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The Global Stability Analysis of a Mathematical Cellular Model of Hepatitis C Virus Infection with Non-Cytolytic Process

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Abstract

The aim of this work is to analyse the global dynamics of an extended mathematical model of Hepatitis C virus (HCV) infection *in vivo* with cellular proliferation, spontaneous cure and hepatocyte homeostasis. We firstly prove the existence of local and global solutions of the model and establish some properties of this solution as positivity and asymptotic behaviour. Secondly we show, by the construction of appropriate Lyapunov functions, that the uninfected equilibrium and the unique infected equilibrium of the mathematical model of HCV are globally asymptotically stable respectively when the threshold number $\mathcal{R}_0 < 1 - \frac{q}{d_I + q}$ and when $\mathcal{R}_0 > 1$.

Keywords

HCV Model, Global Solutions, Non-Cytolytic Process, Invariant Set, Lyapunov Functions, Basic Reproduction Number, Equilibrium Points

1. Introduction

According to [1] [2], approximately 200 million people worldwide are persistently infected with the hepatitis C virus (HCV) and are at risk of developing chronic liver disease, cirrhosis, and hepatocellular carcinoma. HCV infection therefore represents a significant global public health problem. HCV establishes chronic hepatitis in 60% - 80% of infected adults [3]. A vaccine against infection with HCV does not exist yet, and standard treatment with interferon-α and ribavirin has produced sustained virological response rates of approximately 50%, with no effective alternative treatment for nonresponders to this treatment pro-

tocol. A model of human immunodeficiency virus infection was adapted by Neumann *et al.* [4] to study the kinetics of chronic HCV infection during treatment and some mathematical analysis was done by [5]. Since then viral kinetics modeling has played an important role in the analysis of HCV RNA decay during antiviral therapy (see Perelson [6], Perelson *et al.* [7]). The original Neumann *et al.* model for HCV infection included three differential equations representing the populations of target cells, productively infected cells, and virus. In this paper we are going to study global dynamics of an HCV infection mathematical model with full logistic terms, antivirus treatments and homeostasis phenomenon. A similar work has been done by A. Nangue [8] concerning a mathematical intracellular HCV infection model with therapy.

1.1. The Compartmental Model

There are too many mathematical models of HCV dynamics amongst those, the original model or model of Newmann [4] and its extended models as those in [5] [9] for example. Each model can be represented by a compartmental scheme. A compartmental scheme is a scheme for estimating the variation in the number of individuals in each compartment over time. **Figure 1** is the schematic representation of the extended model, which we will study, of HCV with cellular proliferation and spontaneous healing designed by T. C. Reluga *et al.* [10]. This model expands the viral dynamics of the original model of infection and the disappearance of HCV by incorporating the proliferation and death density dependence. In addition to cell proliferation, the number of uninfected hepatocytes may increase through immigration or differentiation of hepatocyte precursors that develop into hepatocytes at a constitutive rate of *s* or by spontaneous infected

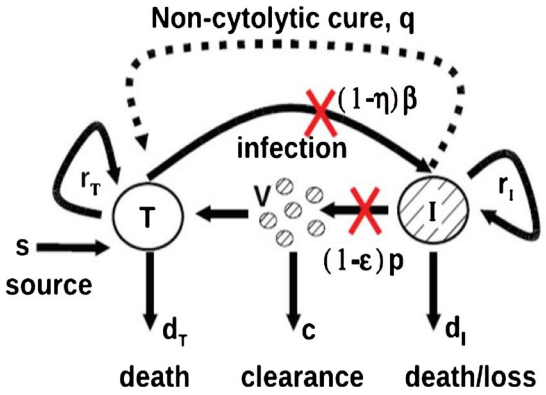

Figure 1. Schematic representation of HCV infection models. T and I represent target and infected cells, respectively, and V represents free virus. The parameters shown in the figure are defined in the text. The original model of Neumann *et al.* [4] assumed that there is no proliferation of target and infected cells (*i.e.* $r_T = r_I = 0$) and no spontaneous cure (*i.e.* $q = 0$). The extended model of Dahari, Ribeiro, and Perelson [11], which was used for predicting complex HCV kinetics under therapy, includes target and infected cell proliferation without cure ($r_T > 0$, $r_I > 0$ and $q = 0$). A model including both proliferation and the spontaneous cure of infected cells (dashed line; $q > 0$) was used to explain the kinetics of HCV in primary infection in chimpanzees [12].

hepatocyte healing by a non-cytolytic process at the rate q.

The model proposed by Dahari and coworkers [11] [13] expands on the standard HCV viral-dynamic model [4] of infection and clearance by incorporating density-dependent proliferation and death. Uninfected hepatocytes or noninfected hepatocytes, T, are infected at a rate β per free virus per hepatocyte. Infected cells, I, produce free virus at rate p per cell but also die with rate d_I. Free virus, V, is cleared at rate c by immune and other degradation processes. Besides infection processes, hepatocyte numbers are influenced by homeostatic processes. Uninfected hepatocytes die at rate d_T. Both infected and uninfected hepatocytes proliferate logistically with maximum rates r_I and r_T, respectively, as long as the total number of hepatocytes is less than $T_{\max}$. Besides proliferation, uninfected hepatocytes may increase in number through immigration or differentiation of hepatocyte precursors that develop into hepatocytes at constitutive rate s, or by spontaneous cure of infected hepatocytes through a noncytolytic process at rate q. Treatment with antiviral drugs reduces the infection rate by a fraction η and the viral production rate by a fraction ε. It should be noted that η and ε are parameters which values are non-negative and less than one. A further comprehensive survey on the description of the model is given in [10] [14] [15]. Given the meanings of η and β, the term $(1-\eta)\beta VT$ represents the mass action principle; βVT is the rate of infection of healthy hepatocytes T by interaction with virus V.

1.2. The Mathematical Model

According to Reluga *et al.* [10] and more precisely according to the schematic representation of HCV infection model in **Figure 1** we have the following dynamics:

- the variation of the healthy hepatocytes or uninfected hepatocytes, T, is expressed by the following equation:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = s + r_T T\left(1-\frac{T+I}{T_{\max}}\right) - d_T T - (1-\eta)\beta VT + qI. \tag{1}$$

- the variation of infected hepatocytes, I, is expressed by the following equation:

$$\frac{\mathrm{d}I}{\mathrm{d}t} = r_I I\left(1-\frac{T+I}{T_{\max}}\right) - d_I I - (1-\eta)\beta VT - qI. \tag{2}$$

- the variation of free virions or virus, V, is expressed by the following equation:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = (1-\varepsilon)pI - cV. \tag{3}$$

Thus, the phenomenon described above is governed by the following mathematical model (4), which is a system of three differential autonomous equations:

$$\begin{cases} \dfrac{\mathrm{d}T}{\mathrm{d}t} = s + r_T T\left(1 - \dfrac{T+I}{T_{\max}}\right) - d_T T - (1-\eta)\beta VT + qI; \\ \dfrac{\mathrm{d}I}{\mathrm{d}t} = r_I I\left(1 - \dfrac{T+I}{T_{\max}}\right) - d_I I - (1-\eta)\beta VT - qI; \\ \dfrac{\mathrm{d}V}{\mathrm{d}t} = (1-\varepsilon)pI - cV \end{cases} \tag{4}$$

To analyse the system (4) we need the following initial conditions:

$$T_0 = T(t_0),\ I_0 = I(t_0) \text{ and } V_0 = V(t_0) \quad \text{where } t_0 \in [0, +\infty[. \tag{5}$$

For biological significance of the parameters, three assumptions are employed. (a) Due to the burden of supporting virus replication, infected cells may proliferate more slowly than uninfected cells, *i.e.* $r_I \le r_T$. (b) To have a physiologically realistic model, in an uninfected liver when $T_{\max}$ is reached, liver size should no longer increase, *i.e.* $s \le d_T T_{\max}$. (c) Infected cells have a higher turnover rate than uninfected cells, *i.e.* $d_I \ge d_T$. The interpretations and biologically plausible values of other parameters and a further comprehensive survey on the description of (4) is given in [10]. Besides HCV infection, the similar model of (4) is also used to describe the dynamics of HBV or HIV infection, in which the full logistic terms mean the proliferation of uninfected/infected hepatocytes [12] [16] [17], or the mitotic transmission of uninfected/infected CD^{4+} T cells.

Our goal is therefore to analyze the stability of an extended model of HCV infection in a patient with cell proliferation and spontaneous healing given by (4) to reveal significant information on pathogenesis and dynamics of this virus. The paper is organized as follows: In Section 1, first focuses on some properties of the solutions of the model, then we calculate the basic reproduction ratio $\mathcal{R}_0$, which is an indispensable element in the study and analysis of the models. We theoretically analyze the local stability where we widely use the works of A. Nangue *et al.* [18] in Section 2. In Section 3 we theoretically analyze with some assumptions the global stability of the model by constructing appropriate Lyapounov's functions.

2. Properties of Solutions to the Initial Value Problem (4), (5)

2.1. Positivity, Global Solutions and Asymptotic Behaviour

Theorem 1. *Let* $T_0, I_0, V_0 \in \mathbb{R}$. *There exists* $t_1 > 0$ *and functions* $T, I, V : [t_0; t_1[\to \mathbb{R}$ *continuously differentiable such that* (T, I, V) *is a solution of system* (1) *satisfying* (4).

Theorem 2. *Let* (T, I, V) *be a solution of the system* (1) *over an interval* $[t_0, t_1[$ *such that* $T(t_0) = T_0, I(t_0) = I_0$ *et* $V(t_0) = V_0$.

If T_0, I_0, V_0 are positive, then $T(t)$, $I(t)$ and $V(t)$ are also positive for all $t \in [t_0, t_1[$.

Proof. We are going to prove by contradiction. so suppose there is $t \in [t_0, t_1[$ such that $T(t) = 0$ or $I(t) = 0$ or $V(t) = 0$.

Let $x=(x_1,x_2,x_3)=(T,I,V)$

Let also t_* be the smallest of all t in the interval $[t_0,t_1[$ such that $x_i(t)>0$, $\forall t\in[t_0,t_*[$, $\forall t\in[t_0,t_*[$ and $x_i(t_*)=0$ for a certain i.

Then each of the equations of the system (4) can be written $\dot{x}_i=-h_i(x)+g_i(x)$ where g_i is a non negative function and h_i any function. As a consequence $\frac{\mathrm{d}x_i(t)}{\mathrm{d}t}\geq -x_i f(x)$ and $x_i(t)>0$, $\forall t\in[t_0,t_*[$. A contradiction. □

Theorem 3. [18] *The solutions of the Cauchy problem* (4), (5), *with positive initial data, exist globally in time in the future that is on* $[t_0,+\infty[$.

Theorem 4. *For any positive solution* (T,I,V) *of system* (4), (5) *we have*:

$$T(t)\leq \tilde{T}_0,\ I(t)\leq \tilde{T}_0 \text{ and } V(t)\leq \lambda_0$$

where

$$\tilde{T}_0=\frac{T_{\max}}{2r_I}\left(\sqrt{(r_T-d_T)^2+\frac{4sr_I}{T_{\max}}}+r_T-d_T\right),\lambda_0=\lambda_0=\max\left\{V_0,\frac{1-\varepsilon}{c}p\tilde{T}_0\right\}.$$

Proof. Summing Equations (6) and (7), we get:

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}(T+I)&=s+\left(1-\frac{T+I}{T_{\max}}\right)(r_TT-r_II)-d_TT-d_II\\&=s+(r_T-d_T)T+(r_I-d_I)I-\frac{T+I}{T_{\max}}(r_TT+r_II)\\&\leq s+(r_T-d_T)(T+I)-\frac{T+I}{T_{\max}}(r_TT+r_II)\quad \text{since } r_T-d_T\geq r_I-d_I,\end{aligned}$$

thus $\frac{\mathrm{d}}{\mathrm{d}t}(T+I)\leq s+(r_T-d_T)(T+I)-\frac{r_I}{T_{\max}}(T+I)^2$ since $r_I\leq r_T$.

Let $N_1=T+I$, $a=s>0$, $b=(r_T-d_T)>0$, $d=-\frac{r_I}{T_{\max}}<0$ and let us solve the following equation

$$\frac{\mathrm{d}N_1}{\mathrm{d}t}=a+bN_1+dN_1^2 \tag{6}$$

Coupled to Equation (6) the initial condition:

$$N_1(t_0)=N_1^0. \tag{7}$$

The solving of the problem (6), (7) gives for all $t\in[t_0,+\infty[$,

$$N_1(t)=-\frac{1}{2d}\left[\tanh\left(\frac{1}{2}\sqrt{-4ad+b^2}-\frac{1}{2}t_0\sqrt{-4ad+b^2}-\arctan\left(\frac{2N_1^0+b}{\sqrt{-4ad+b^2}}\right)\right)\sqrt{-4ad+b^2}\right]-\frac{b}{2d}.$$

As for all $x\in\mathbb{R}$, $-1\leq\tanh x\leq 1$, it follows that:

$$N_1(t)\leq\frac{T_{\max}}{2r_I}\left(\sqrt{(r_T-d_T)^2+\frac{4sr_I}{T_{\max}}}+r_T-d_T\right).$$

Let

$$\tilde{T}_0 = \frac{T_{\max}}{2r_I}\left(\sqrt{\left(r_T - d_T\right)^2 + \frac{4sr_I}{T_{\max}}} + r_T - d_T\right).$$

Therefore

$$T + I \le \tilde{T}_0.$$

Since T and I are positive $I \le T + I$ and $T \le T + I$, so it follows that $T(t) \le \tilde{T}_0$ and $I(t) \le \tilde{T}_0$.

Equation (3), according to Gromwall inequality, leads to:

$$V(t) \le \lambda_0.$$

where

$$\lambda_0 = \max\left\{V_0, \frac{1-\varepsilon}{c} p\tilde{T}_0\right\}.$$

This completes the proof of theorem 4. □

2.2. Basic Reproduction Ratio $\mathcal{R}_0$, Invariant Set of the Model and Equilibria

Proposition 5. *The uninfected equilibrium point* E^0 *of the system* (4) *is given by*

$$E^0 = \left(T^0, 0, 0\right)$$

where:

$$T^0 = \frac{T_{\max}}{2r_T}\left(r_T - d_T + \sqrt{\left(r_T - d_T\right)^2 + \frac{4r_T s}{T_{\max}}}\right).$$

We use the method proposed in [19] [20] to compute the basic reproduction number $\mathcal{R}_0$.

Proposition 6. *The expression of the basic reproduction number* $\mathcal{R}_0$ *associated to the system* (4) *is given by*:

$$\mathcal{R}_0 = \frac{r_I}{d_I + q}\left(1 - \frac{T^0}{T_{\max}}\right) + \frac{(1-\theta)\beta T^0 p}{c\left(d_I + q\right)}. \tag{8}$$

where

$$1 - \theta = (1-\varepsilon)(1-\eta).$$

Remark 1. $\theta \in]0,1[$ *denotes the overall effectiveness rate of the drug.*

Remark 2. *Henceforth, we will let* $\delta = d_I + q$ *and* $1 - \theta = (1-\varepsilon)(1-\eta)$.

Theorem 7. *Let* $\left(t_0, S_0 = \left(T_0, I_0, V_0\right)\right) \in R \times R_+^3$ *and* $\left([t_0, T[, S = (T, I, V)\right)$ *be a maximal solution of the Cauchy problem* (1), (4) ($T \in]t_0, +\infty[$). *If* $T(t_0) + I(t_0) \le \tilde{T}_0$ *and* $V(t_0) \le \lambda_0$ *then the set*:

$$\Omega = \left\{(T, I, V) \in \mathbb{R}; 0 < T + I \le \tilde{T}_0; 0 < V \le \lambda_0\right\},$$

where:

$$\tilde{T}_0 = \frac{T_{\max}}{2r_I}\left(\sqrt{\left(r_T - d_T\right)^2 + \frac{4sr_I}{T_{\max}}} + r_T - d_T\right) \text{ and } \lambda_0 \max\left\{V_0, \frac{1-\varepsilon}{c} p\tilde{T}_0\right\},$$

is a positively invariant set by system (4).

When it exists, the infected equilibrium point is given by: $E^* = \left(T^*, I^*, V^*\right)$ where T^*, I^* and V^* are positive constants that we are going to determine.

Lemma 1. [18] *T^* exists if and only if*

$$s + q\frac{T_{\max}}{r_I}\left(r_I - \delta\right) > 0.$$

Lemma 2. [18] *When it exists, T^* is defined by*:

$$T^* = \frac{1}{2}\left(-\frac{D}{H} + \sqrt{\left(\frac{D}{H}\right)^2 + F + \frac{4sT_{\max}}{r_T}H}\right)$$

where:

$$D = AT_{\max}\left(\frac{1}{r_T}\left(1 + \frac{d_T + q}{A}\right) - \frac{\delta}{r_I}\left(\frac{1}{r_T} + \frac{1}{A}\right) - \frac{q}{r_T r_I}\right);$$

$$F = \frac{4AqT_{\max}^2}{H^2 r_T^2 r_I^2}\left(A\left(\delta - r_I\right) - d_I\left(r_I - r_T\right) - r_I\left(q - r_I - r_T\right) + r_I q\right);$$

and

$$H = \frac{A^2}{r_I r_T} + \frac{A}{r_I} - \frac{A}{r_T};\ A = \frac{\left(1-\theta\right)\beta pT_{\max}}{c}$$

The combination of the lemma 1 and the lemma 2 leads to the following theorem:

Theorem 8. *The model* (4) *admits a unique infected equilibrium $E^* = \left(T^*, I^*, V^*\right)$ if and only if $\mathcal{R}_0 > 1$, where*

$$T^* = \frac{1}{2}\left(-\frac{D}{H} + \sqrt{\left(\frac{D}{H}\right)^2 + F + \frac{4sT_{\max}}{r_T}H}\right),$$

$$I^* = T^*\left(\frac{A}{r_I} - 1\right) + T_{\max}\left(1 - \frac{\delta}{r_I}\right),$$

$$V^* = \frac{\left(1-\varepsilon\right)pI^*}{c};$$

When $\mathcal{R}_0 \le 1$ the unique equilibrium is the uninfected equilibrium point or the infection-free steady state $E^0 = \left(T^0, 0, 0\right)$.

3. Local Stability Analyses

3.1. Case of the Uninfected Equilibrium Point or Infection-Free Steady State

Theorem 9. *The infection-free steady state $E^0 = \left(T^0, 0, 0\right)$ of model* (4) *is locally asymptotically stable if $\mathcal{R}_0 \le 1$ and unstable if $\mathcal{R}_0 > 1$.*

Proof. See the appendice of [18]. □

3.2. Case of Infected Equilibrium Point

We start this section by this lemma where the proof can be found in [18].

Lemma 3 *The characteristic equation of the Jacobian matrix* $J\left(E^*\right)$ *of the system* (4) *at* E^* *is given by the following cubic equation*:

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0;$$

where:

$$A_1 = c + \frac{s}{T^*} + \frac{r_T T^* + r_I I^* + AT^*}{T_{\max}} + q\frac{I^*}{T^*},$$

$$A_2 = \frac{cs}{T^*} + \frac{cr_T T^* + sA + cr_I I^*}{T_{\max}} + q\frac{I^*}{T^*}\left(r_I - \delta\right) + \frac{sr_I I^*}{T^* T_{\max}} + \frac{r_T AT^*\left(T^* + I^*\right)}{T_{\max}^2} + \frac{cqI^*}{T^*} + q\frac{I^*}{T_{\max}},$$

$$A_3 = \frac{csr_I I^*}{T^* T_{\max}} + \frac{cA^2 I^* T^*}{T_{\max}^2} - \frac{cAr_I I^* T^*}{T_{\max}^2} + \frac{cAr_T I^* T^*}{T_{\max}^2} + q\frac{cI^*}{T^*}\left(r_I - \delta\right).$$

Proof. See [18]. □

Now let:

$$\Delta_2 = \begin{vmatrix} A_1 & 1 \\ A_3 & A_2 \end{vmatrix}$$

According to lemma 3 combined with the Routh-Hurwitz criterion [21], we have the following results where the proofs can be found in [18].

Theorem 10. *For model* (4), *when* $\mathcal{R}_0 > 1$ *is valid, the unique endemic equilibrium* E^* *is locally asymptotically stable if* $\Delta_2 > 0$ *and unstable if* $\Delta_2 < 0$.

Especially, we have:

Corollary 1. *The infected steady state during the therapy* E^* *of the model* (4) *is locally asymptotically stable if* $\mathcal{R}_0 > 1$ *and unstable if* $\mathcal{R}_0 > 1$.

4. Global Stability Analyses

The global stability analysis of a dynamical system is usually a very complex problem. One of the most efficient methods to solve this problem is Lyapunov's theory. To build the functions of Lyapunov we will follow the method proposed by A. Korobeinikov [22] [23] [24]. In the proofs of the results that follow, to simplify the writings, we can use differently $\frac{\mathrm{d}}{\mathrm{d}t}$ or $\dot{\cdot}$ for the derivation with respect to time.

4.1. Case of Infection-Free Steady State

Theorem 11. *The infection-free steady state* $E^0 = \left(T^0, 0, 0\right)$ *of the model* (4) *is globally asymptotically stable if the basic reproduction number* $R_0 < 1 - \frac{q}{\delta}$ *and unstable if* $R_0 > 1 - \frac{q}{\delta}$.

Proof. Consider the Lyapunov function:

$$L(T,I,V)=T-T^0-T^0\ln\frac{T}{T^0}+I+\frac{(1-\eta)\beta T^0}{c}V.$$

L is defined, continuous and positive definite for all $T>0$, $I>0$, $V>0$. Also, the global minimum $L=0$ occurs at the infection free equilibrium E^0. Further, function L, along the solutions of system (4), satisfies:

$$\begin{aligned}\frac{\mathrm{d}L}{\mathrm{d}t}&=\frac{\partial L}{\partial T}\frac{\mathrm{d}T}{\mathrm{d}t}+\frac{\partial L}{\partial I}\frac{\mathrm{d}I}{\mathrm{d}t}+\frac{\partial L}{\partial V}\frac{\mathrm{d}V}{\mathrm{d}t}\\&=\left(1-\frac{T^0}{T}\right)\dot{T}+\dot{I}+\frac{(1-\eta)\beta T^0}{c}\dot{V}\\&=\left(T-T^0\right)\frac{\dot{T}}{T}+\dot{I}+\frac{(1-\eta)\beta T^0}{c}\dot{V}\\&=\left(T-T^0\right)\left(\frac{s}{T}+r_T-\frac{r_T(T+I)}{T_{\max}}-\mathrm{d}T-(1-\eta)\beta V+q\frac{I}{T}\right)+(1-\eta)\beta VT\\&\quad+r_II\left(1-\frac{T+I}{T_{\max}}\right)-\delta I+\frac{1-\theta}{c}\beta pT^0T-(1-\eta)\beta T^0V\\&=\left(T-T^0\right)\left(\frac{s}{T}+r_T-dT-\frac{r_T(T+I)}{T_{\max}}+q\frac{I}{T}\right)-T(1-\eta)\beta V+T^0(1-\eta)\beta V\\&\quad+(1-\eta)\beta VT+r_II\left(1-\frac{T+I}{T_{\max}}\right)-\delta I+\frac{1-\theta}{c}\beta pT^0I-(1-\eta)\beta T^0V,\end{aligned}$$

i.e.

$$\begin{aligned}\frac{\mathrm{d}L}{\mathrm{d}t}&=\left(T-T^0\right)\left(\frac{s}{T}+r_T-dT-\frac{r_T(T+I)}{T_{\max}}\right)+qI-qI\frac{T^0}{T}\\&\quad+r_II\left(1-\frac{T+I}{T_{\max}}\right)+\left(\frac{1-\theta}{c}\beta pT^0-\delta\right)I;\end{aligned}$$

yet

$$r_T-d_T=\frac{rT^0}{T_{\max}}-\frac{s}{T^0};$$

hence, Further collecting terms, we have:

$$\begin{aligned}\frac{\mathrm{d}L}{\mathrm{d}t}&=\left(T-T^0\right)\left(\frac{s}{T}+\frac{rT^0}{T_{\max}}-\frac{s}{T^0}-\frac{r_T(T+I)}{T_{\max}}\right)\\&\quad+r_II\left(1-\frac{T+I}{T_{\max}}\right)+\left(\frac{1-\theta}{c}\beta pT^0-\delta\right)I\\&=\left(T-T^0\right)\left(-\frac{s}{TT^0}\left(T-T^0\right)-\frac{r_T}{T_{\max}}\left(T-T^0\right)-\frac{r_TI}{T_{\max}}\right)\\&\quad+r_II\left(1-\frac{T+I}{T_{\max}}\right)+\left(\frac{1-\theta}{c}\beta pT^0-\delta\right)I+qI-qI\frac{T^0}{T}\\&=-\frac{s}{TT^0}\left(T-T^0\right)^2-\frac{r_T}{T_{\max}}\left(\left(T-T^0\right)^2+\left(T-T^0\right)I\right)+r_II-\frac{r_IIT}{T_{\max}}\\&\quad-\frac{r_II^2}{T_{\max}}+\left(\frac{1-\theta}{c}\beta pT^0-\delta\right)I+qI-qI\frac{T^0}{T}\end{aligned}$$

$$
\begin{aligned}
&= -\frac{s}{TT^0}\left(T-T^0\right)^2 - \frac{r_T}{T_{\max}}\left(\left(T-T^0\right)^2 + \left(T-T^0\right)I + \frac{r_I IT}{r_T} + \frac{r_I I^2}{r_T}\right) \\
&\quad + r_I I + \left(\frac{1-\theta}{c}\beta pT_0 - \delta\right)I + qI - qI\frac{T^0}{T} \\
&= -\frac{s}{TT_0}\left(T-T^0\right)^2 - \frac{r_T}{T_{\max}}\left[\left(T-T^0\right)^2 + \left(T-T^0\right)I + \frac{r_I IT}{r_T} + \frac{r_I I^2}{r_T}\right. \\
&\quad \left. + \frac{r_I}{r_T}IT^0 - \frac{r_I}{r_T}IT^0\right] + r_I I + \left(\frac{1-\theta}{c}\beta pT^0 - \delta\right)I + qI - qI\frac{T^0}{T} \\
&= -\frac{s}{TT^0}\left(T-T^0\right)^2 - \frac{r_T}{T_{\max}}\left(\left(T-T^0\right)^2 + \left(T-T^0\right)I + \frac{r_I IT}{r_T}\left(T-T^0\right)\right. \\
&\quad \left. + \frac{r_I I^2}{r_T} + \frac{r_I}{r_T}IT^0\right) + r_I I + \left(\frac{1-\theta}{c}\beta pT^0 - \delta\right)I + qI - qI\frac{T^0}{T} \\
&= -\frac{s}{TT^0}\left(T-T^0\right)^2 - \frac{r_T}{T_{\max}}\left(T+I-T^0\right)\left(T+\frac{r_I}{r_T}I-T^0\right) \\
&\quad - \frac{r_I}{T_{\max}}IT^0 + r_I I + \left(\frac{1-\theta}{c}\beta pT^0 - \delta\right)I + qI - qI\frac{T^0}{T} \\
&= -\frac{s}{TT^0}\left(T-T^0\right)^2 - \frac{r_T}{T_{\max}}\left(T+I-T^0\right)\left(T+\frac{r_I}{r_T}I-T^0\right) \\
&\quad + \delta I\left(\frac{r_I}{\delta} - \frac{r_I T^0}{\delta T_{\max}}\frac{1-\theta}{c\delta}\beta pT^0 - 1\right) + qI - qI\frac{T^0}{T}.
\end{aligned}
$$

Furthermore,

$$
\mathcal{R}_0 = \frac{1-\theta}{c\delta}\beta pT^0 + \frac{r_I}{\delta}\left(1-\frac{T^0}{T_{\max}}\right),
$$

hence

$$
\begin{aligned}
\frac{\mathrm{d}L}{\mathrm{d}t} &= -\frac{s}{TT^0}\left(T-T^0\right)^2 - \frac{r_T}{T_{\max}}\left(T+I-T^0\right)\left(T+\frac{r_I}{r_T}I-T^0\right) \\
&\quad - qI\frac{T^0}{T} + \delta I\left(\mathcal{R}_0 - 1\right) + qI \\
&= -\frac{s}{TT^0}\left(T-T^0\right)^2 - \frac{r_T}{T_{\max}}\left(T+I-T^0\right)\left(T+\frac{r_I}{r_T}I-T^0\right) \\
&\quad - qI\frac{T^0}{T} + \delta I\left(\mathcal{R}_0 - 1 + \frac{q}{\delta}\right).
\end{aligned}
$$

Since $r_I \le r_T$ and $\mathcal{R}_0 < 1-\frac{q}{\delta}$, we have $\frac{\mathrm{d}L}{\mathrm{d}t} \le 0$ and $\frac{\mathrm{d}L}{\mathrm{d}t} = 0$ if and only if $T = T^0$ and $I = 0$ simultaneously.

Therefore, the largest compact invariant subset of the set

$$
M = \left\{(T, I, V) \in \Omega : \frac{\mathrm{d}L}{\mathrm{d}t} = 0\right\}
$$

is the singleton $\left\{E^0\right\}$. By the Lasalle invariance principle [25], the infection-free equilibrium is globally asymptotically stable if $\mathcal{R}_0 < 1 - \frac{q}{\delta}$. We have seen previously that if $\mathcal{R}_0 > 1$, 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 $\mathcal{R}_0 > 1$. This completes the proof of the theorem.

Remark 3. *The Lyapunov function defined in the proof of theorem* 11 *has been obtained following the general form giving by Korobonikov* [22] [23] [24] *for the dynamic virus fondamental model.*

4.2. Case of Infected Equilibrium Point

We recall:

Remark 4. *The infected equilibrium point* $E^* = \left(T^*, I^*, V^*\right)$ *satisfies*:

$$r_T - d_T = -\frac{s}{T^*} + (1-\eta)\beta V^* + \frac{r_T}{T_{\max}}\left(T^* + I^*\right) - q\frac{I^*}{T^*}, \tag{9}$$

$$r_I - \delta = -\frac{(1-\eta)\beta V^* T^*}{I^*} + \frac{r_I}{T_{\max}}\left(T^* + I^*\right), \tag{10}$$

$$c = \frac{(1-\varepsilon)pI^*}{V^*}. \tag{11}$$

Now we are stating and demonstrating one of the most important results of this work.

Theorem 12. *Suppose that* $r_I = r_T$, $s = d_T T_{\max}$ *and* $\delta = d_T$. *Then the infected steady state during therapy* E^* *of model* (4) *is globally asymptotically stable as soon as it exists.*

Proof. Consider the Lyapunov function defined by:

$$L(T,I,V) = T - T^* - T^* \ln\frac{T}{T^*} + I - I^* - I^* \ln\frac{I}{I^*} + \frac{(1-\eta)\beta T^* V^*}{(1-\varepsilon)pI^*}\left(V - V^* - V^* \ln\frac{V}{V^*}\right).$$

Let us show that $\frac{\mathrm{d}L}{\mathrm{d}t} \le 0$ and $\frac{\mathrm{d}L}{\mathrm{d}t} = 0$ if and only if $T = T^*$, $I = I^*$, $V = V^*$ simultaneously.

The time derivative of L along the trajectories of system (1) is:

$$\begin{aligned}\frac{\mathrm{d}L}{\mathrm{d}t} &= \frac{\partial L}{\partial T}\frac{\mathrm{d}T}{\mathrm{d}t} + \frac{\partial L}{\partial I}\frac{\mathrm{d}I}{\mathrm{d}t} + \frac{\partial L}{\partial V}\frac{\mathrm{d}V}{\mathrm{d}t} \\ &= \left(1 - \frac{T^*}{T}\right)\dot{T} + \left(1 - \frac{I^*}{I}\right)\dot{I} + \frac{(1-\eta)\beta T^* V^*}{(1-\varepsilon)pI^*}\left(1 - \frac{V^*}{V}\right)\dot{V} \\ &= \left(T - T^*\right)\frac{\dot{T}}{T} + \left(I - I^*\right)\frac{\dot{I}}{I} + \frac{(1-\eta)\beta T^* V^*}{(1-\varepsilon)pI^*}\left(V - V^*\right)\frac{\dot{V}}{V}.\end{aligned}$$

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

$$\begin{aligned}\frac{\mathrm{d}L}{\mathrm{d}t} &= \left(T-T^*\right)\left(\frac{s}{T}+r_T-\frac{r_T\left(T+I\right)}{T_{\max}}-d_T-\left(1-\eta\right)\beta V+q\frac{I}{T}\right)\\ &+\frac{\left(1-\eta\right)\beta T^*V^*}{\left(1-\varepsilon\right)pI^*}\left(\frac{V-V^*}{V}\right)\left(\left(1-\varepsilon\right)pI-cV\right)\\ &+\left(I-I^*\right)\left(\left(1-\eta\right)\frac{\beta VT}{I}+r_I\left(1-\frac{T+I}{T_{\max}}\right)-\delta\right).\end{aligned} \tag{12}$$

Reporting equalities (9), (10) and (11) of the remark 4 into (12), we have:

$$\begin{aligned}\frac{\mathrm{d}L}{\mathrm{d}t} &= \left(T-T^*\right)\left[\frac{s}{T}-\frac{s}{T^*}+\left(1-\eta\right)\beta V^*+\frac{r_T}{T_{\max}}\left(T^*+I^*\right)-q\frac{I^*}{T^*}\right.\\ &\left.-\frac{r_T\left(T+I\right)}{T_{\max}}-\left(1-\eta\right)\beta V+q\frac{I}{T}\right]+\left(I-I^*\right)\left[\left(1-\eta\right)\frac{\beta VT}{I}\right.\\ &\left.-r_I\frac{T}{T_{\max}}-r_I\frac{I}{T_{\max}}-\frac{\left(1-\eta\right)\beta V^*T^*}{I^*}+\frac{r_I}{T_{\max}}\left(T^*+I^*\right)\right]\\ &+\left(1-\eta\right)\beta+\frac{T^*V^*}{\left(1-\varepsilon\right)pI^*}\left(\frac{V-V^*}{V}\right)\left(\left(1-\varepsilon\right)pI-\frac{\left(1-\varepsilon\right)pI^*}{V^*}V\right)\\ &= -\frac{s}{TT^*}\left(T-T^*\right)^2-\frac{r_T}{T_{\max}}\left(T-T^*\right)^2-\frac{r_T}{T_{\max}}\left(T-T^*\right)\left(I-I^*\right)\\ &-\left(1-\eta\right)\beta\left(T-T^*\right)\left(V-V^*\right)+\left(1-\eta\right)\beta\left[\left(\frac{VT}{I}-\frac{V^*T^*}{I^*}\right)\left(I-I^*\right)\right.\\ &\left.+\frac{T^*V^*}{\left(1-\varepsilon\right)pI^*}\frac{V-V^*}{V}\left(\left(1-\varepsilon\right)pI-\frac{\left(1-\varepsilon\right)}{V^*}pI^*V\right)\right]-q\frac{I^*}{T^*}\left(T-T^*\right)\\ &+q\frac{I}{T}\left(T-T^*\right)-\frac{r_I}{T_{\max}}\left(T-T^*\right)\left(I-I^*\right)-\frac{r_I}{T_{\max}}\left(I-I^*\right)^2\\ &= -\frac{s}{TT^*}\left(T-T^*\right)^2-\frac{r_T}{T_{\max}}\left(T-T^*\right)^2-\frac{r_T+r_I}{T_{\max}}\left(T-T^*\right)\left(I-I^*\right)\\ &-\frac{r_I}{T_{\max}}\left(I-I^*\right)^2+\left(1-\eta\right)\beta\left[\left(\frac{VT}{I}-\frac{V^*T^*}{I^*}\right)\left(I-I^*\right)\right.\\ &\left.-\left(T-T^*\right)\left(V-V^*\right)+\frac{T^*V^*}{\left(1-\varepsilon\right)pI^*}\frac{V-V^*}{V}\left(\left(1-\varepsilon\right)pI-\frac{1-\varepsilon}{V^*}pI^*V\right)\right]\\ &-q\frac{1}{TT^*}\left(T^2I^*+\left(T^*\right)^2I-T^*TI-T^*TI^*\right)\\ &= -\frac{s}{TT^*}\left(T-T^*\right)^2-\frac{1}{T_{\max}}\left(r_TT+r_II-r_TT^*-r_II^*\right)\left(T+I-T^*-I^*\right)\\ &+\left(1-\eta\right)\beta T^*V^*\left(\frac{VT}{V^*T^*}-\frac{VTI^*}{IV^*T^*}-\frac{V^*T^*I}{I^*V^*T^*}+\frac{V^*T^*I^*}{V^*T^*I^*}-\frac{TV}{T^*V^*}\right.\\ &\left.+\frac{TV^*}{T^*V^*}+\frac{T^*V}{T^*V^*}-\frac{T^*V^*}{T^*V^*}+\frac{IV}{I^*V}-\frac{I^*V^2}{I^*VV^*}-\frac{V^*I}{I^*V}+\frac{V^*I^*V}{V^*I^*V}\right)\\ &-q\frac{1}{TT^*}\left(\left(T-T^*\right)^2I^*+\left(T^*\right)^2\left(I-I^*\right)+TT^*\left(I^*-I\right)\right)\end{aligned}$$

$$= -\frac{s}{TT^*}\left(T-T^*\right)^2 - \frac{1}{T_{\max}}\left(r_T T + r_I I - r_T T^* - r_I I^*\right)\left(T + I - T^* - I^*\right)$$
$$+\left(1-\eta\right)\beta T^* V^*\left(1+\frac{T}{T^*}-\frac{VTI^*}{IV^*T^*}-\frac{V^*I}{I^*V}\right)$$
$$-q\frac{1}{TT^*}\left(\left(T-T^*\right)^2 I^* + T^*\left(I-I^*\right)\left(T^*-T\right)\right).$$

Note that

$$1+\frac{T}{T^*}-\frac{VTI^*}{IV^*T^*}-\frac{V^*I}{I^*V} = \left(3-\frac{T^*}{T}-\frac{VTI^*}{IV^*T^*}-\frac{V^*I}{I^*V}\right)+\left(\frac{T}{T^*}+\frac{T^*}{T}-2\right)$$

and

$$\left(\frac{T}{T^*}+\frac{T^*}{T}-2\right) = \frac{\left(T-T^*\right)^2}{TT^*}.$$

Recall that:

$$s = \left(1-\eta\right)\beta T^* V^* + \left(d_T - r_T + r_T\frac{T^*+I^*}{T_{\max}}\right)T^* - qI^*.$$

furthermore,

$$T^* + I^* = T_{\max};$$

hence,

$$s = \left(1-\eta\right)\beta T^* V^* + d_T T^* - qI^*.$$

By hypothesis, $r_T = r_I$ this leads to:

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \left(-\frac{d_T}{T} + q\frac{I^*}{TT^* - \frac{\left(1-\eta\right)\beta V^*}{T}}\right)\left(T-T^*\right)^2 - \frac{r_T}{T_{\max}}\left(T+I-T^*-I^*\right)^2$$
$$+\left(1-\eta\right)\beta V^* T^*\left(3-\frac{T^*}{T}-\frac{VTI^*}{IV^*T^*}-\frac{V^*I}{I^*V}\right)+\left(1-\eta\right)\beta V^* T^*\frac{\left(T-T^*\right)^2}{TT^*}$$
$$-q\frac{1}{TT^*}\left(\left(T-T^*\right)^2 I^* + T^*\left(I-I^*\right)\left(T^*-T\right)\right)$$
$$= -\frac{d_T}{T}\left(T-T^*\right)^2 - \frac{r_T}{T_{\max}}\left(T+I-T^*-I^*\right)^2 - q\frac{1}{T}\left(I-I^*\right)\left(T^*-T\right)$$
$$+\left(1-\eta\right)\beta V^* T^*\left(3-\frac{T^*}{T}-\frac{VTI^*}{IV^*T^*}-\frac{V^*I}{I^*V}\right)$$
$$= -\frac{d_T}{T}\left(T-T^*\right)^2 - \frac{r_T}{T_{\max}}\left(T+I-T^*-I^*\right)^2 - q\frac{1}{T}\left(I-I^*\right)\left(T^*-T\right)$$
$$+\left(1-\eta\right)\beta V^* T^*\left(3-\frac{\left(T^*\right)^2 II^* VV^* + \left(I^* VT\right)^2 + \left(IV^*\right)^2 TT^*}{TT^* II^* VV^*}\right)$$
$$= -\frac{d_T}{T}\left(T-T^*\right)^2 - \frac{r_T}{T_{\max}}\left(T+I-T^*-I^*\right)^2 - q\frac{1}{T}\left(I-I^*\right)\left(T^*-T\right)$$
$$+\frac{3\left(1-\eta\right)\beta V^* T^*}{TT^* II^* VV^*}\left(TT^* II^* VV^* - \frac{1}{3}\left(\left(T^*\right)^2 II^* VV^* + \left(I^* VT\right)^2 + \left(IV^*\right)^2 TT^*\right)\right).$$

Yet

$$\frac{1}{3}\left(\left(T^*\right)^2 II^*VV^* + \left(I^*VT\right)^2 + \left(IV^*\right)^2 TT^*\right) \geq TT^* II^* VV^*$$

since the geometric mean is less than or equal to the arithmetic mean.

It should be noted that $\frac{\mathrm{d}L}{\mathrm{d}t} \leq 0$ and $\frac{\mathrm{d}L_2}{\mathrm{d}t} = 0$ holds if and only if (T, I, V) take the steady states values $\left(T^*, I^*, V^*\right)$. Therefore, By the Lasalle invariance principle [22], the infected equilibrium point E^* is globally asymptotically stable. This completes the proof of this theorem. □

5. Concluding Remark

To understand the dynamics of HCV infection and its infectious processes, mathematical models are present as an important and unavoidable tool. Global stability analysis has been done, by the technique of Lyapunov, to the model of HCV infection with proliferation cell and spontaneous healing, for revealing significant information for making good decision for the fighting against hepatitis C. This work is a starting point to many interesting other future investigations. We plan to extend our study by focusing on more realistic models such as: 1) mathematical models with delay which involve delay ordinary differential equations. 2) mathematical models taking into account space which involve Partial differential equations. 3) mathematical models taking into account random phenomena which evolve stochastic differential equations. We also plan to focus on others methods of studying global stability like the geometric method that can provide results with fewer hypotheses on mathematical model (4).

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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