Stability and Bifurcation analysis of Hepatitis B-type virus infection model

M. Prakash[†], R. Rakkiyappan[*], A. Manivannan[‡], Haitao Zhu[**], Jinde Cao[***]
[†] Division of Mathematics, School of Advanced Sciences, VIT Vellore, Tamil Nadu India.
[*]Department of Mathematics, Bharathiar University, Coimbatore, India.
[‡]Division of Mathematics, School of Advanced Sciences, VIT-Chennai Campus, Tamil Nadu India.
[**]School of Mathematics and Statistics, Shandong Normal University, Jinan, 250014, PR China.
[***]School of Mathematics, and Research Center for Complex Systems and Network Sciences, Southeast University, Nanjing, 210096, PR China.
Corresponding Author. Email address : zhtmath@163.com (H. Zhu), jdcao@seu.edu.cn (J. Cao)

Abstract: The objective of the present paper is to investigate the dynamics of Hepatitis B-type virus (HBV) infection through mathematical model. Distinct to the existing mathematical models on HBV, the present model considers the various factors such as immune impairment, the maximum number of T-cells (total carrying capacity), logistic growth term. Besides, for more accuracy, the role of antiretroviral therapies are also involved in the analysis. In addition, time delays are inevitable during the activation of immune response and during the antiretroviral therapy. Considering these factors while formulating the mathematical model which helps to gain insights into the disease progression. With the derived model, the qualitative analysis such as stability analysis, bifurcation analysis and stabilization analysis can be performed to investigate the performance of the model over the period of time. The significance of the model parameters are revealed through Hopf-type bifurcation analysis and the global stability analysis of the proposed model. With the help of dataset values that are extracted from the literature the efficiency of the derived theoretical results are explored. **Keywords:** Global Stability, Hepatitis B virus, Hopf Bifurcation, Time delay.

1 Introduction

In general, replication of HBV are processed with liver cells, however, it does not involve in the physical harm of the liver cells, as a result, its determination is highly complicated with the tests. Instead of that, the virus may trigger an immune response which tries to eradicate the viral cells and with a large number of immune response cells is an indication of chronic HBV. The level of immune response cells indicated the stages of the disease progression, for an instance, high replication of HBV dominant the production of antiviral immune response that ends in weak antivirals. The role of HBV-encoded antigens is mainly responsible for controlling further replication and to eradicate the viral cells ([14, 16, 17]). In this regard, there is two different types of immune cells are activated, one is HBV-specific and other is non-specific helper T-cells. The HBV-specific antigen may fail during the chronic infection of HBV. ([18, 20]). Therefore, it is evident, that the outcome of HBV infection is determined by the vigor and the quality of the immune response ([21]) and it is a requirement to control the production and loss of immune response during the viral replication.

Based on the above discussions, it is clear that an immune response against the HBV

plays a remarkable role while modeling the progression of the disease. A mathematical model is a convenient tool which helps to analyze the disease progression and a pathway to obtain the long term treatment options for HBV. Numerous mathematical models have been reported in the literature which explores the basic relation between the various factors such as uninfected and infected hepatocytes, viral cells, Cytotoxic T lymphocytes (CTLs) and HBV cells. However, based on the authors knowledge, still now, the mathematical model which considered the factors include immune impairment (differentiation of CTLs) [7, 31], effect of time delays, logistic growth term, and effect of treatment are not yet formulated and these factors play a vital role in the chronic HBV which is the main objective of the present study.

As we all know, time delays are unavoidably encountered, and it is hard to handle[11, 15, 19]. Time delays play a significant role while modeling infection progress of HBV through a foreign agent, for more details, kindly see [12, 13, 23, 24, 25, 26, 27, 28]. In the view of existing literatures, it is clear that time delays have a significant role in the viral infections, say, time delay during the infection of a healthy hepatocyte and the production of infected hepatocyte (intracellular delay) and time delay in the activation of immune response which helps to eradicate the foreign agent (immune activation delay). Based on the above discussion, the consideration these time delays into the model will reflect much more effective results while compared to the model without these time delays [4, 5, 6].

Recently, most of the clinical studies have been focused on infected patients with elevated aminotransferase levels and circulating hepatitis B "e" antigen (HBeAg). The main idea behind the consideration of the effect of antiviral therapies into the model is because of the access to the antiviral therapies becomes regular. Hence the model should involve the effect of antiviral therapies.

Based on the aforementioned discussions and by considering the above-defined facets, the mathematical model for HBV infection is formulated which helps gain insights into the progression of viral cells. Center manifold theory and normal form method are utilized in the analysis of delay differential model. Further, the time delay is chosen as a bifurcation parameter because it has an ability to cause instability to the differential model.

The remainder of the paper is structured as follows. The section 2 contains the formulation of the mathematical model which involves all the above factors and also the derivation of basic reproduction number. In section 3, the local stability of the model is proved by ignoring the two delays. Further, the global stability of the intracellular delayed model has proven by constructing suitable Lyapunov functions and applying the LaSalle invariance principle. The existence of Hopf bifurcation is analyzed through two different cases, that is, without and with immune activation delay. Section 4 contains the numerical evaluations of the proposed mathematical model which shows the effect of time delays during the progression of the disease.

2 Modeling of HBV

The mathematical model which describes the interactions between HBV, healthy hepatocytes and immune cells and the effect of time delay that provides a new explanation for evolution

of disease progression.

$$
\begin{aligned}
\dot{x}(t) &= \overbrace{\Lambda}^{\text{Hepatocytes production}} - \overbrace{\delta_1 x(t)}^{\text{natural death}} - \overbrace{(1-\epsilon)\beta x(t)v(t)}^{\text{infectious transmission}} + \overbrace{rx(t)\Big(1-\frac{x(t)+l(t)+y(t)}{T_{max}}\Big)}^{\text{Full logistic growth}} \\
\dot{l}(t) &= \overbrace{\eta(1-\epsilon)\beta x(t)v(t)}^{\text{infectious transmission}} - \overbrace{dl(t)}^{\text{natural death}} - \overbrace{al(t)}^{\text{Spontaneous activation}} \\
\dot{y}(t) &= \overbrace{(1-\eta)(1-\epsilon)\beta x(t-\tau)v(t-\tau)}^{\text{Delayed infectious transmission}} - \overbrace{\delta_2 y(t)}^{\text{natural death}} - \overbrace{py(t)z(t)}^{\text{CTL-mediated lysis}} + \overbrace{al(t)}^{\text{Spontaneous activation}} \qquad (1) \\
\dot{v}(t) &= \overbrace{ky(t)}^{\text{Free virions}} - \overbrace{uv(t)}^{\text{natural death}} \\
\dot{w}(t) &= \overbrace{c(1-q)y(t-\omega)w(t-\omega)}^{\text{CTL-Precursors}} - \overbrace{bw(t)}^{\text{natural death}} \\
\dot{z}(t) &= \overbrace{cqy(t-\omega)w(t-\omega)}^{\text{CTL-Effectors}} - \overbrace{hz(t).}^{\text{natural death}}
\end{aligned}
$$

where $x(t)$ represents the uninfected hepatocytes, $l(t)$ stands for the immature viral cells (latent infection), $y(t)$ represents the infected hepatocytes, production of new virus from infected hepatocytes are denoted by $v(t)$. $z(t)$ represents effector cells and $w(t)$ denotes the precursor cells. The representation of the remaining parameters is clearly defined below.

Healthy Cells: Λ denotes the source term of the uninfected hepatocytes. r represents the logistic growth term and T_{max} is the total carrying capacity of the liver cells. β denotes contact rate between the healthy hepatocyte and HBV. The drug therapy is considered as ϵ, whereas $\epsilon \in [0, 1]$.

Infected Cells: The rate of infection of uninfected cells is the source term of infected cells (β). η denotes the number of infections that lies in the latent stage. a is the number of matured infectious cells. d represents the death rate of latently infected cells. δ_2 denotes the natural death rate of infected cells. p denotes the depletion of infected cells from immune response cells.

Free Virions: k denotes the rate of free virions produced from infected cells. The death rate of free virions is denoted by u.

Immune Responses: When the pathogen is detected by the immune system, a signal is sent in order to proliferate immune response cells CTLs to invade foreign agents [30, 31, 32]. In general, the production of CTLs can be categorized into two, that is, CTL precursors (CTLp) and CTL effectors (CTLe). CTLp is not responsible for eradicating virus whereas CTLe has an ability to eliminate the viral infections. In order to acquire the complete knowledge on immune activations it is necessary to consider both CTLp and CTL2 into the mathematical models, In this regard, the population of CTLp is defined as w and the population of CTLe is given as z. If foreign agent interact with antigens then the corresponding CTLp will proliferate at the rate of cyw and evolve into effector cells at a rate $cqyw$. The death rate of CTL precursors is denoted by bw and effectors die at a rate hz. In this model, CTL memory lies in the population of precursors w.

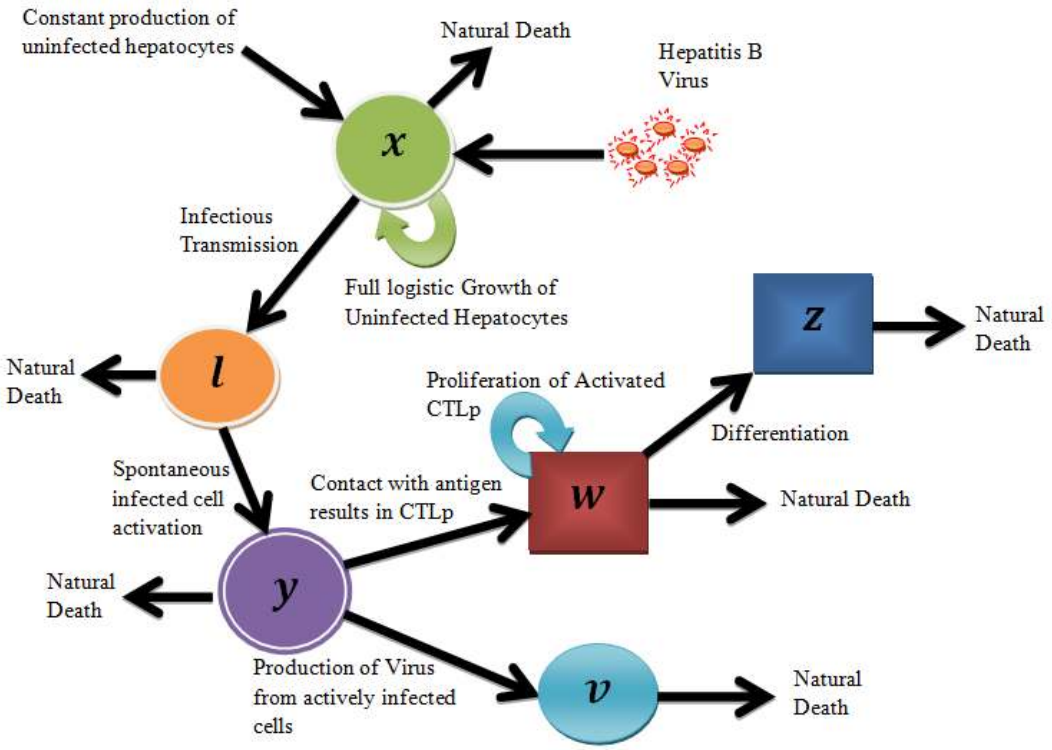

Figure 1: A schematic representation of the model(1).

2.1 Steady States (Equilibrium) of model

This section comprises the derivation of steady states of the cells and it is obvious that level of infections can be known through different type of equilibrium states. However, in this manuscript, we consider two possible states of infection that is infection-free and infection equilibrium. Technically, for the derivation of steady states, we assume that there is no possibility for the realization of time delays.
Consider that there is no symptoms based on HBV infection. So, model (1) has an infection-free (healthy) steady state with equilibrium in the following form

$$E^* = \Big(x^*_{\pm}, 0, 0, 0, 0, 0\Big),$$

where

$$x^*_{\pm} = \frac{T_{max}}{2r}\Big(r - \delta_1 \pm \sqrt{(r-\delta_1)^2 + \frac{4\Lambda r}{T_{max}}}\Big).$$

The main goal of this manuscript is to analyze the interaction and the infection process of hepatocytes with HBV. Hence, it is necessary to consider the coexistence of healthy hepatocytes and HBV. Now, evaluating the model (1) by substituting the numerical values of the parameters, one can obtain the endemic equilibrium $\bar{E}$ of the model which will be provided in the numerical simulation section.

2.2 The basic reproduction number R_0

Generally, the expected number of secondary infections are defined as the basic reproduction number R_0 produced by an index case in a completely susceptible population. The level of R_0 indicates the progression of diseases within a population. If $R_0 < 1$, then a infected individuals lies into a completely susceptible population and able to control in the region as a result epidemics of diseases is controlled. On the other hand, $R_0 > 1$, then the number of infected individuals will increase with each generation and the disease will spread [29]. Here, the system has a unique disease-free equilibrium x^* and now taking the infected compartments to be l, y and v then, one can derive

$$F = \begin{bmatrix} 0 & 0 & -\beta\eta x^*(\epsilon-1) \\ 0 & 0 & -\beta x^*(\epsilon-1) \\ 0 & 0 & 0 \end{bmatrix}, V = \begin{bmatrix} a+d & 0 & 0 \\ -a & \delta_2 & 0 \\ 0 & -k & u \end{bmatrix}.$$

and we apply that $K = FV^{-1}$ which leads to the following matrix

$$K = FV^{-1} = \begin{bmatrix} \frac{ak(\beta\eta x^* - \beta\epsilon\eta x^*)}{\delta_2 u(a+d)} & \frac{k(\beta\eta x^* - \beta\epsilon\eta x^*)}{\delta_2 u} & \frac{\beta\eta x^* - \beta\epsilon\eta x^*}{u} \\ \frac{ak(\beta x - \beta\epsilon x^*)}{\delta_2 u(a+d)} & \frac{k(\beta x^* - \beta\epsilon x^*)}{\delta_2 u}, & \frac{\beta x^* - \beta\epsilon x^*}{u} \\ 0 & 0 & 0 \end{bmatrix}.$$

Therefore, one can find the reproduction number R_0 during the progress of infection through the eigen-values of the above matrix K

$$\begin{pmatrix} 0 \\ 0 \\ \frac{-\beta k x^*(\epsilon-1)(a+d+a\eta)}{\delta_2 u(a+d)} \end{pmatrix},$$

$$R_0 = \frac{-\beta k x^*(\epsilon-1)(a+d+a\eta)}{\delta_2 u(a+d)}. \tag{2}$$

3 Dynamic Analysis of model

This section briefly discuss about the derivation of suitable stability conditions for endemic equilibria, which are derived by assuming the production of viral particles be be positive, that is, $R_0 > 1$. In this manuscript, we considered the following situations in the infection:

(a). If two delays are ignored.

(b). For $\tau > 0$ and $\omega = 0$.

(c). For $\tau = 0, \omega > 0$.

(d). For $\tau > 0, \omega > 0$.

To evaluate the infection model under the above situations, we start with linearizing the proposed model because the nonlinear models are much more complex while solving. Now, we can linearize the model (1) through finding the Jacobian matrix as follows

$$\begin{vmatrix} -\left(\delta_1+(1-\epsilon)\beta\bar{v}-r+\frac{2r\bar{x}}{T_{max}}+\frac{r\bar{y}}{T_{max}}\right)-\lambda & 0 & -\frac{r\bar{x}}{T_{max}} & -(1-\epsilon)\beta\bar{x} & 0 & 0 \\ \eta(1-\epsilon)\beta\bar{v} & -(d+a)-\lambda & 0 & \eta(1-\epsilon)\beta\bar{x} & 0 & 0 \\ (1-\eta)(1-\epsilon)\beta\bar{v}e^{-\lambda\tau} & a & -(\delta_2+p\bar{z})-\lambda & (1-\eta)(1-\epsilon)\beta\bar{x}e^{-\lambda\tau} & 0 & -p\bar{y} \\ 0 & 0 & k & -u-\lambda & 0 & 0 \\ 0 & 0 & c(1-q)\bar{w}e^{-\lambda\omega} & 0 & c(1-q)\bar{y}e^{-\lambda\omega}-b-\lambda & 0 \\ 0 & 0 & cq\bar{w}e^{-\lambda\omega} & 0 & cq\bar{y}e^{-\lambda\omega} & -h-\lambda \end{vmatrix}. \quad (3)$$

The characteristic equation is calculated as follows,

$$\lambda^6 + P_1\lambda^5 + P_2\lambda^4 + P_3\lambda^3 + P_4\lambda^2 + P_5\lambda + P_6 + e^{-\lambda\omega}\Big(R_1\lambda^4 + R_2\lambda^3 + R_3\lambda^2 + R_4\lambda + R_5\Big)$$
$$+e^{-\lambda\tau}\Big(Q_1\lambda^5 + Q_2\lambda^4 + Q_3\lambda^3 + Q_4\lambda^2 + Q_5\lambda + Q_6\Big) + e^{-\lambda(\tau+\omega)}\Big(K_1\lambda^3 + K_2\lambda^2 + K_3\lambda + K_4\Big) = 0.$$

For brevity, the above equation can be rewritten in the simplified form as follows

$$D(\lambda,\tau,\omega) = P(\lambda) + e^{-\lambda\tau}Q(\lambda) + e^{-\lambda\omega}R(\lambda) + e^{-\lambda(\tau+\omega)}K(\lambda), \quad (4)$$

where $P(\lambda) = \lambda^6+P_1\lambda^5+P_2\lambda^4+P_3\lambda^3+P_4\lambda^2+P_5\lambda+P_6, Q(\lambda) = Q_1\lambda^5+Q_2\lambda^4+Q_3\lambda^3+Q_4\lambda^2+Q_5\lambda+Q_6, R(\lambda) = R_1\lambda^4+R_2\lambda^3+R_3\lambda^2+R_4\lambda+R_5$ and $K(\lambda) = K_1\lambda^3+K_2\lambda^2+K_3\lambda+K_4$. The remaining coefficients are provided in the **Appendix 1**.

3.1 For $\tau = 0,\ R_0 > 1$and $\omega = 0$

This section discusses the situation where both delays are assumed to be void. Then the corresponding characteristic equation (4) is simplified into

$$P(\lambda) + Q(\lambda) + R(\lambda) + K(\lambda) = 0. \quad (5)$$

Therefore the equilibrium is proved to be locally asymptotically stable only if the roots of the equation (5) have negative real parts. Equivalently,

$$\lambda^6 + v_1\lambda^5 + v_2\lambda^4 + v_3\lambda^3 + v_4\lambda^2 + v_5\lambda + v_6 = 0.$$

where
$v_1 = P_1 + Q_1, v_2 = P_2 + R_1 + Q_2, v_3 = P_3 + R_2 + Q_3 + K_1, v_4 = P_4 + R_3 + Q_4 + K_2, v_5 = P_5 + R_4 + Q_5 + K_3, v_6 = P_6 + R_5 + Q_6 + K_4$.
The model is asymptotically stable if the above inequalities hold in terms of Routh-Hurwitz criterion.
(H_1) $v_1 > 0, v_1v_2 - v_3 > 0, v_1(v_2v_3 - v_1v_4) - v_3^2 + v_5v_1 > 0,$
$v_1v_2v_3v_4 - v_1v_2^2v_5 + v_1^2v_2v_6 - v_1^2v_4^2 + 2v_1v_4v_5 - v_1v_3v_6 - v_3^2v_4 + v_3v_2v_5 - v_5^2 > 0,$
$v_1v_2v_3v_4v_5 - v_1v_2v_3^2v_6 - v_1v_2^2v_5^2 + 2v_2v_1^2v_5v_6 - v_1^2v_4^2v_5 + v_1^2v_4v_3v_6 - v_1^3v_6^2 + 2v_1v_5^2v_4 - 3v_3v_1v_5v_6 - v_3^2v_4v_5 + v_3^3v_6 + v_3v_2v_5^2 - v_5^3 > 0,$
$(v_1v_2v_3v_4v_5 - v_1v_2v_3^2v_6 - v_1v_2^2v_5^2 + 2v_2v_1^2v_5v_6 - v_1^2v_4^2v_5 + v_1^2v_4v_3v_6 - v_1^3v_6^2 + 2v_1v_5^2v_4 - 3v_3v_1v_5v_6 - v_3^2v_4v_5 + v_3^3v_6 + v_3v_2v_5^2 - v_5^3)v_6 > 0.$
Consequently, all the roots of (4) have negative real parts if and only if all of the inequalities are satisfied.
Theorem 4.1: In the absence of delays, the infection free equilibrium of model (1) is asymptotically stable if and only if H_1 is satisfied.

3.2 For $\tau > 0$ and $\omega = 0$.

For the above case the corresponding model can be derived as

$$\begin{aligned}
\dot{x}(t) &= \Lambda - \delta_1 x(t) - (1-\epsilon)\beta x(t)v(t) + rx\Big(1 - \frac{x(t)+y(t)+l(t)}{T_{max}}\Big),\\
\dot{l}(t) &= \eta(1-\epsilon)\beta x(t)v(t) - dl(t) - al(t),\\
\dot{y}(t) &= (1-\eta)(1-\epsilon)\beta x(t-\tau)v(t-\tau) - \delta_2 y - py(t)z(t) + al(t),\\
\dot{v}(t) &= ky(t) - uv(t),\\
\dot{w}(t) &= c(1-q)y(t)w(t) - bw(t),\\
\dot{z}(t) &= cqy(t)w(t) - hz(t).
\end{aligned} \tag{6}$$

Different types strategies have been followed to obtain the stability conditions of the proposed model. In this study, we have utilise the Lyapunov stability theory to derive the sufficient conditions for the model (6). Now, let us consider the following energy function

$$G(t) = \tilde{G}(t) + (1-\epsilon)(1-\eta)\beta\bar{x}\bar{v}G_+(t)$$

,
where

$$\tilde{G} = \int_{\bar{x}}^{x} \frac{\sigma-\bar{x}}{\sigma}d\sigma + \int_{\bar{l}}^{l} \frac{\sigma-\bar{l}}{\sigma}d\sigma + \int_{\bar{y}}^{y} \frac{\sigma-\bar{y}}{\sigma}d\sigma + \int_{\bar{v}}^{v} \frac{\sigma-\bar{v}}{\sigma}d\sigma + \int_{\bar{w}}^{w} \frac{\sigma-\bar{w}}{\sigma}d\sigma + \int_{\bar{z}}^{z} \frac{\sigma-\bar{z}}{\sigma}d\sigma,$$

and

$$G_+ = \int_0^{\tau} \Big(\frac{x(t-\eta)v(t-\eta)}{\bar{x}\bar{v}} - 1 - \ln\frac{x(t-\eta)v(t-\eta)}{\bar{x}\bar{v}}\Big)d\eta.$$

Along with endemic equilibrium

$$\begin{aligned}
-\delta_1 + r = -\frac{\Lambda}{\bar{x}} + (1-\epsilon)\beta\bar{v} + \frac{r}{T_{max}}(\bar{x}+\bar{y}+\bar{l}); d + a = \frac{\eta(1-\epsilon)\beta\bar{x}\bar{v}}{\bar{l}}; h = \frac{cq\bar{w}\bar{y}}{\bar{z}};\\
\delta_2 = \frac{(1-\eta)(1-\epsilon)\beta\bar{x}\bar{v}}{\bar{y}} - p\bar{z} + \frac{a\bar{l}}{\bar{y}}; u = \frac{k\bar{y}}{\bar{v}}; b = c\bar{y}(1-q).
\end{aligned}$$

Taking the derivate of the above equation leads to the following

$$\begin{aligned}
\frac{d\tilde{G}}{dt} &= \frac{(x-\bar{x})}{x}\frac{dx}{dt} + \frac{(l-\bar{l})}{l}\frac{dl}{dt} + \frac{(y-\bar{y})}{y}\frac{dy}{dt} + \frac{(v-\bar{v})}{v}\frac{dv}{dt} + \frac{(w-\bar{w})}{w}\frac{dw}{dt} + \frac{(z-\bar{z})}{z}\frac{dz}{dt}\\
&= (x-\bar{x})\Big(\frac{\Lambda}{x} - \delta_1 - (1-\epsilon)\beta v + r - \frac{r}{T_{max}}\big(x+y+l\big)\Big) + (l-\bar{l})\Big(\frac{\eta(1-\epsilon)\beta xv}{l} - (d+a)\Big)\\
&\quad +(y-\bar{y})\Big(\frac{\beta x_\tau v_\tau(1-\eta)(1-\epsilon)}{y} - \delta_2 - pz + a\frac{l}{y}\Big) + (v-\bar{v})\Big(\frac{ky}{v} - u\Big)\\
&\quad +(w-\bar{w})\Big(c(1-q)y - b\Big) + (z-\bar{z})\Big(\frac{cqwy}{z} - h\Big).
\end{aligned} \tag{7}$$

Substitute the values of $u, d+a, -\delta_1+r, b, h, \delta_2$ in the equation (7) one can obtain that

$$\begin{aligned}\frac{d\tilde{G}}{dt} &= -\Lambda\frac{(x-\bar{x})^2}{x\bar{x}} - \frac{r}{T_{max}}\frac{(x-\bar{x})^2}{x\bar{x}} + (1-\epsilon)\beta\bar{x}\bar{v}\Big(2 + \frac{(x-\bar{x})^2}{x\bar{x}} + \frac{(v-\bar{v})^2}{v\bar{v}} - \frac{(y-\bar{y})^2}{y\bar{y}} - \frac{\bar{x}}{x} + \frac{\bar{y}}{y} \\ &- \frac{\bar{v}}{v} - \frac{xv}{\bar{v}\bar{x}} + \frac{x_\tau v_\tau}{\bar{x}\bar{v}} + \frac{x_\tau v_\tau \bar{y}}{\bar{x}\bar{v}y}\Big) - \eta(1-\epsilon)\beta\bar{x}\bar{y}\Big(- \frac{(y-\bar{y})^2}{y\bar{y}} + \frac{(l-\bar{l})^2}{l\bar{l}} + \frac{\bar{y}}{y} - \frac{\bar{l}}{l} - \frac{xv}{\bar{x}\bar{v}} + \frac{xv\bar{l}}{\bar{x}\bar{v}l} \\ &- \frac{x_\tau v_\tau \bar{y}}{\bar{x}\bar{v}y} + \frac{x_\tau v_\tau}{\bar{x}\bar{v}}\Big) \quad + \frac{r}{T_{max}}\bar{x}\bar{l}\Big(3 - \frac{xl}{\bar{x}\bar{l}} - \frac{\bar{l}}{l} - \frac{\bar{x}}{x} + \frac{(x-\bar{x})^2}{x\bar{x}} + \frac{(l-\bar{l})^2}{l\bar{l}}\Big) + \frac{r}{T_{max}}\Big(3 - \frac{\bar{x}}{x} \\ &- \frac{\bar{y}}{y} - \frac{xy}{\bar{x}\bar{y}} + \frac{(x-\bar{x})^2}{x\bar{x}} + \frac{(y-\bar{y})^2}{y\bar{y}}\Big)\bar{x}\bar{y} + a\bar{l}\Big(1 - \frac{l\bar{y}}{\bar{l}y} - \frac{\bar{l}}{l} + \frac{\bar{y}}{y} - \frac{(y-\bar{y})^2}{y\bar{y}} + \frac{(l-\bar{l})^2}{l\bar{l}}\Big) \\ &+ p\bar{y}\bar{z}\Big(3 - \frac{\bar{y}}{y} - \frac{\bar{z}}{z} + \frac{(y-\bar{y})^2}{y\bar{y}} - \frac{(z-\bar{z})^2}{z\bar{z}} - \frac{yz}{\bar{y}\bar{z}}\Big) + k\bar{y}\Big(1 - \frac{\bar{y}}{y} + \frac{\bar{v}}{v} + \frac{(y-\bar{y})^2}{y\bar{y}} - \frac{(v-\bar{v})^2}{v\bar{v}} - \frac{y\bar{v}}{\bar{y}v}\Big) \\ &- c\bar{w}\bar{y}\Big(3 - \frac{wy}{\bar{w}}\bar{y} + \frac{(y-\bar{y})^2}{y\bar{y}} + \frac{(w-\bar{w})^2}{w\bar{w}} - \frac{\bar{y}}{y} - \frac{\bar{w}}{w}\Big) + cq\bar{w}\bar{y}\Big(2 + \frac{(y-\bar{y})^2}{y\bar{y}} - \frac{(z-\bar{z})^2}{z\bar{z}} \\ &+ \frac{(w-\bar{w})^2}{w\bar{w}} + \frac{\bar{z}}{z} - \frac{\bar{y}}{y} - \frac{\bar{w}}{w} - \frac{wy\bar{z}}{\bar{w}\bar{y}z}\Big).\end{aligned}$$

Considering $x_\tau = x(t-\tau)$ and $v_\tau = v(t-\tau)$ can leads to

$$\begin{aligned}\frac{dG_+}{dt} &= \frac{d}{dt}\int_0^\tau \Big(\frac{x_\tau v_\tau}{\bar{x}\bar{v}} - 1 - \ln\frac{x_\tau v_\tau}{\bar{x}\bar{y}}\Big)d\tau = \int_0^\tau \frac{d}{dt}\Big(\frac{x_\tau v_\tau}{\bar{x}\bar{v}} - 1 - \ln\frac{x_\tau v_\tau}{\bar{x}\bar{y}}\Big)d\tau \\ &= -\int_0^\tau \frac{d}{d\tau}\Big(\frac{x_\tau v_\tau}{\bar{x}\bar{v}} - 1 - \ln\frac{x_\tau v_\tau}{\bar{x}\bar{y}}\Big)d\tau = -\Big[\frac{x_\tau v_\tau}{\bar{x}\bar{v}} - 1 - \ln\frac{x_\tau v_\tau}{\bar{x}\bar{y}}\Big]_0^\tau \\ &= -\frac{x_\tau v_\tau}{\bar{x}\bar{v}} + \frac{xv}{\bar{x}\bar{v}} + \ln\frac{x_\tau v_\tau}{\bar{x}\bar{v}} + \ln\frac{\bar{x}\bar{v}}{xv} = -\frac{x_\tau v_\tau}{\bar{x}\bar{v}} + \frac{xv}{\bar{x}\bar{v}} + \ln\frac{x_\tau \bar{y} v_\tau}{\bar{x}y\bar{v}} + \ln\frac{\bar{x}}{x} + \ln\frac{y\bar{v}}{\bar{y}v}.\end{aligned}$$

Since

$$\frac{dG}{dt} = \frac{d\tilde{G}}{dt} + (1-\epsilon)(1-\eta)\beta\bar{x}\bar{v}\frac{dG_+}{dt},$$

we obtain that

$$\begin{aligned}
\frac{dG}{dt} = &-\Big(\delta_1 - r + \frac{r}{T_{max}}(\bar{x}+\bar{y}+\bar{l})\Big)\frac{(x-\bar{x})^2}{x} - c\bar{w}\bar{y}\Big(3 + \frac{(y-\bar{y})^2}{y\bar{y}} - \frac{\bar{y}}{y} + \frac{(w-\bar{w})^2}{w\bar{w}} - \frac{\bar{w}}{w} - \frac{wy}{\bar{w}\bar{y}}\Big)\\
&- (1-\epsilon)\beta\bar{x}\bar{v}\big(\frac{\bar{x}}{x} - 1 - \ln\frac{\bar{x}}{x}\big) - (1-\epsilon)\beta\bar{x}\bar{v}\big(\frac{x_\tau\bar{y}v_\tau}{\bar{x}y\bar{v}} - 1 - \ln\frac{x_\tau\bar{y}v_\tau}{\bar{x}y\bar{v}}\big) - (1-\epsilon)\beta\bar{x}\bar{v}\big(\frac{\bar{y}}{y} - 1 - \ln\frac{\bar{y}}{y}\big)\\
&- (1-\epsilon)\beta\bar{x}\bar{v}\big(\frac{\bar{v}}{v} - 1 - \ln\frac{\bar{v}}{v}\big) - \eta(1-\epsilon)\beta\bar{x}\bar{v}\big(\frac{\bar{y}}{y} - 1 - \ln\frac{\bar{y}}{y}\big) + \eta(1-\epsilon)\beta\bar{x}\bar{v}\big(\frac{\bar{l}}{l} - 1 - \ln\frac{\bar{l}}{l}\big)\\
&- \eta(1-\epsilon)\beta\bar{x}\bar{v}\big(\frac{\bar{l}xv}{\bar{x}l\bar{v}} - 1 - \ln\frac{\bar{l}xv}{\bar{x}l\bar{v}}\big) + \eta(1-\epsilon)\beta\bar{x}\bar{v}\big(\frac{\bar{y}x_\tau v_\tau}{\bar{x}y\bar{v}} - 1 - \ln\frac{\bar{y}x_\tau v_\tau}{\bar{x}y\bar{v}}\big)\\
&+ \eta(1-\epsilon)\beta\bar{x}\bar{v}\Big((l-\bar{l})^2 l\bar{l} + \frac{(y-\bar{y})^2}{y\bar{y}}\Big) + \frac{r}{T_{max}}\bar{x}\bar{l}\Big(3 - \frac{xl}{\bar{x}\bar{l}} - \frac{\bar{l}}{l} - \frac{\bar{x}}{x} + \frac{(x-\bar{x})^2}{x\bar{x}} + \frac{(l-\bar{l})^2}{l\bar{l}}\Big)\\
&+ \eta(1-\epsilon)\beta\bar{x}\bar{v}\Big(3 + \frac{(l-\bar{l})^2}{l\bar{l}} - \frac{\bar{l}}{l} - \frac{xvl}{\bar{x}\bar{l}\bar{v}} + \frac{xv}{\bar{x}\bar{v}}\Big) + \frac{r}{T_{max}}\Big(3 - \frac{\bar{x}}{x} - \frac{\bar{y}}{y} - \frac{xy}{\bar{x}\bar{y}} + \frac{(x-\bar{x})^2}{x\bar{x}} + \frac{(y-\bar{y})^2}{y\bar{y}}\Big)\bar{x}\bar{y}\\
&+ p\bar{y}\bar{z}\Big(3 - \frac{\bar{y}}{y} - \frac{\bar{z}}{z} + \frac{(y-\bar{y})^2}{y\bar{y}} - \frac{(z-\bar{z})^2}{z\bar{z}} - \frac{yz}{\bar{y}\bar{z}}\Big) + a\bar{l}\Big(1 - \frac{l\bar{y}}{\bar{l}y} - \frac{\bar{l}}{l} + \frac{\bar{y}}{y} - \frac{(y-\bar{y})^2}{y\bar{y}} + \frac{(l-\bar{l})^2}{l\bar{l}}\Big)\\
&- k\bar{y}\Big(1 - \frac{\bar{y}}{y} + \frac{\bar{v}}{v} + \frac{(y-\bar{y})^2}{y\bar{y}} - \frac{(v-\bar{v})^2}{v\bar{v}} - \frac{y\bar{v}}{\bar{y}v}\Big)\\
&+ cq\bar{w}\bar{y}\Big(2 - \frac{(z-\bar{z})^2}{z\bar{z}} + \frac{\bar{z}}{z} + \frac{(y-\bar{y})^2}{y\bar{y}} - \frac{\bar{y}}{y} - \frac{wy\bar{z}}{\bar{w}\bar{y}z} + \frac{(w-\bar{w})^2}{w\bar{w}} - \frac{\bar{w}}{w}\Big).
\end{aligned}$$

Thus, if

$$r - \delta_1 + \frac{r}{T_{max}}(\bar{x}+\bar{y}+\bar{l}) \leq 0 \tag{8}$$

will results in $\frac{dG}{dt}$ is negative for $\{x(t), l(t), y(t), v(t), w(t), z(t)\} > 0$, and $\frac{dG}{dt} = 0$ and $x(t) = x(t-\tau) = \bar{x}, v(t) = v(t-\tau) = \bar{v}, y(t) = \bar{y}, l(t) = \bar{l}, w(t) = \bar{w}, z(t) = \bar{z}$.
From LaSalle invariance principle, it is clear that equilibrium $\bar{E}$ is globally asymptotically stable for all $\tau > 0$.
Theorem 4.2: The considered system is said to be globally asymptotically stable for $\omega = 0$ and $R_0 > 1$ if the condition (8) holds.

Remark 3.1 *Similarly, the stability analysis and bifurcation analysis have performed for the case of $\tau > 0$ and $\omega = 0$ and it is observed that the solutions of the model are independent to intracellular time-delay when the immmune activation delay is considered to be null.*

3.3 For the case $\tau = 0$ and $\omega > 0$ under $R_0 > 1$.

Consider the situation that only the immune activation delay persists then the model (1) transformed into the following.

$$\begin{aligned}
\dot{x}(t) &= \Lambda - \delta_1 x(t) - (1-\epsilon)\beta x(t)v(t) + rx(t)\Big(1 - \frac{x(t)+l(t)+y(t)}{T_{max}}\Big),\\
\dot{l}(t) &= \eta(1-\epsilon)\beta x(t)v(t) - dl(t) - al(t),\\
\dot{y}(t) &= (1-\eta)(1-\epsilon)\beta x(t)v(t) - \delta_2 y - py(t)z(t) + al(t),\\
\dot{v}(t) &= ky(t) - uv(t),\\
\dot{w}(t) &= c(1-q)y(t-\omega)w(t-\omega) - bw(t),\\
\dot{z}(t) &= cqy(t-\omega)w(t-\omega) - hz(t).
\end{aligned} \tag{9}$$

Now, the characteristic polynomial is derived as

$$\begin{aligned}
&\lambda^6 + (P_1+Q_1)\lambda^5 + (P_2+Q_2)\lambda^4 + (P_3+Q_3)\lambda^3 + (P_4+Q_4)\lambda^2 + (P_5+Q_5)\lambda + (P_6+Q_6)\\
&\quad + e^{-\lambda\omega}\Big(Q_1\lambda^5 + Q_2\lambda^4 + (Q_3+K_1)\lambda^3 + (Q_4+K_2)\lambda^2 + (Q_5+K_3)\lambda + (Q_6+K_4)\Big) = 0.
\end{aligned} \tag{10}$$

For $\omega = 0$, if all the roots of the characteristic polynomial (4) shows then it is concluded that $\bar{E}$ is stable. Let $\omega > 0$ and if $\lambda = i\gamma$ is a purely imaginary root of (10). Solving the characteristic equation (10) and separating real and imaginary roots one can get,

$$\begin{aligned}
&-\gamma^6 + \gamma^4(P_2+Q_2) - \gamma^2(P_4+Q_4) + P_6 + Q_6 + \cos(\omega\gamma)\big(Q_2\gamma^4 - \gamma^2(Q_4+K_2) + Q_6 + K_4\big)\\
&+ \sin(\omega\gamma)\big(Q_1\gamma^5 - \gamma^3(Q_3+K_1) + \gamma(Q_5+K_3)\big) = 0,\\
&\gamma^5 P_1 - (P_3+R_2)\gamma^3 + \gamma(P_5+R_4) - \sin(\omega\gamma)\big(Q_2\gamma^4 - \gamma^2(Q_4+K_2) + Q_6 + K_4\big)\\
&+ \cos(\omega\gamma)\big(Q_1\gamma^5 - \gamma^3(Q_3+K_1) + \gamma(Q_5+K_3)\big) = 0.
\end{aligned} \tag{11}$$

Squaring and adding the above equation can leads into the following

$$\gamma^{12} + J_1\gamma^{10} + J_2\gamma^8 + J_3\gamma^6 + J_4\gamma^4 + J_5\gamma^2 + J_6 = 0, \tag{12}$$

where

$$\begin{aligned}
J_1 =& P_1^2 - Q_1^2 - 2(P_2+R_1),\\
J_2 =& (P_2+R_1)^2 - Q_2^2 + 2\Big(P_4 + R_3 - P_1(P_3+R_2) + Q_1(Q_3+K_1)\Big),\\
J_3 =& (P_3+R_2)^2 - (Q_3+K_1)^2 + 2\Big(P_1(P_5+R_4) - Q_1(Q_5+K_3) - P_6 - R_5\\
&- (P_2+R_1)(P_4+R_3) + Q_2(Q_4+K_2)\Big),\\
J_4 =& (P_4+R_3)^2 - (Q_4+K_2)^2 + 2\Big((P_2+R_1)(P_6+R_5) - Q_2(K_4+Q_6) - (P_3+Q_2)(P_5+R_4)\\
&+ (Q_3+K_1)(Q_5+K_3)\Big),\\
J_5 =& (P_5+R_4)^2 - (Q_5+K_3)^2 - 2\Big((P_4+R_3)(P_6+R_5) + (Q_4+K_2)(Q_6+K_4)\Big),\\
J_6 =& (P_6+R_5)^2 - (Q_6+K_4)^2.
\end{aligned}$$

Here, substitute $u = \gamma^2$ and the equation (12) can be rewritten as follows

$$k(u) = u^6 + J_1u^5 + J_2u^4 + J_3u^3 + J_4u^2 + J_5u + J_6. \tag{13}$$

Since $J_6 < 0$, then equation (13) has atleast one positive root. Here, the equation (13) contains six positive roots, say, $u_1, u_2, u_3, u_4, u_5, u_6$, and it is denoted by

$$\gamma_1 = \sqrt{u_1},\ \gamma_2 = \sqrt{u_2},\ \gamma_3 = \sqrt{u_3},\ \gamma_4 = \sqrt{u_4}, \gamma_5 = \sqrt{u_5}, \gamma_6 = \sqrt{u_6}.$$

Solve for $\sin(\omega\gamma)$ gives on equation (11), we have

$$\omega_n^{(j)} = \frac{1}{\gamma_k} \arccos\Big(\frac{F_1}{F_2}\Big) + \frac{2n\pi}{\gamma_k},$$

where $n = 1, 2, 3, 4, 5, 6.,\ j = 1, 2, 3, \cdots$ and

$$\begin{aligned}
F_1 &= \gamma^{10}(Q_1P_1 - Q_2) + \gamma^8\big(Q_4 + K_2 - P_1(Q_3 + K_1) - (P_3 + R_2)Q_1 + (P_2 + R_1)Q_2\big) \\
&\quad +\gamma^6\Big((P_2 + R_1)(R_6 + K_4) - (Q_4 + K_2)(P_2 + R_1) - Q_2(P_4 + R_3) + P_1(Q_5 + K_3) \\
&\quad +(Q_3 + K_1)(P_3 + R_2) - (P_5 + R_4)Q_1\Big) + \gamma^4\Big((P_2 + R_1)(Q_6 + K_4) + (R_4 + K_2)(P_4 + R_3) \\
&\quad +(P_6 + R_5)Q_2 - (P_3 + R_2)(Q_5 + K_3) + (Q_3 + K_1)(P_5 + R_4)\Big) + \gamma^2\Big(- (Q_4 + K_2)(P_6 + R_5) \\
&\quad -(P_4 + R_3)(Q_6 + K_4) - (Q_5 + K_3)(P_5 + R_4)\Big) + (P_6 + R_5)(Q_6 + K_4), \\
F_2 &= \big(\gamma^5Q_1 - \gamma^3(Q_3 + K_1) + \gamma(Q_5 + K_3)\big)^2 + \big(Q_2\gamma^4 - \gamma^2(Q_4 + K_2) + Q_6 + K_4\big)^2.
\end{aligned}$$

We choose

$$\bar{\omega} = \min\{\omega_n\} \qquad n = 1, 2, 3 \cdots . \tag{14}$$

If the following conditions hold then it is clear the Hopf-type bifurcation will be realized if the threshold of the bifurcation parameter exceeds.

$$sgn\Big[\frac{d\Re\lambda}{d\omega}\Big]_{\omega=\bar{\omega}} = sgn\{k'(\gamma_0^2)\}.$$

Then from the above factors, it is concluded that there exists at least one eigenvalue having positive real part for the condition $\omega > \bar{\omega}$. Now taking the derivation of the above equation, one can have

$$\begin{aligned}
\Big(\frac{d\lambda}{d\omega}\Big)^{-1} = \quad & \frac{6\lambda^5 + 5\lambda^4P_1 + 4\lambda^3(P_2 + R_1) + 3\lambda^2(P_3 + R_2) + 2\lambda(P_4 + R_3) + P_5 + R_4}{\lambda\big(Q_1\lambda^5 + Q_2\lambda^4 + (Q_3 + K_1)\lambda^3 + (Q_4 + K_2)\lambda^2 + (Q_5 + K_3)\lambda + Q_6 + K_4\big)e^{-\lambda\omega}} \\
& + \frac{5\lambda^4Q_1 + 4\lambda^3Q_2 + 3\lambda^2(Q_3 + K_1) + 2\lambda(Q_4 + K_2) + Q_5 + K_3}{\lambda\big(Q_1\lambda^5 + Q_2\lambda^4 + (Q_3 + K_1)\lambda^3 + (Q_4 + K_2)\lambda^2 + (Q_5 + K_3)\lambda + Q_6 + K_4\big)} \\
& - \frac{\omega}{\lambda},
\end{aligned}$$

which implies that

$$\begin{aligned}
sgn\Big[\frac{d\Re\lambda}{d\omega}\Big]^{-1}_{\omega=\bar{\omega}} &= sgn\Big[\Re\Big(\frac{d\lambda}{d\omega}\Big)^{-1}\Big]_{\lambda=i\gamma_0} \\
&= sgn\Big[\Re\Big(\frac{6\lambda^5+5\lambda^4P_1+4\lambda^3(P_2+R_1)+3\lambda^2(P_3+R_2)+2\lambda(P_4+R_3)+P_5+R_4}{\lambda\big(Q_1\lambda^5+Q_2\lambda^4+(Q_3+K_1)\lambda^3+(Q_4+K_2)\lambda^2+(Q_5+K_3)\lambda+r_6+k_4\big)e^{-\lambda\omega}} \\
&\quad +\frac{5\lambda^4Q_1+4\lambda^3Q_2+3\lambda^2(Q_3+K_1)+2\lambda(Q_4+K_2)+Q_5+K_3}{\lambda\big(Q_1\lambda^5+Q_2\lambda^4+(Q_3+K_1)\lambda^3+(Q_4+K_2)\lambda^2+(Q_5+K_3)\lambda+Q_6+K_4\big)} \\
&\quad -\frac{\omega}{\lambda}\Big)\Big]_{\lambda=iu} \\
&= sgn\frac{1}{\Gamma}\Big(6u^5+5u^4J_1+4u^3J_2+3u^2J_3+2uJ_4+J_5\Big) \\
&= sgn\frac{1}{\Gamma}\big\{k'(\gamma_0^2)\big\} = sgn\big\{k'(\gamma_0^2)\big\},
\end{aligned}$$

where $\Gamma = \big(Q_1u^5-(Q_3+K_1)u^3+(Q_5+K_3)u\big)^2+\big(r_2u^4-\gamma^2(Q_4+K_2)+Q_6+K_4\big)^2$. Hence, we prove that $k'(\gamma_0^2)\neq 0$, therefore, transversality condition holds as follows.

$$\frac{d(\Re\lambda)}{d\omega}\Big|_{\omega=\bar{\omega}} > 0.$$

The overall results are summarized in the following theorem.
Theorem 4.3 Suppose that H_1 is satisfied.

i. The proposed model is said to be asymptotically stable only if the immune activation delay lies within an interval $\omega \in [0, \bar{\omega})$.

ii. If $\omega = \bar{\omega}$ then the solution of the model experiences Hopf-type bifurcation.

Remark 3.2 *The objective of the paper is to prove the siginifance of immune activation and intracellular time delays in the HBV infection progress. The intracellular delays are less effective when compared to the immune activation time delays, however, if it occurs along with immune activation delays then it has an ability to destabilize the system. The paper numerically validates the possibilities of both immune response and intracellular time delays.*

4 Numerical Simulation

This section comprises the numerical evaluation of the proposed model to show the effectiveness of the proposed model. Firstly, we chose the parameter values as $\lambda = 10, \delta_1 = 0.06, \delta_2 = 0.5, \beta = 0.1, p = 1, c = 0.1, b = 0.2, q = 0.02, \eta = 0.2, h = 0.1, d = 0.004, a = 0.05, r = 0.03, \epsilon = (0, 1), k = 1, u = 1, T_{max} = 1500$. Further we prove that $\bar{E} = (273.8119, 1.0348, 0.2041, 0.2041, 207.95$ is asymptotically stable that is the roots of the characteristic equation (4) are $-1.4827, -0.1380, -0.8478, -0.0$ $0.0151i$,
$-0.0182 + 0.0151i$ for the non-delayed model, which are also depicted in the Figure 2. Further, we assured that the endemic equilibrium $\bar{E}$ is globally asymptotically stable in the case $\tau > 0, \omega = 0$, by satisfying the condition that derivative of a Lyapunov function is non-positive. Figure 3 shows that the solutions of the model are independent for $\tau > 0, \omega = 0$. If

delay crosses the threshold value $\omega > \bar{\omega}$ then the model (1) shows the unstable behavior as shown in Figure 4 and 5. Figures 6 and 7 show the nature of solutions while both the delay occur simultaneously. Figures 8 and 9 depicts the effect of antiviral therapy along with the presence of two delays.

5 Results and Conclusions

In this paper, the generalized HBV infection model has been proposed and analyzed by incorporating cause of immune impairment, logistic growth term, effect of antiviral therapy. The the influence of intracellular and immune activation time delays while modeling the infection process of HBV has been theoretically validated with the help of necessary and sufficient conditions. In addition, the formulated mathematical model considers the fact that the presence of HBV can stimulate with time delay and immune response cells may differentiate into two types of sub-populations called precursors and effectors. Section 3 dealt the positivity and boundedness of cell populations and the derivation of the basic reproduction number.

Subsection 4.2 dealt with the analysis of delayed model (1) that explores the role of intracellular and immune activation delays. In section 6 we have numerically studied the effects of delays and compared them with the derived analytical results. We have listed the contributions for more understanding.

1. For $\tau > 0$ and $\omega = 0$, the global stability of $\bar{E}$ has been proved through Lyapunov stability theory.

2. For $\tau = 0$ and $\omega > 0$, its is clear from the numerical evaluations that the immune activation delay has an ability to destabilize the model once the immune activation time delay exceeds its threshold value. In detail, the roots of the characteristic polynomial explains the nature of cells which is evaluated with the particular dataset values. Section 4.2 demonstrates that increasing the immune activation delay ω will cause the stability switch and lead the model to exhibit the complex behavior. For controlling the viral load, it is recommend that antiretrovirals should helps to activate the CTLs in a timely manner which eliminates the further spread of the disease.

3. Satisfied results in the antiviral therapy may stabilize the equilibrium even in the presence of immune activation ω and intracellular delays τ.

From the Biological perspective, the derived necessary and sufficient conditions have become an evident to prove the importance of involving the cause of immune impairment, immaturation stage and time delays. Therefore, it is concluded that, the developed model contains the more information about the HBV infection progress which provides a new pathway to find the antiretroviral treatments.

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Appendix 1:

$$C_1 = \beta v(\epsilon-1) - r\Big(\frac{l+x+y}{T_{max}} - 1\Big) - \frac{rx}{T_{max}} - \delta_1, C_2 = -\frac{rx}{T_{max}}, C_3 = -\frac{rx}{T_{max}}, C_4 = \beta x(\epsilon-1),$$
$$C_5 = -\beta\eta v(\epsilon-1) C_6 = -a-d, C_7 = -\beta\eta x(\epsilon-1), C_8 = \beta v(\epsilon-1)(\eta-1), C_9 = a,$$
$$C_{10} = -\delta_2 - pz, C_{11} = \beta x(\epsilon-1)(\eta-1), C_{12} = -py, C_{13} = k, C_{14} = -u, C_{15} = -b, C_{16} = -h,$$
$$P_1 = -(C_6 + C_{10} + C_{14} + C_{16} + C_{15} + C_1),$$
$$P_2 = C_1(C_6 + C_{10} + C_{14} + C_{16} + C_{15}) + C_6(C_{10} + C_{14} + C_{16} + C_{15}) + C_{10}(C_{14} + C_{16} + C_{15}) + C_{14}(C_{16} + C_{15}) + C_{16}C_{15} - C_2C_5,$$
$$P_3 = (-C_1C_6 + C_2C_5)(C_{10} + C_{14} + C_{16} + C_{15}) - C_1C_{10}(C_{14} + C_{16} + C_{15}) - C_3C_5C_9 - C_7C_9C_{13} - C_6C_{14}(C_{16} + C_{10} + C_{15}) - (C_1C_{14} + C_6C_{10} + C_{10}C_{14})(C_{16} + C_{15}) - (C_1 + C_6 + C_{10} + C_{14})C_{16}C_{15},$$
$$P_4 = C_1C_7C_9C_{13} + C_1C_6C_{10}C_{14} - C_2C_5C_{10}C_{14} + C_3C_5C_9C_{14} - C_4C_5C_9C_{13} + C_1C_6C_{10}C_{16} - C_2C_5C_{10}C_{16} + C_3C_5C_9C_{16} + C_1C_6C_{10}C_{15} - C_2C_5C_{10}C_{15} + C_3C_5C_9C_{15} + C_1C_6C_{14}C_{16} - C_2C_5C_{14}C_{16} + C_1C_6C_{14}C_{15} - C_2C_5C_{14}C_{15} + C_1C_{10}C_{14}C_{16} + C_1C_{10}C_{14}C_{15} + C_1C_6C_{16}C_{15} - C_2C_5C_{16}C_{15} + C_7C_9C_{13}C_{16} + C_6C_{10}C_{14}C_{16} + C_7C_9C_{13}C_{15} + C_1C_{10}C_{16}C_{15} + C_6C_{10}C_{14}C_{15} + C_1C_{14}C_{16}C_{15} + C_6C_{10}C_{16}C_{15} + C_6C_{14}C_{16}C_{15} + C_{10}C_{14}C_{16}C_{15},$$
$$P_5 = C_2C_5C_{10}C_{14}C_{16} - C_1C_6C_{10}C_{14}C_{16} - C_1C_7C_9C_{13}C_{15} - C_1C_7C_9C_{13}C_{16} - C_3C_5C_9C_{14}C_{16} + C_4C_5C_9C_{13}C_{16} - C_1C_6C_{10}C_{14}C_{15} + C_2C_5C_{10}C_{14}C_{15} - C_3C_5C_9C_{14}C_{15} + C_4C_5C_9C_{13}C_{15} - C_1C_6C_{10}C_{16}C_{15} + C_2C_5C_{10}C_{16}C_{15} - C_3C_5C_9C_{16}C_{15} - C_1C_6C_{14}C_{16}C_{15} + C_2C_5C_{14}C_{16}C_{15} - C_1C_{10}C_{14}C_{16}C_{15} - C_7C_9C_{13}C_{16}C_{15} - C_6C_{10}C_{14}C_{16}C_{15},$$
$$P_6 = C_1C_7C_9C_{13}C_{16}C_{15} + C_1C_6C_{10}C_{14}C_{16}C_{15} - C_2C_5C_{10}C_{14}C_{16}C_{15} + C_3C_5C_9C_{14}C_{16}C_{15} - C_4C_5C_9C_{13}C_{16}C_{15},$$
$$Q_1 = cqy - cy,$$
$$Q_2 = (C_1 + C_6 + C_{10} + C_{14} + C_{16})cy(1-q) - C_{12}cqw,$$
$$Q_3 = C_1C_{12}cqw + C_6C_{12}cqw + C_{12}C_{14}cqw + C_{12}C_{15}cqw - \big(C_1C_6 + C_2C_5 + C_1C_{10} + C_1C_{14} + C_6C_{10} + C_1C_{16} + C_6C_{14} + C_{10}C_{14} + C_6C_{16} + C_{10}C_{16} + C_{14}C_{16}\big)cy(1-q),$$

$$
\begin{aligned}
Q_4 &= -(C_1C_6C_{10} + C_2C_5C_{10} - C_3C_5C_9 - C_1C_6C_{14} + C_2C_5C_{14} - C_1C_{10}C_{14} - C_1C_6C_{16} + C_2C_5C_{16} \\
&\quad + C_7C_9C_{13} + C_1C_{10}C_{16} - C_6C_{10}C_{14} - C_1C_{14}C_{16} - C_6C_{10}C_{16} - C_6C_{14}C_{16} - C_{10}C_{14}C_{16})cy(1-q) \\
&\quad - C_1C_6C_{12}cqw + C_2C_5C_{12}cqw - C_1C_{12}C_{14}cqw - C_6C_{12}C_{14}cqw - C_1C_{12}C_{15}cqw - C_6C_{12}C_{15}cqw \\
&\quad - C_{12}C_{14}C_{15}cqw - C_1C_6C_{16}cqy - C_7C_9C_{13}cqy - C_6C_{10}C_{16}cqy - C_6C_{14}C_{16}cqy - C_{10}C_{14}C_{16}cqy, \\
Q_5 &= \big(C_2C_5C_{10}C_{14} - C_1C_6C_{10}C_{14} - C_1C_7C_9C_{13} - C_3C_5C_9C_{14} + C_4C_5C_9C_{13} - C_1C_6C_{10}C_{16} \\
&\quad + C_2C_5C_{10}C_{16} - C_3C_5C_9C_{16} - C_1C_6C_{14}C_{16} + C_2C_5C_{14}C_{16} - C_1C_{10}C_{14}C_{16} - C_7C_9C_{13}C_{16} \\
&\quad - C_6C_{10}C_{14}C_{16}\big)c(1-q)y + (C_1C_6C_{12}C_{14} - C_2C_5C_{12}C_{14} + C_1C_6C_{12}C_{15} - C_2C_5C_{12}C_{15} \\
&\quad + C_1C_{12}C_{14}C_{15} + C_6C_{12}C_{14}C_{15})cqw, \\
Q_6 &= (C_1C_7C_9C_{13}C_{16} + C_1C_6C_{10}C_{14}C_{16} - C_2C_5C_{10}C_{14}C_{16} + C_3C_5C_9C_{14}C_{16} \\
&\quad - C_4C_5C_9C_{13}C_{16})c(1-q)y + (-C_1C_6C_{12}C_{14}C_{15} + C_2C_5C_{12}C_{14}C_{15})cqw, \\
R_1 &= -C_3C_8 - C_{11}C_{13}, \\
R_2 &= (C_6 + C_{14} + C_{16} + C_{15})C_3C_8 + (C_1 + C_6 + C_{16} + C_{15})C_{11}C_{13} - C_4C_8C_{13} \\
R_3 &= \big(C_2C_5 - C_1C_6 - C_1C_{16} - C_1C_{15} - C_6C_{16} - C_6C_{15} - C_{16}C_{15}\big)C_{11}C_{13} \\
&\quad + (-C_6C_{14} - C_6C_{16} - C_6C_{15} - C_{14}C_{16} - C_{14}C_{15} - C_{16}C_{15})C_3C_8 \\
&\quad + (-C_2C_7 + C_4C_6 + C_4C_{16} + C_4C_{15})C_8C_{13}, \\
R_4 &= (C_2C_7C_8 + C_1C_6C_{11} - C_2C_5C_{11} - C_4C_6C_8 + C_1C_{11}C_{15} - C_4C_8C_{15} + C_6C_{11}C_{15})C_{13}C_{16} \\
&\quad + (C_6C_{14}C_{16} + C_6C_{14}C_{15} + C_6C_{16}C_{15} + C_{14}C_{16}C_{15})C_3C_8 \\
&\quad + (C_1C_6C_{11} - C_2C_5C_{11} - C_4C_6C_8 + C_2C_7C_8)C_{13}C_{15}, \\
R_5 &= \big((-C_2C_7C_8 - C_1C_6C_{11} + C_4C_6C_8 + C_2C_5C_{11})C_{13} - C_3C_6C_8C_{14}\big)C_{16}C_{15},
\end{aligned}
$$

$$
\begin{aligned}
K_1 &= (C_3C_8 + C_{11}C_{13})c(1-q)y, \\
K_2 &= -\big((C_6 + C_{14} + C_{16})C_3C_8 - C_4C_8C_{13} + (C_6 + C_{16} + C_1)C_{11}C_{13}\big)cy(1-q), \\
K_3 &= \big(C_2C_7C_8C_{13} + C_1C_6C_{11}C_{13} - C_2C_5C_{11}C_{13} + C_3C_6C_8C_{14} - C_4C_6C_8C_{13} + C_3C_6C_8C_{16} \\
&\quad + C_1C_{11}C_{13}C_{16} + C_3C_8C_{14}C_{16} - C_4C_8C_{13}C_{16} + C_6C_{11}C_{13}C_{16}\big)c(1-q)y, \\
K_4 &= \big(- C_2C_7C_8C_{13}C_{16} - C_1C_6C_{11}C_{13}C_{16} + C_2C_5C_{11}C_{13}C_{16} - C_3C_6C_8C_{14}C_{16} \\
&\quad + C_4C_6C_8C_{13}C_{16}\big)cy(1-q).
\end{aligned}
$$

Table 1: Parameter definitions and estimations used in this manuscript

Parameter	Notes	Estimated	Unit
Λ	Source of uninfected hepatocytes	10	$\mu l^{-1} day^{-1}]$
β	Rate of infection	$10^{-5} - 0.5$	$\mu l^{-1} day^{-1}$
r	Logistic Growth term	0.03	day^{-1}
δ_1	Mortality rate of uninfected hepatocytes	0.07	day^{-1}
ϵ	Antiviral Therapy	[0,1]	
T	Total carrying capacity	1500	$\mu l^{-1} day^{-1}$
η	Fraction of latent infections	0.05	$\mu l^{-1} day^{-1}$
d	Death rate of latently infected cells	0.004	day^{-1}
a	Transition rate of infected cells become infectious	0.1	day^{-1}
δ_2	Infected cells died out naturally	0.5–1.4	day^{-1}
p	Immune-induced clearance rate of Infected cells	1	$\mu l^{-1} day^{-1}$
u	Death rate of free virions	23	day^{-1}
c	Average Rate of CTLs proliferation	0.001–1	$\mu l^{-1} day^{-1}$
b	Mortality rate or Precursors due to life-cycle	0.05–0.15	day^{-1}
h	Mortality rate or Effectors due to life-cycle	0.05–0.15	day^{-1}
$x(0)$	Uninfected hepatocytes	1	μl^{-1}
$l(0)$	Latently infected hepatocytes	5	μl^{-1}
$y(0)$	Infected hepatocytes	3	μl^{-1}
$v(0)$	Free virions	1	μl^{-1}
$w(0)$	Precursors	2	μl^{-1}
$z(0)$	Effectors	4	μl^{-1}

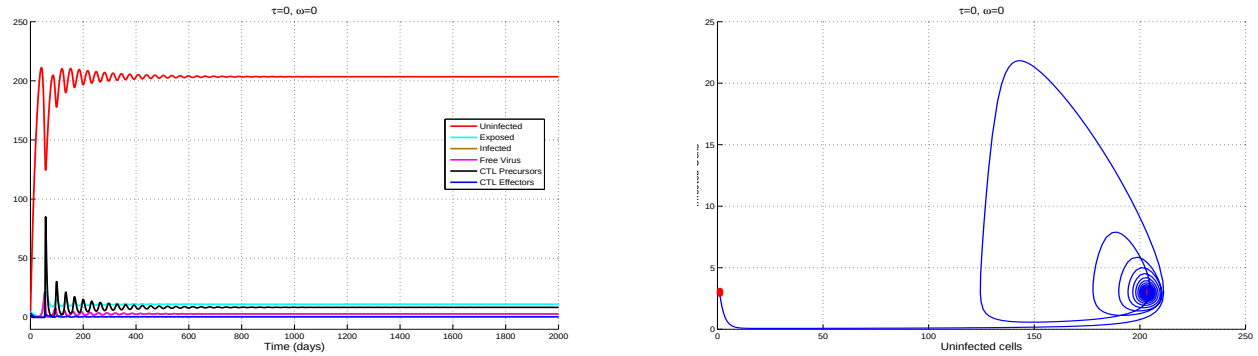

Figure 2: The solutions of the model (1) with $\omega = 0, \tau = 0$. It show the asymptotic stability of the endemic equilibrium.

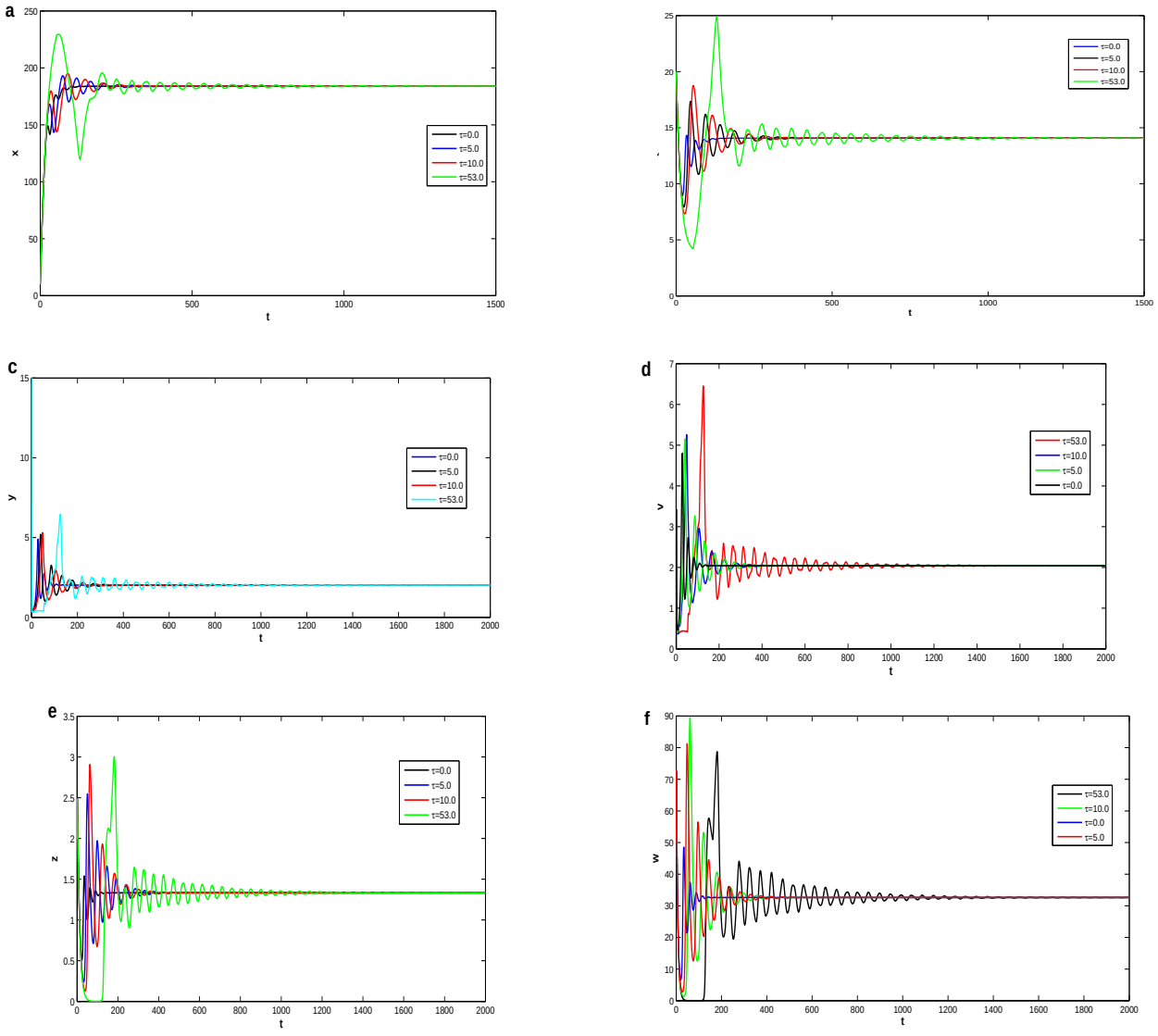

Figure 3: (a)-(f) show the solutions of model (1) for different values of τ : $(\tau = 0, \tau = 5, \tau = 10, \tau = 53)$ when $\omega = 0$ and effect of antiviral therapy is considered to be $\epsilon = 0.9$. It show the stability of the endemic equilibrium where there is no delay in the immune response.

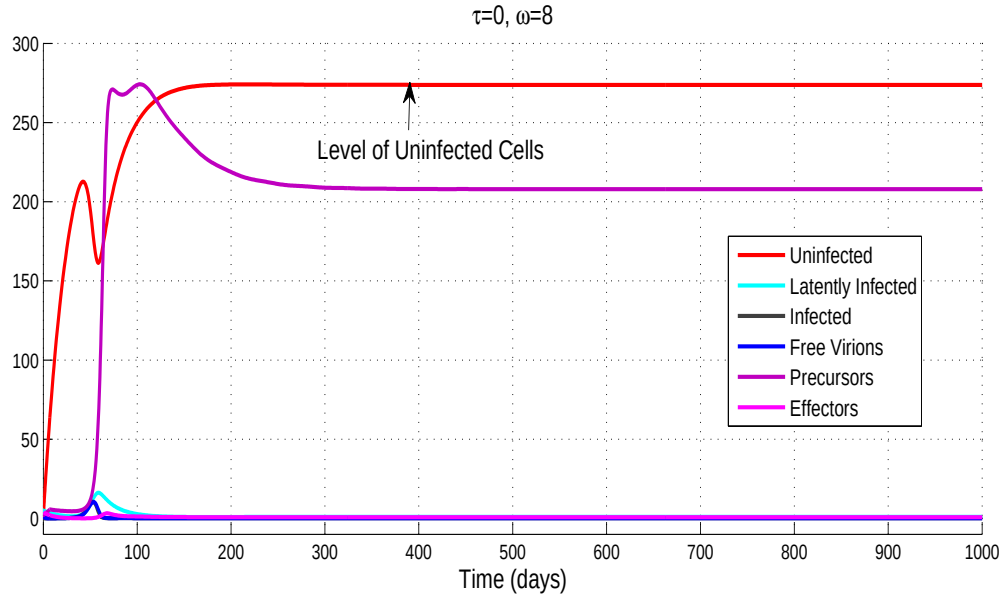

Figure 4: Equilibrium $\bar{E}$ of the model (1) is asymptotically stable when the effect of immune activation time delay is less than its critical value $\bar{\omega}$, that is $\omega = 8 < 8.5224$ and $\tau = 0$.

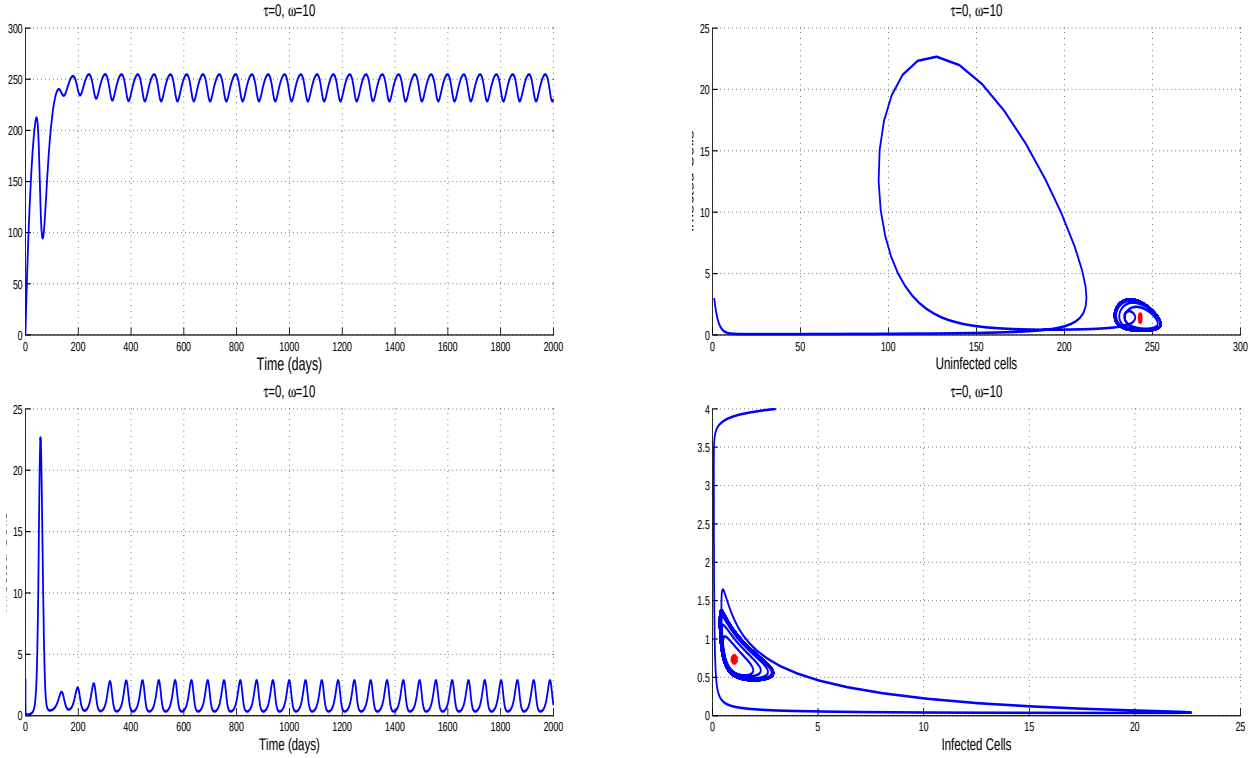

Figure 5: Equilibrium $\bar{E}$ of the model (1) is periodically oscillatory behavior when immune activation time delay exceeds the critical value $\bar{\omega}$, that is $\omega = 10 > 8.5224$ and $\tau = 0$.

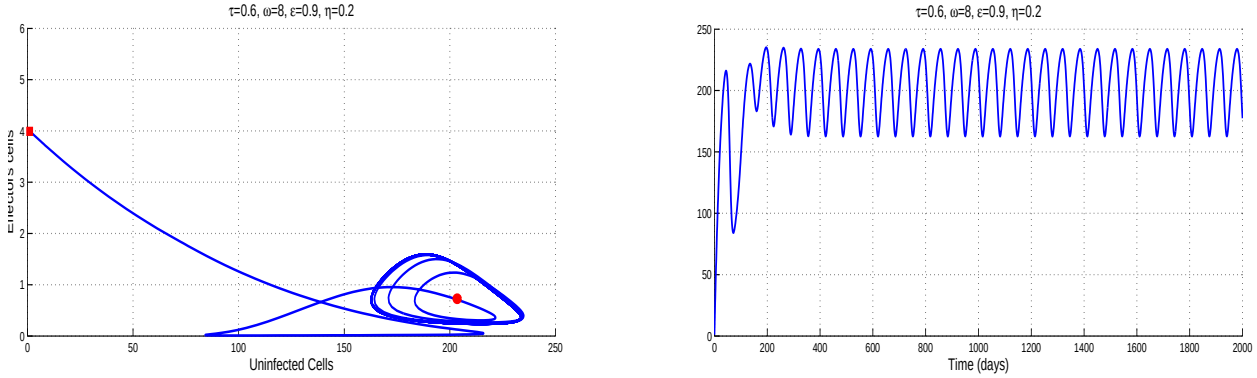

Figure 6: The solutions of the model (1) with $\omega = 8 < 8.5224$ and $\tau = 0.6$, show that existence of intracellular delay disturbs the asymptotic stability of the endemic equilibrium $\bar{E}$. Even though immune activation time delay is less than its critical value $\bar{\omega}$, and the effect of antiviral treatment is considered as $\epsilon = 0.1$.

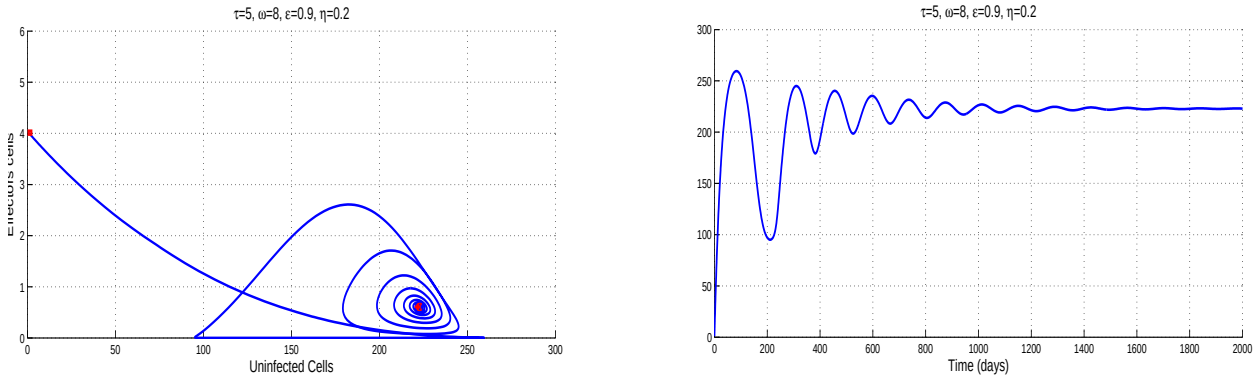

Figure 7: The solutions of the model (1) shows that increasing the $\tau = 5$ with $\omega = 8.9$ results in the asymptotic stability of the endemic equilibria $\bar{E}$ and the effect of antiviral treatment is considered as $\epsilon = 0.1$.

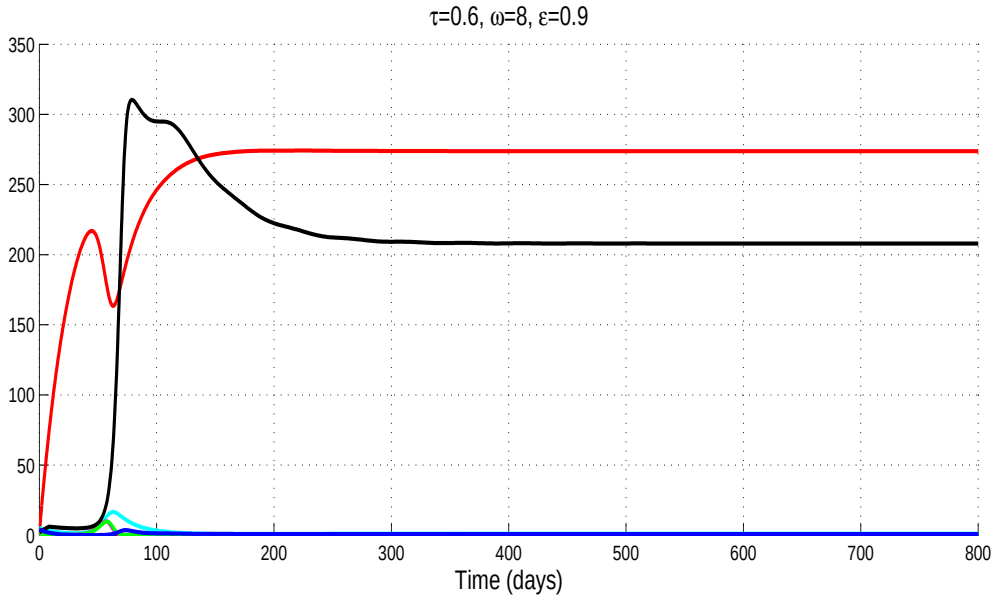

Figure 8: If the antiviral treatment results in satisfactory that is $\epsilon = 0.9$ then the solutions of the model (1) show the asymptotic stability of the endemic equilibria for $\tau = 0.6$ and $\omega = 8$. It indicates that level of uninfected cells is to be increased by suitable antiviral therapy.

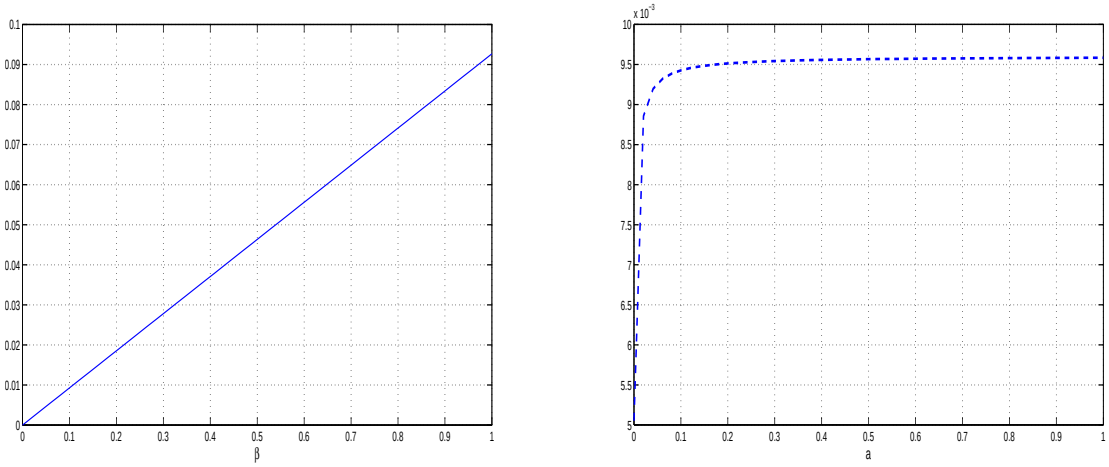

Figure 9: Relation between the reproduction number R_0 and the parameters β, a.