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Global dynamics of an Hepatitis C Virus mathematical cellular model with a logistic term

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Abstract. In this paper, the aim is to analyze the global dynamics of Hepatitis C Virus (HCV) cellular mathematical model under therapy with uninfected hepatocytes proliferation. We prove that the solution of the model with positive initial values are global, positive and bounded. In addition, firstly we show that the model is locally asymptotically stable at free virus equilibrium and also at infected equilibrium. Secondly we show that the model is globally asymptotically stable at the free virus equilibrium by using an appropriate lyapunov function.

2010 Mathematics Subject Classifications: 92B99, 34D23, 92D25

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1. Introduction

Viral hepatitis C is an infectious disease caused by the hepatitis C virus (HCV). It is among the causes of liver cancer, the latter being one of the biggest causes of death in the world. In particular, according to the 2018 WHO report, 10,000 people die each year from hepatitis with a prevalence rate of around 13% for hepatitis C versus 10% for hepatitis B. Mathematical and computer models have become essential tools for analyzing, predicting and controlling infectious diseases (hepatitis, HIV, ebola, dengue, chikungunya...), both at the population level and at the individual level. These models can be used to construct and test hypotheses, make predictions and evaluate effective measures to make drugs effective. Numerous mathematical models describing the temporal dynamics of hepatitis C virus (HCV) have been proposed by various authors, such as: Neumann et al. [8] in 1998; Guedj and Neumann [5] in 2010; Chatterjee et al. [1] in 2012 and J. Rong and al. [6] in 2013. Our model is inspired by the model of Guedj and Neumann [5] which considers two levels of the infection namely: extracellular infection and intracellular infection. Stability is a

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central issue in the study of the dynamics of cellular models. Our work will consist to study the global dynamics of the model (1). The mathematical properties of a certain number of models of hepatitis C virus infection have already been studied, for example in [2].

The Neumann et al. [8] model of viral dynamics, named here the cell infection(CI) model is the standard description for HCV kinetics during treatment. In this model, the change in viral load, $V(t)$, is occurring on the level of cell infection and involves de novo infection (with constant rate β), infected cell loss (with constant rate d), virus particle production (with constant rate per infected cell p), and virus clearance from circulation (with rate constant c), in Figure 1 [8] by the following compartmental model :

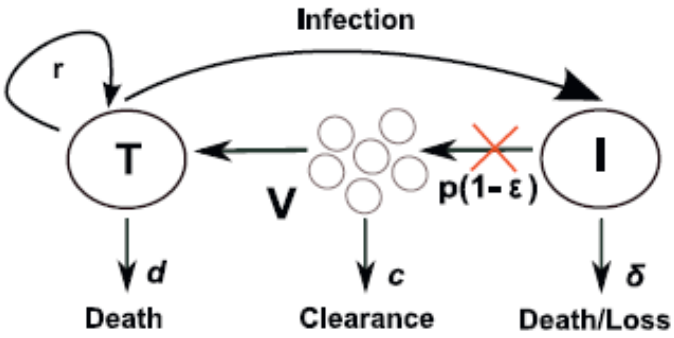

Figure 1: The CI model (1)comprises of de novo infection and loss of infected cells (I), production and clearance of virus in circulation (V) and target cell (T) dynamics.

In the original model, the target cells $T(t)$ are produced at a constant rate s and die with death rate constant d. In this new model we taking into account a logistic rate, $r\left(1-\frac{T+I}{T_{max}}\right)$, that allows for a more realistic growth of hepatocytes by proliferation. It should be noted that T_{max} is the maximum hepatocyte density or 'carrying capacity' which is based on both uninfected and infected hepatocyte in the liver. It is implicitly assumed that the vast majority of hepatocytes are susceptible to infection, consistent with experimental findings that a large proportion of hepatocytes can be infected (Rodriguez-Inigo et al. [9] ; Stiffler et al. [10]). Initially, the model neglects the fact that when a cell is infected the number of virions outside the cells is reduced by one. For this reason the equation for $\frac{dV}{dt}$ should contain an extra term $-(1-\eta)\beta VT$. It is argued, however, that this term is small in comparison to other terms in the same equation, so that it is justified to omit it. From a mathematical point of view including this effect leads to a new system which we call the 'modified fundamental model of virus dynamics'. The additional term can be written as $-\alpha(1-\eta)\beta VT$, where the Parameter α takes the value zero or one.

The phenomenon described above is governed according to J. Guedj and A. U. Neumann [5] by a set of three autonomous ordinary differential equations :

$$\frac{dT}{dt} = rT\left(1 - \frac{T+I}{T_{max}}\right) - (1-\eta)\beta VT - dT; \tag{1a}$$

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

$$\frac{dV}{dt} = (1-\varepsilon)pI - cV - \alpha(1-\eta)\beta VT; \tag{1c}$$

where the equations relate the dynamics relationship between, T as the uninfected target cells (hepatocytes), I as the infected cells and V as the viral load (amount of viruses present in the blood). The efficacy of treatment in blocking virion production and reducing new infections is described by the parameters, ε and η, respectively, which values are non-negative and less than one. For biological significance of the parameters, one assumption is employed. Infected cells have a higher turnover rate than uninfected cells, i.e. $d \leq \delta$ and we also suppose that $r \geq d$.
Let $T_0,\ I_0,\ V_0 \in \mathbb{R}$ be given real numbers. we look for solutions T, I and V of the mathematical model (1) over $[t_0, +\infty[$, $T \leq +\infty$ satisfying :

$$T(t_0) = T_0,\ I(t_0) = I_0, \text{ and } V(t_0) = V_0,\ \ t_0 \in [0, +\infty[. \tag{2}$$

(2) are called initial conditions and the given numbers T_0, I_0, V_0 being the initial data.
The aim of this paper is to analyze the global dynamics of Hepatitis C Virus (HCV) cellular mathematical model under therapy with uninfected hepatocytes proliferation described by system (1). To achieve this, we will organized the paper as follows : we study in section 1 some properties of the solutions of the studied model. Section 2 is devoted to the study of the local stability of equilibrium points and we end with the global stability of the uninfected equilibrium point in Section 3

2. Properties of solutions to the Cauchy problem (1), (2)

2.1. Existence of local and global solutions, positivity

Our objective is to prove the existence of global solution T, I V defined over the whole interval $[t_0, +\infty[$ and satisfying (2). The first step in examining model (1) is to prove that local solution to the initial-value problem does, in fact, exist, and that this solution is unique.

Proposition 1. *Let $T_0,\ I_0,\ V_0 \in \mathbb{R}$ be given. There exists $t_1 > t_0 > 0$ and continuously differentiable functions $T,\ I,\ V : [0, t_0) \longrightarrow \mathbb{R}$ such that the ordered triple (T, I, V) satisfies (1) and $(T(t_0), I(t_0), V(t_0)) = (T_0, I_0, V_0)$.*

Proof. To prove the result, we use the classical Cauchy-Lipschitz theorem. Since the first order system of ordinary differential equations (1) is autonomous, it is enough to show

that the function $f : \mathbb{R}^3 \longrightarrow \mathbb{R}^3$ defined by :

$$f(x,y,z) = \begin{pmatrix} f_1(x,y,z) \\ f_2(x,y,z) \\ f_3(x,y,z) \end{pmatrix} = \begin{pmatrix} rx(1-\frac{x+y}{T_{max}}) - dx - (1-\eta)\beta zx \\ (1-\eta)\beta zx - \delta y \\ (1-\varepsilon)py - cz - \alpha(1-\eta)\beta zx \end{pmatrix}$$

is locally Lipschitz in its $u = (x,y,z)$ argument. In fact, it suffices to notice that the jacobian matrix

$$\nabla f(x,y,z) = \begin{bmatrix} r(1-\frac{2x+y}{T_{max}}) & -\frac{rx}{T_{max}} & -(1-\eta)\beta x \\ (1-\eta)\beta z & -\delta & (1-\eta)\beta x \\ -\alpha(1-\eta)\beta x & (1-\varepsilon)p & -c-\alpha(1-\eta)\beta x \end{bmatrix}$$

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

$$u'(t) = f(x(t))$$

with initial value $u(t_0) = u_0 = (x_0, y_0, z_0)$ on $[t_0, t_1]$ for some time $t_1 > t_0 \geq 0$. This completes the proof of the proposition.

Remark 1. *Since f is a continuously differentiable function, we deduce a unique maximal solution of initial value problem* (1), (2). *In addition, f, being indefinitely continuously differentiable, we can also deduce that this solution is indefinitely continuously differentiable.*

Additionally, we may show that for positive initial data, solutions of Cauchy problem (1), (2) remain positive as long as they exist.

Theorem 1. *Let (T,I,V) be a solution of the Cauchy problem* (1), (2) *on an interval $[t_0, t_1[$. Assume the initial data of (1), (2) satisfy $T_0 > 0$, $I_0 > 0$, and $V_0 > 0$ then $T(t)$, $T(t)$ and $V(t)$ remain positive for all $t \in [t_0, t_1[$.*

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

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

where $g(x)$ is non-negative. As a consequence $\frac{dx_i(t)}{dt} \geq -x_i f(x)$ and $x_i(t) > 0$, $\forall t \in [t_0, t_*]$. A contradiction. This completes the proof of the theorem.

Remark 2. *With this, we have a general idea that the model is sustainable, and can say with assurance that it remains biologically valid as long as it began with biologically-reasonable (i.e, positive) data. This also shows that once infected, it is entirely possible that the virus may continue to exist beneath a detectable threshold without doing any damage.*

Remark 3. *One reason why we choose the strict inequalities for the initial data is that often in biological (or chemical) applications we are interested in the case of solutions where all unknowns are positive. This means intuitively that all elements of the model are 'active'. On the other hand it is sometimes relevant to consider solutions with non-strict inequalities. The fact the statement of the theorem with strict inequalities implies the corresponding statement with non-strict inequalities is based on continuous dependence of the solution on initial data.*

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

Theorem 2. *If* $(1-\varepsilon)p-\delta>0$ *the solution of the initial value problem* (1), (2), *with positive initial data, exists globally in time in the future, i.e. on* $[t_0,+\infty[$.

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

The sum of equations (1a), (1b) and (1c) leads to :

$$\frac{d}{dt}(T+I+V) = rT\left(1-\frac{T+I}{T_{max}}\right)-dT+((1-\varepsilon)p-\delta)I-cV-\alpha(1-\eta)\beta VT.$$

Hence

$$\frac{d}{dt}(T+I+V) \leq \frac{rT_{max}}{4}-\left(\frac{\sqrt{r}T}{\sqrt{T_{max}}}-\frac{\sqrt{rT_{max}}}{2}\right)^2+A(T+I+V)$$

where

$$A=\max\{c,d,(1-\varepsilon)p-\delta\}.$$

It follows that :

$$\frac{d}{dt}(T+I+V)\leq \frac{rT_{max}}{4}+A(T+I+V). \tag{3}$$

From differential inequation (3), $T(t)+I(t)+V(t)$ should verify :

$$T(t)+I(t)+V(t)\leq N(t),$$

where the function N is the solution of the following initial value problem (4), (5):

$$\frac{dN}{dt} = AN+\frac{rT_{max}}{4} \tag{4}$$

$$N(t_0) = N_0=T_0+I_0+V_0. \tag{5}$$

The solution of the initial value problem (4), (5) is given by :

$$N(t) = -\frac{rT_{max}}{4A} + \left(N_0 + \frac{rT_{max}}{4A}\right) e^{A(t-t_0)}.$$

It follows that,

$$T(t) + I(t) + V(t) \leq -\frac{rT_{max}}{4A} + \left(T_0 + I_0 + V_0 + \frac{rT_{max}}{4A}\right) e^{A(t-t_0)}.$$

This last equation leads to :

$$T(t) + I(t) + V(t) \leq \left(T_0 + I_0 + V_0 + \frac{rT_{max}}{4A}\right) e^{A(t-t_0)}.$$

Therefore,

$$T(t) + I(t) + V(t) \leq g(t) \tag{6}$$

where :

$$g(t) = \left(T_0 + I_0 + V_0 + \frac{rT_{max}}{4A}\right) e^{A(t-t_0)}.$$

g is a continuous function thus g is bounded function on $[t_0, t]$. Furthermore according to the positivity result and inequation (6), we have : $0 < N(t) \leq g(t)$ on $[t_0, t]$. Therefore, since N is bounded on any finite interval, T , I ,V are also bounded. This completes the proof of the theorem.

2.2. Asymptotic behaviour and invariant set

The following theorem shows that all solutions of model (1) in $\mathbb{R}^3_+$ are ultimately bounded and that solutions with positive initial value conditions are positive, which indicates that model (1) is well-posed. Otherwise for biological reasons only initial data are considered for which at the initial time $T + I \leq T_{max}$. Then we will prove that if the initial data satisfy this previous inequality the solution also does so.

Theorem 3. *For any positive initial data T_0, I_0 and V_0 of the Cauchy problem* (1)*, we have :*

$$T(t) \leq C_1,\ I(t) \leq C_1 \text{ and } V(t) \leq C_2,$$

where

$$C_1 = \frac{(r-d)T_{max}}{r},$$
$$C_2 = \max\left(\frac{(1-\varepsilon)p}{c}C_1, V_0\right)$$

when t tends to $+\infty$.

Proof. Adding equations (1a) and (1b) implies, since $d \leq \delta$:

$$\begin{aligned}
\frac{d}{dt}(T+I) &= r\left(1-\frac{T+I}{T_{max}}\right)T - dT - \delta I \\
&\leq r\left(1-\frac{T+I}{T_{max}}\right)T - d(T+I) \\
&\leq r\left(1-\frac{T+I}{T_{max}}\right)T + r\left(1-\frac{T+I}{T_{max}}\right)I - d(T+I) \\
\frac{d}{dt}(T+I) &\leq r\left(1-\frac{T+I}{T_{max}}\right)(T+I) - d(T+I). \qquad (7)
\end{aligned}$$

We know that $T(t) + I(t) \leq M(t)$, where M satisfies :

$$\begin{aligned}
\frac{dM}{dt} &= (r-d)M - \frac{r}{T_{max}}M^2 \qquad (8) \\
M(t_0) &= T(t_0) + I(t_0) = T_0 + I_0. \qquad (9)
\end{aligned}$$

(8) is a first order differential equation of Bernoulli type. Hence, by direct calculation, using (9), we obtain the following expression of M :

$$M(t) = \frac{(r-d)T_{max}}{r + (r-d)T_{max}\left(z_0 - \frac{r}{(r-d)T_{max}}\right)e^{-(r-d)(t-t_0)}}$$

which shows that $M(t) \longrightarrow \frac{(r-d)T_{max}}{r}$ as $t \longrightarrow +\infty$ and hence, M is bounded. Since

$$0 \leq T(t) + I(t) \leq M(t),$$

$T + I$ is bounded and therefore $T(t) \leq \frac{(r-d)T_{max}}{r}$, $I(t) \leq \frac{(r-d)T_{max}}{r}$.

Moreover, as far as V is concerned, according to 1c, we have :

$$\begin{aligned}
\frac{dV}{dt} &= (1-\varepsilon)pI - cV - \alpha(1-\eta)\beta VT \\
&\leq (1-\varepsilon)pI - cV \\
&\leq (1-\varepsilon)pC_1 - cV \\
\text{i.e. } \frac{dV}{dt} &\leq -cV + (1-\varepsilon)pC_1 \qquad (10)
\end{aligned}$$

We know, by differential calculus, that

$$V(t) \leq N(t),$$

where N satisfies :

$$\begin{aligned}
\frac{dN}{dt} &\leq -cV + (1-\varepsilon)pC_1, \qquad (11) \\
N(t_0) &= V(t_0)) = V_0. \qquad (12)
\end{aligned}$$

(11) is a non homogeneous first order differential equation. Hence, by direct calculation, using (12), we obtain the following expression of N :

$$\begin{aligned} N(t) &= \frac{(1-\varepsilon)pC_1}{c} + e^{-c(t-t_0)}\left(V_0 - \frac{(1-\varepsilon)pC_1}{c}\right); \\ &= \max\left(\frac{(1-\varepsilon)p}{c}C_1, V_0\right)\left(1 + e^{-c(t-t_0)} - e^{-c(t-t_0)}\right), \end{aligned}$$

which shows that:

$$N(t) \leq \max\left(\frac{(1-\varepsilon)p}{c}C_1, V_0\right)$$

and therefore, N is bounded as t tends to $+\infty$. Since

$$0 \leq V(t) \leq N(t),$$

V is bounded and hence $V(t) \leq \max\left(\frac{(1-\varepsilon)p}{c}C_1, V_0\right)$. At the end we achieve the proof of theorem 3 .

As consequences of Theorem 3 we have the followings :

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

Theorem 4. *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 (1), (2) ($T \in]t_0, +\infty[$). If $T(t_0) + I(t_0) \leq C_1$ and $V(t_0) \leq C_2$ then the set :*

$$\Omega = \left\{(T(t), I(t), V(t)) \in \mathbb{R}^3_+ : T(t) + I(t) \leq C_1,\ V(t) \leq C_2\right\},$$

where

$$C_1 = \frac{(r-d)T_{max}}{r},\ \ C_2 = \max\left(\frac{(1-\varepsilon)p}{c}C_1, V_0\right),$$

is a positively invariant set by system (1).

3. Equilibria and Basic reproduction number $\mathcal{R}_0$

In this section, we will derive the basic reproduction number, and compute the equilibria of model (1).

When there is no viral infection, the uninfected hepatocytes dynamics is determined by :

$$\frac{dT}{dt} = rT\left(1 - \frac{T}{T_{max}}\right) - dT. \tag{13}$$

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

$$T^0 = \frac{r-d}{r} T_{max} \leq T_{max}. \tag{14}$$

Now, using the idea of next generation matrix for a general compartmental disease transmission model in [4], we can obtain the basic reproduction ratio of (1).

Proposition 2. *The basic reproduction ratio $\mathcal{R}_0$ of model (1) is given by :*

$$\mathcal{R}_0 = \frac{(1-\varepsilon)(1-\eta)p\beta T^0}{\delta(c+(1-\eta)\alpha\beta T^0)}.$$

Proof. Using (13) and (14), we know that $E^0 = (T^0, 0, 0)$ is the virus-free equilibrium or uninfected equilibrium, which exists for all positive parameter values. Based on the notations in [4], we have

$$DF = \begin{bmatrix} 0 & (1-\eta)\beta T^0 \\ (1-\varepsilon)p & 0 \end{bmatrix}, \; DV = \begin{bmatrix} \delta & 0 \\ 0 & c+\alpha(1-\eta)\beta T^0 \end{bmatrix} \; and \; DV^{-1} = \begin{bmatrix} \frac{1}{\delta} & 0 \\ 0 & \frac{1}{c+\alpha(1-\eta)\beta T^0} \end{bmatrix}.$$

and the next generation matrix is :

$$\begin{aligned} DF.DV^{-1} &= \begin{bmatrix} 0 & (1-\eta)\beta T^0 \\ (1-\varepsilon)p & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{\delta} & 0 \\ 0 & \frac{1}{c+\alpha(1-\eta)\beta T^0} \end{bmatrix} \\ &= \begin{bmatrix} 0 & \frac{(1-\eta)\beta T^0}{c+\alpha(1-\eta)\beta T^0} \\ \frac{(1-\varepsilon)p}{\delta} & 0 \end{bmatrix}. \end{aligned}$$

According to [4, Theorem 2], the basic reproduction number of (1) is defined by

$$\mathcal{R}_0 = \rho(DF.DV^{-1}) = \frac{(1-\theta)p\beta T^0}{\delta(c+(1-\eta)\alpha\beta T^0)},$$

where $\rho(A)$ denotes the spectral radius of a matrix A and $1-\theta = (1-\varepsilon)(1-\eta)$.

Remark 5. *Henceforth $(1-\varepsilon)(1-\eta) = (1-\theta)$ and θ denotes the overall drug effectiveness [3].*

Besides the virus-free equilibrium point E^0, we now discuss the existence of the infected equilibrium point $E^+ = (T^*, I^*, V^*)$, in which X^* means a positive constant. To determine T^*, I^* and V^* we should solve the following algebraic system :

$$\begin{cases} rT\left(1-\dfrac{T+I}{T_{max}}\right) - (1-\eta)\beta VT - dT = 0; \\ (1-\eta)\beta VT - \delta I = 0; \\ (1-\varepsilon)pI - cV - \alpha(1-\eta)\beta VT = 0. \end{cases} \tag{15}$$

We have the following result by easy way :

Proposition 3. *If $\mathcal{R}_0 > 1$ and $(1-\varepsilon)p - \alpha\delta > 0$ then the mathematical model (1) admits an infected equilibrium point $E^+ = (T^*, I^*, V^*)$*
where

$$T^* = \frac{c\delta}{(1-\eta)\beta[(1-\varepsilon)p - \alpha\delta]};$$

$$V^* = \frac{c}{(1-\varepsilon)p - \alpha\delta}\left\{\frac{(1-\eta)k\beta[(1-\varepsilon)p - \alpha\delta](r-d) - cr\delta}{(1-\eta)\beta cr + (1-\eta)^2 k\beta^2[(1-\varepsilon)p - \alpha\delta]}\right\} = \frac{c}{(1-\varepsilon)p - \alpha\delta}I^*$$

and

$$I^* = \frac{(1-\eta)k\beta[(1-\varepsilon)p - \alpha\delta](r-d) - cr\delta}{(1-\eta)\beta cr + (1-\eta)^2 k\beta^2[(1-\varepsilon)p - \alpha\delta]}.$$

Remark 6. *(i) The point $(0,0,0)$ is also an equilibrium of the model (1).*

(ii) T^* can be expressed with respect to $\mathcal{R}_0$, thus we have:

$$T^* = \frac{c\delta T_0}{\mathcal{R}_0\delta c + (1-\eta)\alpha\beta T_0(\mathcal{R}_0 - 1)}$$

This means that T^* exists if and only if $\mathcal{R}_0 > 1$.

4. Local stability analysis

In this subsection, we investigate the local stability of the equilibria E^0 and E^+ by finding the eigenvalues of the associated Jacobian matrices.

The jacobian matrix $J(T, I, V)$ of model (1) is given by :

$$J(T,I,V) = \begin{bmatrix} p_1 & \frac{rT}{T_{max}} & -(1-\eta)\beta T \\ (1-\eta)\beta V & -\delta & (1-\eta)\beta T \\ -\alpha(1-\eta)\beta V & (1-\varepsilon)p & p_2 \end{bmatrix} \tag{16}$$

where

$$p_1 = r\left(1 - \frac{2T+I}{T_{max}}\right) - d - (1-\eta)\beta V \text{ and } p_2 = -\left(c + \alpha(1-\eta)\right)\beta T.$$

First, we have

Theorem 5. *For model (1), the virus-free equilibrium point $E^0 = (T^0, 0, 0)$ is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$*

Proof. The local stability of the uninfected steady state $E^0 = (T^0, 0, 0)$ is governed by the eigenvalues of the matrix

$$J(E_0) = \begin{bmatrix} -(r-d) & 0 & -\frac{(1-\eta)(r-d)\beta}{r} \\ 0 & -\delta & \frac{(1-\eta)(r-d)\beta}{r} \\ 0 & (1-\varepsilon)p & b_2 \end{bmatrix}$$

where

$$b_2 = -\left(c + \alpha\frac{(1-\eta)(r-d)\beta}{r}\right).$$

The characteristic equation of the linearised system is given by the following equation :

$$[-\lambda-(r-d)][\lambda^2+\frac{\lambda}{r}[cr+\delta r+\alpha\beta(1-\eta)(r-d)]-\frac{\beta}{r}(1-\eta)(r-d)[(1-\varepsilon)p-\delta\alpha]+cr\delta] = 0$$

i.e.

$$[-\lambda-(r-d)][\lambda^2+\lambda a_1+a_2] = 0$$

where coefficients are given by :

$$a_1 = \frac{1}{r}[cr+\delta r+\alpha\beta(1-\eta)(r-d)]$$
$$a_2 = -\frac{\beta}{r}(1-\eta)(r-d)[(1-\varepsilon)p-\delta\alpha]+c\delta.$$

$\lambda = -(r-d)$ is already a negative eigenvalue of the jacobian matrix J (E_0) and to achieve the study we will use the Routh-Hurwitz criterion. If a_1 and a_2 are all positive, then applying the Routh-Hurwitz criterion to the quadratic equation guarantees the eigenvalues to have negative real part, and that two conditions must be satisfied for local asymptotic stability of the uninfected steady state :
$a_1 > 0$ i.e. $\frac{1}{r}[cr+\delta r+\alpha\beta(1-\eta)(r-d)] > 0$ is satisfied.

$a_2 > 0$ i.e. $-\frac{\beta}{r}(1-\eta)(r-d)[(1-\varepsilon)p-\delta\alpha]+c\delta > 0$
i.e.

$$\frac{\beta}{r}(1-\eta)(r-d)[(1-\varepsilon)p+\alpha\delta] < c\delta$$

it follows that :

$$\frac{\beta}{r}(1-\eta)(r-d)(1-\varepsilon)p < c\delta+\frac{\alpha\delta\beta}{r}(1-\eta)(r-d)$$

which yields

$$p\beta(1-\eta)(r-d)(1-\varepsilon) < \delta(cr + \alpha\beta(1-\eta)(r-d)).$$

that leads to :

$$\frac{p\beta(1-\eta)(r-d)(1-\varepsilon)}{\delta(cr + \alpha\beta(1-\eta)(r-d))} < 1$$

$$\Rightarrow \qquad \mathcal{R}_0 < 1.$$

All conditions are satisfied if and only if $\mathcal{R}_0 < 1$ for local asymptotic stability of the uninfected steady state. This completes the proof.

Next we consider the local stability of the unique infected equilibrium pont E^+ when $\mathcal{R}_0 > 1$ and $(1-\varepsilon)p - \alpha\delta > 0$.
Using (16) and the following equation :

$$rT^*\left(1 - \frac{T^* + I^*}{T_{max}}\right) - (1-\eta)\beta V^* T^* - dT^* = 0,$$

the jacobian matrix of model (1) at infected equilibrium point E^+ is :

$$J(E^+) = \begin{bmatrix} -\frac{rT}{T_{max}} & -\frac{rT}{T_{max}} & -(1-\eta)\beta T \\ (1-\eta)\beta V & -\delta & (1-\eta)\beta T \\ -\alpha(1-\eta)\beta V & (1-\varepsilon)p & -c - \alpha(1-\eta)\beta T. \end{bmatrix}.$$

We have the following characteristic equation associated with the above jacobian matrix $J(E^+)$:

$$|J(E^+) - \lambda I| = \lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0,$$

Where :

$$A_1 = \alpha\,(1-\eta)\,\beta T^* + c + \delta + \frac{T^* r}{T_{max}},$$

$$\begin{aligned} A_2 &= \alpha\,(-\eta+1)\,T^* V^* \beta^2 \eta - \alpha\,(-\eta+1)\,T^* V^* \beta^2 - T^*\beta\,\epsilon\eta p + \alpha\,(1-\eta)\,T^*\beta\delta + T^*\beta\epsilon\,p \\ &\quad + T^*\beta\eta p - T^*\beta p + c\delta + \frac{1}{T_{max}}\left(T^{*2}\beta r\alpha\,(1-\eta) - T^* V^*\beta\eta r + T^* V^*\beta r + T^* cr + T^*\delta\,r\right), \end{aligned}$$

i.e.

$$\begin{aligned} A_2 &= \alpha(1-\eta)\beta T^*\,(\delta - (1-\eta)\beta V^*) + \frac{rT^*}{T_{max}}(1-\eta)\beta V^* + (1-\eta)\beta T^*\left(\alpha\frac{rT^*}{T_{max}} - (1-\varepsilon)p\right) \\ &\quad + \frac{rT^*}{T_{max}}(c+\delta) + \delta c \end{aligned}$$

$$A_3 = \left(-V^*\beta^2\epsilon\eta^2 p + \alpha\,(1-\eta)\,V^*\beta^2\delta\eta + 2V^*\beta^2\epsilon\eta p + V^*\beta^2\eta^2 p - \alpha\,(1-\eta)\,V^*\beta^2\delta - V^*\beta^2\epsilon p\right)T^*$$

$$+\frac{T^*}{T_{max}}\left(-T^*\beta\epsilon\eta pr+T^*\beta\delta r\alpha\left(1-\eta\right)+T^*\beta\epsilon pr+T^*\beta\eta pr-V^*\beta c\eta r-T^*\beta pr+V^*\beta cr+c\delta r\right)$$
$$-\left(2V^*\beta^2\eta p-V^*\beta^2 p\right)T^*.$$

Obviously we have :

$$A_1>0$$

and

$$A_2>0 \text{ if and only if } \alpha\frac{rT^*}{T_{max}}-(1-\varepsilon)p>0 \text{ and } \delta-(1-\eta)\beta V^*>0.$$

Let

$$\Delta=\begin{vmatrix} A_1 & 1\\ A_3 & A_2\end{vmatrix}=A_1A_2-A_3.$$

Then, by Routh-Hurwitz criterion, we have the following result.

Theorem 6. *For model* (1)*, when* $\alpha\frac{rT^*}{T_{max}}-(1-\varepsilon)p>0$ *and* $\delta-(1-\eta)\beta V^*>0$ *are valid, then the unique infected equilibrium* E^+ *is locally asymptotically stable if* $\Delta>0$ *and unstable if* $\Delta<0$*.*

Especially we have :

Corollary 1. *Suppose that* $\frac{rT^*}{T_{max}}c-(1-\eta)\beta T^*(\alpha\delta+(1-\varepsilon)p)>0$*, then* $\Delta>0$ *is always valid, i.e.* E^+ *is locally asymptotically stable only if it exists in this case.*

Proof. We have :

$$\begin{aligned}\Delta &= \begin{vmatrix} A_1 & 1\\ A_3 & A_2\end{vmatrix}=A_1A_2-A_3\\
&= T^*\beta\delta\eta p-T^*V^*\beta^2\eta^2p+T^*V^*\beta^2\epsilon\eta p+2T^*V^*\beta^2\eta p+T^*\beta c\epsilon p+T^*\beta\, c\eta p+T^*\beta\delta\epsilon p+c^2\delta+c\delta^2\\
&+ T^*\left(\alpha\left(1-\eta\right)T^*\beta^2\epsilon\, p+\alpha\left(1-\eta\right)T^*\beta^2\eta p-\alpha\left(1-\eta\right)V^*\beta^2c+2\alpha\left(1-\eta\right)\beta c\delta+\left(\alpha\left(1-\eta\right)\right)^2T^*V^*\beta^3\eta\right)\\
&+ T^*\left(\alpha\left(1-\eta\right)V^*\beta^2c\eta+V^*\beta^2\epsilon\eta^2p-2V\beta^2\epsilon\eta p-\beta c\epsilon\eta p-\beta\delta\epsilon\eta p-\alpha\left(1-\eta\right)T^*\beta^2\epsilon\eta p\right)\\
&+ \frac{T^*}{T_{max}}\left(\left(\alpha\left(1-\eta\right)\right)^2T^{*2}\beta^2r+2\alpha\left(1-\eta\right)T^*\beta cr+2\alpha\left(1-\eta\right)T^*\beta\delta r-V^*\beta\delta\eta r+V^*\beta\delta r+c^2r\right)\\
&+ \frac{T^*}{T_{max}}\left(\alpha\left(1-\eta\right)T^{*2}\beta r^2-T^*V^*\beta\eta r^2+T^*V^*\beta r^2+T^*cr^2+T^*\delta r^2+2c\delta r+\delta^2r\right)\\
&- \left(\alpha\left(1-\eta\right)\right)^2T^{*2}V^*\beta^3+\left(\alpha\left(1-\eta\right)\right)^2T^{*2}\beta^2\delta-\alpha\left(1-\eta\right)T^{*2}\beta^2p+\alpha\left(1-\eta\right)T^*\beta\delta^2-T^*V^*\beta^2p\\
&- T^*\beta cp-T^*\beta\delta p,\end{aligned}$$

i.e,

$$\begin{aligned}\Delta &= (1-\eta)\beta T^*\left(\alpha\frac{rT^*}{T_{max}}-(1-\varepsilon)p\right)(c+\alpha(1-\eta)\beta T^*+\delta)+\delta c^2+\delta^2c+(1-\eta)\beta T^*\alpha\delta c\\
&+(c+\delta)\frac{rT^*}{T_{max}}\left(\frac{rT^*}{T_{max}}+c+\alpha(1-\eta)\beta T^*+\delta\right)+(1-\eta)\beta V^*\left(\frac{rT^*}{T_{max}}c-(1-\eta)\beta T^*(\alpha\delta+(1-\varepsilon)p)\right)\\
&+\alpha(1-\eta)\beta T^*(\delta-(1-\eta)\beta V^*)\left(\frac{rT^*}{T_{max}}+c+\alpha(1-\eta)\beta T^*+\delta\right).\end{aligned}$$

Clearly $\Delta>0$ if and only if $\frac{rT^*}{T_{max}}c-(1-\eta)\beta T^*(\alpha\delta+(1-\varepsilon)p)>0$. As a result, $\Delta>0$ is always valid. This completes the proof of this corollary.

5. Global stability analysis of the model (1) at uninfected steady state

For the global stability of the equilibria, we have :

Theorem 7. *The infection-free steady state E^0 of model (1) is globally asymptotically stable if the basic reproduction number $\mathcal{R}_0 < \frac{c}{c+\alpha(1-\eta)\beta T^0}$.*

Remark 7. *Since*

$$\mathcal{R}_0 = \frac{(1-\varepsilon)(1-\eta)p\beta T^0}{\delta(c+(1-\eta)\alpha\beta T^0)} = \frac{(1-\theta)p\beta T^0}{\delta(c+(1-\eta)\alpha\beta T^0)}$$

and

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

Then

$$(1-\theta)p\beta T^0 = \mathcal{R}_0\delta(c+(1-\eta)\alpha\beta T^0)).$$

therefore

$$\begin{aligned}\frac{(1-\theta)p\beta T^0 I}{c} - \delta < 0 &\iff \frac{\mathcal{R}_0\delta(c+\alpha(1-\eta)\beta T^0)}{c} - \delta < 0\\ &\iff \mathcal{R}_0 < \frac{c}{c+\alpha(1-\eta)\beta T^0}.\end{aligned}$$

Proof. Consider the Lyapunov function :

$$L_1(T,I,V) = T - T^0 - T^0\ln\frac{T}{T^0} + I + \frac{(1-\eta)\beta T^0}{c}V$$

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

$$\begin{aligned}\frac{dL_1}{dt} &= \frac{\partial L_1}{\partial T}\frac{dT}{dt} + \frac{\partial L_1}{\partial I}\frac{dI}{dt} + \frac{\partial L_1}{\partial V}\frac{dV}{dt}\\ &= \frac{dT}{dt} - \frac{dT^0}{dt}\frac{dT}{dt} + \frac{dI}{dt} + \frac{(1-\eta)\beta T_0}{c}\frac{dV}{dt}\\ &= \left(1-\frac{dT^0}{dt}\right)\dot{T} + \dot{I} + \frac{(1-\eta)\beta T_0}{c}\dot{V}.\end{aligned}$$

Further collecting terms, we have

$$\begin{aligned}\frac{dL_1}{dt} &= (T-T_0)\left[r - \frac{r(T+I)}{T_{max}} - d - (1-\eta)\beta V\right] + (1-\eta)\beta VT - \delta I\\ &\quad + \frac{(1-\eta)\beta T_0}{c}\left[(1-\varepsilon)pI - cV - \alpha(1-\eta)\beta VT\right].\end{aligned}$$

Hence:

$$\begin{aligned}\frac{dL_1}{dt} &= (T-T^0)\left[-\frac{r}{T_{max}}(T-T^0)-\frac{r}{T_{max}}I\right]-\delta I+\frac{(1-\eta)(1-\varepsilon)p\beta T^0 I}{c}\\ &\quad -\alpha\frac{(1-\eta)^2\beta^2 VTT^0}{c}\\ &= -\frac{r}{T_{max}}[(T-T^0)^2-(T-T^0)I]+\left(\frac{(1-\eta)(1-\varepsilon)p\beta T^0 I}{c}-\delta\right)I\\ &\quad -\alpha\frac{(1-\eta)^2\beta^2 VTT^0}{c}\end{aligned}$$

This leads to :

$$\frac{dL_1}{dt} = -\frac{r}{T_{max}}[(T-T^0)(T+I-T^0)]+\left(\frac{(1-\theta)p\beta T^0 I}{c}-\delta\right)I-\alpha\frac{(1-\eta)^2\beta^2 VTT^0}{c},$$

since $1-\theta=(1-\eta)(1-\varepsilon)$.
Furthermore, we have :

$$\frac{dL_1}{dt} \leq -\frac{r}{T_{max}}[(T-T^0)(T+I-T^0)]+I(\mathcal{R}_0-\frac{c}{c+\alpha(1-\eta)\beta T^0})-\alpha\frac{(1-\eta)^2\beta^2 VTT^0}{c}.$$

$R_0 \leq \frac{c}{c+\alpha(1-\eta)\beta T^0}$ and theorem 4 ensure $\frac{dL_1}{dt}\leq 0$ for all $T>0$, $I>0$, $V>0$. The equality $\frac{dL_1}{dt}=0$ holds only at the free equilibrium E^0 .
Therefore, the largest compact invariant subset of the set

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

is the singleton $\{E^0\}$. By the Lasalle invariance principle, the infection-free equilibrium is globally asymptotically stable if $R_0 \leq \frac{c}{c+\alpha(1-\eta)\beta T^0}$. This completes the proof of theorem 7.

6. Concluding remark

It is clear that this paper is a starting point for further investigations. In a very near future we will attempt to solve the case of the global asymptotic stability of the infected equilibrium point. Constructing a Lyapunov function for this infected equilibrium model appears to be very complex. We will think about Li-Muldowney global-stability criterion [7] for example.

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