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Global Stability Analysis of the Original Cellular Model of Hepatitis C Virus Infection Under Therapy

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Abstract: In this work, we investigate the hepatitis C virus infection under treatment. We first derive a nonlinear ordinary differential equation model for the studied biological phenomenon. The obtained initial value problem is completely analysed. To begin with the analysis of the model, we use the standard theory of ordinary differential equations to prove existence, uniqueness and boundedness of the solution. Morever, the basic reproduction number R_0 determining the extinction or the persistence of the HCV infection is computed and used to express the equilibrium points. Also the global asymptotic stability of the HCV-uninfected equilibrium point and the HCV-infected equilibrium point of the model are derived by means of appropriate Lyapunov functions. Finally numerical simulations are carried out to confirm theoretical results obtained at HCV-unfected equilibrium.

Keywords: HCV Cellular Model, Differential System, Therapy, Local and Global Solution, Invariant Set, Stability

1. Introduction

According to [15] recent estimates, more than 185 million people around the world have been infected with the hepatitis C virus (HCV), of whom 350 000 die each year. One third of those who become chronically infected are predicted to develop liver cirrhosis or hepatocellular carcinoma. Despite the high prevalence of disease, most people infected with the virus are unaware of their infection. For many who have been diagnosed, treatment remains unavailable. Treatment is successful in the majority of persons treated, and treatment success rates among patients treated in low- and middle-income countries are similar to those in high-income countries Hepatitis C virus (HCV) infects liver cells (hepatocytes). Approximately 200 million people worldwide are persistently infected with the HCV and are at risk of developing chronic liver disease, cirrhosis and hepatocellular carcinoma. HCV infection therefore represents a significants global public health problem. HCV established chronic hepatitis in 60%-80% of infected adults [12].

In literature, several mathematical models have been introduced for understanding HCV temporal dynamics [4, 9, 10].

In this article, we consider the basic extracellular model with therapy presented by Neumann et al. in [9]. Given the

recent surge in the development of new direct acting antivirals agents for HCV therapy, mathematical modelling of viral kinetics under treatment continues to play an instrumental role in improving our knowledge and understanding of virus pathogenesis and in guiding drug development [2, 7, 11].
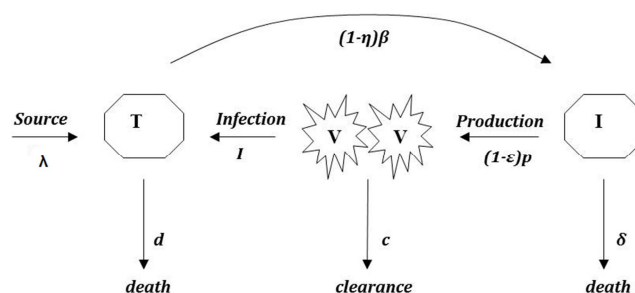
Figure 1. Schematic representation of the original viral kinetic model of HCV infection under treatment. T represents the target uninfected cells, I is the infected cells and V represents the free virus.

To proceed, we assume that the uninfected target cells are produced at a rate λ, die at constant rate d per cell. On the other hand, the target cells are infected with de novo infection rate constant of β and the infected cells die at a constant rate of δ per cell. The hepatitis C virions are produced inside the infected cells at an average rate p per infected cell and have a constant

clearance rate c per virion. Thereby, viral persistence will occur when rate of viral production (p), de novo infection (β), and production of target cells (λ) exceeds the clearance rate (c), death rate of infected cells (δ) and target cells death rate (d). In addition, the therapeutic effect of IFN treatment in this model involved blocking virions production and reducing new infections which, are described in fractions $(1 - \varepsilon)$ and $(1 - \eta)$, respectively. $(0 \le \varepsilon \le 1, 0 \le \eta \le 1)$.

According to [3, 9], the above assumptions lead to the following differential equations:

$$\frac{dT}{dt} = \lambda - dT - (1 - \eta)\beta VT; \tag{1}$$

$$\frac{dI}{dt} = (1 - \eta)\beta VT - \delta I; \tag{2}$$

$$\frac{dV}{dt} = (1 - \varepsilon)pI - cV; \tag{3}$$

where the equations relate the dynamics relationship between, T as the uninfected target cells (hepatocytes), I as the infected cells and V as the viral load (amount of viruses present in the blood). In this article, model system (1) is taken as the original model used to analyse the HCV dynamics.

The initial conditions associated to system (1) are given by:

$$T(t_0) = T_0, I(t_0) = I_0, V(t_0) = V_0, t_0 \in [0, +\infty]. \tag{4}$$

This paper is organized as follows: The global properties of the solutions to the mathematical model is carried out in Section 2. The stability of the disease non-infected steady state, and the infected steady state is analysed in section 3 and finally in section 4, some numerical simulations are carried out.

2. Properties of Solutions of the Initial Value Problem (1)-(4)

2.1. Existence of Local Solutions

The first step in examining model (1), (2), (3) is to prove that local solution of the initial-value problem does, in fact, exist, and that this solution is unique.

Theorem 2.1 *Let T_0, I_0, $V_0 \in R$ be given. There exists $t_1 > t_0 > 0$ and continuously differentiable functions T, I, $V: [0, t_0) \rightarrow R$ such that the ordered triple (T, I, V) satisfies (1), (2), (3) and $(T(t_0), I(t_0), V(t_0)) = (T_0, I_0, V_0)$.*

To prove the result, we use the classical Cauchy-Lipschitz theorem. Since the first order system of ordinary differential equations (1), (2), (3) is autonomous, it suffices to show that the function $H: R^3 \rightarrow R^3$ defined by:

$$H(x) = \begin{pmatrix} h_1(x_1, x_2, x_3) \\ h_2(x_1, x_2, x_3) \\ h_3(x_1, x_2, x_3) \end{pmatrix} = \begin{pmatrix} \lambda - dx_1 - (1 - \eta)\beta x_3 x_1 \\ (1 - \eta)\beta x_3 x_1 - \delta x_2 \\ (1 - \varepsilon)px_2 - cx_3 \end{pmatrix} \tag{5}$$

is locally Lipschitz in its x argument. In fact, it is enough to notice that the jacobian matrix

$$\nabla H(x) = \begin{bmatrix} -d - (1 - \eta)\beta x_3 & 0 & -(1 - \eta)\beta x_1 \\ (1 - \eta)\beta x_3 & -\delta & (1 - \eta)\beta x_1 \\ (1 - \varepsilon)p & 0 & -c \end{bmatrix}$$

is locally bounded for every $x \in R^3$. Hence, H has a continuous, bounded derivative on any compact subset of R^3 and so H is locally Lipschitz in x; In addition H is continuous. By Cauchy-Lipschitz theorem, there exists a unique solution, $x(t)$, to the ordinary differential equation

$$x'(t) = H(x(t))$$

with initial value $x(t_0) = x_0$ on $[t_0, t_1]$ for some time $t_1 > t_0 \ge 0$.

Remark 1 The model (1), (2), (3) can be rewrite in the form

$$S'(t) = H(S(t))$$

where $S(t) = (T(t), I(t), V(t))^t$ and H is defined by (5).

Remark 2 Since H is a continuously differentiable function, we deduce a unique maximal solution of initial value problem (1)-(4). In addition, F, being indefinitely continuously differentiable, we can also deduce that this solution is also only if indefinitely continuously differentiable.

Additionally, we may show that for positive initial data, solutions of ininitial value problem (1)- (4) remain positive as long as they exist.

2.2. Positivity

Theorem 2.2 *Let (T, I, V) be a solution of the Cauchy problem (1)-(4) on an interval $[t_0, t_1]$. Assume the initial data of problem (1)- (4) satisfy $T_0 > 0$, $I_0 > 0$, and $V_0 > 0$ then $T(t)$, $T(t)$ and $V(t)$ remain positive for all $t \in [t_0, t_1]$.*

Proof. Call the variables x_i. If there is an index i and a time t for which $x_i(t) = 0$, let t_* be the infimum of all such t for any i. Then the restriction of the solution to the interval $[t_0; t_*]$ is positive and $x_i(t_*) = 0$ for a certain value of i. The equation for x_i in the system (1), (2), (3) can be written in the form:

$$\frac{dx_i(t)}{dt} = -x_i f(x) + g(x),$$

where $g(x)$ is non-negative. As a consequence $\frac{dx_i(t)}{dt} \ge -x_i f(x)$ and $x_i(t) > 0, \forall t \in [t_0, t_*]$. In fact:

Recall that all constants in the system (1), (2), (3) are non-negative. Using this and the solutions on $[t_0, t_*]$, we have:

$$\begin{cases} \dfrac{dI}{dt} = -I\delta + (1 - \eta)\beta VT \\ \dfrac{dV}{dt} = -Vc + (1 - \varepsilon)pI \end{cases} \Rightarrow \begin{cases} \dfrac{dI}{dt} \ge -I\delta \\ \dfrac{dV}{dt} \ge -Vc \end{cases} \Rightarrow \begin{cases} \dfrac{d}{dt}(\ln I(t)) \ge -\delta \\ \dfrac{d}{dt}(\ln V(t)) \ge -c, \end{cases}$$

which yields:

$$I(t) \geq I_0 e^{-\delta(t-t_0)},$$

$$V(t) \geq V_0 e^{-c(t-t_0)} \ for \ all \ t \in [t_0, t^*].$$

Similarly, in one hand we have:

$$\frac{d}{dt}(I + V) = -I\delta + (1 - \eta)\beta VT - Vc + (1 - \varepsilon)pI \leq \beta VT + pI.$$

Recall that we have a bound on T, so

$$\frac{d}{dt}(I + V) \leq A_1(1 + (t - t_0))\beta T + pI \leq A_2(1 + (t - t_0))(T + I)$$

where $A_2 \geq \max\{A_1\beta, p\}$. Solving the differential inequation yields:

$$I(t) + V(t) \leq A_3 H_1(t), \forall t \in [t_0, t^*] \qquad (6)$$

where $A_3 > 0$ depends upon A_2, I_0 and V_0 only, and $H_1(t) = e^{\int_{t_0}^{t}(1+(t-t_0))d\tau} > 0$, $t \in [t_0, t_*]$. Using the fact that $I(t)$ and $V(t)$ are positive, (6) yields:

$$A_3 H_1(t) \geq I(t) + V(t) \geq V(t), A_3 H_1(t) \geq I(t) + V(t) \geq I(t).$$

With these bounds in place, we can now examine $T(t)$ and bound it from below using:

$$\frac{dT}{dt} = \lambda - dT - (1 - \eta)\beta VT$$

$$\geq -dT - (1 - \eta)\beta VT$$

$$\geq -dT - (1 - \eta)\beta A_3 H_1(t)T$$

$$\frac{dT}{dt} \geq -A_4(1 + H_1(t))T$$

for $t \in [t_0, t^*]$, where $A_4 \geq \max\{d, (1 - \eta)\beta A_3\}$. Shifting that last term to the other side of the equation yields:

$$\frac{dT(t)}{dt} + A_4(1 + H_1(t))T(t) \geq 0.$$

Since we know

$$\frac{d}{dt}\left(T(t) + e^{A_4 \int_{t_0}^{t}(1+H_1(\tau))d\tau}\right) \geq 0,$$

we find that for $t \in [t_0, t^*]$,

$$T(t) \geq e^{-A_4 \int_{t_0}^{t}(1+H_1(\tau))d\tau} > 0$$

Therefore $x_i(t) > 0$, for all $t \in [t_0, t^*]$. In particular $x_i(t^*) > 0$, which is a contradiction and the theorem is proven.

Remark 3
1. With this, we have a general idea that the model is sustainable, and can say with certainty that it remains biologically valid as long as it began with biologically-reasonable (i.e, positive) data. This also shows that once infected, it is entirely possible that the virus may continue to exist beneath a detectable threshold without doing any damage.
2. One reason why we choose the strict inequalities for the initial data is that often in biological (or chemical) applications we are interested in the case of solutions where all unknowns are positive. This means intuitively that all elements of the model are 'active'. On the other hand it is sometimes relevant to consider solutions with non-strict inequalities. In fact the statement of the theorem with strict inequalities implies the corresponding statement with non-strict inequalities by using continuous dependence of solutions with respect to initial Data.

2.3. Existence of Global Solutions

It will now be shown, with the help of the continuation criterion the existence of global solutions.

Theorem 2.3 *The solutions of the Cauchy problem (1)-(4), with positive initial data, exist globally in time in the future that is: on $[t_0, +\infty]$.*

Proof. To prove this it is enough to show that all variables are bounded on an arbitrary finite interval $[t_0; t]$. Using the positivity of the solutions is suffices to show that all variables are bounded above.

Taking the sum of equations (1) and (2) shows that:

$$\frac{d}{dt}(T + I) \leq \lambda$$

and hence that $T(t) + I(t) \leq T_0 + I_0 + \lambda(t - t_0)$. Thus T and I are bounded on any finite interval. The third equation i.e. equation (3), then shows that $V(t)$ cannot grow faster than linearly and is also bounded on any finite interval.

2.4. Global Boundedness of Solutions

Theorem 2.4 *For any positive solution (T, I, V) of initial value problem (1)-(4) we have:*

$$T(t) + I(t) \leq C_1 \ and \ V(t) \leq C_2$$

where

$$\frac{dT}{dt} = \lambda - dT - red(1 - \eta)\beta VT \leq \lambda.$$

Solving for T yields

$$T(t) \leq T_0 + \lambda(t - t_0) \leq A_1(1 + (t - t_0))$$

where $A_1 \geq \max\{T_0, \lambda\}$. In other hand we have:

$$C_1 = \max\left\{T_0 + I_0, \frac{\lambda}{\min\{d, \delta\}}\right\}, C_2 = \max\left\{V_0, \frac{(1-\varepsilon)pC_1}{c}\right\}.$$

Proof. According to equations (1) and (2), we have:

$$\frac{d}{dt}(T + I) = \lambda - dT - \delta I \leq \lambda - \min\{d, \delta\}(T + I).$$

Gronwall inequality [13] yields:

$$T + I \leq (T(t_0) + I(t_0))e^{-\min\{d,\delta\}(t-t_0)} + \int_{t_0}^{t} \lambda e^{-\int_u^t -\min\{d,\delta\}dr}\,du$$

$$\leq (T_0 + I_0)e^{-\min\{d,\delta\}(t-t_0)} + \lambda\int_{t_0}^{t} e^{-\min\{d,\delta\}(t-u)}\,du$$

$$\leq (T_0 + I_0)e^{-\min\{d,\delta\}(t-t_0)} + \lambda\frac{e^{-\min\{d,\delta\}(t-t)} - e^{-\min\{d,\delta\}(t-t_0)}}{\min\{d, \delta\}}$$

$$\leq \max\left\{(T_0 + I_0), \frac{\lambda}{\min\{d, \delta\}}\right\}e^{-\min\{d,\delta\}(t-t_0)} + \max\left\{(T_0 + I_0), \frac{\lambda}{\min{d, \delta}}\right\}(1 - e^{-\min\{d,\delta\}(t-t_0)})$$

$$\leq \max\left\{(T_0 + I_0), \frac{\lambda}{\min\{d, \delta\}}\right\}\left(e^{-\min\{d,\delta\}(t-t_0)} + 1 - e^{-\min\{d,\delta\}(t-t_0)}\right)$$

therefore $T + I \leq \max\left\{(T_0 + I_0), \frac{\lambda}{\min\{d,\delta\}}\right\}$.

Another hand, from equation (3), we have:

$$\frac{dV}{dt} = (1-\varepsilon)pI - cV \leq (1-\varepsilon)p(I + T) - cV$$

$$\leq (1-\varepsilon)p\max\left\{(T_0 + I_0), \frac{\lambda}{\min\{d, \delta\}}\right\} - cV$$

$$\leq (1-\varepsilon)pC_1 - cV.$$

Once more Gronwall inequality yields:

$$V(t) \leq V(t_0)e^{-c(t-t_0)} + \int_{t_0}^{t}(1-\varepsilon)pC_1 e^{\int_u^t cdr}\,du$$

$$\leq V_0 e^{-c(t-t_0)} + (1-\varepsilon)pC_1\int_{t_0}^{t} e^{-c(t-u)}\,du$$

$$\leq V_0 e^{-c(t-t_0)} + (1-\varepsilon)pC_1\frac{e^{-c(t-t)} - e^{-c(t-t_0)}}{c}$$

$$\leq V_0 e^{-c(t-t_0)} + (1-\varepsilon)pC_1\frac{1 - e^{-c(t-t_0)}}{c}$$

$$\leq \max\left\{V_0, \frac{(1-\varepsilon)pC_1}{c}\right\}\left(e^{-c(t-t_0)} + 1 - e^{-c(t-t_0)}\right)$$

$$V(t) \leq \max\left\{V_0, \frac{(1-\varepsilon)pC_1}{c}\right\}$$

Therefore the theorem is proven.

As consequences of Theorem 2.4 we have:

Remark 4 *Let S be a solution of system (1), (2), (3). If $S_0 \in R \times R_+^3$ then, the limit of $S(t)$ exits when $t \rightarrow +\infty$. In other words the solution is globally bounded in the future. In particular, S is periodic if and only if S is stationary under the condition that $S(t)$ admits a finite limit when t tends to infinity.*

Theorem 2.5 *Let $(t_0, S_0 = (T_0, I_0, V_0)) \in R \times R_+^3$ and $([t_0, T_1], S = (T, I, V))$ be a maximal solution of the Cauchy problem (1)-(4) ($T_1 \in [t_0, +\infty]$). If $T(t_0) + I(t_0) \leq C_3$ and $V(t_0) \leq C_4$ then the set:*

$\Omega = \{(T(t), I(t), V(t)) \in R_+^3 : T(t) + I(t) \le C_3, V(t) \le C_4\},$

where $C_3 = \frac{\lambda}{\min\{d,\delta\}}$ and $C_4 = \frac{(1-\varepsilon)p\lambda}{c\min\{d,\delta\}}$, is a positively invariant set by system (1), (2), (3).

Proof. Let $t_1 \in [t_0, T_1]$. We shall show that:

1. If $T(t_1) + I(t_1) \le C_3$ then for all $t_1 \le t < T_1$, $T(t) + I(t) \le C_3$.
2. If $V(t_1) \le C_4$ then for all $t_1 \le t < T_1$, $V(t) \le C_4$.

1. Let us suppose that there exists $\varepsilon_1 > 0$ such that: $t_1 \le t_1 + \varepsilon_1 < T_1$,

$$(T + I)(t_1 + \varepsilon_1) > C_3.$$

Let $t_1^* = \inf\{t \ge t_1 \,/\, (T + I)(t) > C_3\}$.

Since $(T + I)(t_1^*) = C_3$, hence

$(T + I)(t) = C_3 + \frac{d}{dt}(T(t_1^*) + I(t_1^*))(t - t_1^*) + o(t - t_1^*)$, $t \to t_1^*$. In addition, according to equations (1) and (2) of the system we have:

$$\frac{d}{dt}(T(t) + I(t)) = \lambda - dT - \delta I$$

which yields:

$$\frac{d}{dt}(T + I)(t_1^*) \le \lambda - \min\{d, \delta\}(T + I)(t_1^*)$$

$$\le \lambda - \min\{d, \delta\}C_3$$

$$\le \lambda - \min\{d, \delta\}\frac{\lambda}{\min\{d, \delta\}}$$

$$\le 0,$$

hence, there exists $\tilde{\varepsilon} > 0$ such that for all $t_1^* \le t < t_1^* + \tilde{\varepsilon}$, $(T + I)(t) \le C_3$, a contradiction. therefore for all $t \in [t_0, T_1]$, $(T + I)(t) \le C_3$.

2. Let us suppose that there exists $\varepsilon_1 > 0$ such that: $t_1 \le t_1 + \varepsilon_1 < T_1$,

$$V(t_1 + \varepsilon_1) > C_4.$$

Let $t_1^* = \inf\{t \ge t_1 \,/\, V(t) > C_3\}$.

Since $V(t_1^*) = C_3$, hence

$V(t) = C_4 + \frac{dV(t_1^*)}{dt}(t - t_1^*) + o(t - t_1^*)$, $t \to t_1^*$. In addition, according to equation (3), we have:

$$\frac{dV(t)}{dt} = (1 - \varepsilon)pI - cV$$

which yields:

$$\frac{d}{dt}V(t_1^*) \le (1 - \varepsilon)p(I + T)(t_1^*) - cV(t_1^*)$$

$$\le (1 - \varepsilon)pC_3 - cC_4$$

$$\le (1 - \varepsilon)p\frac{\lambda}{\min\{d, \delta\}} - c\frac{(1 - \varepsilon)p\lambda}{c\min\{d, \delta\}}$$

$$\frac{d}{dt}V(t_1^*) \le 0,$$

hence, there exists $\tilde{\varepsilon} > 0$ such that for all $t_1^* \le t < t_1^* + \tilde{\varepsilon}$, $V(t) \le C_4$, a contradiction. therefore for all $t \in [t_0, T_1]$, $V(t) \le C_3$.

3. Stability Analyses

3.1. Equilibria, Basic Reproduction Number R_0 and Local Stability

According to [3], apart from an infection-free equilibrium

$$E^0 = (T^0, 0, 0) \; where \; T^0 = \frac{\lambda}{d} \tag{7}$$

the system (1), (2), (3) has an infected equilibrium during therapy $E^* = (T^*, I^*, V^*)$, where:

$$T^* = \frac{c\delta}{(1-\eta)\beta(1-\varepsilon)p}, I^* = \frac{(1-\varepsilon)(1-\eta)\lambda p\beta - dc\delta}{(1-\eta)(1-\varepsilon)p\beta\delta}$$

$$V^* = \frac{(1-\eta)(1-\varepsilon)\lambda p\beta - dc\delta}{(1-\eta)\delta c\beta} = \frac{p(1-\varepsilon)}{c}I^*. \tag{8}$$

The basic reproduction number R_0 has been defined in the introduction as the average number of secondary infections that occur when one infective is introduced into a completely susceptible host population [5, 6, 14]. Note that R_0 is also called the basic reproduction ratio [5] or basic reproductive rate [1]. It is implicitly assumed that the infected outsider is in the host population for the entire infectious period and mixes with the host population in exactly the same way that a population native would mix. Following the method done by [14], we have:

Proposition 3.1 *The basic reproduction number R_0 for model (1) is given by:*

$$R_0 = (1 - \eta)(1 - \varepsilon)\frac{\lambda p\beta}{cd\delta}.$$

Now we can express the components of infected equilibrium in term of R_0. Hence (8) becomes:

$$T^* = \frac{1}{R_0}\frac{\lambda}{d}, I^* = \frac{cd}{(1-\eta)(1-\varepsilon)p\beta}(R_0 - 1), V^* = \frac{d}{(1-\eta)(R_0-1)\beta} \tag{9}$$

The following results summarize the main results regarding the local stability of the disease-free steady state E^0, and the local stability of the infected steady state during therapy E^*. The proof of these results can be found in [3].

Theorem 3.2 *The infection-free steady state E^0 of model (1), (2), (3) is locally asymptotically stable if $R_0 \le 1$ and unstable if $R_0 > 1$.*

Theorem 3.3 *The infected steady state during the therapy E^* of model (1), (2), (3) is locally asymptotically stable if $R_0 > 1$ and unstable if $R_0 > 1$.*

3.2. Global Stability

In this section, firstly we prove the global stability of the infection-free equilibrium E^0 of model (1), (2), (3) when the basic reproduction number is less than or equal to unity. And secondly we prove the global stability of infected equilibrium E^* whenever it exists. We have seen previously [3] that the unique positive endemic equilibrium exits when the basic

reproduction number is greater than or equal to unity.

Theorem 3.4

1. The infection-free steady state E^0 of model (1), (2), (3) is globally asymptotically stable if the basic reproduction number $R_0 \leq 1$ and unstable if $R_0 > 1$.
2. The infected steady state during therapy E^* of model (1), (2), (3) is globally asymptotically stable if the basic reproduction number $R_0 \leq 1$.

Proof.

1. Consider the Lyapunov function:

$$L_1(T,I,V) = T - T^0 - T^0 \ln\frac{T}{T^0} + I + \frac{\delta}{(1-\varepsilon)p}V.$$

L_1 is defined, continuous and positive definite for all $T > 0$, $I > 0$, $V > 0$. Also, the global minimum $L_1 = 0$ occurs at the infection free equilibrium E^0. Further, function L_1, along the solutions of system (1), (2), (3) satisfies:

$$\frac{dL_1}{dt} = \lambda - dT - \frac{T^0}{T}\lambda + dT^0 + (1-\eta)\beta VT^0 - \frac{c\delta}{(1-\varepsilon)p}V.$$

Further collecting terms, we have

$$\frac{dL_1}{dt} = \lambda\left(2 - \frac{T}{T^0} - \frac{T^0}{T}\right) + (R_0 - 1)\frac{c\delta}{(1-\varepsilon)p}V.$$

Since the arithmetical mean is greater than or equal to the geometrical mean,

$$\sqrt{a_1 a_2} - (a_1 + a_2) \leq 0, a_i \geq 0, i = 1,2.$$

the function $2 - \frac{T}{T^0} - \frac{T^0}{T}$ are non-positive for all $T > 0$. In addition, since $R_0 \leq 1$ ensures $\frac{dL_1}{dt} \leq 0$ for all $T > 0$, $V > 0$. The equality $\frac{dL_1}{dt} = 0$ holds only

(a) at the free equilibrium E^0 or
(b) when $R_0 = 1$ and $T = T^0$.

The latter case implies $I = V = 0$.

Therefore, the largest compact invariant subset of the set

$$M = \{(T,I,V) \in \Omega : \frac{dL_1}{dt} = 0\}$$

is the singleton $\{E^0\}$. By the Lasalle invariance principle [8], the infection-free equilibrium is globally asymptotically stable if $R_0 \leq 1$. We have seen previously that if $R_0 > 1$, at least one of the eigenvalues of the Jacobian matrix evaluated at E^0 has a positive real part. Therefore, the infection-free equilibrium E^0 is unstable when $R_0 > 1$.

2. Consider the Lyapunov function:

$$L_2(T,I,V) = T - T^* - T^*\ln\frac{T}{T^*} + I - I^* - I^*\ln\frac{I}{I^*} + \frac{\delta}{(1-\varepsilon)p}\left(V - V^* - V^*\ln\frac{V}{V^*}\right).$$

The time derivative of L_2 along the trajectories of system (1), (2), (3) is:

$$\frac{dL_2}{dt} = \frac{dT}{dt} - \frac{T^*}{T}\frac{dT}{dt} + \frac{dI}{dt} - \frac{I^*}{I}\frac{dI}{dt} + \frac{\delta}{(1-\varepsilon)p}\frac{dV}{dt} - \frac{\delta}{(1-\varepsilon)p}\frac{V^*}{V}\frac{dV}{dt}.$$

Collecting terms, and canceling identical terms with opposite signs, yields

$$\frac{dL_2}{dt} = \lambda - dT - \lambda\frac{T^*}{T} + dT^* + (1-\eta)\beta VT^* - (1-\eta)\beta VT\frac{I^*}{I} + \delta I^* - \frac{cV\delta}{(1-\varepsilon)p} - \delta\frac{V^*}{V}I + \frac{c\delta}{(1-\varepsilon)p}V^*$$

$$= dR_0 T^* - dT^*\frac{T}{T^*} - dR_0 T^*\frac{T^*}{T} + dT^* + (1-\eta)\beta V^*T^*\frac{V}{V^*} + \delta I^* - (1-\eta)\beta V^*T^*\frac{T}{T^*}\frac{V}{V^*}\frac{I^*}{I} - \frac{c\delta}{(1-\varepsilon)p}\frac{V}{V^*}V^* - \delta\frac{V^*}{V}\frac{I}{I^*}I^* + \frac{c\delta}{(1-\varepsilon)p}V^*,$$

$$according\ to\ (9),$$

$$= dT^*\left(R_0 - \frac{T}{T^*} - R_0\frac{T^*}{T} + 1\right) + (1-\eta)\beta V^*T^*\left(\frac{V}{V^*} - \frac{VTI^*}{V^*T^*I}\right) + \delta I^*\left(2 + \frac{V}{V^*} - \frac{V^*I}{VI^*}\right)$$

$$= dT^*\left(R_0 - \frac{T}{T^*} - R_0\frac{T^*}{T} + 1\right) + \delta I^*\left(\frac{V}{V^*} - \frac{VTI^*}{V^*T^*I}\right) + \delta I^*\left(2 + \frac{V}{V^*} - \frac{V^*I}{VI^*}\right),$$

$$since\ (1-\eta)\beta\ V^*T^* = \ \delta\ I^*$$

$$\frac{dL_2}{dt} = dT^*\left(R_0 - \frac{T}{T^*} - R_0\frac{T^*}{T} + 1\right) + \delta I^*\left(2 - \frac{V^*I}{VI^*} - \frac{VTI^*}{V^*T^*I}\right) + \delta I^*\left(1 - \frac{T^*}{T}\right) - \delta I^*\left(1 - \frac{T^*}{T}\right)$$

$$= dT^*\left(R_0 - \frac{T}{T^*} - R_0\frac{T^*}{T} + 1\right) + \delta I^*\left(3 - \frac{T^*}{T} - \frac{V^*I}{VI^*} - \frac{VTI^*}{V^*T^*I}\right) - dT^*(R_0 - 1)\left(1 - \frac{T^*}{T}\right),$$

$$since\ \delta\ I^* = dT^*(R_0 - 1),$$

$$\frac{dL_2}{dt} = dT^*\left(2 - \frac{T}{T^*} - \frac{T^*}{T}\right) + \delta I^*\left(3 - \frac{T^*}{T} - \frac{V^*I}{VI^*} - \frac{VTI^*}{V^*T^*I}\right). \leq 0.$$

Since the terms between the brackets are less than or equal to zero by the inequality (the geometric mean is less than or equal to the arithmetic mean)

$$\sqrt[3]{a_1 a_2 a_3} - (a_1 + a_2 + a_3) \le 0, a_i \ge 0, i = 1,2,3.$$

It should be noted that $\frac{dL_2}{dt} = 0$ holds if and only if (T, I, V) take the steady states values (T^*, X^*, V^*) Therefore, according to Lasalle invariance principle, the infected equilibrium E^* is globally asymptotically stable.

4. Numerical Simulation

Some numerical simulations have been done in the case $R_0 < 1$ to confirm theoretical result obtain on global stability for the uninfected equilibrium.
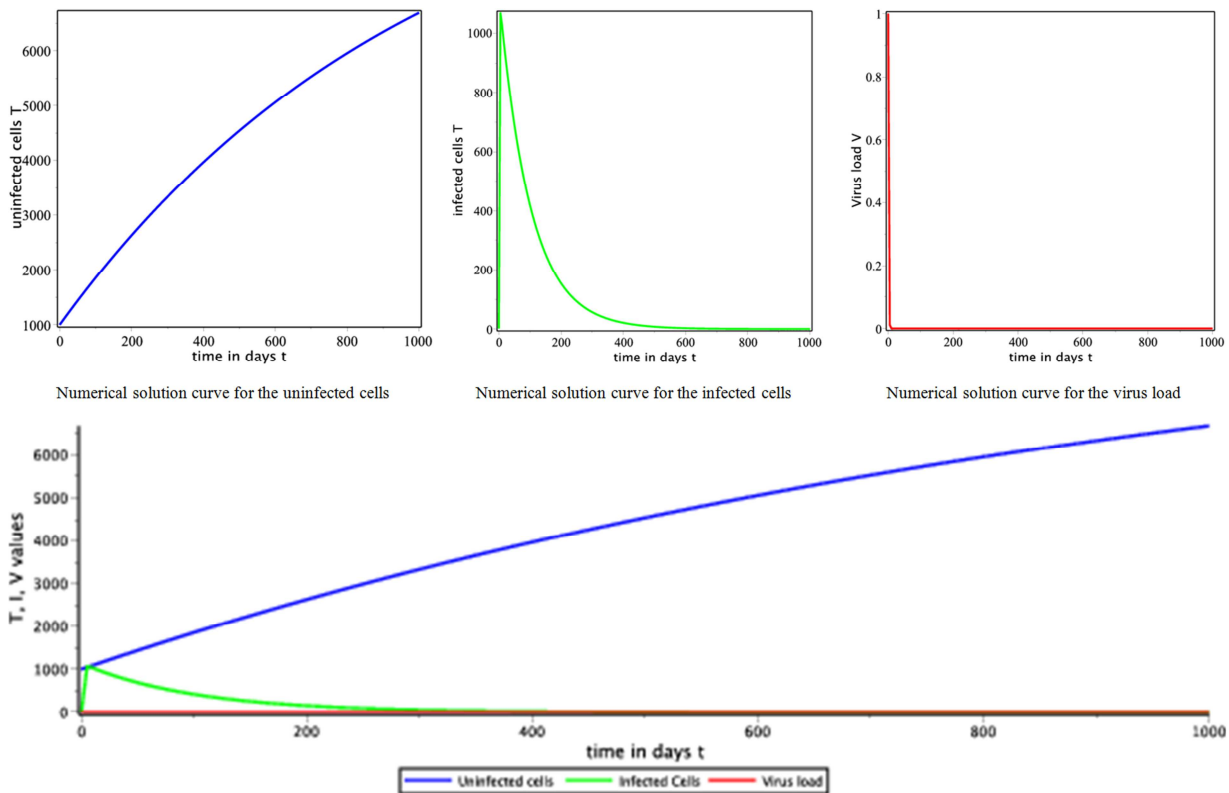

Numerical solution curve for the uninfected cells   Numerical solution curve for the infected cells   Numerical solution curve for the virus load

Figure 2. *Numerical simulation of the HCV model in 1000 days.*

We run simulations using the initial conditions: $T = 10^3$, $I = 2$ and $V = 1$ and the following parameter values: $\lambda = 10$; $\eta = \frac{1}{10000000}$; $\beta = 2.4 \times 10^{-8}$; $\delta = 0.01$; $d = 0.001$; $\varepsilon = 0.00000001$; $c = 0.9$, $p = 0.000000001$.

5. Conclusion

In this paper, we have extended the first part of the work done by Chong et al. in [3] where they only studied the local stability of the fundamental mathematical model of hepatitis C virus infection with treatment. We constructed suitable Lyapunov functions to prove that if the reproduction number $R_0 \le 1$ the HCV- uninfected equilibrium point is globally asymptocally stable; and if $R_0 > 1$ the HCV-infected equilibrium point is globally asymptotically stable. Finally we performed numerical simulations to illustrate theoretical results obtained at HCV-uninfected equilibrium point. It would be interesting to incorporate time delay, diffusion phenomenon or random phenomenon into the cyrrent model. Also, using the standard incidence function instead of mass action principle could be a serious issue. These two challenges will be the concerns of future investigation.

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