Theorem 7. Hence, $\lim_{t\to\infty} T(t) = \frac{\delta_1}{\delta_3} = 7.5188$,

$\lim_{t\to\infty} V(t) = 0$, and $\lim_{t\to\infty} C(t) = 0$. a) Time series of $T(t)$, b) Time series of $V(t)$, c) Time series of $C(t)$.

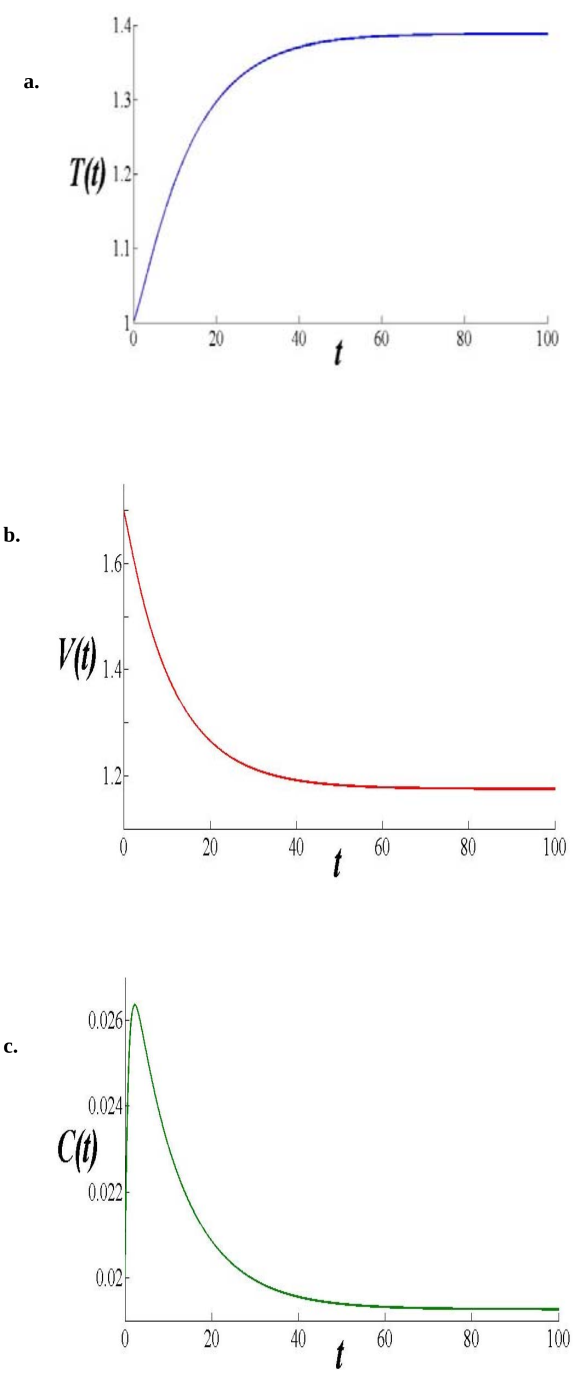

Figure 2. For δ_1 = 1, δ_2 = 0.5, δ_3 = 0.133, δ_4 = 0.05, δ_5 = 0.05, δ_6 = 1, δ_7 = 0.02, δ_8 = 1.22, b = 0.01, with $T(0) = 1$, $V(0) = 1.7$, and $C(0) = 0.02$. Therefore, we have $\delta_5 + b^{-1} = 100.5 > \delta_3 = 0.133$ and $R_n = 1.385 < \frac{\delta_1}{\delta_3} = 7.5188$, satisfying all conditions in Theorem 8. a) Time series of $T(t)$, b) Time series of $V(t)$, c) Time series of $C(t)$.

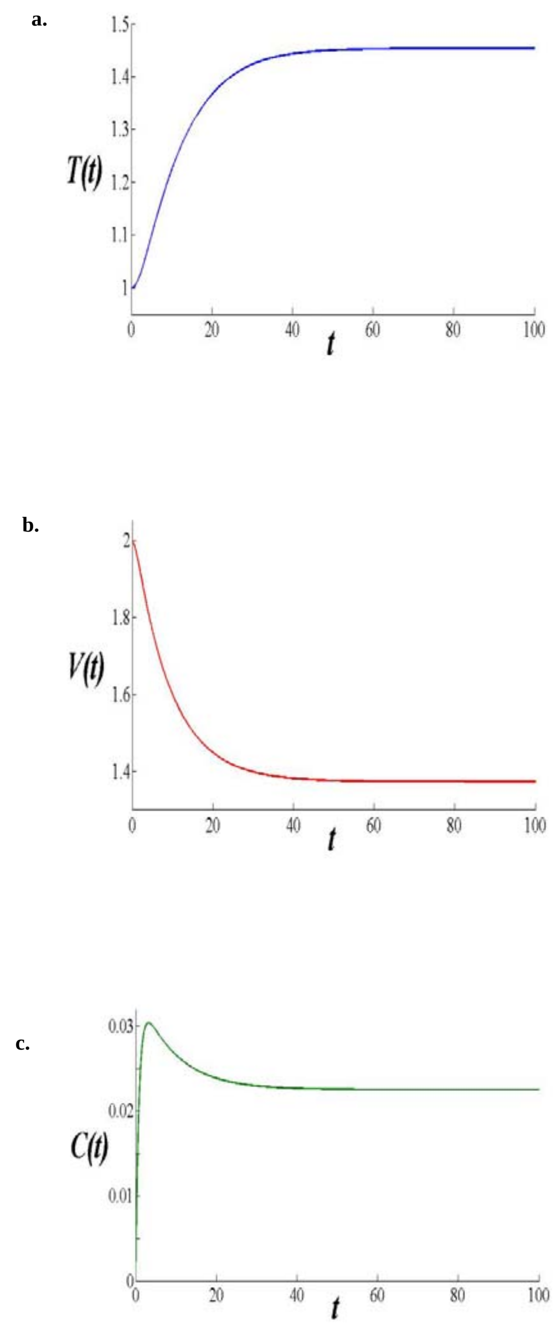

Figure 3: for δ_1 = 1, δ_2 = 0.5, δ_3 = 0.01, δ_4 = 0.05, δ_5 = 0.05, δ_6 = 1, δ_7 = 0.02, δ_8 = 1.22, b = 0.01 and $T(0) = 1$, $V(0) = 2$, $C(0) = 0.02$. Therefore $\delta_5 + b^{-1} = 100.5 > \delta_3 = 0.01$ and $R_n = 1.423 \ll \frac{\delta_1}{\delta_3} = 1000$ satisfy conditions in Theorem 8. a) Time series of $T(t)$, b) Time series of $V(t)$, c) Time series of $C(t)$.

Comparing Figures 2 and 3, we observe that the time series for $V(t)$ and $C(t)$ in Figure 3, where $R_n = 1.423 \ll \frac{\delta_1}{\delta_3} = 1000$, tend to a noticeably higher steady state levels than those in Figure 2.

V. Conclusion

We have proposed and analyzed an HIV infection model with continuous time delay. We provide some conditions which guarantee that the virus will vanish in the long run. The condition $\delta_5 + b^{-1} > \delta_3$ is reasonable since for biological interpretation, we may explain it as follows. It is natural to assume that the average time of virus emission from a CD4+ T-cell is less than the average life time of a CD4+ T-cell. Otherwise, the CD4+ T-cell will die before new virus particles may be produced. The expectation of the life time of a CD4+ T-cell is $1/\delta_3$ and the expectation time of virus emission is nb. Hence $nb < 1/\delta_3$ leads to $b^{-1} > n\delta_3$, which implies that $b^{-1} > \delta_3$, since $n \geq 1$. Numerical simulations have also been presented to illustrate the results.

Acknowledgement

This work was supported by Chiang Mai University.

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