

Time-since-infection Immunological Model for Hepatitis C and Observed Treatment Profiles

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Abstract

Hepatitis C infection becomes chronic in most patients leading to end-stage liver disease. The standard-of-care treatment for HCV patients is only suboptimal. Several patients who exhibit undetectable viral load during, at the end of, or six months after cessation of therapy, observe relapse over variable time. This suggests that there may exist, a sub-clinical threshold, which governs the achievement of lasting cure. We propose an immunological model of hepatocytes and HCV to investigate this threshold behavior, where the infected hepatocytes are differentiated by the age of infection in them. The goal of the model is to obtain observed patient profiles if treatment is provided. Preliminary analysis of the model provides conditions for existence of two endemic equilibria for $\mathfrak{R}_0 < 1$. Analysis of a reduced model without age of infection suggests backward bifurcation at $\mathfrak{R}_0 = 1$. Artificial values of the parameters are taken to show bistability region for $\mathfrak{R}_0 < 1$. However, it may not be possible to observe the patient profile in this region without treatment. The critical reproduction number below which the disease free equilibrium is stable may lead us to the decisive sub-clinical viral load threshold.

KEYWORDS: Interferon, ribavirin, Hepatitis C, HCV,

ABBREVIATIONS: HCV, *Hepatitis C virus*, peg-IFN, *pegylated Interferon*, RBV, *Ribavirin*,

1 Introduction

About one hundred and seventy million people live with Hepatitis C virus (HCV) infection worldwide [?]. Currently, there is no vaccine for HCV. The major mode of transmission of HCV is by exposure to infected blood. Sexual transmission is observed only in people coinfecting with HIV and vertical transmission of HCV is rare [?]. The HCV infects hepatocytes which form a major portion of the cytoplasmic mass of the liver. Although HCV predominantly replicates in hepatocytes, traces of it have been detected in other cell types [?, ?]. Around 15-30% of the acutely infected Hepatitis C patients who are asymptomatic and more than 50% of patients with symptoms spontaneously clear the virus [?], observed more in infants and young women. Whereas, in 55-75% people who develop acute Hepatitis C remain infected [?]. In the the Hep-C patients where the immune system cannot clear the virus by itself medical intervention is necessary. A combination of drugs, Interferon ($\text{IFN-}\alpha$) and ribavirin (RBV) is prescribed for 24 to 48 weeks [?].

Hepatitis C virus (HCV) is a very slowly evolving disease, where chronic HCV infection can continue for decades, with or without treatment. Due to this reason it has not been proved beyond doubt that treatment provides absolute cure and halts progression to adverse liver infections like cirrhosis and hepatocellular carcinoma among others. Thus therapy of HCV is primarily targeted towards restricting deterioration of liver condition necessitating liver transplant or causing patient's death.

As a consequence, response in patients to treatment are measured by "surrogate virological parameter", instead of a specific "clinical end-point". Several types of virological response thresholds are defined depending on time, relative to treatment duration, having differential degree of reliability as a prescient of long term clinical cure [?].

The most important among these is the sustained virological response (SVR), which is the absence of HCV viral load after six months beyond therapy cessation. SVR is largely considered as "virological cure" and usually followed by years of no drastic decline in liver health. The probability of achievement of SVR is dependent on the genotype of the viral HCV-RNA. The $\text{IFN-}\alpha$ and RBV treatment is very effective with SVR rates of about 45-50% in genotype-1 patients and 85-90% in genotype 2 and 3 patients [?].

The rapid virological response (RVR) is defined as observation of undetectable viral load four weeks into treatment with a lower limit of 50 IU/ml^{-1} . Fulfillment of this threshold indicates a high probability of successful achievement of SVR [?, ?].

Another therapeutic landmark is end-of-treatment response (ETR), which is defined by undetectable viral load at the end of 24 or 48-week course of therapy. ETR is a necessary but not sufficient condition to achieve SVR .

An early virological response (EVR) characterized by ≥ 2 log reduction or undetectable viral load at week 12 of therapy is yet another necessary but insufficient predictor of achievement of SVR [?, ?].

It is remarkable that several patients who achieve undetectable viral load in EVR, ETR or even RVR do not always achieve SVR. Some typically observed patient profiles can be see in the Figure 1.

This leads us to believe that there exists other viral-load threshold below detectable levels which

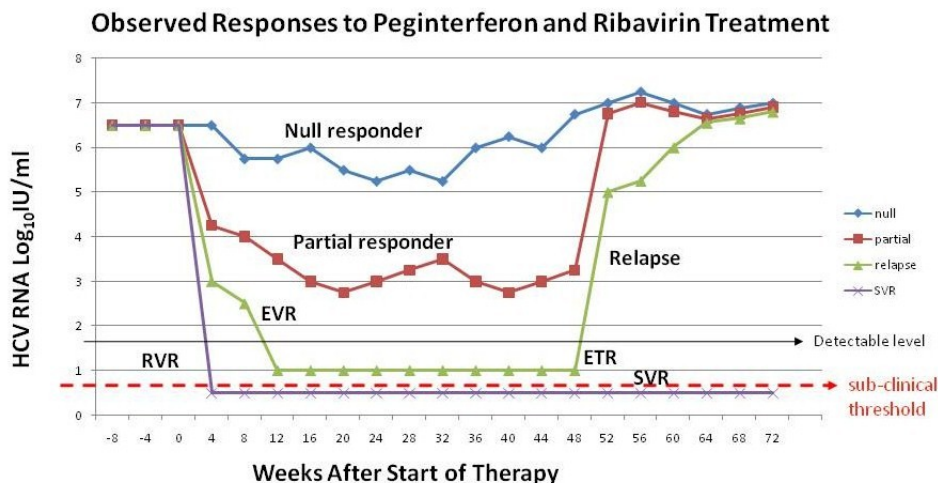


Figure 1: Shows the different observed HCV-RNA dynamics in treated patients. Figure modified from [?]. The red dotted line shows the possible sub-clinical threshold that determines cure.

determine attainment of SVR.

Previous immunological models of HCV as in Dahari et. al. [?] have provided considerable headway in determining the efficacy of peg-IFN and RBV treatment using mathematical ODE models. In their model, all parameters related to infected hepatocyte proliferation, viral production and death rate are considered constant throughout the period of infection. It has been noted in clinical trials that difference in patient's response to treatment, including cases when they achieve ETR and do not proceed to successful achievement of SVR is often due to their different strength of immune system. And since in simple immunological models the aforesaid parameters bear the immune system implicitly, we think that it is important to study them in more details. Moreover, in-vivo and in-vitro observations suggest that, once a virus enters a susceptible host, the normal functions of the host cell is shut down to conserve energy for production of viral material. It takes some time for the virus to complete its life cycle in the cell and finally start budding off to produce new viruses. This differential intra-cellular viral behavior with respect to age of infection affects every natural event related to the host cell, including self-proliferation rate, death rate and viral production rate of infected hepatocytes. The probability of death of an infected cell increases with age of infection. Since it is beneficial to the virus that the life-span of their host cell is longer, the virus does not directly kill the infected hepatocyte. The cell dies due to exhaustion caused by excessive proliferation and extensive budding of viruses formed inside it. Sometimes, the virus may induce the infected hepatocyte to proliferate to produce more infected hepatocytes, presumably to build more cells to produce more viruses [?]. These biological time delay can be easily incorporated into a deterministic mathematical model by including age of infection into the infected hepatocyte population.

The use of age-structured mathematical models to understand infectious disease dynamics at

the cellular level is not uncommon. Age of infection models were used to study various aspects of HIV infection by Thieme and Castillo-Chavez, Rong *et al* and Nelson *et al* [?, ?, ?]. We attempt to use similar techniques to further our understanding of HCV immunology and analyze effects of standard antiviral treatment of peg-IFN- α +RBV to possibly estimate the sub-clinical threshold that dictates the long-term cure in a Hepatitis C patient. Also if we wish to characterize each individual patient as a separate parameter set, the age of infection model gives us more flexibility to study a variety of patient profiles.

In this paper, we introduce an age of infection model for Hepatitis C infection in the liver and give preliminary results at equilibrium. Then we simplify into an ordinary differential equation model which is similar to the extended Dahari *et al* (2007) [?], modified by incorporate the differential proliferation rates of healthy and infected hepatocytes as in [?]. We also present preliminary results and observations.

2 Age of Infection Model

In the following model, T and V represent the density of healthy hepatocytes and free virus respectively in a HCV patient at time t . τ is the age of infection of an infected hepatocyte and $i(\tau, t)$ represents the number of infected hepatocytes with age of infection τ at time t . The scheme of the model can be seen in Figure 2.

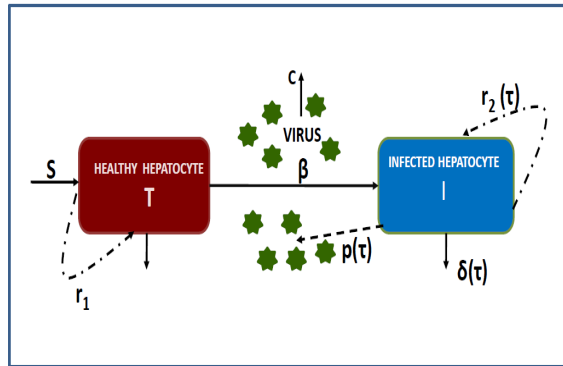


Figure 2: Shows the schematic model.

The moment a hepatocyte gets infected is at $\tau = 0$. Thus, the term $i(\tau, t)$ is the density of hepatocytes which have been infected for time τ at chronological time t . Therefore, the total number of infected cells at time t should be given by

$$I(t) = \int_0^{\infty} i(\tau, t) d\tau.$$

Then the system of equations which represent the HCV dynamics in the liver cells is given by the following.

$$\begin{aligned}
\frac{dT}{dt} &= s + r_1 T \left(1 - \frac{T + I}{T_{max}} \right) - dT - \beta TV \\
\frac{\partial i}{\partial \tau} + \frac{\partial i}{\partial t} &= -\delta(\tau) i(\tau, t) \\
i(0, t) &= \beta TV + R_2(t) \left(1 - \frac{T + I}{T_{max}} \right) \\
\frac{dV}{dt} &= P(t) - cV
\end{aligned} \tag{1}$$

where,

$$\begin{aligned}
R_2(t) &= \int_0^\infty r_2(\tau) i(\tau, t) d\tau \\
P(t) &= \int_0^\infty p(\tau) i(\tau, t) d\tau
\end{aligned}$$

Here s denotes the constant recruitment rate of healthy hepatocytes and r_1 is its maximum possible density dependent proliferation rate. T_{max} is the maximum number of hepatocytes a liver can support including the healthy and infected hepatocytes, thus acting as the 'carrying capacity' in the logistic growth term of T . The natural death rate of T is given by d . β is the number of healthy hepatocytes one virus will infect in a completely susceptible population per unit time. Thus, βTV is the the number of hepatocytes getting infected per unit time. These infected hepatocytes move into the infected population per unit time.

The function $\delta(\tau)$ gives the probability that an infected hepatocyte will die at the age of infection τ . Thus the total number of death among the infected hepatocyte cohort of age of infection τ is equal to $\delta(\tau) i(\tau, t)$, in the time interval t to $t + \Delta t$, which is the same as the time interval between τ and $\tau + \Delta \tau$. Hence we obtain Equation (1). The functional form of this function can be considered linear for simplicity. For example,

$$\delta(\tau) = d + d_1 \tau,$$

where d is the natural death rate of healthy hepatocytes, as defined before and d_1 is the rate of increase in the chances of dying with age of infection.

The number of new infections at a time point t is given by $i(0, t)$. This includes the hepatocytes which got infected at time t represented by the rate of new infection βTV with age of infection $\tau = 0$, and the number of infected hepatocytes born out of previously infected hepatocytes. The latter is represented by a logistic term, with the rate of this proliferation depending on age of infection being $r_2(\tau)$. The rate of change of virus density with respect to chronological time is given by the number of new virus particles produced from infected hepatocyte at the rate of $p(\tau)$ depending on age of infection again. The rates $r_2(\tau)$ and $p(\tau)$ have to be considered as piecewise functions, since these processes get arrested or do not initiate, respectively, immediately after infection.

Although the actual expression of infected hepatocyte's proliferation rate with respect to age of infection r_2 , has not been experimentally determined, it is thought to be initiated by the virus inside the hepatocyte to create more reservoirs of itself. So, a possible function could be of the form,

$$r_2(\tau) = \begin{cases} \frac{(\tau-\tau_0)^2}{K+(\tau-\tau_0)^2} & , \tau > \tau_0 \\ 0 & , elsewhere \end{cases}$$

Here, τ_0 gives the time necessary for the virus to gain control over the cell to initiate and complete infected hepatocyte replication and K giving the half maximum mark of proliferation rate.

The expression for $p(\tau)$ used in [?] for production of HIV which can also be used for HCV is as follows,

$$p(\tau) = \begin{cases} p_{max} (1 - e^{\pi(\tau-\tau_1)}) & , \tau > \tau_1 \\ 0 & , elsewhere \end{cases}$$

Here, p_{max} is the maximum level of possible proliferation, π determines how quickly $p(\tau)$ reaches saturation and τ_1 is the time necessary for the virus to complete replication inside the infected hepatocyte.

Now we move on to analyze this model at equilibrium with respect to chronological time.

2.1 Analysis of Time-since-Infection Model

To find the equilibrium points of the system (1), we equate all the time derivatives to zero. That gives us the following system.

$$\begin{aligned} 0 &= s + r_1 T \left(1 - \frac{T+I}{T_{max}}\right) - dT - \beta TV \\ \frac{\partial i}{\partial \tau} &= -\delta(\tau) i(\tau, t) \end{aligned} \tag{2}$$

$$\begin{aligned} i_0 := i(0, 0) &= \beta TV + R_2(t) \left(1 - \frac{T+I}{T_{max}}\right) \\ 0 &= P(t) - cV \end{aligned} \tag{3}$$

Now we solve for $i^*(\tau)$ from equation (2) to get

$$i^*(\tau) = i_0 e^{-\int_0^\tau \delta(\eta) d\eta}. \tag{4}$$

Using this value we can define the following at equilibrium.

$$I^* := \int_0^\infty e^{-\int_0^\tau \delta(\eta) d\eta} d\tau \tag{5}$$

$$R_2^* := \int_0^\infty r_2(\tau) e^{-\int_0^\tau \delta(\eta) d\eta} d\tau \tag{6}$$

$$P^* := \int_0^\infty p(\tau) e^{-\int_0^\tau \delta(\eta) d\eta} d\tau \tag{7}$$

These constants when multiplied with i_0 essentially represent the total number of infected hepatocytes (of all ages of infection), rate of proliferation of infected hepatocytes and rate of production of viruses respectively, when an equilibrium is reached with respect to chronological time.

Result 1:-

The **Infection Free Equilibrium** is $(T_0^*, 0, 0)$, where,

$$T_0^* = \frac{(r_1 - d) + \sqrt{(r_1 - d)^2 + 4s\frac{r_1}{T_{max}}}}{\frac{2r_1}{T_{max}}} \quad (8)$$

Observation 1:- The *Basic Reproduction Number*, \mathfrak{R}_0^* is calculated by establishing the stability of the Infection free equilibrium, given by,

$$\mathfrak{R}_0^* = \frac{\beta P^*}{c} T_0^* + \left(1 - \frac{T_0^*}{T_{max}}\right) R_2^* \quad (9)$$

(Derivation shown in Appendix.)

The basic reproduction number can be interpreted as the number of secondary infections (hepatocyte or virus) that are caused when a single infected hepatocyte (or virus) is introduced into a completely susceptible population of hepatocytes in its entire lifetime. The first term accounts for the fact that the infected hepatocyte can produce up to P^* virions in its lifetime of $\frac{1}{\delta(\tau)}$ units of time, at age of infection τ , and each virus can infect a healthy hepatocyte at the rate β over its life time of $\frac{1}{c}$ units of time. The second term accounts for the total number of infected hepatocytes being produced by proliferation from the introduced infected hepatocyte, at all ages of infection, over its lifetime.

Now we proceed to investigate the existence of endemic equilibria. Solving out we can get two possible endemic equilibria (T_1^*, I_1^*, V_1^*) and (T_2^*, I_2^*, V_2^*) given by the following.

$$I_{1,2}^* = \int_0^\infty i_{1,2}^*(\tau, 0) d\tau$$

where,

$$i_{1,2}^*(\tau, 0) = i_{01,02} e^{-\int_0^\tau \delta(\eta) d\eta}.$$

Now,

$$i_{01,02} = \frac{-B \pm \sqrt{B^2 - 4AC}}{2A}$$

where,

$$\begin{aligned} A &:= -\frac{r_1}{T_{max}} \gamma_1^2 - \frac{r_1}{T_{max}} \gamma_1 I^* - \frac{\beta P^*}{c} \gamma_1 \\ B &:= r_1 \gamma_1 - 2\frac{r_1}{T_{max}} \gamma_1 - \frac{r_1}{T_{max}} I^* \gamma_2 - d\gamma_1 - \frac{\beta P^*}{c} \gamma_2 \\ C &:= s + r_1 \gamma_2 - \frac{r_1}{T_{max}} \gamma_2^2 - d\gamma_2 \end{aligned}$$

and also,

$$\begin{aligned}\gamma_1 &:= \frac{R_2^* I^*}{T_{max}} \\ \gamma_2 &:= 1 - R_2^*\end{aligned}$$

Then we have,

$$\begin{aligned}T_{1,2}^* &= \gamma_2 + i_{01,02} \gamma_1 \\ V_{1,2}^* &= \frac{P^*}{c} i_{01,02}.\end{aligned}$$

If we have, $A, C > 0$ and $B < 0$ we have $T_1^*, I_1^*, V_1^*, T_2^*, I_2^*$ and V_2^* positive, giving us two endemic states. Further exploration of conditions under which these equilibria will be biologically relevant needs to be made.

3 Ordinary Differential Equation Model

To study the dynamics of the previous system at equilibrium with respect to time in more details, we propose the following ordinary differential equation, which is a modified version of the first model in Reluga *et al*, [?]. The state variables, T, I, V here also represent the concentrations of healthy and infected hepatocytes, and viral load respectively. However in this model all the parameters related to the infected hepatocytes and the virus are constants. For example, an infected hepatocyte starts proliferating and budding out viruses at a constant rate, starting from the moment it is infected to the moment it dies. Thus the model becomes the following.

$$\frac{dT}{dt} = s + r_1 T \left(1 - \frac{T+I}{T_{max}}\right) - dT - \beta TV \quad (10)$$

$$\frac{dI}{dt} = \beta TV + r_2 I \left(1 - \frac{T+I}{T_{max}}\right) - \delta I \quad (11)$$

$$\frac{dV}{dt} = pI - cV \quad (12)$$

In the first equation, s is the natural production and r_1 the maximum proliferation rate of healthy hepatocytes due to a body's effort to homeostasis. The proliferation rate is capped by a carrying capacity of T_{max} , which is the maximum concentration of hepatocytes (both healthy and infected included) a liver can sustain. And d is its death rate. β is the number of infections caused by one infected cell per unit time. βT is the number of healthy hepatocytes infected by one virion per unit of time. βTV is the total number of healthy hepatocytes infected by the amount of virus, V , per unit of time. The total number of infected hepatocytes, i.e. βTV , goes into the second class of hepatocytes which is the infected hepatocytes, I . The rate of proliferation of the infected hepatocytes are given by r_2 with the same carrying capacity of T_{max} . Here, δ is the per-capita rate of clearance of infected hepatocytes including natural death and the effect of immune response, per

unit time. δI is the total number of infected hepatocytes cleared per unit of time. The per capita proliferation rate of HCV is represented by p , i.e. the number of virions produced by one infected hepatocyte, per unit time. pI is the number of virions produced by the total population of infected hepatocytes per unit time. Since c is the death rate of virion in absence of treatment, cV is the total number of deaths of virions per unit time. A list of the parameters with a brief description is given in the Table 1.

Parameter	Interpretation
s	natural rate of production of healthy hepatocytes
$r1$	maximum proliferation rate of healthy hepatocytes
T_{max}	maximum hepatocyte concentration a liver can support
d	natural death rate of healthy hepatocytes
β	rate of new infections per virion
$r2$	maximum proliferation rate of infected hepatocytes
δ	clearance rate of infected hepatocytes
p	proliferation rate of virus
c	clearance rate of virus

Table 1: Parameter Interpretation Table

3.1 Analytic Results

Analysis of the system reveals at most three equilibriums, viz. a unique infection free equilibrium and at most two infected equilibriums.

The *Basic Reproduction Number* is calculated as

$$\bar{\mathfrak{R}}_0 = \frac{\beta p \bar{T}_0}{c \delta} + \frac{r_2}{\delta} \left(1 - \frac{\bar{T}_0}{T_{max}} \right) \quad (13)$$

reproduction number can be interpreted as before. Derived in appendix.

We compute the unique *infection free equilibrium* $(\bar{T}_0, 0, 0)$ where,

$$\bar{T}_0 = \frac{T_{max}}{2r_1} \left((r_1 - d) + \sqrt{(r_1 - d)^2 + 4s \frac{r_1}{T_{max}}} \right)$$

The see two possible *endemic states*, $(\bar{T}_1, \bar{I}_1, \bar{V}_1)$ and $(\bar{T}_2, \bar{I}_2, \bar{V}_2)$ where,

$$\bar{T}_{1,2} = \frac{\delta - r_2 \left(1 - \frac{\bar{I}_{1,2}}{T_{max}} \right)}{\tilde{\beta} - \frac{r_2}{T_{max}}},$$

$$\bar{V}_{1,2} = \frac{p}{c} \bar{I}_{1,2},$$

$$\bar{I}_1 = \frac{-B + \sqrt{B^2 - 4AC}}{2A},$$

$$\bar{I}_2 = \frac{-B - \sqrt{B^2 - 4AC}}{2A},$$

$$\bar{A} = \frac{r_2}{T_{max}}\alpha_1 \quad (14)$$

$$\bar{B} = (\delta - r_2)\alpha_1 + \frac{r_2}{T_{max}}\alpha_2 \quad (15)$$

$$\bar{C} = (\delta - r_2)\alpha_2 - 2s \quad (16)$$

$$(17)$$

and

$$\alpha_1 = \frac{r_1}{T_{max}} \frac{r_2}{T_{max}} + \left(\tilde{\beta} - \frac{r_2}{T_{max}} \right) \left(\frac{r_1}{T_{max}} + \tilde{\beta} \right)$$

$$\alpha_2 = \frac{r_1}{T_{max}} (\delta - r_2) - (r_1 - d) \left(\tilde{\beta} - \frac{r_2}{T_{max}} \right)$$

$$\tilde{\beta} = \frac{\beta p}{c}.$$

The conditions under which the system has zero, one or two endemic equilibriums are investigated. Firstly, we observe that, when $\bar{A}, \bar{C} > 0$ and $\bar{B} > 0$, the values $\bar{T}_i, \bar{I}_i, \bar{V}_i$ are positive $i = 1, 2$.

We define the function $f(\bar{I})$ and $F(\bar{I})$ from the nonlinear system

$$0 = s + r_1 f(\bar{I}) \left(1 - \frac{f(\bar{I}) + \bar{I}}{T_{max}} \right) - d f(\bar{I}) - \tilde{\beta} f(\bar{I}) \bar{I}, \quad (18)$$

$$F(\bar{I}) = \frac{\tilde{\beta}}{\delta} f(\bar{I}) + \frac{r_2}{\delta} \left(1 - \frac{f(\bar{I}) + \bar{I}}{T_{max}} \right). \quad (19)$$

We see that,

$$F(0) = \frac{\tilde{\beta}}{\delta} \bar{T}_0 + \frac{r_2}{\delta} \left(1 - \frac{\bar{T}_0}{T_{max}} \right) = \mathfrak{R}_0$$

, where, $f(0) = \bar{T}_0$.

A non-trivial solution for \bar{I} exists only when $F(\bar{I}) = 1$ has a real solution. If we consider $F(\bar{I})$ as a curve on the $F - \bar{I}$ plane, we have the aforesaid solution only when $F(\bar{I})$ intersects the horizontal line $F = 1$. To explore the conditions under which that happens we calculate $F'(\bar{I})$. Since, $F(\bar{I})$ is an implicit function of $f(\bar{I})$, we first calculate $f'(\bar{I})$ from the equation (18). We get,

$$f'(\bar{I}) = - \left(\frac{r_1}{T_{max}} + \tilde{\beta} \right) \left(\frac{r_1}{T_{max} + \frac{s}{f(\bar{I})^2}} \right)^{-1}, \quad (20)$$

which is < 0 for all \bar{I} . Then

$$F'(\bar{I}) = (\tilde{\beta} - r_2) \frac{f'(\bar{I})}{\delta T_{max}} - \frac{r_2}{\delta T_{max}}. \quad (21)$$

Since, $f'(\bar{I}) < 0$ always, the sign of $F'(\bar{I})$ depends on $(\tilde{\beta} - r_2)$. Hence we make the following observation.

Observation 1. *For $\mathfrak{R}_0 > 1$, a unique endemic equilibrium exists and for $\mathfrak{R}_0 < 1$ we have two possibilities.*

1. *when $(\tilde{\beta} - r_2) > 0$, there is no non-negative Endemic Equilibrium.*
2. *when $(\tilde{\beta} - r_2) < 0$, at most 2 non-negative Endemic Equilibria may exist.*

Proof given in Appendix.

3.2 Conditions for Hysteresis

In this section we explore the existence of multiple equilibria and their stability. We have already seen before that there will exist atmost 2 endemic equilibrium if $\mathfrak{R}_0 < 1$. Since, the existence of a bistability region under backward bifurcation may lead us to the 'sub-clinical' threshold, we investigate conditions under which it shall be possible.

Here we take the maximum proliferation rate of the infected hepatocytes r_2 as the bifurcation parameter. Mainly because it is the introduction of this parameter which results in existence of multiple equilibria. Using the expression of the function $F(\bar{I})$ from equation (21) and equating it to 1, we get,

$$r_2(\bar{I}) = \delta \left(1 - \frac{\tilde{\beta}}{\delta} f(\bar{I}) \right) \left(1 - \frac{f(\bar{I}) + \bar{I}}{T_{max}} \right)^{-1} \quad (22)$$

From this we calculate the following expression for $r_2(0)$.

$$r_2^0 := r_2(0) = (\delta - \tilde{\beta} \bar{T}_0) \left(1 - \frac{\bar{T}_0}{T_{max}} \right)^{-1} \quad (23)$$

Firstly, for the backward bifurcation to exist, it is necessary that $r_2^0 > 0$ and $\frac{\partial r_2}{\partial \bar{I}}|_{\bar{I}=0} < 0$. Since $\left(1 - \frac{\bar{T}_0}{T_{max}} \right) > 0$, the condition $r_2^0 > 0$ reduces to

$$\delta - \tilde{\beta} \bar{T}_0 > 0. \quad (24)$$

Using equation 22, we have,

$$\frac{\partial r_2}{\partial \bar{I}} \Big|_{\bar{I}=0} = \left(\frac{r_2^0}{T_{max}} - (\tilde{\beta}T_{max} - r_2^0) \frac{f'(0)}{T_{max}} \right) \left(1 - \frac{\bar{T}_0}{T_{max}} \right)^{-1} \quad (25)$$

Since, $f'(0) < 0$, we need $\tilde{\beta}T_{max} - r_2^0 < 0$ for $\frac{\partial r_2}{\partial \bar{I}} \Big|_{\bar{I}=0} < 0$. Using the expression for r_2^0 we get,

$$\tilde{\beta}T_{max} - (\delta - \tilde{\beta}\bar{T}_0) \left(1 - \frac{\bar{T}_0}{T_{max}} \right)^{-1} < 0.$$

This condition reduces to

$$\tilde{\beta}T_{max} - \delta < 0. \quad (26)$$

$$\mathfrak{R}_* := \frac{\beta p}{c\delta} T_{max}. \quad (27)$$

We can interpret \mathfrak{R}_* as the *maximum reproduction number*.

The sufficient condition for backward bifurcation would be that both the infectious equilibrium $(\bar{T}_1, \bar{I}_1, \bar{V}_1)$ and $(\bar{T}_2, \bar{I}_2, \bar{V}_2)$ lie in the first quadrant.

Also note that, since $\mathfrak{R}_0 = F(0) < 1$, when the two positive solutions for \bar{I} , we will have, $F'(\bar{I}_1) > 0$ and $F'(\bar{I}_2) < 0$.

Observation 2. *Multiple endemic states when $\mathfrak{R}_0 < 1$, exists in the system (10-12) iff the conditions given by, equation (24), (27) hold together with positive solutions for \bar{I}_1 and \bar{I}_2 .*

3.3 Numerical Results of ODE Model

In this section we use parameters values taken from Dahari et. al. [?] and [?], except for δ and r_2 . We use the parameters listed in the third column of Table 2 to calculate $r_2^0 = 3.70 \text{ day}^{-1}$. We also numerically calculate the value for r_2^{crit} , which marks the lower boundary of the bistability region. Now with

$$r_2 \in [1.01, 3.70]$$

we generate the backward bifurcation graph in (Fig 3).

We know that the value of $\mathfrak{R}_0 = 1$ at r_2^0 and we calculate the value of \mathfrak{R}_0 at the lower limit of r_2 as, $\mathfrak{R}_{crit} = 0.8331$.

For the parameter values in the column 1 in the Table 2, we have $\mathfrak{R}_0 = 0.9437$. Thus here, $\mathfrak{R}_{crit} < \mathfrak{R}_0 < 1$. Simulating the ODE system with these parameter values, we note that the change in initial values of the state variables causes the viral load to either go below detectable levels Fig 4 or go to a non-zero equilibrium in Fig 5.

But if we have our $\mathfrak{R}_0 = 0.8322 < \mathfrak{R}_{crit}$, the system converges to the infection free equilibrium, even when we start with a large viral load, as seen in Figure 6.

For the set of parameters in the column 2 of the Table 2 we get $\mathfrak{R}_0 = 1.2386$. Here even if we start with very low viral load and infected hepatocyte concentration these state variables go to a non-zero endemic equilibrium. The graph of all the state variables are in the Figure 7.

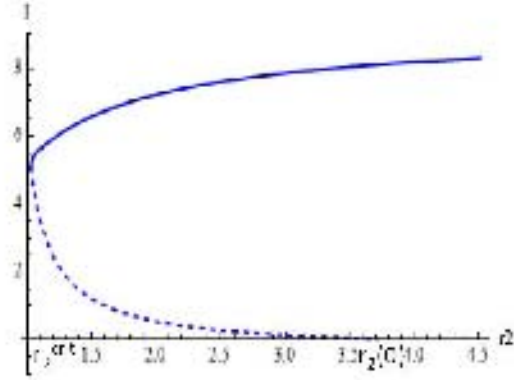


Figure 3: The bifurcation graph of I with respect to parameter r_2 within the interval $[1.01, 3.7]$. Software *Mathematica* is used to generate this graph.

Parameter	Values when $\mathfrak{R}_0 < 1$	Values when $\mathfrak{R}_0 > 1$	Units
s	4×10^{-6}	4×10^{-6}	$nL^{-1} day^{-1}$
r_1	0.5	0.5	day^{-1}
T_{max}	9.13	9.13	$cells nL^{-1}$
d	0.013	0.013	day^{-1}
β	0.5×10^{-1}	0.5×10^{-1}	$nL day^{-1} virion^{-1}$
r_2	2.8	2.8	day^{-1}
δ	0.42	0.32	day^{-1}
p	4.0	4.0	$virion cell^{-1} day^{-1}$
c	5.5	5.5	day^{-1}

Table 2: Parameter Estimation Table. The parameters have been estimated primarily from [?] and [?].

4 Discussion

Chronic Hepatitis-C virus (HCV) infection is a global health problem affecting 3.2 million individuals in the United States alone. The importance of HCV infection is its proclivity to cause insidious liver damage including chronic hepatitis, cirrhosis and liver cancer [?]. The financial burden of this viral infection is staggering with projected medical costs of \$10.7 billion in adults in the years 2010-2019 in the US [?]. Achieving a sustained virological response (SVR) confers long-term viral clearance and represents a cure. However, with current standard-of-care drug regimens, this critical therapeutic milestone is achieved in only 50% of treated patients. It has been observed that several patients who exhibit undetectable viral load in response to treatment at the during therapy, often do not achieve sustained virological response in the long run. Although, therapeutic virological

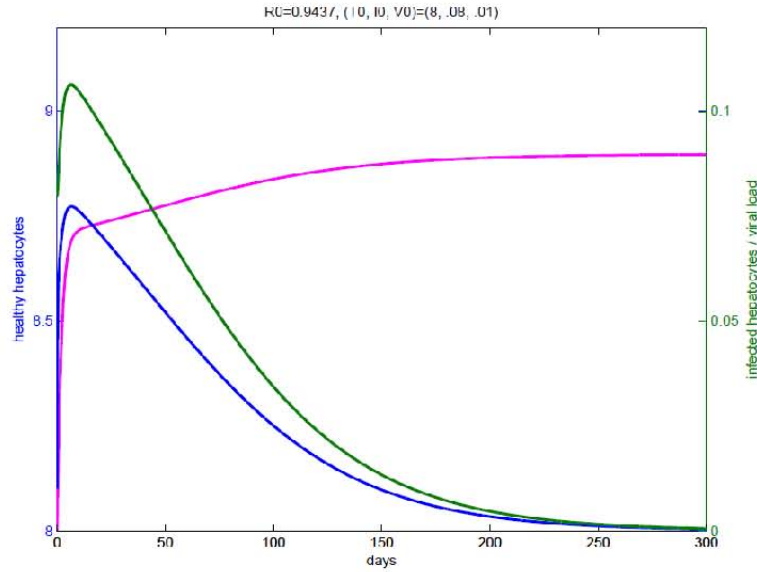


Figure 4: Here $\mathfrak{R}_c < \mathfrak{R}_0 < 1$ and the initial conditions (8, 0.08, 0.01) cause the infected hepatocyte concentration and viral load to go below detectable levels. Software `Matlab` is used to generate this graph.

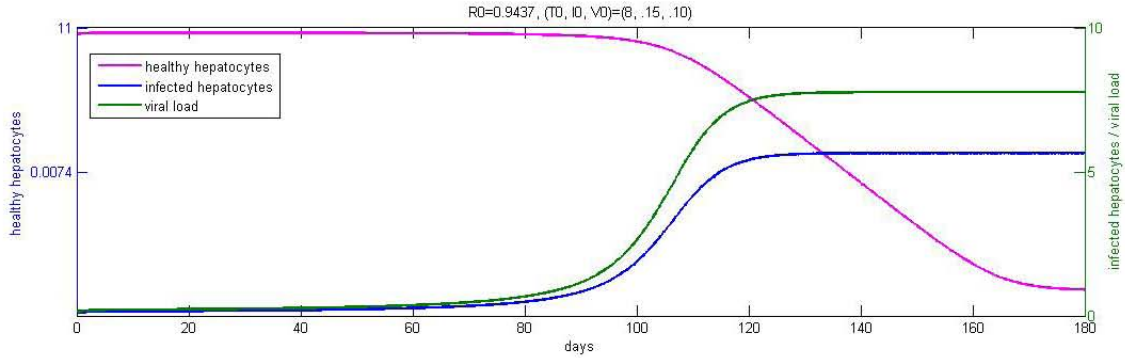


Figure 5: Here although $\mathfrak{R}_c < \mathfrak{R}_0 < 1$, the initial conditions (8, 1, 1) cause the infected hepatocyte concentration and viral load to settle at a non-zero infectious equilibrium. Software `Matlab` is used to generate this graph.

thresholds like RVR and ETR are necessary conditions for successful attainment of SVR, there is no medical estimate that will confirm eventual SVR to a great extent. In addition, PEG-RBV combination therapy is expensive and is associated with treatment-limiting side-effects including anemia, neutropenia, thrombocytopenia, flu-like symptoms, depression and a general "on treatment" poor quality of life [?]. Clearly, there is an urgent need to define a precise thresholds that will improve the likelihood of establishing cure . This will help doctors to formulate an effective dosing strategy,

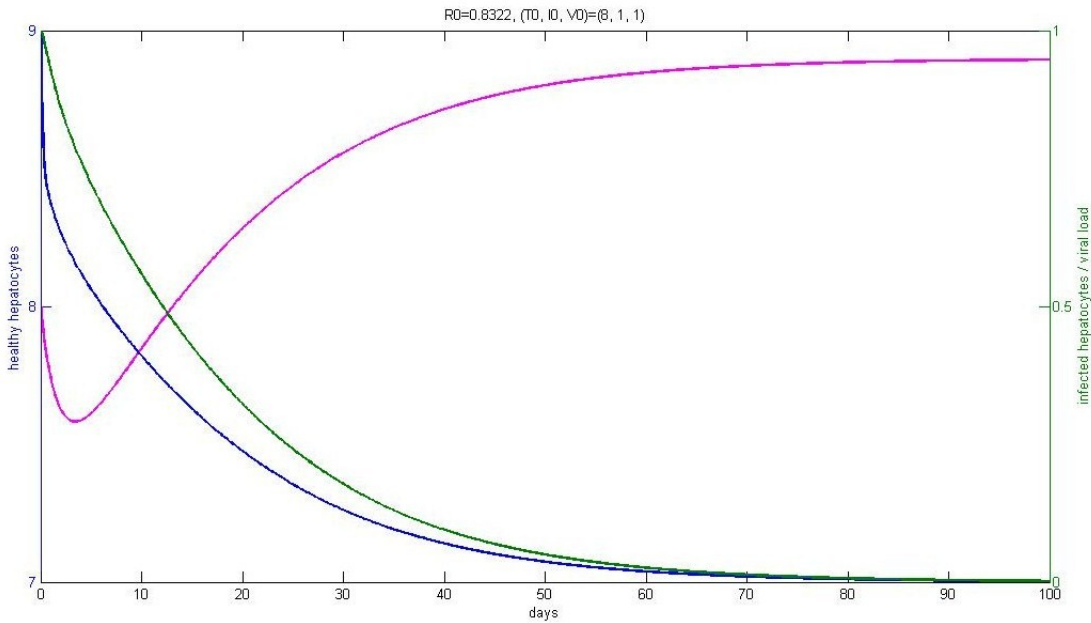


Figure 6: Here $\mathfrak{R}_0 < \mathfrak{R}_c$, the initial conditions (8, 1, 1) cause the infected hepatocyte concentration and viral load to settle at a non-zero infectious equilibrium. Software **Matlab** is used to generate this graph.

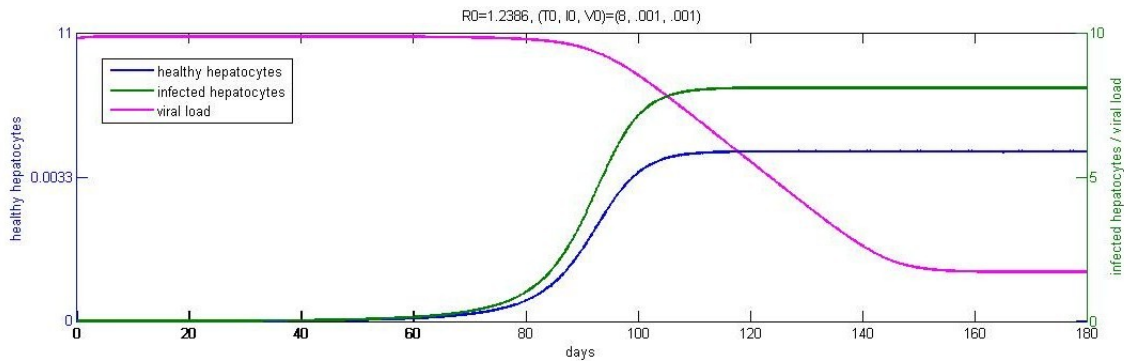


Figure 7: Here $\mathfrak{R}_0 > 1$ and the initial conditions (8, 0.01, 0.01) cause the infected hepatocyte concentration and viral load to go to a non-zero infectious equilibrium. Software **Matlab** is used to generate this graph.

take precautions against possible drug related toxicities and in general help patients to take an informed decision about whether they want to go through the financial and physical perils of the upcoming 24 or 48 weeks of rigorous treatment.

Mathematical modeling has emerged as an important tool in medicine. Models of HCV infection have been effectively used to predict SVR (8-9) and to assess factors associated with favorable responses. Viral and pharmacokinetic studies using mathematical models have shed light on our

understanding of HCV pathobiology and standardizing its treatment [?, ?]. In aggregate, these studies have contributed enormously to improve patient care. In this paper the four distinct patient profiles were generated giving an idea of the functional property of the sub-clinical threshold. It might be possible to calculate the sub-clinical threshold using \mathfrak{R}_{crit} , the lower boundary of the bistability region. The age of infection model with comparable dynamics should allow study of wide range of HCV patients under various assumptions hence leading to more precision in formulating treatment strategies.

For future work, I would like to replicate a wide range of HCV infected patient profiles from real patient data and investigate the presence of the sub-clinical threshold. I would further like to study the effects of different treatment regimes on each typical profile and include drug-related toxicities due to adequate antiviral dosing, to find optimal individualized and therapeutic solutions.

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6 Appendix

6.1 Analysis of Age of Infection Model

Observation 3. *The infection free equilibrium is locally asymptotically stable for $\mathfrak{R}_0 < 1$ and unstable for $\mathfrak{R}_0 > 1$.*

To investigate the stability of the disease free equilibrium we introduce the following perturbations.

$$\begin{aligned} T(t) &= T^* + \tilde{x}(t) \\ i(\tau, t) &= \tilde{y}(\tau, t) \\ V(t) &= \tilde{z}(t) \end{aligned}$$

Now substituting this in the system 2 and applying the conditions from disease-free equilibrium

we get the following system.

$$\begin{aligned}
\frac{d\tilde{x}}{dt} &= r_1\tilde{x} \left(1 - \frac{T_0^*}{T_{max}}\right) - d\tilde{x} - \beta T_0^* \tilde{z} - r_1 T_0^* \frac{\tilde{x} + Y}{T_{max}} \\
\frac{\partial \tilde{y}}{\partial t} + \frac{\partial \tilde{y}}{\partial \tau} &= -\delta(\tau)\tilde{y}(\tau, t) \\
\frac{d\tilde{z}}{dt} &= \int_0^\infty p(\tau)\tilde{y}(\tau, t)d\tau - c\tilde{z} \\
\tilde{y}(0, t) &= \beta T_0^* \tilde{z} + \left(1 - \frac{T_0^*}{T_{max}}\right) \int_0^\infty r_2(\tau)\tilde{y}(\tau, t)d\tau
\end{aligned} \tag{28}$$

where,

$$Y(t) = \int_0^\infty \tilde{y}(\tau, t)d\tau.$$

Now we look for exponential solutions of the form

$$\begin{aligned}
\tilde{x}(t) &= e^{\lambda t} x \\
\tilde{y}(\tau, t) &= e^{\lambda t} y(\tau) \\
\tilde{z}(t) &= e^{\lambda t} z,
\end{aligned}$$

where λ is a constant. Substituting this we get the following system.

$$\begin{aligned}
\lambda x &= r_1 x \left(1 - \frac{T_0^*}{T_{max}}\right) - dx - \beta T_0^* z - r_1 T_0^* \frac{x + Y}{T_{max}} \\
\lambda y + \frac{dy}{d\tau} &= -\delta(\tau)y(\tau) \\
\lambda z &= \int_0^\infty p(\tau)y(\tau)d\tau - cz \\
y(0) &= \beta T_0^* z + \left(1 - \frac{T_0^*}{T_{max}}\right) \int_0^\infty r_2(\tau)y(\tau)d\tau
\end{aligned} \tag{29}$$

We solve the second differential equation to get,

$$y(\tau) = y(0)e^{-\lambda\tau} e^{-\int_0^\tau \delta(\eta)d\eta}$$

Using this we solve the third equation giving this expression for z ,

$$z = y(0) \frac{P_\lambda}{c + \lambda},$$

where,

$$P(\lambda) = \int_0^{\infty} p(\tau) e^{-\lambda\tau} e^{-\int_0^{\tau} \delta(\eta) d\eta} d\tau.$$

Now canceling out $y(0)$ from the last equation in system (29) we get the following *characteristic equation*,

$$1 = \frac{\beta T_0^*}{\lambda + c} P_\lambda + \left(1 - \frac{T_0^*}{T_{max}}\right) R_{2\lambda}$$

where,

$$R_{2\lambda} = \int_0^{\infty} r_2(\tau) e^{-\lambda\tau} e^{-\int_0^{\tau} \delta(\eta) d\eta} d\tau.$$

Now we define,

$$G(\lambda) := \frac{\beta T_0^*}{\lambda + c} P_\lambda + \left(1 - \frac{T_0^*}{T_{max}}\right) R_{2\lambda}. \quad (30)$$

Differentiating with respect to λ we get,

$$\begin{aligned} G'(\lambda) &= -\frac{\beta T_0^*}{\lambda + c} \lambda P_\lambda - \frac{\beta T_0^*}{(\lambda + c)^2} P_\lambda - \left(1 - \frac{T_0^*}{T_{max}}\right) \lambda R_{2\lambda} \\ &< 0, \forall \lambda \end{aligned}$$

If we consider λ as a real variable we get that $G(\lambda)$ is a decreasing function of λ with

$$\lim_{\lambda \rightarrow \infty} G(\lambda) = 0$$

Thus, if $G(0) > 1$ then $G(\lambda)$ will definitely intersect $G(\lambda) = 1$ at least once. That would imply that the infection free equilibrium will become unstable.

Now if $G(0) < 1$, $G(\lambda) = 1$ does not have any real solutions. In that case, we explore the sign of the real part of the solution of λ in the complex field. If possible, let $\lambda = a + ib$, where $a > 0$.

$$\begin{aligned} |G(\lambda)| &\leq \frac{\beta T_0^*}{|\lambda + c|} |P_\lambda| + \left(1 - \frac{T_0^*}{T_{max}}\right) |R_{2\lambda}| \\ &\leq \frac{\beta T_0^*}{Re\lambda + c} P_{Re\lambda} + \left(1 - \frac{T_0^*}{T_{max}}\right) R_{2Re\lambda} \\ &\leq \frac{\beta T_0^*}{c} P^* + \left(1 - \frac{T_0^*}{T_{max}}\right) R_2^* \\ &= G(0) \\ &< 1 \end{aligned}$$

Here, $P_{Re\lambda}$ and $R_{2Re\lambda}$ are the values of P_λ and $R_{2\lambda}$ at $\lambda = a$ respectively. We equate λ to 0 to get the last inequality, giving us $G(0)$. Thus, $G(\lambda) = 1$ does not have any solutions with the

$Re\lambda \geq 0$. Thus, here the Infection free equilibrium is locally asymptotically stable. Thus, since $G(0) < 1$ is the criterion for local stability of the infection free equilibrium, we define, $G(0)$ as the *basic reproduction number*, \mathfrak{R}_0 .

$$\mathfrak{R}_0 = \frac{\beta T_0^*}{c} P^* + \left(1 - \frac{T_0^*}{T_{max}}\right) R_2^*.$$

6.2 Analysis of ODE Model

Proof of Observation (1).

First we calculate $\lim_{\bar{I} \rightarrow F(\bar{I})\infty}$.

$$F(\bar{I}) = \frac{\tilde{\beta}}{\delta} f(\bar{I}) + \frac{r_2}{\delta} \left(1 - \frac{f(\bar{I}) + \bar{I}}{T_{max}}\right) - \delta \quad (31)$$

$$\leq \frac{\tilde{\beta} T_{max}}{\delta} - \frac{r_2 \bar{I}}{\delta T_{max}}, \quad (32)$$

since, $\frac{f(\bar{I})}{T_{max}} < 1$ at any moment of time, we have

$$\lim_{\bar{I} \rightarrow \infty} F'(\bar{I}) \rightarrow -\infty.$$

When, $\mathfrak{R}_0 > 1$, i. e. $F(0) > 1$, $F(\bar{I})$ can intersect $F = 1$ only odd number of times, since $F(\bar{I})$ has to eventually decrease. Moreover, since from previous computations we see that \bar{I} has atmost 2 solutions, we conclude that, under this case, there exists a unique endemic equilibrium.

But when, $\mathfrak{R}_0 < 1$, we consider 2 possible scenarios.

If we have $\tilde{\beta} - r_2 > 0$, we have from Equation (21) that $F'(\bar{I}) < 0$, for all \bar{I} , since $f'(\bar{I}) < 0$, for all \bar{I} also, from Equation (20). Thus, $F(\bar{I})$ does not intersect $F = 1$, hence no endemic equilibrium exists.

But if we have $\tilde{\beta} - r_2 < 0$, we may expect the existence of two endemic equilibria.

Stability of Infection Free Equilibrium

To linearize the ordinary differential equation system we construct the Jacobian and simplify certain terms.

$$J = \begin{bmatrix} -\frac{s}{T} - \frac{r_1 \bar{T}}{T_{max}} - \lambda & -\frac{r_1 \bar{T}}{T_{max}} & -\beta \bar{T} \\ \beta \bar{V} - \frac{r_2 \bar{I}}{T_{max}} & r_2 \left(1 - \frac{\bar{T} + \bar{I}}{T_{max}}\right) - \frac{r_2}{T_{max}} \bar{I} - \delta - \lambda & \beta \bar{T} \\ 0 & p & -c - \lambda \end{bmatrix}$$

At the Infection free equilibrium $(\bar{T}_0, \bar{I}_0, \bar{V}_0)$ the Jacobian reduces to,

$$J_{(\bar{T}_0, \bar{I}_0, \bar{V}_0)} = \begin{bmatrix} -\frac{s}{T_0} - \frac{r_1 \bar{T}_0}{T_{max}} - \lambda & -\frac{r_1 \bar{T}_0}{T_{max}} & -\beta \bar{T}_0 \\ 0 & r_2 \left(1 - \frac{\bar{T}_0}{T_{max}}\right) - \delta - \lambda & \beta \bar{T}_0 \\ 0 & p & -c - \lambda \end{bmatrix}$$

Thus the first eigenvalue is

$$\lambda = -\frac{s}{\bar{T}} - \frac{r_1 \bar{T}}{T_{max}}$$

is always negative, owing to the positivity of our parameters. In the remaining 2×2 matrix, the trace,

$$tr J_{(\bar{T}_0, \bar{I}_0, \bar{V}_0)} = r_2 \left(1 - \frac{\bar{T}_0}{T_{max}} \right) - \delta - c$$

is negative and the determinant,

$$det J_{(\bar{T}_0, \bar{I}_0, \bar{V}_0)} = c \left(r_2 \left(1 - \frac{\bar{T}_0}{T_{max}} \right) - \delta \right) - p\beta \bar{T}_0$$

For the Infection free equilibrium to be stable we require the determinant to be positive. Hence, we derive the following condition.

$$\frac{\beta p}{c\delta} \bar{T}_0 + \frac{r_2}{\delta} \left(1 - \frac{\bar{T}_0}{T_{max}} \right) < 1,$$

giving us *Basic reproduction number*.

Now going back to the Jacobian, J we investigate the stability of the endemic equilibriums. First we define the following,

$$\begin{aligned} \phi_1 &= \frac{s}{\bar{T}} - \frac{r_1 \bar{T}}{T_{max}} \\ \phi_2 &= \frac{\beta p}{c\delta} \bar{T} + \frac{r_2}{T_{max}} \bar{I} \\ \phi_3 &= c \end{aligned}$$

We note that ϕ_1, ϕ_2, ϕ_3 are all positive.

Then the determinant of the Jacobian can be reduced to be,

$$\lambda^3 + A1\lambda^2 + A2\lambda + A3 = 0$$

where,

$$\begin{aligned} A1 &= (\phi_1 + \phi_2 + \phi_3) \\ A2 &= \left(\phi_1\phi_2 + \phi_2\phi_3 + \phi_3\phi_1 - p\beta\bar{T} + \frac{r_1\bar{T}}{T_{max}} \left(\frac{\beta p}{c} - \frac{r_2}{T_{max}} \right) \bar{I} \right) \\ A3 &= \phi_1\phi_2\phi_3 - p\beta\bar{T} + \frac{r_1\bar{T}}{T_{max}} \left(\frac{\beta p}{c} - \frac{r_2}{T_{max}} \right) \bar{I}c + \beta p \left(\frac{\beta p}{c} - \frac{r_2}{T_{max}} \right) \bar{I}\bar{T} \end{aligned}$$

It can be easily verified that A_1, A_2 is always positive and

$$A_3 > 0 \text{ when } F'(\bar{I}_1) < 0$$

$$A_3 < 0 \text{ when } F'(\bar{I}_1) > 0$$

Now applying the Routh-Hurwitz Criterion we show that, under the conditions for backward bifurcation we have that \bar{I}_1 is unstable and \bar{I}_2 is locally asymptotically stable in the bistability region.