DYNAMICS OF A STOCHASTIC HEPATITIS C VIRUS SYSTEM WITH HOST IMMUNITY

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Abstract. In this paper, stochastic differential equations that model the dynamics of a hepatitis C virus are derived from a system of ordinary differential equations. The stochastic model incorporates the host immunity. Firstly, the existence of a unique ergodic stationary distribution is derived by using the theory of Hasminskii. Secondly, sufficient conditions are obtained for the destruction of hepatocytes and the convergence of target cells. Moreover based on realistic parameters, numerical simulations are carried out to show the analytical results. These results highlight the role of environmental noise in the spread of hepatitis C viruses. The theoretical work extend the results of the corresponding deterministic system.

1. Introduction. Hepatitis C virus (HCV) is a small, enveloped, positive-sense single-stranded RNA virus of the family Flaviviridae. It is the cause of hepatitis C and some cancers such as liver cancer and lymphomas in humans. An estimated 143 million (2%) people are affected with hepatitis C worldwide. About 167,000 deaths due to liver cancer and 326,000 deaths due to cirrhosis occurred in 2015. HCV is the leading cause of liver transplantation in developed countries, and the most common chronic bloodborne infection in the USA [30, 32].

Mathematical models produced deep understanding of disease dynamics, and played a fundamental role in the fight against the diseases [1, 9, 17, 20, 21, 28, 34]. In recent decades, many successful mathematical models investigating fundamental Hepatitis C viruses dynamics have been developed, among which we may mention...
the papers by Banerjee et al. [2], Dixit et al. [12], Neumann et al. [27] and Rong et al. [29] to cite only a few. In 2018, Blé et al. [5] investigated the dynamics of a hepatitis C virus system with the host immune. The system contains four variables, namely the target cells, the infected liver cells, the viral load and the T killer cells. At time \( t \), the population in each of these classes are denoted by \( H_s(t) \), \( H_i(t) \), \( V(t) \) and \( T(t) \), respectively. Target cells are produced at a constant rate \( \beta_s \) and die at a constant rate \( \mu_s \). The scaled transmission rate between target cells and infected liver cells is \( k \), and death rate of infected liver cells is \( \mu_i \). The destroy rate of T killer cells to infected liver cells is \( \delta \). HCV virions are produced within the infected liver cells at a rate of \( \rho \) virions per infected cell per day, and viral load die with a death rate \( \mu_v \). T killer cells are produced at a reproduction rate \( \beta_T \) and die at a constant rate \( \mu_T \), and \( T_{\text{max}} \) is the maximum of T killer cells in the body. In terms of those variables and parameters the ordinary differential equations system takes the form

\[
\begin{align*}
\dot{H}_s &= \beta_s - kH_s V - \mu_s H_s, \\
\dot{H}_i &= kH_s V - \delta H_i T - \mu_i H_i, \\
\dot{V} &= \rho H_i - \mu_v V, \\
\dot{T} &= \beta_T V(1 - \frac{T}{T_{\text{max}}}) - \mu_T T.
\end{align*}
\]

For the deterministic system (1), Blé et al. [5] stated that the global stability is determined in terms of the basic reproduction number \( R_0 = \frac{k\beta_s p}{\mu_s \mu_v} \). When \( R_0 \leq 1 \), the system (1) admits a unique infection-free equilibrium \( E_0 = (\frac{\beta_s}{\mu_s}, 0, 0, 0) \), which is globally asymptotically stable. When \( R_0 > 1 \), then infection-free equilibrium \( E_0 \) is unstable and there is a globally asymptotically stable endemic equilibrium \( E_1 \) given by

\[
E_1 = \left( \frac{\beta}{kV^* + \mu_s}, \frac{\mu_v V^*}{p}, V^*, \frac{\beta_T T_{\text{max}} V^*}{\beta_T V^* + \mu_T T_{\text{max}}} \right),
\]

where \( V^* \) is the positive solution of the equation \( AV^2 + BV + C = 0 \) and

\[
A = k\beta_T \rho (\delta T_{\text{max}} + \mu_i), \\
B = -k\beta_s \rho p + \delta \beta_T \mu_s \mu_v T_{\text{max}} + k\mu_i \mu_v \mu_T T_{\text{max}} + \beta_T \mu_i \mu_s \mu_v, \\
C = \mu_i \mu_s \mu_v \mu_T T_{\text{max}} - K\beta_s \rho \mu_T T_{\text{max}}.
\]

The system (1) and its variations have made considerable contribution to our understanding of HCV dynamics. However, the system (1) is deterministic, ignoring the possible importance of environmental noise. In fact, stochastic effects can be significant during the spread of hepatitis C viruses, because different cells and infective virus particles reacting in the same environment can often give different results. Virus invasion is often highly stochastic, and stochastic noise is also the cause leading to extinction from an endemic setting. By running a stochastic system several times, we can obtain the distribution of the predicted number of infected cells, while a deterministic system will just give a single predicted value [6, 10, 16, 15, 25]. Recently, theoretical studies on disease dynamics and population dynamics with stochastic noise have produced several useful results [4, 7, 8, 13, 19, 23, 24, 26, 31, 35, 36, 38]. The effects of stochastic noise on the dynamics of hepatitis C viruses have not been studied to the best of our knowledge. With the theory of Hasminskii and the stochastic Lyapunov functions, we are able to carefully analyze the corresponding stochastic models.
There are several types of approaches for applying stochastic noise into the system (1), both from mathematical and biological perspectives. In this paper, we assume that the stochastic noise is proportional to the variables $H_s(t), H_i(t), V(t)$ and $T(t)$. This is a standard technique in stochastic modeling (see e.g. [37]). In view of this consideration, we construct a stochastic HCV model as follows:

$$
\begin{align*}
    dH_s(t) &= (\beta_s - kH_sV - \mu_sH_s)dt + \sigma_1 H_s dB_1(t), \\
    dH_i(t) &= (kH_sV - \delta H_i T - \mu_i H_i)dt + \sigma_2 H_i dB_2(t), \\
    dV(t) &= (pH_i - \mu_V V)dt + \sigma_3 V dB_3(t), \\
    dT(t) &= (\beta_T V (1 - \frac{T}{T_{max}}) - \mu_T T)dt + \sigma_4 T dB_4(t),
\end{align*}
$$

(2)

where $B_i(t)$ are standard Brownian motions with intensities $\sigma_i^2$, $i = 1, \ldots, 4$.

This paper is aimed at extending the work of Blé [5] in understanding the dynamics of a deterministic hepatitis C virus model with host immunity, and further studying how environmental noise affect the dynamics of hepatitis C viruses. The rest of the paper is organized as follows: In Section 2, we introduce some preliminary lemmas for further studies. In Section 3, we obtain sufficient conditions for the existence of a unique ergodic stationary distribution of the stochastic system. In Section 4, we explore sufficient conditions ensuring the extinction of viruses. In Section 5, we perform some numerical simulations to show the dynamics of cells predicted by our model. The last section summarizes the findings and conclusions.

2. Preliminaries. Throughout this paper, let $(\Omega, \mathcal{F}, \mathbb{P})$ be a complete probability space with a filtration $\{\mathcal{F}_t\}_{t \geq 0}$ satisfying the usual conditions. The Brownian motions are defined on the complete probability space $(\Omega, \mathcal{F}, \mathbb{P})$. $\mathbb{R}^n$ is the $n$-dimensional Euclidean space, $\mathbb{R}_+^n = \{(x_1, x_2, \ldots, x_n) \in \mathbb{R}^n : x_i > 0, i = 1, \ldots, n\}$. $C^{2,1}(\mathbb{R}^n \times \mathbb{R}_+; \mathbb{R})$ denotes the family of all real-valued functions $V(x, t)$ defined on $\mathbb{R}^n \times \mathbb{R}_+$ such that they are continuously twice differentiable in $x$ and once in $t$.

Let $X(t)$ be a regular time-homogeneous Markov process in $\mathbb{R}^n$ given by the stochastic differential equation:

$$
    dX(t) = b(X)dt + \sum_{m=1}^k \sigma_m(X)dB_m(t),
$$

(3)

where $b$ and $\sigma_m$ are vectors in $\mathbb{R}^n$. The diffusion matrix of $X(t)$ is described by

$$
    A(x) = (a_{ij}(x)), \quad a_{ij}(x) = \sum_{m=1}^k \sigma_m^i(x)\sigma_m^j(x).
$$

In addition, for any continuously twice differentiable real value function $V(x)$, the differential operator $\mathcal{L}V$ is define by

$$
    \mathcal{L}V = \sum_{i=1}^l b_i(x) \frac{\partial V(x)}{\partial x_i} + \frac{1}{2} \sum_{i,j=1}^l a_{ij}(x) \frac{\partial^2 V(x)}{\partial x_i \partial x_j}.
$$

Definition 2.1. The solution $X(t)$ of the system (3) is said to be almost surely exponentially stable if

$$
    \limsup_{t \to \infty} \frac{1}{t} \ln |X(t; t_0, X_0)| < 0 \text{ for all } X_0 \in \mathbb{R}^n \text{ a.s.}
$$
Lemma 2.2 ([22]). The Markov process $X(t)$ has a unique ergodic stationary distribution $\mu(\cdot)$, if there exists a bounded open domain $U \subset \mathbb{R}^n$ with regular boundary $\Gamma$, having the following properties:

(B1) In the domain $U$ and some neighborhood thereof, the smallest eigenvalue of the diffusion matrix $A(x)$ is bounded away from zero.

(B2) If $x \in \mathbb{R}^n \setminus U$, the mean time $\tau$ at which a path issuing from $x$ reaches the set $U$ is finite, and $\sup_{x \in K} \mathbb{E}^x \tau < \infty$ for every compact subset $K \subset \mathbb{R}^n$, where $\mathbb{E}^x \tau$ is the expectation of $\tau$ with initial $x$.

Remark 2.1 ([22],[39]). In Lemma 2.2,

1. Condition (B2) guarantees the existence of a stationary distribution $\mu(\cdot)$. To verify Lemma 2.2 (B2), it is sufficient to show that there exists a nonnegative $C^2$-function $\mathcal{V}$ such that the differential operator $\mathcal{L} \mathcal{V}$ is negative on $\mathbb{R}^n \setminus U$.

2. Conditions (B1) and (B2) together ensure ergodicity, that is, the uniqueness of the stationary distribution $\mu(\cdot)$.

We refer to [22] for the definitions and properties of stationary distribution, ergodicity and positive recurrence.

Lemma 2.3 ([3, 11]). Let $\nu^*$ be the distribution of a random variable $\ln X(t)$ provided that $X(t)$ admits $\mu^*$ as its distribution. $Y(t)$ is another random variable. If

$$
\mathbb{E}g(\ln Y(t)) \rightarrow \bar{g} := \int_{\mathbb{R}} g(x)\nu^*(dx) = \int_0^\infty g(\ln x)\mu^*(dx) \text{ as } t \rightarrow \infty
$$

holds for any

$$
g(\cdot) : \mathbb{R} \rightarrow \mathbb{R} : |g(x) - g(y)| \leq |x - y|, |g(x)| < 1, \forall x, y \in \mathbb{R},
$$

then the distribution of random variable $Y(t)$ converges weakly to the measure $\mu^*$.

Lemma 2.4. For any given initial value $(H_s(0), H_i(0), V(0), T(0)) \in \mathbb{R}^4_+$, there is a unique solution of the system (1) on $t \geq 0$, and the solution will remain in $\mathbb{R}^4_+$ with probability one.

Lemma 2.4 ensures the existence and uniqueness of global positive solution. Define $\mathcal{V} = H_s - 1 - \ln H_s + m_2(H_i - 1 - \ln H_i) + m_3(V - 1 - \ln V) + m_4(T - 1 - \ln T)$, $m_2, m_3, m_4 > 0$, the proof is similar to [14] by using standard arguments. Hence we omit it here.

In the following, we study the dynamics of the system (2). In order to state the main results, we define two criteria $R_0^*$ and $R_1^*$ as follows:

$$
R_0^* = \frac{\beta_s kp}{(\mu_s + \frac{1}{2}\sigma_1^2)(\mu_v + \frac{1}{2}\sigma_2^2)},
$$

$$
R_1^* = \frac{2\beta_s kp}{\mu_s \mu_v \left( \min \left\{ \frac{\mu_s}{2}, \frac{\mu_v}{2}, \mu_T \right\} + \frac{1}{6} \min \left\{ \sigma_2^2, \sigma_3^2, \sigma_4^2 \right\} \right)},
$$

where $R_0^*$ is used to study the stationary distribution and ergodicity, and $R_1^*$ is used to study the extinction.
3. Stationary distribution and ergodicity. To obtain the stationary distribution and ergodicity of the system (2), we aim to apply Lemma 2.2. In order to do that, we construct a nonnegative $C^2$-function $\mathcal{V}$ satisfying that

$$\sup_{(H_s, H_i, V, T) \in \mathbb{R}_+^4 \setminus \mathcal{U}_k} \mathcal{L}\mathcal{V}(H_s, H_i, V, T) < -1,$$

where $U_k = \prod_{i=1}^{4} \left( \frac{1}{k}, k \right)$ is a bounded closed set and $k$ is a sufficiently large integer. We also have to prove that the smallest eigenvalue of the diffusion matrix $A(H_s, H_i, V, T)$ is bounded away from zero in the domain $U_k$ and some neighborhood thereof, i.e., there is a positive number $N > 0$ such that

$$\sum_{i,j=1}^{4} a_{i,j}(H_s, H_i, V, T) \xi_i \xi_j \geq N|\xi|^2, (H_s, H_i, V, T) \in U_k, \xi = (\xi_1, \xi_2, \xi_3, \xi_4) \in \mathbb{R}^4.$$

**Theorem 3.1.** For any given initial value $(H_s(0), H_i(0), V(0), T(0)) \in \mathbb{R}_+^4$, the system (2) admits a unique ergodic stationary distribution if $R_0^* > 1$.

**Proof.** Consider the Lyapunov function

$$\mathcal{Q}_1 = -\ln H_s - m_1 \ln H_i - m_2 \ln V + m_3 T.$$

By directly calculating the differential operator $\mathcal{L}\mathcal{Q}_1$ associated with (2), we obtain

$$\mathcal{L}\mathcal{Q}_1 = -\frac{1}{H_s} (\beta_s - kH_s V - \mu_s H_s) - \frac{m_1}{H_i} (kH_s V - \delta H_s T - \mu_i H_i)$$

$$- m_2 \frac{pH_i - \mu_v V}{V} + m_3 \beta_T V (1 - T/T_{max}) - \mu_T T$$

$$+ \frac{1}{2} \sigma_1^2 + \frac{m_1}{2} \sigma_2^2 + \frac{m_2}{2} \sigma_3^2$$

$$\leq - \frac{\beta_s}{H_s} - m_1 \frac{H_s V}{H_i} - m_2 \frac{pH_i}{V} + (k + m_3 \beta_T) V + (m_1 \delta - m_3 \mu_T) T$$

$$+ 3(\mu_s + \frac{1}{2} \sigma_1^2)$$

$$\leq - 3 \sqrt{m_1 m_2 \beta_s k p} + (k + m_3 \beta_T) V + 3(\mu_s + \frac{1}{2} \sigma_1^2)$$

$$= - 3(\mu_s + \frac{1}{2} \sigma_1^2)(\sqrt{m_1 m_2 \beta_s k p} - 1) + (k + m_3 \beta_T) V$$

$$= - 3(\mu_s + \frac{1}{2} \sigma_1^2)(\sqrt{R_0^*} - 1) + (k + m_3 \beta_T) V$$

$$= - C_1 + (k + m_3 \beta_T) V,$$

where

$$m_1 = \frac{\mu_s + \frac{1}{2} \sigma_1^2}{\mu_i + \frac{1}{2} \sigma_2^2}, m_2 = \frac{\mu_s + \frac{1}{2} \sigma_2^2}{\mu_v + \frac{1}{2} \sigma_3^2}, m_3 = \frac{m_1 \delta}{\mu_T},$$

and

$$C_1 = 3(\mu_s + \frac{1}{2} \sigma_1^2)(\sqrt{R_0^*} - 1) > 0.$$
An application of Itô’s formula to \( Q_2 = (H_s + H_i + m_4V + m_5T)^2 \) yields

\[
\mathcal{L}Q_2 = (H_s + H_i + m_4V + m_5T)(\beta_s - \mu_s H_s - \delta H_s T - \mu_i H_i + m_4pH_i \\
- m_4\mu_v V + m_5\beta_T V - \frac{m_5\beta_T V T}{T_{\max}} - m_5\mu_T T) \\
\leq (H_s + H_i + m_4V + m_5T)[\beta_s - \mu_s H_s - (\mu_i - m_4p)H_i \\
- (m_4\mu_v - m_5\beta_T)V - m_5\mu_T T] \\
\leq \beta_s(H_s + H_i + m_4V + m_5T) - \phi(H_s + H_i + m_4V + m_5T)^2 \\
\leq C_2 - \frac{1}{2}\phi(H_s^2 + H_i^2 + m_4^2V^2 + m_5^2T^2),
\]

where

\[
m_4 = \frac{\mu_i}{2p}, \quad m_5 = \frac{\mu_i\mu_v}{4p\beta_T}, \quad \phi = \min\{\mu_s, \frac{1}{2}\mu_i, \frac{3}{4}\mu_v, \mu_T\}
\]

and

\[
C_2 = \max_{(H_s, H_i, V, T) \in \mathbb{R}_+^4} \{\beta_s(H_s + H_i + m_4V + m_5T) - \frac{1}{2}\phi(H_s + H_i + m_4V + m_5T)^2\} < \infty.
\]

Similarly, let \( Q_3 = -\ln H_s - \ln H_i - \ln T \) we have

\[
\mathcal{L}Q_3 = -\frac{\beta_s}{H_s} - \frac{kH_s V}{H_i} - \frac{\beta_T V}{T} + (\frac{\beta_T}{T_{\max}} + k)V + \delta T + \mu_s + \mu_i + \mu_v + \frac{3}{2}\sum_{i=1}^3 \sigma_i^2 \\
:= -\frac{\beta_s}{H_s} - \frac{kH_s V}{H_i} - \frac{\beta_T V}{T} + (\frac{\beta_T}{T_{\max}} + k)V + \delta T + C_3.
\]

Define \( Q = M Q_1 + Q_2 + Q_3 \), where \( M > 0 \) is sufficiently large. It follows that

\[
\liminf_{k \to \infty, (H_s, H_i, V, T) \in \mathbb{R}_+^4 \setminus U_k} Q(H_s, H_i, V, T) = +\infty.
\]

According to the continuity of \( Q \), it must have a minimum point \((\tilde{H}_s, \tilde{H}_i, \tilde{V}, \tilde{T})\) \( \in \mathbb{R}_+^4 \). Therefore, the \( C^2 \) function \( V : \mathbb{R}_+^4 \to \mathbb{R}_+ \)

\[
V(H_s, H_i, V, T) = Q(H_s, H_i, V, T) - Q(\tilde{H}_s, \tilde{H}_i, \tilde{V}, \tilde{T})
\]

is a positive definite function.

Applying Itô formula to \( V \), we have

\[
\mathcal{L}V \leq -MC_1 - \frac{\beta_s}{H_s} - \frac{kH_s V}{H_i} - \frac{\beta_T V}{T} + M(k + m_4\beta_T)V + (\frac{\beta_T}{T_{\max}} + k)V \\
+ \delta T - \frac{1}{2}\phi(H_s^2 + H_i^2 + m_4^2V^2 + m_5^2T^2) + C_2 + C_3.
\]

Define a bounded closed set as

\[
D_\varepsilon = \{\varepsilon \leq H_s \leq 1/\varepsilon, \varepsilon^3 \leq H_i \leq 1/\varepsilon^3, \varepsilon \leq V \leq 1/\varepsilon, \varepsilon^2 \leq T \leq 1/\varepsilon^2\},
\]

where \( 0 < \varepsilon < 1 \) is a sufficiently small constant. For convenience, we divide the complementary set of \( D_\varepsilon \) into eight domains as

\[
\mathbb{R}_+^4 \setminus D_\varepsilon = \bigcup_{i=1}^8 D_{i, \varepsilon}, (H_s, H_i, V, T) \in \mathbb{R}_+^4,
\]
where
\[ D^1_\varepsilon = \{ 0 < H_s < \varepsilon \}, \quad D^2_\varepsilon = \{ 0 < V < \varepsilon \}, \]
\[ D^3_\varepsilon = \{ \varepsilon < H_s, \varepsilon < V, \varepsilon < H_i < \varepsilon^3 \}, \quad D^4_\varepsilon = \{ \varepsilon < V, 0 < T < \varepsilon^2 \}, \]
\[ D^5_\varepsilon = \{ H_i > 1/\varepsilon \}, \quad D^6_\varepsilon = \{ H_i > 1/\varepsilon^3 \}, \]
\[ D^7_\varepsilon = \{ V > 1/\varepsilon \}, \quad D^8_\varepsilon = \{ T > 1/\varepsilon^2 \}. \]

Now we analyze the range of differential operators \( \mathcal{L} \mathcal{V}(H_s, H_i, V, T) \) on each domain.

**Case 1.** If \((H_s, H_i, V, T) \in D^1_\varepsilon\), we derive from (4) that
\[
\mathcal{L} \mathcal{V} \leq - \frac{\beta_s}{H_s} + M(k + m_4 \beta_T) V + \left( \frac{\beta_T}{T_{\max}} + k \right) V - \frac{1}{2} \phi m_4^2 V^2 + \delta T - \frac{1}{2} \phi m_3^2 T^2 + C_2 + C_3 \]
\[
\leq - \frac{\beta_s}{\varepsilon} + J_1 + C_2 + C_3,
\]
where
\[
J_1 = \sup_{(V,T)\in\mathbb{R}^2_+} \{ M(k + m_4 \beta_T) V + \left( \frac{\beta_T}{T_{\max}} + k \right) V - \frac{1}{2} \phi m_4^2 V^2 + \delta T - \frac{1}{2} \phi m_3^2 T^2 \}.
\]

**Case 2.** If \((H_s, H_i, V, T) \in D^2_\varepsilon\), in view of (4), we have
\[
\mathcal{L} \mathcal{V} \leq - M C_1 + M(k + m_4 \beta_T) \varepsilon + \left( \frac{\beta_T}{T_{\max}} + k \right) \varepsilon + C_2 + C_3 - \frac{1}{2} \phi m_3^2 T^2 + \delta T - \frac{1}{2} \phi m_3^2 T^2 + C_2 + C_3 + J_2,
\]
where \( J_2 = \sup_{T\in\mathbb{R}^+} \{ \delta T - \frac{1}{2} \phi m_3^2 T^2 \} \).

**Case 3.** If \((H_s, H_i, V, T) \in D^3_\varepsilon\), we see from (4) that
\[
\mathcal{L} \mathcal{V} \leq - \frac{k H_s V}{H_i} + M(k + m_4 \beta_T) V + \left( \frac{\beta_T}{T_{\max}} + k \right) V - \frac{1}{2} \phi m_4^2 V^2 + \delta T - \frac{1}{2} \phi m_5^2 T^2 + C_2 + C_3 \]
\[
\leq - \frac{k}{\varepsilon} + J_1 + C_2 + C_3.
\]

**Case 4.** If \((H_s, H_i, V, T) \in D^4_\varepsilon\), making use of (4) one obtains that
\[
\mathcal{L} \mathcal{V} \leq - \frac{\beta_T}{T} V + M(k + m_4 \beta_T) V + \left( \frac{\beta_T}{T_{\max}} + k \right) V - \frac{1}{2} \phi m_4^2 V^2 + \delta \varepsilon + C_2 + C_3 \]
\[
\leq - \frac{\beta_T}{\varepsilon} + \delta \varepsilon + J_3 + C_2 + C_3,
\]
where
\[
J_3 = \sup_{V\in\mathbb{R}^+} \{ M(k + m_4 \beta_T) V + \left( \frac{\beta_T}{T_{\max}} + k \right) V - \frac{1}{2} \phi m_4^2 V^2 \}.
\]

**Case 5.** If \((H_s, H_i, V, T) \in D^5_\varepsilon\), by (4) we obtain
\[
\mathcal{L} \mathcal{V} \leq - \frac{1}{2} \phi H_s^2 + J_1 + C_2 + C_3 \leq - \frac{\phi}{\varepsilon^2} + J_1 + C_2 + C_3.
\]
Case 6. If \((H_s, H_i, V, T) \in D^6\), it follows from (4) that
\[
\mathcal{L}V \leq -\frac{1}{2} \phi H_i^2 + J_1 + C_2 + C_3 \leq -\frac{\phi}{\varepsilon^2} + J_1 + C_2 + C_3. \tag{10}
\]

Case 7. If \((H_s, H_i, V, T) \in D^7\), by virtue of (4), we have
\[
\mathcal{L}V \leq -\frac{1}{4} \phi m_4^2 V^2 + M (k + m_4 \beta T) V + \left( \frac{\beta T}{T_{max}} + k \right) V - \frac{1}{4} \phi m_4^2 V^2 + \delta T 
- \frac{1}{2} \phi m_5^2 T^2 + C_2 + C_3 
\leq -\frac{\phi m_5^2}{4 \varepsilon^2} + J_4 + C_2 + C_3, \tag{11}
\]
where
\[
J_4 = \sup_{(V,T) \in \mathbb{R}_+^4} \{ M (k + m_4 \beta T) V + \left( \frac{\beta T}{T_{max}} + k \right) V - \frac{1}{4} \phi m_4^2 V^2 + \delta T - \frac{1}{2} \phi m_5^2 T^2 \}.
\]

Case 8. If \((H_s, H_i, V, T) \in D^7\), making use of (4) one obtains that
\[
\mathcal{L}V \leq -\frac{1}{4} \phi m_3^2 T^2 + M (k + m_4 \beta T) V + \left( \frac{\beta T}{T_{max}} + k \right) V - \frac{1}{4} \phi m_4^2 V^2 + \delta T 
- \frac{1}{4} \phi m_3^2 T^2 + C_2 + C_3 
\leq -\frac{\phi m_5^2}{4 \varepsilon^2} + J_5 + C_2 + C_3, \tag{12}
\]
where
\[
J_5 = \sup_{(V,T) \in \mathbb{R}_+^4} \{ M (k + m_4 \beta T) V + \left( \frac{\beta T}{T_{max}} + k \right) V - \frac{1}{4} \phi m_4^2 V^2 + \delta T - \frac{1}{4} \phi m_5^2 T^2 \}.
\]

In the set \(\mathbb{R}_+^4 \setminus D_\varepsilon\), we can choose \(\varepsilon\) sufficiently small such that the following conditions hold
\[
-\frac{\beta_s}{\varepsilon} + J_1 + C_2 + C_3 < -1, \\
-M C_1 + M (k + m_4 \beta T) \varepsilon + \left( \frac{\beta T}{T_{max}} + k \right) \varepsilon + J_2 + C_2 + C_3 < -1, \\
-k \varepsilon / \varepsilon + J_1 + C_2 + C_3 < -1, \\
-\frac{\beta T}{\varepsilon} + \delta \varepsilon + J_3 + C_2 + C_3 < -1, \\
-\frac{\phi}{\varepsilon^2} + J_1 + C_2 + C_3 < -1, \\
-\frac{\phi}{\varepsilon^2} + J_1 + C_2 + C_3 < -1, \\
-\frac{\phi m_4^2}{4 \varepsilon^2} + J_4 + C_2 + C_3 < -1, \\
-\frac{\phi m_4^2}{4 \varepsilon^2} + J_5 + C_2 + C_3 < -1. \tag{13}
\]
It follows from (5)-(13) that
\[
\sup_{(H_s, H_i, V, T) \in \mathbb{R}_+^4 \setminus D_\varepsilon} \mathcal{L}V(H_s, H_i, V, T) < -1.
\]
Next, we show that the smallest eigenvalue of the diffusion matrix \( A(H_s, H_i, V, T) \) is bounded away from zero in the domain \( U_k \) and some neighborhood thereof. From the definition of diffusion matrix we have

\[
A(H_s, H_i, V, T) = \begin{pmatrix}
\sigma_1^2 H_s^2 & 0 & 0 & 0 \\
0 & \sigma_2^2 H_i^2 & 0 & 0 \\
0 & 0 & \sigma_3^2 V^2 & 0 \\
0 & 0 & 0 & \sigma_4^2 T^2
\end{pmatrix}.
\] (14)

Choose \( N = \min_{(H_s, H_i, V, T) \in U_k} \{ \sigma_1^2 H_s^2, \sigma_2^2 H_i^2, \sigma_3^2 V^2, \sigma_4^2 T^2 \} > 0 \), we have

\[
\sum_{i,j=1}^4 a_{i,j}(H_s, H_i, V, T) \xi_i \xi_j = \sigma_1^2 H_s^2 \xi_1^2 + \sigma_2^2 H_i^2 \xi_2^2 + \sigma_3^2 V^2 \xi_3^2 + \sigma_4^2 T^2 \xi_4^2
\]

\[
\geq N |\xi|^2, (H_s, H_i, V, T) \in U_k, \xi = (\xi_1, \xi_2, \xi_3, \xi_4) \in \mathbb{R}^4.
\]

It follows from Lemma 2.2 that the system (2) admits a unique ergodic stationary distribution.

Remark 3.1. The system (2) is positive recurrent by the definition of positive recurrence and Lemma 4.1 in [22]. This indicates that the target cells, the infected liver cells, the viral load and the T killer cells are persistent in vivo.

Remark 3.2. It is noteworthy that the critical condition \( R_0^* \) for the system (2) becomes the same as the critical condition \( R_0 \) for the system (1) if \( \sigma_i = 0, i = 1, \cdots, 4 \), which indicates that we generalize the results of the deterministic system (1).

4. Extinction of viruses.

Theorem 4.1. Let \((H_s(t), H_i(t), V(t), T(t)) \in \mathbb{R}_+^4 \) be the solution of the system (2) with initial value \((H_s(0), H_i(0), V(0), T(0)) \in \mathbb{R}_+^4 \). If \( R_1^* < 1 \), then we have

\[
\limsup_{t \to \infty} \frac{\ln H_i(t)}{t} < 0, \quad \limsup_{t \to \infty} \frac{\ln V(t)}{t} < 0, \quad \limsup_{t \to \infty} \frac{\ln T(t)}{t} < 0 \text{ a.s.}
\]

In addition, the distribution of \( H_s(t) \) converges weakly to the unique invariant probability measure \( \mu^* \) with density

\[
\pi(x) = \frac{2\beta_a}{\sigma_1^2} x^{2\mu_a + \sigma_1^2} \Gamma^{-1}\left(\frac{2\mu_a + \sigma_1^2}{\sigma_1^2}\right) e^{-\frac{2x}{\sigma_1^2}} e^{-\frac{2x}{\sigma_1^2}}, \quad x > 0,
\]

where \( \Gamma(\cdot) \) is the Gamma function.

Proof. Consider the following equation

\[
d\hat{H}_s(t) = (\beta_a - \mu_s \hat{H}_s)dt + \sigma_1 \hat{H}_s dB_1(t), \quad \hat{H}_s(0) = H_s(0).
\] (15)

Making use of the comparison theorem for stochastic differential equation, we have

\[
\mathbb{P}(H_s(t) \leq \hat{H}_s(t), \ t \geq 0) = 1.
\] (16)

By solving the Fokker-Planck equation we obtain that the system (15) has a unique stationary distribution with density \( \pi(x) \). It then follows from the ergodic property [33] that

\[
\lim_{t \to \infty} \frac{1}{t} \int_0^t \hat{H}_s(\theta)d\theta = \int_0^\infty x\pi(x)dx = \frac{\beta_a}{\mu_s} \text{ a.s.}
\] (17)
An application of Itô’s formula to $Q = \ln(H_t + \frac{\mu}{2p}V + \frac{\mu \mu_v}{4\beta_r}T) = \ln G$ yields that
\[
dQ(t) = \mathcal{L}Q dt + \frac{1}{2} (\sigma_2 H_t dB_2(t) + \frac{\mu_1 \sigma_3}{2p} V dB_3(t) + \frac{\mu_1 \mu_v \sigma_4}{4\beta_r} T dB_4(t)),
\]
where
\[
\mathcal{L}Q \leq \frac{1}{2} (k H_t V - \delta H_t T - \frac{\mu_2}{2} H_t - \frac{\mu_v}{2} V - \mu T \frac{\mu \mu_v}{4\beta_r} T) - \frac{1}{2G} (\sigma_2^2 H_t^2 + \frac{\mu_2^2 \sigma_3^2}{4p^2} V^2 + \frac{\mu_2^2 \mu_v^2 \sigma_4^2}{16\beta_r^2 p^2} T^2)
\]
\[
\leq \frac{2pk}{\mu_i} H_s - \min\{\frac{\mu_i}{2}, \frac{\mu_v}{2}, \mu_T\} - \frac{1}{6} \min\{\sigma_2^2, \sigma_3^2, \sigma_4^2\}.
\]
Integrating (18) from 0 to $t$ and then dividing by $t$ on both sides, we have
\[
\frac{Q(t) - Q(0)}{t} \leq \frac{2pk}{\mu_i} t \int_0^t H_s(\theta) d\theta - \min\{\frac{\mu_i}{2}, \frac{\mu_v}{2}, \mu_T\} - \frac{1}{6} \min\{\sigma_2^2, \sigma_3^2, \sigma_4^2\} + \frac{M_1(t)}{t} + \frac{M_2(t)}{t} + \frac{M_3(t)}{t},
\]
where
\[
M_1(t) = \int_0^t \frac{\sigma_2 H_s(\theta)}{G(\theta)} dB_2(\theta), \quad M_2(t) = \int_0^t \frac{\mu_1 \sigma_3 V(\theta)}{2p G(\theta)} dB_3(\theta)
\]
and
\[
M_3(t) = \int_0^t \frac{\mu_1 \mu_v \sigma_4 T(\theta)}{4\beta_r p G(\theta)} dB_4(\theta)
\]
are continuous local martingales vanishing at $t = 0$ and
\[
\limsup_{t \to \infty} \frac{\langle M_i, M_i \rangle_t}{t} < \infty, \quad i = 1, 2, 3.
\]
It follows from the strong law of large numbers that
\[
\lim_{t \to \infty} \frac{M_i}{t} = 0, \quad i = 1, 2, 3 \text{ a.s.} \quad (20)
\]
Taking upper limit on both sides of (19), it then follows from (16), (17) and (20) that
\[
\limsup_{t \to \infty} \frac{Q(t)}{t} \leq \frac{2pk \beta_s}{\mu_1 \mu_\psi} - \min\{\frac{\mu_i}{2}, \frac{\mu_v}{2}, \mu_T\} - \frac{1}{6} \min\{\sigma_2^2, \sigma_3^2, \sigma_4^2\} \\
= \psi(\frac{2pk \beta_s}{\mu_1 \mu_\psi} - 1) = \psi(R_1^* - 1) < 0 \text{ a.s.,} \quad (21)
\]
where $\psi = \min\{\frac{\mu_i}{2}, \frac{\mu_v}{2}, \mu_T\} + \frac{1}{6} \min\{\sigma_2^2, \sigma_3^2, \sigma_4^2\}$.

That is
\[
\limsup_{t \to \infty} \frac{\ln(H_t(t) + \frac{\mu_v}{2p} V(t) + \frac{\mu_1 \mu_v \sigma_4}{4\beta_r} T(t))}{t} < 0 \text{ a.s.}
\]
By Lemma 2.4, $H_t(t), V(t)$ and $T(t)$ remain non-negative on $t \geq 0$. It follows that
\[
\limsup_{t \to \infty} \frac{\ln H_t(t)}{t} < 0, \quad \limsup_{t \to \infty} \frac{\ln V(t)}{t} < 0, \quad \limsup_{t \to \infty} \frac{\ln T(t)}{t} < 0 \text{ a.s.} \quad (22)
\]
Set $\Omega_\epsilon = \{\ln V(t) \leq \frac{\psi(R_1^* - 1)}{2} t\}$, by (22) we obtain that for any $\epsilon > 0$, there is a $t_0$ such that $\mathbb{P}(\Omega_\epsilon) > 1 - \epsilon$ for all $t \geq t_0$.

Applying Itô’s formula to $\ln H_s(t)$, we have
\[
d\ln H_s(t) = (\frac{\beta_s}{H_s} - \mu_s - \frac{\sigma_2^2}{2}) dt + \sigma_1 dB_1(t).
\]
Similarly, we obtain
\[ d \ln H_s(t) = \left( \frac{\beta_s}{H_s} - kV - \mu_s - \frac{\sigma_1^2}{2} \right) dt + \sigma_1 dB_1(t). \]

Straightforward calculation yields that
\[ 0 \leq \ln \hat{H}_s(t) - \ln H_s(t) = \beta_s \int_{t_0}^t \frac{1}{H_s(\theta)} - \frac{1}{H_s(\theta)} d\theta + k \int_{t_0}^t V(\theta) d\theta \leq k \int_{t_0}^t V(\theta) d\theta \]
\[ \leq \frac{2k}{\psi(1 - R_1^*)} e^{-\frac{\psi(1 - R_1^*) t_0}{2}}. \]

Choose \( t_0 \) sufficiently large such that \( \frac{2k}{\psi(1 - R_1^*)} e^{-\frac{\psi(1 - R_1^*) t_0}{2}} < \epsilon \) then we have
\[ P\{ |\ln \hat{H}_s(t) - \ln H_s(t)| > \epsilon \} < 1 - P(\Omega_e) < \epsilon \] for all \( t \geq t_0 \). (24)

In order to show that the distribution of \( H_s(t) \) converges weakly to \( \mu^* \), by Lemma 2.3 we just need to verify
\[ \mathbb{E}g(\ln H_s(t)) \to \bar{g} := \int_{\mathbb{R}} g(x) \nu^*(dx) = \int_{0}^{\infty} g(\ln x) \mu^*(dx) \] as \( t \to \infty \).

Since the distribution of \( \hat{H}_s(t) \) converges to \( \mu^* \) as \( t \to \infty \), it follows that
\[ \lim_{t \to \infty} \mathbb{E}g(\ln \hat{H}_s(t)) = \bar{g}. \] (25)

An entirely straightforward calculation yields
\[ |\mathbb{E}g(\ln H_s(t)) - \bar{g}| \leq |\mathbb{E}g(\ln H_s(t)) - \mathbb{E}g(\ln \hat{H}_s(t))| + |\mathbb{E}g(\ln \hat{H}_s(t)) - \bar{g}| \leq \epsilon \mathbb{P}\{ |\ln H_s(t) - \ln \hat{H}_s(t)| \leq \epsilon \} + 2 \mathbb{P}\{ |\ln H_s(t) - \ln \hat{H}_s(t)| > \epsilon \} + |\mathbb{E}g(\ln \hat{H}_s(t)) - \bar{g}|. \] (26)

In view of (24)-(26), we have
\[ \limsup_{t \to \infty} \mathbb{E}g(\ln H_s(t)) - \bar{g} \leq 3\epsilon. \]

We obtain the desired conclusion and the proof is complete. \( \square \)

5. Numerical examples. In this section, we use the Euler-Maruyama method [18] to illustrate the results found in the previous sections. The simulation was carried out using \( \odot \)Matlab2014b. The initial setting for variables and parameters was shown in Table 1. The system (2) can be rewritten as
\[ X_{k+1} = X_k + f(X_k)\Delta t + g(X_k)\xi_k \sqrt{\Delta t} + \frac{1}{2} \Delta t (\xi_k^2 - 1)(g(X_k + \sqrt{\Delta t}g(X_k)) - g(X_k)), \]
where \( \Delta t = 0.001 \), \( \xi_k, k = 1, 2, \cdots \) obey the Gaussian distribution \( N(0, 1) \), \( X_k = (H_{s,k}, H_{i,k}, V_k, T_k)' \), \( x = (x_1, x_2, x_3, x_4)' \in \mathbb{R}_+^4 \) and vector-valued functions \( f, g : \mathbb{R}_+^4 \to \mathbb{R}_+^4 \) are given by
\[ f(x) = \begin{bmatrix} \beta_s - kx_1 x_3 - \mu_s x_1 \\ kx_1 x_3 - \delta x_2 x_4 - \mu_i x_2 \\ px_2 - \mu_u x_3 \\ \beta_T x_3 (1 - x_4/T_{max}) - \mu_T x_4 \end{bmatrix}, \quad g(x) = \begin{bmatrix} \sigma_1 x_1 \\ \sigma_2 x_2 \\ \sigma_3 x_3 \\ \sigma_4 x_4 \end{bmatrix}. \]
Table 1. Variables and parameters for HCV spread

| Initial values |
|----------------|
| 1000 mm$^{-3}$ |
| 0 | 10$^{-2}$ mm$^{-3}$ |
| 0 |
| 20 day$^{-1}$ mm$^{-3}$ |
| $3.5 \times 10^{-5}$ mm$^3$ day$^{-1}$ |
| 0.03 day$^{-1}$ |
| 2.5 $\times 10^{-5}$ mm$^3$ day$^{-1}$ |
| 0.02 day$^{-1}$ |
| 0.003 day$^{-1}$ |
| 3.0 $\times 10^{-5}$ mm$^3$ day$^{-1}$ |
| 2000 mm$^{-3}$ |
| 0.01 day$^{-1}$ |

5.1. Stationary distribution and ergodicity. In order to analyze the stationary distribution and ergodicity of the system (2), we simulate the trajectories and density distribution of the solution with 10000 times, in which the parameters $\sigma_i = 0.003$, $i = 1, ..., 4$. As a comparison, we also present the simulations of the deterministic system (1).

By direct calculation, we obtain that $R_0 = 3.4971$ and $R_0 = 3.4971$. It follows from Theorem 3.1 that the system (2) admits a unique ergodic stationary distribution. In addition, the viruses are persistent in vivo. The numerical results of the trajectories and density distribution of the system (2) are shown in Figure 1 and Figure 2, respectively. It is shown that the trajectories of the stochastic system (2) oscillates around the positive equilibrium of the deterministic system (1), and the distribution of the system (2) appears close to a normal distribution.

In order to study the influence of noise on the system (2), we increase the noise intensity to case (a): $\sigma_i = 0.03$, $i = 1, ..., 4$ and case (b): $\sigma_i = 0.05$, $i = 1, ..., 4$, respectively. By straightforward calculations we obtain that (a): $R_0^s = 3.2272$ and (b): $R_0^s = 2.811$, respectively. By Theorem 3.1, the system (2) admits a unique ergodic stationary distribution. The numerical results of the trajectories for case (a) and case (b) are shown in Figure 3 and Figure 5, respectively. The numerical results of the density distributions for case (a) and case (b) are shown in Figure 4 and Figure 6, respectively. It is shown that the solution of the system (2) oscillates around the positive equilibrium of the deterministic system (1), and the intensity of the oscillation is positively correlated with the intensity of noise. In addition, with the increase of noise intensity, the distribution of the system (2) becomes far from the normal distribution.

5.2. Extinction of viruses. In order to study the effect of large noise on the system (2), we increase the noise intensity to $\sigma_i = 0.65$, $i = 1, ..., 4$ and keep other parameters unchanged. By direct calculation, we obtain that $R_1^s = 0.9282$. By
Figure 1. Trajectories of the system (2) and its deterministic system (1)

Figure 2. Density distribution of the system (2)
Figure 3. Trajectories of the system (2) and its deterministic system (1)

Figure 4. Density distribution of the system (2)
Figure 5. Trajectories of the system (2) and its deterministic system (1)

Figure 6. Density distribution of the system (2)
6. **Concluding remarks.** In this paper, we study the effect of environmental noise on the dynamics of a hepatitis C virus model with host immune. The results extend the paper of Blé [5] in understanding the dynamics of a deterministic hepatitis C virus. Various types of Lyapunov functions are designed to study the stationary distribution and ergodicity as well as the extinction of the stochastic system. More precisely,

- When $R_0^s > 1$, the system (2) admits a unique ergodic stationary distribution, which indicates that the hepatitis C viruses persistent in the body. In this case, the solution of the system (2) oscillates around the positive equilibrium of the deterministic system (1), and the oscillation intensity is positively correlated with the intensity of environmental noise. It is noteworthy that $R_0^s \leq R_0$ and the equal sign holds if and only if $\sigma_i = 0, i = 1, ..., 3$, which indicates that we generalize the results of the deterministic system (1).
- When $R_1^s < 1$, the infected liver cells die out and the distribution of the target cells converges weakly to a unique invariant probability measure.
- In the numerical simulations, we change the noise intensity and keep the other parameters unchanged. The results show that when the noise intensity is small, the system admits a unique ergodic stationary distribution, while when the noise intensity is large, the system becomes extinct. Biologically, this means that small environmental disturbances do not lead to the extinction of viruses, while large environmental disturbances do.
The results we obtain may facilitate further investigation of such virus systems.

- There is currently no vaccine to prevent hepatitis C infection. It is meaningful to consider the therapeutic effect of drugs on hepatitis C viruses.
- Hepatitis C viruses can be transmitted through mother to child. Therefore, in order to describe the dynamics of the hepatitis C viruses more accurately, the role of mother-to-child transmission can be considered.
- In reality, target cells, infected liver cells, viral load, and T killer cells may subject to the same kind of noise. Therefore, it is meaningful to study the following system with degenerate diffusion:

\[
\begin{align*}
    dH_s(t) &= (\beta_s - k H_s V - \mu_s H_s)dt + \sigma_1 H_s dB(t), \\
    dH_i(t) &= (k H_s V - \delta H_i T - \mu_i H_i)dt + \sigma_2 H_i dB(t), \\
    dV(t) &= (p H_i - \mu_v V)dt + \sigma_3 V dB(t), \\
    dT(t) &= (\beta T V (1 - T/T_{max}) - \mu_T T)dt + \sigma_4 T dB(t).
\end{align*}
\] (27)

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