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Analysis and Control of a Hepatitis B Virus Model

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Abstract

In this study, bifurcation analysis and multi-objective nonlinear model predictive control are performed on a Hepatitis B Virus model. Bifurcation analysis is a powerful mathematical tool used to deal with the nonlinear dynamics of any process. Several factors must be considered, and multiple objectives must be met simultaneously. The MATLAB program MATCONT was used to perform the bifurcation analysis. The MNLMPC calculations were performed using the optimization language PYOMO in conjunction with the state-of-the-art global optimization solvers IPOPT and BARON. The bifurcation analysis revealed the existence of branch points. The MNLMC converged to the Utopia solution. The branch points (which causes multiple steady-state solutions from a singular point) are very beneficial because they enable the Multiobjective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in the model.

Keywords: Bifurcation; Optimization; Control; Hepatitis

BACKGROUND

Hepatitis B virus (HBV) is a major global health concern, responsible for significant morbidity and mortality across the world. It is one of the most serious types of viral hepatitis, causing inflammation of the liver that can progress to chronic infection, liver cirrhosis, and hepatocellular carcinoma. Despite advances in prevention and treatment, HBV remains a persistent threat, particularly in low- and middle-income countries where vaccination coverage and medical infrastructure are limited. Understanding the biology, transmission, symptoms, diagnosis, prevention, and treatment of HBV is essential for controlling its impact on public health.

Hepatitis B virus is a member of the Hepadnaviridae family, characterized by its unique partially double-stranded DNA genome. It is a small, enveloped virus with a spherical structure containing a surface antigen (HBsAg), a core antigen (HBcAg), and an e antigen (HBeAg). The viral genome encodes several proteins crucial for replication and infection, including the surface protein, core protein, polymerase, and X protein, which plays a role in viral transcription and oncogenesis. HBV replicates in hepatocytes, the main cells of the liver, through a complex mechanism involving reverse transcription, similar to retroviruses. Once the virus enters the host cell, its DNA is transported to the nucleus, where it forms a covalently closed circular DNA (cccDNA) that serves as a template for viral RNA synthesis. This cccDNA is particularly important because it can persist in hepatocytes even after the resolution of infection, making complete eradication of the virus difficult.

Transmission of HBV occurs through exposure to infected blood or body fluids. The main routes include perinatal transmission from mother to child during childbirth, unprotected sexual contact, sharing of contaminated needles or syringes, unsafe medical practices, and blood transfusions with unscreened blood. In highly endemic regions, such as sub-Saharan Africa and parts of Asia, perinatal and early childhood transmission are predominant. In contrast, in low-endemic areas like North America and Western Europe, transmission more often occurs through sexual activity and injection drug use. The virus is highly infectious, much more than HIV, and can survive outside the body for up to seven days, maintaining its ability to cause infection.

After infection, the disease can manifest as either acute or chronic hepatitis. The acute phase occurs within six months of exposure and can present with symptoms such as fever, fatigue, nausea, vomiting, abdominal pain, dark urine, clay-colored stools, joint pain, and jaundice. However, many infections in adults are asymptomatic, and the immune system can clear the virus in most cases. Chronic HBV infection is defined as the persistence of HBsAg in the blood for more than six months. Chronic infection is more likely when the virus is acquired in infancy or early childhood due to the immaturity of the immune response. Over time, chronic hepatitis B can lead to serious complications, including liver fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma. Approximately 15–25% of chronically infected individuals die from HBV-related liver disease, making it one of the leading causes of liver-related deaths globally.

The immune response plays a central role in determining the course of HBV infection. In acute infection, a strong and coordinated immune response involving cytotoxic T lymphocytes, helper T cells, and neutralizing antibodies typically leads to viral clearance. In contrast, chronic infection results from an inadequate immune response that fails to eliminate infected hepatocytes. HBV has evolved mechanisms to evade the immune system, including suppression of interferon signaling and modulation of host immune cells. This ability to persist in the host underscores the challenges in achieving a complete cure.

Diagnosis of hepatitis B infection relies on serological and molecular tests that detect specific viral antigens, antibodies, and DNA. The presence of HBsAg indicates an active infection, while the antibody to HBsAg (anti-HBs) signifies immunity either from recovery or vaccination. Detection of HBeAg suggests active viral replication and higher infectivity, whereas the antibody to the core antigen (anti-HBc) indicates previous or ongoing infection. Quantification of HBV DNA through Polymerase Chain Reaction (PCR) techniques helps assess viral load and monitor treatment response. Liver function tests, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are used to evaluate liver inflammation and damage. Imaging studies and liver biopsy may also be performed in cases of chronic infection to assess the extent of fibrosis or cirrhosis.

Prevention of hepatitis B is highly effective through vaccination. The hepatitis B vaccine, which contains recombinant HBsAg, induces the production of protective antibodies in the body. It is considered one of the safest and most effective vaccines available, offering more than 95% protection against infection and its chronic consequences. The World

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Health Organization (WHO) recommends that all infants receive the first dose of the hepatitis B vaccine within 24 hours of birth, followed by two or three additional doses as part of routine immunization schedules. In addition to vaccination, preventive measures include safe injection practices, blood screening, use of condoms during sexual activity, and education on avoiding the sharing of personal items such as razors and toothbrushes. For newborns born to infected mothers, the combination of the hepatitis B vaccine and Hepatitis B Immunoglobulin (HBIG) given within 12 hours of birth can prevent nearly all perinatal transmissions.

Treatment for hepatitis B depends on the stage and severity of the infection. For acute infections, treatment is mainly supportive, as most adults recover spontaneously. In chronic hepatitis B, the goal of therapy is to suppress viral replication, prevent disease progression, and reduce the risk of complications such as cirrhosis and liver cancer. Antiviral medications such as tenofovir disoproxil fumarate, tenofovir alafenamide, and entecavir are first-line treatments due to their high potency and low risk of resistance. These drugs inhibit the viral polymerase enzyme, effectively reducing HBV DNA levels in the blood. Interferon-alpha, an immune-modulating therapy, can also be used in selected patients, especially those with a good immune response, but it often causes significant side effects and is less well tolerated. Lifelong monitoring of viral load, liver function, and fibrosis progression is essential for chronic patients, as treatment rarely results in complete eradication of the virus.

Despite the availability of effective vaccines and antiviral therapies, hepatitis B remains a global public health challenge. The World Health Organization estimates that approximately 296 million people were living with chronic HBV infection in 2022, with about 820,000 deaths annually, mostly due to complications such as cirrhosis and liver cancer. The burden is disproportionately higher in regions with limited access to healthcare and vaccination. Elimination of hepatitis B as a public health threat by 2030 is one of the WHO's global health targets, which requires strengthening vaccination programs, expanding access to testing and treatment, and improving public awareness.

Recent advances in research are bringing hope for a functional cure, defined as sustained loss of HBsAg with or without the development of anti-HBs antibodies. Novel therapeutic approaches include drugs targeting cccDNA, RNA interference agents that block viral replication, and immune modulators that enhance the host response. Combination therapies aiming to both suppress viral replication and restore immune control are under investigation. These efforts reflect a growing global commitment to ending the burden of HBV once and for all.

Hepatitis B virus represents one of the most important infectious diseases affecting humanity, with profound health and economic consequences. Its unique biology and persistence in the liver make it particularly difficult to eradicate, but prevention through vaccination remains the most powerful tool in controlling its spread. Early diagnosis, effective antiviral therapy, and sustained public health initiatives can dramatically reduce the incidence of infection and associated complications. Continued research, global collaboration, and awareness are essential to achieving the ultimate goal of a world free from hepatitis B.

Tedder et al [1], studied the Hepatitis B transmission from a contaminated cryopreservation tank. Qesmi et al. [2], investigated the, influence of backward bifurcation in a model of hepatitis B and C viruses. Pang et al. [3], discussed the importance of immune responses in a model of hepatitis B virus. Pollicino et al. [4], discussed the impact of Hepatitis B Virus (HBV) preS/S genomic variability on HBV surface antigen and HBV DNA serum levels. Caccamo et al. [5], investigated the effects of the dual infection of Hepatitis B and hepatitis C virus.

Cornberg et al. [6], performed additional investigations of the role of quantitative hepatitis B surface antigen. Butler et al. [7], discussed the hepatitis B virus serum DNA and RNA levels in nucleos (t)ide analog-treated or untreated patients during chronic and acute Infections. Webb et al. [8], discussed the clinical and epidemiological features, diagnosis, treatment, and prevention of Hepatitis A and Hepatitis E. Di Cola et al. [9], discussed the foodborne transmission of hepatitis A and hepatitis E viruses. Li et al. [10], researched the continuous and discrete stability characterization of Hepatitis B deterministic model. Qadeer Khan et al. [11], discussed the bifurcation analysis and chaos in a discrete Hepatitis B virus model [J].

In this work, bifurcation analysis and multiobjective nonlinear model predictive control is performed on a Hepatitis B virus model described in Qadeer Khan et al [11]. The paper is organized as follows. First, the model equations are presented, followed by a discussion of the numerical techniques involving bifurcation analysis and Multiobjective Nonlinear Model Predictive Control (MNLMPC). The results and discussion are then presented, followed by the conclusions.

Model Equations (Qadeer Khan et al [11])

zv, vv, sv, and iv represent the quantity of virus-specific CTLs, free virus particles, uninfected cells, and infected cells. β represents the efficiency of infection of cells (sv) by the cells vv. whereas $\alpha, \delta,$ and u denotes death rates of cells iv, sv, and free virus vv, respectively. ϑ is the constant rate at which cells sv are produced. μ represents the death rate of zv. The CTLs responsiveness is indicated by the parameter c. The parameter pv determines how quickly CTLs eliminate iv. K represents the production rate of vv by the cells iv.

The model equations are

$$\begin{aligned}
\frac{d(sv)}{dt} &= \upsilon - \delta(sv) - \beta(sv)vv \\
\frac{d(iv)}{dt} &= \beta(sv)vv - \alpha(iv) - pv(iv)zv \\
\frac{d(vv)}{dt} &= k(iv) - u(vv) \\
\frac{d(zv)}{dt} &= c(iv)zv - \mu(zv)
\end{aligned} \tag{1}$$

The base parameter values are

υ =4.3; β =2.5; alfa α =0.41; k=5.5; u=4.6; δ =3.004; c=8.4;

μ =4.432768; pv=1.9.

Bifurcation Analysis

The MATLAB software MATCONT is used to perform the bifurcation calculations. Bifurcation analysis deals with multiple steady-states and limit cycles. Multiple steady states occur because of the existence of branch and limit points. Hopf bifurcation points cause limit cycles. A commonly used MATLAB program that locates limit points, branch points, and Hopf bifurcation points is MATCONT (Dhooge, Govaerts, and Kuznetsov, [12]; Dhooge, Govaerts, Kuznetsov, Mestrom and Riet, [13]). This program detects Limit Points (LP), Branch Points (BP), and Hopf bifurcation points (H) for an ODE system

$$\frac{dx}{dt} = f(x, \alpha) \tag{2}$$

$x \in R^n$ Let the bifurcation parameter be α . Since the gradient is orthogonal to the tangent vector,

The tangent plane at any point $w = [w_1, w_2, w_3, w_4, \ldots w_{n+1}]$ must satisfy

$$Aw = 0 \tag{3}$$

Where A is

$$A = [\partial f / \partial x \quad | \partial f / \partial \alpha] \tag{4}$$

where $\partial f / \partial x$ is the Jacobian matrix. For both limit and branch points, the Jacobian matrix $J = [\partial f / \partial x]$ must be singular.

For a limit point, there is only one tangent at the point of singularity. At this singular point, there is a single non-zero vector, y, where Jy=0. This vector is of dimension n. Since there is only one tangent the vector

$y = (y_1, y_2, y_3, y_4, \ldots y_n)$ must align with $\hat{w} = (w_1, w_2, w_3, w_4, \ldots w_n)$. Since

$$J\hat{w} = Aw = 0 \tag{5}$$

the n+1 th component of the tangent vector w_{n+1} = 0 at a Limit Point (LP).

For a branch point, there must exist two tangents at the singularity. Let the two tangents be z and w. This implies that

$$\begin{aligned} Az &= 0 \\ Aw &= 0 \end{aligned} \tag{6}$$

Consider a vector v that is orthogonal to one of the tangents (say w). v can be expressed as a linear combination of z and w ($v = \alpha z + \beta w$). Since $Az = Aw = 0$; $Av = 0$ and since w and v are orthogonal,

$w^T v = 0$. Hence $Bv = \begin{bmatrix} A \\ w^T \end{bmatrix} v = 0$ which implies that B is singular.

Hence, for a Branch Point (BP) the matrix $B = \begin{bmatrix} A \\ w^T \end{bmatrix}$ must be singular.

At a Hopf bifurcation point,

$$\det(2 f_x(x,\alpha) @ I_n) = 0 \tag{7}$$

@ Indicates the bialternate product while I_n is the n-square identity matrix. Hopf bifurcations cause limit cycles and should be eliminated because limit cycles make optimization and control tasks very difficult. More details can be found in Kuznetsov ([14,15]), and Govaerts [16].

Multiobjective Nonlinear Model Predictive Control (MNLMPC)

The rigorous multiobjective nonlinear model predictive control (MNLMPC) method developed by Flores Tlacuahuaz et al. [17], was used.

Consider a problem where the variables $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ (j=1, 2..n) have to

be optimized simultaneously for a dynamic problem

$$\frac{dx}{dt} = F(x,u) \tag{8}$$

t_f being the final time value, and n the total number of objective variables and u the control parameter. The single objective optimal control problem is solved individually optimizing each of the variables $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ The optimization of $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ will lead to the values q_j^*.

Then, the Multiobjective Optimal Control (MOOC) problem that will be solved is

$$\begin{aligned} &\min \left(\sum_{j=1}^{n} \left(\sum_{t_i=0}^{t_i=t_f} q_j(t_i) - q_j^*\right)\right)^2 \\ &subject\ to\ \frac{dx}{dt} = F(x,u); \end{aligned} \tag{9}$$

This will provide the values of u at various times. The first obtained control value of u is implemented and the rest are discarded. This procedure is repeated until the implemented and the first obtained control values are the same or if the Utopia point where ($\sum_{t_i=0}^{t_i=t_f} q_j(t_i) = q_j^*$ for all j) is obtained.

Pyomo (Hart et al. [18], is used for these calculations. Here, the differential equations are converted to a Nonlinear Program (NLP) using the orthogonal collocation method The NLP is solved using IPOPT (Wächter And Biegler, [19] and confirmed as a global solution with BARON (Tawarmalani, M. and N. V. Sahinidis [20].

The steps of the algorithm are as follows

Optimize $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ and obtain q_j^*.

Minimize $\left(\sum_{j=1}^{n} \left(\sum_{t_i=0}^{t_i=t_f} q_j(t_i) - q_j^*\right)\right)^2$ and get the control values at various times.

Implement the first obtained control values

Repeat steps 1 to 3 until there is an insignificant difference between the implemented and the first obtained value of the control variables or if the Utopia point is achieved. The Utopia point is when

$$\sum_{t_i=0}^{t_i=t_f} q_j(t_i) = q_j^* \text{ for all j.}$$

Sridhar [21], demonstrated that when the bifurcation analysis revealed the presence of limit and branch points the MNLMPC calculations to converge to the Utopia solution. For this, the singularity condition, caused by the presence of the limit or branch points was imposed on the co-state equation (Upreti, [22]. If the minimization of q_1 lead to the value q_1^* and the minimization of q_2 lead to the value q_2^* The MNLPMC calculations will minimize the function $(q_1 - q_1^*)^2 + (q_2 - q_2^*)^2$. The multiobjective optimal control problem is

$$\min \quad (q_1 - q_1^*)^2 + (q_2 - q_2^*)^2 \quad subject\ to\ \frac{dx}{dt} = F(x,u) \tag{10}$$

Differentiating the objective function results in

$$\frac{d}{dx_i}\left((q_1 - q_1^*)^2 + (q_2 - q_2^*)^2\right) = 2(q_1 - q_1^*)\frac{d}{dx_i}(q_1 - q_1^*) + 2(q_2 - q_2^*)\frac{d}{dx_i}(q_2 - q_2^*) \tag{11}$$

The Utopia point requires that both $(q_1 - q_1^*)$ and $(q_2 - q_2^*)$ are zero. Hence

$$\frac{d}{dx_i}\left((q_1 - q_1^*)^2 + (q_2 - q_2^*)^2\right) = 0 \tag{12}$$

The optimal control co-state equation (Upreti; [22] is

$$\frac{d}{dt}(\lambda_i) = -\frac{d}{dx_i}\left((q_1 - q_1^*)^2 + (q_2 - q_2^*)^2\right) - f_x \lambda_i; \quad \lambda_i(t_f) = 0 \tag{13}$$

λ_i is the Lagrangian multiplier. t_f is the final time. The first term in this equation is 0 and hence

$$\frac{d}{dt}(\lambda_i) = -f_x\lambda_i; \lambda_i(t_f) = 0 \quad (14)$$

At a limit or a branch point, for the set of ODE $\frac{dx}{dt} = f(x,u)$ f_x is

singular. Hence there are two different vectors-values for $[\lambda_i]$ where

$\frac{d}{dt}(\lambda_i) > 0$ and $\frac{d}{dt}(\lambda_i) < 0$. In between there is a vector $[\lambda_i]$

where $\frac{d}{dt}(\lambda_i) = 0$. This coupled with the boundary condition

$\lambda_i(t_f) = 0$ will lead to $[\lambda_i] = 0$ This makes the problem an unconstrained optimization problem, and the optimal solution is the Utopia solution.

RESULTS AND DISCUSSION

Theorem

If one of the functions in a dynamic system is separable into two distinct functions, a branch point singularity will occur in the system.

Proof

Consider a system of equations

$$\frac{dx}{dt} = f(x,\alpha) \quad (2)$$

$x \in R^n$. Defining the matrix A as

$$A = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_3} & \frac{\partial f_1}{\partial x_4} \ldots\ldots \frac{\partial f_1}{\partial x_n} & \frac{\partial f_1}{\partial \alpha} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \frac{\partial f_2}{\partial x_3} & \frac{\partial f_2}{\partial x_4} \ldots\ldots \frac{\partial f_2}{\partial x_n} & \frac{\partial f_2}{\partial \alpha} \\ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \\ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \frac{\partial f_n}{\partial x_3} & \frac{\partial f_n}{\partial x_4} \ldots\ldots \frac{\partial f_n}{\partial x_n} & \frac{\partial f_n}{\partial \alpha} \end{bmatrix} \quad (3)$$

α is the bifurcation parameter. The matrix A can be written in a compact form as

$$A = [\frac{\partial f_p}{\partial x_q} . | \quad \frac{\partial f_p}{\partial \alpha}] \quad (4)$$

The tangent at any point x; ($z = [z_1, z_2, z_3, z_4, \ldots, z_{n+1}]$) must satisfy

$$Az = 0 \quad (5)$$

The matrix $\{\frac{\partial f_p}{\partial x_q}\}$ must be singular at both limit and branch points..

The n+1 th component of the tangent vector z_{n+1} = 0 at a limit point (LP) and for a branch point (BP) the matrix $B = \begin{bmatrix} A \\ z^T \end{bmatrix}$ must be singular. Any tangent at a point y that is defined by $z = [z_1, z_2, z_3, z_4, \ldots, z_{n+1}]$) must satisfy

$$Az = 0 \quad (6)$$

For a branch point, there must exist two tangents at the singularity.

Let the two tangents be z and w. This implies that

$$Az = 0 \quad (7)$$
$$Aw = 0$$

Consider a vector v that is orthogonal to one of the tangents (say z). v can be expressed as a linear combination of z and w ($v = \alpha z + \beta w$). Since $Az = Aw = 0$; $Av = 0$ and since z and v are orthogonal,

$z^T v = 0$. Hence $Bv = \begin{bmatrix} A \\ z^T \end{bmatrix} v = 0$ which implies that B is singular

where $B = \begin{bmatrix} A \\ z^T \end{bmatrix}$

Let any of the functions f_i are separable into 2 functions ϕ_1, ϕ_2 as

$$f_i = \phi_1\phi_2 \quad (8)$$

At steady-state $f_i(x,\alpha) = 0$ and this will imply that either

$\phi_1 = 0$ or $\phi_2 = 0$ or both ϕ_1 and ϕ_2 must be 0. This implies that two branches $\phi_1 = 0$ and $\phi_2 = 0$ will meet at a point where both ϕ_1 and ϕ_2 are 0.

At this point, the matrix B will be singular as a row in this matrix would be

$$[\frac{\partial f_i}{\partial x_k} | \frac{\partial f_i}{\partial \alpha}] \quad (9)$$

However,

$$[\frac{\partial f_i}{\partial x_k} = \phi_1(=0)\frac{\partial \phi_2}{\partial x_k} + \phi_2(=0)\frac{\partial \phi_1}{\partial x_k} = 0(\forall k = 1.,,n)$$
$$\frac{\partial f_i}{\partial \alpha} = \phi_1(=0)\frac{\partial \phi_2}{\partial \alpha} + \phi_2(=0)\frac{\partial \phi_1}{\partial \alpha}] = 0 \quad (10)$$

This implies that every element in the row $[\frac{\partial f_i}{\partial x_k} | \frac{\partial f_i}{\partial \alpha}]$ would be 0,

and hence the matrix B would be singular. The singularity in B implies that there exists a branch point.

When β is the bifurcation parameter; two branch points are found (Figure 1a) at (sv, iv, vv, zv, β) values of (431425, 0, 0, 0, 0.239558) and (1.3594. 0.52771, 0.630958, 0, 0.252250)

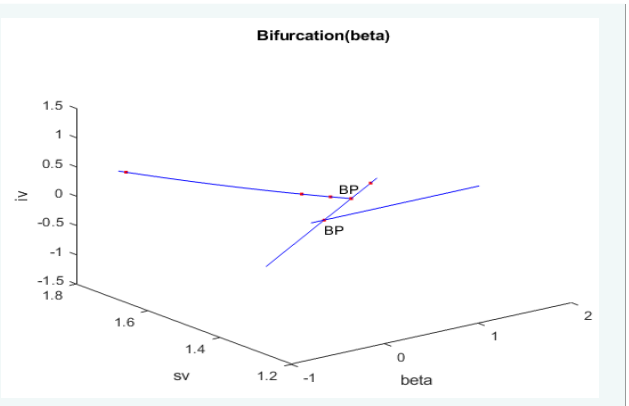

Figure 1a: β i is the bifurcation parameter

The second branch point is because of the two separable functions in the fourth ODE in the model equations.

$$\frac{d(zv)}{dt} = c(iv)zv - \mu(zv) \quad (11)$$

The two distinct equations are

$$zv = 0$$
$$c(iv) - \mu = 0 \quad (12)$$

With zv = 0, iv= 0.0.52771, c=8.4; μ =4.432768 both the distinct equations are satisfied, validating the theorem.

When δ is the bifurcation parameter; two branch points are found (Figure 1b) at (sv, iv, vv, zv, δ) values of (0.137164, 0, 0, 0, 31.349417) and (0.137164, 0.52771, 0.630958, 0, 29.772021)

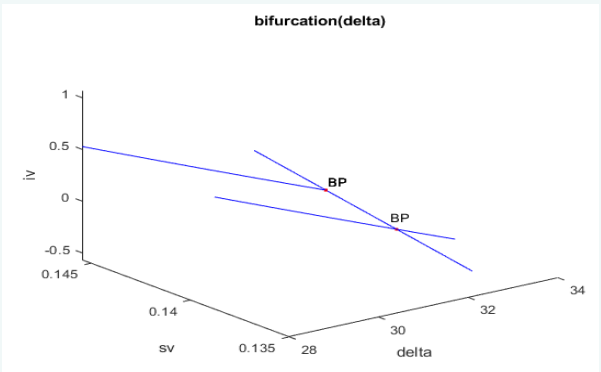

Figure 1b: δ is the bifurcation parameter

The second branch point arises from the two separable functions in the fourth ODE in the model equations.

$$\frac{d(zv)}{dt} = c(iv)zv - \mu(zv) \quad (11)$$

The two distinct equations are

$$zv = 0$$
$$c(iv) - \mu = 0 \quad (12)$$

With zv = 0, iv= 0.0.52771, c=8.4; μ =4.432768, both the distinct equations are satisfied, validating the theorem.

When c is the bifurcation parameter, two branch points are found (Figure 1c) at (sv, iv, vv, zv, c) values of (0.137164, 9.48283, 11.338167, 0, 0.467452). This branch point arises from the two separable functions in the fourth ODE in the model equations.

$$\frac{d(zv)}{dt} = c(iv)zv - \mu(zv) \quad (11)$$

The two distinct equations are

$$zv = 0$$
$$c(iv) - \mu = 0 \quad (12)$$

With zv = 0, iv=, 9.48283, c=0.467452; μ =4.432768, both the distinct equations are satisfied, validating the theorem.

When μ is the bifurcation parameter; two branch points are found (Figure 1d) at (sv, iv, vv, zv, μ) values of (0.137164, 9.482830, 11.338167,

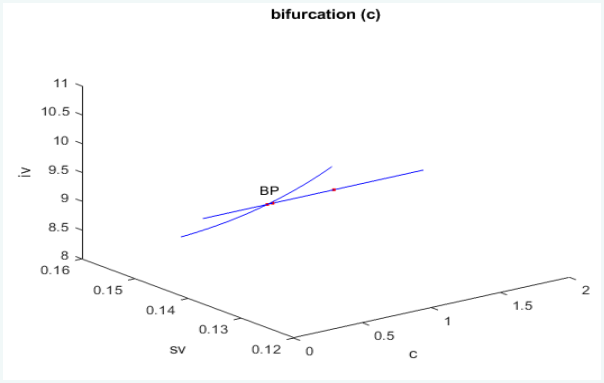

Figure 1c: c is the bifurcation parameter

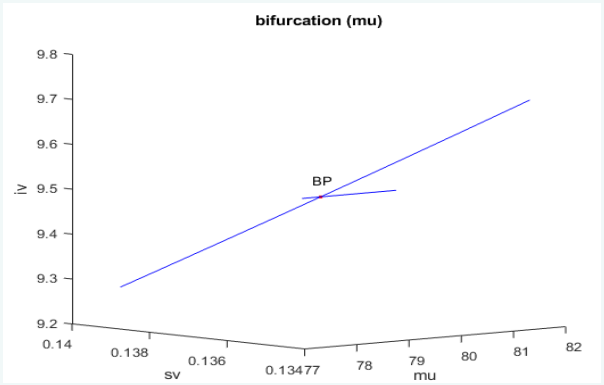

Figure 1d: μ is the bifurcation parameter

0, 79.655775)

This branch point arises from the two separable functions in the fourth ODE in the model equations.

$$\frac{d(zv)}{dt} = c(iv)zv - \mu(zv) \quad (11)$$

The two distinct equations are

$$zv = 0$$
$$c(iv) - \mu = 0 \quad (12)$$

With zv = 0, iv= , 9.482830, c=8.4; μ =79.655775, both the distinct equations are satisfied, validating the theorem. For the MNLMPC, β, δ are the control parameters, and

$\sum_{t_i=0}^{t_i=t_f} iv(t_i), \sum_{t_i=0}^{t_i=t_f} vv(t_i)$ were minimized individually, and each led

to a value of 0. The overall optimal control problem will involve the

minimization of $(\sum_{t_i=0}^{t_i=t_f} vv(t_i) - 0)^2 + (\sum_{t_i=0}^{t_i=t_f} iv(t_i) - 0)^2$ was

minimized subject to the equations governing the model. This led to a value of zero (the Utopia point). The MNLMPC profiles are shown

in Figure 2a-2b. The control profiles of β, δ exhibited noise (Figure 2c), and this was remedied using the Savitzky-Golay filter to produce the smooth profiles $\beta sg, \delta sg$ (Figure 2d).

The presence of the branch point causes the MNLMPC calculations to converge to the Utopia solution, validating the analysis by Sridhar [21].

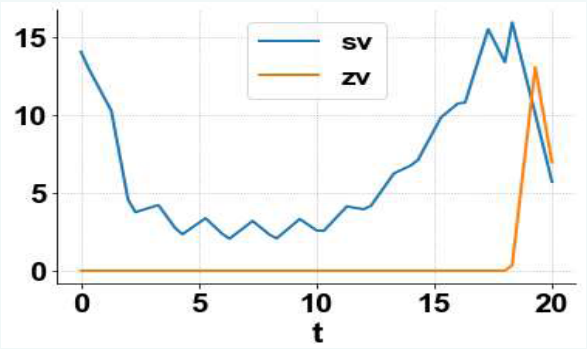

Figure 2a: MNLMC sv, zv profiles

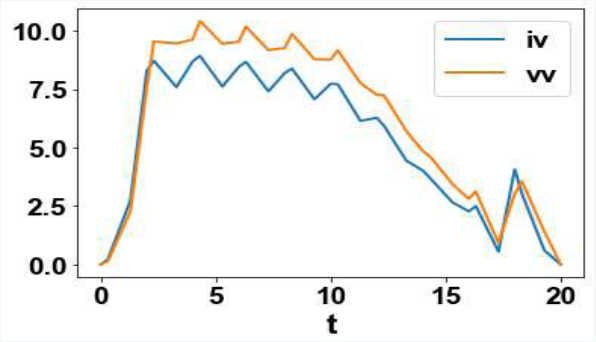

Figure 2b: MNLMC iv, vv profiles

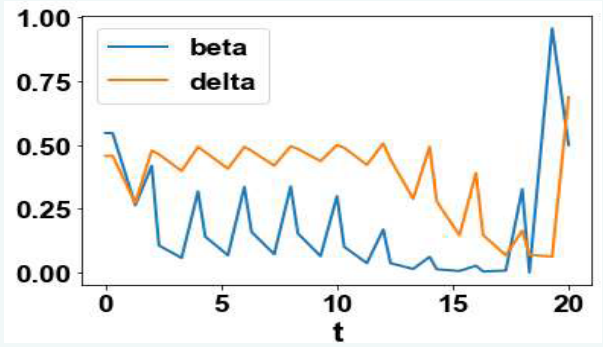

Figure 2c: MNLMPC, β, δ profiles

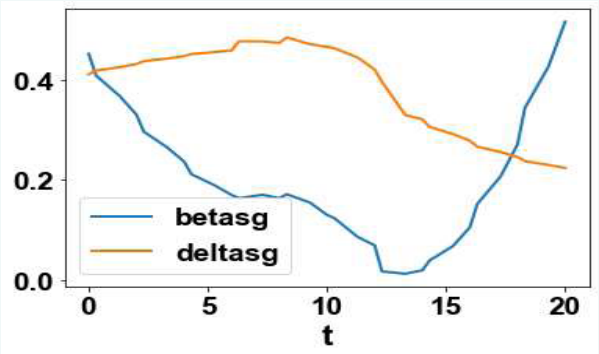

Figure 2d: $\beta sg, \delta sg$ profiles

CONCLUSIONS

Bifurcation analysis and Multi objective Nonlinear Control (MNLMPC) studies on a Hepatitis B virus model. The bifurcation analysis revealed the existence of branch points. The branch points (which cause multiple steady-state solutions from a singular point) are very beneficial because they enable the Multi objective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in the model. A combination of bifurcation analysis and Multi objective Nonlinear Model Predictive Control (MNLMPC) on a Hepatitis B virus model is the main contribution of this paper.

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