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Global Properties of Secondary DENV Infection Models with Pre-Existing CTL Immunity and Discrete/Distributed Delays

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Abstract. Dengue, caused by the dengue virus (DENV), is a serious vector-borne disease mainly prevalent in tropical areas. In certain cases, it can lead to death, especially when a person is infected a second time, resulting in a secondary infection. This research begins by presenting an in-host model for secondary DENV infection under the effect of two types of cytotoxic T lymphocytes (CTLs), non-specific and strain-specific CTLs. The first model is incorporating two distinct discrete-time delays. Additionally, the model is refined by integrating two forms of distributed time delays to provide a more realistic representation of secondary DENV infection dynamics. The main objective is to examine the dynamic behavior of both models, including the non-negativity and boundedness of solutions. A qualitative stability analysis is conducted for their steady states, revealing that the uninfected steady state in both models remains globally asymptotically stable when the basic reproduction number (R_0) is below one but becomes unstable when R_0 exceeds this threshold. Additionally, an infected steady state emerges and is globally asymptotically stable when R_0 is greater than one. The stability conditions for the two steady states are determined using the Lyapunov method. To confirm the qualitative results, comprehensive numerical simulations are conducted, offering valuable biological insights. To assess the influence of specific parameters, we conduct a sensitivity analysis on the model. The results indicate that the infection rate and viral production rate significantly impact the sensitivity of R_0, ultimately affecting the dynamics of DENV. These insights could contribute to the development of antiviral treatments aimed at inhibiting viral entry and replication. Furthermore, the study explores the impact of time delays on DENV infection dynamics, highlighting that prolonged delays can mimic the effects of antiviral treatments. A sufficiently long delay slows down the virus's progression, aiding in its control and eventual eradication. These findings suggest potential strategies for developing new treatments that could extend the viral replication or maturation.

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1. Introduction

Vector-borne viral infections are diseases transmitted to humans through the bite of infected mosquitoes. Common examples include dengue fever, zika virus, west nile virus, and chikungunya. The transmission typically occurs when an infected vector feeds on a human, introducing the virus into the bloodstream. These viruses are often RNA-based and replicate in both the vector and the human host. Upon entering the human body, the virus can infect various organs and tissues, leading to symptoms ranging from mild fever to severe complications such as neurological disorders or hemorrhagic fever.

Dengue which is caused by dengue virus (DENV) is one of the most widespread vector-borne viral infections, especially in tropical and subtropical regions. The risk of dengue outbreaks has risen significantly in recent years [1], largely due to the effects of climate change and global warming [2], [3]. In 2024, more than 14 million people worldwide were diagnosed with dengue, with over 10,000 fatalities linked to the disease [4]. Dengue symptoms can involve an intense headache, a high fever reaching 40°C, skin rash, muscle and joint discomfort, nausea, eye pain, swollen lymph nodes, and episodes of vomiting [5]. Dengue infection causes severe harm to public health, society, and the economy, particularly in low-income countries worldwide. Currently, no antiviral medications have been approved for the treatment of dengue infections [6]. Understanding the virology, transmission dynamics, and environmental factors that influence DENV is essential for developing effective prevention strategies, including vector control, vaccines, and antiviral treatments. DENV is a single-stranded RNA virus belongs to the *Flavivirus* genus and the *Flaviviridae* family and is mainly spread by blood-feeding mosquitoes of the Aedes genus [7], [8]. The DENV has four distinct serotypes (DENV 1-4), each exhibiting a 30-35% variation in amino acid composition [7]. Typically, infection with one serotype provides long-term immunity against that specific strain but does not offer protection against the others [9]. Moreover, a second infection with a different serotype tends to result in a more severe illness [10]. At the onset of a primary infection, the virus enters the bloodstream, targeting monocytes and beginning its replication process [11].

Studying the interactions between viruses, host cells, and immune cells through experiments can be costly. As a result, mathematical models of viral infections have emerged as valuable tools for analyzing the dynamic behavior of viruses and their interactions with target and immune cells. Moreover, models can provide insight into how prior infections influence disease severity and assess the effectiveness of interventions like vaccines or antiviral therapies [12]. Over the past few years, various mathematical models have been designed to describe within-host DENV infection. While some models focus on capturing the dynamics of primary DENV infection (see, e.g., [9], [13], [14]- [23]), others are tailored to represent secondary DENV infection [24]- [29]. DENV infection models have been constructed by integrating different immune responses, including:

- Antibody-mediated immunity, which relies on B cells producing antibodies to neutralize DENV particles (see e.g., [19], [24], [25], [26], [28], [30]).

- Cell-mediated immunity, driven by cytotoxic T lymphocytes (CTLs) that eliminate DENV-infected monocytes (see e.g., [14], [15], [16], [18], [20], [31]).
- A combination of antibody-mediated and cell-mediated immunity, which incorporates both B cell and CTL responses (see e.g., [9], [20], [21], [22], [27], [29]).
- A combination of innate and cell-mediated immunity, where the innate immune system provides an immediate defense before CTLs take action (see e.g., [17]).
- A combination of innate and antibody immunity, integrating the rapid innate response with antibody production to combat DENV (see e.g., [13]).

A primary dengue infection results in lifelong immunity to the initial virus strain [14]. However, upon subsequent infection with a different serotype, two types of CTL responses are triggered: non-specific CTLs carried over from the first infection and strain-specific CTLs that target the newly encountered serotype [14]. In [14], a target cell-limited model was proposed to describe secondary DENV infection, incorporating both non-specific and strain-specific CTLs:

$$\frac{dM(t)}{dt} = -\underbrace{\alpha M(t)V(t)}_{\text{infection rate}}, \tag{1.1}$$

$$\frac{dE(t)}{dt} = \underbrace{\alpha M(t)V(t)}_{\text{formation rate of infected monocytes}} - \underbrace{\mu E(t)}_{\text{mortality rate}} - \underbrace{\kappa_1 E(t)T^N(t)}_{\text{killing rate by non-specific CTLs}}, \tag{1.2}$$

$$- \underbrace{\kappa_2 E(t)T^S(t)}_{\text{killing rate by strain-specific CTLs}}, \tag{1.3}$$

$$\frac{dV(t)}{dt} = \underbrace{\eta E(t)}_{\text{burst size}} - \underbrace{\beta V(t)}_{\text{clearance rate of DENV}}, \tag{1.4}$$

$$\frac{dT^N(t)}{dt} = \underbrace{\xi}_{\text{production of non-specific CTLs}} + \underbrace{\gamma_1 E(t)T^N(t)}_{\text{proliferation of non-specific CTLs}} - \underbrace{\nu T^N(t)}_{\text{mortality rate}}, \tag{1.5}$$

$$\frac{dT^S(t)}{dt} = \underbrace{\xi}_{\text{production of strain-specific CTLs}} + \underbrace{\gamma_2 E(t)T^S(t)}_{\text{proliferation of strain-specific CTLs}} - \underbrace{\nu T^S(t)}_{\text{death rate}}. \tag{1.6}$$

This model was developed based on the following principles:

P1 It was presumed that CTLs targeting the primary DENV infection are generated through immunological memory.

P2 It considers five distinct populations: uninfected monocytes (M), DENV-infected monocytes (E), free DENV particles (V), non-specific CTLs (T^N), and strain-specific CTLs (T^S).

P3 Uninfected monocytes, the primary targets of DENV, are infected by DENV at a rate of αMV.

P4 DENV-infected monocytes are eliminated by non-specific CTLs and strain-specific CTLs at rates $\kappa_1 ET^N$ and $\kappa_2 ET^S$, respectively. Studies have shown that during heterologous dengue virus infections, non-specific CTLs respond are less effective at eliminating infected cells (i.e. $\kappa_1 < \kappa_2$) [14], [32].

P5 The production of DENV particles is given by linear function, ηE.

P6 CTLs are generated through self-regulated mechanisms as well as a predator-prey-like interaction model. Non-specific CTLs and strain-specific CTLs are generated at the same rate, ξ, and their expansion follows the rates $\gamma_1 ET^N$ and $\gamma_2 ET^S$, respectively.

P7 The mortality rates of M, E, V, T^N and T^S are expressed as linear functions of their respective concentrations, represented by σM, μE, βV, νT^N, and νT^S, respectively.

In model (1.1)-(1.6), the following points were noted: (i) The regeneration and death of uninfected monocytes are not considered. However, several DENV infection models in the literature include these factors (e.g., [24], [26], [27], [28]), (ii) both non-specific CTLs and strain-specific CTLs share the same regeneration rate, ξ, however, these rates could differ in other models, and (iii) the mortality rates of non-specific CTLs and strain-specific CTLs are assumed to be equal, though they may not necessarily be the same. To overcome such points Raezah et al. [33] developed the following model:

$$\frac{dM(t)}{dt} = \rho - \sigma M(t) - \alpha M(t)V(t), \tag{1.7}$$

$$\frac{dE(t)}{dt} = \alpha M(t)V(t) - \mu E(t) - \kappa_1 E(t)T^N(t) - \kappa_2 E(t)T^S(t), \tag{1.8}$$

$$\frac{dV(t)}{dt} = \eta E(t) - \beta V, \tag{1.9}$$

$$\frac{dT^N(t)}{dt} = \xi_1 + \gamma_1 ET^N - \nu_1 T^N, \tag{1.10}$$

$$\frac{dT^S(t)}{dt} = \xi_2 + \gamma_2 ET^S - \nu_2 T^S, \tag{1.11}$$

where ρ and σM represent the regeneration and death rates of the uninfected monocytes, respectively. Models (1.1)-(1.6) and (1.7)-(1.11) do not incorporate time delays in the infection process or viral maturation. However, time delays are crucial for accurately capturing the progression of infections, particularly in relation to how the virus infects host cells and matures over time. In our proposed model, we introduce time delays to account for these natural lags in the infection and maturation processes. This modification provides a more precise representation of the time-dependent dynamics of the infection.

The objective of this paper is to develop two models for secondary DENV infection, incorporating both non-specific and strain-specific CTLs. We introduce two types of time delays into the models, with the second model being an extension of the first, incorporating two classes of distributed time delays. The study includes an analysis of both the basic and global properties

of the models, sensitivity analysis, and validation of the theoretical results through numerical simulations.

2. DENV Infection Model With Discrete-Time Delays

In this section we study the dynamics of DENV infection model with discrete-time delays.

2.1. **Model formulation.** This section provides a detailed explanation of the proposed model. The model includes two types delay parameters τ_1 and τ_2 are defined as: τ_1 is the time from the DENV particles contacting uninfected monocytes to become DENV-infected monocytes. τ_2 is the time of maturation of new produced virions. We formulate a DENV dynamics model with discrete-time delays, represented as a system of five delay differential equations (DDEs):

$$\frac{dM(t)}{dt} = \rho - \sigma M(t) - \alpha M(t)V(t), \tag{2.1}$$

$$\frac{dE(t)}{dt} = e^{-m_1\tau_1}\alpha M(t-\tau_1)V(t-\tau_1) - \mu E(t) - \kappa_1 E(t)T^N(t) - \kappa_2 E(t)T^S(t), \tag{2.2}$$

$$\frac{dV(t)}{dt} = e^{-m_2\tau_2}\eta E(t-\tau_2) - \beta V, \tag{2.3}$$

$$\frac{dT^N(t)}{dt} = \xi_1 + \gamma_1 E T^N - \nu_1 T^N, \tag{2.4}$$

$$\frac{dT^S(t)}{dt} = \xi_2 + \gamma_2 E T^S - \nu_2 T^S. \tag{2.5}$$

Here, $m_i, i = 1,2$ are positive constants and the factor $e^{-m_i\tau_i}$ indicates the likelihood of a cell or virion surviving during the delay period $[t-\tau_i, t]$.

The initial conditions for system (2.1)-(2.5) are given as:

$$\begin{aligned} &M(\theta) = \varphi_1(\theta), E(\theta) = \varphi_2(\theta), V(\theta) = \varphi_3(\theta), T^N(\theta) = \varphi_4(\theta), T^S(\theta) = \varphi_5(\theta), \\ &\varphi_i(\theta) \geq 0, \quad \theta \in [-\tau^*, 0], \quad \varphi_i(\theta) \in C\left([-\tau^*, 0], \mathbb{R}_{\geq 0}\right), \quad i = 1,2,\cdots,5, \end{aligned} \tag{2.6}$$

where $\tau^* = \max\{\tau_1, \tau_2\}$, and C is the Banach space of continuous functions mapping from $[-\tau^*, 0]$ to $\mathbb{R}_{\geq 0}$ with the norm

$$\left\|\varphi_i\right\| = \sup_{-\tau^* \leq \theta \leq 0} \left|\varphi_i(\theta)\right| \quad \text{for } \varphi_i \in C, i = 1,2,\cdots,5.$$

The system (2.1)-(2.5), along with the initial conditions given in (2.6), has a unique solution [34], [35]. The values of parameters of model (2.1)-(2.5) are given in Table 1.

2.2. **Preliminaries.** This section addresses the non-negativity and ultimately boundedness of the solutions for system (2.1)-(2.5). We also illustrate the existence of steady states for the system and identify the threshold parameters. Let's use the following notations:

$$\begin{aligned} &\left(M, E, V, T^N, T^S\right) = \left(M, E, V, T^N, T^S\right)(t), \\ &M_{\tau_1} = M(t-\tau_1), V_{\tau_1} = V(t-\tau_1), E_{\tau_2} = E(t-\tau_2). \end{aligned}$$

TABLE 1. Model parameters.

Parameter	Value	Source	Parameter	Value	Source
ρ	10^7	[23]	γ_1	4.44×10^{-4}	[14]
σ	0.14	[23] [14]	γ_2	1.53×10^{-3}	[14]
α	Varied		ν_1	0.5	[14] [37]
μ	0.14	[23] [14]	ν_2	0.5	[14] [37]
η	10^4	[23] [14] [36]	ξ_1	30	[14] [37]
β	3.48	[23] [14]	ξ_2	30	[14] [37]
κ_1	2.77×10^{-6}	[14]	κ_2	1.04×10^{-5}	[14]
m_i	1				

Lemma 2.1. *The solutions of system (2.1)-(2.5) with the initial conditions (2.6) are nonnegative and ultimately bounded.*

Proof. Let's demonstrate the non-negativity of the solutions for the system (2.1)-(2.5). Obviously, Eqs. (2.1), (2.4), and (2.5) give

$$\frac{dM}{dt}|_{M=0} = \rho > 0, \frac{dT^N}{dt}\Big|_{T^N=0} = \xi_1 > 0, \frac{dT^S}{dt}\Big|_{T^S=0} = \xi_2 > 0.$$

Hence $M(t) > 0$, $T^N(t) > 0$ and $T^S(t) > 0$ for any $t \geq 0$. Additionally, we have

$$E(t) = e^{-\int_0^t \left(\mu+\kappa_1 T^N(x)+\kappa_2 T^S(x)\right)dx}\varphi_2(0) + \alpha e^{-m_1\tau_1}\int_0^t e^{-\int_\theta^t \left(\mu+\kappa_1 T^N(x)+\kappa_2 T^S(x)\right)dx} M(\theta-\tau_1)V(\theta-\tau_1)d\theta \geq 0,$$

$$V(t) = e^{-\beta t}\varphi_3(0) + \eta e^{-m_2\tau_2}\int_0^t e^{-\beta(t-\theta)}E(\theta-\tau_2)d\theta \geq 0,$$

for any $t \in [0, \tau^*]$. Therefore, through recursive argumentation, we conclude that $(M, E, V, T^N, T^S)(t) \geq 0$ for any $t \geq 0$. Hence, M, E, V, T^N and T^S are nonnegative.

Next, let's establish the ultimate boundedness of the solution (M, E, V, T^N, T^S). From Eq. (2.1) we have,

$$\limsup_{t\to\infty} M(t) \leq \frac{\rho}{\sigma} = \omega_1.$$

To prove the ultimate boundedness of $E(t)$, $T^N(t)$, and $T^S(t)$, we define

$$\ell = e^{-m_1\tau_1}M_{\tau_1} + E + \frac{\kappa_1}{\gamma_1}T^N + \frac{\kappa_2}{\gamma_2}T^S,$$

then

$$\begin{aligned}
\frac{d\ell}{dt} &= e^{-m_1\tau_1}\frac{dM_{\tau_1}}{dt} + \frac{dE}{dt} + \frac{\kappa_1}{\gamma_1}\frac{dT^N}{dt} + \frac{\kappa_2}{\gamma_2}\frac{dT^S}{dt} \\
&= e^{-m_1\tau_1}\left[\rho - \sigma M_{\tau_1} - \alpha M_{\tau_1} V_{\tau_1}\right] + e^{-m_1\tau_1}\alpha M_{\tau_1} V_{\tau_1} - \mu E - \kappa_1 E T^N \\
&- \kappa_2 E T^S + \frac{\kappa_1}{\gamma_1}\left[\xi_1 + \gamma_1 E T^N - \nu_1 T^N\right] + \frac{\kappa_2}{\gamma_2}\left[\xi_2 + \gamma_2 E T^S - \nu_2 T^S\right] \\
&= e^{-m_1\tau_1}\left[\rho - \sigma M_{\tau_1}\right] - \mu E + \frac{\kappa_1}{\gamma_1}\left[\xi_1 - \nu_1 T^N\right] + \frac{\kappa_2}{\gamma_2}\left[\xi_2 - \nu_2 T^S\right] \\
&= e^{-m_1\tau_1}\rho - \sigma e^{-m_1\tau_1} M_{\tau_1} - \mu E + \frac{\kappa_1\xi_1}{\gamma_1} - \frac{\kappa_1\nu_1}{\gamma_1} T^N + \frac{\kappa_2\xi_2}{\gamma_2} - \frac{\kappa_2\nu_2}{\gamma_2} T^S \\
&= e^{-m_1\tau_1}\rho + \frac{\kappa_1\xi_1}{\gamma_1} + \frac{\kappa_2\xi_2}{\gamma_2} - \left[\sigma e^{-m_1\tau_1} M_{\tau_1} + \mu E + \frac{\kappa_1\nu_1}{\gamma_1} T^N + \frac{\kappa_2\nu_2}{\gamma_2} T^S\right] \\
&\leq \rho + \frac{\kappa_1\xi_1}{\gamma_1} + \frac{\kappa_2\xi_2}{\gamma_2} - \epsilon\left[e^{-m_1\tau_1} M_{\tau_1} + E + \frac{\kappa_1}{\gamma_1} T^N + \frac{\kappa_2}{\gamma_2} T^S\right] \\
&= \rho + \frac{\kappa_1\xi_1}{\gamma_1} + \frac{\kappa_2\xi_2}{\gamma_2} - \epsilon\ell,
\end{aligned}$$

where $\epsilon = \min\{\sigma, \mu, \nu_1, \nu_2\}$. It follows that,

$$\limsup_{t\to\infty} \ell(t) \leq \frac{\rho}{\epsilon} + \frac{\kappa_1\xi_1}{\epsilon\gamma_1} + \frac{\kappa_2\xi_2}{\epsilon\gamma_2} = \omega_2$$

and then $\limsup_{t\to\infty} E(t) \leq \omega_2$, $\limsup_{t\to\infty} T^N(t) \leq \omega_3$, and $\limsup_{t\to\infty} T^S(t) \leq \omega_4$ where $\omega_3 = \frac{\gamma_1\omega_2}{\kappa_1}$ and $\omega_4 = \frac{\gamma_2\omega_2}{\kappa_2}$. Finally, from Eq. (2.3), we obtain

$$\begin{aligned}
\frac{dV}{dt} &= e^{-m_2\tau_2}\eta E_{\tau_2} - \beta V \\
&\leq e^{-m_2\tau_2}\eta\omega_2 - \beta V \\
&\leq \eta\omega_2 - \beta V,
\end{aligned}$$

and hence $\limsup_{t\to\infty} V(t) \leq \omega_5$ where $\omega_5 = \frac{\eta\omega_2}{\beta}$. Based on Lemma 2.1 we can demonstrate that the set

$$\Omega = \left\{(M, E, V, T^N, T^S) \in C^5_{\geq 0} : \|M\| \leq \omega_1, \|E\| \leq \omega_2, \|V\| \leq \omega_5, \|T^N\| \leq \omega_3, \|T^S\| \leq \omega_4\right\}$$

is positively invariant with respect to system (2.1)-(2.5). □

Lemma 2.2. *For the DENV dynamics system (2.1)-(2.5), there exists a threshold parameter $R_0 > 0$ such that*

(i): *If $R_0 \leq 1$, then there is a unique uninfected steady state $\mathcal{SS}_0$,*

(ii): *If $R_0 > 1$, then there is an infected steady state $\mathcal{SS}_1$ in addition to $\mathcal{SS}_0$.*

Proof. The steady states $\mathcal{SS} = (M, E, V, T^N, T^S)$ of system (2.1)-(2.5) can be computed by solving the following system of algebraic equations:

$$0 = \rho - \sigma M - \alpha MV, \tag{2.7}$$

$$0 = e^{-m_1\tau_1}\alpha MV - \mu E - \kappa_1 ET^N - \kappa_2 ET^S, \tag{2.8}$$

$$0 = e^{-m_2\tau_2}\eta E - \beta V, \tag{2.9}$$

$$0 = \xi_1 + \gamma_1 ET^N - \nu_1 T^N, \tag{2.10}$$

$$0 = \xi_2 + \gamma_2 ET^S - \nu_2 T^S. \tag{2.11}$$

Eqs. (2.7), (2.9), (2.10) and (2.11) give

$$\begin{aligned} M &= \frac{\rho}{\sigma + \alpha V}, \quad V = \frac{\eta e^{-m_2\tau_2}E}{\beta}, \\ T^N &= \frac{\xi_1}{\nu_1 - \gamma_1 E}, \quad T^S = \frac{\xi_2}{\nu_2 - \gamma_2 E}. \end{aligned} \tag{2.12}$$

By substituting into Eq. (2.8), we obtain

$$\left(-\mu + \frac{\eta\alpha\rho e^{-(m_1\tau_1+m_2\tau_2)}}{\beta\sigma + \eta\alpha e^{-m_2\tau_2}E} + \frac{\kappa_1\xi_1}{\gamma_1 E - \nu_1} + \frac{\kappa_2\xi_2}{\gamma_2 E - \nu_2}\right)E = 0. \tag{2.13}$$

Eq. (2.13) presents two possibilities: the first is $E = 0$, which leads to the infection-free steady state $\mathcal{SS}_0\left(M_0, 0, 0, T_0^N, T_0^S\right)$, where $M_0 = \frac{\rho}{\sigma}, T_0^N = \frac{\xi_1}{\nu_1}$ and $T_0^S = \frac{\xi_2}{\nu_2}$. The other possibility is that $E \neq 0$ and

$$-\mu + \frac{\eta\alpha\rho e^{-(m_1\tau_1+m_2\tau_2)}}{\beta\sigma + \eta\alpha e^{-m_2\tau_2}E} + \frac{\kappa_1\xi_1}{\gamma_1 E - \nu_1} + \frac{\kappa_2\xi_2}{\gamma_2 E - \nu_2} = 0$$

which leads to

$$\frac{c_3E^3 + c_2E^2 + c_1E + c_0}{(\beta\sigma + \eta\alpha e^{-m_2\tau_2}E)(\gamma_1 E - \nu_1)(\gamma_2 E - \nu_2)} = 0, \tag{2.14}$$

where

$$\begin{aligned} c_3 &= \mu\eta\alpha\gamma_1\gamma_2 e^{-m_2\tau_2}, \\ c_2 &= -\kappa_2\xi_2\eta\alpha\gamma_1 e^{-m_2\tau_2} - \kappa_1\xi_1\eta\alpha\gamma_2 e^{-m_2\tau_2} + \mu\gamma_1\gamma_2\beta\sigma - \eta\alpha\gamma_1\gamma_2\rho e^{-(m_1\tau_1+m_2\tau_2)} \\ &\quad - \mu\eta\alpha\gamma_2\nu_1 e^{-m_2\tau_2} - \mu\eta\alpha\gamma_1\nu_2 e^{-m_2\tau_2}, \\ c_1 &= -\kappa_2\xi_2\gamma_1\beta\sigma - \kappa_1\xi_1\gamma_2\beta\sigma + \kappa_2\xi_2\eta\alpha\nu_1 e^{-m_2\tau_2} - \mu\gamma_2\beta\sigma\nu_1 + \eta\alpha\gamma_2\rho\nu_1 e^{-(m_1\tau_1+m_2\tau_2)} + \kappa_1\xi_1\eta\alpha\nu_2 e^{-m_2\tau_2} \\ &\quad - \mu\gamma_1\beta\sigma\nu_2 + \eta\alpha\gamma_1\rho\nu_2 e^{-(m_1\tau_1+m_2\tau_2)} + \mu\eta\alpha\nu_1\nu_2 e^{-m_2\tau_2}, \\ c_0 &= \kappa_2\xi_2\beta\sigma\nu_1 + \kappa_1\xi_1\beta\sigma\nu_2 + \mu\beta\sigma\nu_1\nu_2 - \eta\alpha\rho\nu_1\nu_2 e^{-(m_1\tau_1+m_2\tau_2)}. \end{aligned}$$

Define a function $\Gamma(E) = c_3E^3 + c_2E^2 + c_1E + c_0$, then

$$\Gamma(0) = -\beta\sigma\left(\kappa_2\xi_2\nu_1 + \kappa_1\xi_1\nu_2 + \mu\nu_1\nu_2\right)\left(\frac{\eta\alpha\rho e^{-(m_1\tau_1+m_2\tau_2)}}{\mu\sigma\beta\left(\frac{\kappa_1\xi_1}{\nu_1\mu} + \frac{\kappa_2\xi_2}{\nu_2\mu} + 1\right)} - 1\right),$$

$$\Gamma\left(\frac{\nu_1}{\gamma_1}\right) = \frac{\kappa_1\xi_1\gamma_2\left(\beta\sigma\gamma_1 + \alpha\nu_1\eta e^{-m_2\tau_2}\right)}{\gamma_1}\left(\frac{\nu_2}{\gamma_2} - \frac{\nu_1}{\gamma_1}\right)$$
$$\Gamma\left(\frac{\nu_2}{\gamma_2}\right) = \frac{\kappa_2\xi_2\gamma_1\left(\beta\sigma\gamma_2 + \alpha\nu_2\eta e^{-m_2\tau_2}\right)}{\gamma_2}\left(\frac{\nu_1}{\gamma_1} - \frac{\nu_2}{\gamma_2}\right),$$
$$\lim_{E\to\infty}\Gamma(E) = \infty.$$

We have $\Gamma(0) < 0$ if the following condition is met

$$\frac{\eta\alpha\rho e^{-(m_1\tau_1+m_2\tau_2)}}{\mu\sigma\beta\left(\frac{\kappa_1\xi_1}{\nu_1\mu} + \frac{\kappa_2\xi_2}{\nu_2\mu} + 1\right)} > 1. \tag{2.15}$$

Observe that

$$\frac{\nu_2}{\gamma_2} > \frac{\nu_1}{\gamma_1} \Longrightarrow \Gamma\left(\frac{\nu_1}{\gamma_1}\right) > 0 \text{ and } \Gamma\left(\frac{\nu_2}{\gamma_2}\right) < 0,$$
$$\frac{\nu_2}{\gamma_2} < \frac{\nu_1}{\gamma_1} \Longrightarrow \Gamma\left(\frac{\nu_1}{\gamma_1}\right) < 0 \text{ and } \Gamma\left(\frac{\nu_2}{\gamma_2}\right) > 0.$$

Hence,

$$\Gamma\left(\min\left\{\frac{\nu_1}{\gamma_1}, \frac{\nu_2}{\gamma_2}\right\}\right) > 0 \text{ and } \Gamma\left(\max\left\{\frac{\nu_1}{\gamma_1}, \frac{\nu_2}{\gamma_2}\right\}\right) < 0.$$

If condition (2.15) is satisfied, then $\Gamma(0) < 0$ and Eq. (2.14) has three positive roots

$$E_1 \in \left(0, \min\left\{\frac{\nu_1}{\gamma_1}, \frac{\nu_2}{\gamma_2}\right\}\right),$$
$$\bar{E} \in \left(\min\left\{\frac{\nu_1}{\gamma_1}, \frac{\nu_2}{\gamma_2}\right\}, \max\left\{\frac{\nu_1}{\gamma_1}, \frac{\nu_2}{\gamma_2}\right\}\right),$$
$$\tilde{E} \in \left(\max\left\{\frac{\nu_1}{\gamma_1}, \frac{\nu_2}{\gamma_2}\right\}, \infty\right).$$

From Eq. (2.12), we observe that the solution $\bar{E}$ results in $T^N < 0$ or $T^S < 0$. Furthermore, $\tilde{E}$ leads to both $T^N < 0$ and $T^S < 0$. Therefore, the only viable solution is E_1 which gives

$$M_1 = \frac{\rho}{\sigma + \alpha V_1} > 0, \quad V_1 = \frac{\eta e^{-m_2\tau_2}E_1}{\beta} > 0$$
$$T_1^N = \frac{\xi_1}{\nu_1 - \gamma_1 E_1} > 0, T_1^S = \frac{\xi_2}{\nu_2 - \gamma_2 E_1} > 0.$$

The basic reproduction number, denoted as R_0, is defined as:

$$R_0 = \frac{\eta\alpha M_0 e^{-(m_1\tau_1+m_2\tau_2)}}{\mu\beta\left(\frac{\kappa_1 T_0^N}{\mu} + \frac{\kappa_2 T_0^S}{\mu} + 1\right)}.$$

In a biological context, R_0 represents the average number of secondary DENV-infected monocytes generated by a single infected monocyte cell throughout its lifespan. The infected steady state $\mathcal{SS}_1\left(M_1, E_1, V_1, T_1^N, T_1^S\right)$, therefore exists if and only if $R_0 > 1$. □

2.3. **Global stability.** This section employs the Lyapunov technique and utilizes LaSalle's invariant principle, as proposed in the work of [38,39], to examine the global asymptotic stability of the two steady states of system (2.1)-(2.5). We define a function $\mathcal{L}(\theta) = \theta - 1 - \ln\theta$. By using $\mathcal{Z}_i$ as the potential Lyapunov function, we identify $\mathcal{H}_i'$ as the largest invariant set of

$$\mathcal{H}_i = \left\{\left(M, E, V, T^N, T^S\right) : \frac{d\mathcal{Z}_i}{dt} = 0\right\}, \quad i = 0, 1.$$

Theorem 2.1. *The DENV dynamics system (2.1)-(2.5) is globally asymptotically stable (GAS) around the uninfected steady state $\mathcal{SS}_0\left(M_0, 0, 0, T_0^N, T_0^S\right)$ if $R_0 \leq 1$ and if $R_0 > 1$ then $\mathcal{SS}_0$ is unstable.*

Proof. Define

$$\mathcal{Z}_0 = M_0\mathcal{L}\left(\frac{M}{M_0}\right) + e^{m_1\tau_1}E + \frac{\alpha M_0}{\beta}V + \frac{\kappa_1 e^{m_1\tau_1}}{\gamma_1}T_0^N\mathcal{L}\left(\frac{T^N}{T_0^N}\right) + \frac{\kappa_2 e^{m_1\tau_1}}{\gamma_2}T_0^S\mathcal{L}\left(\frac{T^S}{T_0^S}\right)$$
$$+ \alpha\int_{t-\tau_1}^{t} M(\theta)V(\theta)d\theta + \frac{\alpha\eta M_0 e^{-m_2\tau_2}}{\beta}\int_{t-\tau_2}^{t} E(\theta)d\theta.$$

Obviously, $\mathcal{Z}_0\left(M, E, V, T^N, T^S\right) > 0$ for any $\left(M, E, V, T^N, T^S\right) > 0$ and $\mathcal{Z}_0\left(M_0, 0, 0, T_0^N, T_0^S\right) = 0$. Calculating $\frac{d\mathcal{Z}_0}{dt}$ as:

$$\frac{d\mathcal{Z}_0}{dt} = \left(1 - \frac{M_0}{M}\right)\frac{dM}{dt} + e^{m_1\tau_1}\frac{dE}{dt} + \frac{\alpha M_0}{\beta}\frac{dV}{dt} + \frac{\kappa_1 e^{m_1\tau_1}}{\gamma_1}\left(1 - \frac{T_0^N}{T^N}\right)\frac{dT^N}{dt} + \frac{\kappa_2 e^{m_1\tau_1}}{\gamma_2}\left(1 - \frac{T_0^S}{T^S}\right)\frac{dT^S}{dt}$$
$$+ \alpha\left(MV - M_{\tau_1}V_{\tau_1}\right) + \frac{\alpha\eta M_0 e^{-m_2\tau_2}}{\beta}\left(E - E_{\tau_2}\right).$$

By substituting the equations from system (2.1)-(2.5), we obtain

$$\frac{d\mathcal{Z}_0}{dt} = \left(1 - \frac{M_0}{M}\right)(\rho - \sigma M - \alpha MV) + e^{m_1\tau_1}\left(e^{-m_1\tau_1}\alpha M_{\tau_1}V_{\tau_1} - \mu E - \kappa_1 E T^N - \kappa_2 E T^S\right)$$
$$+ \frac{\alpha M_0}{\beta}(e^{-m_2\tau_2}\eta E_{\tau_2} - \beta V) + \frac{\kappa_1 e^{m_1\tau_1}}{\gamma_1}\left(1 - \frac{T_0^N}{T^N}\right)\left(\xi_1 + \gamma_1 E T^N - \nu_1 T^N\right)$$
$$+ \frac{\kappa_2 e^{m_1\tau_1}}{\gamma_2}\left(1 - \frac{T_0^S}{T^S}\right)\left(\xi_2 + \gamma_2 E T^S - \nu_2 T^S\right) + \alpha\left(MV - M_{\tau_1}V_{\tau_1}\right) + \frac{\alpha\eta M_0 e^{-m_2\tau_2}}{\beta}\left(E - E_{\tau_2}\right).$$

Then

$$\frac{d\mathcal{Z}_0}{dt} = \left(1 - \frac{M_0}{M}\right)(\rho - \sigma M) - e^{m_1\tau_1}\mu E + \frac{\kappa_1 e^{m_1\tau_1}}{\gamma_1}\left(1 - \frac{T_0^N}{T^N}\right)\left(\xi_1 - \nu_1 T^N\right) - \kappa_1 e^{m_1\tau_1}T_0^N E$$
$$+ \frac{\kappa_2 e^{m_1\tau_1}}{\gamma_2}\left(1 - \frac{T_0^S}{T^S}\right)\left(\xi_2 - \nu_2 T^S\right) - \kappa_2 e^{m_1\tau_1}T_0^S E + \frac{\alpha\eta M_0 e^{-m_2\tau_2}}{\beta}E.$$

Using $\rho = \sigma M_0, \xi_1 = \nu_1 T_0^N$ and $\xi_2 = \nu_2 T_0^S$, we get

$$\frac{d\mathcal{Z}_0}{dt} = -\frac{\sigma\left(M - M_0\right)^2}{M} - \frac{\kappa_1\nu_1 e^{m_1\tau_1}}{\gamma_1}\frac{\left(T^N - T_0^N\right)^2}{T^N} - \frac{\kappa_2\nu_2 e^{-m_1\tau_1}}{\gamma_2}\frac{\left(T^S - T_0^S\right)^2}{T^S}$$
$$+ \left(\frac{\alpha\eta M_0 e^{-m_2\tau_2}}{\beta} - \kappa_1 e^{m_1\tau_1}T_0^N - \kappa_2 e^{m_1\tau_1}T_0^S - e^{m_1\tau_1}\mu\right)E$$

$$= -\frac{\sigma\left(M-M_0\right)^2}{M} - \frac{\kappa_1\nu_1 e^{m_1\tau_1}}{\gamma_1}\frac{\left(T^N-T_0^N\right)^2}{T^N} - \frac{\kappa_2\nu_2 e^{-m_1\tau_1}}{\gamma_2}\frac{\left(T^S-T_0^S\right)^2}{T^S}$$
$$+\left(\frac{\alpha\eta M_0 e^{-m_2\tau_2}}{\beta} - e^{m_1\tau_1}\mu\left(\frac{\kappa_1 T_0^N}{\mu}+\frac{\kappa_2 T_0^S}{\mu}+1\right)\right)E.$$

It follows that

$$\frac{d\mathcal{Z}_0}{dt} = -\frac{\sigma\left(M-M_0\right)^2}{M} - \frac{\kappa_1\nu_1 e^{m_1\tau_1}}{\gamma_1}\frac{\left(T^N-T_0^N\right)^2}{T^N} - \frac{\kappa_2\nu_2 e^{-m_1\tau_1}}{\gamma_2}\frac{\left(T^S-T_0^S\right)^2}{T^S}$$
$$- e^{m_1\tau_1}\mu\left(\frac{\kappa_1 T_0^N}{\mu}+\frac{\kappa_2 T_0^S}{\mu}+1\right)\left(\frac{\alpha\eta M_0 e^{-m_2\tau_2}}{\beta e^{m_1\tau_1}\mu\left(\frac{\kappa_1 T_0^N}{\mu}+\frac{\kappa_2 T_0^S}{\mu}+1\right)}-1\right)E.$$

In conclusion, we derive

$$\frac{d\mathcal{Z}_0}{dt} = -\frac{\sigma\left(M-M_0\right)^2}{M} - \frac{\kappa_1\nu_1 e^{m_1\tau_1}}{\gamma_1}\frac{\left(T^N-T_0^N\right)^2}{T^N} - \frac{\kappa_2\nu_2 e^{-m_1\tau_1}}{\gamma_2}\frac{\left(T^S-T_0^S\right)^2}{T^S}$$
$$- e^{m_1\tau_1}\mu\left(\frac{\kappa_1 T_0^N}{\mu}+\frac{\kappa_2 T_0^S}{\mu}+1\right)\left(R_0-1\right)E.$$

Thus, when $R_0 \leq 1$, we deduce that $\frac{d\mathcal{Z}_0}{dt} \leq 0$ for any $M, E, I, T^N, T^S > 0$. Moreover, $\frac{d\mathcal{Z}_0}{dt} = 0$ if $M = M_0$, $T^N = T_0^N$, $T^S = T_0^S$, and $\left(R_0-1\right)E$. The system's solutions converge to $\mathcal{H}_0'$ [34], where $M = M_0$, $T^N = T_0^N$, $T^S = T_0^S$, and

$$\left(R_0-1\right)E = 0. \tag{2.16}$$

Two scenarios are under consideration:

(I): $R_0 = 1$, then from Eq. (2.1) we obtain

$$0 = \frac{dM}{dt} = \rho - \sigma M_0 - \alpha M_0 V \quad \Longrightarrow \quad V(t) = 0 \text{ for any } t. \tag{2.17}$$

Additionally, Eq. (2.3) implies that

$$0 = \frac{dV}{dt} = e^{-m_2\tau_2}E_{\tau_2} \quad \Longrightarrow \quad E(t) = 0 \text{ for any } t. \tag{2.18}$$

Consequently, $\mathcal{H}_0' = \{\mathcal{SS}_0\}$.

(II): $R_0 < 1$. Then from Eq. (2.16) we have $E = 0$ and Eq. (2.17) leads to $V = 0$ and hence $\mathcal{H}_0' = \{\mathcal{SS}_0\}$.

The global stability of $\mathcal{SS}_0$ follows from LaSalle's invariance principle (LIP) [40]- [42].

The characteristic equation of model (2.1)-(2.5) at the steady state $\mathcal{SS}_0$ is given by

$$(x+\sigma)(x+\nu_1)(x+\nu_2)(\hbar_2 x^2+\hbar_1 x+\hbar_0) = 0, \tag{2.19}$$

where x is the eigenvalue, and

$$\hbar_2 = \sigma\nu_1\nu_2,$$
$$\hbar_1 = \sigma\nu_1\nu_2(\beta+\mu) + \kappa_1\xi_1\sigma\nu_2 + \kappa_2\xi_2\sigma\nu_1,$$

$$\begin{aligned}\hbar_0 &= \kappa_2\xi_2\beta\sigma\nu_1 + \kappa_1\xi_1\beta\sigma\nu_2 + \mu\beta\sigma\nu_1\nu_2 - \eta\alpha\rho\nu_1\nu_2 e^{-(\bar{m}_1\tau_1+\bar{m}_2\tau_2)}\\ &= \beta\sigma\left(\kappa_2\xi_2\nu_1 + \kappa_1\xi_1\nu_2 + \mu\nu_1\nu_2\right)\left(1 - \frac{\eta\alpha\rho e^{-(\bar{m}_1\tau_1+\bar{m}_2\tau_2)}}{\mu\sigma\beta\left(\frac{\kappa_1\xi_1}{\nu_1\mu} + \frac{\kappa_2\xi_2}{\nu_2\mu} + 1\right)}\right)\\ &= \beta\sigma\left(\kappa_2\xi_2\nu_1 + \kappa_1\xi_1\nu_2 + \mu\nu_1\nu_2\right)(1 - R_0),\end{aligned}$$

where $e^{-\bar{m}_i\tau_i} = e^{-(x+m_i)\tau_i}, i = 1, 2$. Obviously, if $R_0 > 1$, then $\hbar_0 < 0$. This indicates that Eq. (2.19) has a positive real root. Consequently, $\mathcal{SS}_0$ is unstable. □

Theorem 2.2. *The DENV dynamics system (2.1)-(2.5) is GAS around the infected steady state* $\mathcal{SS}_1\left(M_1, E_1, V_1, T_1^N, T_1^S\right)$ *if* $R_0 > 1$.

Proof. Define

$$\begin{aligned}\mathcal{Z}_1 &= M_1\mathcal{L}\left(\frac{M}{M_1}\right) + e^{m_1\tau_1}E_1\mathcal{L}\left(\frac{E}{E_1}\right) + \frac{\alpha M_1}{\beta}V_1\mathcal{L}\left(\frac{V}{V_1}\right) + \frac{\kappa_1 e^{m_1\tau_1}}{\gamma_1}T_1^N\mathcal{L}\left(\frac{T^N}{T_1^N}\right) + \frac{\kappa_2 e^{m_1\tau_1}}{\gamma_2}T_1^S\mathcal{L}\left(\frac{T^S}{T_1^S}\right)\\ &+ \alpha M_1V_1\int_{t-\tau_1}^{t}\mathcal{L}\left(\frac{M(\theta)V(\theta)}{M_1V_1}\right)d\theta + \frac{\alpha\eta M_1 e^{-m_2\tau_2}}{\beta}E_1\int_{t-\tau_2}^{t}\mathcal{L}\left(\frac{E(\theta)}{E_1}\right)d\theta.\end{aligned}$$

Taking the derivative of $\mathcal{Z}_1$ along the solution of system (2.1)-(2.5) as:

$$\begin{aligned}\frac{d\mathcal{Z}_1}{dt} &= \left(1 - \frac{M_1}{M}\right)\frac{dM}{dt} + e^{m_1\tau_1}\left(1 - \frac{E_1}{E}\right)\frac{dE}{dt} + \frac{\alpha M_1}{\beta}\left(1 - \frac{V_1}{V}\right)\frac{dV}{dt} + \frac{\kappa_1 e^{m_1\tau_1}}{\gamma_1}\left(1 - \frac{T_1^N}{T^N}\right)\frac{dT^N}{dt}\\ &+ \frac{\kappa_2 e^{m_1\tau_1}}{\gamma_2}\left(1 - \frac{T_1^S}{T^S}\right)\frac{dT^S}{dt} + \alpha M_1V_1\left(\frac{MV}{M_1V_1} - \frac{M_{\tau_1}V_{\tau_1}}{M_1V_1} + \ln\left(\frac{M_{\tau_1}V_{\tau_1}}{MV}\right)\right)\\ &+ \frac{\alpha\eta M_1 e^{-m_2\tau_2}}{\beta}E_1\left(\frac{E}{E_1} - \frac{E_{\tau_2}}{E_1} + \ln\left(\frac{E_{\tau_2}}{E}\right)\right).\end{aligned}$$

Substituting equations of system (2.1)-(2.5), we get

$$\begin{aligned}\frac{d\mathcal{Z}_1}{dt} &= \left(1 - \frac{M_1}{M}\right)(\rho - \sigma M - \alpha MV) + e^{m_1\tau_1}\left(1 - \frac{E_1}{E}\right)\left(e^{-m_1\tau_1}\alpha M_{\tau_1}V_{\tau_1} - \mu E - \kappa_1 ET^N - \kappa_2 ET^S\right)\\ &+ \frac{\alpha M_1}{\beta}\left(1 - \frac{V_1}{V}\right)(e^{-m_2\tau_2}\eta E_{\tau_2} - \beta V) + \frac{\kappa_1 e^{m_1\tau_1}}{\gamma_1}\left(1 - \frac{T_1^N}{T^N}\right)\left(\xi_1 + \gamma_1 ET^N - \nu_1 T^N\right)\\ &+ \frac{\kappa_2 e^{m_1\tau_1}}{\gamma_2}\left(1 - \frac{T_1^S}{T^S}\right)\left(\xi_2 + \gamma_2 ET^S - \nu_2 T^S\right) + \alpha M_1V_1\left(\frac{MV}{M_1V_1} - \frac{M_{\tau_1}V_{\tau_1}}{M_1V_1} + \ln\left(\frac{M_{\tau_1}V_{\tau_1}}{MV}\right)\right)\\ &+ \frac{\alpha\eta M_1 e^{-m_2\tau_2}}{\beta}E_1\left(\frac{E}{E_1} - \frac{E_{\tau_2}}{E_1} + \ln\left(\frac{E_{\tau_2}}{E}\right)\right).\end{aligned}$$

Collecting terms leads to

$$\begin{aligned}\frac{d\mathcal{Z}_1}{dt} &= \left(1 - \frac{M_1}{M}\right)(\rho - \sigma M) - \mu e^{m_1\tau_1}E - \alpha M_{\tau_1}V_{\tau_1}\frac{E_1}{E} + e^{m_1\tau_1}\mu E_1 + \kappa_1 e^{m_1\tau_1}E_1T^N + \kappa_2 e^{m_1\tau_1}E_1T^S\\ &- \frac{\alpha\eta M_1 e^{-m_2\tau_2}}{\beta}E_{\tau_2}\frac{V_1}{V} + \alpha M_1V_1 + \frac{\kappa_1 e^{m_1\tau_1}}{\gamma_1}\left(1 - \frac{T_1^N}{T^N}\right)\left(\xi_1 - \nu_1 T^N\right) - \kappa_1 e^{m_1\tau_1}T_1^N E\\ &+ \frac{\kappa_2 e^{m_1\tau_1}}{\gamma_2}\left(1 - \frac{T_1^S}{T^S}\right)\left(\xi_2 - \nu_2 T^S\right) - \kappa_2 e^{m_1\tau_1}T_1^S E + \alpha M_1V_1\ln\left(\frac{M_{\tau_1}V_{\tau_1}}{MV}\right) + \frac{\alpha\eta M_1 e^{-m_2\tau_2}}{\beta}E_1\left(\frac{E}{E_1} + \ln\left(\frac{E_{\tau_2}}{E}\right)\right).\end{aligned}$$

Applying the steady state conditions

$$\begin{aligned}
\rho &= \sigma M_1 + \alpha M_1 V_1, \\
\mu E_1 &= e^{-m_1\tau_1}\alpha M_1 V_1 - \kappa_1 E_1 T_1^N - \kappa_2 E_1 T_1^S, \\
e^{-m_2\tau_2}\eta E_1 &= \beta V_1, \\
\xi_1 &= \nu_1 T_1^N - \gamma_1 E_1 T_1^N, \\
\xi_2 &= \nu_2 T_1^S - \gamma_2 E_1 T_1^S.
\end{aligned}$$

Then we obtain

$$\begin{aligned}
\frac{d\mathcal{Z}_1}{dt} &= -\frac{\sigma\left(M-M_1\right)^2}{M} - \frac{\kappa_1\nu_1 e^{m_1\tau_1}}{\gamma_1}\frac{\left(T^N-T_1^N\right)^2}{T^N} - \frac{\kappa_2\nu_2 e^{-m_1\tau_1}}{\gamma_2}\frac{\left(T^S-T_1^S\right)^2}{T^S} + \left(1-\frac{M_1}{M}\right)\alpha M_1 V_1 \\
&\quad - \kappa_1 e^{m_1\tau_1}\left(1-\frac{T_1^N}{T^N}\right)E_1 T_1^N - \kappa_2 e^{m_1\tau_1}\left(1-\frac{T_1^S}{T^S}\right)E_1 T_1^S + e^{m_1\tau_1}\left[\frac{\alpha\eta M_1 E_1}{\beta}e^{-(m_1\tau_1+m_2\tau_2)}\right. \\
&\quad \left.-\kappa_1 E_1 T_1^N - \kappa_2 E_1 T_1^S - \mu E_1\right]\frac{E}{E_1} - \alpha M_{\tau_1} V_{\tau_1}\frac{E_1}{E} + \alpha M_1 V_1 - \kappa_1 e^{m_1\tau_1}E_1 T_1^N - \kappa_2 e^{m_1\tau_1}E_1 T_1^S + \kappa_1 e^{m_1\tau_1}E_1 T^N \\
&\quad + \kappa_2 e^{m_1\tau_1}E_1 T^S - \frac{\alpha\eta M_1 e^{-m_2\tau_2}}{\beta}E_{\tau_2}\frac{V_1}{V} + \alpha M_1 V_1 + \alpha M_1 V_1 \ln\left(\frac{M_{\tau_1}V_{\tau_1}}{MV}\right) + \alpha M_1 V_1 \ln\left(\frac{E_{\tau_2}}{E}\right).
\end{aligned}$$

It follows that

$$\begin{aligned}
\frac{d\mathcal{Z}_1}{dt} &= -\frac{\sigma\left(M-M_1\right)^2}{M} - \frac{\kappa_1\nu_1 e^{m_1\tau_1}}{\gamma_1}\frac{\left(T^N-T_1^N\right)^2}{T^N} - \frac{\kappa_2\nu_2 e^{-m_1\tau_1}}{\gamma_2}\frac{\left(T^S-T_1^S\right)^2}{T^S} + \left(3-\frac{M_1}{M}\right)\alpha M_1 V_1 \\
&\quad - \kappa_1 e^{m_1\tau_1}\left(2-\frac{T_1^N}{T^N}-\frac{T^N}{T_1^N}\right)E_1 T_1^N - \kappa_2 e^{m_1\tau_1}\left(2-\frac{T_1^S}{T^S}-\frac{T^S}{T_1^S}\right)E_1 T_1^S - \alpha M_1 V_1\frac{M_{\tau_1}V_{\tau_1}E_1}{M_1 V_1 E} \\
&\quad - \alpha M_1 V_1\frac{E_{\tau_2}V_1}{E_1 V} + \alpha M_1 V_1 \ln\left(\frac{M_{\tau_1}V_{\tau_1}}{MV}\right) + \alpha M_1 V_1 \ln\left(\frac{E_{\tau_2}}{E}\right).
\end{aligned}$$

Using the following inequalities

$$\ln\left(\frac{M_{\tau_1}V_{\tau_1}}{MV}\right) = \ln\left(\frac{M_{\tau_1}V_{\tau_1}E_1}{M_1 V_1 E}\right) + \ln\left(\frac{M_1}{M}\right) + \ln\left(\frac{EV_1}{E_1 V}\right),$$

$$\ln\left(\frac{E_{\tau_2}}{E}\right) = \ln\left(\frac{E_{\tau_2}V_1}{E_1 V}\right) + \ln\left(\frac{E_1 V}{EV_1}\right).$$

We obtain

$$\begin{aligned}
\frac{d\mathcal{Z}_1}{dt} &= -\frac{\sigma\left(M-M_1\right)^2}{M} - \frac{\kappa_1\nu_1 e^{m_1\tau_1}}{\gamma_1}\frac{\left(T^N-T_1^N\right)^2}{T^N} - \frac{\kappa_2\nu_2 e^{-m_1\tau_1}}{\gamma_2}\frac{\left(T^S-T_1^S\right)^2}{T^S} + \alpha M_1 V_1\left(3-\frac{M_1}{M}\right. \\
&\quad \left.-\frac{M_{\tau_1}V_{\tau_1}E_1}{M_1 V_1 E} - \frac{E_{\tau_2}V_1}{E_1 V} + \ln\left(\frac{M_{\tau_1}V_{\tau_1}E_1}{M_1 V_1 E}\right) + \ln\left(\frac{M_1}{M}\right) + \ln\left(\frac{E_{\tau_2}V_1}{E_1 V}\right)\right) \\
&\quad + \kappa_1 e^{m_1\tau_1}\frac{\left(T^N-T_1^N\right)^2}{T^N}E_1 + \kappa_2 e^{m_1\tau_1}\frac{(T^S-T_1^S)^2}{T^S}E_1.
\end{aligned}$$

From the steady state conditions, we have

$$\xi_1 = \nu_1 T_1^N - \gamma_1 E_1 T_1^N \Rightarrow E_1 - \frac{\nu_1}{\gamma_1} = -\frac{\xi_1}{\gamma_1 T_1^N}.$$

Similarly, $E_1 - \frac{\nu_2}{\gamma_2} = -\frac{\xi_2}{\gamma_2 T_1^S}$. It follows that

$$\frac{d\mathcal{Z}_1}{dt} = -\frac{\sigma\left(M - M_1\right)^2}{M} - \frac{\kappa_1 \xi_1 e^{m_1\tau_1}}{\gamma_1}\frac{\left(T^N - T_1^N\right)^2}{T^N T_1^N} - \frac{\kappa_2 \xi_2 e^{m_1\tau_1}}{\gamma_2}\frac{\left(T^S - T_1^S\right)^2}{T^S T_1^S} - \alpha M_1 V_1\left[\mathcal{L}\left(\frac{M_1}{M}\right) + \mathcal{L}\left(\frac{M_{\tau_1} V_{\tau_1} E_1}{M_1 V_1 E}\right) + \mathcal{L}\left(\frac{E_{\tau_2} V_1}{E_1 V}\right)\right].$$

Obviously, we deduce that $\frac{d\mathcal{Z}_1}{dt} \leq 0$ for any $\left(M, E, V, T^N, T^S\right) > 0$ and $\frac{d\mathcal{Z}_1}{dt} = 0$ if $M = M_1$, $T^N = T_1^N$, $T^S = T_1^S$, and $\frac{M_{\tau_1} V_{\tau_1} E_1}{M_1 V_1 E} = \frac{E_{\tau_2} V_1}{E_1 V} = 1$. Thus, solutions of system (2.1)-(2.5) converge to $\mathcal{H}_1'$. For each element in $\mathcal{H}_1'$, we have $M = M_1$, $T^N = T_1^N$, and $T^S = T_1^S$. Then $\frac{dM}{dt} = \frac{dT^N}{dt} = \frac{dT^S}{dt} = 0$ and from Eqs. (2.1) and (2.4), we get

$$0 = \frac{dM}{dt} = \rho - \sigma M_1 - \alpha M_1 V \quad \Longrightarrow \quad V(t) = V_1 \text{ for any } t,$$

$$0 = \frac{dT^N}{dt} = \xi_1 + \gamma_1 E T_1^N - \nu_1 T_1^N \quad \Longrightarrow \quad E(t) = E_1 \text{ for any } t.$$

Thus, by using LIP, $\mathcal{H}_1' = \{\mathcal{SS}_1\}$ and $\mathcal{SS}_1$ is GAS. □

3. DENV Infection Model With Distributed-Time Delays

In the previous section, we made the following assumptions:

(i): The time it takes for each infected cell to form is constant;

(ii): The maturation time for each newly released virion is also constant.

Incorporating distributed delays, where the time delay is represented as a random variable from a probability distribution, allows models to reflect the complexities and variabilities found in real-world situations, making them more robust and applicable.

3.1. **Model formulation.** In this section, we build upon the DENV dynamics system that discussed earlier by introducing two distributed time delays, as follows:

$$\frac{dM}{dt} = \rho - \sigma M - \alpha M V, \tag{3.1}$$

$$\frac{dE}{dt} = \alpha \int_0^{h_1} f_1(\tau) e^{-m_1\tau} M_\tau V_\tau d\tau - \mu E - \kappa_1 E T^N - \kappa_2 E T^S, \tag{3.2}$$

$$\frac{dV}{dt} = \eta \int_0^{h_2} f_2(\tau) e^{-m_2\tau} E_\tau d\tau - \beta V, \tag{3.3}$$

$$\frac{dT^N}{dt} = \xi_1 + \gamma_1 E T^N - \nu_1 T^N, \tag{3.4}$$

$$\frac{dT^S}{dt} = \xi_2 + \gamma_2 E T^S - \nu_2 T^S, \tag{3.5}$$

Here, τ is a random variable drawn from the probability distribution function $f_i(\tau)$ over the time interval $[0, h_i]$, where h_i represents the upper limit of the delay period for $i = 1, 2$. We make the following assumptions:

(I): The probability that uninfected monocytes contacted by DENV at time $t - \tau$ survive for τ time units and become DENV-infected monocytes at time t is expressed by the factor $f_1(\tau)e^{-m_1\tau}$.

(II): The probability of newly immature DENV at time $t - \tau$ surviving for τ time units and maturing at time t is represented by the factor $f_2(\tau)e^{-m_2\tau}$.

Functions $f_i(\tau), i = 1, 2$, satisfy $f_i(\tau) > 0$ and

$$\int_0^{h_i} f_i(\tau)d\tau = 1, \ \int_0^{h_i} f_i(\tau)e^{n\tau}d\tau < \infty,$$

where $n > 0$ [43]. Let us denote $\Pi_i(\tau) = f_i(\tau)e^{-m_i\tau}$ and $F_i = \int_0^{h_i} \Pi_i(\tau)d\tau$, for $i = 1, 2$. This implies that $0 < F_i \leq 1$, and the initial conditions for the system (3.1)-(3.5) are the same as those specified in Eq (2.6). Here $\tau^* = \max\{h_1, h_2\}$.

3.2. **Preliminaries.**

Lemma 3.1. *The solutions of system (3.1)-(3.5) with the initial conditions (2.6) are nonnegative and ultimately bounded.*

Proof. Eqs. (3.1), (3.4), and (3.5) provide

$$\frac{dM}{dt}\,|_{M=0} = \rho > 0, \frac{dT^N}{dt}\,\big|_{T^N=0} = \xi_1 > 0, \frac{dT^S}{dt}\,\big|_{T^S=0} = \xi_2 > 0.$$

Hence, $M(t) > 0, T^N(t) > 0$, and $T^S(t) > 0$ for any $t \geq 0$. Moreover, we have

$$E(t) = e^{-\int_0^t (\mu+\kappa_1 T^N(x)+\kappa_2 T^S(x))dx}\varphi_2(0) + \alpha \int_0^t e^{-\int_\theta^t (\mu+\kappa_1 T^N(x)+\kappa_2 T^S(x))dx} \int_0^{h_1} \Pi_1(\tau)M(t-\theta)V(t-\theta)d\tau d\theta \geq 0,$$

$$V(t) = e^{-\beta t}\varphi_3(0) + \eta \int_0^t e^{-\beta(t-\theta)} \int_0^{h_2} \Pi_2(\tau)E(t-\theta)d\tau d\theta \geq 0,$$

for any $t \in [0, \tau^*]$. Through recursive argumentation, we obtain $E(t), V(t) \geq 0$, for any $t \geq 0$. Consequently, M, E, V, T^N and T^S are nonnegative. Let us prove the ultimate boundedness of M, E, V, T^N and T^S. From Eq. (3.1), we have

$$\lim_{t\to\infty} \sup M(t) \leq \frac{\rho}{\sigma} = \omega_1.$$

Let us prove the ultimate boundedness of E, T^N, and T^S. Define

$$\Phi = \int_0^{h_1} \Pi_1(\tau)M_\tau d\tau + E + \frac{\kappa_1}{\gamma_1}T^N + \frac{\kappa_2}{\gamma_2}T^S.$$

Then,

$$\frac{d\Phi}{dt} = \int_0^{h_1} \Pi_1(\tau)\frac{dM_\tau}{dt}d\tau + \frac{dE}{dt} + \frac{\kappa_1}{\gamma_1}\frac{dT^N}{dt} + \frac{\kappa_2}{\gamma_2}\frac{dT^S}{dt}$$

$$
\begin{aligned}
&= \int_0^{h_1} \Pi_1(\tau)\ \left[\rho - \sigma M_\tau - \alpha M_\tau V_\tau\right] d\tau + \alpha \int_0^{h_1} \Pi_1(\tau)\, M_\tau V_\tau d\tau - \mu E - \kappa_1 E T^N - \kappa_2 E T^S \\
&+ \frac{\kappa_1}{\gamma_1}\left[\xi_1 + \gamma_1 E T^N - \nu_1 T^N\right] + \frac{\kappa_2}{\gamma_2}\left[\xi_2 + \gamma_2 E T^S - \nu_2 T^S\right] \\
&= \rho \int_0^{h_1} \Pi_1(\tau) d\tau - \sigma \int_0^{h_1} \Pi_1(\tau) M_\tau d\tau - \mu E + \frac{\kappa_1 \xi_1}{\gamma_1} - \frac{\kappa_1 \nu_1}{\gamma_1} T^N + \frac{\kappa_2 \xi_2}{\gamma_2} - \frac{\kappa_2 \nu_2}{\gamma_2} T^S \\
&= \rho F_1 + \frac{\kappa_1 \xi_1}{\gamma_1} + \frac{\kappa_2 \xi_2}{\gamma_2} - \left[\sigma \int_0^{h_1} \Pi_1(\tau)\, M_\tau d\tau + \mu E + \frac{\kappa_1 \nu_1}{\gamma_1} T^N + \frac{\kappa_2 \nu_2}{\gamma_1} T^S\right] \\
&\leq \rho + \frac{\kappa_1 \xi_1}{\gamma_1} + \frac{\kappa_2 \xi_2}{\gamma_2} - \epsilon \left[\int_0^{h_1} \Pi_1(\tau) M_\tau d\tau + E + \frac{\kappa_1}{\gamma_1} T^N + \frac{\kappa_2}{\gamma_1} T^S\right] \\
&= \rho + \frac{\kappa_1 \xi_1}{\gamma_1} + \frac{\kappa_2 \xi_2}{\gamma_2} - \epsilon \Phi.
\end{aligned}
$$

It follows that

$$\limsup_{t\to\infty} \Phi \leq \frac{\rho}{\epsilon} + \frac{\kappa_1 \xi_1}{\gamma_1 \epsilon} + \frac{\kappa_2 \xi_2}{\gamma_2 \epsilon} = \omega_2.$$

Hence, $\limsup_{t\to\infty} E(t) \leq \omega_2$, $\limsup_{t\to\infty} T^N(t) \leq \omega_3$, and $\limsup_{t\to\infty} T^S(t) \leq \omega_4$. Ultimately, from Eq. (3.3), we obtain

$$
\begin{aligned}
\frac{dV}{dt} &= \eta \int_0^{h_2} \Pi_2(\tau) E_\tau d\tau - \beta V \\
&\leq \eta F_2 \omega_2 - \beta V \\
&\leq \eta \omega_2 - \beta V,
\end{aligned}
$$

and hence $\limsup_{t\to\infty} V(t) \leq \omega_5$. According to Lemma 3.1, we can demonstrate that Ω is positively invariant for the system (3.1)-(3.5). □

Lemma 3.2. *For the DENV dynamics system (3.1)-(3.5), there exists a threshold parameter $\bar{\mathcal{R}}_0 > 0$ such that*

(i): *If $\bar{\mathcal{R}}_0 \leq 1$, then there is a unique uninfected steady state $\mathcal{SS}_0$,*

(ii): *If $\bar{\mathcal{R}}_0 > 1$, then there is an infected steady state $\mathcal{SS}_1$ in addition to $\mathcal{SS}_0$.*

Proof. We calculate the steady states of the model (3.1)-(3.5) and determine the conditions under which they exist. Any steady state $\mathcal{SS} = (M, E, V, T^N, T^S)$ satisfies:

$$0 = \rho - \sigma M - \alpha M V, \tag{3.6}$$

$$0 = \alpha F_1 M V - \mu E - \kappa_1 E T^N - \kappa_2 E T^S, \tag{3.7}$$

$$0 = \eta F_2 E - \beta V, \tag{3.8}$$

$$0 = \xi_1 + \gamma_1 E T^N - \nu_1 T^N, \tag{3.9}$$

$$0 = \xi_2 + \gamma_2 E T^S - \nu_2 T^S. \tag{3.10}$$

From Eqs. (3.6), (3.8), (3.9) and (3.10) we have

$$\begin{aligned} M &= \frac{\rho}{\sigma + \alpha V}, \quad V = \frac{\eta F_2 E}{\beta}, \\ T^N &= \frac{\xi_1}{\nu_1 - \gamma_1 E}, \quad T^S = \frac{\xi_2}{\nu_2 - \gamma_2 E}. \end{aligned} \tag{3.11}$$

Substituting in Eq. (3.7) we get

$$\left(-\mu + \frac{\eta\alpha\rho F_1 F_2}{\beta\sigma + \eta\alpha F_2 E} + \frac{\kappa_1\xi_1}{\gamma_1 E - \nu_1} + \frac{\kappa_2\xi_2}{\gamma_2 E - \nu_2}\right) E = 0. \tag{3.12}$$

Eq. (3.12) presents two possibilities: the first is $E = 0$, which corresponds to the uninfected steady state $\mathcal{SS}^0\left(M_0, 0, 0, T_0^N, T_0^S\right)$. The other possibility of Eq. (3.12) is $E \neq 0$ and

$$-\mu + \frac{\eta\alpha\rho F_1 F_2}{\beta\sigma + \eta\alpha F_2 E} + \frac{\kappa_1\xi_1}{\gamma_1 E - \nu_1} + \frac{\kappa_2\xi_2}{\gamma_2 E - \nu_2} = 0$$

which gives

$$\frac{\bar{a}_3 E^3 + \bar{a}_2 E^2 + \bar{a}_1 E + \bar{a}_0}{(\beta\sigma + \eta\alpha E)(\gamma_1 E - \nu_1)(\gamma_2 E - \nu_2)} = 0, \tag{3.13}$$

where

$$\begin{aligned} \bar{a}_3 &= \mu\eta\alpha\gamma_1\gamma_2 F_2, \\ \bar{a}_2 &= -\kappa_2\xi_2\eta\alpha\gamma_1 F_2 - \kappa_1\xi_1\eta\alpha\gamma_2 F_2 + \mu\gamma_1\gamma_2\beta\sigma - \eta\alpha\gamma_1\gamma_2\rho F_1 F_2 - \mu\eta\alpha\gamma_2\nu_1 F_2 - \mu\eta\alpha\gamma_1\nu_2 F_2, \\ \bar{a}_1 &= -\kappa_2\xi_2\gamma_1\beta\sigma - \kappa_1\xi_1\gamma_2\beta\sigma + \kappa_2\xi_2\eta\alpha\nu_1 F_2 - \mu\gamma_2\beta\sigma\nu_1 + \eta\alpha\gamma_2\rho\nu_1 F_1 F_2 + \kappa_1\xi_1\eta\alpha\nu_2 F_2 \\ &\quad - \mu\gamma_1\beta\sigma\nu_2 + \eta\alpha\gamma_1\rho\nu_2 F_1 F_2 + \mu\eta\alpha\nu_1\nu_2 F_2, \\ \bar{a}_0 &= \kappa_2\xi_2\beta\sigma\nu_1 + \kappa_1\xi_1\beta\sigma\nu_2 + \mu\beta\sigma\nu_1\nu_2 - \eta\alpha\rho\nu_1\nu_2 F_1 F_2. \end{aligned}$$

We define a function $\bar{\Gamma}(E) = \bar{a}_3 E^3 + \bar{a}_2 E^2 + \bar{a}_1 E + \bar{a}_0$, then we get

$$\bar{\Gamma}(0) = -\beta\sigma\left(\kappa_2\xi_2\nu_1 + \kappa_1\xi_1\nu_2 + \mu\nu_1\nu_2\right)\left(\frac{\eta\alpha\rho F_1 F_2}{\mu\sigma\beta\left(\frac{\kappa_1\xi_1}{\nu_1\mu} + \frac{\kappa_2\xi_2}{\nu_2\mu} + 1\right)} - 1\right),$$

$$\begin{aligned} \bar{\Gamma}\left(\frac{\nu_1}{\gamma_1}\right) &= \frac{\kappa_1\xi_1\gamma_2\left(\beta\sigma\gamma_1 + \alpha\nu_1\eta F_2\right)}{\gamma_1}\left(\frac{\nu_2}{\gamma_2} - \frac{\nu_1}{\gamma_1}\right) \\ \bar{\Gamma}\left(\frac{\nu_2}{\gamma_2}\right) &= \frac{\kappa_2\xi_2\gamma_1\left(\beta\sigma\gamma_2 + \alpha\nu_2\eta F_2\right)}{\gamma_2}\left(\frac{\nu_1}{\gamma_1} - \frac{\nu_2}{\gamma_2}\right), \\ \lim_{E\to\infty} \bar{\Gamma}(E) &= \infty. \end{aligned}$$

We have $\bar{\Gamma}(0) < 0$ if the following condition is satisfied

$$\frac{\eta\alpha\rho F_1 F_2}{\mu\sigma\beta\left(\frac{\kappa_1\xi_1}{\nu_1\mu} + \frac{\kappa_2\xi_2}{\nu_2\mu} + 1\right)} > 1. \tag{B}$$

Similar to the proof of Lemma 2.2, one can prove that there exists $E_1 \in \left(0, \min\left\{\frac{v_1}{\gamma_1}, \frac{v_2}{\gamma_2}\right\}\right)$ satisfies Eq. (3.13). It follows that

$$M_1 = \frac{\rho}{\sigma + \alpha V*}, \quad V_1 = \frac{\eta F_2 E_1}{\beta},$$
$$T_1^N = \frac{\xi_1}{\nu_1 - \gamma_1 E_1}, T_1^S = \frac{\xi_2}{\nu_2 - \gamma_2 E_1}.$$

We define the basic reproduction number $\bar{\mathcal{R}}_0$ as:

$$\bar{\mathcal{R}}_0 = \frac{\eta\alpha M_0 F_1 F_2}{\mu\beta\left(\frac{\kappa_1 T_0^N}{\mu} + \frac{\kappa_2 T_0^S}{\mu} + 1\right)}$$

Then, the infected steady state $\mathcal{SS}^*\left(M_1, E_1, V_1, T_1^N, T_1^S\right)$ exists when $\bar{\mathcal{R}}_0 > 1$. □

3.3. **Global stability.** Let Q_i be the potential Lyapunov function and $\mathcal{J}_i'$ be the largest invariant set of

$$\mathcal{J}_i = \left\{\left(M, E, V, T^N, T^S\right) : \frac{dQ_i}{dt} = 0\right\}, \quad i = 0, 1.$$

Theorem 3.1. *The DENV dynamics system (3.1)-(3.5) is GAS around the uninfected steady state* $\mathcal{SS}_0\left(M_0, 0, 0, T_0^N, T_0^S\right)$ *if* $\bar{\mathcal{R}}_0 \leq 1$.

Proof. Construct Lyapunov function as:

$$Q_0 = M_0\mathcal{L}\left(\frac{M}{M_0}\right) + \frac{1}{F_1}E + \frac{\alpha M_0}{\beta}V + \frac{\kappa_1}{\gamma_1 F_1}T_0^N\mathcal{L}\left(\frac{T^N}{T_0^N}\right) + \frac{\kappa_2}{\gamma_2 F_1}T_0^S\mathcal{L}\left(\frac{T^S}{T_0^S}\right)$$
$$+ \frac{\alpha}{F_1}\int_0^{h_1}\Pi_1(\tau)\int_{t-\tau}^{t}M(\theta)V(\theta)d\theta d\tau + \frac{\alpha\eta M_0}{\beta}\int_0^{h_2}\Pi_2(\tau)\int_{t-\tau}^{t}E(\theta)d\theta d\tau.$$

We observe that $Q_0\left(M, E, V, T^N, T^S\right) > 0$ for all $\left(M, E, V, T^N, T^S\right) > 0$ and $Q_0\left(M_0, 0, 0, T_0^N, T_0^S\right) = 0$. Calculating $\frac{dQ_0}{dt}$ along the solutions of (3.1)-(3.5) as:

$$\frac{dQ_0}{dt} = \left(1 - \frac{M_0}{M}\right)(\rho - \sigma M - \alpha MV) + \frac{1}{F_1}\left(\alpha\int_0^{h_1}\Pi_1(\tau)M_\tau V_\tau d\tau - \mu E - \kappa_1 ET^N - \kappa_2 ET^S\right)$$
$$+ \frac{\alpha M_0}{\beta}\left(\eta\int_0^{h_2}\Pi_2(\tau)E_\tau - \beta V\right) + \frac{\kappa_1}{\gamma_1 F_1}\left(1 - \frac{T_0^N}{T^N}\right)\left(\xi_1 + \gamma_1 ET^N - \nu_1 T^N\right)$$
$$+ \frac{\kappa_2}{\gamma_2 F_1}\left(1 - \frac{T_0^S}{T^S}\right)\left(\xi_2 + \gamma_2 ET^S - \nu_2 T^S\right) + \frac{\alpha}{F_1}\int_0^{h_1}\Pi_1(\tau)\left(MV - M_\tau V_\tau\right)d\tau$$
$$+ \frac{\alpha\eta M_0}{\beta}\int_0^{h_2}\Pi_2(\tau)\left(E - E_\tau\right)d\tau.$$

Then

$$\frac{dQ_0}{dt} = \left(1 - \frac{M_0}{M}\right)(\rho - \sigma M) - \frac{\mu}{F_1}E + \frac{\kappa_1}{\gamma_1 F_1}\left(1 - \frac{T_0^N}{T^N}\right)\left(\xi_1 - \nu_1 T^N\right) - \frac{\kappa_1}{F_1}T_0^N E$$
$$+ \frac{\kappa_2}{\gamma_2 F_1}\left(1 - \frac{T_0^S}{T^S}\right)\left(\xi_2 - \nu_2 T^S\right) - \frac{\kappa_2}{F_1}T_0^S E + \frac{\alpha\eta M_0}{\beta}F_2 E d\tau.$$

Using $\rho = \sigma M_0, \xi_1 = \nu_1 T_0^N$ and $\xi_2 = \nu_2 T_0^S$ we obtain

$$\frac{dQ_0}{dt} = -\frac{\sigma\left(M - M_0\right)^2}{M} - \frac{\kappa_1\nu_1}{\gamma_1 F_1}\frac{\left(T^N - T_0^N\right)^2}{T^N} - \frac{\kappa_2\nu_2}{\gamma_2 F_1}\frac{\left(T^S - T_0^S\right)^2}{T^S} + \left(\frac{\alpha\eta M_0 F_2}{\beta} - \frac{\kappa_1}{F_1}T_0^N - \frac{\kappa_2}{F_1}T_0^S - \frac{\mu}{F_1}\right)E.$$

Ultimately, we obtain

$$\frac{dQ_0}{dt} = -\frac{\sigma\left(M - M_0\right)^2}{M} - \frac{\kappa_1\nu_1}{\gamma_1 F_1}\frac{\left(T^N - T_0^N\right)^2}{T^N} - \frac{\kappa_2\nu_2}{\gamma_2 F_1}\frac{\left(T^S - T_0^S\right)^2}{T^S} - \frac{\mu}{F_1}\left(\frac{\kappa_1 T_0^N}{\mu} + \frac{\kappa_2 T_0^S}{\mu} + 1\right)\left(\bar{\mathcal{R}}_0 - 1\right)E.$$

Hence, If $\bar{\mathcal{R}}_0 \leq 1$, we conclude that $\frac{dQ_0}{dt} \leq 0$ for any $M, E, I, T^N, T^S > 0$. Moreover, $\frac{dQ_0}{dt} = 0$ if $M = M_0$, $T^N = T_0^N$, $T^S = T_0^S$, and $\left(\bar{\mathcal{R}}_0 - 1\right)E$. The system's solutions converge to $\mathcal{J}_0'$ where $M = M_0$, $T^N = T_0^N$, $T^S = T_0^S$, and

$$\left(\bar{\mathcal{R}}_0 - 1\right)E = 0. \tag{3.14}$$

Two scenarios are being considered:

(I): $\bar{\mathcal{R}}_0 = 1$, then from Eq. (3.1) we obtain

$$0 = \frac{dM}{dt} = \rho - \sigma M_0 - \alpha M_0 V \quad \Longrightarrow \quad V(t) = 0 \text{ for any } t, \tag{3.15}$$

and from Eq. (3.3) we obtain

$$0 = \frac{dV}{dt} = \eta\int_0^{h_2}\Pi_2(\tau)E_\tau d\tau \quad \Longrightarrow \quad E(t) = 0 \text{ for any } t. \tag{3.16}$$

Thus, $\mathcal{J}_0' = \{\mathcal{SS}_0\}$.

(II): $\bar{\mathcal{R}}_0 < 1$. Then from Eq. (3.14) we have $E = 0$ and Eq. (3.15) leads to $V = 0$ and hence $\mathcal{J}_0' = \{\mathcal{SS}_0\}$.

Then, the global stability of $\mathcal{SS}_0$ follows from LIP. □

Theorem 3.2. *The DENV dynamics system (3.1)-(3.5) is GAS around the infected steady state* $\mathcal{SS}_1\left(M_1, E_1, V_1, T_1^N, T_1^S\right)$ *if* $\bar{\mathcal{R}}_0 > 1$.

Proof. Define

$$Q_1 = M_1\mathcal{L}\left(\frac{M}{M_1}\right) + \frac{1}{F_1}E_1\mathcal{L}\left(\frac{E}{E_1}\right) + \frac{\alpha M_1}{\beta}V_1\mathcal{L}\left(\frac{V}{V_1}\right) + \frac{\kappa_1}{\gamma_1 F_1}T_1^N\mathcal{L}\left(\frac{T^N}{T_1^N}\right) + \frac{\kappa_2}{\gamma_2 F_1}T_1^S\mathcal{L}\left(\frac{T^S}{T_1^S}\right)$$
$$+ \frac{\alpha}{F_1}M_1V_1\int_0^{h_1}\Pi_1(\tau)\int_{t-\tau}^{t}\mathcal{L}\left(\frac{M(\theta)V(\theta)}{M_1V_1}\right)d\theta d\tau + \frac{\alpha\eta M_1}{\beta}E_1\int_0^{h_2}\Pi_2(\tau)\int_{t-\tau}^{t}\mathcal{L}\left(\frac{E(\theta)}{E_1}\right)d\theta d\tau.$$

Taking the derivative of Q_1 along the solution of system (3.1)-(3.5) as:

$$\begin{aligned}\frac{dQ_1}{dt} &= \left(1-\frac{M_1}{M}\right)\frac{dM}{dt} + \frac{1}{F_1}\left(1-\frac{E_1}{E}\right)\frac{dE}{dt} + \frac{\alpha M_1}{\beta}\left(1-\frac{V_1}{V}\right)\frac{dV}{dt} + \frac{\kappa_1}{\gamma_1 F_1}\left(1-\frac{T_1^N}{T^N}\right)\frac{dT^N}{dt} \\ &+ \frac{\kappa_2}{\gamma_2 F_1}\left(1-\frac{T_1^S}{T^S}\right)\frac{dT^S}{dt} + \frac{\alpha}{F_1}M_1V_1\int_0^{h_1}\Pi_1(\tau)\left(\frac{MV}{M_1V_1} - \frac{M_\tau V_\tau}{M_1V_1} + \ln\left(\frac{M_\tau V_\tau}{MV}\right)\right)d\tau \\ &+ \frac{\alpha\eta M_1}{\beta}E_1\int_0^{h_2}\Pi_2(\tau)\left(\frac{E}{E_1} - \frac{E_\tau}{E_1} + \ln\left(\frac{E_\tau}{E}\right)\right)d\tau.\end{aligned}$$

Substituting equations of system (3.1)-(3.5), we get

$$\begin{aligned}\frac{dQ_1}{dt} &= \left(1-\frac{M_1}{M}\right)(\rho - \sigma M - \alpha MV) + \frac{1}{F_1}\left(1-\frac{E_1}{E}\right)\left(\alpha\int_0^{h_1}\Pi_1(\tau)M_\tau V_\tau d\tau - \mu E - \kappa_1 E T^N - \kappa_2 E T^S\right) \\ &+ \frac{\alpha M_1}{\beta}\left(1-\frac{V_1}{V}\right)\left(\eta\int_0^{h_2}\Pi_2(\tau)E_\tau d\tau - \beta V\right) + \frac{\kappa_1}{\gamma_1 F_1}\left(1-\frac{T_1^N}{T^N}\right)\left(\xi_1 + \gamma_1 E T^N - \nu_1 T^N\right) \\ &+ \frac{\kappa_2}{\gamma_2 F_1}\left(1-\frac{T_1^S}{T^S}\right)\left(\xi_2 + \gamma_2 E T^S - \nu_2 T^S\right) + \frac{\alpha}{F_1}M_1V_1\int_0^{h_1}\Pi_1(\tau)\left(\frac{MV}{M_1V_1} - \frac{M_\tau V_\tau}{M_1V_1} + \ln\left(\frac{M_\tau V_\tau}{MV}\right)\right)d\tau \\ &+ \frac{\alpha\eta M_1}{\beta}E_1\int_0^{h_2}\Pi_2(\tau)\left(\frac{E}{E_1} - \frac{E_\tau}{E_1} + \ln\left(\frac{E_\tau}{E}\right)\right)d\tau.\end{aligned}$$

Collecting terms leads to

$$\begin{aligned}\frac{dQ_1}{dt} &= \left(1-\frac{M_1}{M}\right)(\rho - \sigma M) - \frac{\mu}{F_1}E - \frac{\alpha}{F_1}\int_0^{h_1}\Pi_1(\tau)\frac{M_\tau V_\tau E_1}{E}d\tau + \frac{\mu}{F_1}E_1 + \frac{\kappa_1}{F_1}E_1T^N + \frac{\kappa_2}{F_1}E_1T^S \\ &- \frac{\alpha\eta M_1}{\beta}\int_0^{h_2}\Pi_2(\tau)\frac{E_\tau V_1}{V}d\tau + \alpha M_1V_1 + \frac{\kappa_1}{\gamma_1 F_1}\left(1-\frac{T_1^N}{T^N}\right)\left(\xi_1 - \nu_1 T^N\right) - \frac{\kappa_1}{F_1}T_1^N E \\ &+ \frac{\kappa_2}{\gamma_2 F_1}\left(1-\frac{T_1^S}{T^S}\right)\left(\xi_2 - \nu_2 T^S\right) - \frac{\kappa_2}{F_1}T_1^S E + \frac{\alpha}{F_1}M_1V_1\int_0^{h_1}\Pi_1(\tau)\ln\left(\frac{M_\tau V_\tau}{MV}\right)d\tau \\ &+ \frac{\alpha\eta M_1}{\beta}E_1\int_0^{h_2}\Pi_2(\tau)\left(\frac{E}{E_1} + \ln\left(\frac{E_\tau}{E}\right)\right)d\tau.\end{aligned}$$

Applying the steady state conditions

$$\begin{aligned}\rho &= \sigma M_1 + \alpha M_1V_1, \\ \mu E_1 &= \alpha F_1 M_1V_1 - \kappa_1 E_1 T_1^N - \kappa_2 E_1 T_1^S, \\ F_2\eta E_1 &= \beta V_1, \\ \xi_1 &= \nu_1 T_1^N - \gamma_1 E_1 T_1^N, \\ \xi_2 &= \nu_2 T_1^S - \gamma_2 E_1 T_1^S.\end{aligned}$$

Then we obtain

$$\begin{aligned}\frac{dQ_1}{dt} &= -\frac{\sigma\left(M-M_1\right)^2}{M} - \frac{\kappa_1\nu_1}{\gamma_1 F_1}\frac{\left(T^N-T_1^N\right)^2}{T^N} - \frac{\kappa_2\nu_2}{\gamma_2 F_1}\frac{\left(T^S-T_1^S\right)^2}{T^S} + \left(1-\frac{M_1}{M}\right)\alpha M_1 V_1 \\ &- \frac{\kappa_1}{F_1}\left(1-\frac{T_1^N}{T^N}\right)E_1T_1^N - \frac{\kappa_2}{F_1}\left(1-\frac{T_1^S}{T^S}\right)E_1T_1^S + \frac{1}{F_1}\left[\frac{\alpha\eta M_1F_1F_2E_1}{\beta} - \kappa_1T_1^NE_1 - \kappa_2T_1^SE_1 - \mu E_1\right]\frac{E}{E_1} \\ &- \frac{\alpha}{F_1}M_1V_1\int_0^{h_1}\Pi_1(\tau)\frac{M_\tau V_\tau E_1}{M_1V_1E}d\tau + \alpha M_1V_1 - \frac{\kappa_1}{F_1}E_1T_1^N - \frac{\kappa_2}{F_1}E_1T_1^S + \frac{\kappa_1}{F_1}E_1T^N \\ &+ \frac{\kappa_2}{F_1}E_1T^S - \frac{\alpha\eta M_1}{\beta}E_1\int_0^{h_2}\Pi_2(\tau)\frac{E_\tau V_1}{E_1V}d\tau + \alpha M_1V_1 + \frac{\alpha}{F_1}M_1V_1\int_0^{h_1}\Pi_1(\tau)\ln\left(\frac{M_\tau V_\tau}{MV}\right)d\tau \\ &+ \frac{\alpha M_1V_1}{F_2}\int_0^{h_2}\Pi_2(\tau)\ln\left(\frac{E_\tau}{E}\right)d\tau.\end{aligned}$$

It follows that

$$\begin{aligned}\frac{dQ_1}{dt} &= -\frac{\sigma\left(M-M_1\right)^2}{M} - \frac{\kappa_1\nu_1}{\gamma_1 F_1}\frac{\left(T^N-T_1^N\right)^2}{T^N} - \frac{\kappa_2\nu_2}{\gamma_2 F_1}\frac{\left(T^S-T_1^S\right)^2}{T^S} + \left(3-\frac{M_1}{M}\right)\alpha M_1V_1 \\ &- \frac{\kappa_1}{F_1}\left(2-\frac{T_1^N}{T^N}-\frac{T^N}{T_1^N}\right)E_1T_1^N - \frac{\kappa_2}{F_1}\left(2-\frac{T_1^S}{T^S}-\frac{T^S}{T_1^S}\right)E_1T_1^S - \frac{\alpha}{F_1}M_1V_1\int_0^{h_1}\Pi_1(\tau)\frac{M_\tau V_\tau E_1}{M_1V_1E}d\tau \\ &- \frac{\alpha M_1V_1}{F_2}\int_0^{h_2}\Pi_2(\tau)\frac{E_\tau V_1}{E_1V}d\tau + \frac{\alpha}{F_1}M_1V_1\int_0^{h_1}\Pi_1(\tau)\ln\left(\frac{M_\tau V_\tau}{MV}\right)d\tau + \frac{\alpha M_1V_1}{F_2}\int_0^{h_2}\Pi_2(\tau)\ln\left(\frac{E_\tau}{E}\right)d\tau.\end{aligned}$$

Using the following inequalities

$$\ln\left(\frac{M_\tau V_\tau}{MV}\right) = \ln\left(\frac{M_\tau V_\tau E_1}{M_1V_1E}\right) + \ln\left(\frac{M_1}{M}\right) + \ln\left(\frac{EV_1}{E_1V}\right),$$

$$\ln\left(\frac{E_\tau}{E}\right) = \ln\left(\frac{E_\tau V_1}{E_1V}\right) + \ln\left(\frac{E_1V}{EV_1}\right).$$

We obtain

$$\begin{aligned}\frac{dQ_1}{dt} &= -\frac{\sigma\left(M-M_1\right)^2}{M} - \frac{\kappa_1\nu_1}{\gamma_1 F_1}\frac{\left(T^N-T_1^N\right)^2}{T^N} - \frac{\kappa_2\nu_2}{\gamma_2 F_1}\frac{\left(T^S-T_1^S\right)^2}{T^S} \\ &+ \frac{\alpha}{F_1}M_1V_1\int_0^{h_1}\Pi_1(\tau)\left(2-\frac{M_1}{M}-\frac{M_\tau V_\tau E_1}{M_1V_1E}+\ln\left(\frac{M_\tau V_\tau E_1}{M_1V_1E}\right)+\ln\left(\frac{M_1}{M}\right)\right)d\tau \\ &+ \frac{\alpha}{F_2}M_1V_1\int_0^{h_2}\Pi_2(\tau)\left(1-\frac{E_\tau V_1}{E_1V}+\ln\left(\frac{E_\tau V_1}{E_1V}\right)\right)d\tau \\ &+ \frac{\kappa_1}{F_1}\frac{\left(T^N-T_1^N\right)^2}{T^N}E_1 + \frac{\kappa_2}{F_1}\frac{\left(T^S-T_1^S\right)}{T^S}E_1.\end{aligned}$$

From the steady state conditions, we have

$$E_1 - \frac{\nu_1}{\gamma_1} = -\frac{\xi_1}{\gamma_1 T_1^N} \text{ and } E_1 - \frac{\nu_2}{\gamma_2} = -\frac{\xi_2}{\gamma_2 T_1^S}.$$

It follows that

$$\frac{d\mathcal{Q}_1}{dt} = -\frac{\sigma\left(M-M_1\right)^2}{M} - \frac{\kappa_1\xi_1}{\gamma_1 F_1}\frac{\left(T^N-T_1^N\right)^2}{T^N T_1^N} - \frac{\kappa_2\xi_2}{\gamma_2 F_1}\frac{\left(T^S-T_1^S\right)^2}{T^S T_1^S} - \frac{\alpha}{F_1}M_1V_1\int_0^{h_1}\Pi_1(\tau)\left(\mathcal{L}\left(\frac{M_1}{M}\right)\right.$$
$$\left.+\mathcal{L}\left(\frac{M_\tau V_\tau E_1}{M_1V_1E}\right)\right)d\tau - \frac{\alpha}{F_2}M_1V_1\int_0^{h_2}\Pi_2(\tau)\mathcal{L}\ln\left(\frac{E_\tau V_1}{E_1V}\right)d\tau.$$

Clearly, $\frac{d\mathcal{Q}_1}{dt} \leq 0$ for any $\left(M,E,V,T^N,T^S\right) > 0$ and $\frac{d\mathcal{Q}_1}{dt} = 0$ if $M = M_1$, $T^N = T_1^N$, $T^S = T_1^S$, and $\frac{M_\tau V_\tau E_1}{M_1V_1E} = \frac{E_\tau V_1}{E_1V} = 1$. Solutions of system (3.1)-(3.5) converge to $\mathcal{J}_1'$. Any element in $\mathcal{J}_1'$ satisfies $M = M_1$, $T^N = T_1^N$, and $T^S = T_1^S$. Then $\frac{dM}{dt} = \frac{dT^N}{dt} = \frac{dT^S}{dt} = 0$ and from Eqs. (3.1) and (3.4), we get

$$0 = \frac{dM}{dt} = \rho - \sigma M_1 - \alpha M_1 V \quad \Longrightarrow \quad V(t) = V_1 \text{ for any } t,$$

$$0 = \frac{dT^N}{dt} = \xi_1 + \gamma_1 E T_1^N - \nu_1 T_1^N \quad \Longrightarrow \quad E(t) = E_1 \text{ for any } t.$$

Consequently, by using LIP, $\mathcal{J}_1' = \{\mathcal{SS}_1\}$ and $\mathcal{SS}_1$ is GAS. □

We note that if we chose $f_i(\tau) = D\left(\tau - \tau_i\right), i = 1,2$, and $h_i \to \infty$, then model (3.1)-(3.5) will lead to model (2.1)-(2.5).

4. Numerical Simulation

In this section, we conduct numerical simulations for the model with discrete-time delays (2.1)-(2.5) to enhance the theoretical findings given in Theorem 2.1-2.2.

4.1. **Numerical simulations for system (2.1)-(2.5).** In this subsection, we utilize the parameter values listed in Table 1 and use MATLAB's dde23 solver to numerically solve the system of DDEs. For simplicity, we assign $\tau_i = 0.1$ for $i = 1,2$, and we also select the three following initial points (IPs) as described below:

$$\textbf{IP-1}: M(\theta) = 6\times10^7, E(\theta) = 0.5, V(\theta) = 150, T^N(\theta) = 90, T^S(\theta) = 90,$$
$$\textbf{IP-2}: M(\theta) = 4\times10^7, E(\theta) = 1, V(\theta) = 357, T^N(\theta) = 60, T^S(\theta) = 60,$$
$$\textbf{IP-3}: M(\theta) = 2\times10^7, E(\theta) = 3, V(\theta) = 500, T^N(\theta) = 30, T^S(\theta) = 30,$$

where $\theta \in [-0.1, 0]$. Choosing among the three sets of starting points is optional to make sure our choice does not impact the overall stability of any steady states. By changing the parameter α, we obtain two distinct circumstances:

Circumstance-1: (Stability of $\mathcal{SS}_0$): We set $\alpha = 1.72\times10^{-13}$. In this scenario, we have $R_0 = 0.21 < 1$. Figure 1 illustrates that the solutions starting from initial points IP-1, IP-2, and IP-3 converge to the uninfected steady state $\mathcal{SS}_0 = \left(7.143\times10^7, 0, 0, 60, 60\right)$. This provides $\mathcal{SS}_0$ is GAS which is consistent with the result in Theorem 2.1. Thus, the DENV will eventually be eradicated, and the count of uninfected monocytes will return to its normal level.

TABLE 2. The variation of R_0 with respect to the delay parameters $\tau_i, i = 1, 2$.

$\tau_1 = \tau_2$	R_0
0	25.0755
0.5	9.22474
1.5	1.24843
1.61094	1
1.7	0.83685
1.9	0.560957

Circumstance-2: (Stability of $\mathcal{SS}_1$): By setting $\alpha = 1.72 \times 10^{-11}$, we find $R_0 = 20.53 > 1$. Figure 2 shows that the solutions starting from initial points IP-1, IP-2, and IP-3 converge to the infected steady state $\mathcal{SS}_1 = \left(7.142 \times 10^7, 326.72, 849516, 84.52, 264413\right)$ and then $\mathcal{SS}_1$ is GAS as we have proven in Theorem 2.2.

4.2. **Effect of time delays on the DENV dynamics system.** By fixing the parameter $\alpha = 1.72 \times 10^{-11}$ and varying τ_i (for $i = 1, 2$), we investigate the effect of incorporating time delays on the stability of $\mathcal{SS}_0$. Since R_0 influenced by τ_i, any alterations to these parameters will impact the stability of $\mathcal{SS}_0$. Even a small increase in the values of τ_i will lead to a decrease in R_0 (see Table 2). We will consider the following cases:

T.D-1 : $\tau_1 = \tau_2 = 0$,
T.D-2 : $\tau_1 = \tau_2 = 0.5$,
T.D-3 : $\tau_1 = \tau_2 = 1.5$,
T.D-4 : $\tau_1 = \tau_2 = 1.7$,
T.D-5 : $\tau_1 = \tau_2 = 1.9$.

Let us solve system (2.1)-(2.5) under the following initial condition:

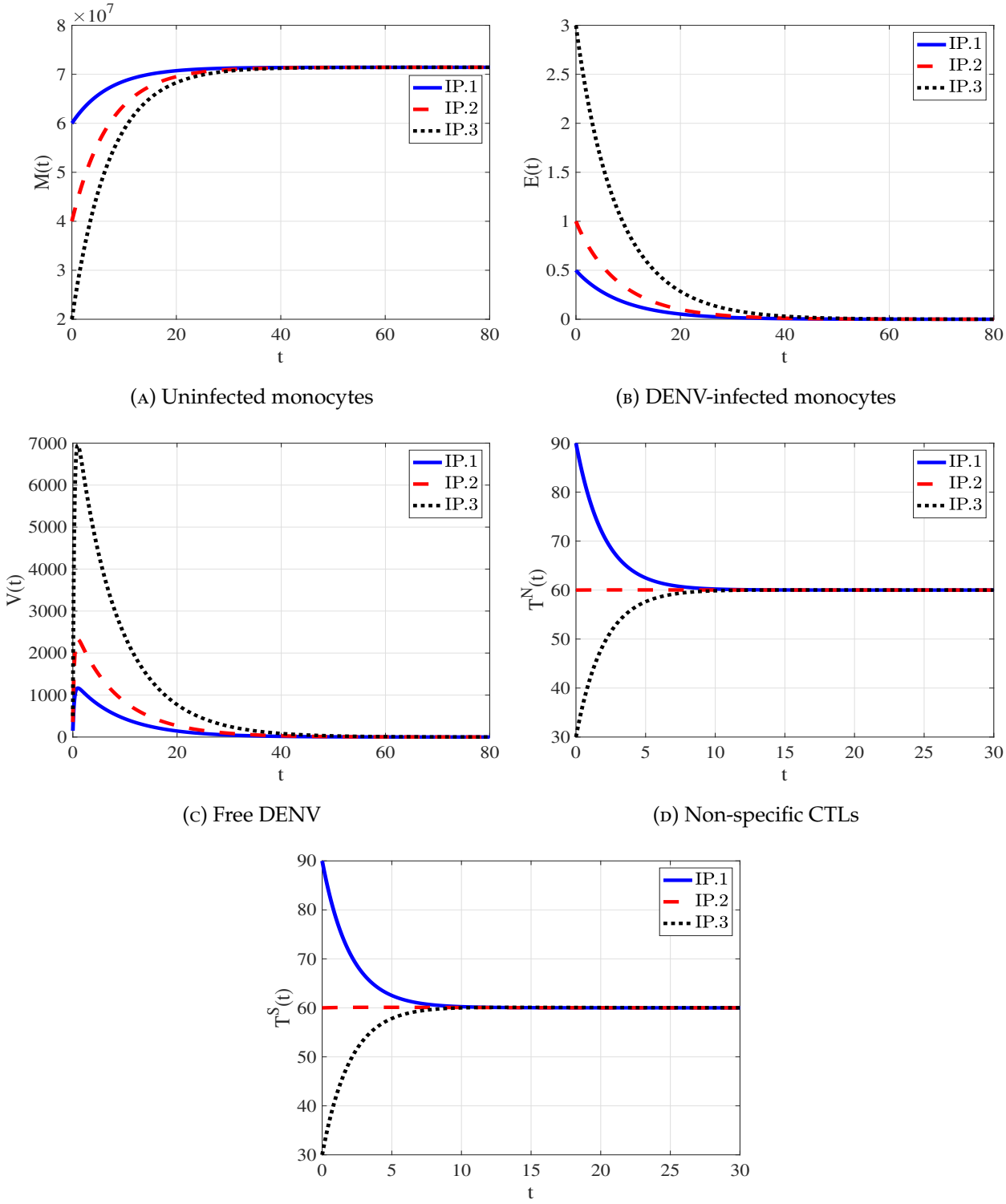
$$\mathbf{IP-4}: M(\theta) = 4 \times 10^7, E(\theta) = 200, V(\theta) = 100, T^N(\theta) = 100, T^S(\theta) = 500,$$

where $\theta \in [-1.9, 0]$. Let's calculate the critical value of the time delay that affects the stability of $\mathcal{SS}_0$. For the sake of simplicity, we assume that $\tau_1 = \tau_2 = \tau_{12}$. By keeping the other parameters constant, R_0 can be expressed as functions of τ_{12} as follows:

$$R_0(\tau_{12}) = \frac{\eta \alpha M_0 e^{-(m_1+m_2)\tau_{12}}}{\mu\beta\left(\frac{\kappa_1 T_0^N}{\mu} + \frac{\kappa_2 T_0^S}{\mu} + 1\right)}.$$

To fulfill that $R_0(\tau_{12}) \leq 1$, we take τ_{12} as:

$$\tau_{12} \geq \tau_{12}^{cr} \text{ where } \tau_{12}^{cr} = \max\left\{0, \frac{1}{m_1 + m_2} \ln\left(\frac{\eta \alpha M_0}{\mu\beta\left(\frac{\kappa_1 T_0^N}{\mu} + \frac{\kappa_2 T_0^S}{\mu} + 1\right)}\right)\right\}.$$



(A) Uninfected monocytes

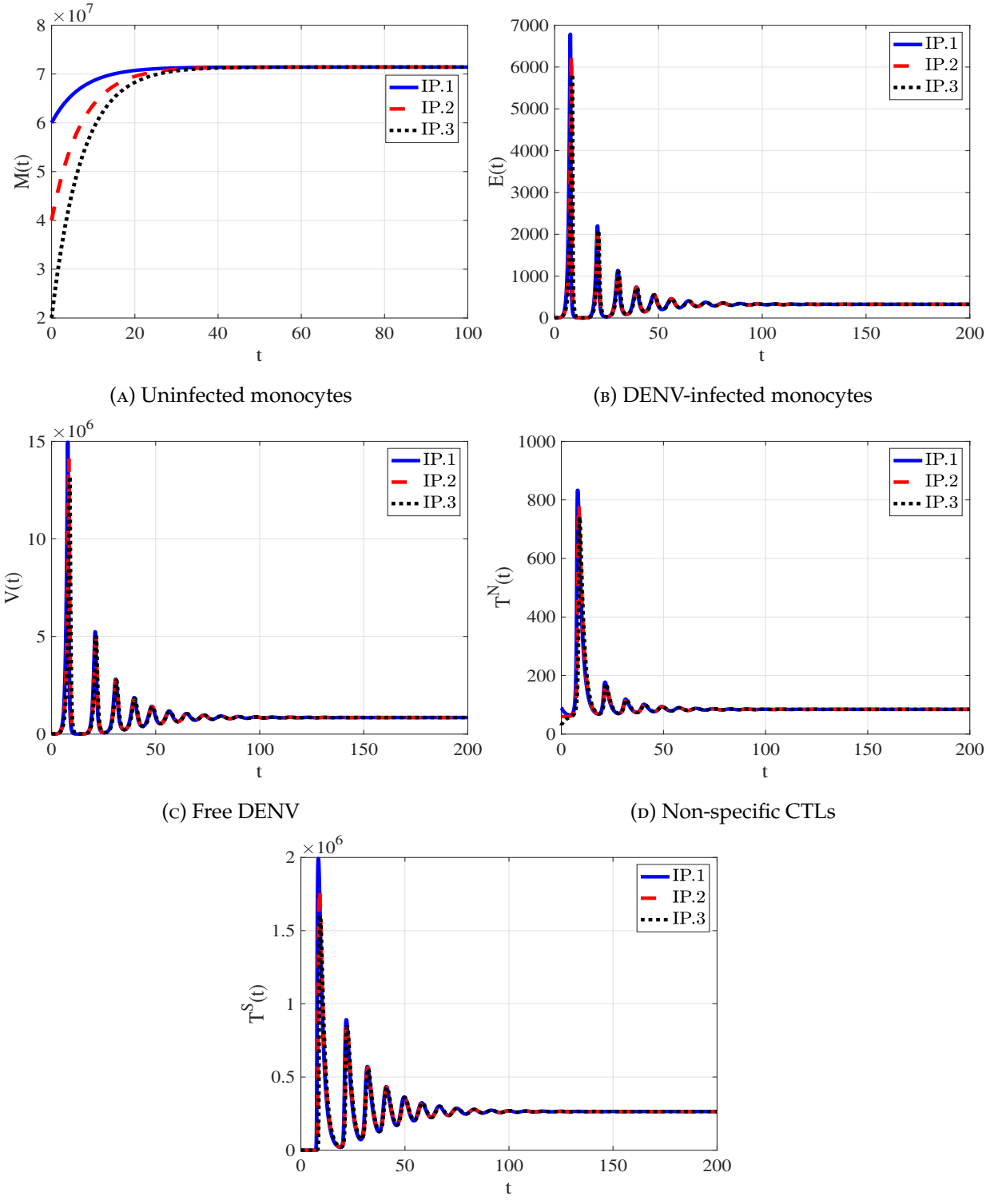
(B) DENV-infected monocytes

(C) Free DENV

(D) Non-specific CTLs

(E) Strain-specific CTLs

FIGURE 1. Solutions of system (2.1)-(2.5) arrive uninfected steady state $\mathcal{SS}_0 = \left(7.143 \times 10^7, 0, 0, 60, 60\right)$ using three distinct initial points (Circumstance-1).



(A) Uninfected monocytes

(B) DENV-infected monocytes

(C) Free DENV

(D) Non-specific CTLs

(E) Strain-specific CTLs

FIGURE 2. Solutions of system (2.1)-(2.5) arrive infected steady state $\mathcal{SS}_1 = \left(7.142 \times 10^7, 326.72, 849516, 84.52, 264413\right)$ using three distinct initial points (Circumstance-2).

Thus, if $\tau_{12} \geq \tau_{12}^{cr}$, then $\mathcal{SS}_0$ is GAS. Using the values of parameters given in Table 1, we obtain $\tau_{12}^{cr} = 1.61094$. Consequently,

(i): If $\tau_{12} \geq 1.61094$, then $R_0(\tau_{12}) \leq 1$, and $\mathcal{SS}_0$ is GAS. This shows that the DENV will be cleared.

(ii): If $0 \leq \tau_{12} < 1.61094$, then $R_1(\tau_{12}) > 1$, and $\mathcal{SS}_0$ will lose its stability and in this case $\mathcal{SS}_1$ will be GAS. In this case the infection will be presented.

Figure 3 presents the numerical solutions for system (2.1)-(2.5). It shows that the including of time delays helps maintain the concentration of uninfected monocytes, while simultaneously reducing the concentrations of other compartments such as E, V, T^N, and T^S. As the delay period increases, it becomes apparent that time delays can help manage DENV progression in patients, demonstrating an effect similar to that of drug efficacy. Therefore, incorporating time delays may play a significant role in the development of new and effective treatment strategies.

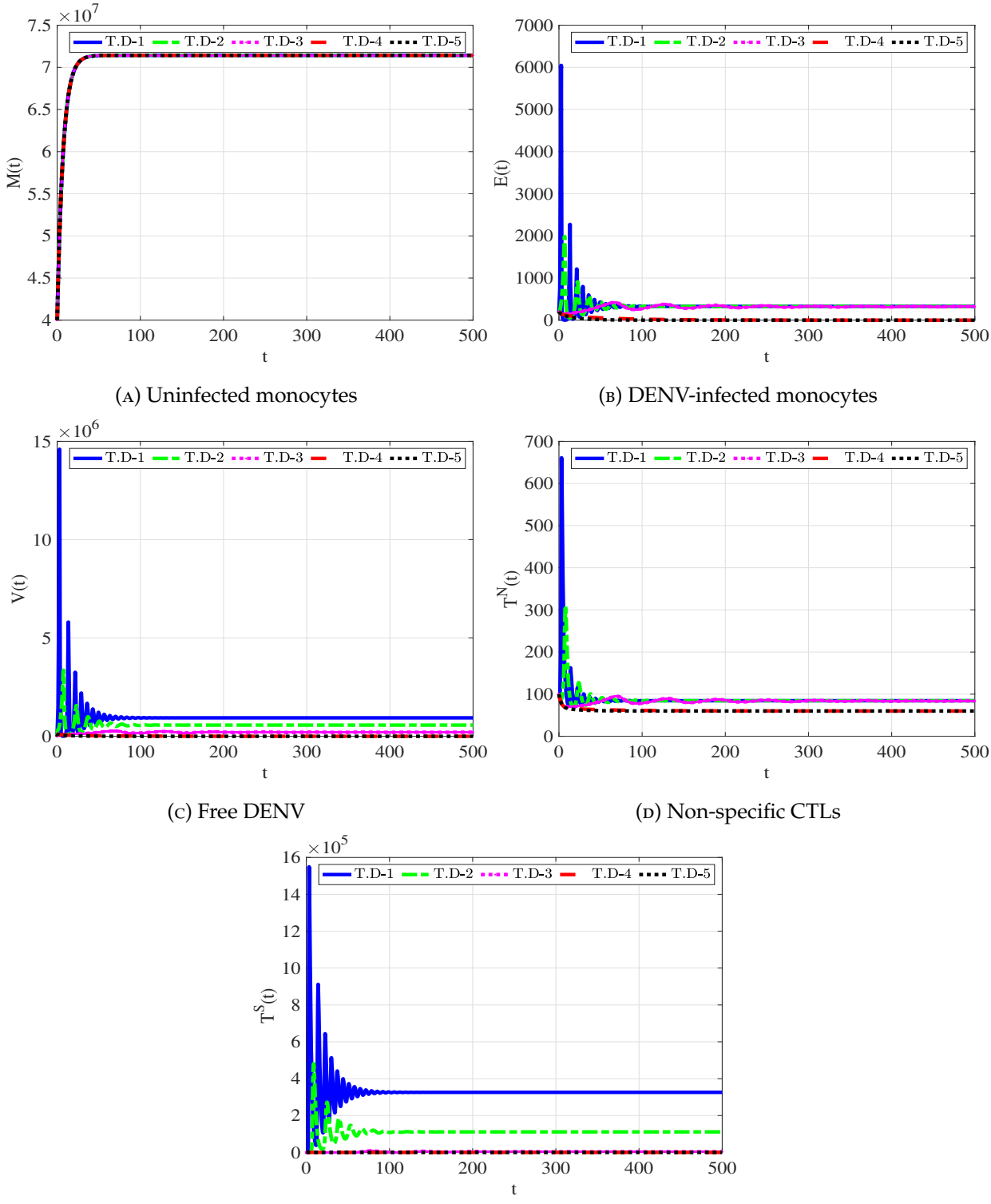
4.3. **Sensitivity analysis.** A sensitivity analysis will be performed to assess how different parameters affect the spread of Dengue infection in a host. This section emphasizes the critical parameters that notably influence our model, assisting researchers in the development of new antiviral drugs. The normalized forward sensitivity index for R_0 is defined as follows:

$$H_{\omega}^{R_i} = \frac{\partial R_i}{\partial \delta} \times \frac{\delta}{R_i} \tag{4.1}$$

where δ is given parameter. The influence of R_0 on the stability of the uninfected steady state $\mathcal{SS}_0$ is quite substantial, which encourages further investigation into the sensitivity analysis of these variables. Using Eq. (4.1) and setting $\alpha = 1.72 \times 10^{-12}$, the sensitivity indices of R_0 with respect to each parameter are determined and presented in Table 3. Based on the signs indicated in the table, we can interpret the level of influence each parameter has in our model as follow:

- Parameters η, α, ρ, ν_1 and ν_2 demonstrate positive indices. This indicates that changes in these parameters will result in corresponding adjustments to the basic reproduction number R_0. As a result, increasing or decreasing these parameters will lead to a rise or fall in R_0 accordingly. The findings suggest that both the infection rate, α, and viral replication rate, η, play a crucial role in determining the sensitivity of R_0. Lowering the values of parameters α and η can be accomplished through a control strategy designed to inhibit both viral infection and production. These findings could be valuable in creating antiviral therapies focused on preventing viral entry and replication.
- Conversely, the parameters β, σ, μ, κ_1,κ_2, ξ_1, ξ_2, m_1, m_2, τ_1, and τ_2 have negative signs, resulting in a negative impact on R_0. From Table 3, we find that a 10% increase (or decrease) the values of β, σ, μ, κ_1,κ_2, ξ_1, ξ_2, m_1, m_2, τ_1 and τ_2 decreases (or increases) R_0 by 10%, 10%, 9.944%, 0.012%, 0.044%, 0.012%, 0.044%, 1%, 1%, 1%, and 1%, respectively.

4.4. **Impact of non-specific CTLs and strain-specific CTL responses on the DENV dynamics.** This section examines how the stimulated rate constants of non-specific CTLs and strain-specific



(A) Uninfected monocytes

(B) DENV-infected monocytes

(C) Free DENV

(D) Non-specific CTLs

(E) Strain-specific CTLs

FIGURE 3. Solutions of system (2.1)-(2.5) for different delays τ_1 and τ_2.

TABLE 3. Sensitivity index of R_0.

Parameter	$H_\delta^{R_0}$	Parameter	$H_\delta^{R_0}$
η	1	ξ_1	−0.0012
α	1	ξ_2	−0.0044
ρ	1	ν_1	0.0012
β	−1	ν_2	0.0044
σ	−1	m_1	−0.1000
μ	−0.9944	m_2	−0.1000
κ_1	−0.0012	τ_1	−0.1000
κ_2	−0.0044	τ_2	−0.1000

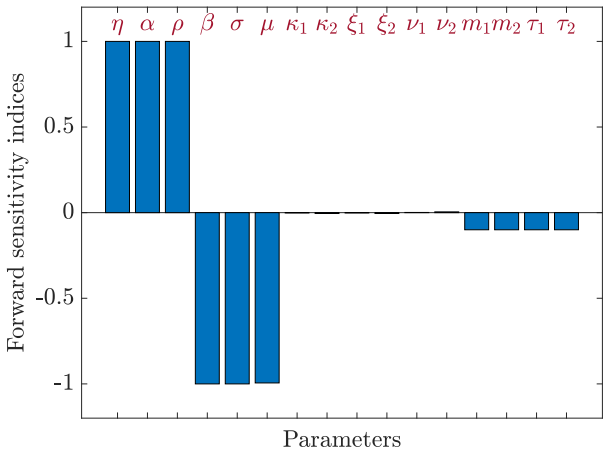
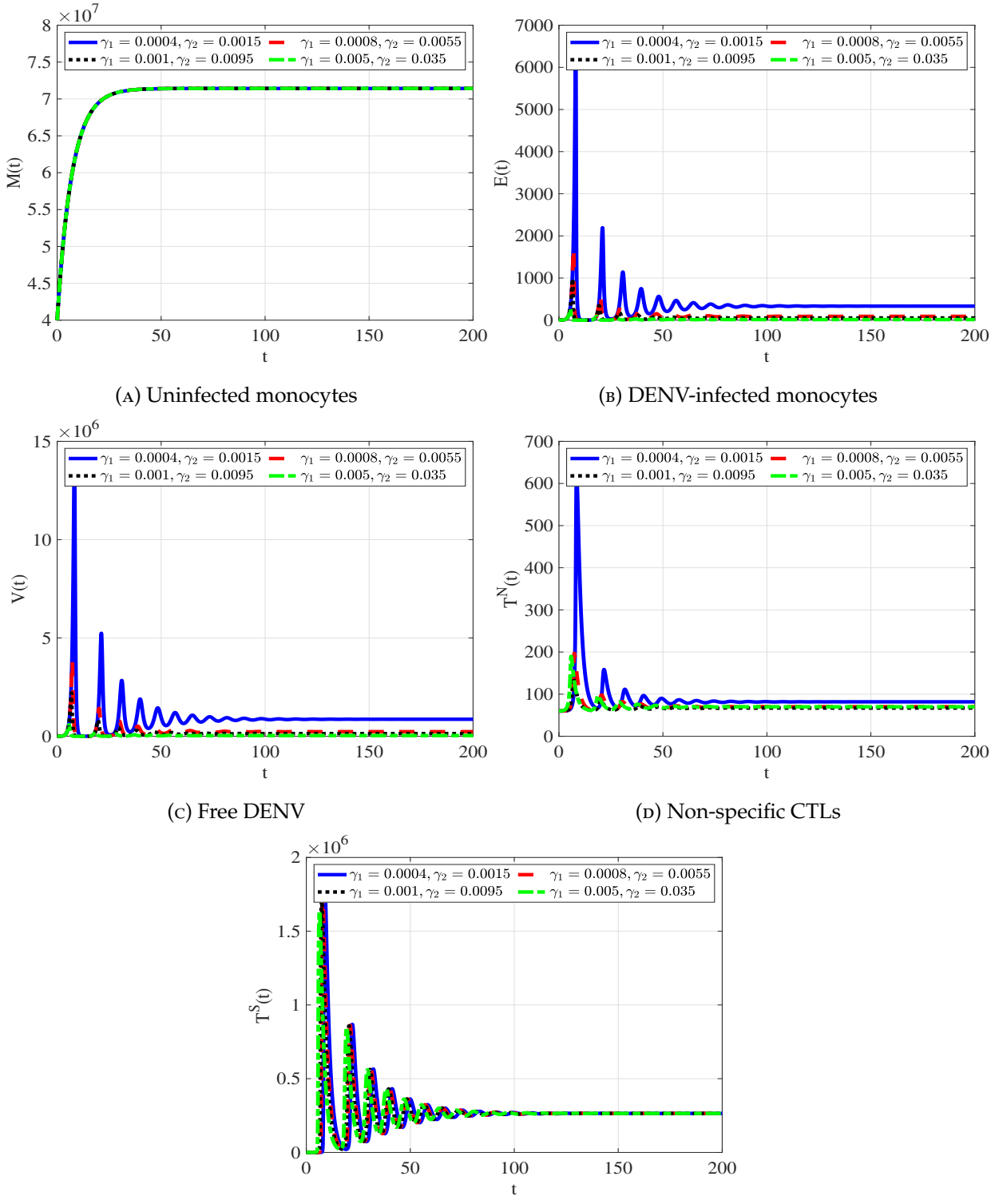


FIGURE 4. Sensitivity of R_2.

CTLs, denoted as γ_1 and γ_2, affect the system dynamics outlined in model (2.1)-(2.5) . To investigate the impact of γ_1 and γ_2 on the model's solutions, we will maintain the values of $\alpha = 1.72 \times 10^{-11}$, and $\tau_i = 0.1$ for $i = 1, 2$, constant while varying the parameter γ_1 and γ_2. We will begin with the following initial point:

$$\mathbf{IP-5}: M(\theta) = 4 \times 10^7, E(\theta) = 1, V(\theta) = 357, T^N(\theta) = 60, T^S(\theta) = 60,$$

where $\theta \in [-0.1, 0]$. Figure 5 shows that as the parameters γ_1 and γ_2 increase, the levels of uninfected monocytes remain unchanged. In contrast, the quantities of DENV-infected monocytes and free DENV decrease. Therefore, these CTLs primarily contribute to controlling DENV infection. Since R_0 is not influenced by changes in γ_1 and γ_2, increasing these parameters does not lead to reaching $\mathcal{SS}_0$. Thus, non-specific CTLs and strain-specific CTL cells cannot completely eliminate DENV infections, but they are effective in slowing down DENV progression.



(A) Uninfected monocytes

(B) DENV-infected monocytes

(C) Free DENV

(D) Non-specific CTLs

(E) Strain-specific CTLs

FIGURE 5. Impact of non-specific CTLs and strain-specific CTL responses on the dynamics of the DENV model.

5. Conclusions and Discussion

This paper explored two DENV dynamics models that include both non-specific and strain-specific CTLs. The models describe the interaction between five populations: uninfected monocytes, infected monocytes, free DENV particles, non-specific CTLs, and strain-specific CTLs. Two types of discrete/distributed delays were included into the models: Delay in the formation of infected monocytes and delay in the maturation of newly released dengue virions.

The study established that the solutions for the proposed models remain non-negative and bounded. Two steady states are identified: the uninfected steady state ($\mathcal{SS}_0$) and the infected steady state ($\mathcal{SS}_1$), with the stability of these points being influenced by the basic reproduction number, R_0. Using the Lyapunov method and LaSalle's invariance principle, the global asymptotic stability of both steady states is demonstrated. We proved that

(i) The uninfected steady state ($\mathcal{SS}_0$) always exists and is GAS when $R_0 \leq 1$. This indicates that DENV will be eradicated in this scenario.

(ii) The infected steady state exists and is GAS when $R_0 > 1$. This represents that an individual infected with DENV.

The theoretical results are verified through numerical simulations. Additionally, sensitivity analysis is performed to examine the effect of various parameters on R_0 based on available data. The findings suggest that both the infection rate and viral production rate play a crucial role in influencing the sensitivity of R_0, thereby shaping the dynamics of DENV. This understanding may aid in the design of antiviral therapies targeting viral entry and replication.The study also examines the role of CTL immune responses and the effect of time delays, leading to several key conclusions:

- Increasing the delay period can help manage the progression of DENV in patients.
- Both non-specific and strain-specific CTLs play distinct roles in controlling DENV infection.

Conflicts of Interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

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