Research Article

Global Dynamics of Secondary DENV Infection with Diffusion

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During the past eras, many mathematicians have paid their attentions to model the dynamics of dengue virus (DENV) infection but without taking into account the mobility of the cells and DENV particles. In this study, we develop and investigate a partial differential equations (PDEs) model that describes the dynamics of secondary DENV infection taking into account the spatial mobility of DENV particles and cells. The model includes five nonlinear PDEs describing the interaction among the target cells, DENV-infected cells, DENV particles, heterologous antibodies, and homologous antibodies. In the beginning, the well-posedness of solutions, including the existence of global solutions and the boundedness, is justified. We derive three threshold parameters which govern the existence and stability of the four equilibria of the model. We study the global stability of all equilibria based on the construction of suitable Lyapunov functions and usage of Lyapunov-LaSalle's invariance principle (LLIP). Last, numerical simulations are carried out in order to verify the validity of our theoretical results.

1. Introduction

Mathematical models and their analysis have been proven to be an efficient and significant approach to understand the within-host dynamics of viral infections such as dengue virus (DENV), human immunodeficiency virus (HIV), hepatitis C and B virus (HCV/HBV), human T lymphotropic virus type I (HTLV-I), and recently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). DENV is the casual of dengue fever which is one of the morbidity and mortality diseases. It can transmit to humans via *Aedes aegypti* and *Aedes albopictus* mosquitoes. Annually, about 50–100 million infected individuals by DENV are reported worldwide. The most epidemic regions are sub-Saharan Africa and Southeast Asia [1]. Several symptoms of dengue that can appear on the infected individual are high fever, vomiting, nausea, joint pains, headache, and pain behind the eyes [2]. DENV aims and infects the following types of cells: monocytes, dendritic cells, hepatocytes, macrophages, and mast cells

[3–6]. There are four serologically various dengue viruses DENV (1–4) that can infect the human [7]. When a DENV enters the human body first time, the immune response is enhanced [8]. Cytotoxic T lymphocytes (CTLs) and antibody immune responses are two main components of the immune system against viruses. CTLs destroy the DENV-infected cells, while antibodies kill DENV particles and clear it from the body.

During the recent years, several mathematical models have been developed which describe within-host DENV primary infection [9–17]. These models are based on the virus dynamics model introduced by Nowak and Bangham [18]. The World Health Organization (WHO) [19] has reported that an infected individual by one serotype will have lifelong immunity against that serotype but only temporary and partial cross-immunity to the other three serotypes. Mathematical models of DENV dynamics pertaining to secondary infection with another serotype have been developed in [20–25]. Gujarati and Ambika [20] have formulated the following DENV infection model:

$$\begin{aligned}
\frac{dK(t)}{dt} &= \delta - \mu K(t)M(t) - \xi K(t), \\
\frac{dL(t)}{dt} &= \mu K(t)M(t) - \varrho L(t), \\
\frac{dM(t)}{dt} &= \tau L(t) - \eta M(t) - \omega_1 M(t)N(t) - \omega_2 M(t)P(t), \\
\frac{dB(t)}{dt} &= \beta - \gamma B(t) + \varphi B(t)M(t), \\
\frac{dN(t)}{dt} &= \vartheta \epsilon B(t) - \kappa_1 N(t)M(t) - \alpha_1 N(t), \\
\frac{dP(t)}{dt} &= \epsilon B(t) - \kappa_2 P(t)M(t) - \alpha_2 P(t),
\end{aligned} \tag{1}$$

where $t > 0$ is the time, and $K(t)$, $L(t)$, $M(t)$, $B(t)$, $N(t)$, and $P(t)$ are the concentrations of the target cells, DENV-infected cells, DENV particles, B cells, heterologous antibody previously formed on primary infection, and homologous antibody against the new virus serotype of the secondary infection, respectively. The parameter δ represents the creation rate of the target cells. The DENV particles infect the target cells at rate μKM . The DENV-infected cells produce viruses at rate τL . The B cells are created at constant rate β and proliferated at rate φBM . The death rates of the compartments K , L , M , B , N , and P are given by ξK , ϱL , ηM , γB , $\alpha_1 N$, and $\alpha_2 P$, respectively. The two types of antibodies N and P are generated from the B cells at rates $\vartheta \epsilon B$ and ϵB and neutralize the DENV at rates $\omega_1 MN$ and $\omega_2 MP$. The terms $\kappa_1 NM$ and $\kappa_2 PM$ represent the rates at which antibody virus complex affects the antibody growth. $\vartheta \in (0, 1)$ is a correlation factor that quantifies the similarity between the individual serotypes. We observe that the global stability of the models presented in [20–25] is not well studied.

All of the DENV infection models in the above-mentioned works are given by ordinary or delay differential equations under the assumption that the cells and DENV particles are well mixed. Spatial structure plays an important role in understanding the dynamical behavior of viral infection within a host. In recent years, spatial dependence has been incorporated into mathematical models of several viral infections such as hepatitis B virus (HBV) [26], hepatitis C virus (HCV) [27, 28], human immunodeficiency virus (HIV) [29–31], and human T lymphotropic virus type I (HTLV-I) [32]. To the best of our knowledge, the DENV infection model with diffusion has not been studied before. Therefore, the aim of the present study is to focus on the dynamical behavior of DENV infection with diffusion. Following the work of Hattaf [33], our proposed model takes into account the spatial mobility of all compartments.

2. Mathematical DENV Dynamics Model

We develop a DENV infection model with secondary infection and diffusion as

$$\frac{\partial K(u, t)}{\partial t} = d_K \Delta K(u, t) + \delta - \mu K(u, t)M(u, t) - \xi K(u, t), \tag{2}$$

$$\frac{\partial L(u, t)}{\partial t} = d_L \Delta L(u, t) + \mu K(u, t)M(u, t) - \varrho L(u, t), \tag{3}$$

$$\begin{aligned}
\frac{\partial M(u, t)}{\partial t} &= d_M \Delta M(u, t) + \tau L(u, t) - \eta M(u, t) \\
&\quad - \omega_1 M(u, t)N(u, t) - \omega_2 M(u, t)P(u, t),
\end{aligned} \tag{4}$$

$$\frac{\partial N(u, t)}{\partial t} = d_N \Delta N(u, t) + \lambda_1 M(u, t)N(u, t) - \alpha_1 N(u, t), \tag{5}$$

$$\frac{\partial P(u, t)}{\partial t} = d_P \Delta P(u, t) + \lambda_2 M(u, t)P(u, t) - \alpha_2 P(u, t), \tag{6}$$

where $u \in \Gamma$ is the position. The heterologous and homologous antibodies are activated at rates $\lambda_1 MN$ and $\lambda_2 MP$, respectively. Here, Δ is the Laplacian operator and d_x is the diffusion coefficient, where $x \in \{K, L, M, N, P\}$. The spatial domain $\Gamma \subset \mathbb{R}^m$ (where $m \geq 1$) is bounded and connected; moreover, its boundary $\partial\Gamma$ is smooth.

The initial conditions are given by

$$\begin{aligned}
K(u, 0) &= \mathcal{G}_1(u), \\
L(u, 0) &= \mathcal{G}_2(u), \\
M(u, 0) &= \mathcal{G}_3(u), \\
N(u, 0) &= \mathcal{G}_4(u), \\
P(u, 0) &= \mathcal{G}_5(u), \quad u \in \bar{\Gamma},
\end{aligned} \tag{7}$$

where $\mathcal{G}_\ell(u) \geq 0$, $\ell = 1, \dots, 5$, are the continuous functions. In addition, we take the following homogeneous Neumann boundary conditions:

$$\frac{\partial K}{\partial \vec{\mathcal{B}}} = \frac{\partial L}{\partial \vec{\mathcal{B}}} = \frac{\partial M}{\partial \vec{\mathcal{B}}} = \frac{\partial N}{\partial \vec{\mathcal{B}}} = \frac{\partial P}{\partial \vec{\mathcal{B}}} = 0, \quad t > 0, u \in \partial\Gamma, \tag{8}$$

where $\partial/\partial \vec{\mathcal{B}}$ is the outward normal derivative on the boundary $\partial\Gamma$. These boundary conditions indicate that cells and viruses cannot cross the isolated boundary [34].

3. Well-Posedness of Solutions

Theorem 1. Assume that $d_K = d_L = d_M = d_N = d_P = \tilde{d}$. Then, models (2)–(6) with any initial satisfying (7) has a unique, nonnegative, and bounded solution defined on $\bar{\Gamma} \times [0, +\infty)$.

Proof. We denote $\mathcal{X} = BUC(\bar{\Gamma}, \mathbb{R}^5)$, the set of all bounded and uniformly continuous functions from $\bar{\Gamma}$ to $\mathbb{R}^5$, with norm $\|\theta\|_{\mathcal{X}} = \sup_{u \in \bar{\Gamma}} |\theta(u)|$. We define the positive cone $\mathcal{X}_+ = BUC(\bar{\Gamma}, \mathbb{R}_+^5) \subset \mathcal{X}$ which induces a partial order on $\mathcal{X}$. This shows that the space $(\mathcal{X}, \|\cdot\|_{\mathcal{X}})$ is a Banach lattice [35, 36].

For any initial data $\mathcal{G} = (\mathcal{G}_1, \mathcal{G}_2, \mathcal{G}_3, \mathcal{G}_4, \mathcal{G}_5)^T \in \mathcal{X}_+$, we define $H = (H_1, H_2, H_3, H_4, H_5)^T: \mathcal{X}_+ \longrightarrow \mathcal{X}$ by

$$\begin{aligned} H_1(\mathcal{G})(u) &= \delta - \mu \mathcal{G}_1(u) \mathcal{G}_3(u) - \xi \mathcal{G}_1(u), \\ H_2(\mathcal{G})(u) &= \mu \mathcal{G}_1(u) \mathcal{G}_3(u) - \varrho \mathcal{G}_2(u), \\ H_3(\mathcal{G})(u) &= \tau \mathcal{G}_2(u) - \eta \mathcal{G}_3(u) - \varpi_1 \mathcal{G}_3(u) \mathcal{G}_4(u) - \varpi_2 \mathcal{G}_3(u) \mathcal{G}_5(u), \\ H_4(\mathcal{G})(u) &= \lambda_1 \mathcal{G}_3(u) \mathcal{G}_4(u) - \alpha_1 \mathcal{G}_4(u), \\ H_5(\mathcal{G})(u) &= \varpi \mathcal{G}_3(u) \mathcal{G}_5(u) - \alpha_2 \mathcal{G}_5(u). \end{aligned} \quad (9)$$

It is clear that H is locally Lipschitz on $\mathcal{X}_+$. We can rewrite systems (2)–(6) with initial conditions (7) and boundary conditions (8) as the following abstract functional differential equation:

$$\begin{cases} \frac{d\overline{\mathcal{U}}}{dt} = \Theta \overline{\mathcal{U}} + H(\overline{\mathcal{U}}), & t > 0, \\ \overline{\mathcal{U}}(0) = \mathcal{G} \in \mathcal{X}_+, \end{cases} \quad (10)$$

where $\overline{\mathcal{U}} = (K, L, M, N, P)^T$ and $\Theta \overline{\mathcal{U}} = (d_K \Delta K, d_L \Delta L, d_M \Delta M, d_N \Delta N, d_P \Delta P)^T$. One can show that

$$\lim_{q \rightarrow 0^+} \frac{1}{q} \text{dist}(\mathcal{G}(0) + qH(\mathcal{G}), \mathcal{X}_+) = 0, \quad \forall \mathcal{G} \in \mathcal{X}_+. \quad (11)$$

Hence, for any $\mathcal{G} \in \mathcal{X}_+$, systems (2)–(6) with (7)–(8) has a unique nonnegative mild solution $(K(u, t), L(u, t), M(u, t), N(u, t), P(u, t))$ defined on $\overline{\Gamma} \times [0, \mathcal{T}_m)$, where $[0, \mathcal{T}_m)$ is the maximal existence time interval on which the solution exists [35–37]. In addition, this solution also is a classical solution for the given problem.

We define

$$\begin{aligned} \Psi(u, t) &= K(u, t) + L(u, t) + \frac{\varrho}{2\tau} M(u, t) + \frac{\varrho \varpi_1}{2\tau \lambda_1} N(u, t) \\ &\quad + \frac{\varrho \varpi_2}{2\tau \lambda_2} P(u, t). \end{aligned} \quad (12)$$

Then, using systems (2)–(6), we obtain

$$\begin{aligned} \frac{\partial \Psi(u, t)}{\partial t} &= d_K \Delta K(u, t) + \delta - \mu K(u, t) M(u, t) - \xi K(u, t) \\ &\quad + d_L \Delta L(u, t) + \mu K(u, t) M(u, t) - \varrho L(u, t), \\ &\quad \frac{\varrho}{2\tau} [d_M \Delta M(u, t) + \tau L(u, t) - \eta M(u, t) - \varpi_1 M(u, t) N(u, t) - \varpi_2 M(u, t) P(u, t)] \\ &\quad + \frac{\varrho \varpi_1}{2\tau \lambda_1} [d_N \Delta N(u, t) + \lambda_1 M(u, t) N(u, t) - \alpha_1 N(u, t)] \\ &\quad + \frac{\varrho \varpi_2}{2\tau \lambda_2} [d_P \Delta P(u, t) + \lambda_2 M(u, t) P(u, t) - \alpha_2 P(u, t)]. \end{aligned} \quad (13)$$

Since $d_K = d_L = d_M = d_N = d_P = \tilde{d}$, then we get

$$\begin{aligned} \frac{\partial \Psi(u, t)}{\partial t} - \tilde{d} \Delta \Psi(u, t) &= \delta - \xi K(u, t) - \frac{\varrho}{2} L(u, t) - \frac{\varrho \eta}{2\tau} M(u, t) - \frac{\varrho \varpi_1 \alpha_1}{2\tau \lambda_1} N(u, t) - \frac{\varrho \varpi_2 \alpha_2}{2\tau \lambda_2} \\ &\quad P(u, t) \leq \delta - \sigma \left(K(u, t) + L(u, t) + \frac{\varrho}{2\tau} M(u, t) + \frac{\varrho \varpi_1}{2\tau \lambda_1} N(u, t) + \frac{\varrho \varpi_2}{2\tau \lambda_2} P(u, t) \right) \\ &= \delta - \sigma \Psi(u, t), \end{aligned} \quad (14)$$

where $\sigma = \min\{\xi, (1/2)\varrho, \eta, \alpha_1, \alpha_2\}$. Thus, $\Psi(u, t)$ satisfies

$$\begin{cases} \frac{\partial \Psi(u, t)}{\partial t} - \tilde{d}\Delta \Psi(u, t) \leq \delta - \sigma \Psi(u, t), \\ \Psi(u, 0) = \mathcal{G}_1(u) + \mathcal{G}_2(u) + \frac{\varrho}{2\tau} \mathcal{G}_3(u) + \frac{\varrho \omega_1}{2\tau \lambda_1} \mathcal{G}_4(u) + \frac{\varrho \omega_2}{2\tau \lambda_2} \mathcal{G}_5(u) \geq 0, \\ \frac{\partial \Psi}{\partial \mathcal{B}} = 0. \end{cases} \quad (15)$$

Let $\tilde{\Psi}(t)$ be a solution of the following ODE:

$$\begin{cases} \frac{d\tilde{\Psi}(t)}{dt} = \delta - \sigma \tilde{\Psi}(t), \\ \tilde{\Psi}(0) = \max_{u \in \bar{\Gamma}} \Psi(u, 0). \end{cases} \quad (16)$$

This gives that $\tilde{\Psi}(t) \leq \max\{(\delta/\sigma), \max_{u \in \bar{\Gamma}} \Psi(u, 0)\}$. On the basis of comparison principle [38], we obtain $\Psi(u, t) \leq \tilde{\Psi}(t)$. Hence,

$$\Psi(u, t) \leq \max\left\{\frac{\delta}{\sigma}, \max_{u \in \bar{\Gamma}} \Psi(u, 0)\right\}, \quad (17)$$

which implies that $K(u, t)$, $L(u, t)$, $M(u, t)$, $N(u, t)$, and $P(u, t)$ are bounded on $\bar{\Gamma} \times [0, \mathcal{T}_m]$. The standard theory for semilinear parabolic systems implies that $\mathcal{T}_m = +\infty$ [39]. This shows that solution $(K(u, t), L(u, t), M(u, t), N(u, t), P(u, t))$ is defined for all $u \in \Gamma$, $t > 0$, and also is unique and nonnegative. $\square$

4. Equilibria

Theorem 2. *There exist three threshold parameters $\mathcal{R}_0$, $\mathcal{R}_1$, and $\mathcal{R}_2$ with $\mathcal{R}_0 > \mathcal{R}_1$ and $\mathcal{R}_0 > \mathcal{R}_2$, such that*

- (i) *If $\mathcal{R}_0 \leq 1$, then the system has a single equilibrium Ω_0*
- (ii) *If $\mathcal{R}_1 \leq 1 < \mathcal{R}_0$ and $\mathcal{R}_2 \leq 1 < \mathcal{R}_0$, then the system contains only two equilibria Ω_0 and Ω_1*
- (iii) *If $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$, then the system contains three equilibria Ω_0 , Ω_1 , and Ω_2*
- (iv) *If $\mathcal{R}_2 > 1$ and $\mathcal{R}_1 < 1$, then the system contains three equilibria Ω_0 , Ω_1 , and Ω_3*
- (v) *If $\mathcal{R}_2 > 1$ and $\mathcal{R}_1 > 1$, then the system contains four equilibria Ω_0 , Ω_1 , Ω_2 , and Ω_3*

Proof. To calculate the equilibria of systems (2)–(6), we let

$$0 = \delta - \mu KM - \xi K, \quad (18)$$

$$0 = \mu KM - \varrho L, \quad (19)$$

$$0 = \tau L - \eta M - \omega_1 MN - \omega_2 MP, \quad (20)$$

$$0 = \lambda_1 MN - \alpha_1 N, \quad (21)$$

$$0 = \lambda_2 MP - \alpha_2 P. \quad (22)$$

Then, solving the system of algebraic equations (18)–(22), we get four equilibria such as the following:

- (i) Infection-free equilibrium $\Omega_0(K_0, 0, 0, 0, 0, 0)$, where $K_0 = \delta/\xi$
- (ii) Persistent DENV infection equilibrium with ineffective antibodies is $\Omega_1(K_1, L_1, M_1, 0, 0)$, where

$$\begin{aligned} K_1 &= \frac{K_0}{\mathcal{R}_0}, \\ L_1 &= \frac{\eta \xi}{\tau \mu} (\mathcal{R}_0 - 1), \\ M_1 &= \frac{\xi}{\mu} (\mathcal{R}_0 - 1). \end{aligned} \quad (23)$$

- (iii) Persistent DENV infection equilibrium with only effective heterologous antibody is $\Omega_2(K_2, L_2, M_2, N_2, 0)$, where

$$\begin{aligned} K_2 &= \frac{\lambda_1 \delta}{\xi \lambda_1 + \mu \alpha_1}, \\ L_2 &= \frac{\mu \delta \alpha_1}{\varrho (\xi \lambda_1 + \mu \alpha_1)}, \\ M_2 &= \frac{\alpha_1}{\lambda_1}, \\ N_2 &= \frac{\eta}{\omega_1} (\mathcal{R}_1 - 1). \end{aligned} \quad (24)$$

- (iv) Persistent DENV infection equilibrium with only effective homologous antibody is $\Omega_3(K_3, L_3, M_3, 0, P_3)$, where

$$\begin{aligned} K_3 &= \frac{\lambda_2 \delta}{\xi \lambda_2 + \mu \alpha_2}, \\ L_3 &= \frac{\mu \delta \alpha_2}{\varrho (\xi \lambda_2 + \mu \alpha_2)}, \\ M_3 &= \frac{\alpha_2}{\lambda_2}, \\ P_3 &= \frac{\eta}{\omega_2} (\mathcal{R}_2 - 1). \end{aligned} \quad (25)$$

Where

$$\begin{aligned} \mathcal{R}_0 &= \frac{K_0 \tau \mu}{\varrho \eta}, \\ \mathcal{R}_1 &= \frac{\mathcal{R}_0}{1 + (\mu \alpha_1 / \xi \lambda_1)}, \\ \mathcal{R}_2 &= \frac{\mathcal{R}_0}{1 + (\mu \alpha_2 / \xi \lambda_2)}. \end{aligned} \quad (26)$$

Clearly, $\mathcal{R}_0 > \mathcal{R}_1$ and $\mathcal{R}_0 > \mathcal{R}_2$

- (v) Clearly from (iii) and (iv), if $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$, then $\Omega_0, \Omega_1, \Omega_2$, and Ω_3 all exist

Here, $\mathcal{R}_0$ represents the basic infection reproduction number, $\mathcal{R}_1$ represents the heterologous antibody immune response activation number, and $\mathcal{R}_2$ is the homologous antibody immune response activation number. $\square$

5. Global Stability

In this section, we investigate the global asymptotic stability of all equilibria by the Lyapunov method. The construction of Lyapunov functions are based on the works presented in [40–44]. To prove Theorems 1–4, we need to define a function $g(s) = s - 1 - \ln s$ and the arithmetic-geometric mean inequality:

$$\frac{1}{s} \sum_{\ell=1}^s \chi_\ell \geq \sqrt[n]{\prod_{\ell=1}^s \chi_\ell}, \quad \chi_\ell \geq 0, \ell = 1, 2, \dots, \quad (27)$$

which implies

$$\frac{1}{3} \left[\frac{K_\ell}{K} + \frac{LM_\ell}{L_\ell M} + \frac{MKL_\ell}{M_\ell K_\ell L} \right] \geq 1, \quad \ell = 1, 2, 3. \quad (28)$$

Neumann boundary conditions (8) and divergence theorem imply that

$$\begin{aligned} 0 &= \int_{\partial \Gamma} \nabla \mathcal{U} \cdot \vec{\mathcal{B}} \, du = \int_{\Gamma} \operatorname{div}(\nabla \mathcal{U}) \, du = \int_{\Gamma} \Delta \mathcal{U} \, du, \\ 0 &= \int_{\partial \Gamma} \frac{1}{\mathcal{U}} \nabla \mathcal{U} \cdot \vec{\mathcal{B}} \, du = \int_{\Gamma} \operatorname{div} \left(\frac{1}{\mathcal{U}} \nabla \mathcal{U} \right) \, du = \int_{\Gamma} \left(\frac{\Delta \mathcal{U}}{\mathcal{U}} - \frac{\|\nabla \mathcal{U}\|^2}{\mathcal{U}^2} \right) \, du, \end{aligned} \quad (29)$$

for $\mathcal{U} \in \{K, L, M, N, P\}$. Thus, we obtain

$$\begin{aligned} \int_{\Gamma} \Delta \mathcal{U} \, du &= 0, \\ \int_{\Gamma} \frac{\Delta \mathcal{U}}{\mathcal{U}} \, du &= \int_{\Gamma} \frac{\|\nabla \mathcal{U}\|^2}{\mathcal{U}^2} \, du. \end{aligned} \quad (30)$$

For convenience, we drop the input notation, i.e., $(K, L, M, N, P) = (K(u, t), L(u, t), M(u, t), N(u, t), P(u, t))$.

Consider a function $\Pi_\ell(K, L, M, N, P)$ and define

$$\tilde{\Pi}_\ell(t) = \int_{\Gamma} \Pi_\ell(u, t) \, du, \quad \ell = 0, 1, 2, 3. \quad (31)$$

Let Y'_ℓ be the largest invariant subset of

$$Y_\ell = \left\{ (K, L, M, N, P) : \frac{d\tilde{\Pi}_\ell}{dt} = 0 \right\}, \quad \ell = 0, 1, 2, 3. \quad (32)$$

Theorem 3. Let $\mathcal{R}_0 \leq 1$, then Ω_0 is globally asymptotically stable (GAS).

Proof. Define $\Pi_0(u, t)$ as

$$\Pi_0(u, t) = K_0 g\left(\frac{K}{K_0}\right) + L + \frac{\varrho}{\tau} M + \frac{\varrho \omega_1}{\tau \lambda_1} N + \frac{\varrho \omega_2}{\tau \lambda_2} P. \quad (33)$$

Clearly, $\tilde{\Pi}_0(K, L, M, N, P) > 0$ for all $(K, L, M, N, P) > 0$ and $\tilde{\Pi}_0(K_0, 0, 0, 0, 0) = 0$. We calculate $\partial \Pi_0 / \partial t$ along the solutions of model (2)–(6) as

$$\begin{aligned}
\frac{\partial \Pi_0}{\partial t} = & \left(1 - \frac{K_0}{K}\right) (d_K \Delta K + \delta - \xi K - \mu KM) + d_L \Delta L + \mu KM - \varrho L \\
& + \frac{\varrho}{\tau} (d_M \Delta M + \tau L - \eta M - \varpi_1 MN - \varpi_2 MP) + \frac{\varrho \varpi_1}{\tau \lambda_1} (d_N \Delta N + \lambda_1 MN - \alpha_1 N) \\
& + \frac{\varrho \varpi_2}{\tau \lambda_2} (d_P \Delta P + \lambda_2 MP - \alpha_2 P).
\end{aligned} \tag{34}$$

Collecting terms of equation (34), we obtain

$$\begin{aligned}
\frac{\partial \Pi_0}{\partial t} = & -\frac{\xi(K - K_0)}{K^2} + \left(\mu K_0 - \frac{\varrho \eta}{\tau}\right) M - \frac{\varrho \varpi_1 \alpha_1}{\tau \lambda_1} N - \frac{\varrho \varpi_2 \alpha_2}{\tau \lambda_2} P \\
& + \left(1 - \frac{K_0}{K}\right) d_K \Delta K + d_L \Delta L + \frac{\varrho}{\tau} d_M \Delta M + \frac{\varrho \varpi_1}{\tau \lambda_1} d_N \Delta N + \frac{\varrho \varpi_2}{\tau \lambda_2} d_P \Delta P \\
= & -\frac{\xi(K - K_0)}{K^2} + \frac{\varrho \eta}{\tau} (\mathcal{R}_0 - 1) M - \frac{\varrho \varpi_1 \alpha_1}{\tau \lambda_1} N - \frac{\varrho \varpi_2 \alpha_2}{\tau \lambda_2} P \\
& + \left(1 - \frac{K_0}{K}\right) d_K \Delta K + d_L \Delta L + \frac{\varrho}{\tau} d_M \Delta M + \frac{\varrho \varpi_1}{\tau \lambda_1} d_N \Delta N + \frac{\varrho \varpi_2}{\tau \lambda_2} d_P \Delta P.
\end{aligned} \tag{35}$$

Consequently, we calculate $d\tilde{\Pi}_0/dt$ as follows:

$$\begin{aligned}
\frac{d\tilde{\Pi}_0}{dt} = & -\xi \int_{\Gamma} \frac{(K - K_0)}{K^2} du + \frac{\varrho \eta}{\tau} (\mathcal{R}_0 - 1) \int_{\Gamma} M du - \frac{\varrho \varpi_1 \alpha_1}{\tau \lambda_1} \int_{\Gamma} N du - \frac{\varrho \varpi_2 \alpha_2}{\tau \lambda_2} \int_{\Gamma} P du \\
& + d_K \int_{\Gamma} \left(1 - \frac{K_0}{K}\right) \Delta K du + d_L \int_{\Gamma} \Delta L du + \frac{\varrho}{\tau} \int_{\Gamma} \Delta M du \\
& + \frac{\varrho \varpi_1}{\tau \lambda_1} d_N \int_{\Gamma} \Delta N du + \frac{\varrho \varpi_2}{\tau \lambda_2} d_P \int_{\Gamma} \Delta P du.
\end{aligned} \tag{36}$$

Using equality (30), equation (36) is reduced to the following form:

$$\begin{aligned}
\frac{d\tilde{\Pi}_0}{dt} = & -\xi \int_{\Gamma} \frac{(K - K_0)}{K^2} du + \frac{\varrho \eta}{\tau} (\mathcal{R}_0 - 1) \int_{\Gamma} M du \\
& - \frac{\varrho \varpi_1 \alpha_1}{\tau \lambda_1} \int_{\Gamma} N du \\
& - \frac{\varrho \varpi_2 \alpha_2}{\tau \lambda_2} \int_{\Gamma} P du - d_K K_0 \int_{\Gamma} \frac{\|\nabla K\|^2}{K^2} du.
\end{aligned} \tag{37}$$

Therefore, $(d\tilde{\Pi}_0/dt) \leq 0$, for all $K, M, N, P > 0$, and $(d\tilde{\Pi}_0/dt) = 0$ with equality holding when $(K, M, N, P) = (K_0, 0, 0, 0)$. The solutions of models (2)–(6) converge to Y'_0 . The elements of Y'_0 satisfy $(K, M, N, P) = (K_0, 0, 0, 0)$, and then, $(\partial M/\partial t) = \Delta M = 0$. Equation (6) reduces to

$$0 = \frac{\partial M}{\partial t} = \tau L. \tag{38}$$

This yields $L = 0$. Hence, $Y'_0 = \{\Omega_0\}$, and by applying LLIP [45–47], we get that Ω_0 is GAS. $\square$

Theorem 4. If $\mathcal{R}_1 \leq 1 < \mathcal{R}_0$ and $\mathcal{R}_2 \leq 1$, then Ω_1 is GAS.

Proof. Define $\Pi_1(u, t)$ as

$$\begin{aligned}
\Pi_1(u, t) = & K_1 g\left(\frac{K}{K_1}\right) + L_1 g\left(\frac{L}{L_1}\right) + \frac{\varrho}{\tau} M_1 g\left(\frac{M}{M_1}\right) \\
& + \frac{\varrho \varpi_1}{\tau \lambda_1} N + \frac{\varrho \varpi_2}{\tau \lambda_2} P.
\end{aligned} \tag{39}$$

Calculate $\partial \Pi_1/\partial t$ as

$$\begin{aligned}
\frac{\partial \Pi_1}{\partial t} &= \left(1 - \frac{K_1}{K}\right) (d_K \Delta K + \delta - \xi K - \mu K M) + \left(1 - \frac{L_1}{L}\right) (d_L \Delta L + \mu K M - \varrho L) \\
&\quad + \frac{\varrho}{\tau} \left(1 - \frac{M_1}{M}\right) (d_M \Delta M + \tau L - \eta M - \varpi_1 M N - \varpi_2 M P) \\
&\quad + \frac{\varrho \varpi_1}{\tau \lambda_1} (d_N \Delta N + \lambda_1 M N - \alpha_1 N) + \frac{\varrho \varpi_2}{\tau \lambda_2} (d_P \Delta P + \lambda_2 M P - \alpha_2 P) \\
&= \left(1 - \frac{K_1}{K}\right) (\delta - \xi K) + \mu K_1 M - \frac{\mu K M L_1}{L} + \varrho L_1 - \frac{\varrho \eta}{\tau} M - \varrho \frac{M_1 L}{M} \\
&\quad + \frac{\varrho \eta}{\tau} M_1 + \frac{\varrho \varpi_1}{\tau} M_1 N + \frac{\varrho \varpi_2}{\tau} M_1 P - \frac{\varrho \varpi_1 \alpha_1}{\tau \lambda_1} N - \frac{\varrho \varpi_2 \alpha_2}{\tau \lambda_2} P \\
&\quad + d_K \left(1 - \frac{K_1}{K}\right) \Delta K + d_L \left(1 - \frac{L_1}{L}\right) \Delta L + \frac{\varrho d_M}{\tau} \left(1 - \frac{M_1}{M}\right) \Delta M \\
&\quad + \frac{\varrho \varpi_1 d_N}{\tau \lambda_1} \Delta N + \frac{\varrho \varpi_2 d_P}{\tau \lambda_2} \Delta P.
\end{aligned} \tag{40}$$

The equilibrium conditions of Ω_1 imply that

$$\begin{aligned}
\delta &= \xi K_1 + \mu K_1 M_1, \\
\varrho L_1 &= \mu K_1 M_1, \\
\tau L_1 &= \eta M_1,
\end{aligned} \tag{41}$$

We get $\mu K_1 M - (\varrho \eta / \tau) M = 0$ and

$$\begin{aligned}
\frac{\partial \Pi_1}{\partial t} &= -\frac{\xi (K - K_1)^2}{K} + \varrho L_1 \left(1 - \frac{K_1}{K}\right) - \varrho L_1 \frac{K M L_1}{K_1 M_1 L} + 2 \varrho L_1 - \varrho L_1 \frac{M_1 L}{M L_1} \\
&\quad + \frac{\varrho \varpi_1}{\tau} \left(M_1 - \frac{\alpha_1}{\lambda_1}\right) N + \frac{\varrho \varpi_2}{\tau} \left(M_1 - \frac{\alpha_2}{\lambda_2}\right) P + d_K \left(1 - \frac{K_1}{K}\right) \Delta K + d_L \left(1 - \frac{L_1}{L}\right) \Delta L \\
&\quad + \frac{\varrho d_M}{\tau} \left(1 - \frac{M_1}{M}\right) \Delta M + \frac{\varrho \varpi_1 d_N}{\tau \lambda_1} \Delta N + \frac{\varrho \varpi_2 d_P}{\tau \lambda_2} \Delta P = -\frac{\xi (K - K_1)^2}{K} \\
&\quad + \varrho L_1 \left[3 - \frac{K_1}{K} - \frac{K M L_1}{K_1 M_1 L} - \frac{M_1 L}{M L_1}\right] + \frac{\varrho \varpi_1 (\xi \lambda_1 + \mu \alpha_1)}{\tau \lambda_1 \mu} (\mathcal{R}_1 - 1) N \\
&\quad + \frac{\varrho \varpi_2 (\xi \lambda_2 + \mu \alpha_2)}{\tau \lambda_2 \mu} (\mathcal{R}_2 - 1) P + d_K \left(1 - \frac{K_1}{K}\right) \Delta K + d_L \left(1 - \frac{L_1}{L}\right) \Delta L + \frac{\varrho d_M}{\tau} \left(1 - \frac{M_1}{M}\right) \Delta M \\
&\quad + \frac{\varrho \varpi_1 d_N}{\tau \lambda_1} \Delta N + \frac{\varrho \varpi_2 d_P}{\tau \lambda_2} \Delta P.
\end{aligned} \tag{42}$$

Calculate the time derivative of $\tilde{\Pi}_1(t)$ and use equality (30) to get

$$\begin{aligned}
 \frac{d\tilde{\Pi}_1}{dt} = & -\xi \int_{\Gamma} \frac{(K - K_1)^2}{K} du + \varrho L_1 \int_{\Gamma} \left[3 - \frac{K_1}{K} - \frac{KML_1}{K_1M_1L} - \frac{M_1L}{ML_1} \right] du \\
 & + \frac{\varrho\omega_1(\xi\lambda_1 + \mu\alpha_1)}{\tau\lambda_1\mu} (\mathcal{R}_1 - 1) \int_{\Gamma} N du + \frac{\varrho\omega_2(\xi\lambda_2 + \mu\alpha_2)}{\tau\lambda_2\mu} (\mathcal{R}_2 - 1) \int_{\Gamma} P du \\
 & + d_K \int_{\Gamma} \left(1 - \frac{K_1}{K} \right) \Delta K du + d_L \int_{\Gamma} \left(1 - \frac{L_1}{L} \right) \Delta L du + \frac{\varrho d_M}{\tau} \int_{\Gamma} \left(1 - \frac{M_1}{M} \right) \Delta M du \\
 & + \frac{\varrho\omega_1 d_N}{\tau\lambda_1} \int_{\Gamma} \Delta N du + \frac{\varrho\omega_2 d_P}{\tau\lambda_2} \int_{\Gamma} \Delta P du = -\xi \int_{\Gamma} \frac{(K - K_1)^2}{K} du \\
 & + \varrho L_1 \int_{\Gamma} \left[3 - \frac{K_1}{K} - \frac{KML_1}{K_1M_1L} - \frac{M_1L}{ML_1} \right] du + \frac{\varrho\omega_1(\xi\lambda_1 + \mu\alpha_1)}{\tau\lambda_1\mu} (\mathcal{R}_1 - 1) \int_{\Gamma} N du \\
 & + \frac{\varrho\omega_2(\xi\lambda_2 + \mu\alpha_2)}{\tau\lambda_2\mu} (\mathcal{R}_2 - 1) \int_{\Gamma} P du - d_K K_1 \int_{\Gamma} \frac{\|\nabla K\|^2}{K^2} du - d_L L_1 \int_{\Gamma} \frac{\|\nabla L\|^2}{L^2} du \\
 & - \frac{\varrho d_M}{\tau} M_1 \int_{\Gamma} \frac{\|\nabla M\|^2}{M^2} du.
 \end{aligned} \tag{43}$$

Since $\mathcal{R}_1 \leq 1$ and $\mathcal{R}_2 \leq 1$, then utilizing inequality (28), we obtain $d\tilde{\Pi}_1/dt \leq 0$ for all $K, L, M, N, P > 0$. Furthermore, $d\tilde{\Pi}_1/dt = 0$ at $(K, L, M, N, P) = (K_1, L_1, M_1, 0, 0)$. The solutions of (2)–(6) tend to $Y'_1 = \{\Omega_1\}$. It follows that Ω_1 is GAS by using LLIP. $\square$

Theorem 5. Let $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 \leq \mathcal{R}_1$ then Ω_2 is GAS.

Proof. Define $\Pi_2(u, t)$ as

$$\begin{aligned}
 \Pi_2(u, t) = & K_2 g\left(\frac{K}{K_2}\right) + L_2 g\left(\frac{L}{L_2}\right) + \frac{\varrho}{\tau} M_2 g\left(\frac{M}{M_2}\right) \\
 & + \frac{\varrho\omega_1}{\tau\lambda_1} N_2 g\left(\frac{N}{N_2}\right) + \frac{\varrho\omega_2}{\tau\lambda_2} P.
 \end{aligned} \tag{44}$$

Calculate $\partial\Pi_2/\partial t$ as

$$\begin{aligned}
 \frac{\partial\Pi_2}{\partial t} = & \left(1 - \frac{K_2}{K}\right) (d_K \Delta K + \delta - \xi K - \mu KM) + \left(1 - \frac{L_2}{L}\right) (d_L \Delta L + \mu KM - \varrho L) \\
 & + \frac{\varrho}{\tau} \left(1 - \frac{M_2}{M}\right) (d_M \Delta M + \tau L - \eta M - \omega_1 MN - \omega_2 MP) \\
 & + \frac{\varrho\omega_1}{\tau\lambda_1} \left(1 - \frac{N_2}{N}\right) (d_N \Delta N + \lambda_1 MN - \alpha_1 N) + \frac{\varrho\omega_2}{\tau\lambda_2} (d_P \Delta P + \lambda_2 MP - \alpha_2 P).
 \end{aligned} \tag{45}$$

Collecting terms of equation (45), we get

$$\begin{aligned}
 \frac{\partial\Pi_2}{\partial t} = & \left(1 - \frac{K_2}{K}\right) (\delta - \xi K) + \mu K_2 M - \frac{\mu KML_2}{L} + \varrho L_2 - \frac{\varrho\eta}{\tau} M - \varrho \frac{M_2 L}{M} + \frac{\varrho\eta}{\tau} M_2 \\
 & + \frac{\varrho\omega_1}{\tau} M_2 N + \frac{\varrho\omega_2}{\tau} M_2 P - \frac{\varrho\omega_1\alpha_1}{\tau\lambda_1} N - \frac{\varrho\omega_1}{\tau} N_2 M + \frac{\varrho\omega_1\alpha_1}{\tau\lambda_1} N_2 - \frac{\varrho\omega_2\alpha_2}{\tau\lambda_2} P \\
 & + d_K \left(1 - \frac{K_2}{K}\right) \Delta K + d_L \left(1 - \frac{L_2}{L}\right) \Delta L + \frac{\varrho d_M}{\tau} \left(1 - \frac{M_2}{M}\right) \Delta M + \frac{\varrho\omega_1 d_N}{\tau\lambda_1} \left(1 - \frac{N_2}{N}\right) \Delta N
 \end{aligned}$$

$$\begin{aligned}
& + \frac{\varrho \omega_2 d_P}{\tau \lambda_2} \Delta P = \left(1 - \frac{K_2}{K}\right) (\delta - \xi K) + \left(\mu K_2 - \frac{\varrho \eta}{\tau} - \frac{\varrho \omega_1}{\tau} N_2\right) M + \frac{\varrho \omega_1}{\tau} \left(M_2 - \frac{\alpha_1}{\lambda_1}\right) N \\
& - \frac{\mu K M L_2}{L} + \varrho L_2 - \varrho \frac{M_2 L}{M} + \frac{\varrho \eta}{\tau} M_2 + \frac{\varrho \omega_2}{\tau} M_2 P + \frac{\varrho \omega_1 \alpha_1}{\tau \lambda_1} N_2 - \frac{\varrho \omega_2 \alpha_2}{\tau \lambda_2} P \\
& + d_K \left(1 - \frac{K_2}{K}\right) \Delta K + d_L \left(1 - \frac{L_2}{L}\right) \Delta L + \frac{\varrho d_M}{\tau} \left(1 - \frac{M_2}{M}\right) \Delta M \\
& + \frac{\varrho \omega_1 d_N}{\tau \lambda_1} \left(1 - \frac{N_2}{N}\right) \Delta N + \frac{\varrho \omega_2 d_P}{\tau \lambda_2} \Delta P.
\end{aligned} \tag{46}$$

Applying the equilibrium conditions,

we get

$$\begin{aligned}
\delta &= \xi K_2 + \mu K_2 M_2, \\
\varrho L_2 &= \mu K_2 M_2, \\
\tau L_2 &= \eta M_2 + \omega_1 M_2 N_2, \\
M_2 &= \frac{\alpha_1}{\lambda_1},
\end{aligned} \tag{47}$$

$$\begin{aligned}
\frac{\partial \Pi_2}{\partial t} &= \frac{\xi (K - K_2)^2}{K} + \varrho L_2 \left(1 - \frac{K_2}{K}\right) - \varrho L_2 \frac{K M L_2}{K_2 M_2 L} - \varrho L_2 \frac{M_2 L}{M L_2} + 2 \varrho L_2 + \frac{\varrho \omega_2}{\tau} \\
&\cdot (M_2 - M_3) P + d_K \left(1 - \frac{K_2}{K}\right) \Delta K + d_L \left(1 - \frac{L_2}{L}\right) \Delta L + \frac{\varrho d_M}{\tau} \left(1 - \frac{M_2}{M}\right) \Delta M + \frac{\varrho \omega_1 d_N}{\tau \lambda_1} \\
&\cdot \left(1 - \frac{N_2}{N}\right) \Delta N + \frac{\varrho \omega_2 d_P}{\tau \lambda_2} \Delta P = \frac{\xi (K - K_2)^2}{K} + \varrho L_2 \left[3 - \frac{K_2}{K} - \frac{K M L_2}{K_2 M_2 L} - \frac{M_2 L}{M L_2} \right] \\
&+ \frac{\varrho \omega_2 (\xi \lambda_2 + \mu \alpha_2)}{\tau \mu \lambda_2 \mathcal{R}_1} (\mathcal{R}_2 - \mathcal{R}_1) P + d_K \left(1 - \frac{K_2}{K}\right) \Delta K + d_L \left(1 - \frac{L_2}{L}\right) \Delta L \\
&+ \frac{\varrho d_M}{\tau} \left(1 - \frac{M_2}{M}\right) \Delta M + \frac{\varrho \omega_1 d_N}{\tau \lambda_1} \left(1 - \frac{N_2}{N}\right) \Delta N + \frac{\varrho \omega_2 d_P}{\tau \lambda_2} \Delta P.
\end{aligned} \tag{48}$$

Calculate the time derivative of $\tilde{\Pi}_2(t)$ and use equality (30) to get

$$\begin{aligned}
\frac{d\tilde{\Pi}_2}{dt} &= -\xi \int_{\Gamma} \frac{(K - K_2)^2}{K} du + \varrho L_2 \int_{\Gamma} \left[3 - \frac{K_2}{K} - \frac{K M L_2}{K_2 M_2 L} - \frac{M_2 L}{M L_2} \right] du + \frac{\varrho \omega_2 (\xi \lambda_2 + \mu \alpha_2)}{\tau \mu \lambda_2 \mathcal{R}_1} \\
&\cdot (\mathcal{R}_2 - \mathcal{R}_1) \int_{\Gamma} P du + d_K \int_{\Gamma} \left(1 - \frac{K_2}{K}\right) \Delta K du + d_L \int_{\Gamma} \left(1 - \frac{L_2}{L}\right) \Delta L du + \frac{\varrho d_M}{\tau} \int_{\Gamma} \left(1 - \frac{M_2}{M}\right) \Delta M du \\
&+ \frac{\varrho \omega_1 d_N}{\tau \lambda_1} \int_{\Gamma} \left(1 - \frac{N_2}{N}\right) \Delta N du + \frac{\varrho \omega_2 d_P}{\tau \lambda_2} \int_{\Gamma} \Delta P du = -\xi \int_{\Gamma} \frac{(K - K_2)^2}{K} du
\end{aligned}$$

$$\begin{aligned}
& + \varrho L_2 \int_{\Gamma} \left[3 - \frac{K_2}{K} - \frac{KML_2}{K_2M_2L} - \frac{M_2L}{ML_2} \right] du + \frac{\varrho \bar{\omega}_2 (\xi \lambda_2 + \mu \alpha_2)}{\tau \mu \lambda_2 \mathcal{R}_1} (\mathcal{R}_2 - \mathcal{R}_1) \int_{\Gamma} P du \\
& - d_K K_2 \int_{\Gamma} \frac{\|\nabla K\|^2}{K^2} du - d_L L_2 \int_{\Gamma} \frac{\|\nabla L\|^2}{L^2} du - \frac{\varrho d_M M_2}{\tau} \int_{\Gamma} \frac{\|\nabla M\|^2}{M^2} du - \frac{\varrho \bar{\omega}_1 d_N N_2}{\tau \lambda_1} \int_{\Gamma} \frac{\|\nabla N\|^2}{N^2} du.
\end{aligned} \tag{49}$$

Since $\mathcal{R}_2 \leq \mathcal{R}_1$, then using inequality (28), we obtain $d\tilde{\Pi}_2/dt \leq 0$ for all $(K, L, M, N, P) > 0$. Furthermore, $d\tilde{\Pi}_2/dt \leq 0$ at $(K, L, M, N, P) = (K_2, L_2, M_2, N_2, 0)$. The solutions of (2)–(6) tend to $Y'_2 = \{\Omega_2\}$. It follows that Ω_2 is GAS by using LLIP. $\square$

Theorem 6. Let $\mathcal{R}_2 > 1$ and $\mathcal{R}_1 \leq \mathcal{R}_2$, then Ω_3 is GAS.

Proof. Define $\Pi_3(u, t)$ as

$$\begin{aligned}
\Pi_3(u, t) &= K_3 g\left(\frac{K}{K_3}\right) + L_3 g\left(\frac{L}{L_3}\right) + \frac{\varrho}{\tau} M_3 g\left(\frac{M}{M_3}\right) \\
&+ \frac{\varrho \bar{\omega}_1}{\tau \lambda_1} N + \frac{\varrho \bar{\omega}_2}{\tau \lambda_2} P_3 g\left(\frac{P}{P_3}\right).
\end{aligned} \tag{50}$$

Calculating $\partial \Pi_3 / \partial t$ along the solutions of models (2)–(6), we get

$$\begin{aligned}
\frac{\partial \Pi_3}{\partial t} &= \left(1 - \frac{K_3}{K}\right) (d_K \Delta K + \delta - \xi K - \mu KM) + \left(1 - \frac{L_3}{L}\right) (d_L \Delta L + \mu KM - \varrho L) \\
&+ \frac{\varrho}{\tau} \left(1 - \frac{M_3}{M}\right) (d_M \Delta M + \tau L - \eta M - \bar{\omega}_1 MN - \bar{\omega}_2 MP) \\
&+ \frac{\varrho \bar{\omega}_1}{\tau \lambda_1} (d_N \Delta N + \lambda_1 MN - \alpha_1 N) + \frac{\varrho \bar{\omega}_2}{\tau \lambda_2} \left(1 - \frac{P_3}{P}\right) (d_P \Delta P + \lambda_2 MP - \alpha_2 P).
\end{aligned} \tag{51}$$

Collecting terms, we get

$$\begin{aligned}
\frac{\partial \Pi_3}{\partial t} &= \left(1 - \frac{K_3}{K}\right) (\delta - \xi K) + \mu K_3 M - \frac{\mu KML_3}{L} + \varrho L_3 - \frac{\varrho \eta}{\tau} M - \varrho \frac{M_3 L}{M} \\
&+ \frac{\varrho \eta}{\tau} M_3 + \frac{\varrho \bar{\omega}_1}{\tau} M_3 N + \frac{\varrho \bar{\omega}_2}{\tau} M_3 P - \frac{\varrho \bar{\omega}_1 \alpha_1}{\tau \lambda_1} N - \frac{\varrho \bar{\omega}_2 \alpha_2}{\tau \lambda_2} P \\
&- \frac{\varrho \bar{\omega}_2}{\tau} P_3 M + \frac{\varrho \bar{\omega}_2 \alpha_2}{\tau \lambda_2} P_3 + d_K \left(1 - \frac{K_3}{K}\right) \Delta K + d_L \left(1 - \frac{L_3}{L}\right) \Delta L \\
&+ \frac{\varrho d_M}{\tau} \left(1 - \frac{M_3}{M}\right) \Delta M + \frac{\varrho \bar{\omega}_1 d_N}{\tau \lambda_1} \Delta N + \frac{\varrho \bar{\omega}_2 d_P}{\tau \lambda_2} \left(1 - \frac{P_3}{P}\right) \Delta P.
\end{aligned} \tag{52}$$

Applying the equilibrium conditions of Ω_3 ,

$$\begin{aligned}
\delta &= \xi K_3 + \mu K_3 M_3, \\
\varrho L_3 &= \mu K_3 M_3, \\
\tau L_3 &= \eta M_3 + \bar{\omega}_2 M_3 P_3, \\
\alpha_2 P_3 &= \lambda_2 M_3 P_3,
\end{aligned} \tag{53}$$

we get

$$\begin{aligned}
\frac{\partial \Pi_3}{\partial t} = & -\frac{\xi(K-K_3)^2}{K} + \varrho L_3 \left(1 - \frac{K_3}{K}\right) - \varrho L_3 \frac{KML_3}{K_3M_3L} - \varrho L_3 \frac{M_3L}{ML_3} + 2\varrho L_3 \\
& + \frac{\varrho \bar{\omega}_1}{\tau} (M_3 - M_2)N + d_K \left(1 - \frac{K_3}{K}\right) \Delta K + d_L \left(1 - \frac{L_3}{L}\right) \Delta L + \frac{\varrho d_M}{\tau} \left(1 - \frac{M_3}{M}\right) \Delta M \\
& + \frac{\varrho \bar{\omega}_1 d_N}{\tau \lambda_1} \Delta N + \frac{\varrho \bar{\omega}_2 d_P}{\tau \lambda_2} \left(1 - \frac{P_3}{P}\right) \Delta P = -\frac{\xi(K-K_3)^2}{K} + \varrho L_3 \left[3 - \frac{K_3}{K} - \frac{KML_3}{K_3M_3L} - \frac{M_3L}{ML_3}\right] \\
& + \frac{\varrho \bar{\omega}_1 (\xi \lambda_2 + \mu \alpha_2)}{\tau \mu \lambda_2 \mathcal{R}_1} (\mathcal{R}_1 - \mathcal{R}_2)N + d_K \left(1 - \frac{K_3}{K}\right) \Delta K + d_L \left(1 - \frac{L_3}{L}\right) \Delta L \\
& + \frac{\varrho d_M}{\tau} \left(1 - \frac{M_3}{M}\right) \Delta M + \frac{\varrho \bar{\omega}_1 d_N}{\tau \lambda_1} \Delta N + \frac{\varrho \bar{\omega}_2 d_P}{\tau \lambda_2} \left(1 - \frac{P_3}{P}\right) \Delta P.
\end{aligned} \tag{54}$$

Calculating the time derivative of $\tilde{\Pi}_3(t)$ and using equality (30), we obtain

$$\begin{aligned}
\frac{d\tilde{\Pi}_3}{dt} = & -\xi \int_{\Gamma} \frac{(K-K_3)^2}{K} du + \varrho L_3 \int_{\Gamma} \left[3 - \frac{K_3}{K} - \frac{KML_3}{K_3M_3L} - \frac{M_3L}{ML_3}\right] du + \frac{\varrho \bar{\omega}_1 (\xi \lambda_2 + \mu \alpha_2)}{\tau \mu \lambda_2 \mathcal{R}_1} \\
& \cdot (\mathcal{R}_1 - \mathcal{R}_2) \int_{\Gamma} N du + d_K \int_{\Gamma} \left(1 - \frac{K_3}{K}\right) \Delta K du + d_L \int_{\Gamma} \left(1 - \frac{L_3}{L}\right) \Delta L du + \frac{\varrho d_M}{\tau} \int_{\Gamma} \left(1 - \frac{M_3}{M}\right) \Delta M du \\
& + \frac{\varrho \bar{\omega}_1 d_N}{\tau \lambda_1} \int_{\Gamma} \Delta N du + \frac{\varrho \bar{\omega}_2 d_P}{\tau \lambda_2} \int_{\Gamma} \left(1 - \frac{P_3}{P}\right) \Delta P du = -\xi \int_{\Gamma} \frac{(K-K_3)^2}{K} du \\
& + \varrho L_3 \int_{\Gamma} \left[3 - \frac{K_3}{K} - \frac{KML_3}{K_3M_3L} - \frac{M_3L}{ML_3}\right] du + \frac{\varrho \bar{\omega}_1 (\xi \lambda_2 + \mu \alpha_2)}{\tau \mu \lambda_2 \mathcal{R}_1} (\mathcal{R}_1 - \mathcal{R}_2) \\
& \cdot \int_{\Gamma} N du - d_K K_3 \int_{\Gamma} \frac{\|\nabla K\|^2}{K^2} du - d_L L_3 \int_{\Gamma} \frac{\|\nabla L\|^2}{L^2} du - \frac{\varrho d_M M_3}{\tau} \int_{\Gamma} \frac{\|\nabla M\|^2}{M^2} du \\
& - \frac{\varrho \bar{\omega}_2 d_P P_3}{\tau \lambda_2} \int_{\Gamma} \frac{\|\nabla P\|^2}{P^2} du.
\end{aligned} \tag{55}$$

Since $\mathcal{R}_1 \leq \mathcal{R}_2$, then using inequality (28), we obtain $d\tilde{\Pi}_3/dt \leq 0$, for all $(K, L, M, N, P) > 0$. Furthermore, $d\tilde{\Pi}_3/dt \leq 0$ at $(K, L, M, N, P) = (K_3, L_3, M_3, 0, P_3)$. The solutions of (2)–(6) tend to $Y'_3 = \{\Omega_3\}$. It follows that Ω_3 is GAS by using LLIP. $\square$

6. Numerical Simulations

In this section, we numerically illustrate the global stability of equilibria by choosing the domain Γ as $\Gamma = [0, 2]$ with a step size 0.02. The step size for time is given by 0.1. Following the works presented in [31, 48–50], we consider the following initial conditions for systems (2)–(6):

$$\begin{aligned}
K(u, 0) &= 500 \left[1 + 0.4 \cos^2(\pi u)\right], \\
L(u, 0) &= 30 \left[1 + 0.5 \cos^2(\pi u)\right], \\
M(u, 0) &= 4 \left[1 + 0.5 \cos^2(\pi u)\right], \\
N(u, 0) &= 2 \left[1 + 0.5 \cos^2(\pi u)\right], \\
P(u, 0) &= 2 \left[1 + 0.5 \cos^2(\pi u)\right], \quad u \in [0, 2].
\end{aligned} \tag{56}$$

The initial values are arbitrarily chosen as the global stability of the equilibria presented in Theorems 3–6 guarantees the convergence regardless of the selected initial conditions.

In addition, we consider the following homogeneous Neumann boundary conditions:

FIGURE 1: Taking Strategy 1 ($\mathcal{R}_0 \leq 1$), the equilibrium $\Omega_0 = (1000, 0, 0, 0, 0)$ is asymptotically stable. (a) Target cells. (b) DENV-infected cells. (c) DENV particles. (d) Heterologous antibodies. (e) Homologous antibodies.

$$\frac{\partial K}{\partial \mathcal{B}} = \frac{\partial L}{\partial \mathcal{B}} = \frac{\partial M}{\partial \mathcal{B}} = \frac{\partial N}{\partial \mathcal{B}} = \frac{\partial P}{\partial \mathcal{B}} = 0, \quad t > 0, u = 0, 2. \quad (57)$$

We are using the following values of the parameters: $\delta = 10$, $\xi = 0.01$, $\varrho = 0.3$, $\tau = 5$, $\eta = 3$, $\omega_1 = 0.3$, $\omega_2 = 0.1$, $\alpha_1 = 0.1$, and $\alpha_2 = 0.1$. The parameters μ , λ_1 , and λ_2 will be selected according to the following strategies:

Strategy 1. (Stability of Ω_0) $\mu = 0.00004$, $\lambda_1 = 0.0005$, and $\lambda_2 = 0.001$. For this set of parameters, we have $\mathcal{R}_0 = 0.2778 < 1$, $\mathcal{R}_1 = 0.1389 < 1$, and $\mathcal{R}_2 = 0.1852 < 1$. Figure 1 shows that the solution of systems (2)–(6) converges to the equilibrium $\Omega_0 = (1000, 0, 0, 0, 0)$. This shows that Ω_0 is GAS according to Theorem 3. In this case, the DENV will be cleared.

Strategy 2. (Stability of Ω_1) $\mu = 0.0004$, $\lambda_1 = 0.0005$, and $\lambda_2 = 0.001$. With such choice, we get $\mathcal{R}_0 = 2.2222 > 1$, $\mathcal{R}_1 = 0.2469 < 1$, and $\mathcal{R}_2 = 0.4444 < 1$. Theorem 4 implies that $\Omega_1 = (450, 18.333, 30.556, 0, 0)$ is GAS which is displayed in Figure 2. This will lead to the situation of persistent DENV infection but with an ineffective antibody immune response.

Strategy 3. (Stability of Ω_2) $\mu = 0.0004$, $\lambda_1 = 0.005$, and $\lambda_2 = 0.001$. Then, we compute $\mathcal{R}_0 = 2.2222 > 1$, $\mathcal{R}_1 = 1.2346 > 1$, and $\mathcal{R}_2 = 0.4444 < \mathcal{R}_1$. Numerical results show that $\Omega_2 = (555.556, 14.815, 20, 2.346, 0)$ exists. Moreover, Figure 3 shows that Ω_2 is GAS which supports Theorem 5. Therefore, a persistent DENV infection with only effective heterologous antibody immune response is reached.

FIGURE 2: Taking Strategy 1 ($\mathcal{R}_1 \leq 1 < \mathcal{R}_0$ and $\mathcal{R}_2 \leq 1$), the equilibrium $\Omega_1 = (450, 18.333, 30.556, 0, 0)$ is asymptotically stable. (a) Target cells. (b) DENV-infected cells. (c) DENV particles. (d) Heterologous antibodies. (e) Homologous antibodies.

FIGURE 3: Continued.

FIGURE 3: Taking Strategy 1 ($\mathcal{R}_1 > 1$ and $\mathcal{R}_2 \leq \mathcal{R}_1$), the equilibrium $\Omega_2 = (555.556, 14.815, 20, 2.346, 0)$ is asymptotically stable. (a) Target cells. (b) DENV-infected cells. (c) DENV particles. (d) Heterologous antibodies. (e) Homologous antibodies.

FIGURE 4: Continued.

FIGURE 4: Taking Strategy 1 ($\mathcal{R}_2 > 1$ and $\mathcal{R}_1 \leq \mathcal{R}_2$), the equilibrium $\Omega_3 = (833.333, 5.556, 5, 0, 25.556)$ is asymptotically stable. (a) Target cells. (b) DENV-infected cells. (c) DENV particles. (d) Heterologous antibodies. (e) Homologous antibodies.

Strategy 4. (Stability of Ω_3) $\mu = 0.0004$, $\lambda_1 = 0.01$, and $\lambda_2 = 0.02$. Then, we compute $\mathcal{R}_0 = 2.2222 > 1$, $\mathcal{R}_1 = 1.5873 > 1$, and $\mathcal{R}_2 = 0.8519 > \mathcal{R}_1$. According to these data, Ω_3 exists with $\Omega_3 = (833.333, 5.556, 5, 0, 25.556)$. In Figure 4, we show that Ω_3 is GAS which is consistent with Theorem 6. In this case, a persistent DENV single infection with only effective homologous antibody immune response is reached.

7. Conclusion

A dynamical model to capture the behavior of secondary DENV infection was studied. The model incorporated the spatial mobility of DENV particles and cells. The model was given by five PDEs to describe the interaction between five compartments, target cells, DENV-infected cells, DENV particles, heterologous antibodies, and homologous antibodies. We first established that the model is biologically relevant by showing that the key variables of the model are nonnegative and bounded. We found that the model has four equilibria Ω_i , $i = 1, 2, 3, 4$, and their existence and global stability are governed by three threshold parameters, $\mathcal{R}_i$, $i = 1, 2, 3$. We performed the global stability analysis of the four equilibria by constructing suitable Lyapunov functions. We conducted some numerical simulations and found that

the numerical results are fully aligned with the theoretical results. We summarize the obtained results in the following:

- (i) The infection-free equilibrium Ω_0 always exists, and it is GAS if $\mathcal{R}_0 \leq 1$. This case corresponds to the healthy state where the DENV particles are cleared.
- (ii) The persistent DENV infection equilibrium with ineffective antibodies Ω_1 exists if $\mathcal{R}_0 > 1$, and it is GAS if $\mathcal{R}_1 \leq 1$ and $\mathcal{R}_2 \leq 1$. At this point, the DENV infection exists while the immune response is not active.
- (iii) The persistent DENV infection equilibrium with only effective heterologous antibody Ω_2 exists if $\mathcal{R}_1 > 1$, and it is GAS if $\mathcal{R}_2 \leq \mathcal{R}_1$. This case leads to the situation where the DENV infection is chronic, while only heterologous antibody immune response is working.
- (iv) The persistent DENV infection equilibrium with only effective homologous antibody Ω_3 exists if $\mathcal{R}_2 > 1$, and it is GAS if $\mathcal{R}_1 \leq \mathcal{R}_2$. At this point, the DENV infection is chronic with only an active homologous antibody immune response.

Our model can be extended to take into account the time delays during the DENV infection as

$$\begin{aligned}
 \frac{\partial K(u, t)}{\partial t} &= d_K \Delta K(u, t) + \delta - \mu K(u, t)M(u, t) - \xi K(u, t), \\
 \frac{\partial L(u, t)}{\partial t} &= d_L \Delta L(u, t) + \mu e^{-k_1 \psi_1} K(u, t - \psi_1)M(u, t - \psi_1) - \varrho L(u, t), \\
 \frac{\partial M(u, t)}{\partial t} &= d_M \Delta M(u, t) + \tau e^{-k_2 \psi_2} L(u, t - \psi_2) - \eta M(u, t) - \omega_1 M(u, t) \\
 &\quad \cdot N(u, t) - \omega_2 M(u, t)P(u, t), \\
 \frac{\partial N(u, t)}{\partial t} &= d_N \Delta N(u, t) + \lambda_1 M(u, t)N(u, t) - \alpha_1 N(u, t), \\
 \frac{\partial P(u, t)}{\partial t} &= d_P \Delta P(u, t) + \lambda_2 M(u, t)P(u, t) - \alpha_2 P(u, t).
 \end{aligned} \tag{58}$$

Here, it is assumed that a DENV contacts a target cell at time $t - \psi_1$, and the cell becomes infected at time t . Moreover, an infected cell at $t - \psi_2$ produces new infectious DENV particles at time t . The factors $e^{-k_i \psi_i}$, $i = 1, 2$, represent the survival rates of the cells during the delay periods.

Data Availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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