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Research article

Mathematical analysis of an HBV model with antibody and spatial heterogeneity

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Abstract: In this paper, we modify the HBV model proposed in [1] to include the spatial variations of free antibody, virus-antibody complexes, and free virus. By using comparison arguments and theory of uniform persistence, we can show that the persistene/extinction of HBV can be determined by the reproduction number(s).

Keywords: HBV; antibody; spatial heterogeneity; uniform persistence; reproduction number

1. Introduction

There has been some work in the study of the relationship between persistent infection with hepatitis B virus and immune responses (see, e.g., [2]). Hepatitis B virus (HBV) is a major cause of various liver diseases around the world. Except acute and chronic hepatitis, it causes liver fibrosis and even hepatocellular carcinoma. When an adult gets first infected with the hepatitis B virus during the early period of six months, it is called an acute infection. On the other hand, innate immune responses on persons may drive huge effector immune cells (CD8 T cells, help T cells, B cells) against infection. It is probably due to such immune system, in clinical observations, only 5–10 percent of healthy adults will develop a chronic hepatitis B infection after they get infection. This motivates researchers to investigate the topic that whether antibodies against hepatitis B play a central role in virus clearance (see, e.g., [1,2]).

It is practically difficult to obtain experimental results in the study of the antibody response to hepatitis B virus (HBV) infection. Thus, developing suitable mathematical models is an alternative way since it can be used to estimate some crucial factors for the viral infection, and to explore possible mechanisms of protection and viral infection process (see, e.g., [1–7] and the references therein). We first mention a model of virus infection in the absence of antibody responses, namely, the following model consists of three compartments of populations, corresponding to target hepatocytes (T), infected hepatocytes (I), and virus (V).

$$\begin{cases} \frac{dT(t)}{dt} = rT(1 - \frac{T+I}{T_m}) - \beta VT + \rho I, \\ \frac{dI(t)}{dt} = \beta VT - \delta I - \rho I, \\ \frac{dV(t)}{dt} = \pi I - cV. \end{cases} \tag{1.1}$$

The growth of target cells (T) in system (1.1) is described by a logistic term with carrying capacity T_m and and maximal growth rate r (see, e.g., [8,9]); target cells (T) also get infected at a rate βVT. Infected cells (I) are gained at rate βVT, and die at rate δ. Infected cells (I) produce virus (V) at rate π, and virus clearance rate is denoted by c. Further, system (1.1) also assumes that infected class (I) can get recovery and move back into the target class at rate ρ.

In order to incorporate antibody response, the authors in [1] ignore the curing of infected cells by setting $\rho = 0$, and introduce two additional classes, free antibody (A) and virus-antibody complexes (X), into system (1.1). Then the governing system takes the following form:

$$\begin{cases} \frac{dT(t)}{dt} = rT(1 - \frac{T+I}{T_m}) - \beta VT, \\ \frac{dI(t)}{dt} = \beta VT - \delta I, \\ \frac{dA(t)}{dt} = p_A(1+\theta)V + r_A A(1 - \frac{A}{A_m}) + (1+\theta)k_m X - (1+\theta)k_p AV - d_A A, \\ \frac{dX(t)}{dt} = -k_m X + k_p AV - c_{AV} X, \\ \frac{dV(t)}{dt} = \pi I - cV + k_m X - k_p AV. \end{cases} \tag{1.2}$$

The free antibody (A) is produced at rate p_A proportional to the viral and subviral concentrations, and is degraded at rate d_A. Without virus, we also introduce a logistic term with maximum growth rate r_A and carrying capacity A_m for the antibody maintenance. In system (1.2), for simplicity, we have imposed the assumption that the concentration of subviral particles is proportional to the concentration of free virus V, and θ is a constant proportionality. Antigen clearance is caused by the constitution of antigen-antibody complexes. The binding rate with antigen-antibody is k_p that causes the free antibody population to descend; k_m represents the disassociation rate for antibody reacting to viral particles. The complexes (X) are produced by a productive combination rate k_p and it decreases at a disassociation rate k_m and a degradation rate c_{AV}. During infection, free virus (V) are gained at a rate π and binding rate k_m with complexes, and are degraded by a rate c and binding rate k_p with antibody.

In [1], the authors also mention that it can be a further topic in the investigation of spatial effects in HBV infection. In fact, spatial clustering of infected cells has recently been observed for hepatitis C virus (HCV) infection (see, e.g., [10]). The effects of spatial heterogeneity was also added to within-host HIV models, see [11,12]. Motivated by those previous works, we intend to consider system (1.2) with spatial variations. For this purpose, we add diffusion terms $D_A\Delta A$, $D_X\Delta X$ and $D_V\Delta V$ into the model, which reflects the spatial variations of free antibody (A), virus-antibody complexes (X) and free virus (V), respectively. Then the modified version of system (1.2) is as follows

$$\begin{cases} \frac{\partial T}{\partial t} = rT(1-\frac{T+I}{T_m}) - \beta VT, \ x \in \Omega, \ t > 0, \\ \frac{\partial I}{\partial t} = \beta VT - \delta I, \ x \in \Omega, \ t > 0, \\ \frac{\partial A}{\partial t} = D_A\Delta A + p_A(1+\theta)V + r_A(x)A(1-\frac{A}{A_m}) + (1+\theta)k_m X \\ \qquad -(1+\theta)k_p AV - d_A(x)A, \ x \in \Omega, \ t > 0, \\ \frac{\partial X}{\partial t} = D_X\Delta X - k_m X + k_p AV - c_{AV}X, \ x \in \Omega, \ t > 0, \\ \frac{\partial V}{\partial t} = D_V\Delta V + \pi I - cV + k_m X - k_p AV, \ x \in \Omega, \ t > 0, \\ \frac{\partial A}{\partial \nu} = \frac{\partial X}{\partial \nu} = \frac{\partial V}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0, \\ u(x,0) = u^0(x), \ u = T, I, A, X, V, \ x \in \Omega. \end{cases} \tag{1.3}$$

Here, we consider a general bounded domain $\Omega \subset \mathbb{R}^3$ where virus and cells stay and interact, and pose zero-flux condition on the boundary of Ω (i.e., homogeneous Neumann boundary condition). The notation $\frac{\partial}{\partial \nu}$ denotes the differentiation along the outward normal ν to $\partial\Omega$. The location dependent parameters are continuous and strictly positive functions on $\bar{\Omega}$.

The dynamics of system (1.3) is challenging since there are no diffusion terms in the first two equations, resulting in the loss of compactness of the solution maps. In order to determine the disease-free steady state of system (1.3), we also need to investigate the following system:

$$\begin{cases} \frac{\partial T}{\partial t} = rT(1-\frac{T}{T_m}), \ x \in \Omega, \ t > 0, \\ T(x,0) = T^0(x), \ x \in \Omega. \end{cases} \tag{1.4}$$

It is easy to see that $T = 0$ and $T = T_m$ are two steady states of (1.4). However, the global dynamics of system(1.4) is still open to us, due to the loss of compactness of the solution maps. This stops us from using persistence theory in the investigation of the dynamics of system (1.3). Instead, we will focus on the study of the existence of the positive steady states of system (1.3), $(\hat{T}(x), \hat{I}(x), \hat{A}(x), \hat{X}(x), \hat{V}(x))$, which satisfies the following equations:

$$\begin{cases} r\hat{T}(1-\frac{\hat{T}+\hat{I}}{T_m}) - \beta\hat{V}\hat{T} = 0, \ x \in \Omega, \\ \beta\hat{V}\hat{T} - \delta\hat{I} = 0, \ x \in \Omega, \\ D_A\Delta\hat{A} + p_A(1+\theta)\hat{V} + r_A(x)\hat{A}(1-\frac{\hat{A}}{A_m}) + (1+\theta)k_m\hat{X} \\ \qquad -(1+\theta)k_p\hat{A}\hat{V} - d_A(x)\hat{A} = 0, \ x \in \Omega, \\ D_X\Delta\hat{X} - k_m\hat{X} + k_p\hat{A}\hat{V} - c_{AV}\hat{X} = 0, \ x \in \Omega, \\ D_V\Delta\hat{V} + \pi\hat{I} - c\hat{V} + k_m\hat{X} - k_p\hat{A}\hat{V} = 0, \ x \in \Omega, \\ \frac{\partial \hat{A}}{\partial \nu} = \frac{\partial \hat{X}}{\partial \nu} = \frac{\partial \hat{V}}{\partial \nu} = 0, \ x \in \partial\Omega. \end{cases} \tag{1.5}$$

In view of the first two equations of (1.5), it follows that

$$\hat{T} + \hat{I} = T_m(1-\frac{\beta}{r}\hat{V}), \ \hat{I} = \frac{\beta}{\delta}\hat{V}\hat{T}. \tag{1.6}$$

Then

$$\begin{cases}\hat{T} = T_m\frac{1-\frac{\beta}{r}\hat{V}}{1+\frac{\beta}{\delta}\hat{V}},\\ \hat{I} = \frac{\beta}{\delta}T_m\frac{(1-\frac{\beta}{r}\hat{V})\hat{V}}{1+\frac{\beta}{\delta}\hat{V}}.\end{cases} \tag{1.7}$$

Substituting the second equality of (1.7) into the fifth equation of (1.5), we arrive at the following elliptic system

$$\begin{cases}D_A\Delta\hat{A} + p_A(1+\theta)\hat{V} + r_A(x)\hat{A}(1-\frac{\hat{A}}{A_m}) + (1+\theta)k_m\hat{X}\\ \qquad -(1+\theta)k_p\hat{A}\hat{V} - d_A(x)\hat{A} = 0,\ x\in\Omega,\\ D_X\Delta\hat{X} - k_m\hat{X} + k_p\hat{A}\hat{V} - c_{AV}\hat{X} = 0,\ x\in\Omega,\\ D_V\Delta\hat{V} + \pi\frac{\beta}{\delta}T_m\frac{1-\frac{\beta}{r}\hat{V}}{1+\frac{\beta}{\delta}\hat{V}}\hat{V} - c\hat{V} + k_m\hat{X} - k_p\hat{A}\hat{V} = 0,\ x\in\Omega,\\ \frac{\partial\hat{A}}{\partial\nu} = \frac{\partial\hat{X}}{\partial\nu} = \frac{\partial\hat{V}}{\partial\nu} = 0,\ x\in\partial\Omega.\end{cases} \tag{1.8}$$

The standard approach in seeking for the positive steady states of system (1.8) is the bifurcation argument. Here, we are going to adopt another approach, using the persistence theory, to study the following parabolic system associated with (1.8):

$$\begin{cases}\frac{\partial A}{\partial t} = D_A\Delta A + p_A(1+\theta)V + r_A(x)A(1-\frac{A}{A_m}) + (1+\theta)k_mX\\ \qquad -(1+\theta)k_pAV - d_A(x)A,\ x\in\Omega,\ t>0,\\ \frac{\partial X}{\partial t} = D_X\Delta X - k_mX + k_pAV - c_{AV}X,\ x\in\Omega,\ t>0,\\ \frac{\partial V}{\partial t} = D_V\Delta V + \pi f(V)V - cV + k_mX - k_pAV,\ x\in\Omega,\ t>0,\\ \frac{\partial A}{\partial\nu} = \frac{\partial X}{\partial\nu} = \frac{\partial V}{\partial\nu} = 0,\ x\in\partial\Omega,\ t>0,\\ A(x,0) = A^0(x),\ X(x,0) = X^0(x),\ V(x,0) = V^0(x),\ x\in\Omega,\end{cases} \tag{1.9}$$

where

$$f(V) = \frac{\beta}{\delta}T_m\frac{1-\frac{\beta}{r}V}{1+\frac{\beta}{\delta}V}. \tag{1.10}$$

If one can show that system (1.9) is uniformly persistent, then (1.9) must admit a positive steady state (see, e.g., [13, CH1]). We point out that the dynamics of systems (1.3) and (1.9) may be different, but they admit the same positive steady states. Thus, we will focus on the search for positive steady state(s) of system (1.9) via the establishment of uniform persistence of system (1.9).

2. Persistence of HBV with antibody

Let $\mathbb{Y} := C(\bar{\Omega},\mathbb{R}^3)$ be the Banach space with the supremum norm $\|\cdot\|_{\mathbb{Y}}$. Define $\mathbb{Y}^+ := C(\bar{\Omega},\mathbb{R}^3_+)$, then $(\mathbb{Y},\mathbb{Y}^+)$ is a strongly ordered space. By the similar arguments in [14, Lemma 2.2] (see also [15]), together with [16, Corollary 4] (see also [17, Theorem 7.3.1]), we have the following result:

Lemma 2.1. *For every initial value function $\phi\in\mathbb{Y}^+$, system* (1.9) *has a unique mild solution $u(x,t,\phi)$ on $(0,\tau_\phi)$ with $u(\cdot,0,\phi)=\phi$, where $\tau_\phi\le\infty$. Furthermore, $u(\cdot,t,\phi)\in\mathbb{Y}^+$, $\forall\ t\in(0,\tau_\phi)$ and $u(x,t,\phi)$ is a classical solution of* (1.9).

Next, we show that solutions of system (1.9) are ultimately bounded, and system (1.9) admits a compact attractor in $\mathbb{Y}^+$.

Lemma 2.2. *For every initial value function $\phi \in \mathbb{Y}^+$, system* (1.9) *admits a unique solution $u(x, t, \phi)$ on* $[0, \infty)$ *with $u(\cdot, 0, \phi) = \phi$. Furthermore,*

(i) *$u(x, t, \phi)$ is ultimately bounded;*
(ii) *The semiflow $\Psi(t) : \mathbb{Y}^+ \to \mathbb{Y}^+$ generated by* (1.9) *is defined by $\Psi(t)\phi = u(\cdot, t, \phi)$, $t \geq 0$, which admits a global compact attractor in $\mathbb{Y}^+$, $\forall\, t \geq 0$.*

Proof. In view of (1.10), it is not hard to see that

$$f(V)V \leq \frac{\beta}{\delta} T_m \frac{V}{1 + \frac{\beta}{\delta} V} \leq \frac{\beta}{\delta} T_m \frac{V}{\frac{\beta}{\delta} V} = T_m, \ \forall\, V > 0.$$

Thus,

$$f(V)V \leq T_m, \ \forall\, V \geq 0. \tag{2.1}$$

Setting

$$U(t) = \int_\Omega [X(x, t) + V(x, t)]\, dx.$$

Then it follows from system (1.9) and (2.1) that

$$\begin{aligned} \frac{dU(t)}{dt} &= \int_\Omega \pi f(V(x, t))V(x, t) dx - \int_\Omega [c_{AV} X(x, t) + cV(x, t)]\, dx \\ &\leq \pi T_m |\Omega| - c_{\min} U(t), \end{aligned}$$

where $c_{\min} := \min\{c_{AV}, c\}$. Thus, we have

$$U(t) \leq U(0) e^{-c_{\min}\, t} + \frac{\pi T_m |\Omega|}{c_{\min}} (1 - e^{-c_{\min}\, t}). \tag{2.2}$$

Using (2.2) and the similar arguments to those in the end of [18, Proposition 2.3], we can show that $X(\cdot, t, \phi)$ and $V(\cdot, t, \phi)$ are ultimately bounded. Therefore, there exists $\hat{C} > 0$ and $t_1 > 0$ such that

$$p_A(1 + \theta)V(x, t) + (1 + \theta)k_m X(x, t) \leq \hat{C}, \ \forall\, x \in \overline{\Omega}, \ t \geq t_1. \tag{2.3}$$

In view of the first equation of system (1.9) and (2.3), it follows that

$$\begin{cases} \frac{\partial A}{\partial t} \leq D_A \Delta A + \hat{C} + r_A(x) A (1 - \frac{A}{A_m}) - d_A(x) A, \ \forall\, x \in \Omega, \ t \geq t_1, \\ \frac{\partial A}{\partial \nu} = 0, \ x \in \partial\Omega, \ t \geq t_1. \end{cases}$$

Then

$$\limsup_{t \to \infty} A(x, t) \leq \hat{A}, \ \forall\, x \in \overline{\Omega},$$

where $\hat{A} > 0$ is a constant such that

$$\hat{C} + r_A(x) \hat{A} (1 - \frac{\hat{A}}{A_m}) - d_A(x) \hat{A} \leq 0, \ \forall\, x \in \Omega.$$

From the above discussions, we see that $\Psi(t) : \mathbb{Y}^+ \to \mathbb{Y}^+$ is point dissipative. Obviously, $\Psi(t) : \mathbb{Y}^+ \to \mathbb{Y}^+$ is compact, $\forall\, t > 0$. It follows from [19, Theorem 3.4.8] that $\Psi(t) : \mathbb{Y}^+ \to \mathbb{Y}^+$, $t \geq 0$, admits a global compact attractor.

□

Putting $X = V = 0$ into (1.9), we see that

$$\begin{cases} \frac{\partial A}{\partial t} = D_A \Delta A + r_A(x) A(1 - \frac{A}{A_m}) - d_A(x) A, \ x \in \Omega, \ t > 0, \\ \frac{\partial A}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0, \\ A(x,0) = A^0(x), \ x \in \Omega. \end{cases} \tag{2.4}$$

It is easy to see that $A = 0$ is the trivial steady state solution of system (2.4). The stability of the trivial steady state solution $A = 0$ is determined by the following eigenvalue problem:

$$\begin{cases} \mu\varphi(x) = D_A \Delta\varphi(x) + (r_A(x) - d_A(x))\varphi(x), \ x \in \Omega, \\ \frac{\partial \varphi(x)}{\partial \nu} = 0, \ x \in \partial\Omega. \end{cases} \tag{2.5}$$

Assume that μ^0 is the principal eigenvalue of system (2.5). By [20, Proposition 4.4], we see that $\mu^0 > 0$ if the following condition is satisfied

$$\int_\Omega (r_A(x) - d_A(x))dx > 0. \tag{2.6}$$

Thus, trivial steady state solution $A = 0$ is unstable for system (2.4) if condition (2.6) holds. If condition (2.6) is true, then one can use [13, Theorem 2.3.2] to show that system (2.4) admits a unique positive steady state $A^*(x)$ which is globally attractive. Thus, two possible steady states of system (1.9) are as follows:

$$E_0(x) = (A, X, V) = (0, 0, 0),$$

and

$$E_1(x) = (A, X, V) = (A^*(x), 0, 0).$$

Note that $E_0(x)$ always exists, and $E_1(x)$ exists when (2.6) holds. Linearizing system (1.9) around $E_1(x)$, we get the following cooperative system for the infectious compartments:

$$\begin{cases} \frac{\partial X}{\partial t} = D_X \Delta X - k_m X + k_p A^*(x) V - c_{AV} X, \ x \in \Omega, \ t > 0, \\ \frac{\partial V}{\partial t} = D_V \Delta V + \pi f(0) V - cV + k_m X - k_p A^*(x) V, \ x \in \Omega, \ t > 0, \\ \frac{\partial X}{\partial \nu} = \frac{\partial V}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0. \end{cases} \tag{2.7}$$

Substituting $X(x,t) = e^{\lambda t}\psi_X(x)$ and $V(x,t) = e^{\lambda t}\psi_V(x)$ into (2.7) and we get the associated eigenvalue problem:

$$\begin{cases} \lambda\psi_X(x) = D_X \Delta\psi_X(x) - (k_m + c_{AV})\psi_X(x) + k_p A^*(x)\psi_V(x), \ x \in \Omega, \\ \lambda\psi_V(x) = D_V \Delta\psi_V(x) + k_m\psi_X(x) + (\pi f(0) - c - k_p A^*(x))\psi_V(x), \ x \in \Omega, \\ \frac{\partial \psi_X(x)}{\partial \nu} = \frac{\partial \psi_V(x)}{\partial \nu} = 0, \ x \in \partial\Omega. \end{cases} \tag{2.8}$$

It is not hard to see that the linear system (2.7) generates a strongly positive semigroup on $C(\overline{\Omega}, \mathbb{R}^2_+)$ (see, e.g., Section 4 of CH 7 in [17]). In addition, the semigroup associated with system (2.7) is compact. By a similar argument as in [17, Theorem 7.6.1], we have the following result which is related to the existence of the principal eigenvalue of (2.8):

Lemma 2.3. *The eigenvalue problem* (2.8) *admits a principal eigenvalue, denoted by λ^0, which corresponds a strongly positive eigenfunction.*

Next, we shall adopt the theory developed in [21, Section 3] to define the basic reproduction number for system (1.9). For this purpose, we assume

$$\mathbb{F}(x) = \begin{pmatrix} 0 & k_p A^*(x) \\ k_m & \pi f(0) \end{pmatrix}, \tag{2.9}$$

and

$$\mathbb{V}(x) = \begin{pmatrix} k_m + c_{AV} & 0 \\ 0 & c + k_p A^*(x) \end{pmatrix}. \tag{2.10}$$

Let $\mathbf{w} = (X, V)^T$, $\mathbf{D}\Delta\mathbf{w} = (D_X \Delta X, D_V \Delta V)^T$, and $\mathbb{S}(t) : C(\overline{\Omega}, \mathbb{R}^2) \to C(\overline{\Omega}, \mathbb{R}^2)$ be the C_0-semigroup generated by the following system

$$\begin{cases} \frac{\partial \mathbf{w}}{\partial t} = \mathbf{D}\Delta\mathbf{w} - \mathbb{V}(x)\mathbf{w}, \ x \in \overline{\Omega}, \ t > 0, \\ \frac{\partial X}{\partial \nu} = \frac{\partial V}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0. \end{cases} \tag{2.11}$$

Assume that the state variables are near the disease-free steady state $E_1(x)$ and the distribution of initial infection is described by $\varphi \in C(\overline{\Omega}, \mathbb{R}^2)$. Then $\mathbb{S}(t)\varphi(x)$ represents the distribution of those infectious cases as time evolves to time t, and hence, the distribution of new infection at time t is $\mathbb{F}(x)\mathbb{S}(t)\varphi(x)$. Let $\mathbb{L} : C(\overline{\Omega}, \mathbb{R}^2) \to C(\overline{\Omega}, \mathbb{R}^2)$ be defined by

$$\mathbb{L}(\varphi)(\cdot) = \int_0^\infty \mathbb{F}(\cdot)(\mathbb{S}(t)\varphi)(\cdot)dt.$$

It then follows that $\mathbb{L}(\varphi)(\cdot)$ represents the distribution of accumulated infectious cases during the infection period, and hence, $\mathbb{L}$ is the next generation operator. By the idea of next generation operators (see, e.g., [21–23]), we define the spectral radius of $\mathbb{L}$ as the basic reproduction number for system (1.9), that is,

$$\mathcal{R}_0 := r(\mathbb{L}).$$

From [24, Theorem 3.5] or [21, Theorem 3.1], the following observation holds.

Lemma 2.4. *$\mathcal{R}_0 - 1$ and λ^0 have the same sign.*

Next, we are going to find an explicit formula for $\mathcal{R}_0$ when coefficients of system (1.9) are all positive constants. For this special case, we see that $\mathbb{F}(x) = \mathbb{F}$ and $\mathbb{V}(x) = \mathbb{V}$, for all $x \in \bar{\Omega}$, and hence, $\mathcal{R}_0 = r(\mathbb{F}\mathbb{V}^{-1})$ (see e. g., [21, Theorem 3.4]). By direct computations, it follows that

$$\mathbb{F}\mathbb{V}^{-1} = \begin{pmatrix} 0 & k_p A^* \\ k_m & \pi f(0) \end{pmatrix} \begin{pmatrix} \frac{1}{k_m + c_{AV}} & 0 \\ 0 & \frac{1}{c + k_p A^*} \end{pmatrix} = \begin{pmatrix} 0 & \frac{k_p A^*}{c + k_p A^*} \\ \frac{k_m}{k_m + c_{AV}} & \frac{\pi f(0)}{c + k_p A^*} \end{pmatrix}.$$

Thus,

$$\mathcal{R}_0 = \frac{1}{2}\left[\frac{\pi f(0)}{c + k_p A^*} + \sqrt{(\frac{\pi f(0)}{c + k_p A^*})^2 + 4\frac{k_p A^*}{c + k_p A^*}\frac{k_m}{k_m + c_{AV}}}\right]. \tag{2.12}$$

In the establishment of the persistence for (1.9), the following results will be necessary.

Lemma 2.5. *For every initial value function $\phi \in \mathbb{Y}^+$, we assume that system* (1.9) *admits a unique solution $u(x,t,\phi)$ on* $[0,\infty)$ *with $u(\cdot,0,\phi) = \phi$.*

(i) *If $\phi_2(\cdot) \not\equiv 0$ and $\phi_3(\cdot) \not\equiv 0$, then*

$$u_i(x,t,\phi) > 0, \text{ for } x \in \bar{\Omega},\ t > 0,\ \text{and } 1 \le i \le 3.$$

(ii) *Assume that $\phi_i(\cdot) \not\equiv 0$, for $i = 2, 3$. If there exists a $\sigma_1 > 0$ such that*

$$\liminf_{t\to\infty} X(x,t,\phi) \ge \sigma_1 \text{ and } \liminf_{t\to\infty} V(x,t,\phi) \ge \sigma_1, \text{ uniformly for } x \in \bar{\Omega}. \tag{2.13}$$

Then there exists a $\sigma > 0$ such that

$$\liminf_{t\to\infty} u_i(x,t,\phi) \ge \sigma, \text{ uniformly for } x \in \bar{\Omega}, \text{ and } 1 \le i \le 3. \tag{2.14}$$

Proof. Part (i). By the positivity of solutions (see Lemma 2.1), it follows that $X(x,t) \ge 0,\ \forall\, x \in \overline{\Omega},\ t \ge 0$. Suppose, by contradiction, there exists $x_1 \in \overline{\Omega}$ and $t_1 \in (0,\infty)$ such that $X(x_1,t_1) = 0$. Let $\tau_1 > 0$ be such that $t_1 < \tau_1$. Then $(x_1,t_1) \in \overline{\Omega} \times [0,\tau_1]$ and X attains its minimum on $\overline{\Omega} \times [0,\tau_1]$ at the point (x_1,t_1). In view of the second equation of (1.9), it follows that

$$\begin{cases} \frac{\partial X}{\partial t} \ge D_X \Delta X - (k_m + c_{AV})X,\ x \in \Omega,\ t \in (0,\tau_1], \\ \frac{\partial X}{\partial \nu} = 0,\ x \in \partial\Omega,\ t \in (0,\tau_1]. \end{cases}$$

In case $x_1 \in \partial\Omega$, we apply the Hopf boundary lemma (see, e.g., [25, p. 170, Theorem 3]) and we have $\frac{\partial X(x_1,t_1,\phi)}{\partial \nu} < 0$, which is impossible. In case where $x_1 \in \Omega$, then the strong maximum principle (see [25, p. 174, Theorem 7]) implies that

$$X(x,t,\phi) \equiv X(x_1,t_1,\phi) = 0,\ \forall\, (x,t) \in \overline{\Omega} \times [0,\tau_1],$$

which contradicts the assumption that $\phi_2(\cdot) \not\equiv 0$. Thus, $X(x,t,\phi) > 0,\ \forall\, x \in \bar{\Omega},\ t > 0$. Similarly, we see that $V(x,t) \ge 0,\ \forall\, x \in \overline{\Omega},\ t \ge 0$ (see Lemma 2.1). Suppose, by contradiction, there exists $x_2 \in \overline{\Omega}$ and $t_2 \in (0,\infty)$ such that $V(x_2,t_2) = 0$. Let $\tau_2 > 0$ be such that $t_2 < \tau_2$. Then $(x_2,t_2) \in \overline{\Omega} \times [0,\tau_2]$ and V attains its minimum on $\overline{\Omega} \times [0,\tau_2]$ at the point (x_2,t_2). Using the third equation of (1.9) and (1.10), it follows that

$$\begin{cases} \frac{\partial V}{\partial t} \ge D_V \Delta V - \pi[\frac{\beta}{\delta} T_m \frac{\frac{\beta}{r} V}{1+\frac{\beta}{\delta} V} + c + k_p A]V,\ x \in \Omega,\ t \in (0,\tau_2], \\ \frac{\partial V}{\partial \nu} = 0,\ x \in \partial\Omega,\ t \in (0,\tau_2]. \end{cases} \tag{2.15}$$

In case $x_2 \in \partial\Omega$, we apply the Hopf boundary lemma (see, e.g., [25, p. 170, Theorem 3]) and we have $\frac{\partial V(x_2,t_2,\phi)}{\partial \nu} < 0$, which is a contradiction. In case where $x_2 \in \Omega$, then the strong maximum principle (see [25, p. 174, Theorem 7]) implies that

$$V(x,t,\phi) \equiv V(x_2,t_2,\phi) = 0,\ \forall\, (x,t) \in \overline{\Omega} \times [0,\tau_2],$$

which contradicts the assumption that $\phi_3(\cdot) \not\equiv 0$. Thus, $V(x,t,\phi) > 0,\ \forall\, x \in \bar{\Omega},\ t > 0$.

Claim. $A(x,t,\phi) > 0,\ \forall\, x \in \bar{\Omega},\ t > 0$.

By Lemma 2.1, it follows that $A(x,t) \ge 0,\ \forall\, x \in \overline{\Omega},\ t \ge 0$. Suppose, by contradiction, there exists $x_3 \in \overline{\Omega}$ and $t_3 \in (0,\infty)$ such that $A(x_3,t_3) = 0$. Let $\tau_3 > 0$ be such that $t_3 < \tau_3$. Then $(x_3,t_3) \in \overline{\Omega} \times [0,\tau_3]$

and A attains its minimum on $\overline{\Omega} \times [0, \tau_3]$ at the point (x_3, t_3). By the first equation of (1.9), it follows that

$$\begin{cases} \frac{\partial A}{\partial t} \geq D_A \Delta A - [r_A(x)\frac{A}{A_m} + (1+\theta)k_p V + d_A(x)]A, \ x \in \Omega, \ t \in (0, \tau_3], \\ \frac{\partial A}{\partial \nu} = 0, \ x \in \partial\Omega, \ t \in (0, \tau_3]. \end{cases}$$

In case $x_3 \in \partial\Omega$, we apply the Hopf boundary lemma (see, e.g., [25, p. 170, Theorem 3]) and we have $\frac{\partial A(x_3,t_3,\phi)}{\partial \nu} < 0$, which is a contradiction. In case where $x_3 \in \Omega$, then the strong maximum principle (see [25, p. 174, Theorem 7]) implies that

$$A(x, t, \phi) \equiv A(x_3, t_3, \phi) = 0, \ \forall \ (x, t) \in \overline{\Omega} \times [0, \tau_3].$$

This together with the first equation of (1.9) imply that

$$X(x, t, \phi) \equiv 0 \text{ and } V(x, t, \phi) \equiv 0, \ \forall \ (x, t) \in \overline{\Omega} \times [0, \tau_3],$$

which is a contradiction. Thus, $A(x, t, \phi) > 0, \ \forall \ x \in \bar{\Omega}, \ t > 0$.

Part (ii). From Lemma 2.2, we see that $V(x, t)$ is ultimately bounded. This together with assumption (2.13) imply that there exists $t_4 > 0$ and $C > 0$ such that

$$\frac{1}{2}\sigma_1 \leq V(x, t) \leq C, \text{ and } X(x, t) \geq \frac{1}{2}\sigma_1, \ \forall \ \in \bar{\Omega}, \ t \geq t_4.$$

From the above inequalities and the first equation of (1.9), it follows that

$$\begin{cases} \frac{\partial A}{\partial t} \geq D_A \Delta A + \frac{1}{2}(1+\theta)(p_A + k_m)\sigma_1 + r_A(x)A(1 - \frac{A}{A_m}) \\ \qquad -[(1+\theta)k_p C + d_A(x)]A, \ x \in \Omega, \ t \geq t_4, \\ \frac{\partial A}{\partial \nu} = 0, \ x \in \partial\Omega, \ t \geq t_4. \end{cases} \tag{2.16}$$

Let $\underline{A} > 0$ satisfy the following inequality

$$\frac{1}{2}(1+\theta)(p_A + k_m)\sigma_1 + r_A(x)\underline{A}(1 - \frac{A}{A_m}) - [(1+\theta)k_p C + d_A(x)]\underline{A} \geq 0, \ \forall \ x \in \Omega.$$

By (2.16) and the standard parabolic comparison theorem (see, e.g., [17, Theorem 7.3.4]), we deduce that

$$\liminf_{t\to\infty} A(x, t, \phi) \geq \underline{A}, \ \forall \ x \in \bar{\Omega}.$$

Let $\sigma := \min\{\sigma_1, \underline{A}\}$. Then (2.14) holds. □

We show that $\mathcal{R}_0$ is an important index for the persistence of HBV in system (1.9).

Theorem 2.1. *Assume that* (2.6) *holds. For every initial value function* $u^0(\cdot) = (A^0, X^0, V^0)(\cdot) \in \mathbb{Y}^+$, *we assume that system* (1.9) *admits a unique solution*

$$u(x, t, u^0) := (A(x, t), X(x, t), V(x, t))$$

on $[0, \infty)$ *with* $u(\cdot, 0, u^0) = u^0$. *If* $\mathcal{R}_0 > 1$, *then system* (1.9) *admits at least one (componentwise) positive steady state* $\hat{u}(x)$ *and there exists a* $\sigma > 0$ *such that for any* $u^0(\cdot) \in \mathbb{Y}^+$ *with* $X^0(\cdot) \not\equiv 0$ *and* $V^0(\cdot) \not\equiv 0$, *we have*

$$\liminf_{t\to\infty} w(x, t, u^0(\cdot)) \geq \sigma, \ \text{for } w = A, X, V, \tag{2.17}$$

uniformly for $x \in \overline{\Omega}$.

Proof. Let

$$\mathbb{W}_0 = \{u^0(\cdot) = (A^0, X^0, V^0)(\cdot) \in \mathbb{Y}^+ : X^0(\cdot) \not\equiv 0 \text{ and } V^0(\cdot) \not\equiv 0\},$$

and

$$\partial\mathbb{W}_0 = \mathbb{Y}^+ \backslash \mathbb{W}_0 = \{u^0(\cdot) = (A^0, X^0, V^0)(\cdot) \in \mathbb{Y}^+ : X^0(\cdot) \equiv 0 \text{ or } V^0(\cdot) \equiv 0\}.$$

Recall that the semiflow $\Psi(t) : \mathbb{Y}^+ \to \mathbb{Y}^+$ generated by (1.9) is defined in Lemma 2.2. By Lemma 2.5 (i), it follows that for any $u^0(\cdot) \in \mathbb{W}_0$, we have

$$w(x, t, u^0(\cdot)) > 0, \text{ for } x \in \bar{\Omega}, \ t > 0, \text{ and } w = A, X, V.$$

In other words, $\Psi(t)\mathbb{W}_0 \subseteq \mathbb{W}_0, \ \forall\, t \geq 0$. Let

$$M_\partial := \{u^0(\cdot) \in \partial\mathbb{W}_0 : \Psi(t)u^0(\cdot) \in \partial\mathbb{W}_0, \forall\, t \geq 0\},$$

and $\omega(u^0(\cdot))$ be the omega limit set of the orbit $O^+(u^0(\cdot)) := \{\Psi(t)u^0(\cdot) : t \geq 0\}$.

Claim 1. $\omega(v^0(\cdot)) \subseteq \{E_0(x)\} \cup \{E_1(x)\}, \ \forall\, v^0(\cdot) \in M_\partial$.

Since $v^0(\cdot) \in M_\partial$, we have $\Psi(t)v^0(\cdot) \in M_\partial, \ \forall\, t \geq 0$, that is, $X(\cdot, t, v^0(\cdot)) \equiv 0$ or $V(\cdot, t, v^0(\cdot)) \equiv 0, \ \forall\, t \geq 0$.

In case where $V(\cdot, t, v^0(\cdot)) \equiv 0, \ \forall\, t \geq 0$. Then it follows from the third equation in system (1.9) that $X(\cdot, t, v^0(\cdot)) \equiv 0, \ \forall\, t \geq 0$. Thus, $X(x, t, v^0(\cdot))$ satisfies system (2.4), and hence,

$$\text{either } \lim_{t\to\infty} A(x, t, v^0) = 0 \text{ or } \lim_{t\to\infty} A(x, t, v^0) = A^*(x), \text{ uniformly for } x \in \bar{\Omega}.$$

Thus,

$$\text{either } \lim_{t\to\infty} u(x, t, v^0) = E_0(x) \text{ or } \lim_{t\to\infty} u(x, t, v^0) = E_1(x), \text{ uniformly for all } x \in \bar{\Omega}.$$

In case where $V(\cdot, \hat{t}_0, v^0(\cdot)) \not\equiv 0$, for some $\hat{t}_0 \geq 0$. Then we can use similar arguments in Lemma 2.5 to show that $V(x, t, v^0) > 0$, for all $x \in \bar{\Omega}$ and $t > \hat{t}_0$, and hence, $X(\cdot, t, v^0) \equiv 0$, for all $t > \hat{t}_0$. Then it follows from the second equation in system (1.9) that $A(\cdot, t, v^0(\cdot))V(\cdot, t, v^0(\cdot)) \equiv 0, \ \forall\, t > \hat{t}_0$. From the above discussions, it follows that $A(\cdot, t, v^0(\cdot)) \equiv 0, \ \forall\, t > \hat{t}_0$. Thanks to the first equation in system (1.9), it follows that $V(\cdot, t, v^0(\cdot)) \equiv 0, \ \forall\, t > \hat{t}_0$. This is a contradiction, and hence, we cannot allow the possibility that $V(\cdot, \hat{t}_0, v^0(\cdot)) \not\equiv 0$, for some $\hat{t}_0 \geq 0$. Therefore, we complete the proof of Claim 1.

Recall that μ^0 is the principal eigenvalue of the eigenvalue problem (2.5), and $\mu^0 > 0$ since (2.6) holds. By continuity, there is a $\delta_0 > 0$ such that $\mu_{\delta_0} > 0$, where $\mu_{\delta_0} > 0$ is the principal eigenvalue of the following eigenvalue problem:

$$\begin{cases} \mu\varphi(x) = D_A\Delta\varphi(x) + [r_A(x)(1 - \frac{\delta_0}{A_m}) - (1+\theta)k_p\delta_0 - d_A(x)]\varphi(x), \ x \in \Omega, \\ \frac{\partial\varphi(x)}{\partial\nu} = 0, \ x \in \partial\Omega. \end{cases} \tag{2.18}$$

Claim 2. $E_0(x)$ is a uniform weak repeller for $\mathbb{W}_0$ in the sense that

$$\limsup_{t\to\infty} \|\Psi(t)u^0(\cdot) - E_0(\cdot)\| \geq \delta_0, \ \forall\, u^0(\cdot) \in \mathbb{W}_0.$$

Suppose, by contradiction, that there exists $u^0(\cdot) \in \mathbb{W}_0$ such that

$$\limsup_{t\to\infty} \|\Psi(t)u^0(\cdot) - E_0(\cdot)\| < \delta_0.$$

Then there exists $t_0 > 0$ such that

$$0 \le w(x,t,u^0) < \delta_0,\ \forall\ t \ge t_0,\ x \in \bar{\Omega},\ w = A, X, V.$$

From the first equation of (1.9), we see that

$$\begin{cases} \frac{\partial A}{\partial t} \ge D_A \Delta A + [r_A(x)(1 - \frac{\delta_0}{A_m}) - (1+\theta)k_p\delta_0 - d_A(x)]A,\ x \in \Omega,\ t \ge t_0, \\ \frac{\partial A}{\partial \nu} = 0,\ x \in \partial\Omega,\ t \ge t_0. \end{cases} \tag{2.19}$$

Assume that $\varphi_{\delta_0}(x)$ is the positive eigenfunction corresponding to μ_{δ_0}, and there exists a $C_0 > 0$ such that

$$A(x,t_0) \ge C_0 \varphi_{\delta_0}(x),\ \forall\ x \in \bar{\Omega},$$

where we have used the fact that $A(x,t_0) > 0,\ \forall\ x \in \bar{\Omega}$ (see Lemma 2.5). The comparison principle and the inequality (2.19) imply that

$$A(x,t) \ge C_0 e^{\mu_{\delta_0}(t-t_0)} \varphi_{\delta_0}(x),\ \forall\ t \ge t_0,\ x \in \bar{\Omega}.$$

Since $\mu_{\delta_0} > 0$, it follows that $A(x,t)$ is unbounded. This contradiction proves the Claim 2.

Since $\mathcal{R}_0 > 1$, it follows from Lemma 2.4 that $\lambda^0 > 0$. By continuity of the principal eigenvalue, we can find an $\epsilon_1 > 0$ such that $\lambda_{\epsilon_1} > 0$, where λ_{ϵ_1} is the principal eigenvalue of the following eigenvalue problem:

$$\begin{cases} \lambda\psi_X(x) = D_X \Delta\psi_X(x) - (k_m + c_{AV})\psi_X(x) + k_p[A^*(x) - \epsilon_1]\psi_V(x),\ x \in \Omega, \\ \lambda\psi_V(x) = D_V \Delta\psi_V(x) + k_m\psi_X(x) \\ \qquad\qquad + [\pi(f(0) - \epsilon_1) - c - k_p(A^*(x) + \epsilon_1)]\psi_V(x),\ x \in \Omega, \\ \frac{\partial \psi_X(x)}{\partial \nu} = \frac{\partial \psi_V(x)}{\partial \nu} = 0,\ x \in \partial\Omega. \end{cases} \tag{2.20}$$

By continuity of $f(V)$, we can choose a δ_1 with $0 < \delta_1 \le \epsilon_1$ such that

$$f(V) > f(0) - \epsilon_1,\ \forall\ \mid V \mid < \delta_1. \tag{2.21}$$

Claim 3. $E_1(x)$ is a uniform weak repeller for $\mathbb{W}_0$ in the sense that

$$\limsup_{t\to\infty} \|\Psi(t)u^0(\cdot) - E_1(\cdot)\| \ge \frac{1}{2}\delta_1,\ \forall\ u^0(\cdot) \in \mathbb{W}_0.$$

Suppose, by contradiction, there exists $u^0(\cdot) \in \mathbb{W}_0$ such that

$$\limsup_{t\to\infty} \|\Psi(t)u^0(\cdot) - E_1(x)\| < \frac{1}{2}\delta_1.$$

Then there exists $t_1 > 0$ such that

$$A^*(x) - \epsilon_1 < A^*(x) - \frac{1}{2}\delta_1 \le A(x,t,u^0) < A^*(x) + \frac{1}{2}\delta_1 < A^*(x) + \epsilon_1,\ \forall\ t \ge t_1,\ x \in \bar{\Omega},$$

and

$$0 \le w(x,t,u^0) < \frac{1}{2}\delta_1 < \epsilon_1,\ \forall\ t \ge t_1,\ x \in \bar{\Omega},\ w = X, V.$$

From the second and third equations in system (1.9), it follows that

$$\begin{cases} \frac{\partial X}{\partial t} \geq D_X \Delta X - k_m X + k_p [A^*(x) - \epsilon_1] V - c_{AV} X, \ x \in \Omega, \ t \geq t_1, \\ \frac{\partial V}{\partial t} \geq D_V \Delta V + \pi [f(0) - \epsilon_1] V - cV + k_m X \\ \qquad\qquad\qquad -k_p [A^*(x) + \epsilon_1] V, \ x \in \Omega, \ t \geq t_1, \\ \frac{\partial X}{\partial \nu} = \frac{\partial V}{\partial \nu} = 0, \ x \in \partial\Omega, \ t \geq t_1. \end{cases} \tag{2.22}$$

Assume that $(\psi_X^{\epsilon_1}(x), \psi_V^{\epsilon_1}(x))$ is the positive eigenfunction corresponding to λ_{ϵ_1}, and there exists a $C_1 > 0$ such that

$$(X(x, t_1), V(x, t_1)) \geq C_1 (\psi_X^{\epsilon_1}(x), \psi_V^{\epsilon_1}(x)), \ \forall \ x \in \bar{\Omega},$$

where we have used the fact that $X(x, t_1) > 0, \ V(x, t_1) > 0, \ \forall \ x \in \bar{\Omega}$ (see Lemma 2.5). The comparison principle and the inequality (2.22) imply that

$$(X(x, t), V(x, t)) \geq C_1 e^{\lambda_{\epsilon_1}(t - t_1)} (\psi_X^{\epsilon_1}(x), \psi_V^{\epsilon_1}(x)), \ \forall \ t \geq t_1, \ x \in \bar{\Omega}.$$

Since $\lambda_{\epsilon_1} > 0$, it follows that $(X(x, t), V(x, t))$ is unbounded. This contradiction proves Claim 3.

Define a continuous function $\mathbb{P} : \mathbb{Y}^+ \to [0, \infty)$ by

$$\mathbb{P}(u^0(\cdot)) := \min\{\min_{x \in \bar{\Omega}} X^0(x), \ \min_{x \in \bar{\Omega}} V^0(x)\}, \ \forall \ u^0(\cdot) = (A^0, X^0, V^0)(\cdot) \in \mathbb{Y}^+.$$

By Lemma 2.5 (i), it follows that $\mathbb{P}^{-1}(0, \infty) \subseteq \mathbb{W}_0$ and $\mathbb{P}$ has the property that if $\mathbb{P}(u^0(\cdot)) > 0$ or $u^0(\cdot) \in \mathbb{W}_0$ with $\mathbb{P}(u^0(\cdot)) = 0$, then $\mathbb{P}(\Psi(t) u^0(\cdot)) > 0, \ \forall \ t > 0$. That is, $\mathbb{P}$ is a generalized distance function for the semiflow $\Psi(t) : \mathbb{Y}^+ \to \mathbb{Y}^+$ (see, e.g., [26]).

From the above claims, it follows that any forward orbit of $\Psi(t)$ in M_∂ converges to $\{E_0(x)\} \cup \{E_1(x)\}$. For $i = 0, 1$, $\{E_i(x)\}$ is isolated in $\mathbb{Y}^+$ and $W^s(\{E_i(x)\}) \cap \mathbb{W}_0 = \emptyset$, where $W^s(\{E_i(x)\})$ is the stable set of $\{E_i(x)\}$ (see [26]). It is obvious that no subset of $\{E_0(x)\} \cup \{E_1(x)\}$ forms a cycle in $\partial\mathbb{W}_0$. By Lemma 2.2, the semiflow $\Psi(t) : \mathbb{Y}^+ \to \mathbb{Y}^+$ has a global compact attractor in $\mathbb{Y}^+$, $\forall \ t \geq 0$. Then it follows from [26, Theorem 3] that there exists a $\sigma_1 > 0$ such that

$$\min_{\psi \in \omega(u^0(\cdot))} p(\psi) > \sigma_1, \ \forall \ u^0(\cdot) \in \mathbb{W}_0.$$

Hence,

$$\liminf_{t \to \infty} X(\cdot, t, u^0(\cdot)) \geq \sigma_1 \text{ and } \liminf_{t \to \infty} V(\cdot, t, u^0(\cdot)) \geq \sigma_1, \ \forall \ u^0(\cdot) \in \mathbb{W}_0.$$

From Lemma 2.5 (ii), there exists a $\sigma > 0$ such that (2.17) is valid. Hence, the uniform persistence stated in the conclusion (ii) hold. By [27, Theorem 3.7 and Remark 3.10], it follows that $\Psi(t) : \mathbb{W}_0 \to \mathbb{W}_0$ has a global attractor $\mathcal{A}_0$. Using [27, Theorem 4.7], we deduce that $\Psi(t)$ admits a steady-state $\hat{u}(\cdot) \in \mathbb{W}_0$. By Lemma 2.5 (i), we can further conclude that $\hat{u}(\cdot)$ is a positive steady state of (1.9). The proof of Part (ii) is finished.

□

3. Elimination of HBV with antibody

In this section, we focus on the study of elimination of HBV with antibody. Due to technical reasons, we only consider a special case where we assume $k_m = 0$ in system (1.9), and the coefficients in (1.9) are all positive constants. Then the equation of X in system (1.9) is decoupled from the other equations, and hence, it suffices to investigate the following system:

$$\begin{cases} \frac{\partial A}{\partial t} = D_A \Delta A + p_A(1+\theta)V + r_A A(1 - \frac{A}{A_m}) \\ \qquad -(1+\theta)k_p AV - d_A A, \ x \in \Omega, \ t > 0, \\ \frac{\partial V}{\partial t} = D_V \Delta V + \pi f(V)V - cV - k_p AV, \ x \in \Omega, \ t > 0, \\ \frac{\partial A}{\partial \nu} = \frac{\partial V}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0, \\ A(x,0) = A^0(x), \ V(x,0) = V^0(x), \ x \in \Omega. \end{cases} \tag{3.1}$$

We see that two possible steady states of system (3.1) are as follows:

$$\mathcal{E}_0 = (A, V) = (0, 0),$$

and

$$\mathcal{E}_1 = (A, V) = (A^*, 0),$$

where $A^* := A_m(1 - \frac{d_A}{r_A}) > 0$, provided that $r_A > d_A$.

Linearizing system (3.1) around $\mathcal{E}_1$, we get the following scalar system

$$\begin{cases} \frac{\partial V}{\partial t} = D_V \Delta V + \pi f(0)V - cV - k_p A^* V, \ x \in \Omega, \ t > 0, \\ \frac{\partial V}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0. \end{cases} \tag{3.2}$$

Substituting $V(x,t) = e^{\Lambda t}\psi(x)$ into (3.2), and we get the associated eigenvalue problem:

$$\begin{cases} \Lambda\psi(x) = D_V \Delta\psi(x) + (\pi f(0) - c - k_p A^*)\psi(x), \ x \in \Omega, \\ \frac{\partial\psi(x)}{\partial \nu} = 0, \ x \in \partial\Omega. \end{cases} \tag{3.3}$$

By the same argument in [17, Theorem 7.6.1], we can show that the eigenvalue problem (3.3) admits a principal eigenvalue, denoted by Λ^0, which corresponds a strongly positive eigenfunction $\psi^0(x)$. In fact, one can show that $\Lambda^0 = \pi f(0) - c - k_p A^*$ and the associated eigenfunction $\psi(\cdot) \equiv 1$. Note that one can also adopt the theory developed in [21, Section 3] to define the basic reproduction number, $\mathcal{R}_0^0$, for system (3.1). For this purpose, we assume $\mathbf{F} = \pi f(0)$ and $\mathbf{V} = c + k_p A^*$. By [21, Theorem 3.4], it follows that

$$\mathcal{R}_0^0 = \mathbf{F}\mathbf{V}^{-1} = \frac{\pi f(0)}{c + k_p A^*}.$$

Putting $k_m = 0$ in (2.12), and it is easy to see that $\mathcal{R}_0^0 = \mathcal{R}_0$ when $k_m = 0$. This is the reason why the reproduction number in this section is denoted by $\mathcal{R}_0^0$. Further, it is easy to observe that

$$\mathcal{R}_0^0 < 1 \Leftrightarrow \Lambda^0 < 0. \tag{3.4}$$

We impose the following condition:

$$\overline{A} := \frac{p_A}{k_p} \geq A^* := A_m(1 - \frac{d_A}{r_A}) \text{ and } r_A > d_A. \tag{3.5}$$

Let

$$\mathcal{Y}_P := \{(A^0, V^0) \in C(\bar{\Omega}, \mathbb{R}_+^2) : A^0(x) \leq \overline{A},\ \forall\, x \in \bar{\Omega}\}.$$

Theorem 3.1. *Assume that* (3.5) *holds. For any* $(A^0(\cdot), V^0(\cdot)) \in \mathcal{Y}_P$ *with* $A^0(\cdot) \not\equiv 0$*, let* $(A(\cdot, t), V(\cdot, t))$ *be the solution of* (3.1) *with* $(A(\cdot, 0), V(\cdot, 0)) = (A^0(\cdot), V^0(\cdot))$*. If* $\mathcal{R}_0^0 < 1$*, then we have*

$$\lim_{t\to\infty}(A(x, t), V(x, t)) = (A^*, 0),\ \textit{uniformly for } x \in \overline{\Omega}.$$

Proof. Assume $\mathcal{R}_0^0 < 1$, that is, $\Lambda^0 < 0$ (see (3.4)). Then there exists $\xi_0 > 0$ such that $\Lambda_{\xi_0} < 0$, where Λ_{ξ_0} is the principal eigenvalue of the following eigenvalue problem:

$$\begin{cases} \Lambda\psi(x) = D_V\Delta\psi(x) + [\pi f(0) - c - k_p(A^* - \xi_0)]\psi(x),\ x \in \Omega, \\ \frac{\partial\psi(x)}{\partial\nu} = 0,\ x \in \partial\Omega. \end{cases} \tag{3.6}$$

The first equation of (3.1) can be rewritten as follows

$$\frac{\partial A}{\partial t} = D_A\Delta A + k_p[\overline{A} - A](1 + \theta)V + \frac{r_A}{A_m}[A^* - A]A.$$

From (3.5), we see that

$$k_p[\overline{A} - A](1 + \theta)V + \frac{r_A}{A_m}[A^* - \overline{A}\,]\overline{A} < 0.$$

Then it is not hard to show that $\mathcal{Y}_P$ is a positively invariant set for system (3.1). Thus,

$$[p_A - k_pA(x, t)](1 + \theta)V(x, t) \geq 0,\ \forall\, x \in \Omega,\ t \geq 0.$$

In view of the first equation of (3.1), we see that

$$\begin{cases} \frac{\partial A}{\partial t} \geq D_A\Delta A + r_AA(1 - \frac{A}{A_m}) - d_AA,\ x \in \Omega,\ t > 0, \\ \frac{\partial A}{\partial\nu} = 0,\ x \in \partial\Omega,\ t > 0, \end{cases} \tag{3.7}$$

and hence,

$$\liminf_{t\to\infty} A(x, t) \geq A^*,\ \text{uniformly for } x \in \overline{\Omega}.$$

Therefore, we may choose $t_1 > 0$ such that

$$A(x, t) \geq A^*(x) - \xi_0,\ \text{uniformly for } x \in \overline{\Omega},\ t \geq t_1.$$

In view of the second equation of (3.1), we see that

$$\begin{cases} \frac{\partial V}{\partial t} \leq D_V\Delta V + \pi f(0)V - cV - k_p(A^*(x) - \xi_0)V,\ x \in \Omega,\ t \geq t_1, \\ \frac{\partial V}{\partial\nu} = 0,\ x \in \partial\Omega,\ t \geq t_1, \end{cases} \tag{3.8}$$

where we have used the fact that $f(V) \leq f(0),\ \forall\ V \geq 0$. Assume that $\psi_{\xi_0}(x)$ is a strongly positive eigenfunction corresponding to Λ_{ξ_0}, and there exists $\hat{C} > 0$ such that $V(x, t_1) \leq \hat{C}\psi_{\xi_0}(x),\ \forall\ x \in \overline{\Omega}$. From (3.8), the comparison principle implies that

$$V(x,t) \leq \hat{C}e^{\Lambda_{\xi_0}(t-t_1)}\psi_{\xi_0}(x),\ \forall\ t \geq t_1,\ x \in \bar{\Omega}.$$

Since $\Lambda_{\xi_0} < 0$, it follows that

$$\lim_{t\to\infty} V(x,t) = 0,\ \text{uniformly for } x \in \overline{\Omega}.$$

Then $A(x,t)$ in (3.1) is asymptotic to system (2.4). Using $A^0(\cdot) \not\equiv 0$ and the theory for asymptotically autonomous semiflows (see, e.g., [28, Corollary 4.3]), we have

$$\lim_{t\to\infty} A(x,t) = A^*,\ \text{uniformly for } x \in \overline{\Omega}.$$

The proof is complete.

□

4. Discussion

This study presents a reaction-diffusion system (1.3) modeling HBV infection, which consists of five compartments of populations, namely, target cells (T), infected cells (I), free virus (V), free antibody (A), and virus-antibody complexes (X). In system (1.3), we assume that only free virus (V), free antibody (A), and virus-antibody complexes (X) can diffuse, and the host cells (target and infected cells) do not have the ability to move. Thus, the governing equations are coupled by ODEs and PDEs. Due to the lack of diffusion terms of target cells (T) and infected cells (I) in (1.3), the steady-state solutions involved T and I can be explicitly expressed by free virus (V). Thus, investigating the existence of steady-state solutions of (1.3) is equivalent to the study of steady-state solutions of system (1.9).

The standard approach in seeking for positive steady-state solutions of system (1.9) is applying theory of bifurcation to the associated elliptic equations of (1.9). Instead, we adopt dynamical approach in the analysis of (1.9) in the current paper. We define an reproduction number, $\mathcal{R}_0$, for system (1.9), and we show that system (1.9) is uniformly persistent and it admits at least one (componentwise) positive steady state when $\mathcal{R}_0 > 1$ (see Theorem 2.1). Mathematically, it is more difficult to investigate the elimination of HBV in system (1.9). Putting $k_m = 0$ in system (1.9), the equation of X in (1.9) is decoupled from the other equations, and we directly study the system (3.1) for the extinction case of HBV. Imposing the assumption (3.5), we can show that HBV will die out for (3.1) if the associated reproduction number $\mathcal{R}_0^0$ is less than one (Theorem 3.1). Here, we also raise some challenging problems related to system (1.9), which can be future research directions:

- The impact of the diffusion coefficients D_X and D_V on the basic reproduction number $\mathcal{R}_0$;
- The dynamics of system (1.9) for the critical case when $\mathcal{R}_0 = 1$;
- The uniqueness and the global attractiveness of the positive steady state of system (1.9) if it exists;
- The asymptotic profile of positive steady state of system (1.9) when the diffusion rates D_X and D_V both tend to zero.

In order to simplify the modeling in system (1.3), we have ignored two compartments of populations, namely, free subviral particles (S) and subviral particles-antibody complexes (X_s) in [1] by assuming that subviral particles S (resp. subviral particles-antibody complexes X_s) is proportional to the concentration of free virus V (resp. virus-antibody complexes X) with a constant proportionality θ. The authors in [1] developed another more complete model about HBV infection with antibody, which includes the interactions of target cells (T), infected cells(I), free subviral particles (S), free antibody (A), virus-antibody complexes (X), subviral particles-antibody complexes (X_s), and free virus (V). After we add spatial variations into such system, we shall investigate the following more realistic and challenging case in the future:

$$\begin{cases} \frac{\partial T}{\partial t} = rT(1 - \frac{T+I}{T_m}) - \beta VT, \ x \in \Omega, \ t > 0, \\ \frac{\partial I}{\partial t} = \beta VT - \delta I, \ x \in \Omega, \ t > 0, \\ \frac{\partial A}{\partial t} = D_A \Delta A + p_A(V + S) + r_A(x)A(1 - \frac{A}{A_m}) + k_m X \\ \qquad -k_p AV + k_m^s X_S - k_p^s AS - d_A(x)A, \ x \in \Omega, \ t > 0, \\ \frac{\partial X}{\partial t} = D_X \Delta X - k_m X + k_p AV - c_{AV} X, \ x \in \Omega, \ t > 0, \\ \frac{\partial X_S}{\partial t} = D_{XS} \Delta X_S - k_m^s X_S + k_p^s AS - c_{AS} X_S, \ x \in \Omega, \ t > 0, \\ \frac{\partial V}{\partial t} = D_V \Delta V + \pi I - cV + k_m X - k_p AV, \ x \in \Omega, \ t > 0, \\ \frac{\partial S}{\partial t} = D_S \Delta S + \pi\theta I - c_s S + k_m^s X_s - k_p^s AS, \ x \in \Omega, \ t > 0, \\ \frac{\partial A}{\partial \nu} = \frac{\partial X}{\partial \nu} = \frac{\partial X_S}{\partial \nu} = \frac{\partial V}{\partial \nu} = \frac{\partial S}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0, \\ u(x, 0) = u^0(x), \ u = T, I, A, X, X_S, V, S, \ x \in \Omega. \end{cases} \tag{4.1}$$

The meanings of the parameters in system (4.1) were collected in [1, Table 1].

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Conflict of interest

The authors declare there is no conflicts of interest.

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