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MATHEMATICAL MODELING OF HBV WITH THE ANTIVIRAL THERAPY FOR THE IMMUNOCOMPROMISED PATIENTS

ABDESSAMAD TRIDANE[1,*], KHALID HATTAF[2], RADOUANE YAFIA[3], FATHALLAH A. RIHAN[1]

[1]Department of Mathematical Sciences, United Arab Emirates University, P.O. Box 17551, Al-Ain, UAE

[2]Centre Régional des Métiers de l'Education et de la Formation, Derb Ghalef, Casablanca, Morocco

[3]Ibn Zohr University, Polydisciplinary Faculty of Ouarzazate, B.P: 638, Ouarzazate, Morocco

Abstract. In this paper, we study the dynamical behaviour of HBV infection model with antiviral therapy and CTL immune response. The model is given by a system of four ordinary differential equations with discrete time delay which describes the time between infection and the immune response. The existence and stability/unstability of the equilibrium points without treatment are proved with respect to the time delay and the basic reproduction number is estimated. The conditions of occurrence of Hopf bifurcation at the endemic steady state are established when the delay crosses some critical value by using the delay as a parameter of bifurcation. By incorporating interferon-α (IFN) and nucleotside analogs (NAs) treatments, the disappearance of oscillations and appearance of new equilibrium point with maximal value of uninfected cells and minimal value of effector cells and vanishing values of virus and infected cells are investigated via optimality control. Numerical illustrations are given to support theoretical results.

Keywords: HBV infection; antiviral therapy; immune system; delay differential equations; optimal control.

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*Corresponding author

E-mail address: a-tridane@uaeu.ac.ae

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1. Introduction and mathematical model

Hepatitis B virus (HBV) infection is a major human disease and is transmitted by percutaneous and mucosal exposure to infected blood or other body fluids and by area, particularly from mother to child at birth, or between persons in childhood. According to World Health Organisation (WHO) more than 2 billion persons have been infected, among 360 millions chronically infected see [14]. 0.5-1 million of infected population die each year [11] and are infective at the later stage of latent period with an average of 90 days.

Mathematical modelling had played a significant role to better understanding the dynamics of HBV disease and the various drugs therapy strategies to control it (see [18, 2, 16, 9, 19] and references therein). In fact, a wealth of mathematical models were based on the earliest model introduced by Nowak et al. in 1996 [17] which is given by:

$$\begin{cases} \dfrac{dx}{dt} &= r - dx - \gamma vx \\ \dfrac{dy}{dt} &= \gamma vx - ay \\ \dfrac{dv}{dt} &= py - \mu v \end{cases}$$

where $x(t)$, $y(t)$ and $v(t)$ are the total number of healthy cells (hepatocytes), HBV infected hepatocytes, and free virions respectively. The healthy hepatocytes are produced at a constant rate r and d is mortality rate. γvx is the infected number of healthy cells, where γ is the rate of infection and a is the rate of mortality rate of infected hepatocytes. The virus is produced with the rate p, die at rate μ.

This simple model led to study different models that analysis several issues related to the HBV, such as the dynamic of the virus, the adaptive and innate immune responses, the drug therapy and it management.

Understanding the impact of a compromised immune response on the progress of the HBV disease is an important step to improve the effect of the antiviral treatment and to find the best practice to manage the treatment. The actual therapy, which includes pegylated and standard

interferon-α and nucleoside analogues, can not completely eradicate the infection. Instead it reduces the infection to level that does not let the infection progress to point where the patient get lever disease or hepatocellular carcinoma (HCC)[11].

The immune response by $CD8^+$ is not immediate and the presence of the time delay between infection and this immune response was observed in HBV infection [21] and this delay was quantify with a given data [22] and [2]. The problem is that quantification has a lot of uncertainty when consider patients with co-infection and immunocompromise, which is the case for big population of the HBV positive. Therefore our goal is to take this fact into consideration particularly when it comes to antiviral therapy management.

First, we consider the following system delay differential equations:

$$\begin{aligned}
\frac{dT}{dt} &= r_T T\left(1-\frac{T+I}{T_{\max}}\right)-\frac{\gamma TV}{T+I}+\rho I \\
\frac{dI}{dt} &= r_I I\left(1-\frac{T+I}{T_{\max}}\right)+\frac{\gamma TV}{T+I}-bIE-\rho I \\
\frac{dV}{dt} &= pI-\mu_V V \\
\frac{dE}{dt} &= \beta I(t-\tau)E(t-\tau)-\mu_E E.
\end{aligned} \tag{1}$$

Where T represents healthy hepatocytes , I is infected hypatocytes cells, V represents free virus particles and E stands of $CD8^+$ the antigen-specific cells. We assume that in the absence of the infection the number of hepatocytes, T, is maintained by homeostasis described by a logical equation, with carrying capacity T_{max} and maximal growth rate per hepatocyte r_T. These healthy cells get infected with a standard incidence function ([9, 6, 24] at maximum rate γ. Due to the burden of supporting HBV replication, we allow infected cells to proliferate slower than uninfected cells, that is., $r_I \leq r_T$ (One special case is to ignore this proliferation by considering $r_I = 0$ as we did in the previous work [24] and recently in [19]). We also consider the possibility of infected get cured by the noncytolytic processes at a constant rate ρ per cell. The free virus is produced at rate p and it is cleared from circulation by all mechanisms, that include the

antibody neutralization, healthy cell absorption and the dendritic cells effect (APC), at rate μ_V. The antigen specific $CD8^+$ cells are activated with rate β with time delay τ and die at rate μ_E.

This paper is organised as follows: Section 2 introduce some basic results, e.g., positivity and boundedness of solutions, and we give the estimation of parameters values of the model. In Section 3, we study the existence of equilibria and their stability and the occurrence of Hopf bifurcation from the nontrivial steady state by considering the delay as a parameter of bifurcation and the switch of stability via Mikhailov Theorem . In Section 4, we study the optimal control of the antiviral therapy treatment and we introduce the numerical algorithm for the simulation of the effectiveness of the optimal treatment.

2. Basic properties and parameter estimations

2.1. Positivity and boundedness of solutions

Let $C = C([-\tau, 0], \mathbb{R}^4)$ the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^4$ with the topology of uniform convergence. Notice that system (1) is locally Lipschitzian. From the standard theory of DDE [13] there exists a unique solution $(T(t), I(t), V(t), E(t))$ of system (1) on $[0, a[$, for some $a > 0$, with initial data $(T_0, I_0, V_0, E_0) \in C$.
In addition, for biological reasons, we assume that the initial conditions for system (1) satisfy:

$$\text{(2)} \qquad \begin{cases} T_0(s) \geq 0, \;\; I_0(s) \geq 0, \;\; V_0(s) \geq 0, \;\; E_0(s) \geq 0, \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{for all } \; s \in [-\tau, 0] \\ \qquad T_{max} \geq N(s) = T(s) + I(s) > 0 \end{cases}$$

Theorem 2.1. *Each component of the solution of system (1), subject to condition (2), remains non-negative and bounded for all $t \in [0, +\infty[$.*

Proof. Suppose that there exists $t_1 \in]0, a[$ such that $T(t_1) = 0$ and $I(t) > 0, V(t) > 0, E(t) > 0$ for $t \in]0, t_1[$. From the two first equations of (1), we have

$$\frac{dN}{dt} = (r_T T + r_I I)(1 - \frac{N}{T_{\max}}) - bIE$$

It is easy to show that $0 < N(t) \leq T_{\max}$ for $t \in [0,t_1]$. In fact, we can see that $\frac{dN}{dt} > -bEN$ for $t \in [0,t_1]$, which yields

$$N(t) \geq N(0)e^{-b\int_0^t E(s)ds}.$$

Clearly $I(t) \leq T_{\max}$ for $t \in [0,t_1]$, which implies that $V(t) \leq v = \max(V(0), \frac{pT_{\max}}{\mu_V})$ for $t \in [0,t_1]$. Then for $t \in [0,t_1]$, we have

$$\frac{dT}{dt} \geq -(\frac{\gamma v}{N(0)}e^{b\int_0^t E(s)ds})T(t).$$

Hence a contradiction is obtained as

$$T(t_1) \geq T(0)\exp(-\frac{\gamma v}{N(0)}e^{b\int_0^{t_1} E(s)ds}) > 0.$$

We suppose now that there exists $t_1 \in]0,a[$ such that $I(t_1) = 0$ and $T(t) > 0, V(t) > 0, E(t) > 0$ for $t \in]0,t_1[$. From (1), we have $I'(t) \geq -(\rho + bE(t))I(t)$ for $t \in [0,t_1]$ which yields to $I(t_1) \geq I(0)e^{-(\rho t_1 + b\int_0^{t_1} E(s)ds)} > 0$, also a contradiction.

We suppose that there exists $t_1 \in]0,a[$ such that $V(t_1) = 0$ and $T(t) > 0, I(t) > 0, E(t) > 0$ for $t \in]0,t_1[$. From (1), we have $V'(t) \geq -\mu_V V(t)$ for $t \in [0,t_1]$ which yields to $V(t_1) \geq V(0)e^{-\mu_V t_1} > 0$, also a contradiction.

Finally, we suppose that there exists $t_1 \in]0,a[$ such that $E(t_1) = 0$ and $T(t) > 0, I(t) > 0, V(t) > 0$ for $t \in]0,t_1[$. From (1), we have $E'(t) \geq -\mu_E E(t)$ for $t \in [0,t_1]$ which yields to $E(t_1) \geq E(0)e^{-\mu_E t_1} > 0$, also a contradiction.

The above contradictions together show that components of the solution of system (1) subject to condition (2) are non-negative for all $t \in [0,a[$. This together with the uniform boundedness of solutions on $[0,a[$ imply that $a = +\infty$. This completes the proof of the theorem.

2. Estimation of parameters

The estimation of hepatocyte carrying capacity, T_{max}, is 13.6×10^6 cells/ml [20]. For the rate of virion infection of hepatocytes, it was estimated in [4, 22] to be between 3.6×10^{-5} and 1.8×10^{-3} cells virion^{-1} day^{-1}. Ciupe et al. [2], based on clinical date of the virus load using the the Akaike information criterion (AIC), estimated b to be $7 \pm 1.7 \times 10^{-4}$ ml/cell day^{-1} with median 6.4×10^{-4}. The maximum rate of daily virion production p during acute HBV infection

was measured to be between 200 and 1000 virions per infected cell [22], An estimation of the same range was given in [2]. We selected the virus clearance rate to be $\mu_V = 0.67$ [18] by assuming that the half life of virus is about one day. The death rate of $CD8^+$ cells μ_E was estimated to be 0.5 days^{-1} [1]. The activation rate of the $CD8^+$ cells was estimated by [2] by $4.4 \pm 1.5 \times 10^{-7}$ ml/cell days^{-1} with median 4.2×10^{-4}.

Table. Parameters, their symbols and default values used in the model (1)

Param.	Value	Ref.
T_{max}	13.6×10^6 cells/ml	[20]
γ	$3.6 \times 10^{-5} - 1.8 \times 10^{-3}$ cells vir^{-1} day^{-1}	[22, 4]
b	$7 \pm 1.7 \times 10^{-4}$ ml/cell day^{-1}	[2]
p	$200 - 1000$ vir. cell^{-1} day^{-1}	[22]
μ_V	0.67 day^{-1}	[18]
β	$4.4 \pm 1.5 \times 10^{-7}$ ml cell^{-1} day^{-1}	[2]
μ_E	0.5 day^{-1}	[1]
r_T		
r_I		
ρ		
E_0	10 cells/ml/day	[21]

3. Stability analysis

System (1) has the following steady states:

- The empty steady state $S_0 = (0, 0, 0, \frac{E_0}{\mu_E})$.
- The disease free steady state $S_f = (T_{max}, 0, 0, 0)$.
- The immune-free steady state define by:

$$S_1 = (\frac{\rho \mu_V T_{max}}{p\gamma}, (1 - \frac{\rho \mu_V}{p\gamma})T_{max}, \frac{p}{\mu_V}(1 - \frac{\rho \mu_V}{p\gamma})T_{max}, 0),$$

- The endemic steady state $S_2 = (T_2, I_2, V_2, E_2)$ that can find in the following way:

From the equation of T , and using the fact that $I = \frac{\mu_E}{\beta}$ and $V = \frac{p\mu_E}{\beta \mu_V}$, we have

$$\frac{r_T}{T_{\max}} T(T + \frac{\mu_E}{\beta})(T_{\max} - \frac{\mu_E}{\beta} - T) = \frac{\mu_E}{\beta}[(\frac{\gamma p}{\mu_V} - \rho)T - \frac{\rho \mu_E}{\beta}]. \tag{3}$$

The left side of the equality (3) is a third degree polynomial, with a negative sign in $[-\frac{\mu_E}{\beta},0]\cup[T_{\max}-\frac{\mu_E}{\beta},+\infty)$ and positive sign in $(-\infty,-\frac{\mu_E}{\beta}]\cup[0,T_{\max}-\frac{\mu_E}{\beta}]$. Therefore, by examining the intersection of this two graphs, we can conclude that if

$$\frac{\rho\mu_E\mu_V}{\beta(\gamma p-\rho\mu_V)}<T_{\max}-\frac{\mu_E}{\beta} \tag{4}$$

or

$$\frac{\rho\mu_E\mu_V}{\beta(\gamma p-\rho\mu_V)}>T_{\max}-\frac{\mu_E}{\beta}, \tag{5}$$

the two graphs have unique intersection (See Figure.1). In the interval $[-\frac{\mu_E}{\beta},0]$, the two graphs could have one or two points of intersections, but in this case $T<0$ which isnot feasible.
As of E_2, we use the sum of the first and the second equations of system (1), we get

$$E_2=\frac{\beta}{b\mu_E T_{max}}(r_T T_2+r_I\frac{\mu_E}{\beta})(T_{\max}-\frac{\mu_E}{\beta}-T_2). \tag{6}$$

Then E_2 exists when $T_2<T_{\max}-\frac{\mu_E}{\beta}$, this condition satisfied if

$$0<\frac{\rho\mu_E\mu_V}{\beta(\gamma p-\rho\mu_V)}<T_{\max}-\frac{\mu_E}{\beta} \tag{7}$$

Since T_2 is determined in unique way, then E_2 would be the same. and we have the following steady state S_2.

$$S_2=(T_2,\frac{\mu_E}{\beta},\frac{p\mu_E}{\beta\mu_V},E_2).$$

Determining T_2 (resp. S_2) explicitly is not possible, but by parameters estimations we can have the numerical value of these steady states.

Now, we focus on the stability of disease free equilibrium S_f and we have the following result:

Theorem 3.1 *Let us define* $R_0=\frac{p\gamma}{\rho\mu_V}$.

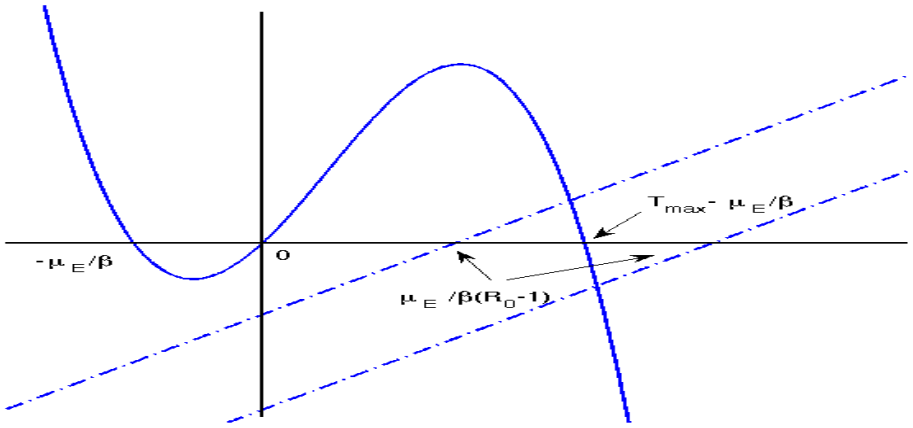

FIGURE 1. The possibility of existence of T_2 under the condition $0 < \frac{\rho\mu_E\mu_V}{\beta(\gamma p-\rho\mu_V)} < T_{\max} - \frac{\mu_E}{\beta}$

- *If $R_0 < 1$, then the disease free equilibrium, E_f, is locally asymptotically stable.*
- *If $R_0 > 1$, then E_f is unstable.*

Proof. The Jacobian matrix of our system at E_f is given by

$$\begin{bmatrix} -r_T & -r_T+\rho & -\gamma & 0 \\ 0 & -\rho & \gamma & 0 \\ 0 & p & -\mu_V & 0 \\ 0 & 0 & 0 & -\mu_E \end{bmatrix} \tag{8}$$

It is clear that this matrix has two negative eigenvalues $-r_T$ and $-\mu_E$. The two other eigenvalues can be negative if and only if $R_0 < 1$ ■

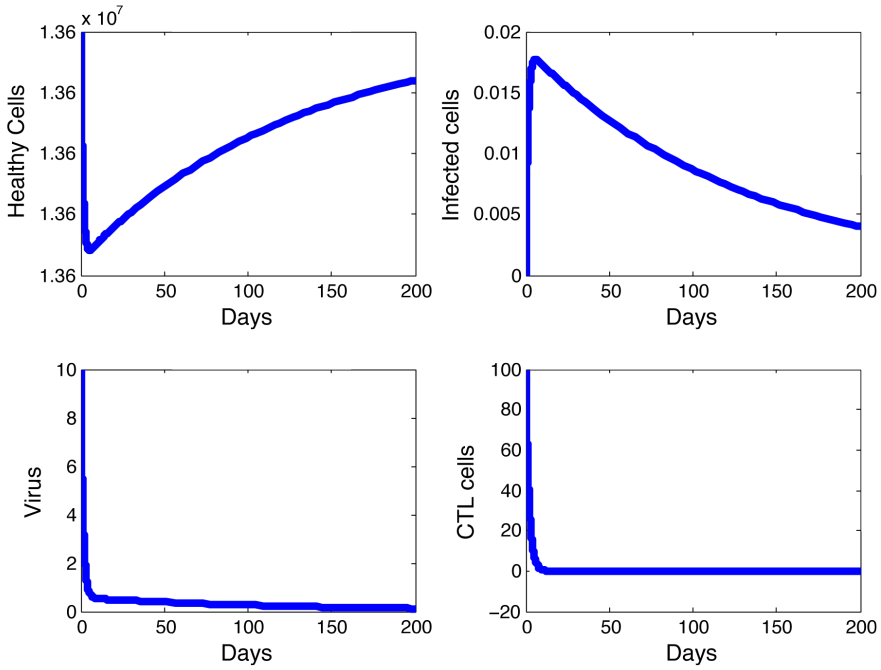

FIGURE 2. Shows the stability of disease free equilibrium S_f. The parameters are $r_T = 0.5$, $r_I = 0.06$, $T_{max} = 13.6 \times 10^6$, $\gamma = 3.6 \times 10^{-5}$, $\rho = 0.01$, $b = 6.4 \times 10^{-4}$, $p = 200$, $\mu_V = 0.67$, $\beta = 2.3 \times 10^{-7}$, $E_0 = 10$, $\mu_E = 0.5$, $\tau = 22.9$. In this case, the basic infection reproduction number R_0 is 0.5166.

Now, we study the stability of S_1. From expression of R_0 we can rewrite the expression of S_1 as follows:

$$S_1 = (\frac{T_{max}}{R_0}, (1 - \frac{1}{R_0})T_{max}, \frac{p}{\mu_V}(1 - \frac{1}{R_0})T_{max}, 0). \tag{9}$$

Therefore, S_1 exists when $R_0 > 1$. Moreover, we if define the threshold R^* by

$$R^* = \frac{T_{max}}{T_{max} - \frac{\mu_E}{\beta}} \tag{10}$$

The following result holds

Theorem 3.2

(1) If $R_0 < 1$, then the point S_1 does not exists and $S_1 = S_f$ when $R_0 = 1$.

(2) If $1 < R_0 < R^*$, then S_1 is locally asymptotically stable.

(3) If $R_0 > R^*$, then S_1 is unstable.

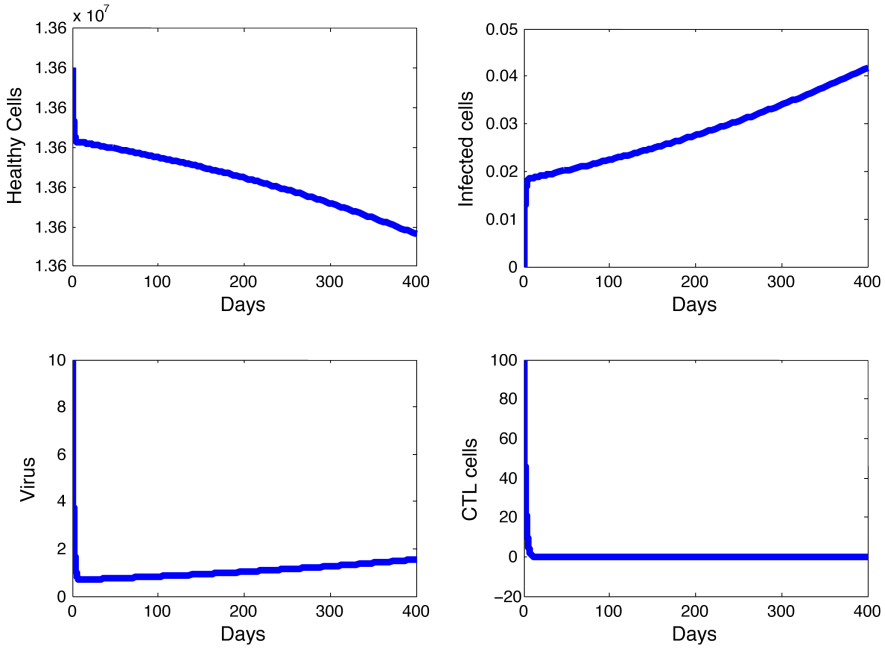

FIGURE 3. Shows the stability of S_1. The parameters values are $r_T = 0.5$, $r_I = 0.01$, $T_{max} = 13.6 \times 10^6$, $\gamma = 3.6 \times 10^{-5}$, $\rho = 0.01$, $b = 5.4 \times 10^{-4}$, $p = 200$, $\mu_V = 0.67$, $\beta = 3.4 \times 10^{-7}$, $E_0 = 0$, $\mu_E = 0.5$, $\tau = 22.9$. In this case, the basic infection reproduction number R_0 is $1.0746 < R^* = 1.1212$.

Proof. It is clear from (9) that if $R_0 < 1$, then the point S_1 does not exists and $S_1 = S_f$ when $R_0 = 1$.

We assume that $R_0 > 1$, then the characteristic equation at S_1 is

$$\begin{vmatrix} -\frac{r_T}{R_0} - \rho R_0(1-\frac{1}{R_0})^2 - \lambda & -\frac{r_T}{R_0} + \rho(2-\frac{1}{R_0}) & -\frac{\gamma}{R_0} & 0 \\ (1-\frac{1}{R_0})(\rho R_0(1-\frac{1}{R_0}) - r_I) & -\frac{r_I}{R_0} - \rho(2-\frac{1}{R_0}) - \lambda & \frac{\gamma}{R_0} & -b(1-\frac{1}{R_0})T_{max} \\ 0 & p & -\mu_V - \lambda & 0 \\ 0 & 0 & 0 & \beta(1-\frac{1}{R_0})T_{max}e^{-\lambda\tau} - \mu_E - \lambda \end{vmatrix} = 0.$$

This equation can be reduce to

$$[\beta(1-\frac{1}{R_0})T_{max}e^{-\lambda\tau} - \mu_E - \lambda](\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3) = 0, \tag{11}$$

where

$$\begin{aligned} a_1 &= \mu_V + \phi + \rho R_0, \\ a_2 &= \phi(\rho R_0 + \mu_V) + \rho \mu_V (R_0 - 1), \\ a_3 &= \rho \phi \mu_V (R_0 - 1), \\ \phi &= \frac{r_T + r_I(R_0 - 1)}{R_0}. \end{aligned}$$

The stability of S_1 is determined by examining the roots of the following equation

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{12}$$

and

$$\beta(1 - \frac{1}{R_0})T_{max}e^{-\lambda\tau} - \mu_E - \lambda = 0. \tag{13}$$

From equation (12) and using $R_0 > 1$, it is clear that a_1 and a_3 are positive and

$$\begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix} = a_1a_2 - a_3 = (\rho R_0 + \mu_V)[\phi^2 + (\rho R_0 + \mu_V)\phi + \rho\mu_V(R_0 - 1)] > 0.$$

By the Routh-Hurwitz Criterion [12], all roots of (12) have negative real parts.

For $\tau = 0$, and from (13), $\beta(1 - \frac{1}{R_0})T_{max} - \mu_E$ is eigenvalue. In fact, It easy to show that the sign of this eigenvalue is negative if $R_0 < R^*$, null if $R_0 = R^*$ and positive if $R_0 > R^*$.

To investigate the switch of stability of S_1, we need to find the pure imaginary roots of equation (13). Let $\lambda = i\omega$, with $\omega > 0$ be a purely imaginary root of (13), then

$$\mu_E + i\omega = \beta(1 - \frac{1}{R_0})T_{max}e^{-i\omega\tau}.$$

Taking moduli in the above equation, we obtain

$$\omega^2 + \mu_E^2 = [\beta(1 - \frac{1}{R_0})T_{max}]^2. \tag{14}$$

Hence, (14) has no positive solution if $1 < R_0 < R^*$. Therefore, there is no purely imaginary root of (13), implying that the roots of (13) can not cross the purely imaginary axis. Thus all roots of (13) have a negative real parts provided $1 < R_0 < R^*$. Then S_1 is locally asymptotically stable when $1 < R_0 < R^*$.

Finally, it easy to show that (11) has a real positive root when $R_0 > R^*$. Indeed, we put

$$f(\lambda) = \beta(1-\frac{1}{R_0})T_{max}e^{-\lambda\tau} - \mu_E - \lambda.$$

We have f is a continuous function on $[0,+\infty[$. Moreover,

$$f(0) = \beta(1-\frac{1}{R_0})T_{max} - \mu_E > 0 \; and \lim_{\lambda\to+\infty} f(\lambda) = -\infty.$$

Consequently, f has a positive real root. Hence, S_1 is unstable. ■

Now, we study the stability of S_2.

From expressions of R_0 and R^* we get

$$S_2 = (T_2, (1-\frac{1}{R^*})T_{max}, \frac{p}{\mu_V}(1-\frac{1}{R^*})T_{max}, \frac{(T_{max}-R^*T_2)[r_T R^* T_2 + r_I(R^*-1)]}{T_{max}^2 R^*(R^*-1)}).$$

Note that the point S_2 exists if

$$0 < \frac{\rho\mu_E\mu_V}{\beta(\gamma p - \rho\mu_V)} < T_{\max} - \frac{\mu_E}{\beta}, \tag{15}$$

i.e, $0 < \dfrac{\mu_E}{\beta(R_0-1)} < \dfrac{T_{max}}{R^*}$. In this case we have

$$\frac{R^*-1}{R^*(R_0-1)} \leq \frac{T_2}{T_{max}} \leq \frac{1}{R^*}. \tag{16}$$

As $R^* > 1$, we conclude that the point S_2 exists when $R_0 > R^*$.

If $R_0 = R^*$, From (16) we have $T_2 = \frac{T_{max}}{R_0}$. Then $E_2 = 0$ and $S_2 = S_1$.

Assume that $R_0 > R^*$, at S_2 (8) reduces to

$$W(\lambda,\tau) = \lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4 - \mu_E(\lambda^3 + c_1\lambda^2 + c_2\lambda + c_3)e^{-\lambda\tau} = 0, \tag{17}$$

where

$$
\begin{aligned}
b_1 &= \mu_V + \mu_E + \varphi(T_2) + \rho(1 - \frac{1}{R^*})\frac{T_{max}}{T_2} + \rho R_0 x(T_2), \\
b_2 &= \mu_E(b_1 - \mu_E) + \chi(T_2) + \mu_V[\varphi(T_2) + \rho(1 - \frac{1}{R^*})\frac{T_{max}}{T_2}], \\
b_3 &= \mu_E[b_2 - \mu_E(b_1 - \mu_E)] + \rho\mu_V R_0(r_T - r_I)(1 - \frac{1}{R^*})x(T_2), \\
b_4 &= \rho\mu_V\mu_E(1 - \frac{1}{R^*})[r_I + r_I(1 - \frac{1}{R^*})\frac{T_{max}}{T_2} + (r_T - r_I)R_0 x(T_2)], \\
c_1 &= b_1 - \mu_E - bE_2, \\
c_2 &= b_2 - \mu_E(b_1 - \mu_E) + bE_2(\psi(T_2) - \mu_V), \\
c_3 &= \frac{b_4}{\mu_E} + \mu_V bE_2\psi(T_2), \\
x(T) &= \frac{R^*T}{R^*T + (R^* - 1)T_{max}}, \\
\varphi(T) &= \frac{r_T T}{T_{max}} + r_I(1 - \frac{1}{R^*}), \\
\psi(T) &= r_T(\frac{1}{R^*} - \frac{2T}{T_{max}}) - \rho R_0\frac{(R^* - 1)^2 T_{max}^2}{[R^*T + (R^* - 1)T_{max}]^2}, \\
\chi(T) &= \rho R_0[\frac{r_T T_2}{T_{max}} - \rho(R^* - 1)T_{max}\frac{R^*(R_0 - 1)T - (R^* - 1)T_{max}}{[R^*T + (R^* - 1)T_{max}]^2}] + \rho r_I\frac{R^* - 1}{R^* x(T)}.
\end{aligned}
$$

When $\tau = 0$, (17) become

$$\lambda^4 + \bar{b}_1\lambda^3 + \bar{b}_2\lambda^2 + \bar{b}_3\lambda + \bar{b}_4 = 0, \tag{18}$$

where

$$\begin{aligned}
\bar{b}_1 &= \mu_V + \varphi(T_2) + \rho(1 - \frac{1}{R^*})\frac{T_{max}}{T_2} + \rho R_0 x(T_2), \\
\bar{b}_2 &= \chi(T_2) + \mu_V[\varphi(T_2) + \rho(1 - \frac{1}{R^*})\frac{T_{max}}{T_2}] + \mu_E b E_2, \\
\bar{b}_3 &= \rho\mu_V R_0(r_T - r_I)(1 - \frac{1}{R^*})x(T_2) + \mu_E b E_2(\mu_V - \psi(T_2)), \\
\bar{b}_4 &= -\mu_V\mu_E b E_2 \psi(T_2).
\end{aligned}$$

If $\psi(T_2) > 0$, then equation (18) has a real positive root. Hence S_2 is unstable.

According to the study of the function ψ, we deduce the following remark.

Remark

- *If* $R_0 < \dfrac{r_T(2R^*-1)^3}{27\rho R^*(R^*-1)^2}$, *then there exists* $T_c < \dfrac{T_{max}}{2R^*}$ *satisfying the equation*

$$\frac{r_T}{T_{max}}(\frac{T_{max}}{R^*} - 2T_c)(T_c + \frac{\mu_E}{\beta}) = \rho R_0(\frac{\mu_E}{\beta})^2,$$

  such that ψ *is positive on* $[0, T_c]$ *and negative on* $[T_c, \dfrac{T_{max}}{R^*}]$.
- *If* $R_0 > \dfrac{r_T(2R^*-1)^3}{27\rho R^*(R^*-1)^2}$, *then* $\psi(T)$ *is negative for all* $T \in [0, \dfrac{T_{max}}{R^*}]$.
- *If* $R^* < R_0 < 2R^* - 1$, *then* $\psi(T_2) < 0$.

From the Routh-Hurwitz Criterion, we have the following Theorem.

Theorem 3.3 *Suppose that* $\tau = 0$ *and* $R_0 > R^*$, *we have :*

(1) If $\psi(T_2) < 0$, $\bar{b}_1\bar{b}_2 - \bar{b}_3 > 0$ *and* $\bar{b}_3(\bar{b}_1\bar{b}_2 - \bar{b}_3) - \bar{b}_1^2\bar{b}_4 > 0$, *then* S_2 *is locally asymptotically stable.*

(2) If $\psi(T_2) > 0$, *then* S_2 *is unstable.*

3.1 Hopf bifurcation analysis

In this subsection, we prove the occurrence Hopf bifurcation by using the time delay τ as the bifurcation parameter. Throughout this subsection, we will assume that $R_0 > R^*$, which means that the endemic equilibrium S_2 exists.

Let $\lambda(\tau) = \alpha(\tau) + i\omega(\tau)$ be the root of (17). If the conditions

$$(H_1) \qquad \psi(T_2) < 0,\ \ \bar{b}_1\bar{b}_2 - \bar{b}_3 > 0,\ \ \bar{b}_3(\bar{b}_1\bar{b}_2 - \bar{b}_3) - \bar{b}_1^2\bar{b}_4 > 0,$$

are satisfied. Then, from Theorem 3.4, we have $\alpha(0) < 0$. By continuity of α, $\alpha(\tau) < 0$ for $0 \leq \tau < \tau_c$ for some critical value $\tau_c > 0$.

Assume $\alpha(\tau_c) = 0$, and $\alpha(\tau) < 0$ for $0 \leq \tau < \tau_c$, then the steady state S_2 may loses it's stability at $\tau = \tau_c$. Let $\lambda = i\omega$In fact, $i\omega$ is a purely imaginary root of equation (17). Then, we have

$$(19) \qquad W(i\omega,\tau) = \omega^4 - b_2\omega + b_4 + i\omega(b_3 - b_1\omega^2) = \mu_E[c_3 - c_1\omega^2 + i\omega(c_2 - \omega^2)]e^{-i\omega\tau}.$$

Equating real parts and imaginary parts, we have the following:

$$(20) \qquad \begin{cases} \omega^4 - b_2\omega^2 + b_4 = \mu_E(c_3 - c_1\omega^2)\cos(\omega\tau) + \mu_E\omega(c_2 - \omega^2)\sin(\omega\tau), \\ \omega(b_3 - b_1\omega^2) = -\mu_E(c_3 - c_1\omega^2)\sin(\omega\tau) + \mu_E\omega(c_2 - \omega^2)\cos(\omega\tau). \end{cases}$$

Squaring and adding both equation of (20), one obtains

$$(21) \qquad \omega^8 + d_1\omega^6 + d_2\omega^4 + d_3\omega^2 + d_4 = 0,$$

where

$$\begin{aligned} d_1 &= b_1^2 - 2b_2 - \mu_E^2, \\ d_2 &= b_2^2 + 2b_4 - 2b_1b_3 + \mu_E^2(2c_2 - c_1^2), \\ d_3 &= b_3^2 - 2b_2b_4 + \mu_E^2(2c_1c_3 - c_2^2), \\ d_4 &= b_4^2 - \mu_E^2c_3^2. \end{aligned}$$

By applying the Mikhailov criterion, we show the switch of stability of the steady state S_2 and we have the following result.

Lemma 3.1 (Mikhailov criterion) *Assume that W has no pair imaginary roots. Then the steady state of the system with the characteristic equation is locally stable if and only if*

$$[arg(W(iw))]_{w=0}^{w=+\infty} = n\frac{\pi}{2},$$

where W is a polynomial with degree n

The calculation of total change of argument of the complex function $W(iw)$ when w increases from 0 to $+\infty$ gives the stability of the corresponding steady state. In delay differential equations, the characteristic equation is written as

$$W(\lambda) = P(\lambda) + \sum_{i=0}^{k} a_i \lambda^i e^{\lambda \tau_i}$$

where P is a polynomial function with $deg(P) = n > k$. Then, the condition which ensures the local stability of the corresponding steady state (See Fig. and Fig.) is given as follows:

$$[arg(W(iw))]_{w=0}^{w=+\infty} = n\frac{\pi}{2}.$$

From equation (19) we can write

$$\sin(W(iw)) = \frac{Im(W(iw))}{\sqrt{Re(W(iw))^2 + Im(W(iw))^2}} \longrightarrow_{w\to+\infty} 0$$

$$\cos(W(iw)) = \frac{Re(W(iw))}{\sqrt{Re(W(iw))^2 + Im(W(iw))^2}} \longrightarrow_{w\to+\infty} 1$$

and

$$W(0) = b_4 - \mu_E c_3$$

Then $arg(W(iw))_{w\to+\infty} \longrightarrow 2\pi$.

If $b_4 > \mu_E c_3$, then $arg(W(0)) = 0$ and

$$[arg(W(iw))]_{w=0}^{w=+\infty} = 2\pi = 4\frac{\pi}{2}$$

If $b_4 < \mu_E c_3$, then $arg(W(0)) = \pi$

$$[arg(W(iw))]_{w=0}^{w=+\infty} = 2\pi - \pi < 4\frac{\pi}{2}$$

which imply that the steady state is unstable for $\tau = 0$ and unstable for all $\tau > 0$ (see Fig.).

In the next we compute the critical value $\tau_c$of the delay τ at which we obtain the switch of stability of the equilibrium point S_2.

Let $z = \omega^2$, then equation (21) becomes

(22) $$g(z) = z^4 + d_1 z^3 + d_2 z^2 + d_3 z + d_4 = 0,$$

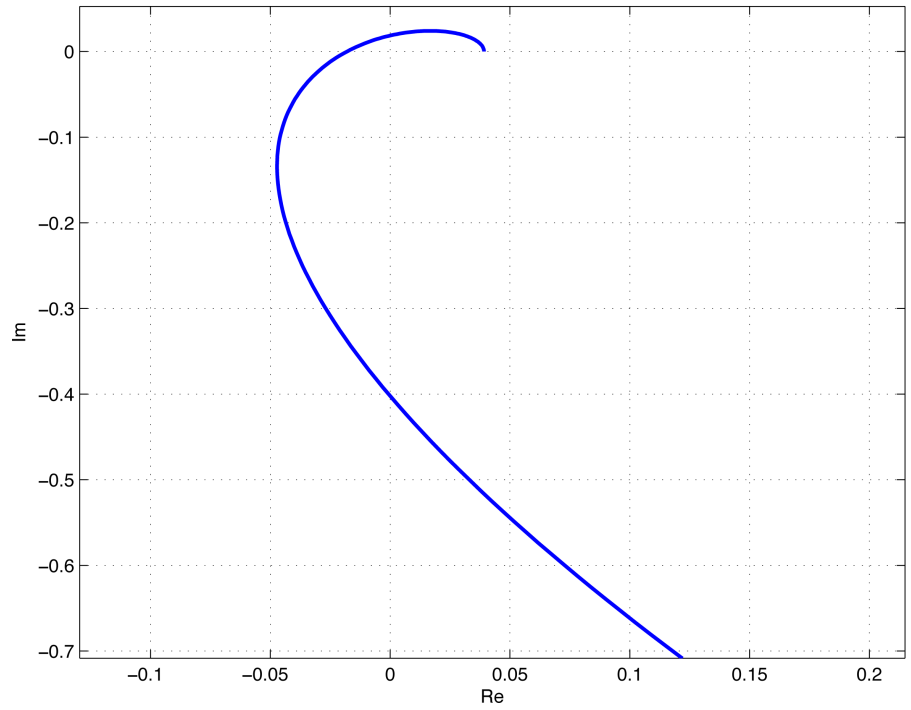

FIGURE 4. Mikailov Hodographs illustrating the stability of the steady state S_2 for $\tau = 0$

Lemma 3.2 *Assume that* $Re(\lambda(0)) < 0$. *If equation (22) has no positive roots. Then, all roots of equation (17) have negative real parts.*

Proof. If (22) has no positive roots, then any real number ω is not a root of equation (21). This ensures that any real number ω is not a root of equation (19). Hence, for any real number ω, $i\omega$ is not a root of equation (17), which implies that there is no τ_c such that $\lambda(\tau_c) = i\omega(\tau_c)$ is a root of equation (17).

Since $Re(\lambda(0)) < 0$ and $Re(\lambda(\tau))$ is a continuous function of τ, we conclude that all roots of (17) have negative real parts. ■

Next, we present conditions which ensure that equation (17) has a positive root or has no positive roots. To this end, we differentiate

$$g'(z) = 4z^3 + 3d_1z^2 + 2d_2z + d_3.$$

We put $x = z + \dfrac{d_1}{4}$, then the equation

$$4z^3 + 3d_1z^2 + 2d_2z + d_3 = 0, \tag{23}$$

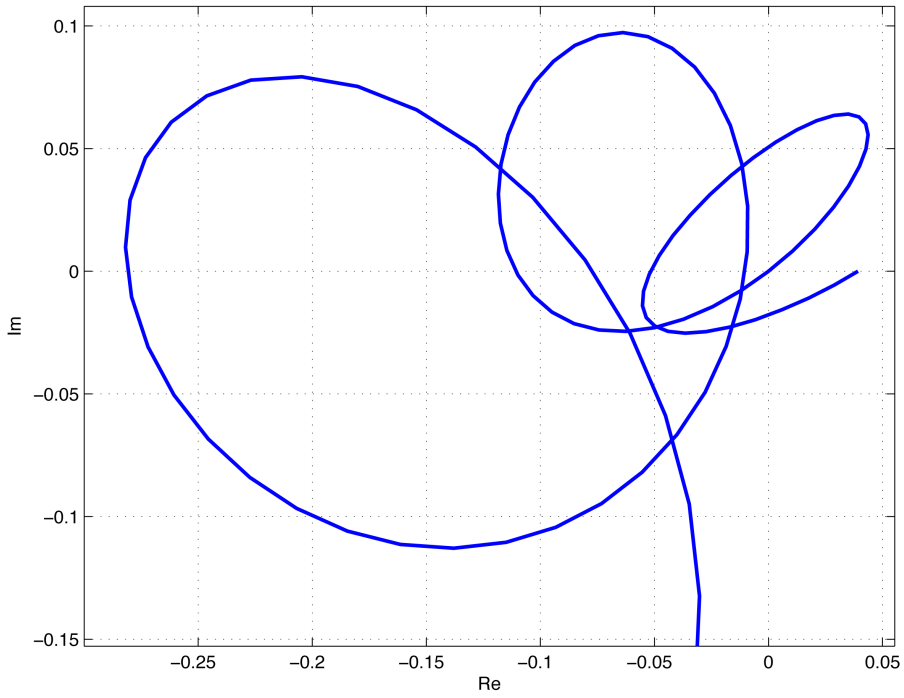

FIGURE 5. Mikailov Hodographs illustrating the stability of the steady state S_2 for $\tau = 40$

becomes

$$z^3 + m_1 z + m_2 = 0, \tag{24}$$

where

$$m_1 = \frac{8d_2 - 3d_1^2}{16}, \text{ and } m_2 = \frac{d_1^3 - 4d_1 d_2 + 8d_4}{27}.$$

From Cardano's method, the discriminant of equation (24) is

$$\Delta = \frac{m_2^2}{4} + \frac{m_1^3}{27},$$

and, solutions of equation (24) are:

$$x_k = j^k \sqrt[3]{\frac{-m_2}{2} + \sqrt{\Delta}} + j^{2k} \sqrt[3]{\frac{-m_2}{2} - \sqrt{\Delta}}, \ k = 0,1,2, \ j = \frac{-1}{2} + \frac{\sqrt{3}}{2} i = e^{i\frac{2\pi}{3}}.$$

Hence,

$$g'(z) = 4 \prod_{k=0}^{k=2} (z - z_k), \ with \ z_k = x_k - \frac{d_1}{3} \tag{25}$$

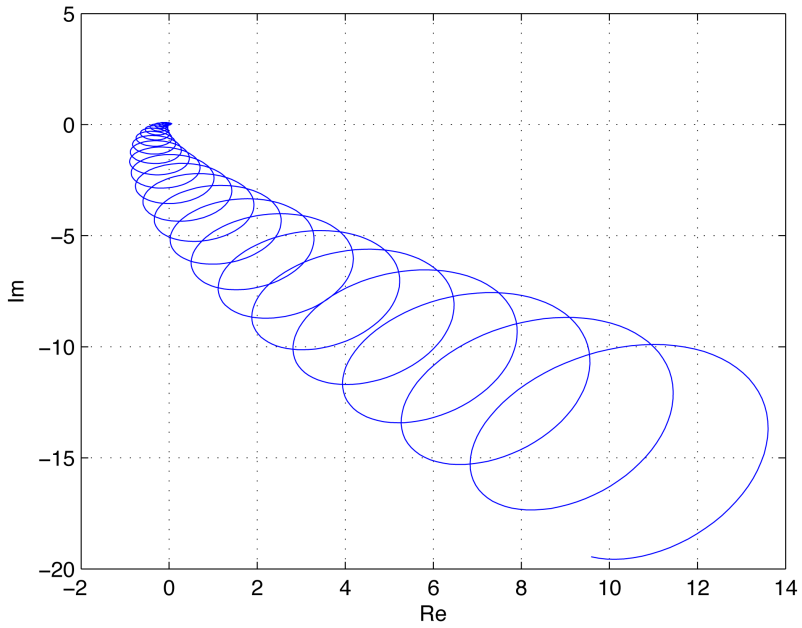

FIGURE 6. Mikailov Hodographs illustrating the instability of the steady state S_2 for $\tau = 80$

According to the sign of the discriminant, we have three cases:

- If $\Delta > 0$, then z_0 is real, z_1 and z_2 are conjugate roots.
- If $\Delta = 0$, then there is one real root (a triple root) or two real roots (a single root and a double root).
- If $\Delta < 0$, then there are three real roots.

Lemma 3.3

(i): *If either (a) $d_4 < 0$, or (b) $d_4 \geq 0$, and there exists $k \in \{0,1,2\}$ such that $z_k > 0$ and $g(z_k) \leq 0$, then equation (22) has a positive root.*

(ii): *If the conditions (a) and (b) are not satisfied, then equation (22) has no positive roots.*

Proof. (i) Suppose that condition (a) holds, that is, $d_4 < 0$. Then, we have that $g(0) = d_4 < 0$. On the other hand, since

$$\lim_{x \longrightarrow +\infty} g(x) = +\infty,$$

by the intermediate value Theorem, equation (22) has a positive root.

Now, suppose that condition (b) holds. Then, there exists $k \in \{0,1,2\}$ such that $z_k > 0$ and

$g(z_k) \leq 0$. Since $g(0) = d_4 < 0$, again by the intermediate value Theorem, g has a zero between the origin and z_k.

(ii) Suppose that condition conditions (a) and (b) are not satisfied. If $\Delta \geq 0$, then

$$g'(z) = 4(z - z_0)Q(x),$$

where Q is a quadratic polynomial with discriminant negative or nul. Hence g' is negative on $]-\infty, z_0]$, positive on $[z_0, +\infty[$. So g is decreasing $]-\infty, z_0]$ and increasing on $[z_0, +\infty[$. Moreover $g(z_0)$ is the global minimum of g on $\mathbb{R}$. If $g(z_0) > 0$, then g is is strictly positive on the real numbers. Thus, equation (22) has no positive roots. If $z_0 \leq 0$, then g is increasing on $[0, +\infty[$. Hence, $g(z) \geq g(0) = d_4 \geq 0$ for all $z \geq 0$. So equation (22) has no positive roots.

If $\Delta < 0$, then (23) are three real roots z_k, $k = 0, 1, 2$, and $g(z_k)$ are three extremums of g. If $g(z_k) > 0$ for all k, then g is is strictly positive on the real numbers. Thus, equation (22) has no positive roots. If $z_k \leq 0$ for all k, then g is increasing on $[0, +\infty[$. Then $g(z) \geq g(0) = d_4 \geq 0$ for all $z \geq 0$. So equation (22) has no positive roots. ■

Using the above lemmas, we have the following result.

Theorem 3.4 *Suppose $R_0 > R^*$ and (H_1) is satisfied.*

If the conditions (a) and (b) of Lemma 3.3 are not satisfied, then S_2 is asymptotically stable for all values of the time delay $\tau \geq 0$.

Next, we will provide the conditions on the parameters to ensure that the Hopf bifurcation occurs at $\tau = \tau_c$. Suppose conditions in Lemma 3.3 hold, then equation (22) has a positive root. Without loss of generality, we assume that it has four positive roots, denoted by p_k, $k = 0, 1, 2, 3$. Therefore equation (21) has four positive roots, $\omega_k = \sqrt{p_k}$ for $k = 0, 1, 2, 3$.

From (20) we know that $\tau_{k,n}$ for $k = 0, 1, 2, 3$ and $n \in \mathbf{N}$, corresponding to ω_k is

$$\tau_{k,n} = \frac{1}{\omega_k} \arcsin \frac{\omega(c_2 - \omega^2)(\omega^4 - b_2\omega + b_4) - \omega(b_3 - b_1\omega^2)(c_3 - c_1\omega^2)}{\mu_E[(c_3 - c_1\omega^2)^2 + \omega^2(c_2 - \omega^2)^2]} + \frac{2n\pi}{\omega_k}.$$

Now, let $\tau_c > 0$ be the smallest τ such that $\alpha(\tau_c) = 0$. Then,

$$\tau_c = \tau_{k_c,n_c} = \min\{\tau_{k,n} > 0,\ 0 \leq k \leq 3,\ n \in \mathbf{N}\} \ \text{ and } \ \omega_c = \omega_{k_c}. \tag{26}$$

Theorem 3.5 *For the time lag τ, let the critical time lag τ_c and ω_c be defined as in (26). Suppose that $R_0 > R^*$, (H_1) and $4\omega_c^6 + 3d_1\omega_c^4 + 2d_2\omega_c^2 + d_3 \neq 0$.*

If one of the conditions (a) *and* (b) *of Lemma 3.3 are satisfied, then* S_2 *is locally asymptotically stable when* $\tau \in [0, \tau_c[$ *and unstable when* $\tau > \tau_c$. *Further, system (1) undergoes Hopf bifurcation at* S_2 *when* $\tau = \tau_c$.

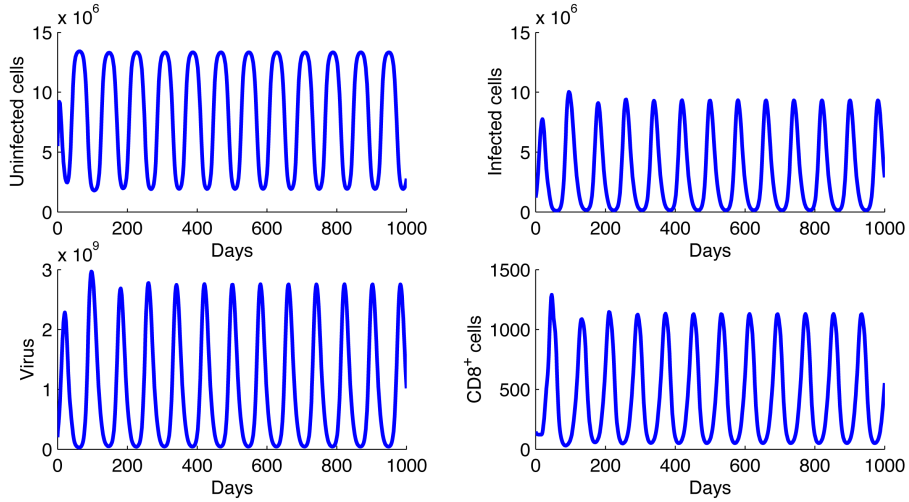

FIGURE 7. Hopf bifurcation occurs and periodic solutions appear. For this simulation,we choose $r_T = 0.5,\ r_I = 0.01,\ T_{max} = 13.6 \times 10^6,\ \gamma = 0.0014,\ \rho = 0.05,\ b = 5.4 \times 10^{-4},\ p = 200,\ \mu_V = 0.67,\ \beta = 3.4 \times 10^{-7},\ E_0 = 0,\ \mu_E = 0.5,\ \tau = 16.$

Proof. From Theorem 3.4, we have S_2 is locally asymptotically stable for $\tau = 0$. Then $\alpha(0) < 0$. Since $\alpha(\tau_c) = 0$, we conclude that $\alpha(\tau) < 0$ for all $\tau \in [0, \tau_c[$. Hence, S_2 is locally asymptotically stable when $\tau \in [0, \tau_c[$. Because otherwise, there exists a $\xi \in [0, \tau_c[$ such that $\alpha(\xi) > 0$. Since $\alpha(0) < 0$, again by the intermediate value theorem, there exists a $\xi' \in [0, \tau_c[$ such that $\alpha(\xi') = 0$. This contradicts the fact that τ_c is the smallest of τ such that $\alpha(\tau_c) = 0$.

Now, we will show that

$$\frac{d\alpha(\tau_c)}{d\tau} > 0,$$

This will signify that there exists at least one eigenvalue with positive real part for $\tau > \tau_c$. Moreover, the conditions for Hopf bifurcation [13] are then satisfied yielding the required periodic solution. We differentiate equation (17) with respect to τ, we obtain

$$(\frac{d\lambda}{d\tau})^{-1} = \frac{4\lambda^3 + 3b_1\lambda^2 + 2b_2\lambda + b_3}{-\mu_E\lambda(\lambda^3 + c_1\lambda^2 + c_2\lambda + c_3)e^{-\lambda\tau}} + \frac{3\lambda^2 + 2c_1\lambda + c_2}{\lambda(\lambda^3 + c_1\lambda^2 + c_2\lambda + c_3)} - \frac{\tau}{\lambda}.$$

As,

$$sign\frac{dRe(\lambda)}{d\tau}\bigg|_{\tau=\tau_c} = sign(Re(\frac{d\lambda}{d\tau})^{-1}\bigg|_{\tau=\tau_c}).$$

Then,

$$sign(\frac{d\alpha(\tau_c)}{d\tau}) = sign[\frac{4\omega_c^6+3d_1\omega_c^4+2d_2\omega_c^2+d_3}{\omega_c^2(b_3-b_1\omega_c^2)^2+(\omega_c^4-b_2\omega_c^2+b_4)^2}] > 0.$$

Because, if $\frac{d\alpha(\tau_c)}{d\tau} < 0$, then equation (17) has a root with positive real part root for $\tau < \tau_c$. This contradicts that S_2 is locally asymptotically stable for $\tau < \tau_c$.

Therefore, the transversally condition holds and hence Hopf bifurcation occurs at $\tau = \tau_c$. This completes the proof of theorem.

4. Control the infection with antiviral therapy

After analyzing this model without treatment, we would like to consider the treatment. Here we will consider two type of treatments: interferon-α (IFN) and nucleotside analogs (NAs). It is well know that there is a correlation between the high virus load and $CD8^+$ failure. It is very important to know which type of therapy regime would allow to reduce the viral load and maintain the dynamic of the peripheral $CD8^+$ at an adequate level. For these reasons we would like to study the following model

$$\begin{aligned}
\frac{dT}{dt} &= r_T T\left(1-\frac{T+I}{T_{\max}}\right)-(1-u_1)\frac{\gamma TV}{T+I}+\rho I \\
\frac{dI}{dt} &= r_I I\left(1-\frac{T+I}{T_{\max}}\right)+(1-u_1)\frac{\gamma TV}{T+I}-bIE-\rho I \\
\frac{dV}{dt} &= (1-u_2)pI-\mu_V V \\
\frac{dE}{dt} &= \beta I(t-\tau)E(t-\tau)+E_0-\mu_E E.
\end{aligned} \tag{27}$$

The INF therapy can lower the virus load p by a factor of $(1-u_2)$ with an effectiveness u_2 and NA can bloke the shedding and bending of the virus to the uninfected cells, by lowering γ by a factor $(1-u_1)$ with an effectiveness u_1. Might also define in our model the total therapy efficacy by $1-u=(1-u_1)(1-u_2)$ and in order to keep our model with in the biological frame we

would also suggest that there are bounds for both therapies that represent the range of the doses of treatment protocols, of course that would change depending of the severity of the infection, age and weight of the patient and other health condition, which means $u_{1\min} \leq u_1 \leq u_{1,\max}$ and $u_{2\min} \leq u_2 \leq u_{2,\max}$

We consider a control problem with objective function defined as follows

$$J(u_1,u_2) = \int_{t_0}^{t_f} [QV(t) - WT(t) + R_1 u_1^2(t) + R_2 u_2^2(t)]dt. \tag{28}$$

The parameters Q, R_1 and W are the weight constants for the virus and control inputs respectively. The second term in (28) represents systemic costs of the drug treatment (i.e., severity of unintended side effects as well as treatment cost). The case when $u_i(t) = u_{i\max}$ represents maximal use of the antiviral therapy. The objective function (28) expresses our goal to minimize both the HBV virus population and systemic costs to body . Therefore, we seek a pair optimal control $u^* = (u_1^*, u_2^*)$ such that

$$J(u^*) = \min\{J(u_1,u_2) : (u_1,u_2) \in U\}, \tag{29}$$

subject to the system of ODE (27) and where

$$U = \{u = (u_1,u_2) \,|u \text{ is measurable, } u_1 \in [u_{1\min}, u_{1\max}], \text{ and } u_2 \in [u_{2\min}, u_{2\max}] \text{ for } t \in [t_0,t_1]\}$$

is the control set.

4.1 Existence of an optimal control pair

The existence result in [7] and Lukes in [15] guarantee existence of the optimal control pair as follows

Theorem 4.1 *There exists an optimal control pair* $(u_1^*, u_2^*) \in U$ *such that*

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

Proof. To use an existence result in [7], we must check the following properties:

(1) The set of controls and corresponding state variables is nonempty.

(2) The control set U is convex and closed.

(3) The right hand side of the state system is bounded by a linear function in the state and control variables.

(4) The integrand of the objective functional is convex on U.

(5) There exist constants $c_1, c_2 > 0$ and $\beta > 1$ such that the integrand $L(T,V,u_1,u_2)$ of the objective functional satisfies

$$L(T,V,u_1,u_2) \geq c_1(|u_1|^2 + |u_2|^2)^{\frac{\beta}{2}} - c_2.$$

To verify the condition 1, we use a result in [15] to show that the existent solutions of (27) with bounded coefficients. the condition 2 is straightforward, the bilinearity of the system with respect to u_1 and u_2 guarantee the condition 3 Our control set satisfies condition 2. Since the state system is bilinear in u_1 and u_2 and the solution is bounded, the right hand side of system (27) satisfies condition 3. Note that the integrand of our objective functional is convex. Since the states are bounded, then there exists c_1, $c_2 > 0$ and $\beta = 2 > 1$ such that

$$L(T,V,u_1,u_2) \geq c_1(|u_1|^2 + |u_2|^2) - c_2.$$

Therefore,existence an optimal control pair.

4.2 Optimality system

Pontryagin's minimum Principle with delay given in [8] provides necessary conditions for an optimal control problem. This principle converts (27), (28) and (29) into a problem of minimizing an Hamiltonian, H, with :

$$\begin{aligned} H(t,T,I,V,E,I_\tau,E_\tau,u_1,u_2,\lambda) &= QV - WT + R_1u_1^2 + R_2u_2^2 \\ &+ \lambda_1[r_T T\left(1 - \frac{T+I}{T_{\max}}\right) - (1-u_1)\frac{\gamma TV}{T+I} + \rho I] \\ &+ \lambda_2[r_I I\left(1 - \frac{T+I}{T_{\max}}\right) + (1-u_1)\frac{\gamma TV}{T+I} - bIE - \rho I] \\ &+ \lambda_3[(1-u_2)pI - \mu_V V] + \lambda_4[\beta I_\tau E_\tau + E_0 - \mu_E E]. \end{aligned}$$

By applying Pontryagin's Minimum Principle with delay in state [8], we obtain the following Theorem.

Theorem 4.2 *Given optimal controls u_1^*, u_2^* and solutions T^*, I^*, V^* and E^* of the corresponding state system (27), there exist adjoint variables λ_1, λ_2, λ_3 and λ_4 satisfying the equations*

$$\begin{aligned}
\lambda_1'(t) &= W - \lambda_1(t) r_T \left(1 - \frac{2T^*(t) + I^*(t)}{T_{\max}}\right) + \lambda_2(t) \frac{r_I I^*(t)}{T_{\max}} \\
&+ (\lambda_1(t) - \lambda_2(t))(1 - u_1^*(t)) \frac{\gamma I^*(t) V^*(t)}{(T^*(t) + I^*(t))^2}, \\
\lambda_2'(t) &= \lambda_2(t)[bE^*(t) - r_I \left(1 - \frac{2I^*(t) + T^*(t)}{T_{\max}}\right)] + \lambda_1(t) \frac{r_T T^*(t)}{T_{\max}} \\
&+ (\lambda_2(t) - \lambda_1(t))[(1 - u_1^*(t)) \frac{\gamma T^*(t) V^*(t)}{(T^*(t) + I^*(t))^2} + \rho] - p(1 - u_2^*(t) \lambda_3(t) \\
&- \chi_{[t_0, t_f - \tau]}(t) \lambda_4(t + \tau) \beta E^*(t), \\
\lambda_3'(t) &= -Q + \mu_V \lambda_3(t) + (\lambda_1(t) - \lambda_2(t))(1 - u_1^*(t)) \frac{\gamma T^*(t)}{T^*(t) + I^*(t)}, \\
\lambda_4'(t) &= \mu_E \lambda_4(t) + bI^*(t) \lambda_2(t) - \chi_{[t_0, t_f - \tau]}(t) \lambda_4(t + \tau) \beta I^*(t),
\end{aligned}$$

with transversality conditions

$$\lambda_i(t_f) = 0, i = 1, ..., 4.$$

Moreover, the optimal control is given by

$$u_1^* = \min(1, \max(0, \frac{1}{2R_1}(\lambda_2(t) - \lambda_1(t)) \frac{\gamma T^*(t) V^*(t)}{T^*(t) + I^*(t)})) \tag{30}$$

and

$$u_2^*(t) = \min(1, \max(0, \frac{1}{2R_2} \lambda_3(t) p I^*(t))). \tag{31}$$

Proof. The adjoint equations and transversality conditions can be obtained by using Pontryagin's Minimum Principle with delay in state [8] such that

$$\lambda_1'(t) = -\frac{\partial H}{\partial T}(t), \quad \lambda_1(t_f) = 0,$$

$$\lambda_2'(t) = -\frac{\partial H}{\partial I}(t) - \chi_{[t_0, t_f - \tau]}(t) \frac{\partial H}{\partial I_\tau}(t + \tau), \quad \lambda_2(t_f) = 0,$$

$$\lambda_3'(t) = -\frac{\partial H}{\partial V}(t), \quad \lambda_3(t_f) = 0.$$

$$\lambda_4^{'}(t) = -\frac{\partial H}{\partial E}(t) - \chi_{[t_0,t_f-\tau]}(t)\frac{\partial H}{\partial E_\tau}(t+\tau), \quad \lambda_4(t_f) = 0,$$

The optimal control u_1^* and u_2^* can be solve from the optimality conditions,

$$\frac{\partial H}{\partial u_1}(t) = 0, \quad \frac{\partial H}{\partial u_2}(t) = 0.$$

That is

$$\frac{\partial H}{\partial u_1}(t) = 2R_1u_1(t) + (\lambda_1(t) - \lambda_2(t))\frac{\gamma T(t)V(t)}{T(t)+I(t)} = 0$$

and

$$\frac{\partial H}{\partial u_2}(t) = 2R_2u_2(t) - pI(t)\lambda_3(t) = 0.$$

By the bounds in U of the controls, it is easy to obtain u_1^* and u_2^* in the form of (30) and (31) respectively. ■

4.3 Numerical results

To solve the optimality system, we use an approach that has been developed in [10] based on improved Gauss-seidel-like implicit finite-difference method and called GSS1 method . This method is given as follows: Let's consider the step size $h > 0$ and integers $(n,m) \in \mathbf{N}^2$ with $\tau = mh$ and $t_f - t_0 = nh$. For reasons of programming, we consider m knots to left of t_0 and right of t_f, we obtains the following partition:

$$\Delta = (t_{-m} = -\tau < ... < t_{-1} < t_0 = 0 < t_1 < ... < t_n = t_f < t_{n+1} < ... < t_{n+m}).$$

Then, we have $t_i = t_0 + ih$ $(-m \leq i \leq n+m)$. Next, we define the state and adjoint variables $T(t)$, $I(t)$, $V(t)$, $E(t)$, $\lambda_1(t)$, $\lambda_2(t)$, $\lambda_3(t)$, $\lambda_4(t)$ and the controls $u_1(t)$, $u_2(t)$ in terms of nodal points T_i, I_i, V_i, E_i, λ_1^i, λ_2^i, λ_3^i, λ_4^i, u_1^i and u_2^i. Now a combination of forward and backward difference approximation, we obtain the following algorithm.

Algorithm

step 1 : for $i=-m,\ldots,0,$ do :

$T_i=T_0, I_i=I_0, V_i=V_0, E_i=E_0, u_1^i=0, u_2^i=0.$

end for

for $i=n,\ldots,n+m,$ do :

$\lambda_1^i=0, \lambda_2^i=0, \lambda_3^i=0, \lambda_4^i=0.$

end for

step 2 : for $i=0,\ldots,n-1,$ do :

$$T_{i+1}=T_i+h[r_T T_i(1-\tfrac{T_i+I_i}{T_{\max}})-(1-u_1^i)\tfrac{\gamma T_i V_i}{T_i+I_i}+\rho I_i],$$
$$I_{i+1}=I_i+h[r_I I_i(1-\tfrac{T_i+I_i}{T_{\max}})+(1-u_1^i)\tfrac{\gamma T_i V_i}{T_i+I_i}-bI_iE_i-\rho I_i],$$
$$V_{i+1}=V_i+h[(1-u_2^i)pI_i-\mu_V V_i],$$
$$E_{i+1}=E_i+h(\beta I_{i-m}E_{i-m}+E_0-\mu_E E_i),$$
$$\lambda_1^{n-i-1}=\lambda_1^{n-i}-h[W-\lambda_1^{n-i}r_T(1-\tfrac{2T_{i+1}+I_{i+1}}{T_{\max}})+\lambda_2^{n-i}\tfrac{r_I I_{i+1}}{T_{\max}}$$
$$+(\lambda_1^{n-i}-\lambda_2^{n-i})(1-u_1^i)\tfrac{\gamma I_{i+1}V_{i+1}}{(T_{i+1}+I_{i+1})^2}],$$
$$\lambda_2^{n-i-1}=\lambda_2^{n-i}-h\{\lambda_2^{n-i}[bE_{i+1}-r_I(1-\tfrac{2I_{i+1}+T_{i+1}}{T_{\max}})]+\lambda_1^{n-i}\tfrac{r_T T_{i+1}}{T_{\max}}$$
$$+(\lambda_2^{n-i}-\lambda_1^{n-i})[(1-u_1^i)\tfrac{\gamma T_{i+1}V_{i+1}}{(T_{i+1}+I_{i+1})^2}+\rho]-p(1-u_2^i\lambda_3^{n-i}$$
$$-\chi_{[0,t_f-\tau]}(t_{n-i})\lambda_4^{n+m-i}\beta E_{i+1}\},$$
$$\lambda_3^{n-i-1}=\lambda_3^{n-i}-h[-Q+\mu_V\lambda_3^{n-i}+(\lambda_1^{n-i}-\lambda_2^{n-i})(1-u_1^i)\tfrac{\gamma T_{i+1}}{T_{i+1}+I_{i+1}}],$$
$$\lambda_4^{n-i-1}=\lambda_4^{n-i}-h[\mu_E\lambda_4^{n-i}+bI_{i+1}\lambda_2^{n-i}-\chi_{[0,t_f-\tau]}(t_{n-i})\lambda_4^{n+m-i}\beta I_{i+1}],$$
$$A_1^{i+1}=\tfrac{1}{2R_1}(\lambda_2^{n-i-1}-\lambda_1^{n-i-1})\tfrac{\gamma T_{i+1}V_{i+1}}{T_{i+1}+I_{i+1}},$$
$$A_2^{i+1}=\tfrac{1}{2R_2}\lambda_3^{n-i-1}pI_{i+1},$$
$$u_1^{i+1}=\min(1,\max(A_1^{i+1},0)),$$
$$u_2^{i+1}=\min(1,\max(A_2^{i+1},0)).$$

end for

step 3 : for $i=1,\ldots,n,$ write

$T^*(t_i)=T_i, I^*(t_i)=I_i, V^*(t_i)=V_i, E^*(t_i)=E_i, u_1^*(t_i)=u_1^i, u_2^*(t_i)=u_2^i.$

end for

The following parameters and initial values conditions used for the simulation are :

$T_0=5.5\times10^6,\ I_0=1.1\times10^6,\ V_0=2\times10^8,\ E_0=500,\ r_T=0.5,\ r_I=0.01,\ T_{max}=13.6\times10^6,\ \gamma=0.0010,\ \rho=0.01,\ b=5.4\times10^{-4},\ p=200,\ \mu_V=0.67,\ \beta=3.4\times10^{-7},\ s=10,\ \mu_E=$

0.5, $\tau = 20$, $Q = 1$, $W = 1$.

The period of the therapy considered is 400 days.

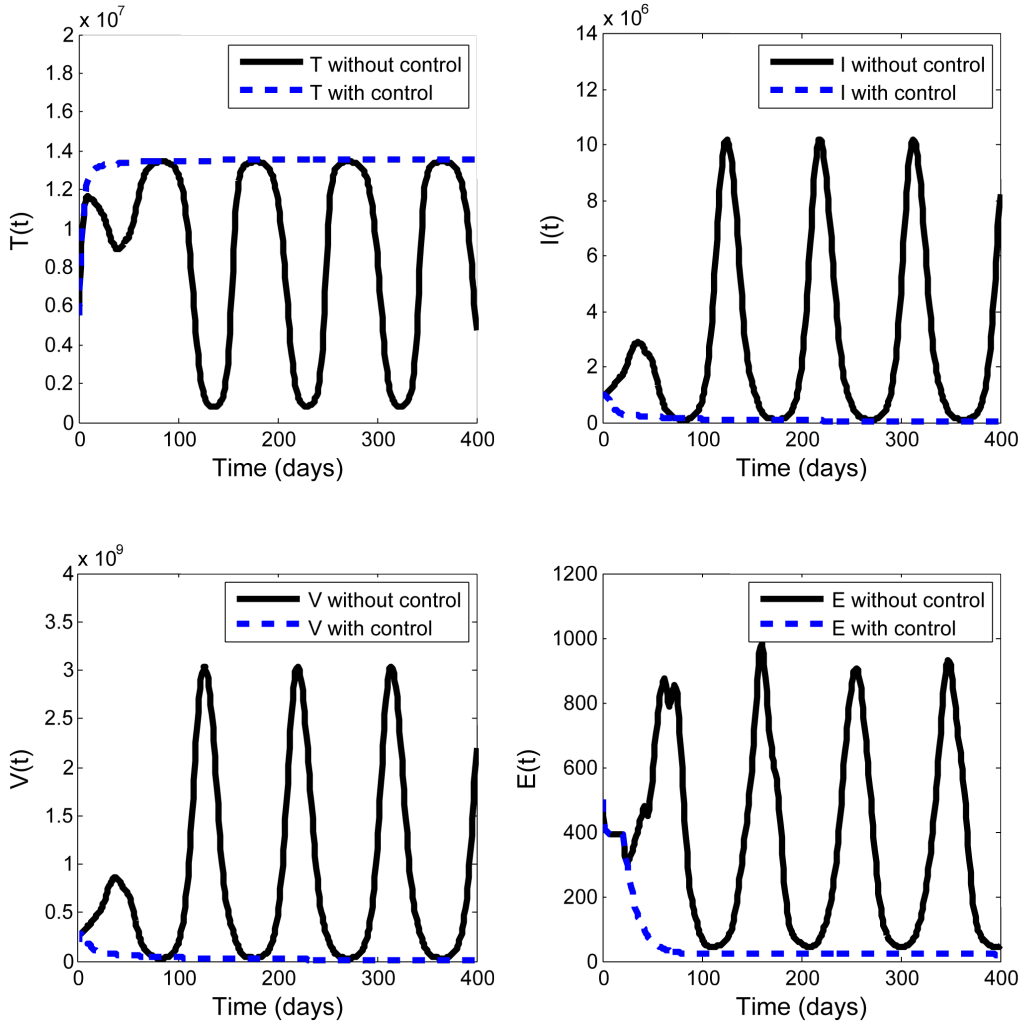

FIGURE 8. HBV population with and without control.

5. Conclusion

The HBV treatment could face several challenges particularly for patient with compromised immune response, such in the case of the HBV/HIV co-infection. In this paper, we studied a mathematical model of HBV dynamic with delay in the activation of the effector CTL cells. To reflect the reality of the growth of hepatocytes, we considered the logistic growth of the healthy cells and infected cells with a homeostatic carrying capacity of T_{max}. We also considered more

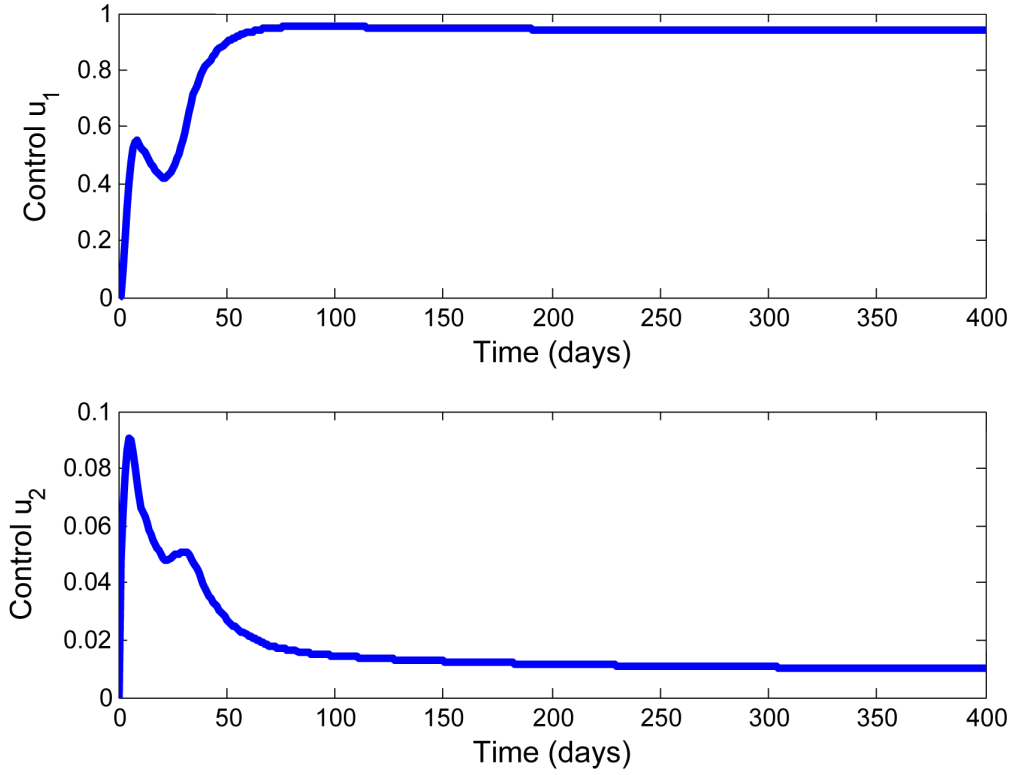

FIGURE 9. The controls u_1 and u_2.

realistic infection rate which proportional to the incidence function.

We showed that there four types of equilibria, three of them are biologically feasible. First, the disease free-equilibrium, which locally asymptotically stable if $R_0 < 1$. Second, the immune-response free-equilibrium which locally asymptotically stable if $1 < R_0 < R^*$. Finally, if $R_0 > R^*$ then there is an endemic equilibria which is locally asymptotically stable for $\tau < \tau_c$ and unstable for $\tau > \tau_c$ and system undergoes Hopf bifurcation when $\tau = \tau_c$. The result show that if the immune response does not response to the infection quickly, the disease dynamic can go to an oscillating behaviour.

We use Mikhailov criterion to illustrate the switch of stability at $\tau = \tau_c$. In fact it clear from Figures (, and) that, the system loses it's stability as τ increases and we get an oscillating behaviour.

When the delay of the activation of the effector immune cells is large to have oscillation in the model, we introduced an optimal control antiviral therapy approach that aimed to minimize the virus count, maximize the health cells and minimizing the drug doses. Our optimal control solution was able to steer the system from oscillating to non-oscillating dynamic (see Fig. 8). In fact, the optimal management of the antiviral therapy was successful to establish the healthy cells and to suppress the infections. To achieve that, the antiviral therapy drugs, interferon-α (IFN) and nucleotside analogs (NAs) must be have an optimal efficacy as represented in Fig. 9. More precisely, our result showed that the optimal efficacy of interferon-α should be 93% with the fifty day of the therapy. Simultaneously, the nucleotside analogs efficacy should be decrease to around 1.3%. This result showed that if there is a weak immune response to HBV treatment, the therapy should aim to suppress the disease by reducing cells susceptibility to the infection more than to reduce of virus production rate.

Conflict of Interests

The authors declare that there is no conflict of interests.

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