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Stability and Hopf Bifurcation Analysis of Hepatitis B Infection Model with CTL Response Delay

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Abstract: In this paper, the Hepatitis B Virus (HBV) infectious model with Cytotoxic T-Lymphocyte (CTL) response delay and its effect on the stability of equilibrium has been investigated. The boundedness and non-negativity solutions of the proposed model were verified. The local stability of virus-free equilibrium and the infected equilibrium were determined by the basic reproduction number R_0. Further, the existence of Hopf bifurcation at the infected equilibrium of CTL response was also observed. Using different set of parameters, the empirical findings in the study are shown with numerical simulations.

Key words: Bifurcation, CTL, delay, HBV, mathematical modeling, stability

1. INTRODUCTION

Hepatitis B virus (HBV) infection has been a global issue which causes the death of approximately two billion people every year. In Asia, almost 400 million people were critically affected by HBV causing severe health issues. Therefore, it is high time find out a medicine to prevent as well as to cure this disease. Having the basic knowledge on immune pathogenesis of HBV would help us to find out an effective way to prevent and give a treatment to this infection. Generally, molecular techniques provide the basic and minute details about the interaction of immune system and HBV, but it does not answer the question biologically [1]. Therefore, mathematical models could answer those questions effectively by explaining the experimental outcomes. Not only it provides experimental outcomes but also supports to understand the fundamental mechanism of the spread of disease. Nowak et al. [2] and Zeuzem et al. [3] proposed a virus infectious model which has been used in several studies without adding immune responses.

Recent studies show the enhanced formation of virus-specific Cytotoxic T-Lymphocytes (CTL) which was demonstrated through the use of HBV pathogenesis animal models. Hepatocellular carcinoma generally affects those who have liver related diseases [4, 5]. Though the models delineate the relationship between the host and virus immune response explaining the acute hepatitis mechanism [6-8], these models do not describe the HBV infection outcomes [9]. The prime function of CTL is not only killing the virus but also

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curing infected hepatocytes through the mechanism of nonlytic effector [10, 11]. CTL play a major part in protecting antiviral through invading infected cells in most virus infections [12]. There has been a substantial concern to population dynamics in viral pathogens with CTL, and several properties have been studied [13-15]. Some researchers suggest that the time delay in the immune response models can never be disregarded. [16, 17, 18, 19].

$$\begin{cases} \dfrac{dx(t)}{dt} = \Lambda - \alpha x(t) - \varphi x(t)v(t), \\ \dfrac{dy(t)}{dt} = \varphi x(t)v(t) - \gamma y(t), \\ \dfrac{dv(t)}{dt} = \delta y(t) - \sigma v(t) - \rho v(t)z(t), \\ \dfrac{dz(t)}{dt} = \mu v(t)z(t) - \omega z(t). \end{cases} \tag{1.1}$$

In our proposed work, the immune response of target cells has been considered including a time delay of the immune response (1.1) to obtain the following model:

$$\begin{cases} \dfrac{dx(t)}{dt} = \Lambda - \alpha x(t) - \varphi x(t)v(t), \\ \dfrac{dy(t)}{dt} = \varphi x(t)v(t) - \gamma y(t), \\ \dfrac{dv(t)}{dt} = \delta y(t) - \sigma v(t) - \rho v(t)z(t), \\ \dfrac{dz(t)}{dt} = \mu v(t-t^*)z(t-t^*) - \omega z(t-t^*). \end{cases} \tag{1.2}$$

In this model, t^* represents the time delay which is considered as the time between antigenic stimulation and the production of CTL cells. The model is taken from the work of Uttam Ghosh et al. [20] in which the fourth compartment is added with a time delay of CTL cells. This model is interrelated with liver cells (uninfected and infected) and the virus, and the immune response of CTL cells is obtained by the mathematical model. Here, $x(t)$ denotes the target uninfected cells (uninfected hepatocytes), $y(t)$ denotes the infected cells (infected hepatocytes), $v(t)$ denotes the HBV virus, and $z(t)$ denotes immune response of CTL cells. This model represents the target cells infecting at the rate φ. Infection happens because of the relation with target cells and virus. Initially, this target cells produce hepatocytes at the rate Λ and the natural death rate is α. The infected cells die at a rate of γ. These infected cells are killed by the immune response of CTL cell at a rate of σ. The decay rate is ρ. CTL cells can maximize immune response to viral antigen. Here the CT proliferate rate is μ and the viral load is δ death rate of CTL cells ω. The immune responses of CTL cells have the effective power to kill the infected cells [21]. These assumptions lead the following model:

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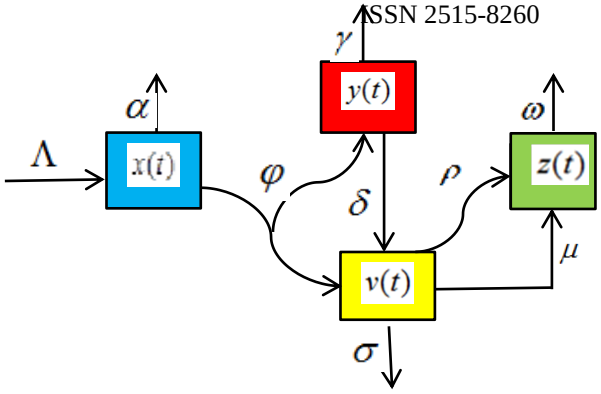

Fig.1. *Compartmental Diagram for the System (Model 1.2)*

1. *Boundedness and Non-Negativity*

The initial conditions for model 1.2 are

$$\begin{cases} x(\theta)=\eta_1(\theta), y(\theta)=\eta_2(\theta), v(\theta)=\eta_3(\theta), z(\theta)=\eta_4(\theta), \\ \eta_i(\theta)\geq 0, \theta\in[-t^*,0], i=1,2,3,4. \end{cases}$$

(2.1)

Here, $\left(\eta_1(\theta),\eta_2(\theta),\ldots\in\left(Q[-t^*,0],R_+\right)\right)$, the Banach space continuous functions mapping the interval $[-t^*,0]$ into R_+^4.

Lemma 2.1. Let $(x(t),y(t),v(t),z(t))$ of (1.2) satisfying conditions (2.1), we have $\limsup_{t\to+\infty} x(t)\leq\frac{\Lambda}{\alpha}$.

Proof. Suppose $t_1>0$ such that $x(t_1)>\frac{\Lambda}{\alpha}$ and $\dot{x}(t_1)>0$, then we have

$$\dot{x}(t_1)=\Lambda-\alpha x(t_1)-\varphi x(t_1)v(t_1)\leq-\varphi x(t)v(t)\leq 0.$$

Here, we used $x(t_1)>\frac{\Lambda}{\alpha}$ which is a contradiction to $\dot{x}(t_1)>0$. Therefore, Lemma 2.1 has been proven.

Theorem 2.1. Let $(x(t),y(t),v(t),z(t))$ be the solution of (1.2) satisfying conditions (2.1). Then $x(t)$, $y(t)$, $v(t)$, and $z(t)$ are positive ; $K>0$ such that $x(t)<K$, $y(t)<K$, $v(t)<K$, and $z(t)<K$ hold after sufficiently large time t.

Proof. From Model1.2, we have

$$x(t)=x(0)e^{-\int_0^t(\alpha+\varphi v(\phi))d\phi}+\int_0^t\Lambda e^{-\int_\tau^t(\alpha+\varphi v(\phi))d\phi}d\tau,$$

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$$y(t) = y(0)e^{-\gamma t} + \int_0^t \varphi x(\tau) v(\tau) e^{-\gamma(t-\tau)} d\tau,$$

$$v(t) = v(0)e^{-\int_0^t (\sigma+\rho z(\phi))d\phi} + \int_0^t \delta y(\tau) e^{-\int_\tau^t (\sigma+\rho z(\phi))d\phi} d\tau,$$

$$z(t) = z(0)e^{-\omega t} + \int_0^t \mu x(\tau - t^*) z(\tau - t^*) e^{\omega t} d\tau.$$

From Model 1.2, we can say that $x(t)$ is positive on the particular interval. Next, we will prove that $y(t)$ is positive. In fact, let $t_1 > 0$ be the first time such that $y(t_1) = 0$.

Also, we get $v(t_1) = v(0)e^{-\int_0^{t_1} (\sigma+\rho z(\phi))d\phi} + \int_0^{t_1} \delta y(\tau) e^{-\int_\tau^{t_1} (\sigma+\rho z(\phi))d\phi} d\tau > 0$ and $\dot{y}(t_1) = \varphi x(t_1) v(t_1) > 0$.

This implies that $y(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$. As ε is an arbitrary small positive constant, this is a contradiction. Therefore, $y(t) > 0$ and $v(t) > 0$. Similarly, we can prove that $z(t)$ is also positive on the existence interval.

Next, we check the boundedness of 1.2.

Let $T(t) = \left[x(t) + y(t) + \frac{\gamma}{2\delta} v(t) + \frac{\rho\alpha}{c\Lambda} z(t + t^*) \right]$,

And let $b = \min\left\{ \alpha, \frac{\gamma}{2}, \sigma, \omega \right\}$. By Lemma 2.1 and the above discussion,

$$\frac{d}{dt}\left[T(t)\right] = \Lambda - \alpha x(t) - \frac{\gamma}{2} y(t) - \frac{\gamma\sigma}{2\delta} v(t) - \rho v(t) z(t) + \frac{\rho\alpha}{\Lambda} v(t) z(t) - \frac{\rho\omega\alpha}{\mu\Lambda}$$

$$\leq \Lambda - \alpha x(t) - \frac{\gamma}{2} y(t) - \frac{\gamma\sigma}{2\delta} v(t) - \frac{\rho\omega\alpha}{\mu\Lambda} z(t + t^*)$$

$$< \Lambda - b\left[x(t) + y(t) + \frac{\gamma}{2\delta} v(t) + \frac{\rho\alpha}{c\Lambda} z(t + t^*) \right] = \Lambda - bT.$$

So, $T \frac{\Lambda}{\alpha} + \varepsilon$ for all large t. Thus, $x(t)$, $y(t)$, $v(t)$, and $z(t)$ are bounded by some positive constant K.

Hence, theorem 2.1 has been proven.

2. *Stability Analysis*

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The basic reproductive number for (1.2) is $R_0 = \frac{\Lambda\varphi\delta}{\gamma\alpha\sigma}$.

Also, we can find the below three equilibria.

Infection-free equilibrium: $A_0 = \left(\frac{\Lambda}{\alpha}, 0, 0, 0\right)$,

CTL-absent infection equilibrium: $A_1 = \left(\frac{\gamma\sigma}{\delta\varphi}, \frac{\Lambda}{\gamma} - \frac{\alpha\sigma}{\delta\varphi}, \frac{\Lambda\delta}{\gamma\sigma} - \frac{\alpha}{\varphi}, 0\right)$,

CTL-present infection equilibrium: $\bar{A} = \left(\frac{\Lambda\mu}{\alpha\mu+\varphi\omega}, \frac{\varphi\omega\Lambda}{\gamma(\alpha\mu+\varphi\omega)}, \frac{\varphi\omega}{\mu}, \frac{\delta\varphi\Lambda\mu}{\gamma\rho(\alpha\mu+\varphi\omega)}\right)$.

The infection-free equilibrium corresponds to maximal levels of healthy CD_4^+T cells. The equilibrium A_1 corresponds to positive levels of healthy CD_4^+T cells, but there is no immune response. The equilibrium corresponds to positive levels of CD_4^+T cells, infected cells, virus and immune response.

3.1 Stability of Infection-Free Equilibrium A_0

For discussing the local asymptotic stability of the infection-free equilibrium A_0, the corresponding linearized equation (1.2) at A_0 is

$$\begin{cases} \frac{dx(t)}{dt} = -\alpha x(t) - \frac{\varphi\Lambda}{\alpha} v(t), \\ \frac{dy(t)}{dt} = \frac{\varphi\Lambda}{\alpha} v(t) - \gamma y(t), \\ \frac{dv(t)}{dt} = \delta y(t) - \sigma v(t), \\ \frac{dz(t)}{dt} = -\omega z(t). \end{cases}$$

(3.1)

The characteristic equation of the above equation is,

$$(\lambda+\omega)(\lambda+\alpha)\left[\lambda^2 + (\gamma+\sigma)\lambda + \gamma\sigma - \frac{\Lambda\varphi\delta}{\alpha}\right] = 0.$$

(3.2)

Solving this characteristic equation we get,

$$\lambda_1 = -\omega, \lambda_2 = -\alpha \text{ and } \lambda_{3,4} = \frac{-(\gamma+\sigma) \pm \sqrt{(\gamma+\sigma)^2 - 4\left(\gamma\sigma - \frac{\Lambda\varphi\delta}{\alpha}\right)}}{2}.$$

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Clearly, all the roots are negative.

Theorem 3.1.

i. If $R_0 < 1$, then the infection-free equilibrium A_0 is locally asymptotically stable;

ii. If $R_0 > 1$, then the infection-free equilibrium A_0 is unstable.
Definitely, when $R_0 < 1$, the global asymptotic stability of A_0 can be obtained by constructing a Lyapunov functional.

Theorem 3.2. The infection-free equilibrium A_0 is globally asymptotically stable if $R_0 < 1$.

*Proof***.** Let us define a Lyapunov functional:

$$L = \frac{1}{2}\left[x(t) - \frac{\Lambda}{\alpha} \right]^2 + \frac{\Lambda}{\alpha} y(t) + pv(t) + \frac{\rho}{\mu} z(t) + \rho \int_{t-t^*}^{t} x(\eta) y(\eta) z(\eta) d\eta,$$

Here, p is a non-negative constant that will be chosen later. In order to calculate the time derivative of L along with the solution of (1.2), we get

$$L' = \left[x(t) - \frac{\Lambda}{\alpha} \right] \left[-\alpha \left(x(t) - \frac{\Lambda}{\alpha} \right) - \varphi x(t) v(t) \right] + \frac{\Lambda}{\alpha} \left[\varphi x(t) v(t) - \gamma y(t) \right]$$

$$+ p\left[\delta y(t) - \sigma v(t) - \rho v(t) z(t) \right] - \frac{\rho \omega}{\mu} z(t) + \rho x(t) y(t) z(t).$$

By applying $\varphi x(t) v(t) = \varphi v(t) \left[x(t) - \frac{\Lambda}{\alpha} \right] + \frac{\varphi \Lambda}{\alpha} v(t)$,

$$L' = -\alpha \left[x(t) - \frac{\Lambda}{\alpha} \right] - \varphi v(t) \left[x(t) - \frac{\Lambda}{\alpha} \right]^2 + \rho y(t) z(t) \left[x(t) - \frac{\Lambda}{\alpha} \right] - \left(\frac{\Lambda \gamma}{\alpha} - \delta p \right) y(t)$$

$$\left(\sigma p - \frac{\varphi \Lambda^2}{\alpha^2} \right) v(t) - \frac{\rho \omega}{\mu} z(t). \text{ can be obtained.}$$

As $R_0 < 1$which reduces to $\frac{\Lambda \gamma}{\delta \alpha} - \frac{\varphi \Lambda^2}{\sigma \alpha^2} > 0$, there is a non-negative constant p $\left(p \in \frac{\varphi \Lambda^2}{\sigma \alpha^2}, \frac{\Lambda \gamma}{\delta \alpha} \right)$, such that $\frac{\Lambda \gamma}{\alpha} - \delta p > 0$ and $\sigma p - \frac{\varphi \Lambda^2}{\alpha^2} > 0$. Assuming $x(t)$, $y(t)$, $v(t)$, $z(t)$ are non-negative and $x(t) \le \frac{\Lambda}{\alpha}$ holds, $L' \le 0$ and $L' = 0$ if and only if $\left(x(t), y(t), v(t), z(t) \right) = \left(\frac{\Lambda}{\alpha}, 0, 0, 0 \right)$.

Then, the global asymptotic stability of A_0 follows from the Lyapunov -LaSalle type theorem [22, 23].

3.2 Stability of CTL-Absent Equilibrium A_1

Let $A_1=(\tilde{x},\tilde{y},\tilde{v},0)=\left(\frac{\gamma\sigma}{\delta\varphi},\frac{\Lambda}{\gamma}-\frac{\alpha\sigma}{\delta\varphi},\frac{\Lambda\delta}{\gamma\sigma}-\frac{\alpha}{\varphi},0\right)$, the linearized equations of (1.2) at A_1 is

$$\begin{cases}\dfrac{dx(t)}{dt}=-(\alpha+\varphi\tilde{v})x(t)-\varphi\tilde{x}v(t),\\ \dfrac{dy(t)}{dt}=\varphi\tilde{v}x(t)-\gamma y(t)+\varphi\tilde{x}v(t),\\ \dfrac{dv(t)}{dt}=\delta y(t)-\sigma v(t)-\rho\tilde{v}z(t),\\ \dfrac{dz(t)}{dt}=\mu\tilde{v}z(t-t^*)-\omega z(t).\end{cases}$$

(3.3)

Now, the transcendental characteristic equation is

$$\left(\lambda-\mu\bar{v}e^{-\lambda t^*}+\omega\right)\left(\lambda^3+e_1\lambda^2+e_2\lambda+e_3\right)=0,$$

Here, $e_1=\gamma+\sigma+\frac{\varphi\Lambda\delta}{\gamma\sigma}$, $e_2=2\gamma\sigma+(\gamma+\sigma)\left(\frac{\Lambda\delta\varphi}{\gamma\sigma}\right)$, $e_3=4(\Lambda\delta\varphi-\alpha\gamma\sigma)$.

The $\lambda^3+e_1\lambda^2+e_2\lambda+e_3=0$ can be considered.

(3.4)

Clearly, if $R_0>1$, we have $e_1=\gamma+\sigma+\frac{\varphi\Lambda\delta}{\gamma\sigma}>0$ and $e_3=4(\Lambda\delta\varphi-\alpha\gamma\sigma)>0$; also

$$e_1e_2-e_3=2\gamma\sigma(\sigma+\gamma)+\Lambda\alpha\varphi\left(\frac{1}{\sigma}+\frac{\sigma}{\gamma}\right)+\frac{\Lambda^2\varphi^2\delta^2}{\gamma\sigma}\left(\frac{1}{\sigma}+\frac{1}{\gamma}\right)-\alpha\gamma\sigma>0.$$

Using Routh-Hurwitz criteria, the roots of eq. 3.4 are negative.

Next, we analyze the transcendental equation $\lambda-\mu\bar{v}e^{-\lambda t^*}+\omega=0$.

(3.5)

For $t^*=0$, $\lambda=\frac{\Lambda\varphi\mu\delta-\alpha\gamma\sigma\mu-\omega\gamma\sigma\varphi}{\gamma\sigma\varphi}$. Obviously, if $R_0<1+\frac{\alpha\gamma\sigma\mu}{\omega\gamma\sigma\varphi}$, then $\beta<0$, which implies that eq.(3.5) has negative roots for $t^*=0$. Let the purely imaginary roots of (3.5) be $\lambda=\pm\beta i$ for $\beta>0$ and $t^*>0$. From 3.5,

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$$\begin{cases} \beta = -\dfrac{\Lambda\varphi\mu\delta - \omega\gamma\sigma\varphi}{\gamma\sigma\varphi}\sin\beta t, \\ c = \dfrac{\Lambda\varphi\mu\delta - \omega\gamma\sigma\varphi}{\gamma\sigma\varphi}\cos\beta t. \end{cases}$$

(3.6)

$\Rightarrow \beta^2 = \left[\dfrac{\Lambda\varphi\mu\delta - \omega\gamma\sigma\varphi}{\gamma\sigma\varphi}\right]^2 - c^2$. can be obtained.

Noting that if $1 < R_0 < 1 + \dfrac{\alpha\gamma\sigma\mu}{\omega\gamma\sigma\varphi}$, then $\beta^2 < 0$.

Theorem 3.3

i. If $1 < R_0 < 1 + \dfrac{\alpha\gamma\sigma\mu}{\omega\gamma\sigma\varphi}$,, then the CTL-absent infection equilibrium A_1 is locally asymptotically stable;

ii. If $R_0 > 1 + \dfrac{\alpha\gamma\sigma\mu}{\omega\gamma\sigma\varphi}$, then the CTL-absent infection equilibrium A_1 is unstable.

3.3 Stability and Hopf Bifurcation at the CTL-Present Equilibrium $\bar{A}$

The bifurcation parameter is the CTL-response delay t^* and this shows that when the delay t^* passes through a critical value, the CTL-present equilibrium $\bar{A}$ loses its linear stability and a Hopf bifurcation occurs. Let $\bar{A} = (\hat{x}, \hat{y}, \hat{v}, \hat{z}) = \left(\dfrac{\Lambda\mu}{\alpha\mu + \varphi\omega}, \dfrac{\varphi\omega\Lambda}{\gamma(\alpha\mu + \varphi\omega)}, \dfrac{\varphi\omega}{\mu}, \dfrac{\delta\varphi\Lambda\mu}{\gamma\rho(\alpha\mu + \varphi\omega)}\right)$ and $x'(t) = x(t) - \hat{x},\ y'(t) = y(t) - \hat{y},\ v'(t) = v(t) - \hat{v},\ z'(t) = z(t) - \hat{z}$. Instead of using $x'(t), y'(t), v'(t), z'(t)$, we use $x(t), y(t), v(t), z(t)$ for simplification. The linearized equations of (1.2) at $\bar{A}$ is

$$\begin{cases} \dfrac{dx(t)}{dt} = -(\alpha + \varphi\hat{v})x(t) - \varphi x(t)v(t) - \varphi\hat{x}v(t), \\ \dfrac{dy(t)}{dt} = \varphi x(t)v(t) + \varphi\hat{v}x(t) - \gamma y(t) + \varphi\hat{x}v(t), \\ \dfrac{dv(t)}{dt} = \delta y(t) - \sigma v(t) - \rho\hat{v}z(t) - \rho\hat{z}v(t) - \rho v(t)z(t), \\ \dfrac{dz(t)}{dt} = \mu v(t - t^*)z(t - t^*) + \mu\hat{v}z(t - t^*) + \mu z\hat{v}(t - t^*) - \omega z(t). \end{cases}$$

(3.7)

The linearized equation at the origin is

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$$\begin{cases} \dfrac{dx(t)}{dt} = -\left(\alpha + \varphi\hat{v}\right)x(t) - \varphi\hat{x}v(t), \\ \dfrac{dy(t)}{dt} = \varphi\hat{v}x(t) - \gamma y(t) + \varphi\hat{x}v(t), \\ \dfrac{dv(t)}{dt} = \delta y(t) - \sigma v(t) - \rho\hat{v}z(t) - \rho\hat{z}v(t), \\ \dfrac{dz(t)}{dt} = \mu\hat{v}z(t-t^*) + \mu\hat{z}v(t-t^*) - \omega z(t). \end{cases}$$

(3.8)

By the theoretical meaning of delay differential equations, if the trivial solution of Equation 3.8 is asymptotically stable, the Equation 3.7 is also the same.

$$C(\lambda) = \lambda^4 + E_1\lambda^3 + E_2\lambda^2 + E_3\lambda + E_4 - \left(F_1\lambda^3 + F_2\lambda^2 + F_3\lambda + F_4\right)e^{-\lambda t^*},$$

(3.9)

The real parts of the roots of Equation 3.9 gives the stability of the trivial solution.

Here, $E_1 = \gamma + \alpha + \sigma + \left(\gamma + \sigma\right)\alpha + \varphi\hat{v},$

$$E_2 = \gamma\sigma + \left(\gamma + \sigma\right)\varphi\hat{v} + \left(\gamma + \sigma\right)\omega + \omega\alpha + \left(\gamma + \sigma\right)\omega\alpha + \omega\varphi\hat{v},$$

$$E_3 = \alpha\sigma\gamma + \delta\varphi\mu\hat{x}\hat{v} + \omega\gamma\sigma + \left(\gamma + \sigma\right)\varphi\omega\hat{v},$$

$$E_4 = \gamma\sigma + \alpha\delta\mu\varphi\hat{x}\hat{v} + \omega\alpha\gamma\sigma + \omega\gamma\sigma,$$

$$F_1 = \mu\hat{v},$$

$$F_2 = \mu\rho\hat{z}\hat{v} + \delta\varphi\hat{x} + \mu\left(\gamma + \sigma\right)\hat{v} + \mu\alpha\hat{v} + \mu\alpha\left(\gamma + \sigma\right)\hat{v} + \mu\varphi\hat{v}^2,$$

$$F_3 = \mu\gamma\rho\hat{z}\hat{v} + \mu\alpha\rho\hat{z}\hat{v} + \mu\varphi\rho\hat{z}\hat{v}^2 + \alpha\delta\varphi\hat{x} + \mu\gamma\sigma\hat{v} + \mu\varphi\left(\gamma + \sigma\right)\hat{v}^2 + \varphi\delta\omega\hat{x},$$

$$F_4 = \mu\alpha\gamma\rho\hat{z}\hat{v} + \mu\rho\gamma\varphi\hat{z}\hat{v}^2 + \mu\alpha\gamma\sigma\hat{v} + \mu\gamma\sigma\hat{v} + \omega\alpha\delta\varphi\hat{x}.$$

Theorem 3.4. The trivial solution of system (3.8) is asymptotically stable, if $R_0 > 1 + \dfrac{\alpha\gamma\sigma\mu}{\omega\gamma\sigma\varphi}$, when $t^* = 0$.

Proof. When $t^* = 0$

$$(3.9) \Rightarrow \lambda^4 + \left(E_1 - F_1\right)\lambda^3 + \left(E_2 - F_2\right)\lambda^2 + \left(E_3 - F_3\right)\lambda + E_4 - F_4 = 0.$$

(3.10)

As $R_0 > 1 + \dfrac{\alpha\gamma\sigma\mu}{\omega\gamma\sigma\varphi}$, $\hat{x} > 0, \hat{y} > 0, \hat{v} > 0, \hat{z} > 0.$

Using Routh-Hurwitz criteria, we have $H_1 = E_1 - F_1 = \gamma + \alpha + \sigma + \left(\gamma + \sigma\right)\alpha + \left(\varphi - \mu\right)\hat{v} > 0,$

$$H_2=\left(E_1-F_1\right)\left(E_2-F_2\right)-\left(E_3-F_3\right)=\left(\gamma+\alpha+\sigma+\left(\gamma+\sigma\right)\alpha+\left(\varphi-\mu\right)\hat{v}\right)\times$$
$$\left(\gamma\sigma+\left(\gamma+\sigma\right)\varphi\hat{v}+\left(\gamma+\sigma\right)\omega+\omega\alpha+\left(\gamma+\sigma\right)\omega\alpha+\omega\varphi\hat{v}-\mu\rho\hat{z}\hat{v}-\delta\varphi\hat{x}-\mu\left(\gamma+\sigma\right)\hat{v}-\mu\alpha\hat{v}-\mu\alpha\left(\gamma+\sigma\right)\hat{v}-\mu\varphi\hat{v}^2\right)$$
$$-\left(\alpha\sigma\gamma+\delta\varphi\mu\hat{x}\hat{v}+\omega\gamma\sigma+\left(\gamma+\sigma\right)\varphi\omega\hat{v}-\mu\gamma\rho\hat{z}\hat{v}-\mu\alpha\rho\hat{z}\hat{v}-\mu\varphi\rho\hat{z}\hat{v}^2-\alpha\delta\varphi\hat{x}-\mu\gamma\sigma\hat{v}-\mu\varphi\left(\gamma+\sigma\right)\hat{v}^2-\varphi\delta\omega\hat{x}\right)>0.$$

$$H_3=\begin{vmatrix}E_1-F_1 & E_3-F_3 & 0\\ 1 & E_2-F_2 & E_4-F_4\\ 0 & E_1-F_1 & E_3-F_3\end{vmatrix}$$
$$=\left(E_1-F_1\right)\left[\left(E_2-F_2\right)\left(E_3-F_3\right)-\left(E_1-F_1\right)\left(E_4-F_4\right)\right]-\left(E_3-F_3\right)^2.$$

Obviously, $H_3>0$.

$$H_4=\begin{vmatrix}E_1-F_1 & E_3-F_3 & 0 & 0\\ 1 & E_2-F_2 & E_4-F_4 & 0\\ 0 & E_1-F_1 & E_3-F_3 & 0\\ 0 & 1 & E_2-F_2 & E_4-F_4\end{vmatrix}=e_4H_3.$$

Where, $e_4=\gamma\alpha\sigma\rho\hat{z}$ also $H_4>0$. Thus, Equation 3.10 has negative real parts. Hence, Theorem 3.4 has been proven.

When $t^*=0$, $C\left(\lambda\right)$ has negative real parts, then there exists a $t_0>0$ for $t^*\in\left[0,t_0\right)$. The roots of equation 3.9 should satisfy $C\left(\lambda\right)=0$, $\quad \mathrm{Re}\left(\lambda\right)<0, \quad$ for $t^*\in\left[0,t_0\right)$,
(3.11)

Suppose $t^*=t_0$, $\mathrm{Re}\left(\lambda\right)=0$. When solving for equation 3.9, we find t_0 and the corresponding imaginary roots $\beta_0 i\left(\beta_0>0\right)$.

$$(3.9)\Rightarrow \beta_0^4-E_1\beta_0^3 i-E_2\beta_0^2+E_3\beta_0 i+E_4-\left(-F_1\beta_0^3 i-F_2\beta_0^2+F_3\beta_0 i+F_4\right)\left(\cos\beta_0 t_0-i\sin\beta_0 t_0\right)=0.$$
(3.12)

Separating the real and imaginary parts, we get

$$\begin{cases}\left(F_4-F_2\beta_0^2\right)\cos\beta_0 t_0+\left(F_3\beta_0-F_1\beta_0^3\right)\sin\beta_0 t_0=\beta_0^4-E_2\beta_0^2+E_4,\\ \left(F_1\beta_0^3-F_3\beta_0\right)\cos\beta_0 t_0+\left(F_4-F_2\beta_0^2\right)\sin\beta_0 t_0=E_1\beta_0^3-E_3\beta_0.\end{cases}$$

(3.13)

$$\Rightarrow\cos\beta_0 t_0=\frac{1}{\Delta}\begin{vmatrix}\beta_0^4-E_2\beta_0^2+E_4 & F_3\beta_0-F_1\beta_0^3\\ F_1\beta_0^3-F_3\beta_0 & F_4-F_2\beta_0^2\end{vmatrix}$$

$$=\frac{1}{\Delta}\left[\left(E_1F_1-F_2\right)\beta_0^6+\left(F_4+E_2F_2-E_1F_3-E_3F_1\right)\beta_0^4+\left(E_3F_3-E_2F_4-E_4F_2\right)\beta_0^2+E_4F_4\right]$$

$$= \frac{1}{\Delta}\left(a_1\beta_0^6 + a_2\beta_0^4 + a_3\beta_0^2 + a_4\right).$$

$$\sin\beta_0 t_0 = \frac{1}{\Delta}\begin{vmatrix} F_4 - F_2\beta_0^2 & \beta_0^4 - E_2\beta_0^2 + E_4 \\ F_1\beta_0^3 - F_3\beta_0 & E_1\beta_0^3 - E_3\beta_0 \end{vmatrix}$$

$$= -\frac{\beta_0}{\Delta}\left[F_1\beta_0^6 + \left(E_1F_2 - F_3 - E_2F_1\right)\beta_0^4 + \left(E_2F_3 + E_4F_1 - E_3F_2 - E_1F_4\right)\beta_0^2 + E_3F_4 - E_4F_3\right]$$

$$= -\frac{\beta_0}{\Delta}\left(b_1\beta_0^6 + b_2\beta_0^4 + b_3\beta_0^2 + b_4\right).$$

$$\text{Here, } \Delta = \begin{vmatrix} F_4 - F_2\beta_0^2 & F_3\beta_0 - F_1\beta_0^3 \\ F_1\beta_0^3 - F_3\beta_0 & F_4 - F_2\beta_0^2 \end{vmatrix}$$

$$= \left(F_4 - F_2\beta_0^2\right)^2 + \left(F_3\beta_0 - F_1\beta_0^3\right)^2 = F_1\beta_0^6 + \left(F_2 - 2F_1F_3\right)\beta_0^4 + \left(F_3^2 - 2F_2F_4\right)\beta_0^2 + F_4^2$$

$$= \left(c_1\beta_0^6 + c_2\beta_0^4 + c_3\beta_0^2 + c_4\right) > 0.$$

But, $\sin^2\beta_0 t_0 + \cos^2\beta_0 t_0 = 1$. Therefore,

$$\beta_0^{14} + d_1\beta_0^{12} + d_2\beta_0^{12} + d_3\beta_0^8 + d_4\beta_0^6 + d_5\beta_0^4 + d_6\beta_0^2 + d_7 = 0,$$

(3.14)

$$\text{Here, } d_1 = \frac{1}{b_1^2}\left(a_1^2 + 2b_1b_2 - c_1^2\right),$$

$$d_2 = \frac{1}{b_1^2}\left(2a_1a_2 + b_2^2 + 2b_1b_3 - 2c_1c_3\right),$$

$$d_3 = \frac{1}{b_1^2}\left(a_2^2 + 2a_1a_3 + 2b_1b_4 + 2b_2b_4 - c_2^2 - 2c_1c_3\right),$$

$$d_4 = \frac{1}{b_1^2}\left(2a_1a_4 + 2a_2a_3 + b_3^2 + 2b_2b_4 - 2c_1c_4 - 2c_2c_3\right),$$

$$d_5 = \frac{1}{b_1^2}\left(a_3^2 + 2a_2a_4 + 2b_3b_4 - c_3^2 - 2c_2c_4\right),$$

$$d_6 = \frac{1}{b_1^2}\left(2a_3a_4 + b_4^2 - 2c_3c_4\right),$$

$$d_7 = \frac{1}{b_1^2}\left(a_4^2 - c_4^2\right).$$

Let $r = \beta_0^2$ and substitute this in equation 3.14,

$r^7 + d_1 r^6 + d_2 r^5 + d_3 r^4 + d_4 r^3 + d_5 r^2 + d_6 r + d_7 = 0$ can be obtained.

(3.15)

Using computational software, the roots of equation 3.15) can be calculated.

If $F_4 \neq 0$, then $r = 0$ is not a root. Suppose equation 3.15 has only a negative real root, then t^* does not exist, because $\beta_0 = \sqrt{r}$ does not exist. Therefore, the Hopf bifurcation is not occurring. For that, H_1: we assume one of the roots is having positive real part.

H_2:

$\Omega \square \left[4\beta_0^6 + 3\left(E_1^2 - 2E_2 - F_1^2\right)\beta_0^4 + 2\left(E_2^2 - F_2^2 + 2E_4 + 2F_1F_3 - 2E_1E_3\right)\beta_0^2 + E_3^2 - F_3^2 + 2F_2F_4 - 2E_2E_4 \right] > 0$

for any $\beta_0 > 0$. Let r_0 be the only positive root and $\beta_0 = \sqrt{r_0}$ we get,

$$t_i = \frac{1}{\beta_0}\left(\arccos \frac{a_1\beta_0^6 + a_2\beta_0^4 + a_3\beta_0^2 + a_4}{c_1\beta_0^6 + c_2\beta_0^4 + c_3\beta_0^2 + c_4} + 2i\pi \right), \qquad i = 0,1,2,...,$$

$$t_0 = \frac{1}{\beta_0} \arccos \frac{a_1\beta_0^6 + a_2\beta_0^4 + a_3\beta_0^2 + a_4}{c_1\beta_0^6 + c_2\beta_0^4 + c_3\beta_0^2 + c_4}, \qquad i = 0.$$

We investigate the nature of the roots of equation 3.9 near t_0 on (β_0, t_0). The implicit differentiation of $C(\lambda)$ with respect to t^*, we get

$$\left[\frac{d\lambda}{dt^*}\right]^{-1} = \frac{-\left(4\lambda^3 + 3E_1\lambda^2 + 2E_2\lambda + E_3\right)e^{\lambda t^*}}{\lambda\left(F_1\lambda^3 + F_2\lambda^2 + F_3\lambda + F_4\right)} + \frac{3F_1\lambda^2 + 2F_2\lambda + F_3}{\lambda\left(F_1\lambda^3 + F_2\lambda^2 + F_3\lambda + F_4\right)} - \frac{t^*}{\lambda}.$$

(3.16)

$$\mathrm{Re}\left[\frac{d\lambda}{dt^*}\right]^{-1} = \frac{1}{\beta_0\nabla}\left\{\begin{array}{l} \left(3E_1\beta_0^2 - E_3\right)\left[\left(F_1\beta_0^3 - F_3\beta_0\right)\cos\beta_0 t^* + \left(F_4 - F_4\beta_0^2\right)\sin\beta_0 t^*\right] \\ + \left(4\beta_0^3 - 2E_2\beta_0\right)\left[\left(F_4 - F_2\beta_0^2\right)\cos\beta_0 t^* - \left(F_1\beta_0^3 - F_3\beta_0\right)\sin\beta_0 t^*\right] \\ + \left(F_3 - 3F_1\beta_0^2\right)\left(F_1\beta_0^3 - F_3\beta_0\right) + 2F_2\beta_0\left(F_4 - F_2\beta_0^2\right) \end{array}\right\}$$

$$= \frac{1}{\nabla}\left[\begin{array}{l} 4\beta_0^6 + 3\left(E_1^2 - 2E_2 - F_1^2\right)\beta_0^4 + 2\left(E_2^2 - F_2^2 + 2E_4 + 2F_1F_3 - 2E_1E_3\right)\beta_0^2 \\ + E_3^2 - F_3^2 + 2F_2F_4 - 2E_2E_4 \end{array}\right].$$

(3.17)

Here, $\nabla = \left(F_1\beta_0^3 - F_3\beta_0\right)^2 + \left(F_4 - F2\beta_0^2\right)^2 > 0.$ If equation $(3.17) > 0$ for $\beta_0 > 0$, then H_2 is satisfied. Therefore,

$$\text{sign}\left\{\mathrm{Re}\left[\frac{d\lambda}{dt^*}\right]_{t^*=t_0}\right\} = \text{sign}\left\{\mathrm{Re}\left[\frac{d\lambda}{dt^*}\right]^{-1}_{t^*=t_0}\right\} \square \text{sign}(.) = 1.$$

So, if the delay $t*$ near t_0 is increased, the root of equation 3.10 has negative real parts. When $t^* = t_0$, there exists a pair of purely imaginary roots for $C(\lambda) = 0$, and other roots have negative real parts. From the above analysis, we have the following

*Theorem 3. 5***.** For system 3.7, when the conditions H_1, H_2 hold,

i. If $t^* \in [0, t_0)$, then the CTL-present equilibrium $\bar{A}$ is locally asymptotically stable;
ii. If $t^* > t_0$, then the CTL-present equilibrium $\bar{P}$ is unstable and system 1.2 undergoes a Hopf bifurcation at $\bar{A}$ when $t^* = t_0$.

Table 1: *Parameter Values*

Parameter	**Description**	**Values**
Λ	Production of uninfected cells	1.0 mm^{-3}/day
φ	Transmission rate of virus	0.9 mm^{-3}
α	Death rate of uninfected cells	2 per day
γ	Death rate of infected cells	5 per day
δ	Virus rate	0.1 mm^{-3}/day
σ	Virus clearance rate	0.1 mm^{-3}/day
ρ	Decay rate of virus by immune system	0.024 mm^{-3}/day
μ	CTL proliferate rate	0.1 mm^{-1}/day
ω	Death rate of CTL cells	0.2 per day

3. NUMERICAL SIMULATION

We use Matlab to perform numerical illustrations in order to ascertain the main results. The parameter values are considered in Table 1. Based on the values of the given parameters, the infected equilibrium is $\bar{A} = (0.026, 0.0165, 1.8, 0.0344)$, the basic reproduction ratio $R_0 = 0.9$, and the critical value $t_0 = 0.012$. Also, if we increase the value of Λ, R_0 value will be increased. By Theorem 3.4, the infected equilibrium $\bar{A}$ is stable when $t^* < t_0$ [Fig.2] $t^* = t_0$ Hopf bifurcation occurs and the equilibrium becomes unstable. If $t^* > t_0$ [Fig.3].

4. CONCLUSION

In this article, we present a model for CTL response delay of an HBV infection. The stability of virus-free equilibrium A_0 and infected equilibrium A_1 were investigated. The existence of Hopf bifurcation was demonstrated and ascertained by numerical representations when the delay was used as the bifurcation parameter. This helped to indicate that the existence of periodic solutions occurs in the system when the delay crosses the critical value. Based on the numerical findings, it is apparent that HBV infection can easily be regulated.

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Availability of Data and Materials

Data sharing not applicable to this data sets were generated or analyzed during the current study.

Competing Interests

The authors declare that there is no conflict of interest.

Authors' Contributions

The authors contributed equally to the writing of this paper. They read and approved the final manuscript.

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5. REFERENCES

[1] Changjiang Long, Huan and Sheng-Hu Huang, "Mathematical Modeling of Cytotoxic Lymphocyte-Mediated Immune Response to Hepatitis B Virus Infection," *Journal of Biomedicine and Biotecnolog*y, Article ID 743690, 9 pages (2008)

[2] M. A. Nowak, S. Bonhoeffer, M. A. Hill, R. Boehme, C. H. Thomas, H. McDade, "Viral dynamics in hepatitis B virus infection*," Proc. Natl. Acad. Sci*. USA **93**, 4398–4402, (1996)

[3] S. Zeuzem, M. J. Schmidt, H. J. Lee, et al., "Effect of inferferomalt on the dynamics of hepatitis C virus turnover in vivo*," J. Hepatol*. **23**, 366–371, (1996)

[4] S. M. Ciupe, R. M. Ribeiro, P. W. Nelson, G. Dusheiko, and A. S. Perelson, "The role of cells refractory to productive infection in acute hepatitis B viral dynamics," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 12, pp. 5050–5055, (2007)

[5] B. Xuli and D. Zhongping, "Advance in viral dynamics of hepatitis B virus infection," *Foreign Medical Science (Section of Virology)*, vol. 11, no. 2, pp. 36–40, (2004)

[6] S. M. Ciupe, R. M. Ribeiro, P. W. Nelson, and A. S. Perelson, "Modeling the mechanisms of acute hepatitis B virus infection," *Journal of Theoretical Biology*, vol. 247, no. 1, pp. 23–35, (2007)

[7] A. S. Perelson, E. Herrmann, F. Micol, and S. Zeuzem, "New kinetic models for the hepatitis C virus," H*epatology*, vol. 42, no. 4, pp. 749–754, (2005)

[8] H. Dahari, M. Major, X. Zhang, et al., "Mathematical modeling of primary hepatitis C infection: noncytolytic clearance and early blockage of virion production," *Gastroenterology*, vol. 128, no. 4, pp. 1056–1066, (2005)

[9] Y. Ilan, "Immune down regulation leads to up regulation of an antiviral response: a lesson from the hepatitis B virus," *Microbes and Infection*, vol. 4, no. 13, pp. 1317–1326, (2002)

[10] A. Bertoletti, M. Maini, and R. Williams, "Role of hepatitis B virus specific cytotoxic T cells in liver damage and viral control," *Antiviral Research*, vol. 60, no. 2, pp. 61–66, (2003)

[11] L. G. Guidotti, "Pathogenesis of viral hepatitis," *Biological Regulators and Homeostatic Agents*, vol. 17, no. 2, pp. 115–119, (2003)

[12] M. A. Nowak, C. R. Bangham, "Population dynamics of immune responses to Persistent viruses," *Appl. Math. Model.* vol. 272, pp. 74–79, (1996)

[13] D. Wodarz, D. C. Krakauer, Defining CTL-induced pathology: Implications for HIV, *Virology*, vol. 274, pp. 94–104, (2000)

[14] Z. Hu, J Zhang, H. Wang, W. Ma, F. Liao, "Dynamics analysis of a delayed viral infection Model with logistic growth and immune impairment," *Applied Mathematical Modelling*,Vol. 38, Issue 2, pp. 524-534, (2014)

[15] A.A. Canabarro, I.M. Gleria, *et al., "*Periodic solutions and chaos in a non-linear model for the delayed cellular immune response," *Physica A*, vol. 342, pp. 234 – 241, (2004)

[16] Y. Wang, Y. Zhou, J. Wu, J. Heffernan, "Oscillatory viral dynamics in a delayed HIV Pathogenesis model," *Math. Biosci*., vol. 219, pp. 104–112, (2009)

[17] S. Wang, X. Song, and Z. Ge, "Dynamics analysis of a delayed viral infection model with Immune impairment," *Applied Mathematical Modelling*, vol. 35, no. 10, pp. 4877–4885, (2011)

[18] N. Bairagi, D. Adak, "Global analysis of HIV-1 dynamics with Hill type infection rate and Intracellular delay," Applied Mathematical Modelling, vol. 38(21), pp. 5047–5066, (2014)

[19] H. Song, W. Jiang, S. Liu, "Virus dynamics model with intracellular delays and immune Response," *Math. Biosci. Eng*., vol. 12, pp. 185–208, (2015)

[20] Zahura Khatun, Md. Shahidul Islam, Uttam Ghosh, " Mathematical Modeling of Hepatitis B Virus Infection Incorporating Immune Responses", Sensors International, vol. 1, (2020)

[21] M. Aniji, N. Kavitha, S. Balamuralitharan," Mathematical modeling of hepatitis B virus infection for antiviral therapy using LHAM". *Adv Differ Equ* 2020, 408 (2020)

[22] Y. Kuang, "Delay Differential Equations with Applicatios in Pupulation Dynamics", *Academic Press*, San Diego, (1993)

[23] M. Aniji, N. Kavitha, S. Balamuralitharan," Approximate solutions for HBV infection with stability analysis using LHAM during antiviral therapy", *Bound Value Probl* 2020, 80 (2020)

Appendices

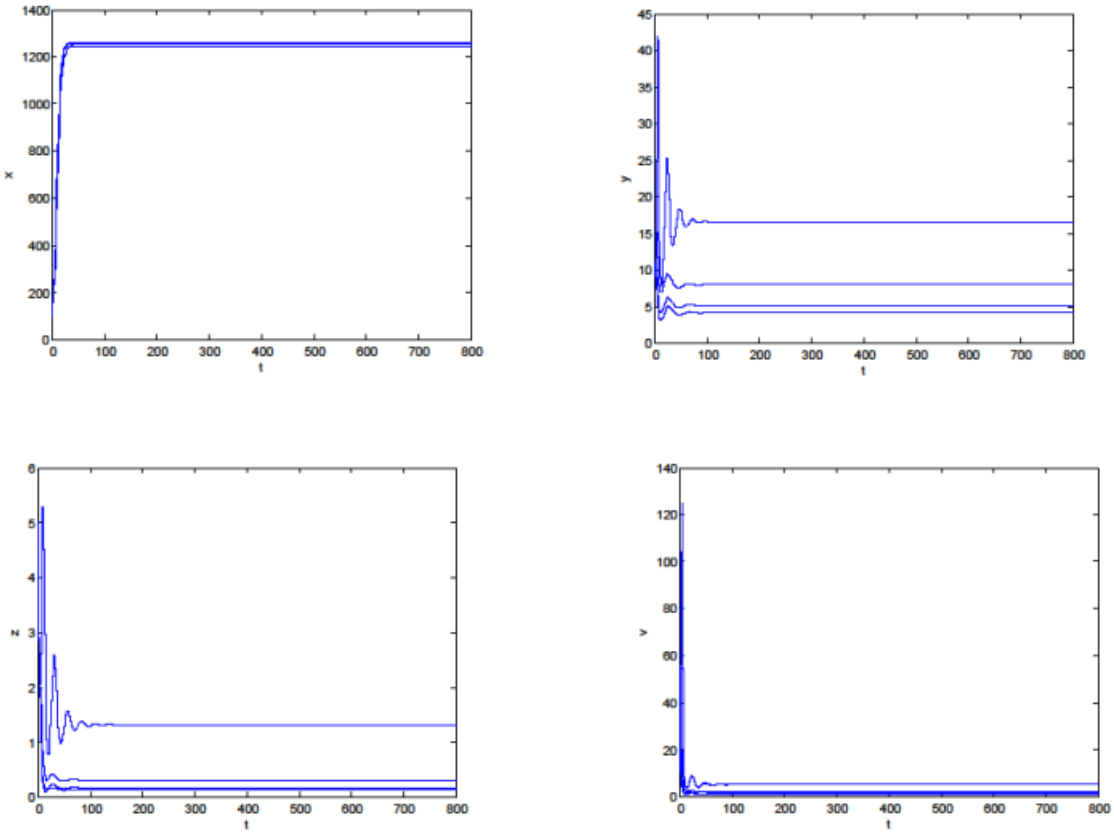

Fig. 2. Shows when $t^* = 1.2$; the system (1.2) is stable with the initial conditions.

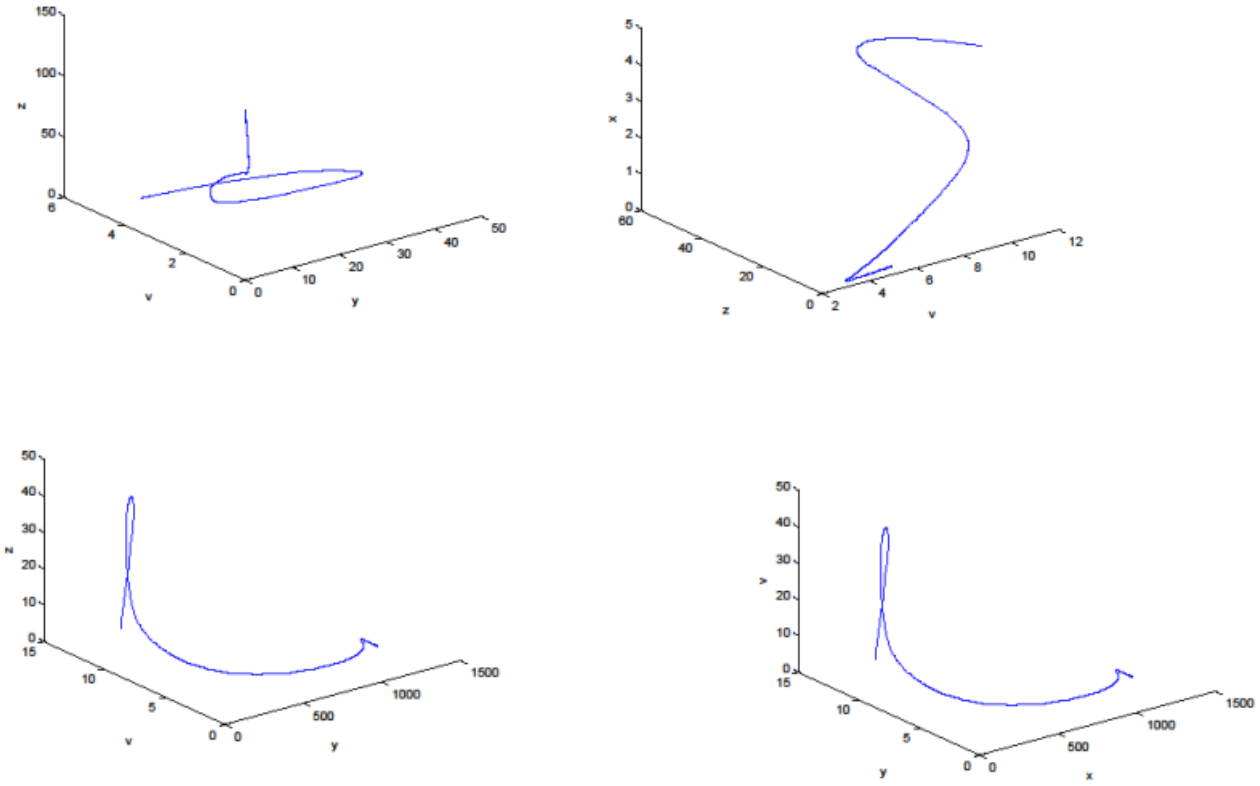

Fig. 3. Shows when $t^* > 2$; the phase diagrams after Hopf bifurcation occurs.