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Analysis of a HCV Model with CTL and Antibody Responses

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Abstract

In this paper, we present the global analysis of a HCV model with CTL and Antibody Responses. We prove that the solutions with positive initial values are all positive, bounded and not display periodic orbits. In addition, we show that the model is globally asymptotically stable, by using appropriate Lyapunov functions.

Keywords: HCV model, CTL and antibody responses, basic infection reproduction number, Lyapunov function, stability.

1 Introduction

Hepatitis C virus (HCV) infects liver cells (hepatocytes). Approximately 200 million people worldwide are persistently infected with the HCV and are at risk of developing chronic liver disease, cirrhosis and hepatocellular carcinoma. HCV infection therefore represents a significant global public health problem. HCV establishes chronic hepatitis in $60\% - 80\%$ of infected adults [6].

In literature, several mathematical models have been introduced for understanding HCV dynamics [1, 5, 9].

In this article, we consider the basic model presented by Wodarz in [9], this model contains five variables, that is, uninfected cells (x), infected cells (y), free virus (v), an antibody response (w) and a CTL response (z). The model is given by

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the following nonlinear system of differential equations

$$\begin{cases} \dot{x} = \lambda - dx - \beta vx \\ \dot{y} = \beta vx - ay - pyz \\ \dot{v} = ky - uv - qvw \\ \dot{w} = gvw - hw \\ \dot{z} = cyz - bz \end{cases} \tag{1}$$

where $x(0) = x_0$, $y(0) = y_0$, $v(0) = v_0$, $w(0) = w_0$ and $z(0) = z_0$ are given. Susceptible host cells (x) are produced at a rate λ, die at a rate dx and become infected by virus at a rate βxv. Infected cells die at a rate ay and are killed by the CTL response at a rate pyz. Free virus is produced by infected cells at a rate ky, decays at a rate uv and is neutralized by antibodies at a rate qvw. Antibodies develop in response to free virus at a rate gvw and decay at a rate hw. CTLs expand in response to viral antigen derived from infected cells at a rate cyz and decay in the absence of antigenic stimulation at a rate bz.
Clearly, the system (1) has a basic infection reproductive number of

$$R_0 = \frac{\lambda\beta k}{dau}$$

In this work, we give a rigorous global analysis of HCV model presented by system (1).

The paper is organized as follows. In Section 2, we give some properties of solutions. The analysis of the model is presented in section 3. Finally, the conclusion are summarized in Section 4.

2 Some properties of solutions

In this section, we give some properties of solutions of system (1).

2.1 Positivity

Proposition 2.1. *Let* $X : [0, +\infty[\to I\!R^5$, $X(t) = (x(t), y(t), v(t), w(t), z(t))$, *be a solution of system (1). If* $X(0) \in I\!R^5_+$ *then* $X(t) \in I\!R^5_+$ *for all* $t \in [0, +\infty[$.

Proof. Simple application of proposition A.1. (see [8]). ■

2.2 Boundedness

We denote by $C_b(I)$ the set of continuous and bounded functions defined on the interval I and taking values in $I\!R^5$.

Proposition 2.2. *Let* $X : [0, +\infty[\to I\!R^5$ *be a solution of system (1). If* $X(0) \in I\!R^5_+$ *then* $X \in C_b([0, +\infty[)$. *Moreover we have*

i) $x(t) \leq x_0 + \frac{\lambda}{d}$,

ii) $y(t) \leq y_0 + \max(1, 2 - \frac{d}{a})x_0 + \max(\frac{\lambda}{a}, \frac{\lambda}{d})$,

iii) $v(t) \leq v_0 + \frac{k}{u}\|y\|_\infty$,

iv) $w(t) \leq w_0 + \frac{g}{q}[\max(1, 2 - \frac{u}{h})v_0 + \max(\frac{k}{u}, \frac{k}{h})\|y\|_\infty]$,

v) $z(t) \leq z_0 + \frac{c}{p}[\max(1, 2 - \frac{d}{b})x_0 + y_0 + \max(\frac{\lambda}{b}, \frac{\lambda}{d}) + \max(0, 1 - \frac{a}{b})\|y\|_\infty]$.

Proof. From Proposition 2.1, we have $X(t) \in \mathbb{R}^5_+$.
As $\dot{x} = \lambda - dx - bvx$, we deduce that $\dot{x} + dx \leq \lambda$, then $\frac{d}{dt}(xe^{dt}) \leq \lambda e^{dt}$.
Hence,

$$x(t) \leq x_0 e^{-dt} + \frac{\lambda}{d}(1 - e^{-dt}), \tag{2}$$

since $0 \leq e^{-dt} \leq 1$, thus *ii)*.
From

$$\dot{y} + ay = bvx - pyz \leq bvx = \lambda - dx - \dot{x},$$

we have that

$$\dot{y} + ay \leq \lambda - (\dot{x} + dx).$$

Thus,

$$y(t)e^{at} - y_0 \leq \frac{\lambda}{a}(e^{at} - 1) - \int_0^t e^{(a-d)s}\frac{d}{ds}(x(s)e^{ds})ds.$$

Using the integration by parts, we get

$$\int_0^t e^{(a-d)s}\frac{d}{ds}(x(s)e^{ds})ds = [x(s)e^{as}]_0^t - (a - d)\int_0^t x(s)e^{as}ds.$$

Hence,

$$y(t) \leq (x_0 + y_0)e^{-at} + \frac{\lambda}{a}(1 - e^{-at}) - x(t) + (a - d)\int_0^t x(s)e^{a(s-t)}ds. \tag{3}$$

If $a - d \leq 0$, then

$$y(t) \leq x_0 + y_0 + \frac{\lambda}{a} \tag{4}$$

If $a - d \geq 0$, then

$$y(t) \leq x_0 + y_0 + \frac{\lambda}{a} + (a - d)\int_0^t x(s)e^{a(s-t)}ds$$

According to i), we have

$$y(t) \leq x_0 + y_0 + \frac{\lambda}{a} + \frac{a-d}{a}(x_0 + \frac{\lambda}{d})(1 - e^{-at}),$$

Hence,

$$y(t) \leq y_0 + (2 - \frac{d}{a})x_0 + \frac{\lambda}{d}. \tag{5}$$

From (4) and (5), we deduce ii).
Now, we show iii). The equation $\dot{v} = ky - uv - qvz$, and $(v(t), z(t)) \in \mathbb{R}^2_+$, implies that

$$v(t) \leq v_0 e^{-ut} + k\int_0^t y(s)e^{(s-t)u}ds. \tag{6}$$

Then,

$$v(t) \leq v_0 + \frac{k}{u}\|y\|_\infty(1 - e^{-tu}).$$

Since $1 - e^{-tu} \leq 1$, we deduce iii).
Using a same technic to show (3), we get

$$w(t) = w_0 e^{-ht} + \frac{g}{q}\{\int_0^t [ky(s) + (h-u)v(s)]e^{h(s-t)}ds - v(t) + v_0 e^{-ht}\}. \tag{7}$$

If $h - u \leq 0$, then

$$w(t) \leq w_0 + \frac{g}{q}(\frac{k}{h}\|y\|_\infty + v_0). \tag{8}$$

If $h - u \geq 0$, using iii), we have

$$w(t) \leq w_0 + \frac{g}{q}[\frac{k}{u}\|y\|_\infty + (2 - \frac{u}{h})v_0]. \tag{9}$$

From (8) and (9), we deduce iv).
Finally, we show v). The equation $\dot{z} = cyz - bz$ implies that

$$\dot{z} + bz = cyz = \frac{c}{p}[\lambda - (\dot{x} + dx) - (\dot{y} + ay)].$$

Using the same technic to show (3) and (7), we get

$$z(t) = [\frac{c}{p}(x_0 + y_0 - \frac{\lambda}{b}) + z_0]e^{-bt} + \frac{c}{p}\{\frac{\lambda}{b} + \int_0^t [(b-d)x(s) + (b-a)y(s)]e^{b(s-t)}ds - x(t) - y(t)\}. \tag{10}$$

If $b-d\leq 0$ and $b-a\leq 0$, we have

$$z(t)\leq z_0+\frac{c}{p}(\frac{\lambda}{b}+x_0+y_0). \tag{11}$$

If $b-d\leq 0$ and $b-a\geq 0$, we have

$$z(t)\leq z_0+\frac{c}{p}[\frac{\lambda}{b}+x_0+y_0+(1-\frac{a}{b})\|y\|_\infty]. \tag{12}$$

If $b-d\geq 0$ and $b-a\leq 0$, we have

$$z(t)\leq z_0+\frac{c}{p}[\frac{\lambda}{d}+(2-\frac{d}{b})x_0+y_0]. \tag{13}$$

If $b-d\geq 0$ and $b-a\geq 0$, we have

$$z(t)\leq z_0+\frac{c}{p}[\frac{\lambda}{d}+(2-\frac{d}{b})x_0+y_0+(1-\frac{a}{b})\|y\|_\infty]. \tag{14}$$

From (10)-(14), we deduce v). ■

2.3 Nonperiodicity and Limiting Behavior

Proposition 2.3. *Let X be a solution of system (1). If $X(0)\in I\!R^5_+$ then, the limit of $X(t)$ exists when $t\to+\infty$. In particular, X is periodic if and only if X is stationary. Moreover we have*

$$\begin{aligned}
\lim_{t\to+\infty} x(t) &\leq \frac{\lambda}{d}, && (15)\\
\lim_{t\to+\infty} z(t) &= \frac{c}{pb}[\lambda-d\lim_{t\to+\infty} x(t)-a\lim_{t\to+\infty} y(t)], && (16)\\
\lim_{t\to+\infty} v(t) &\leq \frac{k}{u}\lim_{t\to+\infty} y(t), && (17)\\
\lim_{t\to+\infty} w(t) &= \frac{g}{qh}[k\lim_{t\to+\infty} y(t)-u\lim_{t\to+\infty} v(t)]. && (18)
\end{aligned}$$

Proof. From (10) and according to Lemma 7 (see [4]), if $\max(a,b,d)=b$, we have

$$\begin{aligned}
\limsup_{t\to+\infty} z(t) &\leq \frac{c}{pb}[\lambda-d\limsup_{t\to+\infty} x(t)-a\limsup_{t\to+\infty} y(t)],\\
\liminf_{t\to+\infty} z(t) &\geq \frac{c}{pb}[\lambda-d\liminf_{t\to+\infty} x(t)-a\liminf_{t\to+\infty} y(t)].
\end{aligned}$$

If $\max(a,b,d)=a$, using the same technic for to obtain (10), we have

$$y(t)=(x_0+y_0+\frac{p}{c}z_0)e^{-at}+\frac{\lambda}{a}(1-e^{-at})-x(t)-\frac{p}{c}z(t)+\int_0^t[(a-d)x(s)+\frac{p}{c}(a-b)z(s)]e^{a(s-t)}ds.$$

then

$$\begin{aligned}\limsup_{t\to+\infty} y(t) &\leq \frac{1}{a}[\lambda - d\limsup_{t\to+\infty} x(t) - \frac{pb}{c}\limsup_{t\to+\infty} z(t)],\\ \liminf_{t\to+\infty} y(t) &\geq \frac{1}{a}[\lambda - d\liminf_{t\to+\infty} x(t) - \frac{pb}{c}\liminf_{t\to+\infty} z(t)].\end{aligned}$$

In the same way we show that, if $\max(a,b,d) = d$, we have

$$x(t) = (x_0+y_0+\frac{p}{c}z_0)e^{-dt}+\frac{\lambda}{d}(1-e^{-dt})-y(t)-\frac{p}{c}z(t)+\int_0^t[(d-a)y(s)+\frac{p}{c}(d-b)z(s)]e^{d(s-t)}ds.$$

then

$$\begin{aligned}\limsup_{t\to+\infty} x(t) &\leq \frac{1}{d}[\lambda - a\limsup_{t\to+\infty} y(t) - \frac{pb}{c}\limsup_{t\to+\infty} z(t)],\\ \liminf_{t\to+\infty} x(t) &\geq \frac{1}{d}[\lambda - a\liminf_{t\to+\infty} y(t) - \frac{pb}{c}\liminf_{t\to+\infty} z(t)].\end{aligned}$$

So, for every parameters $a > 0$, $b > 0$ and $d > 0$, we have

$$\begin{aligned}\limsup_{t\to+\infty} z(t) &\leq \frac{c}{pb}[\lambda - d\limsup_{t\to+\infty} x(t) - a\limsup_{t\to+\infty} y(t)],\\ \liminf_{t\to+\infty} z(t) &\geq \frac{c}{pb}[\lambda - d\liminf_{t\to+\infty} x(t) - a\liminf_{t\to+\infty} y(t)].\end{aligned}$$

Hence,

$$\limsup_{t\to+\infty} z(t)-\liminf_{t\to+\infty} z(t) \leq \frac{c}{pb}[d(\liminf_{t\to+\infty} x(t)-\limsup_{t\to+\infty} x(t))+a(\liminf_{t\to+\infty} y(t)-\limsup_{t\to+\infty} y(t))].$$

Thus,

$$\begin{aligned}\limsup_{t\to+\infty} x(t) &= \liminf_{t\to+\infty} x(t),\\ \limsup_{t\to+\infty} y(t) &= \liminf_{t\to+\infty} y(t),\\ \limsup_{t\to+\infty} z(t) &= \liminf_{t\to+\infty} z(t),\\ \lim_{t\to+\infty} z(t) &= \frac{c}{pb}[\lambda - d\lim_{t\to+\infty} x(t) - a\lim_{t\to+\infty} y(t)].\end{aligned}$$

From (2) we have $\lim_{t\to+\infty} x(t) \leq \frac{\lambda}{d}$, thus (15) and (16).
From (7) and Lemma 7, if $h \geq u$, we have

$$\begin{aligned}\limsup_{t\to+\infty} w(t) &\leq \frac{g}{qh}(k\limsup_{t\to+\infty} y(t) - u\limsup_{t\to+\infty} v(t)),\\ \liminf_{t\to+\infty} w(t) &\geq \frac{g}{qh}(k\liminf_{t\to+\infty} y(t) - u\liminf_{t\to+\infty} v(t)).\end{aligned}$$

If $h < u$, using the same technic for to obtain (7), we have

$$v(t) = v_0 e^{-ut} + \int_0^t [ky(s) + \frac{q}{g}(u-h)w(s)]e^{u(s-t)}ds - \frac{q}{g}w(t) + \frac{q}{g}w_0 e^{-ut}.$$

Then

$$\begin{aligned} \limsup_{t\to+\infty} v(t) &\leq \frac{k}{u}\limsup_{t\to+\infty} y(t) - \frac{qh}{gu}\limsup_{t\to+\infty} w(t), \\ \liminf_{t\to+\infty} v(t) &\geq \frac{k}{u}\liminf_{t\to+\infty} y(t) - \frac{qh}{gu}\liminf_{t\to+\infty} w(t). \end{aligned}$$

So, for every parameters $h > 0$ and $u > 0$, we have

$$\begin{aligned} \limsup_{t\to+\infty} w(t) &\leq \frac{g}{qh}(k\limsup_{t\to+\infty} y(t) - u\limsup_{t\to+\infty} v(t)), \\ \liminf_{t\to+\infty} w(t) &\geq \frac{g}{qh}(k\liminf_{t\to+\infty} y(t) - u\liminf_{t\to+\infty} v(t)). \end{aligned}$$

Since limit $y(t)$ exists, we have

$$\limsup_{t\to+\infty} w(t) - \liminf_{t\to+\infty} w(t) \leq \frac{gu}{qh}(\liminf_{t\to+\infty} v(t) - \limsup_{t\to+\infty} v(t)).$$

Thus,

$$\begin{aligned} \limsup_{t\to+\infty} v(t) &= \liminf_{t\to+\infty} v(t), \\ \limsup_{t\to+\infty} z(t) &= \liminf_{t\to+\infty} z(t), \end{aligned}$$

then limits $v(t)$ and $w(t)$ exist. Moreover

$$\lim_{t\to+\infty} w(t) = \frac{g}{qh}[k\lim_{t\to+\infty} y(t) - u\lim_{t\to+\infty} v(t)].$$

Finally, from (6) we have

$$\lim_{t\to+\infty} v(t) \leq \frac{k}{u}\lim_{t\to+\infty} y(t).$$

In particular, X is periodic if and only if X is stationary. ■

3 Analysis of the model

In this section, we shall study the global asymptotic stability of system (1).

The system (1) always has disease free equilibria of the form $E_0 = (\frac{\lambda}{d}, 0, 0, 0, 0)$ and four endemic equilibrium points:

$$E_1 = (\frac{au}{\beta k}, \frac{\lambda\beta k - dau}{a\beta k}, \frac{\lambda\beta k - dau}{a\beta u}, 0, 0),$$

$$E_2 = (\frac{\lambda uc}{duc + \beta kb}, \frac{b}{c}, \frac{kb}{uc}, 0, \frac{k\beta\lambda c - a(duc + \beta kb)}{p(duc + \beta kb)}),$$

$$E_3 = (\frac{\lambda g}{dg + \beta h}, \frac{\beta h\lambda}{a(dg + \beta h)}, \frac{h}{g}, \frac{k\beta\lambda g - au(dg + \beta h)}{aq(dg + \beta h)}, 0),$$

$$E_4 = (\frac{\lambda g}{dg + \beta h}, \frac{b}{c}, \frac{h}{g}, \frac{kbg - uhc}{cqh}, \frac{hc\beta\lambda - ab(dg + \beta h)}{pb(dg + \beta h)}),$$

We put

$$D_0^w = \frac{\lambda kg}{auh}, \; H_0^w = \frac{1}{\frac{1}{R_0} + \frac{1}{D_0^w}}, \tag{19}$$

$$D_0^z = \frac{\lambda c}{ab}, \; H_0^z = \frac{1}{\frac{1}{R_0} + \frac{1}{D_0^z}}. \tag{20}$$

Then, these equilibria we can be written:

$$E_i = (\frac{\lambda}{d}Q_i^x, \frac{\lambda}{a}Q_i^y, \frac{d}{\beta}Q_i^v, \frac{u}{q}Q_i^w, \frac{a}{p}Q_i^z), \; 0 \leq i \leq 4.$$

where

$$\begin{aligned}
Q_0^x &= 1, \; Q_0^y = Q_0^v = Q_0^w = Q_0^z = 0, \\
Q_1^x &= \frac{1}{R_0}, \; Q_1^y = 1 - \frac{1}{R_0}, \; Q_1^v = R_0 - 1, \; Q_1^w = Q_1^z = 0, \\
Q_2^x &= \frac{H_0^z}{R_0}, \; Q_2^y = \frac{1}{D_0^z}, \; Q_2^v = \frac{R_0}{D_0^z}, \; Q_2^w = 0, \; Q_2^z = H_0^z - 1, \\
Q_3^x &= \frac{H_0^w}{R_0}, \; Q_3^y = \frac{H_0^w}{D_0^w}, \; Q_3^v = \frac{R_0}{D_0^w}, \; Q_3^w = H_0^w - 1, \; Q_3^z = 0, \\
Q_4^x &= \frac{H_0^w}{R_0}, \; Q_4^y = \frac{1}{D_0^z}, \; Q_4^v = \frac{R_0}{D_0^w}, \; Q_4^w = \frac{D_0^w}{D_0^z} - 1, \; Q_4^z = \frac{D_0^z}{D_0^w}H_0^w - 1.
\end{aligned}$$

It easy to remark that

Remark 3.1.

1. *If $R_0 < 1$, then E_1 does not exists and $E_1 = E_0$ when $R_0 = 1$.*
2. *If $H_0^z < 1$, then E_2 does not exists and $E_2 = E_1$ when $H_0^z = 1$.*

3. *If $H_0^w < 1$, then E_3 does not exists and $E_3 = E_1$ when $H_0^w = 1$.*

4. *If $D_0^w < D_0^z$ or $\frac{D_0^z}{D_0^w} H_0^w < 1$, then E_4 does not exists. Moreover $E_4 = E_2$ when $D_0^w = D_0^z$ and $E_4 = E_3$ when $\frac{D_0^z}{D_0^w} H_0^w = 1$.*

The number D_0^w represents the basic defence rate by antibody response, D_0^z represents the basic defence rate by CTL response, H_0^w is the half harmonic mean of R_0 and D_0^w and H_0^z is the half harmonic mean of R_0 and D_0^z.

We put

$$H_0^{w,z} = \frac{H_0^w D_0^z}{D_0^w}.$$

We remark that $H_0^w = H_0^{w,w}$ and $H_0^z = H_0^{z,z}$. The importance of these parameters is related in the following result.

Theorem 3.2.

i) *If $R_0 \leq 1$, then E_0 is globally asymptotically stable.*

ii) *If $R_0 > 1, H_0^w \leq 1$ and $H_0^z \leq 1$, then E_1 is globally asymptotically stable.*

iii) *If $H_0^z > 1$ and $D_0^z > D_0^w$, then E_2 is globally asymptotically stable.*

iv) *If $H_0^w > 1$ and $H_0^{w,z} \leq 1$, then E_3 is globally asymptotically stable.*

v) *If $D_0^w > D_0^z$ and $H_0^{w,z} > 1$, then E_4 is globally asymptotically stable.*

Proof. Using the same technic given in [2] and [7], we consider the following Lyapunov function in $\mathbb{R}_+^5$:

$$\begin{aligned} V(x,y,v,w,z) &= x^*(\frac{x}{x^*} - \ln\frac{x}{x^*}) + y^*(\frac{y}{y^*} - \ln\frac{y}{y^*}) + \frac{\beta x^*}{u+qw^*}[v^*(\frac{v}{v^*} - \ln\frac{v}{v^*}) \\ &\quad + \frac{q}{g}w^*(\frac{w}{w^*} - \ln\frac{w}{w^*})] + \frac{p}{c}z^*(\frac{z}{z^*} - \ln\frac{z}{z^*}), \end{aligned}$$

where $E^* = (x^*, y^*, v^*, w^*, z^*)$ is an equilibrium of system (1) and when $.^*$ is zero for some equilibrium coordinate, the corresponding log term will be absent. It easy to verifies that

$$\begin{aligned} \dot{V}(x,y,v,w,z) &= \lambda[1 + Q_i^x + Q_i^y + \frac{R_0 Q_i^x}{1+Q_i^w}(\frac{Q_i^v}{R_0} + \frac{Q_i^w}{D_0^w}) + \frac{Q_i^z}{D_0^z}] - (dx + \frac{\lambda^2}{dx}Q_i^x) - \frac{\beta\lambda xv}{ay}Q_i^y \\ &\quad - \frac{\lambda ky}{uv}\frac{Q_i^x Q_i^v}{1+Q_i^w} + ay(\frac{R_0 Q_i^x}{1+Q_i^w} - 1 - Q_i^z) + \frac{wq\lambda}{u}\frac{Q_i^x}{1+Q_i^w}(Q_i^v - \frac{R_0}{D_0^w}) \\ &\quad + \frac{p\lambda z}{a}(Q_i^y - \frac{1}{D_0^z}). \end{aligned}$$

For $i = 0$ we have that

$$\dot{V} = 2\lambda - (dx + \frac{\lambda^2}{dx}) + ay(R_0 - 1) - \frac{\lambda qw}{u}\frac{R_0}{D_0^w} - \frac{p\lambda z}{a}\frac{1}{D_0^z}.$$

Since

$$dx + \frac{\lambda^2}{dx} \geq 2\lambda,$$

then $\dot{V} < 0$ and E_0 is globally asymptotically stable, if $R_0 \leq 1$.

For $i = 1$ we have that

$$\begin{aligned}
\dot{V} &= \lambda(3 - \frac{1}{R_0}) - (dx + \frac{\lambda^2}{R_0 dx}) - \frac{\beta\lambda xv}{ay}(1 - \frac{1}{R_0}) - \frac{\lambda ky}{uv}(1 - \frac{1}{R_0}) \\
&\quad + \frac{\lambda qw}{u}(1 - \frac{1}{H_0^w}) + \frac{p\lambda z}{a}(1 - \frac{1}{H_0^z}) \\
&= \lambda[3(1 - \frac{1}{R_0}) + \frac{2}{R_0}] - (dx + \frac{\lambda^2}{R_0^2 dx}) - \frac{\lambda^2}{R_0 dx}(1 - \frac{1}{R_0}) - \frac{\beta\lambda xv}{ay}(1 - \frac{1}{R_0}) - \frac{\lambda ky}{uv}(1 - \frac{1}{R_0}) \\
&\quad + \frac{\lambda qw}{u}(1 - \frac{1}{H_0^w}) + \frac{p\lambda z}{a}(1 - \frac{1}{H_0^z})
\end{aligned}$$

Using the arithmetic-geometric inequality, if $R_0 > 1$, we have that

$$-\frac{\lambda^2}{R_0 dx}(1 - \frac{1}{R_0}) - \frac{\beta\lambda xv}{ay}(1 - \frac{1}{R_0}) - \frac{\lambda ky}{uv}(1 - \frac{1}{R_0}) \leq -3\lambda(1 - \frac{1}{R_0}).$$

Since

$$dx + \frac{\lambda^2}{R_0^2 dx} \geq \frac{2\lambda}{R_0},$$

then $\dot{V} < 0$ and E_1 is globally asymptotically stable, if $R_0 > 1$, $H_0^w \leq 1$ and $H_0^z \leq 1$.

For $i = 2$ we have that

$$\begin{aligned}
\dot{V} &= \lambda(3 - \frac{H_0^z}{R_0}) - (dx + \frac{\lambda^2}{dx}\frac{H_0^z}{R_0}) - \frac{\beta\lambda xv}{ay}\frac{1}{D_0^z} - \frac{\lambda ky}{uv}\frac{H_0^z}{D_0^z} + \frac{\lambda qw}{u}H_0^z(\frac{1}{D_0^z} - \frac{1}{D_0^w}) \\
&= \lambda(3\frac{H_0^z}{D_0^z} + 2\frac{H_0^z}{R_0}) - [dx + \frac{\lambda^2}{dx}(\frac{H_0^z}{R_0})^2] - \frac{\lambda^2}{dx}\frac{H_0^z}{R_0}(1 - \frac{H_0^z}{R_0}) - \frac{\beta\lambda xv}{ay}\frac{1}{D_0^z} - \frac{\lambda ky}{uv}\frac{H_0^z}{D_0^z} \\
&\quad + \frac{\lambda qw}{u}H_0^z(\frac{1}{D_0^z} - \frac{1}{D_0^w})
\end{aligned}$$

Using the arithmetic-geometric inequality, we have that

$$-\frac{\lambda^2}{dx}\frac{H_0^z}{R_0}(1 - \frac{H_0^z}{R_0}) - \frac{\beta\lambda xv}{ay}\frac{1}{D_0^z} - \frac{\lambda ky}{uv}\frac{H_0^z}{D_0^z} \leq -3\lambda\frac{H_0^z}{D_0^z}.$$

Since

$$dx + \frac{\lambda^2}{dx}(\frac{H_0^z}{R_0})^2 \geq 2\lambda\frac{H_0^z}{R_0},$$

then $\dot{V} < 0$ and E_2 is globally asymptotically stable, if $H_0^z > 1$ and $D_0^z > D_0^w$.

For $i = 3$ we have that

$$\begin{aligned}\dot{V} &= \lambda(3\frac{H_0^w}{D_0^w} + 2\frac{H_0^w}{R_0}) - [dx + \frac{\lambda^2}{dx}(\frac{H_0^w}{R_0})^2] - \frac{\lambda^2}{dx}\frac{H_0^w}{R_0}(1 - \frac{H_0^w}{R_0}) - \frac{\beta\lambda xv}{ay}\frac{H_0^w}{D_0^w} - \frac{\lambda ky}{uv}\frac{1}{D_0^w} \\ &\quad + \frac{p\lambda z}{aD_0^z}(H_0^{w,z} - 1)\end{aligned}$$

Using the arithmetic-geometric inequality, we have that

$$-\frac{\lambda^2}{dx}\frac{H_0^w}{R_0}(1 - \frac{H_0^w}{R_0}) - \frac{\beta\lambda xv}{ay}\frac{H_0^w}{D_0^w} - \frac{\lambda ky}{uv}\frac{1}{D_0^w} \leq -3\lambda\frac{H_0^w}{D_0^w}.$$

Since

$$dx + \frac{\lambda^2}{dx}(\frac{H_0^w}{R_0})^2 \geq 2\lambda\frac{H_0^w}{R_0},$$

then $\dot{V} < 0$ and E_3 is globally asymptotically stable, if $H_0^w \geq 1$ and $H_0^{w,z} < 1$.

For $i = 4$ we have that

$$\begin{aligned}\dot{V} &= \lambda(3 - \frac{H_0^w}{R_0}) - (dx + \frac{\lambda^2}{dx}\frac{H_0^w}{R_0}) - \frac{\beta\lambda xv}{ay}\frac{1}{D_0^z} - \frac{\lambda ky}{uv}\frac{H_0^{w,z}}{D_0^w}, \\ &= \lambda(3 - \frac{H_0^w}{R_0}) - [dx + \frac{\lambda^2}{dx}(\frac{H_0^w}{R_0})^2] - \frac{\lambda^2}{dx}\frac{H_0^w}{R_0}(1 - \frac{H_0^w}{R_0}) - \frac{\beta\lambda xv}{ay}\frac{1}{D_0^z} - \frac{\lambda ky}{uv}\frac{H_0^{w,z}}{D_0^w}.\end{aligned}$$

Using the arithmetic-geometric inequality, we have that

$$-\frac{\lambda^2}{dx}\frac{H_0^w}{R_0}(1 - \frac{H_0^w}{R_0}) - \frac{\beta\lambda xv}{ay}\frac{1}{D_0^z} - \frac{\lambda ky}{uv}\frac{H_0^{w,z}}{D_0^w} \leq -3\lambda\frac{H_0^w}{D_0^w}.$$

Since

$$dx + \frac{\lambda^2}{dx}(\frac{H_0^w}{R_0})^2 \geq 2\lambda\frac{H_0^w}{R_0},$$

then $\dot{V} \leq 0$.

The equality holds if and only if

$$x = x^* \quad \textit{and} \quad \frac{v}{y} = \frac{k}{u}\frac{D_0^z}{D_0^w} = \frac{v^*}{y^*}.$$

Let

$$S = \{(x, y, v, w, z) \in \mathbb{R}_+^5 : \dot{V}(x, y, v, w, z) = 0\}.$$

Trajectory $(x(t), y(t), v(t), w(t), z(t)) \in S$ imply that

$$y = y^*, \ v = v^*, \ w = w^* \ \ \textit{and} \ \ z = z^*.$$

From LaSalle's invariance principle [3], we conclude that E_4 is globally asymptotically stable, if $D_0^w > D_0^z$ and $H_0^{w,z} > 1$.

4 Conclusion

In this work, we give the global analysis of a HCV with CTL and antibody responses. The disease free equilibrium is global attractor if the basic infection reproduction number satisfies $R_0 \leq 1$. In addition, the stability of the four endemic equilibrium points is dependent upon both the basic defence rate by antibody response and the basic defence rate by CTL response. These parameters play a crucial role, in order to characterize the stable equilibrium points.

Moreover, we prove that the solutions of this model with positive initial conditions are all positive, bounded and do not admit periodic solutions.

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