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SENSITIVITY ANALYSIS OF HIV-1 VIRAL INTERACTION MODEL WITH SATURATED INFECTION RATE

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ABSTRACT. This paper deals with the sensitivity analysis of Delay-induced model for viral-immune interaction with saturated infection rate. The length of the delay parameter for preserving stability of the system is estimated, which gives the idea about the mode of action for controlling oscillations in viral infection. Sensitivity analysis is performed on a delay differential equation model for viral-immune system. The theoretical and numerical outcomes have been supported through experimental results from literatures.

1. INTRODUCTION

Time delay models of population dynamics in macroscopic models of the immune response are natural and common [1–4]. It is well known that viruses are intracellular parasites that depend on the host cells to survive and duplicate. As in HIV-1, intracellular time delays are intrinsic to the viral infection, replication processes and maturation. In general, multiple delays can naturally occur, and they have been incorporated into in host models (see [5–11]). To incorporate intracellular delays into in-host model may lead to additional insights in the study of complicated biological processes.

Time delays cannot be ignored in models for immune response. Antigenic stimulation generating CTLs may need a period of time τ [12]. Canabarro et. al., [13], studied a non-linear model of the cellular immune response to a viral infection with a time-delayed CTL responsiveness. For using the larger time

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delay value, the dynamic solutions present a series of bifurcations, evolving towards a chaotic behaviour. Buric et. al., [12], investigated the effects of time delay for immune response in a two dimensional system which consists of infected cells and CTLs, the time delay in any other single term of the equations produces stabilization of the transient irregular behaviour onto the simple attractor, i.e., the fixed point or the periodic orbit. Qizhi et. al., [14], discussed when the birth rates of susceptible cells λ is larger than a critical value, complicated dynamic behavior will occur as the time delay τ increases. Our main purpose of this study is to develop a viral-immune with saturation infection for small level of immune delay.

Here, we have considered saturated infection rate model [15], known as Holling type II infection rate and represented by the term $\frac{\beta xy}{1+\alpha y}; \beta > 0, \alpha \geq 0$. Let us we consider the following [15] saturated infection rate for three-dimensional equations with two delays are as follows:

$$
\begin{aligned}
\frac{dx}{dt} &= \lambda - dx - \frac{\beta xy}{1+\alpha y}, \quad \frac{dy}{dt} = \frac{\beta x(t-\tau_1)y(t-\tau_1)}{1+\alpha y(t-\tau_1)} - ay - pyz, \\
\frac{dz}{dt} &= cy(t-\tau_2)z(t-\tau_2) - bz,
\end{aligned} \tag{1.1}
$$

where $x(t)$ is the number of susceptible host cells, $y(t)$ is the number of virus population and $z(t)$ is the number of CTLs. Susceptible host cells are generated at a rate λ, die at a rate d and become infected by the virus at a rate β.

This paper is structured as follows. In Section 2, we estimate the length of the delay to preserve stability of the system (1.1). Sensitivity analysis is discussed in Section 3. Finally, In Section 4, provide the conclusion of this article.

2. Estimation of the length of delay to preserve stability

We linearize the system (1.1) about its steady state E_1, then (1.1) can be written as

(2.1)

$$
\begin{aligned}
&\dot{u}_1 + \left(d + \frac{\beta y_1}{1+\alpha y_1}\right) u_1(t) = -\frac{\beta x_1}{(1+\alpha y_1)^2} u_2(t), \\
&\dot{u}_2 + (a + pz_1)u_2(t) = \frac{\beta y_1}{1+\alpha y_1} u_1(t-\tau_1) + \frac{\beta x_1}{(1+\alpha y_1)^2} u_2(t-\tau_1) - pu_3(t)y_1, \\
&\dot{u}_3 + bu_3(t) = cz_1 u_2(t-\tau_2) + cy_1 u_3(t-\tau_2).
\end{aligned}
$$

Taking Laplace transform of the system (2.1), we get

$$\begin{aligned}
\left(\sigma + d + \frac{\beta y_1}{1+\alpha y_1}\right)\hat{u_1}(s) &= -\frac{\beta x_1}{(1+\alpha y_1)^2}\hat{u_2}(s) + u_1(0), \\
(\sigma + a + p z_1)\,\hat{u_2}(s) &= \frac{\beta y_1}{1+\alpha y_1}e^{-s\tau_1}\hat{u_1}(s) + \frac{\beta y_1}{1+\alpha y_1}e^{-s\tau_1}G_1(s) \\
&\quad + \frac{\beta x_1}{(1+\alpha y_1)^2}e^{-s\tau_1}\hat{u_2}(s) + \frac{\beta x_1}{(1+\alpha y_1)^2}e^{-s\tau_1}G_2(s) \\
&\quad - p y_1 \hat{u_3}(s) + u_2(0), \\
(\sigma + b)\,\hat{u_3}(s) &= c z_1 e^{-s\tau_2}\hat{u_2}(s) + c z_1 e^{-s\tau_2}G_3(s) + c y_1 e^{-s\tau_2}\hat{u_3}(s) \\
&\quad + c y_1 e^{-s\tau_2}G_4(s) + u_3(0).
\end{aligned} \tag{2.2}$$

where

$$G_1(s) = \int_{-\tau_1}^{0} e^{-st}u_1(t)dt; \quad G_2(s) = \int_{-\tau_1}^{0} e^{-st}u_2(t)dt;$$
$$G_3(s) = \int_{-\tau_2}^{0} e^{-st}u_2(t)dt; \quad G_4(s) = \int_{-\tau_2}^{0} e^{-st}u_3(t)dt;$$

$\hat{u_1}(s), \hat{u_2}(s), \hat{u_3}(s)$ are the Laplace transformation of $u_1(t), u_2(t)$ and $u_3(t)$ respectively. Following the lines of [16, 17], and using the Nyquist criterion, it can be shown that the sufficient conditions for the local asymptotic stability at E_1 are given by

$$\begin{aligned}
\Re H(i\omega_0) &= 0 \\
\Im H(i\omega_0) &> 0,
\end{aligned} \tag{2.3}$$

where ω_0 is the smallest positive root of equation (2.3). In [15] we have already shown that $E_1(x_1, y_1, z_1)$ is locally asymptotically stable in absence of delay (by virtue of (**??**))(Ref Thm 5). Hence, by continuity, all eigenvalues will continue to have negative real parts for sufficiently small $\tau_2 > 0$ provided one can guarantee that no eigenvalues with positive real parts bifurcates from infinity as τ increases from zero. This can be proved using Butler's lemma (Freedman and Rao, 1983), already stated before. In our case an equation (2.3) gives

$$M_1\omega_0^2 - M_3 = (M_6 - M_4\omega_0^2)\cos(\omega_0\tau_2) + M_5\omega_0\sin(\omega_0\tau_2) \tag{2.4}$$

$$\omega_0(\omega_0^2 - M_2) > M_5\omega_0\cos(\omega_0\tau_2) + (M_4\omega_0^2 - M_6)\sin(\omega_0\tau_2). \tag{2.5}$$

The sufficient conditions to guarantee the stability are given by (2.4) and (2.5), if these two equations are satisfied simultaneously. we shall utilize them to get an estimate on the length of delay. Our aim is to find an upper bound ω^* to ω_0, independent of τ_2 and then to estimate τ_2 so that the equation(2.5) holds for all values of ω, $0 \le \omega \le \omega^*$ and hence, in particular at $\omega = \omega^*$. Maximizing the R.H.S. of (2.4) subject to $|sin(\omega_0\tau_2)| \le 1$, $|cos(\omega_0\tau_2)| \le 1$, we obtain

$$\big(|M_1| - |M_4|\big)\omega_0^2 \le |M_5|\omega_0 + \big(|M_6| - |M_3|\big) \tag{2.6}$$

and if

$$\omega^* = \frac{|M_5| + \sqrt{|M_5|^2 + 4\big(|M_1| - |M_4|\big)\big(|M_6| - |M_3|\big)}}{2\big(|M_1| - |M_4|\big)} \tag{2.7}$$

then clearly we have $\omega_0 \le \omega^*$.

From (2.5) we obtain,

$$\omega_0^2 > M_2 + M_5\cos(\omega_0\tau_2) + \frac{(M_4\omega_0^2 - M_6)}{\omega_0}\sin(\omega_0\tau_2) \tag{2.8}$$

Since E_1 is locally asymptotically stable for $\tau_2 = 0$, the inequality (2.8) will continue to hold for sufficiently small $\tau_2 > 0$. Substituting equation(2.4) in equation(2.8) and rearranging we get

$$\begin{aligned}\left[\frac{\big(M_6 - M_4\omega_0^2\big)}{M_1} - M_5\right](1 - \cos(\omega_0\tau_2)) + \left[\frac{\big(M_4\omega_0^2 - M_6\big)}{\omega_0} - \frac{M_5\omega_0}{M_1}\right]\sin(\omega_0\tau_2)\\ < \frac{1}{M_1}\big(M_6 - M_4\omega_0^2 - M_1M_5 - M_1M_2 + M_3\big)\end{aligned} \tag{2.9}$$

Using the following bounds,

$$\begin{aligned}\left[\frac{\big(M_6 - M_4\omega_0^2\big)}{M_1} - M_5\right](1 - \cos(\omega_0\tau_2)) &= 2\sin^2\big(\frac{\omega_0\tau_2}{2}\big)\left[\frac{\big(M_6 - M_4\omega_0^2\big)}{M_1} - M_5\right]\\ &\le \frac{1}{2}\left|\frac{M_6 - M_4\omega_0^2 - M_1M_5}{M_1}\right|(\omega^*)^2\tau_2^2\end{aligned}$$

and

$$\left[\frac{\big(M_4\omega_0^2 - M_6\big)}{\omega_0} - \frac{M_5\omega_0}{M_1}\right]\sin(\omega_0\tau_2) \le \left|\left[\left(M_4 - \frac{M_5}{M_1}\right)(\omega^*)^2 - M_6\right]\right|\tau_2$$

in (2.9) we get

$$L_1\tau_2^2 + L_2\tau_2 < L_3$$

where

$$L_1 = \frac{1}{2}\left|\frac{M_6 - M_4\omega_0^2 - M_1M_5}{M_1}\right|(\omega^*)^2,$$

$$L_2 = \left|\left[\left(M_4 - \frac{M_5}{M_1}\right)(\omega^*)^2 - M_6\right]\right|,$$

$$L_3 = \frac{1}{M_1}\Big(M_6 - M_4\omega_0^2 - M_1M_5 - M_1M_2 + M_3\Big).$$

Hence

$$\tau_2^* = \frac{1}{2L_1}\Big(- L_2 + \sqrt{L_2^2 + 4L_1L_3}\Big)$$

Then, for $0 \leq \tau_2 < \tau_2^*$, the Nyquist criterion holds and τ_2^* estimates the maximum length of delay preserving the stability.

3. Sensitivity Analysis

Of considerable importance in assessing the model (1.1) is the sensitivity of the model solution y(t; $\mathbf{q}$) to changes in the parameter $\mathbf{q}$ or the sensitivity of the best to changes in the data. A knowledge of how the solution can vary with respect to small change in the data or the parameters can yield insights into the model behaviour and can assist the modelling process. The sensitivity of the parameter estimate to the observation is low if the sensitivity of the state variable to the parameter estimate is high. There are different approaches to find the sensitivity functions of DDEs [18]. However, for simplicity we will use the so called “direct approach" to find sensitivity functions of model (1.1). Consider model (1.1), with vector parameter $\mathbf{q} = [a, c, \beta, p, d, \alpha]^T$. The sensitivity functions with respect to the parameter $\mathbf{q_i}$ $(i = 1, ..., 6)$, for the model (1.1) are denoted by,

$$\begin{aligned} u_{1,\mathbf{q_i}} &= \frac{\partial u_1(t)}{\partial \mathbf{q_i}}, \\ u_{2,\mathbf{q_i}} &= \frac{\partial u_2(t)}{\partial \mathbf{q_i}}, \\ u_{3,\mathbf{q_i}} &= \frac{\partial u_3(t)}{\partial \mathbf{q_i}}. \end{aligned} \tag{3.1}$$

The corresponding sensitivity of system (1.1), with respect to the parameter 'd' is as follows,

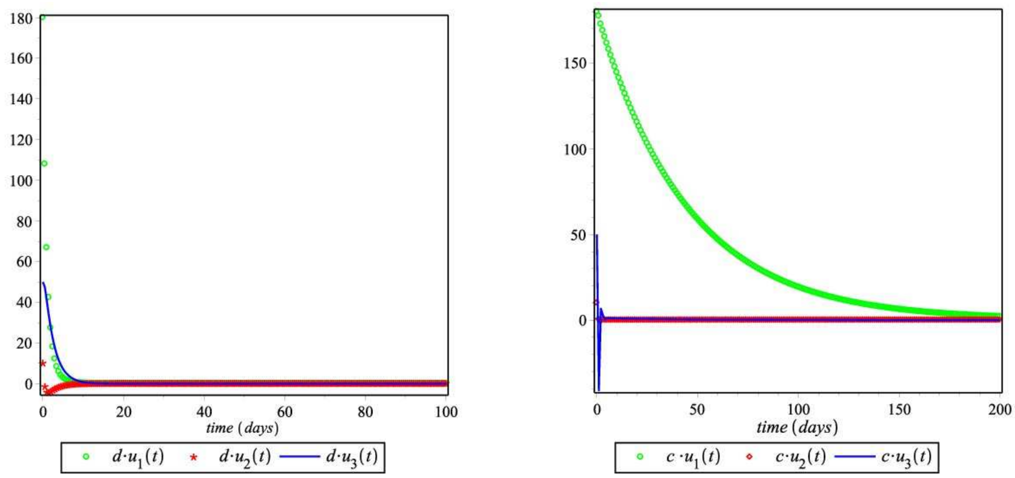
$$
\begin{aligned}
\left(\frac{du_1}{dt}\right)_{t,d} &= -u_1(t) - \frac{\beta y_1}{1+\alpha y_1}u_{1,d}(t,d) \\
&\quad -\frac{\beta x_1}{(1+\alpha y_1)^2}u_{2,d}(t,d), \\
\left(\frac{du_2}{dt}\right)_{t,d} &= \frac{\beta y_1}{1+\alpha y_1}u_{1,d}(t-\tau_1,d) + \frac{\beta x_1}{(1+\alpha y_1)^2}u_{2,d}(t-\tau_1,d) \\
&\quad -au_{2,d}(t,d) - pu_{2,d}(t,d)z_1 - py_1u_{3,d}(t,d), \\
\left(\frac{du_3}{dt}\right)_{t,d} &= cz_1u_{2,d}(t-\tau_2,d) + cy_1u_{3,d}(t-\tau_2,d) - bu_{4,d}(t,d).
\end{aligned}
\tag{3.2}
$$

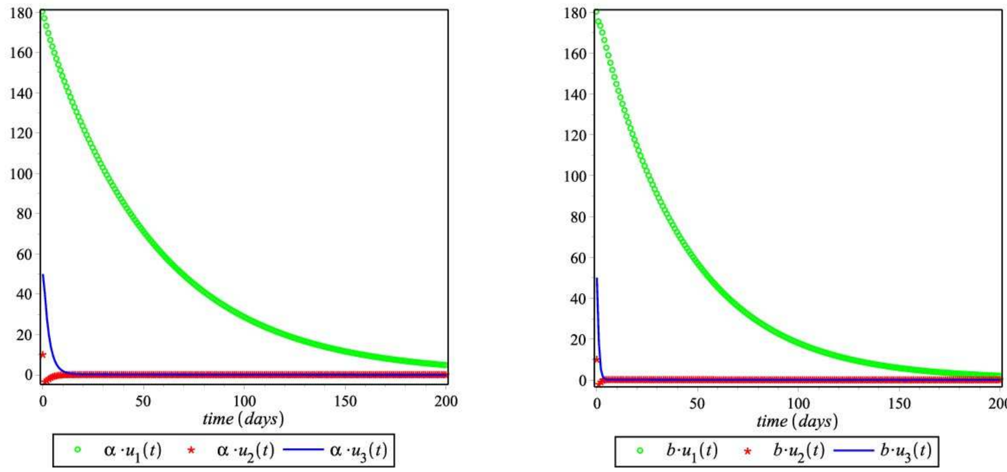
Similarly we can easily obtained the corresponding sensitivity of system (1.1), with respect to the parameter $a,\ p,\ \alpha,\ b,\ c,$ and β.

The semi-relative sensitivity solutions (depicted in Fig.1 and 2) are calculated by simply multiplying the unmodified sensitivity solutions by a chosen parameter which provides information concerning the amount the state will change when that parameter is doubled.

Figure 1

Parameters description and Values [9, 10]





In Fig. 1, we notice that the population of the immune CTL cell is negatively proportion with increasing parameter the parameter “c" and it is very sensitive in the early time intervals and the sensitivity decreases by time to be insensitive in the steady state.

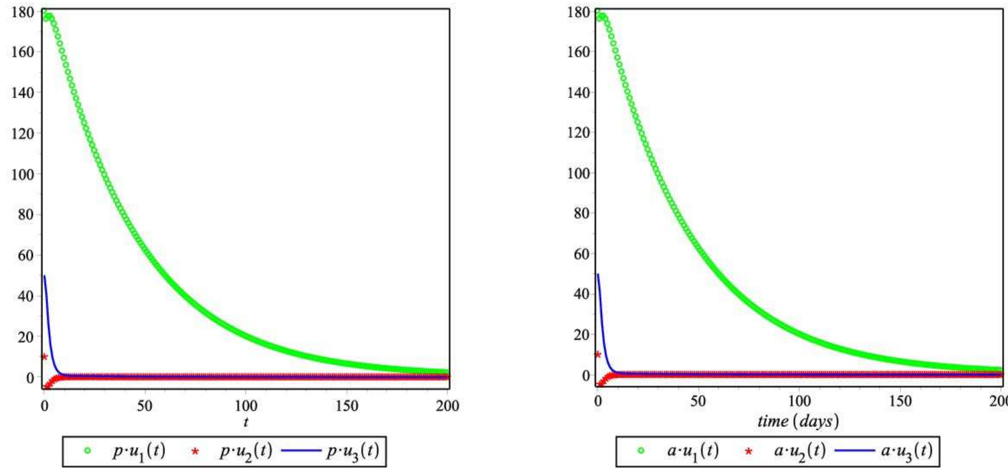


Figure. 2. We notice that the population of the susceptible, virus and CTL immune cells are negatively proportion with increasing parameter the parameter “β’ and it is very sensitive in the early time intervals and the sensitivity decreases by time to be insensitive in the steady state.

We can easily see that the described model is very sensitive with respect to the parameter “b, α, d, a, p". From the above figures, we may observe that a small change in the above said parameters, which can produce significant change in the level of viral infection model.

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