ANALYSIS OF AN INITIAL VALUE PROBLEM FOR AN EXTRACELLULAR AND INTRACELLULAR MODEL OF HEPATITIS C VIRUS INFECTION

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Abstract. In this paper, a mathematical analysis of the global dynamics of a viral infection model in vivo is carried out. We study the dynamics of a hepatitis C virus (HCV) model, under therapy, that considers both extracellular and intracellular levels of infection. At present most mathematical modelling of viral kinetics after treatment only addresses the process of infection of a cell by the virus and the release of virions by the cell, while the processes taking place inside the cell are not included. We prove that the solutions of the new model with positive initial values are positive, exist globally in time and are bounded. The model has two virus-free steady states. They are distinguished by the fact that viral RNA is absent inside the cells in the first state and present inside the cells in the second. There are basic reproduction numbers associated to each of these steady states. If the basic reproduction number of the first steady state is less than one then that state is asymptotically stable. If the basic reproduction number of the first steady state is greater than one and that of the second less than one then the second steady state is asymptotically stable. If both basic reproduction numbers are greater than one then we obtain various conclusions which depend on different restrictions on the parameters of the model. Under increasingly strong assumptions we prove that there is at least one positive steady state (infected equilibrium), that there is a unique positive steady state and that the positive steady state is stable. We also give a condition under which every positive solution converges to a positive steady state. This is proved by methods of Li and Muldowney. Finally we illustrate the theoretical results by numerical simulations.

1. Introduction

Infection with hepatitis C virus (HCV) is one of the most common causes of chronic liver disease. An account of its global epidemiology can be found in [1], where the number of people infected worldwide is estimated as 123 million. Achieving a sustained viral response (SVR), defined as undetectable HCV-RNA in serum (viral load) 24 weeks after the end of treatment, is the most effective way to prevent disease progression [2]. Recently the classical treatment regimes with pegylated interferon (IFN) and ribavirin have been improved on by the use of direct-acting antiviral agents (DAA). The new treatments can produce a cure in more than 90% of chronic cases [3]. In the past, mathematical models of the viral dynamics of HCV have proven useful in describing the interaction between the virus and host...
cells. In recent years, several papers on the dynamics of HCV and other related pathogens such as the human immunodeficiency virus (HIV) and the hepatitis B virus (HBV) have appeared [4, 5, 6, 7, 8, 9]. These studies have provided insights into viral replication, cell death rate and treatment effectiveness but they did not take into account the intracellular level of the infection.

In the basic model of virus dynamics, often used to describe the dynamics of HCV, HBV and HIV infections, a simple view of viral infection is proposed through the coupled evolution of three populations: uninfected cells, infected cells and free virus particles. The viral dynamics is therefore described by the temporal evolution of the three populations. Mathematical modelling of HCV infection and treatment has provided valuable insights into viral-host-IFN dynamics [10] and has helped to improve the treatment of HCV [11]. In this model, the virus is produced and released from productively infected cells into the systemic circulation, where it can be cleared or infect further target cells. It was shown using this model that the first phase of viral decline is due to IFN acting to reduce the average rate of virion production and release per infected cell, whereas the slower second phase viral decline was attributed to the progressive loss of infected cells [10].

Denote by $T, I$ and $V$ the concentrations of healthy hepatocytes, hepatocytes infected with HCV, and free HCV virions. Because of the interpretation of these quantities they are non-negative in any biologically relevant solution. The dynamics of HCV infection is the result of the dynamics of the compartments $T, I$, and $V$, and the various interactions between them. The following system is a modification of an extracellular model given in [12]:

$$\begin{align*}
\frac{dT}{dt} &= s + r_T T \left(1 - \frac{T + I}{T_{\text{max}}} \right) - dT - bTV \frac{T}{T + I} ; \\
\frac{dI}{dt} &= r_I I \left(1 - \frac{T + I}{T_{\text{max}}} \right) + bTV \frac{T}{T + I} - \delta I ; \\
\frac{dV}{dt} &= (1 - \epsilon)pI - cV - \frac{bTV}{T + I} .
\end{align*}$$

(1.1)

Its key features are as follows:

(i) The rate of change of the amount of healthy hepatocytes $T$ is given by the first equation of (1.1). Healthy hepatocytes are produced at a constant rate $s$ from an external source and die at rate $dT$. The model in [12] has $s = 0$. The population of uninfected hepatocytes is assumed to maintain itself logistically, with homeostatic carrying capacity $T_{\text{max}}$ as proposed in [4, 5]. Thus the recruitment of healthy hepatocytes is given by $r_T T \left(1 - \frac{T + I}{T_{\text{max}}} \right)$, where $r_T$ is the maximal per capita growth rate or the proliferation rate. Virions infect the healthy hepatocytes at the rate $bTV \frac{T}{T + I}$, where $b$ is the rate of transmission of the infection, an expression only defined when $T + I > 0$. For the significance of this term in the modelling of hepatitis we refer to [13]. This standard incidence function replaces the mass action function (used in the model of [12]) which has been shown lead to the unrealistic feature that a larger liver mass favours the establishment of a chronic hepatitis infection.

(ii) The second equation of (1.1) gives the rate of change of infected cells $I$. The hepatocytes which are infected with HCV die at rate $\delta$ per day so that $\frac{1}{\delta}$ is the life expectancy of hepatocytes infected with HCV. Healthy hepatocytes become infected at the rate $bTV \frac{T}{T + I}$. As in [4, 5], we assume that hepatocytes infected with HCV
proliferate by a complete logistic term $r_I I\left(1 - \frac{T + I}{T_{\max}}\right)$, where $r_I$ is the proliferation rate or maximal per capita growth rate of hepatocytes infected with HCV. The model of [12] has $r_I = 0$.

(iii) The third equation of (1.1) gives the rate of change of the free virus $V$. The infected hepatocytes produce virus at rate $(1 - \epsilon) p I$, and virus is cleared at the rate $c V$; this is the absorption phenomenon [6], which is not included in the model of [12]. The efficacy of treatment in blocking virion production is described by the parameter, $\epsilon$ whose value is non-negative and less than one.

The intracellular and cellular infection (ICCI) model is a multi-scale model that encompasses the original cellular infection (CI) model (1.1) but includes the viral production rate as a dynamical process that may vary with time according to intracellular treatment pressure and viral evolution. It is also a modification of a model presented in [12] and we adopt some of the terminology of that reference in naming the models. To avoid having too many parameters, the modelling of the intracellular replication cycle is simplified to involve only the two intracellular variables that are essential for RNA replication. Hence the intracellular model is given by :

\begin{align}
\frac{dU}{dt} &= \beta R \left(1 - \frac{U}{U_{\max}}\right) - \gamma U; \\
\frac{dR}{dt} &= \alpha U - \sigma R.
\end{align}

(1.2)

Here $R(t)$ is the number of positive genomic RNA strands that are available for transcription and translation. It does not include RNA which is packaged into the replication units which are responsible for the production of new virus RNA in hepatitis C. $U(t)$ is the number of RNA molecules within the replication units which are available as templates for RNA production with rate constant $\alpha$. On the other hand the RNA included in $R(t)$ serves as a template for the formation of replication units $U(t)$ with a maximal rate constant $\beta$. This leads to a replication feedback loop, where a large number of replication units can be formed and function at the same time in each cell [14]. However, replication units are embedded in a replication complex, including the vesicular membranous structure [15] [16], which requires a large amount of resources. Limitations on these resources give rise to a maximum number of replication units possible within a cell, $U_{\max}$. Thus, we assume here that the formation of replication units $U(t)$ is rate-limited by $\beta R \left(1 - \frac{U}{U_{\max}}\right)$. $R$ is lost by degradation with rate $\gamma$. In addition, we assume that replication units $U$ are intrinsically unstable, and that they are thus lost with a degradation rate constant $\gamma$. Although there are no data in vivo for $\gamma$, there are good indications in vitro that this rate is faster than the loss rate of infected cells ($d$) but slower than the viral clearance ($c$) according to [17].

The link between the intracellular replication dynamics (1.2) and the cellular infection dynamics (1.1) is mediated by replacing the constant production/release rate, $p$, in the cellular infection model with a time-dependent production/release rate $p(t) = \rho R(t)$ [12], where we assume that the packaged virus is exported on a rapid time scale. Thus, in this paper we consider the full intracellular and cellular
infection (ICCI) model in presence of treatment, given by the following system:

\[
\begin{aligned}
\frac{dT}{dt} &= s + r_I T \left(1 - \frac{T + I}{T_{\text{max}}}ight) - dT - \frac{bTV}{T + I}; \\
\frac{dI}{dt} &= r_I I \left(1 - \frac{T + I}{T_{\text{max}}}ight) + \frac{bTV}{T + I} - \delta I; \\
\frac{dV}{dt} &= \rho R I - cV - \frac{bTV}{T + I}; \\
\frac{dU}{dt} &= \beta R \left(1 - \frac{U}{U_{\text{max}}}ight) - \gamma U; \\
\frac{dR}{dt} &= \alpha \left(1 - \epsilon \right) U - \sigma R.
\end{aligned}
\]  

(1.3)

The system (1.3) is a modification of a system used in [12]. Note that the factor \(1 - \epsilon\) which represents the effect of treatment occurs in a different place in (1.3) than in (1.1). This implements the fact that, as discussed in [12], the primary effect of the DAA is to block the synthesis of RNA.

The initial conditions associated to system (1.3) are given by:

\[
T(0) = T_0, \quad I(0) = I_0, \quad V(0) = V_0, \quad U(0) = U_0, \quad R(0) = R_0.
\]  

(1.4)

where the constants \(T_0, I_0, V_0, U_0\) and \(R_0\) are positive. For biological significance of the parameters, four assumptions are employed. (a) Due to the burden of supporting virus replication, infected cells proliferate more slowly than uninfected cells, i.e. \(r_I \leq r_T\). (b) To have a physiologically realistic model, in an uninfected liver when \(T_{\text{max}}\) is reached, liver size should no longer increase, i.e. \(s \leq dT_{\text{max}}\). (c) Infected cells have a higher turnover rate than uninfected cells, i.e. \(\delta \geq \delta\). (d) The rapid first phase of viral decline is limited either by \(c\) or by \(\sigma\). If \(c < \sigma\), then the initial slope of decline is mainly due to the clearance of virus; if \(\sigma < c\), then this is due to the loss rate of genomic RNA and the export. If we assume that the first phase of viral decline is due to the viral clearance [17][18], then \(\sigma > c\). Hence the parameters are such that \(d \leq \delta < \gamma < c < \sigma\).

This paper is organized as follows. The positivity, global existence and boundedness of solutions are obtained in Section 2. The equilibria of system (1.3) are studied in Section 3 and the basic reproduction numbers of the virus-free equilibria are given. The local asymptotic stability of the virus-free steady states is established under appropriate conditions. It is shown that when both reproductive numbers are greater than one and \(r_I > \delta\) there exists at least one infected steady state. We identify conditions on the parameters under which the infected steady state is unique and further conditions under which it is locally asymptotically stable. Section 4 proves a result on the global asymptotic stability of the virus-free steady state \(E_0\). In Section 5 a condition on the parameters is identified under which every positive solution converges to a positive steady state. In Section 6 numerical simulations are carried out to illustrate the theoretical results obtained. Finally, a brief discussion concludes the paper.

2. Existence and global boundedness of solutions of the initial value problem (1.3)-(1.4)

2.1. Existence, uniqueness and positivity of local and global solutions of the initial value problem (1.3), (1.4). The main task of this subsection
is twofold. Firstly we are going to show that the solution cannot approach the boundary of the domain of definition of the system (1.3)-(1.4) arbitrarily closely and from this we deduce the positivity. Secondly we show that the solution of the initial value problem (1.3)-(1.4) is bounded on each finite time interval. It is well known by the fundamental theory of ordinary differential equations (ODE), that the system (1.3) has a unique local solution \((T(t), I(t), V(t), U(t), R(t))\) satisfying the initial conditions (1.4) since the right hand side of the system (1.3) is locally Lipschitz on the region where all the variables are positive.

**Lemma 2.1.** The infimum of \(T(t) + I(t)\) is different from zero for any positive solution on an interval \([0, t_0]\), where \(t_0 = \infty\) is allowed.

**Proof.** The evolution equation of \(T + I\) is given by:

\[
\frac{d}{dt}(T + I) = s + (r_T T + r_I I) \left( 1 - \frac{T + I}{T_{\text{max}}} \right) - dT - \delta I. \tag{2.1}
\]

If the infimum of \(T(t) + I(t)\) were zero then there would have to exist a time \(t_1 \in [0, t_0]\) such that \(T(t_1) + I(t_1) < T_{\text{max}}\). Let \(t_2\) be the infimum of the times \(t\) for which \(T(t) + I(t) < T_{\text{max}}\) on \((t, t_1)\). We do not know a priori if \(t_2 = 0\) or \(t_2 > 0\). Let \(a = \max\{d, \delta\}\). Then from (2.1) on \((t_2, t_1)\) we have

\[
\frac{d}{dt}(T + I) \geq s - a(T + I).
\]

Hence

\[
(T + I)(t_1) \geq (T + I)(t_2)e^{-a(t_1-t_2)} + sa^{-1}(1 - e^{-a(t_1-t_2)}).
\]

- If \(t_2 = 0\) then \((T + I)(t_2) = I(0) + T(0) > 0\).
- If \(t_2 > 0\) then \((T + I)(t_2) = T_{\text{max}} > 0\).

Thus in both cases we get a positive lower bound for \((T + I)(t_2)\). On the other hand \(e^{-a(t_1-t_2)} \geq e^{-a t_1}\). This contradicts the assumption that the infimum of \(T + I\) was zero and completes the proof. \(\square\)

**Remark 2.2.** As a consequence the solution cannot approach those points of the boundary of the domain of definition of system (1.3) where the right hand side of the equations does not have a continuous extension and therefore if a solution exists on an interval \([0, t_1]\) it satisfies a bound of the form \(T + I \geq C > 0\).

We show in the following proposition that solutions of the initial value problem (1.3)-(1.4) are positive which means that the model is well-posed biologically.

**Proposition 2.3.** Let \((T(t), I(t), V(t), U(t), R(t))\) be a solution of the initial value problem (1.3)-(1.4) on an interval \([0, t_1]\) with \(t_1 < +\infty\). If \(T_0 > 0\), \(I_0 > 0\), \(V_0 > 0\), \(U_0 > 0\) and \(R_0 > 0\) then

\[
\liminf_{t \to t_0} \min \{T(t), I(t), V(t), U(t), R(t)\} > 0.
\]

**Proof.** For convenience we introduce the notation \(X_1 = T\), \(X_2 = I\), \(X_3 = V\), \(X_4 = U\), \(X_5 = R\). Let \(t^*\) be the supremum of times \(t\) for which \(X_i(t) > 0\) on \([0, t]\) for all \(i \in \{1, 2, 3, 4, 5\}\). Each \(X_i\) satisfies an ordinary differential equation of the form

\[
\dot{X}_i = -X_i f_i(X) + g_i(X),
\]

where \(g_i\) are some functions of \((T, I, V, U, R)\) and \(g_i \geq 0\) for all \(i \in \{1, 2, 3, 4, 5\}\). As consequence \(\dot{X}_i \geq -X_i f_i(X)\) and \(\frac{d}{dt} \log X_i \geq -f_i(X)\) on \([0, t^*)\). Suppose that
Proof. We first claim that for any solution there is a time existence is positive and admits a positive lower bound for finite interval. By the arguments above the solution on a finite maximum interval of which shows that $t^* < t_1$. Hence $t = t^*$ and this completes the proof of the proposition.

It will now be shown that all solutions of (1.3)-(1.4) with positive initial data exist globally in time in the future.

Theorem 2.4. The initial value problem (1.3)-(1.4) admits a unique global solution defined on $[0, +\infty[$.

Proof. Taking the sum of equations (1.3a) and (1.3b) shows that
\[
\frac{d(T + I)}{dt} \leq s + \lambda(T + I),
\]
where $\lambda = \max\{r_I, r_T\}$. It follows from this differential inequality that $T$ and $I$ are bounded on any finite interval. Moreover, taking the sum of equations (1.3c) and (1.3d) shows that
\[
\frac{d(U + R)}{dt} \leq \kappa(U + R),
\]
where $\kappa = \max\{\alpha, \beta\}$, and hence $R$ and $U$ are bounded on any finite interval. Equation (1.3d) implies that
\[
\frac{dV}{dt} \leq \rho RI - cV,
\]
which shows that $V(t)$ cannot grow faster than linearly and is also bounded on any finite interval. By the arguments above the solution on a finite maximum interval of existence is positive and admits a positive lower bound for $T + I$. By the estimates just proved it is bounded. Hence it remains in a compact subset of the domain of definition of the system. The standard continuation criterion for ODE then implies global existence and this completes the proof of the theorem.

2.2. Global boundedness of the solutions for the initial value problem (1.3)-(1.4). We are now going to prove that the solution is globally bounded.

Theorem 2.5. For any positive solution $(T, I, V, U, R)$ of the initial value problem (1.3)-(1.4) and any $\zeta > 0$, we have that for $t$ sufficiently large:
\[
T(t) + I(t) \leq (1 + \zeta)p_0, \quad V(t) \leq \frac{(1 + \zeta)M}{c}, \quad U(t) \leq M_1 \text{ and } R(t) \leq M_2,
\]
with
\[
p_0 = \left(r_T - d + \left((r_T - d)^2 + \frac{4s r_T}{T_{\max}}\right)^{1/2}\right)\frac{T_{\max}}{2r_T} > 0, \quad M_1 = \max\{U(0), U_{\max}\};
\]
\[
M_2 = \frac{(1 + \zeta)\alpha}{\sigma}(1 - \epsilon)U_{\max} \quad \text{and} \quad M = (1 + \zeta)p_0 M_2.
\]

Proof. We first claim that for any solution there is a time $t_1 \geq 0$ such that $U(t_1) \leq U_{\max}$. Either $U(0) \leq U_{\max}$ in which case we can take $t_1 = 0$ or $U(0) > U_{\max}$. In the latter case let
\[
t_2 = \sup\{t \geq 0 : U(t) > U_{\max}\}.
\]
On interval $(0, t_2)$ we have $U(t) \leq U(0)e^{-\gamma t}$. It follows that $t_2 < +\infty$ and we can take $t_1 = t_2$. At any time where $U = U_{\max}$ the derivative of $U$ is negative. Thus $U$
becomes less than $U_{\text{max}}$ for $t$ slightly greater than $t_1$ and it can never again reach the value $U_{\text{max}}$. Hence $U(t) < U_{\text{max}}$ for all $t > t_1$. In particular $U$ is globally bounded by

$$\max\{U(0), U_{\text{max}}\}.$$  

We can now go with this information to the equation for $R$. From equation (1.3e) we obtain the differential inequality

$$\frac{dR}{dt} \leq \alpha (1 - \epsilon) U_{\text{max}} - \sigma R. \quad (2.2)$$

If we compare this differential inequality with the corresponding differential equation we can see that

$$\lim_{t \to +\infty} R(t) \leq \frac{\alpha}{\sigma} (1 - \epsilon) U_{\text{max}}.$$  

In particular this proves that $R$ is globally bounded.

Now adding the first two equations of system (1.3), yields

$$\frac{d(T + I)}{dt} = s + r_T (T - \frac{T + I}{T_{\text{max}}}) + r_I (1 - \frac{T + I}{T_{\text{max}}}) - dT - \delta I. \quad (2.3)$$

Since $d \leq \delta$ and $r_I \leq r_T$, it follows that

$$\frac{d(T + I)}{dt} \leq s + r_T (T + I) \left(1 - \frac{T + I}{T_{\text{max}}} \right) - d(T + I). \quad (2.4)$$

Setting $P = T + I$ the differential inequality (2.4) becomes

$$\frac{dP}{dt} \leq s + (r_T - d)P - \frac{r_T}{T_{\text{max}}} P^2. \quad (2.5)$$

The right hand side of (2.5) has a unique positive root given by

$$p_0 = \left(r_T - d + \left( (r_T - d)^2 + \frac{4sr_T}{T_{\text{max}}} \right)^{\frac{1}{2}} \right) \frac{T_{\text{max}}}{2r_T} > 0.$$  

Comparing a solution of (2.5) with a solution of the corresponding differential equation gives

$$\lim_{t \to +\infty} P(t) \leq p_0. \quad (2.6)$$

This proves that $T$ and $I$ are globally bounded.

Now consider the third equation of system (1.3). We have

$$\frac{dV}{dt} = \rho IR - cV - \frac{bTV}{T + I} \leq \rho RI - cV \leq M - cV,$$

where $M = (1 + \zeta)p_0 M_2$. Thus for all $t > 0$:

$$\frac{dV(t)}{dt} + cV(t) \leq M. \quad (2.7)$$

Solving (2.7) yields

$$V(t) \leq V(0) \exp(-ct) + \frac{M}{c}. \quad (2.8)$$
We deduce that,
\[
\lim \sup_{t \to +\infty} V(t) \leq \frac{M_c}{c}.
\]
This proves that \(V\) is globally bounded and completes the proof of Theorem 2.5. □

**Remark 2.6.** From the above results we have that any solution of the initial value problem (1.3), (1.4) enters the region:
\[
\Omega = \left\{ (T, I, V, U, R) \in \mathbb{R}^5_+ : 0 < T(t) + I(t) \leq 2p_0, 0 < V(t) \leq (1 + \zeta)M_c, 0 < U(t) \leq M_1, 0 < R(t) \leq M_2 \right\},
\]
and remains there.

### 3. Stability Analysis of the Full ICCI Model

#### 3.1. Equilibria and the basic reproduction numbers.
Consider the equilibria of the ICCI model. One important case is that where \(V = 0\), i.e. no virus is present. In a steady state with \(V = 0\) it follows from (1.3c) that \(R = 0\) or \(I = 0\). Consider first the possibility that \(I \neq 0\). Then (1.3d) implies that
\[
\left(1 - \frac{T + I}{T_{\max}}\right) = \frac{\delta}{r}.\]
Together with (1.3a) this implies that \(s = dT \left(1 - \frac{\delta r}{dT}\right)\). Under the given assumptions on the parameters this is a contradiction. Hence in fact \(I = 0\). It then follows from equation (1.3a) that \(T\) is equal to the quantity \(p_0\) introduced in the statement of Theorem 2.5. The quantities \(R\) and \(T\) are only constrained by the equations (1.3d) and (1.3e). In one solution \(U = R = 0\) and the only other possible solution has the explicit form
\[
U^* = U^*_1 = U_{\max} \left(1 - \frac{1}{\mathcal{R}_0'}\right), \quad R^* = R^*_1 = U_{\max} \frac{\gamma}{\beta} \left(\mathcal{R}_0' - 1\right),
\]
where \(\mathcal{R}_0' = \frac{\alpha \beta (1 - \epsilon)}{\gamma \sigma}\). A positive solution of this type exists precisely when \(\mathcal{R}_0' > 1\). The two virus-free equilibria are \(E_0 = (p_0, 0, 0, 0, 0)\) and \(E'_0 = (p_0, 0, 0, U^*_1, R^*_1)\).

At this point it is appropriate to comment on the notation \(\mathcal{R}_0'\) just introduced. It is an example of a concept often used in models for infection called the basic reproduction number. Intuitively the basic reproduction number \(\mathcal{R}_0\) is defined as the average number of secondary infections that occur when one infective is introduced into a completely susceptible host population [19, 20, 21]. Note that \(\mathcal{R}_0\) is also called the basic reproduction ratio [19] or basic reproductive rate [22]. It is implicitly assumed that the infected outsider is in the host population for the entire infectious period and mixes with the host population in exactly the same way that a population native would mix. A rigorous mathematical definition of the basic reproductive number and a method for calculating it are given in [21]. In fact this quantity is not a feature of a system of ODE as a whole but of a boundary equilibrium of such a system. Since we have just shown that in general the model (1.3) has two boundary equilibria it also has two basic reproduction numbers associated to it. That associated to \(E_0\) is \(\mathcal{R}_0\). It is referred to in [12] as the intracellular basic reproductive number. It defines the critical threshold of antiviral effectiveness for intracellular virus stability. The other, that associated to
$E'_0$, is what is referred to in [12] as the composite basic reproductive number. It is given by

$$R''_0 = \frac{b \rho R}{(b + c)(\delta - r_1(1 - \frac{p_u}{T_{\text{max}}})}).$$

It defines the critical threshold of antiviral effectiveness for extra-cellular virus stability, where $R = U_{\text{max}} \left( \frac{2}{3} - \frac{2}{3} \right)$ is the pre-treatment steady-state value for $R$.

3.2. The existence of infected equilibria. In this subsection, we investigate the existence of infected equilibria of the ODE system (1.3). Thus, let $E^* = (T^*, I^*, V^*, U^*, R^*)$ be an equilibrium point with infection, where $T^* > 0$, $I^* > 0$, $V^* > 0$, $U^* > 0$, $R^* > 0$. Note that a non-negative steady state automatically satisfies $T^* > 0$ and can only satisfy $I^* = 0$ or $R^* = 0$ if $V^* = 0$. In the latter case it is one of the virus-free steady states considered above. Thus any non-negative steady state other than the virus-free steady states is positive. It satisfies the following two algebraic systems:

$$\begin{cases}
  s + r_T T^* \left( 1 - \frac{T^* + I^*}{T_{\text{max}}} \right) - d T^* - \frac{b T^* V^*}{T^* + I^*} = 0, \\
  r_I I^* \left( 1 - \frac{T^* + I^*}{T_{\text{max}}} \right) + \frac{b T^* V^*}{T^* + I^*} - \delta I^* = 0, \\
  \mu I^* - c V^* - \frac{b I^* V^*}{T^* + I^*} = 0,
\end{cases} \tag{3.1}$$

and

$$\begin{cases}
  \beta R^* \left( 1 - \frac{U^*}{U_{\text{max}}} \right) - \gamma U^* = 0, \\
  \alpha (1 - \epsilon) U^* - \sigma R^* = 0.
\end{cases} \tag{3.2}$$

Note that (3.2) is decoupled from (3.1). Its unique positive solution, which only exists when $R'_0 > 1$, was given in the last section. It remains to solve (3.1) after substituting in the value of $R^*$ given by that positive solution.

Now let $\mu = \rho R^*$ and $X = \frac{T^*}{T_{\text{max}} + I^*}$. Thus, since $T^*$ and $I^*$ are positive, it follows that $0 < X < 1$. The system (3.1) can be rewritten in the form

$$\begin{cases}
  s + r_T T^* \left( 1 - \frac{T^* + I^*}{T_{\text{max}} X} \right) - d T^* - \frac{b T^* V^*}{T^* + I^*} = 0, \\
  r_I I^* \left( 1 - \frac{T^* + I^*}{T_{\text{max}} X} \right) + \frac{b T^* V^*}{T^* + I^*} - \delta I^* = 0, \\
  \mu I^* - c V^* - \frac{b I^* V^*}{T^* + I^*} = 0.
\end{cases} \tag{3.3}$$

If a positive steady state $(T^*, I^*, V^*)$ is given a corresponding value of $X$ can be calculated. Conversely, under an additional condition introduced below, $T^*$, $I^*$ and $V^*$ can be expressed in terms of $X$, as will now be shown. Solving the last equation of (3.3) with respect to $V^*$ gives

$$V^* = \frac{\mu}{c + b X} I^*. \tag{3.4}$$
Substituting (3.4) into the second equation of (3.3) yields

$$r_I I^* \left(1 - \frac{T^*}{T_{\max}X}\right) + b\frac{\mu}{c + bX} I^* X - \delta I^* = 0;$$

since $I^* \neq 0$, the previous equation implies that

$$r_I \left(1 - \frac{T^*}{T_{\max}X}\right) + \frac{b\mu X}{c + bX} - \delta = 0.$$

Thus,

$$T^* = \frac{T_{\max}X \left[b\mu X + (c + bX)(r_I - \delta)\right]}{r_I (c + bX)}.$$  \hspace{1cm} (3.5)

A sufficient condition for the positivity of the right hand side of (3.5) is that $r_I - \delta \geq 0$ and this assumption will be made from now on. We are not aware whether the right hand side of (3.5) is always positive in the absence of this assumption. Having calculated $T^*$ in terms of $X$ we can calculate $I^*$ using the relation $I^* = \frac{T^* (1 - X)}{X}$ and $V^*$ using (3.4). Under the assumption $0 < X < 1$ these quantities $(T^*, I^*, V^*)$ are positive. When do quantities defined in this way in terms of $X \in (0, 1)$ define a steady state of (3.1)? The equation defining $I^*$ shows that the equation originally used to define $X$ holds. It follows from (3.4) that the third equation of (3.3) holds and this implies the third equation of (3.1). The defining equation for $T^*$ together with (3.4) implies that the second equation of (3.1) holds. Substituting the expression for $(T^*, I^*, V^*)$ into the first equation of (3.3) and multiplying by $\frac{r_I}{c + bX}^2$ gives

$$sr_I^2 (c + bX)^2 + T_{\max}X \left[b(\mu + r_I - \delta)X + c(r_I - \delta)\right]$$

$$\times \left[b(\delta r_T - dr_I - \mu(r_T - r_I))X + c(\delta r_T - dr_I) - b\mu r_I\right] = 0;$$  \hspace{1cm} (3.6)

We see that under the assumption $r_I - \delta \geq 0$ positive steady states are in one to one correspondence with roots of a cubic polynomial $p(X)$ in the interval $(0, 1)$, where

$$p(X) = a_3 X^3 + a_2 X^2 + a_1 X + a_0$$

and

$$a_0 = c^2 sr_I^2,$$

$$a_1 = 2bc sr_I^2 + c T_{\max}(r_I - \delta)(c(\delta r_T - dr_I) - b\mu r_I),$$

$$a_2 = b^2 sr_I^2 + b T_{\max}((\mu + r_I - \delta)(c(\delta r_T - dr_I) - b\mu r_I)$$

$$+ c(r_I - \delta)(\delta r_T - dr_I - \mu(r_T - r_I))),$$

$$a_3 = b^2 T_{\max}(\mu + r_I - \delta)(\delta r_T - dr_I - \mu(r_T - r_I)).$$

The roots of the polynomial $p$ depend continuously on the parameters. If the parameters vary in a compact set then the roots cannot approach $X = 0$ since $a_0$ is bounded away from zero. On the other hand the roots might approach $X = 1$. Consider a sequence in parameter space which converges to a positive limit and a sequence of roots $X_n \in (0, 1)$ of $p$ corresponding to these parameter values with $\lim_{n \to \infty} X_n = 1$. Let $(T_n^*, I_n^*, V_n^*)$ be the corresponding sequence of positive steady states. $T_n^*$ converges to a positive limit. It follows that $I_n^* \to 0$ and $V_n^* \to 0$. 

Thus this sequence of steady states converges to a steady state on the boundary. We know the steady states on the boundary explicitly. Since in this limit two steady states approach each other the steady state in the limiting case must be degenerate. It will be shown in the next subsection that this can only happen when one of the basic reproduction numbers is one. Consider now a convergent sequence of parameters for which both reproduction numbers remain strictly greater than one. Then the corresponding sequence of roots of $p$ remains in a compact subset of $(0, 1)$. It follows that the number of roots of the polynomial, counting multiplicity, is independent of the parameters in this region modulo two.

Consider next what happens if $s$ tends to zero while the other parameters are held fixed. The polynomial $p$ converges to the product of $X$ with a quadratic polynomial $q$ and the the values of the roots can be read off. When $s = 0$ we have $p_0 = \frac{(r_T - d)T_{\text{max}}}{r_T}$. Under the assumption that $r_T > \delta$ one of the roots of $q$ is negative. The second factor in the denominator of the expression for $R_0''$ can be bounded below by $\delta \left(1 - \frac{r_T}{r_T + \sigma}\right)$, which is positive. Thus $R_0''$ is positive. If we make $\alpha$ large while fixing all other parameters then $R_0'$ and $R_0''$ can be made as large as desired, in particular greater than one. In this situation $\mu$ also becomes arbitrarily large and this implies that the other root of $q$ is also negative. $q$ tends to $-\infty$ when $|X|$ is large and $q(0) < 0$. Hence $p'(0) < 0$. It can be concluded that under these circumstances for $s$ small and positive, where $p'(0)$ remains negative but $p(0) > 0$, the polynomial $p$ has precisely one root in $(0, 1)$ and there exists precisely one infected steady state. Since we have now shown that there are points in this region of parameter space where this number is one it follows that it is always odd. In particular there always exists at least one positive steady state under these assumptions. There are always one, two or three positive steady states but we will not answer the question of whether there can be more than one in this paper.

Let us study the local stability of the uninfected equilibrium $E_0$.

### 3.3. Local stability of HCV uninfected equilibria.

**Proposition 3.1.** If $R_0 < 1$, then the uninfected equilibrium $E_0$ of the ODE model (1.3) is locally asymptotically stable.

**Proof.** The Jacobian matrix at $E_0$ of the ODE model (1.3) is given by

$$J(E_0) = \begin{pmatrix}
-a_{11} & -a_{12} & -b & 0 & 0 \\
0 & a_{22} & b & 0 & 0 \\
0 & 0 & -c - b & 0 & 0 \\
0 & 0 & 0 & -\gamma & \beta \\
0 & 0 & 0 & \alpha(1 - \epsilon) & -\sigma
\end{pmatrix},$$

where

$$a_{11} = \sqrt{(r_T - d)^2 + \frac{4sr_T}{T_{\text{max}}}} > 0, \quad a_{12} = \frac{p_0}{T_{\text{max}}}r_T > 0, \quad a_{22} = -\left[\delta + r_T \left(\frac{p_0}{T_{\text{max}}} - 1\right)\right] < 0.$$  

The characteristic polynomial $P_J$ associated to $J(E_0)$ is given by

$$P_J(X) = (-a_{11} - X)(a_{22} - X)(-c - b - X)\left(X^2 + (\gamma + \sigma)X + \gamma\sigma - \alpha(1 - \epsilon)\beta\right).$$

Since $-a_{11} < 0, a_{22} < 0$ and $-(b + c) < 0$, the real part of the roots of $P_J$ are negative if and only if the roots of the quadratic polynomial defined by:

$$T(X) = X^2 + (\gamma + \sigma)X + \gamma\sigma - \alpha(1 - \epsilon)\beta$$  \hspace{1cm} (3.7)
have negative real part. Applying the Routh-Hurwitz criterion to the previous quadratic equation, the roots of \( T(X) \) have negative real part if and only if

\[
0 < \gamma \sigma - \alpha (1 - \epsilon) \beta,
\]

which is equivalent to

\[
1 > \frac{\alpha \beta (1 - \epsilon)}{\gamma \sigma},
\]

i.e.,

\[
\mathcal{R}_0' < 1.
\]

which completes the proof of the proposition 3.1.

Proposition 3.2. If \( \mathcal{R}_0' > 1 \) and \( \mathcal{R}_0'' < 1 \), then the second uninfected equilibrium \( E_0' \) of the ODE model (1.3) is locally asymptotically stable.

Proof. The Jacobian matrix associated to the ODE model (1.3) at \( E_0' \) is given by

\[
J(E_0') = \begin{pmatrix}
-a_{11} & -a_{12} & -b & 0 & 0 \\
0 & a_{22} & b & 0 & 0 \\
0 & \rho R^* & -c - b & 0 & 0 \\
0 & 0 & 0 & -\beta e_{44} - \gamma & \beta (1 - e_{45}) \\
0 & 0 & 0 & \alpha (1 - \epsilon) & -\sigma
\end{pmatrix},
\]

where

\[
e_{44} = \frac{R^*}{U_{\text{max}}} > 0, \quad e_{45} = \frac{U^*}{U_{\text{max}}} > 0,
\]

and \( a_{11}, a_{12}, a_{22} \) are defined in the same way as in the previous proof. The characteristic polynomial \( P_J(X) \) associated to \( J(E_0') \) is the product of a quadratic polynomial generalizing the polynomial \( T \) introduced above with a cubic polynomial. The signs of the coefficients in the quadratic polynomial remain the same and thus its roots have negative real parts. The cubic contains a factor \( X + a_{11} \) and so to show that all eigenvalues of the linearization have negative real part it suffices to control the roots of the remaining quadratic polynomial. It is given by

\[
X^2 + (-a_{22} + b + c) X - a_{22} (b + c) - b \rho R^*.
\]

The coefficient of \( X \) is negative and so it is enough to show that the constant term is positive.

\[
-a_{22} (b + c) - b \rho R^* = \rho \left( \frac{1}{\mathcal{R}_0'' - 1} \right) b \rho \bar{R} + b \rho (\bar{R} - R^*) > 0
\]

when \( \mathcal{R}_0'' < 1 \) since \( \bar{R} > R^* \). This completes the proof of the proposition 3.2.

Now let us study the local stability of infected equilibria.

3.4. Local stability of HCV infected equilibria.

Proposition 3.3. If \( \mathcal{R}_0 > 1, \mathcal{R}_0'' > 1, s \) is sufficiently small and \( \alpha \) and \( b \) sufficiently large then the unique equilibrium with infection \( E^* \) of the ODE model (1.3) is locally asymptotically stable.
Proof. The Jacobian matrix at $E^*$ of the ODE model (1.3) is given by:

$$
J(E^*) = \begin{pmatrix}
-a_1 & b_1 & -\frac{bT^*}{T^* + I^*} & 0 & 0 \\
\frac{bT^*}{(T^* + I^*)^2} & -a_2 & -b_2 & 0 & 0 \\
-b_2 & \frac{bT^*}{(T^* + I^*)^2} & -c - \frac{\beta R^* - \gamma}{T_{\text{max}}} & 0 & 0 \\
0 & 0 & 0 & -\frac{\beta R^*}{T_{\text{max}}} - \gamma & \beta \left(1 - \frac{U}{T_{\text{max}}}\right)
\end{pmatrix},
$$

where

$$
\begin{align*}
a_1 &= d - r_T + \frac{2r_T T^*}{T_{\text{max}}} + \frac{r_T I^*}{T_{\text{max}}} + \frac{bI^* V^*}{(T^* + I^*)^2}, \\
a_2 &= -\frac{r_T I^*}{T_{\text{max}}} + \frac{bI^* V^*}{(T^* + I^*)^2}, \\
b_1 &= -\frac{r_T T^*}{T_{\text{max}}} + \frac{bI^* V^*}{(T^* + I^*)^2}, \\
b_2 &= \delta - r_T + \frac{r_T T^*}{T_{\text{max}}} + \frac{2r_T I^*}{T_{\text{max}}} + \frac{bT^* V^*}{(T^* + I^*)^2}.
\end{align*}
$$

This matrix is block triangular and thus its characteristic polynomial is the product of those of the top left $3 \times 3$ matrix and the bottom right $2 \times 2$ matrix. The latter is equal to a polynomial we studied in the previous case and thus its roots have negative real parts. It remains to analyse the other factor, call it

$$
P_1(X) = X^3 + \lambda_2 X^2 + \lambda_1 X + \lambda_0 \quad (3.9)
$$

where

$$
\begin{align*}
\lambda_2 &= (\delta - r_I) + (d - r_T) + c + \frac{bT^*}{T^* + I^*} + \frac{bV^* I^*}{(T^* + I^*)^2} + \frac{(T^* + I^*)(r_T + r_I) + r_T T^* + r_I I^*}{T_{\text{max}}} \\
&+ \frac{bT^* V^*}{(T^* + I^*)^2}, \\
\lambda_1 &= c \left( d - r_T + \frac{2r_T T^*}{T_{\text{max}}} + \frac{r_T I^*}{T_{\text{max}}} + \frac{bI^* V^*}{(T^* + I^*)^2} \right) + \left( \delta - r_I + \frac{r_T T^*}{T_{\text{max}}} + \frac{2r_T I^*}{T_{\text{max}}} \right) \left( c + \frac{bT^*}{T^* + I^*} + d - r_T \\
&+ \frac{2r_T T^*}{T_{\text{max}}} + \frac{bV^* I^*}{(T^* + I^*)^2} \right) + \frac{bT^*}{T_{\text{max}}} \left( d - r_T + \frac{2r_T T^*}{T_{\text{max}}} + \frac{r_T I^*}{T_{\text{max}}} \right) + \frac{r_T I^*}{T_{\text{max}}} \left( \delta - r_I + \frac{2r_T T^*}{T_{\text{max}}} \right) \\
&+ \frac{bT^* V^*}{T_{\text{max}}(T^* + I^*)^2} + \frac{bT^* V^*}{(T^* + I^*)^2} \left( \rho R^* + d - r_T + \frac{2r_T T^*}{T_{\text{max}}} + \frac{r_T I^*}{T_{\text{max}}} \right) \\
&+ \frac{bT^*}{T_{\text{max}}(T^* + I^*)^2} - \rho R^* bT^* \\
&+ \frac{bT^*}{T_{\text{max}}(T^* + I^*)^2} - \rho R^* bT^* \\
&+ \frac{bT^*}{T_{\text{max}}(T^* + I^*)^2} - \rho R^* bT^* \\
&+ \frac{bT^*}{T_{\text{max}}(T^* + I^*)^2} - \rho R^* bT^* \\
\lambda_0 &= c \left( d - r_T + \frac{r_T (2T^* + I^*)}{T_{\text{max}}} + \frac{bI^* V^*}{(T^* + I^*)^2} \right) \left( \delta - r_I + \frac{r_T (T^* + 2I^*)}{T_{\text{max}}} \right) \\
&+ \frac{bT^*}{T_{\text{max}} + I^*} \left( d - r_T + \frac{r_T (2T^* + I^*)}{T_{\text{max}}} \right) \left( \delta - r_I + \frac{r_T (T^* + 2I^*)}{T_{\text{max}}} \right) \\
&+ \frac{r_T I^*}{T_{\text{max}}} \left( c + \frac{bT^*}{T^* + I^*} \right) \left( \frac{bT^* V^*}{(T^* + I^*)^2} - \frac{r_T T^*}{T_{\text{max}}(T^* + I^*)^2} \right) \\
&+ \frac{bT^* V^*}{(T^* + I^*)^2} \left( d - r_T + \frac{2r_T I^*}{T_{\text{max}}} + \frac{r_T T^*}{T_{\text{max}}} + \frac{r_T bT^* V^*}{T_{\text{max}}(T^* + I^*)^2} + \frac{bI^* (T^* V^*)^2}{(T^* + I^*)^5} (T^* + I^* - 1) \right) \\
&+ \frac{\rho R^* T^*}{T_{\text{max}}(T^* + I^*)^2} - \frac{\rho T^* R^*}{T_{\text{max}}(T^* + I^*)^2}.
\end{align*}
$$
The expressions for the coefficients $\lambda_i$ are so complicated that we have not succeeded in analyzing them in general. Instead we concentrate on obtaining information in the limiting regime in which the existence of a unique steady state was obtained, i.e. that where $s$ is small. When $s$ tends to zero the steady state tends to the point where the coordinates take the values $T^* = 0$, $I^* = \frac{(r_I - \delta)T_{\text{max}}}{c r_I}$ and $V^* = \frac{\rho R_t(r_I - \delta)T_{\text{max}}}{c r_I}$.

It will be shown that under certain conditions the eigenvalues of the linearization about this point with $s = 0$ all have negative real parts. It then follows by continuity that the same is true for the steady state with $s$ positive and sufficiently small.

When $s = 0$ the coefficients have the following forms

$\lambda_2 = (\delta - r_I) + (d - r_T) + c + \frac{b V^*}{T_{\text{max}}} + \frac{(r_I + 2r_I I^*)}{T_{\text{max}}} \tag{3.10}$

$\lambda_1 = c \left( d - r_T + \frac{r_I I^*}{T_{\text{max}}} + \frac{b V^*}{I^*} \right) + \left( \delta - r_I + \frac{2r_I I^*}{T_{\text{max}}} \right) \tag{3.11}$

$\lambda_0 = c \left( d - r_T + \frac{r_I I^*}{T_{\text{max}}} + \frac{b V^*}{I^*} \right) \left( \delta - r_I + \frac{2r_I I^*}{T_{\text{max}}} \right) \tag{3.12}$

Note that $\delta - r_I + \frac{2r_I I^*}{T_{\text{max}}} = r_I - \delta > 0$. Now choose values of the parameters such that a unique steady state exists. Then make $b$ large while fixing all the other parameters. Then for $b$ large $\lambda_2$, $\lambda_1$ and $\lambda_0$ are all positive for $b$ large and grow like a constant multiple of $b$. The combination $\lambda_1 \lambda_2 - \lambda_0$ is positive for $b$ large and grows like a constant multiple of $b^2$. Applying the Routh-Hurwitz criterion this completes the proof of proposition 3.3. \hfill \square

4. Global stability analysis of the full ICCI model (1.3)

**Theorem 4.1.** Under the conditions $M_2 \leq R_0' \leq 1$ and $R_0'' \leq \tau_0 \leq 1$, where

$$\tau_0 = \frac{b \rho R}{(b + c)(\delta - r_I)}$$

is a positive constant, the uninfected equilibrium point $E_0$ of the full ICCI ODE model (1.3) is globally asymptotically stable in the positively-invariant region $\Omega$.

**Proof.** Consider the Lyapunov function defined on $\mathbb{R}_+$ by

$$L(t) = \rho R I(t) + (\delta - r_I) V(t) + \beta R(t) + \sigma U(t).$$

$L$ is defined, continuously differentiable and positive definite for all $T > 0$, $I > 0$, $V > 0$, $U > 0$, $R > 0$. It is easy to see that $L$ reaches its global minimum when the solution is at the infection-free equilibrium $E_0$. Further, the function $L$, along the
solutions of system (1.3), satisfies:

\[
\frac{dL}{dt} = \rho R r_1 I \left(1 - \frac{T + I}{T_{\text{max}}} \right) + \rho R b TV \frac{T + I}{T_{\text{max}}} - \rho R I (\delta - r_1) - \rho R I (\delta - r_1) - e V (\delta - r_1) - b (\delta - r_1) \frac{TV}{T + I} + \alpha \beta (1 - \epsilon) U - \alpha \beta \rho + \sigma \beta R \left(1 - \frac{U}{U_{\text{max}}} \right) - \sigma \gamma U,
\]

\[
\leq \rho R b TV \frac{T + I}{T_{\text{max}}} - c (\delta - r_1) \frac{TV}{T + I} - b (\delta - r_1) \frac{TV}{T + I} - \rho R r_1 I \frac{T + I}{T_{\text{max}}} + \rho R r_1 I \frac{T + I}{T_{\text{max}}}
\]

\[
+ (M_2 - R) \rho I (\delta - r_1) + \alpha \beta (1 - \epsilon) U - \sigma \beta R + \sigma \beta R \left(1 - \frac{U}{U_{\text{max}}} \right) - \sigma \gamma U.
\]

Since \( \frac{T}{T_{\text{max}}} \leq 1 \), then \(-V \leq -\frac{TV}{T_{\text{max}}} \). Moreover, in the positively invariant set, \( R(t) \leq M_2 \). Thus,

\[
\frac{dL}{dt} \leq \frac{TV}{T + I} (b \rho R (b + c) (\delta - r_1)) + \rho I (M_2 - R) (\delta - r_1),
\]

\[
+ \alpha \beta (1 - \epsilon) U - \sigma \beta R + \sigma \beta R - \sigma \gamma U,
\]

\[
\leq \frac{TV}{T + I} (b \rho R (b + c) (\delta - r_1)) + \rho I (M_2 - R) (\delta - r_1),
\]

\[
+ \alpha \beta (1 - \epsilon) - \sigma \gamma U,
\]

\[
\leq (b + c) (\delta - r_1) \frac{TV}{T + I} \left( \frac{b \rho R}{(b + c) (\delta - r_1)} - 1 \right) + \left( \frac{\alpha \beta (1 - \epsilon)}{\sigma \gamma} - 1 \right) \sigma \gamma U
\]

\[
+ \rho I (M_2 - R) (\delta - r_1).
\]

It follows that

\[
\frac{dL}{dt} \leq (b + c) (\delta - r_1) \frac{TV}{T + I} \left( \frac{b \rho R}{(b + c) (\delta - r_1)} - 1 \right) + (R - R) (\delta - r_1) + (R - R) (\delta - r_1).
\]

\[
\leq (b + c) (\delta - r_1) \frac{TV}{T + I} (\tau - 1) + (R - R) (\delta - r_1) + (R - R) (\delta - r_1).
\]

It is clear that the condition \( \tau_0 \leq 1 \) and \( M_2 \leq R \) \( \leq 1 \) give \( \frac{dL}{dt} \leq 0 \) for all \( T > 0 \), \( I > 0 \), \( V > 0 \), \( U > 0 \), \( R > 0 \). Therefore, the largest compact invariant subset of the set

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

is the singleton \( \{ E_0 \} \). By the Lasalle invariance principle [23], the uninfected equilibrium point is globally asymptotically stable if \( M_2 \leq R \) \( \leq 1 \) and \( \tau_0 \leq 1 \). So, we obtain a sufficient condition \( R_0 \leq \tau_0 \) which ensures that the HCV-uninfected equilibrium \( E_0 \) of ODE-model system (1.3) is globally asymptotically stable if \( \tau_0 < 1 \). This completes the proof of theorem 1.1. \( \square \)
5. Global convergence to infected equilibria

Consider first the system (1.3d)-(1.3e) describing the intracellular dynamics. Its linearization at any point of the positive orthant has the property that both off-diagonal elements are negative. Thus it is a competitive system and since all solutions exist globally and are bounded it follows that any positive solution converges to a steady state [24]. Next consider any positive solution of the full system (1.3a)-(1.3e) and any $\omega$-limit point of that solution. There is a non-negative solution which passes through that $\omega$-limit point. Since the projection of the original solution onto its last two components converges to a steady state, the limiting solution has the property that $U$ and $R$ have the constant values $(0, 0)$ or $(U^*, R^*)$. Its projection onto the first three coordinates is a solution of the system obtained from (1.3a)-(1.3c) by fixing $R$ to be equal to 0 or $R^*$. In the case $R = 0$ the function $V$ is a Lyapunov function for the projected solution and it must converge to zero. If we again pass to an $\omega$-limit point and a solution passing through it we get a solution of the system obtained by setting $V = 0$ and projecting on the first two coordinates. The resulting two-dimensional system is again competitive and so the solution must converge to a steady state. This system has no positive steady states and so the convergence must be to a point of the boundary. On the boundary $I = 0$ the only steady state is given by $T = p_0$. The boundary $T = 0$ consists entirely of steady states. It is a centre manifold of any of its points and the non-zero eigenvalue of the linearization at any of these points is positive. Thus no solution can approach a point of this type. It can be concluded that the original solution converges to the point $E_0$.

It remains to analyse the case $R = R^*$. For this it suffices to study the late time behaviour of the system (1.3a)-(1.3c) with $R = R^*$ and so we will now concentrate on that system and apply the geometric approach of [25]. In doing this we use the quantity

$$\hat{T} = \frac{T_{\text{max}}}{2r_I} \left[ r_I - \delta + \sqrt{(r_I - \delta)^2 + \frac{4sr_I}{T_{\text{max}}}} \right].$$

It follows from Theorem 2.5 that for any constant $\zeta > 0$ any solution satisfies $T + I \leq (1 + \zeta)p_0$ for $t$ sufficiently large. By a very similar argument to that used in the proof of that theorem $T + I \geq (1 - \zeta)\hat{T}$ for $t$ large. To prove the main result of this section we need the following lemma.

**Lemma 5.1.** If $R''_0 > 1$ then the system (1.3a)-(1.3c) with $R = R^*$ is uniformly persistent.

**Proof.** This result follows from an application of Theorem 4.3 in [26] with $X = \mathbb{R}^3$ and $E = \Omega$. The maximal invariant set $M$ on the boundary $\partial\Omega$ is the singleton $\{E_0\}$, and it is isolated. From Theorem 4.3 in [26] we can see that the uniform persistence of the system (1.1) is equivalent to the instability of the disease-free equilibrium $E_0$. On the other hand, we have proved in Theorem 4.1 that $E_0$ is unstable if $R''_0 > 1$. Thus, the system (1.3a)-(1.3c) with $R = R^*$ is uniformly persistent when $R''_0 > 1$. \hfill $\square$

**Theorem 5.2.** Suppose that the following inequality holds

$$\xi = \max \left\{ r_T - d + \frac{(r_T + r_T)p_0}{T_{\text{max}}} - \frac{r_T T_{\text{max}}}{T_{\text{max}}} + 2b; r_I - \delta + \frac{(r_I + r_T)p_0}{T_{\text{max}}} - \frac{r_I T_{\text{max}}}{T_{\text{max}}} + 2b \right\} < 0.$$
Then every positive solution of the system (1.3a)-(1.3c) with $R = R^*$ converges to a steady state. If $R_0^m > 1$ then every positive solution converges to a positive steady state.

**Proof.** Any positive solution of (1.3a)-(1.3c) is bounded and so has a non-empty $\omega$-limit set and that set is connected. Consider an $\omega$-limit point on the boundary of the positive orthant and a solution passing through that point at some time. It lies entirely in the $\omega$-limit set of the original solution and so, in particular, is non-negative. If $V$ were zero at that point and $I \neq 0$ then the evolution equation for $V$ would imply that the limiting solution was negative slightly before the initial time, a contradiction. Hence for a point of this type $V = 0$ implies $I = 0$. By a similar argument the evolution equation for $T$ implies that $T > 0$ at such a point. Finally the evolution equation for $I$ implies that if $I = 0$ then $V = 0$. Thus the only possible $\omega$-limit point is $(p_0, 0, 0)$. The set of steady states is finite and therefore discrete. Hence if a solution does not converge to a steady state then by connectedness its $\omega$-limit set must contain points which are not steady states and which are contained in the positive orthant. These are non-equilibrium non-wandering points (see [25] for the terminology). This implies that there exists a periodic solution of a system which is a small perturbation of the original one ([25], Lemma 2.1). This is impossible if the quantity $\tilde{q}_2$ in [25] is negative ([25], Theorem 3.1). Thus to prove the theorem it suffices to show that the inequality assumed as a hypothesis implies that $\tilde{q}_2 < 0$. This will now be done, following closely an argument given in [25].

The Jacobian matrix $J$ associated with a general solution to (1.3a)-(1.3c) is

$$J = \begin{pmatrix} \frac{bV}{(T+I)^2} - \frac{rT}{T_{\text{max}}} & \frac{bTV}{(T+I)^2} & q \rho R^* + \frac{bTV}{(T+I)^2} - c \frac{bT}{T+I} \\ \frac{bV}{(T+I)^2} - \frac{rT}{T_{\text{max}}} & \frac{bTV}{(T+I)^2} - \frac{bT}{T+I} & \frac{bT}{T+I} \\ \frac{bV}{(T+I)^2} & \frac{bTV}{(T+I)^2} & \frac{bT}{T+I} \end{pmatrix},$$

with $p = rT - d - \frac{2rT}{T_{\text{max}}} - \frac{rT}{T_{\text{max}}} - \frac{bV}{(T+I)^2}$ and $q = rT - \delta - \frac{rT}{T_{\text{max}}} - \frac{2T}{T_{\text{max}}} - \frac{bV}{(T+I)^2}$.

The second additive compound matrix $J^{[2]}$ is

$$J^{[2]} = \begin{pmatrix} \frac{p + q}{(T+I)^2} & \frac{bT}{T+I} & \frac{bT}{T+I} \\ \frac{bV}{(T+I)^2} & \frac{bTV}{(T+I)^2} - \frac{rT}{T_{\text{max}}} & \frac{bT}{T+I} \\ \frac{bV}{(T+I)^2} & \frac{bTV}{(T+I)^2} & \frac{bT}{T+I} \end{pmatrix}.$$

We consider the matrix $P = \text{diag}\{1, \frac{1}{V}, \frac{1}{V}\}$. It follows then that

$$P J P^{-1} - \begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix}$$

with $' = \frac{d}{dt}$ and where the matrix $P J P^{-1}$ is obtained by replacing each entry $p_{ij}$ of $P$ by its derivative in the direction of the solution of (1.1).

Furthermore, we have

$$B = P J P^{-1} + P J^{[2]} P^{-1} = \begin{pmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{pmatrix},$$

where $B_{11} = \frac{bT}{T+I} - \frac{rT}{T_{\text{max}}}$ and $B_{12} = \frac{bTV}{(T+I)^2} - \frac{rT}{T_{\text{max}}}$.
where

\[ B_{11} = p + q, \]
\[ B_{12} = \frac{bTV}{I(T+I)} \frac{bTV}{I(T+I)}, \]
\[ B_{21} = \left( \frac{\rho R^* I}{V} + \frac{bTI}{(T+I)^2} \right), \]
\[ B_{22} = \left( \frac{i}{I} \frac{\dot{V}}{V} - c + p - \frac{bT}{T+I} \left\| I \frac{\dot{V}}{V} - c + q - \frac{bT}{T+I} \right\| \right) \]

Define the norm in \( \mathbb{R}^3 \) as \( ||(x, y, z)|| = \max\{|x|, |y|, |z|\} \) for \((x, y, z) \in \mathbb{R}^3\). Then the Lozinskii measure \( \mu \) with respect to the norm \( \| \cdot \|_1 \) can be estimated as follows (see [27]): we have

\[ \mu(B) \leq \sup\{g_1, g_2\}, \quad (5.1) \]

where:

\[ g_1 = \mu_1(B_{11}) + \|B_{12}\|_1 \text{ and } g_2 = \|B_{21}\|_1 + \mu_1(B_{22}). \]

Here \( \mu_1 \) denotes the Lozinskii measure with respect to the \( \| \cdot \|_1 \) vector norm, and \( B_{12} \) and \( B_{21} \) are matrix norms with respect to the \( \| \cdot \|_1 \) norm. Moreover, we have

\[ \mu_1(B_{11}) = p + q, \quad \|B_{12}\|_1 = \frac{bTV}{I(T+I)}, \quad \|B_{21}\|_1 = \frac{\rho R^* I}{V} + \frac{bT}{T+I}. \]

To calculate \( \mu_1(B_{22}) \), add the absolute value of the off-diagonal elements to the diagonal one in each column of \( B_{22} \), and then take the maximum of two sums. Thus, for \( t \) sufficiently large,

\[ \mu_1(B_{22}) = \max \left\{ \frac{i}{I} \frac{\dot{V}}{V} - c + p - \frac{bT}{T+I} + \left| \frac{bIV}{(T+I)^2} - \frac{r_I I}{T_{\max}} \right|, \frac{i}{I} \frac{\dot{V}}{V} - c + q - \frac{bT}{T+I} \right\} \]

\[ \leq \frac{i}{I} \frac{\dot{V}}{V} - c + \max \left\{ r_T - d - \frac{2r_T}{T_{\max}}, \frac{r_I I}{T_{\max}} \right\} + \left| \frac{bIV}{(T+I)^2} - \frac{r_I I}{T_{\max}} \right| \]

\[ \leq \frac{i}{I} \frac{\dot{V}}{V} - c + \max \left\{ r_T - d - \frac{2r_T}{T_{\max}}, \frac{r_I I}{T_{\max}} \right\} + \left| \frac{bIV}{(T+I)^2} - \frac{r_I I}{T_{\max}} \right| \]

In the last inequality it has been used that any solution satisfies \( T + I \leq (1 + \zeta) p_0 \) and \( T + I \geq (1 - \zeta) \bar{T} \) for \( t \) sufficiently large. Note that the inequality in the statement of the theorem implies that there exists \( \zeta > 0 \) for which the analogous inequality holds where \( p_0 \) is replaced by \( \bar{p}_0 = (1 + \zeta) p_0 \) and \( \bar{T} \) by \( \bar{T} = (1 - \zeta) \bar{T} \).

From the second and third equations of (1.1), we have

\[ \frac{i}{I} = r_T \left( 1 - \frac{T + I}{T_{\max}} \right) + \frac{bTV}{I(T+I)} - \delta, \]
\[ \frac{\dot{V}}{V} = \frac{\rho R^* I}{V} - c - \frac{bT}{T+I}. \]
Hence,

$$g_1 = p + q + \frac{bTV}{T(T+1)},$$

$$= \frac{i}{\bar{T}} + r_T - d - \frac{r_T}{T_{\text{max}}} - \frac{r_T}{T_{\text{max}}} - \frac{bV}{T + T},$$

$$\leq \frac{i}{\bar{T}} + r_T - d + \frac{(r_I + r_T)\bar{p}_0}{T_{\text{max}}} - \frac{r_T}{T_{\text{max}}},$$

$$g_2 \leq \frac{\rho R^2 I}{V} + \frac{bT}{\bar{T} + I} + \frac{i}{\bar{T}} - \frac{\bar{V}}{\bar{T}} - c + \max \left\{ r_T - d + \frac{(r_I + r_T)\bar{p}_0}{T_{\text{max}}} - \frac{r_T}{T_{\text{max}}}; r_I - \delta + \frac{(r_I + r_T)\bar{p}_0}{T_{\text{max}}} - \frac{r_T}{T_{\text{max}}} \right\}.$$

$$\leq \frac{i}{\bar{T}} + \frac{2b}{\bar{T} + I} + \max \left\{ r_T - d + \frac{(r_I + r_T)\bar{p}_0}{T_{\text{max}}} - \frac{r_T}{T_{\text{max}}}; r_I - \delta + \frac{(r_I + r_T)\bar{p}_0}{T_{\text{max}}} - \frac{r_T}{T_{\text{max}}} \right\},$$

$$\leq \frac{i}{\bar{T}} + \max \left\{ r_T - d + \frac{(r_I + r_T)\bar{p}_0}{T_{\text{max}}} - \frac{r_T}{T_{\text{max}}}; r_I - \delta + \frac{(r_I + r_T)\bar{p}_0}{T_{\text{max}}} - \frac{r_T}{T_{\text{max}}} \right\}.$$

Therefore, 

$$\mu(B) \leq \frac{i}{\bar{T}} + \xi,$$

is valid for \( t \geq t_1 \), where \( t_1 \) is a sufficiently large positive constant. Along each solution \( (T(t), I(t), V(t)) \) of model (1.1) with \( (T_0, I_0, V_0) \in K \), where \( K \) is the compact absorbing set and exists by Theorem 2.5 and Lemma 5.1, we have

$$\frac{1}{t} \int_0^t \mu(B) ds \leq \frac{1}{t} \int_0^{t_1} \mu(B) ds + \frac{1}{t} \log \left( \frac{I(t)}{I(t_1)} \right) + (t - t_1) \xi,$$

$$\leq \frac{1}{t} \int_0^{t_1} \mu(B) ds + \frac{1}{t} \log \left( \frac{I(t)}{I(t_1)} \right) + (t - t_1) \xi.$$

The boundedness of \( I \) implies that

$$\lim_{t \to +\infty} \sup_{\gamma_0 \in K} \frac{1}{t} \int_0^t \mu(B) ds \leq \xi < 0.$$

Thus, 

$$q_2 = \lim_{t \to +\infty} \sup_{\gamma_0 \in K} \frac{1}{t} \int_0^t \mu(B) ds \leq \xi < 0.$$

This completes the proof that each solution converges to a steady state. It remains to note that it has already been shown that when \( R_0'' > 1 \) no solution can converge to a steady state on the boundary. \( \square \)

6. Numerical simulations

In this section, we present some numerical simulations to complement the theoretical results obtained in the previous sections.

Figure 1 illustrates the case \( R_0' < 1 \) and \( R_0'' < 1 \). From this figure, we observe that the trajectories converge to the HCV-free equilibrium \( E_0 \). This corresponds to


Figure 1. Simulations of Initial value problem (1.3) using various initial conditions when $s = 3 \times 10^4$; $d = 2 \times 10^{-3}$; $r_T = 3 \times 10^{-2}$; $r_I = 10^{-3}$; $T_{\text{max}} = 10^6$; $b = 5.44 \times 10^{-4}$; $\delta = 0.0987$; $c = 8 \times 10^{-1}$; $\rho = 0.8898$; $\alpha = 30$; $\epsilon = 0.95$; $\sigma = 30$; $U_{\text{max}} = 30$; $\gamma = 0.5$; $E_0 = (9.439273688 \times 10^7, 0, 0, 0, 0)$ (Such that $R_0' = 0.95$ and $R_0'' = 0.0552$).

the case where the equilibrium is globally asymptotically stable. In this case, the infection could disappear within the host.

Figure 2 illustrates the case $R_0'' < 1$ and $R_0' > 1$. We observe that the trajectories converge to the second HCV-free equilibrium $E'_{0}$. This corresponds to the case where $E'_{0}$ is globally asymptotically stable. In this case, the infection could disappear within the host but the viral replication units will persist.

Figure 3 illustrates the case corresponding to $R_0' > 1$ and $R_0'' > 1$. From this figure, it is seen that the trajectories converge to an infected equilibrium $E^*$. In this case, the infection persists within the host.

Apart from, numerical solutions of ODE model system (1.3), we also complete the numerical simulations by phase portrait in TIV space and TUR space.

7. Conclusion

In order to better understand the dynamics of HCV viral infection, this paper presents a mathematical study on the global dynamics of improved HCV models based on system (3) in [12]. In this work, we have studied the models describing the dynamics of the hepatitis C viral cellular and intracellular infection model with logistic cellular growth. The model includes five equations illustrating the
interaction between the uninfected cells, infected cells, HCV virus, positive genomic RNA strands and negative strands. The global existence, the positivity and the boundedness of solutions are established. The existence of an infected steady state is also established for certain values of the parameters. Furthermore, we have studied the local stability of both uninfected equilibrium and infected equilibrium. Concerning global asymptotic stability, that of an uninfected equilibrium point was established by the construction of a suitable Lyapunov function. It was also shown using the Li-Muldowney global-stability criterion that for certain values of the parameters every solution converges to a steady state. Finally, we performed numerical simulations to illustrate the theoretical results obtained. It would be interesting to incorporate time delay or spatial dependence into the current model. These two challenges will be the concerns of future investigation.

A number of the conclusions of the paper required making restrictions on the parameters of the model. It would be desirable to investigate what happens when these restrictions are removed; which of the conclusions extend? It would also be desirable to understand the biological meaning of these restrictions. Let us just comment on one of these, the inequality $r_I - \delta > 0$. This means, roughly speaking, that if all the liver cells were infected the liver would be able to sustain itself. Note that in practise it could be that during a chronic hepatitis C infection most of the
Figure 3. Simulations of Initial value problem (1.3) using various initial conditions when $s = 3 \times 10^5; d = 2 \times 10^{-3}; r_T = 3 \times 10^{-2}; r_I = 10^{-3}; T_{\text{max}} = 10^8; b = 0.01; \delta = 10^{-6}; c = 8 \times 10^{-2}; \rho = 0.8898; \alpha = 50; \beta = 15; \epsilon = 0.5; \sigma = 30; U_{\text{max}} = 30; \gamma = 5; E^* = (0.25 \times 10^6, 5.766414063 \times 10^7, 9.617092746 \times 10^9, 18, 15)$ (Such that $R_0 = 6.9235$ and $R''_0 = 2.5$).

hepatocytes are infected. Thus it seems intuitively that this inequality is related to the condition that a chronic infection persists. Finally it would be desirable to make a broad comparison of the properties of the model in this paper with those of other models for hepatitis C or other related diseases such as hepatitis B in the literature. Note, for instance, that in contrast to what we found here, in the model for hepatitis B in [13], which also uses the standard incidence function, it does sometimes happen that $T + I \to 0$. This is connected to the fact that while we choose $s > 0$ the model of [13] corresponds to the case $s = 0$. This in turn is related to the question whether the population of hepatocytes is maintained by cell division in the liver or whether is also supported by migration of cells from outside.

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