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A Dynamic Intraccelular Differential Equation Model For The Treatment Of Hepatitis B Virus (Hbv) Infection

*Titus Ifeanyi Chinebu[1],RemigiusOkekeAja[2],Godwin C.E. Mbah[3]
[1](Department of Computer Science, Madonna University Nigeria, Elele)
[2](Department of Mathematics, Michael Okpara University of Agriculture Umudike, Abia State, Nigeria)
[3](Department of Mathematics,University Of Nigeria, Nsukka)*

ABSTRACT: *Hepatitis B Virus infects the liver cells thereby causing hepatitis B virus infection and is a major global health problem. We developed a simplified non linear ordinary differential equation model of HBV infection which focuses on the control of the infection through treatment of the infected cells. We performed sensitivity analysis on the parameters of the model and demonstrated that there are three stages in the control of HBV infection using treatment for the infected cells. This includes the lag time corresponding to the finite time taken for the treatment to locate the site of action. At the site of action, the treatment interacts with the virus and once there is success in turning immune response, the infected patient will eliminate the infection.*

Keywords: *Hepatitis B virus, Immune system, Immune Response, Treatment, Lag time and Hepatocyte.*

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I. INTRODUCTION

Hepatitis B virus is a hepadnavirus (from hepa = liver, dna = DNA) (Kidd-lyunggren et al, 2006; Glebe and Bremer, 2013). The virus particle, (virion) consist of an outer lipid envelop and an icosahedral necleocapsid core composed of protein. The nucleocapsid encloses the viral DNA and a DNA polymerase that has reverse transcriptase activity (National Institute of Health (NIH), 2010). The outer envelope contains embedded proteins which are involved in viral binding of and entry into, susceptible cells. The virus is one of the smallest enveloped animal viruses, with a virion diameter of 42nm, but pleomorphic forms exist, including filamentous and spherical bodies lacking a core. These particles are not infectious and are composed of lipid and protein that forms part of the surface of the virion, which is called the surface antigen (HBsAg), and is produced in excess during the life cycle of the virus (Trepo and Guillevin, 2001). According to Pan and Zhang, (2005), isolating the DNA sequence of HBV shows the existence of 8 viral genotypes A – H and these varies in geographical distribution.

An individual can develop hepatitis B virus infection that is acute and achieve complete immune clearance of virus yielding lifelong immunity; however, an alternate fate of the host is the development of chronic hepatitis B. There are two phases of hepatitis B virus infection based on viral – host interaction, namely, the immune tolerant phase and the immune clearance (reactive) phase. After acute infection of HBV, some patients may remain HBeAg positive (a serological marker of viral replication) with high levels of serum HBV DNA (high viral replication rate), little or no symptoms, normal alanine aminotransferase (ALT) levels and minimal histological activity in the liver. This phenomenon is known as the immune tolerant phase and there is little or no inflammation or fibrosis of the liver (Pita et al, 2014).This phase is typical of infection in children and young adults. It usually lasts for 2 – 4 weeks, but can last for years in those that acquired the infection during the perinatal period (Merican et al, 2000; Pita et al, 2014). Individuals in this group are highly contagious and can transmit HBV easily. When the tolerogenic effect is lost during the immunetolerant phase, immune – mediated lysis (destruction of cells through the damage of cell contents) of infected hepatocytes become active and patients enter the second phase defined as immune clearance (reactive) phase. In this phase, the host immune system starts mounting a response against HBV, HBV DNA level decreases, ALT level increases and there is moderate to severe necro inflammatory activity in the liver (pita et al, 2014). The age of the patient at the time of infection determines whether the virus will be cleared and the infection cured during this phase. The immune clearance (reactive) phase ends with the loss of HBeAg and seroconversion to anti HBe status. The loss of HBeAg and seroconversion to anti HBe is usually associated with viral suppression by the host immune system (European association for the study of liver (EASL), 2012). Two disease states, not necessarily static, are possible after seroclearance of HBeAg and they are inactive carrier (IC) state and chronic hepatitis B (CHB) state (Pita et al, 2014). The duration of clearance (reactive) phase last from months to years. In the inactive carrier (IC) state, seroconversion of hepatitis B e antigen (HBeAg) to hepatitis B e antibody (HBeAb) occurs, HBV DNA becomes non detectable or at low level and ALT is usually normal, reflecting very low or no replication of HBV and mild or no hepatic injury (EASL, 2012). The inactive carrier state may last for years or

even lifetime. Patients in this state can have spontaneous resolution of hepatitis B and develop HBsAg, but a portion of them may undergo spontaneous or immunosupression – induced reactivation of chronic hepatitis B. This bring in the second state which is chronic hepatitis B and is usually associated with elevated ALT, high level of DNA, moderate to severe liver histological activity, and with or without HBeAg seroconversion (Pan and Zhang, 2005). Differentiating between inactive carrier (IC) and chronic hepatitis B (CHB) status is very important in clinical practice, because it has an implication in the follow-up, management and prognosis (EASL, 2012).

An additional phase, the recovery phase (Lok and Heath cote, 2001) was proposed during two research workshops on management of chronic hepatitis B in 2000 and 2006 by the National Institutes of Health (NIH) (Mcmahon, 2009). About 0.5% and 0.8% of chronically infected individuals clear HBsAg per year (Mcmahon, 2009; Chu and Liaw, 2007; Liaw et al, 1991) and those that were predicted for the clearance of HBsAg and sustains presence of the inactive hepatitis state are the older age (Mcmahon et al, 2001, and Chu and Liaw, 2007). The clinical outcome after clearance of HBsAg is generally better than in persons who continue to be HBsAg positive as liver inflammation and fibrosis improve over time (Ahn et al, 2003 and Yuen et al, 2004).

Acute hepatitis B infection does not usually require treatment because about 95% of most adults clear the infection spontaneously (Shapiro, 1993 and Lok et al, 2015). Early antiviral treatment may only be required in fewer than one percent of patients, whose infection are of great severity (fulminant hepatitis) or who are immunocompromised. In patients with fulminant infection, intravenous (IV) feeding may be needed, if the patient has persistent vomiting and can't take oral foods. Ninety percent of patients with acute HBV infection have a favorable course and recover completely (Jayapal, 2007).

On the other hand, treatment of chronic HBV infection may be necessary to reduce the risk of cirrhosis and liver cancer. Chronically infected individuals with persistently elevated serum alamine aminotranferase, a marker of liver damage and HBV DNA level are candidates for therapy (Shi et al, 2011). Thirty to forty percent of patients with chronic hepatitis B respond to $IFN\alpha$ treatment.

Immune defense is partially active in chronic hepatitis B patients, since the viral load and HBsAg level are lower (Kosinska et al 2013). Undertaken in various experimental systems is antigen expressing DNA in combination with antiviral therapy or immunotherapy with various HBV derived antigens and example is the work of Michael Roggendorf in infected woodchuck with partial success (Kosinska et al 2013). Hepadnaviral cccNDA silencing or destruction would be the best therapy for control of HBV infection but it is still a science fiction (Gerlich, 2013). The current therapy (GS – 9620) for HBV infection suppresses viral replication and delay progression of liver damage. This GS – 9620 which works by targeting the virus represents the first conceptually new treatment for hepatitis B virus in more than a decade (Texas Biomedical Research Institute, 2013). Other antiviral medicine includes, Lemivudine (Epivir) and the newer neucleotide analogues famciclovir, lobucavir and adefovir (Hepsera), dipivoxil, tenofovir (viread), tesbivudine (Tyzeka), entecavir (Baraclute) (Lok et al, 2015) and they directly block or suppress or destroy the HBV by interfering with its replication (Gerlich, 2013; WHO, 2015). These agents are highly effective and well tolerated. $IFN\alpha$ and lamivudine have been approved by FDA for the treating chronic hepatitis B.

II. RELATED WORKS

Kimbir et al (2014), extended the model of Zou et al (2009) and used it to study the transmission dynamics of HBV infection considering vaccination and treatment as control measure in the host population. They showed from the numerical simulation of their model that effective vaccination and treatment is a good control strategy for HBV infection. But a combination of vaccination and treatment is a better control strategy for the disease. In the recovery of HBV infection, each component of innate and adaptive immune response contributes, but in the absence of one component of innate immunity, the remaining two defense mechanisms are sufficient for viral clearance (Dontwi et al, 2010).

Momoh et al (2012) confirmed that much progress have been made in understanding the transmission dynamics of HBV infection but maintained that more effort is needed if we want to conquer the infection. Obaid and Elaiw (2014) proposed and analyzed two virus infection models with antibody immune response and chronically infected cells. It is not reachable in practice to vaccinate newborns by a rate greater than 96%. Therefore, treatment or additional vaccination strategies are needed to control the spread of HBV infection in population (Moneim and Khalil, 2015). Certainly, controlling HBV infection simply indicates reducing the susceptible by vaccination or reducing the latent and infected by treatment scheme.

In the current study, we provide a detailed analytical study of a mathematical model of the interaction between infective virus, hepatocytes and CTL, which incorporates treatment of the infected hepatocyte.

III. THE MODEL

3.1: The assumptions of the model are`

1. The chronic carrier are treated at the rate k, acute infections are not subjected to treatment because of relapse and resistance (WHO, 2001; Pang et al 2010).
2. The treated individual's hepatocytes recover (Ahmed et al, 1987; Oleary et al, 2008).
3. The eradication of CCCDNA from the vast majority of virally infected cells as well as sustained immune control of HBV replication in a small number of residual HBV – infected cells helps to control the infection.(Chang et al, 2014).
4. Part of the infected hepatocytes recovers through immune response (spontaneous recovery) even before the commencement of treatment (Zou et al, 2010; Kar and Jana 2013).

We proposed a model to understand the effect of detection and control of HBV on the transmission dynamics of the disease. The model is represented with the diagram below.

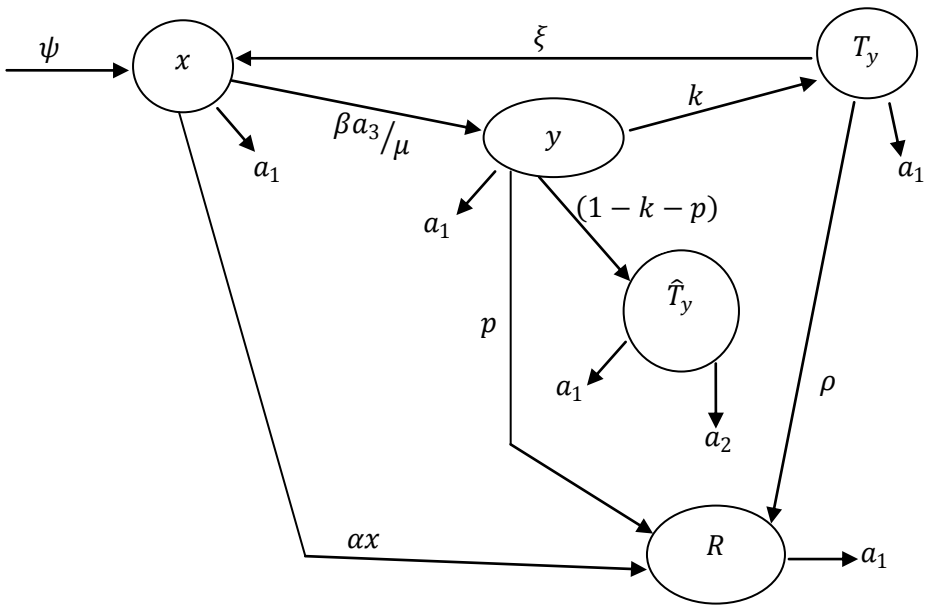


Fig.1: Flow diagram of Hepatitis B Virus Control Model Using Treatment.

The model equations are partitioned into four compartments of susceptible hepatocytes, (x), non treated hepatocytes, $(\hat{T}_y)$, treated hepatocytes, (T_y) and recovered hepatocytes with strong immunity (R). The variable (y) is not included as one of the compartments since we assumed that there is no domicility in (y), that is, infected individuals are classified as either treated or non treated. Individual uninfected hepatocytse enter the cell population with a recruitment rate of ψ. The natural death rate of both infected, uninfected, treated, non treated and recovered hepatocytes is a_1. α is the population of the susceptible hepatocyte entering the recovered class with protective immunity, where as the rate at which the infected cells are treated (efficacy of treatment) is denoted as (k). Also, the rate constant for non treated cells (i.e., decay in efficacy) is $(1-k-p)$. $\frac{\beta a_3}{\mu}$ is the rate constant for uninfected cells to be infected, while infected non treated hepatocytes are assumed to be kill by CTL response due to HBV infection at the rate a_2. The movement of infected cells from treated class to susceptible uninfected class is denoted by $\xi$and ρ is the rate at which treated cells recover with immunity against HBV in the liver and p is the noncytocidal response of the immune system against HBV through which the virus is cleared without harming the hepatocytes.

From the diagram above we obtain the following differential equations;

$$\begin{aligned}
\frac{dx}{dt} &= \psi - \frac{\beta a_3(1-k-p)\hat{T}_y x}{\mu} - a_1 x + \xi T_y \\
\frac{d\hat{T}_y}{dt} &= \frac{\beta a_3(1-k-p)\hat{T}_y x}{\mu} - a_1\hat{T}_y - a_2\hat{T}_y \qquad (3.1)\\
\frac{dT_y}{dt} &= \frac{\beta a_3 k T_y x}{\mu} - \xi T_y - a_1 T_y - \rho T_y \\
\frac{dR}{dt} &= \rho T_y + py + \alpha x - a_1 R \\
& x(t) \geq 0, \quad \hat{T}_y(t) \geq 0, \quad T_y(t) \geq 0, \quad R(t) \geq 0
\end{aligned}$$

Because the models are items of proportions, we have

$$x(t) + \hat{T}_y(t) + T_y(t) + R(t) = N \; for \; all \; time \; t. \qquad (3.2)$$

3.2: Disease Free Equilibrium

We study the equilibrium state and analyze the stability of the system by setting the right hand side of equation (3.1) to zero. Therefore, we obtain

$$\begin{aligned} &\psi - \frac{\beta a_3(1-k-p)\hat{T}_y x}{\mu} - a_1 x + \xi T_y = 0 \\ &\frac{\beta a_3(1-k-p)\hat{T}_y x}{\mu} - a_1\hat{T}_y - a_2\hat{T}_y = 0 \qquad (3.3) \\ &\frac{\beta a_3 k T_y x}{\mu} - \xi T_y - a_1 T_y - \rho T_y = 0 \\ &\rho T_y + py + \alpha x - a_1 R = 0 \end{aligned}$$

If the liver cell population is free of hepatitis B virus, then there will not be any infection and we have that

$$\hat{T}_y\left(\frac{\beta a_3(1-k-p)x}{\mu} - a_1 - a_2\right) = 0 \qquad (3.4)$$

$$T_y\left(\frac{\beta a_3 k x}{\mu} - \xi - a_1 - p\right) = 0$$

$$\Longrightarrow \hat{T}_y = T_y = 0$$

Now, system (3.3) reduces to

$$\begin{aligned} &\psi - a_1 x = 0 \qquad (3.5) \\ &\rho T_y + py + \alpha x - a_1 R = 0 \end{aligned}$$

Since the liver cell population is free of hepatitis B virus i.e., there were no infection, the immune system will be free of clearing the virus from the hepatocyte and this eliminates $py \; and \; \rho T_y$. Then system (3.5) further reduces to

$$\begin{aligned} &\psi - a_1 x = 0 \qquad (3.6) \\ &\alpha x - a_1 R = 0 \end{aligned}$$

Simplifying (3.6) in terms of $x \; and \; R$ gives

$$x = \frac{\psi}{a_1} \; and \; R = \frac{1}{a_1}\left(\frac{\alpha\psi}{a_1}\right)$$

This shows that the disease free equilibrium of the models is given as

$$Q = \left(x, \hat{T}_y, T_y, R\right) = \left(\frac{\psi}{a_1}, 0, 0, \frac{1}{a_1}\left(\frac{\alpha\psi}{a_1}\right)\right) \qquad (3.7)$$

Since the models are items of proportion, we now have from (3.2) that

$$N = x(t) + \hat{T}_y(t) + T_y(t) + R(t)$$

$$\begin{aligned} \Longrightarrow \; &\psi - \frac{\beta a_3(1-k-p)\hat{T}_y x}{\mu} - a_1 x + \xi T_y + \frac{\beta a_3(1-k-p)\hat{T}_y x}{\mu} - a_1\hat{T}_y - a_2\hat{T}_y \\ &+ \frac{\beta a_3 k T_y x}{\mu} - \xi T_y - a_1 T_y - \rho T_y + \rho T_y + py + \alpha x - a_1 R \\ \Longrightarrow \; &\psi - a_1 x - a_1\hat{T}_y - a_2\hat{T}_y + \frac{\beta a_3 k T_y x}{\mu} - a_1 T_y + py + \alpha x - a_1 R \\ \leq \; &\frac{\beta a_3 k T_y x}{\mu} + \psi + \alpha x + py - a_1 x - (a_1 + a_2)\hat{T}_y - a_1 T_y - a_1 R \end{aligned}$$

Note that in the absence of the disease, a_2 will be zero and thus we have;

$$\leq \frac{\beta a_3 k T_y x}{\mu} + \psi + py + \alpha x - a_1 N$$

Therefore,

$$N(t) \leq \frac{\beta a_3 k T_y x + \psi + py + \alpha x}{a_1 \mu} \qquad (3.8)$$

We can at this point omit the equation for R, in our analysis since R is not contained in the other equations of the model. Thus

$$\Gamma = \left\{\left(x, \hat{T}_y, T_y\right) \in \mathbb{R}_+^3 : x \leq \frac{\psi}{a_1}, x + \hat{T}_y + T_y \leq \frac{\beta a_3 k T_y x + \psi + py + \alpha x}{a_1 \mu}\right\}$$

is the feasible region of the model. Once the dynamics of $\left(x, \hat{T}_y, T_y\right)$ are understood, those of R can then be determined from the equation$\frac{dR}{dt} = \rho T_y + py + \alpha x - a_1 R$. The first step in our analysis is to find equilibria where a point $\left(x^*, \hat{T}_y{}^*, T_y{}^*\right)$ is called the steady state of the equations below.

$$\begin{aligned} \psi - \frac{\beta a_3 (1-k-p)\hat{T}_y x}{\mu} - a_1 x + \xi T_y &= 0 \\ \frac{\beta a_3 (1-k-p)\hat{T}_y x}{\mu} - a_1 \hat{T}_y - a_2 \hat{T}_y &= 0 \\ \frac{\beta a_3 k T_y x}{\mu} - \xi T_y - a_1 T_y - \rho T_y &= 0 \end{aligned} \tag{3.9}$$

Notice that system (3.1) always has a disease free equilibrium $Q = \left(\frac{\psi}{a_1}, 0, 0\right)$. An endemic equilibrium $Q = \left(x^*, \hat{T}_y{}^*, T_y{}^*\right)$ satisfies $x^*, \hat{T}_y{}^*, T_y{}^* > 0$. From the equilibrium equations, we can show that a unique Q^* exist by having that

$$\frac{\beta a_3 (1-k-p)\hat{T}_y x}{\mu} = a_1 \hat{T}_y + a_2 \hat{T}_y$$

$$\frac{\beta a_3 (1-k-p) x}{\mu} = a_1 + a_2 \tag{3.10}$$

$$\frac{\beta a_3 k T_y x}{\mu} = \xi T_y + a_1 T_y + \rho T_y$$

$$\frac{\beta a_3 k x}{\mu} = \xi + a_1 + \rho \tag{3.11}$$

The sum of (3.10) and (3.11) gives

$$\frac{\beta a_3 (1-k-p)x^* + \beta a_3 k x^*}{\mu} = 2a_1 + a_2 + \xi + \rho$$

$$\frac{\beta a_3 (1-p)x^*}{\mu} = 2a_1 + a_2 + \xi + \rho$$

$$x^* = \frac{(2a_1 + a_2 + \xi + \rho)\mu}{\beta a_3 (1-p)}$$

For Q^* to exist in the feasible region Γ, it is necessary and sufficient that

$$0 < x^* \leq \frac{\psi}{a_1} \; or \; 1 \leq \frac{\psi}{a_1 x^*}$$

Define

$$R_0 = \frac{1}{x^*}\frac{\psi}{a_1} = \frac{\psi}{a_1}\frac{\beta a_3 (1-p)}{(2a_1 + a_2 + \xi + \rho)\mu} \tag{3.12}$$

This is the basic reproduction number and it represents the average number of secondary infections caused by a single infective hepatocyte in an entirely susceptible hepatocyte population in the liver during its entire infectious period. When a single infective hepatocyte in the liver with infective rate $\frac{\beta a_3}{\mu}$, interact with susceptible cells recruited at the rate ψ, it is straight forward from (3.12) that R_{02} increases with increase in $\frac{\beta a_3}{\mu}$ and decrease in $p \; and \rho$, but decreases with decrease in $\frac{\beta a_3}{\mu}$ and increase in $p \; and \; \rho$. This simply shows that the number of new cases of HBV infected liver cells that occur in a liver cell population during the period of increase in $\frac{\beta a_3}{\mu}$ and decrease in $p \; and \; \rho$ will be high. Conversely, it will be low during the period of decrease in $\frac{\beta a_3}{\mu}$ and increase in $p \; and \; \rho$.

3.3: Stability Analysis Of Disease Free Equilibrium

We find the Jacobian matrix of the model system by differentiating equation (3.1) with respect to $x, \hat{T}_y, T_y, R$ respectively to obtain

$$\frac{dX^*}{dt} = \left[-a_1 - \frac{\beta a_3 (1-k-p)\hat{T}_y}{\mu}\right] X^* + \left[-\frac{\beta a_3 (1-k-p)\hat{T}_y}{\mu}\right] \hat{T}_y{}^* + [\xi] T_y{}^*$$

$$\frac{d\hat{T}_y^{\,*}}{dt} = \left[\frac{\beta a_3(1-k-p)\hat{T}_y}{\mu}\right]X^* + \left[\frac{\beta a_3(1-k-p)x}{\mu} - a_1 - a_2\right]\hat{T}_y^{\,*}$$

$$\frac{dT_y^{\,*}}{dt} = \left[\frac{\beta a_3 k T_y}{\mu}\right]X^* + \left[\frac{\beta a_3 kx}{\mu} - \xi - a_1 - \rho\right]T_y^{\,*}$$

$$\frac{dR^*}{dt} = [\alpha]X^* + [\rho]T_y^{\,*} + [-a_1]R^*$$

To examine the stability of the disease free equilibrium Q, we evaluate the Jacobian matrix at $Q = \left(x, \hat{T}_y, T_y, R\right) = \left(\frac{\psi}{a_1}, 0, 0, \frac{1}{a_1}\left(\frac{\alpha\psi}{a_1}\right)\right)$.

$$J(Q) := \begin{pmatrix} -a_1 & -\beta a_3 \dfrac{\psi(1-k-p)}{a_1\mu} & \xi & 0 \\ 0 & \beta a_3 \dfrac{\psi(1-k-p)}{a_1\mu} - a_1 - a_2 & 0 & 0 \\ 0 & 0 & \beta a_3 \dfrac{k\psi}{a_1\mu} - a_1 - \xi - \rho & 0 \\ \alpha & 0 & \rho & -a_1 \end{pmatrix}$$

Proposition 1: The steady state Q of equation (3.1) is asymptotically stable if $R_0 < 1, p < 1$ *and* $k + p < 1$and unstable if $R_0 > 1, p > 1$ *and* $k + p > 1$.

Proof:

We first remark that the characteristic equation of the matrix $J(Q)$ is given by

$$|Q - \lambda I| = 0$$

This implies

$$\begin{vmatrix} -a_1 - \lambda & -\dfrac{\beta a_3(1-k-p)\psi}{a_1\mu} & \xi & 0 \\ 0 & \dfrac{\beta a_3(1-k-p)\psi}{a_1\mu} - a_1 - a_2 - \lambda & 0 & 0 \\ 0 & 0 & \dfrac{\beta a_3 k\psi}{a_1\mu} - a_1 - \xi - \rho - \lambda & 0 \\ \alpha & 0 & \rho & -a_1 - \lambda \end{vmatrix} = 0$$

If we observe critically the form of the Jacobian matrix, we immediately have that $-a_1$ is a double eigenvalues. The remaining eigenvalues are those of the 2×2 sub matrix

$$\begin{bmatrix} \dfrac{\beta a_3(1-k-p)\psi}{a_1\mu} - a_1 - a_2 - \lambda & 0 \\ 0 & \dfrac{\beta a_3 k\psi}{a_1\mu} - a_1 - \xi - \rho - \lambda \end{bmatrix} \qquad (3.13)$$

To determine the nature of eigenvalue in (3.13), we show that Routh Hurwitz necessary and sufficient conditions hold, that is

$$let\ Q_1 = \begin{bmatrix} F_x(x,y) & F_y(x,y) \\ G_x(x,y) & G_y(x,y) \end{bmatrix}$$

be the Jacobian matrix of the non-linear system,

$$\left.\begin{aligned} \frac{dx}{dt} &= f(x,y) \\ \frac{dy}{dt} &= g(x,y) \end{aligned}\right\}$$

evaluated at critical point (x, y). The critical point (x, y)

1. Is asymptotically stable if $trace\ (Q_1) < 0$ and $det(Q_1) > 0$.
2. Is stable but not asymptotically stable if $trace\ (Q_1) = 0$ and $det(Q_1) > 0$.
3. Is unstable if $trace\ (Q_1) > 0$ and $det(Q_1) > 0$.

$$Let \quad Q_1 = \begin{bmatrix} \frac{\beta a_3(1-k-p)\psi}{a_1\mu} - a_1 - a_2 & 0 \\ 0 & \frac{\beta a_3 k\psi}{a_1\mu} - a_1 - \xi - \rho \end{bmatrix}$$

Simple calculation shows that

$$trace\ (Q_1) = \frac{\beta a_3(1-k-p)\psi}{a_1\mu} - a_1 - a_2 + \frac{\beta a_3 k\psi}{a_1\mu} - a_1 - \xi - \rho$$
$$= \frac{\beta a_3(1-p)\psi}{a_1\mu} - 2a_1 - a_2 - \xi - \rho$$

But $trace\ (Q_1) < 0$

$$\Rightarrow \frac{\beta a_3(1-p)\psi}{a_1\mu} - 2a_1 - a_2 - \xi - \rho < 0$$
$$\frac{\beta a_3(1-p)\psi}{a_1\mu(2a_1 + a_2 + \xi + \rho)} < 1$$

Remember that $R_0 = \frac{\beta a_3(1-p)\psi}{a_1\mu(2a_1+a_2+\xi+\rho)}$, therefore, $R_0 < 1$. This shows that $(Q_1) < 0$ when $R_0 < 1$. We therefore, calculate the determinant of Q_1. That is

$$det(Q_1) = \begin{vmatrix} \frac{\beta a_3(1-k-p)\psi}{a_1\mu} - a_1 - a_2 & 0 \\ 0 & \frac{\beta a_3 k\psi}{a_1\mu} - a_1 - \xi + \rho \end{vmatrix}$$
$$= \left(\frac{\beta a_3(1-k-p)\psi}{a_1\mu} - a_1 - a_2\right)\left(\frac{\beta a_3 k\psi}{a_1\mu} - a_1 - \xi - \rho\right) - (0)(0)$$

$$= \left(\frac{\beta a_3 k\psi}{a_1\mu}\right)\left(\frac{\beta a_3(1-k-p)\psi}{a_1\mu} - a_1 - a_2\right) + (-a_1)\left(\frac{\beta a_3(1-k-p)\psi}{a_1\mu} - a_1 - a_2\right)$$
$$+(-\xi)\left(\frac{\beta a_3(1-k-p)\psi}{a_1\mu} - a_1 - a_2\right) + (-\rho)\left(\frac{\beta a_3(1-k-p)\psi}{a_1\mu} - a_1 - a_2\right)$$
$$= \left(\frac{\beta a_3 k\psi}{a_1\mu}\right)\left(\frac{\beta a_3(1-k-p)\psi}{a_1\mu}\right) + \left(\frac{\beta a_3 k\psi}{a_1\mu}\right)(-a_1 - a_2) - a_1\left(\frac{\beta a_3(1-k-p)\psi}{a_1\mu}\right) + a_1^2 + a_1 a_2$$
$$-\xi\left(\frac{\beta a_3(1-k-p)\psi}{a_1\mu}\right) + \xi a_1 + \xi a_2 - \rho\left(\frac{\beta a_3(1-k-p)\psi}{a_1\mu}\right) + \rho a_1 + \rho a_2$$
$$= \frac{\beta a_3 k\psi}{a_1\mu}\left(\frac{\beta a_3\psi - \beta a_3 k\psi - \beta a_3 p\psi}{a_1\mu}\right) - \frac{\beta a_3 k\psi}{a_1\mu}(a_1 + a_2) - \left(\frac{\beta a_3\psi - \beta a_3 k\psi - \beta a_3 p\psi}{\mu}\right) + a_1^2$$
$$+a_1 a_2 + \xi a_1 + \xi a_2 - \xi\left(\frac{\beta a_3\psi}{a_1\mu} - \frac{\beta a_3 k\psi}{a_1\mu} - \frac{\beta a_3 p\psi}{a_1\mu}\right) - \rho\left(\frac{\beta a_3(1-k-p)\psi}{a_1\mu}\right) + \rho a_1 + \rho a_2$$
$$= \frac{\beta^2 a_3^2\psi^2 k}{a_1^2\mu^2} - \frac{\beta^2 a_3^2\psi^2 k^2}{a_1^2\mu^2} - \frac{\beta^2 a_3^2\psi^2 kp}{a_1^2\mu^2} - \frac{\beta a_3 k\psi}{\mu} - \frac{\beta a_2 a_3 k\psi}{a_1\mu} - \frac{\beta a_3\psi}{\mu} + \frac{\beta a_3 k\psi}{\mu} + \frac{\beta a_3 p\psi}{\mu} + a_1^2$$
$$+a_1 a_2 + \xi a_1 + \xi a_2 + \rho a_1 + \rho a_2 - \frac{\beta a_3\xi\psi}{a_1\mu} + \frac{\beta a_3\xi k\psi}{a_1\mu} + \frac{\beta a_3\xi p\psi}{a_1\mu} - \frac{\beta a_3\rho\psi}{a_1\mu} + \frac{\beta a_3\rho k\psi}{a_1\mu} + \frac{\beta a_3\rho p\psi}{a_1\mu}$$
$$\Rightarrow \frac{\beta^2 a_3^2\psi^2}{a_1^2\mu^2}k\big(1-(k+p)\big) + a_1^2 + a_1 a_2 + \xi a_1 + \xi a_2 + \rho a_1 + \rho a_2 - \frac{\beta a_3\psi}{\mu}(1-p)$$
$$+\frac{\beta a_3\psi}{a_1\mu}\big(\xi(k+p) - (\xi + ka_2)\big) - \frac{\beta a_3\rho\psi}{a_1\mu}\big(1-(k+p)\big)$$
$$But \qquad det(Q_1) > 0$$
$$\Rightarrow \quad \frac{\beta^2 a_3^2\psi^2}{a_1^2\mu^2}k\big(1-(k+p)\big) + a_1^2 + a_1 a_2 + \xi a_1 + \xi a_2 + \rho a_1 + \rho a_2 - \frac{\beta a_3\psi}{\mu}(1-p)$$
$$+\frac{\beta a_3\psi}{a_1\mu}\big(\xi(k+\rho) - (\xi + ka_2)\big) - \frac{\beta a_3\rho\psi}{a_1\mu}\big(1-(k+p)\big) > 0$$

Therefore,

$$\frac{\beta^2 a_3^2\psi^2}{a_1^2\mu^2}k\big(1-(k+p)\big) + \frac{\beta a_3\psi}{a_1\mu}\xi(k+p) + a_1^2 + a_1 a_2 + \xi a_1 + \xi a_2 + \rho a_1 + \rho a_2$$

$$> \frac{\beta a_3\psi}{\mu}(1-p) + \frac{\beta a_3\psi}{a_1\mu}(\xi + ka_2) + \frac{\beta a_3\rho\psi}{a_1\mu}\big(1-(k+p)\big)$$

$$\Longrightarrow \frac{a_1\mu\left[\frac{\beta^2 a_3^2\psi^2}{a_1^2\mu^2}k\big(1-(k+p)\big) + \frac{\beta a_3\psi}{a_1\mu}\xi(k+p) + a_1^2 + a_1a_2 + \xi a_1 + \xi a_2 + \rho a_1 + \rho a_2\right]}{\beta a_3\psi\big(a_1(1-p) + (\xi + ka_2)\big) + \beta a_3\rho\psi\big(1-(k+p)\big)} > 1$$

Thus, our model is asymptotically stable if $p < 1$ *and* $(k+p) < 1$.

3.4: Sensitivity Analysis Of The Basic Reproduction Number (R_0) Of HBV With Treatment

We conduct sensitivity analysis to determine the nature of the model. R_0 is the average number of newly infected cells provided by a single infected cell (in host dynamics). If $R_0 < 1$, each individual cells produces on the average, less than one new infected individual cell and hence the disease dies out. But if $R_0 > 1$, each individual cell produces more than one new infected cell and hence the disease is able to invade the susceptible cell population. Therefore R_0 allows us to determine the effectiveness of control measure.
To calculate the value of R_0, we use the parameters for the chronic states;

Table 3: Parameter Values used for the Calculation of R_0 and Numerical Simulation of the model.

Parameters	Description	Value Range	Reference
a_1	Natural death rate of hepatocytes	0.002	Long et al, 2008.
a_2	Death rate of non - treated hepatocytes due to immune response	40	Long et al, 2008.
a_3	Production rate of free virus from infected hepatocyte	0.8	Long et al, 2008.
p	Rate at which infected cells recover before treatment	0.1 – 0.3	Assumed
ξ	Movement of treated infected cells to susceptible class	100	Long et al, 2008.
ψ	Number of uninfected susceptible hepatocytes	1	Long et al, 2008.
β	Rate at which uninfected cells are being infected	0.2	Long et al, 2008.
μ	Removal (natural death) rate of free virus	0.58	Long et al, 2008.
ρ	Rate of recovery with immunity of treated hepatocytes	0.02	Long et al, 2008.
k	The rate at which infected cell are treatred (efficacy of treatment)	0.5	Assumed
α	Population of the susceptible hepatocytes entering the recovered class with strong immunity	0.025	Zou et al, 2009
y	Infected hepatocytes	1.02	Bocharov, 1994

Remember that

$$x^* = \frac{(2a_1 + a_2 + \rho + \xi)\mu}{\beta a_3(1-p)}$$

Then, if $p = 0.1$, we have that

$$x^* = \frac{(2(0.002) + 40 + 0.02 + 100) \times 0.58}{0.2 \times 0.8(1-0.1)} = 563.9855556$$

$$R_0 = \frac{1}{x^*}\frac{\psi}{a_1} = \frac{\psi}{a_1}\frac{\beta a_3(1-p)}{(2a_1 + a_2 + \rho + \xi)\mu} = 0.886547527$$

if $p = 0.3$, we have that

$$x^* = \frac{(2(0.002) + 40 + 0.02 + 100) \times 0.58}{0.2 \times 0.8(1-0.3)} = 725.1242857$$

$$R_0 = \frac{1}{x^*}\frac{\psi}{a_1} = \frac{\psi}{a_1}\frac{\beta a_3(1-p)}{(2a_1 + a_2 + \rho + \xi)\mu} = 0.689536966$$

- To see the effect of p *on* R_0 we have $\mathrm{Z}_p^{R_0} = \frac{\partial R_0}{\partial p} \times \frac{R_0}{p} = -8.732961315$

Here we observe that $\frac{\partial R_0}{\partial p} < 0$, and this shows that a greater recoverability of hepatocytes with immunity will decrease the basic reproduction number.

- To see the effect of μ *on* R_0 we have

$$\mathrm{Z}_\mu^{R_0} = \frac{\partial R_0}{\partial \mu} \times \frac{R_0}{\mu} = -2.242332773$$

- To see the effect of β *on* R_0 we have

$$\mathrm{Z}_\beta^{R_0} = \frac{\partial R_0}{\partial \beta} \times \frac{R_0}{\beta} = 19.64916295$$

- To see the effect of a_3 *on* R_0 we have

$$\mathrm{Z}_{a_3}^{R_0} = \frac{\partial R_0}{\partial a_3} \times \frac{R_0}{a_3} = 1.228072686$$

- To see the effect of ψ *on* R_0 we have

$$\mathrm{Z}_{\psi}^{R_0} = \frac{\partial R_0}{\partial \psi} \times \frac{R_0}{\psi} = 0.785966512$$

- To see the effect of a_1 *on* R_0 we have

$$\mathrm{Z}_{a_1}^{R_0} = \frac{\partial R_0}{\partial a_1} \times \frac{R_0}{a_1} = -66649.75511$$

- To see the effect of a_2 *on* R_0 we have

$$\mathrm{Z}_{a_2}^{R_0} = \frac{\partial R_0}{\partial a_2} \times \frac{R_0}{a_2} = -1.403271069e^{-4}$$

- To see the effect of ξ *on* R_0 we have

$$\mathrm{Z}_{\xi}^{R_0} = \frac{\partial R_0}{\partial \xi} \times \frac{R_0}{\xi} = -5.613084278\mathrm{e}^{-5}$$

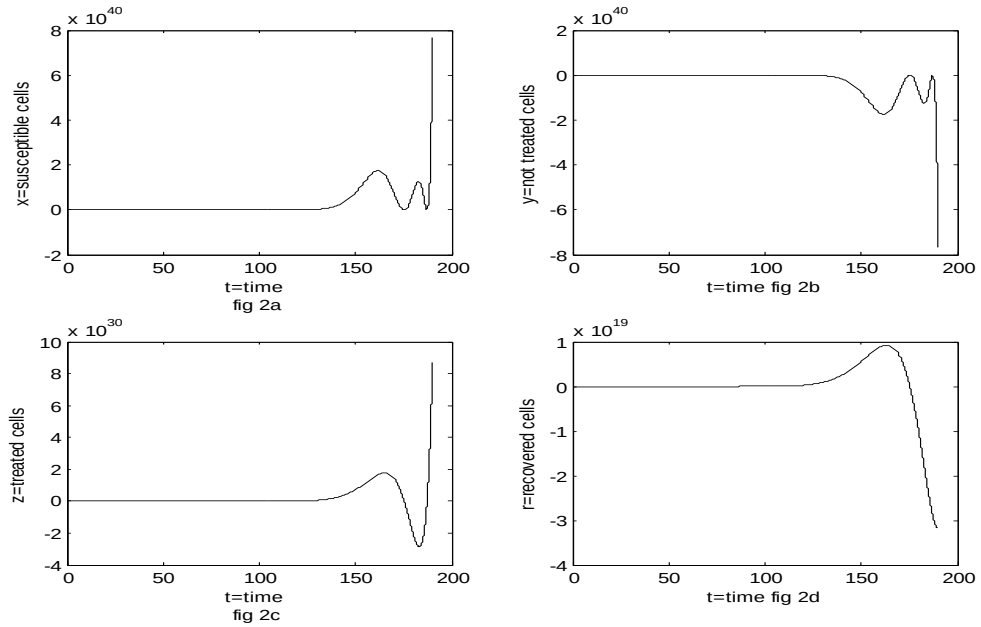
- To see the effect of ρ *on* R_0 we have

$$\mathrm{Z}_{\rho}^{R_0} = \frac{\partial R_0}{\partial \rho} \times \frac{R_0}{\rho} = -0.281379686$$

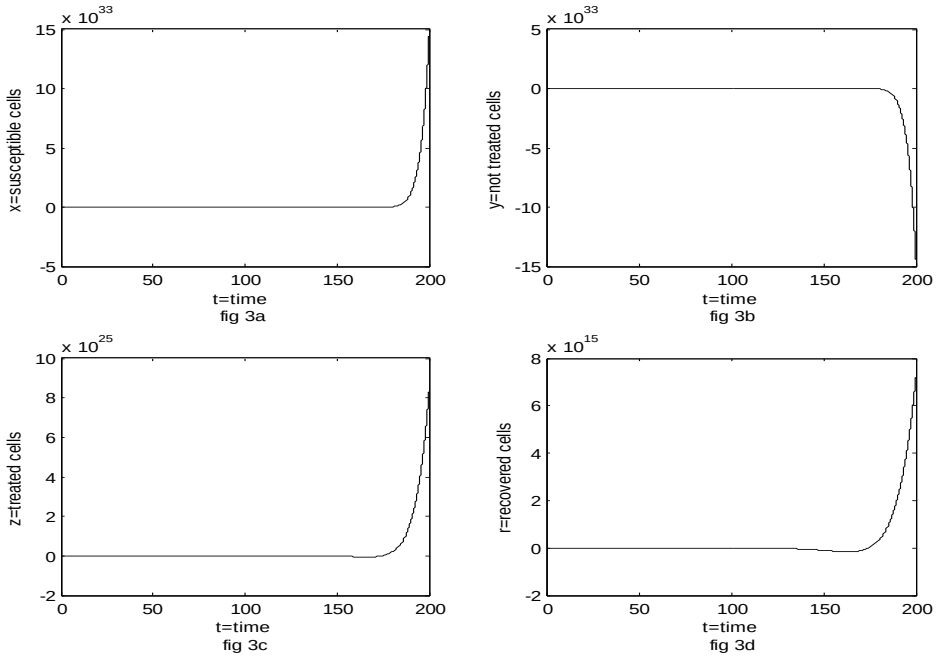
The sensitivity indices $Z(\beta), Z(a_3)\ and\ Z(\psi)$ are positive and this shows that the value of R_0 increases as the value of β, a_3 and ψ increases. The remaining indices $Z(\mu), Z(a_1), Z(a_2)$, $Z(\xi), Z(p) and\ Z(\rho)$ are negative, indicating that the value R_0 decreases as μ, a_1, a_2, ξ, p $and\ \rho$ Increases. This simply means that liver cells will be infected, cured and eventually recover and retain the infection for life, or obtain immunity. This reduces the rate at which the infection multiplies in the liver cell population and may eventually eradicate the disease

IV. ANALYSIS OF RESULT

To show the density of the behavior of the four variables, susceptible hepatocytes, (x), non treated hepatocytes, $(\hat{T}_y)$, treated hepatocytes, (T_y) and recovered hepatocytes with strong immunity(R), we use table 6 and numerically simulate model system (3.1) which is the system for control using the treatment of infected hepatocytes.



Figures (2a – 2d): Numerical simulation of the model system (3.1) where $\psi = 1, a_1 = 0.002, a_3 = 0.8, \beta = 0.2, a_2 = 40, \xi = 100, \mu = 0.58, k = 0.5, p = 0.1, \rho = 0.02, \alpha =$
$0.025\ with\ time\ ranging\ from\ 0\ to\ 180 days.$



Figures (3a – 3d): Numerical simulation of the model system (3.1) where $\psi = 1, a_1 = 0.002, a_3 = 0.8, \beta = 0.2, a_2 = 40, \xi = 100, \mu = 0.58, k = 0.5, p = 0.1, \rho = 0.02, \alpha = 0.025$ *with time ranging from* 0 *to* $200 days$.

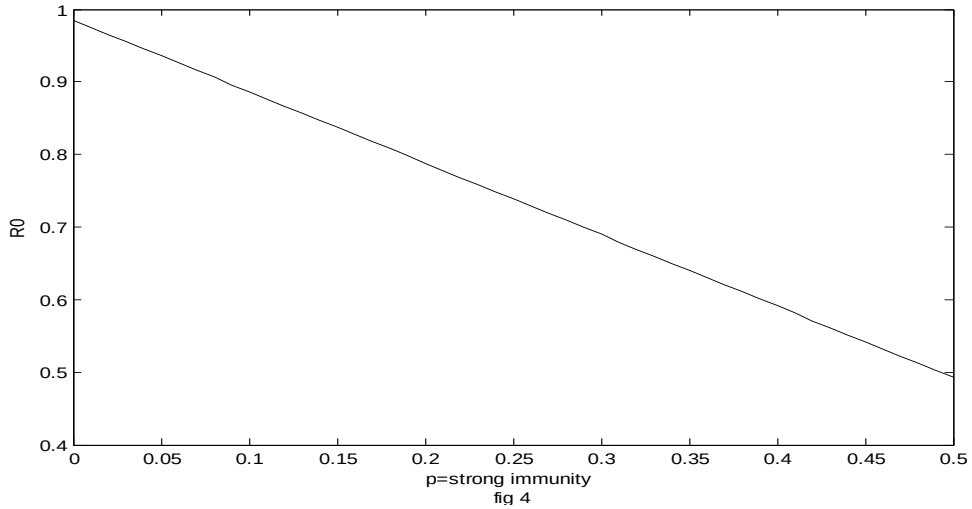
In figures (1a – 1d) and (2a – 2d), we simulated system (3.1) using the parameter values as stated above. Here we assume that the system is in the infected state before treatment is initiated. We therefore observe that when treatment is applied adequately by targeting the infected hepatocytes, the concentration of both the treated and untreated hepatocytes will initially assume a constant before oscillating. Finally, the concentration of the treated hepatocytes will increase while the concentration of the untreated hepatocytes will decay (decreasing). The constant is the lag time (time effect of the drug). In pharmacokinetics, 'lag time' corresponds to the finite time taken for a treatment (drug) to appear in systemic circulation following extravasscular administration and is also a reflection of the processes associated with the absorption phase such as treatment dissolution and/or release from the delivery system and treatment migration to the absorbing surface. During this period, the treatment tries to locate the site of action and the magnitude of response/toxicity depends on the concentration at the site of action. Concentration must be kept high enough to produce a desirable response, but low enough to avoid toxicity and this is known as the therapeutic window. Therapeutic window is the amount of a medication between the amount that gives an effect (effective dose) and the amount that gives more adverse effect than desired effect. More so, it is known that metabolic actions take place in the liver and HBV affects the liver thereby affecting blood flow and function of the hepatocytes leading to decreased treatment clearance, and prolong half-life. Half-life of a treatment is the treatments' elimination from the blood stream which can be caused by metabolism, urine and other forms of excretion. The oscillation is caused by the immune response via the effectiveness of the treatment and tissue repair and it also shows that the treatment is potent enough to elicit desired response which the virus tries to resist. As the treatment is able to overcome the viral resistance, it will inhibit viral replication by blocking the virus from entering the liver cells and preventing those that are already inside the liver cells from releasing new viral particles. This results in viral reduction which reduces the viral load and eliminates the infection.

In other words, efficacy of hepatitis B virus infected cell treatment is how well the cells are treated after the treament is bounded to the receptors thereby initiating a response at cellular and tissue level. Since the potency of the treatment produced the required intensity, we noticed that the density of the susceptible, treated and recovered hepatocytes gradually increases while the untreated hepatocytes decayed continuously and this means that the therapy (treatment) has worked.

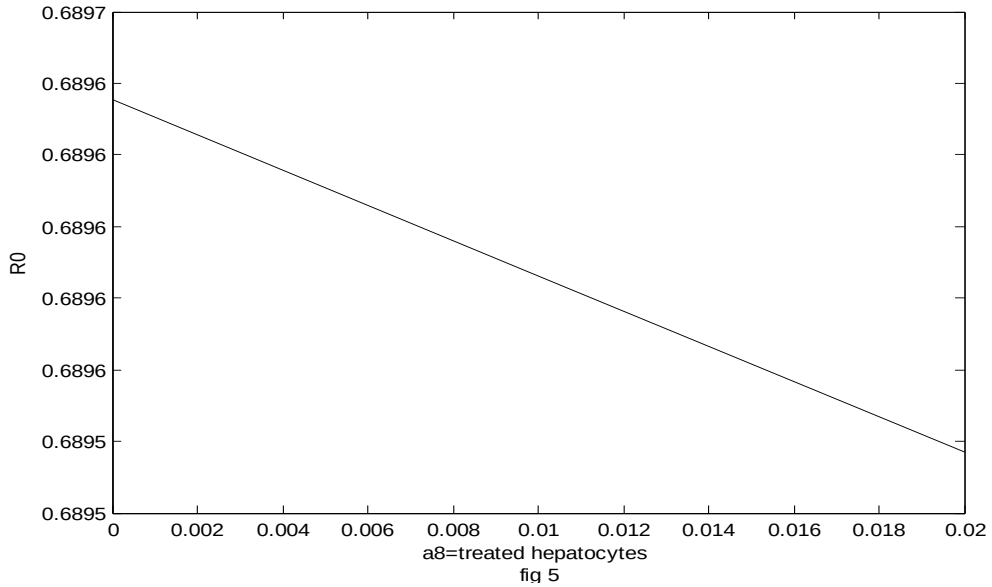
Certainly, the goal of treatment is to reduce HBV replication and to remove the hepatitis B surface and e antigens and of covalently closed circular DNA (CCCDNA). The removal of the hepatitis Be antigen is associated with immunological factors, such as removal of the torelant status of hepatitis B specific T cells (Marrack et al, 1999). From the results, it implies that an increase in CTL response (in acute infection) and

reversal of CTL inactivation (in chronic infection) are very important for prompt control of the HBV from having access to the rest of the liver cells.

Also shown here is the numerical simulation of the basic reproduction number $R_0 = \frac{1}{x^*}\frac{\psi}{a_1} = \frac{\psi}{a_1}\frac{\beta a_3(1-p)}{(2a_1+a_2+\xi+\rho)\mu}$ from which we have figure 3 and 4 and in the later we represented ρ with a_8.



Figures 3: Numerical simulation of the basic reproduction number R_{02} using different rate of $a_1 = 0.002, a_2 = 40, a_3 = 0.8, \xi = 100, \psi = 1, \beta = 0.2, \mu = 0.58, \rho = 0.02$ *and* $p = 0 - 0.5$.



Figures 4: Numerical simulation of the basic reproduction number R_0 using different rate of $a_1 = 0.002, a_2 = 40, a_3 = 0.8, \xi = 100, \psi = 1, \beta = 0.2, \mu = 0.58,\ p = 0.3, and\ \rho = 0 - 0.02$.

From figures 3and 4, we see that as $p\ and\ \rho$ increases, the basic reproduction number R_0 decreases as was indicated by the sensitivity analysis of R_0 in table 2.

V. SUMMARY AND CONCLUSION

From the biological point of view, for HBV infection to be eliminated from the hepatocytes, the treatment must target the infected cells. Changes in the basic reproduction number R_0 can have an influential effect on the endemicity of the infection. Even if the virus is close to maintain the infection, once a strong immune response is turned with appropriate and adequate treatment of the infected cells, the concentration of both the infected cells and free virus will be reduced. Thus, the virus weakly affects liver cells. By this model, patients whose immune response was strengthened with adequate and effective treatment should have a greater reduction in viral concentration and this will help reduce the incidence of hepatocellular carcinoma (liver cancer).

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