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Global Stability of Disease-Free Equilibrium for an Acute Hepatitis C Virus Transmission Dynamics Model

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Abstract:

Global stability of disease-free equilibrium (DFE) of a deterministic epidemiological model describes the state of no infection that can eventually be reached in the absence of intervention, suggesting that the system can be deliberately intervened. This paper presents a global stability analysis of DFE, E_0 obtained from an acute hepatitis C virus (HCV) transmission dynamics model that incorporates the dynamic effectors: immune response, hepatocytes proliferation and spontaneous clearance of the virus. The analysis was accomplished with R_0 calculated from the model system of equations at E_0 using Metzler matrix method. With the parameter threshold R_0, being a determining factor of the transmission of HCV infection, both the analytical results and simulations results have established the conditions for global stability of DEF. Precisely, the results show that the basic reproductive number, R_0 remains below unity, $R_0 < 1$, despite initial values of the state variables. Thus, there should be a timely strategic intervention to eradicate the disease by ensuring that the basic reproductive number is strictly less than unity.

Keywords: *HCV model, Disease free equilibrium, Basic reproductive number, Global stability.*

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1. Introduction

Hepatitis C infection is a disease caused by hepatitis C virus (HCV) that was recognized in 1983 (Choo *et al.*, 1989; Purcell, 1997), which is one of the well-known types of viruses that trigger liver inflammation, ultimately leading to hepatic loss. The disease has been persistently a world health tragedy as about 150 to 200 million people are infected with HCV worldwide. This triggers death of at least 350,000 people each year from HCV-related liver complications caused by liver cirrhosis and hepatocellular carcinoma (Perz *et al.*, 2006). Overall, this is attributed to absence of vaccine as the virus mutates very rapidly and absence of reliable medication that can bring about 100 percent sustained virologic response (SVR) to infected persons. Moreover, poor awareness of existence and mode of transmission of the disease; and insufficient access of medical services by the majority of infected people exceedingly contributes to the world health tragedy. Of the world population, the prevalence rate of HCV infection is below 2 percent in developed countries such as Australia and most West Europe countries(Alter, 2007;Cornberg *et al.*, 2011; Sievert *et al.*, 2011). In most parts of Eastern Europe, Latin America, countries formerly under the Soviet Union, some African countries, the Middle East and South Asia, the HCV prevalence rate is at least 3 percent(Shepard *et al.*, 2005; Qureshi *et al.*, 2010; Kershenobich *et al.*, 2011; Sievert *et al.*, 2011). In Africa, it generally ranges from 0.1 percent to17.5percent depending on the country and genotype. Egypt, for example, has the prevalence rate 17.5 percent whereas Zambia, Kenya, Malawi and South Africa have the lowest rates (less than 1 percent) (Karoney and Siika, 2013).

The channels of HCV transmission are blood, blood products such as red blood cell concentrates, platelets, plasma and cryoprecipitate, tissue and organs and unsafe medical services generally in healthcare provision centers. In developing countries, the most common channels of transmission are injection drug use (IDU) and unsafe injection practices (Williams *et al*., 2011) while IDU is the most common channel in developed countries.

To date, mathematical modeling has proven to be very important and thus a reliable mainstay in the study of the origin and spread of infectious diseases. The analysis of models helps to obtain additional understanding of the diseases dynamics, which can facilitate search for proper control strategies. The study of the disease dynamics through mathematical modeling and analysis of the model helps to address clearly the origination and development of viruses (Liu*et al.*, 2013). Moreover, the analysis of these models helps to examine the dynamic behaviour of diseases from which we can understand how various dynamic effectors influence infection development with time. Therefore, mathematical modeling can help in figuring out decisions that influence theories and practices in relation to disease management and control (Tumwiine *et al.*, 2007).

Similarly, modeling of HCV dynamics has provided further insight into the origination and spread of the virus; and the effect of infection in communities worldwide. This has helped pharmacologists to develop

medicines in an attempt to treat infected people though this has not been 100percent successful (i.e., without 100 percent SVR). In literature, a number of mathematical models have been developed to study the dynamics of HCV with various dynamics effectors, whereby some have combined the effectors: host immune response, hepatocytes proliferation, spontaneous clearance of the virus and antiviral therapy (Newmann *et al*., 1998; Avendano *et al.*, 2002; Dahari et al. 2005c; Dahari et al., 2007a ; Dahari *et al*., 2007b; Ismail *et al.* 2017; Ismail and Luboobi, 2019). Besides, global stability analysis of in-vivo HCV models steady states has been done as shown in literature (Ismail *et al*, 2016a: Ismail and Luboobi *et al*, 2017b; Cheng *et al*, 2015; Miao et all, 2016; Nangue, 2019; Nangue *et al*, 2019a; Nangue, 2019b) and found that they are stable. With these available models, efforts to find suitable control measures have not guaranteed its eradication yet. Thus, research in this area is ongoing. In this paper, no new model has been presented; instead, we have performed global analysis of only DFE of an in-vivo HCV dynamics model developed by Ismail and Luboobi (2019) has been presented in order to acquire further insight of its pathogenesis and thus aid search of suitable control measures. The model steady state DFE has been chosen merely for simplicity of analyses and due to its indication that the disease disappears in the long run, which establishes the fact that early inteventation becomes more successful.

Some significant analytical results of the model are the disease-free equilibrium (DFE), endemic equilibrium (EE) and basic reproductive number R_0. The parameter R_0. is a measure of disease transmissibility in a completely susceptible population; it helps in the investigation of asymptotic behaviour of the model at the states DFE and EE. DFE is the equilibrium state that describes the absence of disease while EE is the state that describes disease prevalence. R_0 has been one of the keys and most frequently used metrics to investigate the dynamics of an infectious disease (Keeling and Grenfell, 2000; Heesterbeek, 2002; Heffernan *et al*., 2005; Roberts, 2007; Pellis *et al.*, 2012). It is an indicator of the transmissibility of disease infectious agents. Definitely, through the model equilibria together with the parameter R_0, one can determine whether or not the DFE is globally asymptotically stable; and so the conditions for either extinction or prevalence of the disease can be established. This paper presents a global stability analysis of the steady state DFE for an in-vivo HCV dynamics model that incorporates the dynamic effectors host body immune system response, spontaneous clearance of the virus and proliferation of hepatocytes (Ismail and Luboobi, 2019). In essence, this will provide further insight into the disease progression, where it is revealed that the disease will go to extinction in the long run in the absence of intervention. Thus, pharmacologists can design appropriate medications that can be used as therapies to combat the disease.

2. The Model

At this juncture ,we briefly reiterate some significant preliminaries and few analytical

results of a deterministic mathematical model formulated to investigate the effect of immune response and hepatocytes proliferation on the transmission dynamics of HCV in the acute stage of infection (Ismail and Luboobi, 2019). These dynamic features are very important for the achievement of global analysis of the model equilibrium state.

2.1 Description of Dynamics

The model incorporated four (4) compartmental dynamic classes: susceptible hepatocytes (S), infected hepatocytes (I), free hepatitis C viruses (V) and $CD8^+$ T cells (T). In the presence of HCV infection, susceptible hepatocytes (S) are produced at a rate Λ, die naturally at a rate $\mu_1 S$ and are infected by the interaction with the virus at a rate σSV. The infected hepatocytes die naturally at a rate $\mu_1 I$ and produce free viruses at a rate βI. The susceptible hepatocytes and infected hepatocytes proliferate logistically at a maximum proliferation rate α to allow the liver grow till a maximum size $N_{\max}$. The infected hepatocytes die due to infection at a rate δI and recover spontaneously at a rate ΣI. The viruses die naturally at a constant rate $\mu_2 V$. In the HCV infection period, the $CD8^+$ T cells are produced logistically at a rate λ so as to kill the infected hepatocytes. The $CD8^+$ T cells kill infected hepatocytes at a rate ωIT and die naturally at a rate $\mu_3 T$.

The state variables and parameters symbols used in the model are defined in Table 1 and Table 2 respectively.

Table 1: Variables' Descriptions

Variable	Definition
S	Susceptible hepatocytes
I	Infected hepatocytes
V	Hepatitis C viruses
T	$CD8^+$ T cells

Table 2: Parameters' Descriptions

Parameter	Definition
σ	Infection rate
β	Production rate of viruses from infected hepatocytes
ω	$CD8^+$ T cells destructive rate of infected hepatocytes
Λ	Recruitment rate of susceptible hepatocytes
λ	Production rate of $CD8^+$ Tcells
μ_1	Natural death rate of susceptible and infected hepatocytes
μ_2	Natural death rate of hepatitis C viruses
μ_3	Natural death rate of $CD8^+$ T cells
Σ	Spontaneous recovery rate of infected hepatocytes
δ	Hepatitis C disease-induced death rate of infected hepatocytes
α	Maximum proliferation rate of susceptible and infected hepatocytes
$N_{\max}$	Maximum level of susceptible hepatocytes population due to cell proliferation
T_m	Maximum level of $CD8^+$ T cells population

From the description of dynamics and the symbols for state variables and parameters defined in Table 1 and Table 2 respectively, we established the system of ordinary differential equations 1-4. In this case, Equation 1 models the uninfected liver cells population; Equation 2, the infected liver cells population; Equation 3, the viral load and Equation 4, the $CD8^+$ T cells population.

$$\frac{dS}{dt} = \Lambda + \Sigma I + \alpha S(1 - \frac{I+S}{N_{\max}}) - \mu_1 S - \sigma SV \quad (1)$$

$$\frac{dI}{dt} = \sigma SV + \alpha I(1 - \frac{I+S}{N_{\max}}) - \mu_1 I - \delta I - \omega IT - \Sigma I \quad (2)$$

$$\frac{dV}{dt} = \beta I - \mu_2 V \quad (3)$$

$$\frac{dT}{dt} = \lambda V(1 - \frac{T}{T_{\max}}) - \mu_3 T \quad (4)$$

with initial conditions: $S(0) \geq 0$, $I(0) \geq 0$, $V(0) \geq 0$ and $T(0) \geq 0$.

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It was proved that all feasible solutions of the model system are positively invariant in the region φ such that $\varphi = \psi_L \times \psi_V \times \psi_T$, where

$$\psi_L = \left\{ N(t) : N(t) \leq \max\left\{ N_0, \frac{(\alpha - \mu_1)N_{\max}}{\alpha} \right\} \right\},$$

$$\psi_V = \left\{ V(t) : V(t) \leq \max\left\{ V_0, \frac{\beta(\alpha - \mu_1)N_{\max}}{\alpha\mu_2} \right\} \right\}$$

$$\psi_T = \left\{ T(t) : T(t) \leq \max\left\{ T_0, \frac{(\alpha - \mu_1)\lambda\beta N_{\max}T_{\max}}{(\alpha - \mu_1)\lambda\beta N_{\max} + \alpha\mu_2\mu_3 T_{\max}} \right\} \right\}$$

provided that $\alpha > \mu_1$. It was also proved that the solution set $\{S(t), I(t), V(t), T(t)\}$ contains only non-negative values in φ $\forall t \geq 0$ .Therefore, it was established that the model system 1-4 is epidemiologically and mathematically realistic (Hethcote, 2000).

3. Analysis of the Model

3.1 Existence of Disease-Free Equilibrium, E_0

The disease-free equilibrium point describes the state of absence of HCV infection. It is obtained by equating the derivatives of the model equations equal to zero. Thus, the model system 1-4 becomes:

$$\begin{cases} \Lambda + \Sigma I + \alpha S\left(1 - \dfrac{S+I}{N_{\max}}\right) - \mu_1 S - \sigma SV = 0 \\ \sigma SV + \alpha I\left(1 - \dfrac{S+I}{N_{\max}}\right) - \mu_1 I - \omega IT - \delta I - \Sigma I = 0 \\ \beta I - \mu_2 V = 0 \\ \lambda V(1 - T/T_{\max}) - \mu_3 T = 0 \end{cases} \quad (5)$$

Let $E_0 = (S^*, I^*, V^*, T^*)$ be the DFE point of the model (1)-(4). Then from the new system of equations (5), we have:

$$S^* = \frac{\Lambda + \Sigma I^*}{\mu_1 + \sigma V^* - \alpha\left(1 - \dfrac{S^* + I^*}{N_{\max}}\right)}$$

, $I^* = \dfrac{\mu_2 V^*}{\beta}$ and $T^* = \dfrac{\lambda T_{\max} V^*}{\lambda V^* + \mu_3 T_{\max}}$

When there is no HCV infection, $V = 0$. Then this produces: $I^* = 0$, $T^* = 0$ and

$$S^* = \frac{\Lambda}{\mu_1 - \alpha\left(1 - \dfrac{S^*}{N_{\max}}\right)}$$

Since $I^* = 0$, then $S^* = N_{\max}$. Thus, the disease-free equilibrium exists at E_0; and is given by

$$E_0 = \left(\frac{\Lambda}{\mu_1}, 0, 0, 0\right)$$

This implies that the whole hepatic cells population consists of merely susceptible hepatocytes at this state.

3.2 Basic Reproductive Number, R_0

The transmission of an infectious disease in a population is a global concern. Thus, Heesterbeek and Dietz (1996) introduced most noteworthy and esteemed ideas to mathematical epidemiology. One of these ideas is the basic reproductive number, R_0, which is a measure of the potential for disease transmission in a population. It represents the average number of new infections caused by an infected individual introduced into an entirely susceptible population. Precisely, it denotes the average number of infected hepatocytes produced by an infectious hepatocyte in an entirely susceptible hepatic cells population.

Using the next generation operator method described by Diekmann and Heesterbeek (2000) and subsequently examined by Van den and Watmough (2005), the basic reproduction number, R_0 of the model system of equations 1-4 was determined. This is the spectral radius of the next generation matrix FY^{-1}, which is given by

$$FY^{-1} = \left[\frac{\partial F_i(E_0)}{\partial X_j}\right]\left[\frac{\partial Y_i(E_0)}{\partial X_j}\right]^{-1},$$

where

$$F = \begin{bmatrix} \alpha\left(1 - \dfrac{\Lambda}{\mu_1 N_{\max}}\right) & \dfrac{\sigma\Lambda}{\mu_1} \\ \beta & 0 \end{bmatrix}$$

and $$Y = \begin{bmatrix} \mu_1 + \delta + \Sigma & 0 \\ 0 & \mu_2 \end{bmatrix}$$

Inverting Y produces

$$Y^{-1} = \begin{bmatrix} \frac{1}{\mu_1 + \delta + \Sigma} & 0 \\ 0 & \frac{1}{\mu_1} \end{bmatrix}$$

Thus, we have:

$$FY^{-1} = \begin{bmatrix} \frac{\alpha\left(1 - \frac{\Lambda}{\mu_1 N_{\max}}\right)}{\mu_1 + \delta + \Sigma} & \frac{\sigma\Lambda}{\mu_1\mu_2} \\ \frac{\beta}{\mu_1 + \delta + \Sigma} & 0 \end{bmatrix}$$

Hence the dominant eigenvalue of FY^{-1}, which is the basic reproductive number R_0, is given by

$$R_0 = \frac{1}{2}\cdot\frac{\alpha(\mu_1 N_{\max} - \Lambda)}{(\mu_1 + \delta + \Sigma)\mu_1 N_{\max}} + \frac{1}{2}\cdot\sqrt{\frac{\alpha^2(\mu_1 N_{\max} - \Lambda)^2}{(\mu_1 N_{\max})^2(\mu_1 + \delta + \Sigma)^2} + \frac{4\beta\Lambda\sigma}{\mu_1\mu_2(\mu_1 + \delta + \Sigma)}} \quad (6)$$

3.3 Asymptotic Stability of Disease-Free Equilibrium, E_0

Here, we determine the conditions under which the disease free equilibrium is asymptotically stable or unstable. Asymptotic stability denotes the state where solutions starting arbitrarily in the close vicinity of the equilibrium remains in the close vicinity of the equilibrium and tends to the equilibrium over time $0 \le t < \infty$ whereas instability means the state where solutions starting arbitrarily in the close vicinity of the equilibrium do not tend to it over indefinite time. Also, if neighboring initial conditions of a fixed point remain in the close vicinity of that point over definite time the point is said to be locally stable; and if they remain in the close vicinity of it over indefinite time it is said to be globally stable

3.4 Global Stability of Disease-Free Equilibrium, E_0

Here, we establish a condition for the global asymptotic stability (GAS) of DFE for Hepatitis C virus infection. This means we have to prove that the condition for the GAS is $R_0 < 1$. The analysis is achieved by the Theorem 1 and Metzler matrix method. Here, a Lyapunov function or Comparison method could be used, but the Lyapunov function method has been extensively used.

Theorem 1: *The disease-free equilibrium, E_0 of the HCV model system* 1-4 *is globally asymptotically stable (GAS) if $R_0 \le 1$.*

Proof: To prove the theorem, we use the equations of the system 1-4 and the approaches of Kamgang and Sallet (2008) and Dumont (2008). Therefore, we can write the system 1-4 in the following manner:

$$\begin{cases} \frac{dX_s}{dt} = A_1(X_s - X_{DFE,s}) + A_3 X_i \\ \frac{dX_i}{dt} = A_2 X_s \end{cases} \quad (7)$$

where X_s is the vector denoting the state of different compartments of non-transmitting classes while the vector X_i denotes the state of different compartments of transmitting classes. Thus, we have

$$X_s = \begin{pmatrix} S \\ T \end{pmatrix}, \; X_i = \begin{pmatrix} I \\ V \end{pmatrix} \text{ and } X_{DFE,s} = \left(\frac{\Lambda}{\mu_1}, 0 \right) \tag{8}$$

It implies that

$$\begin{pmatrix} \Lambda + \Sigma I + \alpha S\left(1 - \frac{I+S}{N_{\max}}\right) - \mu_1 S - \sigma S V \\ \lambda V\left(1 - \frac{T}{T_{\max}}\right) - \mu_3 T \end{pmatrix} = A_1 \begin{pmatrix} S - \frac{\Lambda}{\mu_1} \\ T \end{pmatrix} + A_3 \begin{pmatrix} I \\ V \end{pmatrix} \tag{9}$$

$$\begin{pmatrix} \sigma S V + \alpha I\left(1 - \frac{I+S}{N_{\max}}\right) - \mu_1 I - \delta I - \omega I T - \Sigma I \\ \beta I - \mu_2 V \end{pmatrix} = A_2 \begin{pmatrix} I \\ V \end{pmatrix} \tag{10}$$

From (9), we deduce:

$$A_1 = \begin{pmatrix} -\frac{\alpha\Lambda}{\mu_1 N_{\max}} & 0 \\ 0 & \mu_3 \end{pmatrix} \text{ and } A_3 = \begin{pmatrix} \Sigma & -\frac{\sigma\Lambda}{\mu_1} \\ 0 & \lambda \end{pmatrix}$$

From (10), we deduce that

$$A_2 = \begin{pmatrix} -(\mu_1 + \delta + \Sigma) & \frac{\sigma\Lambda}{\mu_1} \\ \beta & -\mu_2 \end{pmatrix}$$

By direct computation, we find that the eigenvalues of A_1 are $-\sigma\Lambda/\mu_1 N_{\max}$ and $-\mu_3$, which are all negative and real. Furthermore, we see that A_2 is a Metzler matrix as the entries in the leading diagonal are all negative and the off-diagonal entries are all positive. In respect of this, the DFE, E_0 of the model system 1-4 is globally asymptotically stable if $R_0 \leq 1$ in the region $\varphi$and unstable if $R_0 > 1$.

In this case, we find that if the number of new HCV infections is greater than one, the disease will persist. Conversely, the disease will die out if the number of new infections is less than one

3.5 Numerical Simulations

This section presents selected numerical simulations of the HCV dynamic model to certify the analytical results. These are graphical representations demonstrating the dynamical behaviour that reflect variations in the actual physical situations. The simulations have been performed using the ode 45 MATLAB solvers for first order differential equations with most parameter values adopted from literatures. In particular, we have performed simulations of

the state variables and basic reproductive number, R_0 at given constant parameter values so as to illustrate the globally asymptotic behaviour and conditions for the global stability of disease free equilibrium (DFE), E_0 respectively. This was achieved using the following parameter values: $\lambda = 0.0003$, $\Sigma = 0.05$, $\sigma = 0.000001$, $\mu_3 = 0.009$, $\mu_1 = 0.14$, $\alpha = 0.000034$, $\delta = 0.02$, $\Lambda = 100$, $\omega = 0.0001$ and $\beta = 2$, $T_{\max} = 1000$ and $N_{\max} = 1000$. Some of these parameter values were used for the analysis of the HCV dynamics model proposed by Ismail and Luboobi (2019) while others were merely estimated.

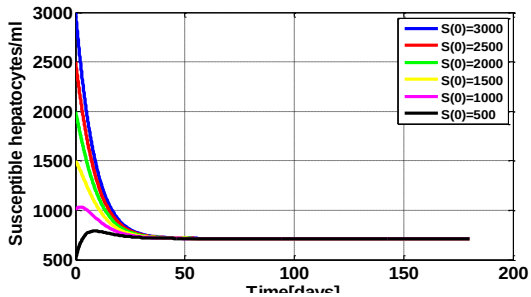

Figure 1: Graph of susceptible hepatocytes load with respect to time at various initial conditions, S_0

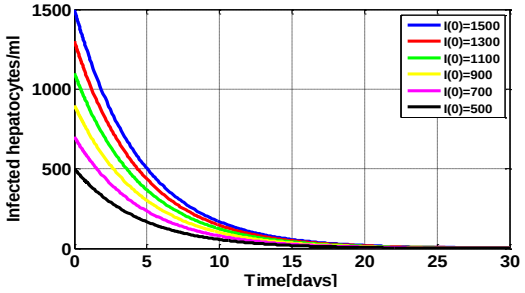

Figure 2: Graph of infected hepatocytes load with respect to time at various initial conditions. I_0

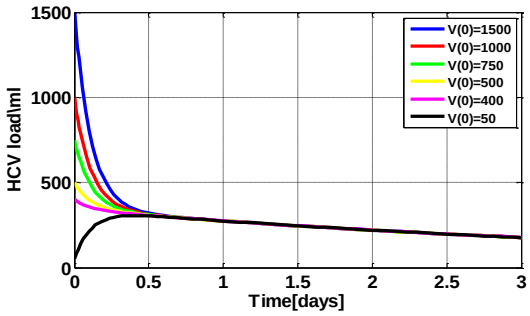

Figure 3(a): Graph at various of HCV load with respect to time initial conditions, V_0

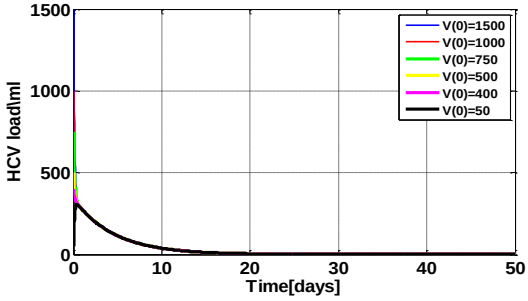

Figure 3(b): Graph of HCV load with respect to time at various initial conditions, V_0

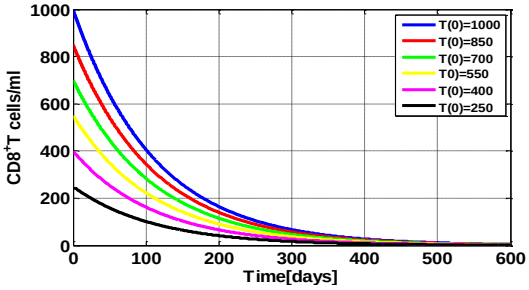

Figure 4: Graph of $CD8^+$T cells load with respect to time at various initial conditions, T_0

Figures $1-4$ illustrate plots of susceptible hepatocytes, infected hepatocytes, HCV and $CD8^+$ T cells loads with respect to time in days respectively. Here, it is observed that from various initial values of each state variable, the value of it approach the same equilibrium point over indefinite time t. Precisely, the susceptible hepatocytes

quantities approaches a non-zero equilibrium point (Figure 1) while the infected hepatocytes, HCV and $CD8^+$ T cells quantities all tend to a zero equilibrium point over indefinite time t (Figures 2, 3(a), 3(b) and 4 respectively). Consequently, all equilibrium quantities of the state variables correspond to the disease-free equilibrium, E_0, as shown in the analytical results.

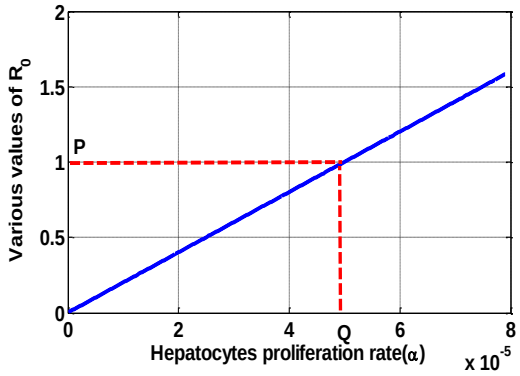

Figure 5: Variation of the basic reproductive number, R_0 with hepatocytes proliferation rate, α.

In Figure 5, it is observed that the basic reproductive number R_0 varies with hepatocytes proliferation rate, α, whereby it is found that the increase of α generally causes the value of R_0 to increase; and vice versa. Moreover, it is seen that at if $a = Q$ the value of R_0 equals to unity; but when $a < Q$ it is seen that $R_0 < 1$. Conversely, when $a > Q$, R_0 is greater than unity, i.e. $R_0 > 1$. In Mathematical Epidemiology, this implies that the disease exterminates if and only if $a < Q$ (or $R_0 < 1$) and prevails in the hepatic cells population if and only if $a > Q$ (or $R_0 > 1$. More accurately, we state that the HCV infection goes to extinction when $R_0 \leq 1$ ($a \leq Q$ and predominates when $R_0 > 1$ ($a > Q$.

4. Conclusion

This paper, presents global stability analysis of a deterministic mathematical model, which is descriptive of the transmission dynamics of hepatitis C virus (HCV) infection with hepatocytes proliferation, body immune response and spontaneous clearance of the virus. In particular, the stability of disease-free equilibrium (DFE) was analyzed and found it to be globally asymptotically stable if $R_0 \leq 1$ and unstable if $R_0 > 1$ irrespective of initial values of the state variables. This means that the disease disappears when the basic reproductive number R_0 is strictly less than or equal to unity; but it prevails if R_0 is greater than unity. Besides, some numerical simulations of the model relating to the global stability of DFE and R_0 were performed and the results found to comply with the analytical ones. Specifically, it was established that the neighboring initial condition of DFE remains in the close vicinity of it over indefinite time, which suggests existence of global asymptotic stability of the model equilibrium point, E_0. Furthermore, we established the condition for global stability of DFE, which is $R_0 \leq 1$ for certain values of hepatic cells proliferation rate, suggesting existence of a fixed set of parameter values for which the condition $R_0 \leq 1$ holds. Thus, it is recommend that there should be found ways to ensure that R_0 is strictly less or

equal to unity for the infection to go to extinction.

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