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VIRAL INFECTION DYNAMICS OF HBV DNA-CONTAINING CAPSIDS WITH LOGISTICS GROWTH AND SATURATED RATE

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Abstract. Knowing more about the dynamics of hepatitis B viral infection with DNA containing capsids, still under research. In this paper, we propose a new mathematical model dealing with the infection of hepatocytes with capsids logistics growth functions and saturated rate. We initiate the work with the description and the well-posedness of the formulation, then we study the stability of different equilibria to get a set of results which express that the system has tree equilibrium points. For the basic reproduction number is less then one ($R_0 < 1$) the disease-free equilibrium is stable and when $R_0 > 1$ other conditions determinate the stability of the endemic equilibrium points. By numerical simulation, we verify numerically the theoretical founding.

Keywords: HBV infection; HBV DNA-containing capsids; logistic growth; saturated rate; stability.

2020 AMS Subject Classification: 92B05, 37M05, 34D20, 37C20.

1. INTRODUCTION

As it known, the hepatitis B virus (HBV) can infect liver cells and can cause acute or chronic infection of healthy hepatocytes [1,2], World Health Organization claims this disease as world-wide public health problem and report it with more than 257 millions infected persons [3,4].

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Several scientific works have been developed in order to study the dynamic of HBV infection from both fields biologic and mathematics one [5–14]. In recent paper, [15] the authors describe the HBV infection stochastically with differential model and they reconize that white noise can influence the treatment of infectious. We can find also that HBV is studied and formulated with ODEs system [6, 16, 17] and FDEs system [18–20], the propagation of HBV with spatial dependence is discussed at [21] to design reaction-diffusion. Motivated by the natural existence of viral genome DNA countaining capsids with hepatocytes B, it is describe as package comprised of an assembly of proteins, many works concider capsids as a contributing factor in the dynamics of the viral infection [8, 16, 17, 22, 23]. After reading and analyzing what was done by the previous research, we propose the formulation of the HBV viral dynamics with DNA countaining capsids as the next nonlinear differential equations system:

$$(1)\qquad \begin{cases} \frac{dH}{dt} &= rH(1-\frac{H+I}{N})-k\frac{HV}{H+I}, \\ \frac{dI}{dt} &= \rho I(1-\frac{H+I}{N})+k\frac{HV}{H+I}-\delta I, \\ \frac{dD}{dt} &= aI-(\beta+\delta)D, \\ \frac{dV}{dt} &= \beta D-cV. \end{cases}$$

This illustrate the dynamic between the healthy hepatocytes (H), the infected hepatocytes (I), DNA containing capsids (D) and free virus (V).

The first equation express the variation over time of the healthy hepatocytes with two functions, logistic growth with r as maximum proliferation and N as population capacity. The other function is saturated rate with k as infection rate due to virus and the polulation of hepatocytes.

The second equation give tree terms to describe the pace of the infected hepatocytes, we find logistic growth with the maximum proliferation of infected cells ρ, $k\frac{HV}{H+I}$ for saturation and the last term to quantify the natural elimination with δ as death rate.

The third equation is for capsids, expressed by linear fonctions, with a as proliferation rate of intracellular capsids associated to infected cells, β production rate of virus due to capsids and δ death rate of capsids.

The fourth equation descrive the variation over time of HBV as linear fonctions, with production rate and elimination rate c of virus.

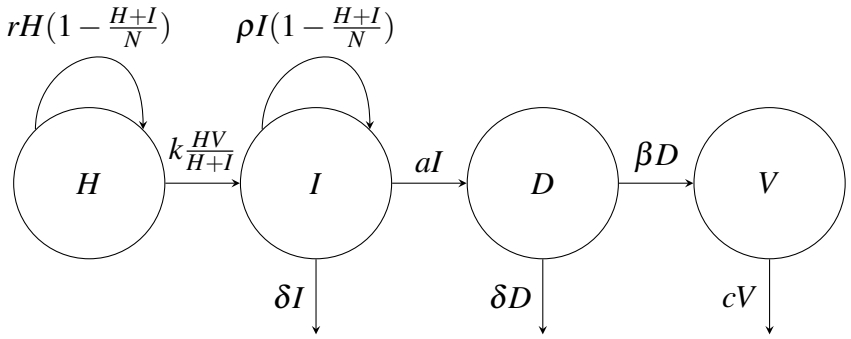

FIGURE 1. Dynamics of HBV schematized by a graphical diagram.

The dynamics of this infection is schematized by the graphical diagram (Fig. 1). The schematic behavior visualises well the interactions between the hepatocyte, infection cell, capsids and B virus of the model (1).

This paper is organized by sections as follows. In section 2, we begin the analysis by showing the non negativity and boundedness of the solution and discussing locally the stability of steady states, in section 3, we present the numerical simulations by discussing the result then we conclude the analysis.

2. ANALYSIS OF HBV INFECTION MODEL

In this section, we try to analyze the well posedness of the HBV dynamics formulation of the model by assuring the positivity and the bordness of the solutions to keep biological identification of the infection.

2.1. Well-posedness of the dynamics. In this paper, the phenomenon of HBV infection is expressed by the equations of the model (1), we will admit that the initial condition of the solutions are positive for biological reasons.

Proposition 1. *The solution of the problem (1) is non negative and bounded for all* $t \geq 0$.

Proof. Firstly, lets show that $\mathbb{R}^4_+ = \{(H,I,D,V) \in \mathbb{R}^4 : H \geq 0, I \geq 0, D \geq 0 \text{ and } V \geq 0\}$ is a positively invariant region.

Indeed, for $(H,I,D,V) \in \mathbb{R}^4_+$, we have:

$$\left.\frac{dH}{dt}\right|_{H=0} = 0 \geq 0,$$

$$\left.\frac{dI}{dt}\right|_{I=0} = KV \geq 0,$$

$$\left.\frac{dD}{dt}\right|_{D=0} = aI \geq 0,$$

$$\left.\frac{dV}{dt}\right|_{V=0} = \beta D \geq 0.$$

Therefore, all solutions initiating are positive, which give the result.

Secondly, for the boundness, from the system (1), we have:

$$\frac{dH}{dt} \leq rH(1-\frac{H}{N}),$$

$$\frac{d(H+I)}{dt} \leq Max(r,\rho)(H+I)(1-\frac{H+I}{N}),$$

$$\frac{dD}{dt} + (\beta+\delta)D \leq aI,$$

$$\frac{dV}{dt} + cV \leq \beta D.$$

We deduce that H, I, D and V are bounded. □

2.2. Existence and local stability of the solution. Before discussing the stability of the viral dynamic, it is necessary to calculate the basic reproduction number (BRN), the average of the new possible cases contaminated by one infected cell and mathematically it is defined by the spectral radius of the next generation matrix.

By a simple calculation we get in our case the following formulation of BRN:

$$R_0 = \frac{ak\beta}{\delta c(\beta+\delta)}.$$

The equations of the model (1) are null at any equilibrium instant $E^*(H^*, I^*, D^*, V^*)$.

$$(2)\qquad \begin{cases} 0 &= rH^*(1-\dfrac{H^*+I^*}{N})-k\dfrac{H^*V^*}{H^*+I^*}, \\ 0 &= \rho I^*(1-\dfrac{H^*+I^*}{N})+k\dfrac{H^*V^*}{H^*+I^*}-\delta I^*, \\ 0 &= aI^*-(\beta+\delta)D^*, \\ 0 &= \beta D^*-cV^*. \end{cases}$$

So, the last two equations of (2) give:

$$\begin{cases} D^* &= \dfrac{a}{(\beta+\delta)}I^*, \\ V^* &= \dfrac{a\beta}{c(\beta+\delta)}I^* = \dfrac{\delta R_0}{k}I^*. \end{cases}$$

For $I^*=0$, that give $D^*=0$, $V^*=0$ and $H^*=N$ which implies:

The disease-free equilibrium $E_0(N,0,0,0)$.

For $H^*=0$ and $\rho \geq \delta$, that give $I^*=\frac{N}{\rho}(\rho-\delta)$, $D^*=\frac{a}{(\beta+\delta)}\frac{N}{\rho}(\rho-\delta)$ and $V^*=\frac{a\beta}{c(\beta+\delta)}\frac{N}{\rho}(\rho-\delta)$ which implies one endemic equilibrium point:

The first endemic equilibrium $E_1(0,I_1,D_1,V_1)$

With:

$$I_1=\frac{N}{\rho}(\rho-\delta),$$

$$D_1=\frac{a}{(\beta+\delta)}\frac{N}{\rho}(\rho-\delta),$$

$$V_1=\frac{\delta R_0}{k}\frac{N}{\rho}(\rho-\delta).$$

From the discussion above we can start the stability analysis studies with the following set of results:

Proposition 2. *If $R_0<1$, the disease-free equilibrium E_0 is locally asymptotically stable.*

Proof. The Jacobian matrix at E_0 is:

$$\begin{pmatrix} -r & -r & 0 & -k \\ 0 & -\delta & 0 & k \\ 0 & a & -\beta-\delta & 0 \\ 0 & 0 & \beta & -c \end{pmatrix}$$

The characteristic polynomial of the matrix is:

$$P_{E_0} = (X+r)[(X+\delta)(X+\beta+\delta)(X+c) - a\beta k]$$

From the Routh–Hurwitz stability criterion, it follows that all roots of P_{E_0} have negative real part, when $R_0 < 1$. □

Proposition 3. *If $\rho > \delta$ and $R_0 > \frac{r}{\rho}$, the endemic equilibrium E_1 exist and it is locally asymptotically stable.*

Proof. The Jacobian matrix at E_1 is:

$$\begin{pmatrix} r(1-\frac{I_1}{N}) - \frac{kV_1}{I_1} & 0 & 0 & 0 \\ -\frac{\rho I_1}{N} + \frac{kV_1}{I_1} & \rho(1-2\frac{I_1}{N}) - \delta & 0 & 0 \\ 0 & a & -\beta-\delta & 0 \\ 0 & 0 & \beta & -c \end{pmatrix}$$

The characteristic polynomial of the matrix is:

$$P_{E_1} = (X+c)(X+\beta+\delta)(X+\delta-\rho(1-2\frac{I_1}{N}))(X+\frac{kV_1}{I_1} - r(1-\frac{I_1}{N})).$$

So, when $\rho > \delta$ and $\rho R_0 > r$, we get the stability criterion of the endemic equilibrium E_1. □

For $H^* \neq 0$, we pose $X^* = H^* + I^* \neq 0$.

So, the first two equations of (2) give:

$$\begin{cases} I^* = \dfrac{r}{\delta R_0} X^* (1 - \dfrac{X^*}{N}), \\ H^* = \dfrac{1}{\delta R_0} X^* \left(\delta - \rho (1 - \dfrac{X^*}{N}) \right) = X^* (1 - \frac{r}{\delta R_0} (1 - \frac{X^*}{N})). \end{cases}$$

That give : $\delta R_0 = (r - \rho)(1 - \frac{X^*}{N}) + \delta$.

We can notice that the discussion will be continued with the differentiation between the proliferating rates of proliferation is essential,

2.2.1. *Same proliferation rates of healthy and infected hepatocytes.* At the case when the healthy and infected hepatocytes proliferate at the same rate $\rho = r$. We can talk over and calculat two equilibruim points, one DFE E_0 and EE E_1 and specially when $R_0 = 1$, we can get an infinity of positive steady states E^*.

For the stability, we can discuss the next results from above as follow:

Proposition 4. *If $R_0 < 1$, the disease-free equilibrium E_0 is locally asymptotically stable.*

Proof. Same as Proposition 2. □

Proposition 5. *If $r > \delta$ and $R_0 > 1$, the endemic equilibrium E_1 exist and it is locally asymptotically stable.*

Proof. Same as it is at Proposition 3 for $\rho = r$. □

To sum up the pervious propositions when the healthy and infected hepatocytes proliferate at the same rate, we present the following bifurcation diagram showing the relation between the basic reproduction number R_0 and steady states obtained in this case, we consider R_0 is varied via δ.

2.2.2. *Different proliferation rates of healthy and infected hepatocytes.* At the case when the infected hepatocytes proliferating at a different rate from the healthy one, we can discuss the existence of an other endemic equilibruim point.

We pose : $R_D = \frac{\delta(R_0 - 1)}{r - \rho} = 1 - \frac{X^*}{N}$.

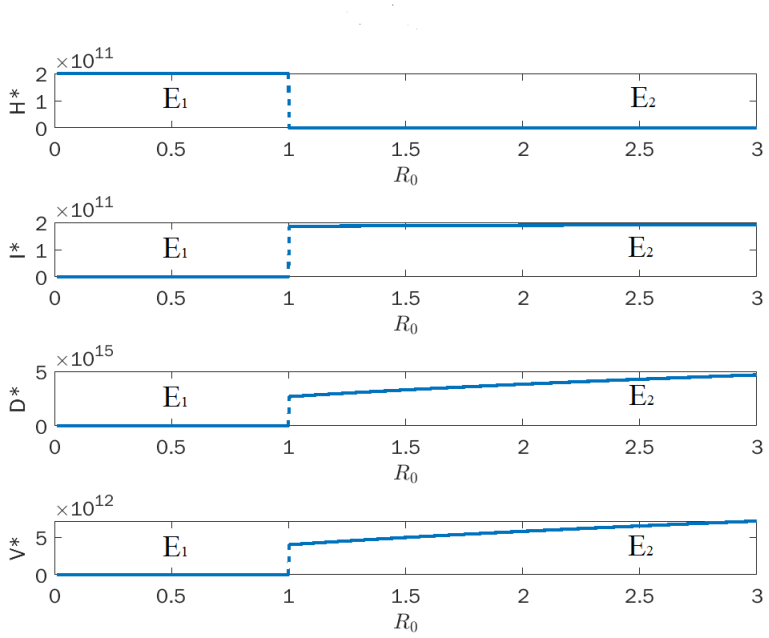

FIGURE 2. Equilibrium healthy hepatocyte, infected hepatocyte, capsid and virus bifurcation diagrams as R_0 functions when the paremeters value are: $r = 0.4, N = 2\times 10^1 1, k = 0.0014, a = 450\delta = 0.0693, \beta = 0.001$ and $c = 0.693$.

The second endemic equilibrium $E_2(H_2, I_2, D_2, V_2)$.

With:

$$H_2 = N(1-R_D)(1-\frac{r}{\delta R_0}R_D),$$
$$I_2 = \frac{rN}{\delta R_0}(1-R_D)R_D,$$
$$D_2 = \frac{ar}{(\beta+\delta)}\frac{N}{\delta R_0}(1-R_D)R_D,$$
$$V_2 = \frac{Nr}{k}(1-R_D)R_D.$$

We can study the stability of this endemic equilibruim and conclude the following results.

Remarque 1. *From the boundness result X can get the maximum value at N. So, R_D is positive, we conclude that ($R_0 > 1$ and $r > \rho$) or ($R_0 < 1$ and $r < \rho$).*

For meaningful interpretation, we consider $R_0 > 1$ and $r > \rho$, the existence of E_2 is also related to the condition giving as follow:

$$1 < R_0 < \frac{r}{\rho}.$$

Fig. 3 helps to search the maximum values of ρ that agree the existence of E_2, it is obvious that ρ is less than r, and to get more details about the relation between R_0 and ρ the following curve give the response.

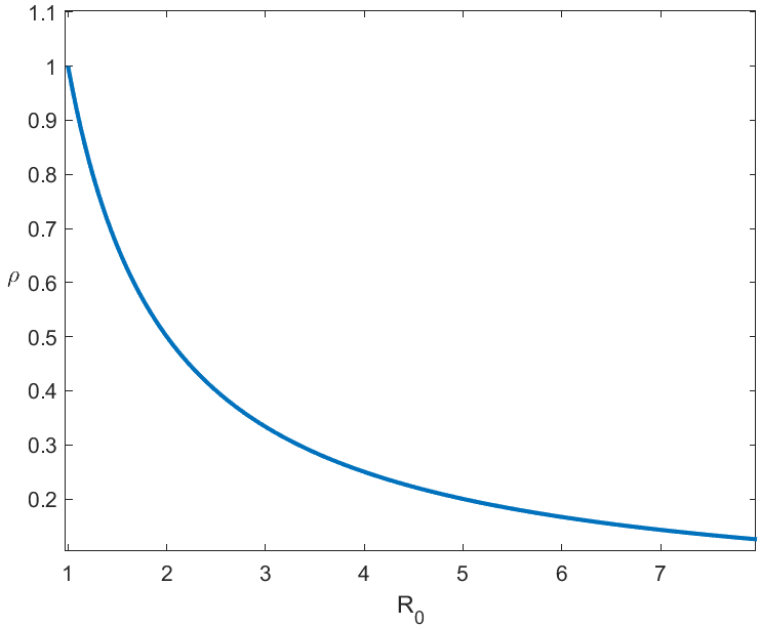

FIGURE 3. Maximum values of ρ for the steady state E_2, with the proliferation rate of healthy hepatocyte is unit ($r = 1$)

Proposition 6. *If* $R_D < Min(1, \frac{\delta R_0}{r}, \frac{2\delta+\beta+c+\frac{r}{\delta R_0}}{\rho+\frac{r}{\delta R_0}})$ *and* $H_i < 1, \forall i \in \{1,2,3\}$, *the endemic equilibrium* E_2 *is locally asymptotically stable.*

Proof. The Jacobian matrix at E_2 is:

$$\begin{pmatrix} r(1-\frac{2H_2+I_2}{N})-\frac{kV_2I_2}{(H_2+I_2)^2} & -\frac{rH_2}{N}+\frac{kV_2H_2}{(H_2+I_2)^2} & 0 & -k\frac{H_2}{H_2+I_2} \\ -\frac{\rho I_2}{N}+\frac{kV_2I_2}{(H_2+I_2)^2} & \rho(1-\frac{H_2+2I_2}{N})-\frac{kV_2H_2}{(H_2+I_2)^2}-\delta & 0 & k\frac{H_2}{H_2+I_2} \\ 0 & a & -\beta-\delta & 0 \\ 0 & 0 & \beta & -c \end{pmatrix}$$

The characteristic polynomial of the matrix is:

$$P_{E_2} = X^4 + AX^3 + BX^2 + CX + D.$$

With:

$A = 2\delta + \beta + c + \frac{r}{R_0}(1-R_D) - \rho R_D,$

$B = (c+\beta+\delta)(\frac{r}{R_0}(1-R_D) - \rho R_D + \delta) + c(\beta+\delta) + r(1-2R_D)(\delta R_0 - rR_D),$

$C = c(\beta+\delta)(\delta + \frac{r}{R_0}(1-R_D) - \rho R_D) + (\delta+\beta+c)r(1-2R_D)(\delta R_0 - rR_D) - ka\beta(1 - \frac{r}{\delta R_0}R_D),$

$D = r(1-2R_D)(\delta R_0 - rR_D)c(\beta+\delta) + ka\beta(1 - \frac{r}{\delta R_0}R_D)(\delta R_0 + \rho R_D - \frac{r}{R_0}(1-R_D) - \delta).$

Again, using Routh-Hurwitz stability criterion, the eigenvalues of the above matrix have negative real parts when $A > 0$, $D > 0$, $AB - C > 0$ and $A(BC - AD) - C^2 > 0$.

We pose:

$$B^+ = (c+\beta+\delta)(\frac{r}{R_0}(1-R_D) + \delta) + c(\beta+\delta) + r(1-R_D)(\delta R_0 - rR_D),$$

$$C^+ = c(\beta+\delta)(\delta + \frac{r}{R_0}(1-R_D)) + (\delta+\beta+c)r(1-R_D)(\delta R_0 - rR_D),$$

$$D^+ = r(1-R_D)(\delta R_0 - rR_D)c(\beta+\delta) + ka\beta(1 - \frac{r}{\delta R_0}R_D)(\delta R_0 + \rho R_D),$$

$$B^- = \rho R_D(c+\beta+\delta) + rR_D(\delta R_0 - rR_D),$$

$$C^- = c\rho R_D(\beta+\delta)(\delta + \frac{r}{R_0}(1-R_D)) + rR_D(\delta+\beta+c)(\delta R_0 - rR_D) + ka\beta(1 - \frac{r}{\delta R_0}R_D),$$

$$D^- = rR_D(\delta R_0 - rR_D)c(\beta+\delta) + ka\beta(1 - \frac{r}{\delta R_0}R_D)(+\frac{r}{R_0}(1-R_D) + \delta),$$

$$H_1 = \frac{C^+ + AB^-}{C^- + AB^+},$$

$$H_2 = \frac{A(B^+C^+ + B^-C^-)}{C^2 + A^2B + B^+C^- + B^-C^+},$$

$$H_3 = \frac{D^+}{D^-}.$$

So, we can be explicite the conditions by: $H_i < 1, \forall i \in \{1,2,3\}$ and $(\rho + \frac{r}{\delta R_0})R_D < 2\delta + \beta + c + \frac{r}{R_0}$. □

3. Numerical Simulations and Discussion

In the present section, several numerical simulations are carried out to exhibit the theoretical results. Using Euler's explicit method, we program numerically the solutions of the model (1) under Matlab to illustrate this result.

With the following parameter values [14, 16, 24]: $r = 1$, $\rho = 1$, $N = 2 \times 10^{11}$, $k = 0.0014$, $\delta = 0.0693$, $a = 30$, $\beta = 0.87$ and $c = 0.693$.

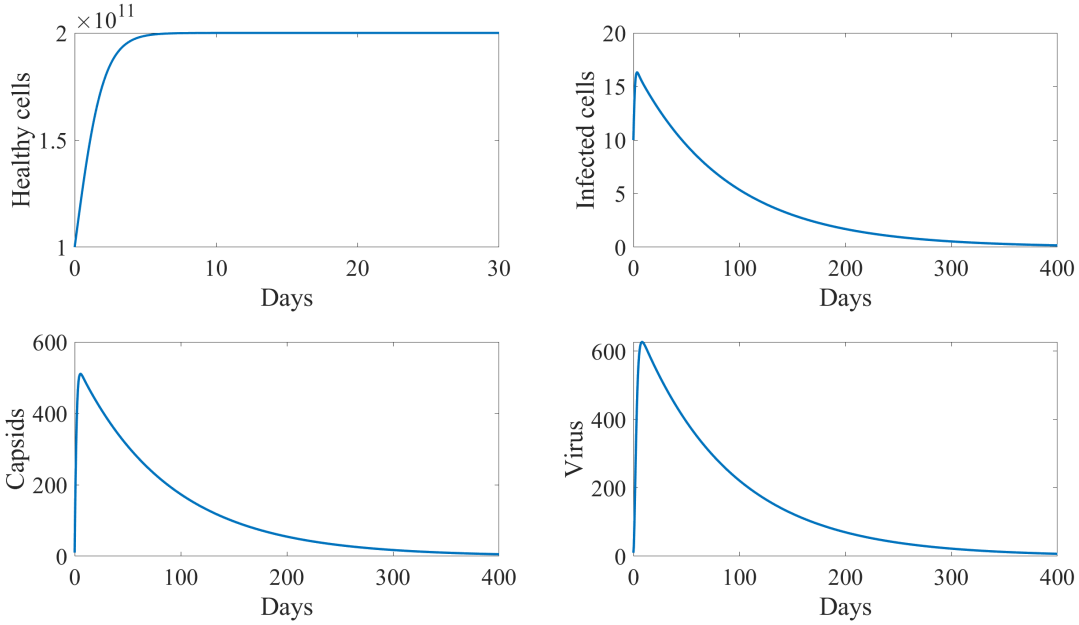

FIGURE 4. The Behavior of the infection at disease-free equilibrium when the proliferation rates of healthy and infected hepatocytes are equal ($\rho = r$)

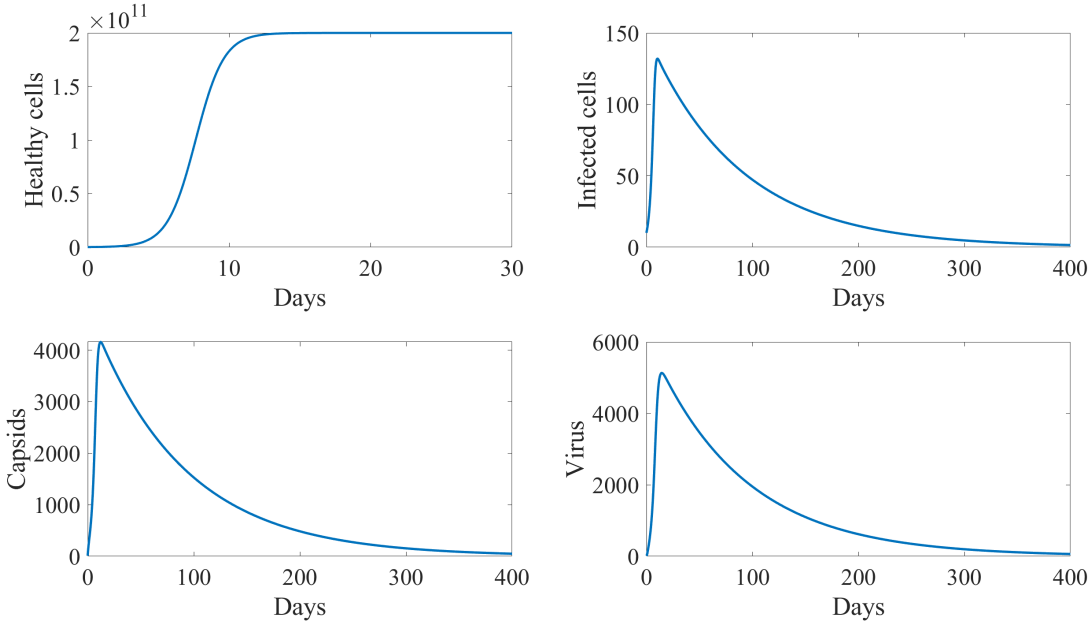

FIGURE 5. The Behavior of the infection at disease-free equilibrium when the proliferation rates of healthy and infected hepatocytes are different ($\rho \neq r$)

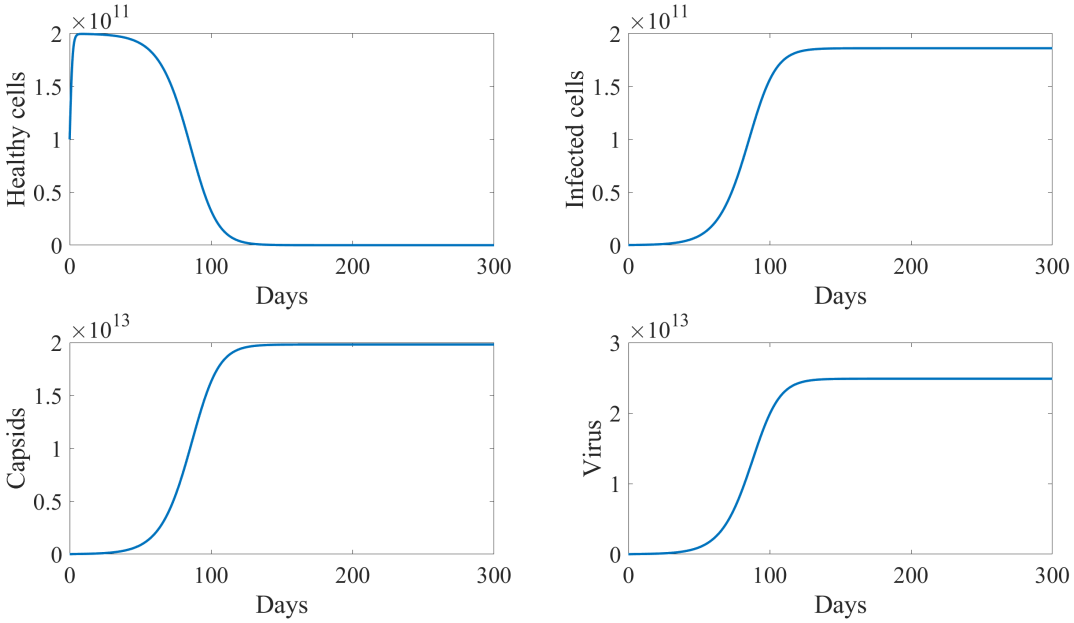

FIGURE 6. The Behavior of the infection at endemic equilibrium when the proliferation rates of healthy and infected hepatocytes are equal ($\rho = r$)

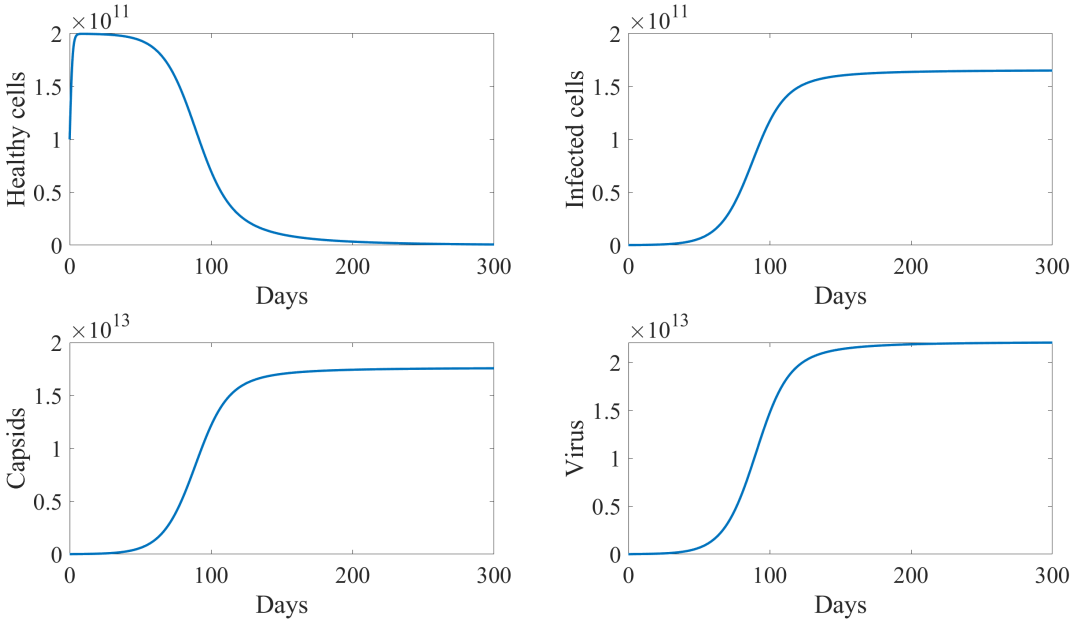

FIGURE 7. The Behavior of the infection at endemic equilibrium when the proliferation rates of healthy and infected hepatocytes are different ($\rho \neq r$)

In Fig. 4, we talk over the disease-free equilibrium, we discuss the case when we have the same proliferation rates of healthy and infected hepatocytes ($\rho = r$), we simulate the solutions and the behavior infection converge to the stable state $E_0 = (2 \times 10^{11}, 0, 0, 0)$. In this case the basic reproduction number is less than unit ($R_0 = 0.8100 < 1$) which is confirmed with our theoretical result of the stability of DFEs.

Next, Fig. 5 shows the results when the proliferation rates of healthy and infected hepatocytes are different ($\rho \neq r$), we choose $\rho = 0.4$ and do not change the other parameter values, the disease dies out and go the same point E_0. Moreover, the stability in this case is different in terme of taking more time to converge and the infected cells, capsids and virus expand more then the first case of the same proliferation rates.

Fig. 6 argues the stability of the endemic equilibrium, we change the paremeter $a = 100$ and let the others as they are, we get the basic reproduction number is greater than unity ($R_0 = 2.7 > 1$). At the case of the same proliferation rates of healthy and infected hepatocytes ($\rho = r$), the curves converge to $E_1 = (0, 0.0186 \times 10^{11}, 1.9817 \times 10^{11}, 2.4878 \times 10^{11})$, we observe the persistence of the capcids and the virus.

Fig. 7 shows, when the proliferation rates of healthy and infected hepatocytes are different ($\rho \neq r$), that the behavior infection converge to $E_1 = (0, 0.0165 \times 10^{11}, 1.7604 \times 10^{11}, 2.2100 \times 10^{11})$, however, the persistente of the virus in this case is less than the case of the same proliferation rates.

4. CONCLUSION

In this work, we investigated the hepatocytes B infection with DNA-containing capsids by considering the proliferating of its dynamics following logistic growth funtions and satureted rates under ordinary differential equation (ODE) model. In accordance with the biological concept, the correct pose of the model is shown to confirm identification of the infection matematically, then we establish the analysis of the problem to prove the existence and the stability of various steady states. At the present study, we give the local stability conditions of differents equilibruim points and to better understand the progression of hepatic B diseases two scenarios possible were discuss, when the healthy and infected hepatocytes proliferate at the same, we conclude that at the disease free equilibrium the virus expand more then the case of different

rates, however, at the endemic equillibruim the persistente result of the virus in this case of different rates is less than the same. Moreover, our numerical summulation confirm the theoretical results concerning the stability of the steady states.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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