

Optimal Control Analysis on the Transmission Dynamics of Hepatitis C Virus Infection with Asymptomatic Carriers

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ABSTRACT

In this paper, the authors develop the transmission dynamics of the acute and chronic hepatitis C virus (HCV) epidemic problem and incorporate optimal control strategy for controlling the spread of the disease. In order to control the spread of the virus, we develop a control strategy by applying three control variables such as protection, treatment of acute infection and treatment of chronic infection to minimize the number of acute infected, chronically infected with HCV individuals and maximize the number of susceptible and recovered individuals. We find the necessary conditions for the optimal solution for controlling the spread of the virus using Pontryagin's Maximum Principle (PMP). Runge-Kutta of order four was used for the numerical simulation to demonstrate the achievability of the control strategies.

(Keywords: transmission, acute, chronic, hepatitis, control, strategy, disease, infection, protection, treatment, susceptible, recovered)

INTRODUCTION

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV): the virus can cause both acute and chronic hepatitis, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. Hepatitis C is a major cause of liver cancer.

The hepatitis C virus is a bloodborne virus: the most common modes of infection are through exposure to small quantities of blood. This may happen through injection drug use, unsafe injection practices, unsafe health care, transfusion of unscreened blood and blood products, and sexual practices that lead to exposure to blood. Globally, an estimated 71 million people have chronic hepatitis C virus infection (WHO, 2019). A

significant number of those who are chronically infected will develop cirrhosis or liver cancer. WHO estimated that in 2016, approximately 399 000 people died from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer).

Antiviral medicines can cure more than 95% of persons with hepatitis C infection, thereby reducing the risk of death from cirrhosis and liver cancer, but access to diagnosis and treatment is low. Hepatitis C virus causes both acute and chronic infection. New HCV infections are usually asymptomatic. Some persons get acute hepatitis which does not lead to a life-threatening disease. Around 30% (15–45%) of infected persons spontaneously clear the virus within 6 months of infection without any treatment. The remaining 70% (55–85%) of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis ranges between 15% and 30% within 20 years, (WHO, 2019).

WHO (2019) reported that the incubation period for hepatitis C ranges from 2 weeks to 6 months. Following initial infection, approximately 80% of people do not exhibit any symptoms. Those who are acutely symptomatic may exhibit fever, fatigue, decreased appetite, nausea, vomiting, abdominal pain, dark urine, grey-colored feces, joint pain and jaundice (yellowing of skin and the whites of the eyes).

New HCV infections are usually asymptomatic, few people are diagnosed when the infection is recent. In those people who go on to develop chronic HCV infection, the infection is also often undiagnosed because it remains asymptomatic until decades after infection when symptoms develop secondary to serious liver damage. HCV infection is diagnosed in 2 steps: (i) testing for anti-HCV antibodies with a serological test identifies people who have been infected with the

virus and (ii) if the test is positive for anti-HCV antibodies, a nucleic acid test for HCV ribonucleic acid (RNA) is needed to confirm chronic infection because about 30% of people infected with HCV spontaneously clear the infection by a strong immune response without the need for treatment. Although no longer infected, they will still test positive for anti-HCV antibodies.

After a person has been diagnosed with chronic HCV infection, they should have an assessment of the degree of liver damage (fibrosis and cirrhosis). This can be done by liver biopsy or through a variety of non-invasive tests. Early diagnosis can prevent health problems that may result from infection and prevent transmission of the virus. A new infection with HCV does not always require treatment, as the immune response in some people will clear the infection. However, when HCV infection becomes chronic, treatment is necessary (WHO, 2019).

Most of the HCV related disease burden in developed countries has resulted from injection drug use, transfusion before donor screening and high-risk sexual activity (Alter, 2007).

Aitken et al., (2007) conducted a study of HCV infection and reinfection in injecting drug users (IDUs), using a much shorter median testing interval and more precise ascertainment of reinfection.

Kalajdziewska and Li (2011) developed a deterministic mathematical model and studied the effect of carriers on general infectious diseases. They further used their model as a crude approximation for the transmission dynamics of chronic hepatitis B infection among an adult population. Their simulation results revealed that, in high HBV prevalence countries, testing and increasing awareness of carriers will have a much greater impact on the disease burden than increasing vaccination rates.

Moffat et al., (2014) developed a mathematical model and studied the effect of carriers in the transmission of typhoid fever in Kisii town Kenya. The numerical results show that reducing the typhoid carriers by 9.5% could assist Kisii county government in Kenya achieve a typhoid free status by 2030.

Several mathematical models of HCV infection were developed and analyzed by many researchers such as (Dontwi et al., 2010),

(Elamin, 2013), (Mather and Crofts, 1999), (Hanafiah, Groeger, Flaxman and Wiersma, 2013), (Pollack, 2001), (Pollack, 2001), (Vickerman, Hickman and Judd, 2006) and (Zeiler, Langlands, Murray and Ritter, 2010).

Echevarria et al., (2015) use a mathematical model to predict the impact of a direct-active antivirals (DAAs) treatment scale-up on HCV prevalence among persons who inject drugs (PWID) and the estimated cost in metropolitan Chicago using empirical data from three epidemiological studies. They show that treatment scale-up will reduce the HCV prevalence by one-half over 10 years of treatment that will cost \$(50-77) for 35 per 1,000 in the overall PWID population.

Natasha, et al., (2011) developed a model of HCV transmission and treatment among active injecting drug users (IDUs) to determine the optimal treatment program strategy over 10 years for two baseline chronic HCV prevalence scenarios (30% and 45%) with a range of maximum annual budgets (£50,000 – £300,000) pounds per 1,000 IDUs. Their objectives are to minimise the costs of health service and health utility losses.

Ainea, Massawe, Makinde and Namkinga (2015) considers an optimal control analysis for HCV model by incorporating education, health care, immunization, screening of immigrants and treatment in their model. Their aim is to minimize the spread of HCV disease in the community with inflows of immigrants and the cost of control strategies. Their result show that the effective use of optimal screening of immigrants together with education, health care, immunization and treatment have a significant impact in reducing the spread of the disease in the community.

Okosun (2014) consider a deterministic hepatitis C virus (HCV) model and study the impact of optimal control on the screening of immigrants and treatment of HCV on the transmission dynamics of the disease in a homogeneous population with constant immigration of susceptible. They investigate the costs associated with each of the strategies by formulating the costs function problem as an optimal control problem using the Pontryagin's Maximum Principle to solve the optimal control problems. Their result shows that the optimal combination of treatment of acute-infected and chronic-

infected individuals control strategy produced the same results as the combination of three control strategies (combination of screening of immigrants, treatment of acute-infected individuals and treatment of chronic-infected individuals).

Khan, Zaman and Chohan (2017) present a mathematical model for the transmission dynamic of the acute and chronic hepatitis B epidemic problem and develop an optimal control strategy to control the spread of hepatitis B in a community by applying three control variables such as isolation of infected and non-infected individuals, treatment and vaccination to minimize the number of acute infected, chronically infected with hepatitis B individuals and maximize the number of susceptible and recovered individuals. Khan, Sail, Imran and Malik (2014) present a rigorous mathematical analysis of a deterministic model for the transmission dynamics of hepatitis C virus using a standard incidence rate. They applied two control strategies (vaccination and isolation) which are designed to control the disease and to reduce the infected population.

Shah, Yeolekar and Shukla (2018) formulated a nonlinear Mathematical Model for Hepatitis C Virus with vertical transmission and effective control on the treatment cost. Numerically, they optimize the maximum amount for treatment cost paid by the Government and minimum amount of treatment paid by the infected individuals that will help in decreasing the burden of HCV in the population.

Therefore, we extended the work of Abdullahi, Momoh, Alhassan and Sajoh (2018) by incorporating control parameters into their model and optimal control was applied to analyse the effectiveness of the control(s) in tackling the transmission of the virus.

MODEL DESCRIPTION

The model is partitioned into five compartments comprises of Susceptible individuals at time t , $S(t)$, Asymptomatic (Acute) HCV infected individuals at time t , $I(t)$, Diagnosed individuals at time t , $D(t)$, Chronic HCV infected individuals, $C(t)$ and Recovered individuals, $R(t)$, and the total population is given as:

$$N(t) = S(t) + I(t) + D(t) + C(t) + R(t) \quad (1)$$

It is assumed that the recruitment rate into the susceptible population is constant, denoted by Λ , and the movement of individuals who recovered from the HCV infection due to loss of immunity at a rate ε . Susceptible individuals can die naturally at a rate μ . Susceptible individuals acquired the virus following effective contact rate β with infected individuals ($I(t)$, $D(t)$ or $C(t)$) at the rate

$$\rho = \frac{\beta(I(t) + \theta_1 D(t) + \theta_2 C(t))}{N(t)}$$

and move to the asymptomatic (acute) infected $I(t)$ compartment but the movement is controlled using sexual protection $u_1(t)$. θ_1 and θ_2 are the modification parameters that assumed to reduce the disease transmission for both diagnosed and chronic infected individuals in comparison to the acute infected individuals $I(t)$.

Individuals in $I(t)$ can die naturally at a rate μ and as a result of the HCV induced death at a rate δ_I . The $I(t)$ can further be reduced by those that had been diagnosed at a rate π and those that progressed to the chronic compartment after manifestation of the symptom at a rate σ . The diagnosed population is generated by those diagnosed from the asymptomatic (acute) infected class (at the rate π). While $u_2(t)$ denotes the control on treatment of diagnosed individuals and it reduces the population at a rate γ_1 due to the recovery from the virus. The diagnosed individuals can die due to the HCV infection at a rate δ_D and through naturally death, at a rate μ .

The chronic individuals are those that progresses from symptomatic compartment as a result of the appearance of the symptoms at a rate σ and it can be reduced when the control on treatment $u_3(t)$ is applied on those who are chronically infected at a rate γ_2 . It can further be decreased due to the HCV induced death at a rate δ_C and through natural death at a rate μ .

Lastly, the recovered population increases due to the treatments on both diagnosed and chronic individuals at a rate γ_1 and γ_2 . But it can be reduced due to natural death rate μ and those who lost immunity after recovery at a rate ε . Thus the model equations are given as:

$$\dot{S}(t) = \Lambda - (1 - u_1(t))\rho S(t) + \varepsilon R(t) - \mu S(t) \quad (2)$$

$$\dot{I}(t) = (1 - u_1(t))\rho S(t) - (\pi + \sigma + \delta_I + \mu)I(t) \quad (3)$$

$$\dot{D}(t) = \pi I(t) - (u_2(t)\gamma_1 + \delta_D + \mu)D(t) \quad (4)$$

$$\dot{C}(t) = \sigma I(t) - (u_3(t)\gamma_2 + \delta_C + \mu)C(t) \quad (5)$$

$$\dot{R}(t) = u_1(t)\gamma_1 D(t) + u_2(t)\gamma_2 C(t) - (\varepsilon + \mu)R(t) \quad (6)$$

Table 1: Parameters and Variables of the Model.

Symbols	Descriptions	Values and References
Λ	Recruitment rate into the Susceptible pool	100 Okosun & Makinde (2014)
μ	Natural death rate	0.00004 Okosun & Makinde (2014)
δ_I	HCV induced death rate of asymptomatic individuals	0.2201 Assumed
δ_D	HCV induced death rate of diagnosed individuals	0.0476 Assumed
δ_C	HCV induced death rate of symptomatic individuals	0.2801 Assumed
β	Transmission coefficient	0.1 Assumed
θ_1	Modification parameter associated with reduced transmission rate by diagnosed infected individuals	0.3 Assumed
θ_2	Modification parameter associated with reduced transmission rate by symptomatic infected individuals	0.5 Assumed
γ_1	Recovery rate of diagnosed individuals	0.13 Okosun & Makinde (2014)
γ_2	Recovery rate of symptomatic individuals	0.3 Okosun & Makinde (2014)
σ	Rate of appearance of symptoms of asymptomatic individuals	0.0588 Assumed
π	Rate of diagnosis (the rate at which asymptomatic individuals are made aware of their infection through testing)	0.5 Okosun & Makinde (2014)
$S(0)$	Susceptible individuals at time t	800 Okosun & Makinde (2014)
$I(0)$	Acute individuals at time t	10 Okosun & Makinde (2014)
$D(0)$	Diagnosed individuals at time t	50 Okosun & Makinde (2014)
$C(0)$	Chronic individuals at time t	10 Assumed
$R(0)$	Recovered individuals at time t	5 Assumed

OPTIMAL CONTROL ANALYSIS

The optimal control problem is formulated for the HCV model by introducing into the models (2 – 6), time-dependent control variables $u_1(t)$, $u_2(t)$ and $u_3(t)$ in order to determine optimal HCV control strategies (Sexual protection and Treatments) with minimal implementation cost.

For the optimal control problem of the given system, we consider the control variables $u(t) = [u_1(t), u_2(t), u_3(t)] \in U$ relative to the state variables $S(t)$, $I(t)$, $D(t)$, $C(t)$, $R(t)$ where control variables are bounded and measured with $\{U = (u_1, u_2, u_3)$ is Lebesgue measurable on $[0, 1]$, $0 \leq u_i(t) \leq 1, t \in [0, tf], i = 1, 2, 3\}$.

The objective functional is given as:

$$J = \min_{u_1, u_2, u_3} \int_0^{tf} \left(A_1 D + A_2 C + \frac{B_1 u_1^2}{2} + \frac{B_2 u_2^2}{2} + \frac{B_3 u_3^2}{2} \right) dt \quad (7)$$

where tf is the final time and the coefficients A_1, A_2, B_1, B_2 and B_3 are positive weights to balance the factors. The terms $A_1 D$ and $A_2 C$ are the cost of infection while $B_1 u_1^2, B_2 u_2^2$ and $B_3 u_3^2$ are the costs associated with u_1 (protection), u_2 (treatment of diagnosed individuals) and u_3 (treatment of symptomatic individuals).

We seek optimal control u_1, u_2, u_3 such that:

$$J(u_1^*, u_2^*, u_3^*) = \min \{ J(u_i, u_2, u_3), (u_i, u_2, u_3 \in U) \} \quad (8)$$

The necessary conditions that an optimal control must satisfy the Pontryagin's Maximum Principle (PMP) that converts (2 – 6) into a problem of minimizing pointwise a Hamiltonian H , with respect to u_1, u_2, u_3 .

$$\begin{aligned} H = & A_1 D + A_2 C + \frac{B_1 u_1^2}{2} + \frac{B_2 u_2^2}{2} + \frac{B_3 u_3^2}{2} \\ & + \lambda_S \{ \Lambda - [1 - u_1(t)] \rho S(t) - \mu S(t) \} \\ & + \lambda_I \{ [1 - u_1(t)] \rho S(t) - (\pi + \sigma) I(t) - (\delta_I + \mu) I(t) \} \quad (9) \\ & + \lambda_D \{ \pi I(t) - u_2(t) \gamma_1 D(t) - (\delta_D + \mu) D(t) \} \\ & + \lambda_C \{ \sigma I(t) - u_3(t) \gamma_2 C(t) - (\delta_C + \mu) C(t) \} \\ & + \lambda_R \{ u_2(t) \gamma_1 D(t) + u_3(t) \gamma_2 C(t) - \mu R(t) \} \end{aligned}$$

where $\lambda_S, \lambda_I, \lambda_D, \lambda_C$ and λ_R are the adjoint variables or co-state variables.

In order to find the necessary conditions for this optimal control, we apply the Pontryagin's Maximum Principle and the existence result for the optimal control as described by (Lenhart & Workman, 2007).

Theorem: The optimal controls u_1^*, u_2^*, u_3^* and solutions S, I, D, C, R of the corresponding state system (2 – 6), then there exist adjoint variables $\lambda_S, \lambda_I, \lambda_D, \lambda_C$ and λ_R satisfying:

$$\begin{aligned} -\frac{d\lambda_S}{dt} &= \frac{\partial H}{\partial S(t)}, \quad -\frac{d\lambda_I}{dt} = \frac{\partial H}{\partial I(t)}, \quad -\frac{d\lambda_D}{dt} = \frac{\partial H}{\partial D(t)}, \\ -\frac{d\lambda_C}{dt} &= \frac{\partial H}{\partial C(t)}, \quad -\frac{d\lambda_R}{dt} = \frac{\partial H}{\partial R(t)} \end{aligned} \quad (10)$$

then,

$$\begin{aligned} \frac{\partial H}{\partial S(t)} &= ([1 - u_1(t)] \lambda) (\lambda_S - \lambda_I) + \mu \lambda_S \\ \frac{\partial H}{\partial I(t)} &= \left([1 - u_1(t)] \frac{\beta S(t)}{N(t)} \right) (\lambda_S - \lambda_I) \\ &+ \pi (\lambda_I - \lambda_D) + \sigma (\lambda_I - \lambda_C) + (\delta_I + \mu) \lambda_I \\ \frac{\partial H}{\partial D(t)} &= \left([1 - u_1(t)] \frac{\theta_1 S(t)}{N(t)} \right) (\lambda_S - \lambda_I) \\ &+ u_2(t) \gamma_1 (\lambda_D - \lambda_R) + (\delta_D + \mu) \lambda_D - A_1 \\ \frac{\partial H}{\partial C(t)} &= \left([1 - u_1(t)] \frac{\theta_2 S(t)}{N(t)} \right) (\lambda_S - \lambda_I) \\ &+ u_3(t) \gamma_2 (\lambda_C - \lambda_R) + (\delta_C + \mu) \lambda_C - A_2 \\ \frac{\partial H}{\partial R(t)} &= \varepsilon (\lambda_R - \lambda_S) + \mu \lambda_R \end{aligned} \quad (11)$$

with transversality conditions,

$$\lambda_S(tf) = \lambda_I(tf) = \lambda_D(tf) = \lambda_C(tf) = \lambda_R(tf) = 0 \quad (12)$$

using the optimality conditions;

$$u_1^* = \max \left\{ 0, \min \left(1, \bar{u}_1 \right) \right\},$$

$$u_2^* = \max \left\{ 0, \min \left(1, \bar{u}_2 \right) \right\} \text{ and}$$

$$u_3^* = \max \left\{ 0, \min \left(1, \bar{u}_3 \right) \right\}$$

we solve the given optimality conditions to find $\bar{u}_1 = u_1, \bar{u}_2 = u_2$ and $\bar{u}_3 = u_3$, we let:

$$\frac{\partial H}{\partial u_1} = 0, \quad \frac{\partial H}{\partial u_2} = 0 \text{ and } \frac{\partial H}{\partial u_3} = 0, \quad (13)$$

we differentiate (9) with respect to u_i , $0 < u_i \leq 1$, where $i = 1, 2, 3$ to obtain:

$$\frac{\partial H}{\partial u_1} = B_1 u_1 + \rho S(t) \lambda_S - \rho S(t) \lambda_I \quad (14)$$

$$u_1 = \rho S(t) (\lambda_I - \lambda_S)$$

$$\frac{\partial H}{\partial u_2} = B_2 u_2 - \gamma_1 D(t) \lambda_D + \gamma_1 D(t) \lambda_R \quad (15)$$

$$u_2 = \frac{\gamma_1 D(t) (\lambda_D - \lambda_R)}{B_2}$$

$$\frac{\partial H}{\partial u_3} = B_3 u_3 - \gamma_2 C(t) \lambda_C + \gamma_2 C(t) \lambda_R \quad (16)$$

$$u_3 = \frac{\gamma_2 C(t) (\lambda_C - \lambda_R)}{B_3}$$

therefore,

$$u_1^* = \max \left\{ 0, \min \left(1, \rho S(t) (\lambda_I - \lambda_S) \right) \right\}, \quad (17)$$

$$u_2^* = \max \left\{ 0, \min \left(1, \frac{\gamma_1 D(t) (\lambda_D - \lambda_R)}{B_2} \right) \right\} \quad (18)$$

$$u_3^* = \max \left\{ 0, \min \left(1, \frac{\gamma_2 C(t) (\lambda_C - \lambda_R)}{B_3} \right) \right\} \quad (19)$$

NUMERICAL SIMULATIONS

In this section, we investigate numerically the effect of the control strategies on the spread of HCV in a population. We solve the optimality system using iterative method which will result into the optimal sexual protection and treatments strategies in controlling the HCV transmission dynamics. The optimal control solution is obtained by solving the optimality system, which consists of the state system and the adjoint system. Because of the transversality conditions, we solve the state equations with a guess for the controls over the simulated time using the fourth-order Runge–Kutta scheme.

First, we consider the application of sexual protection in the susceptible class, the treatment on the acute infected individuals and the treatment on the chronic infected individuals to see the effect of each control in their respective classes.

Implementing Sexual Protection (u_1) as Control

We consider implementing the sexual protection u_1 as a control against the HCV transmission in the population. We use u_1 to optimize the objective functional (J) while we set $u_2 = 0$ and $u_3 = 0$, so we can see the effectiveness of the control in reducing the virus transmission.

We observe from Figures 1(a) - 1(c) a significant decrease in acute, diagnosed and chronic infected individuals as against when there is no control. Therefore, the control is very effective in control the virus transmission. While, figure 1(d) the control profile shows a swift decline in the transmission from 100% to the lower bound at $t = 10$ years.

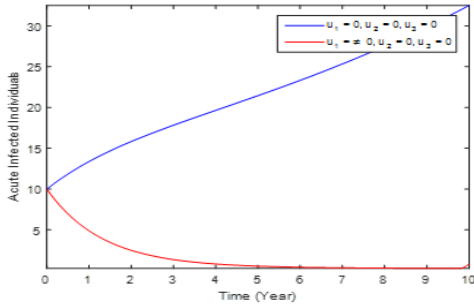


Figure 1(a)

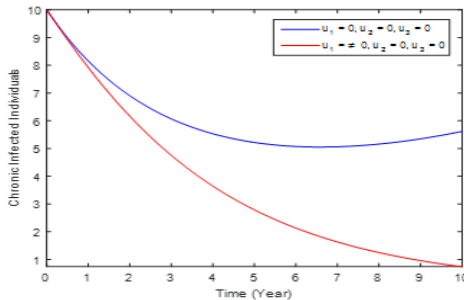


Figure 1(b)

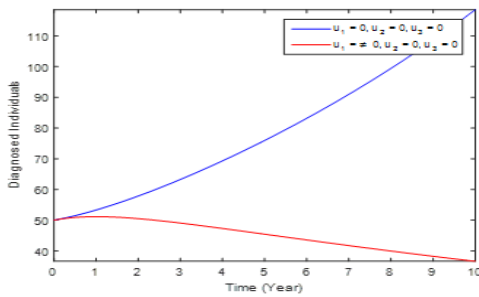


Figure 1(c)

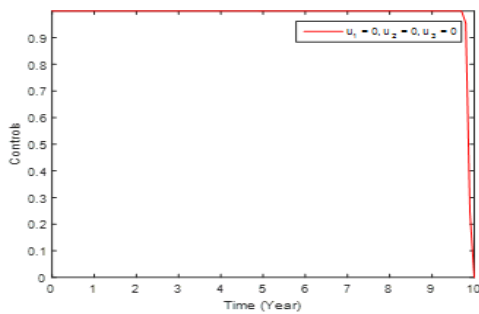


Figure 1(d)

Implementing Treatment on Acute Individuals (u_2) as Control

The treatment control u_2 of acute infected individuals, was used to optimize the objective

functional (J) while we set $u_1 = 0$ and $u_3 = 0$. It has been observed from Figure 2(a) that the number of acute infected individuals declines gradually due to the drug efficacy of acute treatment as compared with when there is no control. While, the control profile, figure 2(b) shows how the control decrease the infection swiftly from the highest bound to the lower bound at $t = 9.9$ years.

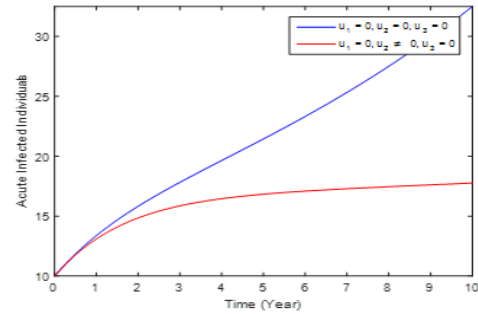


Figure 2(a)

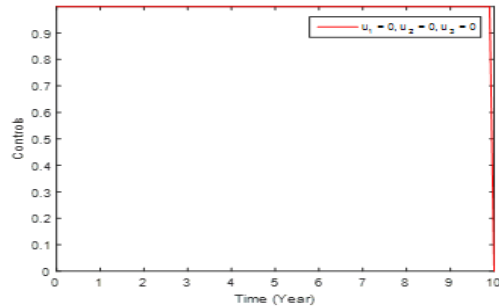


Figure 2(b)

Implementing Treatment on Chronic individuals (u_3) as Control

The treatment control u_3 of chronic infected individuals, was used to optimize the objective functional (J) while we set $u_1 = 0$ and $u_2 = 0$. It has been observed from figure 3(a) that the number of chronic infected individuals decreases more due to the drug efficacy of chronic treatment as compared with when there is no control. While, the control profile, figure 3(b) shows how the control decrease the infection swiftly from the highest bound to the lower bound at $t = 9.8$ years.

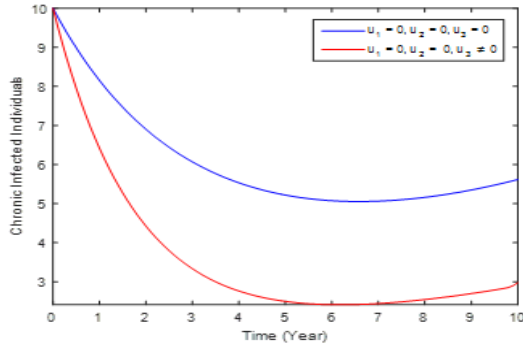


Figure 3(a)

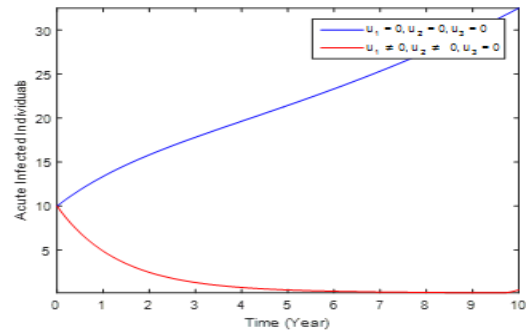


Figure 4(a)

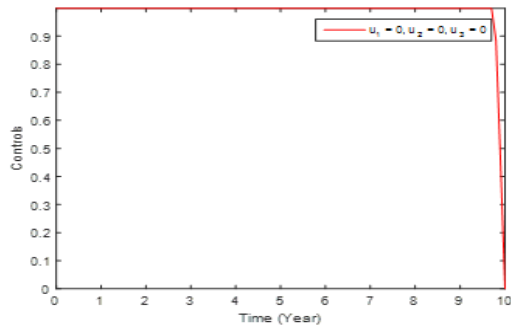


Figure 3(b)

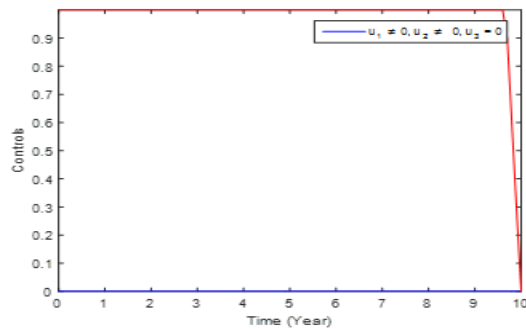


Figure 4(b)

Implementing Sexual Protection u_1 and Treatment for Acute Individuals u_2 at Acute Stage as Control

We use the sexual protection u_1 and the treatment of acute infected individuals u_2 to optimize the objective functional (J) while we set $u_3 = 0$, and it shows clearly the effectiveness of the two controls simultaneously.

Figure 4(a) shows how the number of acute infected individuals declines gradually as compared with when there is no control. While, the control profile, Figure 4(b) shows how the control decrease the infection swiftly from the highest bound to the lower bound at $t = 9.8$ years.

Implementing Sexual Protection u_1 and Treatment of Chronic Individuals u_3 at Chronic Stage as Control

The sexual protection u_1 and the treatment of chronic infected individuals u_3 are used to optimize the objective functional (J) while we set $u_2 = 0$, and it shows clearly the effectiveness of the two controls concurrently.

Figure 5(a) shows how the number of acute infected individuals declines gradually as compared with when there is no control. While, the control profile, Figure 5(b) show that the controls decrease the infection swiftly from the highest bound to the lower bound at $t = 6.6$ years and $t = 9.8$ years.

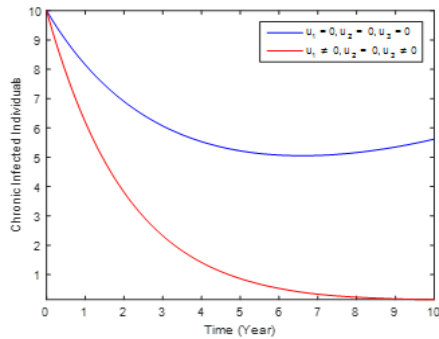


Figure 5(a)

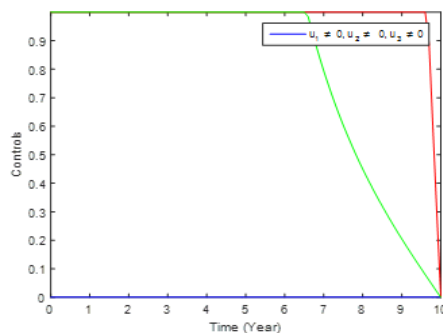


Figure 5(b)

CONCLUSION

In this work, a mathematical model of HCV dynamics was formulated, by incorporating three control parameters that will curtail the transmission of the virus. We considered optimal control strategy using Pontryagin's maximum principle to analyze the effectiveness of the three (3) controls: sexual protection u_1 , treatment of acute individuals u_2 and treatment of chronic individual u_3 . We observe that the implementation of the controls individually or concurrently will have a significant impact in decreasing the transmission of the virus after some time.

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