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STABILITY OF A DELAYED ADAPTIVE IMMUNITY HIV INFECTION MODEL WITH SILENT INFECTED CELLS AND CELLULAR INFECTION

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Abstract In this paper we formulate a mathematical model to investigate the within-host HIV dynamics under the effect of both antibody and Cytotoxic T lymphocytes (CTL) immune responses. The model consists of five components: healthy $CD4^+T$ cells, silent infected cells, active infected cells, free HIV particles, CTLs and antibodies. The healthy $CD4^+T$ cells can be infected when they are contacted by (i) free HIV particles, (ii) active infected cells, and (iii) silent infected cells. The model is an improvement of some existing HIV infection models with both virus-to-cell (VTC) and cell-to-cell (CTC) transmissions by incorporating the incidence between the silent infected cells and healthy $CD4^+T$ cells. The well-posedness of the model is established by showing that the solutions of the model are nonnegative and bounded. We have shown that the model has five equilibria and their existence is governed by five threshold parameters. We prove the global asymptotic stability of all equilibria by utilizing Lyapunov function and LaSalle's invariance principle. We have presented numerical simulations to illustrate the theoretical results. We have studied the effects of CTC transmission and time delays on the dynamical behavior of the system. We have shown that inclusion of time delay can significantly increase the concentration of the uninfected $CD4^+$ T cells and reduce the concentrations of the infected cells and free HIV particles. While the inclusion of CTC transmission decreases the concentration of the uninfected $CD4^+$ T cells and increases the concentrations of the infected cells and free HIV particles.

Keywords HIV infection, cell-to-cell transmission, global stability, silent infected cells, adaptive immune response, Lyapunov function, intracellular delay.

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1. Introduction

Acquired immunodeficiency syndrome (AIDS) is one of dangerous human diseases which are caused by human immunodeficiency virus (HIV). According to global health observatory (GHO, 2018) data of HIV/AIDS published by WHO [55] that,

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globally, 37.9 million people living with HIV in 2018, 1.7 million people newly infected with HIV in 2018 and 770,000 HIV-related death 2018. HIV is a retrovirus that infects the healthy CD4$^+$T cells which play an important role in immune system. Cytotoxic T lymphocytes (CTLs) and antibodies are the two arms of the immune system response to control the HIV infection for long period (10-15 years). However, during this period the concentration of the healthy CD4$^+$T cells declines. The concentration of the CD4$^+$T cells in uninfected individual is 1000 cells/mm^3. When the concentration of the CD4$^+$T cells reaches below a critical value of 200 cells/mm^3, the individual is said to have progressed to AIDS. During the last decades, mathematical modeling of within-host HIV infection has witnessed a significant development [46]. Stability analysis has also become one of the very important and helpful methods for better understanding the within-host HIV dynamics (see e.g. [5,7,8,10,15–17,25,28,33,41]).

During the recent years, great efforts have been made to formulate and analyze within-host HIV dynamics models under the influence of CTL immune response (see e.g. [2,11,35,45,48,53]) or antibody immune response (see e.g. [19,22,24,26,27,37,44]). In 2003, Wodarz [56] has presented a virus dynamics model which considers the effect of antibodies together with CTL immune response. Dubey etc [9] have extended the model in [56] by adding a logistic growth term which represents the proliferation of healthy CD4$^+$T cells. Moreover, the model in [9] incorporates a combination of two classes of antiviral treatment, protease inhibitor and reverse transcriptase. Su at al. [50] have developed the model in [56] by considering Beddington-DeAngelis incidence rate to replace the mass-action incidence rate. Yousfi etc [59] have suggested a model to describe the HBV dynamics. In [9,50,56,59], it has been assumed that infection processes are instantaneous. However, it has been estimated that the time between the HIV enters a target cell until producing new HIV particles is about 0.9 days [47]. Therefore, more realistic virus dynamics model when time delay is incorporated. Yan and Wang [58] have extended the model Wodarz [56] by incorporating a discrete time delay for production of active infected cells as:

$$\begin{cases} \dot{W}(t) = \rho - \alpha W(t) - \eta N(t)W(t), \\ \dot{M}(t) = \eta e^{-\hbar\varphi} N(t-\varphi)W(t-\varphi) - aM(t) - \mu P(t)M(t), \\ \dot{N}(t) = bM(t) - \varepsilon N(t) - \varpi T(t)N(t), \\ \dot{P}(t) = \sigma P(t)M(t) - \pi P(t), \\ \dot{T}(t) = \tau T(t)N(t) - \zeta T(t), \end{cases} \tag{1.1}$$

where $W(t)$, $M(t)$, $N(t)$, $P(t)$ and $T(t)$ are the the concentrations of healthy CD4$^+$T cells, active HIV-infected CD4$^+$T cells, free HIV particles, HIV-specific CTLs and HIV-specific antibodies at time t, respectively. The healthy CD4$^+$T cells are produced at specific constant rate ρ. The term ηWN refers to the rate at which new infectious appears by VTC contact between free HIV particles and healthy CD4$^+$T cells. The term μPM is the killing rate of active HIV-infected cells due to their specific CTLs immunity. The proliferation rate for effective HIV-specific CTLs is given by σPM. The proliferation rate for HIV-specific antibodies is given by τTN. The free HIV particles are generated at rate bM and neutralized from the plasma due to HIV-specific antibodies at rate ϖTN. The fraction $e^{-\hbar\varphi}$ denotes the survive rate of infected cells during the delay period φ. Wang and Liu [54] have developed model (1.1) by considering saturated incidence rate $\frac{\eta NW}{1+\omega N}$, where $\omega > 0$. Model (1.1) assume that the time delay is constant which is not biologically realistic. Wang etc [52] have extended model (1.1) by incorporating two types of distributed time delays.

In [9, 23, 47, 50, 52, 54, 56, 58, 59] it was assumed that the infection occurs due to virus-to-cell transmission (VTC). It has been reported in several works that the healthy CD4$^+$T cells can also be infected due to cell-cell contact known as cell-to-cell transmission (CTC) (see e.g. [36, 38]). Therefore, CTC transmission plays an important role in the HIV infection process even during the antiviral treatment [49]. The CTC transmission has been incorporated into viral infection models by including: (i) CTL immune response [6, 51], (ii) antibody immune response, [14, 32, 43] and (iii) both CTL and antibody immune responses [18, 20, 30, 42].

It is known that highly active anti-retroviral therapy can suppress HIV replication to a low level but cannot enucleate the HIV from the body. One of the main reasons is the presence of silent (latent) CD4$^+$T infected cells where the HIV provirus can reside [57]. Silent CD4$^+$T infected cells live long, but they can be activated to produce new HIV particles. In a very recent work [1], it has been shown that both silent and active infected CD4$^+$T cells can infect the healthy CD4$^+$T cells through CTC mechanism. In all of the above mentioned works, it has been assumed that the CTC transmission is only due to the active infected CD4$^+$T cells. In a very recent work, Elaiw and Alshamrani [21] have investigated an HIV dynamics model with silent and active CTC transmissions and CTL immune response. In [21] the antibody immune response has not been included.

In the present paper we propose an HIV infection model by including (i) both CTL and antibody immune responses, (ii) three types of distributed time delays, (iii) both VTC and CTC transmissions. The CTC transmission is due to the contact of healthy CD4$^+$T cells with silent or active infected cells. The well-posedness of the model is investigated by establishing that the solutions of the model are nonnegative and bounded. We derive five threshold parameters which determine the existence and stability of the five equilibria. Global stability of all equilibria is proven by formulating Lyapunov functions and utilizing LaSalle's invariance principle. We perform some numerical simulations to illustrate the theoretical results.

2. Model formulation

We formulate a distributed delay HIV infection model with both CTL and antibody immune responses. We assume that the HIV virions can replicate by two mechanisms VTC and CTC transmissions. The CTC infection has two sources, (i) the contact between healthy CD4$^+$T cells and silent infected CD4$^+$T cells, and (ii) the contact between healthy CD4$^+$T cells and active infected CD4$^+$T cells. Under these assumptions we propose by the following model:

$$
\begin{cases}
\dot{W}(t) = \rho - \alpha W(t) - \eta_1 W(t)N(t) - \eta_2 W(t)U(t) - \eta_3 W(t)M(t), \\
\dot{U}(t) = \int_0^{\kappa_1} \Lambda_1(\varphi)e^{-\hbar_1\varphi}W(t-\varphi)[\eta_1 N(t-\varphi)+\eta_2 U(t-\varphi)+\eta_3 M(t-\varphi)]d\varphi - (\lambda+\gamma)U(t), \\
\dot{M}(t) = \lambda \int_0^{\kappa_2} \Lambda_2(\varphi)e^{-\hbar_2\varphi}U(t-\varphi)d\varphi - aM(t) - \mu P(t)M(t), \\
\dot{N}(t) = b \int_0^{\kappa_3} \Lambda_3(\varphi)e^{-\hbar_3\varphi}M(t-\varphi)d\varphi - \varepsilon N(t) - \varpi T(t)N(t), \\
\dot{P}(t) = \sigma P(t)M(t) - \pi P(t), \\
\dot{T}(t) = \tau T(t)N(t) - \zeta T(t),
\end{cases}
\tag{2.1}
$$

where $W(t)$, $U(t)$, $M(t)$, $N(t)$, $P(t)$ and $T(t)$ are the the concentrations of healthy CD4$^+$T cells, silent HIV-infected CD4$^+$T cells, active HIV-infected CD4$^+$T cells, free HIV particles, HIV-specific CTLs and HIV-specific antibodies at time t, respectively. The HIV virions can replicate using VTC and CTC transmissions. The healthy CD4$^+$T cells are produced at specific constant rate ρ. The term $\eta_1 WN$ refers to the rate at which new infectious appears by VTC contact between free HIV particles and healthy CD4$^+$T cells. The healthy CD4$^+$T cells are contacted with silent infected CD4$^+$T cells and active infected CD4$^+$T cells and become infected due to CTC transmission at rates $\eta_2 WU$ and $\eta_3 WM$, respectively. The term λU is the rate of silent HIV-infected cells that become actively HIV-infected cells. The term μPM is the killing rate of active HIV-infected cells due to their specific CTLs immunity. The proliferation rates for effective HIV-specific CTLs is given by σPM. The proliferation rate for HIV-specific antibodies which is proportional to the numbers of HIV particles and HIV-specific antibodies is given by τTN. The free HIV particles are generated at rate bM and neutralized from the plasma due to HIV-specific antibodies at rate ϖTN. The factor $\Lambda_1(\varphi)e^{-\hbar_1\varphi}$ represents the probability that healthy CD4$^+$T cells contacted by HIV particles at time $t-\varphi$ survived φ time units and become silent infected at time t. The term $\Lambda_2(\varphi)e^{-\hbar_2\varphi}$ is the probability that silent HIV-infected CD4$^+$T cells survived φ time units before transmitted to be active at time t. Moreover, the factor $\Lambda_3(\varphi)e^{-\hbar_3\varphi}$ demonstrates the probability of new immature HIV particles at time $t-\varphi$ lost φ time units and become mature at time t. Here $\hbar_i$, $i = 1, 2, 3$ are positive constants. The delay parameter φ is random taken from a probability distribution function $\Lambda_i(\varphi)$ over the time interval $[0, \kappa_i]$, $i = 1, 2, 3$, where κ_i is the limit superior of this delay period. The function $\Lambda_i(\varphi)$, $i = 1, 2, 3$ satisfies $\Lambda_i(\varphi) > 0$ and

$$
\int_0^{\kappa_i} \Lambda_i(\varphi)d\varphi = 1 \text{ and } \int_0^{\kappa_i} \Lambda_i(\varphi)e^{-u\varphi}d\varphi < \infty,
$$

where $u > 0$. Let us denote

$$
\bar{\mathcal{H}}_i(\varphi) = \Lambda_i(\varphi)e^{-\hbar_i\varphi} \text{ and } \mathcal{H}_i = \int_0^{\kappa_i} \bar{\mathcal{H}}_i(\varphi)d\varphi,
$$

where $i = 1, 2, 3$. Thus $0 < \mathcal{H}_i \leq 1$, $i = 1, 2, 3$. The initial conditions of system (2.1) is given by:

$$
\begin{aligned}
&W(x) = \epsilon_1(x),\ U(x) = \epsilon_2(x),\ M(x) = \epsilon_3(x),\ N(x) = \epsilon_4(x),\ P(x) = \epsilon_5(x),\\
&T(x) = \epsilon_6(x), \epsilon_j(x) \geq 0,\ x \in [-\kappa, 0],\ j = 1, 2, ..., 6, \quad \kappa = \max\{\kappa_1, \kappa_2, \kappa_3\},
\end{aligned}
\tag{2.2}
$$

where $\epsilon_j(x) \in \mathcal{C}([-\kappa, 0], \mathbb{R}_{\geq 0})$, $j = 1, 2, ..., 6$ and $\mathcal{C} = \mathcal{C}([-\kappa, 0], \mathbb{R}_{\geq 0})$ is the Banach space of continuous functions mapping the interval $[-\kappa, 0]$ into $\mathbb{R}_{\geq 0}$ with norm $\|\epsilon_j\| = \sup\limits_{-\kappa \leq m \leq 0} |\epsilon_j(m)|$ for $\epsilon_j \in \mathcal{C}$. Therefore, system (2.1) with initial conditions (2.2) has a unique solution by using the standard theory of functional differential equations [31, 40]. All parameters and their definitions are summarized in Table 1.

Table 1. Parameters of model (2.1) and their interpretations.

Symbol	Biological meaning
ρ	Recruitment rate for the susceptible $CD4^+T$ cells
α	Natural death rate constant for the susceptible $CD4^+T$ cells
η_1	Virus-cell incidence rate constant between free HIV particles and susceptible $CD4^+T$ cells
η_2	Cell-cell incidence rate constant between silent HIV-infected $CD4^+T$ cells and susceptible $CD4^+T$ cells
η_3	Cell-cell incidence rate constant between active HIV-infected $CD4^+T$ cells and susceptible $CD4^+T$ cells
γ	Death rate constant of silent HIV-infected cells
a	Death rate constant of active HIV-infected cells
μ	Killing rate constant of active HIV-infected cells due to their specific CTL-mediated immunity
λ	Transmission rate constant of silent HIV-infected cells that become active HIV-infected cells
b	Generation rate constant of new HIV particles
ε	Death rate constant of free HIV particles
σ	Proliferation rate constant for effective HIV-specific CTLs
π	Decay rate constant of HIV-specific CTLs
ϖ	Neutralization rate constant of HIV particles due to HIV-specific antibodies immunity
τ	Proliferation rate constant of HIV-specific antibodies
ζ	Decay rate constant of HIV-specific antibodies
φ	Delay parameter
$\Lambda_i(\varphi)$	Probability distribution function

3. Well-posedness of solutions

Proposition 3.1. *All solutions of system (2.1) with initial conditions (2.2) are nonnegative and ultimately bounded.*

Proof. First, we show the nonnegativity of solutions. From the first Eq. of system (2.1), we have $\dot{W}\mid_{W=0}=\rho>0$, then $W(t)>0$ for all $t\geq 0$. Moreover, the rest Eqs. of system (2.1) give us the following

$$U(t)=\epsilon_2(0)e^{-(\lambda+\gamma)t}+\int\limits_0^t e^{-(\lambda+\gamma)(t-\varkappa)}\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)W(\varkappa-\varphi)$$
$$\times\left[\eta_1 N(\varkappa-\varphi)+\eta_2 U(\varkappa-\varphi)+\eta_3 M(\varkappa-\varphi)\right]d\varphi d\varkappa\geq 0,$$
$$M(t)=\epsilon_3(0)e^{-\int_0^t(a+\mu P(y))dy}+\lambda\int\limits_0^t e^{-\int_\varkappa^t(a+\mu P(y))dy}\int\limits_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)U(\varkappa-\varphi)d\varphi d\varkappa\geq 0,$$
$$N(t)=\epsilon_4(0)e^{-\int_0^t(\varepsilon+\varpi T(y))dy}+b\int\limits_0^t e^{-\int_\varkappa^t(\varepsilon+\varpi T(y))dy}\int\limits_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)M(\varkappa-\varphi)d\varphi d\varkappa\geq 0,$$
$$P(t)=\epsilon_5(0)e^{-\int_0^t(\pi-\sigma M(y))dy}\geq 0,$$
$$T(t)=\epsilon_6(0)e^{-\int_0^t(\zeta-\tau N(y))dy}\geq 0,$$

for all $t\in[0,\kappa]$. Thus, by a recursive argument, we get $W(t),U(t),M(t),N(t),P(t)\geq 0$ for all $t\geq 0$. Hence, the solutions of system (2.1) satisfy $(W(t),U(t),M(t),N(t),P(t))\in\mathbb{R}^6_{\geq 0}$ for all $t\geq 0$. Next, we establish the boundedness of the model's solutions. The nonnegativity of the model's solution implies that $\limsup_{t\to\infty}W(t)\leq\frac{\rho}{\alpha}$. To show the ultimate boundedness of $U(t)$ we let $\Psi_1(t)=\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)W(t-\varphi)d\varphi+U(t)$, then

$$\begin{aligned}\dot{\Psi}_1(t)&=\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\rho-\alpha W(t-\varphi)\right]d\varphi-(\lambda+\gamma)U(t)\\&=\rho\mathcal{H}_1-\alpha\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)W(t-\varphi)d\varphi-(\lambda+\gamma)U(t)\\&\leq\rho-\phi_1\left(\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)W(t-\varphi)d\varphi+U(t)\right)=\rho-\phi_1\Psi_1(t),\end{aligned}$$

where $\phi_1=\min\{\alpha,\lambda+\gamma\}$. It follows that, $\limsup_{t\to\infty}\Psi_1(t)\leq\Omega_1$, where $\Omega_1=\frac{\rho}{\phi_1}$. Since $\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)W(t-\varphi)d\varphi$ and $U(t)$ are nonnegative, then $\limsup_{t\to\infty}U(t)\leq\Omega_1$. Moreover, we let $\Psi_2(t)=M(t)+\frac{\mu}{\sigma}P(t)$, then

$$\begin{aligned}\dot{\Psi}_2(t)&=\lambda\int\limits_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)U_\varphi d\varphi-aM(t)-\frac{\mu\pi}{\sigma}P(t)\leq\lambda\mathcal{H}_2\Omega_1-aM(t)-\frac{\mu\pi}{\sigma}P(t)\\&\leq\lambda\Omega_1-aM(t)-\frac{\mu\pi}{\sigma}P(t)\leq\lambda\Omega_1-\phi_2\left(M(t)+\frac{\mu}{\sigma}P(t)\right)=\lambda\Omega_1-\phi_2\Psi_2(t),\end{aligned}$$

where $\phi_2=\min\{a,\pi\}$. It follows that, $\limsup_{t\to\infty}\Psi_2(t)\leq\Omega_2$, where $\Omega_2=\dfrac{\lambda\Omega_1}{\phi_2}$. Since $M(t)\geq 0$ and $P(t)\geq 0$, then $\limsup_{t\to\infty}M(t)\leq\Omega_2$ and $\limsup_{t\to\infty}P(t)\leq$

Ω_3, where $\Omega_3 = \frac{\sigma}{\mu}\Omega_2$. Finally, let $\Psi_3(t) = N(t) + \frac{\varpi}{\tau}T(t)$, then

$$\begin{aligned}\dot{\Psi}_3(t) &= b\int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi)M(t-\varphi)d\varphi - \varepsilon N(t) - \frac{\varpi\zeta}{\tau}T(t) \leq b\mathcal{H}_3\Omega_2 - \varepsilon N(t) - \frac{\varpi\zeta}{\tau}T(t) \\ &\leq b\Omega_2 - \varepsilon N(t) - \frac{\varpi\zeta}{\tau}T(t) \leq b\Omega_2 - \phi_3\left(N(t) + \frac{\varpi}{\tau}T(t)\right) = b\Omega_2 - \phi_3\Psi_3(t),\end{aligned}$$

where $\phi_3 = \min\{\varepsilon, \zeta\}$. It follows that, $\limsup_{t\to\infty}\Psi_3(t) \leq \Omega_4$, where $\Omega_4 = \dfrac{b\Omega_2}{\phi_3}$. Since $N(t) \geq 0$ and $T(t) \geq 0$, then $\limsup_{t\to\infty} N(t) \leq \Omega_4$ and $\limsup_{t\to\infty} T(t) \leq \Omega_5$, where $\Omega_5 = \frac{\tau}{\varpi}\Omega_4$. This complete the proof and insures the ultimate boundedness of all variables contained in the positively invariant region Ξ. $\square$

According to Proposition 3.1 we can show that the region

$$\begin{aligned}\Xi = &\Big\{(W,U,M,N,P,T) \in \mathcal{C}^6_{\geq 0} : \|W\| \leq \Omega_1, \|U\| \leq \Omega_1, \|M\| \leq \Omega_2, \|P\| \leq \Omega_3, \\ &\|N\| \leq \Omega_4, \|T\| \leq \Omega_5\Big\}\end{aligned}$$

is positively invariant with respect to system (2.1).

4. Equilibria

In this section, we derive two threshold parameters which guarantee the existence of the equilibria of the model. Let (W,U,M,N,P,T) be any equilibrium of system (2.1) satisfying the following equations:

$$0 = \rho - \alpha W - \eta_1 WN - \eta_2 WU - \eta_3 WM, \tag{4.1}$$
$$0 = \mathcal{H}_1\left(\eta_1 WN + \eta_2 WU + \eta_3 WM\right) - (\lambda + \gamma)\,U, \tag{4.2}$$
$$0 = \lambda\mathcal{H}_2 U - aM - \mu PM, \tag{4.3}$$
$$0 = b\mathcal{H}_3 M - \varepsilon N - \varpi TN, \tag{4.4}$$
$$0 = (\sigma M - \pi)\,P, \tag{4.5}$$
$$0 = (\tau N - \zeta)\,T. \tag{4.6}$$

The straightforward calculation finds that system (2.1) admits five equilibria.

(I) It is obvious that system (2.1) has an infection-free equilibrium, $Đ_0 = (W_0, 0, 0, 0, 0, 0)$, where $W_0 = \rho/\alpha$. This case describes the situation of healthy state where the HIV infection is absent.

(II) When $P = T = 0$, we have the chronic HIV infection equilibrium with inactive immune response, $Đ_1 = (W_1, U_1, M_1, N_1, 0, 0)$, where

$$\begin{aligned}W_1 &= \frac{a\varepsilon(\gamma+\lambda)}{\mathcal{H}_1\left[a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)\right]}, \\ U_1 &= \frac{a\varepsilon\alpha}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}\left[\frac{W_0\mathcal{H}_1\left\{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)\right\}}{a\varepsilon(\gamma+\lambda)} - 1\right], \\ M_1 &= \frac{\varepsilon\alpha\lambda\mathcal{H}_2}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}\left[\frac{W_0\mathcal{H}_1\left\{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)\right\}}{a\varepsilon(\gamma+\lambda)} - 1\right],\end{aligned}$$

$$N_1 = \frac{\alpha b\lambda\mathcal{H}_2\mathcal{H}_3}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}\left[\frac{W_0\mathcal{H}_1\left\{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)\right\}}{a\varepsilon\left(\gamma+\lambda\right)} - 1\right].$$

Therefore, $Đ_1$ exists when

$$\frac{W_0\mathcal{H}_1\left[a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)\right]}{a\varepsilon\left(\gamma+\lambda\right)} > 1.$$

At the equilibrium $Đ_1$ the chronic HIV infection persists while the immune response is unstimulated. The basic HIV reproduction number of model (2.1) is given as:

$$\Re_0 = \frac{W_0\mathcal{H}_1\left[a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)\right]}{a\varepsilon\left(\gamma+\lambda\right)} = \Re_{01} + \Re_{02} + \Re_{03},$$

where

$$\Re_{01} = \frac{W_0\lambda b\eta_1\mathcal{H}_1\mathcal{H}_2\mathcal{H}_3}{a\varepsilon\left(\gamma+\lambda\right)}, \qquad \Re_{02} = \frac{W_0\eta_2\mathcal{H}_1}{\gamma+\lambda}, \qquad \Re_{03} = \frac{W_0\lambda\eta_3\mathcal{H}_1\mathcal{H}_2}{a\left(\gamma+\lambda\right)}.$$

The parameter $\Re_0$ determines whether or not the infection will chronic. In fact, $\Re_{01}$ determines the average number of secondary HIV infected cells caused by free HIV particles due to VTC transmission, while $\Re_{02}$ and $\Re_{03}$ determine the average numbers of secondary HIV infected cells caused by silent and active HIV-infected CD4$^+$T cell, respectively, due to CTC transmission. In terms of $\Re_0$, we can write

$$\begin{aligned}
W_1 &= \frac{W_0}{\Re_0},\ U_1 = \frac{a\varepsilon\alpha}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}\left(\Re_0 - 1\right),\\
M_1 &= \frac{\varepsilon\alpha\lambda\mathcal{H}_2}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}\left(\Re_0 - 1\right),\\
N_1 &= \frac{\alpha b\lambda\mathcal{H}_2\mathcal{H}_3}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}\left(\Re_0 - 1\right).
\end{aligned} \tag{4.7}$$

(III) When $P \neq 0$, $T = 0$, we consider the chronic HIV infection equilibrium with only active CTL-mediated immune response, $Đ_2 = (W_2, U_2, M_2, N_2, P_2, 0)$, where

$$\begin{aligned}
W_2 &= \frac{\rho\varepsilon\sigma}{b\pi\eta_1\mathcal{H}_3 + \varepsilon\left(\pi\eta_3 + \alpha\sigma + \sigma\eta_2U_2\right)}, \quad M_2 = \frac{\pi}{\sigma},\\
N_2 &= \frac{b\pi\mathcal{H}_3}{\varepsilon\sigma}, \quad P_2 = \frac{a}{\mu}\left(\frac{\lambda\sigma\mathcal{H}_2U_2}{a\pi} - 1\right),
\end{aligned} \tag{4.8}$$

and U_2 satisfies the quadratic equation

$$\tilde{A}U_2^2 + \tilde{B}U_2 + \tilde{C} = 0, \tag{4.9}$$

where

$$\begin{aligned}
\tilde{A} &= \varepsilon\eta_2\sigma\left(\gamma+\lambda\right),\\
\tilde{B} &= \pi\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)\left(\gamma+\lambda\right) + \varepsilon\sigma\left[\alpha\left(\gamma+\lambda\right) - \eta_2\rho\mathcal{H}_1\right],\\
\tilde{C} &= -\pi\rho\mathcal{H}_1\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right).
\end{aligned} \tag{4.10}$$

Since $\tilde{A} > 0$ and $\tilde{C} < 0$, then $\tilde{B}^2 - 4\tilde{A}\tilde{C} > 0$ and there are two distinct real roots of Eq. (4.9). The positive root is given by

$$U_2 = \frac{-\tilde{B} + \sqrt{\tilde{B}^2 - 4\tilde{A}\tilde{C}}}{2\tilde{A}}. \tag{4.11}$$

It follows that $W_2 > 0$ and $P_2 > 0$ only when $\frac{\lambda\sigma\mathcal{H}_2 U_2}{a\pi} > 1$. We define the HIV specific CTL-mediated immunity reproductive ratio as follows:

$$\Re_1 = \frac{\lambda\sigma\mathcal{H}_2 U_2}{a\pi}.$$

Thus, $P_2 = \frac{a}{\mu}(\Re_1 - 1)$. Therefore, Đ$_2$ exists when $\Re_1 > 1$. The parameter $\Re_1$ determines whether or not the HIV-specific CTL-mediated immune response is stimulated.

(IV) When $P = 0$, $T \neq 0$, we consider the chronic HIV infection equilibrium with only active antibody immune response, Đ$_3 = (W_3, U_3, M_3, N_3, 0, T_3)$, where

$$W_3 = \frac{a\rho\tau}{a(\eta_1\zeta + \alpha\tau) + \tau(a\eta_2 + \lambda\eta_3\mathcal{H}_2)U_3}, \ M_3 = \frac{\lambda\mathcal{H}_2 U_3}{a}, \ N_3 = \frac{\zeta}{\tau},$$
$$T_3 = \frac{\varepsilon}{\varpi}\left(\frac{\tau b\lambda\mathcal{H}_2\mathcal{H}_3 U_3}{a\varepsilon\zeta} - 1\right), \tag{4.12}$$

and U_3 satisfies the quadratic equation

$$\hat{A}U_3^2 + \hat{B}U_3 + \hat{C} = 0,$$

where

$$\hat{A} = \tau(a\eta_2 + \lambda\eta_3\mathcal{H}_2)(\gamma + \lambda), \ \hat{B} = a(\gamma + \lambda)(\zeta\eta_1 + \alpha\tau) - \rho\tau\mathcal{H}_1(a\eta_2 + \lambda\eta_3\mathcal{H}_2),$$
$$\hat{C} = -a\rho\zeta\eta_1\mathcal{H}_1. \tag{4.13}$$

Since $\hat{A} > 0$ and $\hat{C} < 0$, then $\hat{B}^2 - 4\hat{A}\hat{C} > 0$ and there are two distinct real roots of Eq. (4.13). The positive root is given by

$$U_3 = \frac{-\hat{B} + \sqrt{\hat{B}^2 - 4\hat{A}\hat{C}}}{2\hat{A}}. \tag{4.14}$$

It follows that $W_3 > 0$, $M_3 > 0$ and $T_3 > 0$ only when $\dfrac{\tau b\lambda\mathcal{H}_2\mathcal{H}_3 U_3}{a\varepsilon\zeta} > 1$. The HIV-specific antibody immune response reproductive ratio is stated as:

$$\Re_2 = \frac{\tau b\lambda\mathcal{H}_2\mathcal{H}_3 U_3}{a\varepsilon\zeta}.$$

Thus, $T_3 = \dfrac{\varepsilon}{\varpi}(\Re_2 - 1)$. The parameter $\Re_2$ determines whether or not the HIV-specific antibody immune response is stimulated.

(V) When $P \neq 0$, $T \neq 0$, we consider the chronic HIV infection equilibrium with active CTL-mediated and antibody immune responses,
Đ$_4 = (W_4, U_4, M_4, N_4, P_4, T_4)$, where

$$W_4 = \frac{\rho\sigma\tau}{\eta_1\zeta\sigma + \pi\eta_3\tau + \sigma\tau(\alpha + \eta_2 U_4)}, \quad M_4 = \frac{\pi}{\sigma}, \quad N_4 = \frac{\zeta}{\tau},$$

$$P_4 = \frac{a}{\mu}\left(\frac{\lambda\sigma\mathcal{H}_2 U_4}{a\pi} - 1\right), \quad T_4 = \frac{\varepsilon}{\varpi}\left(\frac{\tau\pi b\mathcal{H}_3}{\sigma\varepsilon\zeta} - 1\right),$$

and U_4 satisfies the quadratic equation

$$\bar{A}U_4^2 + \bar{B}U_4 + \bar{C} = 0,$$

where

$$\bar{A} = \sigma\tau\eta_2(\gamma+\lambda), \; \bar{B} = (\gamma+\lambda)(\eta_1\zeta\sigma + \pi\eta_3\tau + \sigma\tau\alpha) - \rho\sigma\tau\eta_2\mathcal{H}_1,$$
$$\bar{C} = -\rho\mathcal{H}_1(\eta_1\zeta\sigma + \pi\eta_3\tau). \tag{4.15}$$

Since $\bar{A} > 0$ and $\bar{C} < 0$, then $\bar{B}^2 - 4\bar{A}\bar{C} > 0$ and there are two distinct real roots of Eq. (4.13). The positive root is given by

$$U_4 = \frac{-\bar{B} + \sqrt{\bar{B}^2 - 4\bar{A}\bar{C}}}{2\bar{A}}.$$

It follows that $W_4 > 0$, $P_4 > 0$ and $T_4 > 0$ only when $\frac{\lambda\sigma\mathcal{H}_2 U_4}{a\pi} > 1$ and $\frac{\tau\pi b\mathcal{H}_3}{\sigma\varepsilon\zeta} > 1$. The HIV-specific CTL-mediated immune competitive reproductive ratio and the HIV-specific antibody immune competitive reproductive ratio of system (2.1) are stated respectively as:

$$\Re_3 = \frac{\lambda\sigma\mathcal{H}_2 U_4}{a\pi}, \; \Re_4 = \frac{\tau\pi b\mathcal{H}_3}{\sigma\varepsilon\zeta}.$$

Thus, $P_4 = \frac{a}{\mu}(\Re_3 - 1)$, $T_4 = \frac{\varepsilon}{\varpi}(\Re_4 - 1)$. The parameters $\Re_3$ and $\Re_4$ determine whether or not the HIV-specific CTL-mediated and antibody immune responses are stimulated.

The threshold parameters are given as follows:

$$\Re_0 = \frac{W_0\mathcal{H}_1[a\varepsilon\eta_2 + \lambda\mathcal{H}_2(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3)]}{a\varepsilon(\gamma+\lambda)}, \quad \Re_1 = \frac{\lambda\sigma\mathcal{H}_2 U_2}{a\pi},$$
$$\Re_2 = \frac{\tau b\lambda\mathcal{H}_2\mathcal{H}_3 U_3}{a\varepsilon\zeta}, \quad \Re_3 = \frac{\lambda\sigma\mathcal{H}_2 U_4}{a\pi}, \quad \Re_4 = \frac{\tau\pi b\mathcal{H}_3}{\sigma\varepsilon\zeta}.$$

5. Global stability analysis

In this section we prove the global asymptotic stability of all equilibria by constructing Lyapunov functional following the method presented [34, 39]. Define $F(x) = x - 1 - \ln x$. Denote $(W,U,M,N,P,T) = (W(t),U(t),M(t),N(t),P(t),T(t))$ and $(W_\varphi, U_\varphi, M_\varphi, N_\varphi) = (W(t-\varphi), U(t-\varphi), M(t-\varphi), N(t-\varphi))$.

Theorem 5.1. *If $\Re_0 \le 1$, then $Đ_0$ is globally asymptotically stable (G.A.S).*

Proof. Constructing a Lyapunov functional candidate $\Theta_0(W,U,M,N,P,T)$ as:

$$\Theta_0 = W_0 F\left(\frac{W}{W_0}\right) + \frac{1}{\mathcal{H}_1}U + \frac{W_0(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3)}{a\varepsilon}M + \frac{\eta_1 W_0}{\varepsilon}N + \frac{\mu W_0(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3)}{\sigma a\varepsilon}P$$

$$+\frac{\varpi\eta_1 W_0}{\tau\varepsilon}T+\frac{1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\int_{t-\varphi}^{t}W(\varkappa)\left[\eta_1 N(\varkappa)+\eta_2 U(\varkappa)+\eta_3 M(\varkappa)\right]d\varkappa d\varphi$$
$$+\frac{\lambda W_0\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\int_{t-\varphi}^{t}U(\varkappa)d\varkappa d\varphi+\frac{b\eta_1 W_0}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\int_{t-\varphi}^{t}M(\varkappa)d\varkappa d\varphi.$$

It is seen that, $\Theta_0(W,U,M,N,P,T)>0$ for all $W,U,M,N,P,T>0$, and Θ_0 has a global minimum at $Đ_0$. We calculate $\frac{d\Theta_0}{dt}$ along the solutions of model (2.1) as:

$$\begin{aligned}
\frac{d\Theta_0}{dt}=&\left(1-\frac{W_0}{W}\right)\left(\rho-\alpha W-\eta_1 WN-\eta_2 WU-\eta_3 WM\right)\\
&+\frac{1}{\mathcal{H}_1}\left[\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)W_\varphi\left\{\eta_1 N_\varphi+\eta_2 U_\varphi+\eta_3 M_\varphi\right\}d\varphi-(\lambda+\gamma)U\right]\\
&+\frac{W_0\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}\left[\lambda\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)U_\varphi d\varphi-aM-\mu PM\right]\\
&+\frac{\eta_1 W_0}{\varepsilon}\left[b\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)M_\varphi d\varphi-\varepsilon N-\varpi TN\right]\\
&+\frac{\mu W_0\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}\left(\sigma PM-\pi P\right)+\frac{\varpi\eta_1 W_0}{\tau\varepsilon}\left(\tau TN-\zeta T\right)\\
&+\frac{1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[W\left\{\eta_1 N+\eta_2 U+\eta_3 M\right\}-W_\varphi\left\{\eta_1 N_\varphi+\eta_2 U_\varphi+\eta_3 M_\varphi\right\}\right]d\varphi\\
&+\frac{\lambda W_0\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\left[U-U_\varphi\right]d\varphi+\frac{b\eta_1 W_0}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\left[M-M_\varphi\right]d\varphi.
\end{aligned}\tag{5.1}$$

Collecting terms of Eq. (5.1), we get

$$\begin{aligned}
\frac{d\Theta_0}{dt}=&\left(1-\frac{W_0}{W}\right)(\rho-\alpha W)+\eta_2 W_0 U-\frac{\lambda+\gamma}{\mathcal{H}_1}U+\frac{\lambda W_0\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}U\\
&-\frac{\mu\pi W_0\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}P-\frac{\varpi\zeta\eta_1 W_0}{\tau\varepsilon}T.
\end{aligned}$$

Using $W_0=\rho/\alpha$, we obtain

$$\begin{aligned}
\frac{d\Theta_0}{dt}=&-\alpha\frac{(W-W_0)^2}{W}+\frac{\lambda+\gamma}{\mathcal{H}_1}\left[\frac{W_0\mathcal{H}_1\left\{a\varepsilon\eta_2+\lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)\right\}}{a\varepsilon(\lambda+\gamma)}-1\right]U\\
&-\frac{\mu\pi W_0\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}P-\frac{\varpi\zeta\eta_1 W_0}{\tau\varepsilon}T.\\
=&-\alpha\frac{(W-W_0)^2}{W}+\frac{\lambda+\gamma}{\mathcal{H}_1}\left(\Re_0-1\right)U-\frac{\mu\pi W_0\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}P-\frac{\varpi\zeta\eta_1 W_0}{\tau\varepsilon}T.
\end{aligned}$$

Therefore, $\frac{d\Theta_0}{dt}\leq 0$ for all $W,U,M,N,P,T>0$. Moreover, $\frac{d\Theta_0}{dt}=0$ when $W=W_0$, $P=T=0$ and $(\Re_0-1)U=0$. Let $\Upsilon_0=\left\{(W,U,M,N,P,T):\frac{d\Theta_0}{dt}=0\right\}$ and Υ_0'

be the largest invariant subset of Υ_0. The solutions of system (2.1) converge to $\Upsilon_0^{'}$ [31]. We have two cases:

- $\Re_0 = 1$: In this case we have $\frac{d\Theta_0}{dt} = 0$ occurs at $W = W_0$ and $P = T = 0$. The set $\Upsilon_0^{'}$ contains elements which satisfy $W = W_0$ and $P = T = 0$, then $\dot{W} = 0$ and from the first equation of system (2.1) we get

$$0 = \dot{W}(t) = \rho - \alpha W_0 - W_0\left[\eta_1 N(t) + \eta_2 U(t) + \eta_3 M(t)\right].$$

  Using $W_0 = \rho/\alpha$ we get

$$\eta_1 N(t) + \eta_2 U(t) + \eta_3 M(t) = 0.$$

  The nonnegativity of N, U and M implies that $N(t) = U(t) = M(t) = 0$ for all t. Therefore, $\Upsilon_0^{'} = \{Đ_0\}$ and by applying LaSalle's invariance principle we get that $Đ_0$ is G.A.S [31].

- $\Re_0 < 1$: In this case we have $\frac{d\Theta_0}{dt} = 0$ occurs at $W = W_0$ and $U(t) = P(t) = T(t) = 0$. Hence the set $\Upsilon_0^{'}$ contains elements which satisfy $W(t) = W_0$, $U(t) = P(t) = T(t) = 0$ and

$$\dot{M}(t) = -aM(t), \tag{5.2}$$

$$\dot{N}(t) = b\int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) M_\varphi d\varphi - \varepsilon N(t). \tag{5.3}$$

  Following the method presented in [31] we define a Lyapunov function as:

$$\tilde{\Theta}_0 = M(t) + \frac{a}{2b\mathcal{H}_3} N(t) + \frac{a}{2\mathcal{H}_3}\int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi)\int_{t-\varphi}^{t} M(\varkappa) d\varkappa d\varphi.$$

  Therefore, the time derivative of $\tilde{\Theta}_0$ along the solutions of system (5.2)-(5.3) can be calculated as follows:

$$\frac{d\tilde{\Theta}_0}{dt} = -\frac{a}{2}\left(M(t) + \frac{\varepsilon}{b\mathcal{H}_3} N(t)\right) \le 0.$$

  Clearly $\frac{d\tilde{\Theta}_0}{dt} = 0$ if and only if $M(t) = N(t) = 0$ for all t. Let $\Upsilon_0^{''} = \left\{(W, U, M, N, P, T) \in \Upsilon_0^{'} : \frac{d\tilde{\Theta}_0}{dt} = 0\right\}$ then

$$\Upsilon_0^{''} = \left\{(W, U, M, N, P, T) \in \Upsilon_0^{'} : W = W_0,\ U = M = N = P = T = 0\right\} = \{Đ_0\}.$$

  Hence, all solutions trajectories approach $Đ_0$ and this means that $Đ_0$ is G.A.S.

□

Lemma 5.1. *(i) If $\Re_1 \le 1$, then $M_1 \le M_2$.*

(ii) If $\Re_2 \le 1$, then $N_1 \le N_3$.

Proof. (i) Let $\Re_1 \leq 1$, hence $\frac{\lambda\sigma\mathcal{H}_2 U_2}{a\pi} \leq 1$, where U_2 is given by Eq. (4.11),

$$\begin{aligned} U_2 \leq \frac{a\pi}{\lambda\sigma\mathcal{H}_2} &\Longrightarrow \frac{-\tilde{B}+\sqrt{\tilde{B}^2-4\tilde{A}\tilde{C}}}{2\tilde{A}} \leq \frac{a\pi}{\lambda\sigma\mathcal{H}_2} \\ &\Longrightarrow \sqrt{\tilde{B}^2-4\tilde{A}\tilde{C}} \leq \frac{2\tilde{A}a\pi+\lambda\sigma\mathcal{H}_2\tilde{B}}{\lambda\sigma\mathcal{H}_2} \\ &\Longrightarrow \left(\frac{2\tilde{A}a\pi+\lambda\sigma\mathcal{H}_2\tilde{B}}{\lambda\sigma\mathcal{H}_2}\right)^2 + 4\tilde{A}\tilde{C} - \tilde{B}^2 \geq 0. \end{aligned}$$

Using Eqs. (4.7), (4.8) and (4.10), we obtain

$$\frac{4a\pi\varepsilon\eta_2\sigma(\gamma+\lambda)^2\left[a\varepsilon\eta_2+\lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)\right]}{\lambda^2\mathcal{H}_2^2}\left(M_2-M_1\right) \geq 0.$$

Hence, $M_1 \leq M_2$.

(ii) Let $\Re_2 \leq 1$, hence $\dfrac{\tau b\lambda\mathcal{H}_2\mathcal{H}_3 U_3}{a\varepsilon\zeta} \leq 1$, where U_3 is given by Eq. (4.14).

$$\begin{aligned} L_3 \leq \frac{a\varepsilon\zeta}{\tau b\lambda\mathcal{H}_2\mathcal{H}_3} &\Longrightarrow \frac{-\hat{B}+\sqrt{\hat{B}^2-4\hat{A}\hat{C}}}{2\hat{A}} \leq \frac{a\varepsilon\zeta}{\tau b\lambda\mathcal{H}_2\mathcal{H}_3} \\ &\Longrightarrow \sqrt{\hat{B}^2-4\hat{A}\hat{C}} \leq \frac{2\hat{A}a\varepsilon\zeta+\tau b\lambda\mathcal{H}_2\mathcal{H}_3\hat{B}}{\tau b\lambda\mathcal{H}_2\mathcal{H}_3} \\ &\Longrightarrow \left(\frac{2\hat{A}a\varepsilon\zeta+\tau b\lambda\mathcal{H}_2\mathcal{H}_3\hat{B}}{\tau b\lambda\mathcal{H}_2\mathcal{H}_3}\right)^2 + 4\hat{A}\hat{C} - \hat{B}^2 \geq 0. \end{aligned}$$

Using Eqs. (4.7), (4.12) and (4.13), we obtain

$$\frac{4a^2\varepsilon\zeta\tau\left(a\eta_2+\lambda\eta_3\mathcal{H}_2\right)\left[a\varepsilon\eta_2+\lambda\mathcal{H}_2(b\eta_1\mathcal{H}_3+\varepsilon\eta_3)\right](\gamma+\lambda)^2}{b^2\lambda^2\mathcal{H}_2^2\mathcal{H}_3^2}\left(N_3-N_1\right) \geq 0.$$

Hence, $N_1 \leq N_3$. □

We consider the following equalities to be used in the proceeding theorems:

$$\begin{aligned} &\ln\left(\frac{W_\varphi N_\varphi}{WN}\right) = \ln\left(\frac{W_\varphi N_\varphi U_n}{W_n N_n U}\right) + \ln\left(\frac{W_n}{W}\right) + \ln\left(\frac{N_n U}{N U_n}\right), \\ &\ln\left(\frac{W_\varphi U_\varphi}{WU}\right) = \ln\left(\frac{W_\varphi U_\varphi}{W_n U}\right) + \ln\left(\frac{W_n}{W}\right), \\ &\ln\left(\frac{W_\varphi M_\varphi}{WM}\right) = \ln\left(\frac{W_\varphi M_\varphi U_n}{W_n M_n U}\right) + \ln\left(\frac{W_n}{W}\right) + \ln\left(\frac{M_n U}{M U_n}\right), \\ &\ln\left(\frac{U_\varphi}{U}\right) = \ln\left(\frac{U_\varphi M_n}{U_n M}\right) + \ln\left(\frac{U_n M}{U M_n}\right), \\ &\ln\left(\frac{M_\varphi}{M}\right) = \ln\left(\frac{M_\varphi N_n}{M_n N}\right) + \ln\left(\frac{M_n N}{M N_n}\right). \end{aligned} \tag{5.4}$$

Theorem 5.2. *Suppose that $\Re_0 > 1$, $\Re_1 \leq 1$ and $\Re_2 \leq 1$, then $Đ_1$ is G.A.S.*

Proof. We define a functional $\Theta_1(W,U,M,N,P,T)$ as:

$$\begin{aligned}\Theta_1 =& W_1 F\left(\frac{W}{W_1}\right)+\frac{1}{\mathcal{H}_1}U_1 F\left(\frac{U}{U_1}\right)+\frac{W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}M_1 F\left(\frac{M}{M_1}\right)\\ &+\frac{\eta_1 W_1}{\varepsilon}N_1 F\left(\frac{N}{N_1}\right)+\frac{\mu W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}P+\frac{\varpi\eta_1 W_1}{\tau\varepsilon}T\\ &+\frac{\eta_1 W_1 N_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\int_{t-\varphi}^{t}F\left(\frac{W(\varkappa)N(\varkappa)}{W_1N_1}\right)d\varkappa d\varphi\\ &+\frac{\eta_2 W_1 U_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\int_{t-\varphi}^{t}F\left(\frac{W(\varkappa)U(\varkappa)}{W_1U_1}\right)d\varkappa d\varphi\\ &+\frac{\eta_3 W_1 M_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\int_{t-\varphi}^{t}F\left(\frac{W(\varkappa)M(\varkappa)}{W_1M_1}\right)d\varkappa d\varphi\\ &+\frac{\lambda W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)U_1}{a\varepsilon}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\int_{t-\varphi}^{t}F\left(\frac{U(\varkappa)}{U_1}\right)d\varkappa d\varphi\\ &+\frac{b\eta_1 W_1 M_1}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\int_{t-\varphi}^{t}F\left(\frac{M(\varkappa)}{M_1}\right)d\varkappa d\varphi.\end{aligned}$$

Calculating $\frac{d\Theta_1}{dt}$ as:

$$\begin{aligned}\frac{d\Theta_1}{dt} =& \left(1-\frac{W_1}{W}\right)\left(\rho-\alpha W-\eta_1 WN-\eta_2 WU-\eta_3 WM\right)\\ &+\frac{1}{\mathcal{H}_1}\left(1-\frac{U_1}{U}\right)\left[\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)W_\varphi\left\{\eta_1 N_\varphi+\eta_2 U_\varphi+\eta_3 M_\varphi\right\}d\varphi-(\lambda+\gamma)U\right]\\ &+\frac{W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}\left(1-\frac{M_1}{M}\right)\left[\lambda\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)U_\varphi d\varphi-aM-\mu PM\right]\\ &+\frac{\eta_1 W_1}{\varepsilon}\left(1-\frac{N_1}{N}\right)\left[b\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)M_\varphi d\varphi-\varepsilon N-\varpi TN\right]\\ &+\frac{\mu W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}\left(\sigma PM-\pi P\right)+\frac{\varpi\eta_1 W_1}{\tau\varepsilon}\left(\tau TN-\zeta T\right)\\ &+\frac{\eta_1 W_1 N_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WN}{W_1N_1}-\frac{W_\varphi N_\varphi}{W_1N_1}+\ln\left(\frac{W_\varphi N_\varphi}{WN}\right)\right]d\varphi\\ &+\frac{\eta_2 W_1 U_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WU}{W_1U_1}-\frac{W_\varphi U_\varphi}{W_1U_1}+\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)\right]d\varphi\\ &+\frac{\eta_3 W_1 M_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WM}{W_1M_1}-\frac{W_\varphi M_\varphi}{W_1M_1}+\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)\right]d\varphi\end{aligned}$$

$$+\frac{\lambda W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)U_1}{a\varepsilon}\int\limits_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\left[\frac{U}{U_1}-\frac{U_\varphi}{U_1}+\ln\left(\frac{U_\varphi}{U}\right)\right]d\varphi$$

$$+\frac{b\eta_1 W_1 M_1}{\varepsilon}\int\limits_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\left[\frac{M}{M_1}-\frac{M_\varphi}{M_1}+\ln\left(\frac{M_\varphi}{M}\right)\right]d\varphi. \tag{5.5}$$

Collecting terms of Eq. (5.5), we derive

$$\begin{aligned}\frac{d\Theta_1}{dt}=&\left(1-\frac{W_1}{W}\right)(\rho-\alpha W)+\eta_2W_1U-\frac{\lambda+\gamma}{\mathcal{H}_1}U-\frac{\eta_1}{\mathcal{H}_1}\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi N_\varphi U_1}{U}d\varphi\\
&-\frac{\eta_2}{\mathcal{H}_1}\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi U_\varphi U_1}{U}d\varphi-\frac{\eta_3}{\mathcal{H}_1}\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi M_\varphi U_1}{U}d\varphi\\
&+\frac{\lambda+\gamma}{\mathcal{H}_1}U_1-\frac{\lambda W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}\int\limits_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\frac{U_\varphi M_1}{M}d\varphi+\frac{W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon}M_1\\
&+\frac{\mu W_1(b\eta_1\mathcal{H}_3+\varepsilon\eta_3)}{a\varepsilon}PM_1-\frac{b\eta_1W_1}{\varepsilon}\int\limits_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\frac{M_\varphi N_1}{N}d\varphi+\eta_1W_1N_1+\frac{\varpi\eta_1W_1}{\varepsilon}TN_1\\
&-\frac{\mu\pi W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}P-\frac{\varpi\zeta\eta_1W_1}{\tau\varepsilon}T+\frac{\eta_1W_1N_1}{\mathcal{H}_1}\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi N_\varphi}{WN}\right)d\varphi\\
&+\frac{\eta_2W_1U_1}{\mathcal{H}_1}\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)d\varphi+\frac{\eta_3W_1M_1}{\mathcal{H}_1}\int\limits_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)d\varphi\\
&+\frac{\lambda W_1\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}U+\frac{\lambda W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)U_1}{a\varepsilon}\int\limits_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\ln\left(\frac{U_\varphi}{U}\right)d\varphi\\
&+\frac{b\eta_1W_1M_1}{\varepsilon}\int\limits_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\ln\left(\frac{M_\varphi}{M}\right)d\varphi.\end{aligned}\tag{5.6}$$

Using the equilibrium conditions for $Đ_1$, we get

$$\begin{aligned}&\rho=\alpha W_1+\eta_1W_1N_1+\eta_2W_1U_1+\eta_3W_1M_1,\\
&\eta_1W_1N_1+\eta_2W_1U_1+\eta_3W_1M_1=\frac{\lambda+\gamma}{\mathcal{H}_1}U_1,\\
&\frac{\lambda\mathcal{H}_2U_1}{a}=M_1,\qquad N_1=\frac{b\mathcal{H}_3M_1}{\varepsilon}.\end{aligned}\tag{5.7}$$

In addition,

$$\eta_1W_1N_1+\eta_3W_1M_1=\frac{W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon}M_1=\frac{\lambda W_1\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}U_1.$$

Then, we obtain

$$\frac{d\Theta_1}{dt}=\left(1-\frac{W_1}{W}\right)(\alpha W_1-\alpha W)+\left(\eta_1W_1N_1+\eta_2W_1U_1+\eta_3W_1M_1\right)\left(1-\frac{W_1}{W}\right)$$

$$
\begin{aligned}
&- \frac{\eta_1 W_1 N_1}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \frac{W_\varphi N_\varphi U_1}{W_1 N_1 U} d\varphi - \frac{\eta_2 W_1 U_1}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \frac{W_\varphi U_\varphi}{W_1 U} d\varphi \\
&- \frac{\eta_3 W_1 M_1}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \frac{W_\varphi M_\varphi U_1}{W_1 M_1 U} d\varphi + \eta_1 W_1 N_1 + \eta_2 W_1 U_1 + \eta_3 W_1 M_1 \\
&- \frac{\eta_1 W_1 N_1 + \eta_3 W_1 M_1}{\mathcal{H}_2} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) \frac{U_\varphi M_1}{U_1 M} d\varphi + \eta_1 W_1 N_1 + \eta_3 W_1 M_1 \\
&+ \frac{\mu W_1 \left(b\eta_1 \mathcal{H}_3 + \varepsilon \eta_3\right)}{a\varepsilon} P M_1 - \frac{\eta_1 W_1 N_1}{\mathcal{H}_3} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) \frac{M_\varphi N_1}{M_1 N} d\varphi + \eta_1 W_1 N_1 \\
&+ \frac{\varpi \eta_1 W_1}{\varepsilon} T N_1 - \frac{\mu \pi W_1 \left(b\eta_1 \mathcal{H}_3 + \varepsilon \eta_3\right)}{\sigma a \varepsilon} P - \frac{\varpi \zeta \eta_1 W_1}{\tau \varepsilon} T \\
&+ \frac{\eta_1 W_1 N_1}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \ln\left(\frac{W_\varphi N_\varphi}{W N}\right) d\varphi + \frac{\eta_2 W_1 U_1}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \ln\left(\frac{W_\varphi U_\varphi}{W U}\right) d\varphi \\
&+ \frac{\eta_3 W_1 M_1}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \ln\left(\frac{W_\varphi M_\varphi}{W M}\right) d\varphi + \frac{\eta_1 W_1 N_1 + \eta_3 W_1 M_1}{\mathcal{H}_2} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) \ln\left(\frac{U_\varphi}{U}\right) d\varphi \\
&+ \frac{\eta_1 W_1 N_1}{\mathcal{H}_3} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) \ln\left(\frac{M_\varphi}{M}\right) d\varphi.
\end{aligned}
$$

Using the equalities given by (5.4) in case of $n = 1$, we get

$$
\begin{aligned}
\frac{d\Theta_1}{dt} = &- \alpha \frac{(W - W_1)^2}{W} - \left(\eta_1 W_1 N_1 + \eta_2 W_1 U_1 + \eta_3 W_1 M_1\right) \left[\frac{W_1}{W} - 1 - \ln\left(\frac{W_1}{W}\right)\right] \\
&- \frac{\eta_1 W_1 N_1}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[\frac{W_\varphi N_\varphi U_1}{W_1 N_1 U} - 1 - \ln\left(\frac{W_\varphi N_\varphi U_1}{W_1 N_1 U}\right)\right] d\varphi \\
&- \frac{\eta_2 W_1 U_1}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[\frac{W_\varphi U_\varphi}{W_1 U} - 1 - \ln\left(\frac{W_\varphi U_\varphi}{W_1 U}\right)\right] d\varphi \\
&- \frac{\eta_3 W_1 M_1}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[\frac{W_\varphi M_\varphi U_1}{W_1 M_1 U} - 1 - \ln\left(\frac{W_\varphi M_\varphi U_1}{W_1 M_1 U}\right)\right] d\varphi \\
&- \frac{\eta_1 W_1 N_1 + \eta_3 W_1 M_1}{\mathcal{H}_2} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) \left[\frac{U_\varphi M_1}{U_1 M} - 1 - \ln\left(\frac{U_\varphi M_1}{U_1 M}\right)\right] d\varphi \\
&- \frac{\eta_1 W_1 N_1}{\mathcal{H}_3} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) \left[\frac{M_\varphi N_1}{M_1 N} - 1 - \ln\left(\frac{M_\varphi N_1}{M_1 N}\right)\right] d\varphi \\
&+ \frac{\mu W_1 \left(b\eta_1 \mathcal{H}_3 + \varepsilon \eta_3\right)}{a\varepsilon} \left(M_1 - \frac{\pi}{\sigma}\right) P + \frac{\varpi \eta_1 W_1}{\varepsilon} \left(N_1 - \frac{\zeta}{\tau}\right) T. \qquad (5.8)
\end{aligned}
$$

Therefore, Eq. (5.8) becomes

$$\begin{aligned}\frac{d\Theta_1}{dt} =& -\alpha\frac{(W-W_1)^2}{W} - \frac{\eta_1 W_1 N_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi N_\varphi U_1}{W_1 N_1 U}\right)+F\left(\frac{W_1}{W}\right)\right]d\varphi \\ & - \frac{\eta_2 W_1 U_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi U_\varphi}{W_1 U}\right)+F\left(\frac{W_1}{W}\right)\right]d\varphi \\ & - \frac{\eta_3 W_1 M_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi M_\varphi U_1}{W_1 M_1 U}\right)+F\left(\frac{W_1}{W}\right)\right]d\varphi \\ & - \frac{\eta_1 W_1 N_1+\eta_3 W_1 M_1}{\mathcal{H}_2}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)F\left(\frac{U_\varphi M_1}{U_1 M}\right)d\varphi \\ & - \frac{\eta_1 W_1 N_1}{\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)F\left(\frac{M_\varphi N_1}{M_1 N}\right)d\varphi + \frac{\mu W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}\left(M_1-M_2\right)P \\ & + \frac{\varpi\eta_1 W_1}{\varepsilon}\left(N_1-N_3\right)T.\end{aligned}$$

Using Lemma 5.1 and since $M_1 \le M_2$ and $N_1 \le N_3$ then $\frac{d\Theta_1}{dt} \le 0$ for all $W,U,M,N,P,T > 0$ with equality holding when

$$\left(M_1-M_2\right)P = 0,\ \left(N_1-N_3\right)T = 0, \tag{5.9}$$

$$\frac{W}{W_1} = \frac{W_\varphi N_\varphi U_1}{W_1 N_1 U} = \frac{W_\varphi U_\varphi}{W_1 U} = \frac{W_\varphi M_\varphi U_1}{W_1 M_1 U} = \frac{U_\varphi M_1}{U_1 M} = \frac{M_\varphi N_1}{M_1 N} = 1,\ t\in[0,\kappa]. \tag{5.10}$$

Let Υ_1' be the largest invariant subset of $\Upsilon_1 = \left\{(W,U,M,N,P,T) : \frac{d\Theta_1}{dt} = 0\right\}$. The trajectories of system (2.1) converge to Υ_1'. The set Υ_1 is invariant and contains elements satisfying Eqs. (5.9) and (5.10). Eq. (5.10) is satisfied when $W(t) = W_1$, $U(t) = U_1$, $M(t) = M_1$ and $N(t) = N_1$. Now we show that each element in Υ_1 satisfies $P(t) = T(t) = 0$ for all t. From Eq. (5.9) we have four cases:

- $M_1 = M_2$ and $N_1 = N_3$: From the third and fourth equations of system (2.1) we get

$$0 = \dot{M}(t) = \lambda\mathcal{H}_2 U_1 - aM_1 - \mu P(t)M_1, \tag{5.11}$$

$$0 = \dot{N}(t) = b\mathcal{H}_3 M_1 - \varepsilon N_1 - \varpi T(t)N_1. \tag{5.12}$$

  From the equilibrium conditions (5.7) we get $P(t) = T(t) = 0$ for all t.

- $M_1 = M_2$ and $N_1 < N_3$. From Eq. (5.9) we obtain $T(t) = 0$ for all t. Moreover, from conditions (5.7) and Eq. (5.11) we obtain $P(t) = 0$ for all t.
- $M_1 < M_2$ and $N_1 = N_3$. Eq. (5.9) gives $P(t) = 0$ for all t. Moreover, from conditions (5.7) and Eq. (5.12) we obtain $T(t) = 0$ for all t.
- $M_1 < M_2$ and $N_1 < N_3$. Eq. (5.9) implies $T(t) = P(t) = 0$ for all t.

Then, $\Upsilon_1' = \{Đ_1\}$ and $Đ_1$ is G.A.S using LaSalle's invariance principle. □

Theorem 5.3. *For system (2.1), suppose that $\Re_1 > 1$ and $\Re_4 \le 1$, then $Đ_2$ is G.A.S.*

Proof. Define a function $\Theta_2(W, U, M, N, P, T)$ as:

$$\begin{aligned}
\Theta_2 =& W_2 F\left(\frac{W}{W_2}\right) + \frac{1}{\mathcal{H}_1} U_2 F\left(\frac{U}{U_2}\right) + \frac{W_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}{\varepsilon\left(a + \mu P_2\right)} M_2 F\left(\frac{M}{M_2}\right) \\
&+ \frac{\eta_1 W_2}{\varepsilon} N_2 F\left(\frac{N}{N_2}\right) + \frac{\mu W_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}{\sigma\varepsilon\left(a + \mu P_2\right)} P_2 F\left(\frac{P}{P_2}\right) + \frac{\varpi\eta_1 W_2}{\tau\varepsilon} T \\
&+ \frac{\eta_1 W_2 N_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \int_{t-\varphi}^{t} F\left(\frac{W(\varkappa)N(\varkappa)}{W_2 N_2}\right) d\varkappa d\varphi \\
&+ \frac{\eta_2 W_2 U_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \int_{t-\varphi}^{t} F\left(\frac{W(\varkappa)U(\varkappa)}{W_2 U_2}\right) d\varkappa d\varphi \\
&+ \frac{\eta_3 W_2 M_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \int_{t-\varphi}^{t} F\left(\frac{W(\varkappa)M(\varkappa)}{W_2 M_2}\right) d\varkappa d\varphi \\
&+ \frac{\lambda W_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right) U_2}{\varepsilon\left(a + \mu P_2\right)} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) \int_{t-\varphi}^{t} F\left(\frac{U(\varkappa)}{U_2}\right) d\varkappa d\varphi \\
&+ \frac{b\eta_1 W_2 M_2}{\varepsilon} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) \int_{t-\varphi}^{t} F\left(\frac{M(\varkappa)}{M_2}\right) d\varkappa d\varphi.
\end{aligned}$$

We calculate $\frac{d\Theta_2}{dt}$ as:

$$\begin{aligned}
\frac{d\Theta_2}{dt} =& \left(1 - \frac{W_2}{W}\right)\left(\rho - \alpha W - \eta_1 W N - \eta_2 W U - \eta_3 W M\right) \\
&+ \frac{1}{\mathcal{H}_1}\left(1 - \frac{U_2}{U}\right)\left[\int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) W_\varphi \left\{\eta_1 N_\varphi + \eta_2 U_\varphi + \eta_3 M_\varphi\right\} d\varphi - (\lambda + \gamma) U\right] \\
&+ \frac{W_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}{\varepsilon\left(a + \mu P_2\right)}\left(1 - \frac{M_2}{M}\right)\left[\lambda \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) U_\varphi d\varphi - aM - \mu P M\right] \\
&+ \frac{\eta_1 W_2}{\varepsilon}\left(1 - \frac{N_2}{N}\right)\left[b \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) M_\varphi d\varphi - \varepsilon N - \varpi T N\right] \\
&+ \frac{\mu W_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}{\sigma\varepsilon\left(a + \mu P_2\right)}\left(1 - \frac{P_2}{P}\right)\left(\sigma P M - \pi P\right) + \frac{\varpi\eta_1 W_2}{\tau\varepsilon}\left(\tau T N - \zeta T\right) \\
&+ \frac{\eta_1 W_2 N_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi)\left[\frac{WN}{W_2 N_2} - \frac{W_\varphi N_\varphi}{W_2 N_2} + \ln\left(\frac{W_\varphi N_\varphi}{WN}\right)\right] d\varphi \\
&+ \frac{\eta_2 W_2 U_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi)\left[\frac{WU}{W_2 U_2} - \frac{W_\varphi U_\varphi}{W_2 U_2} + \ln\left(\frac{W_\varphi U_\varphi}{WU}\right)\right] d\varphi
\end{aligned}$$

$$+\frac{\eta_3 W_2 M_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WM}{W_2M_2}-\frac{W_\varphi M_\varphi}{W_2M_2}+\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)\right]d\varphi$$
$$+\frac{\lambda W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)U_2}{\varepsilon\left(a+\mu P_2\right)}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\left[\frac{U}{U_2}-\frac{U_\varphi}{U_2}+\ln\left(\frac{U_\varphi}{U}\right)\right]d\varphi$$
$$+\frac{b\eta_1 W_2 M_2}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\left[\frac{M}{M_2}-\frac{M_\varphi}{M_2}+\ln\left(\frac{M_\varphi}{M}\right)\right]d\varphi. \tag{5.13}$$

Collecting terms of Eq. (5.13), we derive

$$\begin{aligned}\frac{d\Theta_2}{dt}=&\left(1-\frac{W_2}{W}\right)(\rho-\alpha W)+\eta_2W_2U+\eta_3W_2M-\frac{\lambda+\gamma}{\mathcal{H}_1}U\\
&-\frac{\eta_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi N_\varphi U_2}{U}d\varphi\\
&-\frac{\eta_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi U_\varphi U_2}{U}d\varphi-\frac{\eta_3}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi M_\varphi U_2}{U}d\varphi\\
&+\frac{\lambda+\gamma}{\mathcal{H}_1}U_2-\frac{aW_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}M-\frac{\lambda W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\frac{U_\varphi M_2}{M}d\varphi\\
&+\frac{aW_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}M_2+\frac{\mu W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}PM_2\\
&-\frac{b\eta_1W_2}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\frac{M_\varphi N_2}{N}d\varphi+\eta_1W_2N_2+\frac{\varpi\eta_1W_2}{\varepsilon}TN_2-\frac{\mu\pi W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma\varepsilon\left(a+\mu P_2\right)}P\\
&-\frac{\mu W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}P_2M+\frac{\mu\pi W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma\varepsilon\left(a+\mu P_2\right)}P_2-\frac{\varpi\zeta\eta_1W_2}{\tau\varepsilon}T\\
&+\frac{\eta_1W_2N_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi N_\varphi}{WN}\right)d\varphi+\frac{\eta_2W_2U_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)d\varphi\\
&+\frac{\eta_3W_2M_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)d\varphi+\frac{\lambda W_2\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}U\\
&+\frac{\lambda W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)U_2}{\varepsilon\left(a+\mu P_2\right)}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\ln\left(\frac{U_\varphi}{U}\right)d\varphi\\
&+\frac{b\mathcal{H}_3\eta_1W_2}{\varepsilon}M+\frac{b\eta_1W_2M_2}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\ln\left(\frac{M_\varphi}{M}\right)d\varphi.\end{aligned}$$

Using the equilibrium conditions for $Ð_2$:

$$\rho=\alpha W_2+\eta_1W_2N_2+\eta_2W_2U_2+\eta_3W_2M_2,$$
$$\eta_1W_2N_2+\eta_2W_2U_2+\eta_3W_2M_2=\frac{\lambda+\gamma}{\mathcal{H}_1}U_2,$$

$$\lambda \mathcal{H}_2 U_2 = (a + \mu P_2)\, M_2, \qquad M_2 = \frac{\pi}{\sigma}, \qquad N_2 = \frac{b\mathcal{H}_3}{\varepsilon} M_2. \tag{5.14}$$

Further,

$$\eta_1 W_2 N_2 + \eta_3 W_2 M_2 = \frac{W_2\,(b\eta_1 \mathcal{H}_3 + \varepsilon\eta_3)}{\varepsilon} M_2 = \frac{\lambda W_2 \mathcal{H}_2\,(b\eta_1 \mathcal{H}_3 + \varepsilon\eta_3)}{\varepsilon\,(a + \mu P_2)} U_2.$$

Therefore, we obtain

$$\begin{aligned}
\frac{d\Theta_2}{dt} = &\left(1 - \frac{W_2}{W}\right)(\alpha W_2 - \alpha W) + (\eta_1 W_2 N_2 + \eta_2 W_2 U_2 + \eta_3 W_2 M_2)\left(1 - \frac{W_2}{W}\right) \\
&- \frac{\eta_1 W_2 N_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \frac{W_\varphi N_\varphi U_2}{W_2 N_2 U} d\varphi - \frac{\eta_2 W_2 U_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \frac{W_\varphi U_\varphi}{W_2 U} d\varphi \\
&- \frac{\eta_3 W_2 M_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \frac{W_\varphi M_\varphi U_2}{W_2 M_2 U} d\varphi + \eta_1 W_2 N_2 + \eta_2 W_2 U_2 + \eta_3 W_2 M_2 \\
&- \frac{\eta_1 W_2 N_2 + \eta_3 W_2 M_2}{\mathcal{H}_2} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) \frac{U_\varphi M_2}{U_2 M} d\varphi + \eta_1 W_2 N_2 + \eta_3 W_2 M_2 \\
&- \frac{\eta_1 W_2 N_2}{\mathcal{H}_3} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) \frac{M_\varphi N_2}{M_2 N} d\varphi + \eta_1 W_2 N_2 + \frac{\varpi \eta_1 W_2}{\varepsilon} T N_2 - \frac{\varpi \zeta \eta_1 W_2}{\tau \varepsilon} T \\
&+ \frac{\eta_1 W_2 N_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \ln\left(\frac{W_\varphi N_\varphi}{W N}\right) d\varphi + \frac{\eta_2 W_2 U_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \ln\left(\frac{W_\varphi U_\varphi}{W U}\right) d\varphi \\
&+ \frac{\eta_3 W_2 M_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \ln\left(\frac{W_\varphi M_\varphi}{W M}\right) d\varphi \\
&+ \frac{\eta_1 W_2 N_2 + \eta_3 W_2 M_2}{\mathcal{H}_2} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) \ln\left(\frac{U_\varphi}{U}\right) d\varphi \\
&+ \frac{\eta_1 W_2 N_2}{\mathcal{H}_3} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) \ln\left(\frac{M_\varphi}{M}\right) d\varphi.
\end{aligned}$$

Using the equalities given by (5.4) in case of $n = 2$, we get

$$\begin{aligned}
\frac{d\Theta_2}{dt} = &-\alpha \frac{(W - W_2)^2}{W} - (\eta_1 W_2 N_2 + \eta_2 W_2 U_2 + \eta_3 W_2 M_2)\left[\frac{W_2}{W} - 1 - \ln\left(\frac{W_2}{W}\right)\right] \\
&- \frac{\eta_1 W_2 N_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[\frac{W_\varphi N_\varphi U_2}{W_2 N_2 U} - 1 - \ln\left(\frac{W_\varphi N_\varphi U_2}{W_2 N_2 U}\right)\right] d\varphi \\
&- \frac{\eta_2 W_2 U_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[\frac{W_\varphi U_\varphi}{W_2 U} - 1 - \ln\left(\frac{W_\varphi U_\varphi}{W_2 U}\right)\right] d\varphi \\
&- \frac{\eta_3 W_2 M_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[\frac{W_\varphi M_\varphi U_2}{W_2 M_2 U} - 1 - \ln\left(\frac{W_\varphi M_\varphi U_2}{W_2 M_2 U}\right)\right] d\varphi
\end{aligned}$$

$$-\frac{\eta_1 W_2 N_2+\eta_3 W_2 M_2}{\mathcal{H}_2}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\left[\frac{U_\varphi M_2}{U_2 M}-1-\ln\left(\frac{U_\varphi M_2}{U_2 M}\right)\right]d\varphi$$
$$-\frac{\eta_1 W_2 N_2}{\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\left[\frac{M_\varphi N_2}{M_2 N}-1-\ln\left(\frac{M_\varphi N_2}{M_2 N}\right)\right]d\varphi+\frac{\varpi\eta_1 W_2}{\varepsilon}\left(N_2-\frac{\zeta}{\tau}\right)T. \tag{5.15}$$

Eq. (5.15) can be rewritten as follows

$$\begin{aligned}\frac{d\Theta_2}{dt}=&-\alpha\frac{(W-W_2)^2}{W}-\frac{\eta_1 W_2 N_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi))\left[F\left(\frac{W_\varphi N_\varphi U_2}{W_2 N_2 U}\right)+F\left(\frac{W_2}{W}\right)\right]d\varphi\\
&-\frac{\eta_2 W_2 U_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi U_\varphi}{W_2 U}\right)+F\left(\frac{W_2}{W}\right)\right]d\varphi\\
&-\frac{\eta_3 W_2 M_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi M_\varphi U_2}{W_2 M_2 U}\right)+F\left(\frac{W_2}{W}\right)\right]d\varphi\\
&-\frac{\eta_1 W_2 N_2+\eta_3 W_2 M_2}{\mathcal{H}_2}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)F\left(\frac{U_\varphi M_2}{U_2 M}\right)d\varphi\\
&-\frac{\eta_1 W_2 N_2}{\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)F\left(\frac{M_\varphi N_2}{M_2 N}\right)d\varphi+\frac{\varpi\eta_1 W_2}{\varepsilon}\left(N_2-N_4\right)T.\end{aligned}$$

Hence, if $\Re_4\le 1$, then $Đ_4$ does not exists since $T_4=\dfrac{\varepsilon}{\varpi}(\Re_4-1)\le 0$. This implies that, $\dot{T}(t)=\tau\left(N-\frac{\zeta}{\tau}\right)T\le 0$ for all $T>0$. Thus, $N_2\le\frac{\zeta}{\tau}=N_4$. Hence, if $\Re_1>1$, then $\frac{d\Theta_2}{dt}\le 0$ for all $W,U,M,N,P,T>0$ with equality holding when

$$(N_2-N_4)T=0, \tag{5.16}$$
$$\frac{W}{W_2}=\frac{W_\varphi N_\varphi U_2}{W_2 N_2 U}=\frac{W_\varphi U_\varphi}{W_2 U}=\frac{W_\varphi M_\varphi U_2}{W_2 M_2 U}=\frac{U_\varphi M_2}{U_2 M}=\frac{M_\varphi N_2}{M_2 N}=1,\ t\in[0,\kappa]. \tag{5.17}$$

Let Υ_2' be the largest invariant subset of $\Upsilon_2=\left\{(W,U,M,N,P,T):\frac{d\Theta_2}{dt}=0\right\}$. The trajectories of system (2.1) converge to Υ_2'. The set Υ_2 is invariant and contains elements satisfying Eqs. (5.16) and (5.17). Eq. (5.17) is satisfied when $W(t)=W_2$, $U(t)=U_2$, $M(t)=M_2$ and $N(t)=N_2$. Next we show that for each element in Υ_2 we get $P(t)=P_2$ and $T(t)=0$ for all t. From Eq. (5.16) we have two cases:

- $N_2=N_4$: From the third and fourth equations of system (2.1) we get

$$0=\dot{M}(t)=\lambda\mathcal{H}_2 U_2-aM_2-\mu P(t)M_2, \tag{5.18}$$
$$0=\dot{N}(t)=b\mathcal{H}_3 M_2-\varepsilon N_2-\varpi T(t)N_2. \tag{5.19}$$

  From the equilibrium conditions (5.14) we get $P(t)=P_2$ and $T(t)=0$ for all t.

- $N_2 < N_4$: From Eq. (5.16) we get $T(t) = 0$ for all t. Moreover, from conditions (5.14) and Eq. (5.18) we obtain $P(t) = P_2$ for all t.

Therefore, $\Upsilon_2^{'} = \{Đ_2\}$. LaSalle's invariance principle implies that $Đ_2$ is G.A.S. □

Theorem 5.4. *Suppose that $\Re_2 > 1$ and $\Re_3 \leq 1$, then $Đ_3$ is G.A.S.*

Proof. Define a function $\Theta_3(W, U, M, N, P, T)$ as:

$$\begin{aligned}
\Theta_3 =& W_3 F\left(\frac{W}{W_3}\right) + \frac{1}{\mathcal{H}_1} U_3 F\left(\frac{U}{U_3}\right) + \frac{W_3\left[b\eta_1\mathcal{H}_3 + \eta_3\left(\varepsilon + \varpi T_3\right)\right]}{a\left(\varepsilon + \varpi T_3\right)} M_3 F\left(\frac{M}{M_3}\right) \\
&+ \frac{\eta_1 W_3}{\varepsilon + \varpi T_3} N_3 F\left(\frac{N}{N_3}\right) + \frac{\mu W_3\left[b\eta_1\mathcal{H}_3 + \eta_3\left(\varepsilon + \varpi T_3\right)\right]}{\sigma a\left(\varepsilon + \varpi T_3\right)} P \\
&+ \frac{\varpi\eta_1 W_3}{\tau\left(\varepsilon + \varpi T_3\right)} T_3 F\left(\frac{T}{T_3}\right) + \frac{\eta_1 W_3 N_3}{\mathcal{H}_1}\int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi)\int_{t-\varphi}^{t} F\left(\frac{W(\varkappa)N(\varkappa)}{W_3 N_3}\right) d\varkappa d\varphi \\
&+ \frac{\eta_2 W_3 U_3}{\mathcal{H}_1}\int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi)\int_{t-\varphi}^{t} F\left(\frac{W(\varkappa)U(\varkappa)}{W_3 U_3}\right) d\varkappa d\varphi \\
&+ \frac{\eta_3 W_3 M_3}{\mathcal{H}_1}\int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi)\int_{t-\varphi}^{t} F\left(\frac{W(\varkappa)M(\varkappa)}{W_3 M_3}\right) d\varkappa d\varphi \\
&+ \frac{\lambda W_3\left[b\eta_1\mathcal{H}_3 + \eta_3\left(\varepsilon + \varpi T_3\right)\right] U_3}{a\left(\varepsilon + \varpi T_3\right)}\int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi)\int_{t-\varphi}^{t} F\left(\frac{U(\varkappa)}{U_3}\right) d\varkappa d\varphi \\
&+ \frac{b\eta_1 W_3 M_3}{\varepsilon + \varpi T_3}\int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi)\int_{t-\varphi}^{t} F\left(\frac{M(\varkappa)}{M_3}\right) d\varkappa d\varphi.
\end{aligned}$$

We calculate $\frac{d\Theta_3}{dt}$ as:

$$\begin{aligned}
\frac{d\Theta_3}{dt} =& \left(1 - \frac{W_3}{W}\right)\left(\rho - \alpha W - \eta_1 WN - \eta_2 WU - \eta_3 WM\right) \\
&+ \frac{1}{\mathcal{H}_1}\left(1 - \frac{U_3}{U}\right)\left[\int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) W_\varphi \left\{\eta_1 N_\varphi + \eta_2 U_\varphi + \eta_3 M_\varphi\right\} d\varphi - \left(\lambda + \gamma\right) U\right] \\
&+ \frac{W_3\left[b\eta_1\mathcal{H}_3 + \eta_3\left(\varepsilon + \varpi T_3\right)\right]}{a\left(\varepsilon + \varpi T_3\right)}\left(1 - \frac{M_3}{M}\right)\left[\lambda\int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) U_\varphi d\varphi - aM - \mu PM\right] \\
&+ \frac{\eta_1 W_3}{\varepsilon + \varpi T_3}\left(1 - \frac{N_3}{N}\right)\left[b\int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) M_\varphi d\varphi - \varepsilon N - \varpi TN\right] \\
&+ \frac{\mu W_3\left[b\eta_1\mathcal{H}_3 + \eta_3\left(\varepsilon + \varpi T_3\right)\right]}{\sigma a\left(\varepsilon + \varpi T_3\right)}\left(\sigma PM - \pi P\right) + \frac{\varpi\eta_1 W_3}{\tau\left(\varepsilon + \varpi T_3\right)}\left(1 - \frac{T_3}{T}\right)\left(\tau TN - \zeta T\right) \\
&+ \frac{\eta_1 W_3 N_3}{\mathcal{H}_1}\int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi)\left[\frac{WN}{W_3 N_3} - \frac{W_\varphi N_\varphi}{W_3 N_3} + \ln\left(\frac{W_\varphi N_\varphi}{WN}\right)\right] d\varphi
\end{aligned}$$

$$+\frac{\eta_2 W_3 U_3}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WU}{W_3U_3}-\frac{W_\varphi U_\varphi}{W_3U_3}+\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)\right]d\varphi$$

$$+\frac{\eta_3 W_3 M_3}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WM}{W_3M_3}-\frac{W_\varphi M_\varphi}{W_3M_3}+\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)\right]d\varphi$$

$$+\frac{\lambda W_3\left[b\eta_1\mathcal{H}_3+\eta_3\left(\varepsilon+\varpi T_3\right)\right]U_3}{a\left(\varepsilon+\varpi T_3\right)}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\left[\frac{U}{U_3}-\frac{U_\varphi}{U_3}+\ln\left(\frac{U_\varphi}{U}\right)\right]d\varphi$$

$$+\frac{b\eta_1 W_3 M_3}{\varepsilon+\varpi T_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\left[\frac{M}{M_3}-\frac{M_\varphi}{M_3}+\ln\left(\frac{M_\varphi}{M}\right)\right]d\varphi. \tag{5.20}$$

Collecting terms of Eq. (5.20), using the equilibrium conditions for Đ$_3$

$$\begin{aligned}
&\rho=\alpha W_3+\eta_1 W_3 N_3+\eta_2 W_3 U_3+\eta_3 W_3 M_3,\\
&\eta_1 W_3 N_3+\eta_2 W_3 U_3+\eta_3 W_3 M_3=\frac{\lambda+\gamma}{\mathcal{H}_1}U_3,\\
&\frac{\lambda\mathcal{H}_2 U_3}{a}=M_3,\qquad N_3=\frac{\zeta}{\tau},\quad b\mathcal{H}_3 M_3=\left(\varepsilon+\varpi T_3\right)N_3,
\end{aligned} \tag{5.21}$$

and using the equalities given by (5.4) in case of $n=3$, we get

$$\begin{aligned}
\frac{d\Theta_3}{dt}=&-\alpha\frac{(W-W_3)^2}{W}-\frac{\eta_1 W_3 N_3}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi N_\varphi U_3}{W_3 N_3 U}\right)+F\left(\frac{W_3}{W}\right)\right]d\varphi\\
&-\frac{\eta_2 W_3 U_3}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi U_\varphi}{W_3 U}\right)+F\left(\frac{W_3}{W}\right)\right]d\varphi\\
&-\frac{\eta_3 W_3 M_3}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi M_\varphi U_3}{W_3 M_3 U}\right)+F\left(\frac{W_3}{W}\right)\right]d\varphi\\
&-\frac{\eta_1 W_3 N_3+\eta_3 W_3 M_3}{\mathcal{H}_2}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)F\left(\frac{U_\varphi M_3}{U_3 M}\right)d\varphi\\
&-\frac{\eta_1 W_3 N_3}{\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)F\left(\frac{M_\varphi N_3}{M_3 N}\right)d\varphi\\
&+\frac{\mu W_3\left[b\eta_1\mathcal{H}_3+\eta_3\left(\varepsilon+\varpi T_3\right)\right]}{a\left(\varepsilon+\varpi T_3\right)}\left(M_3-M_4\right)P.
\end{aligned}$$

Hence, if $\Re_3\leq 1$, then Đ$_4$ does not exists since $P_4=\frac{a}{\mu}\left(\Re_3-1\right)\leq 0$. This implies that, $\dot{P}(t)=\sigma\left(M-\frac{\pi}{\sigma}\right)P\leq 0$ for all $P>0$. Thus, $M_3\leq\frac{\pi}{\sigma}=M_4$. Then $\frac{d\Theta_3}{dt}\leq 0$ for all $W,U,M,N,P,T>0$ with equality holding when

$$\left(M_3-M_4\right)P=0, \tag{5.22}$$

$$\frac{W}{W_3}=\frac{W_\varphi N_\varphi U_3}{W_3 N_3 U}=\frac{W_\varphi U_\varphi}{W_3 U}=\frac{W_\varphi M_\varphi U_3}{W_3 M_3 U}=\frac{U_\varphi M_3}{U_3 M}=\frac{M_\varphi N_3}{M_3 N}=1,\ t\in[0,\kappa]. \tag{5.23}$$

Let Υ_3' be the largest invariant subset of $\Upsilon_3 = \left\{(W,U,M,N,P,T) : \frac{d\Theta_3}{dt} = 0\right\}$. The trajectories of system (2.1) converge to Υ_3'. The set Υ_3 contains elements satisfying Eqs. (5.22) and (5.23). Eq. (5.23) is satisfied when $W(t) = W_3$, $U(t) = U_3$, $M(t) = M_3$ and $N(t) = N_3$. Next we show that for each element in Υ_3 we get $P(t) = 0$ and $T(t) = T_3$ for all t. From Eq. (5.22) we have two cases:

- $M_3 = M_4$: From the third and fourth equations of system (2.1) we get

$$0 = \dot{M}(t) = \lambda \mathcal{H}_2 U_3 - aM_3 - \mu P(t) M_3, \tag{5.24}$$

$$0 = \dot{N}(t) = b\mathcal{H}_3 M_3 - \varepsilon N_3 - \varpi T(t) N_3. \tag{5.25}$$

  From the equilibrium conditions (5.21) we get $P(t) = 0$ and $T(t) = T_3$ for all t.

- $M_3 < M_4$: From Eq. (5.22) we get $P(t) = 0$ for all t. Moreover, from conditions (5.21) and Eq. (5.25) we obtain $T(t) = T_3$ for all t.

Therefore, $\Upsilon_3' = \{Đ_3\}$. Applying LaSalle's invariance principle we get $Đ_3$ is G.A.S. □

Theorem 5.5. *If $\Re_3 > 1$ and $\Re_4 > 1$, then $Đ_4$ is G.A.S.*

Proof. Define $\Theta_4(W,U,M,N,P,T)$ as:

$$\begin{aligned}
\Theta_4 =& W_4 F\left(\frac{W}{W_4}\right) + \frac{1}{\mathcal{H}_1} U_4 F\left(\frac{U}{U_4}\right) + \frac{W_4\left[b\eta_1\mathcal{H}_3 + \eta_3\left(\varepsilon + \varpi T_4\right)\right]}{\left(\varepsilon + \varpi T_4\right)\left(a + \mu P_4\right)} M_4 F\left(\frac{M}{M_4}\right) \\
&+ \frac{\eta_1 W_4}{\varepsilon + \varpi T_4} N_4 F\left(\frac{N}{N_4}\right) + \frac{\mu W_4\left[b\eta_1\mathcal{H}_3 + \eta_3\left(\varepsilon + \varpi T_4\right)\right]}{\sigma\left(\varepsilon + \varpi T_4\right)\left(a + \mu P_4\right)} P_4 F\left(\frac{P}{P_4}\right) \\
&+ \frac{\varpi \eta_1 W_4}{\tau\left(\varepsilon + \varpi T_4\right)} T_4 F\left(\frac{T}{T_4}\right) + \frac{\eta_1 W_4 N_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \int_{t-\varphi}^{t} F\left(\frac{W(\varkappa)N(\varkappa)}{W_4 N_4}\right) d\varkappa d\varphi \\
&+ \frac{\eta_2 W_4 U_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \int_{t-\varphi}^{t} F\left(\frac{W(\varkappa)U(\varkappa)}{W_4 U_4}\right) d\varkappa d\varphi \\
&+ \frac{\eta_3 W_4 M_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \int_{t-\varphi}^{t} F\left(\frac{W(\varkappa)M(\varkappa)}{W_4 M_4}\right) d\varkappa d\varphi \\
&+ \frac{\lambda W_4\left[b\eta_1\mathcal{H}_3 + \eta_3\left(\varepsilon + \varpi T_4\right)\right] U_4}{\left(\varepsilon + \varpi T_4\right)\left(a + \mu P_4\right)} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) \int_{t-\varphi}^{t} F\left(\frac{U(\varkappa)}{U_4}\right) d\varkappa d\varphi \\
&+ \frac{b\eta_1 W_4 M_4}{\varepsilon + \varpi T_4} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) \int_{t-\varphi}^{t} F\left(\frac{M(\varkappa)}{M_4}\right) d\varkappa d\varphi.
\end{aligned}$$

Calculating $\frac{d\Theta_4}{dt}$ as:

$$\frac{d\Theta_4}{dt} = \left(1 - \frac{W_4}{W}\right)\left(\rho - \alpha W - \eta_1 WN - \eta_2 WU - \eta_3 WM\right)$$

$$
\begin{aligned}
&+\frac{1}{\mathcal{H}_1}\left(1-\frac{U_4}{U}\right)\left[\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)W_\varphi\left\{\eta_1 N_\varphi+\eta_2 U_\varphi+\eta_3 M_\varphi\right\}d\varphi-(\lambda+\gamma)\,U\right]\\
&+\frac{W_4\left[b\eta_1\mathcal{H}_3+\eta_3\left(\varepsilon+\varpi T_4\right)\right]}{\left(\varepsilon+\varpi T_4\right)\left(a+\mu P_4\right)}\left(1-\frac{M_4}{M}\right)\left[\lambda\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)U_\varphi d\varphi-aM-\mu PM\right]\\
&+\frac{\eta_1 W_4}{\varepsilon+\varpi T_4}\left(1-\frac{N_4}{N}\right)\left[b\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)M_\varphi d\varphi-\varepsilon N-\varpi TN\right]\\
&+\frac{\mu W_4\left[b\eta_1\mathcal{H}_3+\eta_3\left(\varepsilon+\varpi T_4\right)\right]}{\sigma\left(\varepsilon+\varpi T_4\right)\left(a+\mu P_4\right)}\left(1-\frac{P_4}{P}\right)\left(\sigma PM-\pi P\right)\\
&+\frac{\varpi\eta_1 W_4}{\tau\left(\varepsilon+\varpi T_4\right)}\left(1-\frac{T_4}{T}\right)\left(\tau TN-\zeta T\right)\\
&+\frac{\eta_1 W_4 N_4}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WN}{W_4N_4}-\frac{W_\varphi N_\varphi}{W_4N_4}+\ln\left(\frac{W_\varphi N_\varphi}{WN}\right)\right]d\varphi\\
&+\frac{\eta_2 W_4 U_4}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WU}{W_4U_4}-\frac{W_\varphi U_\varphi}{W_4U_4}+\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)\right]d\varphi\\
&+\frac{\eta_3 W_4 M_4}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WM}{W_4M_4}-\frac{W_\varphi M_\varphi}{W_4M_4}+\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)\right]d\varphi\\
&+\frac{\lambda W_4\left[b\eta_1\mathcal{H}_3+\eta_3\left(\varepsilon+\varpi T_4\right)\right]U_4}{\left(\varepsilon+\varpi T_4\right)\left(a+\mu P_4\right)}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\left[\frac{U}{U_4}-\frac{U_\varphi}{U_4}+\ln\left(\frac{U_\varphi}{U}\right)\right]d\varphi\\
&+\frac{b\eta_1 W_4 M_4}{\varepsilon+\varpi T_4}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\left[\frac{M}{M_4}-\frac{M_\varphi}{M_4}+\ln\left(\frac{M_\varphi}{M}\right)\right]d\varphi. \qquad (5.26)
\end{aligned}
$$

Collecting terms of Eq. (5.26), we obtain

$$
\begin{aligned}
&\frac{d\Theta_4}{dt}\\
&=\left(1-\frac{W_4}{W}\right)(\rho-\alpha W)+\eta_1 W_4 N+\eta_2 W_4 U+\eta_3 W_4 M-\frac{\lambda+\gamma}{\mathcal{H}_1}U\\
&\quad-\frac{\eta_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi N_\varphi U_4}{U}d\varphi-\frac{\eta_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi U_\varphi U_4}{U}d\varphi\\
&\quad-\frac{\eta_3}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi M_\varphi U_4}{U}d\varphi+\frac{\lambda+\gamma}{\mathcal{H}_1}U_4-\frac{aW_4\left[b\eta_1\mathcal{H}_3+\eta_3\left(\varepsilon+\varpi T_4\right)\right]}{\left(\varepsilon+\varpi T_4\right)\left(a+\mu P_4\right)}M\\
&\quad-\frac{\lambda W_4\left[b\eta_1\mathcal{H}_3+\eta_3\left(\varepsilon+\varpi T_4\right)\right]}{\left(\varepsilon+\varpi T_4\right)\left(a+\mu P_4\right)}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\frac{U_\varphi M_4}{M}d\varphi\\
&\quad+\frac{aW_4\left[b\eta_1\mathcal{H}_3+\eta_3\left(\varepsilon+\varpi T_4\right)\right]}{\left(\varepsilon+\varpi T_4\right)\left(a+\mu P_4\right)}M_4
\end{aligned}
$$

$$+\frac{\mu W_4[b\eta_1\mathcal{H}_3+\eta_3(\varepsilon+\varpi T_4)]}{(\varepsilon+\varpi T_4)(a+\mu P_4)}PM_4-\eta_1 W_4\frac{\varepsilon N}{\varepsilon+\varpi T_4}-\frac{b\eta_1 W_4}{\varepsilon+\varpi T_4}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\frac{M_\varphi N_4}{N}d\varphi$$
$$+\eta_1 W_4\frac{\varepsilon N_4}{\varepsilon+\varpi T_4}+\eta_1 W_4\frac{\varpi T N_4}{\varepsilon+\varpi T_4}-\frac{\mu\pi W_4[b\eta_1\mathcal{H}_3+\eta_3(\varepsilon+\varpi T_4)]}{\sigma(\varepsilon+\varpi T_4)(a+\mu P_4)}P$$
$$-\frac{\mu W_4[b\eta_1\mathcal{H}_3+\eta_3(\varepsilon+\varpi T_4)]}{(\varepsilon+\varpi T_4)(a+\mu P_4)}P_4 M+\frac{\mu\pi W_4[b\eta_1\mathcal{H}_3+\eta_3(\varepsilon+\varpi T_4)]}{\sigma(\varepsilon+\varpi T_4)(a+\mu P_4)}P_4$$
$$-\eta_1 W_4\frac{\varpi\zeta T}{\tau(\varepsilon+\varpi T_4)}$$
$$-\eta_1 W_4\frac{\varpi T_4 N}{\varepsilon+\varpi T_4}+\eta_1 W_4\frac{\varpi\zeta T_4}{\tau(\varepsilon+\varpi T_4)}+\frac{\eta_1 W_4 N_4}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi N_\varphi}{WN}\right)d\varphi$$
$$+\frac{\eta_2 W_4 U_4}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)d\varphi+\frac{\eta_3 W_4 M_4}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)d\varphi$$
$$+\frac{\lambda W_4\mathcal{H}_2[b\eta_1\mathcal{H}_3+\eta_3(\varepsilon+\varpi T_4)]}{(\varepsilon+\varpi T_4)(a+\mu P_4)}U$$
$$+\frac{\lambda W_4[b\eta_1\mathcal{H}_3+\eta_3(\varepsilon+\varpi T_4)]U_4}{(\varepsilon+\varpi T_4)(a+\mu P_4)}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\ln\left(\frac{U_\varphi}{U}\right)d\varphi$$
$$+\frac{b\eta_1\mathcal{H}_3 W_4}{\varepsilon+\varpi T_4}M+\frac{b\eta_1 W_4 M_4}{\varepsilon+\varpi T_4}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\ln\left(\frac{M_\varphi}{M}\right)d\varphi.$$

Using the equilibrium conditions for Đ$_4$:

$$\begin{aligned}
&\rho=\alpha W_4+\eta_1 W_4 N_4+\eta_2 W_4 U_4+\eta_3 W_4 M_4,\\
&\eta_1 W_4 N_4+\eta_2 W_4 U_4+\eta_3 W_4 M_4=\frac{\lambda+\gamma}{\mathcal{H}_1}U_4,\\
&\lambda\mathcal{H}_2 U_4=(a+\mu P_4)M_4,\quad b\mathcal{H}_3 M_4=(\varepsilon+\varpi T_4)N_4,\\
&M_4=\frac{\pi}{\sigma},\qquad N_4=\frac{\zeta}{\tau},
\end{aligned}$$

we obtain

$$\begin{aligned}
\eta_1 W_4 N_4+\eta_3 W_4 M_4&=\frac{W_4[b\eta_1\mathcal{H}_3+\eta_3(\varepsilon+\varpi T_4)]}{\varepsilon+\varpi T_4}M_4\\
&=\frac{\lambda W_4\mathcal{H}_2[b\eta_1\mathcal{H}_3+\eta_3(\varepsilon+\varpi T_4)]}{(\varepsilon+\varpi T_4)(a+\mu P_4)}U_4.
\end{aligned}$$

Moreover, we get

$$\begin{aligned}
\frac{d\Theta_4}{dt}=&\left(1-\frac{W_4}{W}\right)(\alpha W_4-\alpha W)+(\eta_1 W_4 N_4+\eta_2 W_4 U_4+\eta_3 W_4 M_4)\left(1-\frac{W_4}{W}\right)\\
&-\frac{\eta_1 W_4 N_4}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi N_\varphi U_4}{W_4 N_4 U}d\varphi-\frac{\eta_2 W_4 U_4}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi U_\varphi}{W_4 U}d\varphi
\end{aligned}$$

$$- \frac{\eta_3 W_4 M_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \frac{W_\varphi M_\varphi U_4}{W_4 M_4 U} d\varphi + \eta_1 W_4 N_4 + \eta_2 W_4 U_4 + \eta_3 W_4 M_4$$
$$- \frac{\eta_1 W_4 N_4 + \eta_3 W_4 M_4}{\mathcal{H}_2} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) \frac{U_\varphi M_4}{U_4 M} d\varphi + \eta_1 W_4 N_4 + \eta_3 W_4 M_4$$
$$- \frac{\eta_1 W_4 N_4}{\mathcal{H}_3} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) \frac{M_\varphi N_4}{M_4 N} d\varphi + \eta_1 W_4 N_4 + \frac{\eta_1 W_4 N_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \ln\left(\frac{W_\varphi N_\varphi}{WN}\right) d\varphi$$
$$+ \frac{\eta_2 W_4 U_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \ln\left(\frac{W_\varphi U_\varphi}{WU}\right) d\varphi + \frac{\eta_3 W_4 M_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \ln\left(\frac{W_\varphi M_\varphi}{WM}\right) d\varphi$$
$$+ \frac{\eta_1 W_4 N_4 + \eta_3 W_4 M_4}{\mathcal{H}_2} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) \ln\left(\frac{U_\varphi}{U}\right) d\varphi + \frac{\eta_1 W_4 N_4}{\mathcal{H}_3} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) \ln\left(\frac{M_\varphi}{M}\right) d\varphi.$$

Using the equalities given by (5.4) in case of $n = 4$, we get

$$\begin{aligned}
\frac{d\Theta_4}{dt} = & -\alpha \frac{(W - W_4)^2}{W} - (\eta_1 W_4 N_4 + \eta_2 W_4 U_4 + \eta_3 W_4 M_4) \left[\frac{W_4}{W} - 1 - \ln\left(\frac{W_4}{W}\right)\right] \\
& - \frac{\eta_1 W_4 N_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[\frac{W_\varphi N_\varphi U_4}{W_4 N_4 U} - 1 - \ln\left(\frac{W_\varphi N_\varphi U_4}{W_4 N_4 U}\right)\right] d\varphi \\
& - \frac{\eta_2 W_4 U_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[\frac{W_\varphi U_\varphi}{W_4 U} - 1 - \ln\left(\frac{W_\varphi U_\varphi}{W_4 U}\right)\right] d\varphi \\
& - \frac{\eta_3 W_4 M_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[\frac{W_\varphi M_\varphi U_4}{W_4 M_4 U} - 1 - \ln\left(\frac{W_\varphi M_\varphi U_4}{W_4 M_4 U}\right)\right] d\varphi \\
& - \frac{\eta_1 W_4 N_4 + \eta_3 W_4 M_4}{\mathcal{H}_2} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) \left[\frac{U_\varphi M_4}{U_4 M} - 1 - \ln\left(\frac{U_\varphi M_4}{U_4 M}\right)\right] d\varphi \\
& - \frac{\eta_1 W_4 N_4}{\mathcal{H}_3} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) \left[\frac{M_\varphi N_4}{M_4 N} - 1 - \ln\left(\frac{M_\varphi N_4}{M_4 N}\right)\right] d\varphi. \qquad (5.27)
\end{aligned}$$

Eq. (5.27) can be simplified as follows

$$\begin{aligned}
\frac{d\Theta_4}{dt} = & -\alpha \frac{(W - W_4)^2}{W} - \frac{\eta_1 W_4 N_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[F\left(\frac{W_\varphi N_\varphi U_4}{W_4 N_4 U}\right) + F\left(\frac{W_4}{W}\right)\right] d\varphi \\
& - \frac{\eta_2 W_4 U_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[F\left(\frac{W_\varphi U_\varphi}{W_4 U}\right) + F\left(\frac{W_4}{W}\right)\right] d\varphi \\
& - \frac{\eta_3 W_4 M_4}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \left[F\left(\frac{W_\varphi M_\varphi U_4}{W_4 M_4 U}\right) + F\left(\frac{W_4}{W}\right)\right] d\varphi
\end{aligned}$$

$$- \frac{\eta_1 W_4 N_4 + \eta_3 W_4 M_4}{\mathcal{H}_2} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) F \left(\frac{U_\varphi M_4}{U_4 M} \right) d\varphi$$

$$- \frac{\eta_1 W_4 N_4}{\mathcal{H}_3} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) F \left(\frac{M_\varphi N_4}{M_4 N} \right) d\varphi.$$

Hence, if $\Re_3 > 1$ and $\Re_4 > 1$, then $\frac{d\Theta_4}{dt} \leq 0$ for all $W, U, M, N, P, T > 0$. Similar to the previous Theorems one can show that $\frac{d\Theta_4}{dt} = 0$ when $W = W_4$, $U = U_4$, $M = M_4$ and $N = N_4$. The solutions of system (2.1) tend to $\Upsilon_4^{'}$ the largest invariant subset of $\Upsilon_4 = \left\{(W, U, M, N, P, T) : \frac{d\Theta_4}{dt} = 0\right\}$. The set $\Upsilon_4^{'}$ contains elements with $U(t) = U_4$, $M(t) = M_4$, $N(t) = N_4$, then $\dot{M}(t) = \dot{N}(t) = 0$ and from the third and fourth equations of system (2.1) we have

$$\begin{aligned} 0 &= \dot{M}(t) = \lambda U_4 - a M_4 - \mu P(t) M_4, \\ 0 &= \dot{N}(t) = b M_4 - \varepsilon N_4 - \varpi T(t) N_4, \end{aligned}$$

which give $P(t) = P_4$ and $T(t) = T_4$ for all t. Therefore, $\Upsilon_4^{'} = \{Đ_4\}$. Applying LaSalle's invariance principle we get $Đ_4$ is G.A.S. □

6. Numerical results

In this section, we illustrate the results of Theorems 5.1-5.5 by performing numerical simulations. We study the influence of CTC transmission and time delays on the dynamical behavior of the system. We choose dirac delta function $D(.)$ as a special form of $\Lambda_i(.)$:

$$\Lambda_i(x) = D\left(x - \varphi_i\right), \quad \varphi_i \in [0, \kappa_i], \ i = 1, 2, 3,$$

Let κ_i tends to ∞, then the properties of as $D(.)$ implies that:

$$\int_0^\infty \Lambda_j(\varsigma) d\varsigma = 1, \quad \mathcal{H}_j = \int_0^\infty D\left(\varsigma - \varphi_j\right) e^{-\hbar_j \varsigma} d\varsigma = e^{-\hbar_j \varphi_j}, \quad j = 1, 2, 3.$$

Then, model (2.1) will take the following form:

$$\begin{cases} \dot{W} = \rho - \alpha W - \eta_1 W N - \eta_2 W U - \eta_3 W M, \\ \dot{U} = e^{-\hbar_1 \varphi_1} W_{\varphi_1} \left[\eta_1 N_{\varphi_1} + \eta_2 U_{\varphi_1} + \eta_3 M_{\varphi_1}\right] - (\lambda + \gamma) U, \\ \dot{M} = \lambda e^{-\hbar_2 \varphi_2} U_{\varphi_2} - a M - \mu P M, \\ \dot{N} = b e^{-\hbar_3 \varphi_3} M_{\varphi_3} - \varepsilon N - \varpi T N, \\ \dot{P} = \sigma P M - \pi P, \\ \dot{T} = \tau T N - \zeta T. \end{cases} \tag{6.1}$$

For model (6.1), the threshold parameters are given by:

$$\Re_0 = \frac{W_0 e^{-\hbar_1 \varphi_1} \left[a \varepsilon \eta_2 + \lambda e^{-\hbar_2 \varphi_2} \left(b \eta_1 e^{-\hbar_3 \varphi_3} + \varepsilon \eta_3\right)\right]}{a \varepsilon \left(\gamma + \lambda\right)}, \quad \Re_1 = \frac{\lambda \sigma e^{-\hbar_2 \varphi_2} U_2}{a \pi},$$

$$\Re_2 = \frac{\tau b \lambda e^{-(\hbar_2\varphi_2+\hbar_3\varphi_3)}U_3}{a\varepsilon\zeta}, \quad \Re_3 = \frac{\lambda\sigma e^{-\hbar_2\varphi_2}U_4}{a\pi}, \quad \Re_4 = \frac{\tau\pi b e^{-\hbar_3\varphi_3}}{\sigma\varepsilon\zeta}. \tag{6.2}$$

To solve system (6.1) numerically we fix the values of some parameters (see Table 2) and the other will be varied.

Table 2. Some values of the parameters of model (6.1).

Parameter	Value	Parameter	Value	Parameter	Value	Parameter	Value
ρ	10	γ	0.2	σ	Varied	$\hbar_3$	0.3
α	0.01	λ	0.2	τ	Varied	φ_1	Varied
η_1	Varied	b	5	ϖ	0.3	φ_2	Varied
η_2	Varied	π	0.1	ζ	0.2	φ_3	Varied
η_3	Varied	μ	0.2	$\hbar_1$	0.1		
a	0.5	ε	2	$\hbar_2$	0.2		

6.1. Stability of the equilibria

In this subsection, we take the values $\varphi_1 = 3$, $\varphi_2 = 2$ and $\varphi_3 = 1$ and choose the following three different initial conditions for model (6.1):

IV-1 : $(W(\varphi), U(\varphi), M(\varphi), N(\varphi), P(\varphi), T(\varphi)) = (500, 5, 0.8, 0.8, 3, 9)$, (Solid lines in the figures),

IV-2: $(W(\varphi), U(\varphi), M(\varphi), N(\varphi), P(\varphi), T(\varphi)) = (650, 4, 0.6, 0.6, 2, 6)$, (Dashed lines in the figures),

IV-3: $(W(\varphi), U(\varphi), M(\varphi), N(\varphi), P(\varphi), T(\varphi)) = (800, 3, 0.4, 0.4, 1, 3)$. (Dotted lines in the figures), where $\varphi \in [-3, 0]$.

Choosing selected values of η_1, η_2, η_3, σ and τ under the above initial conditions leads to the following cases:

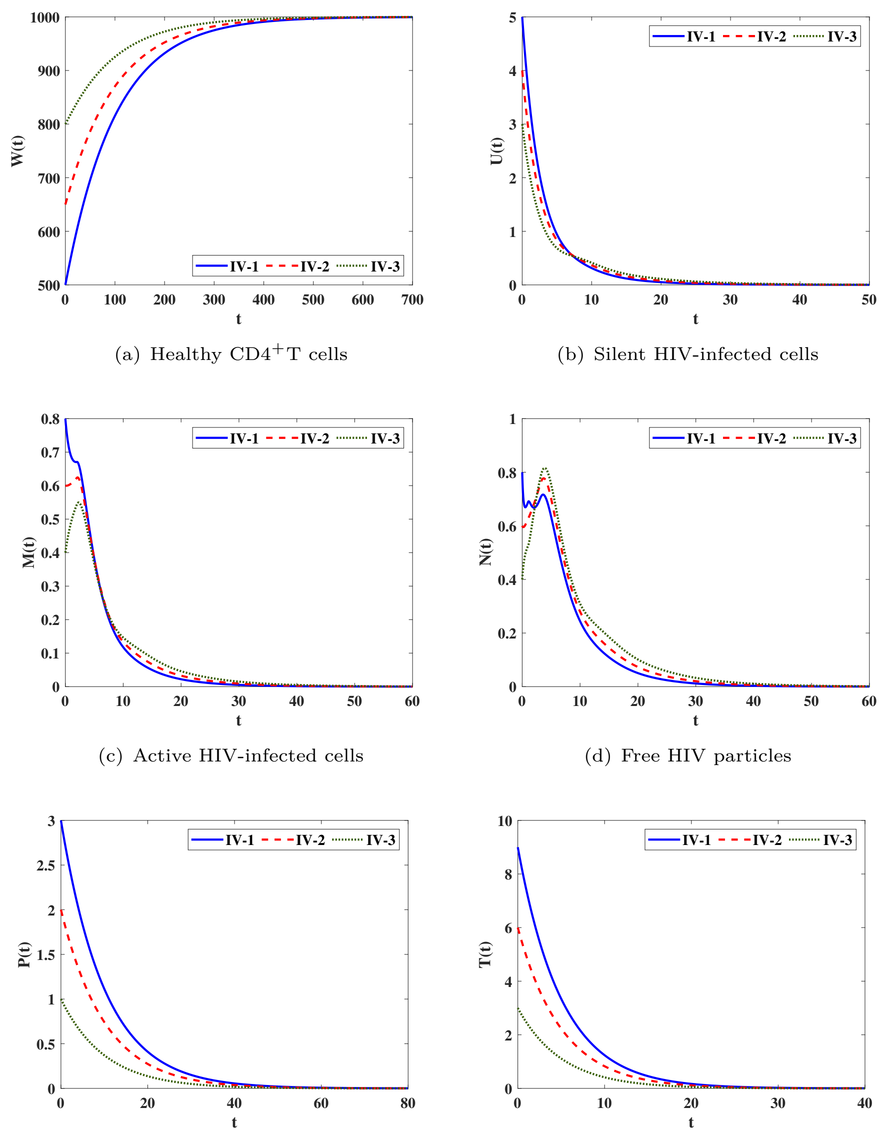
Stability of $Đ_0$**.** $\eta_1 = 0.0003$, $\eta_2 = 0.00001$, $\eta_3 = 0.0001$, $\sigma = 0.002$ and $\tau = 0.003$. For this set of parameters, we have $\Re_0 = 0.34 < 1$. Figure 1 displays that the trajectories initiating with IV-1, IV2 and IV-3 reach the equilibrium $Đ_0 = (1000, 0, 0, 0, 0, 0)$. This show that $Đ_0$ is G.A.S according to Theorem 5.1. In this case the HIV particles will be cleared from the body.

Stability of $Đ_1$**.** $\eta_1 = 0.003$, $\eta_2 = 0.00002$, $\eta_3 = 0.001$, $\sigma = 0.002$ and $\tau = 0.003$. With such choice we get $\Re_0 = 3.29 > 1$, $\Re_1 = 0.10 < 1$ and $\Re_2 = 0.13 < 1$. It is clear that the equilibrium point $Đ_1$ exists with $Đ_1 = (303.7, 12.90, 3.46, 6.40, 0, 0)$. Figure 2 displays that the trajectories initiating with IV-1, IV2 and IV-3 tend to $Đ_1$. Therefore, the numerical results supports Theorem 5.2. This case represents the persistence of the HIV infection but with unstimulated immune responses.

Stability of $Đ_2$**.** $\eta_1 = 0.003$, $\eta_2 = 0.00002$, $\eta_3 = 0.001$, $\sigma = 0.2$ and $\tau = 0.003$. Then, we calculate $\Re_1 = 2.50 > 1$ and $\Re_2 = 0.13 < 1$. In Figure 3 we show that $Đ_2 = (747.86, 4.67, 0.5, 0.93, 3.76, 0)$ exists and it is G.A.S and this agrees Theorem 5.3. Hence a chronic HIV infection with CTL-mediated immune response is attained.

Stability of $Đ_3$**.** $\eta_1 = 0.003$, $\eta_2 = 0.00002$, $\eta_3 = 0.001$, $\sigma = 0.002$ and $\tau = 0.3$. Then, we calculate $\Re_2 = 3.45 > 1$ and $\Re_3 = 0.08 < 1$. The numerical results plotted in Figure 4 show that $Đ_3 = (749.94, 4.63, 1.24, 0.67, 0, 16.33)$ exists and it is G.A.S and this agrees Theorem 5.4. As a result a chronic HIV infection with antibody immune response is attained.

Stability of Đ_4**.** $\eta_1 = 0.003$, $\eta_2 = 0.00002$, $\eta_3 = 0.001$, $\sigma = 0.2$ and $\tau = 0.3$. Then, we calculate $\Re_3 = 2.03 > 1$ and $\Re_4 = 1.39 > 1$. The numerical results displayed in Figure 5 show that $\text{Đ}_4 = (795.17, 3.79, 0.5, 0.67, 2.59, 2.59)$ exists and it is G.A.S according to Theorem 5.5. In this case a chronic HIV infection is attained where both CTL-mediated and antibody immune responses are working.



(a) Healthy CD4$^+$T cells

(b) Silent HIV-infected cells

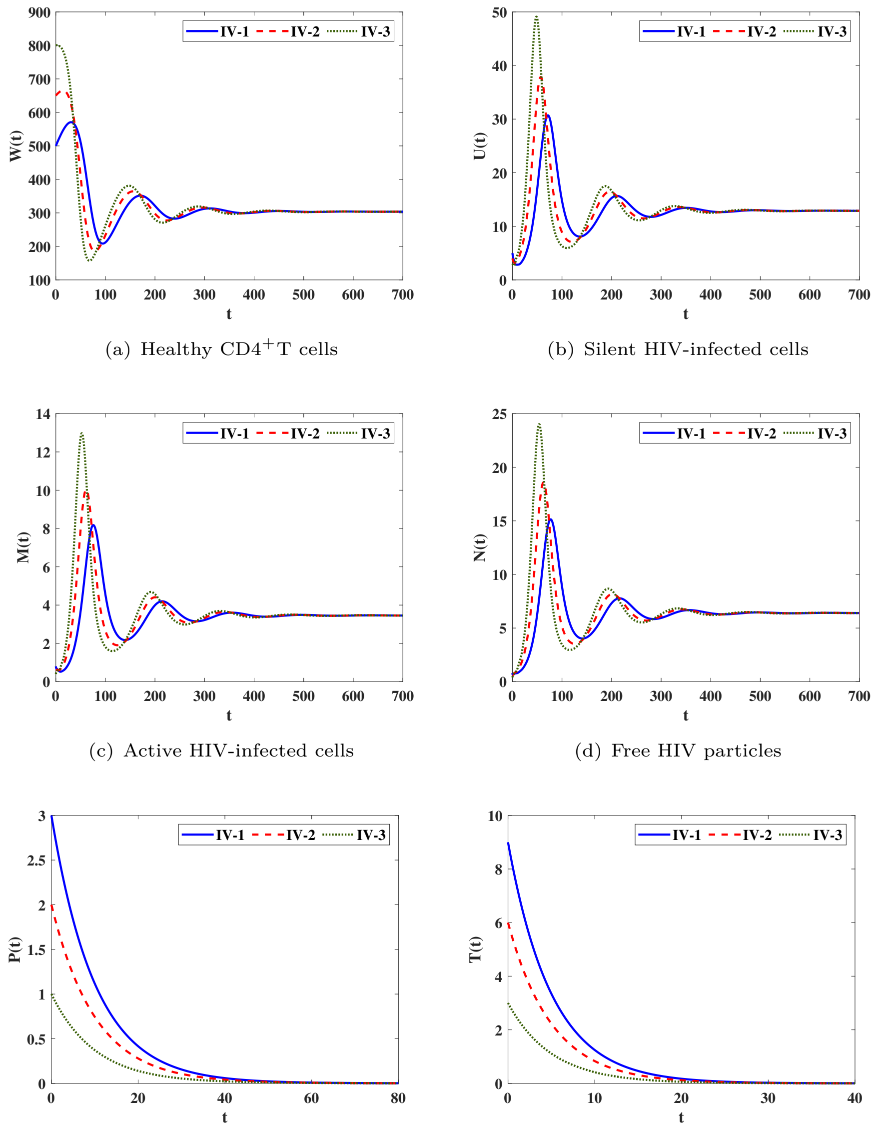
(c) Active HIV-infected cells

(d) Free HIV particles

(e) HIV-specific CTLs

(f) HIV-specific antibodies

Figure 1. The behavior of solution trajectories of system (6.1) in case of $\Re_0 \leq 1$.



(a) Healthy $CD4^+T$ cells

(b) Silent HIV-infected cells

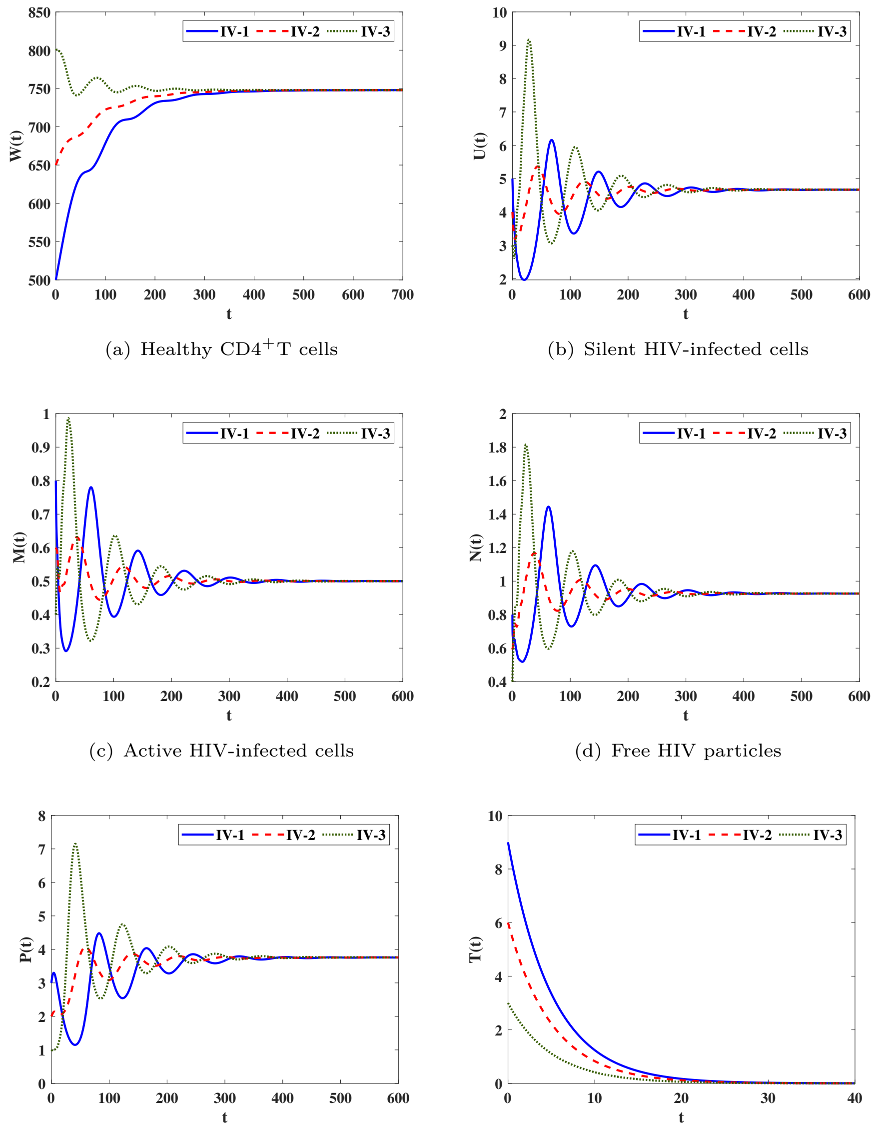
(c) Active HIV-infected cells

(d) Free HIV particles

(e) HIV-specific CTLs

(f) HIV-specific antibodies

Figure 2. The behavior of solution trajectories of system (6.1) in case of $\Re_0 > 1$, $\Re_1 \leq 1$ and $\Re_2 \leq 1$.



(a) Healthy CD4$^+$T cells

(b) Silent HIV-infected cells

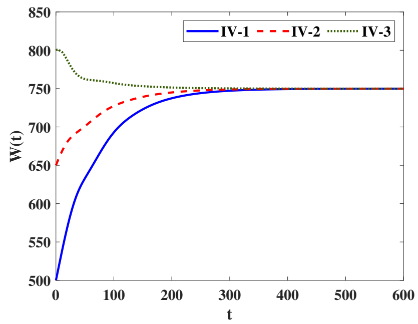
(c) Active HIV-infected cells

(d) Free HIV particles

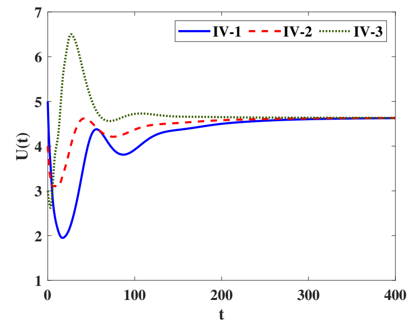
(e) HIV-specific CTLs

(f) HIV-specific antibodies

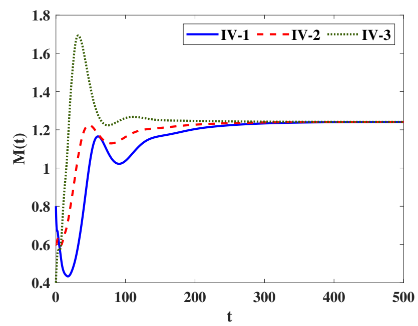
Figure 3. The behavior of solution trajectories of system (6.1) in case of $\Re_1 > 1$ and $\Re_4 \leq 1$.



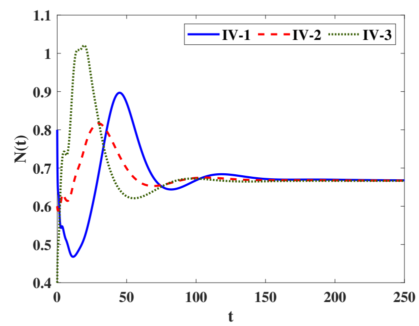
(a) Healthy CD4$^+$T cells



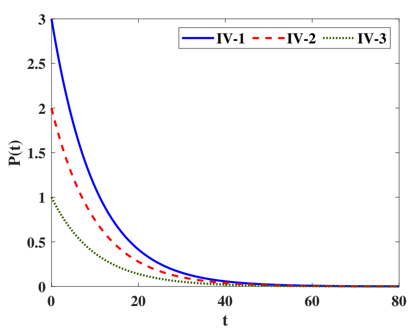
(b) Silent HIV-infected cells



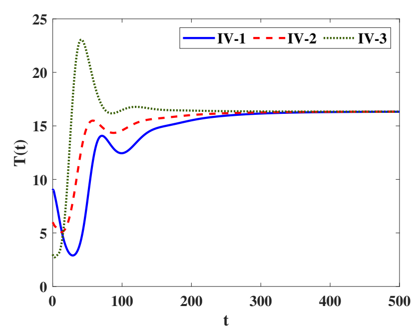
(c) Active HIV-infected cells



(d) Free HIV particles

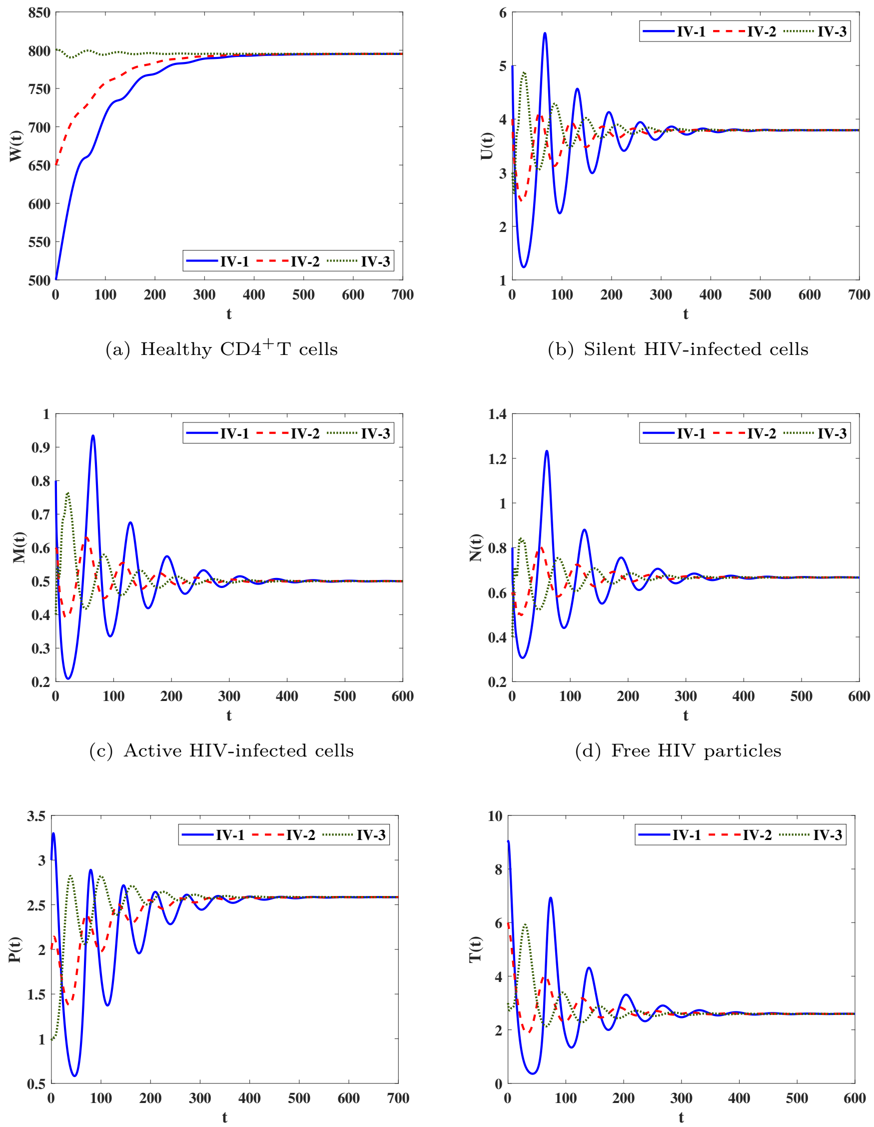


(e) HIV-specific CTLs



(f) HIV-specific antibodies

Figure 4. The behavior of solution trajectories of system (6.1) in case of $\Re_2 > 1$ and $\Re_3 \leq 1$.



(a) Healthy CD4$^+$T cells

(b) Silent HIV-infected cells

(c) Active HIV-infected cells

(d) Free HIV particles

(e) HIV-specific CTLs

(f) HIV-specific antibodies

Figure 5. The behavior of solution trajectories of system (6.1) in case of $\Re_3 > 1$ and $\Re_4 > 1$.

6.2. Effect of time delays on the HIV dynamics

In this part we vary the delays parameters φ_1, φ_2 and φ_3 and fix the parameters $\eta_1 = 0.003$, $\eta_2 = 0.00002$, $\eta_3 = 0.001$, $\sigma = 0.2$ and $\tau = 0.3$. Since $\Re_0$ given by Eq. (6.2) depends on φ_1, φ_2 and φ_3, then changing the parameters φ_1, φ_2 and φ_3 will change the stability of equilibria. Let us take the following values:

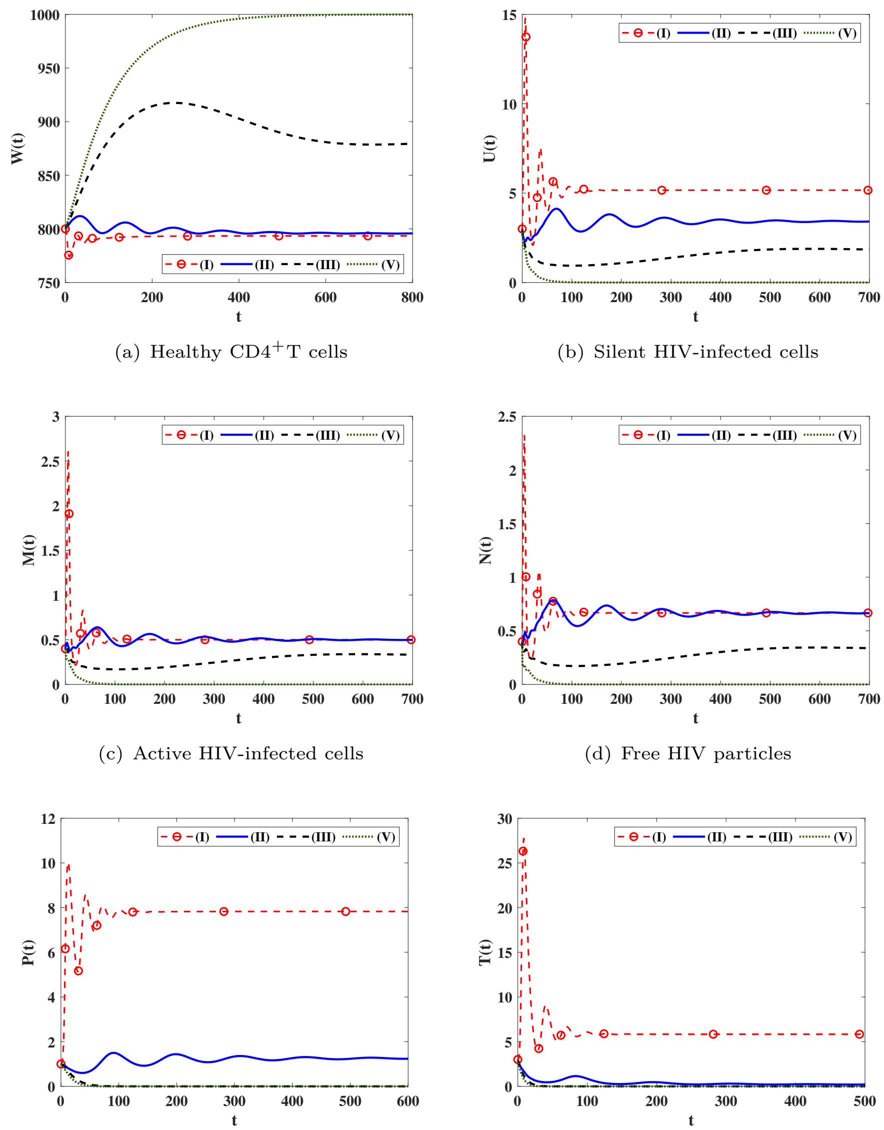
(I) $\varphi_1 = \varphi_2 = \varphi_3 = 0$,

(II) $\varphi_1 = 4$, $\varphi_2 = 3$ and $\varphi_3 = 2$,

(III) $\varphi_1 = 5$, $\varphi_2 = 4$ and $\varphi_3 = 3$,

(V) $\varphi_1 = 7$, $\varphi_2 = 6$ and $\varphi_3 = 5$.

With these values we solve system (6.1) under initial condition IV-3. The numerical solutions are displayed in Figure 6. We observe that inclusion of time delays can significantly increase the concentration of the healthy CD4$^+$ T cells and reduce the concentrations other compartments.



(a) Healthy CD4$^+$T cells

(b) Silent HIV-infected cells

(c) Active HIV-infected cells

(d) Free HIV particles

(e) HIV-specific CTLs

(f) HIV-specific antibodies

Figure 6. The influence of time delay parameters on the behavior of solution trajectories of system (6.1).

In Table 3 we present the values $\Re_0$ for selected values of φ_1, φ_2 and φ_3. It is clear that $\Re_0$ is decreased when φ_1, φ_2 and φ_3 are increased and the stability of $Đ_0$

will be is changed. Now we want to calculate the critical value of the time delay that changes the stability of $Đ_0$. To do so we fix the parameters φ_2 and φ_3 and write $\Re_0$ as a function of φ_1 as:

$$\Re_0(\varphi_1) = \frac{W_0 e^{-\hbar_1\varphi_1}\left[a\varepsilon\eta_2 + \lambda e^{-\hbar_2\varphi_2}\left(b\eta_1 e^{-\hbar_3\varphi_3} + \varepsilon\eta_3\right)\right]}{a\varepsilon\left(\gamma+\lambda\right)}.$$

When $\Re_0\left(\varphi_1\right) \leq 1$, we obtain

$$\varphi_1 \geq \varphi_1^{\min} \text{ where } \varphi_1^{\min} = \max\left\{0, \frac{1}{\hbar_1}\ln\left(\frac{W_0\left\{a\varepsilon\eta_2 + \lambda e^{-\hbar_2\varphi_2}\left(b\eta_1 e^{-\hbar_3\varphi_3} + \varepsilon\eta_3\right)\right\}}{a\varepsilon\left(\gamma+\lambda\right)}\right)\right\}.$$

Therefore, if $\varphi_1 \geq \varphi_1^{\min}$, then $Đ_0$ is G.A.S. Let $\varphi_2 = 5$ and $\varphi_3 = 4$ and compute $\varphi_1^{\min}$ as $\varphi_1^{\min} = 2.22266$. Then we have the following:

(i) If $\varphi_1 \geq 2.22266$, then $\Re_0(\varphi_1) \leq 1$ and $Đ_0$ is G.A.S.

(ii) If $\varphi_1 < 2.22266$, then $\Re_0(\varphi_1) > 1$ and $Đ_0$ will lose it stability and one of the other equilibria will be G.A.S.

Table 3. The values of $\Re_0$ for selected values of delay parameters.

Delay parameters	$\Re_0$
$\varphi_1 = \varphi_2 = \varphi_3, = 0$	8.55
$\varphi_1 = 3,\ \varphi_2 = 2,\ \varphi_3 = 1$	3.29
$\varphi_1 = 4,\ \varphi_2 = 3,\ \varphi_3 = 2,$	1.92
$\varphi_1 = 5,\ \varphi_2 = 4,\ \varphi_3 = 3$	1.13
$\varphi_1 = 6,\ \varphi_2 = 5,\ \varphi_3 = 4$	0.69
$\varphi_1 = 7,\ \varphi_2 = 6,\ \varphi_3 = 5$	0.42

6.3. Effects of CTC transmission

In this subsection, we investigate the influence of different mode of transmissions on the HIV dynamics (6.1). We use the parameters given in Table 2 and choose the values $\sigma = 0.05$, $\tau = 0.3$, $\varphi_1 = 3$, $\varphi_2 = 2$, $\varphi_3 = 1$ with the following initial condition:

IV-4 $(W(\varphi), U(\varphi), M(\varphi), N(\varphi), P(\varphi), T(\varphi)) = (600, 10, 2, 0.5, 1, 20)$, where $\varphi \in [-3, 0]$.

We choose three sets of parameters η_1, η_2 and η_3 and investigate the following illustrative cases:

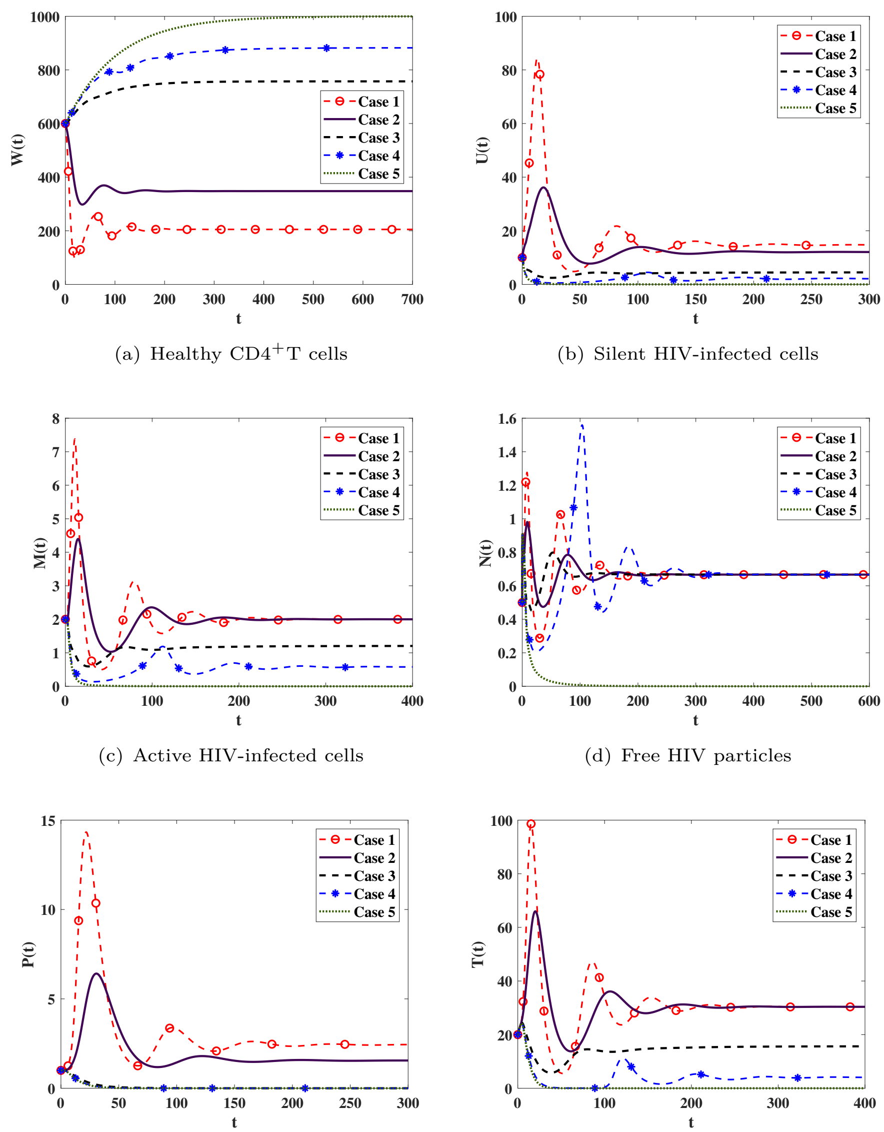
Case 1: HIV dynamics with VTC, silent-CTC and active-CTC transmissions: Here we consider the parameters $\eta_1 = 0.005$, $\eta_2 = 0.002$ and $\eta_3 = 0.003$. Figure 7 shows that the solutions of the system approach the equilibrium $Đ_4 = (205, 14.72, 2, 0.67, 2.43, 30.37)$.

Case 2: HIV dynamics with VTC, silent-CTC and active-CTC transmissions: In this case, we choose the parameters $\eta_1 = 0.004$, $\eta_2 = 0.001$ and $\eta_3 = 0.002$. We can see from Figure 7 that the trajectories of the system tend to the equilibrium $Đ_4 = (347.9006, 12.08, 2, 0.67, 1.55, 30.37)$.

Case 3: HIV dynamics with both VTC and active-CTC transmissions: In this case, we select the values $\eta_1 = 0.003$, $\eta_2 = 0.0$ and $\eta_3 = 0.001$. From

Figure 7, we observe that the solution trajectories converge to the equilibrium $Ð_3 = (757.27, 4.50, 1.21, 0.67, 0, 15.66)$.

Case 4: HIV dynamics with only VTC transmission: Here, we consider the values $\eta_1 = 0.002$, $\eta_2 = \eta_3 = 0.00$. Figure 7 displays that the solution trajectories approach the equilibrium $Ð_3 = (882.35, 2.18, 0.58, 0.67, 0, 4.15)$.



(a) Healthy CD4$^+$T cells
(b) Silent HIV-infected cells
(c) Active HIV-infected cells
(d) Free HIV particles
(e) HIV-specific CTLs
(f) HIV-specific antibodies

Figure 7. The evolution of HIV dynamics (6.1) under different modes of transmissions.

Case 5: HIV dynamics with only VTC transmission: In this situation, we pick the parameters $\eta_1 = 0.001$, $\eta_2 = \eta_3 = 0.0$. It is clear from Figure 7 that the solution trajectories reach the equilibrium $Ð_0 = (1000, 0, 0, 0, 0, 0)$.

From the above we note that the presence of silent-CTC and/or active-CTC transmissions increase the infection rate. As a result, the concentration of the healthy cells is decreased while the concentrations of silent/active infected cells, free HIV particles, CTL cells and antibodies are increased as shown in Figure 7.

7. Conclusion and discussion

In this work, we proposed an HIV dynamics model in the presence of CTLs and antibodies. Three types of distributed-time delays were incorporated into the model. We took into consideration two routes of transmission, VTC and CTC. The CTC transmission is due to (i) the contact between healthy $CD4^{+}T$ cells and silent HIV-infected cells, and (ii) the contact between healthy $CD4^{+}T$ cells and active HIV-infected cells. We proved that the solutions of the model are nonnegative and bounded. We showed that the model has five possible equilibria, and their existence is determined by five threshold parameters. We investigated the global asymptotic stability of all equilibria by constructing Lyapunov functionals and applying LaSalle's invariance principle. We conducted numerical simulations to illustrate the results of Theorems 5.1-5.5. We studied the influence of time delay and CTC transmission on the dynamical behavior of the system. Numerical simulation of our proposed model give the following results. (1) The results indicated that the intracellular delay is one of the key factors in controlling the disease. (2) The presence of CTC transmission poses a challenge to the existing antiviral drug treatments. Thus, such transmission will increase the infection progression within the host. Those findings might be helpful in designing treatment for the control of HIV infection. Our proposed HIV dynamics model can be generalized and extended to incorporate different biological effects such as reaction-diffusion [3, 4, 12, 13] and stochastic interactions [29].

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