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Dynamics of a generalized age-structured model for HBV infection with capsids in presence of two treatments

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Abstract

The main aim of this paper is to propose and analyze the dynamics of a generalized age-structured model for hepatitis B virus (HBV) infection with HBV DNA-containing capsids and two treatments. Such treatments are pegylated interferon and lamivudine drugs which are used to block new infections of liver cells and stop viral infection. We first investigate the existence and uniqueness of solutions to the proposed model, as well as the existence of equilibria. Furthermore, the uniform persistence and the stability analysis are rigorously established by means of characteristic equations and Lyapunov functionals.

Keywords: HBV infection, age-structure, general incidence rate, uniform persistence, stability analysis.

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1. Introduction

Nowadays, hepatitis B caused by hepatitis B virus (HBV) is a dangerous infections that attacks the liver cells called hepatocytes and puts people at high risk of death from cirrhosis and liver cancer. According to World Health Organization (WHO) [24], hepatitis B resulted in an estimated 820000 deaths in 2019, mostly from cirrhosis and liver cancer. Also, 296 millions people were living with chronic hepatitis B infection in the same year.

The treatments for HBV infection depend on several factors, including the phase of the infection (acute or chronic), the level of liver damage, the presence of symptoms, and the overall health of the individual. Actually, there is no specific treatment for acute hepatitis B [24]. Chronic hepatitis B can be treated with antiviral medications and interferon injections like pegylated interferon and lamivudine. The first drug stimulates the body's immune system to control and combat the HBV. However, lamivudine is used to inhibit the replication of HBV and reduce the viral load in the body. Many studies have suggested that the combination of pegylated interferon and lamivudine may result in a more robust virological response compared to monotherapy [17, 20].

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In the literature, various age-structured models have been proposed and developed to understand the dynamics of infectious diseases like HBV. For instance, Hattaf and Yang [8] proposed an age-structured viral infection model with general incidence function that takes account of the loss of viral particles due to their absorption into susceptible cells. Liu and Zhang [11] studied an age-structured HBV with DNA-containing capsids and bilinear incidence rate. Nelson et al. [19] proposed and investigated an age-structured viral model with bilinear incidence rate. An age-structured viral infection model with latency was proposed in [23]. Furthermore, an age-structured HBV infection model with bilinear incidence and cell-to-cell infection was formulated in [10]. In addition, there are other models for HBV with capsids [15, 16, 18].

The present paper is devoted to the construction of a generalized HBV model with capsids and two treatments. To do this, Section 2 deals with model formulation and preliminary results including the existence and uniqueness of solutions by rewriting model (2.1) as an abstract Cauchy problem. Section 3 studies the uniform persistence of solution semi-flow. Section 4 establishes local and global stability of equilibria. Section 5 presents an application in order to illustrate our analytical results. Finally, Section 6 ends the paper with a conclusion.

2. Model formulation and preliminary results

This section presents model formulation and preliminary results. Such model is governed by the following nonlinear system:

$$\begin{cases} \frac{dT(t)}{dt} = \Lambda - \mu_1 T(t) - (1-\eta_1) f\big(T(t), V(t)\big) V(t), \\ \frac{\partial i(t,a)}{\partial t} + \frac{\partial i(t,a)}{\partial a} = -\delta(a) i(t,a), \\ \frac{dD(t)}{dt} = (1-\eta_2) \int_0^\infty p(a) i(t,a) da - (\mu_2 + k) D(t), \\ \frac{dV(t)}{dt} = kD(t) - \mu_3 V(t), \end{cases} \tag{2.1}$$

with the boundary condition

$$i(t,0) = (1-\eta_1) f(T(t), V(t)) V(t),$$

and initial conditions

$$T(0) = T_0, \quad i(0,a) = i_0(a), \quad D(0) = D_0, \quad V(0) = V_0.$$

Here, $T(t)$, $i(t,a)$, $D(t)$, and $V(t)$ denote the densities of uninfected hepatocytes, infected hepatocytes with infection age a, HBV DNA-containing capsids, and free virions at time t, respectively. The biological meanings of the parameters of our model (2.1) are given in Table 1.

Table 1: Biological meanings of parameters.

Parameters	Biological meanings
Λ	Recruitment rate of uninfected hepatocytes
$\delta(a)$	Death rate of infected hepatocytes with infection age a
$p(a)$	Production rate of capsids from infected hepatocytes with infection age a
μ_1	Death rate of uninfected hepatocytes
μ_2	Death rate of capsids
μ_3	Clearance rate of virions
k	Production rate of virions from capsids
η_1	Efficiency of pegylated interferon drug
η_2	Efficiency of lamivudine drug

The general incidence function $f(T,V)$ represents the average number of cells, which are infected by each virus in unit time. As in [7, 21, 22], we assume that $f(T,V)$ is continuously differentiable in the interior of $\mathbb{R}^2_+$ and satisfies the following hypotheses:

(H_1) $f(0,V)=0$, for all $V \geqslant 0$;
(H_2) $f(T,V)$ is a strictly monotone increasing function with respect to T, for any fixed $V \geqslant 0$;
(H_3) $f(T,V)$ is a monotone decreasing function with respect to V.

Notice that the recent model proposed by Liu and Zhang [11] is a special case of system (2.1), it suffices to take $\eta_1=\eta_2=0$ and $f(T,V)=\beta TV$ with β is the infection rate. In this paper, we consider the following assumptions.

(i) $\Lambda, \mu_1, \mu_2, \mu_3, k > 0$.
(ii) The functions $\delta(a), p(a) \in L^{\infty}_{+}(0,\infty)$ and

$$\bar{\delta} = \operatorname{ess}\sup_{a\in[0,\infty)} \delta(a) < \infty, \quad \bar{p} = \operatorname{ess}\sup_{a\in[0,\infty)} p(a) < \infty,$$

where ess sup is essential supremum.
(iii) There exists a $m_0 \in (0,\Lambda]$, such that $\delta(a) \geqslant m_0$ for all $a > 0$.
(iv) There exists a maximum age $a^+ > 0$, such that $p(a) > 0$ for $a \in [0,a^+]$, and $p(a) = 0$ for $a > a^+$.

Integrating the second equation of model (2.1) along the characteristic line $t-a=$ constant, we get

$$i(t,a) = \begin{cases} (1-\eta_1)f\big(T(t-a),V((t-a)\big)V(t-a)\sigma(a), & \text{for } t > a \geqslant 0, \\ i_0(a-t)\frac{\sigma(a)}{\sigma(a-t)}, & \text{for } a \geqslant t > 0, \end{cases}$$

where $\sigma(a) = e^{-\int_0^a \delta(\theta)d\theta}$ is the probability that an infected cell survives to age a. Let

$$N = \int_0^{\infty} p(a)\sigma(a)da,$$

which denotes the total number of capsids produced by an infected hepatocyte in its lifespan. Consider the following function

$$G(t) = T(t) + \int_0^{\infty} i(t,a)da,$$

which leads to

$$\frac{dG(t)}{dt} = \Lambda - \mu_1 T(t) - \int_0^{\infty} \delta(a)i(t,a)da \leqslant s - \gamma G(t),$$

where $\gamma = \min\{\Lambda, m_0\}$. Then

$$\limsup_{t\to+\infty} G(t) \leqslant \frac{\Lambda}{\gamma}.$$

From the third equation of system (2.1), we get

$$\frac{dD(t)}{dt} \leqslant (1-\eta_2)\bar{p}\int_0^{\infty} i(t,a)da - (\mu_2+k)D(t).$$

Hence,

$$\limsup_{t\to+\infty} D(t) \leqslant \frac{(1-\eta_2)\bar{p}\Lambda}{\gamma(\mu_2+k)}.$$

From the fourth equation of system (2.1), we obtain

$$\frac{dV(t)}{dt} = kD(t) - \mu_3 V(t) \leqslant \frac{(1-\eta_2)\bar{p}\Lambda k}{\gamma(\mu_2+k)} - \mu_3 V(t).$$

Then

$$\limsup_{t\to+\infty} V(t) \leqslant \frac{(1-\eta_2)\bar{p}\Lambda}{\gamma\mu_3(\mu_2+k)}.$$

Therefore,

$$\Omega = \left\{(T,i,D,V) \in \mathbb{R}_+ \times L^1_+((0,+\infty),\mathbb{R}) \times (\mathbb{R}_+)^2 : T + \int_0^{+\infty} i(a)da \leqslant \frac{\Lambda}{\gamma}, D \leqslant \frac{(1-\eta_2)\bar{p}\Lambda}{\gamma(\mu_2+k)}, V \leqslant \frac{(1-\eta_2)\bar{p}\Lambda}{\gamma\mu_3(\mu_2+k)}\right\}$$

is a positively invariant set of model (2.1). Consider the following spaces:

$$\begin{aligned}
\mathcal{X} &= \mathbb{R} \times L^1((0,+\infty),\mathbb{R}) \times \mathbb{R} \times \mathbb{R} \times \mathbb{R},\\
\mathcal{X}_0 &= \mathbb{R} \times L^1((0,+\infty),\mathbb{R}) \times \{0\} \times \mathbb{R} \times \mathbb{R},\\
\mathcal{X}_+ &= \mathbb{R}_+ \times L^1_+((0,+\infty),\mathbb{R}) \times \mathbb{R}_+ \times \mathbb{R}_+ \times \mathbb{R}_+,
\end{aligned}$$

and

$$\mathcal{X}_{0+} = \mathcal{X}_+ \cap \mathcal{X}_0.$$

Let $A : \mathrm{Dom}(A) \subset \mathcal{X} \to \mathcal{X}$ be the linear operator defined by

$$A\begin{pmatrix} T \\ \begin{pmatrix} i \\ 0 \end{pmatrix} \\ D \\ V \end{pmatrix} = \begin{pmatrix} -\mu_1 T \\ \begin{pmatrix} -i' - \delta(a)i \\ -i(0) \end{pmatrix} \\ -(\mu_2+k)D \\ -\mu_3 V \end{pmatrix},$$

with $\mathrm{Dom}(A) = \mathbb{R} \times W^{1,1}((0,+\infty),\mathbb{R}) \times \{0\} \times \mathbb{R} \times \mathbb{R}$, where $W^{1,1}$ is a Sobolev space. Consider $F : \mathcal{X}_0 \to \mathcal{X}$,

$$F\begin{pmatrix} T \\ \begin{pmatrix} i \\ 0 \end{pmatrix} \\ D \\ V \end{pmatrix} = \begin{pmatrix} \Lambda - f(T,V)V \\ \begin{pmatrix} 0_{L^1} \\ f(x,v)v \end{pmatrix} \\ \int_0^{\infty} p(a)i(t,a)da \\ kD(t) \end{pmatrix},$$

and

$$u(t) = \begin{pmatrix} T(t) \\ \begin{pmatrix} i(t,.) \\ 0 \end{pmatrix} \\ D(t) \\ V(t) \end{pmatrix}.$$

Hence, system (2.1) can be rewritten as the following abstract Cauchy problem:

$$\begin{cases} \frac{du(t)}{dt} = Au(t) + F(u(t)), \quad t \geqslant 0, \\ u(0) = u_0 \in \mathcal{X}_{0+}. \end{cases} \tag{2.2}$$

Based on the results in [3, 12, 13], we get the following theorem.

Theorem 2.1. *System (2.2) generates a unique continuous semiflow $\{U(t)\}_{t\geqslant 0}$ on $\mathcal{X}_{0+}$ that is bounded dissipative and asymptotically smooth. Moreover, the semiflow $\{U(t)\}_{t\geqslant 0}$ has a global attractor $\mathcal{A}$ in $\mathcal{X}_{0+}$, which attracts the bounded sets of $\mathcal{X}_{0+}$.*

It is obvious that system (2.1) has a unique infection-free equilibrium of the forms $E^0(T^0,0,0,0)$, where $T^0 = \frac{\Lambda}{\mu_1}$. Hence, the basic reproductive number of (2.1) is given as follows:

$$\mathcal{R}_0 = \frac{kN(1-\eta_1)(1-\eta_2)f(T^0,0)}{\mu_3(\mu_2+k)}.$$

Biologically, $\mathcal{R}_0$ represents the average number of secondary infections produced by a single infected cell during the period of infection when all cells are uninfected.

Theorem 2.2.

(i) *If* $\mathcal{R}_0 \leqslant 1$, *then the system (2.1) has a unique infection-free equilibrium of the form* $E^0(T^0, 0, 0, 0)$, *where* $T^0 = \frac{\Lambda}{\mu_1}$.

(ii) *If* $\mathcal{R}_0 > 1$, *then the infection-free equilibrium is still present and model (2.1) has a unique chronic infection equilibrium of the form* $E^*(T^*, i^*(a), D^*, V^*)$, *where* $T^* \in (0, T^0)$, $D^* = \frac{N(1-\eta_2)(\Lambda-\mu_1 T^*)}{\mu_2+k}$, $V^* = \frac{kN(1-\eta_2)(\Lambda-\mu_1 T^*)}{\mu_3(\mu_2+k)}$, *and* $i^*(a) = (1-\eta_1)f(T^*, V^*)V^*\sigma(a)$.

Proof. Any equilibrium of model (2.1) satisfies the following equations:

$$\Lambda - \mu_1 T - (1-\eta_1)f(T,V)V = 0, \tag{2.3}$$

$$\frac{di(a)}{da} = -\delta(a)i(a), \tag{2.4}$$

$$(1-\eta_2)\int_0^\infty p(a)i(a)da - (\mu_2+k)D = 0, \tag{2.5}$$

$$kD - \mu_3 V = 0, \tag{2.6}$$

$$i(0) = (1-\eta_1)f(T,V)V. \tag{2.7}$$

It follows from (2.4) and (2.7) that

$$i(a) = (1-\eta_1)f(T,V)V\sigma(a). \tag{2.8}$$

According to (2.5) and (2.8), we obtain

$$N(1-\eta_1)(1-\eta_2)f(T,V) = \frac{\mu_3(\mu_2+k)}{k}. \tag{2.9}$$

From (2.3), (2.6), and (2.9), we have

$$V = \frac{kN(\Lambda-\mu_1 T)(1-\eta_2)}{\mu_3(\mu_2+k)} \quad \text{and} \quad D = \frac{N(\Lambda-\mu_1 T)(1-\eta_2)}{\mu_2+k}. \tag{2.10}$$

Substituting (2.10) into (2.9) yields

$$N(1-\eta_1)(1-\eta_2)f\left(T, \frac{kN(\Lambda-\mu_1 T)(1-\eta_2)}{\mu_3(\mu_2+k)}\right) = \frac{\mu_3(\mu_2+k)}{k}.$$

Since $V = \frac{kN(\Lambda-\mu_1 T)(1-\eta_2)}{\mu_3(\mu_2+k)} \geqslant 0$, we have $T \leqslant T^0$. Hence, model (2.1) has no biological equilibrium when $T > T^0$. Consider a function g on the interval $[0, x^0]$ as follows:

$$g(T) = N(1-\eta_1)(1-\eta_2)f\left(T, \frac{kN(\Lambda-\mu_1 T)(1-\eta_2)}{\mu_3(\mu_2+k)}\right) - \frac{\mu_3(\mu_2+k)}{k}.$$

We have $g(0) = -\frac{\mu_3(\mu_2+k)}{k} < 0$, $g(T^0) = \frac{\mu_3(\mu_2+k)}{k}(\mathcal{R}_0 - 1)$, and

$$g'(T) = N(1-\eta_1)(1-\eta_2)\left(\frac{\partial f}{\partial T} - \frac{kN\mu_1(1-\eta_2)}{\mu_3(\mu_2+k)}\frac{\partial f}{\partial V}\right) > 0.$$

Therefore, the equation $g(T) = 0$ has a unique solution $T^* \in (0, T^0)$, when $\mathcal{R}_0 > 1$. This completes the proof. □

3. Uniform persistence

This section establishes the uniform persistence of system (2.1). From a biological point of view, this notation signifies the persistence of the virus in the human body. Let

$$\hat{\mathcal{M}} = \left\{ \begin{pmatrix} T \\ \begin{pmatrix} i \\ 0 \end{pmatrix} \\ D \\ V \end{pmatrix} \in \mathcal{X}_{0+} : \int_0^{\bar{a}} i(a)da > 0, D > 0, V > 0 \right\},$$

and $\partial\hat{\mathcal{M}} = \mathcal{X}_{0+} \setminus \hat{\mathcal{M}}$, where $\bar{a} = \inf\left\{a : \int_a^{\infty} p(\theta)d\theta = 0\right\}$.

Theorem 3.1. *$\partial\hat{\mathcal{M}}$ is positively invariant under the semiflow $\{U(t)\}_{t\geqslant 0}$ generated by system (2.2) on $\mathcal{X}_{0+}$. Furthermore, the equilibrium $E^0 \begin{pmatrix} x^0 \\ \begin{pmatrix} 0_{L^1} \\ 0 \end{pmatrix} \\ 0 \\ 0 \end{pmatrix}$ is globally asymptotically stable for the semiflow $\{U(t)\}_{t\geqslant 0}$ restricted to $\partial\hat{\mathcal{M}}$.*

Proof. Let $\begin{pmatrix} x_0 \\ \begin{pmatrix} i_0(.) \\ 0 \end{pmatrix} \\ v_0 \end{pmatrix} \in \partial\hat{\mathcal{M}}$, we have

$$\begin{cases} \frac{\partial i(t,a)}{\partial t} + \frac{\partial i(t,a)}{\partial a} = -\delta(a)i(t,a), \\ \frac{dD(t)}{dt} = (1-\eta_2)\int_0^{\infty} p(a)i(t,a)da - (\mu_2+k)D(t), \\ \frac{dV(t)}{dt} = kD(t) - \mu_3 V(t), \\ i(t,0) = (1-\eta_1)f(T(t),V(t))V(t), \\ i(0,a) = i_0(a), \quad D(0) = 0, \quad V(0) = 0. \end{cases}$$

Since $T(t) \leqslant T^0$ for large enough time t, we get

$$i(t,a) \leqslant \hat{i}(t,a), \quad D(t) \leqslant \hat{D}(t), \quad V(t) \leqslant \hat{V}(t), \tag{3.1}$$

where

$$\begin{cases} \frac{\partial \hat{i}(t,a)}{\partial t} + \frac{\partial \hat{i}(t,a)}{\partial a} = -\delta(a)\hat{i}(t,a), \\ \frac{d\hat{D}(t)}{dt} = (1-\eta_2)\int_0^{\infty} p(a)\hat{i}(t,a)da - (\mu_2+k)\hat{D}(t), \\ \frac{d\hat{V}(t)}{dt} = k\hat{D}(t) - \mu_3\hat{V}(t), \\ \hat{i}(t,0) = (1-\eta_1)f(T^0,0)\hat{V}(t), \\ \hat{i}(0,a) = i_0(a), \quad \hat{D}(0) = 0, \quad \hat{V}(0) = 0. \end{cases} \tag{3.2}$$

Hence,

$$\hat{i}(t,a) = \begin{cases} (1-\eta_1)f(T^0,0)\hat{V}(t-a)\sigma(a), & \text{if } t > a \geqslant 0, \\ i_0(a-t)\frac{\sigma(a)}{\sigma(a-t)}, & \text{if } a \geqslant t > 0. \end{cases} \tag{3.3}$$

According to the second-third equation of (3.2) and (3.3), we deduce that

$$\begin{cases} \frac{d}{dt}\left(\hat{D}(t)+\hat{V}(t)\right) = (1-\eta_1)(1-\eta_2)f(T^0,0)\int_0^t p(a)\hat{V}(t-a)\sigma(a)da + F_v(t) - \mu_2\hat{D}(t) - \mu_3\hat{V}(t), \\ \hat{D}(0) = 0, \hat{V}(0) = 0, \end{cases} \tag{3.4}$$

where $F_v(t) = \int_t^{+\infty} p(a) i_0(a-t) \frac{\sigma(a)}{\sigma(a-t)} da$. It follows from $p(a) \in L^\infty_+((0,+\infty), \mathbb{R}) \setminus \{0_{L^\infty}\}$ that $F_v(t) \equiv 0$ for all $t \geqslant 0$. This system (3.4) has a unique solution $\left(\hat{D}(t), \hat{V}(t)\right) = (0,0)$. By (3.3), we get $\hat{i}(t,a) = 0$ for $t > a$. For $t \leqslant a$, we obtain

$$\|\hat{i}(t,a)\|_{L^1} = \left\| i_0(a-t) \frac{\sigma(a)}{\sigma(a-t)} \right\|_{L^1} \leqslant e^{-\delta_{\min} t} \|i_0\|_{L^1}.$$

This implies that $\hat{i}(t,a) \to 0$ as $t \to \infty$. By (3.1), we have $i(t,a) \to 0$ and $\left(D(t), V(t)\right) = (0,0)$ as $t \to \infty$. Therefore, $\lim_{t\to+\infty} T(t) = T^0$. □

Theorem 3.2. *If $\mathcal{R}_0 > 1$, then the semiflow $\{U(t)\}_{t\geqslant 0}$ generated by system (2.2) is uniformly persistent with respect to the pair $(\partial\hat{\mathcal{M}}, \hat{\mathcal{M}})$, i.e., there exists $\varepsilon > 0$ such that for each $y \in \hat{\mathcal{M}}$, $\liminf_{t\to+\infty} d(U(t)y, \partial\hat{\mathcal{M}}) \geqslant \varepsilon$. Moreover, the semiflow $\{U(t)\}_{t\geqslant 0}$ has a compact global attractor $\mathcal{A}_0 \subset \tilde{\mathcal{M}}$.*

Proof. $E^0 \begin{pmatrix} T^0 \\ \begin{pmatrix} 0_{L^1} \\ 0 \end{pmatrix} \\ 0 \\ 0 \end{pmatrix}$ is globally asymptotically stable in $\partial\hat{\mathcal{M}}$. From Theorem 4.2 in [4], we only need to prove

$$W^s(E^0) \cap \hat{\mathcal{M}} = \emptyset,$$

where $W^s(E^0) = \left\{ y \in \mathcal{X}_{0+} : \lim_{t\to+\infty} U(t)y = E^0 \right\}$. Suppose by contradiction that for each $n \geqslant 0$, there exists

$$y_n = \begin{pmatrix} T_0^n \\ \begin{pmatrix} i_0^n \\ 0 \end{pmatrix} \\ D_0^n \\ V_0^n \end{pmatrix} \in \left\{ y \in \hat{\mathcal{M}} : \|E^0 - y\| \leqslant \frac{1}{n} \right\},$$

such that $\|E^0 - U(t)y_n\| \leqslant \frac{1}{n}$, for all $t \geqslant 0$. Let

$$\begin{pmatrix} T^n(t) \\ \begin{pmatrix} i^n(t,.) \\ 0 \end{pmatrix} \\ D^n(t) \\ V^n(t) \end{pmatrix} := U(t)y_n.$$

Hence,

$$\|T^n(t) - T^0\| \leqslant \frac{1}{n}, \quad \|D^n(t) - 0\| \leqslant \frac{1}{n}, \quad \|V^n(t) - 0\| \leqslant \frac{1}{n}.$$

This implies that $T^0 - \frac{1}{n} > 0$ for large enough $n > 0$. For the given n, there exists a $\hat{t} > 0$ such that for all $t \geqslant \hat{t}$, we have

$$T^0 - \frac{1}{n} < T^n(t) < T^0 + \frac{1}{n}, \quad 0 \leqslant D^n(t) \leqslant \frac{1}{n}, \quad 0 \leqslant V^n(t) \leqslant \frac{1}{n}.$$

According to comparison principle and

$$i^n(t,a) \geqslant (1-\eta_1) f\left(T^0 - \frac{1}{n}, \frac{1}{n}\right) V^n(t-a)\sigma(a),$$

we get $\hat{D}^n(t) \leqslant D^n(t)$, $\hat{V}^n(t) \leqslant V^n(t)$, where $\left(\hat{D}^n(t), \hat{V}^n(t)\right)$ is a solution of the following system

$$\begin{cases} \frac{d\hat{D}^n(t)}{dt} = (1-\eta_1) f\left(x^0 - \frac{1}{n}, \frac{1}{n}\right) \int_0^\infty p(a)\sigma(a)\hat{D}^n(t-a)da - (\mu_2+k)\hat{V}^n(t), \\ \frac{d\hat{V}^n(t)}{dt} = k\hat{D}^n(t) - \mu_3\hat{V}^n(t), \\ \hat{D}^n(0) = D^n(0) \geqslant 0, \quad \hat{V}^n(0) = V^n(0) \geqslant 0. \end{cases}$$

When $\left(\hat{D}^n(0), \hat{V}^n(0)\right) = (0,0)$, we have $\hat{D}^n(t) > 0$ and $\hat{V}^n(t) > 0$. Hence, without loss of generality, we take $\hat{D}^n(0) > 0$ and $\hat{V}^n(0) > 0$. If $\mathcal{R}_0 > 1$, then we can choose the large enough n such that

$$kN(1-\eta_1)(1-\eta_2) f\left(x^0 - \frac{1}{n}, \frac{1}{n}\right) > \mu_3(\mu_2+k).$$

By Lemma 3.5 of Browne and Pilyugin [1], we deduce that $\left(\hat{D}^n(t), \hat{V}^n(t)\right)$ is unbounded. Since $\hat{D}^n(t) \leqslant D^n(t)$ and $\hat{V}^n(t) \leqslant V^n(t)$, we get that $\left(D^n(t), V^n(t)\right)$ is unbounded. This is a contradiction with the boundedness of $\left(D^n(t), V^n(t)\right)$. Thus, $W^s(E^0) \cap \hat{\mathcal{M}} = \emptyset$. Based on the results of [14], we prove that $\{U(t)\}_{t\geqslant 0}$ is uniformly persistent and there exists a compact set $\mathcal{A}_0 \subset \hat{\mathcal{M}}$ that is a global attractor for $\{U(t)\}_{t\geqslant 0}$. □

4. Stability analysis

This section analyzes the local and global stability of equilibria.

4.1. Local stability

We recall that an equilibrium is locally asymptotically stable if all eigenvalues of the characteristic equation have negative real parts and it is unstable if at least one of the eigenvalues has a positive real part.

Theorem 4.1. *The infection-free steady state E^0 is locally asymptotically stable if $\mathcal{R}_0 < 1$ and it is unstable if $\mathcal{R}_0 > 1$.*

Proof. Linearizing system (2.1) about E^0 and defining the perturbation variables

$$T_1(t) = T(t) - \frac{\Lambda}{\mu_1}, \qquad i_1(t,a) = i(t,a), \qquad D_1(t) = D(t), \qquad V_1(t) = V(t),$$

we get

$$\begin{cases} \frac{dT_1(t)}{dt} = -\mu_1 T_1(t) - (1-\eta_1) f(T^0, 0) V_1(t), \\ \frac{\partial i_1(t,a)}{\partial t} + \frac{\partial i_1(t,a)}{\partial a} = -\delta(a) i_1(t,a), \\ \frac{dD_1(t)}{dt} = (1-\eta_2)\int_0^\infty p(a) i_1(t,a) da - (\mu_2 - k) D_1(t), \\ \frac{dV_1(t)}{dt} = k D_1(t) - \mu_3 V_1(t), \end{cases} \tag{4.1}$$

and

$$i_1(t,0) = (1-\eta_1) f(T^0, 0) V_1. \tag{4.2}$$

Look for non-trivial solutions of (4.1) and (4.2) of the form

$$T_1(t) = c_1 e^{\lambda t}, \quad i_1(t,a) = e_1^0(a) e^{\lambda t}, \quad D_1(t) = c_2 e^{\lambda t}, \quad V_1(t) = c_3 e^{\lambda t}. \tag{4.3}$$

Substituting (4.3) into (4.1) and (4.2), we have

$$\begin{cases} (\lambda + \mu_1) c_1 = -(1-\eta_1) f(x^0, 0) c_3, \\ \frac{\partial i_1^0(a)}{\partial a} = -(\lambda + \delta(b)) i_1^0(a), \\ (\lambda + \mu_2 + k) c_2 = (1-\eta_2)\int_0^\infty p(a) i_1^0(a) da, \\ i_1^0(0) = (1-\eta_1) f(T^0, 0) c_3. \end{cases} \tag{4.4}$$

Integrating the second equation of (4.4) yields

$$i_1^0(a) = i_1^0(0)e^{-\int_0^a (\lambda+\delta(\theta))d\theta}. \tag{4.5}$$

According to the fourth equation of (4.4) and (4.5), we get

$$i_1^0(a) = (1-\eta_1)f(T^0,0)c_3e^{-\int_0^a (\lambda+\delta(\theta))d\theta}.$$

Substituting $i_1^0(a)$ into the third equation of (4.4), we have the characteristic equation

$$\left(\frac{\lambda+\mu_2+k}{\mu_2+k}\frac{\lambda+\mu_3}{\mu_3}\frac{N}{N(\lambda)} - \mathcal{R}_0\right) = 0, \tag{4.6}$$

where $N(\lambda) = \int_0^\infty p(a)\sigma(a)e^{-\lambda a}da$. If $\mathcal{R}_0 < 1$, then all roots of equation (4.6) have negative real parts. However, equation (4.6) has at least one root satisfying $Re(\lambda) > 0$, where $\mathcal{R}_0 > 1$. On the other hand, we have

$$\mathcal{R}_0 = \left|\frac{\lambda+\mu_2+k}{\mu_2+k}\frac{\lambda+\mu_3}{\mu_3}\frac{N}{N(\lambda)}\right| = \left|\frac{\lambda+\mu_2+k}{\mu_2+k}\right|\left|\frac{\lambda+\mu_3}{\mu_3}\right|\left|\frac{N}{N(\lambda)}\right| > 1.$$

This contradicts with $\mathcal{R}_0 < 1$. Thus, all roots of equation (4.6) have negative real parts. Therefore, E^0 is locally asymptotically stable when $\mathcal{R}_0 < 1$ and it is unstable when $\mathcal{R}_0 > 1$. □

Now, we establish the local stability of the chronic infection equilibrium E^* by supposing that $\mathcal{R}_0 > 1$ and the incidence function f satisfies the following hypothesis

(H_4) $f(T,V) + V\frac{\partial f(T,V)}{\partial V} \geqslant 0$, for all $T \geqslant 0$ and $V \geqslant 0$.

Theorem 4.2. *Assume that $\mathcal{R}_0 > 1$ and (H_4) holds. Then the chronic infection equilibrium E^* is locally asymptotically stable.*

Proof. Linearizing system (2.1) about E^* and defining the perturbation variables

$$T_2(t) = T(t) - T^*, \qquad i_2(t,a) = i(t,a) - i^*(a), \qquad D_2(t) = D(t) - D^*, \qquad V_2(t) = V(t) - V^*,$$

we get

$$\begin{cases} \frac{dT_2(t)}{dt} = -\left(\mu_1 + (1-\eta_1)V^*\frac{\partial f(T^*,V^*)}{\partial T}\right)T_2(t) - (1-\eta_1)\left(V^*\frac{\partial f(T^*,T^*)}{\partial V} + f(T^*,V^*)\right)V_2(t), \\ \frac{\partial i_2(t,a)}{\partial t} + \frac{\partial i_2(t,a)}{\partial a} = -\delta_2(a)i_2(t,a), \\ \frac{dD_2(t)}{dt} = (1-\eta_2)\int_0^\infty p_2(a)i_2(t,a)da - (\mu_2+k)D_2(t), \\ \frac{dV_2(t)}{dt} = kD_2(t) - \mu_3V_2(t), \end{cases} \tag{4.7}$$

and

$$i_2(t,0) = (1-\eta_1)V^*\frac{\partial f(T^*,V^*)}{\partial T}T_2(t) + (1-\eta_1)\left(f(T^*,V^*) + V^*\frac{\partial f(T^*,V^*)}{\partial T}\right)V_2(t). \tag{4.8}$$

Look for non-trivial solutions of (4.7) and (4.8) of the form

$$T_2(t) = c_1e^{\lambda t}, \quad i_2(t,a) = i_2^0(a)e^{\lambda t}, \quad D_2(t) = c_2e^{\lambda t}, \quad V_2(t) = c_3e^{\lambda t}.$$

Similarly to the proof of Theorem 4.1, we get the characteristic equation as

$$\frac{\lambda+\mu_3}{\mu_3}\frac{\lambda+\mu_2+k}{\mu_2+k} - \frac{N(\lambda)}{N}\frac{f(T^*,V^*)+V^*\frac{\partial f(T^*,V^*)}{\partial V}}{f(T^*,V^*)}\left[\frac{\lambda+\mu_1+(1-\eta_1)\left(f(T^*,V^*)+V^*\frac{\partial f(T^*,V^*)}{\partial V} - V^*\frac{\partial f(T^*,V^*)}{\partial T}\right)}{\lambda+\mu_1+(1-\eta_1)\left(f(T^*,V^*)+V^*\frac{\partial f(T^*,V^*)}{\partial V}\right)}\right] = 0. \tag{4.9}$$

If $Re(\lambda) \geqslant 0$, then we get

$$\left|\frac{\lambda+\mu_3}{\mu_3}\frac{\lambda+\mu_2+k}{\mu_2+k}\right| \geqslant 1,$$

$$\left|\frac{N(\lambda)}{N}\right|\left|\frac{f(T^*,V^*)+V^*\frac{\partial f(T^*,V^*)}{\partial V}}{f(T^*,V^*)}\right|\left|\frac{\lambda+\mu_1+(1-\eta_1)\left(f(T^*,V^*)+V^*\frac{\partial f(T^*,V^*)}{\partial V}-V^*\frac{\partial f(T^*,V^*)}{\partial T}\right)}{\lambda+\mu_1+(1-\eta_1)\left(f(T^*,V^*)+V^*\frac{\partial f(T^*,V^*)}{\partial V}\right)}\right| < 1,$$

which leads a contradiction to (4.9). Therefore, the chronic infection equilibrium E^* is locally asymptotically stable. This completes the proof. □

4.2. Global stability

In this subsection, we study the global asymptotic stability of equilibria by means of Lyapunov functionals.

Theorem 4.3. *The infection-free equilibrium* E^0 *of* (2.1) *is globally asymptotically stable if* $\mathcal{R}_0 \leqslant 1$.

Proof. Consider the following Lyapunov functional

$$L_0(t) = T(t) - T^0 - \int_{T^0}^{T(t)} \frac{f(T^0,0)}{f(\theta,0)}d\theta + \frac{k(1-\eta_1)(1-\eta_2)f(T^0,0)}{\mu_3(\mu_2+k)}\int_0^\infty \alpha(a)i(t,a)da + \frac{k(1-\eta_1)f(T^0,0)}{\mu_3(\mu_2+k)}D(t) + \frac{(1-\eta_1)f(T^0,0)}{\mu_3}V(t),$$

where $\alpha(a) = \int_a^\infty p(\theta)e^{-\int_a^\theta \delta(\xi)d\xi}d\theta$. We have $\alpha(0) = N$. Also, $\alpha(a)$ is bounded and its derivative satisfies

$$\alpha'(a) = \delta(a)\alpha_1(a) - p(a).$$

Since the function $T \mapsto T - T^0 - \int_{T^0}^{T} \frac{f(T^0,0)}{f(\theta,0)}d\theta$ is nonnegative, we easily deduce that the Lyapunov functional L_0 is positive and zero at the equilibrium. Next, calculating the time derivative of L_0 along the solution of system (2.1), we have

$$\begin{aligned}
\frac{dL_0}{dt} &= \left(1-\frac{f(T^0,0)}{f(T,0)}\right)\frac{dT(t)}{dt} + \frac{k(1-\eta_1)(1-\eta_2)f(T^0,0)}{\mu_3(\mu_2+k)}\int_0^\infty \alpha(a)\frac{\partial i(t,a)}{\partial t}da \\
&\quad + \frac{k(1-\eta_1)f(T^0,0)}{\mu_3(\mu_2+k)}\frac{dD(t)}{dt} + \frac{(1-\eta_1)f(T^0,0)}{\mu_3}\frac{dV(t)}{dt} \\
&= \left(1-\frac{f(T^0,0)}{f(T,0)}\right)(\Lambda - \mu_1 T - (1-\eta_1)f(T,V)V) \\
&\quad - \frac{k(1-\eta_1)(1-\eta_2)f(T^0,0)}{\mu_3(\mu_2+k)}\int_0^\infty \alpha(a)\left(\frac{\partial i(t,a)}{\partial a} + i(t,a)\right)da \\
&\quad + \frac{k(1-\eta_1)(1-\eta_2)f(T^0,0)}{\mu_3(\mu_2+k)}\int_0^\infty p(a)i(t,a)da - \frac{k(1-\eta_1)f(T^0,0)}{\mu_3}D(t) \\
&\quad + \frac{k(1-\eta_1)f(T^0,0)}{\mu_3}D(t) - (1-\eta_1)f(T^0,0)V(t).
\end{aligned}$$

Using integration by parts and $\Lambda = \mu_1 T^0$, we obtain

$$\frac{dL_0}{dt} = \Lambda\left(1-\frac{f(T^0,0)}{f(T,0)}\right)\left(1-\frac{T}{T^0}\right) + i(t,0)(\mathcal{R}_0-1) + (1-\eta_1)f(T^0,0)V\left(\frac{f(T,V)}{f(T,0)}-1\right).$$

Since the function $f(T,V)$ is strictly monotonically increasing with respect to T and decreasing function with respect to V, we get

$$\left(\frac{f(T,V)}{f(T,0)}-1\right)\leqslant 0 \quad \text{and} \quad \left(1-\frac{f(T^0,0)}{f(T,0)}\right)\left(1-\frac{T}{T^0}\right)\leqslant 0.$$

Thus, $\frac{dL_0}{dt}\leqslant 0$ for $\mathcal{R}_0\leqslant 1$. In addition, it is obvious to prove that the largest invariant set where $\frac{dL_0(t)}{dt}=0$ is the singleton $\{E^0\}$. By the Lyapunov-LaSalle asymptotic stability theorem, the disease-free equilibrium E^0 is globally asymptotically stable for $\mathcal{R}_0\leqslant 1$. □

Theorem 4.4. *Assume that $\mathcal{R}_0>1$ and (H_4) holds. Then the chronic infection equilibrium E^* is globally asymptotically stable.*

Proof. According to Theorem 3.2, let $u(t)=\left\{\left(T(t),i(t,a),0,D(t),V(t)\right)^T\right\}_{t\in\mathbb{R}}\subset\mathcal{A}_0$ be a given entire solution of $U(t)$. It remains to show that $\mathcal{A}_0=\{u^*\}$. Similarly to the proof of Lemma 3.6 and Claim 5.3 in [2], we deduce that there exist $\Delta_1>0$ and $\Delta_2>0$ such that

$$\Delta_1\leqslant x(t)\leqslant\Delta_2,\quad \Delta_1\leqslant i(t,a)\leqslant\Delta_2,\quad \Delta_1\leqslant D(t)\leqslant\Delta_2,\quad \Delta_1\leqslant V(t)\leqslant\Delta_2,$$

for all $t\in\mathbb{R}$ and $a\geqslant 0$. Now, we consider the following Lyapunov functional

$$\begin{aligned}L_1(t)=(1-\eta_2)&\left(T(t)-T^*-\int_{T^*}^{T(t)}\frac{f(T^*,V^*)}{f(\theta,V^*)}d\theta\right)\\&+\frac{1-\eta_2}{N}\int_0^\infty\alpha(a)i^*(a)\phi\left(\frac{i(t,a)}{i^*(a)}\right)da+\frac{1}{N}D^*\phi\left(\frac{D(t)}{D^*}\right)+\frac{1}{N}\frac{\mu_2+k}{k}V^*\phi\left(\frac{V(t)}{V^*}\right),\end{aligned}$$

where $\phi(x)=x-1-\ln x$, $x\in\mathbb{R}^+$. Clearly, $\phi:\mathbb{R}^+\to\mathbb{R}^+$ attains its strict global minimum at $x=1$ and $\phi(1)=0$. Calculating the time derivative of L_1 along the solution of system (2.1), we get

$$\begin{aligned}\frac{dL_1}{dt}=&(1-\eta_2)\left(1-\frac{f(T^*,V^*)}{f(T,V^*)}\right)\left(\Lambda-\mu_1T(t)-(1-\eta_1)f\big(T(t),V(t)\big)V(t)\right)\\&-\frac{1-\eta_2}{N}\int_0^\infty\alpha(a)\left(1-\frac{i^*(a)}{i(t,a)}\right)\left(\frac{\partial i(t,a)}{\partial a}+\delta(a)i(t,a)\right)da\\&+\frac{1}{N}\left(1-\frac{D^*}{D(t)}\right)\left((1-\eta_2)\int_0^\infty p(a)i(t,a)da-(\mu_2+k)D(t)\right)\\&+\frac{1}{N}\frac{\mu_2+k}{k}\left(1-\frac{V^*}{V(t)}\right)\left(kD(t)-\mu_3V(t)\right).\end{aligned}$$

By using $\Lambda=\mu_1T^*+(1-\eta_1)f(T^*,V^*)V^*$, $D^*=\frac{1-\eta_2}{\mu_2+k}\int_0^\infty p(a)i^*(a)da$, and $\int_0^\infty p(a)i^*(a)da=Ni^*(0)$, we have

$$\begin{aligned}\frac{dL_1}{dt}=&(1-\eta_2)\mu_1T^*\left(1-\frac{T}{T^*}\right)\left(1-\frac{f(T^*,V^*)}{f(T,V^*)}\right)-(1-\eta_1)(1-\eta_2)f(T,V)V\\&+(1-\eta_2)i^*(0)\left(1-\frac{f(T^*,V^*)}{f(T,V^*)}+\frac{V}{V^*}\frac{f(T,V)}{f(T,V^*)}\right)\\&-\frac{1-\eta_2}{N}\int_0^\infty p(a)i^*(a)\left[\phi\left(\frac{i(t,a)}{i^*(a)}\right)-\phi\left(\frac{i(t,0)}{i^*(0)}\right)\right]da\\&-\frac{1-\eta_2}{N}\int_0^\infty p(a)i^*(a)\left[\frac{D}{D^*}-1-\frac{i(t,a)}{i^*(a)}+\frac{i(t,a)D^*}{i^*(a)D}\right]da\\&-\frac{1-\eta_2}{N}\int_0^\infty p(a)i^*(a)\left[\frac{V^*D}{VD^*}-\frac{D}{D^*}+\frac{V}{V^*}-1\right]da.\end{aligned}$$

Hence,

$$\begin{aligned}\frac{dL_1}{dt} &= (1-\eta_2)\mu_1 T^*\left(1-\frac{T}{T^*}\right)\left(1-\frac{f(T^*,V^*)}{f(T,V^*)}\right)\\ &+ i^*(0)\left(-1-\frac{V}{V^*}+\frac{f(T,V^*)}{f(T,V)}+\frac{V}{V^*}\frac{f(T,V)}{f(T,V^*)}\right)-\frac{1-\eta_2}{N}\int_0^\infty p(a)i^*(a)\phi\left(\frac{i(t,a)D^*}{i^*(a)D}\right)da\\ &- (1-\eta_2)i^*(0)\left[\phi\left(\frac{V^*D}{VD^*}\right)+\phi\left(\frac{f(T^*,V^*)}{f(T,V^*)}\right)+\phi\left(\frac{f(T,V^*)}{f(T,V)}\right)\right].\end{aligned}$$

Since $f(T,V)$ is strictly monotonically increasing with respect to T, we have

$$\left(1-\frac{T}{T^*}\right)\left(1-\frac{f(T^*,V^*)}{f(T,V^*)}\right)\leqslant 0.$$

From (H_3) and (H_4), we have

$$-1-\frac{V}{V^*}+\frac{f(T,V^*)}{f(T,V)}+\frac{V}{V^*}\frac{f(T,V)}{f(T,V^*)}=\left(1-\frac{f(T,V)}{f(T,V^*)}\right)\left(\frac{f(T,V^*)}{f(T,V)}-\frac{V}{V^*}\right)\leqslant 0.$$

Since $\phi(x)\geqslant 0$ for $x>0$, we have $\frac{dL_1}{dt}\leqslant 0$. Therefore, L_1 is a bounded and decreasing map. Arguing similarly as the end of the proof of Theorem 2.2 (i) in Demasse and Ducrot [2], we get $u(t)=u^*$, i.e., $\mathcal{A}_0=\{u^*\}$. It follows from Theorem 4.2 that E^* globally asymptotically stable. □

Theorem 4.4 implies that the infection becomes chorionic and the virus persists in the host when $\mathcal{R}_0>1$.

5. Application

In this section, we apply our key results to an age-structured model for HBV infection with Hattaf-Yousfi functional response [9]. In this case, system (2.1) becomes

$$\begin{cases}\frac{dT(t)}{dt}=\Lambda-\mu_1 T(t)-(1-\eta_1)\frac{\beta T(t)V(t)}{\alpha_0+\alpha_1 T(t)+\alpha_2 V(t)+\alpha_3 T(t)V(t)},\\ \frac{\partial i(t,a)}{\partial t}+\frac{\partial i(t,a)}{\partial a}=-\delta(a)i(t,a),\\ \frac{dD(t)}{dt}=(1-\eta_2)\int_0^\infty p(a)i(t,a)da-(\mu_2+k)D(t),\\ \frac{dV(t)}{dt}=kD(t)-\mu_3 V(t),\end{cases}\tag{5.1}$$

where $\alpha_0,\alpha_1,\alpha_2,\alpha_3\geqslant 0$ represent the saturation factors that measure the psychological or inhibitory effects and $\beta>0$ is the infection coefficient. The other parameters have the same biological meanings as those in (2.1). The boundary condition is as follows:

$$i(t,0)=(1-\eta_1)\frac{\beta T(t)V(t)}{\alpha_0+\alpha_1 T(t)+\alpha_2 V(t)+\alpha_3 T(t)V(t)}.$$

The initial conditions of system (5.1) are similar to that of system (2.1). Notice that the Hattaf-Yousfi functional response includes numerous incidence rates existing in the literature like the bilinear incidence rate. Also, it satisfies the four hypotheses (H_1)-(H_4). Furthermore, the basic reproduction number of system (5.1) is as

$$\overline{\mathcal{R}}_0=\frac{kN(1-\eta_1)(1-\eta_2)(\beta\Lambda)}{\mu_3(\mu_2+k)(\mu_1\alpha_0+\Lambda\alpha_1)}.$$

By applying Theorems 4.3 and 4.4, we get the following result.

Corollary 5.1.

(i) *If $\overline{\mathcal{R}}_0\leqslant 1$, then the infection-free equilibrium E^0 of system (5.1) is globally asymptotically stable.*

(ii) *If $\overline{\mathcal{R}}_0>1$, then the infection-free equilibrium E^0 becomes unstable and the chronic infection equilibrium E^* of system (5.1) is globally asymptotically stable.*

6. Conclusion

In this work, we have proposed an age-structured model for HBV infection with capsids, general incidence rate and two treatments in order to block new infections of liver cells and stop viral infection. By a rigorous mathematical analysis, we have proved the well-posedness the model, the existence of equilibria, the uniform persistence, as well as the local and global stability by means of characteristic equations and Lyapunov functionals. On the other hand, immunological memory is an important characteristic of immune system against HBV infection. Therefore, the study of the memory effect on the dynamics of our proposed model by using the new generalized Hattaf fractional operators introduced in [5, 6], will be the main objective of our future works.

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