A THREE DIMENSIONAL HTLV-1 MODEL WITH INTRACELLULAR AND IMMUNE ACTIVATION DELAYS

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ABSTRACT. In this paper, a three dimensional mathematical model for HTLV-1 infection with intracellular delay and immune activation delay is investigated. By applying the frequency domain approach, we show that time delays can destabilize the HAM/TSP equilibrium, leading to Hopf bifurcations and stable or unstable periodic oscillations. At the end, numerical simulations are illustrated.

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1. Introduction

In the last decades, mathematical modelling of infectious diseases has attracted much attentions. Mathematical modelling is a useful tool for better understanding disease dynamics, making prediction of disease outbreak and finding therapeutic strategies against infections. Furthermore, mathematical modelling with delay differential equations (DDEs) is widely used for analysis and predictions of various areas of the life sciences. Time delays in these models take into account a dependence of the present state of the modelled system on its past history [16].

HTLV-1 is an abbreviation for human T-cell lymphotropic virus type 1, also called adult T-cell lymphoma virus type 1. The etiologic agent for the HTLV-1 associated myelopathy (HAM), a chronic inflammatory disease of the central nervous system, also called tropical spastic paraparesis (TSP). HTLV-1 infection can also lead to adult T cell leukemia (ATL) [10]. HTLV-1 belongs to the retroviruses family. It mainly infects the $CD4^+$ T cells, B-lymphocytes, monocytes and fibroblasts results in persistent human infection [9]. In the most of virus infections like HIV-1, HTLV-I and HBV, cytotoxic T lymphocytes (CTLs), $CD8^+$, are the main host immune factor involved the defence against virus infections [1]. The host immune system, especially the cellular response, against HTLV-I exerts critical control over virus replication and the proliferation of infected cells [3]. Understanding the pathogenesis of the HTLV-1 within the host has important implications for the development of therapeutic measures [4].

Several papers are considered the following three dimensional model (1.1) for HTLV-1, we cite as example [6, 10, 14]

$$\begin{cases} \dot{x} = \lambda - \beta xy - \mu_1 x \\ \dot{y} = \sigma\beta xy - \gamma yz - \mu_2 y \\ \dot{z} = \nu f(z, y) - \mu_3 z \end{cases} \tag{1.1}$$

In this model, there are three main types of cells which are critical to the modelling effort: The uninfected $CD4^+$ target cells x, infected $CD4^+$ target cells y, and HTLV-1 specific $CD8^+$ CTLs z, with turnover rates of μ_1, μ_2 and μ_3 respectively. Healthy $CD4^+$ T cells are produced at a constant rate λ. The infection of healthy $CD4^+$ T cells is through direct cell to cell contact with a proviral $CD4^+$ T cell. $\beta > 0$ represents the ability of a proviral cell to transmit HTLV-1 to a susceptible cell.

$\sigma \in [0,1]$ represents the probability of a transmission of HTLV-1 resulting in a new proviral cell. γ is the rate of CTL-initiated lysis. The term $\nu f(z,y)$ represents the production of CTLs in response to HTLV-1, where $f(z,y)$ is the CTL response function. Lang et al in [10] considered a sigmoidal response function in the form of $f(z,y) = \frac{z^2}{z^2+a^2}y$

Moreover, in HTLV-1, the period of contacting the HTLV-1 with a target cell until producing new viruses from infected cell needs a period of time. In more realistic HTLV-1 infection models time delay have been considered [2, 5, 8, 15, 17, 18, 19]. In this regard, we considered the time delay τ_1 as the intracellular delay. In addition, the activation rate of immune cells at time t is assumed to depend on the virus load and the number of immune cells at time $t-\tau_2$. Here τ_2 is the time lag accounting for the time needed for the immune system to trigger a sequence of events such as antigenic activation, selection, and proliferation of the immune cells to produce new immune cells.

So, the desired systems is

$$\begin{cases} \dot{x}(t) = \lambda - \beta x(t)y(t) - \mu_1 x(t) \\ \dot{y}(t) = \sigma\beta x(t-\tau_1)y(t-\tau_1) - \gamma y(t)z(t) - \mu_2 y(t) \\ \dot{z}(t) = \nu \frac{z^2(t-\tau_2)}{z^2(t-\tau_2)+a^2} y(t-\tau_2) - \mu_3 z(t) \end{cases} \tag{1.2}$$

2. Hopf bifurcation and its stability

We denote by $X = C([-\rho, 0], \mathbb{R}^3_+)$, the Banach space of continuous function mapping the interval $[-\rho, 0]$ into $\mathbb{R}^3_+$ equipped with the sup-norm, where $\rho = max\{\tau_1, \tau_2\}$. By the standard theory of functional differential equation [7] we know that for any $\phi \in X$ there exists a unique solution,

$$Y(t,\phi) = (x(t,\phi), y(t,\phi), z(t,\phi)),$$

of the delayed system (1.2), which satisfies $Y_0 = \phi$, where $\phi = (\phi_1, \phi_2, \phi_3) \in \mathbb{R}^3_+$ with $\phi_i(\theta) \geq 0; \theta \in [-\rho, 0], i = 1, 2, 3$. The initial conditions are given by,

$$\begin{cases} x(\theta) = \phi_1(\theta) \\ y(\theta) = \phi_2(\theta) \\ z(\theta) = \phi_3(\theta) \end{cases} \tag{2.1}$$

Lemma 1. *Under initial conditions in* (2.1)*, all solutions of system* (1.2) *are positive and ultimately bounded in* $\mathbb{R} \times C \times C$.

With a same arguments given in [12, 11], it is easy to show the validity of Lemma 1. By Lemma 1, the dynamics of system (1.2) can be analysed in the following bounded feasible region

$$\Gamma = \{(x, y, z) \in \mathbb{R}_+ \times C^+ \times C^+ : |x| \leq \frac{\lambda}{\mu_1}, \|x + y\| \leq \frac{\lambda}{\bar{\mu}}, |z| \leq \frac{\nu\lambda}{\mu_3\bar{\mu}}\}$$

where $\bar{\mu} = min\{\mu_1, \mu_2\}$.

2.1. **Equilibria of system** (1.2)**.** For calculation of the equilibrium points the three different cases will be considered

Case 1. *The equilibria for* $z = 0$ *are*

$$P_0 = (\frac{\lambda}{\mu_1}, 0, 0), \quad P_1 = (\frac{\mu_2}{\sigma\beta}, \frac{\lambda\sigma\beta - \mu_1\mu_2}{\beta\mu_2}, 0) \tag{2.2}$$

P_0 *is called the free disease equilibrium and* P_1 *is called the carrier equilibrium. Furthermore, if* $z \neq 0$

$$\lambda - \beta xy - \mu_1 x = 0 \Rightarrow y = \frac{\lambda - \mu_1 x}{\beta x} \tag{2.3}$$

and

$$\sigma\beta xy - \gamma yz - \mu_2 y = 0 \Rightarrow x = \frac{\mu_2 + \gamma z}{\sigma\beta} \tag{2.4}$$

(2.4) *and* (2.3)*, imply*

$$y = \frac{\lambda\sigma\beta - \mu_1\mu_2 - \mu_1\gamma z}{\beta\mu_2 + \beta\gamma z} \tag{2.5}$$

By substituting (2.5) *in the third equation of* (1.2)*, we obtain*

$$\nu\lambda\sigma\beta z^2 - \nu\mu_1\mu_2 z^2 - \nu\mu_1\gamma z^3 - \beta\mu_2\mu_3 z^3 - \beta\gamma\mu_3 z^4 - \mu_2\mu_3\beta a^2 z - \mu_3\beta\gamma a^2 z^2 = 0 \tag{2.6}$$

$z \neq 0$*, thus* (2.6) *can be rewritten as follows:*

$$g(z) = \beta\gamma\mu_3 z^3 + (\nu\mu_1\gamma + \beta\mu_2\mu_3)z^2 - \nu(\lambda\sigma\beta - \mu_1\mu_2)z + \mu_3\beta\gamma a^2 z + \mu_2\mu_3\beta a^2 = 0 \tag{2.7}$$

Note that $z \geq a$ from biological point of view imply $y > 0$ because, the infection affected on the body. Hence, in (2.5)*:*

$$\lambda\sigma\beta - \mu_1\mu_2 - \mu_1\gamma z > 0 \Rightarrow \lambda\sigma\beta - \mu_1\mu_2 > \mu_1\gamma z \Rightarrow \frac{\lambda\sigma\beta - \mu_1\mu_2}{\mu_1\gamma} > z \geq 0. \tag{2.8}$$

Let

$$R_0 = \frac{\lambda\sigma\beta}{\mu_1\mu_2} \tag{2.9}$$

consequently

$$0 \leq z < \frac{\mu_2}{\gamma}(R_0 - 1) \tag{2.10}$$

The acceptable roots of $g(z)$ is the interval

$$I = \left[0, \frac{\mu_2}{\gamma}(R_0 - 1)\right), \quad R_0 > 1 \tag{2.11}$$

Therefore

$$\lambda\sigma\beta - \mu_1\mu_2 > 0 \tag{2.12}$$

There is at least one root of $g(z)$ in interval (2.11) *([10]). We indicate the corresponding equilibrium with:*

$$P^* = (x^*, y^*, z^*) \tag{2.13}$$

where z^* satisfies in $g(z)$ and x^* and y^* are as (2.4) *and* (2.5) *respectively.*

Remark 1. *We have shown if $R_0 > 1$, the equilibrium P^* exists which is corresponds to the HAM/TSP state. Therefore, the patient has a high risk of developing HTLV-1. In order to preventing the spread of the disease, drug control is an essential tool for the interaction of HTLV-1 infection and the HTLV-1 specific CTL response. Therefore, that is necessary to estimate the values of τ_1 and τ_2 to determine the effective time of the drug therapy. In the following, we apply graphical Hopf bifurcation theory to obtain the region of stability with respect to two parameters τ_1 and τ_2. Hopf bifurcation determines the appearance of multiple limit cycles under system parameter variation. Therefore, the birth and the amplitudes of multiple limit cycles can be controlled by monitoring the corresponding degenerate Hopf bifurcations with respect to parameters. This task would be accomplished in the frequency domain setting.*

2.2. **Existence of Hopf bifurcation at the equilibrium point P^*.** We should mention that, from now on the parameter for the Hopf bifurcation is the time delay parameters τ_1 and τ_2 and the rest of the parameters of the system (1.2) are fix. The system (1.2) can be rewritten in a vector form as:

$$\frac{\mathrm{d}X}{\mathrm{d}t} = AX(t) + H(X) \tag{2.14}$$

where $X = (x, y, z)^T$ and

$$A = \begin{pmatrix} -\mu_1 & 0 & 0 \\ 0 & -\mu_2 & 0 \\ 0 & 0 & -\mu_3 \end{pmatrix} \tag{2.15}$$

Also

$$H(X) = \begin{pmatrix} \lambda - \beta xy \\ \sigma\beta x(t-\tau_1)y(t-\tau_1) - \gamma yz \\ \nu y(t-\tau_2)\frac{z^2(t-\tau_2)}{z^2(t-\tau_2)+a^2} \end{pmatrix} \tag{2.16}$$

choosing a "state feedback control" $(u = g(y(t-\tau_1), y(t-\tau_2); \tau_1; \tau_2))$ and

$$\begin{cases} \frac{\mathrm{d}X}{\mathrm{d}t} = AX + Bu \\ Y = -CX \\ u = g(Y(t-\tau_1), Y(t-\tau_2); \tau_1; \tau_2)) \end{cases} \tag{2.17}$$

where $B = C = I_{3\times 3}$ is a unit matrix and $Y = (y_1, y_2, y_3)$,

$$\begin{aligned} u &= g(Y(t-\tau_1), Y(t-\tau_2); \tau_1; \tau_2)) \\ &= \begin{pmatrix} \lambda - \beta(-y_1(t))(-y_2(t)) \\ \sigma\beta(-y_1(t-\tau_1))(-y_2(t-\tau_1)) - \gamma(-y_2(t))(-y_3(t)) \\ \nu(-y_2(t-\tau_2))\frac{y_3^2(t-\tau_2)}{y_3^2(t-\tau_2)+a^2} \end{pmatrix} \end{aligned} \tag{2.18}$$

Next, taking Laplace transform on (2.15), the standard transfer matrix of the linear part of the system is:

$$G(s; \tau_1; \tau_2) = C[sI - A]^{-1}B = \begin{pmatrix} \frac{1}{s+\mu_1} & 0 & 0 \\ 0 & \frac{1}{s+\mu_2} & 0 \\ 0 & 0 & \frac{1}{s+\mu_3} \end{pmatrix} \tag{2.19}$$

Then the Jacobian of (2.18), is given by

(2.20)

$$J = \frac{\partial g}{\partial Y} = \begin{pmatrix} -\beta y_2(t) & -\beta y_1(t) & 0 \\ \sigma\beta y_2(t-\tau_1)e^{-s\tau_1} & \sigma\beta y_1(t-\tau_1)e^{-s\tau_1} - \gamma y_3(t) & -\gamma y_2(t) \\ 0 & \nu\frac{y_3^2(t-\tau_2)}{y_3^2(t-\tau_2)+a^2}e^{-s\tau_2} & \nu y_2(t-\tau_2)\frac{2y_3(t-\tau_2)a^2}{(y_3^2(t-\tau_2)+a^2)^2}e^{-s\tau_2} \end{pmatrix}$$

Let

$$\begin{cases} P = \mu_2 + \gamma z^* \\ M = \frac{\lambda\sigma\beta - \mu_1 P}{P} \\ N = \frac{z^*}{z^{*2}+a^2}\nu \end{cases} \tag{2.21}$$

Then J in (2.20), at equilibrium point P^* will be obtained as follows

$$J(\tau_1, \tau_2) = \begin{pmatrix} -M & -\frac{P}{\sigma} & 0 \\ \sigma M e^{-s\tau_1} & \mu_2 + \gamma z^*(e^{-s\tau_1} - 1) & -\gamma\frac{M}{\beta} \\ 0 & N z^* e^{-s\tau_2} & \frac{a^2 NM}{\beta(z^{*2}+a^2)}e^{-s\tau_2} \end{pmatrix} \tag{2.22}$$

also

$$G(s;\tau_1;\tau_2)J(\tau_1,\tau_2) = \begin{pmatrix} -\frac{M}{s+\mu_1} & -\frac{P}{\sigma(s+\mu_1)} & 0 \\ \frac{\sigma M e^{-s\tau_1}}{s+\mu_2} & \frac{\mu_2+\gamma z^*(e^{-s\tau_1}-1)}{s+\mu_2} & -\gamma\frac{M}{\beta(s+\mu_2)} \\ 0 & \frac{N z^* e^{-s\tau_2}}{s+\mu_3} & \frac{\frac{NMa^2}{\beta(z^{*2}+a^2)}e^{-s\tau_2}}{s+\mu_3} \end{pmatrix} \tag{2.23}$$

Set $h(\lambda, s; \tau_1; \tau_2) = det[\lambda I - G(s;\tau_1;\tau_2)J(\tau_1,\tau_2)]$ and let $\hat{\lambda} = \hat{\lambda}(i\omega;\tau_1;\tau_2)$ be the eigenvalue of $G(i\omega;\tau_1;\tau_2)J(\tau_1,\tau_2)$ which is $\hat{\lambda}(i\omega_0;\tau_{1_0};\tau_{2_0}) = -1 + 0i$. Considering $s = i\omega$ and $\hat{\lambda}(i\omega_0;\tau_{1_0};\tau_{2_0}) = -1 + 0i$, in $h(\lambda, s;\tau_1;\tau_2)$ gives

$$\begin{aligned} &s^3 + A_1 s^2 + A_2 s + A_3 + e^{-s(\tau_1+\tau_2)}(B_1 s + B_2) + \\ &e^{-s\tau_2}(C_1 s^2 + C_2 s + C_3) + e^{-s\tau_1}(D_1 s^2 + D_2 s + D_3) = 0 \end{aligned} \tag{2.24}$$

where

$$
\begin{cases}
A_1 = z^*\gamma + M - \mu_2 \\
A_2 = 2\mu_2 M + \mu_3 M - \mu_1\mu_2 + \mu_1\gamma z^* + \mu_3\gamma z^* - \mu_2\mu_3 - M\gamma z^* \\
A_3 = 2\mu_2\mu_3 M - \mu_1\mu_2\mu_3 + \mu_1\mu_3\gamma z^* - \mu_3 M\gamma z^* \\
B_1 = \frac{-MNa^2 z^*\gamma}{\beta(z^{*2}+a^2)} \\
B_2 = \frac{-\mu_1 MNa^2 z^{*2}\gamma - \mu_2 a^2 M^2 N}{\beta(z^{*2}+a^2)} \\
C_1 = \frac{-MNa^2}{\beta(z^{*2}+a^2)} \\
C_2 = \frac{-2\mu_2 MNa^2 - \mu_1 MNa^2 + M^2 Na^2 - MNz^{*3}\gamma}{\beta(z^{*2}+a^2)} \\
C_3 = \frac{-2\mu_1\mu_2 MNa^2 - \mu_1 MNz^{*3}\gamma + 2\mu_2 a^2 M^2 N + M^2 Nz^{*3}\gamma}{\beta(z^{*2}+a^2)} \\
D_1 = -z^*\gamma \\
D_2 = -\mu_1 z^*\gamma - \mu_3 z^*\gamma - \mu_2 M \\
D_3 = -\mu_1\mu_3 z^*\gamma - \mu_3\mu_2 M
\end{cases} \tag{2.25}
$$

Now, we study the following three cases:

Case (1) . If $\tau_1 = \tau_2 = 0$, then the characteristic equation (2.24) becomes

$$s^3 + A_1 s^2 + A_2 s + A_3 = 0 \tag{2.26}$$

(H0) . By Routh Hurwitz criterion if $A_1, A_2, A_3 > 0$ and $A_1 A_2 > A_3$, then P^* is locally asymptotically stable.

Case (2) . If $\tau_1 = 0$ and $\tau_2 > 0$ then for the characteristic equation (2.24) one can have

$$s^3 + A_1 s^2 + A_2 s + A_3 + e^{-s\tau_2}(C_1 s^2 + (C_2 + B_1)s + (C_3 + B_2)) = 0 \tag{2.27}$$

If $i\omega(\omega > 0)$ is a root of Eq. (2.27), then

$$-i\omega^3 + A_1\omega^2 + iA_2\omega + A_3 + e^{-i\tau_2\omega}(C_1\omega^2 + i(C_2 + B_1)\omega + (C_3 + B_2)) = 0. \tag{2.28}$$

Separating the real and imaginary parts, we obtain

$$
\begin{cases}
A_1\omega^2 + A_3 = -(C_1\omega^2 + C_3 + B_2)cos(\omega\tau_2) - (C_2 + B_1)\omega sin(\omega\tau_2) \\
-\omega^3 + A_2\omega = -(C_2 + B_1)\omega cos(\omega\tau_2) + (C_1\omega^2 + C_3 + B_2)sin(\omega\tau_2)
\end{cases} \tag{2.29}
$$

Adding up the squares of the corresponding sides of the above equations in (2.29) leads to

(2.30)
$$\omega^6 + (A_1^2 - 2A_2 - C_1^2)\omega^4 + (2A_1A_3 - 2C_1E_2 - E_1^2 + A_2^2)\omega^2 + (A_3^2 - E_2^2) = 0$$

where

(2.31)
$$\begin{cases} E_1 = C_2 + B_1 \\ E_2 = C_3 + B_2 \end{cases}$$

Let

(2.32)
$$z = \omega^2$$

(2.33)
$$\begin{cases} r_1 = (A_1^2 - 2A_2 - C_1^2) \\ r_2 = (2A_1A_3 - 2C_1E_2 - E_1^2 + A_2^2) \\ r_3 = (A_3^2 - E_2^2) \end{cases}$$

Then equation (2.30) can be rewritten as

(2.34)
$$h(z) = z^3 + r_1z^2 + r_2z + r_3 = 0$$

For finding the different cases that will occur for roots, r_1, r_2 and r_3 we do as, [13].

Claim 1. *If $r_3 < 0$, then equation* (2.34) *has at least one positive root*

Proof. : $h(0) = r_3 < 0$ and $\lim_{z\to\infty} h(z) = \infty$, hence there exist a $Z_0 \in (0, \infty)$ so that $h(z_0) = 0$ □

Claim 2. *If $r_3 \geq 0$, then the necessary condition for* (2.34) *to have positive roots is $\Delta = r_1^2 - 3r_2 \geq 0$*

Proof. :

(2.35)
$$\frac{\mathrm{d}h(z)}{\mathrm{d}z} = 3z^2 + 2r_1z + r_2$$

From

(2.36)
$$3z^2 + 2r_1z + r_2 = 0$$

the roots of equation (2.36) are:

$$z_{1,2} = \frac{-r_1 \pm \sqrt{r_1^2 - 3r_2}}{3} \tag{2.37}$$

If $\Delta = r_1^2 - 3r_2 < 0$ then (2.36) does not have real roots. So the function $h(z)$ is monotone increasing in z. It follows from $h(0) = r_3 \geq 0$ that equation (2.34) has no positive real roots. Clearly if $\Delta \geq 0$, then $z_1 = \frac{-r_1+\sqrt{\Delta}}{3}$ is the local minimum of $h(z)$. Then we can state that: □

Claim 3. *If $r_3 \geq 0$ then equation (2.34) has positive roots if and only if $z_1 > 0$ and $h(z_1) \leq 0$*

Proof. : The sufficiency is obvious. We only need to prove the necessity. Otherwise, we assume that either $z_1 \leq 0$ or $z_1 > 0$ and $h(z_1) > 0$. If $z_1 \leq 0$, since $h(z)$ is increasing for $z \geq z_1$ and $h(0) = r_3 \geq 0$, it follows that h(z) has no positive real zeros. □

Let us to have the following condition:

(H1) : Suppose that equation (2.34) has positive roots. Without loss of generality, we assume that it has three positive roots, denoted by z_1, z_2 and z_3. Then equation (2.30) has three positive roots, say

$$\begin{cases} \omega_1 = \sqrt{z_1} \\ \omega_2 = \sqrt{z_2} \\ \omega_3 = \sqrt{z_3} \end{cases} \tag{2.38}$$

From (2.29) and (2.31), one can obtain:

(2.39)

$$\begin{cases} (A_1\omega^2 + A_3)(C_1\omega^2 + E_2) = -(C_1\omega^2 + E_2)^2 cos(\omega\tau_2) - (C_1\omega^2 + E_2)E_1\omega sin(\omega\tau_2) \\ -(\omega^3 + A_2\omega)E_1\omega = -E_1^2\omega^2 cos(\omega\tau_2) + (C_1\omega^2 + E_2)E_1\omega sin(\omega\tau_2) \end{cases}$$

Adding up the two terms of (2.39), implies that

$$cos(\omega\tau_2) = \frac{\delta}{\delta_1} \tag{2.40}$$

where

$$\begin{cases} \delta = (A_1C_1 - E_1)\omega^4 + (A_1E_2 + A_3C_1 - A_2E_1)\omega^2 + A_3E_2 \\ \delta_1 = -(C_1^2\omega^4 + (2C_1E_2 + E_1^2)\omega^2 + E_2^2) \end{cases} \tag{2.41}$$

thus

(2.42)

$$\tau_{2_k}^{(j)} = \frac{1}{\omega_k}[arccos(\frac{(A_1C_1 - E_1)\omega_k^4 + (A_1E_2 + A_3C_1 - A_2E_1)\omega_k^2 + A_3E_2}{-(C_1^2\omega_k^4 + (2C_1E_2 + E_1^2)\omega_k^2 + E_2^2)}) + 2j\pi].$$

$k = 1, 2, 3\,;\ j = 0, 1, 2, ...$

Then $\pm i\omega_k$ is a pair of purely imaginary roots of equation (2.30) with $\tau = \tau_{2_k}^{(j)}$, $k = 1, 2, 3$, $j = 0, 1, 2, ...$ Let

$$\begin{aligned} &\tau_{2_0} = \tau_{2_{k_0}}^{(j_0)} = min\left\{\tau_{2_k}^{(j)}\right\},\ \omega = \omega_k, \\ &k = 1, 2, 3\,;\ j \geq 0 \end{aligned} \tag{2.43}$$

Lemma 2. *Suppose that $z_k = \omega_k^2$ where $k = 1, 2, 3$ and $\frac{\mathrm{d}h(z_k)}{\mathrm{d}z} \neq 0$, then the following condition hold:*

$$\Re[\frac{\mathrm{d}s_k(\tau_2)}{\mathrm{d}\tau_2}] \neq 0 \tag{2.44}$$

Proof. Differentiating of (2.27) with respect to τ_2 and considering the relations (2.31) leads to

(2.45)

$$\begin{aligned} &(3s^2 - 2A_1s + A_2 + (-2C_1s + E_1)e^{-s\tau_2} - \tau_2(-C_1s^2 + E_1s + E_2)e^{-s\tau_2})ds \\ = \ &s(-C_1s^2 + E_1s + E_2)e^{-s\tau_2})d\tau_2 \end{aligned}$$

so

(2.46)

$$(\frac{\mathrm{d}s}{\mathrm{d}\tau_2})^{-1} = \frac{(3s^2 - 2A_1s + A_2)e^{s\tau_2}}{-C_1s^2 + E_1s + E_2)s} + \frac{-2C_1s + E_1}{(-C_1s^2 + E_1s + E_2)s} - \frac{\tau_2}{s} = \frac{M_1}{N_1} + \frac{M_2}{N_1} - \frac{\tau_2}{s}$$

Put $s = i\omega_k$ and $\tau_2 = \tau_{2_j}^k$, $k = 1, 2, 3$, $j = 0, 1, 2, ...$, then each terms in (2.46), will be as follows:

(2.47)

$$\begin{cases} [M_1]_{\tau=\tau_j^k} = (-3\omega_k^2 - 2iA_1\omega_k + A_2)(cos\omega_k\tau_{2_j}^k + isin\omega_k\tau_{2_j}^k) = \\ (-3\omega_k^2 + A_2)cos\omega_k\tau_{2_j}^k + 2A_1 sin\omega_k\tau_{2_j}^k + i[-2A_1\omega_k cos\omega_k\tau_{2_j}^k + (-3\omega_k^2 + A_2)sin\omega_k\tau_{2_j}^k], \\ [M_2]_{\tau=\tau_{2_j}^k} = E_1 - 2iC_1\omega_k, \\ [N_1]_{\tau_2=\tau_{2_j}^k} = (C_1\omega_k^2 + iE_1\omega_k + E_2)i\omega_k = -E_1\omega_k^2 + i(C_1\omega_k^2 + E_2)\omega_k. \end{cases}$$

Suppose that

$$M^* = (-E_1\omega_k^2 + i(E_2 + C_1\omega_k)\omega_k)^2 = E_1^2\omega_k^4 + (E_2 + C_1\omega_k^2)^2\omega_k^2 \tag{2.48}$$

Therefore

$$\Re[(\frac{\mathrm{d}s}{\mathrm{d}\tau_2})^{-1}] = \Re\left\{\frac{(3s^2 - 2A_1s + A_2)e^{s\tau_2}}{(-C_1s^2 + E_1s + E_2)s}\right\} + \Re\left\{\frac{-2C_1s + E_1}{(-C_1s^2 + E_1s + E_2)s}\right\} \tag{2.49}$$

$$\frac{\omega_k^2}{M^*}\left\{3\omega_k^4 + 2(2A_1 + C_1^2)\omega_k^2 + (A_1^2 + 2A_1A_3 + A_2^2 + E_1^2 + 2C_1E_2)\right\}$$

$$= \frac{z_k}{M^*}\frac{\mathrm{d}h(z_k)}{\mathrm{d}z} \neq 0$$

So, $\Re[\frac{\mathrm{d}s_k(\tau_2)}{\mathrm{d}\tau_2}] \neq 0$ since by $(H1)$, $M^* \neq 0$. □

Now, by condition $(H0)$ and $(H1)$ we state the following theorem

Theorem 1. *Suppose that (H0) and (H1) satisfy, then the following results hold:*

(i) *For Eq.*(1.2), P^* *is asymptotically stable when* $\tau_2 \in [0, \tau_{2_0})$

(ii) *Eq.*(1.2), *undergoes Hopf bifurcation at* P^* *when* $\tau_2 = \tau_{2_0}$ *(see* (2.43)*).*

Case (3) . If $\tau_1 > 0$, $\tau_2 > 0$, we consider the characteristic equation (2.24) with τ_2 in its stable interval $[0, \tau_{2_0})$. Choosing τ_1 as a parameter, without loss of generality we study (1.2) under (H1). Let $i\omega(\omega > 0)$ be a root of Eq.(2.24), similarly, we can get

(2.50)

$$\omega^6 + (F_1^2 - 2F_2 - D_1^2)\omega^4 + (2F_1F_3 - 2D_1F_5 - F_4^2 + F_2^2)\omega^2 + (F_3^2 - F_5^2) = 0$$

where

$$\begin{cases} F_1 = A_1 + C_1 e^{-i\omega\tau_2} \\ F_2 = A_2 + C_2 e^{-i\omega\tau_2} \\ F_3 = A_3 + C_3 e^{-i\omega\tau_2} \\ F_4 = D_2 + B_1 e^{-i\omega\tau_2} \\ F_5 = D_3 + B_2 e^{-i\omega\tau_2} \end{cases} \tag{2.51}$$

Assume that Eq.(2.50) has three positive solutions. Then, for every fixed $i\omega(i = 1, 2, 3)$, there exists a sequence $\tau_{1_i}^j > 0$, $(i = 1, 2, 3,\ j = 1, 2, 3, ...)$ such that the characteristic equation (2.24) holds. Let

$$\begin{aligned} &\tau_{1_0} = \tau_{1_{i_0}}^{(j_0)} = min\left\{\tau_{1_i}^{(j)}\right\},\ \omega = \omega_i, \\ &i = 1, 2, 3\ ;\ j \geq 0 \end{aligned} \tag{2.52}$$

When $\tau_1 = \tau_{1_0}$, then the characteristic equation (2.24) has a pair of purely imaginary roots $\pm i\omega_0$. Next, we assume that the condition

(H2)

$$\Re[\frac{\mathrm{d}s_i(\tau_1)}{\mathrm{d}\tau_1}] \neq 0 \tag{2.53}$$

holds. Moreover, when $\tau_1 = 0$, $\tau_2 \in [0, \tau_{2_0})$, one can easily see that Eq.(2.24) can be rewritten as

$$-i\omega^3 + F_1\omega^2 + iF_2\omega + F_3 \tag{2.54}$$

We consider the following condition

(H3) By Routh Hurwitz criterion if $F_1, F_2, F_3 > 0$ and $F_1F_2 > F_3$, then P^* is locally asymptotically stable.

Now we can state the following theorem

Theorem 2. *Let (H1),(H2) and (H3) hold, $\tau_2 \in [0, \tau_{2_0})$. Then the positive equilibrium P^* of system (1.2) is asymptotically stable for $\tau_1 \in [0, \tau_{1_0})$, and is unstable for $\tau_1 \in (\tau_{1_0}, \infty)$; system (1.2) undergoes Hopf bifurcation at the positive equilibrium P^* for $\tau_1 = \tau_{1_0}$. Here, the critical delay τ_{1_0} is clearly a function of τ_2.*

3. Numerical simulation

In this section, we present some numerical simulations regarding our theoretical analysis. Parameters values are chosen as follows:

Table 1. List of parameters values.

Parameter	value	reference	unit
λ	10	[20]	$\text{day}^{-1}\text{mm}^{-3}$
β	1	[10]	$\text{day}^{-1}\text{mm}^{-3}$
μ_1	1	[10]	day^{-1}
μ_2	1	[10]	day^{-1}
μ_3	0.5	[10]	day^{-1}
γ	1.99	[10]	day^{-1}
a	0.45	[10]	day^{-1}
ν	3.85	[10]	day^{-1}
σ	1	[10]	day^{-1}

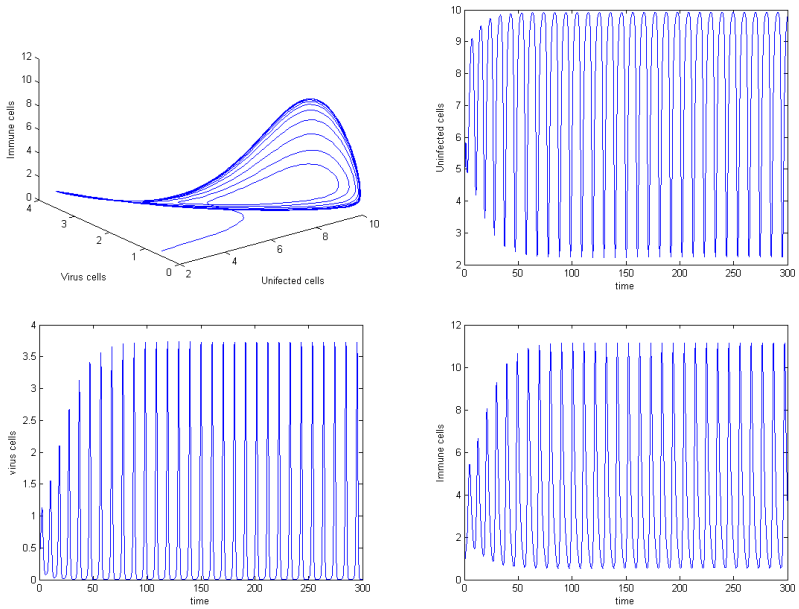

FIGURE 1. An unstable periodic orbits for $\tau_1 = 1.453542882$ and $\tau_2 = 0.4232519849$ with the initial values $(2, 0.5, 0.5)$.

4. Discussion

In this study, we have considered a three dimensional model with intracellular delay and immune activation delay, model (1.2). In the first stage of infection, the viruses enter into a target cell and integrate its viral DNA into the host genome. The second stage is the period from the integration of viral DNA to the transcriptase of viral RNA and translation of viral proteins. The last stage is the period between the transcription of viral RNA and the release and maturation of virus. To evaluate these events in the infection process, we incorporated the time delay τ_1 in the model. Moreover, a time lag is needed for the production of immune cells which was considered with time delay τ_2 for the model (1.2). We used the graphical Hopf bifurcation with time delay τ_1 and τ_2 as the parameters, in order to obtain periodic solutions for system (1.2). From the numerical simulations, one can see, as the delay parameters τ_1 or τ_2 varies, transient or sustained oscillations may be appeared. This shows the sensitivity of the model dynamics to the time delays. A drug therapy is needed when the corresponding viral load and the number of immune cells are

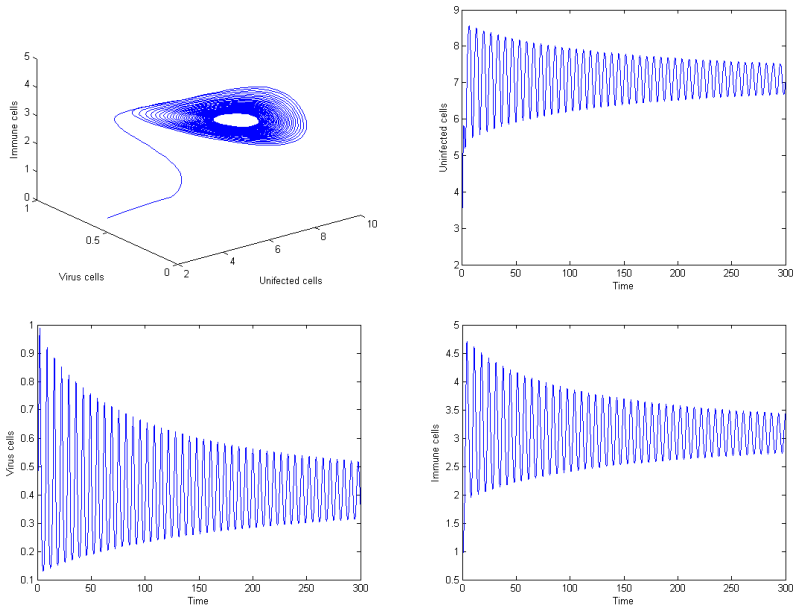

FIGURE 2. A stable periodic orbits when $\tau_1 = 1.0453542882$ and $\tau_2 = 0.4232519849$ with the initial values $(2, 0.5, 0.5)$.

in the basin of P^*. For this purpose, can be estimated the values of τ_1 and τ_2 to determine the effective time of the drug therapy. During the treatment, the virus load and the immune cells should be maintained in a stable state.

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