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THE EFFECT OF IMMUNE RESPONSES IN HCV DISEASE PROGRESSION

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Abstract. In this research article, the discreet role of Cytotoxic T Lymphocyte (CTL) during the Hepatitis C Virus infection has been studied. To explore the implications of the CTL responses, we have formulated a model considering the dynamics of the population of uninfected liver cells, infected liver cells, HCV and CTL responses. Since the actual incidence rate is probably not linear over the entire range of virus and uninfected liver cells. So, here we have assumed that there exists a saturation effect in disease transmission rate. We have analysed the model by both analytical as well as numerical approaches. We have found out the threshold condition that determines the existence and stability of the endemic equilibrium.

Keywords: HCV; CTL; functional response; liver cell; sensitivity analysis.

2010 AMS Subject Classification: 97M60.

1. Introduction

Hepatitis C is an infectious disease caused by Hepatitis C virus. It is highly blood contagious and very low risk of sexual and vertical transmission [1]. Unhygienic clinical conditions and improper sterilization are the main reasons behind the Hepatitis C infection [2].

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According to the World Health Organisation (WHO), an estimated of 71 million people, globally has been suffering from chronic Hepatitis C syndromes, resulting in cirrhosis and liver cancer. And fatality rate is approximately $39,900$ every year. Presently, there is no vaccine available for Hepatitis C, but research on this filed is still being carried on.

The footprints of the disease can be traced across the globe, but Eastern Mediterranean and Europe Regions are the worst affected, affecting 2.3% and 1.5% of the population respectively. Hepatitis C virus was untreated till 1975, but it's presence was traced back in 1989 [3].

Hepatitis C syndromes are multiple and demographically manipulated. The virus generally spreads and affects in between 2 weeks to 6 months in the human body. Fever, fatigue, nausea, vomiting, abdominal pain, dark urine, grey face, joint pain, and jaundice are the symptoms of Hepatitis C affected patient. But the worst part of the disease is that the virus sometime remains undiagnosed for a long time and prolonged Hepatitis C infection leads to liver damage (fibrosis and cirrhosis)

The role of Cytotoxic T Lymphocyte (CTL) and antibody responses in HCV infection is not fully understood yet. Antibody responses have the potential to control infection. But the evolution of antigenic escape allows the virus to persist in the host. CTL responses are required to resolve the infection and that virus persistence is caused by week CTL responses. Due to cellular immune responses against the virus, specifically that of CTLs which activates hepatic stellate cells and, thus leads to liver inflammation and fibrosis.

Appropriate mathematical models can be helpful to answer biological important questions concerned with the dynamics of the immune response to persistence virus. The effectiveness of drug therapy has been formulated by several authors. Various theoretical studies have been carried out on the mathematical model of HCV transmission dynamics. Nowak and Banghum [4] used a mathematical model to explore the effect of individual variation in immune responses on virus load and diversity. They found better indications of CTL responses in the equilibrium virus load, rather than the abundance of virus-specific CTLs. Bonhoeffer et. al. [5] analysed the virus populations role of the immune system and resistance of the drug therapy for the HIV or Hepatitis B virus. Neumann et. al. [6] used a mathematical model to analyse the efficacy of treatment with IFN-a therapy. Avendan et al. [7] formulated a mathematical model to describe

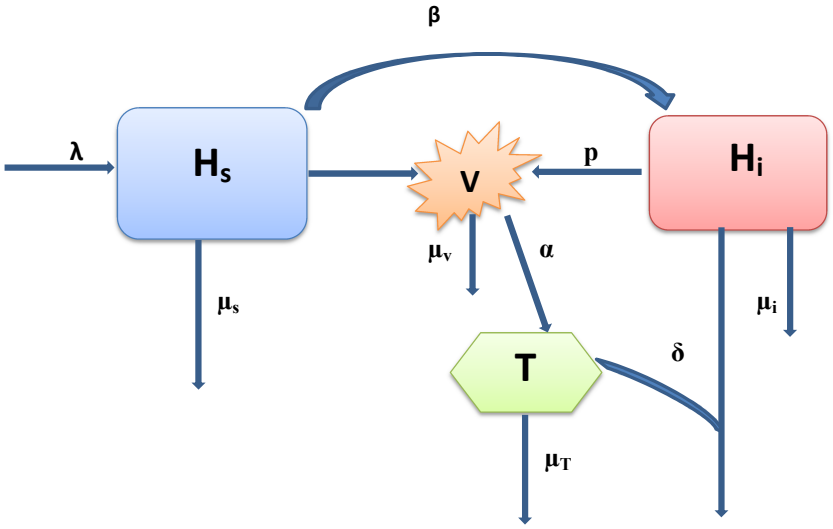

FIGURE 1. Schematic explanation for the model (1) showing the effect of CTL responses

HCV considering four population susceptible or healthy liver cell, infected liver cell, virus, and CTL responses. Zhao et al. [8] assume that the incidence rate of the virus model is described by a Beddington-DeAngelis functional responses. This article is arranged in the following manner: In the first section, we formulate the basic mathematical model on the basis of CTL responses against the infected cells along with saturating infection. Here we show how CTL responses on the human immune system for HCV patients. We have also carriedout the analytical and numerical studies. In the last section, we have discussed the implication of the results which were found in the earlier sections.

2. Formulation of the basic model

In this research article we have considered the basic model proposed by Avendan [7], considering healthy liver cells ($H_s(t)\ mm^{-3}$), infected liver cells ($H_i(t)\ mm^{-3}$), virus population ($V(t)\ mm^{-3}$) and the CTL responses ($T(t)\ mm^{-3}$). Healthy Liver cell H_s are produced at a rate λ and die at a constant rate μ_s. Healthy liver cells become infected at a rate proportional to the product of H_s and V, with constant of proportionality k, and once infected die with a constant

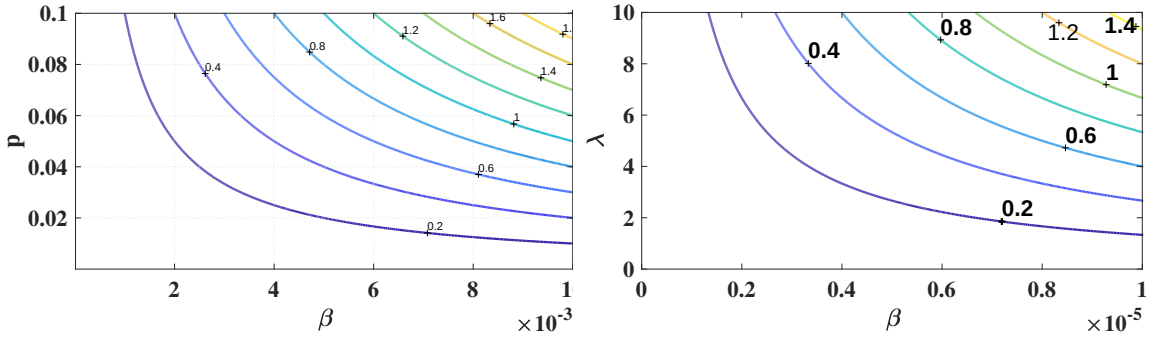

FIGURE 2. Left Panel: Contour plot of R_0 as a function of β and p. Right Panel: Contour plot of R_0 as a function of β and λ.

rate of μ_i. Since the average lifetime of infected cells is shorter than the average lifetime of the healthy cell, thus we assume $\mu_s < \mu_i$. Since the actual viral infection is not linear, then it is better to assume that the infection rate of viral infection model is given by saturated infection rate[9]. Here we assume that the infection rate of the virus dynamics models is given by the Beddington-DeAngelis functional response, $\frac{\beta H_s V}{1+kV}$, where β, and k are constants [8]. Thus the equation of the model becomes

$$\begin{aligned}
\dot{H}_s &= \lambda - \mu_s H_s - \frac{\beta H_s V}{1+kV} \\
\dot{H}_i &= \frac{\beta H_s V}{1+kV} - \mu_i H_i - \delta H_i T \\
\dot{V} &= pH_i - \mu_v V \\
\dot{T} &= \alpha V(1 - \frac{T}{T_m}) - \mu_t T.
\end{aligned} \tag{1}$$

We assume that Hepatitis C virions are produced inside the infected cells at a rate of p virions per infected cell per day. On the other hand, viruses die at a per capita constant rate μ_v. In the presence of HCV, the CTL responses is given by $\alpha V(1 - \frac{T}{T_m})$ [7] and μ_t is the per capita death rate of CTL responses. The killing rate of infected cells via mass action kinetics by the CTL immune responses is denoted by δ. It is also assumed that all parameters of the model are always positive.

3. Existence condition and stability analysis of the basic model

To study the model (1), we have observed that there exist two equilibrium point: (1) The disease free equilibrium point $\bar{E}(\frac{\lambda}{\mu_s},0,0,0)$; and (2) The endemic equilibrium point $E^*(H_s^*,H_i^*,V^*,T^*)$ exist in the region Ω define as

$\{\Omega=\{H_s,H_i,T,V\}\in R^4{}_+ \mid H_s+H_i\leq H_{max},V\leq V_{max},T\leq T_{max}\}$, where $H_{max}=\frac{\lambda}{\mu_s}$, $V_{max}=\frac{p\lambda}{\mu_s\mu_v}$, $T_{max}=\frac{\alpha p\lambda}{\alpha p\lambda+\mu_s\mu_t\mu_v}$, is positively invariant for system (1) for $t>0$. Here we will assume that initial conditions are always given in Ω. Detail description regarding the maximum cell count is given in Section 3.4.

Remark: From the above study we have clearly observed that the maximum value of liver cells is H_{max}, and V_{max} is the maximum value of the HCV. On the other hand, the maximum value of the CTL responses in presence of HCV is T_{max}.

The endemic equilibrium point must satisfy the relations $H_s^*=\frac{\lambda(1+kV^*)}{\beta V^*+\mu_s(1+kV^*)}$, $H_i^*=\frac{\mu_v V^*}{p}$,$T^*=\frac{\alpha V^*T_m}{\alpha V^*+\mu_t T_m}$ and V^* is defined as

$a_1V^{*2}+a_2V^*+a_3=0$, where $a_1=(\beta+k\mu_s)(\alpha\mu_i\mu_v+\alpha\delta\mu_vT_m)$, $a_2=\mu_s(\mu_i\mu_v\alpha+\alpha\delta\mu_vT_m)+\mu_i\mu_v\mu_tT_m(\beta+k\mu_s)-\lambda\beta$, $a_3=\mu_i\mu_v\mu_s\mu_tT_m-\alpha\beta p\mu_tT_m$.

Since $a_1>0$, $a_2>0$, then we can conclude that if $a_3<0$, there exist a positive root of V^*. Now, if $\frac{\alpha\beta p}{\mu_i\mu_v\mu_s}>1$, then $a_3<0$. Hence we can conclude that if the disease transmission rate dominate the death rate of the models, then the endemic equilibrium persist.

3.1. The disease free state

There may exist disease free equilibrium point $\bar{E}$ which is given by $\bar{E}(\frac{\lambda}{\mu_s},0,0,0)$. Now for the system (1), the Jacobian matrix is given by

$$J=\begin{pmatrix}-\mu_s & 0 & -\frac{\beta\lambda}{\mu_s} & 0\\ 0 & -\mu_i & \frac{\beta\lambda}{\mu_s} & 0\\ 0 & p & -\mu_v & 0\\ 0 & 0 & \alpha & -\mu_T\end{pmatrix}.$$

The characteristic equation for the disease free equilibrium is

$$(\Lambda+\mu_s)(\Lambda+\mu_T)[\Lambda^2+(\mu_i+\mu_v)\Lambda+\mu_i\mu_v-\frac{p\beta\lambda}{\mu_s}]=0 \tag{2}$$

For $\mu_i\mu_v - p\beta H_s > 0$, there exist no positive roots and all roots are negative. Hence, the basic reproduction R_0 is $\frac{p\lambda\beta}{\mu_s\mu_i\mu_v}$.

Remark: At disease free equilibrium point $\bar{E}$, the system is locally stable if the basic reproduction number $R_0 < 1$ and the system is unstable when $R_0 > 1$.

3.2. The Endemic state

For endemic equilibrium E^*, the Jacobian is

$$J(E^*)=\begin{pmatrix} -\mu_s+\frac{\beta V^*}{(1+kV^*)^2} & 0 & -\frac{\beta H_s^*}{(1+kV^*)^2} & 0 \\ \frac{\beta V^*}{(1+kV^*)^2} & -\mu_i-\delta T^* & \frac{\beta H_s^*}{(1+kV^*)^2} & 0 \\ 0 & p & -\mu_v+kT^* & 0 \\ 0 & 0 & -\alpha(1-\frac{T}{T_m}) & -\mu_t \end{pmatrix}.$$

The characteristic equation becomes

$$\Lambda^4+a_1\Lambda^3+a_2\Lambda^2+a_3\Lambda+a_4=0 \tag{3}$$

where

$$\begin{aligned} a_1 &= \mu_s+t_1+t_2+t_3+t_5+\mu_v>0, \\ a_2 &= t_3(\mu_s+t_1)+\mu_v t_5+(\mu_s+t_1+t_3)(\mu_v+t_5)-pt_2>0, \\ a_3 &= \mu_v t_5(\mu_s+t_1+t_3)+t_3(\mu_s+t_1)(\mu_v+t_5)-pt_2(t_5+\mu_s)+p\delta H_i^* t_4>0, \\ a_4 &= t_3(\mu_s+t_1)\mu_v t_5+p\delta t_4 t_1 H_i^*-pt_2t_5\mu_5>0, \\ t_1 &= \frac{\beta V^*}{1+kV^*},\ t_2=\frac{\beta H_s^*}{(1+kV^*)^2} \\ t_3 &= \mu_i+\delta T^*,\ t_4=\alpha(1-\frac{T}{T_m}),\ t_5=\frac{\alpha V^*}{T_m}+\mu_T. \end{aligned} \tag{4}$$

Using the Routh-Hwritz criteria [14], the local stability of the endemic equilibrium E^* will be stable if we can show that

$$\Delta_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & a_4 & a_3 \end{pmatrix} > 0.$$

Remark The Endemic equilibrium E^* is exist if $R_0 > 1$ and it is stable if $a_1 > 0,\ a_2 > 0,\ a_3 > 0,\ a_4 > 0,\ a_1a_2 - a_3 > 0$,.

3.3. Global Stability Analysis

The system $\bar{E}$ is globally stable if the system satisfy the following three conditions as follows:

(1) $\bar{E}$ is locally asymptotically stable,

(2) for $\frac{d\Gamma_1}{dt} = f(\Gamma_1, 0)$, ${\Gamma_1}^0$ is globally asymptotically stable, and

(3) $\bar{E}$ satisfies the Liapunov-Lasalle Theorem.

Now we want to prove that the system is locally asymptotically stable. Thus we rewrite the system (1) in the form given below

$$\frac{d\Gamma_1}{dt} = f(\Gamma_1, \Gamma_2), \frac{d\Gamma_2}{dt} = f(\Gamma_1, \Gamma_2) \tag{5}$$

where Γ_1, Γ_2 are defined as follows

$$\Gamma_1 = (H_s), \Gamma_2 = (H_i, V, A). \tag{6}$$

Now if we can show that, $f(\Gamma_1, 0)$ is a limiting function of

$$\frac{d\Gamma_1}{dt} = f(\Gamma_1), i.e. \lim_{t\to\infty} \Gamma_1 = {\Gamma_1}^*, \tag{7}$$

Then we can conclude that the system $\bar{E}$ is globally asymptotically stable.

3.4. Total Cell Count

We consider $H_{tot} = H_s + H_i$

Then

$$\begin{aligned}\frac{dH_{tot}}{dt} &= \frac{dH_s}{dt} + \frac{dH_i}{dt} \\ &\leq \lambda - \mu_s H_s - \mu_i H_i \\ &\leq \lambda - \mu_s H_{tot},\ since\ \mu_s < \mu_i \\ \Rightarrow H_{tot} &\leq \frac{\lambda}{H_{tot}}\ as\ t \to \infty\end{aligned} \tag{8}$$

Hence the total liver cell count is always below $\frac{\lambda}{H_{tot}}$.

For CTL responses,

$$\begin{aligned}\frac{dA}{dt} &= \alpha V(1 - \frac{T}{T_m}) - \mu_t T \\ &\leq \frac{\alpha p \lambda}{\mu_s \mu_v} - \frac{\alpha p \lambda + \mu_s \mu_v \mu_t}{\mu_s \mu_v} T \\ \Rightarrow A(t) &\leq \frac{\alpha p \lambda}{\alpha p \lambda + \mu_s \mu_t \mu_v}.\end{aligned} \tag{9}$$

For HCV population,

$$\begin{aligned}\frac{dV}{dt} &= pH_i - \mu_v V \\ &\leq \frac{p\lambda}{\mu_s} - \mu_v T \\ \Rightarrow V(t) &\leq \frac{p\lambda}{\mu_s \mu_v}\end{aligned} \tag{10}$$

4. Sensitivity Analysis

In this section, we have studied the sensitivity analysis of the reproduction number R_0. Through sensitivity analysis, we can predict the amount and type of change of the model behavior by the change of the parameters. If the basic reproduction number is very sensitive to a particular parameter, then a perturbation of that condition affects the dynamics of the system which may prove useful in identifying policies or helps us to make strategies to reduce the epidemic prevalence. Through this study, we can predict which parameters play the most significant role in HCV transmission dynamics. We have calculated a partial rank correlation coefficient

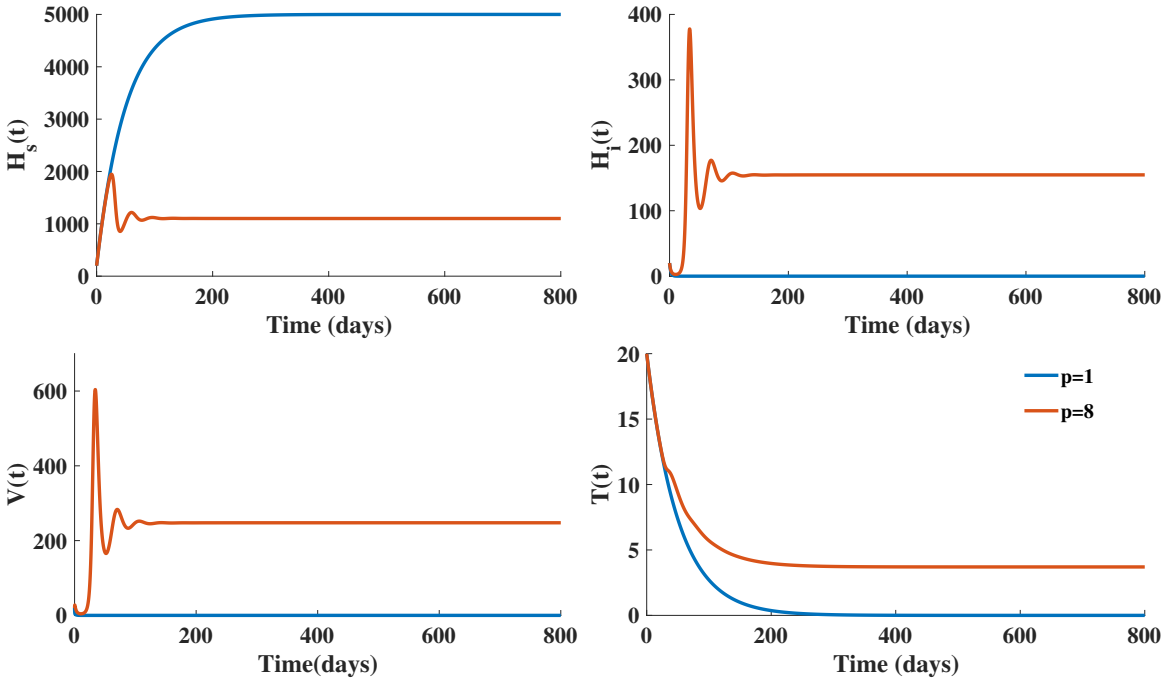

FIGURE 3. Trajectories showing the time dependent changes in concentration of the model variables for $p = 1$ and $p = 8$.

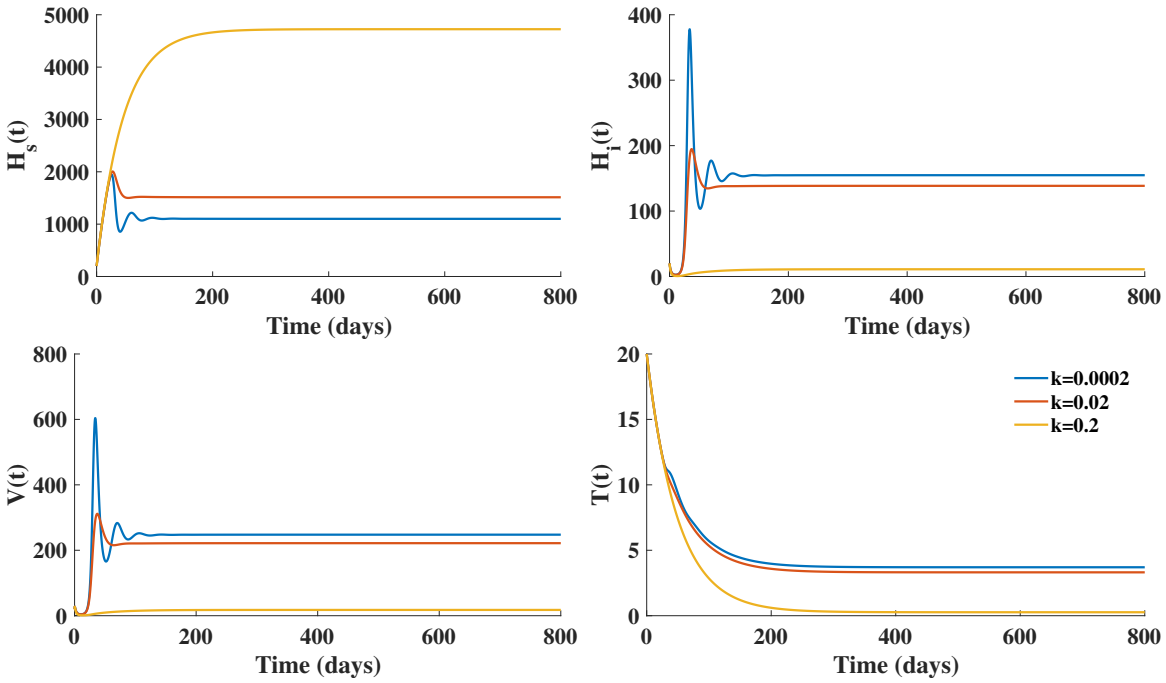

FIGURE 4. Trajectories showing the time dependent changes in concentration of the model variables for $k = 0.0002,\ 0.02$ and $k = 0.2$.

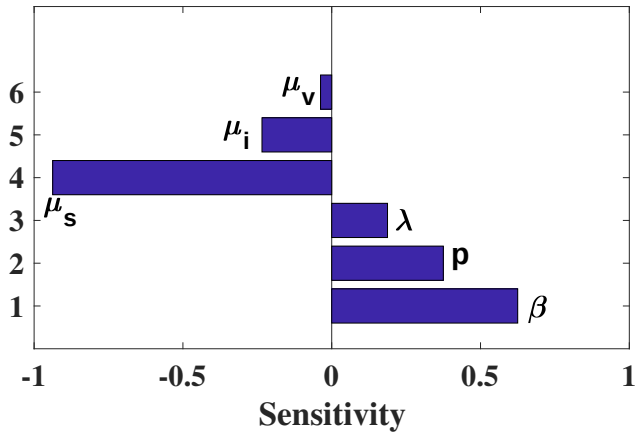

FIGURE 5. Tornado plot of sensitivity analysis of all six parameters that influence R_0. Left panel: $R_0 < 1$. Right panel: $R_0 > 1$

(PRCC) to study the sensitivity analysis of the system. Through the PRCC we can determine the importance of the model parameters. The basic reproduction ratio is defined as $R_0 = \frac{\lambda\beta p}{\mu_s\mu_i\mu_v}$.

$\frac{\partial R_0}{\partial p} = \frac{\lambda\beta}{\mu_s\mu_i\mu_v} > 0$, $\frac{\partial R_0}{\partial \beta} = \frac{\lambda p}{\mu_s\mu_i\mu_v} > 0$, $\frac{\partial R_0}{\partial \lambda} = \frac{p\beta}{\mu_s\mu_i\mu_v} > 0$, $\frac{\partial R_0}{\partial \mu_s} = -\frac{\lambda\beta p}{\mu_s^2\mu_i\mu_v} < 0$, $\frac{\partial R_0}{\partial \mu_i} = -\frac{\lambda\beta p}{\mu_s\mu_i^2\mu_v} < 0$

$\frac{\partial R_0}{\partial \mu_v} = -\frac{\lambda\beta p}{\mu_s\mu_i\mu_v^2} < 0.$

From the above study we can conclude that higher rates of $p,\ \beta,\ \lambda$ lead to increase of R_0 and higher rates of $\mu_s,\ \mu_i,\ \mu_v$ rates leads to the lower R_0 and lower predominance of the epidemic. Since the basic reproduction number, R_0 is inversely related to μ_s, μ_i, μ_v, which means that increasing of death rate uptake for the patients at the acquit stage which is beneficial to control the disease.

5. Numerical Simulation and Discussion

Table 1. *Parameter values used in numerical simulations.*

Parameter	Description	Values Range	Reference
λ	Production rate of healthy liver cell	100	[7, 10, 11, 13]
β	Disease transmission rate	0.0003	[7, 11, 13]
δ	Killing rate of infected liver cell	0.001	[7, 11, 13]
p	Production rate of Hepatitis C virions	1-100	[7, 10, 11, 13]
α	Growth rate of CTL responses	0.0003	[7]
μ_s	Death rate of healthy liver cells	0.02	[7]
μ_i	Death rate of infected liver cells	0.5	[7]
μ_v	Death rate of Hepatitis C virions	5	[7, 10, 11, 13]
μ_t	Removal rate of CTL responses	0.02	[7]
k	Half saturation constant	0.002	-
T_m	Maximum CTL responses level	1000	[7]

In our numerical simulation, we have described the CTL responses against Hepatitis C virions and the functional responses. All the parameters are taken from Table 1. We have assumed that $H_s(0) = 200,\ H_i(0) = 20,\ V(0) = 20,\ T(0) = 20$, and the unit of the concentration are mm^{-3}. From figure 2 (left panel) we have clearly observed that the infection rate β and virus production rate p play a crucial role to fluctuate the basic reproduction number R_0 of the system. It has been observed that for low production rate (p), $R_0 < 1$, i.e. the disease-free state is stable. However, with high virus production rate, $R_0 > 1$ i.e. the system moves towards the endemic state. From figure 2 (right panel), we have observed that the infection rate β and production rate of liver cell λ play a crucial role to fluctuate the basic reproduction number R_0 of the system. For low production rate (λ), $R_0 < 1$, i.e. the disease-free state is stable. However, with high liver cell production rate, $R_0 > 1$ i.e. the system moves towards the endemic state.

From figure 3, we have studied the system behavior for effect of virus production rate p. It is clearly observed, that when $p = 1$, the basic reproduction number becomes below 1, and the system attains its disease-free state. As p increases, the system moves to towards endemic state. Thus we can conclude that disease can be restricted if we can control the production rate of Hepatitis C virions. Figure 4 shows that the infected liver cell population reduces along with

virus load and CTL responses reduces as the half-saturation constant increases. Thus saturation effect plays an important role to restrict the disease progression.

Figure 5 illustrates the PRCCs using R_0 as an output variable. Results here suggest that disease transmission rate as well as virus production rate for HCV infected individuals have the greatest influence on increasing the magnitude of R_0 thereby increasing new secondary HCV cases. Also, the death rate of infected liver cells and death rate of the healthy liver cell have great influence to reduce the magnitude of R_0 which results from reduction of new infection of HCV cases.

In order to understand the outbreak of HCV infection and verify the role of the CTL responses in the disease progression, we have proposed a mathematical model which includes healthy liver cells, infected liver cells, virus population and CTL responses. Theoretically, we have found out the existence and stability condition for disease free as well as endemic state. From our analytical findings, it is clear that the disease-free equilibrium is globally asymptotically stable if $R_0 \leq 1$, which means that hepatitis C virus and infected liver cells can be entirely eliminated from the population. When $R_0 \leq 1$, hepatitis C will persist and the endemic equilibrium is globally asymptotically stable.

From our numerical findings it is clear that CTL responses and saturation effect play an important role to stabilize the disease progression. It is clearly observed that as the saturation effect increases the system moves towards disease-free state and the virus level along with infected liver cell moves towards extinction. However more realistic models about HCV infection along with control theoretic concept will be studied in the future work.

Conflict of Interests

The authors declare that there is no conflict of interests.

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