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\textsuperscript{+} 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:

\[
\begin{align*}
\dot{U}(t) &= \rho - \gamma U(t) - \omega U(t)P(t), \\
\dot{I}(t) &= \omega U(t)P(t) - \beta I(t), \\
\dot{P}(t) &= \beta M_1 I(t) - \xi P(t).
\end{align*}
\]

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

\[
\dot{U}(t) = \rho - \gamma U(t) - \omega U(t)P(t), \\
I(t) = \omega U(t - \tau_1)P(t - \tau_1) - \beta I(t), \\
\dot{P}(t) = \epsilon I(t - \tau_2) - \xi P(t) - \rho P(t)C(t), \\
\dot{C}(t) = \epsilon P(t)C(t) - \mu C(t),
\]

where \( C(t) \) is the concentration of B cells. The term \( \rho P(t)C(t) \) represents the neutralization rate of HIV particles. Parameters \( \epsilon \) and \( \mu \) are the proliferation and natural death rate constants of B cells, respectively. Parameter \( \tau_1 \) represents the time between an HIV contacts an uninfected CD4\(^+\) T cell and the cell becomes infected. The immature virus needs time \( \tau_2 \) 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 \( \epsilon P(t) \) and this leads to \( \dot{C}(t) = \epsilon P(t) - \mu C(t) \).

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:

\[
\dot{U}(t) = \rho - \gamma U(t) - (\omega_1 + \omega_2 + \omega_3)U(t)P(t), \\
\dot{I}(t) = e^{-\theta_1 \tau_1} \omega_1 U(t - \tau_1)P(t - \tau_1) - (\zeta + \gamma)I(t), \\
\dot{I}(t) = e^{-\theta_2 \tau_2} \omega_2 U(t - \tau_2)P(t - \tau_2) + \gamma I(t) - \beta I(t), \\
\dot{O}(t) = e^{-\theta_3 \tau_3} \omega_3 U(t - \tau_3)P(t - \tau_3) - \Lambda O(t), \\
\dot{P}(t) = e^{-\theta_4 \tau_4} \beta M_1 I(t - \tau_4) + e^{-\theta_5 \tau_5} \Lambda M_2 O(t - \tau_5) - \xi P(t) - \rho P(t)C(t), \\
\dot{C}(t) = \epsilon P(t) - \mu C(t) - \delta P(t)C(t),
\]
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 \( \tau L(t) \) 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 \( \Lambda \) is the natural death rate constant of the long lived productively infected cells. The B cell impairment rate is given by \( \delta P(t)C(t) \). All previous described parameters are positive constants. Parameters \( \tau_1, \tau_2, \) and \( \tau_3 \) 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 \( e^{-\theta_1 \tau_k}, k = 1, 2, 3 \) represents the damage of CD4\(^+\) T cells during the interval \([t - \tau_k, t] \). The parameters \( \tau_4 \) and \( \tau_5 \) 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, \( \tau_1, \tau_2, \tau_3, \tau_4, \) and \( \tau_5 \) are positive constants.

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

\[
\begin{align*}
U(s) & = \varphi_1(s), & L(s) & = \varphi_2(s), \\
I(s) & = \varphi_3(s), & O(s) & = \varphi_4(s), \\
P(s) & = \varphi_5(s), & C(s) & = \varphi_6(s), \\
\varphi_1(s) & \geq 0, s \in [-\tau, 0], & i & = 1, 2, \ldots, 6,
\end{align*}
\]

where \( \tau = \max(\tau_1, \tau_2, \tau_3, \tau_4, \tau_5) \) and \( (\varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5, \varphi_6) \in \mathcal{C}[-\tau, 0, \mathbb{R}^6_{\geq 0}] \), where \( \mathcal{C} \) is the Banach space of continuous function mapping the interval \([-\tau, 0] \) into \( \mathbb{R}^6_{\geq 0} \). 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 \( U(t), I(t), O(t), P(t), \) and \( C(t) \) are all non-negative and ultimately bounded for all \( t \geq 0 \).

**Proof.** Assume that \( U(t) \) loses 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 \( U(j^*) = \rho > 0 \). 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 \( t \geq 0 \). Furthermore, for all \( t \in [0, \tau] \), we have

\[
\begin{align*}
L(t) & = \varphi_2(0)e^{-(\zeta + \nu)t} + e^{-\theta_1 \tau_1} \omega_1 \int_0^t e^{-(\zeta + \nu)(t-s)}U(x - \tau_1)P(x - \tau_1) \, dx \geq 0, \\
I(t) & = \varphi_3(0)e^{-\beta t} + \int_0^t e^{-(t-x)}(e^{-\theta_2 \tau_2} \omega_2 U(x - \tau_2) + \nu L(x)) \, dx \geq 0, \\
O(t) & = \varphi_4(0)e^{-\Lambda t} + e^{-\theta_3 \tau_3} \omega_3 \int_0^t e^{-(t-x)}U(x - \tau_3)P(x - \tau_3) \, dx \geq 0, \\
P(t) & = \varphi_5(0)e^{-\int_0^t (\xi + \rho C(1)) \, dx} + \int_0^t e^{-\int_0^s (\xi + \rho C(1)) \, dx} \bigg( e^{-\theta_4 \tau_4} \beta M_1 I(x - \tau_4) + e^{-\theta_5 \tau_5} \Lambda M_2 O(x - \tau_5) \bigg) \, dx \geq 0, \\
C(t) & = \varphi_6(0)e^{-\int_0^t (\mu + \theta P(1)) \, dx} + \int_0^t e^{-\int_0^s (\mu + \theta P(1)) \, dx} P(x) \, dx \geq 0.
\end{align*}
\]

Thus, by a recursive argument, we get \( L(t), I(t), O(t), P(t), C(t) \geq 0 \) for all \( t \geq 0 \). Hence, \( \mathbb{R}^6_{\geq 0} \) is positively invariant for model (2.1)-(2.6). Next, from Eq. (2.1) we obtain \( U(t) \leq \rho - \gamma U(t) \). This implies that

\[
\lim_{t \to \infty} \sup U(t) \leq \frac{\rho}{\gamma}.
\]

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
\[
\dot{F}_1(t) = \frac{\omega_1 e^{-\theta_1 t_1}}{\omega_1 + \omega_2 + \omega_3} \left[ \rho - \gamma U(t - \tau_1) - (\omega_1 + \omega_2 + \omega_3) U(t - \tau_1) P(t - \tau_1) \right] \\
+ \frac{\omega_2 e^{-\theta_2 t_2}}{\omega_1 + \omega_2 + \omega_3} \left[ \rho - \gamma U(t - \tau_2) - (\omega_1 + \omega_2 + \omega_3) U(t - \tau_2) P(t - \tau_2) \right] \\
+ \frac{\omega_3 e^{-\theta_3 t_3}}{\omega_1 + \omega_2 + \omega_3} \left[ \rho - \gamma U(t - \tau_3) - (\omega_1 + \omega_2 + \omega_3) U(t - \tau_3) P(t - \tau_3) \right] \\
e^{-\theta_1 t_1} \omega_1 U(t - \tau_1) P(t - \tau_1) + e^{-\theta_2 t_2} \omega_2 U(t - \tau_2) P(t - \tau_2) + \gamma L(t) - \beta I(t) \\
+ e^{-\theta_3 t_3} \omega_3 U(t - \tau_3) P(t - \tau_3) - \lambda O(t)
\]
\[
= -\sigma_1 \left[ \frac{\omega_1 e^{-\theta_1 t_1}}{\omega_1 + \omega_2 + \omega_3} U(t - \tau_1) + \frac{\omega_2 e^{-\theta_2 t_2}}{\omega_1 + \omega_2 + \omega_3} U(t - \tau_2) \\
\right] \\
\leq -\sigma_1 \left[ \frac{\omega_1 e^{-\theta_1 t_1}}{\omega_1 + \omega_2 + \omega_3} U(t - \tau_1) + \frac{\omega_2 e^{-\theta_2 t_2}}{\omega_1 + \omega_2 + \omega_3} U(t - \tau_2) \\
\right]
\]
where \(\sigma_1 = \min(\gamma, \lambda, \beta, \Lambda)\). Hence, \(\lim_{t \to \infty} \sup F_1(t) \leq s_1\), where \(s_1 = \frac{\rho}{\sigma_1}\). Since \(U(t), L(t), I(t)\) and \(O(t)\) are all non-negative, then \(\lim_{t \to \infty} \sup L(t) \leq s_1\), \(\lim_{t \to \infty} \sup I(t) \leq s_1\) and \(\lim_{t \to \infty} \sup O(t) \leq s_1\) for all \(t \geq 0\). Moreover, let \(F_2(t) = P(t) + \frac{\xi}{2\epsilon} C(t)\). Then
\[
\dot{F}_2(t) = e^{-\theta_1 t_1} \beta M_1 I(t - \tau_4) + e^{-\theta_3 t_3} \Lambda M_2 O(t - \tau_5) - \xi P(t) - \rho P(t) C(t) + \frac{\xi}{2} P(t) - \frac{\xi}{2} \epsilon \frac{P(t) C(t)}{\epsilon}
\]
\[
e^{-\theta_2 t_2} \beta M_1 I(t - \tau_4) + e^{-\theta_3 t_3} \Lambda M_2 O(t - \tau_5) - \frac{\xi}{2} P(t) - \frac{\xi}{2} \epsilon \frac{P(t) C(t)}{\epsilon}
\]
\[
\leq \beta M_1 I(t - \tau_4) + \Lambda M_2 O(t - \tau_5) - \frac{\xi}{2} P(t) - \frac{\xi}{2} \epsilon \frac{P(t) C(t)}{\epsilon}
\]
\[
\leq \beta M_1 s_1 + \Lambda M_2 s_1 - \frac{\xi}{2} P(t) - \frac{\xi}{2} \epsilon \frac{P(t) C(t)}{\epsilon}
\]
where \(s_2 = \min\left\{ \frac{\xi}{2}, \mu \right\}\). Hence, \(\lim_{t \to \infty} \sup F_2(t) \leq s_2\), where \(s_2 = \frac{\beta M_1 s_1 + \Lambda M_2 s_1}{\sigma_2}\). The non-negativity of \(P(t)\) and \(C(t)\) implies \(\lim_{t \to \infty} \sup P(t) \leq s_2\) and \(\lim_{t \to \infty} \sup C(t) \leq s_3\), where \(s_3 = \frac{2 \epsilon s_2}{\xi}\).

The basic reproduction number for model (2.1)-(2.6) is defined as
\[
R_0 = \frac{\rho \left[ \omega_1 \gamma M_1 e^{-\theta_1 t_1} e^{-\theta_4 t_4} + (\xi + \nu) \left( \omega_2 M_1 e^{-\theta_2 t_2} e^{-\theta_4 t_4} + \omega_3 M_2 e^{-\theta_3 t_3} e^{-\theta_5 t_5} \right) \right]}{\xi \gamma (\xi + \nu)}.
\]

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

(i) if \(R_0 \leq 1\), 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

\[
\rho - \gamma U - (\omega_1 + \omega_2 + \omega_3)U = 0, \quad (2.8)
\]

\[
e^{-\theta_1\tau_1}U \rho - (\zeta + \nu)U = 0, \quad (2.9)
\]

\[
e^{-\theta_2\tau_2}U \omega_2 + \nu L - \beta I = 0, \quad (2.10)
\]

\[
e^{-\theta_3\tau_3}U \omega_3 - \Lambda O = 0, \quad (2.11)
\]

\[
e^{-\theta_4\tau_4}I L + e^{-\theta_5\tau_5}M_2O - \xi P - \rho PC = 0, \quad (2.12)
\]

\[
e^{-\mu C - \delta PC} = 0. \quad (2.13)
\]

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

2.1. Global stability of equilibria

Define the function $G(u) = u - 1 - \ln u$. Clearly, $G(u) \geq 0$, 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:

$$W_0 = hU_0G \left( \frac{U(t)}{U_0} \right) + \frac{\nu M_1 e^{-\theta_1\tau_1}}{\zeta + \nu} L(t) + M_1 e^{-\theta_1\tau_1} I(t) + M_2 e^{-\theta_5\tau_5} O(t) + P(t) + \frac{\xi}{\zeta} (1 - R_0) C(t)$$

$$+ \frac{\nu M_1 \omega_1 e^{-\theta_1\tau_1} - \theta_4\tau_4}}{\zeta + \nu} \int_{t-\tau_1}^{t} U(s)P(s)ds + M_1 \omega_2 e^{-\theta_2\tau_2 - \theta_4\tau_4} \int_{t-\tau_2}^{t} U(s)P(s)ds$$

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

where
\[ h = \frac{1}{\omega_1 + \omega_2 + \omega_3} \left( \frac{\nu M_1 \omega_1 e^{-\theta_1 t} - \theta_4 t} {\zeta + \nu} + M_1 \omega_2 e^{-\theta_2 t} - \theta_4 t} + M_2 \omega_3 e^{-\theta_3 t} - \theta_5 t} \right). \]

Calculating \( \frac{dW_0}{dt} \), we get
\[
\frac{dW_0}{dt} = h \left( 1 - \frac{U_0}{U(t)} \right) \left( \rho - \gamma U(t) - (\omega_1 + \omega_2 + \omega_3)U(t)P(t) \right) \\
+ \frac{\nu M_1 e^{-\theta_1 t} - \theta_4 t} {\zeta + \nu} \left( e^{-\theta_1 t} \omega_1 U(t) - (\theta_1 t) \right) - (\zeta + \nu) L(t) \\
+ M_1 e^{-\theta_1 t} - \theta_4 t} \omega_2 U(t) (t) - \theta_2 t)P(t) - \theta_2 t) + \nu L(t) - \beta I(t) \\
+ M_2 e^{-\theta_3 t} - \theta_5 t} \omega_3 U(t) (t) - \theta_3 t)P(t) - \theta_3 t) - \Lambda O(t) \\
+ \beta M_1 e^{-\theta_1 t} - \theta_4 t} I(t) - \theta_4 t) + \Lambda M_2 e^{-\theta_5 t} O(t) - \theta_5 t) - \xi P(t) - \rho P(t) C(t) \\
\frac{\xi}{\varepsilon} (1 - R_0) \left( \varepsilon P(t) - \mu C(t) - \theta P(t) C(t) \right) \\
+ \frac{\nu M_1 \omega_1 e^{-\theta_1 t} - \theta_4 t} {\zeta + \nu} \left( U(t)P(t) - U(t) - \theta_1 t)P(t) - \theta_1 t) \right) \\
+ M_1 \omega_2 e^{-\theta_2 t} - \theta_4 t} \left( U(t)P(t) - U(t) - \theta_2 t)P(t) - \theta_2 t) \right) \\
+ M_2 \omega_3 e^{-\theta_3 t} - \theta_5 t} \left( U(t)P(t) - U(t) - \theta_3 t)P(t) - \theta_3 t) \right) \\
+ \beta M_1 e^{-\theta_1 t} - \theta_4 t} \left( I(t) - I(t) - \theta_4 t) + \Lambda M_2 e^{-\theta_5 t} \left( O(t) - O(t) - \theta_5 t) \right) \\
= h \left( 1 - \frac{U_0}{U(t)} \right) \left( \rho - \gamma U(t) + h(\omega_1 + \omega_2 + \omega_3)U_0 P(t) - \xi P(t) - \rho P(t) C(t) + \xi (1 - R_0) P(t) \\
- \frac{\xi \mu}{\varepsilon} (1 - R_0) C(t) - \frac{\xi \theta}{\varepsilon} (1 - R_0) P(t) C(t). \right) \]

We have \( \xi R_0 = h U_0 (\omega_1 + \omega_2 + \omega_3) \), then
\[ h(\omega_1 + \omega_2 + \omega_3)U_0 P(t) - \xi P(t) + \xi (1 - R_0) P(t) = 0. \]

Then
\[
\frac{dW_0}{dt} = -h \gamma (U(t) - U_0)^2 U(t) - \frac{\xi \mu}{\varepsilon} (1 - R_0) C(t) - \left( \rho + \frac{\xi \theta}{\varepsilon} (1 - R_0) \right) P(t) C(t). \]

Since \( R_0 < 1 \), then for all \( U(t), P(t), C(t) > 0 \) we have \( \frac{dW_0}{dt} \leq 0 \). Moreover, \( \frac{dW_0}{dt} = 0 \) when \( U(t) = U_0 \) and \( C(t) = 0 \). Let \( D_0 = \{ (U(t), L(t), I(t), O(t), P(t), C(t)) : \frac{dW_0}{dt} = 0 \} \) 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
\[ \dot{C}(t) = 0 = \varepsilon P(t) \quad \implies \quad P(t) = 0, \quad \text{for all } t. \]

Also from Eq. \( (2.5) \) we get
\[ 0 = \dot{P}(t) = e^{-\theta_4 t} \beta M_1 I(t - \tau_4) + e^{-\theta_5 t} \Lambda M_2 O(t - \tau_5). \]

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, \( N_0 = \{ E_0 \} \). From LaSalle’s invariance principle (L.I.P), we derive that if \( R_0 < 1 \), then \( E_0 \) is G.A.S. \( \square \)
Theorem 2.4. Let $R_0 > 1$, then $E_1$ 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:

$$W_{11} = hU_1G \left( \frac{U(t)}{U_1} \right) + \frac{\nu M_1e^{-\theta_3\tau_1}}{\zeta + \nu} L_1G \left( \frac{L(t)}{L_1} \right) + M_1e^{-\theta_1\tau_1} I_1G \left( \frac{I(t)}{I_1} \right) + M_2e^{-\theta_3\tau_3} O_1G \left( \frac{O(t)}{O_1} \right) + P_1G \left( \frac{P(t)}{P_1} \right) + \frac{\rho}{2(\varepsilon - \delta C_1)} (C(t) - C_1)^2.$$ 

Note that from the equilibrium condition (2.13) that

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

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

$$\frac{dW_{11}}{dt} = h \left( 1 - \frac{U_1}{U(t)} \right) (\rho - \gamma U(t) - (\omega_1 + \omega_2 + \omega_3)U(t)P(t))$$ 

$$+ \frac{\nu M_1e^{-\theta_3\tau_1}}{\zeta + \nu} \left( 1 - \frac{L_1}{L(t)} \right) (e^{-\theta_1\tau_1} \omega_1 U(t - \tau_1)P(t - \tau_1) - (\zeta + \nu)L(t))$$ 

$$+ M_1e^{-\theta_1\tau_1} \left( 1 - \frac{I_1}{I(t)} \right) (e^{-\theta_1\tau_1} \omega_2 U(t - \tau_2)P(t - \tau_2) + \nu L(t) - \beta I(t))$$ 

$$+ M_2e^{-\theta_3\tau_3} \left( 1 - \frac{O_1}{O(t)} \right) (e^{-\theta_3\tau_3} \omega_3 U(t - \tau_3)P(t - \tau_3) - \Lambda O(t))$$ 

$$+ \left( 1 - \frac{P_1}{P(t)} \right) (e^{-\theta_1\tau_1} \beta M_1 I(t - \tau_4) + e^{-\theta_3\tau_3}M_2O(t - \tau_5) - \xi P(t) - \rho P(t) C(t))$$ 

$$+ \frac{\rho}{\varepsilon - \delta C_1} (C(t) - C_1) (\varepsilon P(t) - \mu C(t) - \delta P(t) C(t)).$$

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

$$W_{12} = \frac{\nu M_1 \omega_1 e^{-\theta_1\tau_1} - \theta_3\tau_1}{\zeta + \nu} U_1 P_1 \int_{t - \tau_1}^{t} G \left( \frac{U(s)p(s)}{U_1 P_1} \right) ds$$ 

$$+ M_1 \omega_2 e^{-\theta_1\tau_2} - \theta_3\tau_1 U_1 P_1 \int_{t - \tau_2}^{t} G \left( \frac{U(s)p(s)}{U_1 P_1} \right) ds$$ 

$$+ M_2 \omega_3 e^{-\theta_3\tau_3} - \theta_3\tau_3 U_1 P_1 \int_{t - \tau_3}^{t} G \left( \frac{U(s)p(s)}{U_1 P_1} \right) ds.$$ 

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

$$\frac{dW_{12}}{dt} = \frac{\nu M_1 \omega_1 e^{-\theta_1\tau_1} - \theta_3\tau_1}{\zeta + \nu} U_1 P_1 \left[ \frac{U(t)P(t)}{U_1 P_1} - \frac{U(t - \tau_1)P(t - \tau_1)}{U_1 P_1} + \ln \left( \frac{U(t - \tau_1)P(t - \tau_1)}{U(t)P(t)} \right) \right]$$ 

$$+ M_1 \omega_2 e^{-\theta_1\tau_2} - \theta_3\tau_1 U_1 P_1 \left[ \frac{U(t)P(t)}{U_1 P_1} - \frac{U(t - \tau_2)P(t - \tau_2)}{U_1 P_1} + \ln \left( \frac{U(t - \tau_2)P(t - \tau_2)}{U(t)P(t)} \right) \right]$$ 

$$+ M_2 \omega_3 e^{-\theta_3\tau_3} - \theta_3\tau_3 U_1 P_1 \left[ \frac{U(t)P(t)}{U_1 P_1} - \frac{U(t - \tau_3)P(t - \tau_3)}{U_1 P_1} + \ln \left( \frac{U(t - \tau_3)P(t - \tau_3)}{U(t)P(t)} \right) \right].$$

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

$$W_{13} = \beta M_1 e^{-\theta_1\tau_1} I_1 \int_{t - \tau_4}^{t} G \left( \frac{I(s)}{I_1} \right) ds + \Lambda M_2 e^{-\theta_3\tau_3} O_1 \int_{t - \tau_5}^{t} G \left( \frac{O(s)}{O_1} \right) ds.$$
Calculating $\frac{dW_{13}}{dt}$ as:

$$\frac{dW_{13}}{dt} = \beta M_1 e^{-\theta_1 \tau_1} I_1 \left[ \frac{I(t) - I(t - \tau_4)}{I_1} + \ln \left( \frac{I(t) - I(t - \tau_4)}{I(t)} \right) \right]$$

$$+ \Lambda M_2 e^{-\theta_5 \tau_5} O_1 \left[ \frac{O(t)}{O_1} - \frac{O(t - \tau_5)}{O(t)} + \ln \left( \frac{O(t) - O(t - \tau_5)}{O(t)} \right) \right].$$

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

$$\frac{dW_1}{dt} = h \left( 1 - \frac{U_1}{U(t)} \right) (\rho - \gamma U(t)) + h(\omega_1 + \omega_2 + \omega_3) U_1 P(t)$$

$$- \frac{\gamma M_1 \omega_1 e^{-\theta_1 \tau_1 - \theta_3 \tau_3}}{\zeta + \nu} U(t - \tau_1) P(t - \tau_1) \frac{L_1}{I(t)} + \nu M_1 e^{-\theta_3 \tau_3} L_1$$

$$- M_1 \omega_2 e^{-\theta_3 \tau_3 - \theta_3 \tau_1} U(t - \tau_2) P(t - \tau_2) \frac{I_1}{I(t)} - \nu M_1 e^{-\theta_3 \tau_3} L_1 \frac{I_1}{I(t)} + \beta M_1 e^{-\theta_3 \tau_3} I_1$$

$$- M_2 \omega_3 e^{-\theta_3 \tau_3 - \theta_4 \tau_5} U(t - \tau_3) P(t - \tau_3) \frac{O_1}{O(t)} + \Lambda M_2 e^{-\theta_4 \tau_4} O_1$$

$$- \beta M_1 e^{-\theta_4 \tau_4} I(t - \tau_4) \frac{P_1}{P(t)} + \Lambda M_2 e^{-\theta_4 \tau_5} O(t - \tau_5) \frac{P_1}{P(t)} - \xi (P(t) - P_1)$$

$$- \rho (P(t) - P_1) C(t) + \frac{\rho}{\epsilon - \theta C_1} (C(t) - C_1) (\epsilon P(t) - \mu C(t) - \theta P(t) C(t))$$

$$+ \frac{\gamma M_1 \omega_1 e^{-\theta_1 \tau_1 - \theta_4 \tau_4}}{\zeta + \nu} U_1 P_1 \ln \left( \frac{U(t - \tau_1) P(t - \tau_1)}{U(t) P(t)} \right)$$

$$+ M_1 \omega_2 e^{-\theta_2 \tau_2 - \theta_4 \tau_4} U_1 P_1 \ln \left( \frac{U(t - \tau_2) P(t - \tau_2)}{U(t) P(t)} \right)$$

$$+ M_2 \omega_3 e^{-\theta_3 \tau_3 - \theta_5 \tau_5} U_1 P_1 \ln \left( \frac{U(t - \tau_3) P(t - \tau_3)}{U(t) P(t)} \right)$$

$$+ \beta M_1 e^{-\theta_4 \tau_4} I_1 \ln \left( \frac{I(t - \tau_4)}{I(t)} \right) + \Lambda M_2 e^{-\theta_5 \tau_5} O_1 \ln \left( \frac{O(t - \tau_5)}{O(t)} \right).$$

From the equilibrium conditions, we have:

$$\rho = \gamma U_1 + (\omega_1 + \omega_2 + \omega_3) U_1 P_1,$$

$$\frac{\gamma M_1 \omega_1 e^{-\theta_1 \tau_1 - \theta_4 \tau_4}}{\zeta + \nu} U_1 P_1 = \nu M_1 e^{-\theta_4 \tau_4} L_1,$$

$$\beta M_1 e^{-\theta_4 \tau_4} I_1 = M_1 \omega_2 e^{-\theta_2 \tau_2 - \theta_4 \tau_4} U_1 P_1 + \nu M_1 e^{-\theta_4 \tau_4} L_1,$$

$$M_2 \omega_3 e^{-\theta_3 \tau_3 - \theta_5 \tau_5} U_1 P_1 = \Lambda M_2 e^{-\theta_5 \tau_5} O_1.$$
\[\begin{align*}
&-\nu M_1 e^{-\theta_1 \tau_1 L_1} \frac{L_1 U(t-t_1)P(t-t_1)}{L(t)U_1 P_1} + \nu M_1 e^{-\theta_2 \tau_2} e^{-\theta_1 \tau_1} U_1 P_1 \frac{I_1 U(t-t_2)P(t-t_2)}{L(t)U_1 P_1} \\
&-\nu M_1 e^{-\theta_1 \tau_1 L_1} \frac{L_1 U(t-t_1)P(t-t_1)}{L(t)U_1 P_1} + \nu M_1 e^{-\theta_2 \tau_2} e^{-\theta_1 \tau_1} U_1 P_1 + \nu M_1 e^{-\theta_1 \tau_1 L_1} - \Lambda M_2 e^{-\theta_5 \tau_5} O_1 \\
&\quad \times \frac{O_1 U(t-t_3)P(t-t_3)}{O(t)U_1 P_1} \\
&+ \Lambda M_2 e^{-\theta_5 \tau_5} O_1 \left( M_1 \omega_2 e^{-\theta_2 \tau_2} e^{-\theta_1 \tau_1} U_1 P_1 + \nu M_1 e^{-\theta_1 \tau_1 L_1} \right) \\
&\frac{P_1 I_1(t-t_4)}{P(t)I_1} - \Lambda M_2 e^{-\theta_5 \tau_5} O_1 \frac{P_1 O(t-t_5)P(t)}{P(t)O_1} \\
&+ \xi(P(t) - P_1) - \rho(P(t) - P_1)C(t) + \rho\frac{(C(t) - C_1)\left(\varepsilon(P(t) - \mu C(t) - \varepsilon P_1 + \mu C_1 + \delta P_1 C_1 - \delta(P(t)C_1 + \delta(P(t)C_1) \\
&+ \frac{\rho}{\varepsilon - \delta C_1} (C(t) - C_1)\left(\varepsilon(P(t) - \mu C(t) - \varepsilon P_1 + \mu C_1 + \delta P_1 C_1 - \delta(P(t)C_1 + \delta(P(t)C_1) \\
&+ \nu M_1 e^{-\theta_1 \tau_1 L_1} \ln\left( \frac{U(t-t_1)P(t-t_1)}{U(t)P(t)} \right) \right) + M_1 \omega_2 e^{-\theta_2 \tau_2} e^{-\theta_1 \tau_1} U_1 P_1 \ln\left( \frac{U(t-t_2)P(t-t_2)}{U(t)P(t)} \right) \\
&+ M_2 \omega_3 e^{-\theta_3 \tau_3} e^{-\theta_1 \tau_1} U_1 P_1 \ln\left( \frac{U(t-t_3)P(t-t_3)}{U(t)P(t)} \right) + M_2 e^{-\theta_5 \tau_5} O_1 \ln\left( \frac{O(t-t_5)}{O(t)} \right) \\
&\left( M_1 \omega_2 e^{-\theta_2 \tau_2} e^{-\theta_1 \tau_1} U_1 P_1 + \nu M_1 e^{-\theta_1 \tau_1 L_1} \right) \ln\left( \frac{I(t-t_4)}{I(t)} \right)
\end{align*}\]

Simplifying the result, we obtain

\[\begin{align*}
\frac{dW_t}{dt} &= -\gamma h \frac{(U(t) - U_1)^2}{U(t)} + \nu M_1 e^{-\theta_1 \tau_1 L_1} \left( 1 - \frac{U_1}{U(t)} \right) + M_1 \omega_2 e^{-\theta_2 \tau_2} e^{-\theta_1 \tau_1} U_1 P_1 \left( 1 - \frac{U_1}{U(t)} \right) \\
&\quad + \Lambda M_2 e^{-\theta_5 \tau_5} O_1 \left( 1 - \frac{U_1}{U(t)} \right) + \left( \nu M_1 e^{-\theta_1 \tau_1 L_1} + M_1 \omega_2 e^{-\theta_2 \tau_2} e^{-\theta_1 \tau_1} U_1 P_1 + \Lambda M_2 e^{-\theta_5 \tau_5} O_1 \right) \frac{P(t)}{P_1} \\
&\quad - \nu M_1 e^{-\theta_1 \tau_1 L_1} \frac{U_1(t-t_1)P(t-t_1)}{L(t)U_1 P_1} + \nu M_1 e^{-\theta_1 \tau_1 L_1} - \Lambda M_2 e^{-\theta_5 \tau_5} O_1 \times \frac{O_1 U(t-t_3)P(t-t_3)}{O(t)U_1 P_1} \\
&\quad + \nu M_1 e^{-\theta_1 \tau_1 L_1} \ln\left( \frac{U(t-t_1)P(t-t_1)}{U(t)P(t)} \right) + \nu M_1 e^{-\theta_1 \tau_1 L_1} \ln\left( \frac{U(t-t_1)P(t-t_1)}{U(t)P(t)} \right) \\
&\quad + \nu M_1 e^{-\theta_1 \tau_1 L_1} \ln\left( \frac{U(t-t_1)P(t-t_1)}{U(t)P(t)} \right) + \Lambda M_2 e^{-\theta_5 \tau_5} O_1 \ln\left( \frac{O(t-t_5)}{O(t)} \right) \\
&\quad + \left( \Lambda M_2 e^{-\theta_5 \tau_5} O_1 \right) \ln\left( \frac{I(t-t_4)}{I(t)} \right)
\end{align*}\]

We have

\[-(\xi + \rho C_1)(P(t) - P_1) = -\frac{1}{P_1} \left( \beta M_1 e^{-\theta_1 \tau_1 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} e^{-\theta_1 \tau_1} U_1 P_1 + \nu M_1 e^{-\theta_1 \tau_1 L_1} + \Lambda M_2 e^{-\theta_5 \tau_5} O_1 \right) \left( 1 - \frac{P(t)}{P_1} \right).

Then \(\frac{dW_t}{dt}\) will be

\[\begin{align*}
\frac{dW_t}{dt} &= -\gamma h \frac{(U(t) - U_1)^2}{U(t)} - \frac{\rho(\mu + \delta P(t))}{\varepsilon - \delta C_1} (C(t) - C_1)^2 \\
&\quad + \nu M_1 e^{-\theta_1 \tau_1 L_1} \left[ 4 - \frac{U_1}{U(t)} - \frac{L_1 U(t-t_1)P(t-t_1)}{L(t)U_1 P_1} - \frac{I_1(t-t_1)P(t-t_1)}{I(t)U_1 P_1} - \frac{P_1 I_1(t-t_4)}{P(t)I_1} \right] \\
&\quad + M_1 \omega_2 e^{-\theta_2 \tau_2} e^{-\theta_1 \tau_1} U_1 P_1 \left[ 3 - \frac{U_1}{U(t)} - \frac{L_1 U(t-t_2)P(t-t_2)}{L(t)U_1 P_1} - \frac{P_1 I_1(t-t_4)}{P(t)I_1} \right]
\end{align*}\]
Then \( dW_t \) will be

\[
\frac{dW_1}{dt} = -\gamma \frac{(U(t) - U_1)^2}{U(t)} - \frac{\rho(\mu + \delta P(t))}{\epsilon - \delta C_1} (C(t) - C_1)^2 \\
- \nu M_1 e^{-\theta_1 t} L_1 \left[ \frac{G(U_t)}{U(t)} + \frac{G(I_t)}{I(t)L_1} \right] + \frac{M_1 \omega_2 e^{-\theta_2 t} \theta \xi_1 U_1 P_1}{P(t)O_1} \left[ \frac{G(U_t)}{U(t)} + \frac{G(I_t)}{I(t)L_1} \right]
\]

Then for all \( U(t), L(t), I(t), O(t), P(t), C(t) > 0 \) we have \( \frac{dW_1}{dt} \leq 0 \). 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:

\[
\dot{U}(t) = -\gamma U(t) - (\omega_1 + \omega_2 + \omega_3)\Theta(U(t), P(t)),
\]

\[
\dot{L}(t) = e^{-\theta_1 t} \omega_1 \Theta(U(t) - \tau_1, P(t) - \tau_1) - (\zeta + \gamma) L(t),
\]

\[
\dot{I}(t) = e^{-\theta_2 t} \omega_2 \Theta(U(t) - \tau_2, P(t) - \tau_2) + \gamma L(t) - \beta I(t),
\]

\[
\dot{O}(t) = e^{-\theta_3 t} \omega_3 \Theta(U(t) - \tau_3, P(t) - \tau_3) - \Lambda O(t),
\]
\[ \dot{P}(t) = e^{-\theta_1 t} \beta M_1 I(t - \tau_4) + e^{-\theta_5 t} \Lambda M_2 O(t - \tau_5) - \xi P(t) - \rho P(t) C(t), \]  
(3.5)

\[ \dot{C}(t) = \varepsilon P(t) - \mu C(t) - \delta P(t) C(t). \]  
(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 \( UP/(1 + \alpha P + \alpha_2 U) \), and Crowley-Martin incidence \( UP/((1 + \alpha_1 P)(1 + \alpha_2 U)) \), where \( \alpha_1 \) and \( \alpha_2 \) are non-negative 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 \( R_0^G \leq 1 \), then the model has only one equilibrium point \( E_0^G \); and

(ii) if \( R_0^G > 1 \), then the model has two equilibria \( E_0^G \) and \( E_1^G \).

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

\[ \rho - \gamma U - (\omega_1 + \omega_2 + \omega_3) \Theta(U, P) = 0, \]  
(3.7)

\[ e^{-\theta_1 t} \omega_1 \Theta(U, P) - (\zeta + \gamma) L = 0, \]  
(3.8)

\[ e^{-\theta_2 t} \omega_2 \Theta(U, P) + \nu L - \beta I = 0, \]  
(3.9)

\[ e^{-\theta_3 t} \omega_3 \Theta(U, P) - \Lambda O = 0, \]  
(3.10)

\[ e^{-\theta_4 t} \beta M_1 I + e^{-\theta_5 t} \Lambda M_2 O - \xi P - \rho PC = 0, \]  
(3.11)

\[ \varepsilon P - \mu C - \delta PC = 0. \]  
(3.12)

From Eq. (3.12), we have

\[ C = \frac{\varepsilon P}{\mu + \delta P}. \]  
(3.13)

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

\[ L = \frac{e^{-\theta_1 t} + \theta_3 t \Lambda \omega_1}{\omega_3 (\zeta + \gamma)} O. \]  
(3.14)

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

\[ I = \frac{e^{-\theta_2 t} + \theta_3 t \Lambda \omega_2 (\zeta + \gamma) + e^{-\theta_1 t} \theta_3 t \Lambda \omega_1 \nu}{\beta \omega_3 (\zeta + \gamma)} O, \]  
(3.15)

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

\[ O = \frac{\omega_3 (\zeta + \gamma)}{\Lambda \phi} \left( \xi P + \frac{\rho \varepsilon P^2}{\mu + \delta P} \right), \]  
(3.16)

where \( \phi = (e^{-\theta_2 t} + \theta_3 t \Lambda - \theta_4 t \omega_2 M_1 + e^{-\theta_5 t} \omega_3 M_2)(\zeta + \gamma) + e^{-\theta_1 t} \theta_3 t \Lambda - \theta_4 t \omega_1 M_1 \nu. \) By substitution into
Thus, the positive solution of Eq. (3.21) is given by
\[ L = e^{-\theta_1\tau_1 + \theta_3\tau_3} \frac{\xi + \rho e \mu^2}{\mu + \theta P}, \]
\[ I = e^{-\theta_2\tau_2 + \theta_3\tau_3} \frac{\xi + \nu + e^{-\theta_1\tau_1 + \theta_3\tau_3} \omega_1 \nu}{\beta \phi} \left( \xi P + \frac{\rho e P^2}{\mu + \theta P} \right). \] (3.17) (3.18)

Then, from Eqs. (3.7), (3.10), and (3.16), we get
\[ U = \frac{P}{\gamma} - \frac{e^{\theta_1\tau_1} (\omega_1 + \omega_2 + \omega_3) (\xi + \nu)}{\gamma \phi} \left( \xi P + \frac{\rho e P^2}{\mu + \theta P} \right). \] (3.19)

Let
\[ \psi(P) = \frac{P}{\gamma} - \frac{e^{\theta_1\tau_1} (\omega_1 + \omega_2 + \omega_3) (\xi + \nu)}{\gamma \phi} \left( \xi P + \frac{\rho e P^2}{\mu + \theta P} \right). \]

Therefore, we can write \( U = \psi(P) \). Note that \( \psi(0) = \frac{P}{\gamma} \). From Eqs. (3.10) and (3.16), we have
\[ e^{-\theta_1\tau_1} \Theta(\psi(P), P) - \frac{\xi + \nu}{\phi} \left( \xi P + \frac{\rho e P^2}{\mu + \theta P} \right) = 0. \] (3.20)

Observe that, \( P = 0 \) is a solution of Eq. (3.20). Then from Eqs. (3.13), (3.16)-(3.19) we have \( U = \psi_0 = \frac{P}{\gamma} \), \( L = 0 \), \( I = 0 \), \( O = 0 \), and \( C = 0 \). Then we get an infection-free equilibrium \( EP_0^G = (U_0, 0, 0, 0, 0, 0) \). Let
\[ H(P) = e^{-\theta_1\tau_1} \Theta(\psi(P), P) - \frac{\xi + \nu}{\phi} \left( \xi P + \frac{\rho e P^2}{\mu + \theta P} \right), \]
then \( H(0) = 0 \). Let \( \overline{P} \) be such that \( \psi(\overline{P}) = 0 \), i.e.,
\[ U_0 - \frac{e^{\theta_1\tau_1} (\omega_1 + \omega_2 + \omega_3) (\xi + \nu)}{\gamma \phi} \left( \xi \overline{P} + \frac{\rho e \overline{P}^2}{\mu + \theta \overline{P}} \right) = 0, \]
which gives
\[ e^{\theta_1\tau_1} (\rho e + \xi \theta)(\xi + \nu)(\omega_1 + \omega_2 + \omega_3) \overline{P}^2 + \left[ e^{\theta_1\tau_1} \xi \mu(\xi + \nu)(\omega_1 + \omega_2 + \omega_3) - \gamma \overline{U_0} \phi \right] \overline{P} - \gamma \mu \overline{U_0} \phi = 0. \] (3.21)

Thus, the positive solution of Eq. (3.21) is given by
\[ \overline{P} = \frac{-b + \sqrt{b^2 - 4ac}}{2a}, \]
where,
\[ a = e^{\theta_1\tau_1} (\rho e + \xi \theta)(\xi + \nu)(\omega_1 + \omega_2 + \omega_3), \]
\[ b = e^{\theta_1\tau_1} \xi \mu(\xi + \nu)(\omega_1 + \omega_2 + \omega_3) - \gamma \overline{U_0} \phi, \]
\[ c = -\gamma \mu \overline{U_0} \phi. \]

We can see from Assumption (A1) that
\[ H(\overline{P}) = e^{-\theta_1\tau_1} \Theta(0, \overline{P}) - \frac{\xi + \nu}{\phi} \left( \xi \overline{P} + \frac{\rho e \overline{P}^2}{\mu + \theta \overline{P}} \right) = -\frac{\xi + \nu}{\phi} \left( \xi \overline{P} + \frac{\rho e \overline{P}^2}{\mu + \theta \overline{P}} \right) < 0. \]
Moreover,
\[
H'(P) = e^{-\theta_3 \psi'(P)} \frac{\partial \Theta(U, P)}{\partial U} + e^{-\theta_3 \psi_u} \frac{\partial \Theta(U, P)}{\partial P} - \frac{\zeta + \nu}{\phi} \left( \zeta + \frac{\rho \varepsilon (2\mu P + \partial P^2)}{(\mu + \partial P)^2} \right).
\]

Assumption (A1) implies that \( \frac{\partial \Theta(U_0, 0)}{\partial U} = 0 \), then
\[
H'(0) = e^{-\theta_3 \psi_u} \frac{\partial \Theta(U_0, 0)}{\partial P} - \frac{\zeta + \nu}{\phi} \left( \frac{\rho \varepsilon (2\mu P + \partial P^2)}{(\mu + \partial P)^2} - 1 \right).
\]

Therefore, if \( \frac{e^{-\theta_3 \psi_u} \frac{\partial \Theta(U_0, 0)}{\partial P}}{\zeta + \nu} > 1 \), then \( H'(0) > 0 \) and \( \exists P_1 \in (0, \bar{P}) \) such that \( H(P_1) = 0 \). Let us define
\[
R_0^G = \left( \omega_2 M_1 e^{-\theta_2 \tau_2 - \theta_4 \tau_4} + \omega_3 e^{-\theta_3 \tau_3 - \theta_5 \tau_5} \right) \frac{(\zeta + \nu) + \nu \omega_1 M_1 e^{-\theta_1 \tau_1 - \theta_4 \tau_4} \frac{\partial \Theta(U_0, 0)}{\partial P}}{\zeta + \nu},
\]
which represents the basic infection reproduction number. Now, let \( P = P_1 \) in Eq. (3.7) and define
\[
g(U) = \rho - \gamma U - (w_1 + w_2 + w_3) \Theta(U, P) = 0.
\]

Then from Assumption (A1) we have \( g(0) = \rho > 0 \) and \( g(U_0) = -(w_1 + w_2 + w_3) \Theta(U_0, P_1) < 0 \). 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
\[
L_1 = \frac{e^{-\theta_1 \tau_1 + \theta_3 \tau_3} \omega_1}{\phi} \left( \zeta P_1 + \frac{\rho \varepsilon P_1^2}{\mu + \partial P_1} \right) > 0,
\]
\[
I_1 = \frac{e^{-\theta_2 \tau_2 + \theta_3 \tau_3} \omega_2 (\zeta + \nu) + e^{-\theta_1 \tau_1 - \theta_4 \tau_4} \omega_1 \nu}{\beta \phi} \left( \zeta P_1 + \frac{\rho \varepsilon P_1^2}{\mu + \partial P_1} \right) > 0,
\]
\[
O_1 = \frac{\omega_3 (\zeta + \nu)}{\Lambda \phi} \left( \zeta P_1 + \frac{\rho \varepsilon P_1^2}{\mu + \partial P_1} \right) > 0,
\]
\[
C_1 = \frac{\varepsilon P_1}{\mu + \partial P_1} > 0.
\]

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
\[
Z_0 = h \left( U(t) - U_0 - \lim_{P \to 0^+} \frac{\Theta(U_0, P)}{\Theta(\eta, P)} \right) + \frac{\gamma M_1 e^{-\theta_4 \tau_4} + \nu M_1 e^{-\theta_4 \tau_4} I(t) + M_2 e^{-\theta_5 \tau_5} O(t) + P(t) + \frac{\xi}{\epsilon} (1 - R_0^G) C(t) + \frac{\nu M_1 \omega_1 e^{-\theta_1 \tau_1 - \theta_4 \tau_4} \int_{t-\tau_4}^t U(s)P(s)ds + M_1 \omega_2 e^{-\theta_2 \tau_2 - \theta_4 \tau_4} \int_{t-\tau_2}^t U(s)P(s)ds + M_2 \omega_3 e^{-\theta_3 \tau_3 - \theta_5 \tau_5} \int_{t-\tau_3}^t U(s)P(s)ds + \beta M_1 e^{-\theta_4 \tau_4} \int_{t-\tau_4}^t I(s)ds + \lambda M_2 e^{-\theta_5 \tau_5} \int_{t-\tau_5}^t O(s)ds. 
\]
Calculating \( \frac{dZ_0}{dt} \) as:

\[
\frac{dZ_0}{dt} = h \left( 1 - \lim_{p \to 0^+} \frac{\Theta(U_0, P)}{\Theta(U(t), P)} \right) (\rho - \gamma U(t) - (\omega_1 + \omega_2 + \omega_3)\Theta(U(t), P(t))) + \frac{\nu M_1 e^{-\theta t \tau_1}}{\xi + \nu} (e^{-\theta_1 t \tau_1} \omega_1 \Theta(U(t - \tau_1), P(t - \tau_1)) - (\xi + \nu)L(t)) + M_1 e^{-\theta t \tau_2} (e^{-\theta_2 t \tau_2} \omega_2 \Theta(U(t - \tau_2), P(t - \tau_2)) + \nu L(t)) + M_2 e^{-\theta t \tau_3} (e^{-\theta_3 t \tau_3} \omega_3 \Theta(U(t - \tau_3), P(t - \tau_3)) - \Lambda O(t)) + \beta M_1 e^{-\theta t \tau_4} (I(t) - I(t - \tau_4)) + \Lambda M_2 e^{-\theta t \tau_5} (O(t) - O(t - \tau_5)).
\]

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

\[
\frac{dZ_0}{dt} = h \left( 1 - \frac{\partial \Theta(U_0, 0)}{\partial P} \right) (\rho - \gamma U(t)) + \lim_{p \to 0^+} \frac{\partial \Theta(U_0, 0)}{\partial P} \frac{\partial \Theta(U(t), P)}{\partial P} \frac{\partial \Theta(U(t), P(t))}{\partial P} - \left( \rho + \frac{\xi \partial \Theta(U_0, 0)}{\partial \Theta(U_0, 0)} \right) P(t) C(t) - \frac{\xi \mu}{\xi (1 - R_0^G)} \left( 1 - \frac{U(t)}{U_0} \right) C(t) + \frac{\xi \mu}{\xi (1 - R_0^G)} \left( 1 - \frac{U(t)}{U_0} \right) C(t) - \frac{\xi \mu}{\xi (1 - R_0^G)} \left( 1 - \frac{U(t)}{U_0} \right) C(t),
\]

where,

\( R_0 = h(\omega_1 + \omega_2 + \omega_3) \).

From the Assumption (A4), we have

\[
\frac{\Theta(U(t), P)}{P} \leq \lim_{p \to 0^+} \frac{\Theta(U(t), P)}{P} = \frac{\partial \Theta(U(t), 0)}{\partial P}
\]

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

\[
\frac{\Theta(U(t), P)}{P} \frac{\partial \Theta(U_0, 0)}{\partial P} \leq \frac{\Theta(U(t), P)}{P} \frac{\partial \Theta(U(t), P(t))}{\partial P} - \left( \rho + \frac{\xi \partial \Theta(U_0, 0)}{\partial \Theta(U_0, 0)} \right) P(t) C(t) - \frac{\xi \mu}{\xi (1 - R_0^G)} \left( 1 - \frac{U(t)}{U_0} \right) C(t).
\]

It implies that

\[
\frac{dZ_0}{dt} \leq h \gamma U_0 \left( 1 - \frac{U(t)}{U_0} \right) \left( 1 - \frac{\partial \Theta(U_0, 0)}{\partial \Theta(U(t), 0)} \right) \left( \rho + \frac{\xi \partial \Theta(U_0, 0)}{\partial \Theta(U_0, 0)} \right) P(t) C(t) - \frac{\xi \mu}{\xi (1 - R_0^G)} \left( 1 - \frac{U(t)}{U_0} \right) C(t).
\]

From (A2) we have

\[
\left( 1 - \frac{U(t)}{U_0} \right) \left( 1 - \frac{\partial \Theta(U_0, 0)}{\partial \Theta(U(t), 0)} \right) \leq 0.
\]

Therefore, if \( R_0^G < 1 \), then \( \frac{dZ_0}{dt} \leq 0 \) 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 \( R^G_0 > 1 \), then the endemic equilibrium \( E^G_1 \) of model (3.1)-(3.6) is G.A.S.

Proof. Define 
\[
Z_{11} = h \left( U(t) - U_1 - \int_{U_1}^{U(t)} \frac{\Theta(U_1, P_1)}{\Theta(U_1, P_1)} \, d\eta \right) + \frac{\nu M_1 e^{-\theta_1 t_4}}{\zeta + \nu} L_1 G \left( \frac{L(t)}{L_1} \right) + M_1 e^{-\theta_1 t_1} I_1 G \left( \frac{I(t)}{I_1} \right)
\]
\[
+ M_2 e^{-\theta_5 t_5} O_1 G \left( \frac{O(t)}{O_1} \right) + P_1 G \left( \frac{P(t)}{P_1} \right) + \rho \frac{P}{2(\varepsilon - \theta C_1)} (C(t) - C_1)^2.
\]

Calculating \( \frac{dZ_{11}}{dt} \) as:
\[
\frac{dZ_{11}}{dt} = h \left( 1 - \frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)} \right) \left( \rho - \gamma U(t) - (\omega_1 + \omega_2 + \omega_3) \Theta(U(t), P(t)) \right)
\]
\[
+ \frac{\nu M_1 e^{-\theta_1 t_4}}{\zeta + \nu} \left( 1 - \frac{L_1}{L(t)} \right) \left( \omega_1 e^{-\theta_1 t_1} \Theta(U(t - t_1), P(t - t_1)) - (\zeta + \nu) L(t) \right)
\]
\[
+ M_1 e^{-\theta_1 t_4} \left( 1 - \frac{L_1}{L(t)} \right) \left( \omega_2 e^{-\theta_2 t_2} \Theta(U(t - t_2), P(t - t_2)) + \nu L(t) - \beta I(t) \right)
\]
\[
+ M_2 e^{-\theta_5 t_5} \left( 1 - \frac{O_1}{O(t)} \right) \left( \omega_3 e^{-\theta_5 t_5} \Theta(U(t - t_5), P(t - t_3)) - \lambda O(t) \right)
\]
\[
+ \left( 1 - \frac{P_1}{P(t)} \right) \left( \beta M_1 e^{-\theta_4 t_4} I(t - t_4) + \lambda M_2 e^{-\theta_5 t_5} O(t - t_5) - \xi P(t) - \rho P(t) C(t) \right)
\]
\[
+ \frac{\rho}{\varepsilon - \theta C_1} (C(t) - C_1) \left( \varepsilon P(t) - \mu C(t) - \theta P(t) C(t) \right) .
\]

Define 
\[
Z_{12} = \frac{\nu M_1 \omega_1 e^{-\theta_1 t_1 - \theta_4 t_4}}{\zeta + \nu} \int_{t - t_1}^{t} G \left( \frac{\Theta(U(s), P(s))}{\Theta(U_1, P_1)} \right) \, ds
\]
\[
+ M_1 \omega_2 e^{-\theta_2 t_2 - \theta_4 t_4} \Theta(U_1, P_1) \int_{t - t_2}^{t} G \left( \frac{\Theta(U(s), P(s))}{\Theta(U_1, P_1)} \right) \, ds
\]
\[
+ M_2 \omega_3 e^{-\theta_3 t_3 - \theta_5 t_5} \Theta(U_1, P_1) \int_{t - t_3}^{t} G \left( \frac{\Theta(U(s), P(s))}{\Theta(U_1, P_1)} \right) \, ds.
\]

We calculate \( \frac{dZ_{12}}{dt} \):
\[
\frac{dZ_{12}}{dt} = \frac{\nu M_1 \omega_1 e^{-\theta_1 t_1 - \theta_4 t_4}}{\zeta + \nu} \Theta(U_1, P_1) \left( \frac{\Theta(U(t), P(t))}{\Theta(U_1, P_1)} - \frac{\Theta(U(t - t_1), P(t - t_1))}{\Theta(U_1, P_1)} \right)
\]
\[
+ \ln \left( \frac{\Theta(U(t - t_1), P(t - t_1))}{\Theta(U(t), P(t))} \right)
\]
\[
+ M_1 \omega_2 e^{-\theta_2 t_2 - \theta_4 t_4} \Theta(U_1, P_1) \left( \frac{\Theta(U(t), P(t))}{\Theta(U_1, P_1)} - \frac{\Theta(U(t - t_2), P(t - t_2))}{\Theta(U_1, P_1)} \right)
\]
\[
+ \ln \left( \frac{\Theta(U(t - t_2), P(t - t_2))}{\Theta(U(t), P(t))} \right)
\]
\[
+ M_2 \omega_3 e^{-\theta_3 t_3 - \theta_5 t_5} \Theta(U_1, P_1) \left( \frac{\Theta(U(t), P(t))}{\Theta(U_1, P_1)} - \frac{\Theta(U(t - t_3), P(t - t_3))}{\Theta(U_1, P_1)} \right)
\]
\[
+ \ln \left( \frac{\Theta(U(t - t_3), P(t - t_3))}{\Theta(U(t), P(t))} \right) .
\]
Define $Z_{13}(U(t), L(t), I(t), O(t), P(t), C(t))$ as

$$Z_{13} = \beta M_1 e^{-\theta_1 t_4} I_1 \int_{t-t_4}^{t} \frac{G}{I_1} \left( \frac{I(s)}{I_1} \right) ds + \Lambda M_2 e^{-\theta_5 t_5} O_1 \int_{t-t_5}^{t} \frac{O(s)}{O_1} \left( \frac{O(t)}{O(t)} \right) ds.$$ 

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

$$\frac{dZ_{13}}{dt} = \beta M_1 e^{-\theta_1 t_4} I_1 \left[ \frac{I(t)}{I_1} - \frac{I(t-t_4)}{I_1} + \ln \left( \frac{I(t-t_4)}{I(t)} \right) \right] + \Lambda M_2 e^{-\theta_5 t_5} O_1 \left[ \frac{O(t)}{O_1} - \frac{O(t-t_5)}{O_1} + \ln \left( \frac{O(t-t_5)}{O(t)} \right) \right].$$

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

$$\frac{dZ_1}{dt} = h \left( 1 - \frac{\Theta(U_1, P_1)}{\Theta(U(t), P_1)} \right) (\rho - \gamma U(t)) + h(\omega_1 + \omega_2 + \omega_3) \Theta(U_1, P_1) \frac{\Theta(U(t), P(t))}{\Theta(U(t), P_1)} - \frac{\gamma M_1 \omega_1 e^{-\theta_1 t_1} - \theta_1 t_1 L_1}{\zeta + \nu} \Theta(U(t-t_1), P(t-t_1)) + \frac{\nu M_1 e^{-\theta_1 t_4} L_1}{I_1}$$

$$- M_1 \omega_2 e^{-\theta_2 t_2 - \theta_4 t_4} \Theta(U(t-t_2), P(t-t_2)) \frac{I_1}{I(t)} - \frac{\nu M_1 e^{-\theta_1 t_4} L_1}{I_1} + \frac{\beta M_1 e^{-\theta_4 t_4} I_1}{I(t)}$$

$$- M_2 \omega_3 e^{-\theta_3 t_3 - \theta_5 t_5} \Theta(U(t-t_3), P(t-t_3)) \frac{O_1}{O(t)} - \Lambda M_2 e^{-\theta_4 t_4} O_1$$

$$- \beta M_1 e^{-\theta_4 t_4} I(t-t_4) \frac{P_1}{P(t)} - \Lambda M_2 e^{-\theta_5 t_5} O(t-t_5) \frac{P_1}{P(t)} - \xi(P(t) - P_1)$$

$$- \rho (P(t) - P_1) C(t) + \frac{\rho}{\epsilon - \theta C_1} (C(t) - C_1) (\epsilon P(t) - \mu C(t) - \delta P(t) C(t))$$

$$+ \frac{\nu M_1 \omega_1 e^{-\theta_1 t_1} - \theta_1 t_1 L_1}{\zeta + \nu} \Theta(U_1, P_1) \ln \left( \frac{\Theta(U(t-t_1), P(t-t_1))}{\Theta(U(t), P(t))} \right)$$

$$+ M_1 \omega_2 e^{-\theta_2 t_2 - \theta_4 t_4} \Theta(U_1, P_1) \ln \left( \frac{\Theta(U(t-t_2), P(t-t_2))}{\Theta(U(t), P(t))} \right)$$

$$+ M_2 \omega_3 e^{-\theta_3 t_3 - \theta_5 t_5} \Theta(U_1, P_1) \ln \left( \frac{\Theta(U(t-t_3), P(t-t_3))}{\Theta(U(t), P(t))} \right)$$

$$+ \beta M_1 e^{-\theta_4 t_4} I_1 \ln \left( \frac{I(t-t_4)}{I(t)} \right) + \Lambda M_2 e^{-\theta_5 t_5} O_1 \ln \left( \frac{O(t-t_5)}{O(t)} \right).$$

From the equilibrium conditions, we have:

$$\rho = \gamma U_1 + (\omega_1 + \omega_2 + \omega_3) \Theta(U_1, P_1),$$

$$\frac{\nu M_1 \omega_1 e^{-\theta_1 t_1} - \theta_1 t_1 L_1}{\zeta + \nu} \Theta(U_1, P_1) = \nu M_1 e^{-\theta_1 t_4} L_1,$$

$$\beta M_1 e^{-\theta_4 t_4} I_1 = M_1 \omega_2 e^{-\theta_2 t_2 - \theta_4 t_4} \Theta(U_1, P_1) + \nu M_1 e^{-\theta_1 t_4} L_1,$$

$$M_2 \omega_3 e^{-\theta_3 t_3 - \theta_5 t_5} \Theta(U_1, P_1) = \Lambda M_2 e^{-\theta_5 t_5} O_1.$$
\[\xi P_1 + \rho P_1 C_1 = \beta M_1 e^{-\theta_1 t \tau_1} I_1 + \Lambda M_2 e^{-\theta_3 t \tau_3} O_1,\]
\[\varepsilon P_1 = \mu C_1 + \delta P_1 C_1.\]

Utilizing these conditions for \(EP_1^C\), we obtain

\[
\frac{dZ_1}{dt} = h \left( 1 - \frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)} \right) \left( \gamma U_1 - \gamma U(t) \right) + \left( v M_1 e^{-\theta_1 t \tau_1} L_1 + M_1 \omega_2 e^{-\theta_2 t \tau_2 - \theta_1 t \tau_1} \Theta(U_1, P_1) + \Lambda M_2 e^{-\theta_3 t \tau_3} O_1 \right) \left( 1 - \frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)} \right) \\
+ \left( v M_1 e^{-\theta_1 t \tau_1} L_1 + M_1 \omega_2 e^{-\theta_2 t \tau_2 - \theta_1 t \tau_1} \Theta(U_1, P_1) + \Lambda M_2 e^{-\theta_3 t \tau_3} O_1 \right) \frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)} \\
- v M_1 e^{-\theta_1 t \tau_1} L_1 \Theta(U(t - \tau_1), P(t - \tau_1)) + v M_1 e^{-\theta_1 t \tau_1} L_1 \\
- M_1 \omega_2 e^{-\theta_2 t \tau_2 - \theta_1 t \tau_1} \Theta(U_1, P_1) \frac{I_1 \Theta(U(t - \tau_2), P(t - \tau_2))}{I(t) \Theta(U_1, P_1)} - v M_1 e^{-\theta_1 t \tau_1} L_1 \frac{I_1 L_1}{I(t) I_1} \\
+ M_1 \omega_2 e^{-\theta_2 t \tau_2 - \theta_1 t \tau_1} \Theta(U_1, P_1) + v M_1 e^{-\theta_1 t \tau_1} L_1 - \Lambda M_2 e^{-\theta_3 t \tau_3} O_1 \frac{O_1 \Theta(U(t - \tau_3), P(t - \tau_3))}{O(t) \Theta(U(t), P(t))} \\
+ \Lambda M_2 e^{-\theta_3 t \tau_3} O_1 - \left( v M_1 e^{-\theta_1 t \tau_1} L_1 + M_1 \omega_2 e^{-\theta_2 t \tau_2 - \theta_1 t \tau_1} \Theta(U_1, P_1) \right) \frac{P_1 I(t - \tau_4)}{P(t) I_1} \\
- \Lambda M_2 e^{-\theta_3 t \tau_3} 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 - \partial C_1} (C(t) - C_1) (\varepsilon P(t) - \mu C(t) - \delta P(t) C(t) - \varepsilon P_1 + \mu C_1 + \delta P_1 C_1 - \delta P(t) C_1) + \delta P(t) C_1) \\
+ v M_1 e^{-\theta_1 t \tau_1} 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_3 t \tau_3} 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 t \tau_2 - \theta_1 t \tau_1} \Theta(U_1, P_1) \ln \left( \frac{\Theta(U(t - \tau_2), P(t - \tau_2))}{\Theta(U(t), P(t))} \right) \\
+ \left( v M_1 e^{-\theta_1 t \tau_1} L_1 + M_1 \omega_2 e^{-\theta_2 t \tau_2 - \theta_1 t \tau_1} \Theta(U_1, P_1) \right) \ln \left( \frac{I(t - \tau_4)}{I(t)} \right) + \Lambda M_2 e^{-\theta_3 t \tau_3} O_1 \ln \left( \frac{O(t - \tau_5)}{O(t)} \right).\]

Simplifying the result, we obtain

\[
\frac{dZ_1}{dt} = -h \gamma U_1 \left( 1 - \frac{U(t)}{U_1} \right) \left( 1 - \frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)} \right) - (\xi + \rho C_1)(P(t) - P_1) \\
- \rho(P(t - P_1))(C(t) - C_1) + \frac{\rho(\varepsilon - \partial C_1)}{\varepsilon - \partial C_1} (C(t) - C_1) (P(t) - P_1) - \frac{\rho(\mu + \rho P(t))}{\varepsilon - \partial C_1} (C(t) - C_1)^2 \\
+ v M_1 e^{-\theta_1 t \tau_1} L_1 \left[ 3 - \frac{\Theta(U_1, P_1)}{\Theta(U(t), P_1)} \right] - \frac{L_1 \Theta(U(t - \tau_1), P(t - \tau_1))}{L(t) \Theta(U_1, P_1)} - \frac{I_1 L(t)}{I(t) I_1} - \frac{P_1 I(t - \tau_4)}{P(t) I_1} \\
+ \ln \left( \frac{\Theta(U(t - \tau_1), P(t - \tau_1))}{\Theta(U(t), P(t))} \right) + \ln \left( \frac{I(t - \tau_4)}{I(t)} \right) \\
+ M_1 \omega_2 e^{-\theta_2 t \tau_2 - \theta_1 t \tau_1} \Theta(U_1, P_1) \left[ 2 - \frac{\Theta(U_1, P_1)}{\Theta(U(t), P_1)} - \frac{P_1 I(t - \tau_4)}{P(t) I_1} - \frac{I_1 \Theta(U(t - \tau_2), P(t - \tau_2))}{I(t) \Theta(U_1, P_1)} \right] \\
+ \ln \left( \frac{\Theta(U(t - \tau_2), P(t - \tau_2))}{\Theta(U(t), P(t))} \right) + \ln \left( \frac{I(t - \tau_4)}{I(t)} \right) \\
+ \Lambda M_2 e^{-\theta_3 t \tau_3} O_1 \left[ 2 - \frac{\Theta(U_1, P_1)}{\Theta(U(t), P_1)} - \frac{O_1 \Theta(U(t - \tau_3), P(t - \tau_3))}{O(t) \Theta(U_1, P_1)} - \frac{P_1 O(t - \tau_5)}{P(t) O_1} \right] \\
+ \ln \left( \frac{\Theta(U(t - \tau_3), P(t - \tau_3))}{\Theta(U(t), P(t))} \right) + \ln \left( \frac{O(t - \tau_5)}{O(t)} \right).\]
\[
\begin{align*}
&+ \left(\nu M_1 e^{-\theta_1 t_1 L_1} + M_1\omega_1 e^{-\theta_2 t_2 - \theta_4 t_4} \Theta(U_1, P_1) + \Lambda M_2 e^{-\theta_5 t_5} O_1\right) \frac{\Theta(U(t), P(t))}{\Theta(U(t), P_1)} \\
&+ \left(\nu M_1 e^{-\theta_1 t_1 L_1} + M_1\omega_1 e^{-\theta_2 t_2 - \theta_4 t_4} \Theta(U_1, P_1) + \Lambda M_2 e^{-\theta_5 t_5} O_1\right) \left(1 - \frac{P(t)\Theta(U(t), P_1)}{P_1\Theta(U(t), P_1)}\right) \\
&- \left(\nu M_1 e^{-\theta_1 t_1 L_1} + M_1\omega_1 e^{-\theta_2 t_2 - \theta_4 t_4} \Theta(U_1, P_1) + \Lambda M_2 e^{-\theta_5 t_5} O_1\right) \left(1 - \frac{P(t)\Theta(U(t), P_1)}{P_1\Theta(U(t), P_1)}\right). 
\end{align*}
\]

Note that

\[-(\xi + \rho C_1)(P(t) - P_1) = -\frac{1}{P_1} \left(\beta M_1 e^{-\theta_1 t_1 L_1} + \Lambda M_2 e^{-\theta_5 t_5} O_1\right) (P(t) - P_1) = \left(\nu M_1 e^{-\theta_1 t_1 L_1} + M_1\omega_1 e^{-\theta_2 t_2 - \theta_4 t_4} \Theta(U_1, P_1) + e^{-\theta_5 t_5} \Lambda M_2 O_1\right) \left(1 - \frac{P(t)}{P_1}\right).
\]

Moreover, we have

\[
\begin{align*}
\ln \left(\frac{\Theta(U(t - \tau_1), P(t - \tau_1))}{\Theta(U(t), P(t))}\right) &= \ln \left(\frac{I_1\Theta(U(t - \tau_1), P(t - \tau_1))}{I(t)\Theta(U_1, P_1)}\right) + \ln \left(\frac{I_1 L(t) I(t)}{I_1 L(t) I(t)}\right) \\
&+ \ln \left(\frac{I(t) P_1}{I_1 P(t)} + \ln \left(\frac{P(t)\Theta(U(t), P_1)}{P_1\Theta(U(t), P_1)}\right) + \ln \left(\frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)}\right),
\end{align*}
\]

\[
\begin{align*}
\ln \left(\frac{\Theta(U(t - \tau_2), P(t - \tau_2))}{\Theta(U(t), P(t))}\right) &= \ln \left(\frac{I_1\Theta(U(t - \tau_2), P(t - \tau_2))}{I(t)\Theta(U_1, P_1)}\right) + \ln \left(\frac{I(t) P_1}{I_1 P(t)} + \ln \left(\frac{P(t)\Theta(U(t), P_1)}{P_1\Theta(U(t), P_1)}\right) + \ln \left(\frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)}\right),
\end{align*}
\]

\[
\begin{align*}
\ln \left(\frac{\Theta(U(t - \tau_3), P(t - \tau_3))}{\Theta(U(t), P(t))}\right) &= \ln \left(\frac{O(t)\Theta(U(t - \tau_3), P(t - \tau_3))}{O(t)\Theta(U_1, P_1)}\right) + \ln \left(\frac{O(t) P_1}{O(t) P(t)} + \ln \left(\frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)}\right)
\end{align*}
\]


d\frac{dZ_1}{dt} \text{ will be}

\[
\begin{align*}
d\frac{dZ_1}{dt} &= -\gamma h U_1 \left(1 - \frac{U(t)}{U_1}\right) \left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U(t), P_1)}\right) - \frac{\rho(\mu + \delta P(t))}{\epsilon - \delta C_1} (C(t) - C_1)^2 \\
&+ \nu M_1 e^{-\theta_1 t_1 L_1} \left[5 - \frac{\Theta(U_1, P_1)}{\Theta(U(t), P_1)} - \frac{I_1\Theta(U(t - \tau_1), P(t - \tau_1))}{I(t)\Theta(U_1, P_1)} + \ln \left(\frac{\Theta(U(t), P_1)}{\Theta(U(t), P(t))}\right)\right]
\end{align*}
\]
\[ \begin{align*}
& + (\nu \delta_1 e^{-\delta_1 t} L_1 + M_1 \omega_2 e^{-\delta_2 t} - \delta_4 \delta_4 \Omega(U_1, P_1) + e^{-\delta_5 t} \Lambda M_2 O_1) \\
& \times \left( \frac{\Theta(U(t), P(t))}{\Theta(U(t), P_1)} - \frac{P(t)}{P_1} - 1 + \frac{P(t) \Theta(U(t), P_1)}{P_1 \Theta(U(t), P(t))} \right). 
\end{align*} \]

Simplifying the result, we get
\[
\frac{dZ_1}{dt} = -\gamma h L_1 \left( 1 - \frac{U(t)}{U_1} \right) \left( 1 - \frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)} \right) - \frac{\rho(\mu + \beta P(t))}{\varepsilon - \beta C_1} (C(t) - C_1)^2 \\
- \nu \delta_1 e^{-\delta_1 t} L_1 \left[ G \left( \frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)} \right) + G \left( \frac{L(t) \Theta(U(t), P_1)}{L(t) \Theta(U(t), P_1)} \right) \right] + G \left( \frac{P(t) \Theta(U(t), P_1)}{P(t) \Theta(U(t), P_1)} \right) \\
- \frac{\Lambda M_2 e^{-\delta_5 t} U_1}{\Theta(U(t), P_1)} \left[ G \left( \frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)} \right) + G \left( \frac{O(t) \Theta(U(t) - \tau_3, P(t) - \tau_3)}{O(t) \Theta(U(t), P_1)} \right) \right] + G \left( \frac{P(t) O(t - \tau_3)}{P(t) O_1} \right) \\
+ G \left( \frac{P(t) \Theta(U(t), P_1)}{P(t) \Theta(U(t), P_1)} \right) \left( \nu \delta_5 e^{-\delta_5 t} L_1 + M_1 \omega_2 e^{-\delta_2 t} - \delta_4 \delta_4 \Theta(U_1, P_1) + e^{-\delta_5 t} \Lambda M_2 O_1 \right) \\
\times \left( \frac{\Theta(U(t), P(t))}{\Theta(U(t), P_1)} - \frac{P(t)}{P_1} \right) \left( 1 - \frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)} \right). 
\]

From (A2) we have
\[
\left( 1 - \frac{U(t)}{U_1} \right) \left( 1 - \frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)} \right) \leq 0. 
\]

In addition, from Assumptions (A1), (A2), and (A4), we have
\[
\left( \frac{\Theta(U(t), P(t))}{P(t)} - \frac{\Theta(U(t), P_1)}{P_1} \right) (\Theta(U(t), P(t)) - \Theta(U(t), P_1) \leq 0, 
\]
which gives
\[
\left( \frac{\Theta(U(t), P(t))}{\Theta(U(t), P_1)} - \frac{P(t)}{P_1} \right) \left( 1 - \frac{\Theta(U(t), P_1)}{\Theta(U(t), P_1)} \right) \leq 0. 
\]

Then we get that for all \( U(t), L(t), I(t), O(t), P(t), C(t) > 0 \) we have \( \frac{dZ_1}{dt} \leq 0 \) and \( \frac{dZ_1}{dt} = 0 \) 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 \( E P_1^G \) is G.A.S.

\[ \square \]

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 \( \rho = 10, \gamma = \mu = 0.01, \zeta = \beta = 0.3, \nu = \varepsilon = 0.2, M_2 = 5, \xi = 6, \Lambda = 0.1, \rho = 0.4, \omega_k = 0.001, \delta_i = 0.6, i = 1, 2, \ldots, 5 \) 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:

\[ \text{IC1: } U(s) = 800, L(s) = 2, I(s) = 4, O(s) = 7, P(s) = 1, C(s) = 8; \]
IC2: \( U(s) = 600, \ L(s) = 3, \ I(s) = 7, \ O(s) = 12, \ P(s) = 2, \ C(s) = 13; \)
IC3: \( U(s) = 400, \ L(s) = 4, \ I(s) = 10, \ O(s) = 15, \ P(s) = 3, \ C(s) = 8, \ s \in [-\tau, 0]. \)

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.

4.1.2. The effect of \( \tau \) on stability of equilibria

In this case, we take \( \vartheta = 0.01, \ M_1 = 10 \) and \( \tau \) 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 \( \tau \)
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 \(\tau > 0.9606\).

![Graphs showing the behavior of uninfected CD4\(^+\) T cells, latently infected cells, short lived productively infected cells, long lived productively infected cells, HIV particles, and B cells over time for different values of \(\tau\).](image)

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

4.1.3. Effect of B cell impairment parameter \(\vartheta\) on the HIV dynamics.

In this case, we take \(\tau = 0.01\), \(M_1 = 10\) and \(\vartheta\) 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 \(\vartheta\) 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 \(\vartheta\) has no effect on the stability of equilibria.

![Graphs showing the behavior of different cell populations](image)

(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 \(\vartheta\).

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 \(\alpha_1\) and \(\alpha_2\) 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

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

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

We also have

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

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

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

In this subsection, we fix $\theta = \tau = 0.01$, $M_1 = 10$ and choose $\alpha_1$ and $\alpha_2$.

4.2.1. Effect of the saturation parameter $\alpha_1$ 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 $\alpha_1$ 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 $\alpha_1$ has no effect on the stability of equilibria. The reason is that $R_0$ does not depend on the parameter $\alpha_1$.

4.2.2. Effect of Holling type-II constant $\alpha_2$ 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 $\alpha_2$ 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 $0 \leq \alpha_2 < 0.0031$;

(ii) $EP_0^G$ is G.A.S. when $\alpha_2 > 0.0031$.

This means that $\alpha_2$ 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:

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

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

$$\dot{I}(t) = (1 - \epsilon_r) \omega_2 e^{-\theta_2 \tau_2} \frac{U(t-\tau_2)P(t-\tau_2)}{1 + \alpha_2 U(t-\tau_2)} + \nu L(t) - \beta I(t).$$
(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 \(\alpha_1\).

\[
\dot{O}(t) = (1 - \epsilon_r) \omega_3 e^{-\theta_3 \tau_3} \frac{U(t - \tau_3) P(t - \tau_3)}{1 + \alpha_2 U(t - \tau_3)} - \Lambda O(t),
\]

\[
\dot{P}(t) = (1 - \epsilon_p) \beta M_1 e^{-\theta_1 \tau_1} I(t - \tau_4) + (1 - \epsilon_p) \Lambda M_2 e^{-\theta_2 \tau_2} O(t - \tau_5) - \xi P(t) - \rho P(t) C(t),
\]

\[
\dot{C}(t) = \epsilon P(t) - \mu C(t) - \theta P(t) C(t),
\]

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

\[
R_0(\epsilon) = (1 - \epsilon)^2 \frac{[\omega_1 \nu M_1 e^{-\theta_1 \tau_1 - \theta_4 \tau_4} + (\zeta + \gamma) (\omega_2 M_1 e^{-\theta_2 \tau_2 - \theta_4 \tau_4} + \omega_3 M_2 e^{-\theta_3 \tau_3 - \theta_5 \tau_5})]}{\xi(\zeta + \gamma)(1 + \alpha_2 U_0)} U_0.
\]
Figure 5: Solution trajectories of model (3.1)-(3.6) for different values of $\alpha_2$.

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 $0 \leq \epsilon \leq 1$, then for $\epsilon_{\min} < \epsilon \leq 1$, $EP_0^{G}$ 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 $0.2849 < \epsilon \leq 1$, then $R_0(\epsilon) < 1$ and $EP_0^{G}$ is G.A.S;

(ii) if $0 \leq \epsilon < 0.2849$, 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 $\epsilon$. Clearly from
the figure we can see that, the increasing of $\epsilon$ 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.

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

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 lose 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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