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Effect of ACE2 receptor and CTL response on within-host dynamics of SARS-CoV-2 infection

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Abstract

Since the end of 2019, scientists and researchers have intensified their efforts to comprehend the within-host dynamics of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus illness 2019 (COVID-19). The dynamics and progression of the SARS-CoV-2 inside the body may be understood with the use of mathematical modeling. In this study, we develop a mathematical model for characterizing the within-host dynamics of SARS-CoV-2 infection under the effect of ACE2 receptor and cytotoxic T lymphocytes (CTL) response. Latently and actively (productively) epithelial infected cells are represented in the model as two distinct classes. We take into account three distributed delays, including (i) the formation of latently infected cells, (ii) the activation of latently infected cells, and (iii) the maturation of newly released virions. We first prove that the model is well-posed, then find all possible equilibria. To determine if an equilibrium exists and is globally asymptotically stable, we derive two threshold parameters: the basic reproduction number ($\mathfrak{R}_0$) and CTL response activation number ($\mathfrak{R}_1$). We demonstrate the global asymptotic stability for all equilibria by constructing the relevant Lyapunov functions and employing LaSalle's invariance principle. To illustrate the theoretical findings, we run numerical simulations. We do sensitivity analysis and determine the most vulnerable parameters. It is discussed how CTL response and ACE2 receptors affect the kinetics of the SARS-CoV-2. Even though $\mathfrak{R}_0$ is independent of CTL response characteristics, it is shown that significant CTL immune activation can impede viral replication. Moreover, we found that, $\mathfrak{R}_0$ is influenced by the rates of ACE2 receptor growth and degradation, and this may offer valuable guidance for the creation of potential receptor-targeted vaccinations and medications. The impact of time delays and the latent period on SARS-CoV-2 infection is finally examined.

Keywords: SARS-CoV-2, ACE2 receptor, COVID-19, CTL response, Lyapunov function, global stability.

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1. Introduction

The pathogen of coronavirus disease 2019 (COVID-19), which began a pandemic over the world in the end of 2019, is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is mostly spread by contact and airborne pathways. The majority of symptomatic infected people may have a variety of symptoms, including as fever, a dry cough, diarrhea, muscular soreness, weariness, trouble swallowing, headache, and nausea [41]. Individuals with severe infections may develop acute respiratory

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distress syndrome (ARDS), which is characterized by breathing problems and low oxygen levels in the blood [41]. Consequently, the severity of the illness and the patients' death are determined by the viral infection and host reactions [41]. The virus infects epithelial (target) cells by attaching its spike protein, S, to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of epithelial cells [20, 45]. SARS-CoV-2 uses the ACE2 receptor to accurately enter host cells, making the host cells more susceptible [11]. Although type II alveolar epithelial cells in the lungs produce ACE2 better and more copiously than other cell types, these cells are believed to be the main targets of SARS-CoV-2 infection [2, 9]. Following viral cell entrance, the RNA of the virus is translated and duplicated in the cytoplasm of the infected cells, after which the replicated viral particles are released to infect further cells [3]. The immune response is crucial for stopping the spread of the illness and getting rid of the SARS-CoV-2 infection. Cytotoxic T lymphocyte (CTL) and antibody are the two primary immune responses to viral infections. While antibodies neutralize the viruses, CTLs are in charge of destroying virus-infected cells.

Mathematical modeling could be a useful approach for identifying the interactions occurring within the host during COVID-19 infection. Within-host models of SARS-CoV-2 infection dynamics allow for the evaluation of the benefits of various antiviral treatment options in terms of specific individuals [13]. In [18, 43], the following target cell-limited model for SARS-CoV-2 infection was presented as:

$$\dot{E} = -\eta ES, \tag{1.1}$$
$$\dot{I} = \eta ES - \delta_I I, \tag{1.2}$$
$$\dot{S} = \delta_I \nu I - \delta_S S, \tag{1.3}$$

where $E = E(t)$, $I = I(t)$ and $S = S(t)$ represent the concentrations of the uninfected epithelial cells, infected cells, and free SARS-CoV-2 particles at time t, respectively. η denotes the infection rate constant, and ν represents number of free SARS-CoV-2 particles produced during the course of an average infected cell's life. The average lifetime of I is denoted by δ_I. Parameter δ_S stand for the clearance rate of viruses. Several works are devoted for extending the model by dividing the infected cells into two populations, latently infected cells and actively (productively) infected cells (see e.g., [13, 15, 18, 22, 36–38, 43]). Li et al. [31] proposed SARS-CoV-2 infection by included the growth and decay of epithelial cells as:

$$\dot{E} = \delta_E (E(0) - E) - \eta ES, \tag{1.4}$$
$$\dot{I} = \eta ES - \delta_I I, \tag{1.5}$$
$$\dot{S} = \delta_I \nu I - \delta_S S, \tag{1.6}$$

where $E(0)$ is the concentration of epithelial cells that are virus-free. The average lifetime of E is denoted by δ_E.

Models (1.1)-(1.3) and (1.4)-(1.6) were expanded upon by taking into account the impact of immune response [4, 11, 12, 14, 17, 22, 30, 34, 38], pharmacological therapy [1, 7, 10, 15] and time delay [12, 21]. When the CTL immune response is considered, model (1.4)-(1.6) becomes

$$\begin{aligned}
\dot{E} &= \lambda_E - \eta ES - \delta_E E,\\
\dot{I} &= \eta ES - \delta_I I - \gamma IU,\\
\dot{S} &= \delta_I \nu I - \delta_S S,\\
\dot{U} &= \Upsilon(I,U) - \delta_U U,
\end{aligned}$$

where $U = U(t)$ denotes the concentration of CTLs and $\lambda_E = \delta_E E(0)$. The responsiveness and death rates of the CTLs are denoted by $\Upsilon(I,U)$ and $\delta_U U$, respectively. The killing rate of infected cells by CTLs is represented by γIU. The most forms of $\Upsilon(I,U)$ that were considered in the literature are (i) self-regulating CTL, $\Upsilon(I,U) = \rho$, [13]; (ii) linear CTL response, $\Upsilon(I,U) = \rho I$, [3]; (iii) predator-prey like CTL, $\Upsilon(I,U) = \rho IU$, [14, 17]; and (iv) saturated CTL expansion, $\Upsilon(I,U) = \frac{\rho I}{I+\mu}$, [34]. Here, ρ and μ denote the responsiveness and half-saturation constant of CTL, respectively.

These works mentioned above did not take into account the kinetics of the ACE2 receptor on epithelial cells. The Middle East respiratory syndrome coronavirus (MERS-CoV) infection was modeled by the authors of [40]-[25] to see how the dipeptidyl peptidase 4 (DPP4) receptor affects it. Chatterjee and Al Basir [6] proposed a system of ODEs for SARS-CoV-2 infection with CTL response and ACE2 receptor. The responsiveness of CTL was given by $\Upsilon(I,U)=\rho IU\left(1-\frac{U}{U_{max}}\right)$, where U_{max} is the maximum concentration of CTL. Lv and Ma [32] formulated a system of delay differential equations (DDEs) for SARS-CoV-2 infection mediated by ACE2 receptor as:

$$\dot{E}=\lambda_E-\eta\Psi(A)ES-\delta_E E, \tag{1.7}$$
$$\dot{I}=e^{-\alpha_1\tau_1}\eta\Psi(A_{\tau_1})E_{\tau_1}S_{\tau_1}-\delta_I I, \tag{1.8}$$
$$\dot{S}=\delta_I\nu I-\delta_S S, \tag{1.9}$$
$$\dot{A}=\lambda_A-\kappa\eta\Psi(A)AS-\delta_A A, \tag{1.10}$$

where $(E_{\tau_1},S_{\tau_1},A_{\tau_1})=(E(t-\tau_1),S(t-\tau_1),A(t-\tau_1))$. The variable $A=A(t)$ represents the concentration of per unit volume of ACE2 receptors at time t. $\Psi(A)$ represents the probability of successful entry of the virion into the epithelial cell mediated by the receptor ACE2. When the concentration of the epithelial cell receptor ACE2 is lower (higher), there are $\Psi(A)\sim 0(\sim 1)$ [32]. The term $\eta\Psi(A)ES$ represents the reduction rate of epithelial cells by SARS-CoV-2 and ACE2. Here, $\eta\Psi(A)ES$ represents the decrease in uninfected epithelial cells (due to free SARS-CoV-2 particles), and the average number of ACE2 receptors carried by each uninfected epithelial cell is A/E. Therefore, the decrease in ACE2 receptors due to the decrease in uninfected epithelial cells (caused by free virions) is $\kappa\eta\Psi(A)ES=\kappa\eta\Psi(A)ES\times(A/E)=\kappa\eta\Psi(A)AS$, where κ is a constant [32]. Here, τ_1 represents the amount of time that has passed since SARS-CoV-2 particles had made contact with healthy epithelial cells before those cells become actively infected. The likelihood that infected cells will survive throughout the delay period is $e^{-\alpha_1\tau_1}$. In [6], the reduction rates of epithelial cells and ACE2 receptors were given by ηAES and $\kappa\eta AES$, respectively.

One of the most effective approaches for giving researchers a better knowledge of the dynamical behavior of the virus inside the host and the immune response is stability analysis of viral infection models. Some recent research investigated the stability analysis of models depicting the dynamics of the SARS-CoV-2 infection inside the host. Nath et al. [35] demonstrated the global stability of model (1.4)-(1.6). Hattaf and Yousfi [17] extended model (1.4)-(1.6) by including cell-to-cell transmission and both lytic and nonlytic CTL immune responses. They investigated the global stability of the model. A two-dimensional SARS-CoV-2 infection model with immune response was proposed in [18], and Almocera et al. [4] investigated its stability. Al-Darabsah et al. [3] investegated the stability of SARS-CoV-2 infection model with CTL and general infection rate. Stability of SARS-CoV-2 dynamics models with both antibody and CTL responses was examined in [12, 34]. Stability of SARS-CoV-2 infection models with antibody-dependent enhancement were studied in [8, 39]. Chatterjee and Al Basir [6] studied the local stability of a SARS-CoV-2 infection with ACE2 receptor and CTL response. The global stability of model is addressed by Lv and Ma [32].

Model (1.7)-(1.10) ignores the immune system's reaction, cells that are latently infected, and the delayed maturity of recently released virions. As a result, this article's goal is to adjust and analyze model (1.7)-(1.10) while taking into consideration the following aspects.

A1. CTL immune response, which act for killing the actively infected cells.

A2. Latently infected cells, which contain virions, but they are not released until the cells are activated.

A3. Three distributed-time delays; (i) delay in development of latently infected epithelial cells; (ii) delay in the latently infected epithelium cells' activation; and (iii) delay in the maturation of recently released SARS-CoV-2 virions. In comparison to discrete-time delay, distributed-time delay is known to be more universal. In this case, the time delay is taken as a random variable drawn from the probability distribution function.

We first examine the essential properties of the DDEs, find the model's equilibria and discussing their existence and global stability. We create suitable Lyapunov functions and employ LaSalle's invariance principle (LIP) to examine the global asymptotic stability of all equilibria. We show the theoretical conclusions using numerical simulations. We wrap up by discussing the outcomes.

2. Model formulation

We propose the following SARS-CoV-2 infection model with ACE2 receptors, CTL response, latent phase, and distributed-time delays:

$$\begin{cases} \dot{E} = \lambda_E - \eta\Psi(A)ES - \delta_E E, \\ \dot{L} = \eta\int_0^{h_1} f_1(\tau)e^{-\alpha_1\tau}\Psi(A_\tau)E_\tau S_\tau d\tau - (a+\delta_L)L, \\ \dot{I} = a\int_0^{h_2} f_2(\tau)e^{-\alpha_2\tau}L_\tau d\tau - \delta_I I - \gamma IU, \\ \dot{S} = \delta_I\nu\int_0^{h_3} f_3(\tau)e^{-\alpha_3\tau}I_\tau d\tau - \delta_S S, \\ \dot{A} = \lambda_A - \kappa\eta\Psi(A)AS - \delta_A A, \\ \dot{U} = \rho IU - \delta_U U, \end{cases} \tag{2.1}$$

where, $(E_\tau, L_\tau, I_\tau, S_\tau, A_\tau) = (E(t-\tau), L(t-\tau), I(t-\tau), S(t-\tau), A(t-\tau))$. The variables $L = L(t)$ and $U = U(t)$ represent the concentrations of per unit volume of latently infected cells and CTLs at time t, respectively. We take τ as a random variable from probability distributed function $f_i(\tau)$, over the interval $[0, h_i]$, where h_i is the limit superior of the delay period, $i = 1, 2, 3$. The likelihood that epithelial cells that were uninfected when the SARS-CoV-2 made contact with them at time $t-\tau$ survived for τ time units and acquired latent infection at time t is represented by $f_1(\tau)e^{-\alpha_1\tau}$. The factor $f_2(\tau)e^{-\alpha_2\tau}$ represents the likelihood that latently infected cells will survive throughout the interval $[t-\tau, t]$. The likelihood that an immature SARS-CoV-2 at time $t-\tau$ survives for τ time units to become a mature SARS-CoV-2 at time t is represented by $f_3(\tau)e^{-\alpha_3\tau}$. A schematic representation of the model in (2.1) is illustrated in Figure 1.

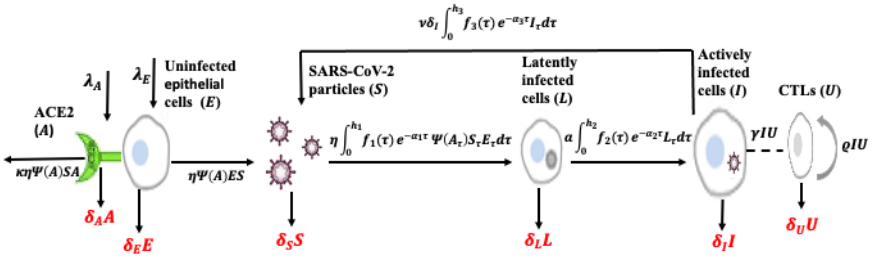


Figure 1: The schematic diagram of the SARS-CoV-2 infection with CTL immune response and intracellular delay.

Functions $f_i(\tau)$, $i = 1, 2, 3$, satisfy the following conditions:

$$f_i(\tau) > 0, \quad \int_0^{h_i} f_i(\tau)d\tau = 1, \quad \int_0^{h_i} f_i(\tau)e^{\ell\tau}d\tau < \infty, \quad \text{where } \ell > 0.$$

Let $\chi_i(\tau) = f_i(\tau)e^{-\alpha_i\tau}$ and $\zeta_i = \int_0^{h_i}\chi_i(\tau)d\tau$, thus $0 < \zeta_i \leqslant 1$, $i = 1, 2, 3$. Usually function $\Psi(A)$ is chosen as the classic Hill function: $\Psi(A) = \frac{A^n}{\mathcal{A}_s^n + A^n}$, where $\mathcal{A}_s$ is the half-saturation constant and n is the Hill coefficient [5, 32]. The function $\Psi(A)$ is continuously differentiable on $[0, +\infty)$ and strictly monotonically increasing.

The initial conditions for model (2.1) are given by:

$$\begin{aligned} &E(\theta) = \phi_1(\theta), \quad L(\theta) = \phi_2(\theta), \quad I(\theta) = \phi_3(\theta), \quad S(\theta) = \phi_4(\theta), \\ &A(\theta) = \phi_5(\theta), \quad U(\theta) = \phi_6(\theta), \quad \phi_i(\theta) \geqslant 0, \ i = 1, 2, \ldots, 6, \quad \theta \in [-\tau^*, 0], \end{aligned} \tag{2.2}$$

where, $\tau^* = \max\{h_1, h_2, h_3\}$, $\phi_i \in C([-\tau^*, 0], \mathbb{R}_{\geqslant 0})$ and C is the Banach space of continuous functions mapping from $[-\tau^*, 0]$ to $\mathbb{R}_{\geqslant 0}$ with the norm $\|\phi_i\| = \sup_{-\tau^* \leqslant \theta \leqslant 0} |\phi_i(\theta)|$ for $\phi_i \in C$, $i = 1, 2, \ldots, 6$. We note that system (2.1) with initial conditions (2.2) has a unique solution [29]. All parameters of model (2.1) are positive.

3. Basic qualitative properties

This section proves the non-negativity and boundedness of the solutions of system (2.1).

Lemma 3.1. *The solutions of model* (2.1) *with the initial states* (2.2) *are non-negative and ultimately bounded.*

Proof. We have $\dot{E}\,|_{E=0} = \lambda_E > 0$, $\dot{A}\,|_{A=0} = \lambda_A > 0$ and $\dot{U}\,|_{U=0} = 0$. Hence, $E(t) > 0$, $A(t) > 0$ and $U(t) \geqslant 0$, for all $t \geqslant 0$. From second, third and fourth equations of system (2.1) we have

$$L(t) = e^{-(a+\delta_L)t}\phi_2(0) + \eta \int_0^t \int_0^{h_1} \chi_1(\tau)\Psi(A(\theta-\tau))E(\theta-\tau)S(\theta-\tau)e^{-(a+\delta_L)(t-\theta)}d\tau d\theta \geqslant 0,$$

$$I(t) = e^{-\int_0^t (\delta_I+\gamma U(r))dr}\phi_3(0) + a\int_0^t \int_0^{h_2} \chi_2(\tau)L(\theta-\tau)e^{-\int_\theta^t (\delta_I+\gamma U(r))dr}d\tau d\theta \geqslant 0,$$

$$S(t) = e^{-\delta_S t}\phi_4(0) + \delta_I \nu \int_0^t \int_0^{h_3} \chi_3(\tau)I(\theta-\tau)e^{-\delta_S(t-\theta)}d\tau d\theta \geqslant 0,$$

for all $t \in [0, \tau^*]$. Hence, by recursive argumentation, we obtain that $L(t), I(t), S(t) \geqslant 0$ for all $t \geqslant 0$. Hence, E, L, I, S, A, and U are non-negative. Now, we prove the ultimately boundedness E, L, I, S, A, and U. From the first equation of system (2.1) we have, $\limsup_{t\to\infty} E(t) \leqslant \frac{\lambda_E}{\delta_E} = \omega_1$. To prove the ultimate boundedness of L, we define

$$\Pi_1 = \int_0^{h_1} \chi_1(\tau)E_\tau d\tau + L.$$

Then, we obtain

$$\begin{aligned}
\dot{\Pi}_1 &= \int_0^{h_1} \chi_1(\tau)\dot{E}_\tau d\tau + \dot{L} \\
&= \int_0^{h_1} \chi_1(\tau)\{\lambda_E - \eta\Psi(A_\tau)E_\tau S_\tau - \delta_E E_\tau\}d\tau + \int_0^{h_1} \chi_1(\tau)\eta\Psi(A_\tau)E_\tau S_\tau d\tau - (a+\delta_L)L \\
&= \lambda_E \int_0^{h_1} \chi_1(\tau)d\tau - \delta_E \int_0^{h_1} \chi_1(\tau)E_\tau d\tau - (a+\delta_L)L \\
&\leqslant \lambda_E\zeta_1 - p_1\left(\int_0^{h_1} \chi_1(\tau)E_\tau d\tau + L\right) \\
&\leqslant \lambda_E - p_1\left(\int_0^{h_1} \chi_1(\tau)E_\tau d\tau + L\right),
\end{aligned}$$

where, $p_1 = \min\{\delta_E, (a+\delta_L)\}$, then

$$\dot{\Pi}_1 \leqslant \lambda_E - p_1\Pi_1.$$

It follows that, $\limsup_{t\to\infty} \Pi_1(t) \leqslant \frac{\lambda_E}{p_1} = \omega_2$. Since $E > 0$ and $L \geqslant 0$, then $\limsup_{t\to\infty} L(t) \leqslant \omega_2$. Now we define

$$\Pi_2 = I + \frac{\gamma}{\rho}U.$$

Then, we obtain

$$\dot{\Pi}_2 = \dot{I} + \frac{\gamma}{\rho}\dot{U} = a\int_0^{h_2} \chi_2(\tau)L_\tau d\tau - \delta_I I - \gamma IU + \frac{\gamma}{\rho}(\rho IU - \delta_U U)$$

$$\begin{aligned}
&= a\int_0^{h_2} \chi_2(\tau) L_\tau d\tau - \delta_I I - \frac{\gamma\delta_U}{\rho} U \\
&\leqslant a\omega_2\zeta_2 - p_2\left(I + \frac{\gamma}{\rho}U\right) \\
&\leqslant a\omega_2 - p_2\left(I + \frac{\gamma}{\rho}U\right),
\end{aligned}$$

where, $p_2 = \min\{\delta_I, \delta_U\}$, then

$$\dot{\Pi}_2 \leqslant a\omega_2 - p_2\Pi_2.$$

Hence, $\lim\limits_{t\to\infty}\sup \Pi_2(t) \leqslant \frac{a\omega_2}{p_2} = \omega_3$. Since $I \geqslant 0$ and $U \geqslant 0$, then $\lim\limits_{t\to\infty}\sup I(t) \leqslant \omega_3$ and $\lim\limits_{t\to\infty}\sup U(t) \leqslant \frac{\rho}{\gamma}\omega_3 = \omega_6$. From the fourth equation we have

$$\dot{S} = \delta_I\nu\int_0^{h_3} f_3(\tau)e^{-\alpha_3\tau} I_\tau d\tau - \delta_S S \leqslant \delta_I\nu\zeta_3\omega_3 - \delta_S S \leqslant \delta_I\nu\omega_3 - \delta_S S.$$

Therefore, $\lim\limits_{t\to\infty}\sup S(t) \leqslant \frac{\delta_I\nu\omega_3}{\delta_S} = \omega_4$. Finally, from fifth equation of system (2.1) we have, $\lim\limits_{t\to\infty}\sup A(t) \leqslant \frac{\lambda_A}{\delta_A} = \omega_5$. □

Based on Lemma 3.1, one can show that

$$\Gamma = \left\{(E, L, I, S, A, U) \in C^6_{\geqslant 0} : \|E\| \leqslant \omega_1, \|L\| \leqslant \omega_2, \|I\| \leqslant \omega_3, \|S\| \leqslant \omega_4, \|A\| \leqslant \omega_5, \|U\| \leqslant \omega_6\right\}$$

is positively invariant for system (2.1).

4. Equilibria and thresholds

This section identifies all of the model (2.1) equilibria as well as the threshold parameters that guarantee their existence. First, by applying the next-generation matrix approach [42], we compute the fundamental infection reproduction number $\mathfrak{R}_0$ for system (2.1). We define the matrices F and V as follows:

$$F = \begin{pmatrix} 0 & 0 & \eta\zeta_1\Psi(A_0)E_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} a+\delta_L & 0 & 0 \\ -a\zeta_2 & \delta_I & 0 \\ 0 & -\zeta_3\delta_I\nu & \delta_S \end{pmatrix},$$

where $E_0 = \lambda_E/\delta_E$ and $A_0 = \lambda_A/\delta_A$. Then, $\mathfrak{R}_0$ can be derived as the spectral radius of FV^{-1}, as

$$\mathfrak{R}_0 = \frac{\eta a\nu\zeta_1\zeta_2\zeta_3\Psi(A_0)E_0}{(a+\delta_L)\delta_S}.$$

A second step is to define $\Delta = (E, L, I, S, A, U)$ as any equilibrium of system (2.1) that may be solved by the set of nonlinear equations that follows:

$$0 = \lambda_E - \eta\Psi(A)ES - \delta_E E, \tag{4.1}$$
$$0 = \eta\zeta_1\Psi(A)ES - (a+\delta_L)L, \tag{4.2}$$
$$0 = a\zeta_2 L - \delta_I I - \gamma IU, \tag{4.3}$$
$$0 = \delta_I\nu\zeta_3 I - \delta_S S, \tag{4.4}$$
$$0 = \lambda_A - \kappa\eta\Psi(A)SA - \delta_A A, \tag{4.5}$$
$$0 = \rho IU - \delta_U U. \tag{4.6}$$

Eq. (4.6) has two solutions, $U = 0$ and $I = \frac{\delta_U}{\rho}$. When $U = 0$, then from Eq. (4.3) we get

$$\delta_I I = a\zeta_2 L. \tag{4.7}$$

Substituting Eq. (4.7) into Eq. (4.4), we get

$$L = \frac{\delta_S}{a\nu\zeta_2\zeta_3} S. \tag{4.8}$$

Substituting Eq. (4.8) into Eq. (4.2), we get

$$\left[\eta\zeta_1\Psi(A)E - \frac{(a+\delta_L)\delta_S}{\nu a\zeta_2\zeta_3}\right] S = 0,$$

and then we have

$$S = 0, \quad \text{or} \quad \eta\zeta_1\Psi(A)E - \frac{(a+\delta_L)\delta_S}{\nu a\zeta_2\zeta_3} = 0.$$

If $S = 0$, then from Eqs. (4.1), (4.2), (4.3), and (4.5), we have $E = \lambda_E/\delta_E$, $L = 0$, $I = 0$, and $A = \lambda_A/\delta_A$. Then, we obtain the uninfected equilibrium $\Delta_0 = (E_0, 0, 0, 0, A_0, 0)$. If $S \neq 0$, then $L \neq 0$ and

$$\eta\zeta_1\Psi(A)E = \frac{(a+\delta_L)\delta_S}{\nu a\zeta_2\zeta_3}.$$

Therefore, we obtain

$$E = \frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}, \quad S = \frac{\nu a\zeta_2\zeta_3}{\delta_S}L, \quad I = \frac{a\zeta_2}{\delta_I}L, \text{ and } A = \frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}. \tag{4.9}$$

Substituting Eq. (4.9) into Eq. (4.2), we have

$$\eta\zeta_1\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right)\left(\frac{\nu a\zeta_2\zeta_3}{\delta_S}L\right) - (a+\delta_L)L = 0.$$

Since $L \neq 0$, then

$$\eta\zeta_1\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right)\left(\frac{\nu a\zeta_2\zeta_3}{\delta_S}\right) - (a+\delta_L) = 0.$$

We define a function $G(L)$ as:

$$G(L) = \eta\zeta_1\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right)\left(\frac{\nu a\zeta_2\zeta_3}{(a+\delta_L)\delta_S}\right) - 1 = 0.$$

We have

$$G(0) = \frac{\eta\nu a\zeta_1\zeta_2\zeta_3}{(a+\delta_L)\delta_S}\Psi\left(\frac{\lambda_A}{\delta_A}\right)\left(\frac{\lambda_E}{\delta_E}\right) - 1 = \Re_0 - 1 > 0, \quad \text{if} \quad \Re_0 > 1, \qquad \lim_{L \to \frac{\lambda_E\zeta_1}{a+\delta_L}} G(L) = -1 < 0,$$

and

$$\frac{d}{dL}\left[\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\right] = -\frac{\kappa(a+\delta_L)\delta_E\lambda_A\lambda_E\zeta_1^{-1}}{[\delta_A\lambda_E + (a+\delta_L)\zeta_1^{-1}L(\kappa\delta_E - \delta_A)]^2}\Psi_L\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)$$
$$= \Theta < 0.$$

So, we have

$$\frac{dG(L)}{dL} = \frac{\eta\nu a\zeta_1\zeta_2\zeta_3}{(a+\delta_L)\delta_S}\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right)\Theta - \frac{\eta\nu a\zeta_2\zeta_3}{\delta_S\delta_E}\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right) < 0.$$

Then, there exists a unique $L_1 \in \left(0, \frac{\lambda_E \zeta_1}{a+\delta_L}\right)$ such that $G(L_1) = 0$.

Therefore, there exists a unique infected equilibrium without CTL response $\Delta_1 = (E_1, L_1, I_1, S_1, A_1, 0)$ when $\Re_0 > 1$, where

$$E_1 = \frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L_1}{\delta_E} \in \left(0, \frac{\lambda_E}{\delta_E}\right), \qquad I_1 = \frac{a\zeta_2}{\delta_I}L_1 \in \left(0, \frac{a\lambda_E\zeta_1\zeta_2}{(a+\delta_L)\delta_I}\right),$$
$$S_1 = \frac{\nu a\zeta_2\zeta_3}{\delta_S}L_1 \in \left(0, \frac{\nu a\lambda_E\zeta_1\zeta_2\zeta_3}{(a+\delta_L)\delta_S}\right), \qquad A_1 = \frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L_1/E_1} \in \left(0, \frac{\lambda_A}{\delta_A}\right).$$

If $U \neq 0$ and $I = \frac{\delta_U}{\rho}$, therefore, we obtain

$$E = \frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}, \quad S = \frac{\nu\zeta_3\delta_I\delta_U}{\rho\delta_S}, \quad A = \frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}, \quad \text{and} \quad U = \frac{\delta_I}{\gamma}\left(\frac{a\rho\zeta_2}{\delta_I\delta_U}L - 1\right). \tag{4.10}$$

Substituting Eq. (4.10) into Eq. (4.2), we obtain

$$\frac{\nu\eta\zeta_1\zeta_3\delta_I\delta_U}{\rho\delta_S}\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right) - (a+\delta_L)L = 0.$$

Define a function $G^*(L)$ as:

$$G^*(L) = \frac{\nu\eta\zeta_1\zeta_3\delta_I\delta_U}{\rho\delta_S}\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right) - (a+\delta_L)L.$$

We have

$$G^*(0) = \frac{\nu\eta\zeta_1\zeta_3\delta_I\delta_U}{\rho\delta_S}\Psi\left(\frac{\lambda_A}{\delta_A}\right)\left(\frac{\lambda_E}{\delta_E}\right) > 0, \qquad \lim_{L \to \frac{\lambda_E\zeta_1}{a+\delta_L}} G^*(L) = -\lambda_E\zeta_1 < 0.$$

Moreover,

$$\frac{d}{dL}\left[\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\right] = -\frac{\kappa(a+\delta_L)\delta_E\lambda_A\lambda_E\zeta_1^{-1}}{[\delta_A\lambda_E + (a+\delta_L)\zeta_1^{-1}L(\kappa\delta_E - \delta_A)]^2}\Psi_L\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)$$
$$= \Theta^* < 0.$$

So, we have

$$\frac{dG^*(L)}{dL} = \Theta^*\frac{\nu\eta\zeta_1\zeta_3\delta_I\delta_U}{\rho\delta_S}\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right) - \left(\frac{\nu\eta\zeta_3\delta_I\delta_U(a+\delta_L)}{\rho\delta_S\delta_E}\right)\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)$$
$$-(a+\delta_L) < 0.$$

Then, there exists a unique $L_2 \in \left(0, \frac{\lambda_E\zeta_1}{a+\delta_L}\right)$ such that $G^*(L_2) = 0$. It follows that, there exists a unique infected equilibrium with CTL response $\Delta_2 = (E_2, L_2, I_2, S_2, A_2, U_2)$, when $\Re_1 > 1$, where $E_2 = \frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L_2}{\delta_E} \in \left(0, \frac{\lambda_E}{\delta_E}\right)$, $I_2 = \frac{\delta_U}{\rho}$, $S_2 = \frac{\nu\zeta_3\delta_I\delta_U}{\rho\delta_S}$, $A_2 = \frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L_2/E_2} \in \left(0, \frac{\lambda_A}{\delta_A}\right)$, and $U_2 = \frac{\delta_I}{\gamma}(\Re_1 - 1)$, where

$$\Re_1 = \frac{a\rho\zeta_2}{\delta_I\delta_U}L_2.$$

Here, $\Re_1$ represents the CTL response activation number.

We have $\Psi(A_2) < \Psi(A_0)$ and $E_2 < E_0$. Therefore

$$\Re_1 = \frac{a\rho\zeta_2 L_2}{\delta_I\delta_U} = \frac{a\rho\zeta_2}{\delta_I\delta_U}\frac{\zeta_1\eta\Psi(A_2)E_2S_2}{a+\delta_L} = \frac{\nu a\zeta_1\zeta_2\zeta_3\eta\Psi(A_2)E_2}{\delta_S(a+\delta_L)} < \frac{\nu a\zeta_1\zeta_2\zeta_3\eta\Psi(A_0)E_0}{\delta_S(a+\delta_L)} = \Re_0.$$

Now we can state the following lemma.

Lemma 4.1. *For system (2.1), there exist two threshold parameters $\Re_0$ and $\Re_1$ such that*

(i) *if $\Re_0 \leqslant 1$, then the uninfected equilibrium $\Delta_0 = (E_0, 0, 0, 0, A_0, 0)$ is the unique equilibrium;*
(ii) *if $\Re_1 \leqslant 1 < \Re_0$, then there exists two equilibria Δ_0 and infected equilibrium without CTL response $\Delta_1 = (E_1, L_1, I_1, S_1, A_1, 0)$;*
(iii) *if $\Re_1 > 1$, then there exist three equilibria Δ_0, Δ_1, and infected equilibrium with CTL response $\Delta_2 = (E_2, L_2, I_2, S_2, A_2, U_2)$.*

5. Global stability

This section formulates Lyapunov function and uses LIP to study the global asymptotic stability of equilibria. We follow the method presented in [19, 28]. We define a function $\Phi(x) = x - 1 - \ln x$. Clearly, $\Phi(1) = 0$ and $\Phi(x) \geqslant 0$ for $x > 0$. Let $\tilde{\Omega}_j$ be the largest invariant subset of

$$\Omega_j = \{(E, L, I, S, A, U) : \frac{d\Lambda j}{dt} = 0\}, \quad j = 0, 1, 2,$$

where, $\Lambda j(E, L, I, S, A, U)$ is a Lyapunov function candidate.

The following result indicates that, given all initial conditions, SARS-CoV-2 infection is likely to vanish when $\Re_0 \leqslant 1$.

Theorem 5.1. *Consider system (2.1) and suppose that $\Re_0 \leqslant 1$, then Δ_0 is globally asymptotically stable (G.A.S) and it is unstable when $\Re_0 > 1$.*

Proof. Define

$$\begin{aligned}\Lambda_0 = {} & \zeta_1 E_0 \Phi\left(\frac{E}{E_0}\right) + L + \frac{a+\delta_L}{a\zeta_2} I + \frac{a+\delta_L}{a\nu\zeta_2\zeta_3} S + \frac{\zeta_1 E_0}{\kappa A_0}\left(A - A_0 - \int_{A_0}^{A(t)} \frac{\Psi(A_0)}{\Psi(\xi)} d\xi\right) \\ & + \frac{\gamma(a+\delta_L)}{a\rho\zeta_2} U + \eta \int_0^{h_1} \chi_1(\tau) \int_{t-\tau}^{t} \Psi(A(s)) E(s) S(s) ds d\tau \\ & + \frac{a+\delta_L}{\zeta_2} \int_0^{h_2} \chi_2(\tau) \int_{t-\tau}^{t} L(s) ds d\tau + \frac{\delta_I(a+\delta_L)}{a\zeta_2\zeta_3} \int_0^{h_3} \chi_3(\tau) \int_{t-\tau}^{t} I(s) ds d\tau.\end{aligned}$$

Clearly, $\Lambda_0(E, L, I, S, A, U) > 0$ for all $E, L, I, S, A, U > 0$ and $\Lambda_0(E_0, 0, 0, 0, A_0, 0) = 0$. We calculate $\frac{d\Lambda_0}{dt}$ along the solutions of model (2.1) as:

$$\begin{aligned}\frac{d\Lambda_0}{dt} = {} & \zeta_1\left(1 - \frac{E_0}{E}\right)\dot{E} + \dot{L} + \frac{a+\delta_L}{a\zeta_2}\dot{I} + \frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\dot{S} + \frac{\zeta_1 E_0}{\kappa A_0}\left(1 - \frac{\Psi(A_0)}{\Psi(A)}\right)\dot{A} \\ & + \frac{\gamma(a+\delta_L)}{a\rho\zeta_2}\dot{U} + \eta\frac{d}{dt}\int_0^{h_1} \chi_1(\tau) \int_{t-\tau}^{t} \Psi(A(s)) E(s) S(s) ds d\tau \\ & + \frac{a+\delta_L}{\zeta_2}\frac{d}{dt}\int_0^{h_2} \chi_2(\tau) \int_{t-\tau}^{t} L(s) ds d\tau + \frac{\delta_I(a+\delta_L)}{a\zeta_2\zeta_3}\frac{d}{dt}\int_0^{h_3} \chi_3(\tau) \int_{t-\tau}^{t} I(s) ds d\tau.\end{aligned}$$

Using system (2.1) we get

$$\begin{aligned}\frac{d\Lambda_0}{dt} = {} & \zeta_1\left(1 - \frac{E_0}{E}\right)[\lambda_E - \eta\Psi(A)ES - \delta_E E] + \eta\int_0^{h_1} \chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau d\tau - (a+\delta_L)L \\ & + \frac{a+\delta_L}{a\zeta_2}\left[a\int_0^{h_2} \chi_2(\tau)L_\tau d\tau - \delta_I I - \gamma I U\right] + \frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\left[\delta_I\nu\int_0^{h_3} \chi_3(\tau)I_\tau d\tau - \delta_S S\right] \\ & + \frac{\zeta_1 E_0}{\kappa A_0}\left(1 - \frac{\Psi(A_0)}{\Psi(A)}\right)[\lambda_A - \kappa\eta\Psi(A)SA - \delta_A A] + \frac{\gamma(a+\delta_L)}{a\rho\zeta_2}[\rho I U - \delta_U U]\end{aligned}$$

$$+\eta\int_0^{h_1}\chi_1(\tau)\left[\Psi(A)ES-\Psi(A_\tau)E_\tau S_\tau\right]d\tau$$
$$+\frac{a+\delta_L}{\zeta_2}\int_0^{h_2}\chi_2(\tau)[L-L_\tau]d\tau+\frac{\delta_I(a+\delta_L)}{a\zeta_2\zeta_3}\int_0^{h_3}\chi_3(\tau)[I-I_\tau]d\tau.$$

Collecting terms we get

$$\begin{aligned}\frac{d\Lambda_0}{dt}&=\zeta_1\left(1-\frac{E_0}{E}\right)[\lambda_E-\delta_E E]+\eta\zeta_1\Psi(A)E_0S-\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\delta_S S+\eta\zeta_1\Psi(A_0)E_0S-\eta\zeta_1\Psi(A_0)E_0S\\&+\frac{\zeta_1E_0}{\kappa A_0}\left(1-\frac{\Psi(A_0)}{\Psi(A)}\right)[\lambda_A-\delta_A A]-\frac{\zeta_1E_0}{A_0}(\Psi(A)-\Psi(A_0))\eta SA-\frac{\gamma(a+\delta_L)\delta_U}{a\rho\zeta_2}U\\&=\zeta_1\left(\frac{E-E_0}{E}\right)[\lambda_E-\delta_E E]+\left(\eta\zeta_1\Psi(A_0)E_0-\frac{(a+\delta_L)\delta_S}{a\nu\zeta_2\zeta_3}\right)S+\eta\zeta_1E_0S(\Psi(A)-\Psi(A_0))\\&+\frac{\zeta_1E_0}{\kappa A_0\Psi(A)}(\Psi(A)-\Psi(A_0))[\lambda_A-\delta_A A]-\frac{\zeta_1E_0}{A_0}(\Psi(A)-\Psi(A_0))\eta SA-\frac{\gamma(a+\delta_L)\delta_U}{a\rho\zeta_2}U.\end{aligned}$$

Using the equilibrium condition $\lambda_E=\delta_E E_0$ and $\lambda_A=\delta_A A_0$, we get:

$$\begin{aligned}\frac{d\Lambda_0}{dt}&=-\zeta_1\delta_E\frac{(E-E_0)^2}{E}+\frac{(a+\delta_L)\delta_S}{a\nu\zeta_2\zeta_3}\left(\frac{a\nu\zeta_1\zeta_2\zeta_3\eta\Psi(A_0)E_0}{(a+\delta_L)\delta_S}-1\right)S\\&+\eta\zeta_1E_0S(\Psi(A)-\Psi(A_0))\frac{A_0}{A_0}+\frac{\zeta_1\delta_AE_0}{\kappa A_0\Psi(A)}(\Psi(A)-\Psi(A_0))(A_0-A)\\&-\frac{\eta\zeta_1E_0}{A_0}S(\Psi(A)-\Psi(A_0))A-\frac{\gamma(a+\delta_L)\delta_U}{a\rho\zeta_2}U\\&=-\zeta_1\delta_E\frac{(E-E_0)^2}{E}+\frac{(a+\delta_L)\delta_S}{a\nu\zeta_2\zeta_3}(\Re_0-1)S\\&+\left(\frac{\eta\zeta_1E_0S}{A_0}+\frac{\zeta_1\delta_AE_0}{\kappa A_0\Psi(A)}\right)(\Psi(A)-\Psi(A_0))(A_0-A)-\frac{\gamma(a+\delta_L)\delta_U}{a\rho\zeta_2}U.\end{aligned}$$

Since $\Re_0\leqslant 1$ and $(\Psi(A)-\Psi(A_0))(A_0-A)\leqslant 0$, then $\frac{d\Lambda_0}{dt}\leqslant 0$ for all $E,S,A,U>0$. In addition $\frac{d\Lambda_0}{dt}=0$ when $E=E_0$, $A=A_0$ and $S=U=0$. Solutions of system (2.1) converge to $\tilde{\Omega}_0$, where $E=E_0$, $A=A_0$, and $S=U=0$, [16]. Thus, $\dot{S}=0$, the fourth equation of system (2.1) gives

$$0=\dot{S}=\delta_I\nu\int_0^{h_3}\chi_3(\tau)I_\tau d\tau\Longrightarrow I=0,\ \text{for all } t.$$

Since $I=0$, then $\dot{I}=0$ and from the third equation of system (2.1) we have:

$$0=\dot{I}=a\int_0^{h_2}\chi_2(\tau)L_\tau d\tau\Longrightarrow L=0,\ \text{for all } t.$$

Therefore, $\tilde{\Omega}_0=\{\Delta_0\}$ and applying LIP [26], we obtain that Δ_0 is G.A.S.

To show that instability of Δ_0 we calculate the characteristic equation of system (2.1) at Δ_0 as:

$$\begin{aligned}0=(c+\delta_E)(c+\delta_U)&\left[c^4+(a+\delta_L+\delta_I+\delta_S+\delta_A)c^3+[(a+\delta_L)(\delta_I+\delta_S+\delta_A)+\delta_S\delta_A+\delta_I(\delta_S+\delta_A)]c^2\right.\\&\left.+(\delta_I\delta_S\delta_A-\eta a\bar{\zeta}_1\bar{\zeta}_2\bar{\zeta}_3\delta_I\nu\Psi(A_0)E_0)c+(a+\delta_L)\delta_I\delta_S\delta_A-\eta a\bar{\zeta}_1\bar{\zeta}_2\bar{\zeta}_3\delta_I\nu\delta_A\Psi(A_0)E_0\right].\end{aligned}$$

Define a function where $\mathcal{T}(c)$ as:

$$\begin{aligned}\mathcal{T}(c)&=c^4+(a+\delta_L+\delta_I+\delta_S+\delta_A)c^3+[(a+\delta_L)(\delta_I+\delta_S+\delta_A)+\delta_S\delta_A+\delta_I(\delta_S+\delta_A)]c^2\\&+(\delta_I\delta_S\delta_A-\eta a\bar{\zeta}_1\bar{\zeta}_2\bar{\zeta}_3\delta_I\nu\Psi(A_0)E_0)c+(a+\delta_L)\delta_I\delta_S\delta_A-\eta a\bar{\zeta}_1\bar{\zeta}_2\bar{\zeta}_3\delta_I\nu\delta_A\Psi(A_0)E_0,\end{aligned}$$

where $\bar{\zeta_i} = \int_0^{h_i} f_i(\tau)e^{-(c+\alpha_i)\tau}d\tau$, $i = 1, 2, 3$, which is continuous on $[0, \infty)$. We have

$$\mathcal{T}(0) = (a + \delta_L)\delta_I\delta_S\delta_A(1 - \Re_0) \ < 0, \quad \text{when} \ \ \Re_0 > 1, \qquad \lim_{c\to\infty} \mathcal{T}(c) = \infty.$$

Hence, $\mathcal{T}(c)$ has a positive real root and thus Δ_0 is unstable.

In order to validate the dynamics of Δ_1 results, we need to make an additional hypothesis [44]:

$$I_1 \leqslant \frac{\delta_U}{\rho}. \tag{H}$$

□

The following result suggests that when $\Re_1 \leqslant 1 < \Re_0$ and $I_1 \leqslant \frac{\delta_U}{\rho}$, the SARSCoV-2 infection is always formed without a CTL immunological response, independent of the initial conditions.

Theorem 5.2. *Suppose that hypothesis (H) is satisfied and $\Re_1 \leqslant 1 < \Re_0$, then Δ_1 is G.A.S.*

Proof. Define Λ_1 as:

$$\begin{aligned}
\Lambda_1 = {} & \zeta_1 E_1 \Phi\left(\frac{E}{E_1}\right) + L_1\Phi\left(\frac{L}{L_1}\right) + \frac{a+\delta_L}{a\zeta_2} I_1\Phi\left(\frac{I}{I_1}\right) + \frac{a+\delta_L}{a\nu\zeta_2\zeta_3} S_1\Phi\left(\frac{S}{S_1}\right) \\
& + \frac{\zeta_1 E_1}{\kappa A_1}\left(A - A_1 - \int_{A_1}^{A} \frac{\Psi(A_1)}{\Psi(\xi)}d\xi\right) + \frac{\gamma(a+\delta_L)}{\rho a\zeta_2} U \\
& + \eta\Psi(A_1)E_1S_1\int_0^{h_1}\chi_1(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_1)E_1S_1}\right)dsd\tau \\
& + \frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{L(s)}{L_1}\right)dsd\tau + \frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_1\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{I(s)}{I_1}\right)dsd\tau.
\end{aligned}$$

We note that, $\Lambda_1(E, L, I, S, A, U) > 0$ for all $E, L, I, S, A, U > 0$ and $\Lambda_1(E_1, L_1, I_1, S_1, A_1, 0) = 0$. Calculate $\frac{d\Lambda_1}{dt}$ as

$$\begin{aligned}
\frac{d\Lambda_1}{dt} = {} & \zeta_1\left(1 - \frac{E_1}{E}\right)\dot{E} + \left(1 - \frac{L_1}{L}\right)\dot{L} + \frac{a+\delta_L}{a\zeta_2}\left(1 - \frac{I_1}{I}\right)\dot{I} \\
& + \frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\left(1 - \frac{S_1}{S}\right)\dot{S} + \frac{\zeta_1 E_1}{\kappa A_1}\left(1 - \frac{\Psi(A_1)}{\Psi(A)}\right)\dot{A} + \frac{\gamma(a+\delta_L)}{\rho a\zeta_2}\dot{U} \\
& + \eta\Psi(A_1)E_1S_1\frac{d}{dt}\int_0^{h_1}\chi_1(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_1)E_1S_1}\right)dsd\tau \\
& + \frac{a+\delta_L}{\zeta_2}L_1\frac{d}{dt}\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{L(s)}{L_1}\right)dsd\tau + \frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_1\frac{d}{dt}\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{I(s)}{I_1}\right)dsd\tau.
\end{aligned}$$

Using system (2.1) we get

$$\begin{aligned}
\frac{d\Lambda_1}{dt} = {} & \zeta_1\left(1 - \frac{E_1}{E}\right)[\lambda_E - \eta\Psi(A)ES - \delta_E E] + \left(1 - \frac{L_1}{L}\right)\left[\eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau d\tau - (a+\delta_L)L\right] \\
& + \frac{a+\delta_L}{a\zeta_2}\left(1 - \frac{I_1}{I}\right)\left[a\int_0^{h_2}\chi_2(\tau)L_\tau d\tau - \delta_I I - \gamma IU\right] + \frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\left(1 - \frac{S_1}{S}\right)\left[\delta_I\nu\int_0^{h_3}\chi_3(\tau)I_\tau d\tau - \delta_S S\right] \\
& + \frac{\zeta_1 E_1}{\kappa A_1}\left(1 - \frac{\Psi(A_1)}{\Psi(A)}\right)[\lambda_A - \kappa\eta\Psi(A)SA - \delta_A A] + \frac{\gamma(a+\delta_L)}{\rho a\zeta_2}[\rho IU - \delta_U U] \\
& + \eta\Psi(A_1)E_1S_1\int_0^{h_1}\chi_1(\tau)\left[\frac{\Psi(A)ES}{\Psi(A_1)E_1S_1} - \frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A_1)E_1S_1}\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)\right]d\tau
\end{aligned}$$

$$+\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\left[\frac{L}{L_1}-\frac{L_\tau}{L_1}+\ln\left(\frac{L_\tau}{L}\right)\right]d\tau+\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_1\int_0^{h_3}\chi_3(\tau)\left[\frac{I}{I_1}-\frac{I_\tau}{I_1}+\ln\left(\frac{I_\tau}{I}\right)\right]d\tau.$$

Collecting terms we get

$$\begin{aligned}\frac{d\Lambda_1}{dt}&=\zeta_1\left(1-\frac{E_1}{E}\right)[\lambda_E-\delta_E E]+\zeta_1\eta\Psi(A)E_1S-\eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau\frac{L_1}{L}d\tau+(a+\delta_L)L_1\\&-\frac{a+\delta_L}{\zeta_2}\int_0^{h_2}\chi_2(\tau)L_\tau\frac{I_1}{I}d\tau+\frac{a+\delta_L}{a\zeta_2}\delta_I I_1+\frac{a+\delta_L}{a\zeta_2}\gamma I_1 U-\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\delta_S S-\frac{a+\delta_L}{a\zeta_2\zeta_3}\delta_I\int_0^{h_3}\chi_3(\tau)I_\tau\frac{S_1}{S}d\tau\\&+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\delta_S S_1+\frac{\zeta_1E_1}{\kappa A_1}\left(1-\frac{\Psi(A_1)}{\Psi(A)}\right)[\lambda_A-\delta_A A]-\frac{\zeta_1E_1}{A_1}\eta SA\left(\Psi(A)-\Psi(A_1)\right)-\frac{\gamma(a+\delta_L)\delta_U}{\rho a\zeta_2}U\\&+\eta\Psi(A_1)E_1S_1\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau\\&+\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau+\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_1\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.\end{aligned}$$

Using the equilibrium condition for Δ_1:

$$\begin{gathered}\lambda_E=\eta\Psi(A_1)E_1S_1+\delta_E E_1,\ \ (a+\delta_L)L_1=\eta\zeta_1\Psi(A_1)E_1S_1,\\ \delta_I I_1=a\zeta_2L_1,\ \ \delta_S S_1=\delta_I\nu\zeta_3I_1,\ \ \lambda_A=\kappa\eta\Psi(A_1)S_1A_1+\delta_A A_1,\end{gathered}$$

we obtain

$$\begin{aligned}\frac{d\Lambda_1}{dt}&=-\zeta_1\delta_E\frac{(E-E_1)^2}{E}+5(a+\delta_L)L_1-(a+\delta_L)L_1\frac{E_1}{E}+\zeta_1\eta\Psi(A)E_1S\\&-\frac{a+\delta_L}{\zeta_1}L_1\int_0^{h_1}\chi_1(\tau)\frac{\Psi(A_\tau)E_\tau S_\tau L_1}{\Psi(A_1)E_1S_1L}d\tau-\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\frac{L_\tau I_1}{L_1I}d\tau\\&-\zeta_1\eta\Psi(A_1)E_1S-\frac{a+\delta_L}{\zeta_3}L_1\int_0^{h_3}\chi_3(\tau)\frac{I_\tau S_1}{I_1S}d\tau+\left(\frac{(a+\delta_L)\gamma}{a\zeta_2}I_1-\frac{(a+\delta_L)\gamma\delta_U}{a\rho\zeta_2}\right)U\\&+\frac{\zeta_1\delta_AE_1}{\kappa A_1\Psi(A)}\left(\Psi(A)-\Psi(A_1)\right)(A_1-A)-(a+\delta_L)L_1\frac{\Psi(A_1)}{\Psi(A)}\\&-\frac{\eta\zeta_1E_1}{A_1}\left(\Psi(A)-\Psi(A_1)\right)SA+\frac{a+\delta_L}{\zeta_1}L_1\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau\\&+\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau+\frac{a+\delta_L}{\zeta_3}L_1\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau\\&=-\zeta_1\delta_E\frac{(E-E_1)^2}{E}+5(a+\delta_L)L_1-(a+\delta_L)L_1\frac{E_1}{E}+\eta\zeta_1E_1S(\Psi(A)-\Psi(A_1))\\&-\frac{a+\delta_L}{\zeta_1}L_1\int_0^{h_1}\chi_1(\tau)\frac{\Psi(A_\tau)E_\tau S_\tau L_1}{\Psi(A_1)E_1S_1L}d\tau-\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\frac{L_\tau I_1}{L_1I}d\tau\\&-\frac{a+\delta_L}{\zeta_3}L_1\int_0^{h_3}\chi_3(\tau)\frac{I_\tau S_1}{I_1S}d\tau+\frac{(a+\delta_L)\gamma}{a\zeta_2}\left(I_1-\frac{\delta_U}{\rho}\right)U\\&+\frac{\zeta_1\delta_AE_1}{\kappa A_1\Psi(A)}\left(\Psi(A)-\Psi(A_1)\right)(A_1-A)-(a+\delta_L)L_1\frac{\Psi(A_1)}{\Psi(A)}\\&-\frac{\eta\zeta_1E_1}{A_1}\left(\Psi(A)-\Psi(A_1)\right)SA+\frac{a+\delta_L}{\zeta_1}L_1\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau\\&+\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau+\frac{a+\delta_L}{\zeta_3}L_1\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.\end{aligned}$$

Using equalities

$$\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)=\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau L_1}{\Psi(A_1)E_1S_1L}\right)+\ln\left(\frac{\Psi(A_1)}{\Psi(A)}\right)+\ln\left(\frac{LS_1}{L_1S}\right)+\ln\left(\frac{E_1}{E}\right),$$
$$\ln\left(\frac{L_\tau}{L}\right)=\ln\left(\frac{L_\tau I_1}{L_1 I}\right)+\ln\left(\frac{L_1 I}{L I_1}\right),$$
$$\ln\left(\frac{I_\tau}{I}\right)=\ln\left(\frac{I_\tau S_1}{I_1 S}\right)+\ln\left(\frac{I_1 S}{I S_1}\right),$$

we obtain

$$\begin{aligned}\frac{d\Lambda_1}{dt}=&-\zeta_1\delta_E\frac{(E-E_1)^2}{E}-(a+\delta_L)L_1\left[\Phi\left(\frac{E_1}{E}\right)+\frac{1}{\zeta_1}\int_0^{h_1}\chi_1(\tau)\Phi\left(\frac{\Psi(A_\tau)E_\tau S_\tau L_1}{\Psi(A_1)E_1S_1L}\right)d\tau\right.\\&\left.+\frac{1}{\zeta_2}\int_0^{h_2}\chi_2(\tau)\Phi\left(\frac{L_\tau I_1}{L_1 I}\right)d\tau+\frac{1}{\zeta_3}\int_0^{h_3}\chi_3(\tau)\Phi\left(\frac{I_\tau S_1}{I_1 S}\right)d\tau+\Phi\left(\frac{\Psi(A_1)}{\Psi(A)}\right)\right]\\&+\frac{(a+\delta_L)\gamma}{a\zeta_2}\left(I_1-\frac{\delta_U}{\rho}\right)U+\left[\frac{\zeta_1\delta_A E_1}{\kappa A_1\Psi(A)}+\frac{\eta\zeta_1E_1S}{A_1}\right](\Psi(A)-\Psi(A_1))(A_1-A).\end{aligned}$$

We have $(\Psi(A)-\Psi(A_1))(A_1-A)\leqslant 0$ and from hypothesis (H) we have $I_1-\frac{\delta_U}{\rho}\leqslant 0$, then $\frac{d\Lambda_1}{dt}\leqslant 0$ for all $E,L,I,S,A,U>0$. In addition, $\frac{d\Lambda_1}{dt}=0$ when $E=E_1$, $A=A_1$, $U=0$, and

$$\frac{L_\tau I_1}{L_1 I}=\frac{I_\tau S_1}{I_1 S}=\frac{\Psi(A_\tau)E_\tau S_\tau L_1}{\Psi(A_1)E_1S_1L}=1,\quad\text{for almost }\tau\in[0,\tau^*].\tag{5.1}$$

Solutions of model (2.1) are attracted to $\tilde{\Omega}_1$. Since $\tilde{\Omega}_1$ is invariant w.r.t (2.1), on $\tilde{\Omega}_1$, we have

$$0=\dot{E}=\lambda_E-\eta\Psi(A_1)E_1S-\delta_E E_1\Longrightarrow S(t)=S_1,\ \text{for any } t,$$

and from Eq. (5.1) we get $I(t)=I_\tau=I_1$ and $L(t)=L_\tau=L_1$ for any t. Therefore, $\tilde{\Omega}_1=\{\Delta_1\}$ and applying LIP, we obtain that Δ_1 is G.A.S. □

The following finding suggests that when $\Re_1>1$, the SARS-CoV-2 infection is always formed with a CTL immunological response, independent of the initial conditions.

Theorem 5.3. *For system (2.1), let $\Re_1>1$, then Δ_2 is G.A.S.*

Proof. Consider

$$\begin{aligned}\Lambda_2=&\zeta_1E_2\Phi\left(\frac{E}{E_2}\right)+L_2\Phi\left(\frac{L}{L_2}\right)+\frac{a+\delta_L}{a\zeta_2}I_2\Phi\left(\frac{I}{I_2}\right)\\&+\left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}+\frac{\gamma(a+\delta_L)U_2}{a\nu\zeta_2\zeta_3\delta_I}\right)S_2\Phi\left(\frac{S}{S_2}\right)+\frac{\zeta_1E_2}{\kappa A_2}\left(A-A_2-\int_{A_2}^{A}\frac{\Psi(A_2)}{\Psi(\xi)}d\xi\right)\\&+\frac{\gamma(a+\delta_L)}{\rho a\zeta_2}U_2\Phi\left(\frac{U}{U_2}\right)+\eta\Psi(A_2)E_2S_2\int_0^{h_1}\chi_1(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_2)E_2S_2}\right)ds d\tau\\&+\frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{L(s)}{L_2}\right)ds d\tau+\left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}+\frac{\gamma(a+\delta_L)U_2}{a\zeta_2\zeta_3}\right)I_2\\&\times\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{I(s)}{I_2}\right)ds d\tau.\end{aligned}$$

We note that, $\Lambda_2(E, L, I, S, A, U) > 0$ for all $E, L, I, S, A, U > 0$ and $\Lambda_2(E_2, L_2, I_2, S_2, A_2, U_2) = 0$. We calculate $\frac{d\Lambda_2}{dt}$ as:

$$\begin{aligned}
\frac{d\Lambda_2}{dt} &= \zeta_1\left(1-\frac{E_2}{E}\right)\dot{E} + \left(1-\frac{L_2}{L}\right)\dot{L} + \frac{a+\delta_L}{a\zeta_2}\left(1-\frac{I_2}{I}\right)\dot{I} \\
&+ \left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3} + \frac{\gamma(a+\delta_L)U_2}{a\nu\zeta_2\zeta_3\delta_I}\right)\left(1-\frac{S_2}{S}\right)\dot{S} + \frac{\zeta_1 E_2}{\kappa A_2}\left(1-\frac{\Psi(A_2)}{\Psi(A)}\right)\dot{A} \\
&+ \frac{\gamma(a+\delta_L)}{\rho a\zeta_2}\left(1-\frac{U_2}{U}\right)\dot{U} + \eta\Psi(A_2)E_2S_2\frac{d}{dt}\int_0^{h_1}\chi_1(\tau) \\
&\times \int_{t-\tau}^{t}\Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_2)E_2S_2}\right)ds\,d\tau + \frac{a+\delta_L}{\zeta_2}L_2\frac{d}{dt}\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{L(s)}{L_2}\right)ds\,d\tau \\
&+ \left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3} + \frac{\gamma(a+\delta_L)U_2}{a\zeta_2\zeta_3}\right)I_2\frac{d}{dt}\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{I(s)}{I_2}\right)ds\,d\tau.
\end{aligned}$$

From system (2.1) we get

$$\begin{aligned}
\frac{d\Lambda_2}{dt} &= \zeta_1\left(1-\frac{E_2}{E}\right)[\lambda_E - \eta\Psi(A)ES - \delta_E E] + \left(1-\frac{L_2}{L}\right)\left[\eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau d\tau - (a+\delta_L)L\right] \\
&+ \frac{a+\delta_L}{a\zeta_2}\left(1-\frac{I_2}{I}\right)\left[a\int_0^{h_2}\chi_2(\tau)L_\tau d\tau - \delta_I I - \gamma UI\right] \\
&+ \left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3} + \frac{\gamma(a+\delta_L)U_2}{a\nu\zeta_2\zeta_3\delta_I}\right)\left(1-\frac{S_2}{S}\right)\left[\delta_I\nu\int_0^{h_3}\chi_3(\tau)I_\tau d\tau - \delta_S S\right] \\
&+ \frac{\zeta_1 E_2}{\kappa A_2}\left(1-\frac{\Psi(A_2)}{\Psi(A)}\right)[\lambda_A - \kappa\eta\Psi(A)SA - \delta_A A] \\
&+ \frac{\gamma(a+\delta_L)}{\rho a\zeta_2}\left(1-\frac{U_2}{U}\right)[\rho IU - \delta_U U] + \eta\Psi(A_2)E_2S_2\int_0^{h_1}\chi_1(\tau)\left[\frac{\Psi(A)ES}{\Psi(A_2)E_2S_2}\right. \\
&\left.-\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A_2)E_2S_2} + \ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)\right]d\tau + \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\left[\frac{L}{L_2} - \frac{L_\tau}{L_2} + \ln\left(\frac{L_\tau}{L}\right)\right]d\tau \\
&+ \left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3} + \frac{\gamma(a+\delta_L)U_2}{a\zeta_2\zeta_3}\right)I_2\int_0^{h_3}\chi_3(\tau)\left[\frac{I}{I_2} - \frac{I_\tau}{I_2} + \ln\left(\frac{I_\tau}{I}\right)\right]d\tau.
\end{aligned}$$

Collecting terms we get

$$\begin{aligned}
\frac{d\Lambda_2}{dt} &= \zeta_1\left(1-\frac{E_2}{E}\right)[\lambda_E - \delta_E E] + \eta\zeta_1\Psi(A)E_2S - \eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau\frac{L_2}{L}d\tau + (a+\delta_L)L_2 \\
&- \frac{a+\delta_L}{\zeta_2}\int_0^{h_2}\chi_2(\tau)L_\tau\frac{I_2}{I}d\tau + \frac{(a+\delta_L)\delta_I}{a\zeta_2}I_2 + \frac{\gamma(a+\delta_L)}{a\zeta_2}I_2U \\
&- \left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3} + \frac{\gamma(a+\delta_L)U_2}{a\nu\zeta_2\zeta_3\delta_I}\right)\delta_S S - \left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3} + \frac{\gamma(a+\delta_L)U_2}{a\zeta_2\zeta_3}\right)\int_0^{h_3}\chi_3(\tau)I_\tau\frac{S_2}{S}d\tau \\
&+ \left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3} + \frac{\gamma(a+\delta_L)U_2}{a\nu\zeta_2\zeta_3\delta_I}\right)\delta_S S_2 + \frac{\zeta_1 E_2}{\kappa A_2}\left(1-\frac{\Psi(A_2)}{\Psi(A)}\right)[\lambda_A - \delta_A A] \\
&- \frac{\zeta_1 E_2}{A_2}(\Psi(A) - \Psi(A_2))\eta SA - \frac{\gamma(a+\delta_L)}{\rho a\zeta_2}\delta_U U + \frac{\gamma(a+\delta_L)\delta_U}{\rho a\zeta_2}U_2 \\
&+ \eta\Psi(A_2)E_2S_2\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau + \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau) \\
&\times \ln\left(\frac{L_\tau}{L}\right)d\tau + \left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3} + \frac{\gamma(a+\delta_L)U_2}{a\zeta_2\zeta_3}\right)I_2\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.
\end{aligned}$$

Using the equilibrium condition for Δ_2:

$$\lambda_E = \eta\Psi(A_2)E_2S_2 + \delta_E E_2, \qquad (a+\delta_L)L_2 = \eta\zeta_1\Psi(A_2)E_2S_2,$$
$$a\zeta_2 L_2 = \delta_I I_2 + \gamma I_2 U_2, \quad \delta_S S_2 = \delta_I \nu \zeta_3 I_2, \quad \lambda_A = \kappa\eta\Psi(A_2)S_2A_2 + \delta_A A_2, \quad I_2 = \frac{\delta_U}{\rho},$$

we obtain

$$\begin{aligned}
\frac{d\Lambda_2}{dt} &= -\delta_E\zeta_1\frac{(E-E_2)^2}{E} + 5(a+\delta_L)L_2 - (a+\delta_L)L_2\frac{E_2}{E} + \zeta_1\eta\Psi(A)E_2S \\
&- \frac{a+\delta_L}{\zeta_1}L_2\int_0^{h_1}\chi_1(\tau)\frac{\Psi(A_\tau)E_\tau S_\tau L_2}{\Psi(A_2)E_2S_2L}d\tau - \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\frac{L_\tau I_2}{L_2 I}d\tau \\
&- \eta\zeta_1\Psi(A_2)E_2S - \frac{a+\delta_L}{\zeta_3}L_2\int_0^{h_3}\chi_3(\tau)\frac{I_\tau S_2}{I_2 S}d\tau + \frac{\zeta_1\delta_A E_2}{\kappa A_2\Psi(A)}\left(\Psi(A)-\Psi(A_2)\right)(A_2-A) \\
&- (a+\delta_L)L_2\frac{\Psi(A_2)}{\Psi(A)} - \frac{\zeta_1 E_2}{A_2}\eta SA\left(\Psi(A)-\Psi(A_2)\right) \\
&+ \frac{a+\delta_L}{\zeta_1}L_2\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau + \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau \\
&+ \frac{a+\delta_L}{\zeta_3}L_2\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau \\
&= -\delta_E\zeta_1\frac{(E-E_2)^2}{E} + 5(a+\delta_L)L_2 - (a+\delta_L)L_2\frac{E_2}{E} + \zeta_1\eta E_2S(\Psi(A)-\Psi(A_2)) \\
&- \frac{a+\delta_L}{\zeta_1}L_2\int_0^{h_1}\chi_1(\tau)\frac{\Psi(A_\tau)E_\tau S_\tau L_2}{\Psi(A_2)E_2S_2L}d\tau - \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\frac{L_\tau I_2}{L_2 I}d\tau \\
&- \frac{a+\delta_L}{\zeta_3}L_2\int_0^{h_3}\chi_3(\tau)\frac{I_\tau S_2}{I_2 S}d\tau + \frac{\zeta_1\delta_A E_2}{\kappa A_2\Psi(A)}\left(\Psi(A)-\Psi(A_2)\right)(A_2-A) \\
&- (a+\delta_L)L_2\frac{\Psi(A_2)}{\Psi(A)} - \frac{\zeta_1 E_2}{A_2}\eta SA\left(\Psi(A)-\Psi(A_2)\right) + \frac{a+\delta_L}{\zeta_1}L_2\int_0^{h_1}\chi_1(\tau) \\
&\times\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau + \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau + \frac{a+\delta_L}{\zeta_3}L_2\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.
\end{aligned}$$

Using equalities

$$\begin{aligned}
\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right) &= \ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau L_2}{\Psi(A_2)E_2S_2L}\right) + \ln\left(\frac{\Psi(A_2)}{\Psi(A)}\right) + \ln\left(\frac{LS_2}{L_2S}\right) + \ln\left(\frac{E_2}{E}\right), \\
\ln\left(\frac{L_\tau}{L}\right) &= \ln\left(\frac{L_\tau I_2}{L_2 I}\right) + \ln\left(\frac{L_2 I}{L I_2}\right), \\
\ln\left(\frac{I_\tau}{I}\right) &= \ln\left(\frac{I_\tau S_2}{I_2 S}\right) + \ln\left(\frac{I_2 S}{I S_2}\right),
\end{aligned}$$

we obtain

$$\begin{aligned}
\frac{d\Lambda_2}{dt} &= -\delta_E\zeta_1\frac{(E-E_2)^2}{E} - (a+\delta_L)L_2\left[\Phi\left(\frac{E_2}{E}\right) + \frac{1}{\zeta_1}\int_0^{h_1}\chi_1(\tau)\Phi\left(\frac{\Psi(A_\tau)E_\tau S_\tau L_2}{\Psi(A_2)E_2S_2L}\right)d\tau\right. \\
&\left. + \frac{1}{\zeta_2}\int_0^{h_2}\chi_2(\tau)\Phi\left(\frac{L_\tau I_2}{L_2 I}\right)d\tau + \frac{1}{\zeta_3}\int_0^{h_3}\chi_3(\tau)\Phi\left(\frac{I_\tau S_2}{I_2 S}\right)d\tau + \Phi\left(\frac{\Psi(A_2)}{\Psi(A)}\right)\right] \\
&+ \left[\frac{\zeta_1\delta_A E_2}{\kappa A_2\Psi(A)} + \frac{\zeta_1\eta S E_2}{A_2}\right]\left(\Psi(A)-\Psi(A_2)\right)(A_2-A).
\end{aligned}$$

If $\mathfrak{R}_1 > 1$, we get $\frac{d\Lambda_2}{dt} \leqslant 0$ for all $E, L, I, S, A > 0$. Further, $\frac{d\Lambda_2}{dt} = 0$, when $E = E_2$, $A = A_2$, and

$$\frac{L_\tau I_2}{L_2 I} = \frac{I_\tau S_2}{I_2 S} = \frac{\Psi(A_\tau)E_\tau S_\tau L_2}{\Psi(A_2)E_2 S_2 L} = 1, \text{ for almost } \tau \in [0, \tau^*]. \tag{5.2}$$

Trajectories of system (2.1) converge to $\tilde{\Omega}_2$ which has $E = E_2$ and $A = A_2$. Then

$$0 = \dot{E} = \lambda_E - \eta\Psi(A_2)E_2 S - \delta_E E_2 \Longrightarrow S(t) = S_2, \text{ for any } t,$$

and from Eq. (5.2) we get $I(t) = I_\tau = I_1$ and $L(t) = L_\tau = L_1$ for any t. The fourth equation of system (2.1) provides

$$0 = \dot{S} = \delta_I \nu \zeta_3 I_2 - \delta_S S_2 - \gamma S_2 U \Longrightarrow U = U_2, \text{ for all } t.$$

Therefore, $\tilde{\Omega}_2 = \{\Delta_2\}$. Applying LIP, we get Δ_2 is G.A.S. □

5.1. Comparison results

In order to illustrate the significance of incorporating latently infected cells and CTL response in our proposed model, we use model (2.1) under the impact of protease inhibitor (PI) drug therapy as an example:

$$\begin{cases} \dot{E} = \lambda_E - \eta\Psi(A)ES - \delta_E E, \\ \dot{L} = \eta \int_0^{h_1} f_1(\tau) e^{-\alpha_1 \tau} \Psi(A_\tau) E_\tau S_\tau d\tau - (a + \delta_L)L, \\ \dot{I} = a \int_0^{h_2} f_2(\tau) e^{-\alpha_2 \tau} L_\tau d\tau - \delta_I I - \gamma I U, \\ \dot{S} = (1-\varepsilon)\delta_I \nu \int_0^{h_3} f_3(\tau) e^{-\alpha_3 \tau} I_\tau d\tau - \delta_S S, \\ \dot{A} = \lambda_A - \kappa\eta\Psi(A)AS - \delta_A A, \\ \dot{U} = \rho I U - \delta_U U, \end{cases} \tag{5.3}$$

where $\varepsilon \in [0, 1]$ is the efficacy of PI drug therapy. The basic reproduction number of system (5.3) is:

$$\mathfrak{R}_0^\varepsilon = \frac{(1-\varepsilon)\eta a \nu \zeta_1 \zeta_2 \zeta_3 \Psi(A_0) E_0}{(a + \delta_L)\delta_S} = (1-\varepsilon)\mathfrak{R}_0.$$

Now, we calculate the drug efficacy ε that makes $\mathfrak{R}_0^\varepsilon \leqslant 1$ and stabilizes Δ_0 of system (5.3) as:

$$1 \geqslant \varepsilon \geqslant \tilde{\varepsilon}_{\min} = \max\left\{0, 1 - \frac{1}{\mathfrak{R}_0}\right\}. \tag{5.4}$$

When we ignore the latent phase in model (5.3) we obtain

$$\begin{cases} \dot{E} = \lambda_E - \eta\Psi(A)ES - \delta_E E, \\ \dot{I} = \eta \int_0^{h_1} f_1(\tau) e^{-\alpha_1 \tau} \Psi(A_\tau) E_\tau S_\tau d\tau - \delta_I I - \gamma I U, \\ \dot{S} = (1-\varepsilon)\delta_I \nu \int_0^{h_3} f_3(\tau) e^{-\alpha_3 \tau} I_\tau d\tau - \delta_S S, \\ \dot{A} = \lambda_A - \kappa\eta\Psi(A)AS - \delta_A A, \\ \dot{U} = \rho I U - \delta_U U, \end{cases} \tag{5.5}$$

and the basic reproduction number of model (5.5) is given by

$$\hat{\mathfrak{R}}_0^\varepsilon = \frac{(1-\varepsilon)\eta \nu \zeta_1 \zeta_3 \Psi(A_0) E_0}{\delta_S} = (1-\varepsilon)\hat{\mathfrak{R}}_0.$$

We determine the drug efficacy ε that makes $\hat{\mathfrak{R}}_0^\varepsilon \leqslant 1$ and stabilizes Δ_0 of system (5.5) as:

$$1 \geqslant \varepsilon \geqslant \hat{\varepsilon}_{\min} = \max\left\{0, 1 - \frac{1}{\hat{\mathfrak{R}}_0}\right\}. \tag{5.6}$$

Since $0 < \zeta_2 \leqslant 1$, then

$$\mathfrak{R}_0 = \frac{\eta a \nu \zeta_1 \zeta_2 \zeta_3 \Psi(A_0) E_0}{(a+\delta_L)\delta_S} \leqslant \frac{\eta a \nu \zeta_1 \zeta_3 \Psi(A_0) E_0}{(a+\delta_L)\delta_S} < \frac{\eta \nu \zeta_1 \zeta_3 \Psi(A_0) E_0}{\delta_S} = \hat{\mathfrak{R}}_0.$$

In the SARS-CoV-2 dynamical model, excluding the latently infected cells would result in an overestimation of the basic reproduction number. By comparing Eqs. (5.4) and (5.6) we get that $\hat{\varepsilon}_{min} > \tilde{\varepsilon}_{min}$. As a result, when using a model with latent phase, less anti-SARS-CoV-2 medication will be required to maintain the system at the uninfected equilibrium and eradicate SARS-CoV-2 from the body.

In the absence of CTL immune response, system (2.1) becomes:

$$\begin{cases} \dot{E} = \lambda_E - \eta \Psi(A) E S - \delta_E E, \\ \dot{L} = \eta \int_0^{h_1} f_1(\tau) e^{-\alpha_1 \tau} \Psi(A_\tau) E_\tau S_\tau d\tau - (a+\delta_L) L, \\ \dot{I} = a \int_0^{h_2} f_2(\tau) e^{-\alpha_2 \tau} L_\tau d\tau - \delta_I I, \\ \dot{S} = \delta_I \nu \int_0^{h_3} f_3(\tau) e^{-\alpha_3 \tau} I_\tau d\tau - \delta_S S, \\ \dot{A} = \lambda_A - \kappa \eta \Psi(A) A S - \delta_A A. \end{cases}$$

This model has only two equilibria:

(i) uninfected equilibrium, $\bar{\Delta}_0 = (E_0, 0, 0, 0, A_0)$, where the SARS-CoV-2 infection is cleared;
(ii) infected equilibrium $\bar{\Delta}_1 = (E_1, L_1, I_1, S_1, A_1)$, where the SARS-CoV-2 infection is present.

As a result, the SARS-CoV-2 infection model may not effectively represent SARS-CoV-2 infection if CTL response is ignored. Therefore, our proposed model are more relevant in describing the SARS-CoV-2 dynamics than the model presented in [32].

6. Numerical simulations

In this section, we conduct numerical simulation for model (2.1) to illustrate the theoretical findings. We perform sensitivity analysis for the model. We demonstrate the effect of CTL response and time delays on the SARS-CoV-2 dynamics. Let us take a particular form of the probability distributed functions as

$$f_i(\tau) = F(\tau - \tau_i), \quad i = 1, 2, 3,$$

where $F(.)$ is the Dirac delta function. When $h_i \to \infty$, $i = 1, 2, 3$, we have

$$\int_0^\infty f_i(\tau) d\tau = 1 \quad \text{and} \quad \int_0^\infty F(\tau - \tau_i) e^{-\alpha_i \tau} d\tau = e^{-\alpha_i \tau_i}, \quad i = 1, 2, 3.$$

Moreover

$$\int_0^\infty F(\tau - \tau_1) e^{-\alpha_1 \tau} \Psi(A_\tau) E_\tau S_\tau d\tau = e^{-\alpha_1 \tau_1} \Psi(A_{\tau_1}) E_{\tau_1} S_{\tau_1},$$
$$\int_0^\infty F(\tau - \tau_2) e^{-\alpha_2 \tau} L_\tau d\tau = e^{-\alpha_2 \tau_2} L_{\tau_2},$$
$$\int_0^\infty F(\tau - \tau_3) e^{-\alpha_3 \tau} I_\tau d\tau = e^{-\alpha_3 \tau_3} I_{\tau_3}.$$

Then, model (2.1) becomes

$$\begin{aligned} \dot{E} &= \lambda_E - \eta \Psi(A) E S - \delta_E E, \\ \dot{L} &= \eta e^{-\alpha_1 \tau_1} \Psi(A_{\tau_1}) E_{\tau_1} S_{\tau_1} - (a+\delta_L) L, \\ \dot{I} &= e^{-\alpha_2 \tau_2} a L_{\tau_2} - \delta_I I - \gamma I U, \\ \dot{S} &= \delta_I \nu e^{-\alpha_3 \tau_3} I_{\tau_3} - \delta_S S, \\ \dot{A} &= \lambda_A - \kappa \eta \Psi(A) A S - \delta_A A, \\ \dot{U} &= \rho U I - \delta_U U. \end{aligned} \tag{6.1}$$

MATLAB's dde23 solver will be used to numerically solve the DDEs system (6.1). Table 1 contains the values of the parameters of model (6.1). We choose the function Ψ as $\Psi(A) = \frac{A^n}{\mathcal{A}_s^n + A^n}$. For $n = 1$, we have

$$\mathfrak{R}_0 = \frac{\eta a \nu e^{-\alpha_1\tau_1-\alpha_2\tau_2-\alpha_3\tau_3}\Psi(A_0)E_0}{(a+\delta_L)\delta_S} = \frac{\eta a \nu e^{-\alpha_1\tau_1-\alpha_2\tau_2-\alpha_3\tau_3}\lambda_E\lambda_A}{(a+\delta_L)\delta_S(\mathcal{A}_s\delta_E\delta_A+\lambda_A\delta_E)}. \tag{6.2}$$

Table 1: Model parameters.

Parameter	Value	Parameter	Value
λ_E	5	ρ	Varied
δ_E	0.1	δ_I	0.1
η	Varied	$\mathcal{A}_s$	50
δ_S	0.1	α_1	1
ν	20	α_2	1
δ_L	0.1	α_3	1
γ	0.04	τ_1	Varied
λ_A	1	τ_2	Varied
κ	0.3	τ_3	Varied
a	0.2	δ_U	0.1
n	1	δ_A	0.1

6.1. Stability of the equilibria

To show the global stability of the equilibria of system (6.1) we take three initials as:

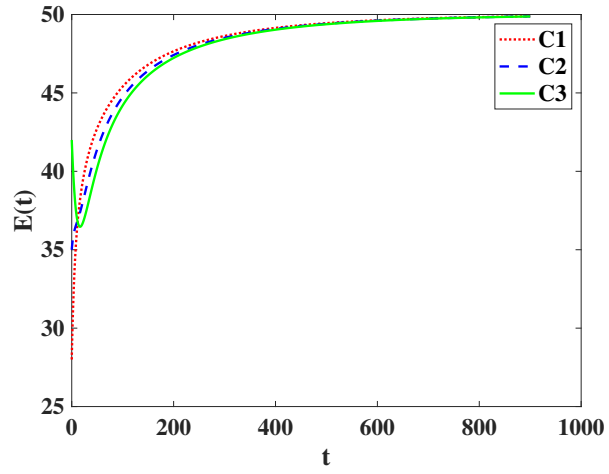
$$\begin{aligned}
&C1 : (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), U(\theta)) = (28, 2.5, 2.4, 21, 8, 0.09),\\
&C2 : (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), U(\theta)) = (35, 3, 3.2, 24, 8.7, 0.15),\\
&C3 : (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), U(\theta)) = (42, 3.5, 4, 27, 9.4, 0.21),
\end{aligned}$$

where $\theta \in [-\max\{\tau_1, \tau_2, \tau_3\}, 0]$. Here, we set $\tau_i = 0.8,\ i = 1, 2, 3$ and select the values of η and ρ as follows.

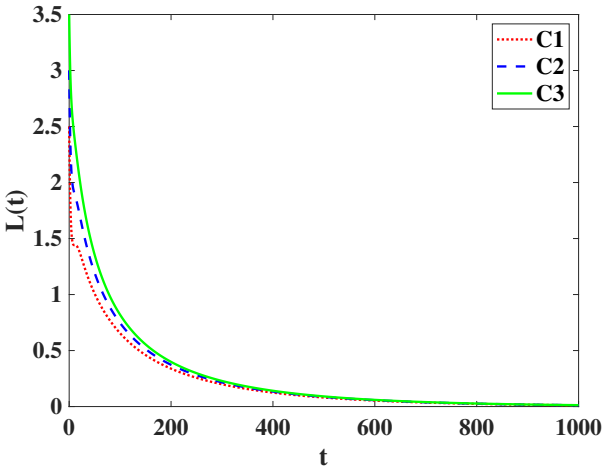
State 1 (Stability of Δ_0)): $\eta = 0.009$ and $\rho = 0.009$. These values give $\mathfrak{R}_0 = 0.90718 < 1$. Figure 2 demonstrates that for all starting values, the trajectories lead to the equilibrium $\Delta_0 = (50, 0, 0, 0, 10, 0)$. This demonstrates that Theorem 5.1's statement that Δ_0 is G.A.S. In this state, the viruses are eventually cleared.

State 2 (Stability of Δ_1)): $\eta = 0.02$ and $\rho = 0.009$. With such selection we obtain $\mathfrak{R}_1 = 0.72305 < 1 < 2.01595 = \mathfrak{R}_0$ and $I_1 = 2.79776 < \frac{\delta_U}{\rho} = \frac{0.1}{0.009} = 11.1111$. The equilibrium point Δ_1 exists with $\Delta_1 = (29.2139, 3.11326, 2.79776, 25.1423, 8.24094, 0)$. Figure 3 clearly demonstrates that the trajectories eventually trend to Δ_1 for all initials, which is consistent with Theorem 5.2. This is the situation of an infected person when CTL response is not engaged.

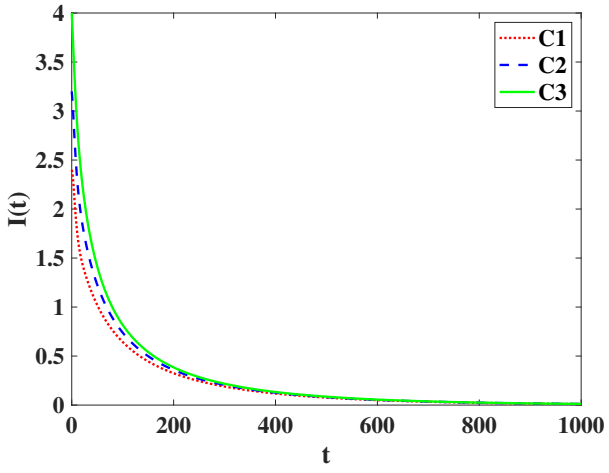
State 3 (Stability of Δ_2): $\eta = 0.02$ and $\rho = 0.04$. This gives $\mathfrak{R}_1 = 1.05541 > 1$. The numerical results show that, $\Delta_2 = (30.3969, 2.93608, 2.5, 22.4664, 8.37892, 0.138535)$ exists. Figure 4 shows that, for all initials, the trajectories eventually converge to Δ_2, which is consistent with Theorem 5.3. This case depicts a person who has SARS-CoV-2 infection and active CTL response.



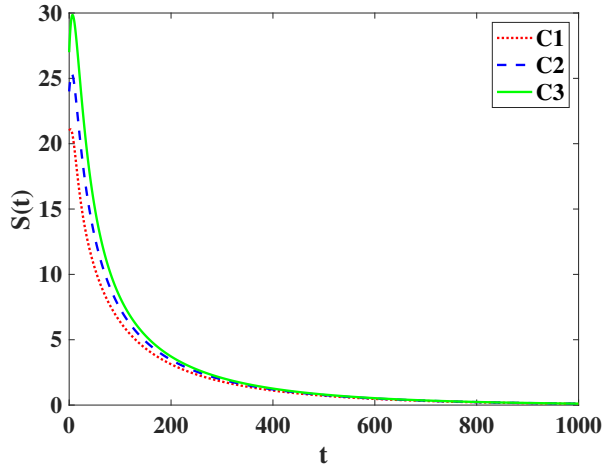
(a) Uninfected epithelial cells



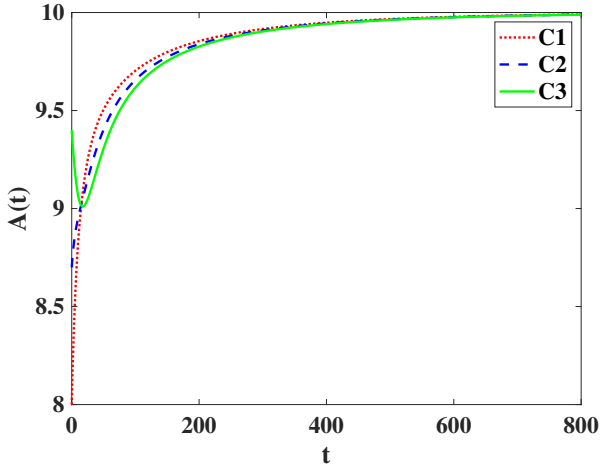
(b) Latent infected epithelial cells



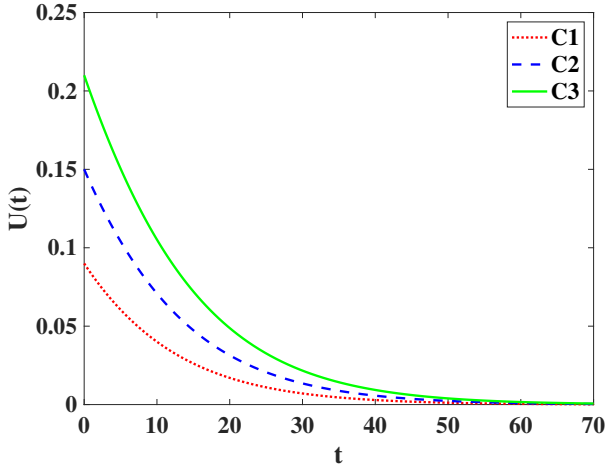
(c) Active infected epithelial cells



(d) SARS-CoV-2 particles

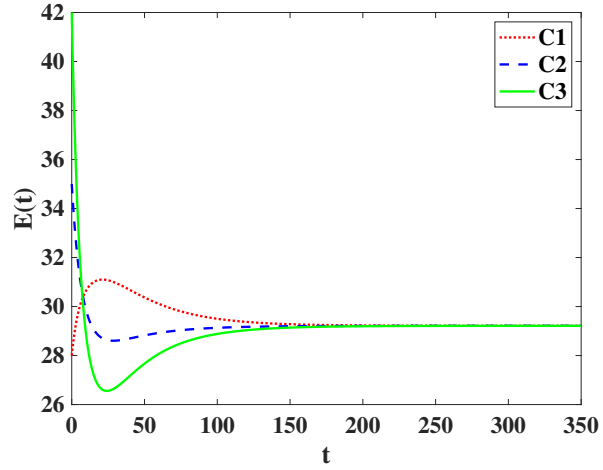


(e) ACE2 receptors

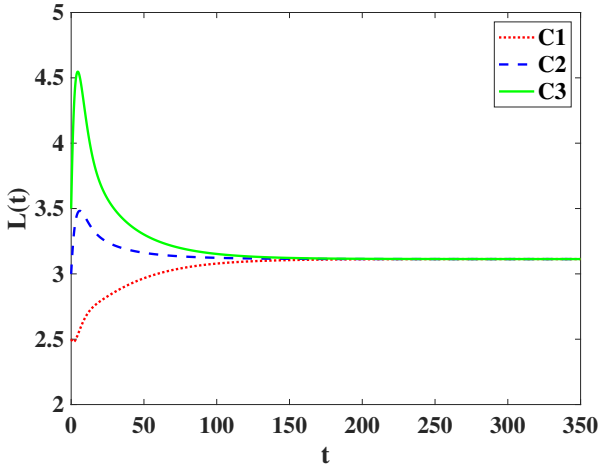


(f) CTLs

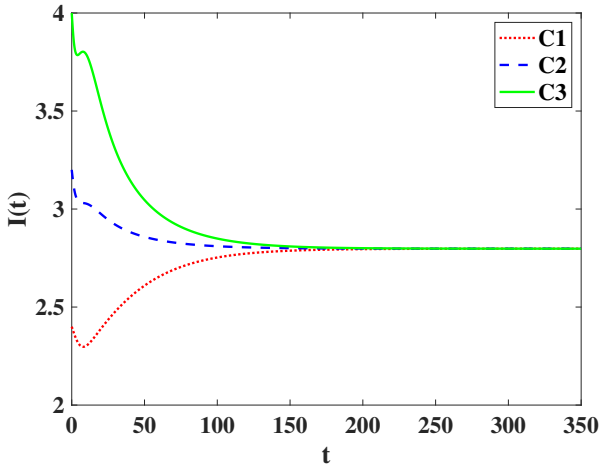
Figure 2: Solutions of model (6.1) with initials C1-C3 converge to $\Delta_0 = (50, 0, 0, 0, 10, 0)$ when $\Re_0 \leqslant 1$ (state 1).



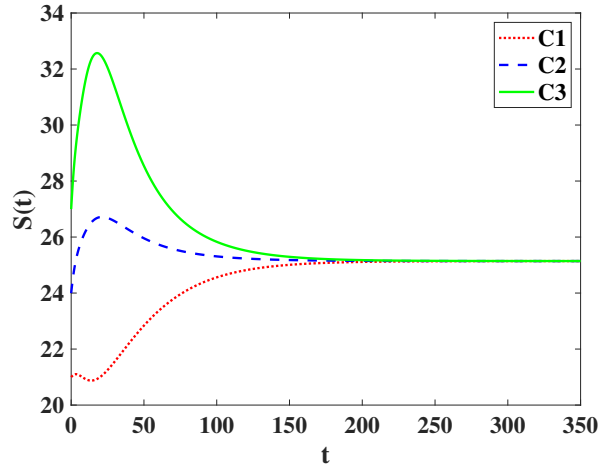
(a) Uninfected epithelial cells



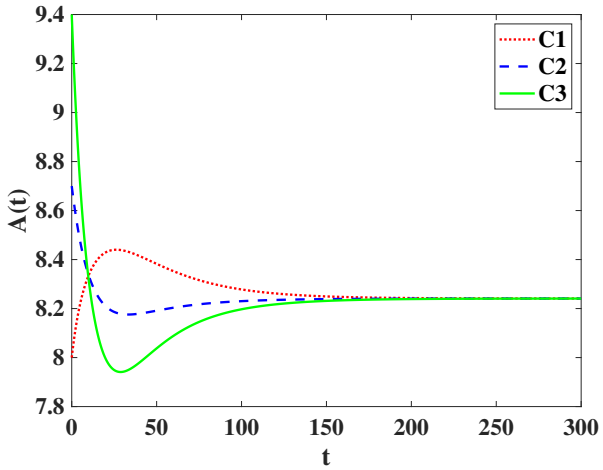
(b) Latent infected epithelial cells



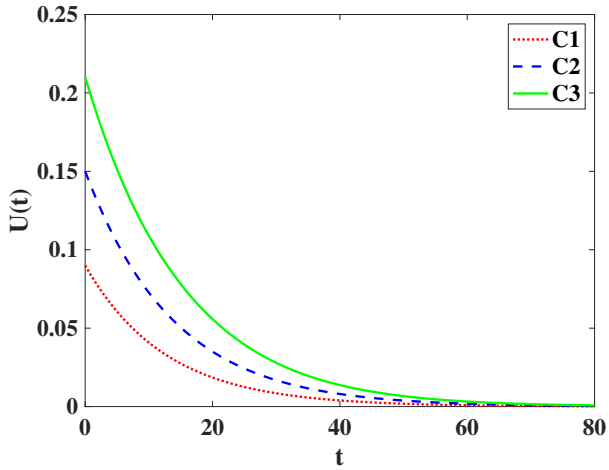
(c) Active infected epithelial cells



(d) SARS-CoV-2 particles

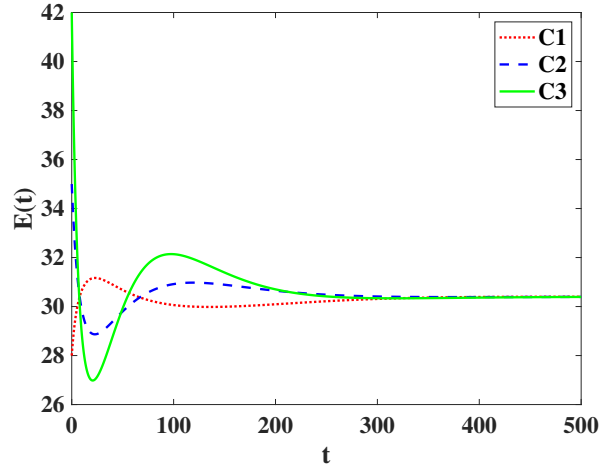


(e) ACE2 receptors

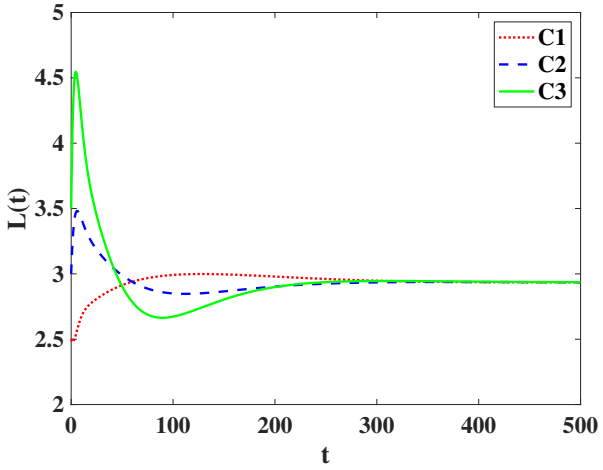


(f) CTLs

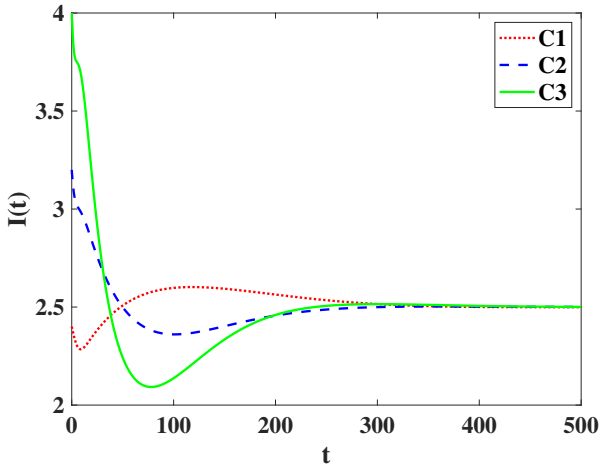
Figure 3: Solutions of model (6.1) with initials C1-C3 converge to $\Delta_1 = (29.2139, 3.11326, 2.79776, 25.1423, 8.24094, 0)$ when $\Re_0 > 1$ and $\Re_1 \leqslant 1$ (state 2).



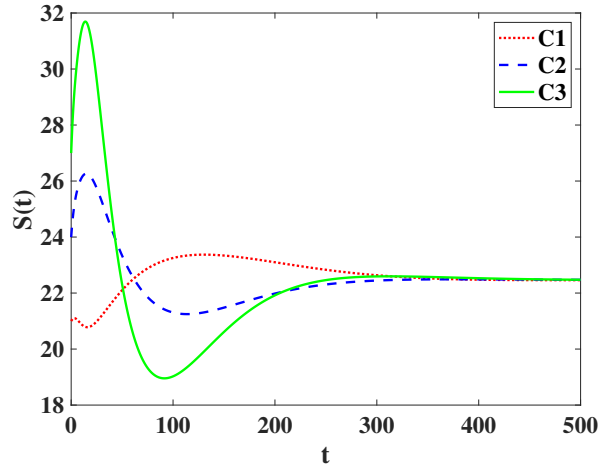
(a) Uninfected epithelial cells



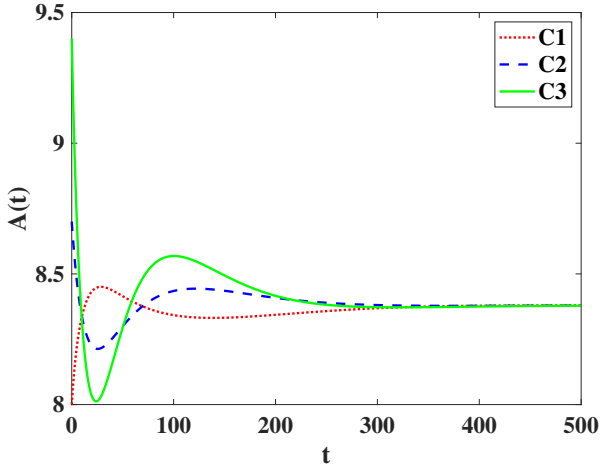
(b) Latent infected epithelial cells



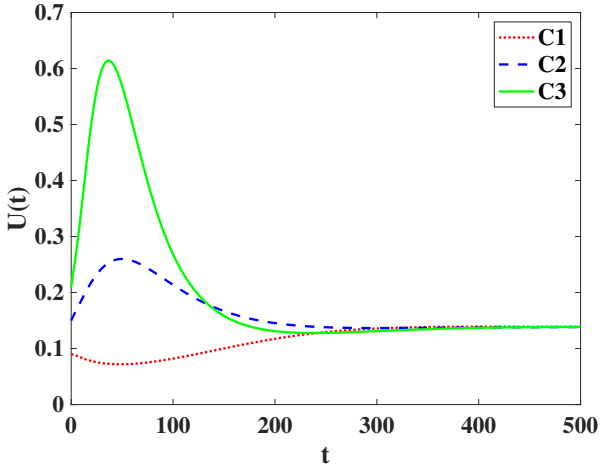
(c) Active infected epithelial cells



(d) SARS-CoV-2 particles



(e) ACE2 receptors



(f) ACTLs

Figure 4: Solutions of model (6.1) with initials C1-C3 converge to $\Delta_2 = (30.3969, 2.93608, 2.5, 22.4664, 8.37892, 0.138535)$ when $\Re_1 > 1$ (state 3).

6.2. Impact of the time delay on the SARS-CoV-2 dynamics

We show the impact of time delays τ_1, τ_2, and τ_3 on solutions of the system as well as stability of Δ_0. We can see from Eq. (6.2) that the parameter $\Re_0$ is decreasing by increasing of the delay parameters τ_1, τ_2, and τ_3 when all other parameters are fixed. Therefore, stability of Δ_0 can significantly be changed based on τ_1, τ_2, and τ_3. Let us fix $\eta = 0.004$, $\rho = 0.01$, and vary τ_1, τ_2, and τ_3 as:

D1: $\tau_1 = \tau_2 = \tau_3 = 0$;
D2: $\tau_1 = \tau_2 = \tau_3 = 0.2$;
D3: $\tau_1 = \tau_2 = \tau_3 = 0.6$;
D4: $\tau_1 = \tau_2 = \tau_3 = 1$.

Further, we consider the initial condition:

$$C4 : (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), U(\theta)) = (30, 5, 10, 200, 8, 1),$$

where $\theta \in [-\max\{\tau_1, \tau_2, \tau_3\}, 0]$. Assume that $\tau = \tau_1 = \tau_2 = \tau_3$, then $\Re_0$ is given by

$$\Re_0 = \frac{\eta a \nu e^{-(\alpha_1+\alpha_2+\alpha_3)\tau} \lambda_E \lambda_A}{(a+\delta_L)\delta_S(\mathcal{A}_s \delta_E \delta_A + \lambda_A \delta_E)}.$$

We see that $\Re_0$ is a decreasing function of τ. Let τ_{cr} be such that $\Re_0(\tau_{cr}) = 1$. Consequently,

$$\Re_0 \leqslant 1 \text{ for all } \tau \geqslant \tau_{cr}.$$

Hence, Δ_0 is G.A.S when $\tau \geqslant \tau_{cr}$. Using the values of the parameters we obtain, $\tau_{cr} = 0.497218$. Therefore, we have the following cases.

(i) If $\tau \geqslant \tau_{cr}$, then $\Re_0 \leqslant 1$ and thus Δ_0 is G.A.S. Therefore, when τ is large enough, then Δ_0 can be stabilized.
(ii) If $\tau < \tau_{cr}$, then $\Re_0 > 1$ and thus Δ_0 will be unstable.

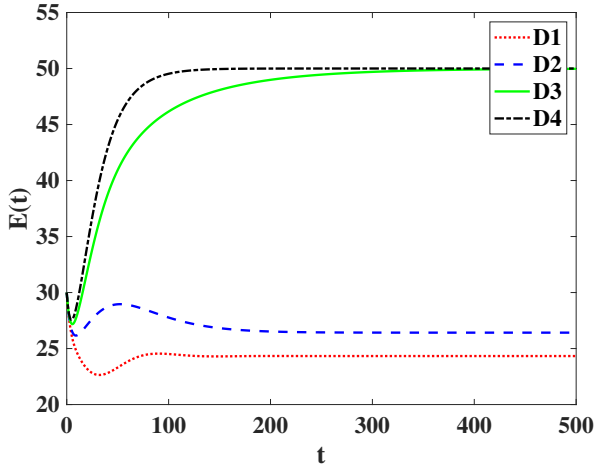
The impact of time delay on the system's trajectories is depicted in Figure 5. It is evident that as τ increases, the proportions of uninfected epithelial cells and ACE2 receptor increase, whereas those of latently and actively infected cells, SARS-CoV-2 particles, and CTLs decrease.

6.3. Impact of CTL response on the SARS-CoV-2 infection

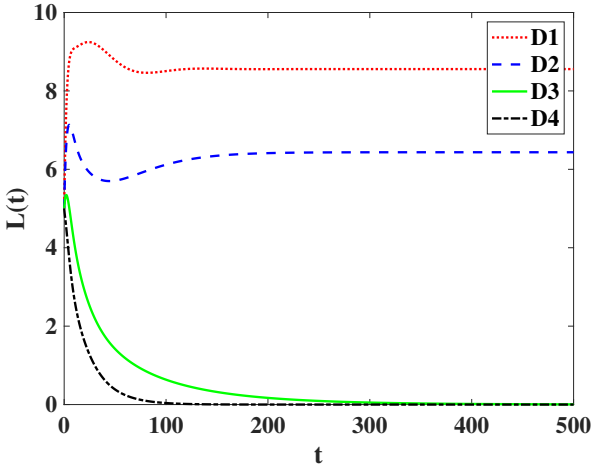
This subsection addresses the effect of stimulated rate constant ρ on the dynamics of system (6.1). We fix the parameters $\eta = 0.02$ and $\tau_1 = \tau_2 = \tau_3 = 0.8$ and vary the parameter ρ as $\rho = 0.009$, $\rho = 0.025$, $\rho = 0.04$, and $\rho = 0.07$. Further, we consider the initial condition:

$$C5 : (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), U(\theta)) = (35, 2, 3, 15, 9, 2), \quad \theta \in [-0.8, 0].$$

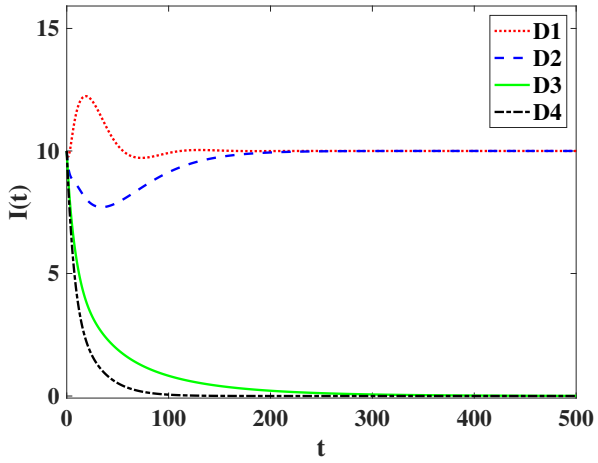
The impact of CTL response can be seen in Figure 6. We observe that, as ρ is increased, the concentrations of uninfected epithelial cells, CTLs and ACE2 receptors are increased, while concentrations of latently infected cells, actively infected cells and SARS-CoV-2 particles are decreased. Therefore, CTL response can control the SARS-CoV-2 infection. Note that, $\Re_0$ dose not depend on ρ, therefore Δ_0 can not be reached by increasing ρ. This might contribute to the development of treatments for SARS-CoV-2 with the potential to boost CTL response.



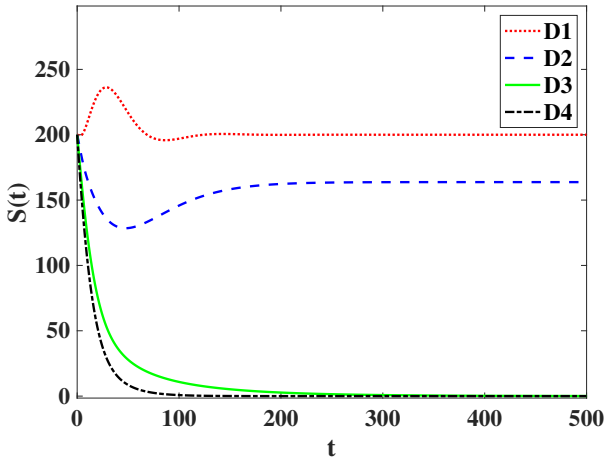
(a) Uninfected epithelial cells



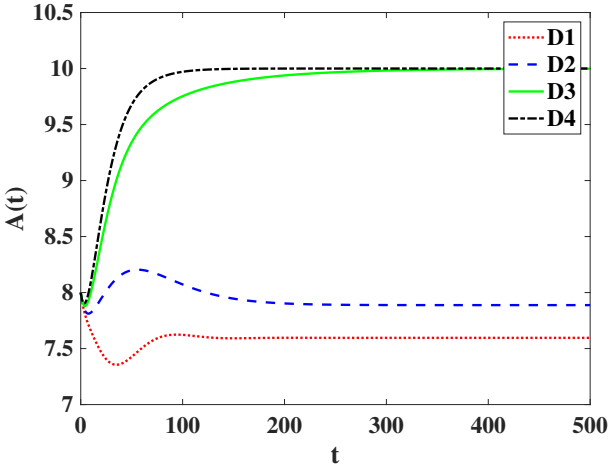
(b) Latent infected epithelial cells



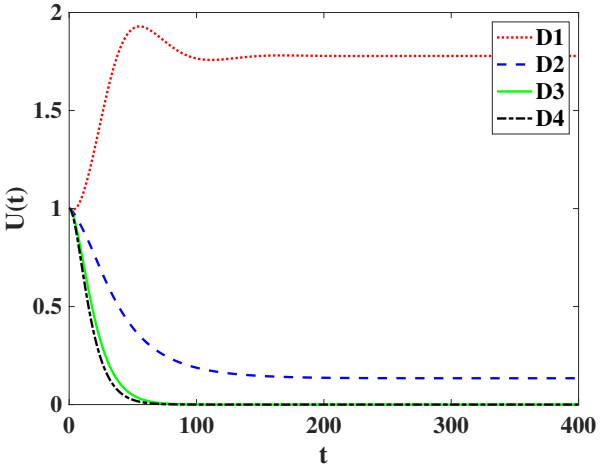
(c) Active infected epithelial cells



(d) SARS-CoV-2 particles

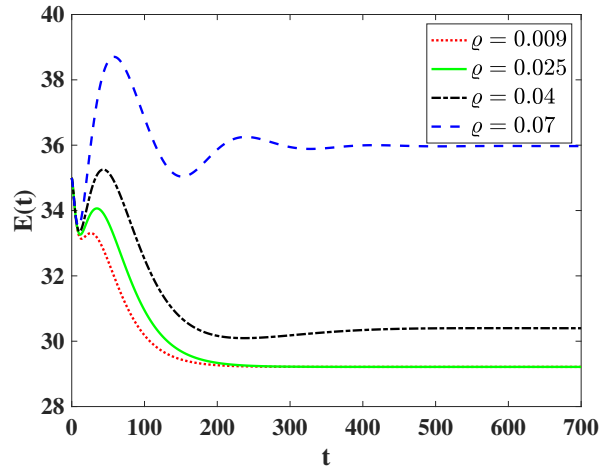


(e) ACE2 receptors

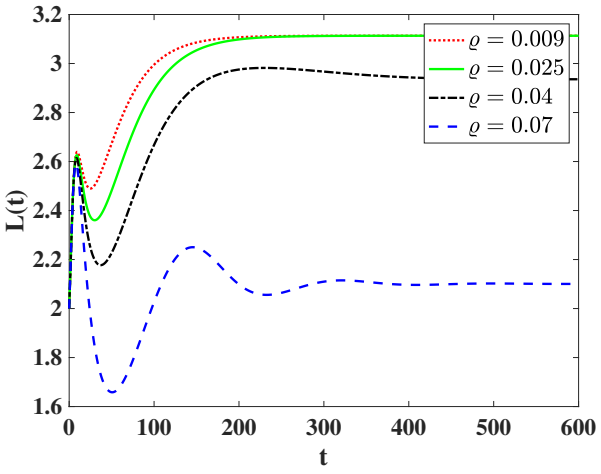


(f) CTLs

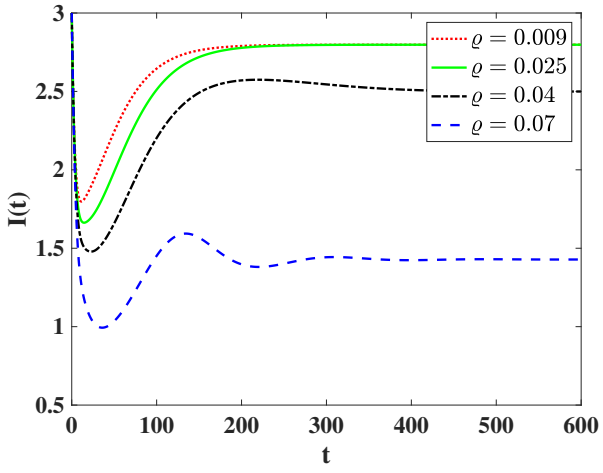
Figure 5: Solutions of model (6.1) under the impact of the time delays τ.



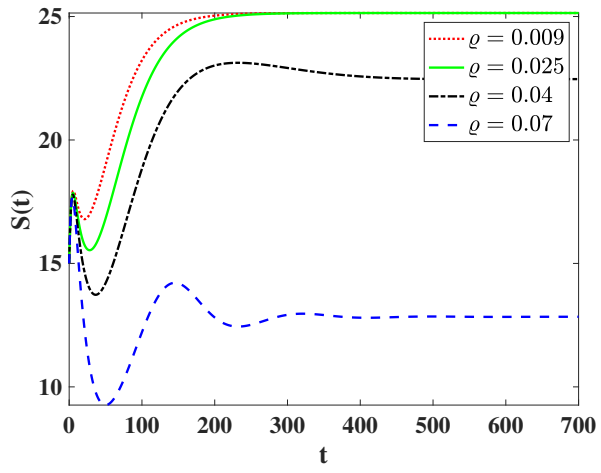
(a) Uninfected epithelial cells



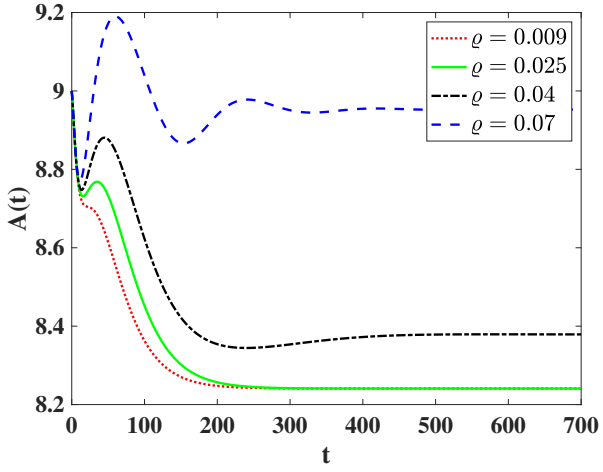
(b) Latent infected epithelial cells



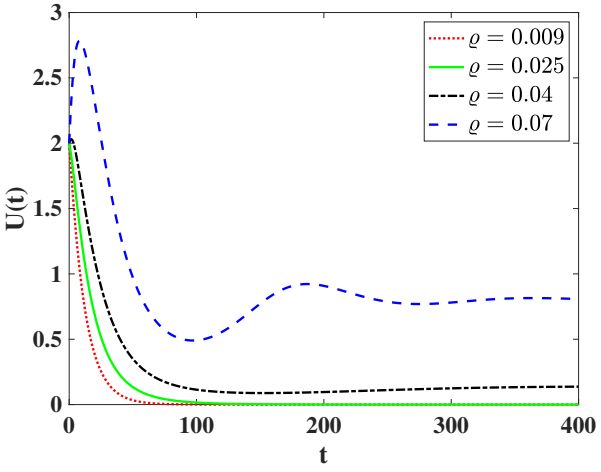
(c) Active infected epithelial cells



(d) SARS-CoV-2 particles



(e) ACE2 receptors



(f) CTLs

Figure 6: Solutions of model (6.1) under the impact of CTL immunity parameter ρ.

6.4. Sensitivity analysis

Sensitivity analysis is crucial in pathology and epidemiology when modeling complex interactions [33]. Sensitivity analysis can help us assess how well we are able to prevent the progression of the disease

between-hosts and within-host. Three techniques may be used to determine sensitivity indices: directly by direct differentiation, with the use of a Latin hypercube sampling technique, or by linearizing the system and resolving the resultant equations [27, 33]. With the use of direct differentiation, the indices in this study may be stated analytically. When variables fluctuate dependent on parameters, you may get the sensitivity index by using partial derivatives. The normalized forward sensitivity index of $\Re_0$ is written in terms of the parameter m:

$$\mathcal{S}_m = \frac{m}{\Re_0}\frac{\partial \Re_0}{\partial m}.$$

Using the values given in Table 1 and $\eta = 0.02$, $\rho = 0.009$, and $\tau_1 = \tau_2 = \tau_3 = 0.8$, we present the sensitivity index $\mathcal{S}_m$ in Table 2 and Figure 7. Obviously, λ_E, η, λ_A, a, and ν have positive indices. Clearly, λ_E, η, and ν, have the most positive sensitivity index. In this state, there is a positive relationship between the progression of COVID-19 and the parameters λ_E, η, λ_A, a, and ν, when all other parameters are fixed. Parameters δ_E, δ_S, δ_A, δ_L, τ_1, τ_2, τ_3, α_1, α_2 α_3, $\mathcal{A}_s$, and n have negative indices, meaning that when the values of these parameters rise, the value of $\Re_0$ declines. Obviously, n has the most negative sensitivity index.

Table 2: Sensitivity index of $\Re_0$.

m	$\mathcal{S}_m$	m	$\mathcal{S}_m$	m	$\mathcal{S}_m$
λ_E	1	δ_A	-0.833	α_1	-0.8
η	1	τ_1	-0.8	ν	1
δ_E	-1	λ_A	0.833	α_2	-0.8
δ_S	-1	τ_2	-0.8	α_3	-0.8
$\mathcal{A}_s$	-0.833	τ_3	-0.8	a	0.333
δ_L	-0.333	n	-1.3412		

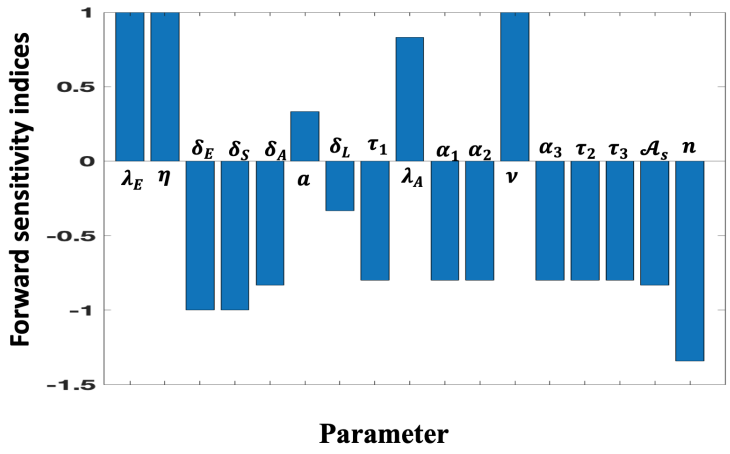


Figure 7: Forward sensitivity analysis of the parameters on $\Re_0$.

7. Conclusion and discussions

In order to understand the dynamics of SARS-CoV-2 in the host, we developed a SARS-CoV-2 infection model in this study that considers the role of the ACE2 receptor. It was taken into account how CTL response and the latent phase impacted the SARS-CoV-2 infection. We toke into account three distributed delays, including (i) the formation of latently infected epithelial cells; (ii) the activation of latently infected epithelial cells; and (iii) the maturation of newly released SARS-CoV-2 virions. We began by displaying

the fundamental properties of the solutions, nonnegativity and boundedness. The model's three equilibria were then determined to be uninfected equilibrium (Δ_0), infected without CTL response (Δ_1), and infection with CTL response (Δ_2). We derived two threshold parameters: the basic reproduction number ($\Re_0$) and CTL response activation number ($\Re_1$). The existence and global stability of the equilibria were demonstrated using $\Re_0$ and $\Re_1$. To illustrate the three equilibria's global asymptotic stability, we made the necessary Lyapunov functions and employed LIP. We proved the following.

- If $\Re_0 \leqslant 1$, then Δ_0 is the only equilibrium and it is G.A.S. In this state, the number of SARS-CoV-2 particles eventually converges to 0 and the COVID-19 patient will recover. Different control strategies can be applied to make

$$\Re_0 = \frac{\eta a \nu e^{-\alpha_1\tau_1-\alpha_2\tau_2-\alpha_3\tau_3}\lambda_E\lambda_A}{(a+\delta_L)\delta_S(\mathcal{A}_s\delta_E\delta_A+\lambda_A\delta_E)} \leqslant 1.$$

  Examples of these strategies are as follows

  (i) employing reverse transcriptase inhibitor (RTI) medications with drug efficacy $\epsilon_{RTI} \in [0,1]$ to lower the parameter η as $(1-\epsilon_{RTI})\eta$ [1];
  (ii) employing protease inhibitor (PI) medications with drug efficacy $\epsilon_{PI} \in [0,1]$ to lower the parameter ν as $(1-\epsilon_{PI})\nu$ [1];
  (iii) employing antiviral remdesivir (RDV) with drug efficacy $\epsilon_{RDV} \in [0,1]$ to lower the parameter a as $(1-\epsilon_{RDV})a$ [10];
  (iv) enlarging the length of delay periods τ_1, τ_2, and τ_3 [19];
  (v) inhibiting the proliferation rate of ACE2 receptors λ_A [32];
  (vi) increasing the degradation rate of ACE2 receptors δ_A [32].

  We note that $\Re_0$ is independent of CTL response parameters; as a result, CTL response only functions to regulate infection rather than to eradicate it.

- If $\Re_1 \leqslant 1 < \Re_0$, then there exist two equilibria Δ_0 and Δ_1, where Δ_0 is unstable and Δ_1 is G.A.S. In this case, the infection is there, but the immune system is not responding. The reason for this is because when the infected cell concentration decreases (i.e., $I \leqslant \delta_U/\rho$), it may not be high enough to trigger an immune response.

- If $\Re_1 > 1$, then in addition to Δ_0 and Δ_1, there exists Δ_2 and it is G.A.S. For this case, the body has enough infected cells (i.e., $I > \delta_U/\rho$) to trigger the immune system's response.

The model was numerically solved, and the outcomes were graphically displayed and found to be consistent with our theoretical conclusions. We looked into the sensitivity analysis to determine how the parameter $\Re_0$ is impacted by the parameters' values in the model. We looked into how the SARS-CoV-2 infection was affected by ACE2 receptors, CTL response, time delay, and latent phase. We demonstrated that the proliferation and degradation rates of ACE2 receptors affect $\Re_0$, which may be important knowledge for the development of potentially receptor-targeted vaccines and drugs. We proved that while CTL response does contribute to the control of infections, SARS-CoV-2 particles are not eventually eliminated by it. Furthermore, extending the time delay can significantly lower $\Re_0$ and inhibit the development of COVID-19. This enables the development of numerous medicines that will lengthen the delay period. Finally, we demonstrated that the model would overestimate $\Re_0$ if the latently infected cells were excluded.

Our inability to determine the values of the model's parameters using actual data from COVID-19 patients is the primary drawback of our study. The explanations are as follows: (i) real data from infected individuals are still scarce; (ii) our results may not be very accurate when compared to a small number of real studies; (iii) it is difficult to gather real data from patients who have SARS-CoV-2 infection; and (iv) doing experiments to get real data is outside the purview of this study.

There are several methods to extend our proposed model, such as by adding the effect of antibody immune response:

$$\begin{aligned}
\dot{E} &= \lambda_E - \eta\Psi(A)ES - \delta_E E,\\
\dot{L} &= \eta\int_0^{h_1} f_1(\tau)e^{-\alpha_1\tau}\Psi(A_\tau)E_\tau S_\tau d\tau - (a+\delta_L)L,\\
\dot{I} &= a\int_0^{h_2} f_2(\tau)e^{-\alpha_2\tau}L_\tau d\tau - \delta_I I - \gamma_U IU,\\
\dot{S} &= \delta_I\nu\int_0^{h_3} f_3(\tau)e^{-\alpha_3\tau}I_\tau d\tau - \delta_S S - \gamma_B SB,\\
\dot{A} &= \lambda_A - \kappa\eta\Psi(A)AS - \delta_A A,\\
\dot{B} &= \rho_B SB - \delta_B B,\\
\dot{U} &= \rho_U IU - \delta_U U,
\end{aligned}$$

where $B = B(t)$ is the concentration of the antibodies. The antibodies are stimulated at rate $\rho_B SB$, die at rate $\delta_B B$ and neutralize the SARS-CoV-2 particles at rate $\gamma_B SB$. Other extentions can also be considered by including reaction diffusion and immunologic memory. It is feasible to aim future research towards integrating the influence of immunizations and antiviral drugs into the model. Additionally, we wish to compare the results with patient data from SARS-CoV-2 affected individuals.

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