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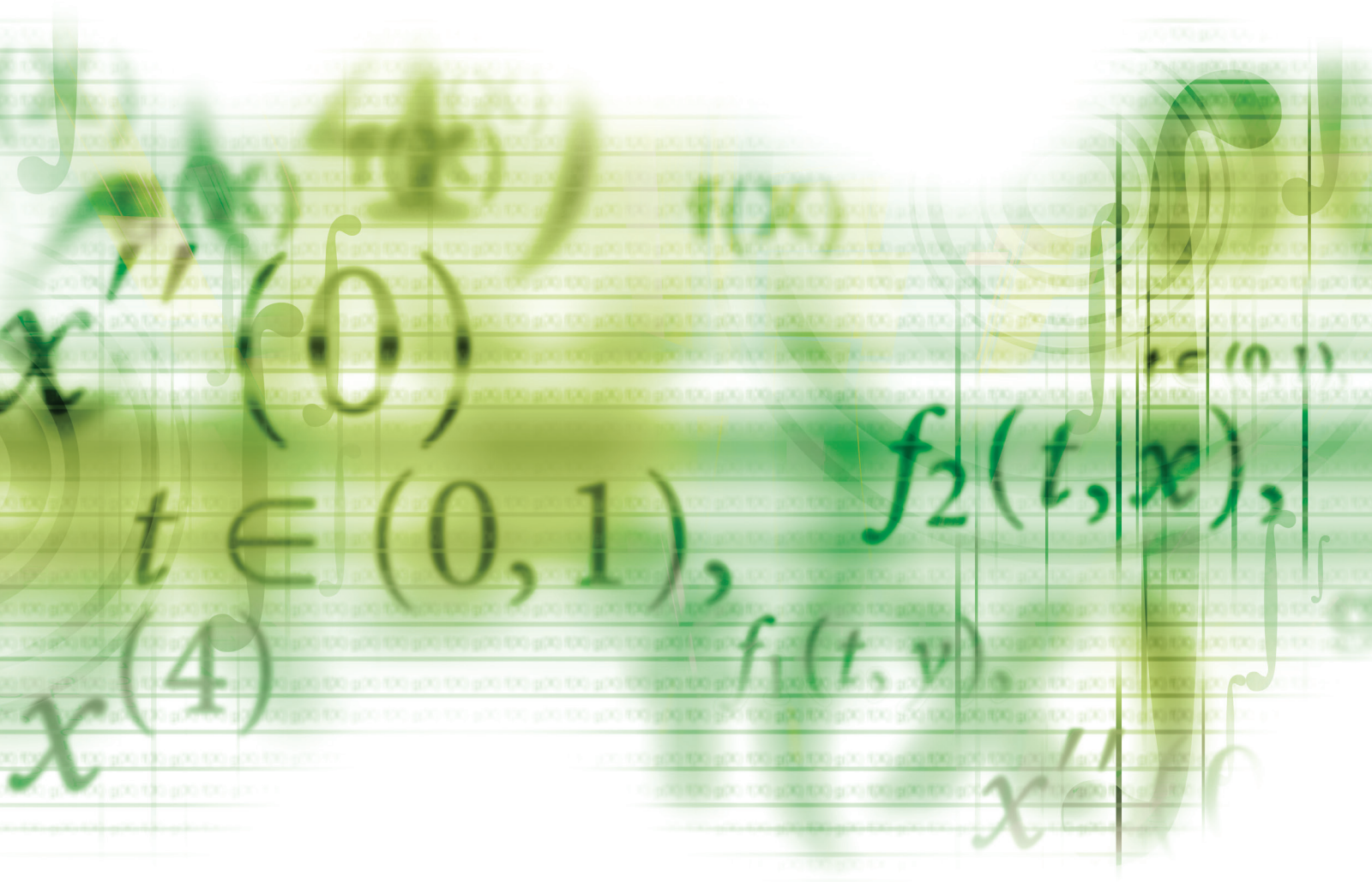
Mathematical Modeling in Virology by Differential Equations

Lead Guest Editor: Khalid Hattaf
Guest Editors: Ahmed M. Elaiw, Abid A. Lashari, and Noura Yousfi



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Editorial Board

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Editorial

Mathematical Modeling in Virology by Differential Equations

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Viruses are microscopic organisms that need to penetrate inside a cell of their host to multiply and replicate. Various viruses infect directly the human body such as the human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). There are also viruses that affect the human body through a living vector such as West Nile virus which is a virus most commonly spread to people by mosquito bites. Infectious diseases caused by these viruses represent a major global health problem by causing mortality of millions of people and expenditure of enormous amount of money in health care and disease control. In this special issue, many mathematical models, ordinary differential equations (ODEs), delay differential equations (DDEs), partial differential equations (PDEs), and fractional differential equations (FDEs), have been proposed and developed to better describe the dynamics of these infectious diseases and establish control strategies to limit their evolution and spread.

One paper of this special issue proposes a mathematical model with ODEs and PDEs to describe the dynamics of vector-borne diseases such as West Nile virus, malaria, and dengue. The proposed model incorporates the waning of vaccine-induced immunity. Furthermore, the global stability of the equilibria of the model is established. More precisely, it is proved that when the basic reproduction number is less than one, the disease-free equilibrium is globally asymptotically stable, which implies that the disease dies out. However, when the basic reproduction number is larger than one, the endemic equilibrium is globally asymptotically stable, which means that the disease persists in the population.

Another paper presents a delayed model formulated by DDEs in order to study the early stage of HBV infection and impact of the delay in the infection process on the adaptive immune response, which includes cytotoxic T lymphocytes (CTL) cells and antibodies. The stability analysis of equilibria and the optimal treatment strategies are investigated.

Another paper focuses on the qualitative analysis of a generalized virus dynamics model with distributed delays and two modes of transmission, one by virus-to-cell infection and the other by cell-to-cell transmission. The infection transmission process is modeled by general incidence functions for both modes of transmission. Moreover, many known viral infection models with discrete and distributed delays are extended and improved.

Another paper deals with a family of periodic SEIRS epidemic models. The global dynamics of these models is fully determined by a threshold parameter, namely, the basic reproduction number. Numerical simulations are carried out to support the theoretical results.

Another paper of this special issue proposes a fractional order model of HIV infection with specific functional response and cure rate. This functional response covers the most functional responses used by several authors such as the saturated incidence rate, the Beddington-DeAngelis functional response, and the Crowley-Martin functional

response. It is shown that the model is mathematically and biologically well-posed. In addition, the local and global stabilities of the equilibria are investigated.

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Research Article

On the Global Dynamics of a Vector-Borne Disease Model with Age of Vaccination

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We study a vector-borne disease with age of vaccination. A nonlinear incidence rate including mass action and saturating incidence as special cases is considered. The global dynamics of the equilibria are investigated and we show that if the basic reproduction number is less than 1, then the disease-free equilibrium is globally asymptotically stable; that is, the disease dies out, while if the basic reproduction number is larger than 1, then the endemic equilibrium is globally asymptotically stable, which means that the disease persists in the population. Using the basic reproduction number, we derive a vaccination coverage rate that is required for disease control and elimination.

1. Introduction

Many of infections that have the important impact on human health in terms of mortality or morbidity are vector-borne disease. Mosquitoes [1] are perhaps the best known disease vectors, with various species playing a role in the transmission of infections such as malaria, yellow fever, dengue fever, and West Nile virus. One of the effective methods in disease prevention is the vaccination [2–5]. Several studies in the literature have been carried out to investigate the role of treatment and vaccination of the spread of diseases ([6–8] and the references therein). An epidemic model with vaccination for measles is derived by Linda [9]. The effect of vaccination on the spread of periodic diseases, using discrete-time model, was studied by Mickens [10].

The impact of vaccination in two SVIR models with permanent immunity is studied by Liu et al. [11]. Xiao and Tang [12] have shown from an SIV model that complex dynamics are induced by imperfect vaccination. Gumel and Moghadas [13] investigated a disease transmission model by considering the impact of a protective vaccine and found the optimal vaccine coverage threshold required for disease control and elimination. The eradicating of an SEIRS epidemic model by using vaccine was studied by Gao et al. [14]. Yang et al. [8] derived a threshold value for the vaccination coverage of an SIVS epidemic model. Many previous studies have shown that the reemergence of some diseases is caused by the waning of vaccine-induced immunity [15–17]. A consequence of this is that it is important for health authorities to take into account waning of vaccine-induced immunity in the disease control and elimination campaign.

In this paper, we consider a vector-borne disease model such as malaria that incorporates the waning of vaccine-induced immunity. Additionally, we use incidences with a nonlinear response to the number of infectious individuals and infectious vectors. The incidences take the form $Sf(I)$ and $Sg(I)$, respectively, for the human and vector populations. We assume that f and g satisfy the following assumptions:

(**H1**) For $x \in \mathbb{R}^+$, $f(x) \geq 0$ with equality if and only if $x = 0$, $f'(x) \geq 0$, and $f''(x) \leq 0$.

(**H2**) For $x \in \mathbb{R}^+$, $g(x) \geq 0$ with equality if and only if $x = 0$, $g'(x) \geq 0$, and $g''(x) \leq 0$.

From the above assumptions and the Mean Value Theorem, it follows that

$$\begin{aligned} f'(x)\,x \leq f(x) \leq f'(0)\,x, \\ g'(x)\,x \leq g(x) \leq g'(0)\,x. \end{aligned} \tag{1}$$

Let S_h, I_h, and R_h denote, respectively, the number of susceptible, infectious, and removed host individuals and S_v, I_v the number of susceptible and infectious vectors. The susceptible individuals are vaccinated at the rate $\theta \geq 0$. $v(t,a)$ denotes the population size of the vaccinated compartment at time t with the vaccine age a. Let $\epsilon(a)$ be the rate at which the vaccine-induced immunity wanes. We assume that $\epsilon(a)$ and the following assumption:

(**H3**) $\epsilon : [0,\infty) \to [0,\infty)$ is bounded, nondecreasing, and piecewise continuous with possibly many finite jumps.

We consider a relatively isolated community where there is no immigration or emigration. Additionally, we assume that all the newly recruited, including the newborns, are susceptibles. Let, at any time t, Λ_h and Λ_v be the recruitment rate of host individuals and vectors, respectively. μ_h and μ_v are, respectively, the natural death rate of host individuals and vectors. Let γ be the natural recovery rate from the infected population and δ the disease induced death rate of host individuals. The number of individuals moving from the vaccinated class into the susceptible class at time t is $\int_0^{+\infty} v(t,a)da$. From the above assumptions, we formulate our vector-borne epidemic model in the following way:

$$\begin{aligned}
\frac{dS_h(t)}{dt} &= \Lambda_h - \mu_h S_h(t) - S_h(t) f\left(I_v(t)\right) \\
&\quad - \theta S_h(t) + \int_0^{\infty} \epsilon(a)\, v(t,a)\, da, \\
\frac{dI_h(t)}{dt} &= S_h(t) f\left(I_v(t)\right) \\
&\quad - \left(\mu_h + \gamma + \delta\right) I_h(t), \\
\frac{dR_h(t)}{dt} &= \gamma I_h(t) - \mu_h R_h(t), \\
\frac{\partial v(t,a)}{\partial t} + \frac{\partial v(t,a)}{\partial a} &= -\left(\mu_h + \epsilon(a)\right) v(t,a), \\
\frac{dS_v(t)}{dt} &= \Lambda_v - \mu_v S_v(t) - S_v(t)\, g\left(I_h(t)\right), \\
\frac{dI_v(t)}{dt} &= S_v(t)\, g\left(I_h(t)\right) - \mu_v I_v(t), \\
v(t,0) &= \theta S_h(t), \\
S_h(0) &= S_{h0} \geq 0, \\
I_h(0) &= I_{h0} > 0, \\
R_h(0) &= R_{h0} \geq 0, \\
v(0,\cdot) &= v_0(\cdot) \in L^1_+, \\
S_v(0) &= S_{v0} \geq 0, \\
I_v(0) &= I_{v0} > 0,
\end{aligned} \tag{2}$$

where L^1_+ is the set of integrable functions from $(0,\infty)$ into $\mathbb{R}^+ = [0,\infty)$. Since the removed host individual population does not appear in the remaining equations of system (2), it is sufficient to consider the following system:

$$\begin{aligned}
\frac{dS_h(t)}{dt} &= \Lambda_h - \mu_h S_h(t) - S_h(t) f\left(I_v(t)\right) \\
&\quad - \theta S_h(t) + \int_0^{\infty} \epsilon(a)\, v(t,a)\, da, \\
\frac{dI_h(t)}{dt} &= S_h(t) f\left(I_v(t)\right) \\
&\quad - \left(\mu_h + \gamma + \delta\right) I_h(t), \\
\frac{\partial v(t,a)}{\partial t} + \frac{\partial v(t,a)}{\partial a} &= -\left(\mu_h + \epsilon(a)\right) v(t,a), \\
\frac{dS_v(t)}{dt} &= \Lambda_v - \mu_v S_v(t) - S_v(t)\, g\left(I_h(t)\right), \\
\frac{dI_v(t)}{dt} &= S_v(t)\, g\left(I_h(t)\right) - \mu_v I_v(t), \\
v(t,0) &= \theta S_h(t), \\
S_h(0) &= S_{h0} \geq 0, \\
I_h(0) &= I_{h0} > 0, \\
R_h(0) &= R_{h0} \geq 0, \\
v(0,\cdot) &= v_0(\cdot) \in L^1_+, \\
S_v(0) &= S_{v0} \geq 0, \\
I_v(0) &= I_{v0} > 0.
\end{aligned} \tag{3}$$

From [18, 19], we state that system (3) has a unique continuous solution if the initial conditions satisfy the compatibility condition

$$v_0(0) = \theta S_{h0}. \tag{4}$$

In the remaining part of this paper, we always assume that condition (4) is satisfied. The existence and the nonnegativity of the solution of (3) can be reached in Browne and Pilyugin [20]. We next introduce a semiflow solution of system (3).

Define

$$\begin{aligned}
\chi &= \mathbb{R} \times \mathbb{R} \times \mathbb{R} \times L^1\left((0,+\infty), \mathbb{R}\right) \times \mathbb{R} \times \mathbb{R}, \\
\chi^+ &= \mathbb{R}^+ \times \mathbb{R}^+ \times \mathbb{R} \times L^1_+\left((0,+\infty), \mathbb{R}\right) \times \mathbb{R}^+ \times \mathbb{R}^+,
\end{aligned} \tag{5}$$

and consider the linear operator $A : \mathrm{dom}(A) \subset \chi \to \chi$ defined by

$$A\begin{pmatrix} S_h \\ I_h \\ \begin{pmatrix} 0 \\ v \end{pmatrix} \\ S_v \\ I_v \end{pmatrix} = \begin{pmatrix} -\left(\mu_h + \theta\right) S_h \\ -\left(\mu_h + \gamma + \delta\right) I_h \\ \begin{pmatrix} -v(0) \\ -v' - \left(\mu_h + \epsilon(a)\right) v \end{pmatrix} \\ -\mu_v S_v \\ -\mu_v I_v \end{pmatrix}, \tag{6}$$

with $\mathrm{dom}(A) = \mathbb{R}\times\mathbb{R}\times\{0\}\times W^{1,1}((0,+\infty),\mathbb{R})\times\mathbb{R}\times\mathbb{R}$, where $W^{1,1}$ is a Sobolev space. Then, $\overline{\mathrm{dom}(A)} = \mathbb{R}\times\mathbb{R}\times\{0\}\times L^1((0,+\infty),\mathbb{R})\times\mathbb{R}\times\mathbb{R}$ is not dense in χ. We consider a nonlinear map $F : \overline{\mathrm{dom}(A)} \to \chi$ which is defined by

$$F\begin{pmatrix} S_h \\ I_h \\ \begin{pmatrix} 0 \\ v \end{pmatrix} \\ S_v \\ I_v \end{pmatrix} = \begin{pmatrix} \Lambda_h - S_h(t) f\left(I_v(t)\right) + \int_0^\infty \epsilon(a) v(t,a)\, da \\ S_h(t) f\left(I_v(t)\right) \\ \begin{pmatrix} \theta S_h(t) \\ 0_{L^1} \end{pmatrix} \\ \Lambda_v - S_v(t) g\left(I_h(t)\right) \\ S_v(t) g\left(I_h(t)\right) \end{pmatrix}, \tag{7}$$

and let

$$u(t) = \left(S_h(t), I_h(t), \begin{pmatrix} 0 \\ v(t,\cdot) \end{pmatrix}, S_v(t), I_v(t)\right)^T. \tag{8}$$

Set

$$\begin{aligned} \chi_0 &:= \overline{\mathrm{dom}(A)} \\ &= \mathbb{R}\times\mathbb{R}\times\{0\}\times L^1((0,+\infty),\mathbb{R})\times\mathbb{R}\times\mathbb{R}, \\ \chi_0^+ &:= \overline{\mathrm{dom}(A)} \cap \chi_+ \\ &= \mathbb{R}^+\times\mathbb{R}^+\times\{0\}\times L^1_+((0,+\infty),\mathbb{R})\times\mathbb{R}^+\times\mathbb{R}^+. \end{aligned} \tag{9}$$

Based on the above, we can reformulate system (3) as the following abstract Cauchy problem:

$$\frac{du(t)}{dt} = Au(t) + Fu(t), \quad \text{for } t \geq 0, \text{with } u(0) \in \chi_0^+. \tag{10}$$

By applying the results given in [19, 21], we derive the existence and uniqueness of the semiflow $\{\Phi(t)\}_{t\geq 0}$ on χ_0^+ generated by system (3). By using the theory for dynamical system (see [19]), we can further obtain the following lemma.

Lemma 1. *System (3) generates a unique continuous semiflow $\{\Phi(t)\}_{t\geq 0}$ on χ_0^+ that is asymptotically smooth and bounded dissipative. Furthermore, the semiflow $\{\Phi(t)\}_{t\geq 0}$ has a compact global attractor $\mathscr{B} \subset \chi_0^+$.*

The total population size of human hosts and vectors is, respectively,

$$\begin{aligned} N_h(t) &= S_h(t) + I_h(t) + \int_0^\infty v(t,a)\, da, \\ N_v(t) &= S_v(t) + I_v(t). \end{aligned} \tag{11}$$

Then, from the time derivative of $N_h(t)$ and $N_v(t)$, we get

$$\begin{aligned} \frac{dN_h(t)}{dt} &\leq \Lambda_h - \mu_h N_h(t), \\ \frac{dN_v(t)}{dt} &= \Lambda_v - \mu_v N_v(t), \end{aligned} \tag{12}$$

which implies

$$\begin{aligned} \limsup_{t\to\infty} N_h(t) &\leq \frac{\Lambda_h}{\mu_h}, \\ \limsup_{t\to\infty} N_v(t) &\leq \frac{\Lambda_v}{\mu_v}. \end{aligned} \tag{13}$$

We hence restrict our attention to solutions of (3) with initial conditions in

$$\begin{aligned} \Gamma = \Big\{ &\left(S_{h0}, I_{h0}, S_{v0}, I_{v0}, v_0(\cdot)\right) \in \mathbb{R}^{4+}\times L^1_+ : v_0(0) \\ &= \theta S_{h0},\ N_h(0) \leq \frac{\Lambda_h}{\mu_h},\ N_v(0) \leq \frac{\Lambda_v}{\mu_v} \Big\}. \end{aligned} \tag{14}$$

The rest of the paper is structured as follows. In Section 2, we study the existence and local stability of equilibria of system (3). In Section 3, we present the results for the global dynamics of equilibria of system (3). In Section 4, the paper closes with conclusion.

2. Existence and Local Stability of Equilibria

In this part, we state the result about the existence and local stability of equilibria of the model (3). We first start by the existence of equilibria. We define

$$\xi : \mathbb{R}^+ \longrightarrow \mathbb{R}^+, \tag{15}$$

as

$$\begin{aligned} \xi(a) &= e^{-\mu_h a - \int_0^a \epsilon(s) ds}, \\ \mathscr{A} &= \int_0^\infty \epsilon(a)\xi(a)\, da. \end{aligned} \tag{16}$$

Then,

$$\mathscr{A} \leq \int_0^\infty \epsilon(a) e^{-\int_0^a \epsilon(s) ds} da = 1. \tag{17}$$

Let $(\overline{S}_h, \overline{I}_h, \overline{S}_v, \overline{I}_v, \overline{v}(\cdot))$ be an equilibrium of (3). This implies

$$\begin{aligned} &\Lambda_h - \mu_h \overline{S}_h - \overline{S}_h f\left(\overline{I}_v\right) - \theta \overline{S}_h + \int_0^\infty \epsilon(a)\overline{v}(a)\, da = 0, \\ &\overline{S}_h f\left(\overline{I}_v\right) - \left(\mu_h + \gamma + \delta\right)\overline{I}_h = 0, \\ &\frac{d\overline{v}(a)}{da} = -\left(\mu_h + \epsilon(a)\right)\overline{v}(a), \\ &\Lambda_v - \mu_v \overline{S}_v - \overline{S}_v g\left(\overline{I}_h\right) = 0, \\ &\overline{S}_v g\left(\overline{I}_h\right) - \mu_v \overline{I}_v = 0, \\ &\overline{v}(0) = \theta \overline{S}_h. \end{aligned} \tag{18}$$

From the third and the sixth equations of (18), we deduce that

$$\overline{v}(a) = \theta \overline{S}_h \xi(a). \tag{19}$$

By the first equation of (18), we get

$$\overline{S}_h = \frac{\Lambda_h}{f\left(\overline{I}_v\right) + \mu_h + \theta(1-\mathscr{A})}. \tag{20}$$

From the fourth equation of (18), we have

$$\overline{S}_v = \frac{\Lambda_v}{g\left(\overline{I}_h\right) + \mu_v}. \tag{21}$$

Substituting $\overline{S}_h$ and $\overline{S}_v$ into the second and the fifth equations of (18) gives

$$\begin{aligned} &\Lambda_h f\left(\overline{I}_v\right) - \left(\mu_h + \gamma + \delta\right)\left(\mu_h + \theta(1-\mathscr{A}) + f\left(\overline{I}_v\right)\right)\overline{I}_h \\ &\quad = 0, \\ &\Lambda_v g\left(\overline{I}_h\right) - \mu_v \overline{I}_v\left(\mu_v + g\left(\overline{I}_h\right)\right) = 0. \end{aligned} \tag{22}$$

From the second equation of (22), we obtain

$$\overline{I}_v = \frac{\Lambda_v g\left(\overline{I}_h\right)}{\mu_v\left(\mu_v + g\left(\overline{I}_h\right)\right)}. \tag{23}$$

Replacing $\overline{I}_v$ in the first equation of (22) yields

$$\begin{aligned} &\left(\Lambda_h - \mu_h \overline{I}_h\right) f\left(\frac{\Lambda_v g\left(\overline{I}_h\right)}{\mu_v\left(\mu_v + g\left(\overline{I}_h\right)\right)}\right) \\ &\quad - \left(\mu_h + \gamma + \delta\right)\left(\mu_h + \theta(1-\mathscr{A})\right)\overline{I}_h = 0. \end{aligned} \tag{24}$$

By (**H1**) and (**H2**), $\overline{I}_h = 0$ is a solution of the above equation. Thus, system (3) has a disease-free equilibrium

$$\mathscr{E}_0 = \left(\frac{\Lambda_h}{\mu_h + \theta(1-\mathscr{A})}, 0, \frac{\Lambda_v}{\mu_v}, 0, \frac{\theta \Lambda_h \xi(a)}{\mu_h + \theta(1-\mathscr{A})}\right). \tag{25}$$

Following the same method as [22], the basic reproduction number for model (3) is

$$\mathscr{R}(\theta) = \sqrt{\frac{\Lambda_h \Lambda_v f'(0) g'(0)}{\mu_v^2\left(\mu_h + \gamma + \delta\right)\left(\mu_h + \theta(1-\mathscr{A})\right)}}. \tag{26}$$

$\mathscr{R}(\theta)$ describes a threshold for endemic persistence/spread of the disease, the rate of increase in the number of cases during an epidemic. Its magnitude allows determining the effort necessary either to prevent an epidemic or to eliminate an infection from a population.

Let $(S_h^*, I_h^*, S_v^*, I_v^*, v^*(\cdot))$ be an endemic equilibrium. Then, $I_h^* \in (0, \Lambda_h/\mu_h)$ and $h(I_h^*) = 0$, where

$$\begin{aligned} h(I_h) &= (\Lambda_h - \mu_h I_h) f\left(\frac{\Lambda_v g(I_h)}{\mu_v(\mu_v + g(I_h))}\right) \\ &\quad - \left(\mu_h + \gamma + \delta\right)\left(\mu_h + \theta(1-\mathscr{A})\right) I_h. \end{aligned} \tag{27}$$

The function h is continuous with $h(0) = 0$ and $h(\Lambda_h/\mu_h) \le 0$.

Moreover, for $I_h \in (0, \Lambda_h/\mu_h)$,

$$\begin{aligned} &\frac{dh}{dI_h} \\ &= (\Lambda_h - \mu_h I_h) \frac{\Lambda_v g'(I_h)}{(\mu_v + g(I_h))^2} f'\left(\frac{\Lambda_v g(I_h)}{\mu_v(\mu_v + g(I_h))}\right) \\ &\quad - \mu_h f\left(\frac{\Lambda_v g(I_h)}{\mu_v(\mu_v + g(I_h))}\right) \\ &\quad - \left(\mu_h + \gamma + \delta\right)\left(\mu_h + \theta(1-\mathscr{A})\right). \end{aligned} \tag{28}$$

The sufficient condition for h to have a zero in $(0, \Lambda_h/\mu_h)$ is that h is increasing at 0. Thus, there is an endemic equilibrium if

$$\begin{aligned} \frac{dh}{dI_h}(0) &= \left(\mu_h + \gamma + \delta\right)\left(\mu_h + \theta(1-\mathscr{A})\right)\left(\mathscr{R}^2(\theta) - 1\right) \\ &> 0, \end{aligned} \tag{29}$$

which is equivalent to $\mathscr{R}(\theta) > 1$. Let I_h^* be a unique solution in $(0, \Lambda_h/\mu_h)$ of $h(I_h) = 0$. Then, system (3) admits a unique endemic equilibrium $\mathscr{E}^* = (S_h^*, I_h^*, S_v^*, I_v^*, v^*(\cdot))$, where

$$\begin{aligned} S_h^* &= \frac{\Lambda_h}{f\left(\Lambda_v g\left(I_h^*\right)/\mu_v\left(\mu_v + g\left(I_h^*\right)\right)\right) + \mu_h + \theta(1-\mathscr{A})}, \\ S_v^* &= \frac{\Lambda_v}{\mu_v + g\left(I_h^*\right)}, \\ I_v^* &= \frac{\Lambda_v g\left(I_h^*\right)}{\mu_v\left(\mu_v + g\left(I_h^*\right)\right)}, \\ v^*(\cdot) &= \frac{\Lambda_h \theta \xi(a)}{f\left(\Lambda_v g\left(I_h^*\right)/\mu_v\left(\mu_v + g\left(I_h^*\right)\right)\right) + \mu_h + \theta(1-\mathscr{A})}. \end{aligned} \tag{30}$$

We summarize the above analysis in the following result.

Theorem 2 (consider system (3)). *If $\mathscr{R}(\theta) \le 1$, then there is a unique equilibrium, which is the disease-free equilibrium $\mathscr{E}_0$.*

If $\mathscr{R}(\theta) > 1$, then there are two equilibria, the disease-free equilibrium $\mathscr{E}_0$ and the endemic equilibrium $\mathscr{E}^*$.

We now deal with the local stability of the disease-free equilibrium. We show the stability of $\mathscr{E}_0$ by linearizing system (3) about $\mathscr{E}_0$. The result is stated as follows.

Theorem 3 (consider system (3)). *If $\mathscr{R}(\theta) < 1$, the disease-free equilibrium $\mathscr{E}_0$ is locally asymptotically stable.*

If $\mathscr{R}(\theta) > 1$, the unique endemic equilibrium $\mathscr{E}^*$ is locally asymptotically stable.

Proof. From the linearization of system (3) at $\mathscr{E}_0$, we deduce the following characteristic equation:

$$\begin{aligned}&(\lambda+\mu_v)\left(\lambda+\mu_h+\theta\left(1-\widehat{\mathscr{A}}(\lambda)\right)\right)\\&\cdot\left((\lambda+\mu_h+\gamma+\delta)(\lambda+\mu_v)\right.\\&\left.-\frac{\Lambda_h}{\mu_h+\theta(1-\mathscr{A})}\frac{\Lambda_v}{\mu_v}f'(0)\,g'(0)\right)=0,\end{aligned}\tag{31}$$

where

$$\widehat{\mathscr{A}}(\lambda)=\int_0^\infty \epsilon(a)\,\xi(a)\,e^{-\lambda a}da.\tag{32}$$

From (31), the eigenvalues are $-\mu_v$ and solutions of

$$\lambda+\mu_h+\theta=\theta\widehat{\mathscr{A}}(\lambda),\tag{33}$$

$$(\lambda+\mu_h+\gamma+\delta)(\lambda+\mu_v)=\frac{\Lambda_h\Lambda_v f'(0)\,g'(0)}{\mu_v(\mu_h+\theta(1-\mathscr{A}))}.\tag{34}$$

All roots of (33) and (34) have negative real parts; otherwise let λ_0 be a root of (33) with $\mathrm{Re}(\lambda_0)\geq 0$. Then, we have

$$\begin{aligned}&\left|\lambda_0+\mu_h+\theta\right|>\theta,\\&\left|\theta\widehat{\mathscr{A}}(\lambda_0)\right|\leq\theta\mathscr{A}\leq\theta.\end{aligned}\tag{35}$$

This leads to a contradiction.

Now, let λ_0 be a root of (34) with $\mathrm{Re}(\lambda_0)\geq 0$. From (26), we have

$$\begin{aligned}\left|\frac{\Lambda_h\Lambda_v f'(0)\,g'(0)}{\mu_v(\mu_h+\theta(1-\mathscr{A}))}\right|&=\mathscr{R}(\theta)^2\,\mu_v(\mu_h+\gamma+\delta)\\&<\mu_v(\mu_h+\gamma+\delta)\\&\leq\left|(\lambda_0+\mu_h+\gamma+\delta)(\lambda_0+\mu_v)\right|.\end{aligned}\tag{36}$$

This also leads to a contradiction by using (34) and then proves that $\mathscr{E}_0$ is locally asymptotically stable.

The characteristic equation at $\mathscr{E}^*$ is

$$0=\begin{vmatrix}\lambda+\mu_h+f(I_v^*)+\theta\left(1-\widehat{\mathscr{A}}(\lambda)\right) & 0 & 0 & S_h^*f'(I_v^*)\\ -f(I_v^*) & \lambda+\mu_h+\gamma+\delta & 0 & -S_h^*f'(I_v^*)\\ 0 & S_v^*g'(I_h^*) & \lambda+\mu_v+g(I_h^*) & 0\\ 0 & -S_v^*g'(I_h^*) & -g(I_h^*) & \lambda+\mu_v\end{vmatrix},\tag{37}$$

$$\begin{aligned}0=(\lambda+\mu_v)&\left[\left(\lambda+\mu_h+f(I_v^*)+\theta\left(1-\widehat{\mathscr{A}}(\lambda)\right)\right)(\lambda+\mu_h+\gamma+\delta)(\lambda+\mu_v+g(I_h^*))+S_h^*S_v^*f'(I_v^*)f(I_v^*)g'(I_h^*)g(I_h^*)\right.\\&\left.-\left(\lambda+\mu_h+f(I_v^*)+\theta\left(1-\widehat{\mathscr{A}}(\lambda)\right)\right)S_h^*S_v^*f'(I_v^*)g'(I_h^*)\right].\end{aligned}$$

By using $S_h^*=(\mu_h+\gamma+\delta)I_h^*/f(I_v^*)$ and $S_v^*=\mu_vI_v^*/g(I_h^*)$, we get

$$\begin{aligned}0=(\lambda+\mu_v)&\left[\left(\lambda+\mu_h+f(I_v^*)+\theta\left(1-\widehat{\mathscr{A}}(\lambda)\right)\right)\right.\\&\cdot(\lambda+\mu_h+\gamma+\delta)(\lambda+\mu_v+g(I_h^*))\\&+\mu_v(\mu_h+\gamma+\delta)I_h^*I_v^*f'(I_v^*)g'(I_h^*)\\&-\left(\lambda+\mu_h+f(I_v^*)+\theta\left(1-\widehat{\mathscr{A}}(\lambda)\right)\right)\\&\left.\times\frac{\mu_v(\mu_h+\gamma+\delta)I_h^*I_v^*}{f(I_v^*)g(I_h^*)}f'(I_v^*)g'(I_h^*)\right].\end{aligned}\tag{38}$$

We show that the characteristic equation has no eigenvalues with nonnegative real parts. The eigenvalues are $-\mu_v$ and solutions of

$$\begin{aligned}&\left(\lambda+\mu_h+f(I_v^*)+\theta\left(1-\widehat{\mathscr{A}}(\lambda)\right)\right)(\lambda+\mu_h+\gamma+\delta)\\&\cdot(\lambda+\mu_v+g(I_h^*))+\mu_v(\mu_h+\gamma+\delta)I_h^*I_v^*f'(I_v^*)\\&\cdot g'(I_h^*)=\left(\lambda+\mu_h+f(I_v^*)+\theta\left(1-\widehat{\mathscr{A}}(\lambda)\right)\right)\\&\times\frac{\mu_v(\mu_h+\gamma+\delta)I_h^*I_v^*}{f(I_v^*)g(I_h^*)}f'(I_v^*)g'(I_h^*).\end{aligned}\tag{39}$$

By way of contradiction, assume that there is one eigenvalue λ_1 with $\mathrm{Re}(\lambda_1)\geq 0$. Then,

$$\begin{aligned}&\left|1+\frac{\mu_v(\mu_h+\gamma+\delta)I_h^*I_v^*f'(I_v^*)g'(I_h^*)}{\left(\lambda_1+\mu_h+f(I_v^*)+\theta\left(1-\widehat{\mathscr{A}}(\lambda_1)\right)\right)(\lambda_1+\mu_h+\gamma+\delta)(\lambda_1+\mu_v+g(I_h^*))}\right|\\&\times\left|(\lambda_1+\mu_h+\gamma+\delta)(\lambda_1+\mu_v+g(I_h^*))\right|=\left|\frac{\mu_v(\mu_h+\gamma+\delta)I_h^*I_v^*}{f(I_v^*)g(I_h^*)}f'(I_v^*)g'(I_h^*)\right|.\end{aligned}\tag{40}$$

From (1), it follows that

$$\left|\frac{\mu_v\left(\mu_h+\gamma+\delta\right)I_h^*I_v^*}{f\left(I_v^*\right)g\left(I_h^*\right)}f'\left(I_v^*\right)g'\left(I_h^*\right)\right| \leq \mu_v\left(\mu_h+\gamma+\delta\right). \tag{41}$$

Since

$$\left|1+\frac{\mu_v\left(\mu_h+\gamma+\delta\right)I_h^*I_v^*f'\left(I_v^*\right)g'\left(I_h^*\right)}{\left(\lambda_1+\mu_h+f\left(I_v^*\right)+\theta\left(1-\widehat{\mathscr{A}}\left(\lambda_1\right)\right)\right)\left(\lambda_1+\mu_h+\gamma+\delta\right)\left(\lambda_1+\mu_v+g\left(I_h^*\right)\right)}\right|>1, \tag{42}$$

we have

$$\begin{aligned}&\left|1+\frac{\mu_v\left(\mu_h+\gamma+\delta\right)I_h^*I_v^*f'\left(I_v^*\right)g'\left(I_h^*\right)}{\left(\lambda_1+\mu_h+f\left(I_v^*\right)+\theta\left(1-\widehat{\mathscr{A}}\left(\lambda_1\right)\right)\right)\left(\lambda_1+\mu_h+\gamma+\delta\right)\left(\lambda_1+\mu_v+g\left(I_h^*\right)\right)}\right|\\&\times\left|\left(\lambda_1+\mu_h+\gamma+\delta\right)\left(\lambda_1+\mu_v+g\left(I_h^*\right)\right)\right|>\mu_v\left(\mu_h+\gamma+\delta\right).\end{aligned} \tag{43}$$

This leads to a contradiction. □

3. Global Stability Analysis of Equilibria

In this section, we prove the global stability of the equilibria of model (3). We first start by the global stability of the disease-free equilibrium $\mathscr{E}_0$. To attend this, we need the Fluctuation Lemma [23].

Let us introduce the notations

$$\begin{aligned}\psi_\infty&=\liminf_{t\to\infty}\psi\left(t\right),\\\psi^\infty&=\limsup_{t\to\infty}\psi\left(t\right).\end{aligned} \tag{44}$$

The Fluctuation Lemma is stated as follows.

Lemma 4 (See [23]). *Let $\psi:\mathbb{R}^+\to\mathbb{R}$ be a bounded and continuously differentiable function. Then, there exist sequences $\{s_n\}$ and $\{t_n\}$ such that $s_n\to\infty$, $t_n\to\infty$, $\psi(s_n)\to\psi_\infty$, $\psi'(s_n)\to 0$, $\psi(t_n)\to\psi^\infty$, and $\psi'(t_n)\to 0$ as $n\to\infty$.*

We also need the following lemma for establishing the global stability of $\mathscr{E}_0$.

Lemma 5 (See [18]). *Suppose that $f:\mathbb{R}^+\to\mathbb{R}$ is a bounded function and $k\in L^1((0,+\infty),\mathbb{R})$. Then,*

$$\limsup_{t\to\infty}\int_0^t k\left(\zeta\right)f\left(t-\zeta\right)d\zeta\leq f^\infty\left\|k\right\|_1, \quad \text{where } \left\|k\right\|_1=\int_0^{+\infty}k\left(s\right)ds. \tag{45}$$

We state the stability result of the disease-free equilibrium $\mathscr{E}_0$ as follows.

Theorem 6. *If $\mathscr{R}(\theta)<1$, then the disease-free equilibrium $\mathscr{E}_0$ is globally asymptotically stable.*

Proof. Using Theorem 3, it is sufficient to show that $\mathscr{E}_0$ is attractive in Γ.

Let $(S_h(t),I_h(t),S_v(t),I_v(t),v(t,a))$ be a solution of (3) with $(S_{h0},I_{h0},S_{v0},I_{v0},v_0(\cdot))\in\Gamma$. We integrate the third equation of (3) with the boundary conditions to obtain

$$v\left(t,a\right)=\begin{cases}\theta S_h\left(t-a\right)\xi\left(a\right), & t\geq a,\\ v_0\left(a-t\right)\dfrac{\xi\left(a\right)}{\xi\left(a-t\right)}, & t<a.\end{cases} \tag{46}$$

Using the Fluctuation Lemma 4, we derive

$$\begin{aligned}S_h^\infty&\leq\frac{\Lambda_h}{\mu_h+\theta\left(1-\mathscr{A}\right)},\\S_v^\infty&\leq\frac{\Lambda_v}{\mu_v}.\end{aligned} \tag{47}$$

From (1) and (3), we get

$$\begin{aligned}\frac{dI_h\left(t\right)}{dt}&=S_h\left(t\right)f\left(I_v\left(t\right)\right)-\left(\mu_h+\gamma+\delta\right)I_h\\&\leq\frac{\Lambda_h}{\mu_h+\theta\left(1-\mathscr{A}\right)}f'\left(0\right)I_v\left(t\right)-\left(\mu_h+\gamma+\delta\right)I_h\left(t\right),\\\frac{dI_v\left(t\right)}{dt}&=S_v\left(t\right)g\left(I_h\left(t\right)\right)-\mu_vI_v\left(t\right)\\&\leq\frac{\Lambda_v}{\mu_v}g'\left(0\right)I_h\left(t\right)-\mu_vI_v\left(t\right).\end{aligned} \tag{48}$$

From (48), we have

$$\begin{pmatrix}\dfrac{dI_h}{dt}\\[2mm]\dfrac{dI_v}{dt}\end{pmatrix}$$

$$\leq \begin{pmatrix} -(\mu_h+\gamma+\delta) & \dfrac{\Lambda_h f'(0)}{\mu_h+\theta(1-\mathscr{A})} \\ \dfrac{\Lambda_v g'(0)}{\mu_v} & -\mu_v \end{pmatrix} \begin{pmatrix} I_h \\ I_v \end{pmatrix}. \tag{49}$$

It is evident that all eigenvalues of the matrix

$$\begin{pmatrix} -(\mu_h+\gamma+\delta) & \dfrac{\Lambda_h f'(0)}{\mu_h+\theta(1-\mathscr{A})} \\ \dfrac{\Lambda_v g'(0)}{\mu_v} & -\mu_v \end{pmatrix} \tag{50}$$

have negative real parts when $\mathscr{R}(\theta) < 1$. This leads to

$$\begin{aligned} I_h^\infty &\longrightarrow 0, \\ I_v^\infty &\longrightarrow 0. \end{aligned} \tag{51}$$

From Lemma 4, it follows that there exists a sequence $\{t_n\}$ such that $t_n \to \infty$, $S_h(t_n) \to S_{h,\infty}$, $S_v(t_n) \to S_{v,\infty}$, and $S_h'(t_n) \to 0$, $S_v'(t_n) \to 0$ as $n \to \infty$.

Note that

$$\begin{aligned} \lim_{n\to\infty} I_h(t_n) &= 0, \\ \lim_{n\to\infty} I_v(t_n) &= 0. \end{aligned} \tag{52}$$

Thus,

$$\begin{aligned} \frac{dS_h(t_n)}{dt} &= \Lambda_h - (\mu_h+\theta) S_h(t_n) - S_h(t_n) f(I_v(t_n)) \\ &\quad + \int_0^{t_n} \epsilon(a) S_h(t_n - a) \xi(a)\, da \\ &\quad + \int_{t_n}^{\infty} \epsilon(a) v_0(a - t_n) \frac{\xi(a)}{\xi(a-t_n)} da, \\ \frac{dS_v(t_n)}{dt} &= \Lambda_v - \mu_v S_v(t_n) - S_v(t_n) g(I_h(t_n)). \end{aligned} \tag{53}$$

Let $n \to \infty$; then

$$\begin{aligned} 0 &\geq \Lambda_h - (\mu_h+\theta) S_{h,\infty} - S_{h,\infty} f(I_v^\infty) \\ &\quad + \int_0^{\infty} \epsilon(a) S_{h,\infty} \xi(a)\, da, \\ 0 &\geq \Lambda_v - \mu_v S_{v,\infty} - S_{v,\infty} g(I_h^\infty), \end{aligned} \tag{54}$$

which gives

$$\begin{aligned} 0 &\geq \Lambda_h - (\mu_h + \theta(1-\mathscr{A})) S_{h,\infty} - S_{h,\infty} f(I_v^\infty), \\ 0 &\geq \Lambda_v - \mu_v S_{v,\infty} - S_{v,\infty} g(I_h^\infty). \end{aligned} \tag{55}$$

Since $I_h^\infty \to 0$ and $I_v^\infty \to 0$, we obtain

$$\begin{aligned} \frac{\Lambda_h}{\mu_h+\theta(1-\mathscr{A})} \leq S_{h,\infty} \leq S_h^\infty \leq \frac{\Lambda_h}{\mu_h+\theta(1-\mathscr{A})}, \\ \frac{\Lambda_v}{\mu_v} \leq S_{v,\infty} \leq S_v^\infty \leq \frac{\Lambda_v}{\mu_v}. \end{aligned} \tag{56}$$

That is,

$$\begin{aligned} \lim_{t\to\infty} S_h(t) &= \frac{\Lambda_h}{\mu_h+\theta(1-\mathscr{A})}, \\ \lim_{t\to\infty} S_v(t) &= \frac{\Lambda_v}{\mu_v}. \end{aligned} \tag{57}$$

From (46), it follows that

$$\lim_{t\to\infty} v(t,a) = \frac{\Lambda_h \theta \xi(a)}{\mu_h+\theta(1-\mathscr{A})}. \tag{58}$$

Therefore, $(S_h(t), I_h(t), S_v(t), I_v(t), v(t,\cdot)) \to \mathscr{E}_0$ in $\mathbb{R}^{4+} \times L_+^1$ as $t \to \infty$. □

We now deal with the global stability of the endemic equilibrium $\mathscr{E}^*$.

A total trajectory of Φ is a function $X : \mathbb{R} \to \mathbb{R}^{4+} \times L_+^1$ such that $\Phi(s, X(t)) = X(t+s)$ for all $t \in \mathbb{R}$ and all $s \in \mathbb{R}^+$.

We define $\phi : (0,\infty) \to \mathbb{R}$ by $\phi(x) = x - 1 - \ln x$. ϕ has a strict global minimum at 1 with $\phi(1) = 0$ and $\phi(x) > 0$, $\forall x \neq 1$.

Lemma 7 (see [24]). *Define*

$$F(X) = \phi\left(\frac{f(X)}{f(X^*)}\right) - \phi\left(\frac{X}{X^*}\right). \tag{59}$$

If assumptions (**H1**) *and* (**H2**) *are satisfied, then* $F(X) \leq 0$, $\forall X > 0$.

The result of the global stability of the endemic equilibrium is stated as follows.

Theorem 8. *If* $\mathscr{R}(\theta) > 1$, *then the endemic equilibrium* $\mathscr{E}^*$ *is globally asymptotically stable in* Γ.

Proof. Evaluating both sides of (3) at $\mathscr{E}_*$ gives

$$\Lambda_h + \int_0^\infty \epsilon(a) v^*(a)\, da = (\mu_h + f(I_v^*) + \theta) S_h^*, \tag{60}$$

$$S_h^* f(I_v^*) = (\mu_h+\gamma+\delta) I_h^*, \tag{61}$$

$$\Lambda_v = (\mu_v + g(I_h^*)) S_v^*, \tag{62}$$

$$g(I_h^*) S_v^* = \mu_v I_v^*, \tag{63}$$

$$v^*(a) = \theta S_h^* \xi(a). \tag{64}$$

Let

$$\alpha(a) = \int_a^\infty \epsilon(s) v^*(s)\, ds. \tag{65}$$

Then,

$$\frac{d\alpha(a)}{da} = -\epsilon(a) v^*(a). \tag{66}$$

Let

$$V_{S_h}(t) = \phi\left(\frac{S_h(t)}{S_h^*}\right),$$
$$V_{I_h}(t) = \phi\left(\frac{I_h(t)}{I_h^*}\right),$$
$$V_{S_v}(t) = \phi\left(\frac{S_v(t)}{S_v^*}\right), \quad (67)$$
$$V_{I_v}(t) = \phi\left(\frac{I_v(t)}{I_v^*}\right),$$
$$V_v(t) = \int_0^\infty \alpha(a)\,\phi\left(\frac{v(t,a)}{v^*(a)}\right).$$

Define

$$V(t) = S_v^* g(I_h^*)\left(S_h^* V_{S_h}(t) + I_h^* V_{I_h}(t)\right) + S_h^* f(I_v^*)\left(S_v^* V_{S_v}(t) + I_v^* V_{I_v}(t)\right) + S_v^* g(I_h^*) V_v(t). \quad (68)$$

We study the behavior of the Lyapunov functional $V(t)$ given by (68). $V(t)$ is bounded and $V(t) \geq 0$ with equality if and only if $S_h(t)/S_h^* = I_h(t)/I_h^* = S_v(t)/S_v^* = I_v(t)/I_v^* = v(t,a)/v^*(a) = 1$.

For clarity, the derivatives of $V_{S_h}(t), V_{I_h}(t), V_{S_v}(t), V_{I_v}(t), V_v(t)$ will be calculated separately and then combined to obtain $dV(t)/dt$. We first have

$$\frac{dV_{S_h}(t)}{dt} = \frac{1}{S_h^*}\left(1 - \frac{S_h^*}{S_h(t)}\right)\frac{dS_h(t)}{dt} = \frac{1}{S_h^*}\left(1 - \frac{S_h^*}{S_h(t)}\right)\left(\Lambda_h - \mu_h S_h(t) - S_h(t) f(I_v(t)) - \theta S_h(t) + \int_0^\infty \epsilon(a)\, v(t,a)\, da\right). \quad (69)$$

Using (60) to replace Λ_h in (69) gives

$$\frac{dV_{S_h}(t)}{dt} = \frac{1}{S_h^*}\left(1 - \frac{S_h^*}{S_h(t)}\right)\left((\mu_h + \theta) S_h^* + S_h^* f(I_v^*) - \int_0^\infty \epsilon(a)\, v^*(a)\, da - (\mu_h + \theta) S_h(t) - S_h(t) \cdot f(I_v(t)) + \int_0^\infty \epsilon(a)\, v(t,a)\, da\right) = -(\mu_h + \theta) \cdot \frac{(S_h(t) - S_h^*)^2}{S_h(t) S_h^*} + f(I_v^*)\left(1 - \frac{S_h(t) f(I_v(t))}{S_h^* f(I_v^*)} - \frac{S_h^*}{S_h(t)} + \frac{f(I_v(t))}{f(I_v^*)}\right) + \int_0^\infty \frac{\epsilon(a) v^*(a)}{S_h^*}\left(\frac{v(t,a)}{v^*(a)} - \frac{S_h^* v(t,a)}{S_h(t) v^*(a)} - 1 + \frac{S_h^*}{S_h(t)}\right) da. \quad (70)$$

Next, we calculate $dV_{I_h}(t)/dt$.

$$\frac{dV_{I_h}(t)}{dt} = \frac{1}{I_h^*}\left(1 - \frac{I_h^*}{I_h(t)}\right)\frac{dI_h}{dt} = \frac{1}{I_h^*}\left(1 - \frac{I_h^*}{I_h(t)}\right) \cdot \left(S_h(t) f(I_v(t)) - (\mu_h + \gamma + \delta) I_h(t)\right) = \frac{1}{I_h^*}\left(1 - \frac{I_h^*}{I_h(t)}\right) \cdot \left(S_h(t) f(I_v(t)) - (\mu_h + \gamma + \delta) I_h^* \frac{I_h(t)}{I_h^*}\right). \quad (71)$$

Using (61) to replace $(\mu_h + \gamma + \delta)I_h^*$ in (71) gives

$$\frac{dV_{I_h}(t)}{dt} = \frac{1}{I_h^*}\left(1 - \frac{I_h^*}{I_h(t)}\right)\left(S_h(t) f(I_v(t)) - S_h^* f(I_v^*)\frac{I_h(t)}{I_h^*}\right) = \frac{S_h^* f(I_v^*)}{I_h^*}\left(1 + \frac{S_h(t) f(I_v(t))}{S_h^* f(I_v^*)} - \frac{S_h(t) f(I_v(t)) I_h^*}{S_h^* f(I_v^*) I_h(t)} - \frac{I_h(t)}{I_h^*}\right). \quad (72)$$

We now calculate the derivative of $V_{S_v(t)}$.

$$\frac{dV_{S_v}(t)}{dt} = \frac{1}{S_v^*}\left(1 - \frac{S_v^*}{S_v(t)}\right)\frac{dS_v}{dt} = \frac{1}{S_v^*}\left(1 - \frac{S_v^*}{S_v(t)}\right)\left(\Lambda_v - \mu_v S_v(t) - S_v(t) g(I_h(t))\right). \quad (73)$$

Using (62) to replace Λ_v in (73) gives

$$\frac{dV_{S_v}(t)}{dt} = \frac{1}{S_v^*}\left(1 - \frac{S_v^*}{S_v(t)}\right)\frac{dS_v}{dt} = \frac{1}{S_v^*}\left(1 - \frac{S_v^*}{S_v(t)}\right) \cdot \left(\mu S_v^* + S_v^* g(I_h^*) - \mu_v S_v(t) - S_v(t) g(I_h(t))\right) = -\mu_v \frac{(S_v(t) - S_v^*)^2}{S_v(t) S_v^*} + g(I_h^*) \cdot \left(1 - \frac{S_v(t) g(I_h(t))}{S_v^* g(I_h^*)} - \frac{S_v^*}{S_v(t)} + \frac{g(I_h(t))}{g(I_h^*)}\right). \quad (74)$$

Differentiating $V_{I_v}(t)$ with respect to t yields

$$\frac{dV_{I_v}(t)}{dt} = \frac{1}{I_v^*}\left(1 - \frac{I_v^*}{I_v(t)}\right)\frac{dI_v}{dt} = \frac{1}{I_v^*}\left(1 - \frac{I_v^*}{I_v(t)}\right)(S_v(t) g(I_h(t)) - \mu_v I_v(t)) = \frac{1}{I_v^*}\left(1 - \frac{I_v^*}{I_v(t)}\right)\left(S_v(t) g(I_h(t)) - \mu_v I_v^* \frac{I_v(t)}{I_v^*}\right). \quad (75)$$

Using (63) to replace $\mu_v I_v^*$ in (75) gives

$$\frac{dV_{I_v}(t)}{dt} = \frac{1}{I_v^*}\left(1-\frac{I_v^*}{I_v(t)}\right)\left(S_v(t)\,g\left(I_h(t)\right) - S_v^* g\left(I_h^*\right)\frac{I_v(t)}{I_v^*}\right) = \frac{S_v^* g\left(I_h^*\right)}{I_v^*}\left(1 + \frac{S_v(t)\,g\left(I_h(t)\right)}{S_v^* g\left(I_h^*\right)} - \frac{S_v(t)\,g\left(I_h(t)\right)I_v^*}{S_v^* g\left(I_h^*\right)I_v(t)} - \frac{I_v(t)}{I_v^*}\right). \tag{76}$$

The derivative of $V_v(t)$ is

$$\begin{aligned}\frac{dV_v(t)}{dt} &= \int_0^\infty \alpha(a)\frac{\partial\phi\left(v(t,a)/v^*(a)\right)}{\partial t}da = \int_0^\infty \alpha(a)\\ &\cdot\left(1-\frac{v^*(a)}{v(t,a)}\right)\frac{1}{v^*(a)}\frac{\partial v(t,a)}{\partial t}da = -\int_0^\infty \alpha(a)\\ &\cdot\left(1-\frac{v^*(a)}{v(t,a)}\right)\frac{v(t,a)}{v^*(a)}\left(\frac{v_a(t,a)}{v(t,a)}+\mu_h+\epsilon(a)\right)da\\ &= -\int_0^\infty \alpha(a)\left(\frac{v(t,a)}{v^*(a)}-1\right)\\ &\cdot\left(\frac{v_a(t,a)}{v(t,a)}+\mu_h+\epsilon(a)\right)da,\end{aligned} \tag{77}$$

where $v_a(t,a) = \partial v(t,a)/\partial a$.

Using $(\partial/\partial a)\phi(v(t,a)/v^*(a)) = (v(t,a)/v^*(a) - 1)(v_a(t,a)/v(t,a)+\mu_h+\epsilon(a))$, $d\alpha(a)/da = -\epsilon(a)v^*(a)$ and integration by parts, we get

$$\begin{aligned}\frac{dV_v(t)}{dt} &= -\int_0^\infty \alpha(a)\frac{\partial}{\partial a}\phi\left(\frac{v(t,a)}{v^*(a)}\right)da\\ &= -\alpha(a)\,\phi\left(\frac{v(t,a)}{v^*(a)}\right)\Big|_{a=0}^{a=\infty}\\ &\quad + \int_0^\infty \phi\left(\frac{v(t,a)}{v^*(a)}\right)\frac{d\alpha(a)}{da}da\\ &= -\alpha(a)\,\phi\left(\frac{v(t,a)}{v^*(a)}\right)\Big|_{a=\infty}\\ &\quad + \alpha(0)\,\phi\left(\frac{v(t,0)}{v^*(0)}\right)\\ &\quad - \int_0^\infty \epsilon(a)\,v^*(a)\,\phi\left(\frac{v(t,a)}{v^*(a)}\right)da.\end{aligned} \tag{78}$$

From $\alpha(0) = \int_0^\infty \epsilon(a)v^*(a)da$, we get

$$\begin{aligned}\frac{dV_v(t)}{dt} &= -\alpha(a)\,\phi\left(\frac{v(t,a)}{v^*(a)}\right)\Big|_{a=\infty}\\ &\quad + \int_0^\infty \epsilon(a)\,v^*(a)\,\phi\left(\frac{v(t,0)}{v^*(0)}\right)da\\ &\quad - \int_0^\infty \epsilon(a)\,v^*(a)\,\phi\left(\frac{v(t,a)}{v^*(a)}\right)da.\end{aligned} \tag{79}$$

Combining (70), (72), (74), (76), and (79) and multiplying appropriately by coefficients determined by (68), we obtain

$$\begin{aligned}\frac{dV(t)}{dt} &= -\left(\mu_h+\theta\right)S_v^* g\left(I_h^*\right)\frac{\left(S_h-S_h^*\right)^2}{S_h(t)}\\ &\quad - \mu_v S_h^* f\left(I_v^*\right)\frac{\left(S_v-S_v^*\right)^2}{S_v(t)} + S_h^* S_v^* f\left(I_v^*\right)g\left(I_h^*\right)\left(4\right.\\ &\quad - \frac{S_h(t)\,f\left(I_v(t)\right)I_h^*}{S_h^* f\left(I_v^*\right)I_h(t)} - \frac{S_h^*}{S_h(t)} + \frac{f\left(I_v(t)\right)}{f\left(I_v^*\right)} - \frac{I_h(t)}{I_h^*}\\ &\quad - \frac{I_v(t)}{I_v^*} - \frac{S_v(t)\,g\left(I_h(t)\right)I_v^*}{S_v^* g\left(I_h^*\right)I_v(t)} - \frac{S_v^*}{S_v(t)}\\ &\quad \left. + \frac{g\left(I_h(t)\right)}{g\left(I_h^*\right)}\right) - \alpha(a)\,S_v^* g\left(I_h^*\right)\phi\left(\frac{v(t,a)}{v^*(a)}\right)\Big|_{a=\infty}\\ &\quad + S_v^* g\left(I_h^*\right)\int_0^\infty \epsilon(a)\,v^*(a)\left(\phi\left(\frac{v(t,0)}{v^*(0)}\right)\right.\\ &\quad - \phi\left(\frac{v(t,a)}{v^*(a)}\right) + \frac{v(t,a)}{v^*(a)} - \frac{S_h^* v(t,a)}{S_h(t)\,v^*(a)} - 1\\ &\quad \left. + \frac{S_h^*}{S_h(t)}\right)da.\end{aligned} \tag{80}$$

By $\int_0^\infty \epsilon(a)v^*(a)da = \theta S_h^* K$, $v(t,0) = \theta S_h(t)$, and $v^*(0) = \theta S_h^*$, it follows that

$$\begin{aligned}\frac{dV(t)}{dt} &= -\left(\mu_h+\theta(1-K)\right)S_v^* g\left(I_h^*\right)\frac{\left(S_h-S_h^*\right)^2}{S_h(t)}\\ &\quad - \mu_v S_h^* f\left(I_v^*\right)\frac{\left(S_v-S_v^*\right)^2}{S_v(t)} + S_h^* S_v^* f\left(I_v^*\right)g\left(I_h^*\right)\\ &\quad \cdot\left(\phi\left(\frac{f\left(I_v(t)\right)}{f\left(I_v^*\right)}\right) - \phi\left(\frac{I_v(t)}{I_v^*}\right) + \phi\left(\frac{g\left(I_h(t)\right)}{g\left(I_h^*\right)}\right)\right.\\ &\quad - \phi\left(\frac{I_h(t)}{I_h^*}\right) - \phi\left(\frac{S_v^*}{S_v(t)}\right)\\ &\quad \left. - \phi\left(\frac{S_v(t)\,g\left(I_h(t)\right)I_v^*}{S_v^* g\left(I_h^*\right)I_v(t)}\right)\right)\\ &\quad - \alpha(a)\,S_v^* g\left(I_h^*\right)\phi\left(\frac{v(t,a)}{v^*(a)}\right)\Big|_{a=\infty} - S_v^* g\left(I_h^*\right)\\ &\quad \cdot\int_0^\infty \epsilon(a)\,v^*(a)\,\phi\left(\frac{S_h^* v(t,a)}{S_h(t)\,v^*(a)}\right).\end{aligned} \tag{81}$$

Thus, from Lemma 7, we deduce that

$$\frac{dV(t)}{dt} \le 0; \tag{82}$$

that is, V is nonincreasing. Denote by $\mathcal{M}$ the largest invariant subset of $\{dV(t)/dt = 0\}$.

Since V is bounded on $X(\cdot)$, the ω-limit set of $X(\cdot)$ must be contained in $\mathscr{M}$.

$dV(t)/dt = 0$ yields $S_h(t) = S_h^*$, $S_v(t) = S_v^*$, and $v(t,a) = v^*(a)$.

Thus, $dS_h(t)/dt = dS_v(t)/dt = 0$ in $\mathscr{M}$. This implies that

$$\begin{aligned}&\Lambda_h - (\mu_h + \theta) S_h^* - S_h^* f(I_v(t)) + \int_0^\infty \epsilon(a) v^*(a)\, da \\ &\quad = 0, \\ &\Lambda_v - \mu_v S_v^* - S_v^* g(I_h(t)) = 0,\end{aligned} \tag{83}$$

for $t \in \mathbb{R}$, which gives $f(I_v(t)) = f(I_v^*)$ and $g(I_h(t)) = g(I_h^*)$ $\forall t \in \mathbb{R}$. The monotonicity of f and g stated in (**H1**) and (**H2**) implies that $I_v(t) = I_v^*$ and $I_h(t) = I_h^*$, $\forall t \in \mathbb{R}$. Therefore, $\mathscr{M} = \{\mathscr{E}^*\}$.

Then, the ω-limit set of $X(\cdot)$ is the endemic equilibrium $\mathscr{E}^*$ and hence $V(X(t)) \geq V(\mathscr{E}^*)$, $\forall t \in \mathbb{R}$. Thus, $\mathscr{B} = \{\mathscr{E}^*\}$. □

4. Conclusion

We have analysed a vector-borne disease model with nonlinear incidences, in which we have incorporated the waning of vaccine-induced immunity. These nonlinear incidences rates include mass action and saturating incidence as special cases. The basic reproduction number denoted by $\mathscr{R}(\theta)$ is derived. The model exhibits two equilibria, namely, the disease-free equilibrium $\mathscr{E}_0$ and the endemic equilibrium $\mathscr{E}^*$. We have shown that if $\mathscr{R}(\theta)$ is less than 1, then the disease-free equilibrium $\mathscr{E}_0$ is globally asymptotically stable; that is, the disease dies out and if $\mathscr{R}(\theta)$ is larger than 1, then the endemic equilibrium $\mathscr{E}^*$ is globally asymptotically stable; that is, the disease persists in the population.

From these results, a critical vaccine coverage rate is obtained by solving the equation $\mathscr{R}(\theta) = 1$, which yields

$$\theta_0 = \frac{1}{1-\mathscr{A}}\left(\frac{\Lambda_h \Lambda_v f'(0)\, g'(0) - \mu_h \mu_v^2 (\mu_h + \gamma + \delta)}{\mu_v^2 (\mu_h + \gamma + \delta)}\right). \tag{84}$$

Then, if the vaccine coverage rate θ is greater than θ_0, then $\mathscr{R}(\theta) < 1$ and the disease will die out. The critical vaccine coverage rate θ_0 is increasing in the waning of vaccine. Then, neglecting the waning of vaccine (i.e., $\mathscr{A} = 0$) when applying a vaccination for vector-borne disease will surely not be sufficient to make the disease die out in the population.

Conflicts of Interest

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

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Research Article

Mathematical Modeling of the Adaptive Immune Responses in the Early Stage of the HBV Infection

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The aim of this paper is to study the early stage of HBV infection and impact delay in the infection process on the adaptive immune response, which includes cytotoxic T-lymphocytes and antibodies. In this stage, the growth of the healthy hepatocyte cells is logistic while the growth of the infected ones is linear. To investigate the role of the treatment at this stage, we also consider two types of treatment: interferon-α (IFN) and nucleoside analogues (NAs). To find the best strategy to use this treatment, an optimal control approach is developed to find the possibility of having a functional cure to HBV.

1. Introduction

It is very well known that the adaptive immune response has a significant impact on the progress of the early stage of HBV [1]. This response can either lead to complete cure from the infection, and it is characterised by the production of neutralizing antibodies against HBV surface antigen (HBsAg) and adequate cytotoxic lymphocyte T-cell (CTL) responses [2–4], or it could result in chronic infection that leads to liver cancer (HHC), cirrhosis, or liver failure.

During the incubation period of HBV, which is 30 to 180 days, the dynamics of the adaptive immune response are not fully understood, since the majority of the cases are clinically known after the infection is established and the patient is in the acute stage [5]. Understanding the dynamics of the two main arms of the adaptive immune response, CTL cells and B-cells [6, 7], will help grasp how the virus escapes the adaptive immunity and improve the ability of the immune system to control the virus in early infection.

Moreover, it is known that the actual therapy, which includes the standard interferon-α (INF) and the nucleoside analogues (NAs), is also initiated during the acute stage of HBV infection. INF helps eliminate the infected cells by reducing cccDNA [8], while NAs' function is to elongate DNA which leads to the inhibition of HBV replication [8]. As monotherapy, the NAs come in different types of drugs (Entecavir, Adefovir, and Lamivudine), which are also known for enhancing the functions of natural killers [8]. The question is, what if we could initiate therapy even earlier? Is it possible to eradicate the virus within this period with the therapy? In fact, recent studies [9, 10] showed that early Lamivudine treatment could lead to better outcome in acute-on-chronic stages and with less liver damage. Therefore, our goal is to understand the dynamics of the adaptive immune response, via the CTL cells and B-cells, in the early stage of HBV, and investigate the impact of early HBV treatment therapy on disease progress via a mathematical model of virus-immune response.

Mathematical modeling of the immune response to HBV is a subject that has been heavily investigated over the years by many authors [11–18], just to name a few. To our knowledge, there is no study that investigates the adaptive immune response in the early stage of the infection and effect of the early treatment on the progress of the disease. In this work, we are aiming to investigate this issue by considering an augmented model of our recent works [18, 19], and we consider the logistic growth only for the healthy hepatocyte cells and the infected hepatocyte cells [11]. This assumption is made to reflect the nature of the growth of these two types of cells in the early stage of the infection. We also did not

consider the latently infected cells, which are established at an acute stage [11], and we did not consider noncytolytic carrying processes since no data support such assumption in this stage. Moreover, we have also considered a more generalized incident function [16] and the delay in this incident function to reflect the time between the infection and the cells becoming productively infected (infected and producing new viruses). The optimal control of the HBV therapy aims to find the optimal strategy of the drugs that allow blocking the virus production and infection. Several papers studied the optimal control of the HBV therapy [16, 20–22]. In our case, the therapy will have an antiviral effect, and we ignore its immunomodulatory effect since we do not know what impact the use of the therapy could have on the immune system in the early stage of HBV infection.

The paper is organized as follows. In Section 2, we introduce our model, and we investigate the basic properties of the model without therapy, which includes positivity and boundedness of solutions. In Section 3, we focus on the stability analysis of the different types of steady states. Next, we will investigate optimal control of the treatment therapy, and we will numerically solve the optimality conditions. Finally, we will give a discussion and a conclusion to our work.

2. Introducing the Model

We defined the dynamics of the early stage of the HBV by the following system:

$$\begin{aligned}
\frac{dx}{dt} &= rx(t)\left(1-\frac{T(t)}{T_m}\right)-\beta\left(1-u_1(t)\right)\frac{v(t)\,x(t)}{T(t)},\\
\frac{dy}{dt} &= \beta e^{-k\tau}\left(1-u_1(t)\right)\frac{v(t-\tau)\,x(t-\tau)}{T(t-\tau)}-ay(t)\\
&\quad -py(t)\,z(t),\\
\frac{dv}{dt} &= \left(1-u_2(t)\right)aNy(t)-\delta v(t)-qv(t)\,w(t),\\
\frac{dw}{dt} &= gv(t)\,w(t)-hw(t),\\
\frac{dz}{dt} &= cy(t)\,z(t)-bz(t)
\end{aligned} \tag{1}$$

with

$$T(t)=x(t)+y(t), \tag{2}$$

where $x(t)$, $y(t)$, $v(t)$, $w(t)$, and $z(t)$ denote the concentrations of uninfected cells, infected cells, viruses, antibodies, and cytotoxic T-lymphocytes (CTLs), respectively. The uninfected hepatocytes grow at a rate that depends on the liver size, T_m, at a maximum per capita proliferation rate r. The healthy hepatocytes become infected by the virus at rate $\beta(vx/T)$, where β is a constant. Infected cells y die at rate a and are killed by the CTLs response at rate p. The infected non-virus-producing cells have a death rate k; these cells start producing viruses after delay time τ, hence $e^{-k\tau}$ is the probability of survival between time $t-\tau$ and t. The free virus particles are produced at rate aN, where N is the number of free virions produced by the infected cells during their lifespan, and decay at rate δ. Parameter c represents the rate of expansion of CTL cell z and b is its decay rate in the absence of antigenic stimulation. The antibodies are developed in response to free virus at rate g and decay at rate h. Finally, u_1 represents the efficiency of IFN in reducing the new infected cells; the infection rate in the presence of the drug is $(1-u_1)\beta$, while u_2 is the efficiency of NAs in blocking the reverse transcription, such that the virions production rate under this drug is $(1-u_2)aN$.

First, we analyse the model without drug therapy (i.e., $u_1=u_2=0$). More precisely, we consider the following model:

$$\begin{aligned}
\frac{dx}{dt} &= rx(t)\left(1-\frac{T(t)}{T_m}\right)-\beta\frac{v(t)\,x(t)}{T(t)},\\
\frac{dy}{dt} &= \beta e^{-k\tau}\frac{v(t-\tau)\,x(t-\tau)}{T(t-\tau)}-ay(t)-py(t)\,z(t),\\
\frac{dv}{dt} &= aNy(t)-\delta v(t)-qv(t)\,w(t),\\
\frac{dw}{dt} &= gv(t)\,w(t)-hw(t),\\
\frac{dz}{dt} &= cy(t)\,z(t)-bz(t).
\end{aligned} \tag{3}$$

Let $X=C([-\tau,0];\mathbb{R}^5)$ be the Banach space of continuous mapping from $[-\tau,0]$ to $\mathbb{R}^5$ with respect to the norm

$$\|\varphi\|=\sup_{-\tau\le t\le 0}\varphi(t). \tag{4}$$

We assume that the initial functions of the system of delayed differential equations (3) verify

$$\left(x(t),y(t),v(t),z(t),w(t)\right)\in X. \tag{5}$$

Following the standard approach, we assume that

$$\begin{aligned}
x(t)&>0,\\
y(t)&\ge 0,\\
v(t)&\ge 0,\\
z(t)&\ge 0,\\
w(t)&\ge 0,\\
&\qquad\qquad \text{for } t\in[-\tau,0],
\end{aligned} \tag{6}$$

$$T_m\ge T(t)=x(t)+y(t)>0,\quad \text{for } t\in[-\tau,0]. \tag{7}$$

Under these initial conditions, the solutions of (3) satisfy the following theorem.

Theorem 1. *System (3) has a unique solution; in addition, this solution is nonnegative and bounded for all $t\ge 0$.*

Proof. Notice that system (3) is locally Lipschitzian at $t = 0$, which implies that the solution of system (3), subject to (7), exists and is unique on $[0, b)$, where b is the maximal existence time for the solution of system (3). Notice that if $x(0) = 0$, then $x(t) \equiv 0$ for all $t > 0$. Hence, we can assume that $x(0) > 0$. Notice also that if $y(0) = 0$, then, from (6), we have $y'(0) = \beta((v(-\tau)x(-\tau))/T(-\tau)) \geq 0$ t, which implies that, for small $t > 0$, we have $y(t) > 0$. Similarly, if $v(0) = 0$, then $v'(0) = aNy(0) > 0$, which implies that, for small $t > 0$, we have $v(t) > 0$. Moreover, if $w(0) = 0$, $z(0) = 0$, then $w(t) \equiv 0$, $z(t) \equiv 0$ for all $t > 0$. Hence, we assume below that $w(0) > 0, z(0) > 0$.

Assume first that there is $b > t_1 > 0$ such that $x(t_1) = 0$ and $x(t) > 0$, $y(t) > 0$, $v(t) > 0$, for $t \in [0, t_1]$. Observe that

$$\frac{dx(t)}{dt} = rx(t)\left(1 - \frac{T(t)}{T_m}\right) - \frac{\beta v(t) x(t)}{T(t)}; \tag{8}$$

it is easy to show that $0 < T(t) < T_m$ for $t \in [0, t_1]$; we can see that $dx(t)/dt \geq -\beta(v(t)x(t)/T(t))$, and clearly $y(t) < T(t)$, for $t \in [0, t_1]$; these observations imply that, for $t \in [0, t_1]$, we have $dx(t)/dt \geq -\beta(v(t)x(t)/y(t))$.

Hence,

$$x(t_1) \geq x(0) e^{-\int_0^{t_1} (\beta v(s)/y(s))ds} > 0, \tag{9}$$

which contradicts our assumption.

Following a similar approach, we can prove that all the variables of system (3) are positive.

In order to prove boundedness of the solutions of system (3), we consider the following function:

$$\begin{aligned} F(t) = {} & Ncge^{-k\tau} x(t) + Ncgy(t+\tau) + \frac{cg}{2} v(t+\tau) \\ & + \frac{cq}{2} w(t+\tau) + Ngpz(t+\tau). \end{aligned} \tag{10}$$

From (3), we have

$$\begin{aligned} \frac{dF(t)}{dt} = {} & Ncge^{-k\tau}\left(rx(t) - rx(t)\frac{T(t)}{T_m}\right. \\ & \left. - \beta\frac{v(t)x(t)}{T(t)}\right) + Ncg\left(\beta e^{-k\tau}\frac{v(t)x(t)}{T(t)}\right. \\ & \left. - ay(t+\tau) - py(t+\tau)z(t+\tau)\right) \\ & + \frac{cg}{2}\left(aNy(t+\tau) - \delta v(t+\tau)\right. \\ & \left. - qv(t+\tau)w(t+\tau)\right) + \frac{cq}{2}\left(gv(t+\tau)w(t+\tau)\right. \\ & \left. - hw(t+\tau)\right) + Ngp\left(cy(t+\tau)z(t+\tau)\right. \\ & \left. - bz(t+\tau)\right); \end{aligned} \tag{11}$$

since $0 < T(t) < T_m$, $x(t) < T_m$, $-x(t)T(t) < -x(t)$ for $t > 0$, it follows that

$$\begin{aligned} \frac{dF(t)}{dt} \leq {} & Ncge^{-k\tau} rT_m - Ncge^{-k\tau}\frac{r}{T_m}x(t) \\ & - \frac{aNcg}{2}y(t+\tau) - \frac{\delta cg}{2}v(t+\tau) \\ & - \frac{hcq}{2}w(t+\tau) - Ngpbz(t+\tau); \end{aligned} \tag{12}$$

if we set $\varrho = \min(r/T_m, a/2, \delta, h, b)$, we will have

$$\frac{dF(t)}{dt} \leq Ncge^{-k\tau} - \varrho F(t). \tag{13}$$

Using Gronwall's Lemma, we have that $F(t)$ is bounded, which makes the variables $x(t)$, $y(t)$, $v(t)$, $w(t)$, and $z(t)$ bounded, which makes us unsure that the solution exists globally.

The above results show that the components of the solution of system (3) are nonnegative for all $t \in [0, b)$. Hence, the boundedness of $T(t), v(t), w(t)$, and $z(t)$ on $[0, b)$ imply that $b = \infty$. This completes the proof of the theorem. □

3. Equilibrium Points and Their Stability

First, we aim to find all possible equilibria points. It is clear that our model (3) has disease-free equilibrium $E_0 = (T_m, 0, 0, 0, 0)$. The second equilibrium $E_1 = (x_1, y_1, v_1, 0, 0)$ represents the no immune response equilibrium with

$$\begin{aligned} x_1 &= \frac{T_m \beta aN}{\mathcal{R}_0 \delta r}(\mathcal{R}_1 - 1), \\ y_1 &= \frac{T_m \beta aN}{\mathcal{R}_0 \delta r}(\mathcal{R}_0 - 1)(\mathcal{R}_1 - 1), \\ v_1 &= \frac{(aN)^2 \beta T_m}{\delta^2 \mathcal{R}_0 r}(\mathcal{R}_0 - 1)(\mathcal{R}_1 - 1). \end{aligned} \tag{14}$$

This equilibrium exits only if $\mathcal{R}_0 > 1$ and $\mathcal{R}_1 > 1$ with

$$\begin{aligned} \mathcal{R}_0 &= \frac{\beta e^{-k\tau} N}{\delta}, \\ \mathcal{R}_1 &= \frac{\delta r \mathcal{R}_0 + \beta aN}{\beta aN \mathcal{R}_0} = \left(\frac{re^{-k\tau}}{a} + 1\right)\frac{1}{\mathcal{R}_0}. \end{aligned} \tag{15}$$

We also have the equilibrium $E_2 = (x_2, y_2, v_2, 0, z_2)$, which represents an equilibrium where CTL cells are the only adaptive immune response and B-cells are zero. To define such equilibrium, we introduce the following thresholds:

$$\mathcal{R}^* = \frac{T_m \delta cr}{4\beta aNb}. \tag{16}$$

If $\mathcal{R}^* \geq 1$, then we define

$$\begin{aligned} \mathcal{R}_2 &= \frac{cT_m}{2b}\left(1 + \sqrt{1 - \frac{1}{\mathcal{R}^*}}\right), \\ \mathcal{R}_z &= \mathcal{R}_0\left(1 - \frac{1}{\mathcal{R}_2}\right). \end{aligned} \tag{17}$$

If $\mathscr{R}_2 > 1$ and $\mathscr{R}_z > 1$, then the coordinates of E_2 are given by

$$\begin{aligned} x_2 &= \frac{b}{c}\left(\mathscr{R}_2 - 1\right), \\ y_2 &= \frac{b}{c}, \\ v_2 &= \frac{aNb}{\delta c}, \\ z_2 &= \frac{a}{p}\left(\mathscr{R}_z - 1\right). \end{aligned} \tag{18}$$

Remark 2. If $\mathscr{R}_0 > 1$, we can easily prove the following:

(1) The equilibrium E_1 exists if and only if

$$1 < \mathscr{R}_0 < \frac{re^{-k\tau}}{a} + 1. \tag{19}$$

(2) $\mathscr{R}^* > 1$ is equivalent to

$$1 < \mathscr{R}_0 < \frac{T_m cre^{-k\tau}}{4ab}. \tag{20}$$

And if $\mathscr{R}_2 > 1$, this condition combined with the condition $\mathscr{R}_z > 1$ could be simplified to

$$1 < \frac{\mathscr{R}_2}{\mathscr{R}_2 - 1} < \mathscr{R}_0 < \frac{T_m cre^{-k\tau}}{4ab}. \tag{21}$$

From the two previous assessments, the model could have two equilibria E_1 and E_2 at same time if

$$1 < \frac{\mathscr{R}_2}{\mathscr{R}_2 - 1} < \mathscr{R}_0 < \min\left(\frac{T_m cre^{-k\tau}}{4ab}, \frac{re^{-k\tau}}{a} + 1\right). \tag{22}$$

Finally, it is easy to see that if $b/c \le T_m/2$ or $b/c \ge T_m$, then $\mathscr{R}_2 > 1$.

The third type of equilibrium, E_3, is characterised by no CTL cells response; that is, $z = 0$. For this reason, we define the threshold by

$$\mathscr{R}^\diamond = \frac{T_m gr}{4\beta h}. \tag{23}$$

If $\mathscr{R}^\diamond \ge 1$, we define T_l and T_h (with $T_l \le T_h$) by

$$\begin{aligned} T^h &= \frac{T_m}{2}\left(1 + \sqrt{1 - \frac{1}{\mathscr{R}^\diamond}}\right), \\ T^l &= \frac{T_m}{2}\left(1 - \sqrt{1 - \frac{1}{\mathscr{R}^\diamond}}\right). \end{aligned} \tag{24}$$

Hence, the coordinates of $E_3^i = (x_3^i, y_3^i, v_3, w_3^i, 0)$, with $i = l, h$, are given by

$$\begin{aligned} x_3^i &= \frac{ag\left(T^i\right)^2}{agT^i + \beta e^{-k\tau}h} \\ y_3^i &= \frac{\beta e^{-k\tau}hT^i}{agT^i + \beta e^{-k\tau}h} \\ v_3 &= \frac{h}{g} \\ w_3^i &= \frac{aNg}{q}\frac{\beta e^{-k\tau}T^i}{agT^i + \beta e^{-k\tau}h} - \frac{\delta}{q}. \end{aligned} \tag{25}$$

Notice that the virus coordinate does not depend on T^i. However, x_3^i, y_3^i, and w_3^i are increase functions with respect to T^i.

Notice that $w_3^i > 0$ require that $\mathscr{R}_0 > 1$ and

$$T^i > \frac{1}{\Phi}\frac{\mathscr{R}_0}{\mathscr{R}_0 - 1} \tag{26}$$

with Φ given by

$$\Phi = \frac{aN}{\delta} \cdot \frac{g}{h}. \tag{27}$$

Remark 3. We consider the threshold $\mathscr{R}_T$ defined by

$$\mathscr{R}_T = \frac{aNgb}{\delta hc} = \Phi\frac{b}{c}, \tag{28}$$

which represents the survival rate of the virus, with ignoring the antibody effect, aN/δ times g/h the survival rate of the antibody, over the survival rate of the CTL cells c/b.

It is easy to see that

$$\begin{gathered} \mathscr{R}^* > \mathscr{R}^\diamond \Longleftrightarrow \\ \mathscr{R}_T < 1 \\ \left(\text{resp. } \mathscr{R}^* < \mathscr{R}^\diamond \Longleftrightarrow \mathscr{R}_T > 1\right). \end{gathered} \tag{29}$$

Finally, we have the endemic equilibria, $E_4 = (x_4, y_4, v_4, w_4, z_4)$, where all the coordinates are nonzero. Using the same condition as the previous case, if $\mathscr{R}^\diamond \ge 1$, then there are two distinct $E_4^i = (x_4^i, y_4, v_4, w_4, z_4^i)$, with $i = l, h$, with the coordinate given by

$$\begin{aligned} x_4^i &= T^i - \frac{b}{c}, \\ y_4 &= \frac{b}{c}, \\ v_4 &= \frac{h}{g}, \end{aligned}$$

$$w^4 = \frac{\delta}{q}\left(\mathscr{R}_T - 1\right),$$
$$z_4^i = \frac{\beta e^{-k\tau} hc}{pbgT^i}\left(T^i - \frac{b}{c}\right) - \frac{a}{p}, \tag{30}$$

and T^l and T^h are defined in (24).

The endemic equilibria are characterised by two possible levels of the healthy cells and corresponding CTL cells. On the other hand, coordinates of the endemic equilibria are constant with respect to the rest of the variables. It is important to mention that the existence of these two endemic equilibria requires $\mathscr{R}^{\diamond} \geq 1$ for T^i to be feasible, and $\mathscr{R}_T > 1$, $T^i > b/c$, and $(\beta h e^{-k\tau}/agT^i)(T^i c/b - 1) > 1$.

3.1. The Stability Analysis. In this section, we investigate the condition of stability of each possible equilibria point. First, the Jacobian matrix of system (3) is given by

$$\begin{pmatrix} r\left(1 - \frac{2x+y}{T_m}\right) - \frac{\beta v y}{(x+y)^2} & \frac{-rx}{T_m} + \frac{\beta v x}{(x+y)^2} & -\frac{\beta x}{x+y} & 0 & 0 \\ \beta e^{-k\tau}\frac{vy}{(x+y)^2} & -\beta e^{-k\tau}\frac{vx}{(x+y)^2} - a - pz & \beta e^{-k\tau}\frac{x}{x+y} & 0 & -py \\ 0 & aN & -\delta - q\omega & -qv & 0 \\ 0 & 0 & g\omega & gv - h & 0 \\ 0 & cz & 0 & 0 & cy - b \end{pmatrix} \tag{31}$$

and we have the following results.

Proposition 4. *The free-equilibrium point E_0 is locally asymptotically stable when $\mathscr{R}_0 < 1$ and unstable when $\mathscr{R}_0 > 1$.*

Proof. The characteristic polynomial of the Jacobian matrix (31) at E_0 is given by

$$P_{E_0}(\lambda) = (\lambda + r)(\lambda + b)(-\lambda - h) \cdot \left(\lambda^2 + (a+\delta)\lambda + a\delta\left(1 - \mathscr{R}_0\right)\right), \tag{32}$$

and then the eigenvalues of the Jacobian matrix at E_f are

$$-r, -b, -h, \frac{-1}{2}\left(a + \delta + \sqrt{(a+\delta)^2 + 4a\delta\left(\mathscr{R}_0 - 1\right)}\right), \frac{-1}{2}\left(a + \delta - \sqrt{(a+\delta)^2 + 4a\delta\left(\mathscr{R}_0 - 1\right)}\right). \tag{33}$$

It is clear that the first four eigenvalues are negative. The fifth one is negative when $\mathscr{R}_0 < 1$. We conclude that the free-equilibrium point E_0 is locally asymptotically stable when $\mathscr{R}_0 < 1$ and unstable when $\mathscr{R}_0 > 1$. □

Next result will give the condition of stability of the no immune response equilibrium $E_1 = (x_1, y_1, v_1, 0, 0)$, where its coordinates are defined in (14).

Theorem 5. *(1) If $\mathscr{R}_0 < 1$, then the point E_1 does not exist.*

(2) If $\mathscr{R}_0 = 1$, then $E_1 = E_0$.

(3) If $1 < \mathscr{R}_0 < 1 + re^{-k\tau}/a$, then E_1 is locally asymptotically stable if $\min(\mathscr{H}_0, (gaN/h\delta)\mathscr{H}_0) < 1$; it is unstable for $\min(\mathscr{H}_0, (gaN/h\delta)\mathscr{H}_0) > 1$, with

$$\mathscr{H}_0 = \frac{T_m \beta a N}{\mathscr{R}_0 \delta r}\left(\mathscr{R}_0 - 1\right)\left(\mathscr{R}_1 - 1\right). \tag{34}$$

Proof. Since the positivity of y_2 and z_2 depends on the positive sign of $\mathscr{R}_0 - 1$, we conclude that E_1 does not exist if $\mathscr{R}_0 < 1$. Moreover, if $\mathscr{R}_0 = 1$, it is easy to say that $E_1 = E_f$. □

Next, we investigate the case where $1 < \mathscr{R}_0 < 1 + re^{-k\tau}/a$. Using the Jacobian matrix (31), the characteristic equation at E_1 is as follows:

$$\begin{aligned} P_{E_1}(\lambda) &= (cy_1 - b - \lambda)(gv_1 - h - \lambda)\left(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3\right), \\ a_1 &= \beta e^{-k\tau} T_v x_1 + \delta + \beta T_v y_1 + \frac{2x_1 + y_1}{T_m} r - r, \\ &= \beta e^{-k\tau} T_v x_1 + \delta + \beta T_v y_1 + \frac{\beta a N}{R_0 \delta r}\left[\left(\frac{re^{-k\tau}}{a} + 1\right)\frac{1}{R_0} - 1\right](R_0 + 1). \\ a_2 &= \beta e^{-k\tau} T_v x_1 \left(\delta + \frac{2x_1 + y_1}{T_m} r - r + \beta T_v y_1\right) + \left(\frac{2x_1 + y_1}{T_m} r - r + \beta T_v y_1\right)(a + \delta) - aN\beta e^{-k\tau} T_x, \\ a_3 &= \left(\frac{\beta a N}{R_0 \delta r}\left[\left(\frac{re^{-k\tau}}{a} + 1\right)\frac{1}{R_0} - 1\right](R_0 + 1) + \beta T_v y_1\right)\left[\delta\beta e^{-k\tau} T_v x_1 + a\delta + aN\beta e^{-k\tau} T_x\right] \\ &\quad + aN\beta^2 e^{-k\tau} T_v y_1 T_x, \end{aligned} \tag{35}$$

with

$$T_v = \frac{v_1}{(x_1 + y_1)^2},$$
$$T_x = \frac{x_1}{(x_1 + y_1)}. \tag{36}$$

Using the form of v_1 and y_1 given in (14), the two first eigenvalues $gv_1 - h$ and $cy_1 - b$ are negative (resp.) if and only if $(gaN/h\delta)\mathcal{H}_0 < 1$ and $\mathcal{H}_0 < 1$ (resp.).

On the other hand, from the Routh-Hurwitz theorem, the other eigenvalues of the above matrix have a negative real part when $1 < \mathcal{R}_0 < 1 + re^{-k\tau}/a$.

Remark 6. (i) If $h\delta/aNg > 1$, the condition $\min(\mathcal{H}_0, (gaN/h\delta)\mathcal{H}_0) < 1$ can be replaced by $\mathcal{H}_0 < 1 < h\delta/aNg$.

(ii) As the delay τ increases, by the inequality $1 < \mathcal{R}_0 < 1 + re^{-k\tau}/a$, the quantity $\mathcal{R}_0$ will be a bit bigger than one.

Next, we study the condition of local stability of the equilibrium E_2.

Theorem 7. *Assume that $\mathcal{R}_0 > 1$; then the following applies:*

(1) *If $\mathcal{R}_2 \le 1$, then E_2 does not exist.*

(2) *If $\mathcal{R}_2 > 1$*

(a) *If $\mathcal{R}_2/(\mathcal{R}_2 - 1) > \mathcal{R}_0$, then E_2 does not exist.*

(b) *If $\mathcal{R}_2/(\mathcal{R}_2 - 1) = \mathcal{R}_0$, then $E_2 = E_1$.*

(c) *If $\mathcal{R}_2/(\mathcal{R}_2 - 1) < \mathcal{R}_0 < T_m cre^{k\tau}/4ab$*

(i) *If $\Phi < 1$, then E_2 is locally asymptotically stable.*

(ii) *If $\Phi > 1$, then E_2 is unstable, where Φ is defined in (27).*

Proof. We can easily notice that $\mathcal{R}_2 \le 1$ and then $\mathcal{R}_z \le 0$, and then $x_2 < 0$ and $z_2 < 0$, which means that E_2 does not exist.

On the other hand, if $\mathcal{R}_2 > 1$ and $1 < \mathcal{R}_0 < \mathcal{R}_2/(\mathcal{R}_2 - 1)$, then $z_2 < 0$, and if $\mathcal{R}_2 > 1$ and $1 < \mathcal{R}_0 = \mathcal{R}_2/(\mathcal{R}_2 - 1)$, then $R_z = 1$ and then $z_2 = w_2 = 0$ and $E_2 = E_1$.

Assume that $\mathcal{R}_2 > 1$ and condition (22) holds. From (31), the characteristic equation at E_2 is given by

$$P_{E_2}(\lambda) = (gv_2 - h - \lambda)\left(\lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4\right), \tag{37}$$

where

$$b_1 = \delta + \beta e^{-k\tau}T_v x_2 + a + pz_2 + \beta T_v y_2 + \frac{2x_2 + y_2}{T_m}r - r,$$

$$b_2 = \delta\beta e^{-k\tau}T_v x_2 + a\delta + p\delta z_2 - aN\beta e^{-k\tau}T_x + py_2 + \left(\beta T_v y_2 + \frac{2x_2 + y_2}{T_m}r - r\right) \cdot \left(\delta + \beta e^{-k\tau}T_v x_2 + a + pz_2\right),$$

$$b_3 = (b - cy_2) \cdot \left(\delta\beta e^{-k\tau}T_v x_2 + a\delta + p\delta z_2 - aN\beta e^{-k\tau}T_x\right) + py_2 cz_2\delta + \left(\beta T_v y_2 + \frac{2x_2 + y_2}{T_m}r - r\right) \cdot \left(\delta\beta e^{-k\tau}T_v x_2 + a\delta + p\delta z_2 - aN\beta e^{-k\tau}T_x + py_2\right),$$

$$b_4 = \left(\beta T_v y_2 + \frac{2x_2 + y_2}{T_m}r - r\right)(cy_2 - b) \cdot \left(\delta\beta e^{-k\tau}T_v x_2 + a\delta + p\delta z_2 - aN\beta e^{-k\tau}T_x\right) - \left(\beta T_v y_2 \frac{2x_2 + y_2}{T_m}r - r\right) py_2 cz_2\delta, \tag{38}$$

with

$$T_v = \frac{v_1}{(x_1 + y_1)^2},$$
$$T_x = \frac{x_1}{(x_1 + y_1)}. \tag{39}$$

It is clear that $gv_2 - h = h(\Phi - 1)$ is an eigenvalue of J_{E_2}. The sign of this eigenvalue is negative if $\Phi < 1$, positive if $\Phi > 1$, and zero when $\Phi = 1$. On the other hand, from the Routh-Hurwitz theorem applied to the fourth-order polynomial in the characteristic equation, the other eigenvalues of the above matrix have negative real parts when $\Phi < 1$. Consequently, if $\mathcal{R}_2 > 1$ and $\mathcal{R}_2/(\mathcal{R}_2 - 1) < \mathcal{R}_0 < T_m cre^{k\tau}/4ab$, then E_2 is unstable when $\Phi > 1$ and locally asymptotically stable when $\Phi < 1$. □

Now, we aim to find the condition of local stability of the equilibrium E_3^h; we have the following result.

Theorem 8. *Assume that $\mathcal{R}_0 > 1$ and $\mathcal{R}^\diamond > 1$:*

(1) *If $T^h < (\beta e^{-\tau k}h/ag)(1/(\mathcal{R}_0 - 1))$, then equilibria E_3^i for $i = l, h$ do not exist and $E_3^h = E_1$ when $T^h = (\beta e^{-\tau k}h/ag)(1/(\mathcal{R}_0 - 1))$.*

(2) *If $(\beta e^{-\tau k}h/ag)(1/(\mathcal{R}_0 - 1)) < T^h < (1/\mathcal{R}_0)(gN/\delta ch + \mathcal{R}_0/c)$, then E_3^h are locally asymptotically stable.*

(3) *If $T^h > \max((\beta e^{-\tau k}h/ag)(1/(\mathcal{R}_0 - 1)), (1/\mathcal{R}_0)(gN/\delta ch + \mathcal{R}_0/c))$, then E_3 is unstable.*

Proof. It is easy to see that if $T^h < (1/\mathcal{R}_0)((g + \beta he^{-\tau k})/ag)$, then the equilibrium E_3^h does not exist and if $T^h = (\beta e^{-\tau k}h/ag)(1/(\mathcal{R}_0 - 1))$ the two points E_3^h and E_1 coincide.

If $T^h > (\beta e^{-\tau k}h/ag)(1/(\mathcal{R}_0 - 1))$, using the Jacobian matrix (31), we get the following characteristic equation at E_3^i:

$$P_{E_3^i}(\lambda) = \left(cy_3^i - b - \lambda\right)\left(\lambda^4 + c_1\lambda^3 + c_2\lambda^2 + c_3\lambda + c_4\right), \quad (40)$$

where

$$\begin{aligned}
c_1 &= \beta e^{-k\tau}T_v x_3^i + a + \delta + \frac{2x_3^i + y_3^i}{T_m}r - r + \beta T_v y_3^i \\
&\quad + qw_3^i, \\
c_2 &= qv_3 g w_3^i + \left(\delta + qw_3^i\right)(h - gv_3) + \left(\beta e^{-k\tau}T_v x_3^i \right. \\
&\quad \left. + a\right)\left(\delta + qw_3^i - gv_3 + h + aN\beta e^{-k\tau}T_x\right) \\
&\quad + \left(\frac{2x_3^i + y_3^i}{T_m}r - r + \beta T_v y_3^i\right)\left(\beta e^{-k\tau}T_v x_3^i + a - qw_3^i \right. \\
&\quad \left. + gv_3 - \delta - h\right) - \beta e^{-k\tau}T_v y_3^i\left(-\frac{rx_1^i}{T_m} + \beta T_v x_3^i\right), \\
c_3 &= \left(-\beta e^{-k\tau}T_v x_3^i - a\right)\left(\delta + qw_3^i\right)(gv_3 - h) \\
&\quad + \left(\beta e^{-k\tau}T_v x_3^i + a\right)qv_3 g w_3^i + aN\beta e^{-k\tau}T_x(gv_3 - h) \\
&\quad + \left(-\frac{2x_3^i + y_3^i}{T_m}r + r - \beta T_v y_3^i\right)\left(-\beta e^{-k\tau}T_v x_3^i - a\right)\left(\delta \right. \\
&\quad \left. + qw_3^i - gv_3 + h + aN\beta e^{-k\tau}T_x\right) + \left(-\frac{2x_3^i + y_3^i}{T_m}r \right. \\
&\quad \left. + r - \beta T_v y_3^i\right)\left(\delta + qw_3^i\right)(gv_3 - h) + \left(\frac{2x_3^i + y_3^i}{T_m}r \right. \\
&\quad \left. - r + \beta T_v y_3^i\right)qv_3 g w_3^i + \beta e^{-k\tau}T_v y_3^i\left(\beta T_x aN \right. \\
&\quad + (gv_3 - h)\left(-\frac{rx_1^i}{T_m} + \beta T_v x_3^i\right) \\
&\quad \left. + \left(-\frac{rx_1}{T_m} + \beta T_v x_3^i\right)\left(\delta + qw_3^i\right)\right), \\
c_4 &= \left(-\frac{2x_3^i + y_3^i}{T_m}r + r - \beta T_v y_3^i\right)\left(-\beta e^{-k\tau}T_v x_3^i - a\right) \\
&\quad \cdot \left(\left(\delta + qw_3^i\right)(h - gv_3) + qv_3 g w_3^i\right) + \left(-\frac{rx_3^i}{T_m} \right. \\
&\quad \left. + \beta T_v x_3^i\right)\left(\delta + qw_3^i\right)gv_3\beta e^{-k\tau}T_v y_3^i \\
&\quad - \beta e^{-k\tau}T_v y_3^i\left(qv_3 g w_3^i\left(-\frac{rx_3^i}{T_m} + \beta T_v x_3^i\right)\right. \\
&\quad \left. + (gv_3 - h)\beta T_x aN\right),
\end{aligned} \quad (41)$$

with

$$\begin{aligned}
T_v &= \frac{v_3}{\left(x_3^i + y_3^i\right)^2}, \\
T_x &= \frac{x_3^i}{\left(x_3^i + y_3^i\right)}.
\end{aligned} \quad (42)$$

It is clear that $cy_3^h - b = b(c\beta h e^{-k\tau}T^h/b(g + \beta e^{-k\tau}h) - 1)$ is an eigenvalue of $J_{E_3^h}$. The sign of this eigenvalue is negative if $T^h < b(g + \beta e^{-k\tau}h)/c\beta h e^{-k\tau}$, which is equivalent to $T^h < (1/\mathcal{R}_0)(gN/\delta ch + \mathcal{R}_0/c)$. The sign of this eigenvalue is positive if $T^h > (1/\mathcal{R}_0)(gN/\delta ch + \mathcal{R}_0/c)$, which will give, with $T^h > (1/\mathcal{R}_0)((g + \beta h e^{-\tau k})/ag)$, the condition of instability of the theorem.

On the other hand, from the Routh-Hurwitz theorem, the other eigenvalues of the above matrix have a negative real part when $T^h < b(g + \beta e^{-k\tau}h)/c\beta h e^{-k\tau}$.

Consequently, if $(\beta e^{-\tau k}h/ag)(1/(\mathcal{R}_0 - 1)) < T^h < (1/\mathcal{R}_0)(gN/\delta ch + \mathcal{R}_0/c)$, then E_3^h is locally asymptotically stable. □

Theorem 9. *(1) If $\Phi < 1$ or $H_i^{w,z} < 1$, then the point E_4^i with $i = l, h$ does not exist. Moreover, $E_4^i = E_2$ when $\Phi = 1$ and $E_4^i = E_2$ when $H_i^{w,z} = 1$.*

(2) If $\Phi > 1$ and $H_i^{w,z} > 1$, then E_4^i is locally asymptotically stable.

Here

$$H_i^{w,z} = \frac{c\beta e^{-k\tau}hT^i}{b\left(g + \beta e^{-k\tau}h\right)}; \quad i = l, h. \quad (43)$$

4. The Optimal Control Therapy Analysis

In this section, we consider the optimal control of the HBV drug therapy; as we mentioned previously, the therapy has an antiviral effect by reducing the viral production rate and blocking the shedding and bending of the virus to the uninfected cells. For this purpose, we consider the controlled version of system (3) defined as follows:

$$\begin{aligned}
\frac{dx}{dt} &= rx(t)\left(1 - \frac{T(t)}{T_m}\right) - \beta\left(1 - u_1(t)\right)\frac{v(t)x(t)}{T(t)}, \\
\frac{dy}{dt} &= \beta e^{-k\tau}\left(1 - u_1(t)\right)\frac{v(t-\tau)x(t-\tau)}{T(t-\tau)} - ay(t) \\
&\quad - py(t)z(t), \\
\frac{dv}{dt} &= \left(1 - u_2(t)\right)aNy(t) - \delta v(t) - qv(t)w(t), \\
\frac{dw}{dt} &= gv(t)w(t) - hw(t), \\
\frac{dz}{dt} &= cy(t)z(t) - bz(t).
\end{aligned} \quad (44)$$

The optimization problem that we consider is to maximize the following objective functional:

$$J(u_1,u_2)=\int_0^{t_f}\left\{x(t)+z(t)+w(t)-\left[\frac{A_1}{2}u_1^2(t)+\frac{A_2}{2}u_2^2(t)\right]\right\}dt, \tag{45}$$

where t_f stands for the time period of treatment. The two positive constants A_1 and A_2 are the weight for the treatment. It is legitimate to assume that two control functions, $u_1(t)$ and $u_2(t)$, are bounded and Lebesgue integrable. These assumptions align with the fact that the drug has a limited dosage and time to use.

The goal is to decrease the viral load while increasing the number of the uninfected cells and maximizing the immune responses. This should be done with minimizing the cost of treatment. We can achieve this goal by maximizing the objective functional defined in (45), which means finding the optimal control pair (u_1^*,u_2^*) such that

$$J(u_1^*,u_2^*)=\max\{J(u_1,u_2):(u_1,u_2)\in U\}, \tag{46}$$

where U is the control set defined by

$$U=\left\{(u_1(t),u_2(t)):u_i(t)\ \text{measurable},\ 0\le u_i(t)\le 1,\ t\in\left[0,t_f\right],\ i=1,2\right\}. \tag{47}$$

First, we need to ensure the existence of the optimal control pair. Using the results in Fleming and Rishel [33] and Lukes [34], we have the following theorem.

Theorem 10. *There exists an optimal control pair* $(u_1^*,u_2^*)\in U$ *such that*

$$J(u_1^*,u_2^*)=\max_{(u_1,u_2)\in U}J(u_1,u_2). \tag{48}$$

The proof of this result is omitted since it is similar to the one in Tridane et al. [16].

Next, via Pontryagin's Minimum Principle [35], we give the necessary conditions for an optimal control problem. We convert solving our optimization problem into maximizing the Hamiltonian $H\equiv H(t,x,y,v,z,w,x_\tau,v_\tau,u_1,u_2,\lambda_i)$ point-wisely with respect to u_1 and u_2 as follows:

$$H=\frac{A_1}{2}u_1(t)^2+\frac{A_2}{2}u_2(t)^2-x(t)-z(t)-w(t)+\sum_{i=0}^{5}\lambda_i f_i \tag{49}$$

with

$$\begin{aligned}
f_1&=rx(t)\left(1-\frac{T(t)}{T_m}\right)-\beta(1-u_1(t))\frac{v(t)x(t)}{T(t)},\\
f_2&=\beta e^{-k\tau}(1-u_1(t))\frac{v(t-\tau)x(t-\tau)}{T(t-\tau)}-ay(t)\\
&\quad-py(t)z(t),\\
f_3&=(1-u_2(t))aNy(t)-\delta v(t)-qv(t)w(t),\\
f_4&=gv(t)w(t)-hw(t),\\
f_5&=cy(t)z(t)-bz(t).
\end{aligned} \tag{50}$$

And λ_i, $i=1,2,3,4,5$, are the adjoint functions to be determined. By applying Pontryagin's Minimum Principle in the case system with delay [35], we have the following theorem.

Theorem 11. *Given optimal controls* u_1^*, u_2^* *and solutions* x^*, y^*, v^*, z^* , *and* w^* *of the corresponding state system (3), there exist adjoint variables,* λ_1, λ_2, λ_3, λ_4, *and* λ_5 *satisfying the equations*

$$\begin{aligned}
\frac{d\lambda_1(t)}{dt}&=1-\lambda_1(t)\left[r\left(1-\frac{T^*(t)}{T_m}\right)-\frac{rx^*(t)}{T_m}-(1-u_1^*(t))\beta v^*(t)\frac{y^*(t)}{T^{*2}}\right]-\chi_{[0,t_f-\tau]}(t)\lambda_2(t\\
&\quad+\tau)(u_1^*(t+\tau)-1)\beta e^{-k\tau}v^*(t)\frac{y^*(t)}{T^{*2}(t)},\\
\frac{d\lambda_2(t)}{dt}&=\lambda_1(t)\left(\frac{rx^*(t)}{T_m}-(1-u_1^*(t))\beta v^*(t)\frac{x^*(t)}{T^{*2}}\right)+\lambda_2(t)(a+pz)\\
&\quad-\lambda_3(t)(1-u_2^*(t))aN-cz^*(t)\lambda_5(t)\\
&\quad-\chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)(u_1^*(t+\tau)-1)\beta e^{-k\tau}v^*(t)\\
&\quad\cdot\frac{x^*(t)}{T^{*2}(t)},\\
\frac{d\lambda_3(t)}{dt}&=\lambda_1(t)\left[\beta(1-u_1^*(t))\frac{x^*(t)}{T^*(t)}\right]+\lambda_3(t)(\delta\\
&\quad+qw(t))-\lambda_4(t)gw^*(t)+\chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)\\
&\quad\cdot\left[\beta e^{-k\tau}(u_1^*(t+\tau)-1)\frac{x^*(t)}{T^*(t)}\right],\\
\frac{d\lambda_4(t)}{dt}&=1+\lambda_3(t)qv^*(t)+\lambda_4(t)\left[h-gv^*(t)\right],\\
\frac{d\lambda_5(t)}{dt}&=1+\lambda_2(t)py^*(t)+\lambda_5(t)\left[b-cy^*(t)\right],
\end{aligned} \tag{51}$$

with χ *being an indicator function and* $T^*(t)=x^*(t)+y^*(t)$ *also the transversality conditions*

$$\lambda_i\left(t_f\right) = 0, \quad i = 1, \ldots, 5. \tag{52}$$

Moreover, the optimal control is given by

$$\begin{aligned} u_1^* &= \min\left(1, \max\left(0, \frac{\beta}{A_1}\left[\lambda_2(t)\, e^{-k\tau}\frac{v^*(t-\tau)\, x^*(t-\tau)}{T^*(t-\tau)} - \lambda_1(t)\,\frac{v^*(t)\, x^*(t)}{T^*}\right]\right)\right) \\ u_2^* &= \min\left(1, \max\left(0, \frac{1}{A_2}\lambda_3(t)\, aNy^*(t)\right)\right). \end{aligned} \tag{53}$$

5. Numerical Simulations

In order to solve our optimization system, we use a numerical schema based on the forward and backward finite difference approximation. This schema was originally presented in the case of ODE system in [36], used similarly by [37] and enhanced for delay differential equation system [38–40].

We consider the step size $h > 0$ and $(n, m) \in \mathbb{N}^2$ with $\tau = mh$ and $t_f - t_0 = nh$. We take m knots to left of t_0 and right of t_f, to get the following partition:

$$\begin{aligned} \Delta = \big(&t_{-m} = -\tau < \cdots < t_{-1} < t_0 = 0 < t_1 < \cdots < t_n = t_f \\ &< t_{n+1} < \cdots < t_{n+m}\big), \end{aligned} \tag{54}$$

which gives $t_i = t_0 + ih$ $(-m \le i \le n + m)$. The state and the adjoint variables are $x(t)$, $y(t)$, $v(t)$, $w(t)$, $z(t)$, $\lambda_1(t)$, $\lambda_2(t)$, $\lambda_3(t)$, $\lambda_4(t)$, and $\lambda_5(t)$ and the controls are $u_1(t)$, $u_2(t)$ in terms of nodal points x_i, y_i, v_i, w_i, z_i, λ_1^i, λ_2^i, λ_3^i, λ_4^i, λ_5^i, u_1^i, and u_2^i. By combining the forward and backward difference approximation, we get Algorithm 1.

For the simulation, we use the parameter values given in Table 1.

As the parameters having been chosen from different references (see Table 1), we use in our numerical simulations a set of parameters that are within the range of the estimation of these references; that is, $r = 1$, $T_m = 2 \times 10^{11}$, $\beta = 0.0018$, $k = 1.1 \times 10^{-2}$, $\tau = 1$, $a = 0.0693$, $N = 480$, $\delta = 0.693$, $q = 0.01$, $p = 0.001$, $c = 4.4 \times 10^{-8}$, $b = 0.5$, $q = 10^{-10}$, $g = 10^{-4}$, $h = 0.1$, $A_1 = 250$, and $A_2 = 2500$.

First, we start our simulation by showing the effect of the delay on the dynamics of the different cells' population as well as the free virions particles. Figure 1 presents the time series of the uninfected cells, the infected cells, the free viruses, and the antibodies. The dashed curves represent the case with delay, while the solid curves show the case without delay. The delay has a clear effect on the dynamics of the early HBV infection by slowing down the overall time series by expending the time between the phases of each curve. However, there is no difference between the two cases as the time passes, which means that the time delay could have an effect on the time scale in planning the treatment period. However, the delay does not lead to periodic dynamics of the model. Hence, the delay cannot cause periodic oscillations.

The next illustrative simulation of the model aims to help in comparing the uninfected cells, the infected cells, the viral load, and the immune response with and without therapy.

Figure 2 shows an increase of the healthy hepatocytes (a) in the first three days, but it is clear that the therapy gives a substantial increase of healthy hepatocytes, with more than 200,000 cells, compared with the case without therapy.

We notice also that, in the absence of the therapy, the number of the infected hepatocytes (b) increases rapidly in the first four days, decreases within twenty days, and increases after 25 days, whereas, in the presence of treatment, the number of infected hepatocytes decreases asymptotically to an undetectable level. More precisely, the number of infected cells with control stabilises at 2.5482, while the number of infected cells without control reaches 2.264×10^5, which makes the drug therapy efficiency in blocking the new infections at 98.73%.

In Figure 2, we see that the number of free virions (a) decreases rapidly towards an undetectable level after introducing the therapy. In fact, with control, the virus stabilises at 1.2112 while without control it reaches 9.768×10^6, which represents a perfect efficiency of the drug therapy in inhibiting the viral production (about 99.99%).

Figure 3(b) shows the antibodies immune response as a function of time. Without the therapy, the antibody level shows relapse in count 50 days after the infection, before it persists over time. We can see clearly that the relapse of the antibody synchronised with the virus peak. On the other hand, the early therapy reduces the burden on the antibody as immune response is barely measured.

The optimal therapy protocol is represented by Figure 4. Each curve presents the optimal drug dosage efficiency and the drug timing during the time of therapy. The optimal therapy requires having a full dosage efficiency for both drugs; the efficiency should be for about 4 days for INF and about 2 weeks for NAs. After 4 days, the INF administration should be stopped and again retaken until it reaches 32% efficiency. Later on, the efficiency can be dropped to less than 10%. For the NAs drugs, after two weeks, the efficiency can be reduced to 50% and eventually dropped to 15% for the rest of the treatment duration.

6. Conclusion

In this paper, we investigated a mathematical model of the adaptive immune response of the early stage of HBV. The early stage is characterised by a delay in the infection process and a logistic growth of the healthy hepatocyte cells. The aim is to study the role of the two arms of the adaptive immune response, represented by the antibodies and the

Step 1:
for $i = -m, \ldots, 0$, do:
$x_i = x_0$, $y_i = y_0$, $T_i = x_0 + y_0$, $v_i = v_0$, $w_i = w_0$, $z_i = z_0$, $u_1^i = 0$, $u_2^i = 0$.
end for
for $i = n, \ldots, n + m$, do:
$\lambda_1^i = 0$, $\lambda_2^i = 0$, $\lambda_3^i = 0$, $\lambda_4^i = 0$, $\lambda_5^i = 0$.
end for
Step 2:
for $i = 0, \ldots, n - 1$, do:

$$x_{i+1} = x_i + h\left[rx_i\left(1 - \frac{T_i}{T_m}\right) - \beta\left(1 - u_1^i\right)\frac{v_i x_i}{T_i}\right],$$

$$y_{i+1} = y_i + h\left[\beta e^{-k\tau}\left(1 - u_1^i\right)v_{i-m}\frac{x_{i-m}}{T_{i-m}} - ay_i - py_i z_i\right],$$

$$v_{i+1} = v_i + h\left[\left(1 - u_2^i\right)aNy_i - \delta v_i - qv_i w_i\right],$$

$$w_{i+1} = w_i + h\left[gv_i w_i - hw_i\right],$$

$$z_{i+1} = z_i + h\left[cy_i z_i - bz_i\right],$$

$$T_{i+1} = x_{i+1} + y_{i+1},$$

$$\lambda_1^{n-i-1} = \lambda_1^{n-i} - h\left[1 - \lambda_1^{n-i}\left(r\left(1 - \frac{T_{i+1}}{T_m}\right) - r\frac{x_{i+1}}{T_m} - \left(1 - u_1^i\right)\beta v_{i+1}\frac{y_{i+1}}{T_{i+1}}\right) - \chi_{[0,t_f-\tau]}\left(t_{n-i}\right)\lambda_2^{n-i+m}\left(u_1^{i+m} - 1\right)\beta e^{-k\tau}v_{i+1}\frac{y_{i+1}}{T_{i+1}^2}\right],$$

$$\lambda_2^{n-i-1} = \lambda_2^{n-i} - h\left[\lambda_1^{n-i}\left(r\frac{x_{i+1}}{T_m} - \left(1 - u_1^i\right)\beta v_{i+1}\frac{x_{i+1}}{T_{i+1}^2}\right) + \lambda_2^{n-i}\left(a + pz_{i+1}\right) - \lambda_3^{n-i}\left(1 - u_2^i\right)aN - cz_{i+1}\lambda_5^{n-i}\right]$$
$$-\chi_{[0,t_f-\tau]}(t_{n-i})\lambda_2^{n-i+m}(u_1^{i+m} - 1)\beta e^{-k\tau}v_{i+1}\frac{x_{i+1}}{T_{i+1}^2},$$

$$\lambda_3^{n-i-1} = \lambda_3^{n-i} - h\left[\lambda_1^{n-i}\left(1 - u_1^i\right)\beta\frac{x_{i+1}}{T_{i+1}} + \lambda_3^{n-i}\left(\delta + qw_{i+1}\right) - \lambda_4^{n-i}gw_{i+1} + \chi_{[0,t_f-\tau]}\left(t_{n-i}\right)\lambda_2^{n-i+m}\left(u_1^{i+m} - 1\right)\beta e^{-k\tau}\frac{x_{i+1}}{T_{i+1}}\right],$$

$$\lambda_4^{n-i-1} = \lambda_4^{n-i} - h\left[1 + q\lambda_3^{n-i}v_{i+1} + \lambda_4^{n-i}\left(h - gv_{i+1}\right)\right],$$

$$\lambda_5^{n-i-1} = \lambda_5^{n-i} - h\left[1 + p\lambda_2^{n-i}y_{i+1} + \lambda_5^{n-i}\left(b - cy_{i+1}\right)\right],$$

$$R_1^{i+1} = \left(\frac{\beta}{A_1}\right)\left(\lambda_2^{n-i-1}e^{-k\tau}v_{i-m+1}\frac{x_{i-m+1}}{T_{i-m+1}} - \lambda_1^{n-i-1}v_{i+1}\frac{x_{i+1}}{T_{i+1}}\right)$$

$$R_2^{i+1} = \left(\frac{1}{A_2}\right)\lambda_3^{n-i-1}aNy_{i+1},$$

$$u_1^{i+1} = \min\left(1, \max\left(R_1^{i+1}, 0\right)\right),$$

$$u_2^{i+1} = \min\left(1, \max\left(R_2^{i+1}, 0\right)\right),$$

end for
Step 3:
for $i = 1, \ldots, n$, write
$x^*(t_i) = x_i$, $y^*(t_i) = y_i$, $T^*(t_i) = T_i$, $v^*(t_i) = v_i$, $z^*(t_i) = z_i$, $w^*(t_i) = w_i$, $u_1^*(t_i) = u_1^i$, $u_2^*(t_i) = u_2^i$.
end for

Algorithm 1

Table 1: Parameters, their symbols, and default values used in Model (3).

Parameters	Meaning	Value	References
r	Maximum hepatocyte growth rate	≤ 1.0 day^{-1}	[23, 24]
T_m	Hepatocyte carrying capacity	2×10^{11} cells	[25]
β	Rate of virion infection of hepatocytes	3.6×10^{-5}–1.8×10^{-3} cells virion^{-1} day^{-1}	[26]
τ	Time delay	1 day	[27, 28]
k	Normal death rate for hepatocytes	.0039 day^{-1}	[27, 28]
a	Infected hepatocyte death rate	0.0693–0.00693 day^{-1}	[25]
p	Clearance rate of infection	$7 \pm 1.7 \times 10^{-4}$ ml/cell day^{-1}	[29]
N	Number of free viruses produced by infected cells	480	[12, 13]
δ	Free virion half-life	0.67 day^{-1}	[30]
q	Neutralization rate of virion and antibodies	10^{-10}–10^{-12} ml day^{-1}	[31]
g	Activation rate of B-cells	1.38×10^{-2}–10^{-4} day^{-1}	[31]
h	Death rate of B-cells	0.03–0.1 day^{-1}	[31]
c	Activation rate of CTL cells	$4.4 \pm 1.5 \times 10^{-7}$ ml cell^{-1} day^{-1}	[29]
b	Death rate of CTL cells	0.5 day^{-1}	[32]

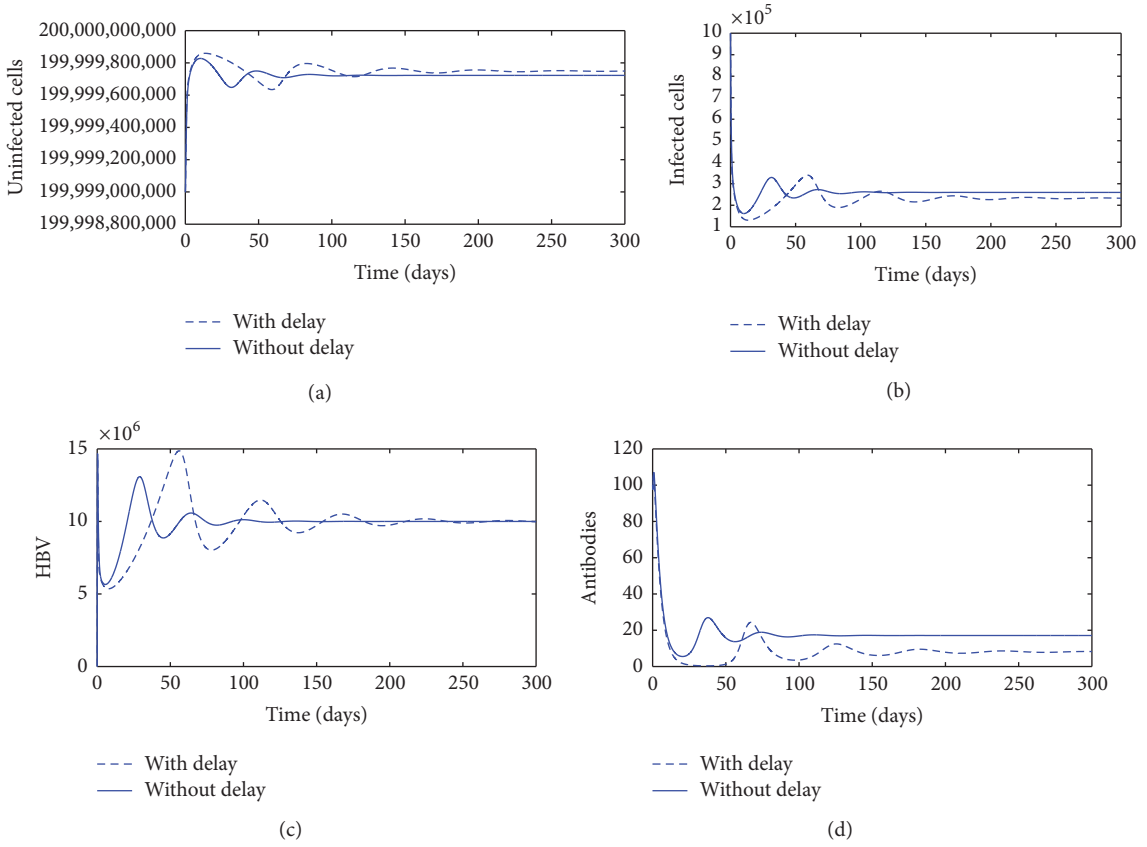

Figure 1: The uninfected cells (a). The infected cells (b). The HBV (c). The antibody response (d).

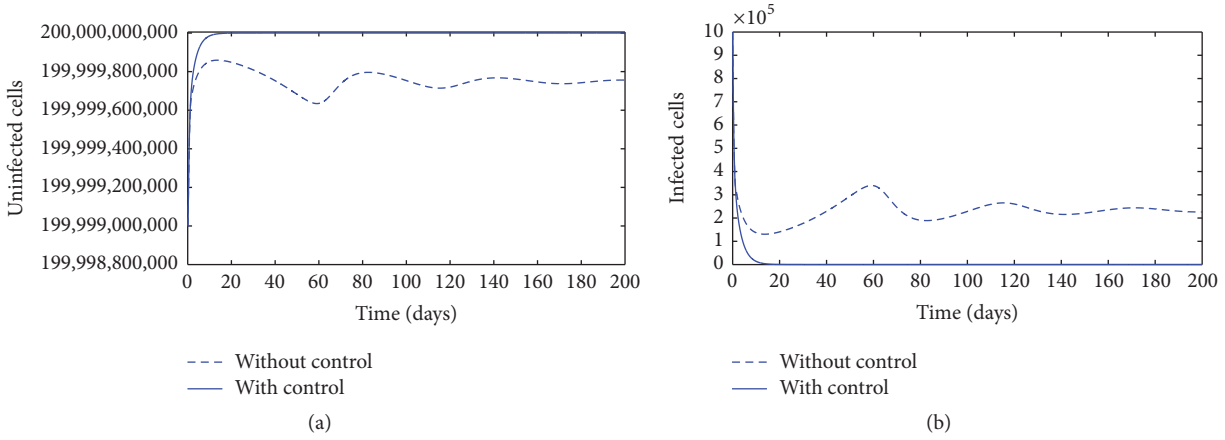

Figure 2: The uninfected cells as a function of time (a). The infected cells as a function of time (b).

CTL cells, in the progress of the HBV infection as the virus gains ground and becomes widespread. Our study showed the possibility of several outcomes depending on many thresholds, which led us to find the conditions of existence of four possible equilibria and investigate their local stability. The stability analysis of these equilibria was very involving and required rigorous calculations. Our mathematical analysis and numerical simulations show that the delay has the effect of slowing down the progress of the disease but does not lead to oscillatory behavior of the dynamics.

As a result of this finding, our next goal was to find the possibility of introducing the actual therapy, which includes standard interferon-α and nucleoside analogues. For this purpose, we investigated the optimal control of this therapy via the proposed model. The implementation of such therapy in the early stage instead of the acute stage of HBV infection could be helpful in reducing the burden of the disease. The optimal therapy aims to increase the efficacy of the drug while keeping the healthy hepatocyte cells at the normal level and enhancing the immune response. To solve this problem,

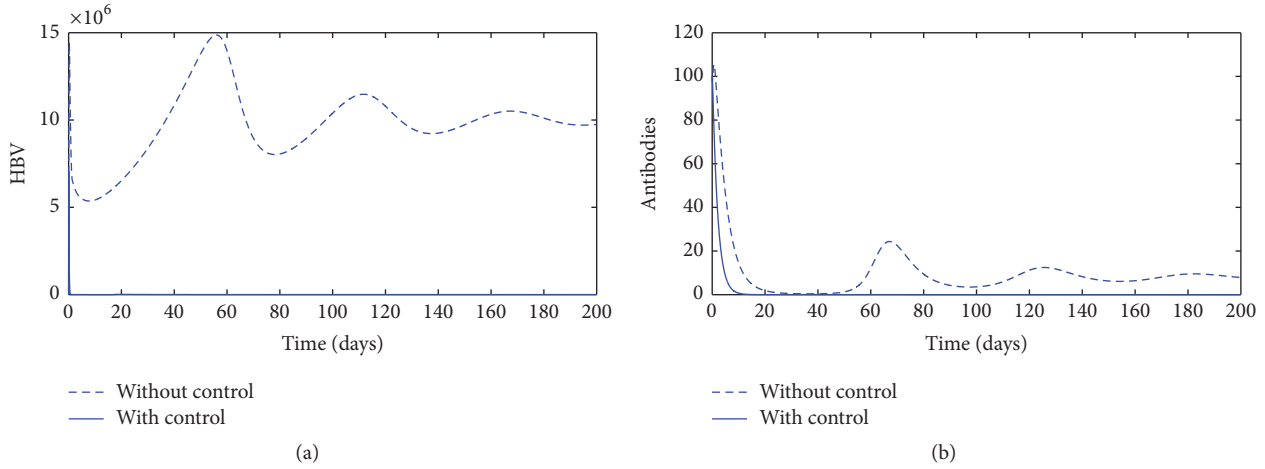

Figure 3: The HBV as a function of time (a). The antibody response as a function of time (b).

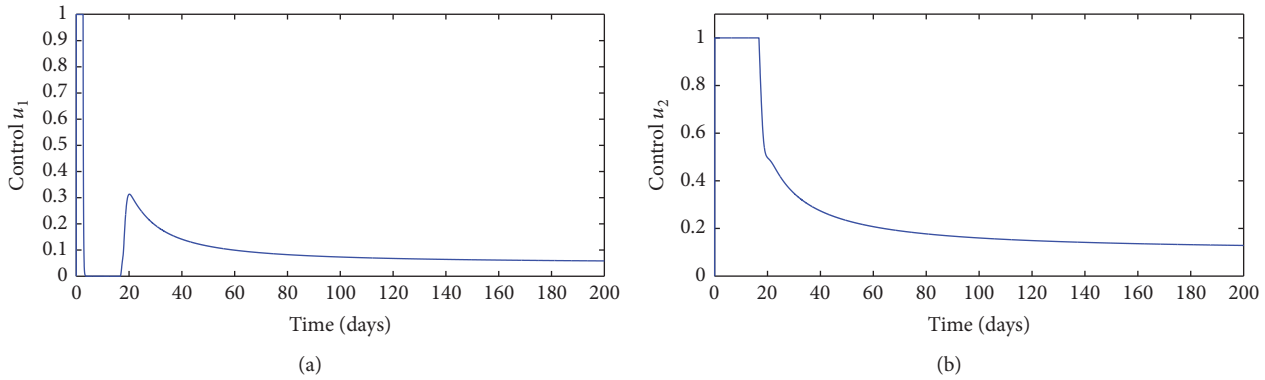

Figure 4: The optimal control u_1 (a) and the optimal control u_2 (b) versus time.

we used the standard techniques to prove the condition of existence of a solution and to find the optimality system. A well-known numerical method was used to solve the optimality system and to identify the best treatment strategy of HBV infection to block new infections and prevent viral production using drug therapy with minimum side effects on the immune response and the healthy hepatocyte cells.

Our numerical results show that the optimal treatment strategies should have high efficiency at the beginning of the therapy, about four days for INF and two weeks for NAs; the efficiency can be adjusted to 10% for INF and to 50% for NAs, and gradually to 15%.

Since there is no clear guideline for the combination therapy in general [41] and for the early infection of HBV in particular, this work should serve as an initial step to consider an early combined use of IFN and NAs in HBV infection. Of course, more pharmacokinetic studies are needed to investigate the long time use of this therapy and the possible risk of treatment failure [8].

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Qualitative Analysis of a Generalized Virus Dynamics Model with Both Modes of Transmission and Distributed Delays

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We propose a generalized virus dynamics model with distributed delays and both modes of transmission, one by virus-to-cell infection and the other by cell-to-cell transfer. In the proposed model, the distributed delays describe (i) the time needed for infected cells to produce new virions and (ii) the time necessary for the newly produced virions to become mature and infectious. In addition, the infection transmission process is modeled by general incidence functions for both modes. Furthermore, the qualitative analysis of the model is rigorously established and many known viral infection models with discrete and distributed delays are extended and improved.

1. Introduction

Viruses are microscopic organisms that need to penetrate into a cell of their host to duplicate and multiply. Many human infections and diseases are caused by viruses such as the human immunodeficiency virus (HIV) that is responsible for acquired immunodeficiency syndrome (AIDS), Ebola that can cause an often fatal illness called Ebola hemorrhagic fever, and the hepatitis B virus (HBV) that can lead to chronic infection, cirrhosis, or liver cancer.

In viral dynamics, infection processes and virus production are not instantaneous. In reality, there are two kinds of delays: one in cell infection and the other in virus production. In the literature, these delays are modeled by discrete time delays [1–6], by finite distributed delays [7–9], and by infinite distributed delays [9–12]. The delay in cell infection can be modeled by an explicit class of latently infected cells (see, e.g., [13–15]).

On the other hand, viruses can spread by two fundamental modes, one by virus-to-cell infection through the extracellular space and the other by cell-to-cell transfer involving direct cell-to-cell contact [16–19]. For these reasons, we propose the following generalized virus dynamics model with both modes of transmission and distributed delays:

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - f\left(x(t), y(t), v(t)\right) v(t) \\
&\quad - g\left(x(t), y(t)\right) y(t), \\
\dot{y}(t) &= \int_0^\infty h_1(\tau) \\
&\quad \cdot e^{-\alpha_1 \tau} \left[f\left(x(t-\tau), y(t-\tau), v(t-\tau)\right) v(t-\tau) \right. \\
&\quad \left. + g\left(x(t-\tau), y(t-\tau)\right) y(t-\tau) \right] d\tau - ay(t), \\
\dot{v}(t) &= k \int_0^\infty h_2(\tau) e^{-\alpha_2 \tau} y(t-\tau)\, d\tau - \mu v(t),
\end{aligned} \tag{1}$$

where $x(t)$, $y(t)$, and $v(t)$ are the concentrations of uninfected cells, infected cells, and free virus particles at time t, respectively. The uninfected cells are produced at rate λ, die at rate dx, and become infected either by free virus at rate $f(x, y, v)v$ or by direct contact with an infected cell at rate $g(x, y)y$. Hence, the term $f(x, y, v)v + g(x, y)y$ denotes

the total infection rate of uninfected cells. The parameters a and μ are, respectively, the death rates of infected cells and free virus. k is the production rate of free virus by an infected cell. In this proposed model, we assume that the virus or infected cell contacts an uninfected target cell at time $t-\tau$, and the cell becomes infected at time t, where τ is a random variable taken from a probability distribution $h_1(\tau)$. The term $e^{-\alpha_1\tau}$ represents the probability of surviving from time $t-\tau$ to time t, where α_1 is the death rate for infected but not yet virus-producing cells. Similarly, we assume that the time necessary for the newly produced virions to become mature and infectious is a random variable with a probability distribution $h_2(\tau)$. The term $e^{-\alpha_2\tau}$ denotes the probability of surviving the immature virions during the delay period, where $1/\alpha_2$ is the average life time of an immature virus. Therefore, the integral $\int_0^\infty h_2(\tau)e^{-\alpha_2\tau}y(t-\tau)d\tau$ describes the mature viral particles produced at time t.

As in [20], the incidence functions $f(x,y,v)$ and $g(x,y)$ for the two modes are continuously differentiable and satisfy the following hypotheses:

- (H_0) $g(0,y)=0$, for all $y\geq 0$; $(\partial g/\partial x)(x,y)\geq 0$ (or $g(x,y)$ is a strictly monotone increasing function with respect to x when $f\equiv 0$) and $(\partial g/\partial y)(x,y)\leq 0$, for all $x\geq 0$ and $y\geq 0$.
- (H_1) $f(0,y,v)=0$, for all $y\geq 0$ and $v\geq 0$.
- (H_2) $f(x,y,v)$ is a strictly monotone increasing function with respect to x (or $(\partial f/\partial x)(x,v,y)\geq 0$ when $g(x,y)$ is a strictly monotone increasing function with respect to x), for any fixed $y\geq 0$ and $v\geq 0$.
- (H_3) $f(x,y,v)$ is a monotone decreasing function with respect to y and v.

Biologically, the four hypotheses are reasonable and consistent with the reality. For more details on the biological significance of these four hypotheses, we refer the reader to the works [20–22]. Further, the general incidence functions $f(x,y,v)$ and $g(x,y)$ include various types of incidence rates existing in the literature.

The probability distribution functions $h_1(\tau)$ and $h_2(\tau)$ are assumed to satisfy $h_i(\tau)\geq 0$ and $\int_0^\infty h_i(\tau)d\tau=1$ for $i=1,2$. When $h_1(\tau)=\delta(\tau-\tau_1)$ and $h_2(\tau)=\delta(\tau-\tau_2)$, where $\delta(\cdot)$ is the Dirac delta function, system (1) becomes a model with two discrete time delays τ_1 and τ_2 which is the generalization of the models presented in [2–6]. When $f(x,y,v)=\beta_1 x$ and $g(x,y)=0$, where β_1 is the virus-to-cell infection rate, we get the HIV infection model with distributed intracellular delays investigated by Xu [11]. On the other hand, the model proposed by Lai and Zou [23] is a special case of our model (1) when $f(x,y,v)=\beta_1 x$, $g(x,y)=\beta_2 x$, and $h_2(\tau)=\delta(\tau)$, where β_2 is the cell-to-cell transmission rate. It is important to note that the model studied by Nelson and Perelson in [10] is a particular case of [23].

The main objective of this work is to investigate the dynamical behavior of system (1). For this end, we start with the existence, the positivity, and boundedness of solutions, which implies that our model is well posed. After that, we determine the basic reproduction number and steady states of the model. The global stability of the disease-free equilibrium and the chronic infection equilibrium is established in Sections 3 and 4 by constructing appropriate Lyapunov functionals. An application of our results is presented in Section 5. Finally, the conclusion is summarized in Section 6.

2. Well-Posedness and Equilibria

For biological reasons, we suppose that the initial conditions of system (1) satisfy

$$\begin{aligned} x(\theta)&=\phi_1(\theta)\geq 0,\\ y(\theta)&=\phi_2(\theta)\geq 0,\\ v(\theta)&=\phi_3(\theta)\geq 0,\\ &\theta\in(-\infty,0]. \end{aligned} \tag{2}$$

Define the Banach space for fading memory type as follows:

$$\begin{aligned} C_\alpha=\Big\{&\varphi\in C\left((-\infty,0],\mathbb{R}_+^3\right):\varphi(\theta)\\ &\cdot e^{\alpha\theta}\ \text{is uniformly continuous on}\ (-\infty,0],\ \|\varphi\|\\ &=\sup_{\theta\leq 0}\left|\varphi(\theta)\right|e^{\alpha\theta}<\infty\Big\}, \end{aligned} \tag{3}$$

where α is a positive constant and $\mathbb{R}_+^3=\{(x_1,x_2,x_3):x_i\geq 0,\ i=1,2,3\}$.

Theorem 1. *For any initial condition $\phi=(\phi_1,\phi_2,\phi_3)\in C_\alpha$ satisfying (2), system (1) has a unique solution on $[0,+\infty)$. Furthermore, this solution is nonnegative and bounded for all $t\geq 0$.*

Proof. By the fundamental theory of functional differential equations [24–26], system (1) with initial condition $\phi\in C_\alpha$ has a unique local solution on $(0,T_{\max})$, where $T_{\max}$ is the maximal existence time for solution of system (1).

First, we prove that $x(t)>0$ for all $t\in(0,T_{\max})$. In fact, supposing the contrary, let $t_1>0$ be the first time such that $x(t_1)=0$ and $\dot{x}(t_1)\leq 0$. From the first equation of system (1), we have $\dot{x}(t_1)=\lambda>0$ which is a contradiction. Then $x(t)>0$ for all $t\in(0,T_{\max})$.

From the second and third equations of system (1), we get

$$\begin{aligned} y(t)&=\phi_2(0)e^{-at}+\int_0^t e^{-a(t-s)}\int_0^\infty h_1(\tau)\\ &\cdot e^{-\alpha_1\tau}\left[f\left(x(s-\tau),y(s-\tau),v(s-\tau)\right)v(s-\tau)\right.\\ &\left.+g\left(x(s-\tau),y(s-\tau)\right)y(s-\tau)\right]d\tau\,ds,\\ v(t)&=\phi_3(0)e^{-\mu t}+k\int_0^t e^{-\mu(t-s)}\int_0^\infty h_2(\tau)e^{-\alpha_2\tau}y(s\\ &-\tau)\,d\tau\,ds, \end{aligned} \tag{4}$$

which implies that $y(t)$ and $v(t)$ are nonnegative for all $t\in(0,T_{\max})$.

Now, we prove the boundedness of the solutions. From the first equation of (1), we have $\dot{x}(t) \leq \lambda - dx(t)$ which implies that

$$\limsup_{t\to+\infty} x(t) \leq \frac{\lambda}{d}. \tag{5}$$

Then $x(t)$ is bounded. Let

$$T(t) = y(t) + \int_0^{\infty} h_1(\tau)\, e^{-\alpha_1\tau} x(t-\tau)\, d\tau. \tag{6}$$

Since $x(t)$ is bounded and $\int_0^{\infty} h_1(\tau)d\tau = 1$, the integral in $T(t)$ is well defined and differentiable with respect to t. Hence,

$$\begin{aligned}\frac{dT(t)}{dt} &= \lambda \int_0^{\infty} h_1(\tau)\, e^{-\alpha_1\tau} d\tau \\ &\quad - d\int_0^{\infty} h_1(\tau)\, e^{-\alpha_1\tau} x(t-\tau)\, d\tau - ay(t) \\ &\leq \lambda\eta_1 - \delta T(t),\end{aligned} \tag{7}$$

where $\delta = \min\{a, d\}$ and

$$\eta_i = \int_0^{\infty} h_i(\tau)\, e^{-\alpha_i\tau} d\tau, \quad i = 1, 2. \tag{8}$$

Thus, $T(t) \leq M := \max\{T(0), \lambda\eta_1/\delta\}$, which implies that $y(t)$ is bounded.

It remains to prove that $v(t)$ is bounded. By third equation of system (1) and the boundedness of $y(t)$, we deduce that

$$\dot{v}(t) \leq kM\eta_2 - \mu v(t). \tag{9}$$

Then $v(t) \leq \max\{v(0), kM\eta_2/\mu\}$. Therefore, $v(t)$ is also bounded. We have proved that all variables of system (1) are bounded which implies that $T_{\max} = +\infty$ and the solution exists globally. □

If in addition to (2) we assume that $\phi_i(0) > 0$ for all $i = 1, 2, 3$, we easily obtain the following result.

Remark 2. When $\phi = (\phi_1, \phi_2, \phi_3) \in C_\alpha$ satisfying (2) with $\phi_i(0) > 0$ $(i = 1, 2, 3)$, all solution of (1) with initial condition ϕ is positive for all $t \geq 0$.

2.1. Equilibria. Obviously, system (1) has always one disease-free equilibrium of the form $E_f(\lambda/d, 0, 0)$. Therefore, the basic reproduction R_0 of system (1) can be defined by

$$R_0 = \frac{k\eta_1\eta_2 f(\lambda/d, 0, 0) + \mu\eta_1 g(\lambda/d, 0)}{a\mu}. \tag{10}$$

As in [20], R_0 can be rewritten as $R_0 = R_{01} + R_{02}$, where $R_{01} = k\eta_1\eta_2 f(\lambda/d, 0, 0)/a\mu$ is the basic reproduction number corresponding to virus-to-cell infection mode and $R_{02} = \eta_1 g(\lambda/d, 0)/a$ is the basic reproduction number corresponding to cell-to-cell transmission mode.

Theorem 3.

(i) *If $R_0 \leq 1$, then system (1) has a unique disease-free equilibrium of the form $E_f(\lambda/d, 0, 0)$.*

(ii) *If $R_0 > 1$, the disease-free equilibrium is still present and system (1) has a unique chronic infection equilibrium of the form $E^*(x^*, y^*, v^*)$ with $x^* \in (0, \lambda/d)$, $y^* > 0$, and $v^* > 0$.*

Proof. It is clear that $E_f(\lambda/d, 0, 0)$ is the unique steady state of system (1) when $R_0 \leq 1$. To find the other equilibria, we resolve the following system:

$$\begin{aligned}\lambda - dx - f(x, y, v)\, v - g(x, y)\, y &= 0, \\ \eta_1\left(f(x, y, v)\, v + g(x, y)\, y\right) - ay &= 0, \\ k\eta_2 y - \mu v &= 0.\end{aligned} \tag{11}$$

From (11), we obtain the equation

$$\begin{aligned}&k\eta_1\eta_2 f\left(x, \frac{\eta_1(\lambda - dx)}{a}, \frac{k\eta_1\eta_2(\lambda - dx)}{a\mu}\right) \\ &\quad + \mu\eta_1 g\left(x, \frac{\eta_1(\lambda - dx)}{a}\right) = a\mu.\end{aligned} \tag{12}$$

We have $y = (\eta_1(\lambda - dx))/a \geq 0$, which implies that $x \leq \lambda/d$. Thus, there is no biological equilibrium when $x > \lambda/d$.

Define the function ψ_1 on the interval $[0, \lambda/d]$ by

$$\begin{aligned}\psi_1(x) &= k\eta_1\eta_2 f\left(x, \frac{\eta_1(\lambda - dx)}{a}, \frac{k\eta_1\eta_2(\lambda - dx)}{a\mu}\right) \\ &\quad + \mu\eta_1 g\left(x, \frac{\eta_1(\lambda - dx)}{a}\right) - a\mu.\end{aligned} \tag{13}$$

Clearly, $\psi_1(0) = -a\mu < 0$, $\psi_1(\lambda/d) = a\mu(R_0 - 1)$, and

$$\begin{aligned}\psi_1'(x) &= k\eta_1\eta_2\left(\frac{\partial f}{\partial x} - \frac{d\eta_1}{a}\frac{\partial f}{\partial y} - \frac{kd\eta_1\eta_2}{a\mu}\frac{\partial f}{\partial v}\right) \\ &\quad + \mu\eta_1\left(\frac{\partial g}{\partial x} - \frac{d\eta_1}{a}\frac{\partial g}{\partial y}\right) > 0.\end{aligned} \tag{14}$$

Hence, if $R_0 > 1$, there exists another biologically meaningful equilibrium $E^*(x^*, y^*, v^*)$ with $x^* \in (0, \lambda/d)$, $y^* > 0$, and $v^* > 0$. This completes the proof. □

3. Stability of the Disease-Free Equilibrium

In this section, we establish the stability of the disease-free equilibrium.

Theorem 4. *The disease-free equilibrium E_f is globally asymptotically stable when $R_0 \leq 1$ and becomes unstable when $R_0 > 1$.*

Proof. To study the global stability of E_f, we consider the following Lyapunov functional:

$$V(t) = \frac{1}{\eta_1} y(t) + \frac{f(\lambda/d, 0, 0)}{\mu} v(t) + \frac{1}{\eta_1} \int_0^\infty h_1(\tau) \cdot e^{-\alpha_1 \tau} \int_{t-\tau}^t \left(f(x(s), y(s), v(s)) v(s) + g(x(s), y(s)) y(s) \right) ds\, d\tau + \frac{kf(\lambda/d, 0, 0)}{\mu} \int_0^\infty h_2(\tau) e^{-\alpha_2 \tau} \int_{t-\tau}^t y(s)\, ds\, d\tau. \tag{15}$$

Calculating the time derivative of V along the positive solution of system (1), we get

$$\dot{V}(t)\Big|_{(1)} = \left(f(x, y, v) - f\left(\frac{\lambda}{d}, 0, 0\right) \right) v + \frac{a}{\eta_1} y \left(\frac{k\eta_1\eta_2 f(\lambda/d, 0, 0) + \mu\eta_1 g(x, y)}{a\mu} - 1 \right). \tag{16}$$

We have $\limsup_{t\to\infty} x(t) \le \lambda/d$, which implies that all omega limit points satisfy $x(t) \le \lambda/d$. Thus, it is sufficient to consider solutions for which $x(t) \le \lambda/d$. By (10) and (H_1)–(H_3), we obtain

$$\dot{V}(t)\Big|_{(1)} \le \left(f(x, 0, 0) - f\left(\frac{\lambda}{d}, 0, 0\right) \right) v + \frac{a}{\eta_1} (R_0 - 1) y \le \frac{a}{\eta_1} (R_0 - 1) y. \tag{17}$$

Therefore, $\dot{V}|_{(1)} \le 0$ when $R_0 \le 1$. In addition, it is not hard to verify that the largest compact invariant set in $\{(x, y, v) \mid \dot{V} = 0\}$ is the singleton $\{E_f\}$. From LaSalle invariance principle [27], we deduce that the disease-free equilibrium E_f is globally asymptotically stable when $R_0 \le 1$.

On the other hand, the characteristic equation at E_f is given by

$$(\xi + d) \left[(\xi + \mu) \left(\xi + a - \overline{\eta}_1(\xi)\, g\left(\frac{\lambda}{d}, 0\right) \right) - \overline{\eta}_1(\xi)\, \overline{\eta}_2(\xi)\, kf\left(\frac{\lambda}{a}, 0, 0\right) \right] = 0, \tag{18}$$

where $\overline{\eta}_i(\xi) = \int_0^\infty h_i(\tau) e^{-(\xi+\alpha_i)\tau} d\tau$. Define a function ψ_2 on $[0, +\infty)$ by

$$\psi_2(\xi) = (\xi + \mu) \left(\xi + a - \overline{\eta}_1(\xi)\, g\left(\frac{\lambda}{d}, 0\right) \right) - \overline{\eta}_2(\xi)\, \overline{\eta}_2(\xi)\, kf\left(\frac{\lambda}{d}, 0, 0\right). \tag{19}$$

We have $\psi_2(0) = a\mu(1 - R_0) < 0$ and $\lim_{\xi\to+\infty} \psi_2(\xi) = +\infty$, which implies that ψ_2 has a positive real root. Consequently, E_f is unstable for $R_0 > 1$. □

4. Stability of the Chronic Infection Equilibrium

In this section, we investigate the global stability of the chronic infection equilibrium E^* by assuming that $R_0 > 1$ and the functions f and g satisfy, for all $x, y, v > 0$, the following hypothesis:

$$\left(1 - \frac{f(x, y, v)}{f(x, y^*, v^*)}\right) \left(\frac{f(x, y^*, v^*)}{f(x, y, v)} - \frac{v}{v^*} \right) \le 0, \quad \left(1 - \frac{f(x^*, y^*, v^*)\, g(x, y)}{f(x, y^*, v^*)\, g(x^*, y^*)}\right) \cdot \left(\frac{f(x, y^*, v^*)\, g(x^*, y^*)}{f(x^*, y^*, v^*)\, g(x, y)} - \frac{y}{y^*} \right) \le 0. \tag{H_4}$$

Therefore, we get the following result.

Theorem 5. *Assume that (H_4) holds. If $R_0 > 1$, then the chronic infection equilibrium E^* is globally asymptotically stable.*

Proof. We define a Lyapunov functional as follows:

$$W(t) = x(t) - x^* - \int_{x^*}^{x(t)} \frac{f(x^*, y^*, v^*)}{f(s, y^*, v^*)} ds + \frac{1}{\eta_1} \cdot y^* H\left(\frac{y(t)}{y^*}\right) + \frac{f(x^*, y^*, v^*)\, v^*}{k\eta_2 y^*} v^* H\left(\frac{v(t)}{v^*}\right) + \frac{1}{\eta_1} f(x^*, y^*, v^*)\, v^* \int_0^\infty h_1(\tau) \cdot e^{-\alpha_1\tau} \int_{t-\tau}^t H\left(\frac{f(x(s), y(s), v(s))\, v(s)}{f(x^*, y^*, v^*)\, v^*} \right) ds\, d\tau + \frac{1}{\eta_1} g(x^*, y^*)\, y^* \int_0^\infty h_1(\tau) \cdot e^{-\alpha_1\tau} \int_{t-\tau}^t H\left(\frac{g(x(s), y(s))\, y(s)}{g(x^*, y^*)\, y^*} \right) ds\, d\tau + \frac{1}{\eta_2} \cdot f(x^*, y^*, v^*)\, v^* \int_0^\infty h_2(\tau) \cdot e^{-\alpha_2\tau} \int_{t-\tau}^t H\left(\frac{y(s)}{y^*} \right) ds\, d\tau, \tag{20}$$

where $H(x) = x - 1 - \ln x$, $x > 0$. Clearly, $H : (0, +\infty) \to [0, +\infty)$ attains its strict global minimum at $x = 1$ and $H(1) = 0$. Hence, $H(x) \ge 0$. Further, the functional W is nonnegative.

In order to simplify the presentation, we will use the following notations: $z = z(t)$ and $z_\tau = z(t - \tau)$ for any $z \in \{x, y, v\}$. The time derivative of W along the positive solution of system (1) is given by

$$\dot{W}(t)\Big|_{(1)} = \left(1 - \frac{f(x^*, y^*, v^*)}{f(x, y^*, v^*)}\right) \dot{x} + \frac{1}{\eta_1} \left(1 - \frac{y^*}{y}\right) \dot{y} + \frac{f(x^*, y^*, v^*)\, v^*}{k\eta_2 y^*} \left(1 - \frac{v^*}{v}\right) \dot{v} + \frac{1}{\eta_1} f(x^*, y^*, v^*)$$

$$\cdot v^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left(H\left(\frac{f(x,y,v)v}{f(x^*,y^*,v^*)v^*} \right) - H\left(\frac{f(x_\tau,y_\tau,v_\tau)v_\tau}{f(x^*,y^*,v^*)v^*} \right) \right) d\tau + \frac{1}{\eta_1} g(x^*,y^*)$$
$$\cdot y^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left(H\left(\frac{g(x,y)y}{g(x^*,y^*)y^*} \right) - H\left(\frac{g(x_\tau,y_\tau)y_\tau}{g(x^*,y^*)y^*} \right) \right) d\tau + \frac{1}{\eta_2} f(x^*,y^*,v^*)$$
$$\cdot v^* \int_0^\infty h_2(\tau) e^{-\alpha_2 \tau} \left(H\left(\frac{y}{y^*} \right) - H\left(\frac{y_\tau}{y^*} \right) \right) d\tau. \tag{21}$$

Applying $\lambda = dx^* + f(x^*,y^*,v^*)v^* + g(x^*,y^*)y^* = dx^* + (a/\eta_1)y^*$ and $k\eta_2 y^* = \mu v^*$, we obtain

$$\begin{aligned}
\dot{W}(t)\big|_{(1)} &= dx^* \left(1 - \frac{x}{x^*}\right)\left(1 - \frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)}\right) \\
&+ \frac{1}{\eta_1} f(x^*,y^*,v^*) v^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left[3 \right. \\
&- \frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)} + \frac{f(x,y,v)v}{f(x,y^*,v^*)v^*} - \frac{v}{v^*} \\
&- \frac{f(x_\tau,y_\tau,v_\tau)v_\tau y^*}{f(x^*,y^*,v^*)v^* y} \\
&\left. + \ln\left(\frac{f(x_\tau,y_\tau,v_\tau)v_\tau}{f(x,y,v)v} \right) \right] d\tau + \frac{1}{\eta_1} g(x^*,y^*) \\
&\cdot y^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left[2 - \frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)} \right. \\
&+ \frac{f(x^*,y^*,v^*) g(x,y) y}{f(x,y^*,v^*) g(x^*,y^*) y^*} - \frac{y}{y^*} \\
&\left. + \frac{g(x_\tau,y_\tau)y_\tau}{g(x^*,y^*)y} + \ln\left(\frac{g(x_\tau,y_\tau)y_\tau}{g(x,y)y} \right) \right] d\tau \\
&- \frac{1}{\eta_2} f(x^*,y^*,v^*) v^* \int_0^\infty h_2(\tau) e^{-\alpha_2 \tau} \left[\frac{v^* y_\tau}{v y^*} \right. \\
&\left. - \ln\left(\frac{y_\tau}{y} \right) \right] d\tau.
\end{aligned} \tag{22}$$

Hence,

$$\begin{aligned}
\dot{W}(t)\big|_{(1)} &= dx^* \left(1 - \frac{x}{x^*}\right)\left(1 - \frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)}\right) \\
&+ f(x^*,y^*,v^*) v^* \left(-1 - \frac{v}{v^*} + \frac{f(x,y^*,v^*)}{f(x,y,v)} \right. \\
&\left. + \frac{f(x,y,v)v}{f(x,y^*,v^*)v^*} \right) + g(x^*,y^*) y^* \left(-1 - \frac{y}{y^*} \right. \\
&+ \frac{f(x,y^*,v^*) g(x^*,y^*)}{f(x^*,y^*,v^*) g(x,y)} \\
&\left. + \frac{f(x^*,y^*,v^*) g(x,y) y}{f(x,y^*,v^*) g(x^*,y^*) y^*} \right) - \frac{1}{\eta_1} f(x^*,y^*,v^*) \\
&\cdot v^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left[H\left(\frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)} \right) \right. \\
&+ H\left(\frac{f(x_\tau,y_\tau,v_\tau)v_\tau y^*}{f(x^*,y^*,v^*)v^* y} \right) \\
&\left. + H\left(\frac{f(x,y^*,v^*)}{f(x,y,v)} \right) \right] d\tau - \frac{1}{\eta_1} g(x^*,y^*) \\
&\cdot y^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left[H\left(\frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)} \right) \right. \\
&+ H\left(\frac{g(x_\tau,y_\tau)y_\tau}{g(x^*,y^*)y} \right) \\
&\left. + H\left(\frac{f(x,y^*,v^*) g(x^*,y^*)}{f(x^*,y^*,v^*) g(x,y)} \right) \right] d\tau - \frac{1}{\eta_2} \\
&\cdot f(x^*,y^*,v^*) v^* \int_0^\infty h_2(\tau) e^{-\alpha_2 \tau} H\left(\frac{v^* y_\tau}{v y^*} \right) d\tau.
\end{aligned} \tag{23}$$

Since the function $f(x,y,v)$ is strictly monotonically increasing with respect to x, we have

$$\left(1 - \frac{x}{x^*}\right)\left(1 - \frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)}\right) \le 0. \tag{24}$$

From (H_4), we have

$$\begin{aligned}
&-1 - \frac{v}{v^*} + \frac{f(x,y^*,v^*)}{f(x,y,v)} + \frac{v}{v^*}\frac{f(x,y,v)}{f(x,y^*,v^*)} \\
&\quad = \left(1 - \frac{f(x,y,v)}{f(x,y^*,v^*)}\right)\left(\frac{f(x,y^*,v^*)}{f(x,y,v)} - \frac{v}{v^*}\right) \le 0, \\
&-1 - \frac{y}{y^*} + \frac{f(x,y^*,v^*) g(x^*,y^*)}{f(x^*,y^*,v^*) g(x,y)} \\
&\quad + \frac{f(x^*,y^*,v^*) g(x,y) y}{f(x,y^*,v^*) g(x^*,y^*) y^*} \\
&\quad = \left(1 - \frac{f(x^*,y^*,v^*) g(x,y)}{f(x,y^*,v^*) g(x^*,y^*)}\right) \\
&\quad \cdot \left(\frac{f(x,y^*,v^*) g(x^*,y^*)}{f(x^*,y^*,v^*) g(x,y)} - \frac{y}{y^*}\right) \le 0.
\end{aligned} \tag{25}$$

Since $H(x) \ge 0$ for $x > 0$, we have $\dot{W}|_{(1)} \le 0$ with equality if and only if $x = x^*$, $y = y^*$, and $v = v^*$. It follows from LaSalle invariance principle that E^* is globally asymptotically stable. □

5. Application

In this section, we consider the following HIV infection model with distributed delays:

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - \frac{\beta_1 x(t) v(t)}{1+\gamma_1 v(t)} - \frac{\beta_2 x(t) y(t)}{1+\gamma_2 y(t)},\\
\dot{y}(t) &= \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left[\frac{\beta_1 x(t-\tau) v(t-\tau)}{1+\gamma_1 v(t-\tau)} \right.\\
&\quad \left. + \frac{\beta_2 x(t-\tau) y(t-\tau)}{1+\gamma_2 y(t-\tau)} \right] d\tau - ay(t),\\
\dot{v}(t) &= k \int_0^\infty h_2(\tau) e^{-\alpha_2 \tau} y(t-\tau)\, d\tau - \mu v(t),
\end{aligned} \tag{26}$$

where γ_1 and γ_2 are nonnegative constants that measure the saturation effect. The parameters β_1 and β_2 are the virus-to-cell infection rate and the cell-to-cell transmission rate, respectively. The other parameters have the same biological meanings as in model (1). Further, system (26) is a special case of (1) with $f(x, y, v) = \beta_1 x/(1+\gamma_1 v)$ and $g(x, y) = \beta_2 x/(1+\gamma_2 y)$. Notice that the HIV infection model presented by Lai and Zou [23] is a particular case of our model (26), it suffices to take $\gamma_1 = \gamma_2 = 0$ and $h_2(\tau) = \delta(\tau)$. In addition, system (26) always has a disease-free equilibrium $E_f(\lambda/d, 0, 0)$ and a unique chronic infection equilibrium $E^*(x^*, y^*, v^*)$ when $R_0 = \beta_1 \lambda k \eta_1 \eta_2 / da\mu + \beta_2 \lambda \eta_1 / da > 1$.

On the other hand, it is easy to see that the hypotheses (H_0)–(H_3) are satisfied. Furthermore, we have

$$\begin{aligned}
&\left(1 - \frac{f(x, y, v)}{f(x, y^*, v^*)}\right)\left(\frac{f(x, y^*, v^*)}{f(x, y, v)} - \frac{v}{v^*}\right)\\
&\quad = \frac{-\delta_1 (v - v^*)^2}{v^* (1+\delta_1 v^*)(1+\delta_1 v)} \le 0,
\end{aligned} \tag{27}$$

$$\begin{aligned}
&\left(1 - \frac{f(x^*, y^*, v^*) g(x, y)}{f(x, y^*, v^*) g(x^*, y^*)}\right)\\
&\quad \cdot \left(\frac{f(x, y^*, v^*) g(x^*, y^*)}{f(x^*, y^*, v^*) g(x, y)} - \frac{y}{y^*}\right)\\
&\quad = \frac{-\delta_2 (y - y^*)^2}{y^* (1+\delta_1 y^*)(1+\delta_1 y)} \le 0.
\end{aligned} \tag{28}$$

Consequently, the hypothesis (H_4) is satisfied. By applying Theorems 4 and 5, we get the following result.

Corollary 6.

(i) *If $R_0 \le 1$, then the disease-free equilibrium E_f of system (26) is globally asymptotically stable.*

(ii) *If $R_0 > 1$, then the disease-free equilibrium E_f becomes unstable and the chronic infection equilibrium E^* of (26) is globally asymptotically stable.*

6. Conclusion

In this work, we have proposed a mathematical model that describes the dynamics of viral infections, such as HIV and HBV, and takes into account the two modes of transmission and the two kinds of delays, one in cell infection and the other in virus production. The transmission process for both modes is modeled by two general incidence functions that include many types of incidence rates existing in the literature. Further, the two delays are modeled by infinite distributed delays. Under some assumptions on the general incidence functions, we have proved that the global stability of the proposed model is fully determined by one threshold parameter that is the basic reproduction number R_0. In addition, the viral infection models with infinite distributed delays and the corresponding results presented in several previous studies are extended and generalized.

In this study, we have neglected the mobility of cells and virus. Motivated by the works in [28–32], we will consider this mobility in our future project in order to improve our present model.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Global Dynamics of a Periodic SEIRS Model with General Incidence Rate

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We consider a family of periodic SEIRS epidemic models with a fairly general incidence rate of the form $Sf(I)$, and it is shown that the basic reproduction number determines the global dynamics of the models and it is a threshold parameter for persistence of disease. Numerical simulations are performed using a nonlinear incidence rate to estimate the basic reproduction number and illustrate our analytical findings.

1. Introduction

Epidemiological models in mathematics have been recognized as valuable tools in analyzing the dynamics of an infectious disease nowadays. They are used to describe the spread of disease and also to make control measures known to avoid its persistence, for example, via vaccination terms or treatment terms. These models consider the total population divided into compartments, given by the biological assumptions on the model and represented by functions depending on time t. The most common categories used are susceptible (S), infected (I), recovered (R), exposed (E), quarantined (Q), and vaccinated (V), and the dynamics of model is given by transmission rates from a compartment to another. We have then indicated that the models could be of type *SIR*, *SIRS*, *SEIR*, *SEIRS*, *SEIVR*, *SEIQV*, and so forth.

To ensure that the model can give a justified qualitative description of the disease, the choice of the incidence rate plays an important role. An incidence rate is defined as the number of new health related events or cases of a disease in a population exposed to the risk in a given time period. Some examples are the bilinear incidence rate, the saturated incidence rate, or a general incidence rate. The bilinear incidence rate has been repeatedly used by several authors. It is given by βSI, where β is the transmission rate and the product SI represents the contact between infected and susceptible individuals (based on the law of mass action). It was introduced by Kermack and McKendrick [1] in 1927, and even when it is mathematically simple to use, it faces multiple problems and challenges when it is used to describe disease propagation among gregarious animals or persons [2], because it goes to infinity when I becomes larger. In order to improve the modelling process to study the dynamics of infection among a large population, Capasso and Serio [3] in 1978 introduced a saturated incidence rate by studying the Cholera epidemic spread in Bari, given by $\beta SI/(1 + kI)$, where β is the transmission rate and k the saturation constant. Unlike the bilinear incidence, saturated incidence does not grow up without a limit, but it goes to a saturation limit as I goes to infinity. Multiple types of saturated incidence have been used in the literature; see, for example, [2] for a list of them. To avoid the use of a single incidence function, the use of a general incidence rate that includes a family of particular functions with similar properties has become a topic of interest by several authors (see, e.g., [4–8]).

The basic reproduction (represented by $\mathcal{R}_0$) is defined as "the average number of secondary cases produced by a single infected case when it is introduced in a susceptible population" and it has an important role in the study of disease transmission. In biological terms, usually when this number is less than one, the disease is eradicated from population, but when it is greater than one, the infection persists. Mathematically, it is of interest to compute a threshold parameter with the properties of the basic reproduction number. A

method to compute this number for certain compartmental disease models is via the next-generation matrix method developed in [9]; however, it is not useful when the model presents time periodic seasonal terms. Authors like [10, 11] have defined its basic reproduction number for periodic models as an average, to give some results about extinction or persistence of infection. However Bacaër and Guernaouni in [12] introduced the definition of basic reproduction number for periodic environments, and, later, Wang and Zhao [13] made a formal definition of it, via the monodromy matrix.

In the present work, we focus on a family of SEIRS epidemic models with a time periodic seasonal term, improving the model of Moneim and Greenhalgh in [14], by introducing an incidence rate with a general function taken from [4] and the references therein.

We propose the following SEIRS model:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N\left(1-p\right) - \beta\left(t\right) Sf\left(I\right) - \left(\mu + r\left(t\right)\right) S + \delta R \\
\frac{dE}{dt} &= \beta\left(t\right) Sf\left(I\right) - \left(\mu + \sigma\right) E \\
\frac{dI}{dt} &= \sigma E - \left(\mu + \gamma\right) I \\
\frac{dR}{dt} &= \mu N p + r\left(t\right) S + \gamma I - \left(\mu + \delta\right) R,
\end{aligned} \tag{1}$$

where $N = S + E + I + R$ is the total population size, with S, E, I, R denoting the fractions of population that are susceptible, exposed, infected, and recovered, respectively. $\beta(t)$ is the transmission rate and it is a continuous, positive T-periodic function. p $(0 \leq p \leq 1)$ is the vaccination rate of all newborn children. $r(t)$ is the vaccination rate of all susceptibles in the population and it is a continuous, positive periodic function with period LT, where L is an integer. μ is the common per capita birth and death rate. σ, γ, and δ are the per capita rates of leaving the latent stage, infected stage, and recovered stage, respectively. It is assumed that all parameters are positive constants.

Bai and Zhou in [5] answered some open problems stated in [14], they also showed that their condition is a threshold between persistence and extinction of the disease via the framework established in [13]. They assumed that the incidence was bilinear. In our study, the nonlinear assumptions on function f are listed below (see [4]).

(A1) $f : \mathbb{R}_+ \to \mathbb{R}_+$ is continuously differentiable.

(A2) $f(0) = 0$, $f'(0) > 0$ and $f(I) > 0$ for all $I > 0$.

(A3) $f(I) - If'(I) \geq 0$.

Under these assumptions, function $f(I)$ includes various types of incidence rate; in particular, when $f(I) = I$, we are on the bilinear case considered in [14].

In addition, we assume the following extra conditions (see [15]).

(A4) $f''(0) \leq 0$.

(A5) There exists $\epsilon^* > 0$ such that when $0 < I < \epsilon^*$, $f(I) \geq f(0) + If'(0) + (1/2)I^2 f''(0)$.

This set of assumptions on the function f allows for more general incidence functions than the bilinear one, like saturated incidence functions and functions of the form $\beta SI/(1 + kI^q)$; in particular, in the case when $q > 1$, they represent psychological or media effects depending on the infected population. In this last case the incidence function is nonmonotone on I. (A3) regulates the value of $f(I)$ comparing it with the value at I of a line containing the origin of slope $f'(I)$ (note that this line varies as I increases), (A4) requires a concave $f(I)$ at the origin, and (A5) imposes the geometrical condition that in a small neighborhood of the origin $f(I)$ must lie between the tangent line of f at I and a concave parabola tangent to f at I.

We consider a family of *SEIRS* epidemic models with periodic coefficients and general incidence rate in epidemiology. Then we show that the global dynamics of solutions is determined by the basic reproduction number $\mathscr{R}_0$, generalizing the results in [5]. The layout of this paper is as follows: In Section 2, we prove the existence of a disease-free periodic solution and we introduce the basic reproduction number via the theory developed in [12, 13]. In Section 3, we adapt the arguments given in [5] to prove that the disease-free periodic solution of system (1) is globally asymptotically stable if $\mathscr{R}_0 < 1$ and it is persistent when $\mathscr{R}_0 > 1$. Finally, in Section 4, we give some numerical simulations of our results, making a comparison between our basic reproduction number $\mathscr{R}_0$ and the average reproduction number $\mathscr{R}_0^T$ used by several authors (see, e.g., [10, 11]).

2. The Basic Reproduction Number

First of all, we prove nonnegativity of the solutions under nonnegative initial conditions.

Theorem 1. *Let $S_0, E_0, I_0, R_0 \geq 0$. The solution $(S(t), E(t), I(t), R(t))$ of (1) with*

$$\left(S\left(0\right), E\left(0\right), I\left(0\right), R\left(0\right)\right) = \left(S_0, E_0, I_0, R_0\right) \tag{2}$$

is nonnegative in the sense that $S(t), E(t), I(t), R(t) \geq 0, \forall t > 0$, and satisfies $S(t) + E(t) + I(t) + R(t) = N$, with N constant.

Proof. Let $N(t) = S(t) + E(t) + I(t) + R(t)$; then, adding all equations of system (1), we can see that $dN/dt = 0$, so the value of N is constant. Now, set $x(t) = (S(t), E(t), I(t), R(t))$ as the solution of system (1) under initial conditions $x_0 = (S(0), E(0), I(0), R(0)) = (S_0, E_0, I_0, R_0) \geq 0$. By the continuity of solutions, for all of $S(t), E(t), I(t)$ and $R(t)$ that have a positive initial value at $t = 0$, we have the existence of an interval $(0, t_0)$ such that $S(t), E(t), I(t), R(t) \geq 0$ for $0 < t < t_0$. We will prove that $t_0 = \infty$.

If $S(t_1) = 0$ for a $t_1 \geq 0$ and other components of $x(t)$ remain nonnegative at $t = t_1$, then

$$\frac{dS}{dt}\left(t_1\right) = \mu N\left(1-p\right) + \delta R\left(t_1\right) \geq 0, \tag{3}$$

implying that whenever the solution $x(t)$ touches the S-axis, the derivative of S is nondecreasing and the function $S(t)$ does

not cross to negative values. Similarly, when $E(t_1) = 0$ for a $t_1 \geq 0$ and other components remain nonnegative, we have

$$\frac{dE}{dt}(t_1) = \beta(t_1) S(t_1) f(I(t_1)) \geq 0. \tag{4}$$

When $I(t_1) = 0$ for a $t_1 \geq 0$ and other components remain nonnegative,

$$\frac{dI}{dt}(t_1) = \sigma E(t_1) \geq 0. \tag{5}$$

Finally, when $R(t_1) = 0$ for a $t_1 \geq 0$ and other components remain nonnegative,

$$\frac{dR}{dt}(t_1) = \mu N p + r(t_1) S(t_1) + \gamma I(t_1) \geq 0. \tag{6}$$

Therefore, whenever $x(t)$ touches any of the axes $S = 0$, $E = 0$, $I = 0$, or $R = 0$, it never crosses them. □

In order to make the analysis of the model in a simpler way from now on, we make a reduction of dimension in system (1) making $R = N - S - E - I$, obtaining the following:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N(1-p) - \beta(t) S f(I) - (\mu + r(t)) S \\
&\quad + \delta(N - S - E - I), \\
\frac{dE}{dt} &= \beta(t) S f(I) - (\mu + \sigma) E, \\
\frac{dI}{dt} &= \sigma E - (\mu + \gamma) I.
\end{aligned} \tag{7}$$

The dynamics of system (1) is equivalent to that of (7); moreover, due to positivity of solutions, we have $S+E+I \leq N$, so we study the dynamics of system (7) in the region

$$X = \left\{(S, E, I) \in \mathbb{R}^3_+ : S + E + I \leq N\right\}. \tag{8}$$

A disease-free periodic solution can be found for (7). To find it, set $E = I = 0$; then, from the first equation of (7) we can obtain the following initial value problem:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N(1-p) - (\mu + r(t)) S + \delta(N - S), \\
S(0) &= S_0 \in \mathbb{R}_+.
\end{aligned} \tag{9}$$

From [5, 14], the equation above admits a unique positive LT-periodic solution given by

$$\begin{aligned}
\widehat{S}(t) = e^{-\int_0^t (\mu + r(s) + \delta) ds} &\left(\widehat{S}(0) \right. \\
&\left. + N(\mu(1-p) + \delta) \int_0^t e^{\int_0^s (\mu + r(\xi) + \delta) d\xi} ds \right),
\end{aligned} \tag{10}$$

where

$$\widehat{S}(0) = \frac{N(\mu(1-p) + \delta) \int_0^{LT} e^{\int_0^s (\mu + r(\xi) + \delta) d\xi} ds}{e^{\int_0^{LT} (\mu + r(s) + \delta) ds} - 1}. \tag{11}$$

Therefore, $(\widehat{S}(t), 0, 0)$ is a disease-free periodic solution of (7); moreover, from [5] we have that $\widehat{S}(t) \leq N$; therefore, $(\widehat{S}(t), 0, 0)$ lives in X.

Using the notation of [9], we sort the compartments so that the first two compartments correspond to infected individuals. Let $x = (E, I, S)$ and define

(i) $\mathscr{F}_i$: the rate of new infection in compartment i,

(ii) $\mathscr{V}_i^+$: the rate of individuals into compartment i by other means,

(iii) $\mathscr{V}_i^-$: the rate of individuals transfer out of compartment i.

System can be written as

$$x'(t) = \begin{pmatrix} \beta(t) S f(I) - (\mu + \sigma) E \\ \sigma E - (\mu + \gamma) I \\ \mu N(1-p) - \beta(t) S f(I) - (\mu + r(t)) S + \delta(N - S - E - I) \end{pmatrix} = \mathscr{F} - \mathscr{V}, \tag{12}$$

where $\mathscr{V} = \mathscr{V}^- - \mathscr{V}^+$,

$$\mathscr{F} = \begin{pmatrix} \beta(t) S f(I) \\ 0 \\ 0 \end{pmatrix},$$

$$\mathscr{V}^+ = \begin{pmatrix} 0 \\ \sigma E \\ \mu N(1-p) + \delta N \end{pmatrix},$$

$$\mathscr{V}^- = \begin{pmatrix} (\mu + \sigma) E \\ (\mu + \gamma) I \\ \beta(t) S f(I) + \delta(S + E + I) + (\mu + r(t)) S \end{pmatrix}. \tag{13}$$

Linearizing system (12) around the disease-free solution, we obtain the matrix of partial derivatives $J(0, 0, \widehat{S}) = D\mathscr{F}(0, 0, \widehat{S}) - D\mathscr{V}(0, 0, \widehat{S})$, where

$$D\mathscr{F}\left(0,0,\widehat{S}\right)=\begin{pmatrix}0 & \beta(t)\widehat{S}f'(0) & 0\\ 0 & 0 & 0\\ 0 & 0 & 0\end{pmatrix}$$

$$D\mathscr{V}\left(0,0,\widehat{S}\right) \tag{14}$$

$$=\begin{pmatrix}\mu+\sigma & 0 & 0\\ -\sigma & \mu+\gamma & 0\\ \delta & \beta(t)\widehat{S}f'(0)+\delta & \delta+\mu+r(t)\end{pmatrix}.$$

Using Lemma 1 of [9], we part $D\mathscr{F}$ and $D\mathscr{V}$ and set

$$F(t)=\begin{pmatrix}0 & \beta(t)\widehat{S}f'(0)\\ 0 & 0\end{pmatrix},$$
$$V(t)=\begin{pmatrix}\mu+\sigma & 0\\ -\sigma & \mu+\gamma\end{pmatrix}. \tag{15}$$

For a compartmental epidemiological model based on an autonomous system, the basic reproduction number is determined by the spectral radius of the next-generation matrix FV^{-1} (which is independent of time) [9]. The definition of basic reproduction number for nonautonomous systems has been studied for multiple authors; see, for example, [12, 13]. Particularly, Wang and Zhao in [13] extended the work of [9] to include epidemiological models in periodic environments. They introduced the next infection operator $\mathscr{L}: C_{LT}\to C_{LT}$ given by

$$\left(\mathscr{L}\phi\right)(t)=\int_0^\infty Y(t,t-a)F(t-a)\phi(t-a)\,da, \tag{16}$$
$$\forall t\in\mathbb{R},\ \phi\in C_{LT},$$

where C_{LT} is the ordered Banach space of all LT periodic functions from $\mathbb{R}$ to $\mathbb{R}^2$, which is equipped with the maximum norm. $\phi(s)\in C_{LT}$ is the initial distribution of infectious individuals in this periodic environment, and $Y(t,s)$, $t\geq s$ is the evolution operator of the linear periodic system:

$$\frac{dy}{dt}=-V(t)y, \tag{17}$$

meaning that, for each $s\in\mathbb{R}$, the 2×2 matrix Y satisfies

$$\frac{dY(t,s)}{dt}=-V(t)Y(t,s),\quad \forall t\geq s,\ Y(s,s)=I_{2\times 2}. \tag{18}$$

$\mathscr{L}\phi$ is the distribution of accumulative new infections at time t produced by all those infected individuals $\phi(s)$ introduced before t, with kernel $K(t,a)=Y(t,t-a)F(t-a)$. The coefficient $K_{i,j}(t,a)$ in row i and column j represents the expected number of individuals in compartment I_i that one individual in compartment I_j generates at the beginning of an epidemic per unit time at time t if it has been in compartment I_j for a units of time, with $I_1=E$, $I_2=I$ [16].

Let $r_0>0$, r_0 is an eigenvalue of $\mathscr{L}$ if there is a nonnegative eigenfunction $v(t)\in C_{LT}$ such that

$$\mathscr{L}v=r_0v. \tag{19}$$

Therefore, the basic reproduction number is defined as

$$\mathscr{R}_0:=\rho(\mathscr{L}), \tag{20}$$

the spectral radius of $\mathscr{L}$. The basic reproduction number can be evaluated by several numerical methods and approximations [15–17]; in Section 4 we discuss this topic.

3. The Threshold Dynamics of R_0

3.1. Disease Extinction

Theorem 2. *Let $\mathscr{R}_0$ be defined as (20); then the disease-free periodic solution $(\widehat{S}(t),0,0)$ is asymptotically stable if $\mathscr{R}_0<1$ and unstable if $\mathscr{R}_0>1$.*

Proof. We use Theorem 2.2 of [13] and check conditions (A1)–(A7). Conditions (A1)–(A5) are clearly satisfied from the definitions of $\mathscr{F}$ and $\mathscr{V}$ given in Section 2. We prove only conditions (A6) and (A7). Define

$$M(t):=-\left(\mu+r(t)+\delta\right), \tag{21}$$

and let $\Phi_M(t)$ be the monodromy matrix of system

$$\frac{dz}{dt}=M(t)z. \tag{22}$$

(A6) $\rho(\Phi_M(LT))<1$. Let Ψ_M be a fundamental matrix for system $dz/dt=M(t)z$, with M defined as before and LT periodic; the monodromy matrix $\Phi_M(LT)$ is given by $\Phi_M(LT)=\Psi_M^{-1}(0)\Psi_M(LT)$. The general solution of (22) is

$$z(t)=K\exp\left(-\int_0^t\left(\mu+r(s)+\delta\right)ds\right), \tag{23}$$

so $\Psi_M=\exp(-\int_0^t(\mu+r(s)+\delta)ds)$ and $\Psi_M^{-1}=\exp(\int_0^t(\mu+r(s)+\delta)ds)$. Note that $\Psi_M^{-1}(0)=1$, so $\Phi_M(LT)=\Psi_M(LT)$ and

$$\Phi_M(LT)=\exp\left(-\int_0^{LT}\left(\mu+r(s)+\delta\right)ds\right). \tag{24}$$

Due to the fact that $\Phi_M(LT)$ is a constant, its eigenvalue is itself and $\rho(\Phi_M(LT))<1$ for $\mu,\delta,r(s)>0$.

(A7) $\rho(\Phi_{-V}(LT))<1$. Solving the system $dz/dt=-V(t)z$, we arrive at the general solution

$$z(t)=c_1\begin{pmatrix}\frac{\gamma-\sigma}{\sigma}\\ 1\end{pmatrix}e^{-(\mu+\sigma)t}+c_2\begin{pmatrix}0\\ 1\end{pmatrix}e^{-(\mu+\gamma)t}, \tag{25}$$

so

$$\Psi_{-V}(t)=\begin{pmatrix}\frac{\gamma-\sigma}{\sigma}e^{-(\mu+\sigma)t} & 0\\ e^{-(\mu+\sigma)t} & e^{-(\mu+\gamma)t}\end{pmatrix}. \tag{26}$$

Computing $\Phi_{-V}(LT) = \Psi_{-V}^{-1}(0)\Psi_{-V}(LT)$, we have

$$\Phi_{-V}(LT) = \begin{pmatrix} e^{-(\mu+\sigma)LT} & 0 \\ 0 & e^{-(\mu+\gamma)LT} \end{pmatrix}. \tag{27}$$

Clearly, $\rho(\Phi_{-V}(LT)) = \max\{e^{-(\mu+\sigma)LT}, e^{-(\mu+\gamma)LT}\} < 1$ for $\mu, \gamma, \sigma > 0$.

□

Note 1. Due to the fact that Ψ_A is a fundamental solution of a periodic system, we can always choose it such that $\Psi(0) = I$, so the monodromy matrix satisfies $\Phi_A(LT) = \Psi_A(LT)$. This property is used in further analysis.

In order to prove the global stability of the disease-free periodic solution, we enunciate some useful definitions and some lemmas.

Let $A(t)$ be continuous, cooperative, irreducible, and ω-periodic $k \times k$ matrix function, and $\Psi_A(t)$ the fundamental matrix of system $x'(t) = A(t)x(t)$. Denote by $\rho(\Psi_A(\omega))$ the spectral radius of $\Psi_A(\omega)$.

Lemma 3. *Let $p = (1/\omega)\ln\rho(\Psi_A(\omega))$. Then there exists a positive, ω-periodic function $v(t)$ such that $e^{pt}v(t)$ is a solution of $x'(t) = A(t)x(t)$ (see proof in Lemma 2.1 of [18]).*

Lemma 4. *Function $f(I)$ of model (1) satisfies $f(I) \le f'(0)I$, $\forall I \ge 0$.*

Proof. Using assumptions on function f, we have

$$\frac{d}{dI}\left(\frac{f(I)}{I}\right) = \frac{If'(I) - f(I)}{I^2} \le 0, \tag{28}$$

so function $f(I)/I$ decreases $\forall I > 0$ and then $f(I)/I \le \lim_{I\to 0^+}(f(I)/I) = f'(0)$. □

Lemma 5. *Let $(S(t), E(t), I(t))$ be a solution of system (7) with initial conditions $(S_0, E_0, I_0) \ge 0$, and $(\widehat{S}(t), 0, 0)$ the disease-free periodic solution of (7); then*

$$\limsup_{t\to\infty}\left(S(t) - \widehat{S}(t)\right) \le 0. \tag{29}$$

Proof. Proof is similar to Lemma 4.1 of [14]. $S(t)$ satisfies the first equation of system (7); then

$$\begin{aligned} \frac{dS}{dt} &= \mu N(1-p) - \beta(t)Sf(I) - (\mu + r(t))S \\ &\quad + \delta(N - S - E - I) \\ &\le N(\mu(1-p) + \delta) - (\mu + r(t) + \delta)S. \end{aligned} \tag{30}$$

Let $X(t) = S(t) - \widehat{S}(t)$; then

$$\begin{aligned} \frac{dX}{dt} &= (\mu + r(t) + \delta)\left(\widehat{S} - S\right) - \beta(t)Sf(I) - \delta(E + I) \\ &\le -(\mu + r(t) + \delta)X. \end{aligned} \tag{31}$$

Using Gronwall's inequality $X(t) \le X(0)e^{-\int_0^t(\mu+r(s)+\delta)ds}$,

$$\begin{aligned} S(t) - \widehat{S}(t) &\le \left(S(0) - \widehat{S}(0)\right)e^{-\int_0^t(\mu+r(s)+\delta)ds} \\ &= \left(S(0) - \widehat{S}(0)\right)e^{-(\mu+\delta)t}e^{-\int_0^t r(s)ds}. \end{aligned} \tag{32}$$

Taking limits in both sides, we obtain that $\limsup_{t\to\infty} S(t) - \widehat{S}(t) \le 0$. □

Now, we are able to enunciate our theorem for global stability of disease-free periodic solution.

Theorem 6. *The disease-free periodic solution $(\widehat{S}(t), 0, 0)$ of system (7) is globally asymptotically stable if $\mathcal{R}_0 < 1$.*

Proof. From Theorem 2 we have that $(\widehat{S}(t), 0, 0)$ is unstable for $\mathcal{R}_0 > 1$ and asymptotically stable for $\mathcal{R}_0 < 1$, so it is sufficient to prove that any solution $(S(t), E(t), I(t))$ with nonnegative initial conditions (S_0, E_0, I_0) approaches $(\widehat{S}, 0, 0)$ as t tends to infinity.

Let $\epsilon > 0$; from Lemma 5 we have

$$\begin{aligned} \limsup_{t\to\infty}\left(S(t) - \widehat{S}(t)\right) &= \lim_{t\to\infty}\sup_{\tau\ge t}\left(S(\tau) - \widehat{S}(\tau)\right) = L \\ &\le 0, \end{aligned} \tag{33}$$

so there exists a $N > 0$ such that for all $t_1 > N$

$$-\epsilon < \sup_{t\ge t_1}\left(S(t) - \widehat{S}(t)\right) - L < \epsilon, \tag{34}$$

which implies that $\sup_{t\ge t_1}(S(t) - \widehat{S}(t)) < \epsilon + L \le \epsilon$. Then, from the definition of supremum, we have that for all $t > t_1$

$$S(t) - \widehat{S}(t) \le \sup_{t\ge t_1}\left(S(t) - \widehat{S}(t)\right) < \epsilon. \tag{35}$$

Then, we have proved that for all $\epsilon > 0$ we can find a $t_1 > 0$ such that $S(t) < \epsilon + \widehat{S}(t)$ for all $t > t_1$.

Now, using Lemma 4, for $\epsilon > 0$ we can find a $t_1 > 0$ such that for $t > t_1$

$$\begin{aligned} \frac{dE}{dt} &= \beta(t)Sf(I) - (\mu + \sigma)E \\ &\le \beta(t)S(t)f'(0)I - (\mu + \sigma)E(t) \end{aligned} \tag{36}$$

$$< \beta(t)f'(0)\left(\widehat{S}(t) + \epsilon\right)I(t) - (\mu + \sigma)E(t). \tag{37}$$

We consider the following perturbed subsystem:

$$\begin{aligned} \frac{d\overline{E}}{dt} &= \beta(t)f'(0)\left(\widehat{S} + \epsilon\right)\overline{I} - (\mu + \sigma)\overline{E}, \\ \frac{d\overline{I}}{dt} &= \sigma\overline{E} - (\mu + \gamma)\overline{I}, \end{aligned} \tag{38}$$

which can be rewritten as

$$\begin{aligned} \left(\frac{d\overline{E}}{dt}, \frac{d\overline{I}}{dt}\right)^T &= (F(t) - V(t))\left(\overline{E}, \overline{I}\right)^T \\ &\quad + \epsilon H(t)\left(\overline{E}, \overline{I}\right)^T, \end{aligned} \tag{39}$$

with $F(t), V(t)$ defined in (15) and

$$H(t) = \begin{pmatrix} 0 & \beta(t) f'(0) \\ 0 & 0 \end{pmatrix}. \tag{40}$$

Matrix $(F - V + \epsilon H)(t)$ is LT-periodic, cooperative, irreducible, and continuous. Using Lemma 3, if $q = (1/LT) \ln \rho(\Psi_{F-V+\epsilon H}(LT))$, then there exists a positive and LT-periodic function $v(t) = (v_1(t), v_2(t))^T$ such that $e^{qt}v(t)$ is solution of system (38). Note that for all $k > 0$, function $ke^{q(t-t_i)}v(t - t_i)$ is also a solution of system (38) with initial condition $kv(0)$ at $t = t_i$.

Choose a $\bar{t} > t_1$ and $\alpha_1 > 0$ such that $(E(\bar{t}), I(\bar{t}))^T \leq \alpha_1 v(0)$; then from (37) we have that

$$\left(\frac{dE}{dt}, \frac{dI}{dt}\right)^T \leq (F - V)(E, I)^T + \epsilon H (E, I)^T, \tag{41}$$

and using a comparison principle (see, e.g., [19] Theorem B.1), we have $(E(t), I(t))^T \leq \alpha_1 e^{q(t-\bar{t})} v(t - \bar{t})$ for all $t > \bar{t}$.

From Theorem 2.2 of [13], $\mathscr{R}_0 < 1$ iff $\rho(\Phi_{F-V}(LT)) < 1$. By the continuity of the spectrum for matrices (see [20], Section II.5.8), we can choose $\epsilon > 0$ small enough so that $\rho(\Phi_{F-V+\epsilon H}(LT)) < 1$ and then $q < 0$ (see Note 1). Thus, using positivity of solutions and comparison,

$$0 \leq \lim_{t\to\infty} E(t) \leq \lim_{t\to\infty} \alpha_1 e^{q(t-\bar{t})} v_1(t - \bar{t}) = 0. \tag{42}$$

And similarly for I, we obtain that

$$\begin{aligned} \lim_{t\to\infty} E(t) &= 0 \\ \lim_{t\to\infty} I(t) &= 0. \end{aligned} \tag{43}$$

We need only to prove that $S(t)$ approaches $\widehat{S}$. At disease-free periodic solution $\widehat{R}(t) = N - \widehat{S}(t)$, where $\widehat{R}$ satisfies

$$\frac{d\widehat{R}}{dt} = \mu N p + r(t)\widehat{S} - (\mu + \delta)\widehat{R}. \tag{44}$$

Thus, $R(t) = N - S(t) - E(t) - I(t)$ satisfies

$$\frac{d\left(R - \widehat{R}\right)}{dt} = r(t)\left(S - \widehat{S}\right) + \gamma I - (\mu + \delta)\left(R - \widehat{R}\right). \tag{45}$$

Let $\epsilon_1 > 0$ be arbitrary and $r_{\max} = \max_{u\in[0,LT]} r(u)$. Due to (43) we can find a $t_2 > 0$ such that $I(t) < \epsilon_1$ for $t > t_2$; moreover, we can find a $t_3 > 0$ such that $S(t) \leq \widehat{S}(t) + \epsilon_1$ for $t > t_3$. Then, let $t_4 = \max\{t_2, t_3\}$; we have for $t > t_4$

$$\frac{d\left(R - \widehat{R}\right)}{dt} \leq (r_{\max} + \gamma)\epsilon_1 - (\mu + \delta)\left(R - \widehat{R}\right). \tag{46}$$

Multiplying in both sides by $e^{(\mu+\delta)t}$ and integrating from t_4 to t, we obtain

$$\begin{aligned} \left(R - \widehat{R}\right) \leq \left(R - \widehat{R}\right)(t_4)\, e^{-(\mu+\delta)(t-t_4)} \\ + \frac{\epsilon_1 (r_{\max} + \gamma)}{\mu + \delta}\left(1 - e^{-(\mu+\delta)(t-t_4)}\right). \end{aligned} \tag{47}$$

So, $\limsup_{t\to\infty}(R - \widehat{R})(t) \leq \epsilon_1(r_{\max} + \gamma)/(\mu + \delta)$, where $\epsilon_1(r_{\max} + \gamma)/(\mu + \delta)$ is arbitrarily small. Then $\limsup_{t\to\infty}(R - \widehat{R})(t) \leq 0$, and using similar arguments for S and $\epsilon_2 > 0$, we can find a $t_5 > 0$ with $R(t) \leq \widehat{R}(t) + \epsilon_2/2$ for $t > t_5$. Also, from (43), we can find $t_6 > 0$ with $E(t) + I(t) < \epsilon_2/2$ for $t > t_6$, so, for $t > \max\{t_5, t_6\}$, we have

$$\begin{aligned} S(t) &= N - E(t) - I(t) - R(t) \geq N - \widehat{R}(t) - \epsilon_2 \\ &= \widehat{S}(t) - \epsilon_2. \end{aligned} \tag{48}$$

Or, equivalently, $S(t) - \widehat{S}(t) \geq -\epsilon_2$, with ϵ_2 being arbitrarily small, and this implies that $\liminf_{t\to\infty}(S - \widehat{S})(t) \geq 0$. We conclude by comparison and using Lemma 5 that $\lim_{t\to\infty} S(t) = \widehat{S}(t)$, completing the proof. □

Theorem 6 shows that disease will completely disappear as long as $\mathscr{R}_0 < 1$. Thus, reducing and keeping $\mathscr{R}_0$ below the unity would be sufficient to eradicate infection, even in a periodic environment and a general incidence rate.

3.2. Disease Persistence. Uniform persistence is an important concept in population dynamics, since it characterizes the long-term survival of some or all interacting species in an ecosystem [21].

In this section we consider the dynamics of the periodic model when $\mathscr{R}_0 > 1$. We will show that actually $\mathscr{R}_0$ is a threshold parameter for the extinction and the uniform persistence of the disease. Our results are inspired by [5, 15, 18, 22].

Let $P : X \to X$ be the Poincaré map associated with system (7); that is,

$$P(x_0) = \phi(LT, x_0), \quad \forall x_0 \in X, \tag{49}$$

where X is defined in (8) and $\phi(t, x_0)$ is the unique solution of system (7) with $\phi(0, x_0) = x_0$. We define the following sets:

$$\begin{aligned} X_0 &:= \{(S, E, I) \in X : E > 0,\ I > 0\}, \\ \partial X_0 &:= X \setminus X_0. \end{aligned} \tag{50}$$

Note that ∂X_0 is not the boundary of X_0, but it is a standard notation of persistence theory.

Lemma 7. *Set X_0 is positively invariant under system (7).*

Proof. Let $x_0 = (S_0, E_0, I_0) \in X_0$, that is, $E_0 > 0,\ I_0 > 0$, and let

$$\phi(t, x_0) = (S(t), E(t), I(t)) \tag{51}$$

be the solution of (7) with $\phi(0, x_0) = x_0$. Due to nonnegativity of solutions and assumptions on function $\beta(t)$ and $f(I)$, we have

$$\begin{aligned} \frac{dE}{dt} &= \beta(t) S f(I) - (\mu + \sigma) E \geq -(\mu + \sigma) E, \\ &\forall t > 0. \end{aligned} \tag{52}$$

Using a comparison theorem (see, e.g., [19] Appendix B.1), we have for all $t > 0$

$$E(t) \geq Ke^{-(\mu+\sigma)t} > 0, \quad \text{with } K = E(0) > 0. \tag{53}$$

Similarly,

$$\frac{dI}{dt} = \sigma E - (\mu+\gamma) I \geq -(\mu+\gamma) I, \tag{54}$$

so,

$$I(t) \geq I(0) e^{-(\mu+\gamma)t} > 0, \quad \forall t > 0. \tag{55}$$

Therefore, $\phi(t, x_0)$ remains on X_0 for all $t > 0$. □

To use persistence theory developed in [21], we show that

$$M_\partial = \{(S, 0, 0) : S \geq 0\}, \tag{56}$$

where

$$M_\partial := \{(S_0, E_0, I_0) \in \partial X_0 : P^m(S_0, E_0, I_0) \in \partial X_0, \ \forall m \geq 0\}. \tag{57}$$

Let $x_0 = (S_0, 0, 0) \in X$ and $(S(t), E(t), I(t))$ be the solution that passes through that initial condition. We have that $\phi(t, x_0) = (S_1(t), 0, 0)$, with $S_1(t)$ being a solution of (9) and $S_1(0) = S_0$ being a solution that satisfies the initial condition. By uniqueness of solutions we have $E(t) = 0 = I(t)$ $\forall t \geq 0$, so x_0 lives on M_∂.

Now, if $x_0 \in M_\partial$, we want $x_0 = (S_0, 0, 0)$. We prove an equivalent sentence: if $x_0 \in \partial X_0 \setminus \{(S, 0, 0) : S \geq 0\}$, then it does not belong to M_∂. Consider an initial point $x_0 = (S_0, E_0, I_0) \in \partial X_0 \setminus \{(S, 0, 0) : S \geq 0\}$; then $E_0 > 0$, $I_0 = 0$, or $E_0 = 0$, $I_0 > 0$. Suppose that $E > 0$ and $I_0 = 0$; then $\phi(t, x_0)$ holds

$$\frac{dI}{dt}(0) = \sigma E(0) > 0. \tag{58}$$

By continuity of $E(t)$ and sign of derivative of I, we have that, for small $0 < t \ll 1$, $E(t) > 0$, $I(t) > 0$, so, for $0 < t \ll 1$, $\phi(t, x_0) \in X_0$. Using invariance of X_0 (Lemma 7) we have $\phi(t, x_0) \in X_0$ for all $t > 1$. Finally, for a $m > 0$ such that $mLT > 1$, we have $P^m(x_0) = \phi(mLT, x_0) \in X_0$ and this implies (56). By the existence of a disease-free periodic solution (proved in Section 2), it is clear that there is one fixed point of P in M_∂ given by $M_0 = (\widehat{S}(0), 0, 0)$ ([23]).

Now, we are in a position to introduce the following result of uniform persistence of the disease.

Theorem 8. *Let $\mathcal{R}_0 > 1$; then there exists an $\epsilon > 0$ such that any solution $(S(t), E(t)I(t))$ of (7) with initial values $(S(0), E(0), I(0)) \in X_0$ satisfies*

$$\liminf_{t\to\infty} E(t) \geq \epsilon, \qquad \liminf_{t\to\infty} I(t) \geq \epsilon. \tag{59}$$

Proof. We first prove that P is uniformly persistent (see Definition 1.3.2 from [21]) with respect to $(X_0, \partial X_0)$, because this implies that the solution of (7) is uniformly persistent with respect to $(X_0, \partial X_0)$ (see [21], Theorem 3.1.1). Clearly, X_0 is relatively open in X, so ∂X_0 is relatively closed.

Define

$$W^s := \left\{x_0 \in X_0 : \lim_{m\to\infty} \left\|P^m(x_0) - M_0\right\| = 0\right\}; \tag{60}$$

we show that $W^s(M_0) \cap X_0 = \emptyset$.

By Theorem 2.2 of [13], $\mathcal{R}_0 > 1$ if and only if $r(\Psi_{F-V}(LT)) > 1$. Choose an $\eta > 0$ small enough with the property $\widehat{S}(t) - \eta > 0, \forall t > 0$ (see Appendix A). For $\alpha > 0$, let us consider the following perturbed equation:

$$\frac{d\overline{S}}{dt} = N(\mu(1-p) + \delta) - 2\delta\alpha - \left(\beta(t) f'(0)\alpha + \mu + r(t) + \delta\right)\overline{S}. \tag{61}$$

System above admits a unique positive LT-periodic solution of the form

$$\widehat{S}(t, \alpha) = e^{-\int_0^t (\beta(s) f'(0)\alpha + \mu + r(s) + \delta) ds} \left(\widehat{S}(0, \alpha) + (N\mu(1-p) + N\delta - 2\delta\alpha) \cdot \int_0^t e^{\int_0^s (\beta(\xi) f'(0)\alpha + \mu + r(\xi) + \delta) d\xi} ds\right) \tag{62}$$

whit $\widehat{S}(t, 0) = \widehat{S}(t)$, which is globally attractive for all solutions of (61) (see Appendix B for proof), and with

$$\widehat{S}(0, \alpha) = \frac{(N\mu(1-p) + N\delta - 2\delta\alpha) \int_0^{LT} e^{\int_0^s (\beta(\xi) f'(0)\alpha + \mu + r(\xi) + \delta) d\xi} ds}{e^{\int_0^{LT} (\beta(s) f'(0)\alpha + \mu + r(s) + \delta) ds} - 1}. \tag{63}$$

Since $\widehat{S}(0, \alpha)$ is continuous in α, for all $\epsilon > 0$ there is a $\delta > 0$ such that for $|\alpha| < \delta$ we have $|\widehat{S}(0, \alpha) - \widehat{S}(0, 0)| < \epsilon$. Moreover, by continuity of solutions with respect to initial values we can find for all $\overline{\eta} > 0$ an $\overline{\epsilon} > 0$ such that if $|\widehat{S}(0, \alpha) - \widehat{S}(0, 0)| < \overline{\epsilon}$, then

$$\left|\widehat{S}(t, \alpha) - \widehat{S}(t, 0)\right| < \overline{\eta}. \tag{64}$$

Therefore, for η established before, we can find α small enough such that $\widehat{S}(t, \alpha) > \widehat{S}(t) - \eta$, $\forall t > 0$.

Again, by continuity of solutions with respect to initial values, for this small $\alpha > 0$, there exists a $\delta > 0$ such that for all $(S_0, E_0, I_0) \in X_0$ with $\|(S_0, E_0, I_0) - M_0\| \leq \delta$ we have $\|\phi(t, (S_0, E_0, I_0)) - \phi(t, M_0)\| < \alpha$, $\forall t \in [0, LT]$.

We now claim that

$$\limsup_{m\to\infty} \left\|P^m(S_0, E_0, I_0) - M_0\right\| \geq \delta, \quad \forall (S_0, E_0, I_0) \in X_0. \tag{65}$$

By contradiction, suppose that

$$\limsup_{m\to\infty} \left\| P^m\left(S_0, E_0, I_0\right) - M_0 \right\| < \delta, \quad \text{for some } \left(S_0, E_0, I_0\right) \in X_0. \tag{66}$$

Without loss of generality, we can assume that $\|P^m(S_0, E_0, I_0) - M_0\| < \delta$ for all $m \geq 0$ (see Appendix C). From the discussion above, $\|\phi(t, P^m(S_0, E_0, I_0)) - \phi(t, M_0)\| < \alpha$, $\forall m \geq 0$ and $t \in [0, LT]$.

For any $t \geq 0$, let $t = mLT + t_1$, where $t_1 \in [0, LT)$ and $m = [t/LT]$ is the greatest integer less than or equal to t/LT. Then, we get

$$\begin{aligned} &\phi\left(t, \left(S_0, E_0, I_0\right)\right) - \phi\left(t, M_0\right) \\ &\quad = \phi\left(t_1, P^m\left(S_0, E_0, I_0\right)\right) - \phi\left(t, M_0\right) < \alpha. \end{aligned} \tag{67}$$

If we set $\phi(t, (S_0, E_0, I_0)) = (S(t), E(t), I(t))$, then we have $E(t) \leq \alpha$, $I(t) \leq \alpha$, $\forall t \geq 0$, and from the first equation of (7) and Lemma 4 we arrive at

$$\begin{aligned} \frac{dS}{dt} &\geq N\left(\mu\left(1-p\right)+\delta\right) - 2\delta\alpha \\ &\quad - \left(\beta\left(t\right) f'\left(0\right)\alpha + \mu + r\left(t\right) + \delta\right)\overline{S}, \end{aligned} \tag{68}$$

which is exactly the equation in (61). Since the unique periodic solution of (61) is globally attractive, we have for $\overline{S}(t, \alpha)$ solution of (61) that $\lim_{t\to\infty} \overline{S}(t, \alpha) = \widehat{S}(t, \alpha)$. So for η given before, there exists $T > 0$ such that for all $t \geq T$

$$\left|\overline{S}\left(t, \alpha\right) - \widehat{S}\left(t, \alpha\right)\right| < \eta, \tag{69}$$

or equivalently $\overline{S}(t, \alpha) > \widehat{S}(t, \alpha) - \eta$. Moreover, from previous analysis, $\widehat{S}(t, \alpha) - \eta > \widehat{S}(t) - \eta$; therefore, using comparison principle on (68) we arrive at

$$S\left(t\right) \geq \widehat{S}\left(t\right) - \eta \tag{70}$$

for $t > T$.

We have $E(t), I(t) \leq \alpha$, and α is fixed small, so we can take $\alpha < \epsilon^*$ and use assumption (A5) in Introduction (see Appendix D) to obtain

$$\begin{pmatrix} \dfrac{dE}{dt} \\ \dfrac{dI}{dt} \end{pmatrix} \geq \left(F - V - \eta H - \alpha K\right)\left(E, I\right)^T, \tag{71}$$

where F, V are defined in (15), H is defined in (40), and

$$K = \begin{pmatrix} 0 & -\dfrac{1}{2}\beta\left(t\right) f''\left(0\right)\left[\widehat{S} - \eta\right] \\ 0 & 0 \end{pmatrix}. \tag{72}$$

By Theorem 2.2 of [13], we have $\mathcal{R}_0 > 1$ iff $\rho(\Phi_{F-V}(LT)) > 1$. By continuity of spectrum (see [20] Section II), we can find α, ϵ such that

$$\rho\left(\Phi_{F-V-\eta H-\alpha K}\right) > 1. \tag{73}$$

Consider the auxiliary system

$$\begin{pmatrix} \dfrac{dE_2}{dt} \\ \dfrac{dI_2}{dt} \end{pmatrix} = \left(F - V - \eta H - \alpha K\right)\left(E_2, I_2\right)^T; \tag{74}$$

then, using Lemma 3 there exists a solution of (71) with the form $e^{p_2 t} v_2(t)$, with $p_2 = (1/LT)\ln(\rho(\Phi_{F-V-\eta H-\alpha K}(LT))) > 0$. Choose a $t_2 > T$ and a small number $\alpha_2 > 0$ such that $(E_2(t_2), I_2(t_2))^T \geq \alpha_2 v_2(0)$. Using comparison principle we get $(E(t), I(t)) \geq \alpha_2 v_2(t - t_2) e^{p_2(t-t_2)}$, which implies $E(t) \to \infty$ and $I(t) \to \infty$. This leads to a contradiction.

The claim above shows that P is weakly uniformly persistent with respect to $(X_0, \partial X_0)$. Note that P has a global attractor $\widehat{S}(0)$ (see Lemma 5). It follows that M_0 is an isolated invariant set in X, $W^s(M_0) \cap X_0 = \emptyset$. Every orbit in M_∂ converges to M_0 and M_0 is acyclic. By the acyclicity theorem on uniform persistence for maps ([21] Theorem 1.3.1 and Remark 1.3.1), it follows that P is uniformly persistent with respect to $(X_0, \partial X_0)$; that is, there exists $\epsilon > 0$ such that any solution of (7) satisfies $\lim_{t\to\infty} E(t) \geq \epsilon$, $\lim_{t\to\infty} I(t) \geq \epsilon$. □

4. Numerical Simulations

In this section we provide some numerical simulations to illustrate the results obtained in our theorems and compare them with previous results.

To improve previous models used in references, we use a particular function

$$f\left(I\right) = \frac{I}{1 + aI}, \quad a \geq 0, \tag{75}$$

which includes the case $f(I) = I$ used in [5]. One can check that function (75) satisfies conditions (A1)–(A5). Using this function, system (7) is rewritten as

$$\begin{aligned} \frac{dS}{dt} &= \mu N\left(1-p\right) - \frac{\beta\left(t\right) SI}{1+aI} - \left(\mu + r\left(t\right)\right) S \\ &\quad + \delta\left(N - S - E - I\right), \\ \frac{dE}{dt} &= \frac{\beta\left(t\right) SI}{1+aI} - \left(\mu + \sigma\right) E, \\ \frac{dI}{dt} &= \sigma E - \left(\mu + \gamma\right) I. \end{aligned} \tag{76}$$

Set an initial population $N = 2{,}200{,}000$ and take time t in years. Suppose $\mu = 0.02$ per year, corresponding to an average human life time of 50 years. Following [5] take the parameters as follows: $\sigma = 38.5$ per year, $\gamma = 100$ per year, $p = 0.85$, $\delta = 0$, and $a = 1$. Choose the periodic transmission as $\beta(t) = \beta_0 + 0.0002\cos(2\pi t)$, with β_0 being the transmission parameter, and the periodic vaccination rate $r(t) = 0.1 + 0.004\cos(2\pi t)$. Both functions have period $LT = 1$.

There exists multiple methods for computing the basic reproduction number, via numerical approximations, or finding a positive solution of the equation $\rho(W(LT, 0, \lambda)) = 1$

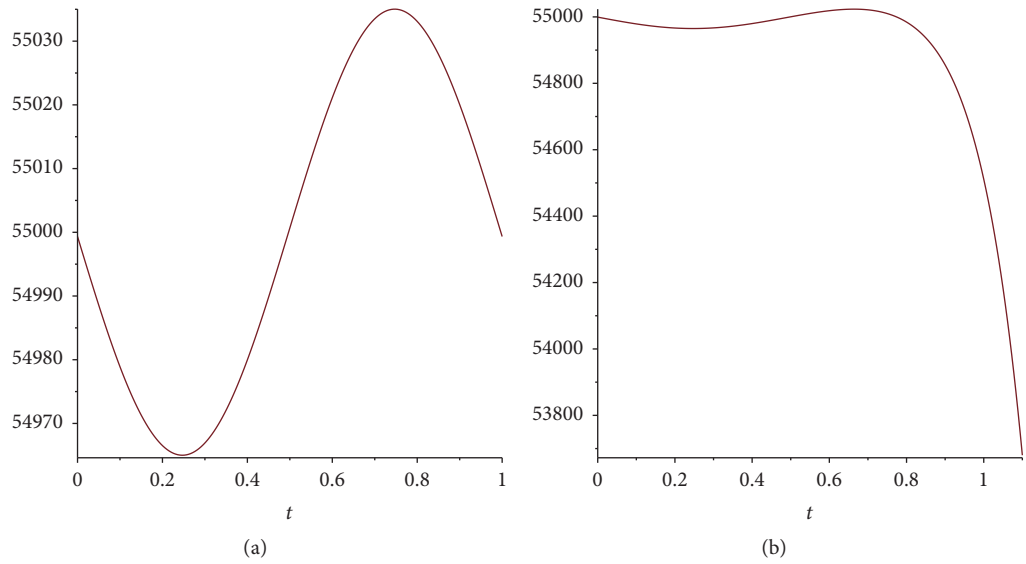

FIGURE 1: S component of infection-free periodic solution. Time t is given in years. (a) $\widehat{S}(t)$, because it is a periodic function of period 1, is plotted only in $[0, 1]$. (b) Taylor expansion of $\widehat{S}$ around $t = 0$ of order t^{10}.

(see Theorem 2.1 of [13]). In order to compare our work with previous works, we approximate the basic reproduction number with its average value $\mathscr{R}_0^T$, used by several authors as the reproduction number (for example [10, 11]), so define

$$R_0^T = \rho\left([F]\,V^{-1}\right), \tag{77}$$

where V is given by (15) and

$$[F] = \begin{pmatrix} 0 & [\beta]\left[\widehat{S}\right] f'(0) \\ 0 & 0 \end{pmatrix}, \tag{78}$$

with $[\beta], [\widehat{S}]$ being the average of functions $\beta, \widehat{S}$ defined as $[\beta] = (1/LT)\int_0^{LT} \beta(t)dt$, $\widehat{S} = (1/LT)\int_0^{LT} \widehat{S}(t)dt$. Computing each average, we obtain

$$R_0^T = 549.6702634\beta_0, \tag{79}$$

so $R_0^T > 1$ for $\beta_0 \in (0.001819272510, \infty)$.

Following Theorem 2.1 of [13], to compute $\mathscr{R}_0$, let $W(t, s, \lambda)$, $t \geq s$, be the evolution operator of the system

$$\frac{dw}{dt} = \left(-V(t) + \frac{F(t)}{\lambda}\right) w \tag{80}$$

that is, for each $\lambda \in (0, \infty)$, $dW(t, s, \lambda)/dt = (-V(t) + F(t)/\lambda)W(t, s, \lambda)$, $\forall t \geq s$, and $W(s, s, \lambda) = I_{2\times 2}$. With this operator, $\mathscr{R}_0 > 0$ is the unique solution of $\rho(W(LT, 0, \lambda)) = 1$.

Example 1. To illustrate our results, fix $\beta_0 = 0.0018$. Computing R_0^T, we have $R_0^T = 0.9894064741$, which is a first approximation of R_0. To solve system (80) numerically, we substitute the terms of expression of $\widehat{S}(t)$ in (10):

$$\begin{aligned} &\widehat{S}(t) \\ &= e^{-0.1200000000t - 0.0006366197724\sin(6.283185307t)}\left(54999.33689\right. \\ &\left. + 6600.0\int_{0.0}^{t} e^{0.1200000000s + 0.0006366197724\sin(6.283185307s)} ds\right) \end{aligned} \tag{81}$$

The previous integral cannot be computed analytically, so we approach $\widehat{S}(t)$ using Taylor expansion around 0 (remember that we want so solve $\rho(W(LT, 0, \lambda)) = 1$, where $LT = 1$), so even when we cannot find an explicit expression for $\widehat{S}(t)$, the Taylor expansion is a good way to estimate it in $(0, 1)$. It could be of interest to also use an approach of $\widehat{S}(t)$ around $t = 1$ and compare the results with those obtained in the present work (see Section 5 for a discussion about this topic).

Setting an initial value $\lambda_0 = 0.98$ and letting $\lambda_i = \lambda_0 + i(0.0001)$, we solve system (80) numerically for each λ_i (using initial conditions $w(0) = (1, 0)$ and $w(0) = (0, 1)$, to satisfy $W(0, 0) = I_{2\times 2}$), and compute $\rho_1 = \rho(W(LT, 0, \lambda_i))$ until $\rho_1 \sim 1$. With previous process we arrive at $\rho_1 = 1.00120166209265$ for $\lambda = 0.9872$ and $\rho_1 = 0.997826338969630$ for $\lambda = 0.9873$; therefore $\mathscr{R}_0 \in (0.9872, 0.9873)$. Using a finer step size 0.0000001 to have more accuracy, we arrive at $\mathscr{R}_0 \sim 0.9872355 < 1$.

Set initial values as $S(0) = 1{,}500{,}000$, $E(0) = 400{,}000$, $I(0) = 40{,}000$, and $R(0) = N - (S(0) + E(0) + I(0))$.

There exist multiple numerical methods to compute and plot the solutions of nonautonomous differential equations; see, for example, the Adomian method, the homotopy analysis method, or the modified homotopy methods (see, e.g., [24, 25]). For this work we use Matlab algorithms (ODE 45) to graph the solution of system (76) with these initial conditions. Figures 2 and 3 shows the results. We can see that $I(t), E(t)$ goes to zero, while $S(t), R(t)$ tend to stabilize; also $S(t)$ is tending to $\widehat{S}(t)$ with values between 54,000 and 56,000 (see Figure 1); this shows the results obtained in Theorem 6.

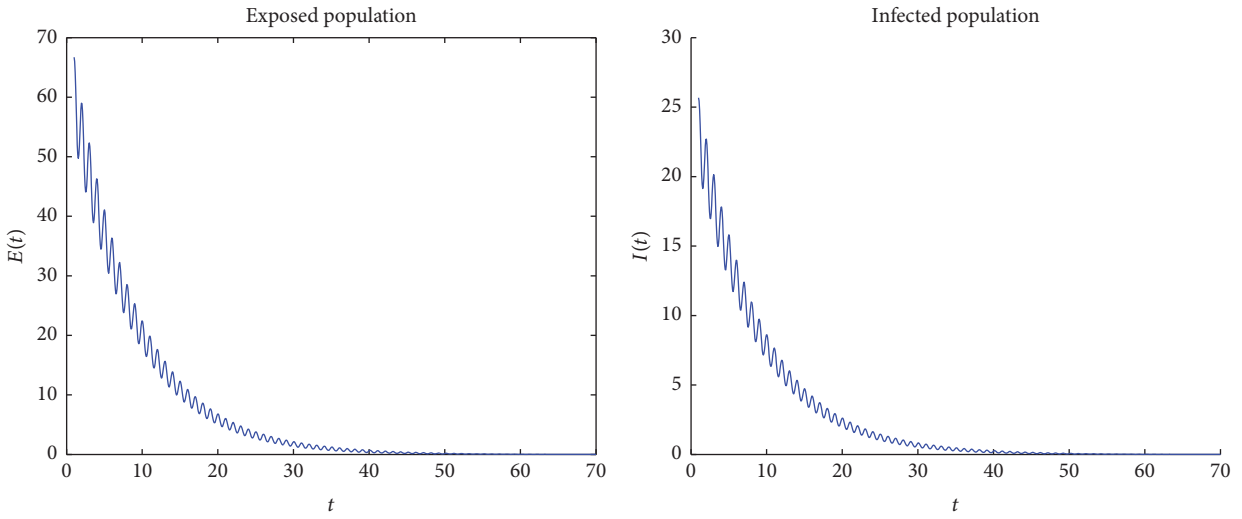

FIGURE 2: Solution of exposed and infected populations of SEIRS system when $\mathscr{R}_0 < 1$. We can see that both approach zero when time goes to infinity. Time t is given in years.

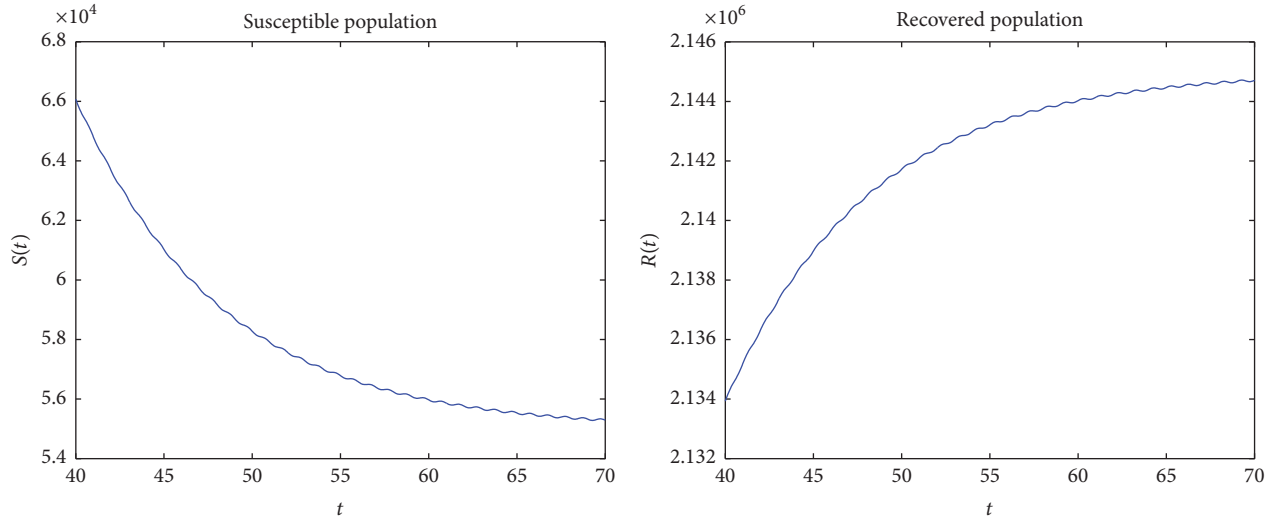

FIGURE 3: Solution of susceptible and recovered populations of SEIRS system when $\mathscr{R}_0 < 1$. We can see that S approaches $\widehat{S}(t)$ (see Figure 1), and R approaches $\widehat{R}(t) = N - \widehat{S}(t)$. Time t is given in years.

Example 2. Now, choose $\beta_0 = 0.005$. As we can see in Figures 4 and 5, the solutions of system (1) remain persistent when t tends to infinity; this fact suggests that $\mathscr{R}_0 > 1$ from Theorem 8. In fact, if we compute the basic reproduction number and its average (using the process described in example 1), $\mathscr{R}_0^T = 3.298021580$ and $\mathscr{R}_0 \in (2.7456, 2.7457)$; therefore it is bigger than one. In fact, this shows the results of persistence obtained in Theorem 8.

5. Conclusion

In this paper we presented a model with seasonal fluctuation with a general incidence function $Sf(I)$ that includes the bilinear case βSI (studied by [5]) and a family of saturated incidence rate of the form $\beta SI/(1 + kI^q)$. We proved the existence of a disease-free periodic solution $(\widehat{S}(t), 0, 0)$ and defined the basic reproduction number $\mathscr{R}_0$, proving that it is a threshold parameter for disease, in the sense that when $\mathscr{R}_0 < 1$, the disease-free periodic solution is globally asymptotically stable, and when $\mathscr{R}_0 > 1$, the disease is persistent. A next step of this work is to consider a family of incidence rates more generally, changing $Sf(I)$ by $f(S, I)$ and trying to obtain results of persistence and stability similar to the ones obtained in this work. Another interesting topic is to ask what the behavior of system at $\mathscr{R}_0 = 1$ is, in order to complete the analysis that we have made.

Several authors (e.g., [10, 11]) define $\mathscr{R}_0$ as an average, which we denoted as $\mathscr{R}_0^T$ to distinguish between it and the basic reproduction number defined by [13], via the monodromy matrix (which is a real threshold parameter

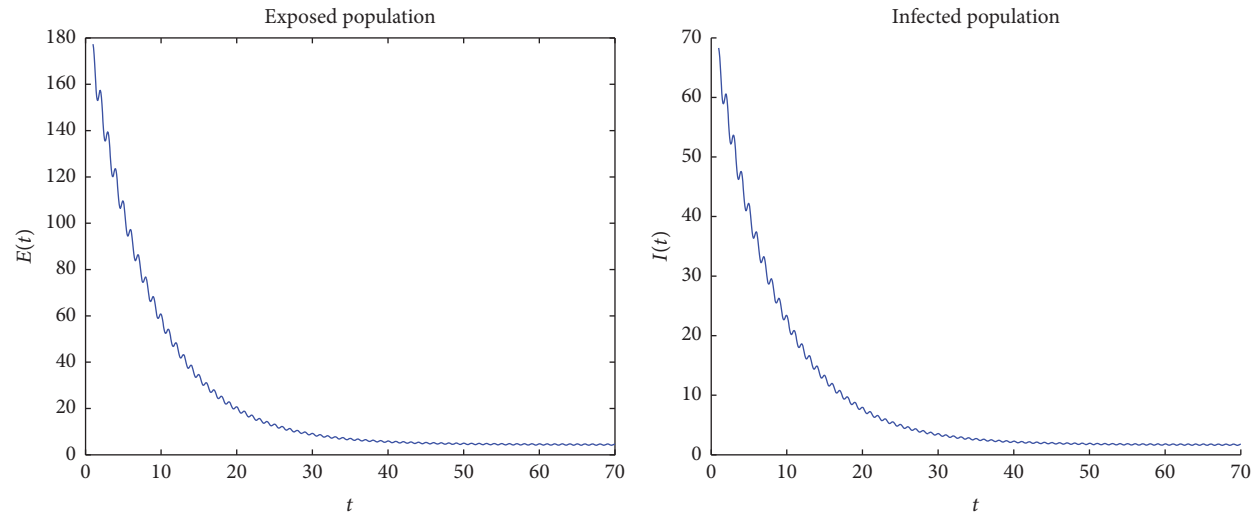

FIGURE 4: Solution of exposed and infected individuals of SEIRS system when $\mathcal{R}_0 > 1$. Both E and I remain persistent when time goes to infinity. Time t is given in years.

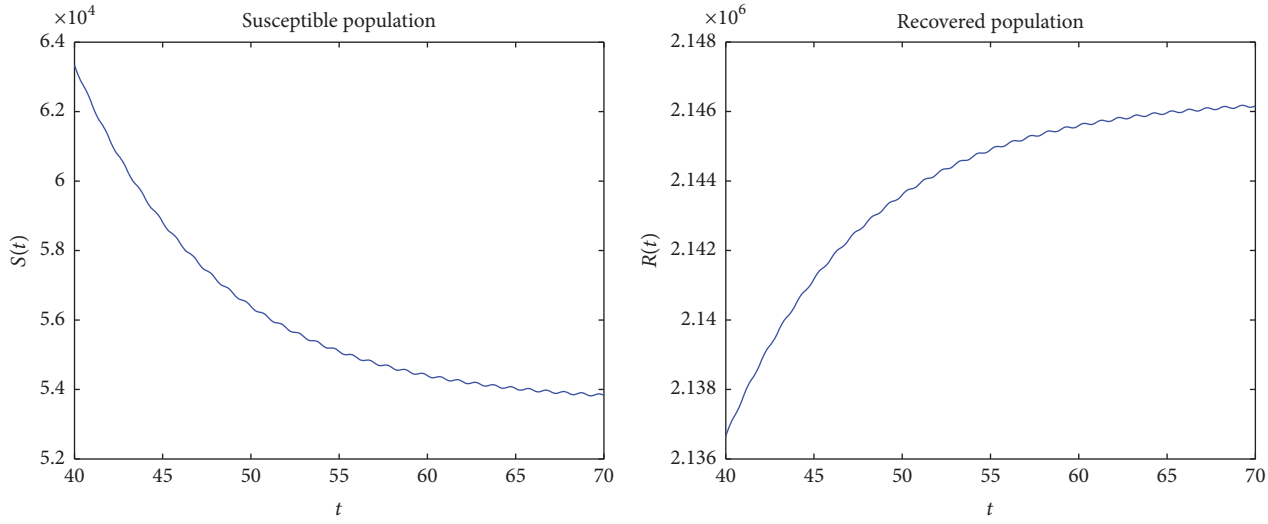

FIGURE 5: Solution of susceptible and recovered populations of SEIRS system when $\mathcal{R}_0 > 1$. Time t is given in years.

for extinction and persistence of disease). We compute $\mathcal{R}_0^T$, approximate $\mathcal{R}_0$ (with the help of Taylor theorem), and compare these values, obtaining that $\mathcal{R}_0^T$ is not equal to $\mathcal{R}_0$; moreover $\mathcal{R}_0^T > \mathcal{R}_0$ in both examples (similar comparisons can be observed also in the works made by [13, 17]). This fact suggests that the use of $\mathcal{R}_0^T$ for persistence overestimates the threshold. To emphasize this conclusion, it would be helpful to find an example where $\mathcal{R}_0 < 1$ but $\mathcal{R}_0^T > 1$ and then compute the solutions to observe the behavior (we affirm that the disease will go extinct due to Theorem 6).

To obtain the estimation of $\mathcal{R}_0$ we used a code in Maple, which is based on numerical computing of $\rho_1 = \rho(W(LT, 0, \lambda_i))$ until $\rho_1 \sim 1$, where $\lambda_i = \lambda_0 + \Delta_\lambda i$, Δ_λ is the step size, and the initial estimation λ_0 is taken as $R_0^T - \epsilon$. For this approximation we have used a Taylor expansion of the periodic solution $\widehat{S}(t)$; another interesting possibility could be varying the approximation used for $\mathcal{R}_0$, for example, changing the Taylor approach of $\widehat{S}(t)$ around $t = 1$ instead of $t = 0$. The graphs of the solutions were obtained with ODE 45 from Matlab, but other methods can be used to improve them, for example, Adomian methods or homotopy methods [24, 25]. The Maple code used to estimate $\mathcal{R}_0$ is available for anyone who wants to use it.

Appendix

A. Assumption on η Used in Theorem 8

Note that $\widehat{S}(t)$ has a positive minimum value $\min(\widehat{S}(t))$ (it is periodic, positive, and continuous, so it is bounded for $t \in [0, LT]$ and then for all $t > 0$) and we can choose a $\eta > 0$

with the property $\min(\widehat{S}(t)) > \eta$, sufficiently small such that $\widehat{S}(t) - \eta > 0$.

B. Periodic Solution of (61)

For each α, (61) used in the proof of Theorem 8 is

$$\frac{d\overline{S}}{dt} = N\left(\mu\left(1-p\right)+\delta\right) - 2\delta\alpha - \left(\beta\left(t\right)f'\left(0\right)\alpha + \mu + r\left(t\right) + \delta\right)\widehat{S}. \tag{B.1}$$

Solving the equation above, we arrive at the general solution

$$\overline{S}\left(t\right) = e^{-\int_{t_0}^{t} p(s)ds}\left[\overline{S}\left(t_0\right) + \left(N\left(\mu\left(1-p\right)+\delta\right) - 2\delta\alpha\right)\int_{t_0}^{t} e^{\int_{t_0}^{s}(p(\zeta)d\zeta)}ds\right], \tag{B.2}$$

where $p(s) = \beta(s)f'(0)\alpha + \mu + r(s) + \delta$. We shall examine the behavior of an arbitrary solution $\overline{S}$. For each $n = 0, 1, \ldots$, we can use an initial time $\overline{t}_0 = t_0 + nLT$ with initial point $\overline{S}(\overline{t}_0)$ and see that

$$\overline{S}\left(t_0 + (n+1)\,LT\right) = e^{-\int_{t_0+nLT}^{(t_0+nLT)+LT} p(s)ds}\left[\overline{S}\left(t_0 + nLT\right) + \left(N\left(\mu\left(1-p\right)+\delta\right) - 2\delta\alpha\right) \cdot \int_{(t_0+nLT)}^{(t_0+nLT)+LT} e^{\int_{t_0+nLT}^{s}(p(\zeta)d\zeta)ds}\right]. \tag{B.3}$$

Since $p(s)$ is a periodic function,

$$\int_{t_0+nLT}^{(t_0+nLT)+LT} p\left(s\right)ds = \int_{t_0}^{t_0+LT} p\left(s\right)ds = \int_{0}^{LT} p\left(s\right)ds, \qquad \int_{t_0+nLT}^{s} p\left(\zeta\right)d\zeta = \int_{t_0}^{s-nLT} p\left(\zeta\right)d\zeta, \tag{B.4}$$

where $s - nLT \geq t_0$. Then

$$\overline{S}\left(t_0 + (n+1)\,LT\right) = e^{-\int_{t_0}^{(t_0+LT)} p(s)ds}\left[\overline{S}\left(t_0 + nLT\right) + \left(N\left(\mu\left(1-p\right)+\delta\right) - 2\delta\alpha\right) \cdot \int_{(t_0+nLT)}^{(t_0+nLT)+LT} e^{\int_{t_0}^{s-LT}(p(\zeta)d\zeta)}ds\right]. \tag{B.5}$$

And using the change of variable $u = s - LT$, we have

$$\overline{S}\left(t_0 + (n+1)\,LT\right) = e^{-\int_{t_0}^{(t_0+LT)} p(s)ds}\left[\overline{S}\left(t_0 + nLT\right) + \left(N\left(\mu\left(1-p\right)+\delta\right) - 2\delta\alpha\right)\int_{t_0}^{t_0+LT} e^{\int_{t_0}^{u}(p(\zeta)d\zeta)}du\right]. \tag{B.6}$$

Equation (B.6) gives a recursive relationship between the solution at $t_0 + nLT$ and after LT times. If we set $S_n = \overline{S}(t_0 + nLT)$, then for each solution $\overline{S}$ this relationship is described by

$$S_{n+1} = F\left(S_n\right), \tag{B.7}$$

with F being on the right side of (B.6). If we take S_i and S_j, two different values of S_n, then

$$\left|F\left(S_i\right) - F\left(S_j\right)\right| = e^{-\int_{T_0}^{t_0+LT} p(s)ds}\left|S_i - S_j\right| \leq \left|S_i - S_j\right| \leq e^{-(\mu+\delta)LT}\left|S_i - S_j\right|. \tag{B.8}$$

Then, $F(S)$ is a contracting map, and by Banach fixed point theorem F has a unique fixed point S_i such that $S_{i+1} = F(S_i) = S_i$ or, equivalently, $\overline{S}(t_0 + iLT) = \overline{S}(t_0 + (i+1)LT)$. This fixed point can be found for any S that is a solution of a differential equation with arbitrary initial condition $S(t_0)$ at any time t_0. The fixed point has the form

$$\overline{S}\left(t_0^*\right) = \frac{\left(N\left(\mu\left(1-p\right)+\delta\right) - 2\delta\alpha\right)\int_{t_0^*}^{t_0^*+LT}\left(e^{\int_{t_0^*}^{u} p(s)ds}\right)du}{e^{\int_0^{LT} p(s)ds} - 1}. \tag{B.9}$$

Thus, define the function

$$\widehat{S}\left(t\right) = \frac{\left(N\left(\mu\left(1-p\right)+\delta\right) - 2\delta\alpha\right)\int_{t}^{t+LT}\left(e^{\int_{t}^{u} p(s)ds}\right)du}{e^{\int_0^{LT} p(s)ds} - 1}. \tag{B.10}$$

$\widehat{S}$ is a periodic function with period LT and is continuously differentiable with respect to t. One can check (by computing the derivative) that $\widehat{S}(t)$ is a solution of differential equation, so by existence and uniqueness of solutions it can be rewritten as

$$\widehat{S}\left(t\right) = e^{-\int_0^t p(s)ds}\left[\widehat{S}\left(0\right) + \left(N\left(\mu\left(1-p\right)+\delta\right) - 2\delta\alpha\right)\int_0^t e^{\int_0^s(p(\zeta)d\zeta)}ds\right], \tag{B.11}$$

with initial condition

$$\widehat{S}\left(0\right) = \frac{\left(N\left(\mu\left(1-p\right)+\delta\right) - 2\delta\alpha\right)\int_0^{LT} e^{\int_0^s(p(\zeta)d\zeta)}ds}{e^{\int_0^{LT} p(s)ds} - 1}. \tag{B.12}$$

If we suppose the existence of another periodic solution $\widehat{S}_2(t)$, then using (B.6) we arrive at $\widehat{S}_2(0) = \widehat{S}(0)$, by uniqueness of solutions $\widehat{S} = \widehat{S}_2$, and the periodic solution is unique. Computing the difference $\overline{S}(t) - \widehat{S}(t)$, we have

$$\overline{S}\left(t\right) - \widehat{S}\left(t\right) = e^{-\int_0^t p(s)ds}\left[\overline{S}\left(0\right) - \widehat{S}\left(0\right)\right], \tag{B.13}$$

so, $\lim(\overline{S}(t) - \widehat{S}(t)) = 0$. Therefore, every solution $\overline{S}(t)$ converges to $\widehat{S}(t)$.

C. Assumption on P^m Used in Theorem 8

Let $f(m) := \|P^m(S_0, E_0, I_0) - M_i\|$. If

$$\limsup_{m\to\infty} f(m) < \delta, \quad \text{for some } (S_0, E_0, I_0) \in X_0,\ i = 1, 2, \tag{C.1}$$

then we have $L = \lim_{m\to\infty}(\sup_{n\geq m} f(n)) < \delta$. For all $\epsilon > 0$ there exists a $M_\epsilon > 0$ such that if $m \geq M_\epsilon$, then $-\epsilon < \sup_{n\geq m} f(n) - L < \epsilon$. In particular, for $\epsilon = (\delta - L)/2 > 0$ we have

$$\sup_{n\geq m} f(n) - L < \delta - L \tag{C.2}$$

or, equivalently, $\sup_{n\geq m} f(n) < \delta$ for $m \geq M_{\delta-L}$. Moreover, for all $n \geq m$ with $m \geq M_{\delta-L}$, we have $f(n) < \sup_{n\geq m} f(n) < \delta$. Therefore, $\|P^n(S_0, E_0, I_0) - M_i\| < \delta$, $\forall n \geq M_{\delta_L}$.

We can take $(S_0^1, E_0^1, I_0^1) = P^{M_{\delta-L}}(S_0, E_0, I_0)$ as initial condition and, therefore,

$$\left\|P^n\left(S_0^1, E_0^1, I_0^1\right) - M_i\right\| < \delta, \quad \forall n \geq 0, \tag{C.3}$$

making our assumption valid.

So, we can assume without loss of generality that $\|P^m(S_0, E_0, I_0) - M_i\| < \delta$ for all $m \geq 0$.

D. Expression (71)

From system (7) $dE/dt = \beta(t)Sf(I) - (\mu + \sigma)E$, with $S(t) > \widehat{S}(t) - \eta$ for $t > T$, so

$$\frac{dE}{dt} \geq \beta(t)\left(\widehat{S}(t) - \eta\right) f(I) - (\mu + \sigma) E, \quad \text{for } t > T. \tag{D.1}$$

Using assumption (A5) for $f(I)$ and positivity of $\widehat{S}(t) - \eta$, we have also

$$\begin{aligned} &f(I)\left(\widehat{S}(t) - \eta\right) \\ &\quad \geq \left(\widehat{S}(t) - \eta\right)\left[If'(0) + \frac{1}{2}I^2 f''(0)\right]. \end{aligned} \tag{D.2}$$

Therefore,

$$\begin{aligned} \frac{dE}{dt} &\geq \beta(t)\left(\widehat{S}(t) - \eta\right)\left[If'(0) + \frac{1}{2}I^2 f''(0)\right] \\ &\quad - (\mu + \sigma) E, \\ &= \beta(t)\left(\widehat{S}(t) - \eta\right) If'(0) \\ &\quad + \frac{1}{2}\beta(t)\left(\widehat{S}(t) - \eta\right) f''(0) I^2 - (\mu + \sigma) E. \end{aligned} \tag{D.3}$$

$0 < I < \alpha$ and $f''(0) \leq 0$, so $I^2 < \alpha I$ and $f''(0)I^2 \geq f''(0)\alpha I$; applying this we arrive at

$$\begin{aligned} \frac{dE}{dt} &\geq \beta(t)\left(\widehat{S}(t) - \eta\right) If'(0) \\ &\quad + \frac{1}{2}\beta(t)\left(\widehat{S}(t) - \eta\right) f''(0)\alpha I, \\ \frac{dI}{dt} &= \sigma E - (\mu + \sigma) I. \end{aligned} \tag{D.4}$$

This expression can be written as (71).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Research Article

Dynamics of a Fractional Order HIV Infection Model with Specific Functional Response and Cure Rate

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We propose a fractional order model in this paper to describe the dynamics of human immunodeficiency virus (HIV) infection. In the model, the infection transmission process is modeled by a specific functional response. First, we show that the model is mathematically and biologically well posed. Second, the local and global stabilities of the equilibria are investigated. Finally, some numerical simulations are presented in order to illustrate our theoretical results.

1. Introduction

Fractional order differential equations (FDEs) are a generalization of ordinary differential equations (ODEs) and they have many applications in various fields such as mechanics, image processing, viscoelasticity, bioengineering, finance, psychology, and control theory [1–7]. In addition, it has been deduced that the membranes of cells of biological organisms have fractional order electrical conductance [8].

Modeling by FDEs has more advantages to describe the dynamics of phenomena with memory which exists in most biological systems, because fractional order derivatives depend not only on local conditions but also on the past. More precisely, calculating the time-fractional derivative of a function $f(t)$ at some time $t = t_1$ requires all the previous history, that is, all $f(t)$ from $t = 0$ to $t = t_1$. In addition, the region of stability of FDEs is larger than that of ODEs. Moreover, some previous study compared between the results of the fractional order model, the results of the integer model, and the measured real data obtained from 10 patients during primary HIV infection [9]. This study proved that the results of the fractional order model give predictions to the plasma virus load of the patients better than those of the integer model.

From the above biological and mathematical reasons, we propose a fractional order model to describe the dynamics of HIV infection that is given by

$$\begin{aligned} D^{\alpha}T(t) &= \lambda - dT - \frac{\beta TV}{1+\alpha_1 T+\alpha_2 V+\alpha_3 TV} + \rho I, \\ D^{\alpha}I(t) &= \frac{\beta TV}{1+\alpha_1 T+\alpha_2 V+\alpha_3 TV} - (a+\rho)I, \\ D^{\alpha}V(t) &= kI - \mu V, \end{aligned} \tag{1}$$

where $T(t)$, $I(t)$, and $V(t)$ represent the concentrations of uninfected $CD4^+$ T-cells, infected cells, and free virus particles at time t, respectively. Uninfected cells are assumed to be produced at a constant rate λ, die at the rate dT, and become infected by a virus at the rate $\beta TV/(1+\alpha_1 T+\alpha_2 V+\alpha_3 TV)$, where $\alpha_1, \alpha_2, \alpha_3 \geq 0$ are the saturation factors measuring the psychological or inhibitory effect. Infected cells die at the rate aI and return to the uninfected state by loss of all covalently closed circular DNA (cccDNA) from their nucleus at the rate ρI. Free virus particles are produced from infected cells at the rate kI and cleared at the rate μV.

The fractional order derivative used in system (1) is in the sense of Caputo. We use this Caputo fractional derivative for

two reasons: the first reason is that the fractional derivative of a constant is zero and the second reason is that the initial value problems depend on the integer order derivative only. In addition, we choose $0 < \alpha \leq 1$ in order to have the same initial conditions as ODE systems.

On the other hand, system (1) generalizes many special cases existing in the literature. For example, when $\alpha_1 = \alpha_2 = \alpha_3 = 0$, we get the model of Arafa et al. [10]. Further, we obtain the model of Liu et al. [11] when $\alpha_3 = 0$. It is very important to note that when $\alpha = 1$, system (1) becomes a model with an ordinary derivative which is the generalization of the ODE models presented in [12–15].

The rest of the paper is organized as follows. In the next section, we give some preliminary results. In Section 3, equilibria and their local stability are investigated. In Section 4, the global stability of the two equilibria is established. Numerical simulations of our theoretical results are presented in Section 5. Finally, the paper ends with conclusion in Section 6.

2. Preliminary Results

We first recall the definitions of the fractional order integral, Caputo fractional derivative, and Mittag-Leffler function that are given in [16].

Definition 1. The fractional integral of order $\alpha > 0$ of a function $f : \mathbb{R}_+ \to \mathbb{R}$ is defined as follows:

$$I^{\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-x)^{\alpha-1} f(x)\, dx, \tag{2}$$

where $\Gamma(\cdot)$ is the Gamma function.

Definition 2. The Caputo fractional derivative of order $\alpha > 0$ of a continuous function $f : \mathbb{R}_+ \to \mathbb{R}$ is given by

$$D^{\alpha} f(t) = I^{n-\alpha} D^n f(t), \tag{3}$$

where $D = d/dt$ and $n - 1 < \alpha \leq n, n \in \mathbb{N}$.

In particular, when $0 < \alpha \leq 1$, we have

$$D^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{f'(x)}{(t-x)^{\alpha}} dx. \tag{4}$$

Definition 3. Let $\alpha > 0$. The function E_{α}, defined by

$$E_{\alpha}(z) = \sum_{j=0}^{\infty} \frac{z^j}{\Gamma(\alpha j + 1)}, \tag{5}$$

is called the Mittag-Leffler function of parameter α.

Let $f : \mathbb{R}^n \to \mathbb{R}^n$ with $n \geq 1$. Consider the fractional order system

$$\begin{aligned} D^{\alpha} x(t) &= f(x), \\ x(t_0) &= x_0, \end{aligned} \tag{6}$$

with $0 < \alpha \leq 1$, $t_0 \in \mathbb{R}$, and $x_0 \in \mathbb{R}^n$. For the global existence of solution of system (6), we need the following lemma.

Lemma 4. *Assume that f satisfies the following conditions:*

(i) *$f(x)$ and $(\partial f/\partial x)(x)$ are continuous for all $x \in \mathbb{R}^n$.*

(ii) *$\|f(x)\| \leq \omega + \lambda\|x\|$ for all $x \in \mathbb{R}^n$, where ω and λ are two positive constants.*

Then, system (6) has a unique solution on $[t_0, +\infty)$.

The proof of this lemma follows immediately from [17]. For biological reasons, we assume that the initial conditions of system (1) satisfy

$$\begin{aligned} T(0) &= \phi_1(0) \geq 0, \\ I(0) &= \phi_2(0) \geq 0, \\ V(0) &= \phi_3(0) \geq 0. \end{aligned} \tag{7}$$

In order to establish the nonnegativity of solutions with initial conditions (7), we need also the following lemmas.

Lemma 5 (see [18]). *Suppose that $g(t) \in C[a,b]$ and $D^{\alpha} g(t) \in C[a,b]$ for $0 < \alpha \leq 1$; then, one has*

$$g(t) = g(a) + \frac{1}{\Gamma(\alpha)} D^{\alpha} g(\xi) (t-a)^{\alpha}, \quad a < \xi < t, \ \forall t \in (a,b]. \tag{8}$$

Lemma 6 (see [18]). *Suppose that $g(t) \in C[a,b]$ and $D^{\alpha} g(t) \in C[a,b]$ for $0 < \alpha \leq 1$. If $D^{\alpha} g(t) \geq 0$ $\forall t \in [a,b]$, then $g(t)$ is nondecreasing for each $t \in [a,b]$. If $D^{\alpha} g(t) \leq 0$ $\forall t \in [a,b]$, then $g(t)$ is nonincreasing for each $t \in [a,b]$.*

Theorem 7. *For any initial conditions satisfying (7), system (1) has a unique solution on $[0, +\infty)$. Moreover, this solution remains nonnegative and bounded for all $t \geq 0$. In addition, one has*

(i) *$N(t) \leq N(0) + \lambda/\delta$,*

(ii) *$V(t) \leq V(0) + (k/\mu)\|I\|_{\infty}$,*

where $N(t) = T(t) + I(t)$ and $\delta = \min\{a, d\}$.

Proof. It is easy to see that the vector function of system (1) satisfies the first condition of Lemma 4. It remains to prove the second condition. Let

$$X(t) = \begin{pmatrix} T(t) \\ I(t) \\ V(t) \end{pmatrix}, \quad \zeta = \begin{pmatrix} \lambda \\ 0 \\ 0 \end{pmatrix}. \tag{9}$$

To this end, we discuss four cases:

(i) If $\alpha_1 \neq 0$, then system (1) can be written as follows:

$$D^{\alpha} X(t) = \zeta + A_1 X + \frac{\alpha_1 T}{1 + \alpha_1 T + \alpha_2 V + \alpha_3 TV} A_2 X, \tag{10}$$

where

$$A_1 = \begin{pmatrix} -d & \rho & 0 \\ 0 & -(a+\rho) & 0 \\ 0 & k & -\mu \end{pmatrix},$$

$$A_2 = \begin{pmatrix} 0 & 0 & -\dfrac{\beta}{\alpha_1} \\ 0 & 0 & \dfrac{\beta}{\alpha_1} \\ 0 & 0 & 0 \end{pmatrix}. \tag{11}$$

Moreover, we have

$$\left\|D^\alpha X(t)\right\| \le \|\zeta\| + \left(\|A_1\| + \|A_2\|\right)\|X\|. \tag{12}$$

(ii) If $\alpha_2 \neq 0$, we have

$$D^\alpha X(t) = \zeta + A_1 X + \frac{\alpha_2 T}{1+\alpha_1 T + \alpha_2 V + \alpha_3 TV} A_3 X, \tag{13}$$

where

$$A_3 = \begin{pmatrix} 0 & 0 & -\dfrac{\beta}{\alpha_2} \\ 0 & 0 & \dfrac{\beta}{\alpha_2} \\ 0 & 0 & 0 \end{pmatrix}. \tag{14}$$

Then,

$$\left\|D^\alpha X(t)\right\| \le \|\zeta\| + \left(\|A_1\| + \|A_3\|\right)\|X\|. \tag{15}$$

(iii) If $\alpha_3 \neq 0$, we have

$$D^\alpha X(t) = \zeta + A_1 X + \frac{\alpha_3 TV}{1+\alpha_1 T + \alpha_2 V + \alpha_3 TV} A_4, \tag{16}$$

where

$$A_4 = \begin{pmatrix} -\dfrac{\beta}{\alpha_3} \\ \dfrac{\beta}{\alpha_3} \\ 0 \end{pmatrix}. \tag{17}$$

Then,

$$\left\|D^\alpha X(t)\right\| \le \left(\|\zeta\| + \|A_4\|\right) + \|A_1\|\|X\|. \tag{18}$$

(iv) If $\alpha_1 = \alpha_2 = \alpha_3 = 0$, we have

$$D^\alpha X(t) = \zeta + A_1 X + V A_5 X, \tag{19}$$

where

$$A_5 = \begin{pmatrix} -\beta & 0 & 0 \\ \beta & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}. \tag{20}$$

Then,

$$\left\|D^\alpha X(t)\right\| \le \|\zeta\| + \left(\|V\|\|A_5\| + \|A_1\|\right)\|X\|. \tag{21}$$

Thus, the second condition of Lemma 4 is satisfied. Then, system (1) has a unique solution on $[0, +\infty)$. Next, we show that this solution is nonnegative. From (1), we have

$$\begin{aligned} D^\alpha T(t)\big|_{T=0} &= \lambda + \rho I \ge 0, \\ D^\alpha I(t)\big|_{I=0} &= \frac{\beta TV}{1+\alpha_1 T + \alpha_2 V + \alpha_3 TV} \ge 0, \\ D^\alpha V(t)\big|_{V=0} &= kI \ge 0. \end{aligned} \tag{22}$$

According to Lemmas 5 and 6, we deduce that the solution of (1) is nonnegative.

Finally, we prove that the solution is bounded. By adding the first two equations of system (1), we get

$$D^\alpha N(t) \le \lambda - \delta N(t). \tag{23}$$

Hence,

$$N(t) \le N(0) E_\alpha\left(-\delta t^\alpha\right) + \frac{\lambda}{\delta}\left[1 - E_\alpha\left(-\delta t^\alpha\right)\right]. \tag{24}$$

Since $0 \le E_\alpha(-\delta t^\alpha) \le 1$, we have

$$N(t) \le N(0) + \frac{\lambda}{\delta}. \tag{25}$$

The third equation of system (1) implies that

$$\begin{aligned} V(t) = {} & V(0) E_\alpha\left(-\mu t^\alpha\right) \\ & + k \int_0^t I(s)\, \alpha (t-s)^{\alpha-1} \frac{dE_\alpha}{ds}\left(-\mu (t-s)^\alpha\right) ds. \end{aligned} \tag{26}$$

Then,

$$V(t) \le V(0) E_\alpha\left(-\mu t^\alpha\right) + \frac{k\|I\|_\infty}{\mu}\left(1 - E_\alpha\left(-\mu t^\alpha\right)\right). \tag{27}$$

Consequently,

$$V(t) \le V(0) + \frac{k\|I\|_\infty}{\mu}. \tag{28}$$

This completes the proof. □

3. Equilibria and Their Local Stability

It is easy to see that system (1) always has a disease-free equilibrium $E_0(\lambda/d, 0, 0)$. Therefore, the basic reproduction number of our system (1) is given by

$$R_0 = \frac{k\beta\lambda}{\mu(a+\rho)(d+\lambda\alpha_1)}. \tag{29}$$

Biologically, this basic reproduction number represents the average number of secondary infections produced by one infected cell during the period of infection when all cells are uninfected. Further, it is not hard to get the following result.

Theorem 8. *(i) If $R_0 \le 1$, system (1) has a unique disease-free equilibrium of the form $E_0(T_0, 0, 0)$, where $T_0 = \lambda/d$. (ii) If $R_0 > 1$, the disease-free equilibrium is still present and system (1) has a unique chronic infection equilibrium of the form $E_1(T_1, (\lambda - dT_1)/a, k(\lambda - dT_1)/a\mu)$, where $T_1 = 2(a+\rho)(a\mu+\alpha_2\lambda k)/(ak\beta+(a+\rho)(\alpha_2 dk-\alpha_1 a\mu-\alpha_3 k\lambda)+\sqrt{\overline{\delta}})$ with*

$$\begin{aligned}\overline{\delta} &= \left(ak\beta + (a+\rho)\left(\alpha_2 dk - \alpha_1 a\mu - \alpha_3 k\lambda\right)\right)^2 \\ &\quad + 4\alpha_3 kd\,(a+\rho)^2\left(a\mu + \alpha_2\lambda k\right).\end{aligned} \tag{30}$$

Next, we investigate the local stability of equilibria. Let $E_e(T, I, V)$ be an arbitrary equilibrium of system (1). Then, the characteristic equation at E_e is given by

$$\begin{vmatrix} -d - V\dfrac{\partial f}{\partial T} - \xi & \rho & -V\dfrac{\partial f}{\partial V} - f(T,V) \\ V\dfrac{\partial f}{\partial T} & -(a+\rho) - \xi & V\dfrac{\partial f}{\partial V} + f(T,V) \\ 0 & k & -\mu - \xi \end{vmatrix} = 0, \tag{31}$$

where

$$f(T,V) = \frac{\beta T}{1 + \alpha_1 T + \alpha_2 V + \alpha_3 TV}. \tag{32}$$

We recall that the equilibrium E_e is locally asymptotically stable if all roots ξ_i of (31) satisfy the following condition [19]:

$$\left|\arg(\xi_i)\right| > \frac{\alpha\pi}{2}. \tag{33}$$

Theorem 9. *(i) If $R_0 < 1$, then E_0 is locally asymptotically stable. (ii) If $R_0 > 1$, then E_0 is unstable.*

Proof. Evaluating (31) at E_0, we have

$$(d+\xi)\left[\xi^2 + (a+\rho+\mu)\,\xi + \mu(a+\rho)(1-R_0)\right] = 0. \tag{34}$$

Obviously, the roots of (34) are

$$\begin{aligned}\xi_1 &= -d, \\ \xi_2 &= \frac{-(a+\rho+\mu) - \sqrt{(a+\rho+\mu)^2 - 4\mu(a+\rho)(1-R_0)}}{2}, \\ \xi_3 &= \frac{-(a+\rho+\mu) + \sqrt{(a+\rho+\mu)^2 - 4u(a+\rho)(1-R_0)}}{2}.\end{aligned} \tag{35}$$

It is clear that ξ_1 and ξ_2 are negative. However, ξ_3 is negative if $R_0 < 1$ and it is positive if $R_0 > 1$. Therefore, E_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. □

Now, we focus on the local stability of the chronic infection equilibrium E_1. It follows from (31) that the characteristic equation at E_1 is given by

$$P(\xi) := \xi^3 + a_1\xi^2 + a_2\xi + a_3 = 0, \tag{36}$$

where

$$\begin{aligned}a_1 &= \mu + d + a + \rho + \frac{\beta V_1(1+\alpha_2 V_1)}{(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)^2}, \\ a_2 &= d(\mu + a + \rho) \\ &\quad + \frac{\beta V_1\left[(a+\mu)(1+\alpha_2 V_1) + kT_1(\alpha_2+\alpha_3 T_1)\right]}{(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)^2}, \\ a_3 &= \frac{\beta V_1\left[a\mu(1+\alpha_2 V_1) + kdT_1(\alpha_2+\alpha_3 T_1)\right]}{(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)^2}.\end{aligned} \tag{37}$$

It is obvious that $a_1 > 0$, $a_2 > 0$, and $a_3 > 0$. Further, we have

$$\begin{aligned}a_1 a_2 - a_3 &= a\left(d(\mu+a+\rho) + \frac{\beta V_1\left[a(1+\alpha_2 V_1) + kT_1(\alpha_2+\alpha_3 T_1)\right]}{(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)^2}\right) \\ &\quad + d\left(d(\mu+a+\rho) + \frac{(a+\mu)\beta V_1(1+\alpha_2 V_1)}{(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)^2}\right) + \left(\mu+\rho + \frac{\beta V_1(1+\alpha_2 V_1)}{(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)^2}\right)h_2 > 0.\end{aligned} \tag{38}$$

So, Routh–Hurwitz conditions are satisfied. Let $D(P)$ denote the discriminant of the polynomial P given by (36); then,

$$D(P) = 18a_1a_2a_3 + (a_1a_2)^2 - 4a_3a_1^3 - 4a_2^3 - 27a_3^2. \tag{39}$$

Using the results in [19], we easily obtain the following result.

Theorem 10. *Assume that $R_0 > 1$.*

(i) *If $D(P) > 0$, then E_1 is locally asymptotically stable for all $\alpha \in (0, 1]$.*

(ii) *If $D(P) < 0$ and $\alpha < 2/3$, then E_1 is locally asymptotically stable.*

4. Global Stability

In this section, we study the global stability of the disease-free equilibrium E_0 and the chronic infection equilibrium E_1.

Theorem 11. *If $R_0 \le 1$, then the disease-free equilibrium E_0 is globally asymptotically stable.*

Proof. Define Lyapunov functional $L_0(t)$ as follows:

$$L_0(t) = \frac{T_0}{1+\alpha_1 T_0}\Phi\left(\frac{T}{T_0}\right) + \frac{\rho}{2(1+\alpha_1 T_0)(a+d)T_0}(T - T_0 + I)^2 + \frac{a+\rho}{k}V, \tag{40}$$

where $\Phi(x) = x - 1 - \ln(x)$, $x > 0$. Calculating the derivative of $L_0(t)$ along solutions of system (1) and using the results in [20], we get

$$D^\alpha L_0(t) \le \frac{1}{1+\alpha_1 T_0}\left(1 - \frac{T_0}{T}\right)D^\alpha T + D^\alpha I \cdot \frac{\rho}{(1+\alpha_1 T_0)(a+d)T_0}(T - T_0 + I) \cdot (D^\alpha T + D^\alpha I) + \frac{a+\rho}{k}D^\alpha V. \tag{41}$$

Using $\lambda = dT_0$, we obtain

$$\begin{aligned} D^\alpha L_0(t) &\le -\frac{d(T-T_0)^2}{(1+\alpha_1 T_0)T} - \frac{1}{1+\alpha_1 T_0}\left(1 - \frac{T_0}{T}\right)f(T,V)V \\ &\quad + \frac{\rho}{1+\alpha_1 T_0}\left(1 - \frac{T_0}{T}\right)I + f(T,V)V \\ &\quad - \frac{d\rho(T-T_0)^2}{(a+d)T_0(1+\alpha_1 T_0)} \\ &\quad - \frac{a\rho I^2}{(a+d)T_0(1+\alpha_1 T_0)} \\ &\quad + \frac{\rho}{T_0(1+\alpha_1 T_0)}I(T_0 - T) - \frac{(a+\rho)\mu}{k}V, \end{aligned} \tag{42}$$

$$\begin{aligned} D^\alpha L_0(t) &\le -\left(\frac{1}{T} + \frac{\rho}{(a+d)T_0}\right)\frac{d(T-T_0)^2}{1+\alpha_1 T_0} \\ &\quad - \frac{\rho I(T-T_0)^2}{TT_0(1+\alpha_1 T_0)} - \frac{a\rho I^2}{(a+d)T_0(1+\alpha_1 T_0)} \\ &\quad + \frac{(a+\rho)\mu}{k}(R_0 - 1)V \\ &\quad - \frac{\beta T_0(\alpha_2 + \alpha_3 T)}{(1+\alpha_1 T_0)(1+\alpha_1 T + \alpha_2 V + \alpha_3 TV)}V^2. \end{aligned}$$

Hence, if $R_0 \le 1$, then $D^\alpha L_0(t) \le 0$. Furthermore, it is clear that the largest invariant set of $\{(T, I, V) \in D : D^\alpha L_0(t) = 0\}$ is the singleton $\{E_0\}$. Therefore, by LaSalle's invariance principle [21], E_0 is globally asymptotically stable. □

Theorem 12. *The chronic infection equilibrium E_1 is globally asymptotically stable if $R_0 > 1$ and*

$$R_0 \le 1 + \frac{d(a+\rho)(\lambda\alpha_2 k + a\mu) + \rho\lambda^2\alpha_3 k}{\rho\mu(a+\rho)(d+\lambda\alpha_1)}. \tag{43}$$

Proof. Define Lyapunov functional $L_1(t)$ as follows:

$$\begin{aligned} L_1(t) &= \frac{1+\alpha_2 V_1}{1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1}T_1\Phi\left(\frac{T}{T_1}\right) \\ &\quad + I_1\Phi\left(\frac{I}{I_1}\right) + \frac{a+\rho}{k}V_1\Phi\left(\frac{V}{V_1}\right) \\ &\quad + \frac{\rho(1+\alpha_2 V_1)}{2T_1(a+d)(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)}(T \\ &\quad - T_1 + I - I_1)^2. \end{aligned} \tag{44}$$

Then, we have

$$\begin{aligned} D^\alpha L_1(t) &\le \frac{1+\alpha_2 V_1}{1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1}\left(1 - \frac{T_1}{T}\right) \\ &\quad \cdot D^\alpha T + \left(1 - \frac{I_1}{I}\right)D^\alpha I \\ &\quad \cdot \frac{\rho(1+\alpha_2 V_1)}{T_1(a+d)(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)}(T - T_1 \\ &\quad + I - I_1)(D^\alpha T + D^\alpha I) + \frac{a+\rho}{k}\left(1 - \frac{V_1}{V}\right)D^\alpha V. \end{aligned} \tag{45}$$

Using $\lambda = dT_1 + aI_1$, $f(T_1, V_1)V_1 = (a+\rho)I_1$, $\mu/k = I_1/V_1$, and $1 - f(T_1,V_1)/f(T,V_1) = ((1+\alpha_2 V_1)/(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1))(1 - T_1/T)$, we get

$$\begin{aligned} D^\alpha L_1(t) &\le d\left(1 - \frac{f(T_1,V_1)}{f(T,V_1)}\right)(T_1 - T) + (a+\rho) \\ &\quad \cdot I_1\left(4 - \frac{f(T_1,V_1)}{f(T,V_1)} - \frac{I_1}{I}\frac{V}{V_1}\frac{f(T,V)}{f(T_1,V_1)} - \frac{I}{I_1}\frac{V_1}{V}\right. \\ &\quad \left. - \frac{f(T,V_1)}{f(T,V)}\right) + (a+\rho)I_1\left(-1 - \frac{V}{V_1} + \frac{f(T,V_1)}{f(T,V)}\right. \\ &\quad \left. + \frac{V}{V_1}\frac{f(T,V)}{f(T,V_1)}\right) \\ &\quad - \frac{d\rho(1+\alpha_2 V_1)}{T_1(a+d)(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)}(T \\ &\quad - T_1)^2 \\ &\quad - \frac{a\rho(1+\alpha_2 V_1)}{T_1(a+d)(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)}(I - I_1)^2 \\ &\quad - \frac{\rho(1+\alpha_2 V_1)}{TT_1(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)}(T - T_1)^2(I \\ &\quad - I_1). \end{aligned} \tag{46}$$

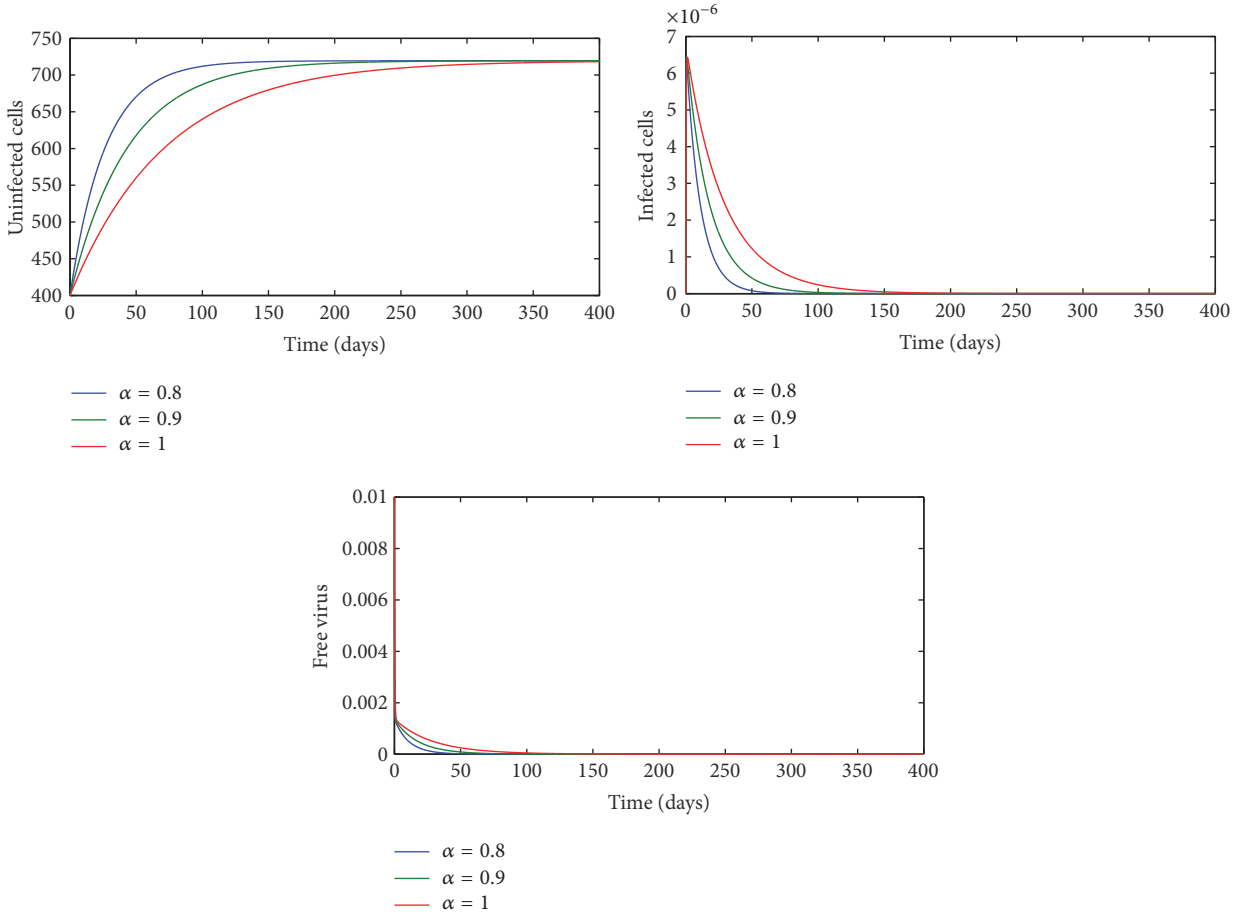

FIGURE 1: Stability of the disease-free equilibrium E_0.

Thus,

$$
\begin{aligned}
&D^{\alpha}L_1(t)\\
&\le -\frac{(1+\alpha_2V_1)(T-T_1)^2}{TT_1(1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1)}\left((dT_1-\rho I_1)\right.\\
&\left.+\frac{d\rho T}{d+a}+\rho I\right)-(a+\rho)I_1\\
&\cdot\frac{(1+\alpha_1T)(\alpha_2+\alpha_3T)(V-V_1)^2}{V_1(1+\alpha_1T+\alpha_2V+\alpha_3TV)(1+\alpha_1T+\alpha_2V_1+\alpha_3TV_1)} \quad (47)\\
&-(a+\rho)I_1\left(\Phi\left(\frac{f(T_1,V_1)}{f(T,V_1)}\right)+\Phi\left(\frac{I_1}{I}\frac{V}{V_1}\frac{f(T,V)}{f(T_1,V_1)}\right)\right.\\
&\left.+\Phi\left(\frac{I}{I_1}\frac{V_1}{V}\right)+\Phi\left(\frac{f(T,V_1)}{f(T,V)}\right)\right)\\
&-\frac{a\rho(1+\alpha_2V_1)}{T_1(a+d)(1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1)}(I-I_1)^2.
\end{aligned}
$$

It is clear that $\Phi(x) \ge 0$. Consequently, $D^{\alpha}L_1(t) \le 0$ if $dT_1 \ge \rho I_1$. In addition, it is easy to see that this condition is equivalent to (43). Further, the largest invariant set of $\{(T,I,V) \in D : D^{\alpha}L_1(t) = 0\}$ is the singleton $\{E_1\}$. By LaSalle's invariance principle, E_1 is globally asymptotically stable. □

It is important to see that

$$
\lim_{\rho\to 0}\frac{d(a+\rho)(\lambda\alpha_2k+a\mu)+\rho\lambda^2\alpha_3k}{\rho\mu(a+\rho)(d+\lambda\alpha_1)}=+\infty. \quad (48)
$$

According to Theorem 12, we obtain the following result.

Corollary 13. *The chronic infection equilibrium E_1 is globally asymptotically stable when $R_0 > 1$ and ρ is sufficiently small.*

5. Numerical Simulations

In this section, we give some numerical simulations in order to illustrate our theoretical results. We discretize system (1) by using fractional Euler's method presented in [22]. Firstly, we take the parameter values as shown in Table 1.

By calculation, we have $R_0 = 0.9283 < 1$. Then, system (1) has a disease-free equilibrium $E_0(719.4245, 0, 0)$. By Theorem 11, the solution of (1) converges to E_0 (see Figure 1). Consequently, the virus is cleared and the infection dies out.

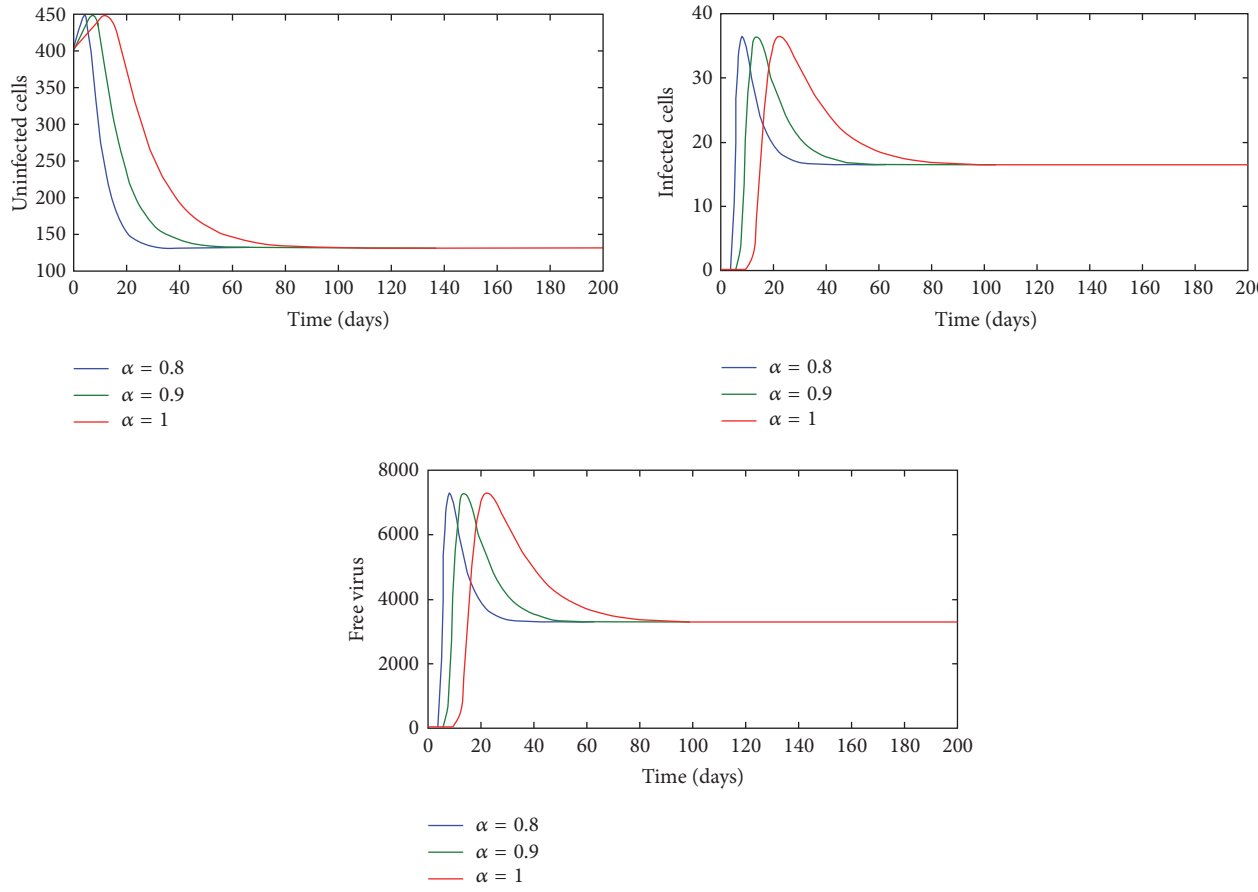

Figure 2: Stability of the chronic infection equilibrium E_1.

Table 1: Parameter values of system (1).

Parameters	Values
λ	10
d	0.0139
β	0.00024
ρ	0.01
a	0.5
k	600
u	3
α_1	0.1
α_2	0.01
α_3	0.00001

Now, we choose $\beta = 0.001$ and we keep the other parameter values. In this case, $R_0 = 3.8678$ and

$$1 + \frac{d(a+\rho)(\lambda\alpha_2 k + a\mu) + \rho\lambda^2\alpha_3 k}{\rho\mu(a+\rho)(d+\lambda\alpha_1)} = 415.885. \quad (49)$$

Hence, condition (43) is satisfied. Therefore, the chronic infection equilibrium $E_1(130.1613, 16.3815, 3276.3)$ is globally asymptotically stable. Figure 2 demonstrates this result.

6. Conclusion

In this paper, we have proposed a fractional order model of HIV infection with specific functional response and cure rate. This functional response covers the most functional responses used by several authors such as the saturated incidence rate, the Beddington-DeAngelis functional response, and the Crowley-Martin functional response. We have shown that the proposed model has a bounded and nonnegative solution as desired in any population dynamics. By using stability analysis of fractional order system, we have proved that if the basic reproduction number $R_0 \leq 1$, the disease-free equilibrium E_0 is globally asymptotically stable for all $\alpha \in (0, 1]$, which means that the virus is cleared and the infection dies out. However, when $R_0 > 1$, the disease-free equilibrium E_0 becomes unstable and there exists another biological equilibrium, namely, chronic infection equilibrium E_1, that is globally asymptotically stable provided that condition (43) is satisfied. In this case, the HIV virus persists in the host and the infection becomes chronic. Furthermore, we have remarked that if the cure rate ρ is equal to zero or is sufficiently small, condition (43) is satisfied and the global stability of E_1 is only characterized by $R_0 > 1$.

According to the above theoretical analysis, we deduce that the global dynamics of the model are fully determined by the basic reproduction number R_0. In addition, we see

that the fractional order parameter α has no effect on the global dynamics of our model, but it can affect the time for arriving at both steady states (see Figures 1 and 2). Moreover, the fractional order model and main results presented by Liu et al. in [11] are generalized and improved.

Conflicts of Interest

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

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