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STABILITY ANALYSIS OF AN IN-VIVO HEPATITIS C DYNAMICS MODEL WITH THERAPY

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Abstract: It is well known that hepatitis C virus (HCV) causes development of end-stage liver disease and hepatocellular carcinoma worldwide, in spite of advances in therapy and improved knowledge of viral factors relating to the disease evolution. In this paper, we review and analyze a deterministic mathematical model developed to assess the effect of antiviral drug on the in-vivo HCV dynamics. We computed the endemic equilibrium point (EE) and performed the stability analysis of the model equilibria using a derived threshold quantity well-known as the effective reproductive number, R_e. The analytical results indicate that the disease free equilibrium point (DFE) is locally asymptotically stable, and globally asymptotically stable by using Metzler Stability Theory, if $R_e < 1$.This implies that antiviral therapy absolutely eradicates the disease in this scenery. Also, we find that the endemic equilibrium point (EE) is globally asymptotically stable if $R_e > 1$ by using the Lyapunov Direct Method with LaSalle Invariance

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Principle. This implies that the disease still persists in the presence of antiviral therapy. Numerical simulations were performed to support the analytical results and the results verify that there is no coexistence of the DFE and EE points and that the model has unique equilibria. Thus, we recommend that the treatment of an individual with HCV infection should be well managed by optimizing therapy regimen such as choice of suitable drug type and combination, dosage and therapy period to stop the transmission by reducing strictly R_e less than unity.

Keywords: Meltzer matrix; endemic equilibrium; Lyapunov function; local stability; global stability.

2010 AMS Subject Classification: 92B05.

1. Introduction

Hepatitis c disease is a blood-borne infection caused by hepatitis C virus (HCV). It is estimated that 130-170 million are infected with HCV worldwide [1]. Literatures show that about 85% of infected individuals progress to chronic hepatitis c infection [2], while the remaining victims undergo just acute hepatitis C infection in six months. Of the acutely infected individuals, about 20% to 50% spontaneously clear the virus in six-month period [3]. Many patients with acute hepatitis c disease are asymptomatic; and hence diagnosis and early intervention of the disease is very rare. Treatment of individuals with chronic hepatitis c has been very difficult to manage. This is associated with worsening prognosis; and requires more therapy and longer therapy period, causing intolerability due to developing side effects attributed to highly dosed drug- taking and drug type. Therapy with peginterferon alpha 2a or 2b and ribavirin drugs, for example, has not been significantly effective as only about 50% of cases attain sustained virologic response (SVR) [4-6]. On the other hand, it has been clinically established that monotherapy of acute HCV infection is far better tolerated, cheaper and takes less time [7] and reduces the chance of disease evolution to chronic state [8].

We know that one goal of mathematical epidemiology is to acquire insight into how to control and exterminate diseases[9]. In this setting, mathematical models have been widely used to study ecological and epidemiological incidences [10]. Also, we see that modeling of *in-vivo* dynamics

of viral infections has been used to inquire into possible mechanisms and dynamical performances of the viral infection course[11, 12]. They can be used to approximate vital parametric values of the viral infection such as virions, rate of clearance, infected cell life-span and viral generation time [13] and guide development of effective antiviral therapies [14].

Stability analysis of model equilibria is a well-known way in mathematical epidemiology that facilitates the understanding of the dynamical behavior of the model. These model equilibria are analyzed for local and global stability by using different methods, namely, the Jacobian stability method, Meltzer Stability Theory, Lyapunov Stability Theory and LaSalle's Invariant Principle. The global stability for a bio-mathematical model equilibria has been very well discussed in the literature [15]. It is also known that the method based on the use of Metzler matrices has been useful for the global stability analysis of the DFE point [16]. Up to now, the Lyapunov Direct Method combined with LaSalle's Invariance Principle has been a classical potent tool for the global stability analysis of autonomous systems of differential equations through construction of appropriate Lyapunov functions. In literature, we find different forms of Lyapunov functions that are employed for global stability analysis of epidemic model equilibria [15, 17-21].

In this paper, we consider the model proposed by [22] for stability analysis of the disease free equilibrium (DFE) and endemic equilibrium (EE) points. We analyze the DFE point for local stability by using the Jacobian stability method and global stability by Meltzer Stability Theory while the global stability analysis of the EE point is performed by using Lyapunov Direct Method combined with LaSalle's Invariance Principle [20, 23].

2. The Model Preliminaries

In this section, we initially introduce a deterministic mathematical model developed by [22], that includes the susceptible hepatocytes (S) and infected hepatocytes (I) sub-populations, HCV population (V) and $CD8^+$ T cells population (T).We believe that some dynamical derivatives of

the model are compulsory for the stability analysis we are presenting in this paper.

2.1 The Description of Interactions

New hepatocytes S are constantly recruited at the rate Π and die naturally at a constant rate d. They are infected at the rate proportional to the product SV, with a constant of proportionality ω. The infected hepatocytes I naturally die at a constant rate d, which produce hepatitis C viruses V are at a constant rate σ. The viruses die naturally at a constant rate c. In the presence of HCV, the $CD8^+$ T cells are activated and supplied at a constant rate g. These $CD8^+$ T cells kill infected hepatocytes at the rate proportional to the product IT, with a constant of proportionality β and naturally die at a constant rate b. Finally, the patient with acute HCV infection is treated with interferon alpha-2b that blocks viral replication within infected hepatocytes by a fraction ε.
The state variables and parameters used in this work are itemized and briefly described in Table 1 and Table 2 respectively.

TABLE 1. List of state variables and their descriptions

Variable	Description
$S(t)$	Number of susceptible hepatocytes at time t
$I(t)$	Number of infected hepatocytes at time t
$V(t)$	Number of hepatitis C virions at time t
$T(t)$	Number of $CD8^+$ T cells at time t

In the formulations and analyses, we merely employ the symbols S, I, V and T to represent the susceptible hepatic sub-population, $S(t)$; infected hepatic sub-population, $I(t)$; hepatitis C viral population, $V(t)$ and $CD8^+$T cells population, $T(t)$ respectively.

TABLE 2**.** List of parameters and their descriptions

Parameter	**Description**
ω	Per capita infection rate
σ	Per capita production rate of viruses from the infected hepatocytes
β	Rate at which the $CD8^+$ T cells destroy the infected hepatocytes
Π	Per capita production rate of susceptible hepatocytes
g	Per capita production rate of the CDB^+ T cells
d	Per capita natural death rate of susceptible and infected hepatocytes
c	Per capita natural death rate of viruses
b	Per capita natural death rate of $CD8^+$ T cells
q	Rate of spontaneous cure of infected hepatocytes by a noncytolytic process
μ	Per capita death rate infected hepatocytes due to HCV infection
ε	Fraction by which antiviral drug reduces viral production rate
T_m	Maximum $CD8^+$ T cells population level

2.2 Model Assumptions and Equations

The model was developed based on the following assumptions:

(i) To study the dynamics of HCV during acute phase of infection.

(ii) New hepatocytes are recruited at a constant rate.

(iii) Susceptible hepatocytes are equally likely infected by the viruses and infected hepatocytes.

(iv) The susceptible and infected hepatocytes die naturally at equal constant rates.

(v) The infected hepatocytes have a constant disease-induced death rate.

(vi) Virions are produced from infected hepatocytes at a constant rate.

(vii) $CD8^+$ T cells are activated and subsequently supplied at a constant rate.

(viii) The virions and the $CD8^+$ T cells die naturally at different constant rates.

(ix) The $CD8^+$ T cells kill infected hepatocytes at a constant rate.

(x) The HCV patient is treated using highly dosed-interferon alpha-2b to block viral replication.

(xi) The patient can either clear the virus spontaneously or not during therapy period.

Then based on the assumptions and description of interactions showing the relationships between the state variables, a system of four non-linear ordinary equations was formulated.

$$\begin{cases} \dfrac{dS}{dt} = \Pi + qI - \omega SV - dS \\ \dfrac{dI}{dt} = \omega SV - \beta IT - dI - \mu I - qI \\ \dfrac{dV}{dt} = (1-\varepsilon)\sigma I - cV \\ \dfrac{dT}{dt} = gV(1-\dfrac{T}{T_{\max}}) - bT \end{cases} \tag{1}$$

with initial conditions $S > 0$, $I \geq 0$, $V \geq 0$ and $T \geq 0$.

2.3 The Disease Free Equilibrium Point and Effective Reproductive Number

We calculated the disease free equilibrium point (DFE) by setting the derivatives of the model system (1) equal to zero. Let $E_0 = (S^*, I^*, V^*, T^*)$ be the DFE point. Thus, we have:

$$\begin{cases} \Pi + qI - \omega SV - dS = 0 \\ \omega SV - \beta IT - dI - \mu I - qI = 0 \\ (1-\varepsilon)\sigma I - cV = 0 \\ gV(1-\dfrac{T}{T_{\max}}) - bT = 0 \end{cases} \tag{2}$$

Using the first, third and fourth equations in (2), we obtain:

$$S = \frac{\Pi + qI}{\omega V + d} \quad , \quad I = \frac{cV}{(1-\varepsilon)\sigma} \quad \text{and} \quad T = \frac{gT_{\max}V}{gV + bT_{\max}} \tag{3}$$

At the DFE point E_0, we assume there is no HCV and hence $V^* = 0$. Then from (3), we obtain:

$$S^* = \frac{\Pi + q(0)}{\omega(0) + d} = \frac{\Pi}{d} \quad , \quad I^* = \frac{c(0)}{(1-\varepsilon)\sigma} = 0 \quad \text{and} \quad T^* = \frac{gT_{\max}(0)}{g(0) + bT_{\max}} = 0 \tag{4}$$

Thus, the disease free equilibrium point of the system (1) exists and is given by

$$E_0 = (\frac{\Pi}{d}, 0, 0, 0)$$

By using the next generation operator method described by [24] and subsequently analyzed by [25], we derived the effective reproduction number, R_e of the model (1). It is the spectral radius (ρ) of the next generation matrix, FY^{-1}, i.e. $R_e = \rho(FY^{-1})$.

where F is a non-negative $n \times n$ matrix and Y is a non –singular N-matrix such that

$$F = \left[\frac{\partial f_i(E_0)}{\partial X_j}\right] \text{ and } Y = \left[\frac{\partial y_i(E_0)}{\partial X_j}\right] \text{ with } 1 \le i, j \le n$$

Thus, we have:

$$F = \begin{bmatrix} 0 & \frac{\omega\Pi}{d} \\ (1-\varepsilon)\sigma & 0 \end{bmatrix}, \quad Y = \begin{bmatrix} d+\mu+q & 0 \\ 0 & c \end{bmatrix} \text{ and hence } FY^{-1} = \begin{bmatrix} 0 & \frac{\omega\Pi}{cd} \\ \frac{(1-\varepsilon)\sigma}{d+\mu+q} & 0 \end{bmatrix}$$

We obtain the effective reproductive number, R_e from $R_e = \rho(FY^{-1})$.Thus, we have:

$$R_e = \sqrt{\frac{(1-\varepsilon)\omega\sigma\Pi}{cd^2 + cd\mu + cdq}} \tag{5}$$

3. Existence of Endemic Equilibrium Point with Therapy

We obtain the endemic equilibrium (EE) point of the mode(1) . Let $E^* = (S^*, I^*, V^*, T^*)$ be the EE point of the model.

Using the first, third and fourth equations of the model system(1) at the EE point E^*, we obtain:

$$S^* = \frac{\Pi + qI^*}{\omega V^* + d} \tag{6a}$$

$$I^* = \frac{cV^*}{(1-\varepsilon)\beta} \tag{6b}$$

$$T^* = \frac{gT_{\max}V^*}{gV^* + bT_{\max}} \tag{6c}$$

Substituting $(6b)$ into $(6a)$ yields:

$$S^* = \frac{\Pi(1-\varepsilon)\sigma + cqV^*}{(1-\varepsilon)\sigma(\omega V^* + d)} \tag{6d}$$

Substituting $(6b),(6c)$ and $(6d)$ into the second equation of the model (1) with simplification produces a quadratic polynomial in terms of V^*.

$$P(V^*) = A(V^*)^2 + B(V^*) + C = 0 \tag{7}$$

The coefficients of the quadratic polynomial (4) are given by

$$A = cqg\omega\sigma - \omega\sigma[cgT_{\max} + cg(d+\mu+q)];$$

$$B = (1-\varepsilon)g\Pi\omega\sigma^2 + bcq\omega T_{\max} - bc\omega\sigma(d+\mu+q)T_{\max}$$

$$-[cdgT_{\max} + cdg(d+\mu+q)];$$

$$C = (1-\varepsilon)b\Pi\sigma^2 T_{\max} - bcd(d+\mu+q)T_{\max}$$

The equation $P(V^*) = 0$ corresponds to a situation when the disease is endemic.

We find that the polynomial (7) has positive real solution V^* under the conditions stipulated in the following theorem:

Theorem 1: *The HCV model system* (1) *with therapy has:*

a) A unique endemic equilibrium point if $C < 0$*, which implies* $R_e > 1$

b) A unique endemic equilibrium point if $B < 0$ *and* $C = 0$ *or* $B^2 - 4AC = 0$

c) Two endemic equilibrium points if $C > 0, B < 0$ *and* $B^2 - 4AC > 0$

d) No solution otherwise.

4. Stability Analysis of the Model Equilibria

In this section, we determine conditions which underlie asymptotic stability or instability of the model equilibria. We initially define asymptotic stability and instability.

Definition 1: *Asymptotic stability of the model system* (1) *is the state where the solutions*

starting arbitrarily in the close vicinity of its equilibrium point remain close to it and converge to it as $t \to \infty$ *whereas instability of an equilibrium point implies that solutions starting arbitrarily in the close vicinity of it do not approach it as* $t \to \infty$.

4.1 Local Stability of the DFE Point

In the general perspective, the local asymptotic stability of an equilibrium point refers to the state where non-linear system trajectories start arbitrarily in the close vicinity of the equilibrium point and converge to it as $t \to \infty$. So, we have to prove that the DFE point of the model (1) is locally asymptotically stable. Nevertheless, we initially evaluate the Jacobian matrix at the DFE point and then compute the trace and determinant of the matrix.

Let J_{E_0} denote the Jacobian matrix at the DFE point E_0. Let $Tr(J_{E_0})$ and $Det(J_{E_0})$ be the trace and determinant of the matrix J_{E_0} respectively. Then the Jacobian matrix J_{E_0} is given by

$$J_{E_0} = \begin{bmatrix} -d & -q & -\dfrac{\omega\Pi}{d} & 0 \\ 0 & -(d+\mu+q) & \dfrac{\omega\Pi}{d} & 0 \\ 0 & (1-\varepsilon)\sigma & -c & 0 \\ 0 & 0 & g & -b \end{bmatrix}$$

Thus, we have:

$$Tr(J_{E_0}) = -(2d + \mu + q + c + b)$$

$$Det(J_{E_0}) = b(cd^2 + cd\mu + cdq - \sigma\omega\Pi + \sigma\omega\Pi\varepsilon)$$

Then $Det(J_{E_0}) > 0$ if $cd^2 + cd\mu + cdq - \sigma\omega\Pi + \sigma\omega\Pi\varepsilon > 0$

That is, $cd^2 + cd\mu + cdq > (1-\varepsilon)\omega\sigma\Pi$

$$(1-\varepsilon)\omega\sigma\Pi < cd^2 + cd\mu + cdq$$

$$\frac{(1-\varepsilon)\omega\sigma\Pi}{cd^2 + cd\mu + cdq} < 1$$

That is,

$$\sqrt{\frac{(1-\varepsilon)\omega\sigma\Pi}{cd^2+cd\mu+cdq}} < \sqrt{1} = 1 \tag{8}$$

Using (5), (8) simplifies to $R_e < 1$.

Since the trace and determinant of the matrix J_{E_0} are strictly negative and positive respectively, the disease free equilibrium point of the model (1) is locally asymptotically stable and so we have proved the following theorem:

Theorem 2: *The disease free equilibrium point is locally asymptotically stable in* Φ *if* $R_e < 1$ *and unstable if* $R_e > 1$.

4.2 Global Stability of the DFE Point

The global stability of the DFE point is analyzed by applying the method of [26].We initially express the model system (1) in the following format:

$$\begin{cases} \dfrac{dX_N}{dt} = P(X_N - X_{E_0,n}) + QX_n \\ \dfrac{dX_n}{dt} = RX_n \end{cases} \tag{9}$$

where X_N is the non-transmitting class, X_n is the transmitting class, $X_{E_0,n}$ is the class of the same size as X_n at the DFE point E_0 and P , Q and R are matrices. Thus, we have:

$$X_N = \begin{pmatrix} S \\ T \end{pmatrix}, \quad X_n = \begin{pmatrix} I \\ V \end{pmatrix}, \quad X_{E_0,n} = \left(\frac{\Pi}{d},0,0\right) \text{ and } X_N - X_{E_0,n} = \begin{pmatrix} S - \dfrac{\Pi}{d} \\ T \end{pmatrix}$$

For global stability of the DFE point, we must show that matrix P has real negative eigenvalues and R is a Meltzer matrix (i.e. the off-diagonal elements of R are non-negative).Then by using the equations of the model (1) and format(9), we obtain:

$$\begin{pmatrix} \Pi + qI - \omega SV - dS \\ gV\left(1 - \dfrac{T}{T_{\max}}\right) - bT \end{pmatrix} = P\begin{pmatrix} S - \dfrac{\Pi}{d} \\ T \end{pmatrix} + Q\begin{pmatrix} I \\ V \end{pmatrix} \text{ and } \begin{pmatrix} \omega SV - \beta IT - dI - \mu I - qI \\ (1-\varepsilon)\sigma I - cV \end{pmatrix} = R\begin{pmatrix} I \\ V \end{pmatrix}$$

Using non-transmitting elements from the Jacobian matrix of the system (1)and the format (9), we find that:

$$P=\begin{pmatrix}-d & 0\\ 0 & -b\end{pmatrix},\ Q=\begin{pmatrix}q & -\frac{\omega\Pi}{d}\\ 0 & g-b\end{pmatrix}\text{and}\ R=\begin{pmatrix}-(d+\mu+q) & \frac{\omega\Pi}{d}\\ (1-\varepsilon)\sigma & -c\end{pmatrix}$$

We find that the matrix P in (9) has real negative eigenvalues $-b$ and $-d$ .We also find that R is a Meltzer matrix as the entries in the leading diagonal are all negative and the off-diagonal elements are positive. So, the DFE point of the system (1) is globally asymptotically stable and therefore we have proved the following theorem:

Theorem 3: *The disease free equilibrium point is globally asymptotically stable in the region* Φ *if* $R_e<1$ *and unstable if* $R_e>1$.

4.3 Global Stability of the EE Point

We know that the DFE point of the model system (1) is locally asymptotically stable if $R_e<1$ and unstable if $R_e>1$,which suggests the local stability of the EE point for the reverse condition [25]. In this section, we only prove the EE point for global stability by constructing a suitable Lyapunov function.

To prove the EE point for the global stability, we use the Lyapunov function of the form (10)

$$H=\sum A_j(y_j-y_j^*\ln\frac{y_j}{y_j^*})\ \text{ for }\ A_j>0\ \text{and}\ \ j=1,...4 \qquad (10)$$

as proposed by [26], where A_j is an appropriately selected constant, y_j is the population of the j^{th} compartment and y_j^* is the value of y_j at equilibrium. The method also holds for more complex compartmental models of the *in-vivo* dynamics [20, 23]. Thus, we have the following Lyapunov function:

$$H=A_1\left(S-S^*\ln\frac{S^*}{S}\right)+A_2\left(I-I^*\ln\frac{I^*}{I}\right)+A_3\left(V-V^*\ln\frac{V^*}{V}\right)+A_4\left(T-T^*\ln\frac{T^*}{T}\right),$$

Differentiation of the function H with respect to t yields:

$$\frac{dH}{dt} = A_1\left(1-\frac{S^*}{S}\right)\frac{dS}{dt} + A_2\left(1-\frac{I^*}{I}\right)\frac{dI}{dt} + A_3\left(1-\frac{V^*}{V}\right)\frac{dV}{dt} + A_4\left(1-\frac{T^*}{T}\right)\frac{dT}{dt} \tag{11}$$

From (1), we have:

$$\begin{aligned}\frac{dH}{dt} &= A_1\left(1-\frac{S^*}{S}\right)[\omega S^* V^* + dS^* - qI^* + qI - \omega SV - dS] \\ &+ A_2\left(1-\frac{I^*}{I}\right)[\frac{(1-\varepsilon)\omega\sigma S^*}{c} - \beta T^* - \frac{(1-\varepsilon)\omega\sigma S}{c} + \beta T]I \\ &+ A_3\left(1-\frac{V^*}{V}\right)[(1-\varepsilon)\sigma I - \frac{(1-\varepsilon)\sigma I^*}{V^*}V] \\ &+ A_4\left(1-\frac{T^*}{T}\right)[gV - \frac{gVT}{T_{\max}} - (\frac{gV^*}{T^*} - \frac{gV^*}{T_{\max}})T]\end{aligned} \tag{12}$$

Simplification of (12) yields:

$$\begin{aligned}\frac{dH}{dt} &= A_1\left(1-\frac{S^*}{S}\right)\left[-(1-\frac{S^*}{S})dS + (1-\frac{I^*}{I})qI - (1-\frac{S^*V^*}{SV})\omega SV\right] \\ &+ A_2\left(1-\frac{I^*}{I}\right)\left[(1-\frac{S^*}{S})\frac{(1-\varepsilon)\omega\sigma}{c}SI - (1-\frac{T^*}{T})\beta IT\right] \\ &+ A_3\left(1-\frac{V^*}{V}\right)\left[(1-\frac{I^*V}{IV^*})(1-\varepsilon)\sigma I\right] \\ &+ A_4\left(1-\frac{T^*}{T}\right)\left[g(1-\frac{V^*T}{VT^*})V - (1-\frac{V^*}{V})\frac{gVT}{T_{\max}}\right]\end{aligned}$$

Further Simplification yields:

$$\begin{aligned}\frac{dH}{dt} &= A_1\left(1-\frac{S^*}{S}\right)^2 dS + A_1\left(1-\frac{S^*}{S}\right)\left[(1-\frac{I^*}{I})qI - (1-\frac{S^*V^*}{SV})\omega SV\right] \\ &+ A_2\left(1-\frac{I^*}{I}\right)\left[(1-\frac{S^*}{S})\frac{(1-\varepsilon)\omega\sigma}{c}SI - (1-\frac{T^*}{T})\beta IT\right]\end{aligned}$$

$$+ A_3(1-\frac{V^*}{V})\left[1-\frac{I^*V}{IV^*}\right](1-\varepsilon)\sigma I$$

$$+ A_4\left(1-\frac{T^*}{T}\right)\left[g(1-\frac{V^*T}{VT^*})V-(1-\frac{V^*}{V})\frac{gVT}{T_{\max}}\right] \quad (13)$$

From (13), we have:

$$\frac{dH}{dt}=-A_1\left(1-\frac{S^*}{S}\right)^2 dS + M(S,I,V,T), \text{ where} \quad (14)$$

$$M(S,I,V,T)=A_1\left(1-\frac{S^*}{S}\right)\left[(1-\frac{I^*}{I})qI-(1-\frac{S^*V^*}{SV})\omega SV\right]$$

$$+ A_2(1-\frac{I^*}{I})\left[(1-\frac{S^*}{S})\frac{(1-\varepsilon)\omega\sigma}{c}SI-(1-\frac{T^*}{T})\beta IT\right]$$

$$+ A_3(1-\frac{V^*}{V})\left[1-\frac{I^*V}{IV^*}\right](1-\varepsilon)\sigma I$$

$$+ A_4\left(1-\frac{T^*}{T}\right)\left[g(1-\frac{V^*T}{VT^*})V-(1-\frac{V^*}{V})\frac{gVT}{T_{\max}}\right]$$

The function $M(S,I,V,T)$ in equation (14) balances the right hand side of equation (13). It is non-negative following the approaches of [27] and [28]. This means that $M \le 0$ for every $S,I,V,T>0$.Thus, $dH/dt \le 0$ for all $S,I,V,T>0$ and zero when $S=S^*$, $I=I^*$,$V=V^*$ and $T=T^*$.Thus, the largest compact set in Φ such that $dH/dt=0$ is the singleton $\{E^*\}$ where the EE point of the model is E^* (1). By the invariance principle [29],we find that E^* is globally asymptotically stable in the region Φ. Hence, we have proved the following theorem:

Theorem 4 : *The endemic equilibrium point is globally asymptotically stable in the region* Φ *if* $R_e>1$ *and unstable if* $R_e<1$.

5. Numerical Simulations and Discussion

The main objective of the original study was to assess the impact of antiviral drug therapy on the hepatitis C disease. Up to now, we have proved that the model equilibria exist and are stable by means of the analytical methods. In this section, we have performed numerical simulations for the model state variables, with various initial values, to support the analytical results, That is, we have performed numerical simulations to analyze the stability of the model equilibria to acquire additional insight into the dynamics of the disease.

5.1 Simulations for the stability analysis of the DFE point

We varied the initial size for each state variable and employed the following parametric values:

$\omega = 0.00001, \sigma = 6, \beta = 0.00000001, \Pi = 100, d = 0.00014, \mu = 0.486 b = 0.02, c = 10, g = 0.0003$

$q = 0$ and $\varepsilon = 0.96$.

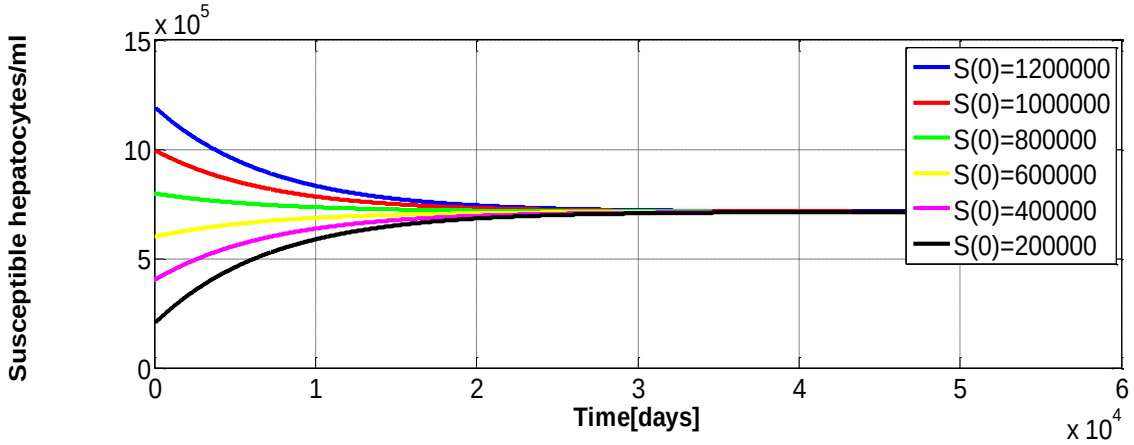

FIGURE 1(a). Graph of susceptible hepatocytes/ml vs. time with therapy varying initial size.

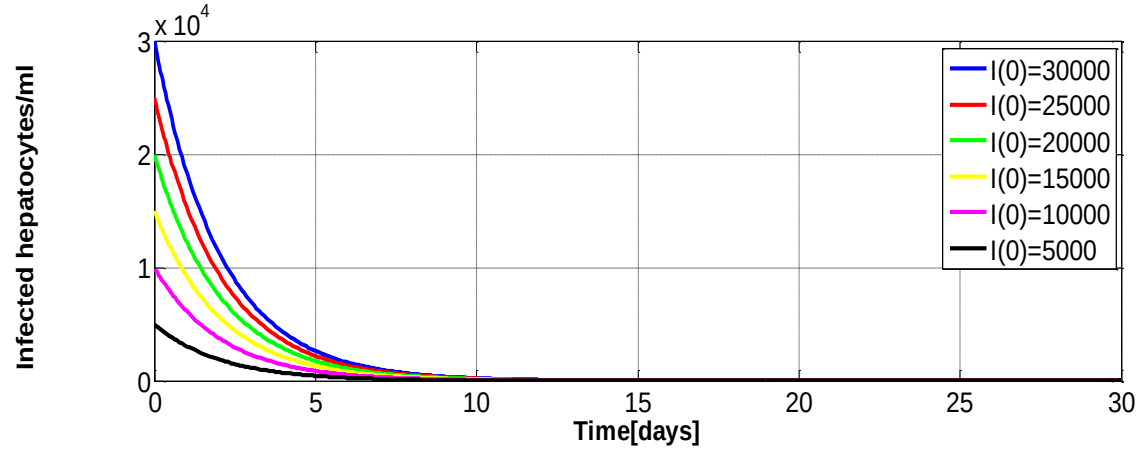

FIGURE 1(b). Graph of Infected hepatocytes/ml vs. time with therapy varying initial size.

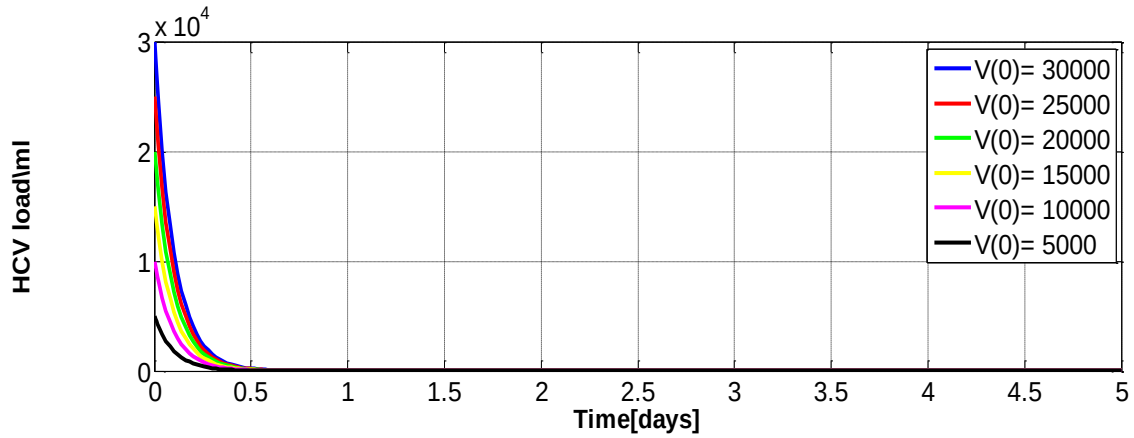

FIGURE 1(c). Graph of HCV load/ml vs. time with therapy varying initial size.

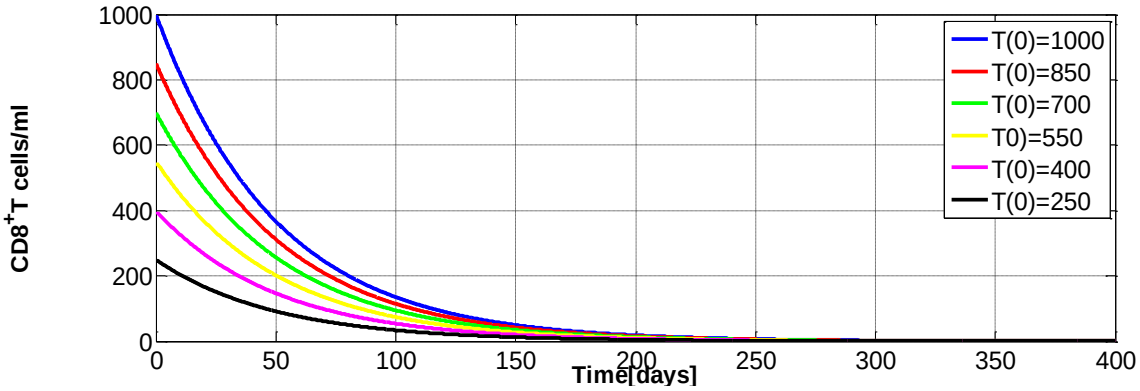

FIGURE 1(d). Graph of $CD8^+$ T cells/ml vs. time with therapy varying initial size.

Figures $1(a)$-$1(d)$ show plots of HCV model with time from the onset of antiviral drug therapy onward. These simulations results verify the existence of a unique disease free equilibrium point and it is stable. That is, the graph of susceptible hepatocytes ultimately attains a non-zero steady state (Fig.1 (a)) whereas the graphs of infected hepatocytes, HCV load and $CD8^+$ T cells attain a zero steady state as shown in Fig.$1(b)$, Fig.$1(b)$ and Fig.$1(d)$ respectively.

5.2 Simulations for the stability analysis of the EE point

We also varied the initial size for each state variable and used the following parametric values:

$\omega = 0.00371, \sigma = 250, \beta = 0.00000001, \Pi = 1000, d = 0.00014, \mu = 0.486 b = 0.02, c = 10, g = 0.0003$

$q = 0$ and $\varepsilon = 0.96$.

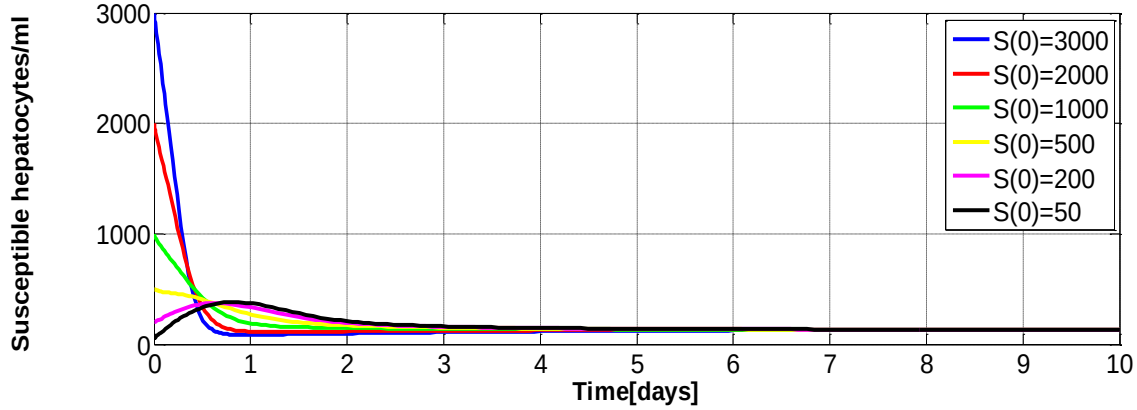

FIGURE 2(a). Graph of susceptible hepatocytes/ml vs. time with therapy varying initial size.

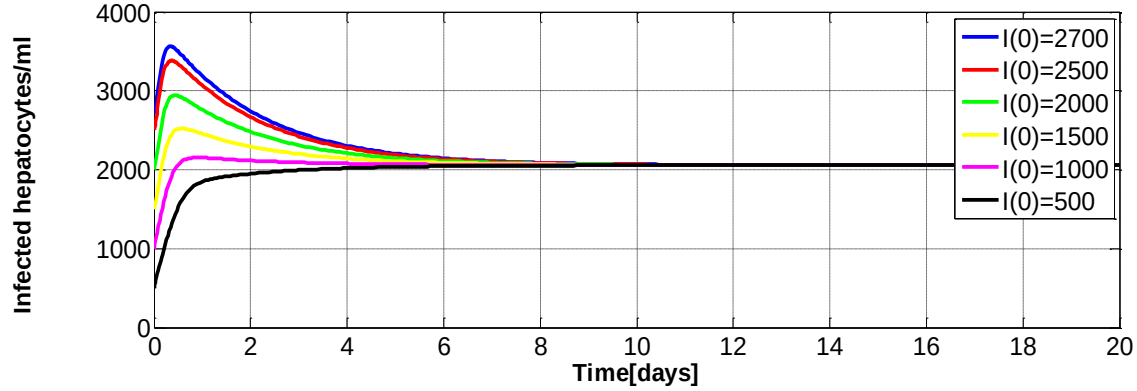

FIGURE 2(b). Graph of Infected hepatocytes/ml vs. time with therapy varying initial size.

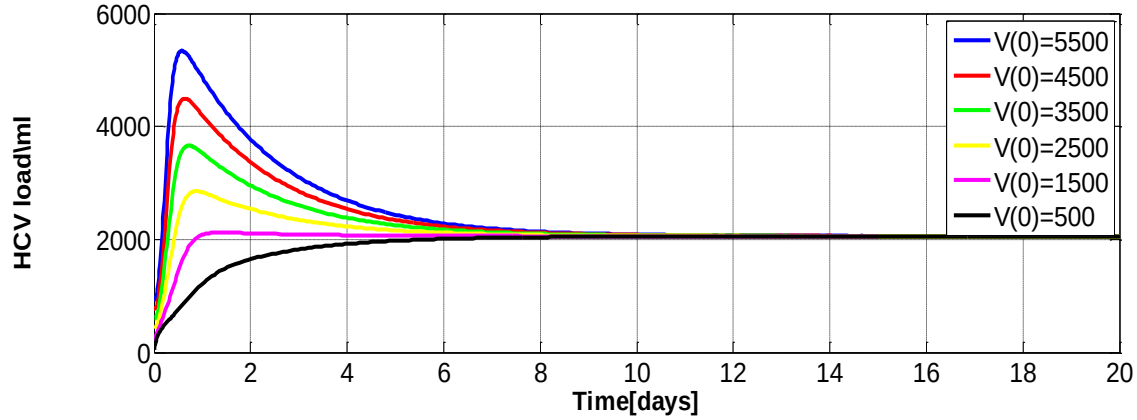

FIGURE 2(c). Graph of HCV load/ml vs. time with therapy varying initial size.

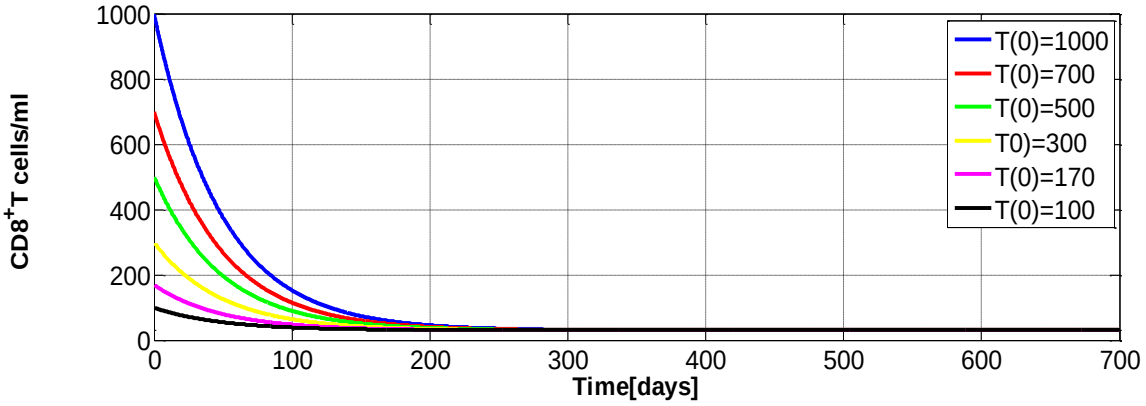

FIGURE 2(d). Graph of $CD8^+$ T cells/ml vs. time with therapy varying initial size.

Figures $2(a)$-$2(d)$ display plots of the HCV model with time from the onset of antiviral therapy and thereafter. The graphs of susceptible hepatocytes, infected hepatocytes, HCV viral load and CD8+ T cells all attain a non-zero steady state in the long run. These simulations results verify the existence of a unique endemic equilibrium point that comprises non-zero values of the state variables. This implies that the EE point is stable whenever it exists

6. Conclusion

A mathematical model was developed to study the *in-vivo* HCV dynamics with therapy [22]. Of the model, the disease free equilibrium point, the basic number and effective reproductive number were computed. The analytical and simulation results of the model showed that antiviral drug therapy is a reliable and effective therapeutic strategy that either eradicates the disease or reduces the intensity of the disease transmission. In this paper, we have established the existence of the endemic equilibrium point and performed the stability analysis of the model equilibria to acquire further insight into the dynamics of HCV with therapy. But, we considered only treatment of the patient who cannot spontaneously clear the virus, as the case would be practical with treatment. From the analysis initially performed using the Jacobian stability technique, Meltzer Stability Theory and Lyapunov Direct Method with LaSalle's Invariance Principle, we find that the disease free and endemic equilibrium points are locally and globally asymptotically stable whenever they exist. Numerical simulations were performed and the results verify the existence of a unique

disease free equilibrium point and a unique endemic equilibrium point in the presence of therapy. Thus, the model equilibria exist and are stable.

We recommend that antiviral therapy should be optimized to reduce strictly R_e less than unity in case the disease still persists with therapy.

Conflict of Interests

The authors declare that there is no conflict of interests.

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REFERENCES

[1] D. Lavanchy, The global burden of hepatitis C, Liver Int. 29 (s1) (2009), 74-81.

[2] S. Merkinaite, J. V. Lazarus and C. Gore, Addressing HCV infection in Europe: reported, estimated and undiagnosed cases, Cent. Eur. J. Public Health, 16 (3) (2008), 106-110.

[3] S. M. Kamal, Acute hepatitis C: a systematic review, Am. J. Gastroenterology, 103 (5) (2008), 1283-1297.

[4] T. Kanda, F. Imazeki and O. Yokosuka, New antiviral therapies for chronic hepatitis C, Hepatology Int. 4 (3) (2010), 548-561.

[5] M. W. Fried., M. L.Shiffman, K. R. Reddy , C.Smith, G. Marinos, Jr, F. L. Gonçales, D. Häussinger, M. Diago, G..Carosi and , D. Dhumeaux., Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection, New England J. Med. 347 (13) (2002), 975-982.

[6] A. J. Muir, J. D. Bornstein and P. G. Killenberg, Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites, New England J. Med. 350 (22) (2004), 2265-2271.

[7] R. P. Myers, C. Regimbeau, T. Thevenot, V. Leroy, P. Mathurin, P. Opolon, J. P. Zarski.and T.Poynard, Interferon for acute hepatitis C, Cochrane Database Syst. Rev. 4(Art. No.: CD000369) (2001), 1-22.

[8] A. Alberti, S. Boccato, A. Vario and L. Benvegnù, Therapy of acute hepatitis C, Hepatology, 36 (S1) (2002), S195-S200.

[9] J. Ma and Z. Ma, Epidemic threshold conditions for seasonally forced seir models, Math. Biosci. Eng. 3 (1) (2006), 161-172.

[10] E. Kaplan and M. Brandeau, Modelling AIDS and the AIDS Epidemic, Raven, New York, 1994.

[11] A. S. Perelson, D. E. Kirschner and R. De Boer, Dynamics of HIV infection of CD4+ T cells, Math. Biosci. 114 (1) (1993), 81-125.

[12] A. S. Perelson and P. W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, SIAM Review, 41 (1) (1999), 3-44.

[13] A. S. Perelson, A. U. Neumann, M. Markowitz, J. M. Leonard and D. D. Ho, HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time, Science, 271 (5255) (1996), 1582.

[14] S. Bonhoeffer, R. M. May, G. M. Shaw and M. A. Nowak, Virus dynamics and drug therapy, Proc. Natl Acad. Sci. 94 (13) (1997), 6971-6976.

[15] A. Korobeinikov and G. C. Wake, Lyapunov functions and global stability for SIR, SIRS, and SIS epidemiological models, Appl. Math. Lett. 15 (8) (2002), 955-960.

[16] J. LaSalle and S. Lefschetz, "The stability by Lyapunovs direct method, New York," ed: Academic, 1961.

[17] C. V. De León, Constructions of Lyapunov functions for classics SIS, SIR and SIRS epidemic model with variable population size, Foro-Red-Mat: Rev. Electr. Cont. Matem. 26 (5) (2009), 1-12.

[18] C. Vargas-De-León, On the global stability of infectious diseases models with relapse, Abstr. Appl. 9 (2013), 50-61.

[19] A. Korobeinikov, Global properties of basic virus dynamics models, Bull. Math. Biol. 66 (4) (2004), 879-883.

[20] A. Korobeinikov, Lyapunov functions and global properties for SEIR and SEIS epidemic models, Math. Med. Biol. 21 (2) (2004), 75-83.

[21] A. Korobeinikov, Global properties of infectious disease models with nonlinear incidence, Bull. Math. Bio. 69 (6) (2007), 1871-1886.

[22] S. Ismail, L. Luboobi and Y. Nkansah-Gyekye, Mathematical Model for the Acute Hepatitis C Virus Infection subject to Immune System Response and Therapy, Asian J. Math. Appl. 2017 (2017), Article ID ama0380.

[23] S. Edward, D. Kuznetsov and S. Mirau, Modeling and stability analysis for a varicella zoster virus model with vaccination, Appl. Comput. Math. 3 (4) (2014), 150-162.

[24] O. Diekmann and J. A. P. Heesterbeek, Mathematical epidemiology of infectious diseases: model building, analysis and interpretation.John Wiley & Sons, 2000.

[25] P. Van den Driessche and J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, Math. Biosci. 180 (1) (2002), 29-48.

[26] C. Castillo-Chavez, Z. Feng, and W. Huang, ON THE COMPUTATION OF Ro AND ITS ROLE ON, Mathematical approaches for emerging and reemerging infectious diseases: an introduction, 1 (2002), 229.

[27] C. C. McCluskey, Lyapunov functions for tuberculosis models with fast and slow progression, Math. Biosci. 3(4) (2006) ,603-614.

[28] Z. Mukandavire, C. Chiyaka, G. Magombedze, G. Musuka and N. J. Malunguza, Assessing the effects of homosexuals and bisexuals on the intrinsic dynamics of HIV/AIDS in heterosexual settings, Math. Comput. Modell. 49 (9) (2009), 1869-1882.

[29] J. La Salle, The Stability of Dynamical Systems, CBMS-NSF Reg. Conf. Ser. Appl. Math. 1976.