Mathematical analysis of an extended cellular model of the Hepatitis C Virus infection with non-cytolytic process

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Abstract

The aims of this work is to analyse of the global stability of the extended model of hepatitis C virus (HCV) infection with cellular proliferation, spontaneous cure and hepatocyte homeostasis. We first give general information about hepatitis C. Secondly, We prove the existence of local, maximal and global solutions of the model and establish some properties of this solution as positivity and asymptotic behaviour. Thirdly we show, by the construction of an appropriate Lyapunov function, that the uninfected equilibrium and the unique infected equilibrium of the model of HCV are globally asymptotically stable respectively when the threshold number $R_0 < 1 − \frac{q}{\alpha_0 + \alpha}$ and when $R_0 > 1$. Finally, some numerical simulations are carried out using Maple software confirm these theoretical results.

keywords: HCV model; global solutions; non-cytolytic process; invariant set; Lyapunov functions; basic reproduction number; equilibrium points.

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1 Introduction

Hepatitis C infection is a viral disease caused by Hepatitis C Virus (HCV) and being transmitted mainly by blood contact between an infected person and a healthy person. This virus that attacks the hepatocytes is one of the main causes of chronic diseases of the liver such as hepatocellular carcinoma, liver cancer and cirrhosis of the liver [1, 19]. According to the WHO [22] global report published in April 2017 on hepatitis, 200 to 300 million people worldwide are infected with HCV, and between 60% et 85% of these people develop chronic liver disease [22, 23]. Although there is considerable progress in the research for the fight against this infection whose virus was discovered in 1989 [1, 19] and which presents today six genotypes, ranked from 1 to 6 according to [19]. There is no vaccine for prevention yet [20, 22]. Concerning the treatment of HCV infection, since 2014, the new direct-acting antivirals combined with Interferon-α and Ribavirin have been able to cure about 90% of cases of chronic infection, but leaves the chronic diseases whose infection has caused. HCV infection is therefore a major public health problem.

To understand the dynamics of HCV viral load and its infectious process, mathematical models have become an important and almost unavoidable tool[2, 16]. A model is a system of mathematical equations accounting for all known experimental data of the studied biological phenomenon. It makes it possible to better understand the phenomenon under consideration and to act on the system optimally. Until 2009, most research work on the modeling of viral dynamics of HCV only took into account the level of circulating virus in a human population, the case in vivo was almost ignored as it provides a better understanding of the pathogenesis of the virus as Harel Dahari et al [8] and Chong et al.[1].

Our goal is therefore to analyze the stability of an extended model of HCV infection in a patient with cell proliferation and spontaneous healing presented in [7, 20] to reveal significant information on pathogenesis and dynamics of this virus. The work is organized as follows : In section 1, first focuses on presentation of the epidemiological model and give some properties of its solutions, then we calculate the basic reproduction ratio $R_0$, which is an indispensable element in the study and analysis of the models. $R_0$ is considered in the virus dynamics as a metric. We theoretically analyze the local stability and the global stability of the model by the linearization and Lyapounov’s functions respectively in section 2 and in section 3 we perform numerical simulations using biologically plausible parameter values in Table 1 to confirm the results obtained theoretically and we complete the work by an appendix.
2 A dynamical model of HCV infection and some properties of the solutions of the differential system associated to the model

Mathematical modeling applies to the study of dynamics of infectious diseases seems to be one of the most interesting tool for designing control or eradication strategies of a disease like hepatitis C. It allows to test on computer different prevention scenarios and so help the decision-making in public health [14]. In the following sections, we will firstly present epidemiology and brief history of HCV dynamics, then describe the model itself, show the existence of solutions and establish some properties of these solutions and finally calculate the basic reproduction rate $R_0$ which is an important tool in epidemiology.

2.1 Epidemiology and history of HCV

2.1.1 HCV infection

HCV is a virus that attacks the cells of the liver and causes inflammation of the latter. This virus is present in the blood of an infected person and is, according to the WHO, mandatory declaration. It can live for about 5 to 7 weeks in the open air. In the long term, there may be very serious consequences such as cirrhosis and in some cases, liver cancer. This virus can remain for decades in the body without any apparent symptoms. According to [14, ?] six main genotypes HCV were identified whereas several subtypes play an important role in the severity of the disease and its response to treatment.

2.1.2 Epidemiology of HCV Infection

HCV infection is a major public health problem. Worldwide, the number of chronic HCV carriers is estimated at about 170 million, or 3\% of the world’s population, and the incidence is between 3 and 4 million infections per year according to the statistics published by the World Health Organization in 2014. The actual incidence is uncertain because the distinction between acute and chronic forms is difficult to make. HCV was only identified in 1989 with the advent of modern molecular cloning techniques.

In Cameroon, about 10,000 people die each year from hepatitis (A, B, C, D, ...). The country is one of the 17 most affected worldwide, with a prevalence rate of about 13\%, that is 2.5 million people infected.

2.1.3 Natural history of HCV infection

According to WHO’s global report on hepatitis C published in April 2017 the first phase of HCV infection is said Acute: It can cause jaundice, but remains asymptomatic in the majority of cases (70 to 80 \%), hence the risk of going unnoticed. It is estimated that 20 to 30 \% people infected will spontaneously clear the virus within the first six months.
after initial contact. If the virus persists, hepatitis progresses to chronicity. The liver reacts to HCV aggression by an inflammatory reaction, one of the components of which is fibrogenesis. Hepatic fibrosis is the main complication of chronic hepatitis C. Hepatitis C is likely to evolve at the chronic phase in about 25\% of cases to cirrhosis within a period of 5 to 20 years. In case of cirrhosis, the incidence of hepatocellular carcinoma is high: on the order of 1 to 4\% per year [14]. (See figure 1).

Figure 1: Natural history of infection with hepatitis C virus.

In order to achieve our various goals, we first describe the model and its parameters.

2.2 Description of the HCV model with compartmental diagram

There are two mathematical models of HCV dynamics: the original model or model of Newmann [17] and its extended models like that of Dahari [1, ?]. 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 2 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. [20]. 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 hepatocyte healing by a non-cytolytic process at the rate $q$.

The model proposed by Dahari and coworkers [8, 4] expands on the standard HCV viral-dynamic model [17] of infection and clearance by incorporating density-dependent proliferation and death. Uninfected hepatocytes or noninfected hepatocytes, $T$, are infected at a rate $\beta$ 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 is cleared at rate $c$ by immune and other degradation processes. Besides infection processes, hepatocyte numbers are influenced
Figure 2: 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.[17] 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[4], 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[5] 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 \( T_{\text{max}} \). 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 \( \eta \) and the viral production rate by a fraction \( \varepsilon \). It should be noted that \( \eta \) and \( \varepsilon \) are parameters which values are non-negative and less than one.

The interpretations and biologically plausible value of other parameters are listed in following Table 1, and a further comprehensive survey on the description of the model is given in [7, 6, 20].

Thus, the variation of healthy hepatocytes \( T \) is expressed by the following expression:

\[
\frac{dT}{dt} = s + r_T T \left(1 - \frac{T + I}{T_{\text{max}}} \right) - d_T T - (1 - \eta) \beta VT + qI. \tag{1}
\]

The variation of infected hepatocytes \( I \) is expressed by the following expression:

\[
\frac{dI}{dt} = r_I I \left(1 - \frac{T + I}{T_{\text{max}}} \right) - d_I I - (1 - \eta) \beta VT - qI. \tag{2}
\]
And the variation of the viral load $V$ is expressed by the following expression:

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

It follows that the dynamics of $T$, $I$ and $V$ is governed by the following differential system:

$$\begin{align*}
\frac{dT}{dt} &= s + r_T T \left( 1 - \frac{T + I}{T_{\text{max}}} \right) - d_T T - (1 - \eta)\beta VT + qI \\
\frac{dI}{dt} &= r_I I \left( 1 - d_T \frac{T + I}{T_{\text{max}}} \right) - d_I I - (1 - \eta)\beta VT - qI \\
\frac{dV}{dt} &= (1 - \varepsilon)pI - cV
\end{align*} \quad (4)$$

System (4) is under the following initial conditions:

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

Given the meanings of $\eta$ and $\beta$, the term $(1 - \eta)\beta VT$ represents the mass action principle; $\beta VT$ is the rate of infection of healthy $T$ cells by interaction with virus $V$.

For biological significance of the parameters, three assumptions are employed. (1) Due to the burden of supporting virus replication, infected cells may proliferate more slowly than uninfected cells, i.e. $r_I \leq r_T$. (2) To have a physiologically realistic model, in an uninfected liver when $T_{\text{max}}$ is reached, liver size should no longer increase, i.e. $s \leq d_T T_{\text{max}}$. (3) Infected cells have a higher turnover rate than uninfected cells, i.e. $d_I \geq d_T$. The interpretations and biologically plausible values of other parameters are listed in Table 1, and a further comprehensive survey on the description of (4) is given in [20]. 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 [3, 15, 5], or the mitotic transmission of uninfected/infected CD4+T.

The range of variation of each parameter is recorded in table 1 [20].

### Table 1

Estimated parameter ranges for hepatitis C when modeled with system [20]. The $r_T$, $T_{\text{max}}$, and
This table tells us in which interval varies each parameter of the model. For the study of stability and for simulations these ranges of values will have to be respected for a good decision-making.

2.3 Theorems of existence and some properties of solution to the cauchy problem (4), (5)

2.3.1 Existence of local solutions

**Theorem 2.1** Let $T_0, I_0, V_0 \in \mathbb{R}$. There exists $t_1 > 0$ and functions $T, I, V : [t_0; t_1] \rightarrow \mathbb{R}$ continuously differentiable such that $(T, I, V)$ is a solution of system (4) satisfying (5).

**Proof.** We will use the local Cauchy-Lipschitz theorem to prove this. Since the system of equations (4) is autonomous, it is enough to show that the function

$$ f : \mathbb{R}^3 \rightarrow \mathbb{R}^3 
\begin{pmatrix}
T, I, V
\end{pmatrix} \mapsto 
\begin{pmatrix}
f_1(T, I, V); f_2(T, I, V); f_3(T, I, V)
\end{pmatrix}
$$

is locally Lipschitzian with:

$$ f_1(T, I, V) = s + r_T T \left(1 - \frac{T + I}{T_{max}}\right) - d_T T - (1 - \eta)\beta VT + q I. \quad (6) $$

$$ f_2(T, I, V) = r_I I \left(1 - \frac{T + I}{T_{max}}\right) + (1 - \eta)\beta VT - d_I I - q I. \quad (7) $$

$$ f_3(T, I, V) = (1 - \varepsilon)p I - c V. \quad (8) $$

According to L. Perko [18], it is also enough to prove that $f$ is a class $C^1$ function. The Jacobian matrix of $f$ at $(T, I, V)$ is:

$$ Df(T, I, V) = 
\begin{pmatrix}
\frac{\partial f_1}{\partial T}(T, I, V) & \frac{\partial f_1}{\partial I}(T, I, V) & \frac{\partial f_1}{\partial V}(T, I, V) \\
\frac{\partial f_2}{\partial T}(T, I, V) & \frac{\partial f_2}{\partial I}(T, I, V) & \frac{\partial f_2}{\partial V}(T, I, V) \\
\frac{\partial f_3}{\partial T}(T, I, V) & \frac{\partial f_3}{\partial I}(T, I, V) & \frac{\partial f_3}{\partial V}(T, I, V)
\end{pmatrix}. $$

$d_T$ parameters are not independently identifiable, so common practice is to fix $d_T$ prior to fitting.
Each component of this matrix being continuous, they are locally bounded for all \((T, I, V) \in \mathbb{R}^3\). Therefore \(f\) possesses continuous and bounded partial derivatives on any compact of \(\mathbb{R}\). Thus \(f\) is locally Lipschitzian with respect to \((T, I, V)\).

By the Cauchy-Lipschitz theorem, there is a local solution defined on \([t_0; t_1[\). This completes the proof of this theorem 2.1.

Remark 1 The function \(f\) in the proof of theorem 2.1 is a class \(C^1\) function so the system (4) has a unique maximal solution.

2.3.2 positivity of the system (4)

**Theorem 2.2** Let \((T, I, V)\) be a solution of the system (4) 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 \(t_\ast\) be the smallest of all \(t\) in the interval \([t_0, t_1]\) such that \(x_i(t) > 0, \forall t \in [t_0, t_\ast[, \forall i \in \{1, 2, 3\}\) and \(x_i(t_\ast) = 0\) 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.

Thus,

\[
\dot{T} = \frac{dT}{dt},
\]

\[
= -T \left( -r_T \left( 1 - \frac{T + I}{T_{\text{max}}} \right) + d_T + (1 - \eta) \beta V \right) + s + q I,
\]

\[
= -Th_1(T, I, V) + g_1(T, I, V).
\]

with

\[
h_1(T, I, V) = \left( -r_T \left( 1 - \frac{T + I}{T_{\text{max}}} \right) + d_T + (1 - \eta) \beta V \right)
\]

and

\[
g_1(T, I, V) = s + q I;
\]
similarly:
\[
\dot{I} = \frac{dI}{dt},
\]
\[
= -I \left( -r_I \left( 1 - \frac{T + I}{T_{\text{max}}} \right) + d_I + q \right) + (1 - \eta) \beta VT,
\]
\[
= -I h_2(T, I, V) + g_2(T, I, V).
\]

with
\[
h_2(T, I, V) = \left( -r_I \left( 1 - \frac{T + I}{T_{\text{max}}} \right) + d_I + q \right)
\]
and
\[
g_2(T, I, V) = (1 - \eta) \beta VT.
\]

and
\[
V = \frac{dV}{dt},
\]
\[
= -V c + (1 - \varepsilon) pI,
\]
\[
= -V h_3(T, I, V) + g_3(T, I, V).
\]

with
\[
h_3(T, I, V) = c
\]
and
\[
g_3(T, I, V) = (1 - \varepsilon) pI.
\]

Without loss the generality, suppose that \(x_1(t_*) = 0\).

As hypothesized, \(g_1(T, I, V)\) is positive on \([t_0, t_*]\), it follows that
\[
\dot{T} \geq -T h_1(T, I, V);
\]
from where
\[
\frac{d}{dt}(\log T) \geq -h_1(T, I, V).
\]

Yet \((T, I, V)\) is a solution of (4). \(T, I, V\) are class \(C^1\) functions. They are continuous on \([t_0, t_*]\) and therefore are bounded on \([t_0, t_*]\). Thus \(h_1(T, I, V)\) is bounded on \([t_0, t_*]\).

There exists a constant \(k > 0\) such that
\[
\frac{d}{dt}(\log T) \geq -h_1(T, I, V) > -k.
\]

By integrating this previous expression on \([t_0, t_*]\), we get
\[
\log T(t_*) - \log T(t_0) \geq -k(t_* - t_0).
\]

Where
\[
T(t_*) \geq T(t_0)e^{-k(t_* - t_0)} > 0.
\]
This is a contradiction because $T(t_*) = 0$.

Similarly, assuming that $x_2(t_*) = 0$, as hypothesized, $g_2(T, I, V)$ is positive on $[t_0, t_*]$, it follows that

$$\dot{I} \geq -h_2(T, I, V).$$

Thus,

$$\frac{d}{dt}(\log I) \geq -h_1(T, I, V).$$

Yet $(T, I, V)$ is a solution of system (4); $T, I, V$ are class $C^1$ functions. They are therefore continuous on $[t_0, t_*]$ and consequently are bounded on $[t_0, t_*]$.

Therefore $h_2(T, I, V)$ is bounded on $[t_0, t_*]$.

Thus, there exists a constant $\lambda > 0$ such that

$$\frac{d}{dt}(\log I) \geq -h_2(T, I, V) > -\lambda.$$

Integrating, the last expression on $[t_0, t_*]$, yields

$$\log I(t_*) - \log I(t_0) \geq -\lambda(t_* - t_0).$$

Therefore

$$I(t_*) \geq I(t_0)e^{-\lambda(t_* - t_0)} > 0.$$

This is a contradiction because $I(t_*) = 0$.

As far as that goes, assuming that $x_3(t_*) = 0$.

By hypothesis, $g_3(T, I, V)$ is positive on $[t_0, t_*]$, we obtain $V \geq -Vc$. i.e

$$\frac{d}{dt}(\log I) \geq -c.$$

Hence integrating on $[t_0, t_*]$ we obtain

$$V(t_*) \geq V(t_0)e^{-k(t_* - t_0)} > 0.$$

This is a contraction.

Conclusion: $T, I, V$ are positive on $[t_0, t_1]$. ■

It will now be shown, with the help of the continuation criterion the existence of global solutions of problem (4), (5).

### 2.3.3 Existence of global solutions

**Theorem 2.3** The solutions of the Cauchy problem (4), (5), with positive initial data, exist globally in time in the future that is on $[t_0, +\infty[$.

**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, by the theorem 2.2, of the solutions it is enough to show that all variables are bounded above.

Taking the sum of equations (1), (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.

\[
\frac{dV}{dt} = (1 - \varepsilon)pI - cV,
\]

then shows that \( V(t) \) cannot grow faster than linearly and is also bounded on any finite interval. This completes the proof of this theorem.

**2.3.4 Asymptotic behaviour**

**Theorem 2.4** For any positive solution \((T, I, V)\) of system (4), (5) we have:

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

where

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

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

**Proof.** Summing equations (1) and (2), we get:

\[
\frac{d}{dt}(T + I) = s + \left( 1 - \frac{T + I}{T_{\max}} \right) (r_T T - r_I I) - d_T T - d_I I,
\]

\[
= s + r_T T - r_I I - d_T T - d_I I - \frac{T + I}{T_{\max}},
\]

\[
= s + (r_T - d_T) T + (r_I - d_I) I - \frac{T + I}{T_{\max}}(r_T T + r_I I),
\]

\[
\leq s + (r_T - d_T) (T + I) - \frac{T + I}{T_{\max}}(T + I)^2 \quad \text{since} \quad r_T - d_T \geq r_I - d_I,
\]

thus \( \frac{d}{dt}(T + I) \leq s + (r_T - d_T) (T + I) - \frac{r_I}{T_{\max}}(T + I)^2 \quad \text{since} \quad r_I \leq r_T. \)

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

\[
\frac{dN_1}{dt} = a + bN_1 + dN_1^2 \quad \text{(9)}
\]

Coupled to equation (9) the initial condition:

\[
N_1(t_0) = N_1^0. \quad \text{(10)}
\]

The resolution of the problem (9), (10) gives for all \( t \in [t_0, +\infty[ \),

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

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

\[
N_1(t) \leq -\frac{1}{2d} \left( \sqrt{-4ad + b^2} + b \right)
\]
i.e.
\[ N_1(t) \leq \frac{T_{\text{max}}}{2r_I} \left( \sqrt{(r_T - d_T)^2 + \frac{4sr_I}{T_{\text{max}}} + r_T - d_T} \right). \]

Let
\[ \tilde{T}_0 = \frac{T_{\text{max}}}{2r_I} \left( \sqrt{(r_T - d_T)^2 + \frac{4sr_I}{T_{\text{max}}} + r_T - d_T} \right), \]
we obtain:
\[ N_1(t) \leq \tilde{T}_0. \]

Therefore
\[ T + I \leq \tilde{T}_0. \]

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

From (3), we have:
\[ \frac{dV}{dt} \leq (1 - \varepsilon)p(T + I) - cV, \]
\[ \leq (1 - \varepsilon)p\tilde{T}_0 - cV \quad \text{since} \quad T + I \leq \tilde{T}_0. \]

According to Gronwall inequality,
\[ V(t) \leq V(t_0)e^{-c(t-t_0)} + \int_{t_0}^{t} (1 - \varepsilon)p\tilde{T}_0 e^\int_{u}^{t} -cdu \, du, \]
\[ \leq V_0e^{-c(t-t_0)} + (1 - \varepsilon)p\tilde{T}_0 \int_{t_0}^{t} e^{-c(u-t)} \, du, \]
\[ V(t) \leq V_0e^{-c(t-t_0)} + (1 - \varepsilon)p\tilde{T}_0 \frac{e^{-c(t-t)} - e^{-c(t-t_0)}}{e}, \]
\[ \leq V_0e^{-c(t-t_0)} + (1 - \varepsilon)p\tilde{T}_0 \frac{1 - e^{-c(t-t_0)}}{e}, \]
\[ \leq \lambda_0 \left( e^{-c(t-t_0)} + 1 - e^{-c(t-t_0)} \right) \]
\[ V(t) \leq \lambda_0. \]

with
\[ \lambda_0 = \max \left\{ V_0, \frac{1 - \varepsilon}{e} p\tilde{T}_0 \right\}. \]

This completes the proof of theorem 2.4. 

**Remark 2** It follows that all solutions of the system (4) are asymptotically uniformly bounded in compact subset \( \Omega \) defined by
\[ \Omega = \{(T, I, V) \in \mathbb{R}; 0 < T + I \leq \tilde{T}_0; \quad 0 < V \leq \lambda_0 \}. \]

**Remark 3** Theorem 2.4 shows that all solutions of model (4) in \( \mathbb{R}^3_+ \) are ultimately bounded and according to theorem 2.2, that solutions with positive initial value conditions are positive, which indicates that model (4) is well-posed and biologically valid.
2.4 Basic reproduction ratio $R_0$

One of the most important concerns about any infectious disease is its ability to invade a population. Many epidemiological models have a disease free equilibrium (DFE) at which the population remains in the absence of disease. These models usually have a threshold parameter, known as the basic reproduction number, $R_0$, such that if $R_0 < 1$, then the DFE is locally asymptotically stable, and the disease cannot invade the population, but if $R_0 > 1$, then the DFE is unstable and invasion is always possible. In other words, we have the following definition:

**Definition 2.5** [9] The basic reproduction ratio or the basic reproduction number or basic reproductive ratio $R_0$ is defined as the expected number of secondary cases produced, in a completely susceptible population, by a typical infected individual during its entire period of infectiousness.

Determine $R_0$ in function of the parameters of the model allow us to guess the conditions under which the disease invade the population.

2.4.1 Determination of the uninfected equilibrium or virus-free equilibrium or non-infected equilibrium

**Proposition 2.6** The uninfected equilibrium point $E^0$ of the system (4) is given by

$$E^0 = (T^0, 0, 0)$$

where :

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

**Proof.** When there is no viral infection, the uninfected hepatocytes dynamic is determined by :

$$\frac{dT}{dt} = s + r_T T \left( 1 - \frac{T}{T_{max}} \right) - d_T T. \quad (11)$$

The quantity $T^0$ of the free-virus equilibrium point $E^0$ is solution of the equation $\frac{dT}{dt} = 0$.

Hence, let us solve the following equation :

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

Its discriminant is given by :

$$\Delta = (r_T - d_T)^2 + 4 \frac{r_T}{T_{max}} s,$$

which yields :

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

Thus, in the absence of viral infection, the amount of susceptible cells or uninfected hepatocytes attend to a positive constant level $T^0$, which is :

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

This completes the proof. ■
2.4.2 **Computation of the basic reproduction number** $R_0$

We are going to use Van Den Driessche and Watmough method \[9, 21\] for calculating the basic reproduction ratio $R_0$ of the model (4).

Let us first present briefly the method.

Considering population whose population are grouped into $n$ homogeneous compartments $X = (X_1, X_2, ..., X_n)$ where $X_i \geq 0$ is the number of individuals in compartment $i$. For clarity we sort the compartments $X_i$, $i = 1, ..., n$ so that the first $m$ ($m \leq n$) compartments correspond to infected individuals. The distinction between infected and uninfected compartments must be determined from the epidemiological interpretation of the model and cannot be deduced from the structure of the equations alone.

We define $X_s$ to be the set of all disease free states. That is:

$$X_s = \{X \geq 0 / X_1 = X_2 = ... = X_m = 0\}.$$

Let $F_i(X)$ be the rate of appearance of new infections in compartment $i$ that is the infected individuals coming from other compartments and enter into $i$.

$V_{i}^+$ be the rate of transfer of individuals into compartment $i$ by all other means (displacement, healing, aging).

$V_{i}^-$ be the rate of transfer of individuals out of compartment $i$ (mortality, change of statut).

It is assumed that each function is continuously differentiable at least twice in each variable.

Figure 3 below shows the variations of the number of individuals in compartment $i$ in a population. The variation of the number of individuals in compartment $i$ is given by:

$$\frac{dX_i}{dt} = F_i(X) - V_i(X)$$

where

$$V_i(X) = V_{i}^- (X) - V_{i}^+ (X).$$

Due to the nature of the epidemiological model, we have the following properties:

$P_1$) If $X_i \geq 0$ then $F_i(X) \geq 0$, $V_{i}^- (X) \geq 0$ and $V_{i}^+ (X) \geq 0$.

Since each function represents a directed transfer of individuals.
If $X_i = 0$ then $V_i^-(X) = 0$.
Indeed, if a compartment is empty, then there can be no transfer of individuals out of the compartment by death, infection, nor any other means: it is the essential property of a compartmental model.

Pour $i > m$, $F_i(X) = 0$.
Indeed, in the compartments with an index greater than $m$ are "uninfected". By definition, it can not appear in these compartments infected individual.

Si $X \in X_s$ alors $F_i(X) = 0$ et pour $i \leq m$, $V_i^+(X) = 0$.
Indeed, to ensure that the disease free subspace is invariant, we assume that if the population is free of disease then the population will remain free of disease. That is, there is no (density independent) immigration of infectives. This is Lavoisier’s principle. There is no spontaneous generation.

Let $F = (F_i)_{i=1,...,n}$ and $V = V^+ - V^- = (V_i^+ - V_i^-)_{i=1,...,n}$.
Let also $x^0$ the uninfected equilibrium point of the corresponding model.
Let $DF(x^0)$ and $DV(x^0)$ denote the jacobian matrices of $F$ and $V$ respectively at the point $x^0$.
It follows that $DF(x^0)$ is a positive matrix and $DV(x^0)$ a Metzler matrix (matrix whose the extra diagonal terms are greater or equal than zero). Thus we have the following equivalent definition of $R_0$:

**Definition 2.7** [9, 21]

$$R_0 = \rho(-DF.DV^{-1})$$

where $\rho$ represents the spectral radius. i.e

$$R_0 = \max |\lambda|$$

with

$$\lambda \in \text{sp}(-DF.DV^{-1}),$$

where $\text{sp}(A)$ is the spectrum of $A$, i.e. the set of eigenvalues associated to a matrix $A$.

### 2.4.3 Expression of the basic reproduction number $R_0$ associated to the system (4)

**Proposition 2.8** The expression of the basic reproduction number $R_0$ associated to the system (4) is given by:

$$R_0 = \frac{r_I}{d_I + q} \left( 1 - \frac{T^0}{T_{\text{max}}} \right) + \frac{(1 - \theta) \beta T^0 p}{c(d_I + q)}.$$ (12)

where

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

**Proof.** Concerning the model (4) that we study here, the system of infected states is the following:

$$\begin{align*}
\frac{dI}{dt} &= r_I I \left( 1 - \frac{T + I}{T_{\text{max}}} \right) + (1 - \eta) \beta VT - d_I I - qI \\
\frac{dV}{dt} &= (1 - \varepsilon) p I - cV
\end{align*}$$
The expression of the quantities $F, V, DF(E^0), DV(E^0)$ and $DV^{-1}(E^0)$ are given by:

$$
F = \left( r_I \left(1 - \frac{T + I}{T_{max}}\right) + (1 - \eta) \beta VT \right),
V = \left( \begin{array}{c} (d_I - q)I \\ (1 - \varepsilon)pI - cV \end{array} \right),
DF(E^0) = \left( \begin{array}{cc} r_I \left(1 - \frac{T^0}{T_{max}}\right) - (1 - \eta) \beta VT^0 \\ 0 \\ 0 \end{array} \right),
DV(E^0) = \left( \begin{array}{cc} -d_I - q & 0 \\ (1 - \varepsilon)p & -c \end{array} \right),
DV^{-1} = \left( \begin{array}{cc} \frac{-1}{d_I + q} & 0 \\ \frac{(1 - \varepsilon)p}{c(d_I + q)} & -\frac{1}{c} \end{array} \right).
$$

From those quantities, we obtain:

$$
DF.DV^{-1} = \left( \begin{array}{cc} -r_I \left(1 - \frac{T^0}{T_{max}}\right) - (1 - \eta) \beta VT^0 \\ 0 \\ 0 \end{array} \right) = \left( \begin{array}{cc} \frac{-1}{d_I + q} & 0 \\ \frac{(1 - \varepsilon)p}{c(d_I + q)} & -\frac{1}{c} \end{array} \right)
$$

Let $1 - \theta = (1 - \varepsilon)(1 - \eta)$. It follows that:

$$
| - DF.DV^{-1} - \lambda I_2 | = 0 \iff -\lambda \left( \frac{r_I}{d_I} + q \left(1 - \frac{T^0}{T_{max}}\right) + \frac{(1 - \theta)\beta T^0 p}{c(d_I + q)} - \lambda \right) = 0
$$

$$
\iff \lambda = 0 \text{ ou } \lambda = \frac{r_I}{d_I} + q \left(1 - \frac{T^0}{T_{max}}\right) + \frac{(1 - \theta)\beta T^0 p}{c(d_I + q)}.
$$

Therefore:

$$
R_0 = \frac{r_I}{d_I + q} \left(1 - \frac{T^0}{T_{max}}\right) + \frac{(1 - \theta)\beta T^0 p}{c(d_I + q)},
$$

which completes the proof of the proposition.

**Remark 4** $\theta \in [0, 1]$ denotes the overall effectiveness rate of the drug.

**Remark 5** Henceforth, we will let $\delta = d_I + q$ and $1 - \theta = (1 - \varepsilon)(1 - \eta)$.

At the end of this section, we note that HCV is a major health problem in the world and particularly in Cameroon where it affects almost 13% of population.

For the model (4) which is the subject of our work, we have shown the existence of the global solution and establish some properties like positivity. The calculation of $R_0$ has been done.

In the next section, we will determine the infected equilibrium point and establish the conditions on $R_0$ for which stability of the model occurs.
3 Stability analysis of the model

In this section, we study the local stability and global stability of the equilibrium points and we present some numerical simulations of the theoretical results obtained. Specifically, we prove by Lyapunov’s theory that the uninfected equilibrium point $E^0$ is globally asymptotically stable if $\mathcal{R}_0 < 1 - \frac{q}{\beta}$ and the infected equilibrium point $E^*$ is globally asymptotically stable when it exists.

Before that we establish a number of essential preliminary results for the next steps

3.1 Invariant set of the model

Theorem 3.1 Let $(t_0, S_0 = (T_0, I_0, V_0)) \in \mathbb{R} \times \mathbb{R}^3_+$ and $([t_0, T], S = (T, I, V))$ be a maximal solution of the Cauchy problem (4), (5) $(T \in ]0, +\infty[)$. If $T(t_0) + I(t_0) \leq \tilde{T}_0$ and $V(t_0) \leq \lambda_0$ then the set :

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

where:

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

is a positively invariant set by system (4).

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

(i) If $T(t_1) + I(t_1) \leq \tilde{T}_0$ then for all $t_1 \leq t < T$, $T(t) + I(t) \leq \tilde{T}_0$.

(ii) If $V(t_1) \leq \lambda_0$ then for all $t_1 \leq t < T$, $V(t) \leq \lambda_0$.

i) Let us show i) by contradiction.

Let us suppose that there exists $\varepsilon_1 > 0$ such that $t_1 < t_1 + \varepsilon_1 < +\infty$ we have

$$(T + I)(t_1 + \varepsilon_1) > T_0.$$

Let $t_1^* = \inf \{ t \geq t_1; (T + I)(t_1 + \varepsilon_1) > T_0 \}.$

If $(T + I)(t_1^*) = T_0$, then since

$$(T + I)(t) = T_0 + \frac{d}{dt} (T(t_1^*) + I(t_1^*)) (t - t_1^*) + o(t - t_1^*)$$

when $t \to t_1^*$. In addition, according to equations (1) and (2) of system (4), we have

$$\frac{d}{dt} ((T + I)(t_1^*)) \leq s + (r_T - d_T)T_0 - \frac{r_I}{T_{\text{max}}}T_0^2.$$

Recall that

$$s + (r_T - d_T)T_0 - \frac{r_I}{T_{\text{max}}}T_0^2 = 0.$$

It follows that :

$$\frac{d}{dt} ((T + I)(t_1^*)) \leq 0.$$

Hence, there exists $\tilde{\varepsilon} > 0$ such that for all $t \in [t_1^*, t_1^* + \tilde{\varepsilon}]$, $(T + I)(t) \leq T_0$, which is a contradiction. Therefore for all $t \in [t_0, +\infty[,(T + I)(t) \leq T_0.$
ii) Let us show ii) by contradiction.

Let us suppose that there exists \( \varepsilon_1 > 0 \) such that \( t_1 < t_1 + \varepsilon_1 < +\infty \) and

\[ T(t_1 + \varepsilon_1) > \lambda_0. \]

Let \( t_2^* = \inf \{ t \geq t_1; V(t) > \lambda_0 \} \).

Since \( V(t_2^*) = \lambda_0 \), since:

\[ V(t) = \lambda_0 + \frac{dV}{dt}(t_2^*)(t - t_2^*) + o(t - t_2^*) \]

with when \( t \to t_2^* \).

Equation (3) yields:

\[ \frac{d}{dt}(V(t_2^*)) \leq (1 - \varepsilon)p(I + T)(t_2^*) - cV(t_2^*) \]

\[ \leq (1 - \varepsilon)pT - c\lambda_0; \]

yet

\[ \lambda_0 = \max \left\{ V_0, \frac{(1 - \varepsilon)pT_0}{c} \right\}; \]

consequently

\[ \frac{d}{dt}(V(t_2^*)) \leq (1 - \varepsilon)pT - c\frac{(1 - \varepsilon)pT_0}{c} \]

\[ \leq 0. \]

Thus, there exists \( \varepsilon > 0 \) such that for all \( t_2^* \leq t \leq t_2^* + \varepsilon, V(t) \leq \lambda_0 \) which is a contradiction. Therefore for all \( t \in [t_0, +\infty[ \), \( V(t) \leq \lambda_0 \). Which completes the proof of Theorem 3.1.

\[ \square \]

### 3.2 Existence of the infected equilibrium point

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

**Lemma 3.2** \( T^* \) exists if and only if

\[ s + q \frac{T_{\text{max}}}{r_I} (r_I - \delta) > 0. \]

**Proof.** Let us consider the following system of algebraic equations:

\[
\begin{align*}
  s + r_T T \left( 1 - \frac{T + I}{T_{\text{max}}} \right) - d_T T - (1 - \eta) \beta V T + q I &= 0; \\
  r_I I \left( 1 - \frac{T + I}{T_{\text{max}}} \right) - d_I I - (1 - \eta) \beta V T - q I &= 0; \\
  (1 - \varepsilon)p I - c V &= 0.
\end{align*}
\]
(15) yields:

\[ V = \frac{(1 - \varepsilon)pI}{c}. \]  

(16)

Reporting (16) in (14), we have:

\[ r_I (1 - \frac{T + I}{T_{max}}) + \frac{(1 - \eta)(1 - \varepsilon)\beta pI}{c} - \delta I = 0. \]

Hence

\[ r_I \left(1 - \frac{T + I}{T_{max}}\right) + \frac{(1 - \theta)\beta pT}{c} - \delta = 0 \quad \text{since} \quad I \neq 0 \quad \text{(there is an infection)} \]

i.e

\[ \frac{r_I}{T_{max}} = \frac{(1 - \theta)\beta pT}{c} - \delta r_I \left(1 - \frac{T}{T_{max}}\right). \]

It follows that:

\[ I = \left(\frac{(1 - \theta)\beta pT_{max}}{cr_I} - 1\right) T + \frac{T_{max}}{r_I} (r_I - \delta). \]  

(17)

Let

\[ g_1(T) = qI = q \left(\frac{(1 - \theta)\beta pT_{max}}{cr_I} - 1\right) T + q \frac{T_{max}}{r_I} (r_I - \delta). \]  

(18)

Reporting (16) and (17) in (13) leads to:

\[ s + r_T T \left(1 - \frac{T}{T_{max}}\right) - \frac{r_T T}{T_{max}} \left(\frac{(1 - \theta)\beta pT_{max}}{cr_I} - 1\right) T + \frac{T_{max}}{r_I} (r_I - \delta) - d_T T \]

\[ - (1 - \eta)\beta \frac{T}{c} T \left(\frac{(1 - \theta)\beta pT_{max}}{cr_I} - 1\right) T + \frac{T_{max}}{r_I} (r_I - \delta) \]

\[ + q \left(\frac{(1 - \theta)\beta pT_{max}}{cr_I} - 1\right) T + q \frac{T_{max}}{r_I} (r_I - \delta) = 0 \]

i.e.

\[ s + T \left(r_T - d_T - \frac{r_T}{r_I} (r_I - \delta) - \frac{(1 - \theta)\beta pT_{max}}{cr_I} (r_I - \delta)\right) - \frac{(1 - \theta)\beta p}{c} \left(\frac{r_T}{r_I} + \frac{(1 - \theta)\beta pT_{max}}{cr_I} - 1\right) \]

\[ + q \left(\frac{(1 - \theta)\beta pT_{max}}{cr_I} - 1\right) T + q \frac{T_{max}}{r_I} (r_I - \delta) = 0. \]

Thus,

\[ s + q \frac{T_{max}}{r_I} (r_I - \delta) + T \left(r_T - d_T - \frac{r_T}{r_I} (r_I - \delta) - \frac{(1 - \theta)\beta pT_{max}}{cr_I} (r_I - \delta)\right) + q \left(\frac{(1 - \theta)\beta pT_{max}}{cr_I} - 1\right) \]

\[ - \frac{(1 - \theta)\beta p}{c} \left(\frac{r_T}{r_I} + \frac{(1 - \theta)\beta pT_{max}}{cr_I} - 1\right) T^2 = 0. \]
It follows that,
\[ s + q \frac{T_{\text{max}}}{r_T} (r_I - \delta) + T \left( r_T - \delta - \frac{r_T}{r_I} (r_I - \delta) - \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} (r_I - \delta) + \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} q \right) \]
\[ - \frac{(1 - \theta) \beta p}{c} \left( \frac{r_T}{r_I} + \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} - 1 \right) T^2 = 0. \]

Let
\[ h_2(T) = s + q \frac{T_{\text{max}}}{r_I} (r_I - \delta) + T \left( r_T - \delta - \frac{r_T}{r_I} (r_I - \delta) - \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} (r_I - \delta) + \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} q \right) \]
\[ - \frac{(1 - \theta) \beta p}{c} \left( \frac{r_T}{r_I} + \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} - 1 \right) T^2; \]
we have:
\[ h_2(T) = g_2(T) + g_1(T) \]   \hspace{1cm} (19)
with:
\[ g_2(T) = s + T \left( r_T - d_T - \frac{r_T}{r_I} (r_I - \delta) - \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} (r_I - \delta) - \frac{(1 - \theta) \beta p}{c} \left( \frac{r_T}{r_I} + \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} - 1 \right) T^2. \]

Since \( r_I \leq r_T \), the polynomial (19) has a unique positive root \( T^* \) if and only if:
\[ s + q \frac{T_{\text{max}}}{r_I} (r_I - \delta) > 0. \]

This completes the proof of Lemma 3.2. \( \blacksquare \)

Suppose that \( \delta \geq r_I \), we have the following results:

**Lemma 3.3** If \( \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} > 1 \), then:

i) \( T^* \leq \tilde{T}_1 \) if and only if \( g_1(T^*) \leq 0 \)

ii) \( T^* > \tilde{T}_1 \) if and only if \( g_1(T^*) > 0 \).

**Remark 6** \( \tilde{T}_1 \) of Lemma 3.3 is the solution of equation \( g_1(T) = 0 \), i.e
\[ \tilde{T}_1 = \frac{c(\delta - r_I) T_{\text{max}}}{(1 - \theta) \beta p T_{\text{max}} - cr_I}. \]

**Proposition 3.4** Suppose that \( \delta \geq r_I \).

- If \( \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} \leq 1 \), then \( g_1(T^*) \leq 0 \). Hence, system (4) admits no infected equilibrium point.

- If \( \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} > 1 \) then:
  i) system (4) admits no infected equilibrium point when \( T^* \leq \tilde{T}_1 \).
  ii) system (4) admits a unique infected equilibrium point \( E^* \) when \( T^* > \tilde{T}_1 \).
Lemma 3.5 \( \tilde{T}_1 = \frac{(r_I - \delta)T^0}{r_I - \delta R_0} \).

**Proof.** Since \( \tilde{T}_1 \) is the root of equation (18), we have :

\[
\tilde{T}_1 = \frac{c(r_I - \delta)T_{\text{max}}}{cr_I - (1 - \theta) \beta p T_{\text{max}}}
\]

\[
= (r_I - \delta) \left( \frac{1}{T_{\text{max}}} - \frac{(1 - \theta) \beta p}{c} \right)
\]

\[
= (r_I - \delta) \left( \frac{T^0}{r_I T_{\text{max}}} - \frac{(1 - \theta) \beta p T^0}{c} \right)
\]

\[
= \frac{(r_I - \delta)T^0}{r_I - \delta R_0}.
\]

Lemma 3.6 \( \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} \leq 1 \) if and only if \( R_0 \leq \frac{r_I}{\delta} \).

**Proof.** We have :

\[
\frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} \leq 1 \iff \frac{(1 - \theta) \beta p}{c} \leq \frac{r_I}{T_{\text{max}}}
\]

\[
\iff \frac{(1 - \theta) \beta p T^0}{c \delta} \leq \frac{r_I T^0}{\delta T_{\text{max}}}
\]

\[
\iff \frac{(1 - \theta) \beta p T^0}{c \delta} - \frac{r_I T^0}{\delta T_{\text{max}}} + \frac{r_I}{\delta} \leq \frac{r_I}{\delta}
\]

\[
\iff R_0 \leq \frac{r_I}{\delta}.
\]

Since \( \frac{r_I}{\delta} \leq 1 \), the equivalence of the Lemma 3.6 allows us to write \( R_0 \leq 1 \).

The following proposition establishes the link between \( R_0 \) and the existence of the equilibrium point \( E^* \) when \( \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} > 1 \).

**Proposition 3.7** Suppose that \( T^* \) exists, \( r_I \leq \delta \) and \( \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} > 1 \), then :

i) \( T^* > \tilde{T}_1 \) if \( R_0 > 1 \).

ii) \( T^* \leq \tilde{T}_1 \) if \( \frac{r_I}{\delta} < R_0 \leq 1 \).

**Proof.** Recall that \( T^* > \tilde{T}_1 \) if and only if \( h_2(\tilde{T}_1) > 0 \) and \( T^* \leq \tilde{T}_1 \) if and only if \( h_2(\tilde{T}_1) \leq 0 \).

Using the expression of \( h_2(T) \) given in (19) we have :

\[
h_2(\tilde{T}_1) = g_2(\tilde{T}_1).
\]

Thus

\[
h_2(\tilde{T}_1) = s + \frac{(\delta - r_I)T^0}{\delta R_0 - r_I} \left( r_T - d_T - \frac{r_T}{r_I} (r_I - \delta) - \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} (r_I - \delta) \right)
\]

\[
- \frac{(1 - \theta) \beta p}{c} \left( \frac{r_T}{r_I} + \frac{(1 - \theta) \beta p T_{\text{max}}}{cr_I} - 1 \right) \left( \frac{(\delta - r_I)T^0}{\delta R_0 - r_I} \right)^2
\]
Yet
\[
s = \left( d_T - r_T \left( 1 - \frac{T^0}{T_{max}} \right) \right) T^0, \\
\frac{(1 - \theta) \beta p T_{max}}{c r_I} = \frac{T_{max}}{T^0} \left( \frac{\delta R_0 - r_I}{r_I} \right) + 1
\]
and
\[
\frac{(1 - \theta) \beta p}{c} = \frac{\delta R_0 - r_I}{T^0} + \frac{r_I}{T_{max}}.
\]
Hence,
\[
h_2(\tilde{T}_1) = \left( d_T - r_T (1 - \frac{T^0}{T_{max}}) \right) T^0 + \left( r_T - d_T - \frac{r_T}{r_I} (r_I - \delta) + \frac{T_{max}}{T^0} \left( \frac{\delta R_0 - r_I}{r_I} \right) (r_I - \delta) - (r_I - \delta) \right) \frac{(\delta - r_I) T^0}{\delta R_0 - r_I} + \\
- \left( \frac{\delta R_0 - r_I}{T^0} + \frac{r_I}{T_{max}} \right) \left( r_T + \frac{T_{max}}{T^0} \left( \frac{\delta R_0 - r_I}{r_I} \right) \right) \left( \frac{(\delta - r_I) T^0}{\delta R_0 - r_I} \right)^2
\]
\[
= \frac{\delta T^0 (R_0 - 1)}{(\delta R_0 - r_I)^2 T_{max}} \left( r_T T^0 (\delta - r_I) + (\delta R_0 - r_I) T_{max} \left( d_T - r_T \left( 1 - \frac{T^0}{T_{max}} \right) \right) \right).
\]
Since \( d_T - r_T (1 - \frac{T^0}{T_{max}}) > 0 \) and \( \delta \geq r_I \), we get :
\[
h_2(\tilde{T}_1) > 0 \quad \text{if} \quad R_0 > 1
\]
and
\[
h_2(\tilde{T}_1) \leq 0 \quad \text{if} \quad \frac{r_I}{\delta} < R_0 \leq 1.
\]
This completes the proof of Proposition 3.7. ■

Suppose now \( \delta < r_I \), then equation (19) admits a unique positive solution \( T^* \) and we have the following results:

**Lemma 3.8** Suppose that \( \frac{(1 - \theta) \beta p T_{max}}{c r_I} < 1 \), then :

- \( T^* \geq \tilde{T}_2 \) if and only if \( g_1(T^*) \leq 0 \).
- \( T^* < \tilde{T}_2 \) if and only if \( g_1(T^*) > 0 \).

**Remark 7** \( \tilde{T}_2 \) of lemma 3.8 is the solution of equation \( g_1(T) = 0 \), i.e
\[
\tilde{T}_2 = \frac{c (r_I - \delta) T_{max}}{c r_I - (1 - \theta) \beta p T_{max}}.
\]

**Proposition 3.9** i) If \( \frac{(1 - \theta) \beta p T_{max}}{c r_I} \geq 1 \), then \( g_1(T) > 0 \) and the system (4) admits in this case a unique infected equilibrium point \( E^* \).
We state the following two lemmas whose the proofs are analogous of those of lemma 3.5 and lemma 3.6 respectively. These lemmas will help us to complete the conditions of existence of the infected equilibrium point $E^*$.

**Lemma 3.10** $\bar{T}_2 = \frac{(r_I - \delta)T^0}{r_I - \delta R_0}$

**Lemma 3.11** $(1 - \theta)\beta p T_{max} < c r_I \geq 1$ if and only if $R_0 \geq \frac{r_I}{\delta}$. 

**Proposition 3.12** Suppose that : $r_I > \delta$ and $(1 - \theta)\beta p T_{max} < c r_I$. Then $T^* \geq \bar{T}_2$ if $R_0 \leq 1$, and $T^* < \bar{T}_2$ if $1 < R_0 < \frac{r_I}{\delta}$.

**Proof.** Recall that $T^* \geq \bar{T}_2$ if and only if $h_2(\bar{T}_2) \geq 0$ and $T^* < \bar{T}_2$ if and only if $h_2(\bar{T}_2) < 0$. From the expression of $h_2(T)$ given by (19) we have :

$$h_2(\bar{T}_2) = g_2(\bar{T}_2).$$

Thus :

$$h_2(\bar{T}_2) = s + \frac{(r_I - \delta)T^0}{r_I - \delta R_0} \left( r_T - d_T - \frac{r_T}{r_I} (\delta - r_I) - \frac{(1 - \theta)\beta p T_{max}}{c r_I} (\delta - r_I) \right)$$

$$- \frac{(1 - \theta)\beta p}{c} \left( \frac{r_T}{r_I} + \frac{(1 - \theta)\beta p T_{max}}{c r_I} - 1 \right) \left( \frac{(r_I - \delta)T^0}{r_I - \delta R_0} \right)^2$$

yet

$$s = \left[ d_T - r_T \left( 1 - \frac{T^0}{T_{max}} \right) \right] T^0,$$

$$\frac{(1 - \theta)\beta p T_{max}}{c r_I} = \frac{T_{max} T^0}{r_I} \left( \frac{r_I - \delta R_0}{r_I} \right) + 1$$

and

$$\frac{(1 - \theta)\beta p}{c} = \frac{r_I - \delta R_0}{T^0} + r_I \frac{T_{max}}{T_{max}}.$$

Hence :

$$h_2(\bar{T}_2) = \left( d_T - r_T \left( 1 - \frac{T^0}{T_{max}} \right) \right) T^0 + \left( r_T - d_T - \frac{r_T}{r_I} (\delta - r_I) + \frac{T_{max}}{T^0} \left( \frac{r_I - \delta R_0}{r_I} \right) (\delta - r_I) \right) \left( \frac{(r_I - \delta)T^0}{r_I - \delta R_0} \right) +$$

$$- \left( \frac{r_I - \delta R_0}{T^0} + \frac{r_I}{T_{max}} \right) \left( \frac{r_T}{r_I} + \frac{T_{max}}{T^0} \left( \frac{r_I - \delta R_0}{r_I} \right) \right) \left( \frac{(r_I - \delta)T^0}{r_I - \delta R_0} \right)^2$$

$$= \frac{\delta T^0 (1 - R_0)}{(r_I - \delta R_0)^2 T_{max}} \left[ r_T T^0 (r_I - \delta) + (r_I - \delta R_0) T_{max} \left( d_T - r_T \left( 1 - \frac{T^0}{T_{max}} \right) \right) \right].$$

Since $d_T - r_T \left( 1 - \frac{T^0}{T_{max}} \right) > 0$ and $\delta < r_I$, we get :
\[ h_2(T_2) \geq 0 \text{ if } R_0 \leq 1. \]
\[ h_2(T_2) < 0 \text{ if } 1 < R_0 < \frac{r_I}{\delta}. \]

This completes the proof. ■

The conditions of existence of an infected equilibrium point \( E^* \) have been established, we are going in the following subsection give its expression.

### 3.3 Expression of the equilibrium points

#### 3.3.1 Uninfected equilibrium point

By the proposition 2.6, the uninfected equilibrium point is given by \( E^0 = (T^0, 0, 0) \) where

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

#### 3.3.2 Infected equilibrium point

**Lemma 3.13** 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 :

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

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

\[
H = \frac{A^2}{r_T r_I} + \frac{A}{r_T} - \frac{A}{r_I}
\]

and

\[
A = \frac{(1 - \theta)\beta p T_{\max}}{c}.
\]

**Proof.** When \( T^* \) exists, it will be a positive solution of the equation of second degree :

\[ h_2(T) = 0, \quad \text{(20)} \]

with :

\[
h_2(T) = s + q \frac{T_{\max}}{r_I} (r_I - \delta) + T \left( r_T - \delta - \frac{r_T}{r_I} (r_I - \delta) - \frac{(1 - \theta)\beta p T_{\max}}{c r_I} (r_I - \delta) + \frac{(1 - \theta)\beta p T_{\max}}{c r_I} q \right)
\]

\[
- \frac{(1 - \theta)\beta p}{c} \left( \frac{r_T}{r_I} + \frac{(1 - \theta)\beta p T_{\max}}{c r_I} - 1 \right) T^2.
\]

Let

\[
A = \frac{(1 - \theta)\beta p T_{\max}}{c}.
\]
then (20) becomes:
\[ s + q \frac{T_{\text{max}}}{r_I} (r_I - \delta) + \left( r_T - (d_T + q) - \frac{r_T}{r_I} (r_I - \delta) - \frac{A}{r_I} \left( r_I - \delta + \frac{Aq}{r_I} \right) \right) T - \frac{r_T}{T_{\text{max}}} \left( \frac{A^2}{r_I r_T} + \frac{A}{r_I} - \frac{A}{r_T} \right) T^2 = 0. \]

Let also:
\[ H = \frac{A^2}{r_I r_T} + \frac{A}{r_I} - \frac{A}{r_T}, \]
then (20) becomes:
\[ s + q \frac{T_{\text{max}}}{r_I} (r_I - \delta) + \left( r_T - (d_T + q) - \frac{r_T}{r_I} (r_I - \delta) - \frac{A}{r_I} \left( r_I - \delta + \frac{Aq}{r_I} \right) \right) T - \frac{r_T}{T_{\text{max}}} HT^2 = 0. \]

Let:
\[ a = -\frac{r_T H}{T_{\text{max}}}, \]
\[ d = s + q \frac{T_{\text{max}}}{r_I} (r_I - \delta), \]
\[ b = r_T - (d_T + q) - \frac{r_T}{r_I} (r_I - \delta) - \frac{A}{r_I} \left( r_I - \delta + \frac{Aq}{r_I} \right), \]
hence the previous equation yields:
\[ aT^2 + bT + d = 0. \]

Its discriminant is:
\[ \Delta = b^2 - 4ad \]
i.e.
\[ \Delta = \left[ r_T - (d_T + q) - \frac{r_T}{r_I} (r_I - \delta) - \frac{A}{r_I} \left( r_I - \delta + \frac{Aq}{r_I} \right) \right]^2 + \left( s + \frac{qT_{\text{max}}}{r_I} \delta \right). \]

Hence
\[ T^* = \frac{r_T - (d_T + q) - \frac{r_T}{r_I} (r_I - \delta) - \frac{A}{r_I} \left( r_I - \delta + \frac{Aq}{r_I} \right) + \sqrt{\Delta}}{2 \frac{H r_T}{T_{\text{max}}}} \]

\[ = \frac{1}{2} \left( \frac{A T_{\text{max}}}{r_I r_T} \left( \frac{r_T - (d_T + q)}{A r_T} - \frac{r_T}{r_I} (r_I - \delta) - \frac{A}{r_I} (r_I - \delta + \frac{Aq}{r_I}) \right) + \frac{q}{r_I r_T} + \frac{T_{\text{max}} \sqrt{\Delta}}{H r_T} \right) \]

\[ = \frac{1}{2} \left( \frac{A T_{\text{max}}}{r_I A} \left( \frac{r_T - (d_T + q)}{r_I} - \frac{1}{r_I} (r_I - \delta) - \left( \frac{1}{r_T} - \frac{\delta}{r_I r_T} \right) \right) + \frac{q}{r_I r_T} + \frac{T_{\text{max}} \sqrt{\Delta}}{H r_T} \right) \]

\[ = \frac{1}{2} \left( \frac{-D}{H} + \frac{T_{\text{max}} \sqrt{\Delta}}{H r_T} \right). \]
Where
\[ D = AT_{\text{max}} \left( \frac{1}{r_T} \left( 1 + \frac{d_T + q}{A} \right) - \frac{\delta}{r_I} \left( \frac{1}{r_T} + \frac{1}{A} \right) - \frac{q}{r_T r_I} \right). \]

We have:
\[ T_{\text{max}} \sqrt{\frac{\Delta}{H r_T}} = \sqrt{\frac{T_{\text{max}}^2 \Delta}{H^2 r_T^2}} = \sqrt{\left( \frac{D}{H} \right)^2 - 4 \frac{H r_T T_{\text{max}}}{H^2 r_T^2} \left( s + \frac{q T_{\text{max}}}{r_I} (r_I - \delta) \right)} = \sqrt{\left( \frac{D}{H} \right)^2 + \frac{4 s T_{\text{max}}}{H r_T} + \frac{4 A q T_{\text{max}}^2}{H^2 r_T^2} \left( \frac{H r_T r_I^2}{A} - \frac{H r_T r_I}{A} \delta \right)} = \sqrt{\left( \frac{D}{H} \right)^2 + \frac{4 s T_{\text{max}}}{r_T} + \frac{4 A q T_{\text{max}}^2}{H^2 r_T^2} \left( A(\delta - r_I) - d_I(r_I - r_T) - r_I(q - r_I - r_T) + r_T q \right) = \sqrt{\left( \frac{D}{H} \right)^2 + F + \frac{4 s T_{\text{max}}}{r_T} H} \]

with
\[ F = \frac{4 A q T_{\text{max}}^2}{H^2 r_T^2} \left( A(\delta - r_I) - d_I(r_I - r_T) - r_I(q - r_I - r_T) + r_T q \right). \]

It follows that:
\[ T^* = \frac{1}{2} \left( -\frac{D}{H} + \sqrt{\left( \frac{D}{H} \right)^2 + F + \frac{4 s T_{\text{max}}}{r_T} H} \right). \]

The combination of the proposition 3.4, proposition 3.12 and the lemma 3.13 leads to the following theorem:

**Theorem 3.14** The model (4) admits a unique infected equilibrium \( E^* = (T^*, I^*, V^*) \) if and only if \( R_0 > 1 \), where

\[ T^* = \frac{1}{2} \left( -\frac{D}{H} + \sqrt{\left( \frac{D}{H} \right)^2 + F + \frac{4 s T_{\text{max}}}{r_T} H} \right), \]
\[ I^* = T^* \left( \frac{A}{r_I} - 1 \right) + T_{\text{max}} \left( 1 - \frac{\delta}{r_I} \right), \]
\[ V^* = \frac{(1 - \varepsilon)p I^*}{c}; \]

where where:
\[ D = AT_{\text{max}} \left( \frac{1}{r_T} \left( 1 + \frac{d_T + q}{A} \right) - \frac{\delta}{r_I} \left( \frac{1}{r_T} + \frac{1}{A} \right) - \frac{q}{r_T r_I} \right); \]
\[ F = \frac{4 A q T_{\text{max}}^2}{H^2 r_T^2 r_I^2} \left( A(\delta - r_I) - d_I(r_I - r_T) - r_I(q - r_I - r_T) + r_T q \right); \]
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\[ H = \frac{A^2}{r_T r_T} + \frac{A}{r_I} - \frac{A}{r_T} \]

and

\[ A = \frac{(1 - \theta)\beta p T_{\text{max}}}{c}. \]

When \( R_0 \leq 1 \) the unique equilibrium is the uninfected equilibrium point or the infection-free steady state \( E^0 = (T^0, 0, 0) \).

3.4 Local stability analysis of the model 1 at the equilibrium points

For the study of local stability of the model (4) at the equilibrium points, let us consider once more the functions \( f_1, f_2 \) et \( f_3 \) given by (6), (7) and (6) respectively.

3.4.1 Case of the uninfected equilibrium point or infection-free steady state

**Theorem 3.15** The infection-free steady state \( E^0 = (T^0, 0, 0) \) of model (4) is locally asymptotically stable if \( R_0 \leq 1 \) and unstable if \( R_0 > 1 \).

**Proof.** The Jacobian matrix \( J(E^0) \) of the system (4) at \( E^0 \) is as the following:

\[
J(E^0) = \begin{pmatrix}
\frac{\partial f_1}{\partial T}(E^0) & \frac{\partial f_1}{\partial I}(E^0) & \frac{\partial f_1}{\partial V}(E^0) \\
\frac{\partial f_2}{\partial T}(E^0) & \frac{\partial f_2}{\partial I}(E^0) & \frac{\partial f_2}{\partial V}(E^0) \\
\frac{\partial f_3}{\partial T}(E^0) & \frac{\partial f_3}{\partial I}(E^0) & \frac{\partial f_3}{\partial V}(E^0)
\end{pmatrix}
\]

i.e.

\[
J(E^0) = \begin{pmatrix}
r_T \left(1 - \frac{2T^0}{T_{\text{max}}} \right) - d_T & -\frac{r_T T^0}{T_{\text{max}}} + q & -(1 - \eta) \beta T^0 \\
0 & r_I \left(1 - \frac{T^0}{T_{\text{max}}} \right) - \delta & (1 - \eta) \beta T^0 \\
0 & (1 - \epsilon)p & -c
\end{pmatrix}
\]

Since

\[ r_T - d_T = -\frac{s}{T^0} + \frac{r_T T^0}{T_{\text{max}}}, \]

it follows that:

\[
J(E^0) = \begin{pmatrix}
-\frac{s}{T^0} - \frac{r_T T^0}{T_{\text{max}}} & -\frac{r_T T^0}{T_{\text{max}}} + q & -(1 - \eta) \beta T^0 \\
0 & r_I \left(1 - \frac{T^0}{T_{\text{max}}} \right) - \delta & (1 - \eta) \beta T^0 \\
0 & (1 - \epsilon)p & -c
\end{pmatrix}
\]
Now let us show that the eigenvalues of the matrix $J(E^0)$ have negative real part if and only if $R_0 < 1$.

Considering the expression of $J(E^0)$, $-\frac{s}{T_0} - \frac{r_y T_0}{T_{max}}$ is a negative eigenvalue of the matrix $J(E^0)$.

Now let us consider the sub-matrix $J_1(E^0)$ defined by:

$$J_1(E^0) = \begin{pmatrix} r_I \left( 1 - \frac{T_0}{T_{max}} \right) - \delta & (1 - \eta) \beta T^0 \\ (1 - \varepsilon) p & -c \end{pmatrix}.$$  \hspace{1cm} (21)

The trace of $J_1(E^0)$ is:

$$Tr(J_1(E^0)) = -c - \delta + r_I \left( 1 - \frac{T_0}{T_{max}} \right) = \delta \left( -\frac{c}{\delta} - 1 + \frac{r_I}{\delta} \left( 1 - \frac{T_0}{T_{max}} \right) \right) = \delta \left( -\frac{c}{\delta} - 1 + R_0 - \frac{(1 - \theta)}{c \delta} \beta p T^0 \right) = -c - \delta (1 - R_0) - \frac{(1 - \theta)}{c} \beta p T^0,$$

and the determinant of $J_1(E^0)$ is:

$$|J_1(E^0)| = -cr_I \left( 1 - \frac{T_0}{T_{max}} \right) + c\delta - (1 - \theta) \beta PT^0 = c\delta \left[ -\frac{r_I}{\delta} \left( 1 - \frac{T_0}{T_{max}} \right) + 1 - \frac{(1 - \theta) \beta PT^0}{c \delta} \right] = c\delta (1 - R_0).$$

The system (4) is locally asymptotically stable at $E^0$ if and only if

$$-c - \delta (1 - R_0) - \frac{(1 - \theta)}{c} \beta p T^0 < 0,$$

and

$$c\delta (1 - R_0) > 0$$

i.e.

$$R_0 < 1.$$

Therefore the model (4), is locally asymptotically stable at $E^0 = (T^0, 0, 0)$ when $R_0 < 1$ and unstable when $R_0 > 1$. This completes the proof of theorem 3.15.

### 3.4.2 Case of infected equilibrium point

We start this subsection by two preliminary lemmas.
Lemma 3.16  The Jacobian matrix $J(E^*)$, of lemma 3.16, of system (4) at $E^*$ is given by:

$$J(E^*) = \begin{pmatrix}
-\frac{s}{T^*} - \frac{v_T T^*}{T_{max}} - q \frac{I^*}{T^*} & -\frac{v_T T^*}{T_{max}} + q & -(1-q) \beta T^* \\
-\frac{r I^*}{T_{max}} + (1-\eta) \beta V^* & -\frac{r I^*}{T_{max}} - \frac{(1-\eta) \beta V^* T^*}{T} & (1-\eta) \beta T^* \\
0 & (1-\varepsilon)p & -c
\end{pmatrix}$$

Proof. See the Appendice for the proof. ■

Lemma 3.17  The characteristic equation of the Jacobian matrix $J(E^*)$ 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:

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

$$A_2 = \frac{c s}{T^*} + \frac{c v_T T^* + s A + c r I^*}{T_{max}} + q \frac{I^*}{T^*} (r I - \delta) + \frac{sr I^*}{T^* T_{max}} + \frac{r AT^* (T^* + I^*)}{T_{max}^2} + c q I^* \frac{T^*}{T_{max}} + q \frac{I^*}{T_{max}},$$

$$A_3 = \frac{c s r T^* I^*}{T^* T_{max}} + \frac{c A^2 I^* T^*}{T_{max}^2} - \frac{c A r I^* T^*}{T_{max}^2} + \frac{c A r T^* I^* T^*}{T_{max}^2} + q \frac{c I^*}{T^*} (r I - \delta).$$

Proof. See the appendice for the proof of lemma 3.17. ■

Now let:

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

By Routh-Hurwitz criteria[16], we have the following results.

Theorem 3.18  For model (4), when $R_0 > 1$ 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 3.19  The infected steady state during the therapy $E^*$ of the model (4) is locally asymptotically stable if $R_0 > 1$ and unstable if $R_0 > 1$.  

\[ \Delta_2 = A_1 A_2 - A_3 \]
\[ = \left( c + \frac{s}{T^*} + \frac{r_T T^*}{T_{\text{max}}} + \frac{r_I I^*}{T_{\text{max}}} + \frac{AT^*}{T_{\text{max}}} + \frac{I^*}{T^*} \right) \left( \frac{cs r_I I^*}{T^* T_{\text{max}}} + \frac{s A}{T_{\text{max}}} + \frac{cr I^*}{T_{\text{max}}} + \frac{cr_T T^*}{T_{\text{max}}} \right) \]
\[ + \frac{c_T A(T^*)^2}{T_{\text{max}}} + \frac{r_T A T^* I^*}{T_{\text{max}}} + \frac{c q I^*}{T^*} + \frac{q I^* (r_I - \delta)}{I^*} \]
\[ - \frac{c r_T A T^* I^*}{T_{\text{max}}} - q c \frac{I^*}{T^*} (r_I - \delta) \]
\[ = \frac{c^2 s}{T^*} + \frac{cs r_I I^*}{T_{\text{max}}} + \frac{cs A}{T_{\text{max}}} + \frac{q A T^*}{T_{\text{max}}} + \frac{q^2 A I^*}{T_{\text{max}}} + \frac{q A I^* T^*}{T_{\text{max}}} + \frac{q A I^* T^*}{T_{\text{max}}} + \frac{q^2 A I^* T^*}{T_{\text{max}}} + \frac{q c I^*}{T_{\text{max}}} \]
\[ = B + D \]
where,

\[
B = \frac{c^2 s}{T^*} + \frac{csrI^*}{T^*T_{max}} + \frac{c^2 \tau I^*}{T_{max}} + \frac{c^2 \tau T^*}{T_{max}} + \frac{crT A(T^*)^2}{T_{max}^2} + \frac{crT A T^* I^*}{T_{max}^2} \\
+ \frac{c^2 q}{T^*} + c q \frac{I^*}{T^*} (r I - \delta) + c q \frac{I^*}{T_{max}} + \frac{cs^2}{(T^*)^2} + \frac{s^2 r I^*}{(T^*)^2 T_{max}} + \frac{s^2 A}{T^* T_{max}} \\
+ \frac{csrI^*}{T^* T_{max}} + \frac{srT A T^*}{T_{max}^2} + \frac{srT A I^*}{T_{max}^2} + \frac{csq I^*}{(T^*)^2} + \frac{sq I^*}{(T^*)^2} (r I - \delta) + \frac{sq I^*}{T^* T_{max}} \\
+ \frac{srI T^*}{T_{max}^2} + \frac{srI T^*}{T_{max}^2} + \frac{crT A T^* T^*}{T_{max}^2} + \frac{crT (T^*)^2}{T_{max}^2} + \frac{r^2 T^* A(T^*)^3}{T_{max}^3} + \frac{r^2 T^* A(T^*)^2 I^*}{T_{max}^3} \\
+ \frac{r T^2 A(T^*)^2 I^*}{T_{max}^3} + \frac{crT I^*}{T^* T_{max}} + q r I^* (r I - \delta) + \frac{q r I^*}{T_{max}} + \frac{csrI^*}{T^* T_{max}} + \frac{s q T^2}{T_{max}} + \frac{sr^2 I^*}{T_{max}} \\
+ \frac{q c T^2}{T^* T_{max}} + \frac{c r I^*}{T^* T_{max}} + \frac{q r I^*}{T_{max}} + \frac{q r I^*}{T_{max}} + \frac{sr T^* A(T^*)^2 I^*}{T_{max}^3} + \frac{r T^* A T^* (T^*)^2 I^*}{T_{max}^3} \\
+ \frac{q A T^* (T^*)^2}{T_{max}^3} + \frac{r T^* A T^* I^*}{T_{max}^3} + \frac{r T^* A T^* I^*}{T_{max}^3} + \frac{r T^* A T^* I^*}{T_{max}^3} + \frac{q r T^* A T^* I^*}{T_{max}^3} \\
+ \frac{q r T^* A I^*}{T_{max}^3} + \frac{q r T^*}{T_{max}^3} + \frac{q r T^*}{T_{max}^3} + \frac{q r T^*}{T_{max}^3} + \frac{q r T^*}{T_{max}^3} + \frac{q r T^*}{T_{max}^3} + \frac{q r T^*}{T_{max}^3} + \frac{q r T^*}{T_{max}^3} \\
+ \frac{r T^2 A I^*}{T^* T_{max}} + \frac{q^2 c I^*}{(T^*)^2} + \frac{q^2 (I^*)^2}{(T^*)^2} + \frac{q^2 (I^*)^2}{(T^*)^2} (r I - \delta) + \frac{q^2 (I^*)^2}{T^* T_{max}} + \frac{csr I^*}{T^* T_{max}} + \frac{cs I^*}{T_{max}^2} - \frac{cs I^*}{T_{max}^2} + \frac{c r T^* A I^*}{T_{max}^2} - \frac{c r T^* A I^*}{T_{max}^2} \\
- \frac{q c}{T^*} (r I - \delta),
\]

and

\[
D = 2 \frac{c s A}{T_{max}} + 2 \frac{c s r T}{T_{max}} + q \frac{c A I^*}{T_{max}} + \frac{c A^2 T^* I^*}{T_{max}^2}.
\]  

(22)

Since $B > 0$, it remains to show that $D > 0$.

From (1) we have:

\[
s + r T^* - \frac{r r(T^*)^2}{T_{max}} - \frac{r r T^* I^*}{T_{max}} - d T^* - (1 - \eta) \beta V^* T^* + q I^* = 0,
\]

yet

\[
V^* = \frac{(1 - \varepsilon) p I^*}{c};
\]
hence,
\[(1 - \eta)\beta V^* T^* = \frac{(1 - \theta) p \beta I^* T^*}{c} = \frac{A I^* T^*}{T_{\max}}.\]

Thus,
\[\frac{A I^* T^*}{T_{\max}} = s + r_T T^* - d_T T^* - \frac{r_T (T^*)^2}{T_{\max}} - \frac{r_T T^* I^*}{T_{\max}} + q I^*\]

it follows that:
\[-\frac{c A^2 I^* T^*}{T_{\max}^2} = -\frac{c s A}{T_{\max}} - \frac{c A r_T T^*}{T_{\max}} + \frac{c A d_T T^*}{T_{\max}} + \frac{c A r_T (T^*)^2}{T_{\max}^2} + \frac{c A r_T T^* I^*}{T_{\max}^2} - \frac{c A q I^*}{T_{\max}}.\]

Reporting this previous expression in (22) yields:
\[D = 2 \frac{c s A}{T_{\max}} + 2 \frac{c s r_T}{T_{\max}} + q \frac{c A I^*}{T_{\max}} - \frac{c s A}{T_{\max}} - \frac{c A r_T T^*}{T_{\max}} + \frac{c A d_T T^*}{T_{\max}} + \frac{c A r_T (T^*)^2}{T_{\max}^2} + \frac{c A r_T T^* I^*}{T_{\max}^2} - \frac{c A q I^*}{T_{\max}}.\]

Taking especially \(s = d_T T_{\max}\) and \(\delta = d_T\), we obtain: \(T^* = \frac{d_T T_{\max}}{A}\). Thus,
\[D = \frac{c s A}{T_{\max}} + c \delta r_T + \frac{c A d_T T^*}{T_{\max}} + \frac{c A r_T (T^*)^2}{T_{\max}^2} + \frac{c A r_T T^* I^*}{T_{\max}^2},\]

and \(D > 0\), therefore the system (4) is locally asymptotically stable at \(E^*\). This completes the proof of Corollary 3.19.

### 3.5 Global stability analysis of the system at equilibrium points

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 [11, 12, 13].

#### 3.5.1 Case of infection-free steady state

**Theorem 3.20** The infection-free steady state \(E^0 = (T^0, 0, 0)\) 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:
\[L(T, I, V) = T - T^0 - T^0 ln \frac{T}{T^0} + I + \frac{(1 - \eta) \beta T^0}{c} V.\]
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$L_1$ 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), satisfies:

$$\frac{dL}{dt} = \frac{\partial L}{\partial T} \frac{dT}{dt} + \frac{\partial L}{\partial I} \frac{dI}{dt} + \frac{\partial L}{\partial V} \frac{dV}{dt},$$

$$= \left(1 - \frac{T^0}{T}\right) \hat{T} + \hat{I} + \frac{(1 - \eta)\beta T^0}{c} \hat{V},$$

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

$$= (T - T^0) \left(\frac{s}{T} + r_T - \frac{r_T(T + I)}{T_{max}} - dT - (1 - \eta)\beta V + \frac{q I}{T}\right) + (1 - \eta)\beta VT$$

$$+ r_I \left(1 - \frac{T + I}{T_{max}}\right) - \delta I + \frac{(1 - \theta)}{c} \beta p T^0 - (1 - \eta)\beta T^0 V,$$

$$= (T - T^0) \left(\frac{s}{T} + r_T - \frac{r_T(T + I)}{T_{max}} + \frac{q I}{T}\right) - T(1 - \eta)\beta V + T^0(1 - \eta)\beta V$$

$$+ (1 - \eta)\beta VT + r_I \left(1 - \frac{T + I}{T_{max}}\right) - \delta I + \frac{(1 - \theta)}{c} \beta p T^0 - (1 - \eta)\beta T^0 V,$$

$$= (T - T^0) \left(\frac{s}{T} + r_T - \frac{r_T(T + I)}{T_{max}}\right) + qI - qI \frac{T^0}{T} + r_I \left(1 - \frac{T + I}{T_{max}}\right) + \frac{(1 - \theta)}{c} \beta p T^0 - \delta I;$$

yet

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

hence, further collecting terms, we have:

$$\frac{dL}{dt} = (T - T^0) \left(\frac{s}{T} + \frac{r T^0}{T_{max}} - \frac{s}{T^0} - \frac{r_T(T + I)}{T_{max}}\right) + r_I \left(1 - \frac{T + I}{T_{max}}\right) + \frac{(1 - \theta)}{c} \beta p T^0 - \delta I;$$

$$= (T - T^0) \left(-\frac{s}{TT^0} (T - T^0) - \frac{r_T}{T_{max}} (T - T^0) - \frac{r_T I}{T_{max}}\right) + r_I \left(1 - \frac{T + I}{T_{max}}\right)$$

$$+ \left(\frac{(1 - \theta)}{c} \beta p T^0 - \delta\right) I + qI - qI \frac{T^0}{T},$$

$$= -\frac{s}{TT^0} (T - T^0)^2 - \frac{r_T}{T_{max}} \left((T - T^0)^2 + (T - T^0)I\right) + r_I - \frac{r_I T}{T_{max}} - \frac{r_I}{T_{max}}$$

$$+ \left(\frac{(1 - \theta)}{c} \beta p T^0 - \delta\right) I + qI - qI \frac{T^0}{T},$$

$$= -\frac{s}{TT^0} (T - T^0)^2 - \frac{r_T}{T_{max}} \left((T - T^0)^2 + (T - T^0)I + \frac{r_I T}{T} + \frac{r_I}{r_T} + \frac{r_I^2}{r_T} + \frac{r_I T}{r_T}\right) + r_I$$

$$+ \left(\frac{(1 - \theta)}{c} \beta p T^0 - \delta\right) I + qI - qI \frac{T^0}{T},$$

$$= -\frac{s}{TT^0} (T - T^0)^2 - \frac{r_T}{T_{max}} \left[(T - T^0)^2 + (T - T^0)I + \frac{r_I T}{r_T} + \frac{r_I^2}{r_T} + \frac{r_I}{r_T} IT^0 - \frac{r_I}{r_T} IT^0\right]$$
+r_1 I + \left( \frac{(1 - \theta)}{c} \beta p T^0 - \delta \right) I + q I - q I T^0 T,

= \frac{s}{T T^0} (T - T^0)^2 - \frac{r_T}{T_{\text{max}}} (T - T^0)^2 + (T - T^0) I + \frac{r_1 I}{r_T} (T - T^0) + \frac{r_1 I^2}{r_T} + \frac{r_1 IT^0}{r_T}

+ r_1 I + \left( \frac{(1 - \theta)}{c} \beta p T^0 - \delta \right) I + q I - q I T^0 T,

= \frac{s}{T T^0} (T - T^0)^2 - \frac{r_T}{T_{\text{max}}} (T + I - T^0) (T + \frac{r_1 I}{r_T} I - T^0) - \frac{r_1 I T^0}{T_{\text{max}}} + r_1 I

+ \left( \frac{(1 - \theta)}{c} \beta p T^0 - \delta \right) I + q I - q I T^0 T,

= \frac{s}{T T^0} (T - T^0)^2 - \frac{r_T}{T_{\text{max}}} (T + I - T^0) (T + \frac{r_1 I}{r_T} I - T^0) + \delta I \left( \frac{r_1 I}{\delta} - \frac{r_1 T^0}{\delta T_{\text{max}}} (1 - \frac{\theta}{c \delta}) \beta p T^0 - 1 \right)

+ q I - q I T^0 T.

Furthermore,

\mathcal{R}_0 = \frac{(1 - \theta)}{c \delta} \beta p T^0 + \frac{r_1 I}{\delta} \left( 1 - \frac{T^0}{T_{\text{max}}} \right),

hence

\frac{dL}{dt} = \frac{s}{T T^0} (T - T^0)^2 - \frac{r_T}{T_{\text{max}}} (T + I - T^0) (T + \frac{r_1 I}{r_T} I - T^0) - q I T^0 T + \delta I (\mathcal{R}_0 - 1) + q I,

= \frac{s}{T T^0} (T - T^0)^2 - \frac{r_T}{T_{\text{max}}} (T + I - T^0) (T + \frac{r_1 I}{r_T} I - T^0) - q I T^0 T + \delta I (\mathcal{R}_0 - 1 + \frac{q}{\delta}).

Since r_I \leq r_T and \mathcal{R}_0 < 1 - \frac{q}{\delta}, we have \frac{dL}{dt} \leq 0

and \frac{dL}{dt} = 0 if and only if T = T^0 and I = 0 simultaneously.

Therefore, the largest compact invariant subset of the set

\[ M = \{ (T, I, V) \in \Omega : \frac{dL}{dt} = 0 \} \]

is the singleton \{E^0\}. By the Lasalle invariance principle[10], 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 8** The Lyapunov function defined in the proof of theorem 3.20 has been obtained following the general giving by Korobonikov \[12, 13, 11\] for the dynamic virus fundamental model.

### 3.5.2 Case of infected equilibrium point

We recall:
Remark 9 According to (13, 14, 15) the infected equilibrium point $E^*$ verify:

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

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

$$c = \frac{(1 - \varepsilon)p I^*}{V^*}.$$

Theorem 3.21 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:

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

Let us show that $\frac{dL}{dt} \leq 0$ and $\frac{dL}{dt} = 0$ if and only if $T = T^*$, $I = I^*$, $V = V^*$ simultaneously.

The time derivative of $L$ along the trajectories of system (4) is:

$$\frac{dL}{dt} = \frac{\partial L}{\partial T} \frac{dT}{dt} + \frac{\partial L}{\partial I} \frac{dI}{dt} + \frac{\partial L}{\partial V} \frac{dV}{dt}$$

$$= \left(1 - \frac{T^*}{T}\right) \dot{T} + \left(1 - \frac{I^*}{I}\right) \dot{I} + \frac{(1 - \eta)\beta T^* V^*}{(1 - \varepsilon)p I^*} \left(1 - \frac{V}{V^*}\right) \dot{V}$$

$$= \left(T - T^*\right) \frac{\dot{T}}{T} + \left(I - I^*\right) \frac{\dot{I}}{I} + \frac{(1 - \eta)\beta T^* V^*}{(1 - \varepsilon)p I^*} \left(V - V^*\right) \frac{\dot{V}}{V}.$$

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

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

$$+ \frac{(1 - \eta)\beta T^* V^*}{(1 - \varepsilon)p I^*} \left(V - V^*\right) \left((1 - \varepsilon)p I - \varepsilon V\right)$$

$$+ (I - I^*) \left(1 - \eta\right) \frac{\beta VT^*}{I} + r_I \left(1 - \frac{T + I}{T_{max}}\right) - \delta.$$  (23)

Reporting equalities of remark 9 into (23), we have:

$$\frac{dL}{dt} = \left(T - T^*\right) \left[\frac{s}{T} - \frac{s}{T^*} + (1 - \eta)\beta V^* + \frac{r_T}{T_{max}}(T^* + I^*) - q \frac{I^*}{T^*} - \frac{r_T(T + I)}{T_{max}} - (1 - \eta)\beta V + q \frac{I}{T}\right]$$
\[ + (I - I^*)(1 - \eta) \frac{\beta VT}{I} - r_I \frac{T}{T_{\text{max}}} - r_I \frac{I}{T_{\text{max}}} - \frac{(1 - \eta)\beta V^* T^*}{I^*} + \frac{r_I}{T_{\text{max}}} (T^* + I^*) \] 
\[ + \frac{T^* V^*}{(1 - \varepsilon)p I^*} \left( \frac{V - V^*}{V} \right) \left( (1 - \varepsilon)p I - \frac{(1 - \varepsilon)p I^*}{V^*} V \right) \]

\[ = - \frac{s}{TT^*} (T - T^*)^2 - \frac{\gamma T}{T_{\text{max}}} (T - T^*)^2 - \frac{\gamma T}{T_{\text{max}}} (T - T^*)(I - I^*) - (1 - \eta)\beta (T - T^*) (V - V^*) \]
\[ + (1 - \eta)\beta \left[ \left( \frac{VT}{I} - \frac{V^* T^*}{I^*} \right) (I - I^*) + \frac{T^* V^*}{(1 - \varepsilon)p I^*} \left( \frac{V - V^*}{V} \right) \left( (1 - \varepsilon)p I - \frac{(1 - \varepsilon)p I^*}{V^*} V \right) \right] \]
\[ - q \frac{I^*}{T^*} (T - T^*) + q \frac{I}{T} (T - T^*) - \frac{r_I}{T_{\text{max}}} (T - T^*)(I - I^*) - \frac{r_I}{T_{\text{max}}} (I - I^*)^2 \]
\[ = - \frac{s}{TT^*} (T - T^*)^2 - \frac{\gamma T}{T_{\text{max}}} (T - T^*)^2 - \frac{\gamma T + r_I}{T_{\text{max}}} (T - T^*)(I - I^*) - \frac{r_I}{T_{\text{max}}} (I - I^*)^2 \]
\[ + (1 - \eta)\beta \left[ \left( \frac{VT}{I} - \frac{V^* T^*}{I^*} \right) (I - I^*) \right. \]
\[ - (T - T^*) (V - V^*) + \frac{T^* V^*}{(1 - \varepsilon)p I^*} \left( \frac{V - V^*}{V} \right) \left( (1 - \varepsilon)p I - \frac{(1 - \varepsilon)p I^*}{V^*} V \right) \]
\[ - q \frac{1}{TT^*} \left( T^2 I^* + (T^*)^2 I - T^* T I - T^* T I^* \right) \]

\[ = - \frac{s}{TT^*} (T - T^*)^2 - \frac{1}{T_{\text{max}}} (\gamma T + r_I T - r_I T^* - r_I I^*) (T + I - T^* - I^*) \]
\[ + (1 - \eta)\beta T^* V^* \left( \frac{VT}{V^* T^*} - \frac{V^* T^*}{I^* V^*} \right. \]
\[ + \frac{V^* V^*}{V^*} \left( \frac{T^* V^*}{I^* V^*} - \frac{IV}{I^* V^*} \right. \]
\[ - \frac{I^* V^*}{V^*} \left( \frac{V^* I^*}{I^* V^*} \right) \left( \frac{V^*}{V^*} \right) \]
\[ - q \frac{1}{TT^*} \left( (T - T^*)^2 I^* + (T^*)^2 (I - I^*) + TT^* (I^* - I) \right) \]
\[ = - \frac{s}{TT^*} (T - T^*)^2 - \frac{1}{T_{\text{max}}} (\gamma T + r_I T - r_I T^* - r_I I^*) (T + I - T^* - I^*) \]
\[ + (1 - \eta)\beta T^* V^* \left( 1 + \frac{T}{T^*} - \frac{VT^*}{IV^* T^*} \right. \]
\[ - \frac{V^* I^*}{I^* V^*} \left( \frac{V^* I}{I^* V} \right) \left( \frac{T}{T^*} \right) \]
\[ - q \frac{1}{TT^*} \left( (T - T^*)^2 I^* \right. \]
\[ + (T^*) (I - I^*) (T^* - T) \right). \]

Note that
\[ 1 + \frac{T}{T^*} - \frac{VT^*}{IV^* T^*} - \frac{V^* I}{I^* V} = \left( 3 - \frac{T}{T^*} - \frac{VT^*}{IV^* T^*} - \frac{V^* I}{I^* V} \right) + \left( \frac{T}{T^*} + \frac{T^*}{T} - 2 \right) \]
and
\[
\left( \frac{T}{T^*} + \frac{T^*}{T} - 2 \right) = \left( \frac{T - T^*}{TT^*} \right)^2.
\]
According to (13),
\[
s = (1 - \eta)\beta T^*V^* + \left( d_T - r_T + r_T \frac{(T^* + I^*)}{T_{\text{max}}} \right)T^* - qI^*.
\]
furthermore,
\[
T^* + I^* = T_{\text{max}};
\]
hence,
\[
s = (1 - \eta)\beta T^*V^* + d_T T^* - qI^*.
\]
By hypothesis, \( r_T = r_I \) this leads to:
\[
\frac{dL}{dT} = \left( - \frac{d_T}{T} + q \frac{I^*}{TT^*} - \frac{(1 - \eta)\beta V^*}{T} \right) (T - T^*)^2 - \frac{r_T}{T_{\text{max}}} (T + I - T^* - I^*)^2
\]
\[+(1 - \eta)\beta V^*T^* \left( 3 - \frac{T^*}{T} - \frac{VTI^*}{IV^*T^*} - \frac{V^*I}{I^*V} \right) + (1 - \eta)\beta V^*T^* \frac{(T - T^*)^2}{TT^*} \]
\[ - q \frac{1}{TT^*} \left( (T - T^*)^2 I^* + T^*(I - I^*)(T^* - T) \right) \]
\[= - \frac{d_T}{T} (T - T^*)^2 - \frac{r_T}{T_{\text{max}}} (T + I - T^* - I^*)^2 - q \frac{1}{T} (I - I^*)(T^* - T) \]
\[+(1 - \eta)\beta V^*T^* \left( 3 - \frac{T^*}{T} - \frac{VTI^*}{IV^*T^*} - \frac{V^*I}{I^*V} \right) \]
\[= - \frac{d_T}{T} (T - T^*)^2 - \frac{r_T}{T_{\text{max}}} (T + I - T^* - I^*)^2 - q \frac{1}{T} (I - I^*)(T^* - T) \]
\[+(1 - \eta)\beta V^*T^* \left( 3 - \frac{(T^*)^2 I^* V^* + (I^*VT)^2 + (IV^*)^2 TT^*}{TT^*II^*VV^*} \right) \]
\[= - \frac{d_T}{T} (T - T^*)^2 - \frac{r_T}{T_{\text{max}}} (T + I - T^* - I^*)^2 - q \frac{1}{T} (I - I^*)(T^* - T) \]
\[+ \frac{3(1 - \eta)\beta V^*T^*}{TT^*II^*VV^*} \left( TT^*II^*VV^* - \frac{1}{3} \left( (T^*)^2 II^*VV^* + (I^*VT)^2 + (IV^*)^2 TT^* \right) \right). \]

Yet
\[
\frac{1}{3} \left( (T^*)^2 II^*VV^* + (I^*VT)^2 + (IV^*)^2 TT^* \right) \geq TT^*II^*VV^*
\]
since the geometric mean is less than or equal to the arithmetic mean.
It should be noted that \( \frac{dL}{dT} \leq 0 \) and \( \frac{dL}{dT} = 0 \) holds if and only if \( (T, X, V) \) take the steady states values \( (T^*, X^*, V^*) \). Therefore the infected equilibrium point \( E^* \) is globally asymptotically stable. This completes the proof of this theorem.
3.6 Some numerical simulations

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

The following curves, obtained using the Maple software, show the real-time evolution of uninfected hepatocytes, infected hepatocytes and viral load. The values of the parameters are taken in the parameter range defined by the table (2.2) and the initial conditions are $T_0 = 10^3$, $I_0 = 2$ and $V_0 = 1$.

3.6.1 Evolution in time of uninfected cells, infected cells and viral load when $R_0 < 1$.

Parameters values: $s = 10$, $r_T = 0.05$, $r_I = 0.112$, $d_T = 0.001$, $d_I = 0.1$, $T_{max} = 10^7$, $\beta = 10^{-7}$, $\eta = 10^{-7}$, $\varepsilon = 10^{-8}$, $p = 1$, $q = 0.5$, $c = 2$. These parameters values yields: $T_0 = 4160020$ and $R_0 = 0.4556 < 1$.

![Numerical solution curves](image)

(a) numerical solution curve for the uninfected hepatocytes. (b) numerical solution curve for the infected hepatocytes. (c) numerical solution curve for the virus load.

Figure 5: Numerical simulations of the extended HCV model in 1000 days.
3.6.2 Evolution in time of uninfected cells, infected cells and viral load when $R_0 > 1$.

Parameters values: $s = 10$, $r_T = 2$, $r_I = 0.112$, $d_T = 0.01$, $d_I = 0.3$, $T_{\text{max}} = 10^7$, $\beta = 10^{-7}$, $\eta = 10^{-4}$, $\varepsilon = 10^{-4}$, $p = 1$, $q = 0.5$, $c = 0.5$. These parameters values yields: $T^0 = 14875270$ et $R_0 = 3.6501 > 1$.

(a) numerical solution curve for the uninfected hepatocytes. (b) numerical solution curve for the infected hepatocytes. (c) numerical solution curve for the virus load.

Figure 7: Numerical simulations of the extended HCV model in 1000 days.

In short, in this section, it was a question to study the global stability of the model (4). We have established that the model (4) is globally asymptotically stable at equilibrium points $E^*$ and $E^0$ when $R_0 < 1$ and unstable when $R_0 > 1$. The numerical simulations has been carried out using the Maple software confirming theoretical results.

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Conclusion and discussions

Having reached the end of our work, it emerges from all the investigations presented that hepatitis C is a major health problem in the world and especially in Cameroon. To understand the dynamics of HCV 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. We first show the existence of the global solution to the Cauchy problem (4), (5); then we have calculated the basic reproduction ratio $R_0$. We finally show that the only infected equilibrium point for the model is globally asymptotically stable when $R_0 > 1$ and unstable when $R_0 < 1$ under others hypotheses. Furthermore uninfected equilibrium point for the model is globally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. These theoretical results have been confirmed by numerical simulations done using the software Maple. Given the results obtained, this work is the beginning point of very interesting other future investigations.

We plan to extend our analysis by focusing on more realistic models such as:

1. models with delay which involve delay ordinary differential equations;
2. models taking into account space which involve Partial differential equations;
3. 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 provides results with less hypotheses on model (4).

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4 Appendices

A Proof lemma 3.16

**Proof.** The Jacobian matrix $J(E^*)$ of the system (4) at $E^*$ is given by:

$$J(E^*) = \begin{pmatrix}
\frac{\partial f_1}{\partial T}(E^*) & \frac{\partial f_1}{\partial T}(E^*) & \frac{\partial f_1}{\partial V}(E^*) \\
\frac{\partial f_2}{\partial T}(E^*) & \frac{\partial f_2}{\partial T}(E^*) & \frac{\partial f_2}{\partial V}(E^*) \\
\frac{\partial f_3}{\partial T}(E^*) & \frac{\partial f_3}{\partial T}(E^*) & \frac{\partial f_3}{\partial V}(E^*)
\end{pmatrix}. $$

Let us determine the coefficients of that Jacobian matrix.

$$\frac{\partial f_1}{\partial T}(E^*) = r_T - \frac{r_T T^*}{T_{max}} - \frac{r_T I^*}{T_{max}} - d_T - (1 - \eta) \beta V^*.$$ 

Yet

$$V^* = \frac{(1 - \varepsilon)}{c} p I^*,$$

$$I^* = \frac{(1 - \theta) \beta p T_{max}}{c r I} - 1) T^* + \frac{T_{max}}{r I} (r I - \delta)$$

and

$$-d_T = + \frac{(1 - \theta)}{c} \beta p \left( \frac{r_T}{r I} + \frac{(1 - \theta) \beta p T_{max}}{c r I} - 1 \right) T^* - \frac{s}{T^*} - \frac{q T_{max}}{T^* r I} (r I - \delta)$$

$$+ \frac{r_T}{r I} (r I - \delta) + \frac{(1 - \theta) \beta p T_{max}}{c r I} (r I - \delta) - \frac{(1 - \theta) \beta p T_{max}}{c r I} q - r_T + q;$$

hence,

$$\frac{\partial f_1}{\partial T}(E^*) = r_T - 2 \frac{r_T T^*}{T_{max}} - \frac{r_T}{T_{max}} \left( \frac{(1 - \theta) \beta p T_{max}}{c r I} - 1 \right) T^* + \frac{T_{max}}{r I} (r I - \delta)$$ 

$$+ \frac{(1 - \theta)}{c} \beta p \left( \frac{r_T}{r I} + \frac{(1 - \theta) \beta p T_{max}}{c r I} - 1 \right) T^* - \frac{s}{T^*} - \frac{q T_{max}}{T^* r I} (r I - \delta)$$
\[\begin{align*}
+ \frac{\eta}{\eta} (r_I - \delta) + \frac{(1 - \theta) \beta p T_{\text{max}}}{c r_I} (r_I - \delta) - \frac{(1 - \theta) \beta p T_{\text{max}}}{c r_I} q - \frac{r_T}{r_I}
+ q - \frac{(1 - \eta) \beta p (1 - \varepsilon)}{c} \left( \left( \frac{(1 - \theta) \beta p T_{\text{max}}}{c r_I} - 1 \right) T^* + \frac{T_{\text{max}}}{r_I} (r_I - \delta) \right),
\end{align*}\]

\[\begin{align*}
= -\frac{s}{T^*} + \frac{2 r_T T^*}{T_{\text{max}}} + \frac{r_T T^*}{T_{\text{max}}} - \frac{r_T}{c r_I} (1 - \theta) \beta p T^* - r_T + \frac{r_T}{r_I} T^*
- \left( \frac{(1 - \theta) \beta p T^*}{c r_I} (1 - \theta) \beta p T^* + \frac{(1 - \theta)^2 \beta^2 p^2 T_{\text{max}}}{c r_I} - \frac{T_{\text{max}}}{T^*} \right)
+ \frac{q T_{\text{max}}}{T^* r_I} \delta + r_T - \frac{r_T}{r_I} \delta + \frac{(1 - \theta) \beta p T_{\text{max}} (r_I - \delta)}{c r_I} - \frac{T_{\text{max}}}{T^*} \delta,
- \frac{(1 - \theta) \beta p T^*}{c r_I} + \left( \frac{(1 - \theta)^2 \beta^2 p^2 T_{\text{max}}}{c r_I} - \frac{T_{\text{max}}}{T^*} \right) - \frac{(1 - \theta) \beta p T_{\text{max}}}{c r_I}
+ \frac{(1 - \theta) \beta p T_{\text{max}} \delta}{c r_I},
\end{align*}\]

\[\begin{align*}
= -\frac{s}{T^*} - \frac{r_T T^*}{T_{\text{max}}} - \frac{q I^*}{T^*};
\end{align*}\]

\[\begin{align*}
\frac{\partial f_1}{\partial I}(E^*) &= -\frac{r_T T^*}{T_{\text{max}}} + q;
\end{align*}\]

\[\begin{align*}
\frac{\partial f_1}{\partial V}(E^*) &= -(1 - \eta) \beta T^*;
\end{align*}\]

\[\begin{align*}
\frac{\partial f_2}{\partial T}(E^*) &= -\frac{r_I I^*}{T_{\text{max}}} + (1 - \eta) \beta V^*;
\end{align*}\]

\[\begin{align*}
\frac{\partial f_2}{\partial I}(E^*) &= r_I \left( 1 - \frac{T^* + I^*}{T_{\text{max}}} \right) - \frac{r_I I^*}{T_{\text{max}}} - \delta,
= r_I - \frac{r_I T^*}{T_{\text{max}}} - \frac{2 r_I I^*}{T_{\text{max}}} - \delta,
= -\frac{r_I I^*}{T_{\text{max}}} + r_I \left( 1 - \frac{T^* + \left( \frac{(1 - \theta) \beta p T_{\text{max}}}{c r_I} - 1 \right) T^* + \frac{T_{\text{max}}}{r_I (r_I - \delta)} \right) - \delta,
= -\frac{r_I I^*}{T_{\text{max}}} + r_I - \frac{r_I T^*}{T_{\text{max}}} + \frac{(1 - \theta) \beta p T^*}{c} + \frac{r_I I^*}{T_{\text{max}}} - r_I + \delta - \delta,
\end{align*}\]
\[ a = \frac{r_I I^*}{T_{\text{max}}} - \frac{(1 - \theta) \beta p T^*}{c}, \]

\[ \frac{\partial f_2}{\partial T}(E^*) = -\frac{r_I I^*}{T_{\text{max}}} - \frac{(1 - \eta) \beta V^* T^*}{I^*}. \]

\[ \frac{\partial f_2}{\partial V}(E^*) = (1 - \eta) \beta T^*; \]

\[ \frac{\partial f_3}{\partial T}(E^*) = 0; \]

\[ \frac{\partial f_3}{\partial I}(E^*) = (1 - \varepsilon) p; \]

\[ \frac{\partial f_3}{\partial V}(E^*) = -c. \]

\[ \frac{\partial f_3}{\partial V}(E^*) = -c. \]

Therefore, \( J(E^*) = \)

\[
\begin{pmatrix}
-\frac{s}{T^*} - \frac{r_I T^*}{T_{\text{max}}} - \frac{\beta T^*}{q} & -\frac{r_I T^*}{T_{\text{max}}} + q & -(1 - q) \beta T^* \\
-\frac{r_I I^*}{T_{\text{max}}} + (1 - \eta) \beta V^* & -\frac{r_I I^*}{T_{\text{max}}} - \frac{(1 - \eta) \beta V^* T^*}{I^*} & (1 - \eta) \beta T^* \\
0 & (1 - \varepsilon) p & -C
\end{pmatrix}.
\]

This completes the proof of the lemma 3.16. \( \blacksquare \)

**B Proof of lemma 3.17**

**Proof.** The characteristic equation is given by \(|J - \lambda I| = 0\), i.e.

\[
\begin{vmatrix}
-\frac{s}{T^*} - \frac{r_I T^*}{T_{\text{max}}} - \frac{\beta T^*}{q} & -\frac{r_I T^*}{T_{\text{max}}} + q & -(1 - q) \beta T^* \\
-\frac{r_I I^*}{T_{\text{max}}} + (1 - \eta) \beta V^* & -\frac{r_I I^*}{T_{\text{max}}} - \frac{(1 - \eta) \beta V^* T^*}{I^*} & (1 - \eta) \beta T^* \\
0 & (1 - \varepsilon) p & -C - \lambda
\end{vmatrix} = 0.
\]

With

\[ q \frac{I^*}{T^*} = \frac{q T_{\text{max}}}{T^*} \left( -\frac{\delta}{r_I} + 1 \right) - q \left( \frac{A}{r_I} - 1 \right), \]
it follows that:

\[ |J - \lambda I| = 0 \]

if and only if

\[ - \left( \frac{s}{\tau^*} - \frac{r_I T^*}{T_{max}} - \frac{q T_{max}}{T^*} \left( - \frac{\delta}{r_I} + 1 \right) - q \left( \frac{A}{r_I} - 1 \right) - \lambda \right) \left( c + \lambda \left( \frac{r_I T^*}{T_{max}} + \frac{1 - \eta V^* T^*}{T^*} + \lambda \right) - (1 - \varepsilon) p(1 - \eta) \beta T^* \right) 
+ \left[ \frac{r_I T^*}{T_{max}} + (1 - \eta) \beta V^* \right] \left[ (c + \lambda) \left( \frac{r_I T^*}{T_{max}} - q \right) + (1 - \varepsilon) p(1 - \eta) \beta T^* \right] = 0, \text{ i.e.} \]

\[ \left[ - \frac{s}{\tau^*} - \frac{r_I T^*}{T_{max}} - \frac{q T_{max}}{T^*} \left( - \frac{\delta}{r_I} + 1 \right) \right] \left( \frac{A}{r_I} - 1 \right) - \lambda^2 \left( c + \frac{r_I I^* + A T^*}{T_{max}} \right) + \frac{c r_I I^*}{T_{max}} \left[ \frac{r_I T^*}{T_{max}} - q \right] + \frac{c r_I T^* + A c T^*}{T_{max}} - q c = 0. \]

By developing the different factors in the previous equation, we get:

\[ \lambda^3 + \lambda^2 \left[ \frac{s}{\tau^*} + \frac{r_I T^*}{T_{max}} + \frac{q T_{max}}{T^*} \left( - \frac{\delta}{r_I} + 1 \right) + q \left( \frac{A}{r_I} - 1 \right) + c + \frac{r_I I^* + A T^*}{T_{max}} \right] + \lambda \left[ \left( c + \frac{r_I I^* + A T^*}{T_{max}} \right) \left( \frac{s}{\tau^*} + \frac{r_I T^*}{T_{max}} + \frac{q T_{max}}{T^*} \left( - \frac{\delta}{r_I} + 1 \right) + q \left( \frac{A}{r_I} - 1 \right) \right) + \frac{c r_I I^*}{T_{max}} \left( \frac{r_I T^*}{T_{max}} - q \right) + \frac{c r_I T^* + A c T^*}{T_{max}} - q c \right] = 0. \]

Let:

\[ A_1 = \frac{s}{\tau^*} + \frac{r_I T^*}{T_{max}} + \frac{q T_{max}}{T^*} \left( - \frac{\delta}{r_I} + 1 \right) + q \left( \frac{A}{r_I} - 1 \right) + c + \frac{r_I I^* + A T^*}{T_{max}} \],

we have:

\[ A_1 = c + \frac{s}{\tau^*} + \frac{r_I T^* + r_I I^* + A T^*}{T_{max}} + q \frac{I^*}{T^*}. \]

Let also:

\[ A_2 = \left( c + \frac{r_I I^* + A T^*}{T_{max}} \right) \left( \frac{s}{\tau^*} + \frac{r_I T^*}{T_{max}} + \frac{q T_{max}}{T^*} \left( - \frac{\delta}{r_I} + 1 \right) + q \left( \frac{A}{r_I} - 1 \right) \right) + \frac{c r_I I^*}{T_{max}} \left( \frac{r_I T^*}{T_{max}} - q \right) + \frac{c r_I T^* + A c T^*}{T_{max}} - q c. \]
we have:

\[ A_2 = \left( c + \frac{r_I I^*}{T_{\text{max}}} + (1 - \eta) \frac{\beta V^* T^*}{I^*} \right) \left( \frac{s}{T^*} + \frac{r_T T^*}{T_{\text{max}}} + \frac{q T_{\text{max}}}{T^*} \left( \frac{-\delta}{r_I} + 1 \right) \right) + q \left( \frac{(1 - \theta)}{c r_I} \beta p T_{\text{max}} - 1 \right) \right) + \frac{c r_I I^*}{T_{\text{max}}} + \frac{c (1 - \eta) \beta V^* T^*}{I^*} - (1 - \theta) \beta p I^*

+ \left( - \frac{r_T T^*}{T_{\text{max}}} + q \right) \left( \frac{r_I I^*}{T_{\text{max}}} - (1 - \eta) \beta V^* \right)

= \frac{cs}{T^*} + \frac{c r_T T^*}{T_{\text{max}}} + \frac{c q T_{\text{max}}}{r_I T^*} (r_I - \delta) + \frac{c q \left( (1 - \theta) \beta p T_{\text{max}} - 1 \right)}{c r_I} + \frac{r_I I^*}{T_{\text{max}}} \frac{s}{T^*} + \frac{r_I I^*}{T_{\text{max}}} \frac{I^*}{T^*} (r_I - \delta)

+ (1 - \eta) \frac{\beta V^* s}{I^*} + \frac{(1 - \eta) \beta V^* (T^*)^2 r_T}{I^* T_{\text{max}}} + \frac{q (1 - \eta) \beta V^* T_{\text{max}}}{r_I I^*} (r_I - \delta)

+ \frac{q (1 - \eta) \beta V^* T^*}{I^*} \left( \frac{(1 - \theta)}{c r_I} \beta p T_{\text{max}} - 1 \right) + \frac{c r_I I^*}{T_{\text{max}}} + \frac{c (1 - \eta) \beta V^* T^*}{I^*}

- (1 - \theta) \beta p I^* - \frac{r_T T^*}{T_{\text{max}}} + (1 - \eta) \beta V^* \frac{r_T T^*}{T_{\text{max}}} + \frac{q r_I I^*}{T_{\text{max}}} - q (1 - \eta) \beta V^* \]

Let once more:

\[ A_3 = \frac{c r_I I^*}{T_{\text{max}}} \left( \frac{s}{T^*} + \frac{r_T T^*}{T_{\text{max}}} + \frac{q T_{\text{max}}}{T^*} \left( \frac{-\delta}{r_I} + 1 \right) + q \left( \frac{A}{r_I} - 1 \right) \right) + \frac{r_I I^* - A I^*}{T_{\text{max}}} \left( \frac{q c r_T T^*}{T_{\text{max}}} + A c T^* \right) \]
We get:

\[
A_3 = \left( \frac{cr_I I^*}{T_{max}} + \frac{c(1 - \eta)\beta V^* T^*}{I^*} - (-\theta)\beta p T^* \right) \left( \frac{s}{T^*} + \frac{r_I T^*}{T_{max}} + \frac{q I^*_{max}}{T^*} (\frac{r_I}{r_I} + 1) \right) \\
+ q \left( \frac{(1 - \theta)\beta p T_{max}}{cr_I} - 1 \right) + \left( - \frac{r_I I^*}{T_{max}} + (1 - \eta)\beta V^* \right) \left( \frac{cr_T T^*}{T_{max}} - cq + (1 - \theta)\beta p T^* \right) \\
= \frac{cs r_I I^*}{T^* T_{max}} + \frac{cr_I r_I T^*}{T_{max}^2} + \frac{c I^*}{T^*} (r_I - \delta) + q \frac{cr_I I^*}{T_{max}} \left( \frac{1 - \theta}{cr_I} \beta p T_{max} - 1 \right) \\
+ \frac{c(1 - \eta)\beta V^* T^*}{I^*} \left( \frac{1 - \theta}{cr_I} \beta p T_{max} - 1 \right) - (1 - \theta) s \beta p - r_T (T^* T_{max})^2 (1 - \theta)\beta p T_{max} \\
- q \frac{(1 - \theta)\beta p}{r_I} T_{max} (r_I - \delta) - q (1 - \theta)\beta p T^* \left( \frac{1 - \theta}{cr_I} \beta p T_{max} - 1 \right) \\
- \frac{cr_I r_I T^*}{T_{max}^2} + q \frac{r_I I^*}{T_{max}} - (1 - \theta) \frac{r_I I^* T^*}{r_I T_{max}} + (1 - \eta)\beta V^* cr_T T^* \\
- qc(1 - \eta)\beta V^* + (1 - \theta) (1 - \eta) \beta^2 p V^* T^* \\
= \frac{cs r_I I^*}{T^* T_{max}} + \frac{c A^2 I^* T^*}{T_{max}^2} - \frac{c A r_I I^* T^*}{T_{max}^2} + \frac{c A r_T I^* T^*}{T_{max}^2} + q \frac{c I^*}{T^*} (r_I - \delta) \\
+ \frac{cr_I I^*}{T_{max}} \left( \frac{1 - \theta}{cr_I} \beta p T_{max} - 1 \right) + q \frac{c(1 - \eta)\beta V^*}{r_I I^*} T_{max} (r_I - \delta) \\
+ q \frac{c(1 - \eta)\beta V^* T^*}{I^*} \left( \frac{1 - \theta}{cr_I} \beta p T_{max} - 1 \right) - q \frac{(1 - \theta)\beta p}{r_I} T_{max} (r_I - \delta) \\
- q (1 - \theta)\beta p T^* \left( \frac{1 - \theta}{cr_I} \beta p T_{max} - 1 \right) + q \frac{r_I I^*}{T_{max}} - qc(1 - \eta)\beta V^* \\
= \frac{cs r_I I^*}{T^* T_{max}} + \frac{c A^2 I^* T^*}{T_{max}^2} - \frac{c A r_I I^* T^*}{T_{max}^2} + \frac{c A r_T I^* T^*}{T_{max}^2} + q \frac{c I^*}{T^*} (r_I - \delta).
\]

Therefore,

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

with

\[
A_1 = c + \frac{s}{T^*} + \frac{r_T T^* + r_I I^* + AT^*}{T_{max}} + \frac{I^*}{T^*};
\]

\[
A_2 = \frac{cs}{T^*} + \frac{cr_T T^* + sA + cr_I I^*}{T_{max}} + \frac{I^*}{T^*} (r_I - \delta) + \frac{sr_I I^*}{T^* T_{max}} + \frac{r_T AT^* (T^* + I^*)}{T_{max}^2} + \frac{cq I^*}{T^*} + \frac{q I^*}{T_{max}}.
\]
and
\[ A_3 = \frac{c s r_I I^*}{T^* T_{\text{max}}} + \frac{c A^2 I^* T^*}{T_{\text{max}}^2} - \frac{c A r_I I^* T^*}{T_{\text{max}}^2} + \frac{c A r_I I^* T^*}{T_{\text{max}}^2} + q \frac{c I^*}{T^*} (r_I - \delta). \]

This completes the proof of the lemma 3.17. ■