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Global dynamics of delayed HIV infection models including impairment of B-cell functions

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Abstract

In this paper, we construct delayed HIV dynamics models with impairment of B-cell functions. Two forms of the incidence rate have been considered, bilinear and general. Three types of infected cells and five-time delays have been incorporated into the models. The well-posedness of the models is justified. The models admit two equilibria, which are determined by the basic reproduction number R_0. The global stability of each equilibrium is proven by utilizing the Lyapunov function and LaSalle's invariance principle. Numerical simulations illustrate the theoretical results.

Keywords: HIV dynamics, global stability, Lyapunov function, B-cell impairment, latent reservoirs, time delay.

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1. Introduction

Modeling the HIV dynamics has received considerable attention from mathematicians during the recent decades. A vast of mathematical models focused on exploring the relation between three main compartments, uninfected $CD4^+$ T cells (U), infected cells producing viruses (I), and HIV particles (P). The first HIV dynamics model was proposed by Nowak and Bangham [45] as:

$$\dot{U}(t) = \rho - \gamma U(t) - \omega U(t)P(t), \tag{1.1}$$

$$\dot{I}(t) = \omega U(t)P(t) - \beta I(t), \tag{1.2}$$

$$\dot{P}(t) = \beta M_1 I(t) - \xi P(t). \tag{1.3}$$

The production and death rate constants of compartments (U, I, P) are give by $(\rho, \omega, \varkappa)$ and (γ, β, ξ), respectively. The term $\omega U(t)P(t)$ represents the incidence rate of infection, where ω is a positive constant. During the recent decades, much more modifications on the basic HIV dynamics model have

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been introduced (see e.g. [2–6, 8–30, 46, 47, 52, 54]). Time delay between the initial virus contacts an uninfected cell and the production of new active viruses plays an important role in virus dynamics modeling. Time delay has been incorporated into the virus dynamics models in several works (see e.g. [6, 13, 14, 32, 35, 36, 38, 39, 44, 48]). Mathematical models which include time delays are more accurate representations of biology when compared to the models without considering time delays.

One of the most important extensions to model (1.1)-(1.3) is to incorporate the population of the B cells. The function of B cells is to produce antibodies which bind to virus particles and mark it as a foreign structure for elimination by other cells of the immune system [46]. The antibodies can neutralize viruses and protect the body from infection [40]. The basic virus dynamics model with B cell immune response has been presented by Murase et al. [43]. Wang and Zou [53] have proposed the following model which takes under consideration the time lag between the virus contacts an uninfected cell and the production of new mature viruses.

$$\begin{aligned}
\dot{U}(t) &= \rho - \gamma U(t) - \omega U(t)P(t),\\
\dot{I}(t) &= \omega U(t-\tau_1)P(t-\tau_1) - \beta I(t),\\
\dot{P}(t) &= \varkappa I(t-\tau_2) - \xi P(t) - \rho P(t)C(t),\\
\dot{C}(t) &= \varepsilon P(t)C(t) - \mu C(t),
\end{aligned}$$

where $C(t)$ is the concentration of B cells. The term $\rho P(t)C(t)$ represents the neutralization rate of HIV particles. Parameters ε and μ are the proliferation and natural death rate constants of B cells, respectively. Parameter τ_1 represents the time between an HIV contacts an uninfected $CD4^+$ T cell and the cell becomes infected. The immature virus needs time τ_2 to be mature. Many delayed viral infection models are developed with B cell immune response (see e.g. [19, 37, 42, 50, 51]). Nowak and May [46] have assumed a linear term for immune stimulation: B cell abundance increases in response to free HIV particles at rate $\varepsilon P(t)$ and this leads to $\dot{C}(t) = \varepsilon P(t) - \mu C(t)$.

On the other hand, there are some factors affect the B-cell function and cause the impairment of the B cells [1, 4, 7]. These factors include malnutrition, tumors, cytotoxic drugs, irradiation, aging, trauma, some diseases, e.g. diabetes, and immunosuppression by microbes, e.g., malaria, measles virus but especially HIV [40]. However, all previous delayed HIV models that constructed with B cell immune response ignoring the B-cell impairment. Miao et al. [41] have proposed a virus dynamics model with humoral impairment, but they did not studied the global stability analysis of the model.

The objective of the present paper is to propose and analyze two delayed HIV dynamics models taking into account the impairment of B cell functions. The infected cells are supposed to divided into three classes, latently infected, short lived productively infected, and long lived productively infected. The linear immune response is considered. In the second model, the incidence rate is given by a general nonlinear function. The nonnegativity and boundedness of the solutions are proven. The global stability of all equilibria of the models are established by constructing Lyapunov functions.

2. Delayed HIV infection model with B-cell impairment

The first suggested delayed HIV infection model with B-cell impairment is given by:

$$\dot{U}(t) = \rho - \gamma U(t) - (\omega_1+\omega_2+\omega_3)U(t)P(t), \tag{2.1}$$

$$\dot{L}(t) = e^{-\theta_1\tau_1}\omega_1 U(t-\tau_1)P(t-\tau_1) - (\zeta+\nu)L(t), \tag{2.2}$$

$$\dot{I}(t) = e^{-\theta_2\tau_2}\omega_2 U(t-\tau_2)P(t-\tau_2) + \nu L(t) - \beta I(t), \tag{2.3}$$

$$\dot{O}(t) = e^{-\theta_3\tau_3}\omega_3 U(t-\tau_3)P(t-\tau_3) - \Lambda O(t), \tag{2.4}$$

$$\dot{P}(t) = e^{-\theta_4\tau_4}\beta M_1 I(t-\tau_4) + e^{-\theta_5\tau_5}\Lambda M_2 O(t-\tau_5) - \xi P(t) - \rho P(t)C(t), \tag{2.5}$$

$$\dot{C}(t) = \varepsilon P(t) - \mu C(t) - \vartheta P(t)C(t), \tag{2.6}$$

where $L(t)$, $I(t)$, and $O(t)$ represent, respectively, the concentration of the latently infected cells, short lived productively infected cells, and long lived productively infected cells at time t. The term $(\omega_1 + \omega_2 + \omega_3)U(t)P(t)$, represents the incidence rate. Latently infected cells die with rate $\zeta L(t)$ and they are transmitted to short lived productively infected cells with rate $\nu L(t)$. Parameters M_1 and M_2 are the average number of HIV particles generated in the lifetime of the short lived productively infected cells and long lived productively infected cells, respectively. Parameter Λ is the natural death rate constant of the long lived productively infected cells. The B cell impairment rate is given by $\vartheta P(t)C(t)$. All previous described parameters are positive constants. Parameters τ_1, τ_2 and τ_3 represent the times between HIV contacts an uninfected $CD4^+$ T cell and the cell becomes latently infected, short lived productively infected and long lived productively infected, respectively. The factor $e^{-\theta_k\tau_k}$, $k = 1, 2, 3$ represents the damage of $CD4^+$ T cells during the interval $[t - \tau_k, t]$. The parameters τ_4 and τ_5 represent the time necessary for producing new mature HIV particles from the short lived productively infected cells and long lived productively infected cells, respectively. The factors $e^{-\theta_4\tau_4}$ and $e^{-\theta_5\tau_5}$ represent the loss of short lived productively infected cells and long lived productively infected cells during the intervals $[t - \tau_4, t]$ and $[t - \tau_5, t]$, respectively. Here, τ_1, τ_2, τ_3, τ_4, and τ_5 are positive constants.

The initial conditions of model (2.1)-(2.6) are

$$\begin{aligned} U(s) &= \varphi_1(s), \quad L(s) = \varphi_2(s), \\ I(s) &= \varphi_3(s), \quad O(s) = \varphi_4(s), \\ P(s) &= \varphi_5(s), \quad C(s) = \varphi_6(s), \\ \varphi_i(s) &\geqslant 0, s \in [-\overline{\tau}, 0], \quad i = 1, 2, \ldots, 6, \end{aligned} \tag{2.7}$$

where $\overline{\tau} = \max\{\tau_1, \tau_2, \tau_3, \tau_4, \tau_5\}$ and $(\varphi_1, \varphi_2, \ldots, \varphi_6) \in \mathcal{C}([-\overline{\tau}, 0], \mathbb{R}^6_{\geqslant 0})$, where $\mathcal{C}$ is the Banach space of continuous function mapping the interval $[-\overline{\tau}, 0]$ into $\mathbb{R}^6_{\geqslant 0}$. By the standard theory of functional differential equations [31, 34], we know that the system has a unique solution satisfying the initial conditions (2.7).

Proposition 2.1. *Let $K(t, \varphi)$ be the solution of the model (2.1)-(2.6) with the initial conditions (2.7), then $U(t)$, $L(t)$, $I(t)$, $O(t)$, $P(t)$, and $C(t)$ are all non-negative and ultimately bounded for all $t \geqslant 0$.*

Proof. Assume that $U(t)$ losses its positivity on some local existence interval $[0, j]$ for some constant j and let $j^* \in [0, j]$ be such that $U(j^*) = 0$. By Eq. (2.1), we have $\dot{U}(j^*) = \rho > 0$. Hence $U(t) > 0$ for some $t \in (j^*, j^* + \kappa)$, where $\kappa > 0$ is sufficiently small. This leads to contradiction and thus $U(t) > 0$, for all $t \geqslant 0$. Furthermore, for all $t \in [0, \overline{\tau}]$ we have

$$\begin{aligned} L(t) &= \varphi_2(0)e^{-(\zeta+\nu)t} + e^{-\theta_1\tau_1}\omega_1 \int_0^t e^{-(\zeta+\nu)(t-x)}U(x - \tau_1)P(x - \tau_1)dx \geqslant 0, \\ I(t) &= \varphi_3(0)e^{-\beta t} + \int_0^t e^{-\beta(t-x)} \left(e^{-\theta_2\tau_2}\omega_2 U(x - \tau_2)P(x - \tau_2) + \nu L(x)\right) dx \geqslant 0, \\ O(t) &= \varphi_4(0)e^{-\Lambda t} + e^{-\theta_3\tau_3}\omega_3 \int_0^t e^{-\Lambda(t-x)}U(x - \tau_3)P(\xi - \tau_3)dx \geqslant 0, \\ P(t) &= \varphi_5(0)e^{-\int_0^t(\xi+\rho C(l))dl} + \int_0^t e^{-\int_x^t(\xi+\rho C(l))dl} \left(e^{-\theta_4\tau_4}\beta M_1 I(x - \tau_4) + e^{-\theta_5\tau_5}\Lambda M_2 O(x - \tau_5)\right) dx \geqslant 0, \\ C(t) &= \varphi_6(0)e^{-\int_0^t(\mu+\vartheta P(l))dl} + \varepsilon \int_0^t e^{-\int_x^t(\mu+\vartheta P(l))dl}P(x)dx \geqslant 0. \end{aligned}$$

Thus, by a recursive argument, we get $L(t), I(t), O(t), P(t), C(t) \geqslant 0$ for all $t \geqslant 0$. Hence, $\mathbb{R}^6_{\geqslant 0}$ is positively invariant for model (2.1)-(2.6). Next, from Eq. (2.1) we obtain $\dot{U}(t) \leqslant \rho - \gamma U(t)$. This implies that $\lim_{t\to\infty} \sup U(t) \leqslant \dfrac{\rho}{\gamma}$. Let

$$F_1(t) = \frac{\omega_1 e^{-\theta_1\tau_1}}{\omega_1 + \omega_2 + \omega_3}U(t - \tau_1) + \frac{\omega_2 e^{-\theta_2\tau_2}}{\omega_1 + \omega_2 + \omega_3}U(t - \tau_2) + \frac{\omega_3 e^{-\theta_3\tau_3}}{\omega_1 + \omega_2 + \omega_3}U(t - \tau_3) + L(t) + I(t) + O(t).$$

Then

$$\begin{aligned}
\dot{F}_1(t) &= \frac{\omega_1 e^{-\theta_1\tau_1}}{\omega_1+\omega_2+\omega_3}\left[\rho-\gamma U(t-\tau_1)-(\omega_1+\omega_2+\omega_3)U(t-\tau_1)P(t-\tau_1)\right]\\
&\quad+\frac{\omega_2 e^{-\theta_2\tau_2}}{\omega_1+\omega_2+\omega_3}\left[\rho-\gamma U(t-\tau_2)-(\omega_1+\omega_2+\omega_3)U(t-\tau_2)P(t-\tau_2)\right]\\
&\quad+\frac{\omega_3 e^{-\theta_3\tau_3}}{\omega_1+\omega_2+\omega_3}\left[\rho-\gamma U(t-\tau_3)-(\omega_1+\omega_2+\omega_3)U(t-\tau_3)P(t-\tau_3)\right]\\
&\quad+e^{-\theta_1\tau_1}\omega_1 U(t-\tau_1)P(t-\tau_1)-(\zeta+\nu)L(t)+e^{-\theta_2\tau_2}\omega_2 U(t-\tau_2)P(t-\tau_2)+\nu L(t)-\beta I(t)\\
&\quad+e^{-\theta_3\tau_3}\omega_3 U(t-\tau_3)P(t-\tau_3)-\Lambda O(t)\\
&=\frac{\omega_1 e^{-\theta_1\tau_1}}{\omega_1+\omega_2+\omega_3}\rho-\frac{\gamma\omega_1 e^{-\theta_1\tau_1}}{\omega_1+\omega_2+\omega_3}U(t-\tau_1)+\frac{\omega_2 e^{-\theta_2\tau_2}}{\omega_1+\omega_2+\omega_3}\rho-\frac{\gamma\omega_2 e^{-\theta_2\tau_2}}{\omega_1+\omega_2+\omega_3}U(t-\tau_2)\\
&\quad+\frac{\omega_3 e^{-\theta_3\tau_3}}{\omega_1+\omega_2+\omega_3}\rho-\frac{\gamma\omega_3 e^{-\theta_3\tau_3}}{\omega_1+\omega_2+\omega_3}U(t-\tau_3)-\zeta L(t)-\beta I(t)-\Lambda O(t)\\
&\leqslant \rho-\sigma_1\left[\frac{\omega_1 e^{-\theta_1\tau_1}}{\omega_1+\omega_2+\omega_3}U(t-\tau_1)+\frac{\omega_2 e^{-\theta_2\tau_2}}{\omega_1+\omega_2+\omega_3}U(t-\tau_2)\right.\\
&\quad\left.+\frac{\omega_3 e^{-\theta_3\tau_3}}{\omega_1+\omega_2+\omega_3}U(t-\tau_3)+L(t)+I(t)+O(t)\right]\\
&=\rho-\sigma_1 F_1(t),
\end{aligned}$$

where $\sigma_1=\min\{\gamma,\zeta,\beta,\Lambda\}$. Hence, $\lim_{t\to\infty}\sup F_1(t)\leqslant s_1$, where $s_1=\dfrac{\rho}{\sigma_1}$. Since $U(t), L(t), I(t)$ and $O(t)$ are all non-negative, then $\lim_{t\to\infty}\sup L(t)\leqslant s_1$, $\limsup_{t\to\infty} I(t)\leqslant s_1$ and $\limsup_{t\to\infty} O(t)\leqslant s_1$ for all $t\geqslant 0$. Moreover, let $F_2(t)=P(t)+\dfrac{\xi}{2\varepsilon}C(t)$. Then

$$\begin{aligned}
\dot{F}_2(t) &= e^{-\theta_4\tau_4}\beta M_1 I(t-\tau_4)+e^{-\theta_5\tau_5}\Lambda M_2 O(t-\tau_5)-\xi P(t)-\rho P(t)C(t)+\frac{\xi}{2}P(t)-\frac{\xi\mu}{2\varepsilon}C(t)-\frac{\xi\vartheta}{2\varepsilon}P(t)C(t)\\
&= e^{-\theta_4\tau_4}\beta M_1 I(t-\tau_4)+e^{-\theta_5\tau_5}\Lambda M_2 O(t-\tau_5)-\frac{\xi}{2}P(t)-\frac{\xi\mu}{2\varepsilon}C(t)-\left(\rho+\frac{\xi\vartheta}{2\varepsilon}\right)P(t)C(t)\\
&\leqslant \beta M_1 I(t-\tau_4)+\Lambda M_2 O(t-\tau_5)-\frac{\xi}{2}P(t)-\frac{\xi\mu}{2\varepsilon}C(t)\\
&\leqslant \beta M_1 s_1+\Lambda M_2 s_1-\frac{\xi}{2}P(t)-\frac{\xi\mu}{2\varepsilon}C(t)\\
&\leqslant \beta M_1 s_1+\Lambda M_2 s_1-\sigma_2 F_2(t),
\end{aligned}$$

where $\sigma_2=\min\left\{\dfrac{\xi}{2},\mu\right\}$. Hence, $\lim_{t\to\infty}\sup F_2(t)\leqslant s_2$, where $s_2=\dfrac{\beta M_1 s_1+\Lambda M_2 s_1}{\sigma_2}$. The non-negativity of $P(t)$ and $C(t)$ implies $\lim_{t\to\infty}\sup P(t)\leqslant s_2$ and $\lim_{t\to\infty}\sup C(t)\leqslant s_3$, where $s_3=\dfrac{2\varepsilon s_2}{\xi}$. $\square$

The basic reproduction number for model (2.1)-(2.6) is defined as

$$R_0=\frac{\rho\left[\omega_1\nu M_1 e^{-\theta_1\tau_1-\theta_4\tau_4}+(\zeta+\nu)\left(\omega_2 M_1 e^{-\theta_2\tau_2-\theta_4\tau_4}+\omega_3 M_2 e^{-\theta_3\tau_3-\theta_5\tau_5}\right)\right]}{\xi\gamma(\zeta+\nu)}.$$

Lemma 2.2. *Consider model (2.1)-(2.6), then*

(i) *if* $R_0\leqslant 1$, *then the model has only one equilibrium point* EP_0;
(ii) *if* $R_0>1$, *then the model has two equilibria* EP_0 *and* EP_1.

Proof. At any equilibrium $EP(U, L, I, O, P, C)$ we have

$$\rho - \gamma U - (\omega_1 + \omega_2 + \omega_3)UP = 0, \tag{2.8}$$
$$e^{-\theta_1\tau_1}\omega_1 UP - (\zeta + \nu)L = 0, \tag{2.9}$$
$$e^{-\theta_2\tau_2}\omega_2 UP + \nu L - \beta I = 0, \tag{2.10}$$
$$e^{-\theta_3\tau_3}\omega_3 UP - \Lambda O = 0, \tag{2.11}$$
$$e^{-\theta_4\tau_4}\beta M_1 I + e^{-\theta_5\tau_5}\Lambda M_2 O - \xi P - \rho PC = 0, \tag{2.12}$$
$$\varepsilon P - \mu C - \vartheta PC = 0. \tag{2.13}$$

From equations (2.8)-(2.13) we get an infection-free equilibrium $EP_0 = (U_0, 0, 0, 0, 0, 0)$, where $U_0 = \dfrac{\rho}{\gamma}$ and a unique endemic equilibrium $EP_1 = (U_1, L_1, I_1, O_1, P_1, C_1)$, where

$$U_1 = \frac{\rho}{\gamma + (\omega_1 + \omega_2 + \omega_3)P_1}, \qquad L_1 = \frac{e^{-\theta_1\tau_1}\rho\omega_1 P_1}{(\zeta+\nu)\left(\gamma + (\omega_1 + \omega_2 + \omega_3)P_1\right)},$$
$$I_1 = \frac{\rho\left(e^{-\theta_2\tau_2}\omega_2(\zeta+\nu) + e^{-\theta_1\tau_1}\nu\omega_1\right)P_1}{\beta(\zeta+\nu)(\gamma + (\omega_1 + \omega_2 + \omega_3)P_1)}, \qquad O_1 = \frac{e^{-\theta_3\tau_3}\rho\omega_3 P_1}{\Lambda(\gamma + (\omega_1 + \omega_2 + \omega_3)P_1)},$$
$$P_1 = \frac{-b + \sqrt{b^2 - 4ac}}{2a}, \qquad C_1 = \frac{\varepsilon P_1}{\vartheta P_1 + \mu},$$

where

$$\begin{aligned}
a = &\frac{1}{\gamma^3\mu^2(\zeta+\nu)}\Big[e^{-\theta_1\tau_1-\theta_4\tau_4}\nu\rho\mu^2 M_1\omega_1^3 + 2e^{-\theta_1\tau_1-\theta_4\tau_4}\nu\rho\mu^2 M_1\omega_1\omega_2\omega_3 + e^{-\theta_1\tau_1-\theta_4\tau_4}\nu\rho\mu^2 M_1\omega_1(\omega_2^2+\omega_3^2)\\
&+ 2e^{-\theta_1\tau_1-\theta_4\tau_4}\nu\rho\mu^2 M_1\omega_1^2(\omega_2+\omega_3) + (\zeta+\nu)\big(e^{-\theta_3\tau_3-\theta_5\tau_5}\rho\mu^2 M_2\omega_3^3 + 2e^{-\theta_2\tau_2-\theta_4\tau_4}\rho\mu^2 M_1\omega_1\omega_2^2\\
&+ 2e^{-\theta_3\tau_3-\theta_5\tau_5}\rho\mu^2 M_2\omega_1\omega_3^2 + e^{-\theta_2\tau_2-\theta_4\tau_4}\rho\mu^2 M_1\omega_2\omega_3^2 + 2e^{-\theta_3\tau_3-\theta_5\tau_5}\rho\mu^2 M_2\omega_2\omega_3^2\\
&+ e^{-\theta_2\tau_2-\theta_4\tau_4}\rho\mu^2 M_1\omega_1^2\omega_2 + e^{-\theta_3\tau_3-\theta_5\tau_5}\rho\mu^2 M_2\omega_1^2\omega_3 + 2e^{-\theta_2\tau_2-\theta_4\tau_4}\rho\mu^2 M_1\omega_2^2\omega_3\\
&+ e^{-\theta_3\tau_3-\theta_5\tau_5}\rho\mu^2 M_2\omega_2^2\omega_3 + 2e^{-\theta_2\tau_2-\theta_4\tau_4}\rho\mu^2 M_1\omega_1\omega_2\omega_3 + 2e^{-\theta_3\tau_3-\theta_5\tau_5}\rho\mu^2 M_2\omega_1\omega_2\omega_3\\
&+ e^{-\theta_2\tau_2-\theta_4\tau_4}\rho\mu^2 M_1\omega_2^3 + \vartheta\varepsilon\rho\gamma^3\big)\Big],\\
b = &-\frac{1}{\gamma^2\mu(\zeta+\nu)}\Big[\gamma^2\varepsilon\rho(\zeta+\nu)\\
&+ \omega_3\rho\mu M_2 e^{-\theta_3\tau_3-\theta_5\tau_5}(\zeta+\nu)(\omega_1+\omega_3) + \omega_2\omega_3\rho\mu(\zeta+\nu)(e^{-\theta_2\tau_2-\theta_4\tau_4}M_1 + e^{-\theta_3\tau_3-\theta_5\tau_5}M_2)\\
&+ \omega_2\rho\mu M_1 e^{-\theta_2\tau_2-\theta_4\tau_4}(\zeta+\nu)(\omega_1+\omega_2) + \omega_1\rho\mu\nu M_1 e^{-\theta_1\tau_1-\theta_4\tau_4}(\omega_1+\omega_2+\omega_3)\Big],\\
c = &\,\xi(1 - R_0).
\end{aligned}$$

Therefore, if $R_0 > 1$, then $c < 0$ and $P_1 > 0$. Then the equilibrium EP_1 exists when $R_0 > 1$. □

2.1. *Global stability of equilibria*

Define the function $G(u) = u - 1 - \ln u$. Clearly, $G(u) \geqslant 0$, for $u > 0$ and $G(1) = 0$.

Theorem 2.3. *Let $R_0 < 1$, then EP_0 of model (2.1)-(2.6) is globally asymptotically stable (G.A.S).*

Proof. Construct a Lyapunov function $W_0(U(t), L(t), I(t), O(t), P(t), C(t))$ as:

$$\begin{aligned}
W_0 = &\hbar U_0 G\left(\frac{U(t)}{U_0}\right) + \frac{\nu M_1 e^{-\theta_4\tau_4}}{\zeta+\nu}L(t) + M_1 e^{-\theta_4\tau_4}I(t) + M_2 e^{-\theta_5\tau_5}O(t) + P(t) + \frac{\xi}{\varepsilon}(1 - R_0)C(t)\\
&+ \frac{\nu M_1\omega_1 e^{-\theta_1\tau_1-\theta_4\tau_4}}{\zeta+\nu}\int_{t-\tau_1}^{t} U(s)P(s)ds + M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\int_{t-\tau_2}^{t} U(s)P(s)ds
\end{aligned}$$

$$+M_2\omega_3 e^{-\theta_3\tau_3-\theta_5\tau_5}\int_{t-\tau_3}^{t}U(s)P(s)ds+\beta M_1 e^{-\theta_4\tau_4}\int_{t-\tau_4}^{t}I(s)ds+\Lambda M_2 e^{-\theta_5\tau_5}\int_{t-\tau_5}^{t}O(s)ds,$$

where

$$\hbar=\frac{1}{\omega_1+\omega_2+\omega_3}\left(\frac{\nu M_1\omega_1 e^{-\theta_1\tau_1-\theta_4\tau_4}}{\zeta+\nu}+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}+M_2\omega_3 e^{-\theta_3\tau_3-\theta_5\tau_5}\right).$$

Calculating $\frac{dW_0}{dt}$, we get

$$\begin{aligned}
\frac{dW_0}{dt}&=\hbar\left(1-\frac{U_0}{U(t)}\right)(\rho-\gamma U(t)-(\omega_1+\omega_2+\omega_3)U(t)P(t))\\
&\quad+\frac{\nu M_1 e^{-\theta_4\tau_4}}{\zeta+\nu}\left(e^{-\theta_1\tau_1}\omega_1 U(t-\tau_1)P(t-\tau_1)-(\zeta+\nu)L(t)\right)\\
&\quad+M_1 e^{-\theta_4\tau_4}\left(e^{-\theta_2\tau_2}\omega_2 U(t-\tau_2)P(t-\tau_2)+\nu L(t)-\beta I(t)\right)\\
&\quad+M_2 e^{-\theta_5\tau_5}\left(e^{-\theta_3\tau_3}\omega_3 U(t-\tau_3)P(t-\tau_3)-\Lambda O(t)\right)\\
&\quad+\beta M_1 e^{-\theta_4\tau_4}I(t-\tau_4)+\Lambda M_2 e^{-\theta_5\tau_5}O(t-\tau_5)-\xi P(t)-\rho P(t)C(t)\\
&\quad+\frac{\xi}{\varepsilon}(1-R_0)(\varepsilon P(t)-\mu C(t)-\vartheta P(t)C(t))\\
&\quad+\frac{\nu M_1\omega_1 e^{-\theta_1\tau_1-\theta_4\tau_4}}{\zeta+\nu}(U(t)P(t)-U(t-\tau_1)P(t-\tau_1))\\
&\quad+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}(U(t)P(t)-U(t-\tau_2)P(t-\tau_2))\\
&\quad+M_2\omega_3 e^{-\theta_3\tau_3-\theta_5\tau_5}(U(t)P(t)-U(t-\tau_3)P(t-\tau_3))\\
&\quad+\beta M_1 e^{-\theta_4\tau_4}(I(t)-I(t-\tau_4))+\Lambda M_2 e^{-\theta_5\tau_5}(O(t)-O(t-\tau_5))\\
&=\hbar\left(1-\frac{U_0}{U(t)}\right)(\rho-\gamma U(t))+\hbar(\omega_1+\omega_2+\omega_3)U_0P(t)-\xi P(t)-\rho P(t)C(t)+\xi(1-R_0)P(t)\\
&\quad-\frac{\xi\mu}{\varepsilon}(1-R_0)C(t)-\frac{\xi\vartheta}{\varepsilon}(1-R_0)P(t)C(t).
\end{aligned}$$

We have $\xi R_0=\hbar U_0(\omega_1+\omega_2+\omega_3)$, then

$$\hbar(\omega_1+\omega_2+\omega_3)U_0P(t)-\xi P(t)+\xi(1-R_0)P(t)=0.$$

Then

$$\frac{dW_0}{dt}=\frac{-\hbar\gamma(U(t)-U_0)^2}{U(t)}-\frac{\xi\mu}{\varepsilon}(1-R_0)C(t)-\left(\rho+\frac{\xi\vartheta}{\varepsilon}(1-R_0)\right)P(t)C(t).$$

Since $R_0<1$, then for all $U(t),P(t),C(t)>0$ we have $\frac{dW_0}{dt}\leqslant 0$. Moreover, $\frac{dW_0}{dt}=0$ when $U(t)=U_0$ and $C(t)=0$. Let $D_0=\left\{(U(t),L(t),I(t),O(t),P(t),C(t)):\frac{dW_0}{dt}=0\right\}$ and N_0 be the largest invariant subset of D_0. The trajectory of model (2.1)-(2.6) tend to N_0 [31]. All the elements of N_0 satisfy $U(t)=U_0$ and $C(t)=0$. Then Eq. (2.6) yields

$$\dot{C}(t)=0=\varepsilon P(t)\qquad\Longrightarrow\qquad P(t)=0,\quad\text{for all } t.$$

Also from Eq. (2.5) we get

$$0=\dot{P}(t)=e^{-\theta_4\tau_4}\beta M_1 I(t-\tau_4)+e^{-\theta_5\tau_5}\Lambda M_2 O(t-\tau_5).$$

The nonnegativity of I and O implies that $I(t)=O(t)=0$ for all t. Then from Eq. (2.3), we have $0=\dot{I}(t)=\nu L(t)$. It follows that, $L(t)=0$ for all t. Hence, $N_0=\{EP_0\}$. From LaSalle's invariance principle (L.I.P), we derive that if $R_0<1$, then EP_0 is G.A.S. □

Theorem 2.4. *Let* $R_0 > 1$, *then* EP_1 *of model* (2.1)-(2.6) *is G.A.S.*

Proof. Define $W_{11}(U(t), L(t), I(t), O(t), P(t), C(t))$ as:

$$W_{11} = \hbar U_1 G\left(\frac{U(t)}{U_1}\right) + \frac{\nu M_1 e^{-\theta_4\tau_4}}{\zeta+\nu} L_1 G\left(\frac{L(t)}{L_1}\right) + M_1 e^{-\theta_4\tau_4} I_1 G\left(\frac{I(t)}{I_1}\right) + M_2 e^{-\theta_5\tau_5} O_1 G\left(\frac{O(t)}{O_1}\right)$$
$$+ P_1 G\left(\frac{P(t)}{P_1}\right) + \frac{\rho}{2(\varepsilon - \vartheta C_1)}\left(C(t) - C_1\right)^2.$$

Note that from the equilibrium condition (2.13) that

$$\varepsilon - \vartheta C_1 = \frac{\mu C_1}{P_1} > 0.$$

Calculating $\frac{dW_{11}}{dt}$, we obtain

$$\begin{aligned}
\frac{dW_{11}}{dt} &= \hbar\left(1 - \frac{U_1}{U(t)}\right)\left(\rho - \gamma U(t) - (\omega_1+\omega_2+\omega_3)U(t)P(t)\right)\\
&+ \frac{\nu M_1 e^{-\theta_4\tau_4}}{\zeta+\nu}\left(1 - \frac{L_1}{L(t)}\right)\left(e^{-\theta_1\tau_1}\omega_1 U(t-\tau_1)P(t-\tau_1) - (\zeta+\nu)L(t)\right)\\
&+ M_1 e^{-\theta_4\tau_4}\left(1 - \frac{I_1}{I(t)}\right)\left(e^{-\theta_2\tau_2}\omega_2 U(t-\tau_2)P(t-\tau_2) + \nu L(t) - \beta I(t)\right)\\
&+ M_2 e^{-\theta_5\tau_5}\left(1 - \frac{O_1}{O(t)}\right)\left(e^{-\theta_3\tau_3}\omega_3 U(t-\tau_3)P(t-\tau_3) - \Lambda O(t)\right)\\
&+ \left(1 - \frac{P_1}{P(t)}\right)\left(e^{-\theta_4\tau_4}\beta M_1 I(t-\tau_4) + e^{-\theta_5\tau_5}\Lambda M_2 O(t-\tau_5) - \xi P(t) - \rho P(t)C(t)\right)\\
&+ \frac{\rho}{\varepsilon - \vartheta C_1}\left(C(t) - C_1\right)\left(\varepsilon P(t) - \mu C(t) - \vartheta P(t)C(t)\right).
\end{aligned}$$

Define $W_{12}(U(t), L(t), I(t), O(t), P(t), C(t))$ as:

$$\begin{aligned}
W_{12} = &\frac{\nu M_1\omega_1 e^{-\theta_1\tau_1-\theta_4\tau_4}}{\zeta+\nu} U_1 P_1 \int_{t-\tau_1}^{t} G\left(\frac{U(s)p(s)}{U_1 P_1}\right) ds\\
&+ M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1 P_1 \int_{t-\tau_2}^{t} G\left(\frac{U(s)p(s)}{U_1 P_1}\right) ds\\
&+ M_2\omega_3 e^{-\theta_3\tau_3-\theta_5\tau_5} U_1 P_1 \int_{t-\tau_3}^{t} G\left(\frac{U(s)p(s)}{U_1 P_1}\right) ds.
\end{aligned}$$

Calculating $\frac{dW_{12}}{dt}$, we get

$$\begin{aligned}
\frac{dW_{12}}{dt} = &\frac{\nu M_1\omega_1 e^{-\theta_1\tau_1-\theta_4\tau_4}}{\zeta+\nu} U_1 P_1\left[\frac{U(t)P(t)}{U_1 P_1} - \frac{U(t-\tau_1)P(t-\tau_1)}{U_1 P_1} + \ln\left(\frac{U(t-\tau_1)P(t-\tau_1)}{U(t)P(t)}\right)\right]\\
&+ M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1 P_1\left[\frac{U(t)P(t)}{U_1 P_1} - \frac{U(t-\tau_2)P(t-\tau_2)}{U_1 P_1} + \ln\left(\frac{U(t-\tau_2)P(t-\tau_2)}{U(t)P(t)}\right)\right]\\
&+ M_2\omega_3 e^{-\theta_3\tau_3-\theta_5\tau_5} U_1 P_1\left[\frac{U(t)P(t)}{U_1 P_1} - \frac{U(t-\tau_3)P(t-\tau_3)}{U_1 P_1} + \ln\left(\frac{U(t-\tau_3)P(t-\tau_3)}{U(t)P(t)}\right)\right].
\end{aligned}$$

Define $W_{13}(U(t), L(t), I(t), P(t), P(t), C(t))$ as:

$$W_{13} = \beta M_1 e^{-\theta_4\tau_4} I_1 \int_{t-\tau_4}^{t} G\left(\frac{I(s)}{I_1}\right) ds + \Lambda M_2 e^{-\theta_5\tau_5} O_1 \int_{t-\tau_5}^{t} G\left(\frac{O(s)}{O_1}\right) ds.$$

Calculating $\frac{dW_{13}}{dt}$ as:

$$\begin{aligned}\frac{dW_{13}}{dt} &= \beta M_1 e^{-\theta_4\tau_4} I_1 \left[\frac{I(t)}{I_1} - \frac{I(t-\tau_4)}{I_1} + \ln\left(\frac{I(t-\tau_4)}{I(t)}\right)\right] \\ &\quad + \Lambda M_2 e^{-\theta_5\tau_5} O_1 \left[\frac{O(t)}{O_1} - \frac{O(t-\tau_5)}{O_1} + \ln\left(\frac{O(t-\tau_5)}{O(t)}\right)\right].\end{aligned}$$

Construct a Lyapunov function $W_1(U(t), L(t), I(t), O(t), P(t), C(t))$ as

$$W_1 = W_{11} + W_{12} + W_{13}.$$

Then

$$\frac{dW_1}{dt} = \frac{dW_{11}}{dt} + \frac{dW_{12}}{dt} + \frac{dW_{13}}{dt}.$$

Now we have

$$\begin{aligned}\frac{dW_1}{dt} &= \hbar\left(1 - \frac{U_1}{U(t)}\right)(\rho - \gamma U(t)) + \hbar(\omega_1+\omega_2+\omega_3)U_1 P(t) \\ &\quad - \frac{\nu M_1 \omega_1 e^{-\theta_1\tau_1-\theta_4\tau_4}}{\zeta+\nu} U(t-\tau_1)P(t-\tau_1)\frac{L_1}{L(t)} + \nu M_1 e^{-\theta_4\tau_4} L_1 \\ &\quad - M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U(t-\tau_2)P(t-\tau_2)\frac{I_1}{I(t)} - \nu M_1 e^{-\theta_4\tau_4} L(t)\frac{I_1}{I(t)} + \beta M_1 e^{-\theta_4\tau_4} I_1 \\ &\quad - M_2\omega_3 e^{-\theta_3\tau_3-\theta_5\tau_5} U(t-\tau_3)P(t-\tau_3)\frac{O_1}{O(t)} + \Lambda M_2 e^{-\theta_4\tau_4} O_1 \\ &\quad - \beta M_1 e^{-\theta_4\tau_4} I(t-\tau_4)\frac{P_1}{P(t)} - \Lambda M_2 e^{-\theta_5\tau_5} O(t-\tau_5)\frac{P_1}{P(t)} - \xi(P(t)-P_1) \\ &\quad - \rho(P(t)-P_1)C(t) + \frac{\rho}{\varepsilon - \vartheta C_1}(C(t)-C_1)(\varepsilon P(t) - \mu C(t) - \vartheta P(t)C(t)) \\ &\quad + \frac{\nu M_1\omega_1 e^{-\theta_1\tau_1-\theta_4\tau_4}}{\zeta+\nu} U_1 P_1 \ln\left(\frac{U(t-\tau_1)P(t-\tau_1)}{U(t)P(t)}\right) \\ &\quad + M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1 P_1 \ln\left(\frac{U(t-\tau_2)P(t-\tau_2)}{U(t)P(t)}\right) \\ &\quad + M_2\omega_3 e^{-\theta_3\tau_3-\theta_5\tau_5} U_1 P_1 \ln\left(\frac{U(t-\tau_3)P(t-\tau_3)}{U(t)P(t)}\right) \\ &\quad + \beta M_1 e^{-\theta_4\tau_4} I_1 \ln\left(\frac{I(t-\tau_4)}{I(t)}\right) + \Lambda M_2 e^{-\theta_5\tau_5} O_1 \ln\left(\frac{O(t-\tau_5)}{O(t)}\right).\end{aligned}$$

From the equilibrium conditions, we have:

$$\begin{aligned}\rho &= \gamma U_1 + (\omega_1+\omega_2+\omega_3)U_1P_1, \\ \frac{\nu M_1\omega_1 e^{-\theta_1\tau_1-\theta_4\tau_4}}{\zeta+\nu} U_1P_1 &= \nu M_1 e^{-\theta_4\tau_4} L_1, \\ \beta M_1 e^{-\theta_4\tau_4} I_1 &= M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1 P_1 + \nu M_1 e^{-\theta_4\tau_4} L_1, \\ M_2\omega_3 e^{-\theta_3\tau_3-\theta_5\tau_5} U_1 P_1 &= \Lambda M_2 e^{-\theta_5\tau_5} O_1, \\ \xi P_1 + \rho P_1 C_1 &= e^{-\theta_4\tau_4}\beta M_1 I_1 + e^{-\theta_5\tau_5}\Lambda M_2 O_1, \\ \varepsilon P_1 &= \mu C_1 + \vartheta P_1 C_1.\end{aligned}$$

Utilizing the equilibrium conditions for EP_1, we get

$$\frac{dW_1}{dt} = \hbar\left(1 - \frac{U_1}{U(t)}\right)(\gamma U_1 + (\omega_1+\omega_2+\omega_3)U_1P_1 - \gamma U(t)) + \hbar(\omega_1+\omega_2+\omega_3)U_1P(t)$$

$$
\begin{aligned}
&-\nu M_1 e^{-\theta_4\tau_4} L_1 \frac{L_1 U(t-\tau_1)P(t-\tau_1)}{L(t)U_1P_1} + \nu M_1 e^{-\theta_4\tau_4} L_1 - M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 \frac{I_1 U(t-\tau_2)P(t-\tau_2)}{I(t)U_1P_1} \\
&-\nu M_1 e^{-\theta_4\tau_4} L_1 \frac{I_1 L(t)}{I(t)L_1} + M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 + \nu M_1 e^{-\theta_4\tau_4} L_1 - \Lambda M_2 e^{-\theta_5\tau_5} O_1 \frac{O_1 U(t-\tau_3)P(t-\tau_3)}{O(t)U_1P_1} \\
&+\Lambda M_2 e^{-\theta_5\tau_5} O_1 - \left(M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 + \nu M_1 e^{-\theta_4\tau_4} L_1\right) \frac{P_1 I(t-\tau_4)}{P(t)I_1} - \Lambda M_2 e^{-\theta_5\tau_5} O_1 \frac{P_1 O(t-\tau_5)}{P(t)O_1} \\
&-\xi(P(t)-P_1) - \rho(P(t)-P_1)C(t) + \rho(P(t)-P_1)C_1 - \rho(P(t)-P_1)C_1 \\
&+\frac{\rho}{\varepsilon-\vartheta C_1}(C(t)-C_1)\left(\varepsilon P(t) - \mu C(t) - \vartheta P(t)C(t) - \varepsilon P_1 + \mu C_1 + \vartheta P_1 C_1 - \vartheta P(t) C_1 + \vartheta P(t) C_1\right) \\
&+\nu M_1 e^{-\theta_4\tau_4} L_1 \ln\left(\frac{U(t-\tau_1)P(t-\tau_1)}{U(t)P(t)}\right) + M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 \ln\left(\frac{U(t-\tau_2)P(t-\tau_2)}{U(t)P(t)}\right) \\
&+M_2\omega_3 e^{-\theta_3\tau_3-\theta_5\tau_5} U_1P_1 \ln\left(\frac{U(t-\tau_3)P(t-\tau_3)}{U(t)P(t)}\right) + \Lambda M_2 e^{-\theta_5\tau_5} O_1 \ln\left(\frac{O(t-\tau_5)}{O(t)}\right) \\
&+\left(M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 + \nu M_1 e^{-\theta_4\tau_4} L_1\right) \ln\left(\frac{I(t-\tau_4)}{I(t)}\right).
\end{aligned}
$$

Simplifying the result, we obtain

$$
\begin{aligned}
\frac{dW_1}{dt} =& -\gamma\hbar \frac{(U(t)-U_1)^2}{U(t)} + \nu M_1 e^{-\theta_4\tau_4} L_1 \left(1-\frac{U_1}{U(t)}\right) + M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 \left(1-\frac{U_1}{U(t)}\right) \\
&+\Lambda M_2 e^{-\theta_5\tau_5} O_1 \left(1-\frac{U_1}{U(t)}\right) + \left(\nu M_1 e^{-\theta_4\tau_4} L_1 + M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 + \Lambda M_2 e^{-\theta_5\tau_5} O_1\right) \frac{P(t)}{P_1} \\
&-\nu M_1 e^{-\theta_4\tau_4} L_1 \frac{L_1 U(t-\tau_1)P(t-\tau_1)}{L(t)U_1P_1} + \nu M_1 e^{-\theta_4\tau_4} L_1 - M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 \frac{I_1 U(t-\tau_2)P(t-\tau_2)}{I(t)U_1P_1} \\
&-\nu M_1 e^{-\theta_4\tau_4} L_1 \frac{I_1 L(t)}{I(t)L_1} + M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 + \nu M_1 e^{-\theta_4\tau_4} L_1 - \Lambda M_2 e^{-\theta_5\tau_5} O_1 \frac{O_1 U(t-\tau_3)P(t-\tau_3)}{O(t)U_1P_1} \\
&+\Lambda M_2 e^{-\theta_5\tau_5} O_1 - \left(M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 + \nu M_1 e^{-\theta_4\tau_4} L_1\right) \frac{P_1 I(t-\tau_4)}{P(t)I_1} - \Lambda M_2 e^{-\theta_5\tau_5} O_1 \frac{P_1 O(t-\tau_5)}{P(t)O_1} \\
&-(\xi+\rho C_1)(P(t)-P_1) - \rho(P(t)-P_1)(C(t)-C_1) + \frac{\rho(\varepsilon-\vartheta C_1)}{\varepsilon-\vartheta C_1}(C(t)-C_1)(P(t)-P_1) \\
&-\frac{\rho(\mu+\vartheta P(t))}{\varepsilon-\vartheta C_1}(C(t)-C_1)^2 + \nu M_1 e^{-\theta_4\tau_4} L_1 \ln\left(\frac{U(t-\tau_1)P(t-\tau_1)}{U(t)P(t)}\right) \\
&+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 \ln\left(\frac{U(t-\tau_2)P(t-\tau_2)}{U(t)P(t)}\right) + M_2\omega_3 e^{-\theta_3\tau_3-\theta_5\tau_5} U_1P_1 \ln\left(\frac{U(t-\tau_3)P(t-\tau_3)}{U(t)P(t)}\right) \\
&+\left(M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 + \nu M_1 e^{-\theta_4\tau_4} L_1\right) \ln\left(\frac{I(t-\tau_4)}{I(t)}\right) + \Lambda M_2 e^{-\theta_5\tau_5} O_1 \ln\left(\frac{O(t-\tau_5)}{O(t)}\right).
\end{aligned}
$$

We have

$$
\begin{aligned}
-(\xi+\rho C_1)(P(t)-P_1) &= -\frac{1}{P_1}\left(\beta M_1 e^{-\theta_4\tau_4} I_1 + \Lambda M_2 e^{-\theta_5\tau_5} O_1\right)(P(t)-P_1) \\
&= \left(M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 + \nu M_1 e^{-\theta_4\tau_4} L_1 + \Lambda M_2 e^{-\theta_5\tau_5} O_1\right)\left(1-\frac{P(t)}{P_1}\right).
\end{aligned}
$$

Then $\frac{dW_1}{dt}$ will be

$$
\begin{aligned}
\frac{dW_1}{dt} =& -\gamma\hbar \frac{(U(t)-U_1)^2}{U(t)} - \frac{\rho(\mu+\vartheta P(t))}{\varepsilon-\vartheta C_1}(C(t)-C_1)^2 \\
&+\nu M_1 e^{-\theta_4\tau_4} L_1 \left[4 - \frac{U_1}{U(t)} - \frac{L_1 U(t-\tau_1)P(t-\tau_1)}{L(t)U_1P_1} - \frac{I_1 L(t)}{I(t)L_1} - \frac{P_1 I(t-\tau_4)}{P(t)I_1}\right] \\
&+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1 \left[3 - \frac{U_1}{U(t)} - \frac{I_1 U(t-\tau_2)P(t-\tau_2)}{I(t)U_1P_1} - \frac{P_1 I(t-\tau_4)}{P(t)I_1}\right]
\end{aligned}
$$

$$
\begin{aligned}
&+\Lambda M_2 e^{-\theta_5\tau_5} O_1\left[3-\frac{U_1}{U(t)}-\frac{O_1 U(t-\tau_3)P(t-\tau_3)}{O(t)U_1P_1}-\frac{P_1 O(t-\tau_5)}{P(t)O_1}\right]\\
&+\nu M_1 e^{-\theta_4\tau_4} L_1\left[\ln\left(\frac{U(t-\tau_1)P(t-\tau_1)}{U(t)P(t)}\right)+\ln\left(\frac{I(t-\tau_4)}{I(t)}\right)\right]\\
&+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4} U_1P_1\left[\ln\left(\frac{U(t-\tau_2)P(t-\tau_2)}{U(t)P(t)}\right)+\ln\left(\frac{I(t-\tau_4)}{I(t)}\right)\right]\\
&+\Lambda M_2 e^{-\theta_5\tau_5} O_1\left[\ln\left(\frac{U(t-\tau_3)P(t-\tau_3)}{U(t)P(t)}\right)+\ln\left(\frac{O(t-\tau_5)}{O(t)}\right)\right].
\end{aligned}
$$

Note that

$$
\begin{aligned}
\ln\left(\frac{U(t-\tau_1)P(t-\tau_1)}{U(t)P(t)}\right)&=\ln\left(\frac{L_1U(t-\tau_1)P(t-\tau_1)}{L(t)U_1P_1}\right)+\ln\left(\frac{I_1L(t)}{I(t)L_1}\right)+\ln\left(\frac{I(t)P_1}{I_1P(t)}\right)+\ln\left(\frac{U_1}{U(t)}\right),\\
\ln\left(\frac{U(t-\tau_2)P(t-\tau_2)}{U(t)P(t)}\right)&=\ln\left(\frac{I_1U(t-\tau_2)P(t-\tau_2)}{I(t)U_1P_1}\right)+\ln\left(\frac{I(t)P_1}{I_1P(t)}\right)+\ln\left(\frac{U_1}{U(t)}\right),\\
\ln\left(\frac{U(t-\tau_3)P(t-\tau_3)}{U(t)P(t)}\right)&=\ln\left(\frac{O_1U(t-\tau_3)P(t-\tau_3)}{O(t)U_1P_1}\right)+\ln\left(\frac{O(t)P_1}{O_1P(t)}\right)+\ln\left(\frac{U_1}{U(t)}\right),\\
\ln\left(\frac{I(t-\tau_4)}{I(t)}\right)&=\ln\left(\frac{P_1I(t-\tau_4)}{P(t)I_1}\right)+\ln\left(\frac{P(t)I_1}{P_1I(t)}\right),\\
\ln\left(\frac{O(t-\tau_5)}{O(t)}\right)&=\ln\left(\frac{P_1O(t-\tau_5)}{P(t)O_1}\right)+\ln\left(\frac{P(t)O_1}{P_1O(t)}\right).
\end{aligned}
$$

Then $\frac{dW_1}{dt}$ will be

$$
\begin{aligned}
\frac{dW_1}{dt}=&-\gamma\hbar\frac{(U(t)-U_1)^2}{U(t)}-\frac{\rho(\mu+\vartheta P(t))}{\varepsilon-\vartheta C_1}(C(t)-C_1)^2\\
&-\nu M_1 e^{-\theta_4\tau_4}L_1\left[G\left(\frac{U_1}{U(t)}\right)+G\left(\frac{L_1U(t-\tau_1)P(t-\tau_1)}{L(t)U_1P_1}\right)+G\left(\frac{I_1L(t)}{I(t)L_1}\right)+G\left(\frac{P_1I(t-\tau_4)}{P(t)I_1}\right)\right]\\
&-M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}U_1P_1\left[G\left(\frac{U_1}{U(t)}\right)+G\left(\frac{I_1U(t-\tau_2)P(t-\tau_2)}{I(t)U_1P_1}\right)+G\left(\frac{P_1I(t-\tau_4)}{P(t)I_1}\right)\right]\\
&-\Lambda M_2 e^{-\theta_5\tau_5}O_1\left[G\left(\frac{U_1}{U(t)}\right)+G\left(\frac{O_1U(t-\tau_3)P(t-\tau_3)}{O(t)U_1P_1}\right)+G\left(\frac{P_1O(t-\tau_5)}{P(t)O_1}\right)\right].
\end{aligned}
$$

Then for all $U(t), L(t), I(t), O(t), P(t), C(t) > 0$ we have $\frac{dW_1}{dt} \leqslant 0$. In addition, $\frac{dW_1}{dt} = 0$ when $U(t) = U_1$, $L(t) = L_1$, $I(t) = I_1$, $O(t) = O_1$, $P(t) = P_1$, and $C(t) = C_1$. Let $D_1 = \{(U(t), L(t), I(t), O(t), P(t), C(t)) : \frac{dW_1}{dt} = 0\}$ and N_1 be the largest invariance subset of D_1. Clearly $N_1 = \{EP_1\}$. Applying L.I.P we obtain that if $R_0 > 1$, then EP_1 is G.A.S. □

3. Model with general infection rate

We generalize the model presented in the previous section by considering a more general incidence rate function $\Theta(U(t), P(t))$ as:

$$\dot{U}(t)=\rho-\gamma U(t)-(\omega_1+\omega_2+\omega_3)\Theta(U(t),P(t)), \tag{3.1}$$

$$\dot{L}(t)=e^{-\theta_1\tau_1}\omega_1\Theta(U(t-\tau_1),P(t-\tau_1))-(\zeta+\nu)L(t), \tag{3.2}$$

$$\dot{I}(t)=e^{-\theta_2\tau_2}\omega_2\Theta(U(t-\tau_2),P(t-\tau_2))+\nu L(t)-\beta I(t), \tag{3.3}$$

$$\dot{O}(t)=e^{-\theta_3\tau_3}\omega_3\Theta(U(t-\tau_3),P(t-\tau_3))-\Lambda O(t), \tag{3.4}$$

$$\dot{P}(t) = e^{-\theta_4\tau_4}\beta M_1 I(t-\tau_4) + e^{-\theta_5\tau_5}\Lambda M_2 O(t-\tau_5) - \xi P(t) - \rho P(t)C(t), \tag{3.5}$$
$$\dot{C}(t) = \varepsilon P(t) - \mu C(t) - \vartheta P(t)C(t). \tag{3.6}$$

We need the following assumptions on the function $\Theta(U,P)$ [18, 33, 49].

(A1) $\Theta(U,P)$ is continuously differentiable, $\Theta(U,P) > 0$, and $\Theta(0,P) = \Theta(U,0) = 0$ for all $U > 0$ and $P > 0$.

(A2) $\frac{\partial\Theta(U,P)}{\partial U} > 0$, $\frac{\partial\Theta(U,P)}{\partial P} > 0$, and $\frac{\partial\Theta(U,0)}{\partial P} > 0$ for all $U > 0$ and $P > 0$.

(A3) $\frac{d}{dU}\left(\frac{\partial\Theta(U,0)}{\partial P}\right) > 0$ for all $U > 0$.

(A4) $\frac{\Theta(U,P)}{P}$ is decreasing with respect to P for all $P > 0$.

This form of the incident rate $\Theta(U,P)$ with the above-mentioned Assumptions generalizes many popular forms like: bilinear incidence UP, saturated incidence $UP/(1+\alpha_1 P)$, Beddington-DeAngelis incidence $UP/(1+\alpha_1 P+\alpha_2 U)$, and Crowley-Martin incidence $UP/((1+\alpha_1 P)(1+\alpha_2 U))$, where, α_1 and α_2 are nonnegative constants.

One can show that $U(t)$, $L(t)$, $I(t)$, $O(t)$, $P(t)$ and $C(t)$ are all nonnegative and ultimately bounded under initial conditions (2.7).

Lemma 3.1. *Assume that Assumptions* (A1)-(A4) *are satisfied, then there exists a threshold parameter* $R_0^G > 0$ *such that:*

(i) *if* $R_0^G \leqslant 1$, *then the model has only one equilibrium point* EP_0^G; *and*

(ii) *if* $R_0^G > 1$, *then the model has two equilibria* EP_0^G *and* EP_1^G.

Proof. At any equilibrium $EP^G(U,L,I,O,P,C)$ we have

$$\rho - \gamma U - (\omega_1+\omega_2+\omega_3)\Theta(U,P) = 0, \tag{3.7}$$
$$e^{-\theta_1\tau_1}\omega_1\Theta(U,P) - (\zeta+\nu)L = 0, \tag{3.8}$$
$$e^{-\theta_2\tau_2}\omega_2\Theta(U,P) + \nu L - \beta I = 0, \tag{3.9}$$
$$e^{-\theta_3\tau_3}\omega_3\Theta(U,P) - \Lambda O = 0, \tag{3.10}$$
$$e^{-\theta_4\tau_4}\beta M_1 I + e^{-\theta_5\tau_5}\Lambda M_2 O - \xi P - \rho PC = 0, \tag{3.11}$$
$$\varepsilon P - \mu C - \vartheta PC = 0. \tag{3.12}$$

From Eq. (3.12), we have

$$C = \frac{\varepsilon P}{\mu + \vartheta P}, \tag{3.13}$$

and from Eqs. (3.8) and (3.10), we obtain

$$L = \frac{e^{-\theta_1\tau_1+\theta_3\tau_3}\Lambda\omega_1}{\omega_3(\zeta+\nu)}O. \tag{3.14}$$

Now, from Eqs. (3.9)-(3.10) and (3.14), we get

$$I = \frac{e^{-\theta_2\tau_2+\theta_3\tau_3}\Lambda\omega_2(\zeta+\nu) + e^{-\theta_1\tau_1+\theta_3\tau_3}\Lambda\omega_1\nu}{\beta\omega_3(\zeta+\nu)}O, \tag{3.15}$$

and from Eqs. (3.11), (3.13), and (3.15), we have

$$O = \frac{\omega_3(\zeta+\nu)}{\Lambda\phi}\left(\xi P + \frac{\rho\varepsilon P^2}{\mu+\vartheta P}\right), \tag{3.16}$$

where $\phi = (e^{-\theta_2\tau_2+\theta_3\tau_3-\theta_4\tau_4}\omega_2 M_1 + e^{-\theta_5\tau_5}\omega_3 M_2)(\zeta+\nu) + e^{-\theta_1\tau_1+\theta_3\tau_3-\theta_4\tau_4}\omega_1 M_1\nu$. By substitution into

Eqs. (3.14)-(3.15), we obtain

$$L = \frac{e^{-\theta_1\tau_1+\theta_3\tau_3}\omega_1}{\phi}\left(\xi P + \frac{\rho\varepsilon P^2}{\mu+\vartheta P}\right), \tag{3.17}$$

$$I = \frac{e^{-\theta_2\tau_2+\theta_3\tau_3}\omega_2(\zeta+\nu) + e^{-\theta_1\tau_1+\theta_3\tau_3}\omega_1\nu}{\beta\phi}\left(\xi P + \frac{\rho\varepsilon P^2}{\mu+\vartheta P}\right). \tag{3.18}$$

Then, from Eqs. (3.7), (3.10), and (3.16), we get

$$U = \frac{\rho}{\gamma} - \frac{e^{\theta_3\tau_3}(\omega_1+\omega_2+\omega_3)(\zeta+\nu)}{\gamma\phi}\left(\xi P + \frac{\rho\varepsilon P^2}{\mu+\vartheta P}\right). \tag{3.19}$$

Let

$$\Psi(P) = \frac{\rho}{\gamma} - \frac{e^{\theta_3\tau_3}(\omega_1+\omega_2+\omega_3)(\zeta+\nu)}{\gamma\phi}\left(\xi P + \frac{\rho\varepsilon P^2}{\mu+\vartheta P}\right).$$

Therefore, we can write U as $U = \Psi(P)$. Note that $\Psi(0) = \frac{\rho}{\gamma}$. From Eqs. (3.10) and (3.16), we have

$$e^{-\theta_3\tau_3}\Theta(\Psi(P), P) - \frac{\zeta+\nu}{\varphi}\left(\xi P + \frac{\rho\varepsilon P^2}{\mu+\vartheta P}\right) = 0. \tag{3.20}$$

Observe that, $P = 0$ is a solution of Eq. (3.20). Then from Eqs. (3.13), (3.16)-(3.19) we have $U = U_0 = \frac{\rho}{\gamma}$, $L = 0$, $I = 0$, $O = 0$, and $C = 0$. Then we get an infection-free equilibrium $EP_0^G = (U_0, 0, 0, 0, 0, 0)$. Let

$$H(P) = e^{-\theta_3\tau_3}\Theta(\Psi(P), P) - \frac{\zeta+\nu}{\phi}\left(\xi P + \frac{\rho\varepsilon P^2}{\mu+\vartheta P}\right),$$

then $H(0) = 0$. Let $\overline{P}$ be such that $\Psi(\overline{P}) = 0$, i.e.,

$$U_0 - \frac{e^{\theta_3\tau_3}(\omega_1+\omega_2+\omega_3)(\zeta+\nu)}{\gamma\phi}\left(\xi\overline{P} + \frac{\rho\varepsilon\overline{P}^2}{\mu+\vartheta\overline{P}}\right) = 0,$$

which gives

$$e^{\theta_3\tau_3}(\rho\varepsilon+\xi\vartheta)(\zeta+\nu)(\omega_1+\omega_2+\omega_3)\overline{P}^2 + \left[e^{\theta_3\tau_3}\xi\mu(\zeta+\nu)(\omega_1+\omega_2+\omega_3) - \gamma\vartheta U_0\phi\right]\overline{P} - \gamma\mu U_0\phi = 0. \tag{3.21}$$

Thus, the positive solution of Eq. (3.21) is given by

$$\overline{P} = \frac{-\overline{b} + \sqrt{\overline{b}^2 - 4\overline{a}\overline{c}}}{2\overline{a}},$$

where,

$$\begin{aligned}
\overline{a} &= e^{\theta_3\tau_3}(\rho\varepsilon+\xi\vartheta)(\zeta+\nu)(\omega_1+\omega_2+\omega_3),\\
\overline{b} &= e^{\theta_3\tau_3}\xi\mu(\zeta+\nu)(\omega_1+\omega_2+\omega_3) - \gamma\vartheta U_0\phi,\\
\overline{c} &= -\gamma\mu U_0\phi.
\end{aligned}$$

We can see from Assumption (A1) that

$$H(\overline{P}) = e^{-\theta_3\tau_3}\Theta(0, \overline{P}) - \frac{\zeta+\nu}{\phi}\left(\xi\overline{P} + \frac{\rho\varepsilon\overline{P}^2}{\mu+\vartheta\overline{P}}\right) = -\frac{\zeta+\nu}{\phi}\left(\xi\overline{P} + \frac{\rho\varepsilon\overline{P}^2}{\mu+\vartheta\overline{P}}\right) < 0.$$

Moreover,

$$H'(P) = e^{-\theta_3\tau_3}\Psi'(P)\frac{\partial\Theta(U,P)}{\partial U} + e^{-\theta_3\tau_3}\frac{\partial\Theta(U,P)}{\partial P} - \frac{\zeta+\nu}{\phi}\left(\xi + \frac{\rho\varepsilon(2\mu P+\vartheta P^2)}{(\mu+\vartheta P)^2}\right).$$

Assumption (A1) implies that $\dfrac{\partial\Theta(U_0,0)}{\partial U} = 0$, then

$$H'(0) = e^{-\theta_3\tau_3}\frac{\partial\Theta(U_0,0)}{\partial P} - \frac{\xi(\zeta+\nu)}{\phi} = \frac{\xi(\zeta+\nu)}{\phi}\left(\frac{e^{-\theta_3\tau_3}\phi}{\xi(\zeta+\nu)}\frac{\partial\Theta(U_0,0)}{\partial P} - 1\right).$$

Therefore, if $\dfrac{e^{-\theta_3\tau_3}\phi}{\xi(\zeta+\nu)}\dfrac{\partial\Theta(U_0,0)}{\partial P} > 1$, then $H'(0) > 0$ and $\exists P_1 \in (0,\overline{P})$ such that $H(P_1) = 0$. Let us define

$$R_0^G = \frac{(\omega_2 M_1 e^{-\theta_2\tau_2-\theta_4\tau_4} + \omega_3 M_2 e^{-\theta_3\tau_3-\theta_5\tau_5})(\zeta+\nu) + \nu\omega_1 M_1 e^{-\theta_1\tau_1-\theta_4\tau_4}}{\xi(\zeta+\nu)}\frac{\partial\Theta(U_0,0)}{\partial P},$$

which represents the basic infection reproduction number. Now, let $P = P_1$ in Eq. (3.7) and define $g(U) = \rho - \gamma U - (\omega_1+\omega_2+\omega_1)\Theta(U,P_1) = 0$. Then from Assumption (A1) we have $g(0) = \rho > 0$ and $g(U_0) = -(\omega_1+\omega_2+\omega_3)\Theta(U_0,P_1) < 0$. Assumption (A2) implies that $g(U)$ is strictly decreasing function of U, and then there exists a unique $U_1 \in (0,U_0)$ such that $g(U_1) = 0$. Moreover, from Eqs. (3.13) and (3.16)-(3.18), we have

$$\begin{aligned}
L_1 &= \frac{e^{-\theta_1\tau_1+\theta_3\tau_3}\omega_1}{\phi}\left(\xi P_1 + \frac{\rho\varepsilon P_1^2}{\mu+\vartheta P_1}\right) > 0,\\
I_1 &= \frac{e^{-\theta_2\tau_2+\theta_3\tau_3}\omega_2(\zeta+\nu) + e^{-\theta_1\tau_1+\theta_3\tau_3}\omega_1\nu}{\beta\phi}\left(\xi P_1 + \frac{\rho\varepsilon P_1^2}{\mu+\vartheta P_1}\right) > 0,\\
O_1 &= \frac{\omega_3(\zeta+\nu)}{\Lambda\phi}\left(\xi P_1 + \frac{\rho\varepsilon P_1^2}{\mu+\vartheta P_1}\right) > 0,\\
C_1 &= \frac{\varepsilon P_1}{\mu+\vartheta P_1} > 0.
\end{aligned}$$

Therefore, the endemic equilibrium $EP_1^G = (U_1, L_1, I_1, O_1, P_1, C_1)$ exists if $R_0^G > 1$. □

3.1. *Global stability of equilibria*

The global stability analysis of the two equilibria of model (3.1)-(3.6) will be investigated in this subsection.

Theorem 3.2. *Let $R_0^G < 1$, then the infection-free equilibrium EP_0^G of model (3.1)-(3.6) is G.A.S.*

Proof. Construct a Lyapunov function $Z_0(U(t), L(t), I(t), O(t), P(t), C(t))$ as

$$\begin{aligned}
Z_0 = \hbar&\left(U(t) - U_0 - \int_{U_0}^{U(t)}\lim_{P\to 0^+}\frac{\Theta(U_0,P)}{\Theta(\eta,P)}d\eta\right) + \frac{\nu M_1 e^{-\theta_4\tau_4}}{\zeta+\nu}L(t) + M_1 e^{-\theta_4\tau_4}I(t)\\
&+ M_2 e^{-\theta_5\tau_5}O(t) + P(t) + \frac{\xi}{\varepsilon}\left(1-R_0^G\right)C(t) + \frac{\nu M_1\omega_1 e^{-\theta_1\tau_1-\theta_4\tau_4}}{\zeta+\nu}\int_{t-\tau_1}^{t}U(s)P(s)ds\\
&+ M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\int_{t-\tau_2}^{t}U(s)P(s)ds + M_2\omega_3 e^{-\theta_3\tau_3-\theta_5\tau_5}\int_{t-\tau_3}^{t}U(s)P(s)ds\\
&+ \beta M_1 e^{-\theta_4\tau_4}\int_{t-\tau_4}^{t}I(s)ds + \Lambda M_2 e^{-\theta_5\tau_5}\int_{t-\tau_5}^{t}O(s)ds.
\end{aligned}$$

Calculating $\dfrac{dZ_0}{dt}$ as:

$$\begin{aligned}\frac{dZ_0}{dt} &= \hbar\left(1-\lim_{P\to 0^+}\frac{\Theta(U_0,P)}{\Theta(U(t),P)}\right)(\rho-\gamma U(t)-(\omega_1+\omega_2+\omega_3)\Theta(U(t),P(t)))\\ &\quad+\frac{\nu M_1 e^{-\theta_4\tau_4}}{\zeta+\nu}(e^{-\theta_1\tau_1}\omega_1\Theta(U(t-\tau_1),P(t-\tau_1))-(\zeta+\nu)L(t))\\ &\quad+M_1e^{-\theta_4\tau_4}\left(e^{-\theta_2\tau_2}\omega_2\Theta(U(t-\tau_2),P(t-\tau_2)+\nu L(t)-\beta I(t)\right)\\ &\quad+M_2e^{-\theta_5\tau_5}(e^{-\theta_3\tau_3}\omega_3\Theta(U(t-\tau_3),P(t-\tau_3))-\Lambda O(t))\\ &\quad+\beta M_1e^{-\theta_4\tau_4}I(t-\tau_4)+\Lambda M_2e^{-\theta_5\tau_5}O(t-\tau_5)-\xi P(t)-\rho P(t)C(t)\\ &\quad+\frac{\xi}{\varepsilon}\left(1-R_0^G\right)(\varepsilon P(t)-\mu C(t)-\vartheta P(t)C(t))\\ &\quad+\frac{\nu M_1\omega_1 e^{-\theta_1\tau_1-\theta_4\tau_4}}{\zeta+\nu}(U(t)P(t)-U(t-\tau_1)P(t-\tau_1))\\ &\quad+M_1\omega_2e^{-\theta_2\tau_2-\theta_4\tau_4}(U(t)P(t)-U(t-\tau_2)P(t-\tau_2))\\ &\quad+M_2\omega_3e^{-\theta_3\tau_3-\theta_5\tau_5}(U(t)P(t)-U(t-\tau_3)P(t-\tau_3))\\ &\quad+\beta M_1e^{-\theta_4\tau_4}(I(t)-I(t-\tau_4))+\Lambda M_2e^{-\theta_5\tau_5}(O(t)-O(t-\tau_5)).\end{aligned}$$

Using L'Hospital's Rule and simplifying the result, we get

$$\begin{aligned}\frac{dZ_0}{dt} &= \hbar\left(1-\frac{\partial\Theta(U_0,0)/\partial P}{\partial\Theta(U,0)/\partial P}\right)(\rho-\gamma U(t))+\hbar(\omega_1+\omega_2+\omega_3)\Theta(U(t),P(t))\frac{\partial\Theta(U_0,0)/\partial P}{\partial\Theta(U,0)/\partial P}\\ &\quad-\left(\rho+\frac{\xi\vartheta}{\varepsilon}\left(1-R_0^G\right)\right)P(t)C(t)-\xi R_0^G P(t)-\frac{\xi\mu}{\varepsilon}\left(1-R_0\right)C(t)\\ &=\hbar\gamma U_0\left(1-\frac{U(t)}{U_0}\right)\left(1-\frac{\partial\Theta(U_0,0)/\partial P}{\partial\Theta(U,0)/\partial P}\right)-\left(\rho+\frac{\xi\vartheta}{\varepsilon}\left(1-R_0^G\right)\right)P(t)C(t)\\ &\quad+\xi R_0^G\left(\frac{\bar{\hbar}}{\xi R_0^G}\frac{\Theta(U(t),P(t))}{P(t)}\frac{\partial\Theta(U_0,0)/\partial P}{\partial\Theta(U,0)/\partial P}-1\right)P(t)-\frac{\xi\mu}{\varepsilon}\left(1-R_0^G\right)C(t),\end{aligned}$$

where,

$$\bar{\hbar}=\hbar(\omega_1+\omega_2+\omega_3).$$

From the Assumption (A4), we have

$$\frac{\Theta(U,P)}{P}\leqslant\lim_{P\to 0^+}\frac{\Theta(U,P)}{P}=\frac{\partial\Theta(U,0)}{\partial P}$$

for all $U(t)>0$. Then

$$\frac{\bar{\hbar}}{\xi R_0^G}\frac{\Theta(U,P)}{P}\frac{\partial\Theta(U_0,0)/\partial P}{\partial\Theta(U,0)/\partial P}\leqslant\frac{\bar{\hbar}}{\xi R_0^G}\frac{\partial\Theta(U_0,0)}{\partial P}=1.$$

It implies that

$$\frac{dZ_0}{dt}\leqslant\hbar\gamma U_0\left(1-\frac{U(t)}{U_0}\right)\left(1-\frac{\partial\Theta(U_0,0)/\partial P}{\partial\Theta(U,0)/\partial P}\right)-\left(\rho+\frac{\xi\vartheta}{\varepsilon}\left(1-R_0^G\right)\right)P(t)C(t)-\frac{\xi\mu}{\varepsilon}\left(1-R_0^G\right)C(t).$$

From (A2) we have

$$\left(1-\frac{U}{U_0}\right)\left(1-\frac{\partial\Theta(U_0,0)/\partial P}{\partial\Theta(U,0)/\partial P}\right)\leqslant 0.$$

Therefore, if $R_0^G<1$, then $\dfrac{dZ_0}{dt}\leqslant 0$ for all $U(t),P(t),C(t)>0$. Similar to the proof of Theorem 2.3, one can show that EP_0^G is G.A.S. □

Theorem 3.3. *Let $R_0^G > 1$, then the endemic equilibrium EP_1^G of model (3.1)-(3.6) is G.A.S.*

Proof. Define $Z_{11}(U(t), L(t), I(t), O(t), P(t), C(t))$ as

$$Z_{11} = \hbar\left(U(t) - U_1 - \int_{U_1}^{U(t)} \frac{\Theta(U_1, P_1)}{\Theta(\eta, P_1)}\, d\eta\right) + \frac{\nu M_1 e^{-\theta_4\tau_4}}{\zeta+\nu} L_1 G\left(\frac{L(t)}{L_1}\right) + M_1 e^{-\theta_4\tau_4} I_1 G\left(\frac{I(t)}{I_1}\right)$$
$$+ M_2 e^{-\theta_5\tau_5} O_1 G\left(\frac{O(t)}{O_1}\right) + P_1 G\left(\frac{P(t)}{P_1}\right) + \frac{\rho}{2(\varepsilon - \vartheta C_1)}\left(C(t) - C_1\right)^2.$$

Calculating $\dfrac{dZ_{11}}{dt}$ as:

$$\begin{aligned}
\frac{dZ_{11}}{dt} &= \hbar\left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U(t), P_1)}\right)\left(\rho - \gamma U(t) - (\omega_1+\omega_2+\omega_3)\Theta(U(t), P(t))\right) \\
&\quad + \frac{\nu M_1 e^{-\theta_4\tau_4}}{\zeta+\nu}\left(1 - \frac{L_1}{L(t)}\right)\left(\omega_1 e^{-\theta_1\tau_1}\Theta(U(t-\tau_1), P(t-\tau_1)) - (\zeta+\nu)L(t)\right) \\
&\quad + M_1 e^{-\theta_4\tau_4}\left(1 - \frac{I_1}{I(t)}\right)\left(\omega_2 e^{-\theta_2\tau_2}\Theta(U(t-\tau_2), P(t-\tau_2)) + \nu L(t) - \beta I(t)\right) \\
&\quad + M_2 e^{-\theta_5\tau_5}\left(1 - \frac{O_1}{O(t)}\right)\left(\omega_3 e^{-\theta_3\tau_3}\Theta(U(t-\tau_3), P(t-\tau_3)) - \Lambda O(t)\right) \\
&\quad + \left(1 - \frac{P_1}{P(t)}\right)\left(\beta M_1 e^{-\theta_4\tau_4} I(t-\tau_4) + \Lambda M_2 e^{-\theta_5\tau_5} O(t-\tau_5) - \xi P(t) - \rho P(t)C(t)\right) \\
&\quad + \frac{\rho}{\varepsilon - \vartheta C_1}\left(C(t) - C_1\right)\left(\varepsilon P(t) - \mu C(t) - \vartheta P(t)C(t)\right).
\end{aligned}$$

Define $Z_{12}(U(t), L(t), I(t), O(t), P(t), C(t))$ as:

$$\begin{aligned}
Z_{12} &= \frac{\nu M_1 \omega_1 e^{-\theta_1\tau_1 - \theta_4\tau_4}}{\zeta+\nu}\Theta(U_1, P_1)\int_{t-\tau_1}^{t} G\left(\frac{\Theta(U(s), P(s))}{\Theta(U_1, P_1)}\right) ds \\
&\quad + M_1\omega_2 e^{-\theta_2\tau_2 - \theta_4\tau_4}\Theta(U_1, P_1)\int_{t-\tau_2}^{t} G\left(\frac{\Theta(U(s), P(s))}{\Theta(U_1, P_1)}\right) ds \\
&\quad + M_2\omega_3 e^{-\theta_3\tau_3 - \theta_5\tau_5}\Theta(U_1, P_1)\int_{t-\tau_3}^{t} G\left(\frac{\Theta(U(s), P(s))}{\Theta(U_1, P_1)}\right) ds.
\end{aligned}$$

We calculate $\dfrac{dZ_{12}}{dt}$

$$\begin{aligned}
\frac{dZ_{12}}{dt} &= \frac{\nu M_1 \omega_1 e^{-\theta_1\tau_1 - \theta_4\tau_4}}{\zeta+\nu}\Theta(U_1, P_1)\left(\frac{\Theta(U(t), P(t))}{\Theta(U_1, P_1)} - \frac{\Theta(U(t-\tau_1), P(t-\tau_1))}{\Theta(U_1, P_1)}\right. \\
&\quad \left. + \ln\left(\frac{\Theta(U(t-\tau_1), P(t-\tau_1))}{\Theta(U(t), P(t))}\right)\right] \\
&\quad + M_1\omega_2 e^{-\theta_2\tau_2 - \theta_4\tau_4}\Theta(U_1, P_1)\left[\frac{\Theta(U(t), P(t))}{\Theta(U_1, P_1)} - \frac{\Theta(U(t-\tau_2), P(t-\tau_2))}{\Theta(U_1, P_1)}\right. \\
&\quad \left. + \ln\left(\frac{\Theta(U(t-\tau_2), P(t-\tau_2))}{\Theta(U(t), P(t))}\right)\right] \\
&\quad + M_2\omega_3 e^{-\theta_3\tau_3 - \theta_5\tau_5}\Theta(U_1, P_1)\left[\frac{\Theta(U(t), P(t))}{\Theta(U_1, P_1)} - \frac{\Theta(U(t-\tau_3), P(t-\tau_3))}{\Theta(U_1, P_1)}\right. \\
&\quad \left. + \ln\left(\frac{\Theta(U(t-\tau_3), P(t-\tau_3))}{\Theta(U(t), P(t))}\right)\right].
\end{aligned}$$

Define $Z_{13}(U(t), L(t), I(t), O(t), P(t), C(t))$ as

$$Z_{13} = \beta M_1 e^{-\theta_4\tau_4} I_1 \int_{t-\tau_4}^{t} G\left(\frac{I(s)}{I_1}\right) ds + \Lambda M_2 e^{-\theta_5\tau_5} O_1 \int_{t-\tau_5}^{t} G\left(\frac{O(s)}{O_1}\right) ds.$$

Calculating $\frac{dZ_{13}}{dt}$ as:

$$\begin{aligned}\frac{dZ_{13}}{dt} &= \beta M_1 e^{-\theta_4\tau_4} I_1 \left[\frac{I(t)}{I_1} - \frac{I(t-\tau_4)}{I_1} + \ln\left(\frac{I(t-\tau_4)}{I(t)}\right)\right] \\ &\quad + \Lambda M_2 e^{-\theta_5\tau_5} O_1 \left[\frac{O(t)}{O_1} - \frac{O(t-\tau_5)}{O_1} + \ln\left(\frac{O(t-\tau_5)}{O(t)}\right)\right].\end{aligned}$$

Construct a Lyapunov function $Z_1(U(t), L(t), I(t), O(t), P(t), C(t))$ as

$$Z_1 = Z_{11} + Z_{12} + Z_{13}.$$

It follows that

$$\frac{dZ_1}{dt} = \frac{dZ_{11}}{dt} + \frac{dZ_{12}}{dt} + \frac{dZ_{13}}{dt}.$$

Now we have

$$\begin{aligned}\frac{dZ_1}{dt} &= \hbar\left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U(t), P_1)}\right)(\rho - \gamma U(t)) + \hbar(\omega_1 + \omega_2 + \omega_3)\Theta(U_1, P_1)\frac{\Theta(U(t), P(t))}{\Theta(U(t), P_1)} \\ &\quad - \frac{\nu M_1 \omega_1 e^{-\theta_1\tau_1 - \theta_4\tau_4}}{\zeta + \nu}\Theta(U(t-\tau_1), P(t-\tau_1))\frac{L_1}{L(t)} + \nu M_1 e^{-\theta_4\tau_4} L_1 \\ &\quad - M_1\omega_2 e^{-\theta_2\tau_2 - \theta_4\tau_4}\Theta(U(t-\tau_2), P(t-\tau_2))\frac{I_1}{I(t)} - \nu M_1 e^{-\theta_4\tau_4} L(t)\frac{I_1}{I(t)} + \beta M_1 e^{-\theta_4\tau_4} I_1 \\ &\quad - M_2\omega_3 e^{-\theta_3\tau_3 - \theta_5\tau_5}\Theta(U(t-\tau_3), P(t-\tau_3))\frac{O_1}{O(t)} + \Lambda M_2 e^{-\theta_4\tau_4} O_1 \\ &\quad - \beta M_1 e^{-\theta_4\tau_4} I(t-\tau_4)\frac{P_1}{P(t)} - \Lambda M_2 e^{-\theta_5\tau_5} O(t-\tau_5)\frac{P_1}{P(t)} - \xi(P(t) - P_1) \\ &\quad - \rho(P(t) - P_1)C(t) + \frac{\rho}{\varepsilon - \vartheta C_1}(C(t) - C_1)(\varepsilon P(t) - \mu C(t) - \vartheta P(t)C(t)) \\ &\quad + \frac{\nu M_1 \omega_1 e^{-\theta_1\tau_1 - \theta_4\tau_4}}{\zeta + \nu}\Theta(U_1, P_1)\ln\left(\frac{\Theta(U(t-\tau_1), P(t-\tau_1))}{\Theta(U(t), P(t))}\right) \\ &\quad + M_1\omega_2 e^{-\theta_2\tau_2 - \theta_4\tau_4}\Theta(U_1, P_1)\ln\left(\frac{\Theta(U(t-\tau_2), P(t-\tau_2))}{\Theta(U(t), P(t))}\right) \\ &\quad + M_2\omega_3 e^{-\theta_3\tau_3 - \theta_5\tau_5}\Theta(U_1, P_1)\ln\left(\frac{\Theta(U(t-\tau_3), P(t-\tau_3))}{\Theta(U(t), P(t))}\right) \\ &\quad + \beta M_1 e^{-\theta_4\tau_4} I_1 \ln\left(\frac{I(t-\tau_4)}{I(t)}\right) + \Lambda M_2 e^{-\theta_5\tau_5} O_1 \ln\left(\frac{O(t-\tau_5)}{O(t)}\right).\end{aligned}$$

From the equilibrium conditions, we have:

$$\begin{aligned}\rho &= \gamma U_1 + (\omega_1 + \omega_2 + \omega_3)\Theta(U_1, P_1), \\ \frac{\nu M_1 \omega_1 e^{-\theta_1\tau_1 - \theta_4\tau_4}}{\zeta + \nu}\Theta(U_1, P_1) &= \nu M_1 e^{-\theta_4\tau_4} L_1, \\ \beta M_1 e^{-\theta_4\tau_4} I_1 &= M_1\omega_2 e^{-\theta_2\tau_2 - \theta_4\tau_4}\Theta(U_1, P_1) + \nu M_1 e^{-\theta_4\tau_4} L_1, \\ M_2\omega_3 e^{-\theta_3\tau_3 - \theta_5\tau_5}\Theta(U_1, P_1) &= \Lambda M_2 e^{-\theta_5\tau_5} O_1,\end{aligned}$$

$$\xi P_1 + \rho P_1 C_1 = \beta M_1 e^{-\theta_4\tau_4} I_1 + \Lambda M_2 e^{-\theta_5\tau_5} O_1,$$
$$\varepsilon P_1 = \mu C_1 + \vartheta P_1 C_1.$$

Utilizing these conditions for EP_1^G, we obtain

$$\begin{aligned}
\frac{dZ_1}{dt} &= \hbar\left(1-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right)(\gamma U_1-\gamma U(t))\\
&+\left(\nu M_1 e^{-\theta_4\tau_4}L_1 + M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)+\Lambda M_2 e^{-\theta_5\tau_5}O_1\right)\left(1-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right)\\
&+\left(\nu M_1 e^{-\theta_4\tau_4}L_1 + M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)+\Lambda M_2 e^{-\theta_5\tau_5}O_1\right)\frac{\Theta(U(t),P(t))}{\Theta(U(t),P_1)}\\
&-\nu M_1 e^{-\theta_4\tau_4}\frac{L_1\Theta(U(t-\tau_1),P(t-\tau_1))}{L(t)\Theta(U_1,P_1)}+\nu M_1 e^{-\theta_4\tau_4}L_1\\
&-M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)\frac{I_1\Theta(U(t-\tau_2),P(t-\tau_2))}{I(t)\Theta(U_1,P_1)}-\nu M_1 e^{-\theta_4\tau_4}L_1\frac{I_1L(t)}{I(t)L_1}\\
&+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)+\nu M_1 e^{-\theta_4\tau_4}L_1-\Lambda M_2 e^{-\theta_5\tau_5}O_1\frac{O_1\Theta(U(t-\tau_3),P(t-\tau_3))}{O(t)\Theta(U_1,P_1)}\\
&+\Lambda M_2 e^{-\theta_5\tau_5}O_1-\left(\nu M_1 e^{-\theta_4\tau_4}L_1+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)\right)\frac{P_1I(t-\tau_4)}{P(t)I_1}\\
&-\Lambda M_2 e^{-\theta_5\tau_5}O_1\frac{P_1O(t-\tau_5)}{P(t)O_1}-\xi(P(t)-P_1)-\rho(P(t)-P_1)C(t)+\rho(P(t)-P_1)C_1-\rho(P(t)-P_1)C_1\\
&+\frac{\rho}{\varepsilon-\vartheta C_1}(C(t)-C_1)\left(\varepsilon P(t)-\mu C(t)-\vartheta P(t)C(t)-\varepsilon P_1+\mu C_1+\vartheta P_1C_1-\vartheta P(t)C_1+\vartheta P(t)C_1\right)\\
&+\nu M_1 e^{-\theta_4\tau_4}L_1\ln\left(\frac{\Theta(U(t-\tau_1),P(t-\tau_1))}{\Theta(U(t),P(t))}\right)+\Lambda M_2 e^{-\theta_5\tau_5}O_1\ln\left(\frac{\Theta(U(t-\tau_3),P(t-\tau_3))}{\Theta(U(t),P(t))}\right)\\
&+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)\ln\left(\frac{\Theta(U(t-\tau_2),P(t-\tau_2))}{\Theta(U(t),P(t))}\right)\\
&+\left(\nu M_1 e^{-\theta_4\tau_4}L_1+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)\right)\ln\left(\frac{I(t-\tau_4)}{I(t)}\right)+\Lambda M_2 e^{-\theta_5\tau_5}O_1\ln\left(\frac{O(t-\tau_5)}{O(t)}\right).
\end{aligned}$$

Simplifying the result, we obtain

$$\begin{aligned}
\frac{dZ_1}{dt} &= -\gamma\hbar U_1\left(1-\frac{U(t)}{U_1}\right)\left(1-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right)-(\xi+\rho C_1)(P(t)-P_1)\\
&-\rho(P(t)-P_1)(C(t)-C_1)+\frac{\rho(\varepsilon-\vartheta C_1)}{\varepsilon-\vartheta C_1}(C(t)-C_1)(P(t)-P_1)-\frac{\rho(\mu+\vartheta P(t))}{\varepsilon-\vartheta C_1}(C(t)-C_1)^2\\
&+\nu M_1 e^{-\theta_4\tau_4}L_1\left[3-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}-\frac{L_1\Theta(U(t-\tau_1),P(t-\tau_1))}{L(t)\Theta(U_1,P_1)}-\frac{I_1L(t)}{I(t)L_1}-\frac{P_1I(t-\tau_4)}{P(t)I_1}\right.\\
&\left.+\ln\left(\frac{\Theta(U(t-\tau_1),P(t-\tau_1))}{\Theta(U(t),P(t))}\right)+\ln\left(\frac{I(t-\tau_4)}{I(t)}\right)\right]\\
&+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)\left[2-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}-\frac{P_1I(t-\tau_4)}{P(t)I_1}-\frac{I_1\Theta(U(t-\tau_2),P(t-\tau_2))}{I(t)\Theta(U_1,P_1)}\right.\\
&\left.+\ln\left(\frac{\Theta(U(t-\tau_2),P(t-\tau_2))}{\Theta(U(t),P(t))}\right)+\ln\left(\frac{I(t-\tau_4)}{I(t)}\right)\right]\\
&+\Lambda M_2 e^{-\theta_5\tau_5}O_1\left[2-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}-\frac{O_1\Theta(U(t-\tau_3),P(t-\tau_3))}{O(t)\Theta(U_1,P_1)}-\frac{P_1O(t-\tau_5)}{P(t)O_1}\right.\\
&\left.+\ln\left(\frac{\Theta(U(t-\tau_3),P(t-\tau_3))}{\Theta(U(t),P(t))}\right)+\ln\left(\frac{O(t-\tau_5)}{O(t)}\right)\right]
\end{aligned}$$

$$
\begin{aligned}
&+\left(\nu M_1 e^{-\theta_4\tau_4}L_1+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)+\Lambda M_2 e^{-\theta_5\tau_5}O_1\right)\frac{\Theta(U(t),P(t))}{\Theta(U(t),P_1)}\\
&+\left(\nu M_1 e^{-\theta_4\tau_4}L_1+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)+\Lambda M_2 e^{-\theta_5\tau_5}O_1\right)\left(1-\frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}\right)\\
&-\left(\nu M_1 e^{-\theta_4\tau_4}L_1+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)+\Lambda M_2 e^{-\theta_5\tau_5}O_1\right)\left(1-\frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}\right).
\end{aligned}
$$

Note that

$$
\begin{aligned}
-(\xi+\rho C_1)(P(t)-P_1)&=-\frac{1}{P_1}\left(\beta M_1 e^{-\theta_4\tau_4}I_1+\Lambda M_2 e^{-\theta_5\tau_5}O_1\right)(P(t)-P_1)\\
&=\left(\nu M_1 e^{-\theta_4\tau_4}L_1+M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)+e^{-\theta_5\tau_5}\Lambda M_2 O_1\right)\left(1-\frac{P(t)}{P_1}\right).
\end{aligned}
$$

Moreover, we have

$$
\begin{aligned}
\ln\left(\frac{\Theta(U(t-\tau_1),P(t-\tau_1))}{\Theta(U(t),P(t))}\right)&=\ln\left(\frac{L_1\Theta(U(t-\tau_1),P(t-\tau_1))}{L(t)\Theta(U_1,P_1)}\right)+\ln\left(\frac{I_1L(t)}{I(t)L_1}\right)\\
&\quad+\ln\left(\frac{I(t)P_1}{I_1P(t)}\right)+\ln\left(\frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}\right)+\ln\left(\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right),\\
\ln\left(\frac{\Theta(U(t-\tau_2),P(t-\tau_2))}{\Theta(U(t),P(t))}\right)&=\ln\left(\frac{I_1\Theta(U(t-\tau_2),P(t-\tau_2))}{I(t)\Theta(U_1,P_1)}\right)+\ln\left(\frac{I(t)P_1}{I_1P(t)}\right)+\ln\left(\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right)\\
&\quad+\ln\left(\frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}\right),\\
\ln\left(\frac{\Theta(U(t-\tau_3),P(t-\tau_3))}{\Theta(U(t),P(t))}\right)&=\ln\left(\frac{O_1\Theta(U(t-\tau_3),P(t-\tau_3))}{O(t)\Theta(U_1,P_1)}\right)+\ln\left(\frac{O(t)P_1}{O_1P(t)}\right)+\ln\left(\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right)\\
&\quad+\ln\left(\frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}\right),\\
\ln\left(\frac{I(t-\tau_4)}{I(t)}\right)&=\ln\left(\frac{P_1I(t-\tau_4)}{P(t)I_1}\right)+\ln\left(\frac{P(t)I_1}{P_1I(t)}\right),\\
\ln\left(\frac{O(t-\tau_5)}{O(t)}\right)&=\ln\left(\frac{P_1O(t-\tau_5)}{P(t)O_1}\right)+\ln\left(\frac{P(t)O_1}{P_1O(t)}\right).
\end{aligned}
$$

Then $\frac{dZ_1}{dt}$ will be

$$
\begin{aligned}
\frac{dZ_1}{dt}&=-\gamma\hbar U_1\left(1-\frac{U(t)}{U_1}\right)\left(1-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right)-\frac{\rho(\mu+\vartheta P(t))}{\varepsilon-\vartheta C_1}(C(t)-C_1)^2\\
&\quad+\nu M_1e^{-\theta_4\tau_4}L_1\left[5-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}-\frac{L_1\Theta(U(t-\tau_1),P(t-\tau_1))}{L(t)\Theta(U_1,P_1)}-\frac{I_1L(t)}{I(t)L_1}\right.\\
&\quad\left.-\frac{P_1I(t-\tau_4)}{P(t)I_1}-\frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}+\ln\left(\frac{\Theta(U(t-\tau_1),P(t-\tau_1))}{\Theta(U(t),P(t))}\right)+\ln\left(\frac{I(t-\tau_4)}{I(t)}\right)\right]\\
&\quad+M_1\omega_2e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)\left[4-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}-\frac{P_1I(t-\tau_4)}{P(t)I_1}-\frac{I_1\Theta(U(t-\tau_2),P(t-\tau_2))}{I(t)\Theta(U_1,P_1)}\right.\\
&\quad\left.-\frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}+\ln\left(\frac{\Theta(U(t-\tau_2),P(t-\tau_2))}{\Theta(U(t),P(t))}\right)+\ln\left(\frac{I(t-\tau_4)}{I(t)}\right)\right]\\
&\quad+\Lambda M_2e^{-\theta_5\tau_5}O_1\left[4-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}-\frac{O_1\Theta(U(t-\tau_3),P(t-\tau_3))}{O(t)\Theta(U_1,P_1)}\right.\\
&\quad\left.-\frac{P_1O(t-\tau_5)}{P(t)O_1}-\frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}+\ln\left(\frac{\Theta(U(t-\tau_3),P(t-\tau_3))}{\Theta(U(t),P(t))}\right)+\ln\left(\frac{O(t-\tau_5)}{O(t)}\right)\right]
\end{aligned}
$$

$$+\left(\nu M_1 e^{-\theta_4\tau_4}L_1 + M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1) + e^{-\theta_5\tau_5}\Lambda M_2 O_1\right)$$
$$\times\left(\frac{\Theta(U(t),P(t))}{\Theta(U(t),P_1)} - \frac{P(t)}{P_1} - 1 + \frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}\right).$$

Simplifying the result, we get

$$\begin{aligned}
\frac{dZ_1}{dt} &= -\gamma\hbar U_1\left(1-\frac{U(t)}{U_1}\right)\left(1-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right) - \frac{\rho(\mu+\vartheta P(t))}{\varepsilon-\vartheta C_1}(C(t)-C_1)^2\\
&-\nu M_1 e^{-\theta_4\tau_4}L_1\left[G\left(\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right) + G\left(\frac{L_1\Theta(U(t-\tau_1),P(t-\tau_1))}{L(t)\Theta(U_1,P_1)}\right) + G\left(\frac{I_1L(t)}{I(t)L_1}\right)\right.\\
&\left.+G\left(\frac{P_1I(t-\tau_4)}{P(t)I_1}\right) + G\left(\frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}\right)\right]\\
&-M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1)\left[G\left(\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right) + G\left(\frac{I_1\Theta(U(t-\tau_2),P(t-\tau_2))}{I(t)\Theta(U_1,P_1)}\right)\right.\\
&\left.+G\left(\frac{P_1I(t-\tau_4)}{P(t)I_1}\right) + G\left(\frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}\right)\right]\\
&-\Lambda M_2 e^{-\theta_5\tau_5}u_1\left[G\left(\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right) + G\left(\frac{O_1\Theta(U(t-\tau_3),P(t-\tau_3))}{O(t)\Theta(U_1,P_1)}\right) + G\left(\frac{P_1O(t-\tau_5)}{P(t)O_1}\right)\right.\\
&\left.+G\left(\frac{P(t)\Theta(U(t),P_1)}{P_1\Theta(U(t),P(t))}\right)\right] + \left(\nu M_1 e^{-\theta_4\tau_4}L_1 + M_1\omega_2 e^{-\theta_2\tau_2-\theta_4\tau_4}\Theta(U_1,P_1) + e^{-\theta_5\tau_5}\Lambda M_2 O_1\right)\\
&\times\left(\frac{\Theta(U(t),P(t))}{\Theta(U(t),P_1)} - \frac{P(t)}{P_1}\right)\left(1-\frac{\Theta(U(t),P_1)}{\Theta(U(t),P(t))}\right).
\end{aligned}$$

From (A2) we have

$$\left(1-\frac{U(t)}{U_1}\right)\left(1-\frac{\Theta(U_1,P_1)}{\Theta(U(t),P_1)}\right) \leqslant 0.$$

In addition, from Assumptions (A1), (A2), and (A4), we have

$$\left(\frac{\Theta(U(t),P(t))}{P(t)} - \frac{\Theta(U(t),P_1)}{P_1}\right)(\Theta(U(t),P(t)) - \Theta(U(t),P_1) \leqslant 0,$$

which gives

$$\left(\frac{\Theta(U(t),P(t))}{\Theta(U(t),P_1)} - \frac{P(t)}{P_1}\right)\left(1-\frac{\Theta(U(t),P_1)}{\Theta(U(t),P(t))}\right) \leqslant 0.$$

Then we get that for all $U(t), L(t), I(t), O(t), P(t), C(t) > 0$ we have $\frac{dZ_1}{dt} \leqslant 0$, moreover $\frac{dZ_1}{dt} = 0$ if and only if $U(t) = U_1$, $L(t) = L_1$, $I(t) = I_1$, $O(t) = O_1$, $P(t) = P_1$ and $C(t) = C_1$. Applying L.I.P, we obtain that if $R_0^G > 1$, then EP_1^G is G.A.S. □

4. Numerical simulations

In this section we perform numerical simulation for systems (2.1)-(2.6) and (3.1)-(3.6). We let $\tau = \tau_i$, $i = 1, 2, \ldots, 5$. In addition, we fix the values of parameters $\rho = 10$, $\gamma = \mu = 0.01$, $\zeta = \beta = 0.3$, $\nu = \varepsilon = 0.2$, $M_2 = 5$, $\xi = 6$, $\Lambda = 0.1$, $\rho = 0.4$, $\omega_k = 0.001$, $\theta_i = 0.6$, $i = 1, 2, \ldots, 5$ and $k = 1, 2, 3$ and the remaining parameters will be changed.

4.1. Numerical simulations for model (2.1)-(2.6)

In this subsection we conduct numerical simulations for model (2.1)-(2.6).

4.1.1. Stability of equilibria for different values of M_1

We choose three different initial conditions as:

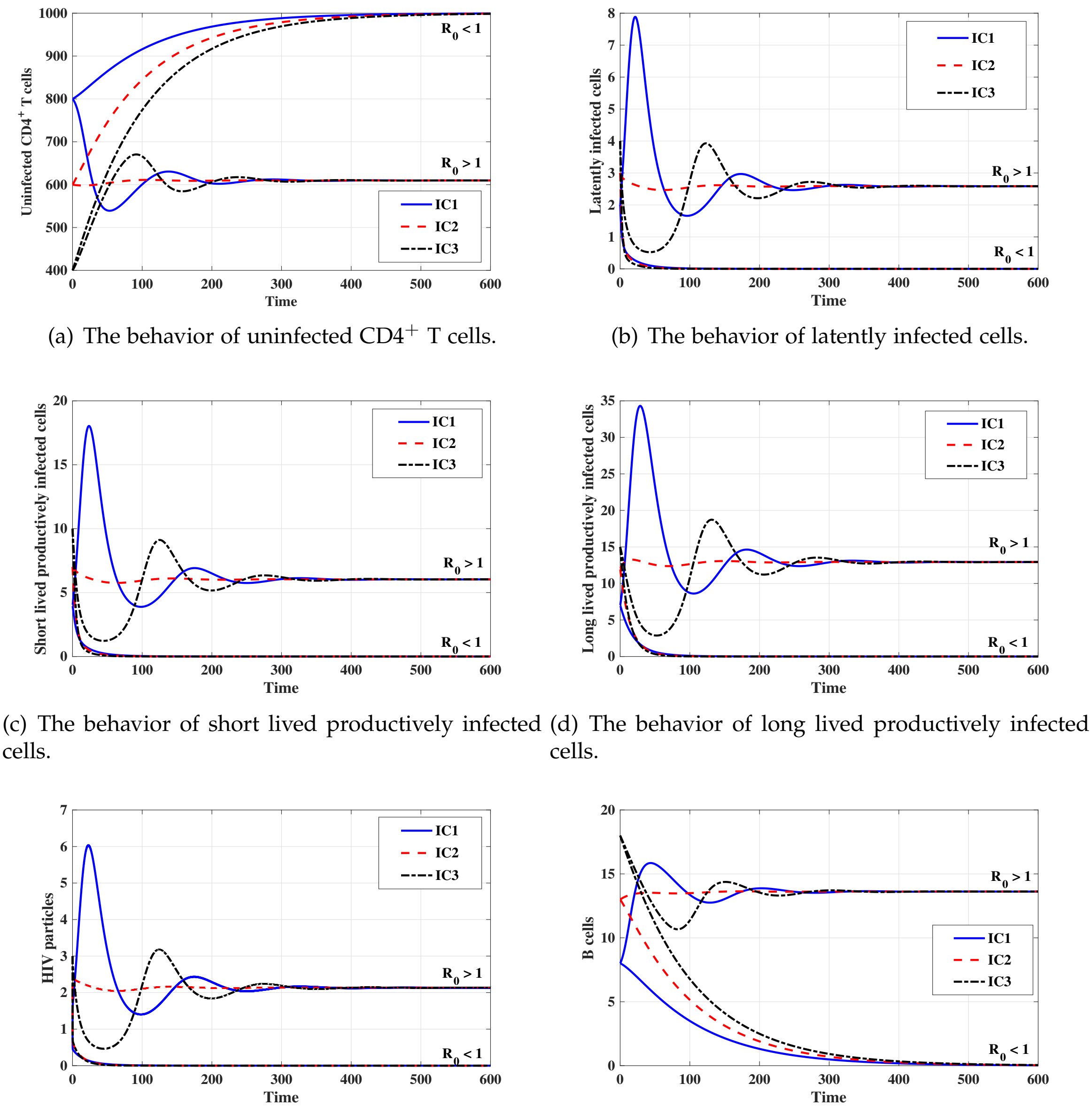
IC1: $U(s) = 800$, $L(s) = 2$, $I(s) = 4$, $O(s) = 7$, $P(s) = 1$, $C(s) = 8$;

IC2: $U(s) = 600$, $L(s) = 3$, $I(s) = 7$, $O(s) = 12$, $P(s) = 2$, $C(s) = 13$;
IC3: $U(s) = 400$, $L(s) = 4$, $I(s) = 10$, $O(s) = 15$, $P(s) = 3$, $C(s) = 18$, $s \in [-\tau, 0]$.

We take $\tau = \vartheta = 0.01$. Moreover, we consider two values of the parameter M_1 as:

(i) $M_1 = 0.5$, then we compute $R_0 = 0.9387 < 1$. Figure 1 shows that, for all IC1-IC3, the solution of the model tends to $EP_0 = (1000, 0, 0, 0, 0, 0)$. It means that, EP_0 is G.A.S .

(ii) $M_1 = 10$, then we compute $R_0 = 3.1289 > 1$. Figure 1 shows that the solutions of the model converge to the equilibrium $EP_1 = (609.7, 2.587, 6.037, 12.94, 2.137, 13.62)$ for all IC1-IC3. Then, EP_1 is G.A.S.



(a) The behavior of uninfected CD4$^+$ T cells.

(b) The behavior of latently infected cells.

(c) The behavior of short lived productively infected cells.

(d) The behavior of long lived productively infected cells.

(e) The behavior of HIV particles.

(f) The behavior of B cells.

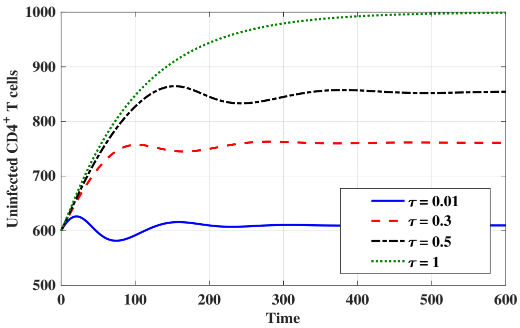
Figure 1: Solution trajectories of model (2.1)-(2.6) for different values of M_1.

4.1.2. *The effect of τ on stability of equilibria*

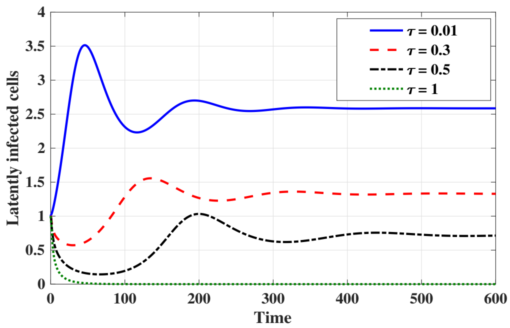
In this case, we take $\vartheta = 0.01$, $M_1 = 10$ and τ is varied. Moreover, we consider the following initial condition $U(s) = 600$, $L(s) = 1$, $I(s) = 2$, $O(s) = 4$, $P(s) = 1$, $C(s) = 8$, $s \in [-\tau, 0]$. Figure 2 shows that as τ

is increased, the concentrations of latently infected cells, short lived productively infected cells, long lived productively infected cells, HIV particles and B cells are decreased, while the concentration of uninfected $CD4^+$ T cells is increased until they reach the equilibrium point EP_0. Moreover, we have the following observations:

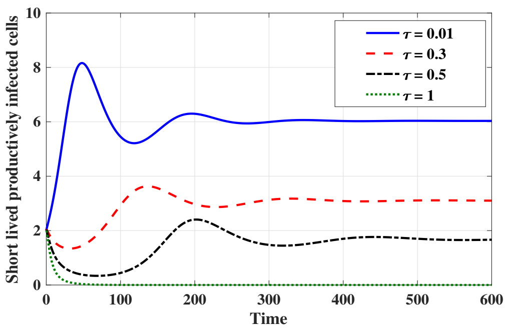
(i) EP_1 is G.A.S when $0 < \tau < 0.9606$;
(ii) EP_0 is G.A.S when $\tau > 0.9606$.



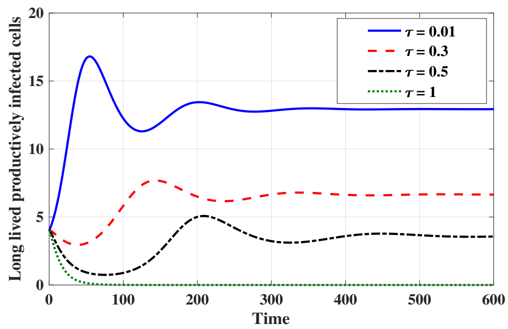
(a) The behavior of uninfected $CD4^+$ T cells.



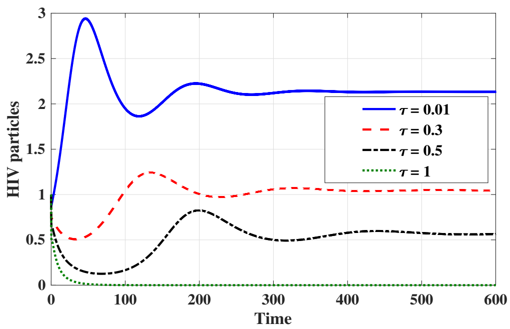
(b) The behavior of latently infected cells.



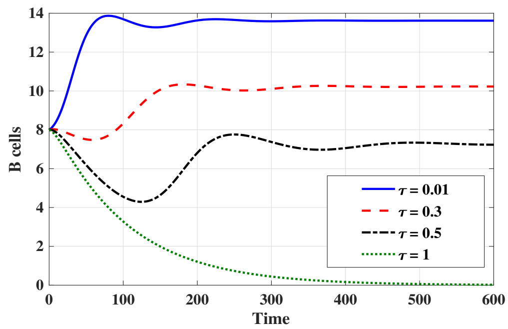
(c) The behavior of short lived productively infected cells.



(d) The behavior of long lived productively infected cells.



(e) The behavior of HIV particles.

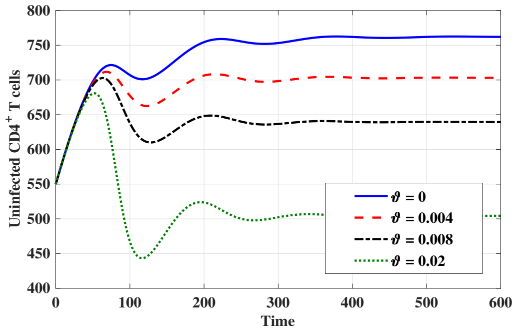


(f) The behavior of B cells.

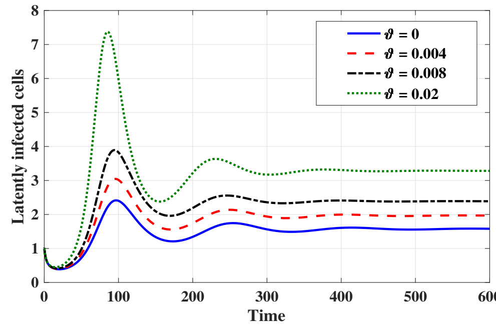
Figure 2: Solution trajectories of model (2.1)-(2.6) for different values of τ.

4.1.3. Effect of B cell impairment parameter ϑ on the HIV dynamics.

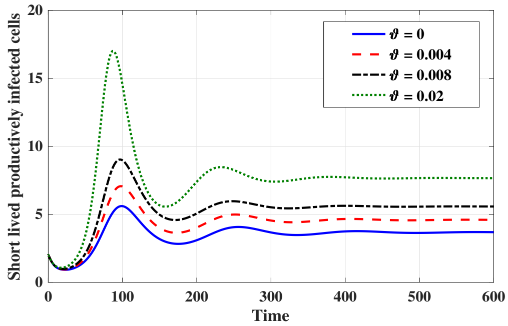
In this case, we take $\tau = 0.01$, $M_1 = 10$ and ϑ is varied. Moreover, we consider the following initial condition $U(s) = 550$, $L(s) = 1$, $I(s) = 2$, $O(s) = 1$, $P(s) = 1$, $C(s) = 16$, $s \in [-\tau, 0]$. Figure 3 shows that as ϑ is increased, the concentrations of latently infected cells, short lived productively infected cells, long lived productively infected cells and HIV particles are increased, while the concentrations of uninfected $CD4^+$ T cells and B cells are decreased. We note that the parameter ϑ has no effect on the stability of equilibria.



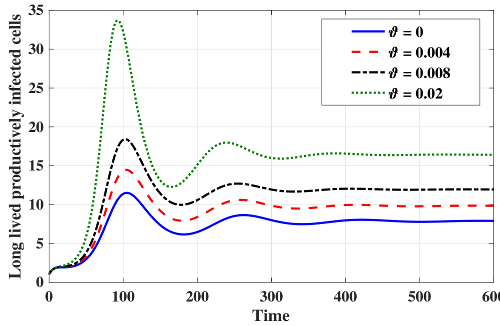
(a) The behavior of uninfected $CD4^+$ T cells.



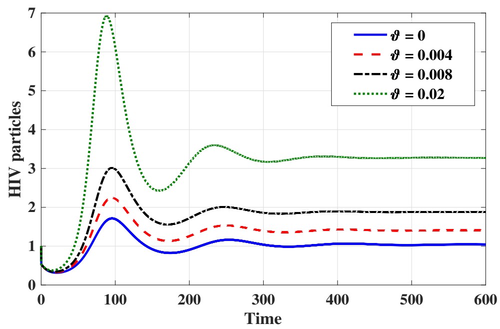
(b) The behavior of latently infected cells.



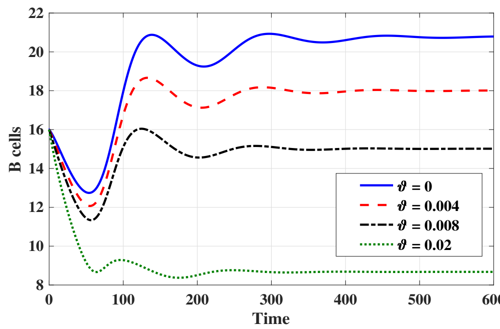
(c) The behavior of short lived productively infected cells.



(d) The behavior of long lived productively infected cells.



(e) The behavior of HIV particles.



(f) The behavior of B cells.

Figure 3: Solution trajectories of model (2.1)-(2.6) for different values of ϑ.

4.2. Numerical simulations for model (3.1)-(3.6)

We conduct numerical simulations for model (3.1)-(3.6) with specific incidence rate function

$$\Theta(U, P) = \frac{UP}{1 + \alpha_1 P + \alpha_2 U},$$

where α_1 and α_2 are nonnegative parameters. We note that if $\alpha_1 = \alpha_2 = 0$, then we obtain bilinear incidence which are given in model (2.1)-(2.6), if $\alpha_1 \neq 0$ and $\alpha_2 = 0$, then we get saturated incidence, and if $\alpha_1 = 0$ and $\alpha_2 \neq 0$, then we obtain Holling type-II incidence. We can easily see that $\Theta(U, P)$ is continuously differentiable function. Moreover, $\Theta(U,P)$ satisfies $\Theta(U,P) > 0$, and $\Theta(0,P) = \Theta(U,0) = 0$ for all $U(t) > 0$ and $P(t) > 0$. Thus (A1) is satisfied. We have

$$\frac{\partial\Theta(U,P)}{\partial U} = \frac{P+\alpha_1 P^2}{(1+\alpha_1 P+\alpha_2 U)^2} > 0, \qquad \frac{\partial\Theta(U,P)}{\partial P} = \frac{U+\alpha_2 U^2}{(1+\alpha_1 P+\alpha_2 U)^2} > 0,$$

for all $U(t) > 0$ and $P(t) > 0$. Moreover, $\dfrac{\partial\Theta(U,0)}{\partial P} = \dfrac{U}{1+\alpha_2 U} > 0$ for all $U(t) > 0$, then (A2) is satisfied.

We also have

$$\frac{d}{dU}\left(\frac{\partial\Theta(U,0)}{\partial P}\right) = \frac{1}{(1+\alpha_2 U)^2} > 0, \quad \text{for all } U(t) \geqslant 0.$$

Then (A3) is satisfied. Finally we have

$$\frac{\partial}{\partial P}\left(\frac{\Theta(U,P)}{P}\right) = \frac{-\alpha_1 U}{(1+\alpha_1 P+\alpha_2 U)^2} < 0, \quad \text{for all } \ U(t), P(t) > 0.$$

Then (A4) is also satisfied. The basic reproduction number is given by

$$R_0 = \frac{\omega_1 \nu M_1 e^{-\theta_1\tau_1-\theta_4\tau_4} + (\zeta+\nu)\left[\omega_2 M_1 e^{-\theta_2\tau_2-\theta_4\tau_4} + \omega_3 M_2 e^{-\theta_3\tau_3-\theta_5\tau_5}\right]}{\xi(\zeta+\nu)(1+\alpha_2 U_0)} U_0.$$

In this subsection, we fix $\vartheta = \tau = 0.01$, $M_1 = 10$ and choose α_1 and α_2.

4.2.1. Effect of the saturation parameter α_1 on the HIV dynamics

In this case, we take $\alpha_2 = 0$ then $\Theta(U,P)$ represents the saturation incidence. We choose the following condition: $U(s) = 700$, $L(s) = 1.5$, $I(s) = 2$, $O(s) = 4$, $P(s) = 1$, $C(s) = 10$, $s \in [-\tau, 0]$. Figure 4 shows that as α_1 is increased, the concentration of the uninfected $CD4^+$ T cells is increased, while the concentrations of latently infected cells, short lived productively infected cells, long lived productively infected cells, HIV particles, and B cells are decreased. We note that the parameter α_1 has no effect on the stability of equilibria. The reason is that R_0 does not depend on the parameter α_1.

4.2.2. Effect of Holling type-II constant α_2 on HIV dynamics

For this case, we take $\alpha_1 = 0$ then $\Theta(U,P)$ represents the Holling type-II incidence. Let us choose the following condition: $U(s) = 700$, $L(s) = 2$, $I(s) = 2$, $O(s) = 4$, $P(s) = 1$, $C(s) = 10$, $s \in [-\tau, 0]$. We suggest different values of α_2 to see its effect on the solution of the model as we can see in Figure 5. Moreover, we conclude the following results:

(i) EP_1^G is G.A.S, when $0 \leqslant \alpha_2 < 0.0031$;
(ii) EP_0^G is G.A.S, when $\alpha_2 > 0.0031$.

This means that α_2 can play the role of controller which can be designed to stabilize the system around the infection-free equilibrium EP_0^G.

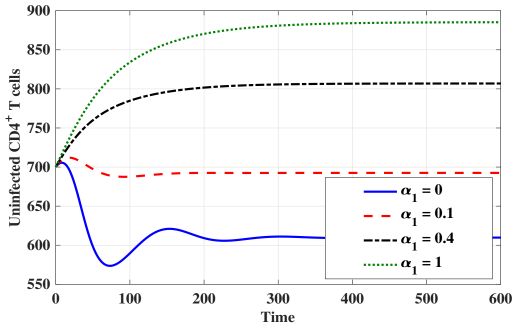
4.2.3. Effect of antiviral treatment on the HIV dynamics

Let us introduce the HIV dynamics model under the effect of highly active antiretroviral therapies (HAART) as:

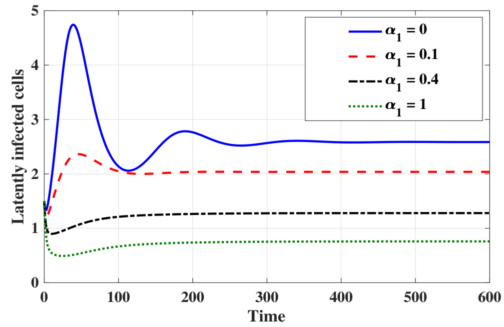
$$\dot{U}(t) = \rho - \gamma U(t) - (1-\epsilon_r)(\omega_1+\omega_2+\omega_3)\frac{U(t)P(t)}{1+\alpha_2 U(t)}, \tag{4.1}$$

$$\dot{L}(t) = (1-\epsilon_r)\omega_1 e^{-\theta_1\tau_1}\frac{U(t-\tau_1)P(t-\tau_1)}{1+\alpha_2 U(t-\tau_1)} - (\zeta+\nu)L(t), \tag{4.2}$$

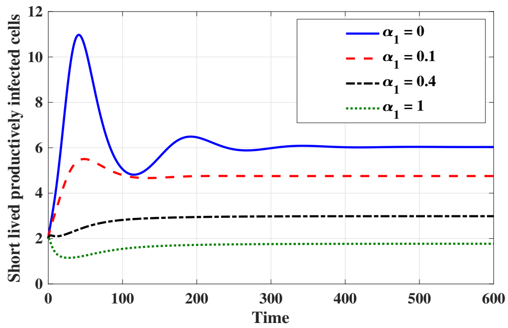
$$\dot{I}(t) = (1-\epsilon_r)\omega_2 e^{-\theta_2\tau_2}\frac{U(t-\tau_2)P(t-\tau_2)}{1+\alpha_2 U(t-\tau_2)} + \nu L(t) - \beta I(t), \tag{4.3}$$



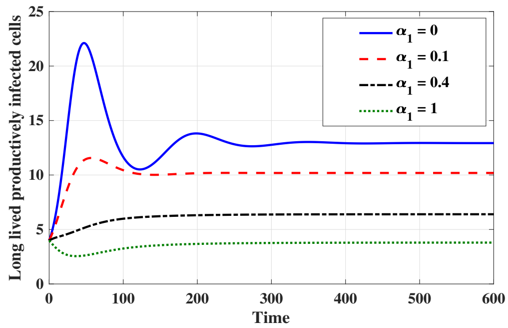
(a) The behavior of uninfected CD4$^+$ T cells.



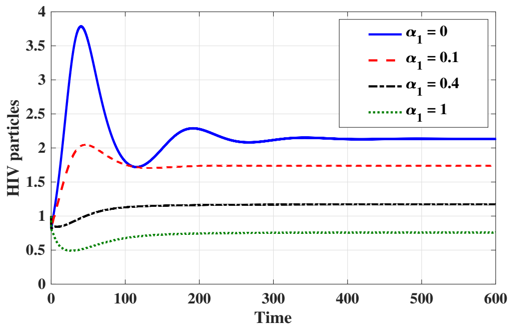
(b) The behavior of latently infected cells.



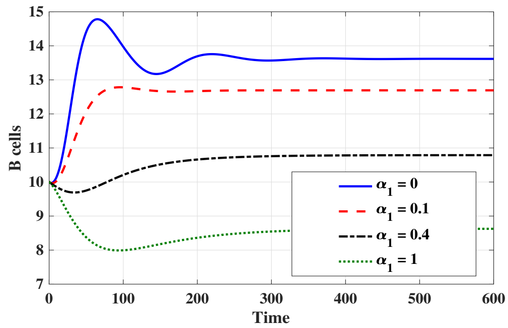
(c) The behavior of short lived productively infected cells.



(d) The behavior of long lived productively infected cells.



(e) The behavior of HIV particles.



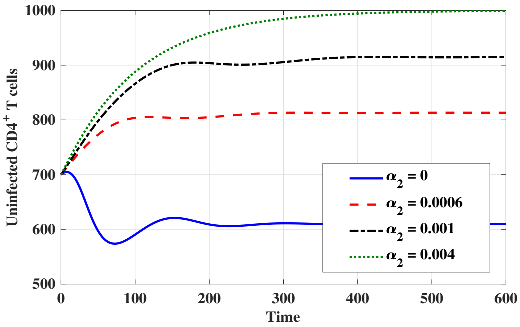
(f) The behavior of B cells.

Figure 4: Solution trajectories of model (3.1)-(3.6) for different values of α_1.

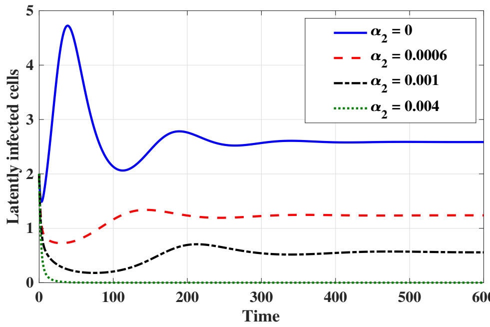
$$\dot{O}(t) = (1-\epsilon_r)\omega_3 e^{-\theta_3\tau_3}\frac{U(t-\tau_3)P(t-\tau_3)}{1+\alpha_2 U(t-\tau_3)} - \Lambda O(t), \tag{4.4}$$
$$\dot{P}(t) = (1-\epsilon_p)\beta M_1 e^{-\theta_4\tau_4} I(t-\tau_4) + (1-\epsilon_p)\Lambda M_2 e^{-\theta_5\tau_5} O(t-\tau_5) - \xi P(t) - \rho P(t)C(t), \tag{4.5}$$
$$\dot{C}(t) = \varepsilon P(t) - \mu C(t) - \vartheta P(t)C(t), \tag{4.6}$$

where $\epsilon_r \in [0,1]$ is the efficacy of the reverse transcriptase inhibitor drug, while $\epsilon_p \in [0,1]$ is the efficacy of the protease inhibitor drug. If $\epsilon_r = \epsilon_p = 0$, then the HAART has no effect, if $\epsilon_r = \epsilon_p = 1$, the HIV growth is completely stopped. Let $\epsilon = \epsilon_r = \epsilon_p$, consequently, the parameter $R_0(\epsilon)$ is given by

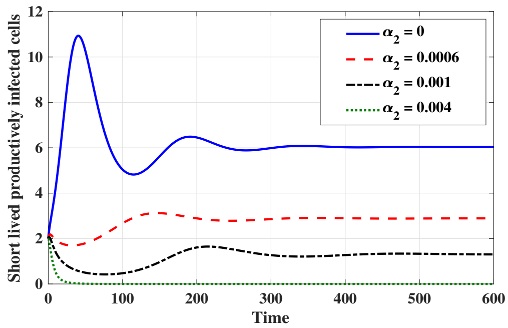
$$R_0(\epsilon) = \frac{(1-\epsilon)^2\left[\omega_1 \nu M_1 e^{-\theta_1\tau_1-\theta_4\tau_4} + (\zeta+\nu)\left(\omega_2 M_1 e^{-\theta_2\tau_2-\theta_4\tau_4} + \omega_3 M_2 e^{-\theta_3\tau_3-\theta_5\tau_5}\right)\right]}{\xi(\zeta+\nu)(1+\alpha_2 U_0)} U_0.$$



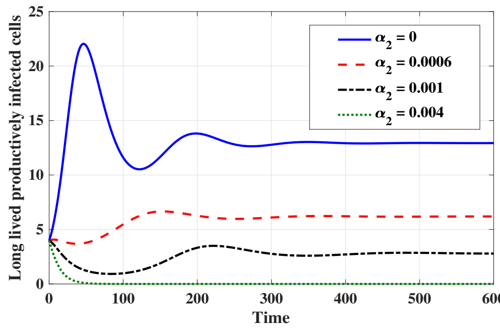
(a) The behavior of uninfected CD4$^+$ T cells.



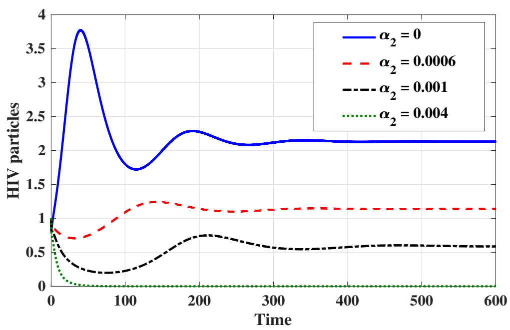
(b) The behavior of latently infected cells.



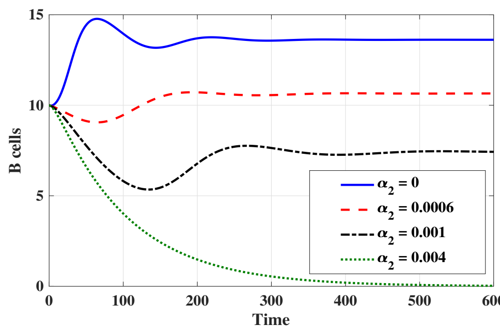
(c) The behavior of short lived productively infected cells.



(d) The behavior of long lived productively infected cells.



(e) The behavior of HIV particles.



(f) The behavior of B cells.

Figure 5: Solution trajectories of model (3.1)-(3.6) for different values of α_2.

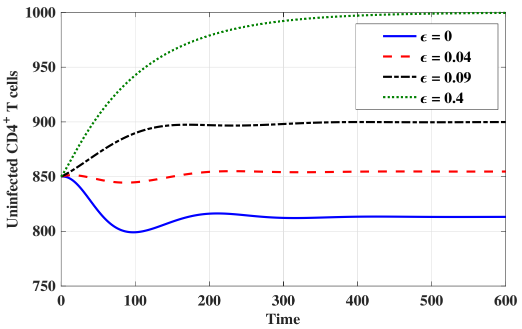
Since the goal is to clear the HIV from the body, then we have to determine the drug efficacies that make $R_0(\epsilon) < 1$ for model (4.1)-(4.6). Then

$$(1-\epsilon)^2 < \frac{1}{R_0(0)}.$$

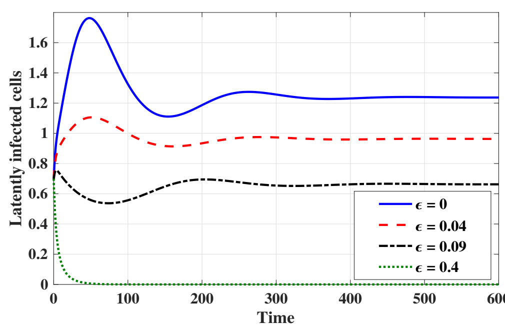
Since, $0 \leqslant \epsilon \leqslant 1$, then for $\epsilon^{\min} < \epsilon \leqslant 1$, EP_0^G is G.A.S, where $\epsilon^{\min} = \max\left\{0, 1 - \frac{1}{\sqrt{R_0(0)}}\right\}$. We take $\alpha_2 = 0.0006$, then, we find the following:

(i) if $0.2849 < \epsilon \leqslant 1$, then $R_0(\epsilon) < 1$ and EP_0^G is G.A.S;
(ii) if $0 \leqslant \epsilon < 0.2849$, then $R_0(\epsilon) > 1$ and EP_1^G is G.A.S.

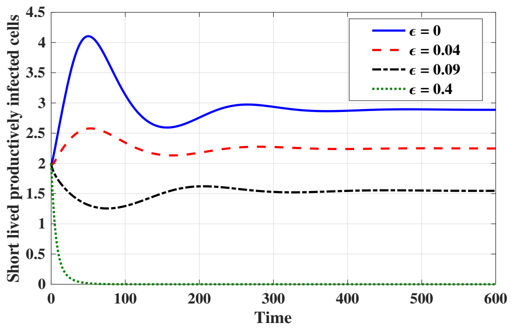
We consider the following initial condition $U(0) = 850$, $L(0) = 0.7$, $I(0) = 2$, $O(0) = 4$, $P(0) = 0.6$, $C(0) = 8$ to show in Figure 6 the solution trajectories of model (4.1)-(4.6) for different values of ϵ. Clearly from the figure we can see that, the increasing of ϵ will increase the concentration of the uninfected CD4$^+$ T cells and decrease the concentrations of latently infected cells, short lived productively infected cells, long lived productively infected cells, HIV particles, and B cells.



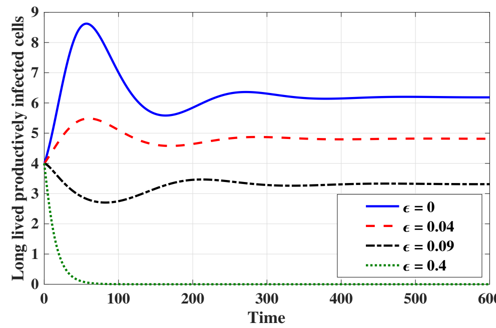
(a) The behavior of uninfected CD4$^+$ T cells.



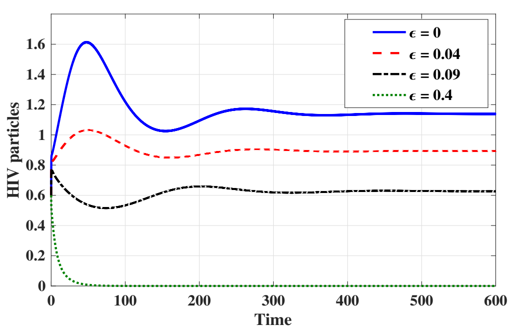
(b) The behavior of latently infected cells.



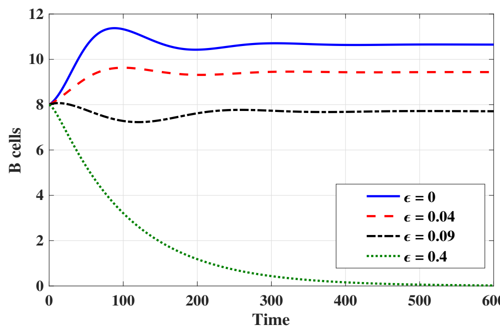
(c) The behavior of short lived productively infected cells.



(d) The behavior of long lived productively infected cells.



(e) The behavior of HIV particles.



(f) The behavior of B cells.

Figure 6: Solution trajectories of model (4.1)-(4.6) for different values of ϵ.

5. Conclusion

In the literature, various mathematical models of virus dynamics have investigated the impairment of CTL functions. However, the dysfunction of B cell could happened during the HIV infection as it has been reported in several papers. In this work, we have studied HIV infection models with five delays including the impairment of B cell functions. We have taken into account three types of infected cells: short-lived productively infected cells (these cells live for short time and produce large amount of HIV particles), long-lived productively infected cells (which live for long time and produce small amount of

HIV particles) and latently infected cells (such cells contain the HIV but are not producing it). Bilinear and general incidence rates have been considered in the first and second model, respectively. We have shown that, the solutions of the models are non-negative and ultimately bounded which ensure the well-posedness of the models. We have derived the basic reproduction number R_0 which fully determines the existence and stability of the two equilibria of the models. We have examined the global stability of the two equilibria of the models by using Lyapunov method and LaSalle's invariance principle. We have proven that (i) if $R_0 < 1$, then the infection-free equilibrium is G.A.S and the HIV is predicted to be completely cleared from the HIV infected individuals, (ii) if $R_0 > 1$, then the endemic equilibrium is G.A.S and a chronic HIV infection is attained. We have conducted numerical simulations and have shown that both the theoretical and numerical results are consistent. The results show that, when the B cells loss their functions during the HIV infection, the number of antibodies produced from the B cells are decreased and then the number of HIV particles are increased. Therefore, HAART is needed to improve the health of the HIV infected patient.

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