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Research article

Stability of an adaptive immunity viral infection model with multi-stages of infected cells and two routes of infection

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Abstract: This paper studies an $(n+4)$-dimensional nonlinear viral infection model that characterizes the interactions of the viruses, susceptible host cells, n-stages of infected cells, CTL cells and B cells. Both viral and cellular infections have been incorporated into the model. The well-posedness of the model is justified. The model admits five equilibria which are determined by five threshold parameters. The global stability of each equilibrium is proven by utilizing Lyapunov function and LaSalle's invariance principle. The theoretical results are illustrated by numerical simulations.

Keywords: viral and cellular infections; global stability; adaptive immune response; Lyapunov function; multi-staged infected cells.

1. Introduction

In the last decades, many researchers have formulated various mathematical models to characterize the human immune system reaction on invading viruses [1–6]. The two mean immune system reactions are the cell-mediated immunity and the humoral immunity. The cell-mediated immunity is based on Cytotoxic T Lymphocytes (CTLs) which kill the infected cells, while the humoral immunity is based on antibodies which are produced by B cells and neutralize the free viruses from the plasma. Some existing models describe the virus dynamics under the effect of cell-mediated immune response (see e.g., [7–10], see also [11] and the references therein) or humoral immune response [12–17]. Wodarz [18] has formulated a virus dynamics model with five compartments; susceptible cells (S), infected

cells (I), virus particles (V), B cells (A) and CTL cells (B) as:

$$\begin{cases} \dot{S}(t) = \rho - \alpha S(t) - \eta S(t)V(t), \\ \dot{I}(t) = \eta S(t)V(t) - bI(t) - \mu C(t)I(t), \\ \dot{V}(t) = dI(t) - \gamma A(t)V(t) - \varepsilon V(t), \\ \dot{A}(t) = \tau A(t)V(t) - \zeta A(t), \\ \dot{C}(t) = \sigma C(t)I_n(t) - \pi C(t). \end{cases} \tag{1.1}$$

The model has been extended in [19–23], but with virus-to-cell transmission. Cell-to-cell infection plays an important role in increasing the number of infected cells. Mathematical models of virus dynamics with both virus-to-cell and cell-to-cell transmissions have been studied in several works (see e.g., [24–34]). In very recent works [35], both CTL cells and B cells have been incorporated into the viral infection models with both cell-to-cell and virus-to-cell transmissions. However, in [35], only one class of infected cells (actively infected cells) is considered. It has been reported in [36] and [37] that the time from the contact of viruses and susceptible cells to the death of the cells can be modeled by dividing the process into n short stages $I_1 \to I_2 \to .... \to I_n$. In [38], virus dynamics models with multi-staged infected cells, humoral immunity and with only virus-to-cell infection have been studied.

The aim of the present paper is to formulate a virus dynamics model by incorporating (i) multi-staged infected cells, (ii) both cell-mediated and humoral immune responses (ii) both cell-to-cell and virus-to-cell infections as:

$$\begin{cases} \dot{S}(t) = \rho - \alpha S(t) - \eta_1 S(t)V(t) - \eta_2 S(t)I_n(t), \\ \dot{I}_1(t) = \eta_1 S(t)V(t) + \eta_2 S(t)I_n(t) - b_1 I_1(t), \\ \dot{I}_k(t) = d_{k-1}I_{k-1}(t) - b_k I_k(t), \qquad k = 2, ..., n-1, \\ \dot{I}_n(t) = d_{n-1}I_{n-1}(t) - b_n I_n(t) - \mu C(t)I_n(t), \\ \dot{V}(t) = d_n I_n(t) - \gamma A(t)V(t) - \varepsilon V(t), \\ \dot{A}(t) = \tau A(t)V(t) - \zeta A(t), \\ \dot{C}(t) = \sigma C(t)I_n(t) - \pi C(t), \end{cases} \tag{1.2}$$

where, I_k, $k = 1, 2, ..., n$ represents the concentration of the i-th stage of infected cells. The model assumes that the susceptible cells are infected by virus particles at rate $\eta_1 S(t)V(t)$ and by infected cells at rate $\eta_2 S(t)I_n(t)$.

2. Well-Posedness of solutions

Let $\Omega_j > 0$, $j = 1, 2, ..., n+3$ and define

$$\Theta = \Big\{(S, I_1, ..., I_n, V, A, C) \in \mathbb{R}^{n+4}_{\geq 0} : 0 \leq S, I_1 \leq \Omega_1, 0 \leq I_k \leq \Omega_k, 0 \leq C \leq \Omega_{n+1}, \\ 0 \leq V \leq \Omega_{n+2}, 0 \leq A \leq \Omega_{n+3},\ k = 2, ..., n\Big\}.$$

Proposition 1. The compact set Θ is positively invariant for system (1.2).

Proof. We have

$$\dot{S}\ |_{S=0} = \rho > 0, \qquad \dot{I}_1\ |_{I_1=0} = \eta_1 S V + \eta_2 S I_n \geq 0 \quad \forall\ S, V, I_n \geq 0,$$
$$\dot{I}_k\ |_{I_k=0} = d_{k-1}I_{k-1} \geq 0, \qquad \forall\ I_{k-1} \geq 0, k = 2, ..., n,$$

$$\dot{V}\mid_{V=0}= d_n I_n \geq 0, \quad \forall I_n \geq 0, \quad \dot{A}\mid_{A=0}= 0, \quad \dot{C}\mid_{C=0}= 0.$$

This insures that, $S(t) > 0$, $I_k(t) \geq 0$, $k = 1, ..., n$, $V(t) \geq 0$, $A(t) \geq 0$, and $C(t) \geq 0$ for all $t \geq 0$.

To show the boundedness of $S(t)$ and $I_1(t)$ we let $\Psi_1(t) = S(t) + I_1(t)$, then

$$\dot{\Psi}_1 = \rho - \alpha S - b_1 I_1 \leq \rho - \phi_1 (S + I_1) = \rho - \phi_1 \Psi_1,$$

where $\phi_1 = \min\{\alpha, b_1\}$. It follows that,

$$\Psi_1(t) \leq e^{-\phi_1 t}\left(\Psi_1(0) - \frac{\rho}{\phi_1}\right) + \frac{\rho}{\phi_1}.$$

Hence, $0 \leq \Psi_1(t) \leq \Omega_1$ if $\Psi_1(0) \leq \Omega_1$ for $t \geq 0$, where $\Omega_1 = \frac{\rho}{\phi_1}$. Since $S(t) > 0$ and $I_1(t) \geq 0$, then $0 \leq S(t), I_1(t) \leq \Omega_1$ if $S(0) + I_1(0) \leq \Omega_1$. From the fourth equation of system (1.2) in case of $k = 2$, we have

$$\dot{I}_2 = d_1 I_1 - b_2 I_2 \leq d_1 \Omega_1 - b_2 I_2.$$

It follows that, $0 \leq I_2(t) \leq \Omega_2$ if $I_2(0) \leq \Omega_2$, where $\Omega_2 = \dfrac{d_1\Omega_1}{b_2}$. Similarly, we can show $0 \leq I_k(t) \leq \Omega_k$ if $I_k(0) \leq \Omega_k$, where $\Omega_k = \dfrac{d_{k-1}\Omega_{k-1}}{b_k}$, $k = 3, ..., n-1$. Further, we let $\Psi_2(t) = I_n(t) + \frac{\mu}{\sigma}C(t)$, then

$$\dot{\Psi}_2 = d_{n-1} I_{n-1} - b_n I_n - \frac{\mu\pi}{\sigma} C \leq d_{n-1}\Omega_{n-1} - \phi_2\left(I_n + \frac{\mu}{\sigma}C\right) = d_{n-1}\Omega_{n-1} - \phi_2\Psi_2,$$

where $\phi_2 = \min\{b_n, \pi\}$. It follows that, $0 \leq \Psi_2(t) \leq \Omega_n$ if $\Psi_2(0) \leq \Omega_n$, where $\Omega_n = \dfrac{d_{n-1}\Omega_{n-1}}{\phi_2}$. Since $I_n(t) \geq 0$ and $C(t) \geq 0$, then $0 \leq I_n(t) \leq \Omega_n$ and $0 \leq C(t) \leq \Omega_{n+1}$ if $I_n(0) + \frac{\mu}{\sigma}C(0) \leq \Omega_n$, where $\Omega_{n+1} = \frac{\sigma}{\mu}\Omega_n$. Finally, let $\Psi_3(t) = V(t) + \frac{\gamma}{\tau}A(t)$, then

$$\dot{\Psi}_3 = d_n I_n - \varepsilon V - \frac{\gamma\zeta}{\tau} A \leq d_n\Omega_n - \phi_3\left(V + \frac{\gamma}{\tau}A\right) = d_n\Omega_n - \phi_3\Psi_3,$$

where $\phi_3 = \min\{\varepsilon, \zeta\}$. It follows that, $0 \leq \Psi_3(t) \leq \Omega_{n+2}$ if $\Psi_3(0) \leq \Omega_{n+2}$, where $\Omega_{n+2} = \dfrac{d_n\Omega_n}{\phi_3}$. It follows that, $0 \leq V(t) \leq \Omega_{n+2}$ and $0 \leq A(t) \leq \Omega_{n+3}$ if $V(0) + \frac{\gamma}{\tau}A(0) \leq \Omega_{n+2}$, where $\Omega_{n+3} = \frac{\tau}{\gamma}\Omega_{n+2}$. □

3. Threshold parameters and equilibria

In this section, we derive five threshold parameters which guarantee the existence of the equilibria of the model.

Lemma 1. System (1.2) has five threshold parameters $\mathfrak{R}_0 > 0$, $\mathfrak{R}_1^A > 0$, $\mathfrak{R}_1^C > 0$, $\mathfrak{R}_2^C > 0$ and $\mathfrak{R}_2^A > 0$ with $\mathfrak{R}_1^C < \mathfrak{R}_0$ such that

(i) if $\mathfrak{R}_0 \leq 1$, then there exists only one steady state $Ð_0$,

(ii) if $\mathfrak{R}_1^A \leq 1$ and $\mathfrak{R}_1^C \leq 1 < \mathfrak{R}_0$, then there exist only two equilibria $Ð_0$ and $\bar{Ð}$,

(iii) if $\mathfrak{R}_1^A > 1$ and $\mathfrak{R}_2^C \leq 1$, then there exist only three equilibria $Ð_0$, $\bar{Ð}$ and $\hat{Ð}$,

(iv) if $\mathfrak{R}_1^C > 1$ and $\mathfrak{R}_2^A \leq 1$, then there exist only three equilibria $Ð_0$, $\bar{Ð}$ and $\check{Ð}$, and

(v) if $\mathfrak{R}_2^A > 1$ and $\mathfrak{R}_2^C > 1$, then there exist five equilibria $Ð_0$, $\bar{Ð}$, $\hat{Ð}$, $\check{Ð}$ and $\tilde{Ð}$.

Proof. Let $(S, I_1, ..., I_n, V, A, C)$ be any equilibrium of system (1.2) satisfying the following equations:

$$\rho - \alpha S - \eta_1 S V - \eta_2 S I_n = 0, \tag{3.1}$$
$$\eta_1 S V + \eta_2 S I_n - b_1 I_1 = 0, \tag{3.2}$$
$$d_{k-1} I_{k-1} - b_k I_k = 0, \qquad k = 2, ..., n-1, \tag{3.3}$$
$$d_{n-1} I_{n-1} - b_n I_n - \mu C I_n = 0, \tag{3.4}$$
$$d_n I_n - \gamma A V - \varepsilon V = 0, \tag{3.5}$$
$$(\tau V - \zeta) A = 0, \tag{3.6}$$
$$(\sigma I_n - \pi) C = 0. \tag{3.7}$$

We find that system (1.2) admits five equilibria.

(i) Infection-free equilibrium $Ð_0 = (S_0, \overbrace{0, ..., 0, 0}^{n+3})$, where $S_0 = \rho/\alpha$.

(ii) Chronic-infection equilibrium with inactive immune response $\bar{Ð}= (\bar{S}, \bar{I}_1, ..., \bar{I}_n, \bar{V}, 0, 0)$, where

$$\bar{S} = \left(\prod_{i=1}^{n} \frac{b_i}{d_i}\right) \frac{\varepsilon d_n}{\eta_1 d_n + \eta_2 \varepsilon},$$
$$\bar{I}_k = \frac{\varepsilon \alpha d_n}{d_k (\eta_1 d_n + \eta_2 \varepsilon)} \left(\prod_{i=1}^{k} \frac{d_i}{b_i}\right)\left(\prod_{i=1}^{n} \frac{b_i}{d_i}\right)\left(\frac{(\eta_1 d_n + \eta_2 \varepsilon) S_0}{\varepsilon d_n} \left(\prod_{i=1}^{n} \frac{d_i}{b_i}\right) - 1\right), \ k = 1, 2, ..., n,$$
$$\bar{V} = \frac{\alpha d_n}{\eta_1 d_n + \eta_2 \varepsilon} \left(\frac{(\eta_1 d_n + \eta_2 \varepsilon) S_0}{\varepsilon d_n} \left(\prod_{i=1}^{n} \frac{d_i}{b_i}\right) - 1\right).$$

Therefore, $\bar{Ð}$ exists when

$$\frac{(\eta_1 d_n + \eta_2 \varepsilon) S_0}{\varepsilon d_n} \left(\prod_{i=1}^{n} \frac{d_i}{b_i}\right) > 1.$$

At the equilibrium $\bar{Ð}$ the disease persists while the immune response is inhibited. The basic infection reproductive ratio for system (1.2) is defined as:

$$\mathfrak{R}_0 = \frac{(\eta_1 d_n + \eta_2 \varepsilon) S_0}{\varepsilon d_n} \left(\prod_{i=1}^{n} \frac{d_i}{b_i}\right).$$

The parameter $\mathfrak{R}_0$ determines whether the disease will progress or not. In terms of $\mathfrak{R}_0$, we can write

$$\bar{S} = \frac{S_0}{\mathfrak{R}_0},$$
$$\bar{I}_k = \frac{\varepsilon \alpha d_n}{d_k (\eta_1 d_n + \eta_2 \varepsilon)} \left(\prod_{i=1}^{k} \frac{d_i}{b_i}\right)\left(\prod_{i=1}^{n} \frac{b_i}{d_i}\right)(\mathfrak{R}_0 - 1), \ k = 1, 2, ..., n,$$
$$\bar{V} = \frac{\alpha d_n}{\eta_1 d_n + \eta_2 \varepsilon} (\mathfrak{R}_0 - 1).$$

(iii) Chronic-infection equilibrium with only active humoral immune response $\hat{\text{D}}= (\hat{S}, \hat{I}_1, ..., \hat{I}_n, \hat{V}, \hat{A}, 0)$, where

$$\hat{S} = \frac{\tau\rho}{\alpha\tau + \eta_1\zeta + \eta_2\tau\hat{I}_n}, \quad \hat{I}_k = \left(\prod_{i=1}^{k}\frac{d_i}{b_i}\right)\frac{\rho\left(\eta_1\zeta + \eta_2\tau\hat{I}_n\right)}{d_k\left(\alpha\tau + \eta_1\zeta + \eta_2\tau\hat{I}_n\right)},\ k = 1, 2, ..., n-1,$$
$$\hat{V} = \frac{\zeta}{\tau}, \quad \hat{A} = \frac{\varepsilon}{\gamma}\left(\frac{d_n\tau}{\varepsilon\zeta}\hat{I}_n - 1\right),$$

where

$$\hat{I}_n = \frac{-\varpi_2 + \sqrt{\varpi_2^2 - 4\varpi_1\varpi_3}}{2\varpi_1} \tag{3.8}$$

is the positive solution of

$$\varpi_1\hat{I}_n^2 + \varpi_2\hat{I}_n + \varpi_3 = 0,$$

with

$$\varpi_1 = \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_n\eta_2\tau,\ \varpi_2 = \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_n\left(\eta_1\zeta + \alpha\tau\right) - \rho\eta_2\tau,\ \varpi_3 = -\eta_1\rho\zeta. \tag{3.9}$$

We note that $\hat{\text{D}}$ exists when $\frac{d_n\tau}{\varepsilon\zeta}\hat{I}_n > 1$. Let us define the active humoral immunity reproductive ratio

$$\mathfrak{R}_1^A = \frac{d_n\tau}{\varepsilon\zeta}\hat{I}_n = \frac{d_n\hat{I}_n}{\varepsilon\hat{V}}, \tag{3.10}$$

which determines when the humoral immune response is activated. Thus, $\hat{A} = \frac{\varepsilon}{\gamma}\left(\mathfrak{R}_1^A - 1\right)$.

(iv) Chronic-infection equilibrium with only active cell-mediated immune response $\check{\text{D}}= (\check{S}, \check{I}_1, ..., \check{I}_n, \check{V}, 0, \check{C})$, where

$$\check{S} = \frac{\varepsilon\sigma\rho}{\pi\left(\eta_1 d_n + \eta_2\varepsilon\right) + \alpha\varepsilon\sigma}, \quad \check{I}_n = \frac{\pi}{\sigma}, \quad \check{V} = \frac{d_n\pi}{\varepsilon\sigma} = \frac{d_n}{\varepsilon}\check{I}_n,$$
$$\check{I}_k = \left(\prod_{i=1}^{k}\frac{d_i}{b_i}\right)\frac{\rho\pi\left(\eta_1 d_n + \eta_2\varepsilon\right)}{d_k\left[\pi\left(\eta_1 d_n + \eta_2\varepsilon\right) + \alpha\varepsilon\sigma\right]},\ k = 1, 2, ..., n-1,$$
$$\check{C} = \frac{b_n}{\mu}\left[\frac{\sigma\rho\left(\eta_1 d_n + \eta_2\varepsilon\right)}{d_n\left[\pi\left(\eta_1 d_n + \eta_2\varepsilon\right) + \alpha\varepsilon\sigma\right]}\left(\prod_{i=1}^{n}\frac{d_i}{b_i}\right) - 1\right].$$

We note that $\check{\text{D}}$ exists when $\frac{\sigma\rho\left(\eta_1 d_n + \eta_2\varepsilon\right)}{d_n\left[\pi\left(\eta_1 d_n + \eta_2\varepsilon\right) + \alpha\varepsilon\sigma\right]}\left(\prod_{i=1}^{n}\frac{d_i}{b_i}\right) > 1$. The active cell-mediated immunity reproductive ratio is stated as:

$$\mathfrak{R}_1^C = \frac{\sigma\rho\left(\eta_1 d_n + \eta_2\varepsilon\right)}{d_n\left[\pi\left(\eta_1 d_n + \eta_2\varepsilon\right) + \alpha\varepsilon\sigma\right]}\left(\prod_{i=1}^{n}\frac{d_i}{b_i}\right) = \frac{\mathfrak{R}_0}{1 + \frac{\pi\left(\eta_1 d_n + \eta_2\varepsilon\right)}{\alpha\varepsilon\sigma}}.$$

The parameter $\mathfrak{R}_1^C$ determines when the cell-mediated immune response is activated. Thus, $\check{C} = \frac{b_n}{\mu}(\mathfrak{R}_1^C - 1)$ and $\mathfrak{R}_1^C < \mathfrak{R}_0$.

(v) Chronic-infection equilibrium with both active humoral and cell-mediated immune responses $\tilde{\text{Đ}}= (\tilde{S}, \tilde{I}_1, ..., \tilde{I}_n, \tilde{V}, \tilde{A}, \tilde{C})$, where

$$\tilde{S} = \frac{\rho\tau\sigma}{\alpha\tau\sigma + \eta_1\zeta\sigma + \eta_2\tau\pi}, \quad \tilde{I}_n = \frac{\pi}{\sigma} = \check{I}_n, \quad \tilde{V} = \frac{\zeta}{\tau} = \hat{V},$$
$$\tilde{I}_k = \left(\prod_{i=1}^{k}\frac{d_i}{b_i}\right)\frac{\rho\left(\eta_1\zeta\sigma + \eta_2\tau\pi\right)}{d_k\left[\alpha\tau\sigma + \eta_1\zeta\sigma + \eta_2\tau\pi\right]},\ k = 1, 2, ..., n-1,$$
$$\tilde{C} = \frac{b_n}{\mu}\left[\frac{\sigma\rho\left(\eta_1\zeta\sigma + \eta_2\tau\pi\right)}{d_n\pi\left[\alpha\tau\sigma + \eta_1\zeta\sigma + \eta_2\tau\pi\right]}\left(\prod_{i=1}^{n}\frac{d_i}{b_i}\right) - 1\right],$$
$$\tilde{A} = \frac{\varepsilon}{\gamma}\left(\frac{d_n\pi\tau}{\varepsilon\sigma\zeta} - 1\right).$$

It is obvious that $\tilde{\text{Đ}}$ exists when $\frac{\sigma\rho\left(\eta_1\zeta\sigma + \eta_2\tau\pi\right)}{d_n\pi\left[\alpha\tau\sigma + \eta_1\zeta\sigma + \eta_2\tau\pi\right]}\left(\prod_{i=1}^{n}\frac{d_i}{b_i}\right) > 1$ and $\frac{d_n\pi\tau}{\varepsilon\sigma\zeta} > 1$. Now we define

$$\mathfrak{R}_2^C = \frac{\sigma\rho\left(\eta_1\zeta\sigma + \eta_2\tau\pi\right)}{d_n\pi\left[\alpha\tau\sigma + \eta_1\zeta\sigma + \eta_2\tau\pi\right]}\left(\prod_{i=1}^{n}\frac{d_i}{b_i}\right) \text{ and } \mathfrak{R}_2^A = \frac{d_n\pi\tau}{\varepsilon\sigma\zeta} = \frac{\tau}{\zeta}\check{V},$$

where $\mathfrak{R}_2^C$ refers to the competed cell-mediated immunity reproductive ratio and appears as the average number of T cells activated due to infectious cells in the scene that the humoral immune response has been constructed, while, $\mathfrak{R}_2^A$ refers to the competed humoral immunity reproductive ratio and appears as the average number of B cells activated due to mature viruses in the scene that the cell-mediated immune response has been constructed. Clearly, $\tilde{\text{Đ}}$ exists when $\mathfrak{R}_2^C > 1$ and $\mathfrak{R}_2^A > 1$ and we can write $\tilde{C} = \frac{b_n}{\mu}\left(\mathfrak{R}_2^C - 1\right)$ and $\tilde{A} = \frac{\varepsilon}{\gamma}\left(\mathfrak{R}_2^A - 1\right)$.□

The five threshold parameters are given as follows:

$$\mathfrak{R}_0 = \frac{\left(\eta_1 d_n + \eta_2\varepsilon\right)S_0}{\varepsilon d_n}\left(\prod_{i=1}^{n}\frac{d_i}{b_i}\right),\ \mathfrak{R}_1^A = \frac{d_n\tau}{\varepsilon\zeta}\hat{I}_n = \frac{d_n\hat{I}_n}{\varepsilon\hat{V}},\ \mathfrak{R}_1^C = \frac{\sigma\rho\left(\eta_1 d_n + \eta_2\varepsilon\right)}{d_n\left[\pi\left(\eta_1 d_n + \eta_2\varepsilon\right) + \alpha\varepsilon\sigma\right]}\left(\prod_{i=1}^{n}\frac{d_i}{b_i}\right)$$
$$\mathfrak{R}_2^C = \frac{\sigma\rho\left(\eta_1\zeta\sigma + \eta_2\tau\pi\right)}{d_n\pi\left[\alpha\tau\sigma + \eta_1\zeta\sigma + \eta_2\tau\pi\right]}\left(\prod_{i=1}^{n}\frac{d_i}{b_i}\right) \text{ and } \mathfrak{R}_2^A = \frac{d_n\pi\tau}{\varepsilon\sigma\zeta} = \frac{\tau}{\zeta}\check{V}.$$

We define the active humoral immunity reproductive ratio $\mathfrak{R}_{humoral}^A$ which comes from the limiting (linearized) A-dynamics near $A = 0$ as:

$$\mathfrak{R}_{humoral}^A = \frac{\bar{V}}{\hat{V}}.$$

Lemma 2. (i) if $\mathfrak{R}_1^A < 1$, then $\mathfrak{R}_{humoral}^A < 1$,
(ii) if $\mathfrak{R}_1^A > 1$, then $\mathfrak{R}_{humoral}^A > 1$,
(iii) if $\mathfrak{R}_1^A = 1$, then $\mathfrak{R}_{humoral}^A = 1$,

Proof. (i) Let $\mathfrak{R}_1^A < 1$, then from Eq. 3.10 we have $\hat{I}_n < \frac{\varepsilon\hat{V}}{d_n}$. Then, using Eq. 3.8 we get

$$\frac{-\varpi_2 + \sqrt{\varpi_2^2 - 4\varpi_1\varpi_3}}{2\varpi_1} < \frac{\varepsilon\hat{V}}{d_n},$$

which leads to

$$\left(\frac{2\varpi_1\varepsilon\hat{V}}{d_n}+\varpi_2\right)^2-\left(\varpi_2^2-4\varpi_1\varpi_3\right)>0.$$

Using Eq. 3.9 we derive

$$4\eta_2\tau\zeta\varepsilon\hat{V}\left(\eta_1 d_n+\eta_2\varepsilon\right)\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)^2\left[1-\frac{\rho\left(\eta_1 d_n+\eta_2\varepsilon\right)-\varepsilon\alpha d_n\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)}{\varepsilon\hat{V}\left(\eta_1 d_n+\eta_2\varepsilon\right)}\left(\prod_{i=1}^{n}\frac{d_i}{b_i}\right)\right]>0$$

$$\Longrightarrow 4\eta_2\tau\zeta\varepsilon\hat{V}\left(\eta_1 d_n+\eta_2\varepsilon\right)\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)^2\left[1-\frac{\rho\left(\eta_1 d_n+\eta_2\varepsilon\right)\left(\prod_{i=1}^{n}\frac{d_i}{b_i}\right)-\varepsilon\alpha d_n}{\varepsilon\hat{V}\left(\eta_1 d_n+\eta_2\varepsilon\right)}\right]>0$$

$$\Longrightarrow 4\eta_2\tau\zeta\varepsilon\hat{V}\left(\eta_1 d_n+\eta_2\varepsilon\right)\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)^2\left[1-\frac{\bar{V}}{\hat{V}}\right]>0$$

$$\Longrightarrow 4\eta_2\tau\zeta\varepsilon\hat{V}\left(\eta_1 d_n+\eta_2\varepsilon\right)\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)^2\left[1-\mathfrak{R}^{A}_{humoral}\right]>0.$$

Thus, $\mathfrak{R}^{A}_{humoral}<1$. Using the same argument one can easily confirm part (ii) and (iii). □

4. Global stability analysis

The global stability of the each equilibria will be investigated by constructing Lyapunov functions using the method presented [39–45]. Let us define the function $F:(0,\infty)\to[0,\infty)$ as $F(\upsilon)=\upsilon-1-\ln\upsilon$. Denote $(S,I_1,...,I_n,V,A,C)=(S(t),I_1(t),...,I_n(t),V(t),A(t),C(t))$. The following equalities will be used:

$$\prod_{i=1}^{0}\frac{b_i}{d_i}=1,\ \prod_{i=1}^{0}d_i=1, \tag{4.1}$$

$$\begin{aligned}
&b_1I_1^*+\sum_{k=2}^{n-1}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)b_kI_k^*+\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)b_nI_n^*=\sum_{k=1}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)b_kI_k^*=\sum_{k=1}^{n}\left(\prod_{i=1}^{k}\frac{b_i}{d_i}\right)d_kI_k^*,\\
&\sum_{k=2}^{n-1}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)d_{k-1}I_{k-1}+\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)d_{n-1}I_{n-1}=\sum_{k=2}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)d_{k-1}I_{k-1},\\
&\sum_{k=2}^{n-1}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)b_kI_k+\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)b_nI_n=\sum_{k=2}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)b_kI_k,\\
&\sum_{k=2}^{n-1}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)d_{k-1}I_{k-1}\frac{I_k^*}{I_k}+\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)d_{n-1}I_{n-1}\frac{I_n^*}{I_n}=\sum_{k=2}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)d_{k-1}I_{k-1}\frac{I_k^*}{I_k},
\end{aligned} \tag{4.2}$$

$$\sum_{k=2}^{n-1}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\left(d_{k-1}I_{k-1}-b_kI_k\right)=b_1I_1-\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)d_{n-1}I_{n-1}, \tag{4.3}$$

where $I^* \in \left\{\bar{I}, \hat{I}, \check{I}, \tilde{I}\right\}$.

Theorem 1. If $\mathfrak{R}_0 \leq 1$, then the infection-free equilibrium $Ð_0$ is globally asymptotically stable.

Theorem 2. Suppose that $\mathfrak{R}_1^A \leq 1$ and $\mathfrak{R}_1^C \leq 1 < \mathfrak{R}_0$, then the chronic-infection equilibrium with inactive immune response $\bar{Ð}$ is globally asymptotically stable.

Theorem 3. If $\mathfrak{R}_1^A > 1$ and $\mathfrak{R}_2^C \leq 1$, then the chronic-infection equilibrium with only active humoral immune response $\hat{Ð}$ is globally asymptotically stable.

Theorem 4. Suppose that $\mathfrak{R}_1^C > 1$ and $\mathfrak{R}_2^A \leq 1$, then the chronic-infection equilibrium with only active cell-mediated immune response $\check{Ð}$ is globally asymptotically stable.

Theorem 5. If $\mathfrak{R}_2^A > 1$ and $\mathfrak{R}_2^C > 1$, then the chronic-infection equilibrium with both active humoral and cell-mediated immune responses $\tilde{Ð}$ is globally asymptotically stable.

The proofs of Theorems 1–5 are given in a Supplementary.

5. Numerical simulations

In this section, we perform some numerical simulations in case of three stages of infected cells i.e. $n = 3$.

$$\begin{cases} \dot{S} = \rho - \alpha S - \eta_1 S V - \eta_2 S I_3, \\ \dot{I}_1 = \eta_1 S V + \eta_2 S I_3 - b_1 I_1, \\ \dot{I}_2 = d_1 I_1 - b_2 I_2, \\ \dot{I}_3 = d_2 I_2 - b_3 I_3 - \mu C I_3, \\ \dot{V} = d_3 I_3 - \gamma A V - \varepsilon V, \\ \dot{A} = \tau A V - \zeta A, \\ \dot{C} = \sigma C I_3 - \pi C. \end{cases} \tag{5.1}$$

The threshold parameters $\mathfrak{R}_0$, $\mathfrak{R}_1^A$, $\mathfrak{R}_1^C$, $\mathfrak{R}_2^C$, and $\mathfrak{R}_2^A$ for system (5.1) are given by:

$$\mathfrak{R}_0 = \frac{d_1 d_2 (\eta_1 d_3 + \eta_2 \varepsilon) S_0}{b_1 b_2 b_3 \varepsilon}, \quad \mathfrak{R}_1^A = \frac{d_3 \tau}{\varepsilon \zeta} \hat{I}_3, \quad \mathfrak{R}_1^C = \frac{d_1 d_2 \sigma \rho (\eta_1 d_3 + \eta_2 \varepsilon)}{b_1 b_2 b_3 [\pi (\eta_1 d_3 + \eta_2 \varepsilon) + \alpha \varepsilon \sigma]},$$
$$\mathfrak{R}_2^C = \frac{d_1 d_2 \sigma \rho (\eta_1 \zeta \sigma + \eta_2 \tau \pi)}{b_1 b_2 b_3 \pi [\alpha \tau \sigma + \eta_1 \zeta \sigma + \eta_2 \tau \pi]}, \text{ and } \mathfrak{R}_2^A = \frac{d_3 \pi \tau}{\varepsilon \sigma \zeta},$$

where

$$\hat{I}_3 = \frac{d_1 d_2 \eta_2 \rho \tau - b_1 b_2 b_3 (\zeta \eta_1 + \alpha \tau) + \sqrt{-4 b_1 b_2 b_3 d_1 d_2 C \eta_1 \tau + (\eta_2 \rho \tau d_1 d_2 - b_1 b_2 b_3 (\zeta \eta_1 + \alpha \tau))^2}}{2 b_1 b_2 b_3 \eta_1 \tau}.$$

Table 1 contains the values of the parameters of model (5.1).

The results of Theorems 1–5 will be investigated by choosing the values of η_1, η_2, τ and σ under three different initial conditions for model (5.1) as follows:

Initial–1: $(S(0), I_1(0), I_2(0), I_3(0), V(0), A(0), C(0)) = (800, 3, 1, 1, 2, 3, 10)$, (Solid lines in the figures)

Initial–2: $(S(0), I_1(0), I_2(0), I_3(0), V(0), A(0), C(0)) = (700, 0.5, 2, 2, 3, 4, 5)$, (Dashed lines in the figures)

Initial–3: $(S(0), I_1(0), I_2(0), I_3(0), V(0), A(0), C(0)) = (300, 0.1, 0.5, 0.5, 1.5, 2, 2.5)$. (Dotted lines in the figures)

Table 1. Some values of the parameters of model (5.1).

Parameter	Value	Parameter	Value	Parameter	Value
ρ	10	b_3	0.8	γ	0.05
α	0.01	d_1	0.2	τ	Varied
η_1	Varied	d_2	1	ζ	0.1
η_2	Varied	d_3	5	σ	Varied
b_1	0.6	μ	0.1	π	0.1
b_2	0.7	ε	1.5		

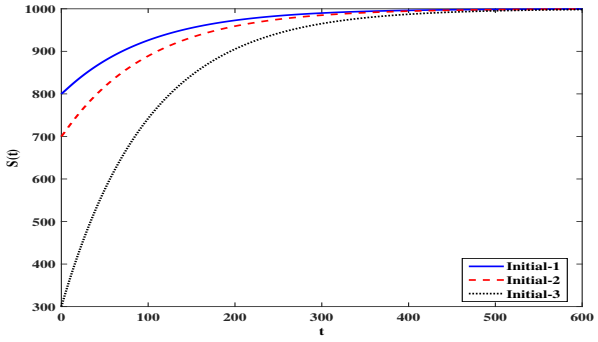
Stability of Đ_0: $\eta_1 = \eta_2 = 0.0001$**,** $\tau = 0.001$ and $\sigma = 0.01$. For this set of parameters, we have $\mathfrak{R}_0 = 0.26 < 1$, $\mathfrak{R}_1^A = 0.10 < 1$, $\mathfrak{R}_1^C = 0.18 < 1$ and $\mathfrak{R}_2^C = 0.31 < 1$. Figure 1 illustrates that the solution trajectories starting from different initial conditions reach the equilibrium $\text{Đ}_0 = (1000, 0, 0, 0, 0, 0, 0)$. This ensures that Đ_0 is globally asymptotically stable according to the result of Theorem 1. In this situation the viruses will be died out.

Stability of $\bar{\text{Đ}}$: $\eta_1 = \eta_2 = 0.001$**,** $\tau = 0.001$ and $\sigma = 0.01$. With such choice we get, $\mathfrak{R}_1^A = 0.18 < 1$ and $\mathfrak{R}_1^C = 0.48 < 1 < \mathfrak{R}_0 = 2.58$ and $\bar{\text{Đ}}$ exists with $\bar{\text{Đ}}$= $(387.68, 10.21, 2.92, 3.65, 12.15, 0, 0)$. Thus, Lemma 1 is verified. Figure 2 shows that the solution trajectories starting from different initial conditions tend to $\bar{\text{Đ}}$ and this support Theorem 2. This case represents the persistence of the viruses but with inhibited humoral and cell-mediated immune responses.

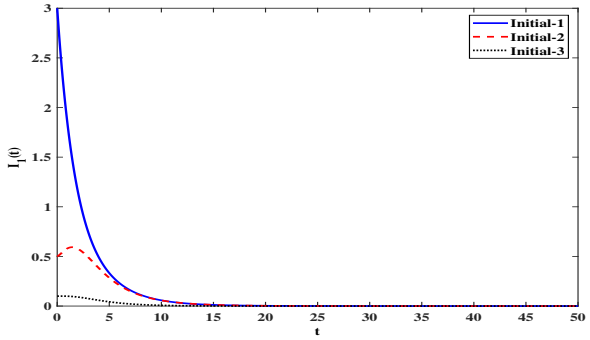
Stability of $\hat{\text{Đ}}$: $\eta_1 = \eta_2 = 0.001$**,** $\tau = 0.07$ and $\sigma = 0.05$. Then, we calculate $\mathfrak{R}_0 = 2.58 > 1$, $\mathfrak{R}_1^A = 2.94 > 1$ and $\mathfrak{R}_2^C = 0.76 < 1$. The numerical results show that $\hat{\text{Đ}}$= $(787.99, 3.53, 1.01, 1.26, 1.43, 58.34, 0)$ which confirm Lemma 1. The global stability result given in Theorem 3 is illustrated by Figure 3. This situation represents the case when the infection is chronic and the humoral immune response is active, while the cell-mediated immune response is inhibited.

Stability of $\check{\text{Đ}}$: $\eta_1 = \eta_2 = 0.001$**,** $\tau = 0.05$ and $\sigma = 0.2$. Then, we calculate $\mathfrak{R}_0 = 2.58 > 1$, $\mathfrak{R}_1^C = 2.12 > 1$ and $\mathfrak{R}_2^A = 0.83 < 1$. The results presented in Lemma 1 and Theorem 4 show that the equilibrium $\check{\text{Đ}}$ exists and it is globally asymptotically stable. Figure 4 supports the results of Theorem 4, where the solution trajectories of the system starting from different initial conditions reach the equilibrium point $\check{\text{Đ}}$= $(821.91, 2.97, 0.85, 0.50, 1.67, 0, 8.96)$. This situation represents the case when the infection is chronic and the cell-mediated immune response is active, while the humoral immune response is inhibited.

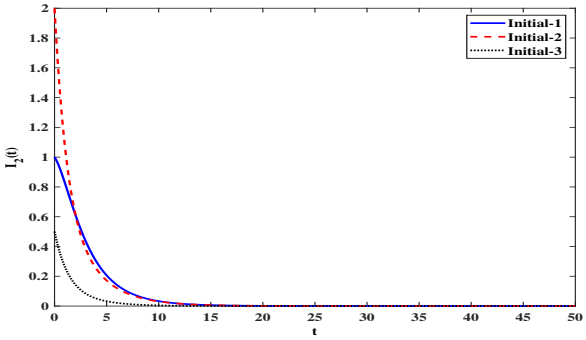
Stability of $\tilde{\text{Đ}}$: $\eta_1 = \eta_2 = 0.001$**,** $\tau = 0.07$ and $\sigma = 0.2$. Then, we calculate $\mathfrak{R}_0 = 2.58 > 1$ and $\mathfrak{R}_2^A = 1.17 > 1$, $\mathfrak{R}_2^C = 1.92 > 1$. The numerical results show that $\tilde{\text{Đ}}$= $(838.32, 2.69, 0.77, 0.50, 1.43, 5.00, 7.40)$ which ensure Lemma 1. Moreover, the global stability result given in Theorem 5 is demonstrated in Figure 5. It can be seen that the solution trajectories of the system starting from different initial conditions converge to the equilibrium $\tilde{\text{Đ}}$. This situation represents the case when the infection is chronic and both immune responses are active.



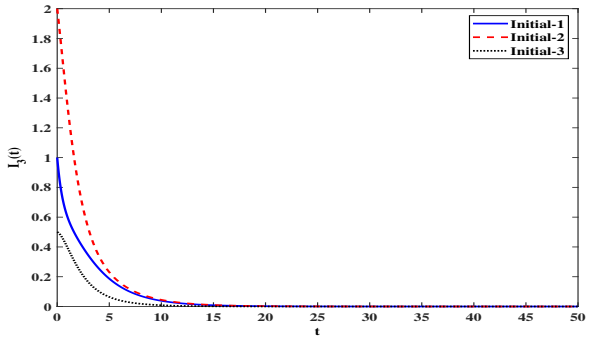
(a) The behavior of susceptible cells



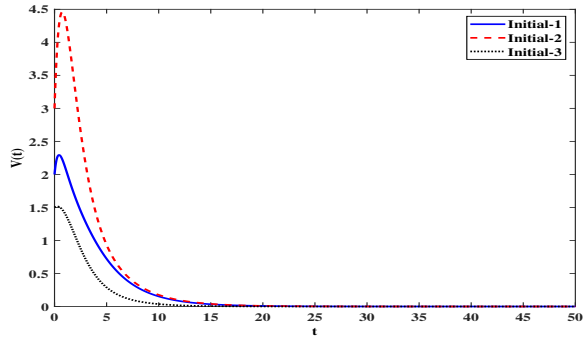
(b) The behavior of first stage of infected cells



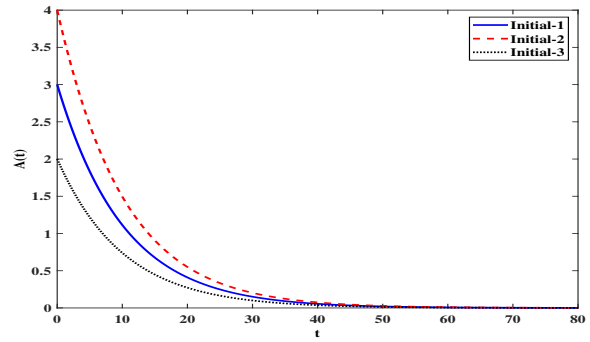
(c) The behavior of second stage of infected cells



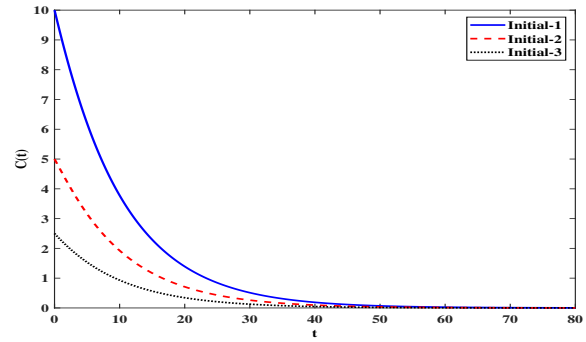
(d) The behavior of third stage of infected cells



(e) The behavior of virus particles

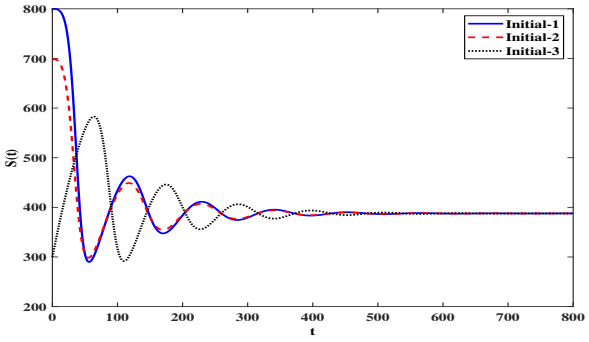


(f) The behavior of B cells

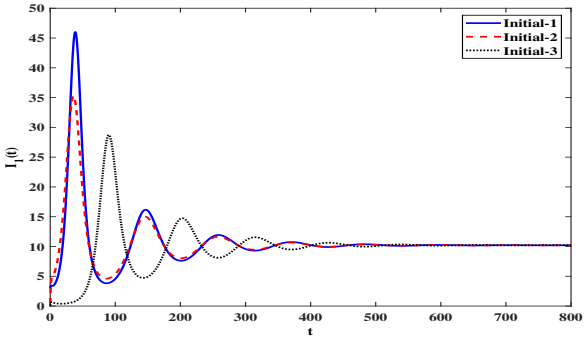


(g) The behavior of CTLs

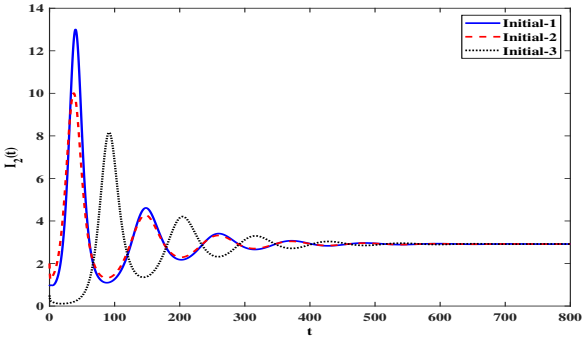
Figure 1. Solution trajectories of system (5.1) when $\mathfrak{R}_0 \leq 1$.



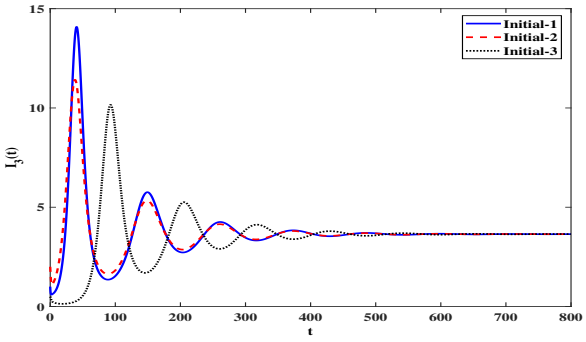
(a) The behavior of susceptible cells



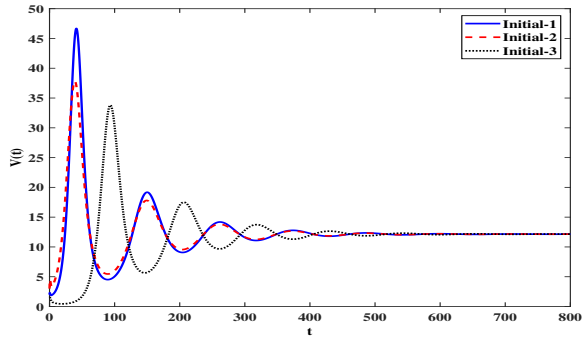
(b) The behavior of first stage of infected cells



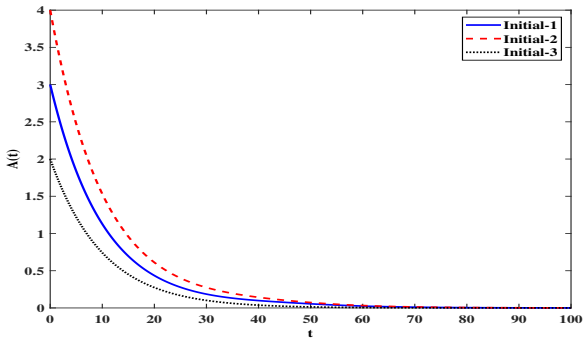
(c) The behavior of second stage of infected cells



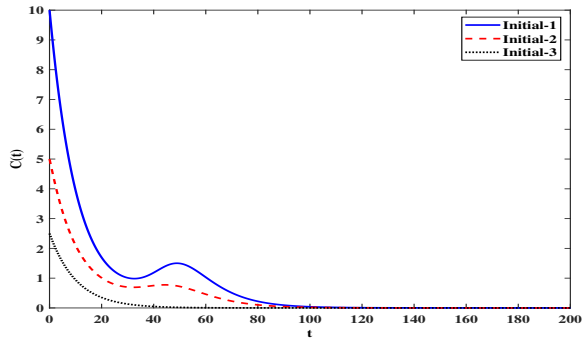
(d) The behavior of third stage of infected cells



(e) The behavior of virus particles

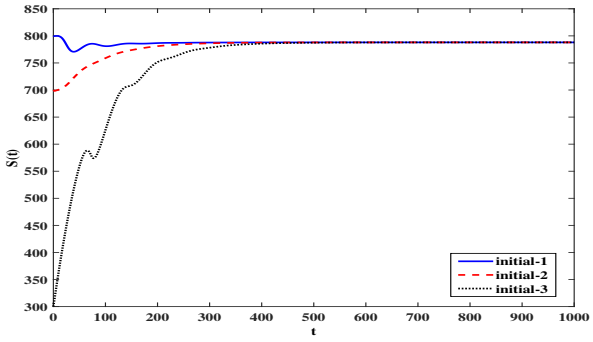


(f) The behavior of B cells

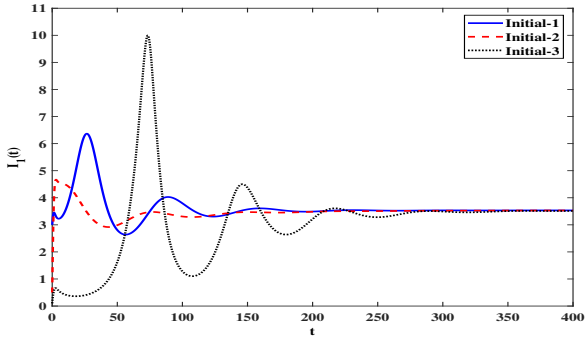


(g) The behavior of CTLs

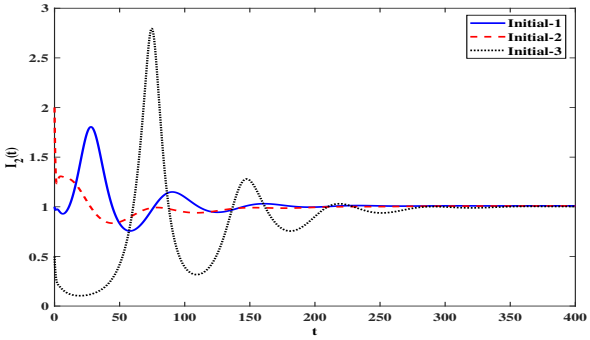
Figure 2. Solution trajectories of system (5.1) when $\mathfrak{R}_1^A \leq 1$ and $\mathfrak{R}_1^C \leq 1 < \mathfrak{R}_0$.



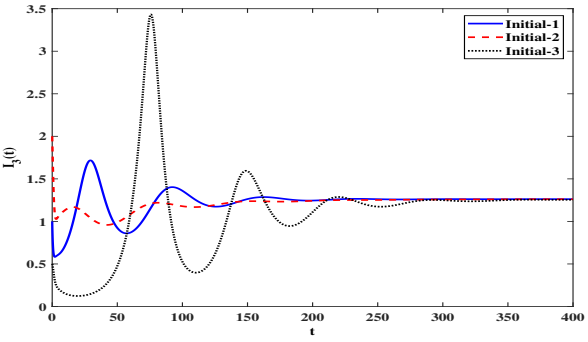
(a) The behavior of susceptible cells



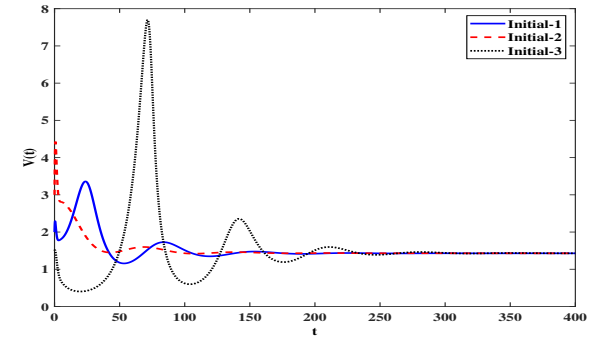
(b) The behavior of first stage of infected cells



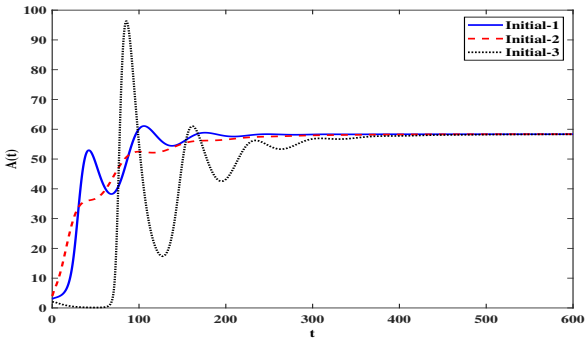
(c) The behavior of second stage of infected cells



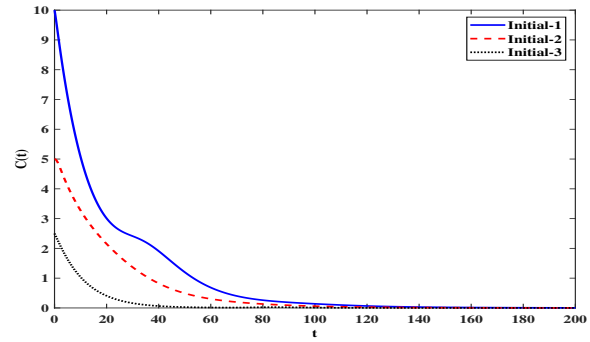
(d) The behavior of third stage of infected cells



(e) The behavior of virus particles

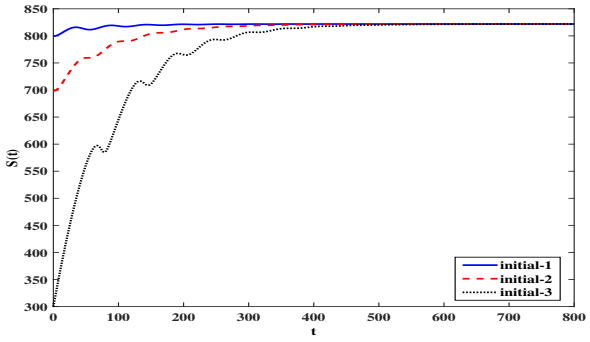


(f) The behavior of B cells

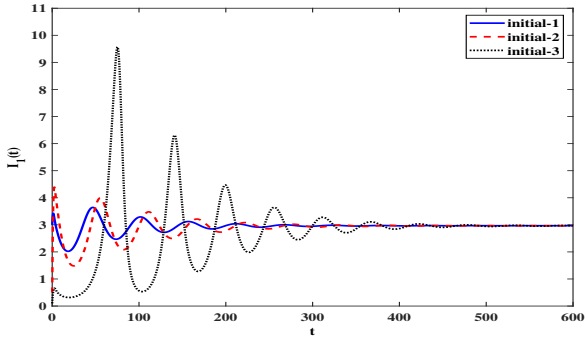


(g) The behavior of CTLs

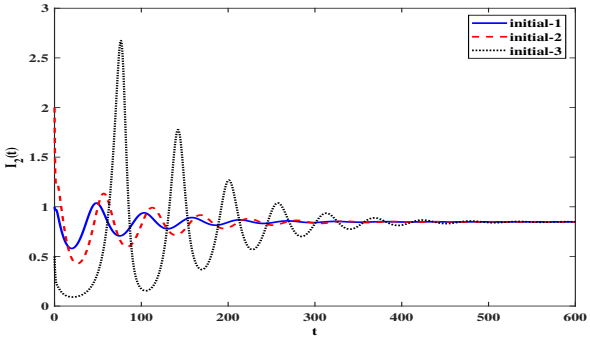
Figure 3. Solution trajectories of system (5.1) when $\Re_1^A > 1$ and $\Re_2^C \leq 1$.



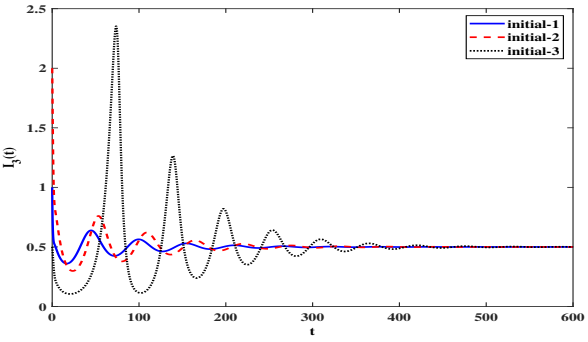
(a) The behavior of susceptible cells



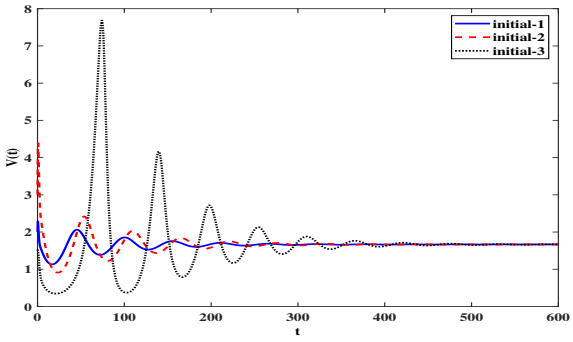
(b) The behavior of first stage of infected cells



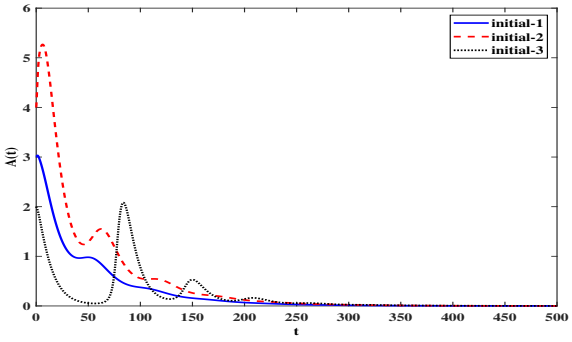
(c) The behavior of second stage of infected cells



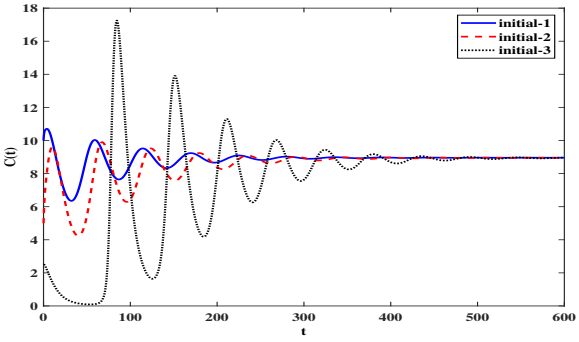
(d) The behavior of third stage of infected cells



(e) The behavior of virus particles

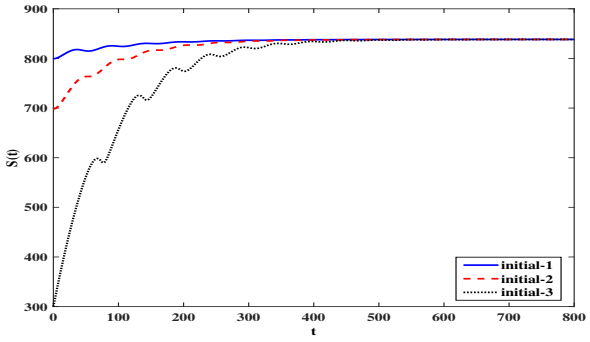


(f) The behavior of B cells

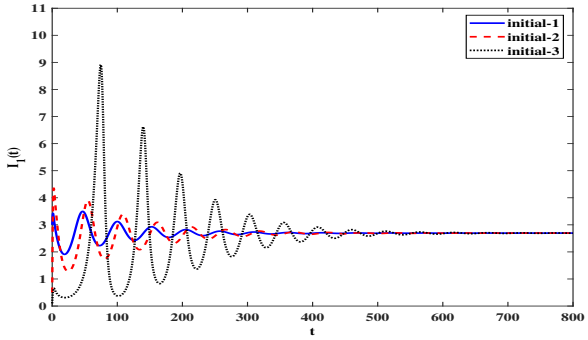


(g) The behavior of CTLs

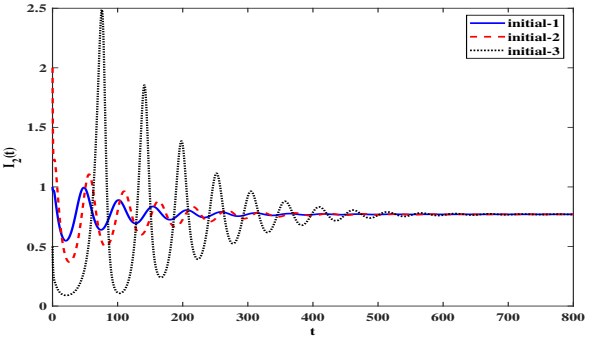
Figure 4. Solution trajectories of system (5.1) when $\Re_1^C > 1$ and $\Re_2^A \leq 1$.



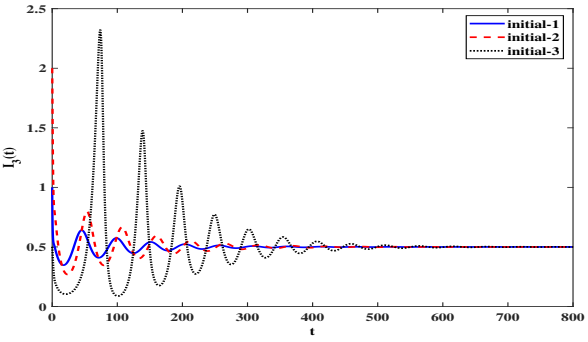
(a) The behavior of susceptible cells



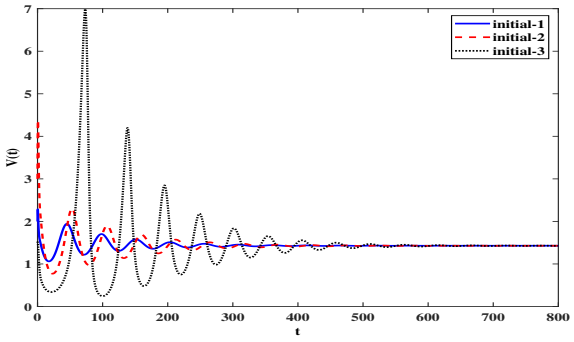
(b) The behavior of first stage of infected cells



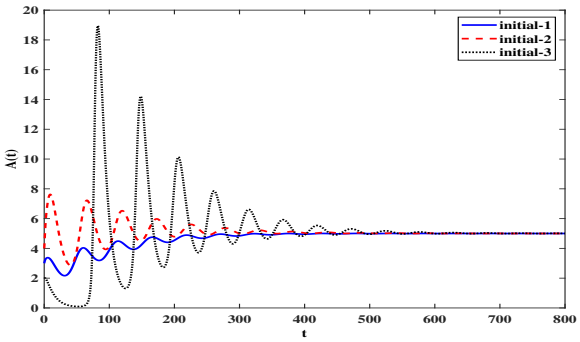
(c) The behavior of second stage of infected cells



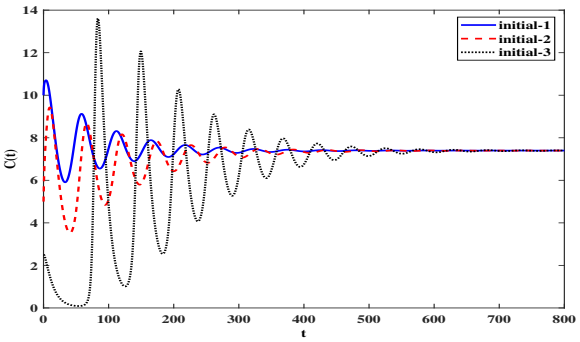
(d) The behavior of third stage of infected cells



(e) The behavior of virus particles



(f) The behavior of B cells



(g) The behavior of CTLs

Figure 5. Solution trajectories of system (5.1) when $\Re_2^A > 1$ and $\Re_2^C > 1$.

5.1. Comparison results

We consider system (5.1) under the effect of two types of treatment as:

$$\begin{cases} \dot{S} = \rho - \alpha S - (1-\epsilon_1)\eta_1 S V - (1-\epsilon_2)\eta_2 S I_3, \\ \dot{I}_1 = (1-\epsilon_1)\eta_1 S V + (1-\epsilon_2)\eta_2 S I_3 - b_1 I_1, \\ \dot{I}_2 = d_1 I_1 - b_2 I_2, \\ \dot{I}_3 = d_2 I_2 - b_3 I_3 - \mu C I_3, \\ \dot{V} = d_3 I_3 - \gamma A V - \varepsilon V, \\ \dot{A} = \tau A V - \zeta A, \\ \dot{C} = \sigma C I_3 - \pi C, \end{cases} \tag{5.2}$$

where, the parameter $\epsilon_1 \in [0,1]$ is the efficacy of antiretroviral therapy in blocking infection by virus-to-cell mechanism, and $\epsilon_2 \in [0,1]$ is the efficacy of therapy in blocking infection by cell-to-cell mechanism [47].

The basic reproduction number of system (5.2) is given by

$$\mathfrak{R}_{0,(5.2)}(\epsilon_1,\epsilon_2) = (1-\epsilon_1)\mathfrak{R}_{01} + (1-\epsilon_2)\mathfrak{R}_{02},$$

where

$$\mathfrak{R}_{01} = \frac{d_1 d_2 d_3 \eta_1 S_0}{b_1 b_2 b_3 \varepsilon}, \qquad \mathfrak{R}_{02} = \frac{d_1 d_2 \eta_2 S_0}{b_1 b_2 b_3}.$$

When the cell-to-cell transmission is neglected, system (5.2) leads to the following system:

$$\begin{cases} \dot{S} = \rho - \alpha S - (1-\epsilon_1)\eta_1 S V, \\ \dot{I}_1 = (1-\epsilon_1)\eta_1 S V - b_1 I_1, \\ \dot{I}_2 = d_1 I_1 - b_2 I_2, \\ \dot{I}_3 = d_2 I_2 - b_3 I_3 - \mu C I_3, \\ \dot{V} = d_3 I_3 - \gamma A V - \varepsilon V, \\ \dot{A} = \tau A V - \zeta A, \\ \dot{C} = \sigma C I_3 - \pi C. \end{cases} \tag{5.3}$$

The basic reproduction number of system (5.3) is given by

$$\mathfrak{R}_{0,(5.3)}(\epsilon_1) = (1-\epsilon_1)\mathfrak{R}_{01}.$$

Without loss of generality we let $\epsilon_1 = \epsilon_2 = \epsilon$. Now we calculate the minimum drug efficacy ϵ which stabilize the infection-free equilibrium for systems (5.2) and (5.3). For system (5.2) one can determine the minimum drug efficacy $\epsilon^{\min}_{(5.2)}$ such that $\mathfrak{R}_{0,(5.2)}(\epsilon) \leq 1$ for all $\epsilon^{\min}_{(5.2)} \leq \epsilon \leq 1$ as:

$$\epsilon^{\min}_{(5.2)} = \max\left\{1 - \frac{1}{\mathfrak{R}_{01} + \mathfrak{R}_{02}}, 0\right\}. \tag{5.4}$$

For system (5.3) the minimum drug efficacy $\epsilon^{\min}_{(5.3)}$ such that $\mathfrak{R}_{0,(5.3)}(\epsilon) \leq 1$, $\epsilon^{\min}_{(5.3)} \leq \epsilon \leq 1$ is given by:

$$\epsilon^{\min}_{(5.3)} = \max\left\{1 - \frac{1}{\mathfrak{R}_{01}}, 0\right\}. \tag{5.5}$$

Comparing Eqs. (5.5) and (5.4) we get that $\epsilon^{\min}_{(5.3)} \leq \epsilon^{\min}_{(5.2)}$. Therefore, if we apply drugs with ϵ such that $\epsilon^{\min}_{(5.3)} \leq \epsilon < \epsilon^{\min}_{(5.2)}$, this guarantee that $\mathfrak{R}_{0,(5.3)}(\epsilon) \leq 1$ and then $Ð_0$ of system (5.3) is globally asymptotically stable, however, $\mathfrak{R}_{0,(5.2)} > 1$ and then $Ð_0$ of system (5.2) is unstable. Therefore, more accurate drug efficacy ϵ is determined when using the model with both virus-to-cell and cell-to-cell transmissions. This shows the importance of considering the effect of the cell-to-cell transmission in the virus dynamics.

Now we perform numerical simulation for both systems (5.2) and (5.3). Using the values given in Table 1 and choosing $\eta_1 = 0.001$, $\eta_2 = 0.005$, $\tau = 0.07$ and $\sigma = 0.2$. Then we get

$$\epsilon^{\min}_{(5.3)} = 0.496, \qquad \epsilon^{\min}_{(5.2)} = 0.7984.$$

Now we select $\epsilon = 0.5$ and choose the initial condition as follows:

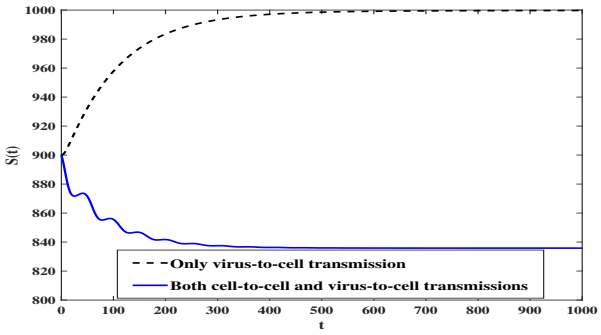
Initial–4: $(S(0), I_1(0), I_2(0), I_3(0), V(0), A(0), C(0)) = (900, 3, 1, 0.5, 2, 3, 5)$.

From Figure 6 we can see that the trajectory of model (5.3) tends to $Ð_0$, while the trajectory of model (5.2) tends to $\tilde{Ð}$. It means that if one design treatment using model (5.3) where the cell-to-cell transmission is neglected, then this treatment will not suffice to clear the viruses from the body.

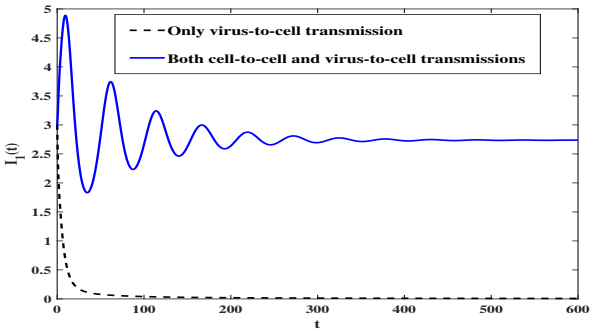
On the other hand, we choose $\epsilon = 0.8$ and consider the following initial condition:

Initial–5: $(S(0), I_1(0), I_2(0), I_3(0), V(0), A(0), C(0)) = (920, 0.5, 0.5, 0.5, 2, 3, 3)$.

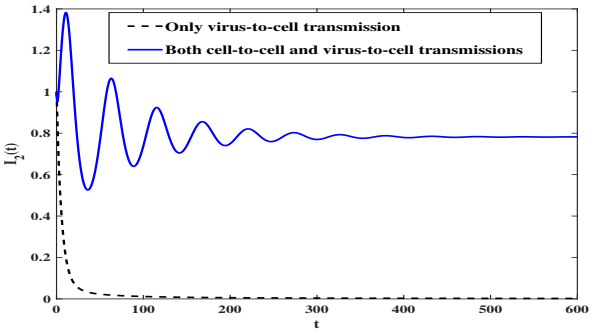
From Figure 7 we can see that the trajectories of both systems (5.2) and (5.3) tend to $Ð_0$. Therefore, this treatment will suffice to clear the viruses from the body.



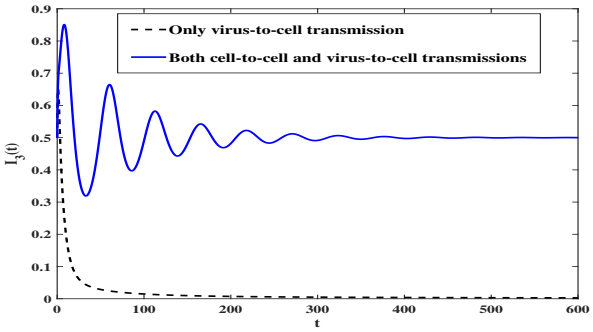
(a) The behavior of susceptible cells



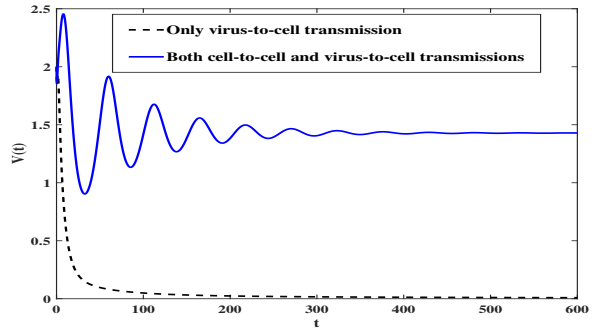
(b) The behavior of first stage of infected cells



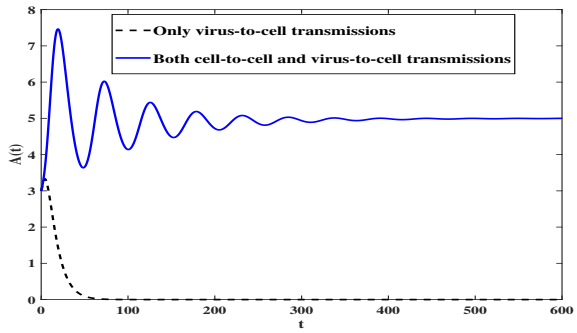
(c) The behavior of second stage of infected cells



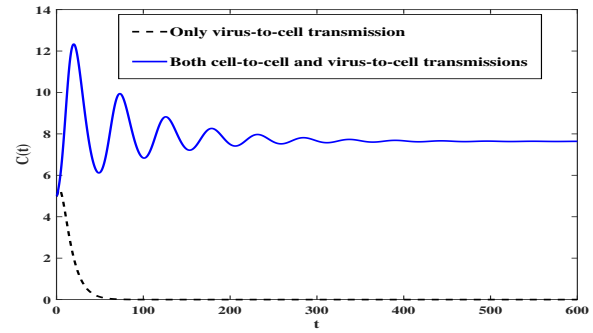
(d) The behavior of third stage of infected cells



(e) The behavior of virus particles

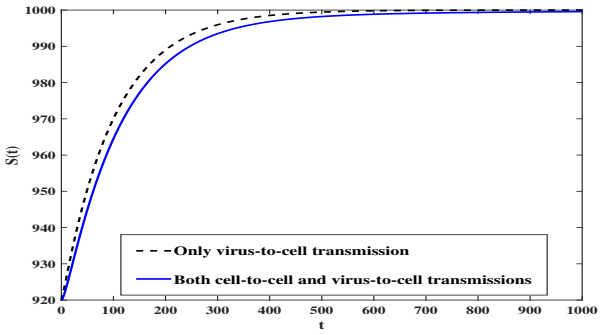


(f) The behavior of B cells

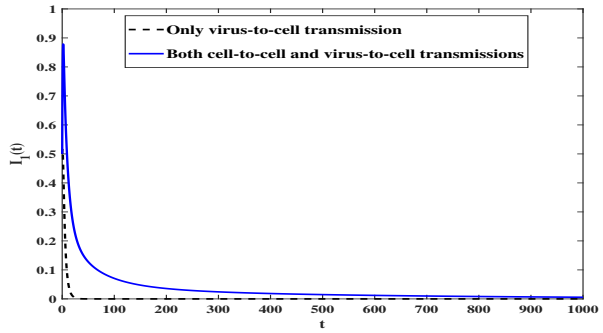


(g) The behavior of CTLs

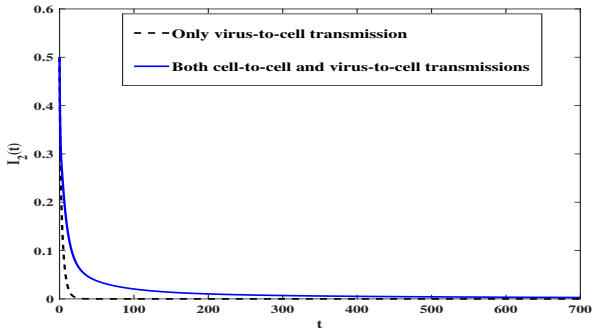
Figure 6. Effect of treatment when $\epsilon = 0.5$ on the behaviour of the solution trajectories of systems (5.2) and (5.3).



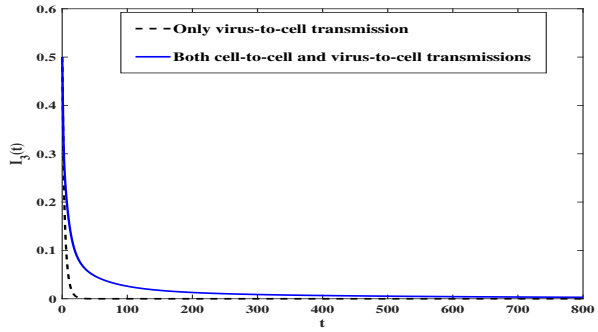
(a) The behavior of susceptible cells



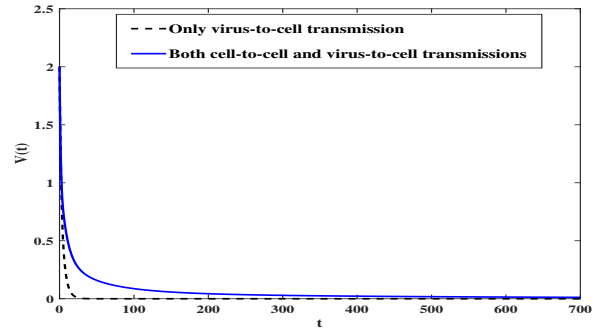
(b) The behavior of first stage of infected cells



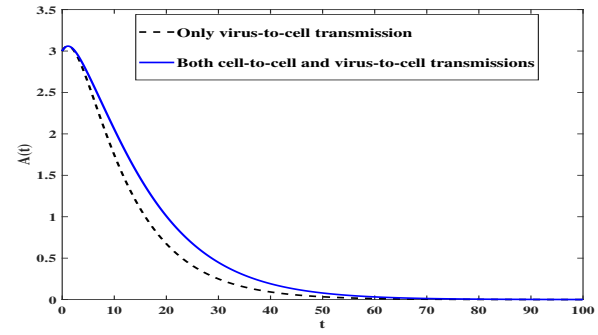
(c) The behavior of second stage of infected cells



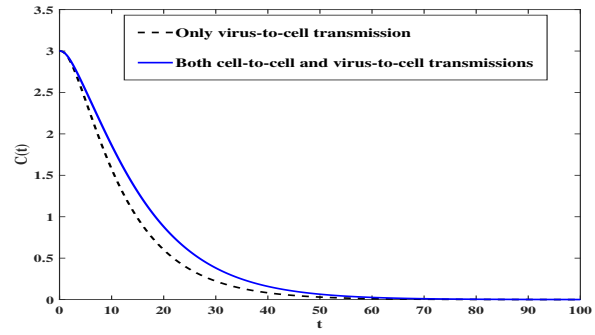
(d) The behavior of third stage of infected cells



(e) The behavior of virus particles



(f) The behavior of B cells



(g) The behavior of CTLs

Figure 7. Effect of treatment when $\epsilon = 0.8$ on the behaviour of the solution trajectories of systems (5.2) and (5.3).

6. Conclusion and discussion

In this paper, we formulated and analyzed a virus dynamics model with both CTL and humoral immune responses. We incorporated both virus-to-cell and cell-to-cell transmissions. We assumed that the infected cells pass through n stages to produce mature viruses. We showed that the solutions of the system are nonnegative and bounded, which ensures the well-posedness of the proposed model. Further, we obtained five threshold parameters, $\mathfrak{R}_0$ (the basic infection reproductive ratio), $\mathfrak{R}_1^A$ (the active humoral immunity reproductive ratio), $\mathfrak{R}_1^C$ (the active cell-mediated immunity reproductive ratio), $\mathfrak{R}_2^C$ (the competed cell-mediated immunity reproductive ratio), and $\mathfrak{R}_2^A$ (the competed humoral immunity reproductive ratio). The global asymptotic stability of the five equilibria $Đ_0$, $\bar{Đ}$, $\hat{Đ}$, $\check{Đ}$, $\tilde{Đ}$ was investigated by constructing Lyapunov functions and applying LaSalle's invariance principle. To support our theoretical results, we conducted some numerical simulations. We note that the incorporation of cell-to-cell transmission mechanism into the viral infection model increases the basic reproduction number $\mathfrak{R}_0$, since $\mathfrak{R}_0 = \mathfrak{R}_{01} + \mathfrak{R}_{02} > \mathfrak{R}_{01}$. Therefore, neglecting the cell-to-cell transmission will lead to under-evaluated basic reproduction number. Model with two types of treatment was presented. We showed that more accurate drug efficacy which is required to clear the virus from the body is calculated by using our proposed model.

There are some factors that can extend our model (1.2):

a. The infected cells may begin to present the viral antigen earlier than when they reach the terminal stage n (i.e. at stage m where $m \leq n$). Therefore, infected cells $I_m, I_{m+1}, ..., I_n$ are subject to be targeted by the CTL immune response.

b. Model (1.2) is formulated by assuming that the virus is purely lytic, that is, only the bursting cells are capable of releasing the free virions. However, many viruses are somewhat mixed, in the sense that they are partially lytic and partially budding, where the release of free virions can be from the infected cells $I_m, I_{m+1}, ..., I_n$.

c. The cell-to-cell infection mechanism can also be expanded to the contact between susceptible cells with infected cells $I_m, I_{m+1}, ..., I_n$.

d. The loss of virions upon the infection could also be added to the model. In fact, there is some speculation that the virions may be indiscriminately entering not only the susceptible cells, but also the cells that are already infected [26, 53].

Then, taking into account the above factors will leads to the following model:

$$\begin{cases} \dot{S}(t) = \rho - \alpha S(t) - \eta_1 S(t)V(t) - \sum\limits_{k=m}^{n} \eta_k S(t) I_k(t), \\ \dot{I}_1(t) = \eta_1 S(t)V(t) + \eta_2 S(t) I_n(t) - b_1 I_1(t), \\ \dot{I}_2(t) = d_1 I_1(t) - b_2 I_2(t) \\ \vdots \\ \dot{I}_{m-1}(t) = d_{m-2} I_{m-2}(t) - b_{m-1} I_{m-1}(t), \\ \dot{I}_k(t) = d_{k-1} I_{k-1}(t) - b_k I_k(t) - \mu_k C(t) I_k(t), \qquad k = m, m+1, ..., n, \\ \dot{V}(t) = \sum\limits_{k=m}^{n} \delta_k I_k(t) - \gamma A(t)V(t) - \varepsilon V(t) - \bar{\eta}_1 S(t)V(t) - V(t) \sum\limits_{k=1}^{n} \varkappa_k I_k(t), \\ \dot{A}(t) = \tau A(t)V(t) - \zeta A(t), \\ \dot{C}(t) = \sum\limits_{k=m}^{n} \sigma_k C(t) I_k(t) - \pi C(t), \end{cases} \tag{6.1}$$

where, $\sum_{k=m}^{n} \eta_k S I_k$ represent the incidence rates due to the contact of the infected cells $I_m, I_{m+1}, ..., I_n$ with susceptible cells. The term $\bar{\eta}_1 S V$ is the loss of virus upon entry of a susceptible cell. The term $V \sum_{k=1}^{n} \varkappa_k I_k$ represents the absorption of free virions into already infected cells $I_1, I_2, ..., I_n$. The production rate of the viruses and the activation rate of the CTL cells are modeled by $\sum_{k=m}^{n} \delta_k I_k$ and $\sum_{k=m}^{n} \sigma_k C I_k$, respectively. The k-stage infected cells I_k, are attacked by CTL cells at rate $\mu_k C I_k$, $k = m, m+1, ..., n$. Analysis of system (6.1) is not straightforward, therefore we leave it for future works.

It is commonly observed that in viral infection processes, time delay is inevitable. Herz et al. [59] formulated an HIV infection model with intracellular delay and they obtained the analytic expression of the viral load decline under treatment and used it to analyze the viral load decline data in patients. Several viral infection models presented in the literature incorporated discrete delays (see, e.g., [36] and [44]) or distributed delays (see, e.g., [7, 23] and [48–50]). In these papers, the global stability of equilibria was proven by utilizing global Lyapunov functional that was motivated by the work in [51] and [52]. Model (6.1) can be extended to incorporate distributed time delays. Moreover, considering age structure of the infected class or diffusion in the virus dynamics model will lead to PDE model [54–58]. These extensions require more investigations, therefore we leave it for future works.

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Conflict of interest

There is no conflicts of interest.

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Supplementary

Proof of Theorem 1. Constructing a Lyapunov function:

$$\Phi_0(S, I_1, ..., I_n, V, A, C) = S_0 F\left(\frac{S}{S_0}\right) + \sum_{k=1}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right) I_k + \frac{\eta_1 S_0}{\varepsilon} V + \frac{\gamma\eta_1 S_0}{\tau\varepsilon} A + \frac{\mu}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right) C. \tag{6.2}$$

It is seen that, $\Phi_0(S, I_1, ..., I_n, V, A, C) > 0$ for all $S, I_1, ..., I_n, V, A, C > 0$, and Φ_0 has a global minimum at $Ð_0$. We calculate $\frac{d\Phi_0}{dt}$ along the solutions of model (1.2) as:

$$\frac{d\Phi_0}{dt} = \left(1 - \frac{S_0}{S}\right)\dot{S} + \dot{I}_1 + \sum_{k=2}^{n-1}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\dot{I}_k + \left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\dot{I}_n + \frac{\eta_1 S_0}{\varepsilon}\dot{V} + \frac{\gamma\eta_1 S_0}{\tau\varepsilon}\dot{A} + \frac{\mu}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\dot{C}. \tag{6.3}$$

Using (4.3), we have

$$\begin{aligned}\sum_{k=1}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\dot{I}_k &= \eta_1 S V + \eta_2 S I_n - b_1 I_1 + \sum_{k=2}^{n-1}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)(d_{k-1}I_{k-1} - b_k I_k)\\ &\quad + \left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)(d_{n-1}I_{n-1} - b_n I_n - \mu C I_n)\\ &= \eta_1 S V + \eta_2 S I_n - \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right) d_n I_n - \mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right) C I_n.\end{aligned}$$

Then,

$$\frac{d\Phi_0}{dt} = \left(1 - \frac{S_0}{S}\right)(\rho - \alpha S) + \frac{\eta_1 S_0}{\varepsilon} d_n I_n + \eta_2 S_0 I_n - \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right) d_n I_n - \frac{\gamma\zeta\eta_1 S_0}{\tau\varepsilon} A - \frac{\mu\pi}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right) C.$$

Using $S_0 = \rho/\alpha$, we obtain

$$\frac{d\Phi_0}{dt} = -\alpha\frac{(S - S_0)^2}{S} + \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right) d_n\left(\Re_0 - 1\right) I_n - \frac{\gamma\zeta\eta_1 S_0}{\tau\varepsilon} A - \frac{\mu\pi}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right) C. \tag{6.4}$$

Therefore, $\frac{d\Phi_0}{dt} \leq 0$ for all $S, I_n, A, C > 0$ with equality holding when $S(t) = S_0$ and $I_n(t) = A(t) = C(t) = 0$ for all t. Let $\Upsilon_0 = \left\{(S(t), I_1(t), ..., I_n(t), V(t), A(t), C(t)) : \frac{d\Phi_0}{dt} = 0\right\}$ and Υ_0' is the largest invariant subset of Υ_0. We note that, the solutions of system (1.2) are confined to Υ_0 [46]. The set Υ_0 is invariant and contains elements which satisfy $I_n(t) = 0$. Then, $\dot{I}_n(t) = 0$ and from Eq. 3.4 we have

$$0 = \dot{I}_n(t) = d_{n-1} I_{n-1}(t).$$

It follows that, $I_{n-1}(t) = 0$ for all t. Since we have $I_{n-1}(t) = 0$, then $\dot{I}_{n-1}(t) = 0$ and from Eq. 3.3, we have $\dot{I}_{n-1}(t) = d_{n-2} I_{n-2} = 0$ which yields $I_{n-2}(t) = 0$. Consequently, we obtain $I_k(t) = 0$, where $k = 1, ..., n$. Moreover, since $S(t) = S_0$ we have $\dot{S}(t) = 0$ and Eq. 3.1 implies that

$$0 = \dot{S}(t) = \rho - \alpha S_0 - \eta_1 S_0 V.$$

which insures that $V(t) = 0$. Noting that $\mathfrak{R}_0 \leq 1$, then $\mathrm{Đ}_0$ is globally asymptotically stable using LaSalle's invariance principle. □

Proof of Theorem 2. Let us define a function $\Phi_1(S, I_1, ..., I_n, V, A, C)$ as:

$$\Phi_1 = \bar{S}F\left(\frac{S}{\bar{S}}\right) + \sum_{k=1}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\bar{I}_k F\left(\frac{I_k}{\bar{I}_k}\right) + \frac{\eta_1\bar{S}}{\varepsilon}\bar{V}F\left(\frac{V}{\bar{V}}\right) + \frac{\gamma\eta_1\bar{S}}{\tau\varepsilon}A + \frac{\mu}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)C.$$

Calculating $\frac{d\Phi_1}{dt}$ as:

$$\begin{aligned}\frac{d\Phi_1}{dt} &= \left(1-\frac{\bar{S}}{S}\right)(\rho - \alpha S - \eta_1 S V - \eta_2 S I_n) + \left(1-\frac{\bar{I}_1}{I_1}\right)(\eta_1 S V + \eta_2 S I_n - b_1 I_1)\\ &+ \sum_{k=2}^{n-1}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\left(1-\frac{\bar{I}_k}{I_k}\right)(d_{k-1}I_{k-1} - b_k I_k) + \left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\left(1-\frac{\bar{I}_n}{I_n}\right)(d_{n-1}I_{n-1} - b_n I_n - \mu C I_n)\\ &+ \frac{\eta_1\bar{S}}{\varepsilon}\left(1-\frac{\bar{V}}{V}\right)(d_n I_n - \gamma A V - \varepsilon V) + \frac{\gamma\eta_1\bar{S}}{\tau\varepsilon}(\tau V A - \zeta A) + \frac{\mu}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)(\sigma I_n C - \pi C). \qquad (6.5)\end{aligned}$$

Collecting terms of Eq. 6.5 and using Eqs. 4.2 and 4.3, we derive

$$\begin{aligned}\frac{d\Phi_1}{dt} &= \left(1-\frac{\bar{S}}{S}\right)(\rho - \alpha S) + \eta_2\bar{S}I_n - \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_n I_n - \eta_1 S V\frac{\bar{I}_1}{I_1} - \eta_2 S I_n\frac{\bar{I}_1}{I_1}\\ &- \sum_{k=2}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\frac{d_{k-1}I_{k-1}\bar{I}_k}{I_k} + \sum_{k=1}^{n}\left(\prod_{i=1}^{k}\frac{b_i}{d_i}\right)d_k\bar{I}_k + \left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\mu C\bar{I}_n + \frac{\eta_1\bar{S}}{\varepsilon}d_n I_n - \frac{\eta_1\bar{S}}{\varepsilon}d_n I_n\frac{\bar{V}}{V}\\ &+ \eta_1\bar{S}\bar{V} + \frac{\eta_1\bar{S}}{\varepsilon}\gamma A\bar{V} - \frac{\gamma\eta_1\bar{S}}{\tau\varepsilon}\zeta A - \frac{\mu\pi}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)C. \qquad (6.6)\end{aligned}$$

Using the equilibrium conditions for $\bar{\mathrm{Đ}}$:

$$\rho = \alpha\bar{S} + \eta_1\bar{S}\bar{V} + \eta_2\bar{S}\bar{I}_n, \qquad \eta_1\bar{S}\bar{V} + \eta_2\bar{S}\bar{I}_n = \left(\prod_{i=1}^{k}\frac{b_i}{d_i}\right)d_k\bar{I}_k = \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)\varepsilon\bar{V}, \quad k = 1, ..., n.$$

We obtain

$$\begin{aligned}\frac{d\Phi_1}{dt} &= \left(1-\frac{\bar{S}}{S}\right)\left(\alpha\bar{S} - \alpha S\right) + \left(\eta_1\bar{S}\bar{V} + \eta_2\bar{S}\bar{I}_n\right)\left(1-\frac{\bar{S}}{S}\right) + \eta_2\bar{S}I_n - \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_n I_n + \frac{\eta_1\bar{S}}{\varepsilon}d_n I_n\\ &- \eta_1\bar{S}\bar{V}\frac{S V\bar{I}_1}{\bar{S}\bar{V}I_1} - \eta_2\bar{S}\bar{I}_n\frac{S I_n\bar{I}_1}{\bar{S}\bar{I}_n I_1} - \left(\eta_1\bar{S}\bar{V} + \eta_2\bar{S}\bar{I}_n\right)\sum_{k=2}^{n}\frac{I_{k-1}\bar{I}_k}{\bar{I}_{k-1}I_k} + n\left(\eta_1\bar{S}\bar{V} + \eta_2\bar{S}\bar{I}_n\right)\\ &+ \eta_1\bar{S}\bar{V} - \frac{\eta_1\bar{S}}{\varepsilon}d_n I_n\frac{\bar{V}}{V} + \mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\left(\bar{I}_n - \frac{\pi}{\sigma}\right)C + \frac{\eta_1\bar{S}\gamma}{\varepsilon}\left(\bar{V} - \frac{\zeta}{\tau}\right)A. \qquad (6.7)\end{aligned}$$

Since we have

$$\bar{S} = \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)\frac{\varepsilon d_n}{\eta_1 d_n + \eta_2\varepsilon},$$

then

$$\eta_2 \bar{S} I_n - \left(\prod_{i=1}^{n} \frac{b_i}{d_i}\right) d_n I_n + \frac{\eta_1 \bar{S}}{\varepsilon} d_n I_n = 0.$$

Also we have when $k = n$,

$$\frac{d_n}{\varepsilon} = \frac{\bar{V}}{\bar{I}_n} \Longrightarrow \frac{\eta_1 \bar{S}}{\varepsilon} d_n I_n \frac{\bar{V}}{V} = \eta_1 \bar{S} \bar{V} \frac{I_n \bar{V}}{\bar{I}_n V}.$$

Therefor Eq. 6.7 becomes

$$\begin{aligned}
\frac{d\Phi_1}{dt} &= -\alpha \frac{(S - \bar{S})^2}{S} + \eta_1 \bar{S} \bar{V} \left[(n+2) - \frac{\bar{S}}{S} - \frac{S V \bar{I}_1}{\bar{S} \bar{V} I_1} - \sum_{k=2}^{n} \frac{I_{k-1} \bar{I}_k}{\bar{I}_{k-1} I_k} - \frac{I_n \bar{V}}{\bar{I}_n V}\right] \\
&\quad + \eta_2 \bar{S} \bar{I}_n \left[(n+1) - \frac{\bar{S}}{S} - \frac{S I_n \bar{I}_1}{\bar{S} \bar{I}_n I_1} - \sum_{k=2}^{n} \frac{I_{k-1} \bar{I}_k}{\bar{I}_{k-1} I_k}\right] + \mu \left(\prod_{i=1}^{n-1} \frac{b_i}{d_i}\right) \left(\bar{I}_n - \check{I}_n\right) C + \frac{\eta_1 \bar{S} \gamma}{\varepsilon} \left(\bar{V} - \hat{V}\right) A \\
&= -\alpha \frac{(S - \bar{S})^2}{S} + \eta_1 \bar{S} \bar{V} \left[(n+2) - \frac{\bar{S}}{S} - \frac{S V \bar{I}_1}{\bar{S} \bar{V} I_1} - \sum_{k=2}^{n} \frac{I_{k-1} \bar{I}_k}{\bar{I}_{k-1} I_k} - \frac{I_n \bar{V}}{\bar{I}_n V}\right] \\
&\quad + \eta_2 \bar{S} \bar{I}_n \left[(n+1) - \frac{\bar{S}}{S} - \frac{S I_n \bar{I}_1}{\bar{S} \bar{I}_n I_1} - \sum_{k=2}^{n} \frac{I_{k-1} \bar{I}_k}{\bar{I}_{k-1} I_k}\right] + \frac{\varepsilon \alpha \sigma + \pi (\eta_1 d_n + \eta_2 \varepsilon)}{\sigma (\eta_1 d_n + \eta_2 \varepsilon)} \left(\mathfrak{R}_1^C - 1\right) C + \frac{\eta_1 \bar{S} \gamma}{\varepsilon} \left(\bar{V} - \hat{V}\right) A.
\end{aligned} \tag{6.8}$$

Since the arithmetical mean is greater than or equal to the geometrical mean, then

$$\frac{\bar{S}}{S} + \frac{S V \bar{I}_1}{\bar{S} \bar{V} I_1} + \sum_{k=2}^{n} \frac{I_{k-1} \bar{I}_k}{\bar{I}_{k-1} I_k} + \frac{I_n \bar{V}}{\bar{I}_n V} \geq n + 2 \text{ and } \frac{\bar{S}}{S} + \frac{S I_n \bar{I}_1}{\bar{S} \bar{I}_n I_1} + \sum_{k=2}^{n} \frac{I_{k-1} \bar{I}_k}{\bar{I}_{k-1} I_k} \geq n + 1.$$

From Lemma 2 we have $\bar{V} < \hat{V}$ and since $\mathfrak{R}_1^C \leq 1 < \mathfrak{R}_0$ then $\frac{d\Phi_1}{dt} \leq 0$ for all $S, I_k, V, A, C > 0$ with equality holding when $S(t) = \bar{S}$, $I_k(t) = \bar{I}_k$, $k = 1, 2, ..., n$, $V(t) = \bar{V}$, and $A(t) = C(t) = 0$ for all t. It can be easily verified that $\Upsilon_1' = \left\{\bar{\mathfrak{D}}\right\}$ is the largest invariant subset of $\Upsilon_1 = \left\{(S(t), I_1(t), ..., I_n(t), V(t), A(t), C(t)) : \frac{d\Phi_1}{dt} = 0\right\}$ [46]. Then, $\bar{\mathfrak{D}}$ is globally asymptotically stable using LaSalle's invariance principle. □

Proof of Theorem 3. The candidate Lyapunov function is

$$\begin{aligned}
\Phi_2(S, I_1, ..., I_n, V, A, C) &= \hat{S} F\left(\frac{S}{\hat{S}}\right) + \sum_{k=1}^{n} \left(\prod_{i=1}^{k-1} \frac{b_i}{d_i}\right) \hat{I}_k F\left(\frac{I_k}{\hat{I}_k}\right) + \frac{\eta_1 \hat{S} \hat{V}}{d_n \hat{I}_n} \hat{V} F\left(\frac{V}{\hat{V}}\right) \\
&\quad + \frac{\gamma \eta_1 \hat{S} \hat{V}}{\tau d_n \hat{I}_n} \hat{A} F\left(\frac{A}{\hat{A}}\right) + \frac{\mu}{\sigma} \left(\prod_{i=1}^{n-1} \frac{b_i}{d_i}\right) C.
\end{aligned} \tag{6.9}$$

We calculate $\frac{d\Phi_2}{dt}$ as:

$$\frac{d\Phi_2}{dt} = \left(1 - \frac{\hat{S}}{S}\right) (\rho - \alpha S - \eta_1 S V - \eta_2 S I_n) + \left(1 - \frac{\hat{I}_1}{I_1}\right) (\eta_1 S V + \eta_2 S I_n - b_1 I_1)$$

$$+\sum_{k=2}^{n-1}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\left(1-\frac{\hat{I}_k}{I_k}\right)(d_{k-1}I_{k-1}-b_kI_k)+\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\left(1-\frac{\hat{I}_n}{I_n}\right)(d_{n-1}I_{n-1}-b_nI_n-\mu CI_n)$$
$$+\frac{\eta_1\hat{S}\,\hat{V}}{d_n\hat{I}_n}\left(1-\frac{\hat{V}}{V}\right)(d_nI_n-\gamma AV-\varepsilon V)+\frac{\gamma\eta_1\hat{S}\,\hat{V}}{\tau d_n\hat{I}_n}\left(1-\frac{\hat{A}}{A}\right)(\tau VA-\zeta A)$$
$$+\frac{\mu}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)(\sigma I_nC-\pi C)\,. \tag{6.10}$$

Collecting terms of Eq. 6.10 and using Eqs. 4.2 and 4.3, we derive

$$\frac{d\Phi_2}{dt}=\left(1-\frac{\hat{S}}{S}\right)(\rho-\alpha S)+\eta_1\hat{S}\,V+\eta_2\hat{S}\,I_n-\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_nI_n-\eta_1SV\frac{\hat{I}_1}{I_1}-\eta_2SI_n\frac{\hat{I}_1}{I_1}$$
$$-\sum_{k=2}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\frac{d_{k-1}I_{k-1}\hat{I}_k}{I_k}+\sum_{k=1}^{n}\left(\prod_{i=1}^{k}\frac{b_i}{d_i}\right)d_k\hat{I}_k+\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\mu C\hat{I}_n+\eta_1\hat{S}\,\hat{V}\frac{I_n}{\hat{I}_n}$$
$$-\frac{\eta_1\hat{S}\,\hat{V}}{d_n\hat{I}_n}\varepsilon V-\eta_1\hat{S}\,\hat{V}\frac{I_n\hat{V}}{\hat{I}_nV}+\frac{\eta_1\hat{S}\,\hat{V}}{d_n\hat{I}_n}\varepsilon\hat{V}+\frac{\eta_1\hat{S}\,\hat{V}}{d_n\hat{I}_n}\gamma\hat{V}A-\frac{\gamma\eta_1\hat{S}\,\hat{V}}{\tau d_n\hat{I}_n}\zeta A-\frac{\gamma\eta_1\hat{S}\,\hat{V}}{d_n\hat{I}_n}V\hat{A}$$
$$+\frac{\gamma\eta_1\hat{S}\,\hat{V}}{\tau d_n\hat{I}_n}\zeta\hat{A}-\frac{\mu\pi}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)C. \tag{6.11}$$

Using the equilibrium conditions for $\hat{\mathbf{D}}$:

$$\rho=\alpha\hat{S}+\eta_1\hat{S}\,\hat{V}+\eta_2\hat{S}\,\hat{I}_n,$$
$$\eta_1\hat{S}\,\hat{V}+\eta_2\hat{S}\,\hat{I}_n=\left(\prod_{i=1}^{k}\frac{b_i}{d_i}\right)d_k\hat{I}_k=\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)\left[\varepsilon\hat{V}+\gamma\hat{V}\hat{A}\right],\quad k=1,...,n. \tag{6.12}$$

We obtain

$$\frac{d\Phi_2}{dt}=\left(1-\frac{\hat{S}}{S}\right)\left(\alpha\hat{S}-\alpha S\right)+\left(\eta_1\hat{S}\,\hat{V}+\eta_2\hat{S}\,\hat{I}_n\right)\left(1-\frac{\hat{S}}{S}\right)+\eta_1\hat{S}\,\hat{V}\frac{V}{\hat{V}}+\eta_2\hat{S}\,\hat{I}_n\frac{I_n}{\hat{I}_n}$$
$$-\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_nI_n-\eta_1\hat{S}\,\hat{V}\frac{SV\hat{I}_1}{\hat{S}\,\hat{V}I_1}-\eta_2\hat{S}\,\hat{I}_n\frac{SI_n\hat{I}_1}{\hat{S}\,\hat{I}_nI_1}-\left(\eta_1\hat{S}\,\hat{V}+\eta_2\hat{S}\,\hat{I}_n\right)\sum_{k=2}^{n}\frac{I_{k-1}\hat{I}_k}{\hat{I}_{k-1}I_k}$$
$$+n\left(\eta_1\hat{S}\,\hat{V}+\eta_2\hat{S}\,\hat{I}_n\right)+\eta_1\hat{S}\,\hat{V}\frac{I_n}{\hat{I}_n}-\frac{\eta_1\hat{S}\,\hat{V}}{d_n\hat{I}_n}\left[\varepsilon\hat{V}+\gamma\hat{V}\hat{A}\right]\frac{V}{\hat{V}}$$
$$-\eta_1\hat{S}\,\hat{V}\frac{I_n\hat{V}}{\hat{I}_nV}+\frac{\eta_1\hat{S}\,\hat{V}}{d_n\hat{I}_n}\left[\varepsilon\hat{V}+\gamma\hat{V}\hat{A}\right]+\mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\left(\hat{I}_n-\frac{\pi}{\sigma}\right)C$$
$$=-\alpha\frac{\left(S-\hat{S}\right)^2}{S}+\left(\eta_1\hat{S}\,\hat{V}+\eta_2\hat{S}\,\hat{I}_n\right)\left(1-\frac{\hat{S}}{S}\right)+\left(\eta_1\hat{S}\,\hat{V}+\eta_2\hat{S}\,\hat{I}_n\right)\frac{I_n}{\hat{I}_n}$$
$$-\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_nI_n-\eta_1\hat{S}\,\hat{V}\frac{SV\hat{I}_1}{\hat{S}\,\hat{V}I_1}-\eta_2\hat{S}\,\hat{I}_n\frac{SI_n\hat{I}_1}{\hat{S}\,\hat{I}_nI_1}-\left(\eta_1\hat{S}\,\hat{V}+\eta_2\hat{S}\,\hat{I}_n\right)\sum_{k=2}^{n}\frac{I_{k-1}\hat{I}_k}{\hat{I}_{k-1}I_k}$$

$$+ n\left(\eta_1\hat{S}\,\hat{V} + \eta_2\hat{S}\,\hat{I}_n\right) - \eta_1\hat{S}\,\hat{V}\frac{I_n\hat{V}}{\hat{I}_n V} + \eta_1\hat{S}\,\hat{V} + \mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\left(\hat{I}_n - \frac{\pi}{\sigma}\right)C. \tag{6.13}$$

Using Eq. 6.12 in case of $k = n$ we get

$$\left(\eta_1\hat{S}\,\hat{V} + \eta_2\hat{S}\,\hat{I}_n\right)\frac{I_n}{\hat{I}_n} - \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_n I_n = \left(\eta_1\hat{S}\,\hat{V} + \eta_2\hat{S}\,\hat{I}_n\right)\frac{I_n}{\hat{I}_n} - \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_n\hat{I}_n\frac{I_n}{\hat{I}_n} = 0.$$

Thus, Eq. 6.13 will become

$$\begin{aligned}\frac{d\Phi_2}{dt} = &-\alpha\frac{\left(S-\hat{S}\right)^2}{S} + \left(\eta_1\hat{S}\,\hat{V} + \eta_2\hat{S}\,\hat{I}_n\right)\left(1 - \frac{\hat{S}}{S}\right) - \eta_1\hat{S}\,\hat{V}\frac{S\,V\hat{I}_1}{\hat{S}\,\hat{V}I_1} - \eta_2\hat{S}\,\hat{I}_n\frac{S\,I_n\hat{I}_1}{\hat{S}\,\hat{I}_n I_1}\\ &- \left(\eta_1\hat{S}\,\hat{V} + \eta_2\hat{S}\,\hat{I}_n\right)\sum_{k=2}^{n}\frac{I_{k-1}\hat{I}_k}{\hat{I}_{k-1}I_k} + n\left(\eta_1\hat{S}\,\hat{V} + \eta_2\hat{S}\,\hat{I}_n\right) + \eta_1\hat{S}\,\hat{V} - \eta_1\hat{S}\,\hat{V}\frac{I_n\hat{V}}{\hat{I}_n V}\\ &+ \mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\left(\hat{I}_n - \tilde{I}_n\right)C.\end{aligned} \tag{6.14}$$

Eq. 6.14 can be written as

$$\begin{aligned}\frac{d\Phi_2}{dt} = &-\alpha\frac{\left(S-\hat{S}\right)^2}{S} + \eta_1\hat{S}\,\hat{V}\left[(n+2) - \frac{\hat{S}}{S} - \frac{S\,V\hat{I}_1}{\hat{S}\,\hat{V}I_1} - \sum_{k=2}^{n}\frac{I_{k-1}\hat{I}_k}{\hat{I}_{k-1}I_k} - \frac{I_n\hat{V}}{\hat{I}_n V}\right]\\ &+ \eta_2\hat{S}\,\hat{I}_n\left[(n+1) - \frac{\hat{S}}{S} - \frac{S\,I_n\hat{I}_1}{\hat{S}\,\hat{I}_n I_1} - \sum_{k=2}^{n}\frac{I_{k-1}\hat{I}_k}{\hat{I}_{k-1}I_k}\right] + \mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\left(\hat{I}_n - \tilde{I}_n\right)C.\end{aligned} \tag{6.15}$$

Thus, if $\mathfrak{R}_2^C \leq 1$, then $\tilde{\mathrm{D}}$ dose not exist since $\tilde{C} = \frac{b_n}{\mu}\left(\mathfrak{R}_2^C - 1\right) \leq 0$. This guarantee that $\dot{C}(t) = \sigma\left(I_n(t) - \frac{\pi}{\sigma}\right)C(t) = \sigma\left(I_n(t) - \tilde{I}_n\right)C(t) \leq 0$ for all $C > 0$, which implies that $\hat{I}_n < \tilde{I}_n$. Hence $\frac{d\Phi_2}{dt} \leq 0$ for all $S, I_k, V, A, C > 0$ with equality holding when $S(t) = \hat{S}$, $I_k(t) = \hat{I}_k$, $k = 1, 2, ..., n$, $V(t) = \hat{V}$, and $C(t) = 0$ for all t. We note that, the solutions of system (1.2) are tend to Υ_2' the largest invariant subset of $\Upsilon_2 = \left\{(S(t), I_1(t), ..., I_n(t), V(t), A(t), C(t)) : \frac{d\Phi_2}{dt} = 0\right\}$ [46]. For each element of Υ_2' we have $I_n(t) = \hat{I}_n$, $V(t) = \hat{V}$, then $\dot{V}(t) = 0$ and from Eq. 3.5 we have

$$0 = \dot{V}(t) = d_n\hat{I}_n - \gamma A(t)\hat{V} - \varepsilon\hat{V} = 0,$$

which gives $A(t) = \hat{A}$. Therefore, $\Upsilon_2' = \left\{\hat{\mathrm{D}}\right\}$. Applying LaSalle's invariance principle we get $\hat{\mathrm{D}}$ is globally asymptotically stable. □

Proof of Theorem 4. Define a function $\Phi_3(S, I_1, ..., I_n, V, A, C)$ as:

$$\Phi_3 = \check{S}F\left(\frac{S}{\check{S}}\right) + \sum_{k=1}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\check{I}_k F\left(\frac{I_k}{\check{I}_k}\right) + \frac{\eta_1\check{S}}{\varepsilon}\check{V}F\left(\frac{V}{\check{V}}\right) + \frac{\gamma\eta_1\check{S}}{\tau\varepsilon}A + \frac{\mu}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\check{C}F\left(\frac{C}{\check{C}}\right).$$

We calculate $\frac{d\Phi_3}{dt}$ as:

$$\frac{d\Phi_3}{dt} = \left(1 - \frac{\check{S}}{S}\right)(\rho - \alpha S - \eta_1 S\,V - \eta_2 S\,I_n) + \left(1 - \frac{\check{I}_1}{I_1}\right)(\eta_1 S\,V + \eta_2 S\,I_n - b_1 I_1)$$

$$+\sum_{k=2}^{n-1}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\left(1-\frac{\check{I}_k}{I_k}\right)(d_{k-1}I_{k-1}-b_kI_k)+\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\left(1-\frac{\check{I}_n}{I_n}\right)(d_{n-1}I_{n-1}-b_nI_n-\mu CI_n)$$
$$+\frac{\eta_1\check{S}}{\varepsilon}\left(1-\frac{\check{V}}{V}\right)(d_nI_n-\gamma AV-\varepsilon V)+\frac{\gamma\eta_1\check{S}}{\tau\varepsilon}(\tau VA-\zeta A)+\frac{\mu}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\left(1-\frac{\check{C}}{C}\right)(\sigma I_nC-\pi C). \tag{6.16}$$

Collecting terms of Eq. 6.16 and using Eqs. 4.2 and 4.3, we derive

$$\begin{aligned}\frac{d\Phi_3}{dt}&=\left(1-\frac{\check{S}}{S}\right)(\rho-\alpha S)+\eta_2\check{S}I_n-\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_nI_n-\eta_1SV\frac{\check{I}_1}{I_1}-\eta_2SI_n\frac{\check{I}_1}{I_1}\\&-\sum_{k=2}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\frac{d_{k-1}I_{k-1}\check{I}_k}{I_k}+\sum_{k=1}^{n}\left(\prod_{i=1}^{k}\frac{b_i}{d_i}\right)d_k\check{I}_k+\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\mu C\check{I}_n+\frac{\eta_1\check{S}}{\varepsilon}d_nI_n-\frac{\eta_1\check{S}}{\varepsilon}d_nI_n\frac{\check{V}}{V}\\&+\eta_1\check{S}\check{V}+\frac{\eta_1\check{S}}{\varepsilon}\gamma A\check{V}-\frac{\gamma\eta_1\check{S}}{\tau\varepsilon}\zeta A-\frac{\mu\pi}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)C-\mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\check{C}I_n+\frac{\mu\pi}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\check{C}.\end{aligned} \tag{6.17}$$

Using the equilibrium conditions for $\check{\mathrm{D}}$:

$$\rho=\alpha\check{S}+\eta_1\check{S}\check{V}+\eta_2\check{S}\check{I}_n,\quad \check{I}_n=\frac{\pi}{\sigma},\quad \check{V}=\frac{d_n\pi}{\varepsilon\sigma}=\frac{d_n}{\varepsilon}\check{I}_n,$$
$$\eta_1\check{S}\check{V}+\eta_2\check{S}\check{I}_n=\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)d_{k-1}\check{I}_{k-1}=\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_n\check{I}_n+\mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\check{C}\check{I}_n,\quad k=1,...,n,$$

we obtain

$$\begin{aligned}\frac{d\Phi_3}{dt}&=\left(1-\frac{\check{S}}{S}\right)\left(\alpha\check{S}-\alpha S\right)+\left(\eta_1\check{S}\check{V}+\eta_2\check{S}\check{I}_n\right)\left(1-\frac{\check{S}}{S}\right)+\eta_2\check{S}I_n-\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_nI_n+\frac{\eta_1\check{S}}{\varepsilon}d_nI_n\\&-\mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\check{C}I_n-\eta_1\check{S}\check{V}\frac{SV\check{I}_1}{\check{S}\check{V}I_1}-\eta_2\check{S}\check{I}_n\frac{SI_n\check{I}_1}{\check{S}\check{I}_nI_1}-\left(\eta_1\check{S}\check{V}+\eta_2\check{S}\check{I}_n\right)\sum_{k=2}^{n}\frac{I_{k-1}\check{I}_k}{\check{I}_{k-1}I_k}\\&+n\left(\eta_1\check{S}\check{V}+\eta_2\check{S}\check{I}_n\right)-\eta_1\check{S}\check{V}\frac{I_n\check{V}}{\check{I}_nV}+\eta_1\check{S}\check{V}+\frac{\eta_1\check{S}\gamma\zeta}{\varepsilon\tau}\left(\frac{\tau\check{V}}{\zeta}-1\right)A.\end{aligned} \tag{6.18}$$

Since we have in case of $k=n$:

$$\begin{aligned}&\eta_2\check{S}I_n-\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_nI_n+\frac{\eta_1\check{S}}{\varepsilon}d_nI_n-\mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\check{C}I_n\\&=\left[\eta_2\check{S}\check{I}_n-\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_n\check{I}_n+\frac{\eta_1\check{S}}{\varepsilon}d_n\check{I}_n-\mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\check{C}\check{I}_n\right]\frac{I_n}{\check{I}_n}\\&=\left[\eta_1\check{S}\check{V}+\eta_2\check{S}\check{I}_n-\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_n\check{I}_n-\mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\check{C}\check{I}_n\right]\frac{I_n}{\check{I}_n}=0.\end{aligned}$$

Then,

$$\frac{d\Phi_3}{dt} = -\alpha\frac{\left(S-\check{S}\right)^2}{S} + \eta_1\check{S}\check{V}\left[(n+2) - \frac{\check{S}}{S} - \frac{SV\check{I}_1}{\check{S}\check{V}I_1} - \sum_{k=2}^{n}\frac{I_{k-1}\check{I}_k}{\check{I}_{k-1}I_k} - \frac{I_n\check{V}}{\check{I}_nV}\right]$$
$$+ \eta_2\check{S}\check{I}_n\left[(n+1) - \frac{\check{S}}{S} - \frac{SI_n\check{I}_1}{\check{S}\check{I}_nI_1} - \sum_{k=2}^{n}\frac{I_{k-1}\check{I}_k}{\check{I}_{k-1}I_k}\right] + \frac{\eta_1\check{S}\gamma\zeta}{\varepsilon\tau}\left(\Re_2^A - 1\right)A. \tag{6.19}$$

Hence, if $\Re_2^A = \frac{\tau\check{V}}{\zeta} \leq 1$, then $\frac{d\Phi_3}{dt} \leq 0$ for all $S, I_k, V, A, C > 0$ with equality holding when $S(t) = \check{S}$, $I_k(t) = \check{I}_k$, $k = 1, 2, ..., n$, $V(t) = \check{V}$ and $A(t) = 0$ for all t. It can be easily verified that the largest invariant subset of $\Upsilon_3 = \left\{(S(t), I_1(t), ..., I_n(t), V(t), A(t), C(t)) : \frac{d\Phi_3}{dt} = 0\right\}$ is $\Upsilon_3' = \left\{\check{\mathrm{D}}\right\}$ [46]. Applying LaSalle's invariance principle we get that $\check{\mathrm{D}}$ is globally asymptotically stable. □

Proof of Theorem 5. Define $\Phi_4(S, I_1, ..., I_n, V, A, C)$ as:

$$\Phi_4 = \tilde{S}F\left(\frac{S}{\tilde{S}}\right) + \sum_{k=1}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\tilde{I}_kF\left(\frac{I_k}{\tilde{I}_k}\right) + \frac{\eta_1\tilde{S}\tilde{V}}{d_n\tilde{I}_n}\tilde{V}F\left(\frac{V}{\tilde{V}}\right) + \frac{\gamma\eta_1\tilde{S}\tilde{V}}{\tau d_n\tilde{I}_n}\tilde{A}F\left(\frac{A}{\tilde{A}}\right) + \frac{\mu}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\tilde{C}F\left(\frac{C}{\tilde{C}}\right).$$

Calculating $\frac{d\Phi_4}{dt}$ as:

$$\frac{d\Phi_4}{dt} = \left(1-\frac{\tilde{S}}{S}\right)(\rho - \alpha S - \eta_1 SV - \eta_2 SI_n) + \left(1-\frac{\tilde{I}_1}{I_1}\right)(\eta_1 SV + \eta_2 SI_n - b_1I_1)$$
$$+ \sum_{k=2}^{n-1}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\left(1-\frac{\tilde{I}_k}{I_k}\right)(d_{k-1}I_{k-1} - b_kI_k) + \left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\left(1-\frac{\tilde{I}_n}{I_n}\right)(d_{n-1}I_{n-1} - b_nI_n - \mu CI_n)$$
$$+ \frac{\eta_1\tilde{S}\tilde{V}}{d_n\tilde{I}_n}\left(1-\frac{\tilde{V}}{V}\right)(d_nI_n - \gamma AV - \varepsilon V) + \frac{\gamma\eta_1\tilde{S}\tilde{V}}{\tau d_n\tilde{I}_n}\left(1-\frac{\tilde{A}}{A}\right)(\tau VA - \zeta A)$$
$$+ \frac{\mu}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\left(1-\frac{\tilde{C}}{C}\right)(\sigma I_nC - \pi C). \tag{6.20}$$

Collecting terms of Eq. 6.20 and using Eqs. 4.2 and 4.3, we obtain

$$\frac{d\Phi_4}{dt} = \left(1-\frac{\tilde{S}}{S}\right)(\rho - \alpha S) + \eta_1\tilde{S}V + \eta_2\tilde{S}I_n - \left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_nI_n - \eta_1SV\frac{\tilde{I}_1}{I_1} - \eta_2SI_n\frac{\tilde{I}_1}{I_1}$$
$$- \sum_{k=2}^{n}\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)\frac{d_{k-1}I_{k-1}\tilde{I}_k}{I_k} + \sum_{k=1}^{n}\left(\prod_{i=1}^{k}\frac{b_i}{d_i}\right)d_k\tilde{I}_k + \left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\mu C\tilde{I}_n + \eta_1\tilde{S}\tilde{V}\frac{I_n}{\tilde{I}_n}$$
$$- \frac{\eta_1\tilde{S}\tilde{V}}{d_n\tilde{I}_n}\varepsilon V - \eta_1\tilde{S}\tilde{V}\frac{I_n\tilde{V}}{\tilde{I}_nV} + \frac{\eta_1\tilde{S}\tilde{V}}{d_n\tilde{I}_n}\varepsilon\tilde{V} + \frac{\eta_1\tilde{S}\tilde{V}}{d_n\tilde{I}_n}\gamma\tilde{V}A - \frac{\gamma\eta_1\tilde{S}\tilde{V}}{\tau d_n\tilde{I}_n}\zeta A - \frac{\gamma\eta_1\tilde{S}\tilde{V}}{d_n\tilde{I}_n}V\hat{A}$$
$$+ \frac{\gamma\eta_1\tilde{S}\tilde{V}}{\tau d_n\tilde{I}_n}\zeta\hat{A} - \frac{\mu\pi}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)C - \mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\tilde{C}I_n + \frac{\mu\pi}{\sigma}\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\tilde{C}. \tag{6.21}$$

Using the equilibrium conditions for $\tilde{\mathrm{D}}$:

$$\rho = \alpha\tilde{S} + \eta_1\tilde{S}\tilde{V} + \eta_2\tilde{S}\tilde{I}_n, \quad \tilde{I}_n = \frac{\pi}{\sigma} = \check{I}_n, \quad \tilde{V} = \frac{\zeta}{\tau} = \hat{V}, \quad d_n\tilde{I}_n = \varepsilon\tilde{V} + \gamma\tilde{V}\tilde{A},$$

$$\eta_1\tilde{S}\,\tilde{V}+\eta_2\tilde{S}\,\tilde{I}_n=\left(\prod_{i=1}^{k-1}\frac{b_i}{d_i}\right)d_{k-1}\tilde{I}_{k-1}=\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_n\tilde{I}_n+\mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\tilde{C}\tilde{I}_n,\quad k=1,...,n.$$

We obtain

$$\begin{aligned}\frac{d\Phi_4}{dt}&=\left(1-\frac{\tilde{S}}{S}\right)\left(\alpha\tilde{S}-\alpha S\right)+\left(\eta_1\tilde{S}\,\tilde{V}+\eta_2\tilde{S}\,\tilde{I}_n\right)\left(1-\frac{\tilde{S}}{S}\right)+\eta_1\tilde{S}\,V+\eta_2\tilde{S}\,I_n-\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_nI_n\\&-\eta_1\tilde{S}\,\tilde{V}\frac{S\,V\tilde{I}_1}{\tilde{S}\,\tilde{V}I_1}-\eta_2\tilde{S}\,\tilde{I}_n\frac{S\,I_n\tilde{I}_1}{\tilde{S}\,\tilde{I}_nI_1}-\left(\eta_1\tilde{S}\,\tilde{V}+\eta_2\tilde{S}\,\tilde{I}_n\right)\sum_{k=2}^{n}\frac{I_{k-1}\tilde{I}_k}{\tilde{I}_{k-1}I_k}+n\left(\eta_1\tilde{S}\,\tilde{V}+\eta_2\tilde{S}\,\tilde{I}_n\right)\\&+\eta_1\tilde{S}\,\tilde{V}\frac{I_n}{\tilde{I}_n}-\frac{\eta_1\tilde{S}\,\tilde{V}}{d_n\tilde{I}_n}\left[\varepsilon\tilde{V}+\gamma\tilde{V}\tilde{A}\right]\frac{V}{\tilde{V}}-\eta_1\tilde{S}\,\tilde{V}\frac{I_n\tilde{V}}{\tilde{I}_nV}+\frac{\eta_1\tilde{S}\,\tilde{V}}{d_n\tilde{I}_n}\left[\varepsilon\tilde{V}+\gamma\tilde{V}\tilde{A}\right]-\mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\tilde{C}I_n.\end{aligned}\tag{6.22}$$

Since we have

$$\eta_1\tilde{S}\,V-\frac{\eta_1\tilde{S}\,\tilde{V}}{d_n\tilde{I}_n}\left[\varepsilon\tilde{V}+\gamma\tilde{V}\tilde{A}\right]\frac{V}{\tilde{V}}=0,$$

and

$$\begin{aligned}&\eta_2\tilde{S}\,I_n-\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_nI_n-\mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\tilde{C}I_n+\eta_1\tilde{S}\,\tilde{V}\frac{I_n}{\tilde{I}_n}\\&=\left[\eta_1\tilde{S}\,\tilde{V}+\eta_2\tilde{S}\,\tilde{I}_n-\left(\prod_{i=1}^{n}\frac{b_i}{d_i}\right)d_n\tilde{I}_n-\mu\left(\prod_{i=1}^{n-1}\frac{b_i}{d_i}\right)\tilde{C}\tilde{I}_n\right]\frac{I_n}{\tilde{I}_n}=0.\end{aligned}$$

Then, Eq. 6.22 will be reduced to the form

$$\begin{aligned}\frac{d\Phi_4}{dt}&=-\alpha\frac{\left(S-\tilde{S}\right)^2}{S}+\left(\eta_1\tilde{S}\,\tilde{V}+\eta_2\tilde{S}\,\tilde{I}_n\right)\left(1-\frac{\tilde{S}}{S}\right)-\eta_1\tilde{S}\,\tilde{V}\frac{S\,V\tilde{I}_1}{\tilde{S}\,\tilde{V}I_1}-\eta_2\tilde{S}\,\tilde{I}_n\frac{S\,I_n\tilde{I}_1}{\tilde{S}\,\tilde{I}_nI_1}\\&-\left(\eta_1\tilde{S}\,\tilde{V}+\eta_2\tilde{S}\,\tilde{I}_n\right)\sum_{k=2}^{n}\frac{I_{k-1}\tilde{I}_k}{\tilde{I}_{k-1}I_k}+n\left(\eta_1\tilde{S}\,\tilde{V}+\eta_2\tilde{S}\,\tilde{I}_n\right)-\eta_1\tilde{S}\,\tilde{V}\frac{I_n\tilde{V}}{\tilde{I}_nV}+\eta_1\tilde{S}\,\tilde{V}\\&=-\alpha\frac{\left(S-\tilde{S}\right)^2}{S}+\eta_1\tilde{S}\,\tilde{V}\left[(n+2)-\frac{\tilde{S}}{S}-\frac{S\,V\tilde{I}_1}{\tilde{S}\,\tilde{V}I_1}-\sum_{k=2}^{n}\frac{I_{k-1}\tilde{I}_k}{\tilde{I}_{k-1}I_k}-\frac{I_n\tilde{V}}{\tilde{I}_nV}\right]\\&+\eta_2\tilde{S}\,\tilde{I}_n\left[(n+1)-\frac{\tilde{S}}{S}-\frac{S\,I_n\tilde{I}_1}{\tilde{S}\,\tilde{I}_nI_1}-\sum_{k=2}^{n}\frac{I_{k-1}\tilde{I}_k}{\tilde{I}_{k-1}I_k}\right].\end{aligned}\tag{6.23}$$

Hence, $\frac{d\Phi_4}{dt}\leq 0$ for all $S,I_k,V,A,C>0$ with equality holding when $S(t)=\tilde{S}$, $I_k(t)=\tilde{I}_k$, $k=1,2,...,n$, and $V(t)=\tilde{V}$ for all t. It can be easily verified that the largest invariant subset of $\Upsilon_4=\left\{(S(t),I_1(t),...,I_n(t),V(t),A(t),C(t)):\frac{d\Phi_3}{dt}=0\right\}$ is $\Upsilon_4'=\left\{\tilde{\mathrm{D}}\right\}$ [46]. LaSalle's invariance principle implies that $\tilde{\mathrm{D}}$ is globally asymptotically stable. □