Bol. Soc. Paran. Mat.
©SPM – E-ISSN-2175-1188
SPM: www.spm.uem.br/bspm

(3s.) **v. 2026 (44) 8** : 1–11.
ISSN-0037-8712
doi:10.5269/bspm.83941

Stochastic Simulation of Hepatitis B Virus Infection: Modeling the Impact of Environmental Noise on Viral Persistence and Clearance

G. Sathyamurthy and N. Vijayasankar

ABSTRACT: Hepatitis B virus (HBV) infection has remained an important health concern in the world with its dynamics being complex with deterministic biological processes as well as stochastic environmental changes. This study formulates and examines a holistic stochastic differential equation (SDE)-based model to establish how environmental noise influences the dynamics of viral persistence and clearance. Building on the classical deterministic HBV model whereby the multiplicative noise terms are added to account for the random variation of viral replication, human immunity and cell dynamics. Deriving the conditions under which the disease will be eliminated or remain, using intensive mathematical analysis and widespread numerical simulations, in terms of a stochastic basic reproduction number R_0^s. Obtaining explicit formulas of the stationary distributions, investigate the average time to extinction, and measure the dependence of the noise parameters and clinical outcomes. This model is tested on longitudinal HBV DNA data of chronic carriers of hepatitis B who demonstrate great consistency between the simulated trajectories and clinical observations of HBV DNA. The stochastic effects cannot be overlooked in HBV modeling and give theoretical justification to the use of treatment strategies that utilize the variability of the environment to improve viral clearance. Keywords: Hepatitis B virus, stochastic differential equations, environmental noise, viral persistence, extinction probability, Itô calculus, basic reproduction number

Keywords: Hepatitis B virus, stochastic differential equations, environmental noise, viral persistence, extinction probability, Itô calculus, basic reproduction number.

Contents

2020 *Mathematics Subject Classification:* 92D30, 60H10.
Submitted May 02, 2026. Published June 05, 2026.

1. Introduction

Hepatitis B virus (HBV) infection is one of the greatest global public health issues, with around 296 million individuals having chronic HBV virus infection and an estimated 820, 000 cases of the deaths caused by HBV-related liver disease, cirrhosis, and hepatocellular carcinoma annually (World Health Organization, 2021). Although efficacious vaccine and antiviral treatments exist, the intricate nature of the HBV infection, especially the mechanisms involved in the persistence and clearance of the virus, are yet to be fully comprehended. Mathematical modeling has become a potent tool of HBV Dynamics and prediction of treatment outcome. Many deterministic models of the interactions of viral particle, immune responses, infected cells, and target hepatocytes have since been modeled following the original work of Nowak et al. (1996) on viral dynamics. These models are often described as systems of ordinary differential equations (ODEs), and have been very useful in understanding how the virus replicates, the role of immunity, and the effectiveness of antiviral treatment (Ciupe et al., 2007; Murray et al., 2005; Ribeiro et al., 2002). Inherently, biological systems experience random variability due to many causes, such as environmental variability, stochasticity in small demographic populations, and random molecular events at the cellular level (Allen, 2010). In the case of HBV infection, these stochastic effects arise due to time-varying efficacy of immune system, random changes in entry rates of virus, stochastic expression of the virus in the hepatocytes that were infected, and non-deterministic effects of the environment on hepatocyte homeostasis (Guedj et al., 2013; Rong and Perelson, 2009). The effect of these random perturbations can have a profound impact on the dynamics of a disease especially around the critical point, where minor changes can lead the system to persistent or extinction. . Stochastic models have been used to HIV (Ding and Jiang, 2017; Tuckwell and Le Corfec, 1998), influenza (Yan and Zhou, 2019), and hepatitis C virus (HCV) infection (Zhou and Zhang, 2016). In the case of HBV, stochastic modeling has been suggested (Hattaf et al., 2016; Khan et al., 2018; Miao et al., 2017), but a detailed study of the impact of various forms and levels of environmental noise on the critical threshold of viral persistence and clearance has not been performed.

2. Mathematical Model Formulation

2.1. Deterministic Model

Our model starts by a deterministic compartmental model of the within-host dynamics of HBV infection. The four state variables comprise the uninfected target hepatocytes (T), the infected hepatocytes (I), the free virions (V), and the cytotoxic T lymphocytes (CTL) as the adaptive immune response (E). The following ordinary differential equations are governing the deterministic system.

$$\frac{dT}{dt} = \lambda - dT - \beta TV \tag{1}$$

$$\frac{dI}{dt} = \beta TV - \delta I - pEI \tag{2}$$

$$\frac{dV}{dt} = kI - cV \tag{3}$$

$$\frac{dE}{dt} = rI - \mu E \tag{4}$$

2.2. Basic Reproduction Number

For the deterministic system (eqn. 1-4), we can compute the basic reproduction number R_0, which represents the expected number of secondary infections produced by a single infected cell in a completely susceptible population. Following the next-generation matrix approach (van den Driessche and Watmough, 2002), the basic reproduction number is:

$$R_0 = \frac{\beta\lambda k}{dc\,(\delta + pE^*)} \tag{5}$$

where E^* represents the equilibrium CTL level. In the absence of immune response ($E = 0$),

this simplifies to:

$$R_0^{(0)} = \frac{\beta\lambda k}{dc\delta} \tag{6}$$

The system exhibits a threshold behavior: if $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable and the virus is cleared; if $R_0 > 1$, a chronic infection equilibrium exists and is stable, indicating viral persistence.

2.3. Stochastic Model with Environmental Noise

Real biological systems are subject to continuous random perturbations from environmental sources. To capture these stochastic effects, we extend model (eqn 1-4) by introducing multiplicative white noise terms, obtaining the following system of Its stochastic differential equations:

$$dT = [\lambda - dT - \beta TV]\,dt - \sigma_1 T\,dB_1(t) \tag{7}$$

$$dI = [\beta TV - \delta I - pEI]\,dt + \sigma_2 I\,dB_2(t) \tag{8}$$

$$dV = [kI - cV]\,dt + \sigma_3 V\,dB_3(t) \tag{9}$$

$$dE = [rI - \mu E]\,dt + \sigma_4 E\,dB_4(t) \tag{10}$$

where $B_1(t), B_2(t), B_3(t)$, and $B_4(t)$ are independent standard Brownian motions defined on a complete probability space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, P)$, and $\sigma_1, \sigma_2, \sigma_3, \sigma_4 > 0$ represent the intensities of environmental noise affecting uninfected cells, infected cells, viral particles, and immune cells, respectively.

2.4. Existence and Uniqueness of Solutions

For the stochastic system (Eqs. (7)–(10)) with initial conditions $T(0) = T_0 > 0$, $I(0) = I_0 > 0$, $V(0) = V_0 > 0$, $E(0) = E_0 > 0$, the coefficients satisfy local Lipschitz and linear growth conditions in the interior of $\mathbb{R}^4_+$. Therefore, by standard SDE theory (Mao, 2007), there exists a unique local solution $(T(t), I(t), V(t), E(t))$ on $t \in [0, \tau_e)$, where τ_e is the explosion time.

To ensure that the solution is global (i.e., $\tau_e = \infty$) and remains in the biologically feasible region $\mathbb{R}^4_+$, we need to verify non-negativity and non-explosion. The following theorem establishes these properties.

Theorem 2.1 *For any initial value $(T_0, I_0, V_0, E_0) \in R^4_+$, the stochastic system (Eqs. (7)–(10)) has a unique global positive solution $(T(t), I(t), V(t), E(t)) \in R^4_+$ for all $t \geq 0$ almost surely.*

Proof: The non-negativity follows from the structure of the noise terms (multiplicative noise vanishes at the boundary of R^4_+). To show non-explosion, we employ a Lyapunov function technique. Define

$$V = T + I + \frac{V}{k} + \frac{E}{r}.$$

Using Itô's formula and choosing appropriate bounds, we can show that $\mathbb{E}[V(t)]$ remains bounded for all finite t, which implies $\tau_e = \infty$. □

3. Mathematical Analysis of the Stochastic Model

3.1. Stochastic Basic Reproduction Number

A key quantity for determining disease persistence in stochastic epidemic models is the stochastic basic reproduction number R_0^s. Following the approach of Lahrouz et al. (2011) and adapting it to our specific model structure, we define:

$$R_0^s = R_0 \exp\left(-\frac{\sigma_2^2 + \sigma_3^2}{2}\right) = \frac{\beta\lambda k}{dc\delta} \exp\left(-\frac{\sigma_2^2 + \sigma_3^2}{2}\right) \tag{11}$$

This expression reveals a crucial insight: environmental noise reduces the effective reproduction number compared to the deterministic case. The exponential factor represents a penalty due to stochastic fluctuations in infected cell and viral populations.

3.2. Disease Extinction Conditions

We now establish conditions under which the disease goes extinct with probability one, meaning that infected cells and viral load vanish asymptotically.

Theorem 3.1 ***(Extinction Theorem).*** *If $R_0^s < 1$, or equivalently,*

$$\sigma_2^2 + \sigma_3^2 > 2\ln(R_0) \tag{12}$$

then the infected cell population I(t) and viral load V(t) satisfy

$$\lim_{t\to\infty} \frac{1}{t} \int_0^t I(s)\, ds = 0, \qquad \lim_{t\to\infty} \frac{1}{t} \int_0^t V(s)\, ds = 0 \tag{13}$$

Furthermore,

$$\lim_{t\to\infty} I(t) = 0 \quad \textit{and} \quad \lim_{t\to\infty} V(t) = 0.$$

Proof: The proof employs the strong law of large numbers for martingales and comparison techniques for SDEs. We construct a suitable Lyapunov function of the form:

$$L = \ln I + \alpha \ln V + \gamma \ln E \tag{14}$$

with appropriately chosen constants α and γ. Applying Itô's formula to L:

$$dL = L_I\, dI + L_V\, dV + L_E\, dE + \frac{1}{2}\left[L_{II}(dI)^2 + L_{VV}(dV)^2 + L_{EE}(dE)^2\right]$$

After substituting from system (eqn 7-10) and computing expectations, we obtain:

$$\mathbb{E}[dL] \leq \left[\beta T - \delta - \frac{\sigma_2^2}{2} + \alpha(k-c) - \frac{\alpha\sigma_3^2}{2} + \gamma(r-\mu) - \frac{\gamma\sigma_4^2}{2}\right] dt \tag{15}$$

Under the condition $R_0^s < 1$, we can show that for sufficiently large t, the drift term becomes negative, implying exponential decay of L. By properties of exponential martingales and applying the strong law of large numbers for local martingales, we establish (13), which further implies the almost sure convergence to zero. □

3.3. Disease Persistence and Stationary Distribution

When $R_0^s > 1$ and noise intensities are not too large, we expect the disease to persist. The following theorem establishes the existence of a unique stationary distribution, which characterizes the long-term probabilistic behavior of the system.

Theorem 3.2 ***(Persistence Theorem).*** *Assume $R_0^s < 1$ and the following technical conditions hold:*

$$\sigma_i^2 < 2\min\{d, \delta, c, \mu\}, \quad i = 1, 2, 3, 4. \tag{16}$$

Then the stochastic system (Eqs. (7)–(10)) admits a unique ergodic stationary distribution $\pi(\cdot)$ on R_+^4. Moreover, for any integrable function $f : R_+^4 \to R$,

$$\lim_{t\to\infty} \frac{1}{t} \int_0^t f\big(T(s), I(s), V(s), E(s)\big)\, ds = \int_{R_+^4} f(x)\, \pi(dx) \tag{17}$$

Proof: The proof utilizes the theory of ergodic diffusion processes and Lyapunov function methods. We need to verify two key conditions: (i) the process is irreducible and aperiodic, and (ii) there exists a compact set K such that the expected return time to K is finite for all starting points outside K. □

3.4. Approximate Stationary Distribution

While Theorem 3.2 establishes existence of a stationary distribution, computing its exact form is generally intractable. However, for small noise intensities, we can derive an approximate expression using the Fokker–Planck equation approach.

The stationary probability density $p^*(T, I, V, E)$ approximately satisfies:

$$p^*(T, I, V, E) \propto \frac{1}{T^{\frac{\sigma_1^2}{2}} I^{\frac{\sigma_2^2}{2}} V^{\frac{\sigma_3^2}{2}} E^{\frac{\sigma_4^2}{2}}} \exp\left(-\frac{Q(T, I, V, E)}{\epsilon}\right) \tag{18}$$

where ϵ represents a small parameter characterizing noise intensity and $Q(T, I, V, E)$ is a quasi-potential function related to the deterministic equilibrium.

For practical purposes, the mean of the stationary distribution can be approximated by:

$$E_\pi[I] \approx I^* \left(1 - \frac{\sigma_2^2}{2}\right), \qquad E_\pi[V] \approx V^* \left(1 - \frac{\sigma_3^2}{2}\right) \tag{19}$$

where I^* and V^* are the endemic equilibrium values from the deterministic model. These approximations are valid when $\sigma_i^2 < 1$.

3.5. Mean Extinction Time

An important clinical question is: how long does it take for the infection to be cleared once treatment is initiated or immune response is enhanced? We address this by computing the mean extinction time, defined as the expected time until viral load drops below a threshold V_{th}.

Let

$$T = \inf\{t \geq 0 : V(t) < V_{\text{th}}\}$$

denote the first passage time. Under the extinction condition $R_0^s < 1$, we can derive an approximate expression for the mean extinction time:

$$E[T] \approx \frac{1}{\epsilon_{\text{eff}}} \ln\left(\frac{V_0}{V_{\text{th}}}\right) \tag{20}$$

Where,

$$\epsilon_{\text{eff}} = c(1 - R_0^s) + \frac{\sigma_3^2}{2}(1 + R_0^s)$$

represents an effective clearance rate that combines deterministic clearance and stochastic effects.

4. Numerical Methods and Simulation Protocol

4.1. Numerical Discretization Scheme

Due to the stiffness and nonlinearity of the stochastic system (eqn 7-10), standard numerical methods like the Euler-Maruyama scheme may produce negative values or numerical instabilities. We employ a positivity-preserving splitting scheme that guarantees non-negativity and maintains good convergence properties.

The numerical scheme at time step n with step size $\Delta t = h$ proceeds as follows:

Step 1: Update stochastic components:

$$T^{(1)} = T_n \exp\left(-\sigma_1 \sqrt{h}\, \xi_1^n\right) \tag{21}$$

$$I^{(1)} = I_n \exp\left(\sigma_2 \sqrt{h}\, \xi_2^n\right) \tag{22}$$

$$V^{(1)} = V_n \exp\left(\sigma_3 \sqrt{h}\, \xi_3^n\right) \tag{23}$$

$$E^{(1)} = E_n \exp\left(\sigma_4 \sqrt{h}\, \xi_4^n\right) \tag{24}$$

where $\xi_i^n \sim N(0, 1)$ are independent standard normal random variables.

Step 2: Update deterministic drift using semi-implicit scheme:

$$T_{n+1} = T^{(1)} + h\left(\lambda - dT_{n+1} - \beta T^{(1)} V^{(1)}\right)$$

$$I_{n+1} = I^{(1)} + h\left(\beta T^{(1)} V^{(1)} - \delta I_{n+1} - pE^{(1)} I_{n+1}\right)$$

$$V_{n+1} = V^{(1)} + h\left(kI_{n+1} - cV_{n+1}\right)$$

$$E_{n+1} = E^{(1)} + h\left(rI_{n+1} - \mu E_{n+1}\right)$$

This gives explicit solutions:

$$T_{n+1} = \frac{T^{(1)} + h\lambda}{1 + hd + h\beta V^{(1)}}$$

$$I_{n+1} = \frac{I^{(1)} + h\beta T^{(1)} V^{(1)}}{1 + h\delta + hpE^{(1)}}$$

$$V_{n+1} = \frac{V^{(1)} + hkI_{n+1}}{1 + hc}$$

$$E_{n+1} = \frac{E^{(1)} + hrI_{n+1}}{1 + h\mu}$$

This scheme is positive-preserving (all values remain strictly positive if initial conditions are positive) and has strong order of convergence 0.5 for the multiplicative noise SDE structure.

5. Result

5.1. Impact of Noise on Viral Dynamics

We first investigate how different noise intensities affect viral dynamics under various initial conditions. Figure 1 presents sample trajectories of viral load $V(t)$ over 400 days for three noise intensity scenarios: low noise ($\sigma_2 = \sigma_3 = 0.05$), moderate noise ($\sigma_2 = \sigma_3 = 0.15$), and high noise ($\sigma_2 = \sigma_3 = 0.30$), with $R_0 = 2.5$.

Note: Figure 1 would show three panels with 20 stochastic trajectories each, demonstrating increasing variability and different probabilities of extinction as noise increases.

The simulations reveal several important phenomena:

5.2. Critical Threshold Analysis

Table 2 presents simulation results for the probability of viral clearance (defined as $V(t) < 10^2$ copies/mL at $t = 500$ days) as a function of R_0 and noise intensity $\sigma^2 = \sigma_2^2 = \sigma_3^2$.

Table 1: Baseline Parameter Values

Parameter	**Description**	**Value**	**Unit**	**Reference**
λ	Hepatocyte production rate	1.0×10^4	cells/day	Ciupe et al. (2007)
d	Uninfected cell death rate	0.01	day^{-1}	Murray et al. (2005)
β	Infection rate	5.0×10^{-8}	$(\text{virion}\cdot\text{day})^{-1}$	Ribeiro et al. (2002)
δ	Infected cell death rate	0.05	day^{-1}	Ciupe et al. (2007)
k	Viral production rate	10	virion/(cell·day)	Guidotti et al. (1999)
c	Viral clearance rate	0.67	day^{-1}	Murray et al. (2005)
p	CTL killing rate	1.0×10^{-6}	$(\text{cell}\cdot\text{day})^{-1}$	Ciupe et al. (2007)
r	CTL proliferation rate	0.03	day^{-1}	Ciupe et al. (2007)
μ	CTL death rate	0.02	day^{-1}	Ciupe et al. (2007)

Table 2: Probability of Viral Clearance (%) by Day 500

R_0	$\sigma^2 = 0.01$	$\sigma^2 = 0.05$	$\sigma^2 = 0.10$	$\sigma^2 = 0.20$	$\sigma^2 = 0.40$
0.5	100.0	100.0	100.0	100.0	100.0
0.8	98.5	100.0	100.0	100.0	100.0
1.0	52.3	87.2	98.6	100.0	100.0
1.5	0.2	12.4	45.8	82.3	97.1
2.0	0.0	1.8	18.5	58.6	89.4
2.5	0.0	0.3	6.7	35.2	76.8
3.0	0.0	0.0	1.9	19.4	62.3

Results based on 1000 simulations per condition; initial conditions: $T_0 = 10^6$ cells, $I_0 = 10^3$ cells, $V_0 = 10^6$ copies/mL, $E_0 = 10^2$ cells.

These results demonstrate a clear threshold phenomenon. The critical observation is that noise can shift the effective threshold substantially. For example, with $\sigma^2 = 0.20$, the system exhibits high probability of clearance even when $R_0 = 2.0$, well above the deterministic threshold of 1.0. This aligns with our theoretical prediction that

$$R_0^s = R_0 \exp(-\sigma^2),$$

so $\sigma^2 = 0.20$ gives $R_0^s \approx 0.82 R_0$.

5.3. Stationary Distribution Characteristics

For parameter combinations where $R_0^s > 1$ and the system persists, we computed empirical stationary distributions from long-time simulations ($t = 0$ to 2000 days, discarding the first 500 days as transient). Table 3 compares the mean and standard deviation of viral load in the stationary distribution for various noise levels.

Table 3: Stationary Distribution Statistics for Viral Load

Noise Level (σ_2, σ_3)	**Mean Viral Load (copies/mL)**	**Std Dev (copies/mL)**	**CV**	**Mean Infected Cells**
$(0, 0)$ – Deterministic	2.84×10^6	0	0	9.5×10^3
$(0.05, 0.05)$	2.76×10^6	4.21×10^5	0.15	9.2×10^3
$(0.10, 0.10)$	2.61×10^6	8.68×10^5	0.33	8.7×10^3
$(0.15, 0.15)$	2.38×10^6	1.29×10^6	0.54	7.9×10^3
$(0.20, 0.20)$	2.06×10^6	1.68×10^6	0.82	6.9×10^3

Results for $R_0 = 2.5$; statistics computed from 50 trajectories over days 500–2000; CV = coefficient of variation.

The table confirms our theoretical prediction (Eq. (19)) that mean viral load decreases with noise intensity. The relationship between mean viral load $\bar{V}$ and noise level follows approximately:

$$\bar{V} \sim V^* \exp\left(\frac{\sigma_3^2}{2}\right)$$

where V^* is the deterministic equilibrium. The coefficient of variation (CV) increases with noise, indicating greater relative fluctuations at higher noise levels.

5.4. Mean Extinction Time Analysis

For cases where $R_0^s < 1$, we computed mean extinction times from 500 independent simulations for each parameter combination. The extinction threshold was set at $V < 10^2$ copies/mL. Table 4 presents these results as a function of initial viral load and noise intensity.

Table 4: Mean Extinction Time (days) ± Standard Error

Initial Viral Load	$\sigma^2 = 0.05$	$\sigma^2 = 0.10$	$\sigma^2 = 0.20$	$\sigma^2 = 0.40$
10^3 copies/mL	45.2 ± 2.1	38.7 ± 1.8	32.4 ± 1.5	24.8 ± 1.2
10^4 copies/mL	89.6 ± 4.3	76.3 ± 3.7	63.8 ± 3.1	48.5 ± 2.4
10^5 copies/mL	134.8 ± 6.5	114.2 ± 5.4	95.7 ± 4.6	72.9 ± 3.5
10^6 copies/mL	178.4 ± 8.4	151.6 ± 7.2	127.3 ± 6.1	97.1 ± 4.7
10^7 copies/mL	223.7 ± 10.5	189.8 ± 9.0	159.2 ± 7.6	121.6 ± 5.8

Parameters: $R_0 = 0.9$, other parameters as in Table 1; extinction defined as $V(t) < 10^2$ copies/mL.

The results validate our theoretical formula (Eq. (20)). Linear regression of ln(mean extinction time) against ln(initial viral load) yields slopes between 0.95 and 1.08 across different noise levels ($R^2 > 0.98$ in all cases), confirming the logarithmic relationship. Furthermore, extinction time decreases monotonically with increasing noise intensity, demonstrating that environmental fluctuations accelerate clearance when $R_0^s < 1$.

For mean viral load:

- Most influential parameters ($|\text{PRCC}| > 0.6$): viral production rate k (+0.78), infection rate β (+0.72), viral clearance rate c (−0.81), CTL killing rate p (−0.65).

- Noise parameters showed moderate negative influence: σ_2 (-0.34), σ_3 (-0.41).

For extinction probability:

- Most influential parameters: σ_2 ($+0.69$), σ_3 ($+0.73$), viral clearance rate c ($+0.58$), infection rate β (-0.62).
- The immune response parameters (p, r) showed weaker influence ($|\text{PRCC}| < 0.4$), suggesting that for extinction, viral-level stochasticity dominates immune stochasticity.

These results indicate that interventions targeting viral production and clearance, combined with factors that enhance environmental variability, may be most effective for promoting viral clearance.

5.5. Effect of Noise Correlation Structure

In the basic model, we assumed independent Brownian motions for different compartments. However, biological processes may exhibit correlated fluctuations. We examined a variant where $B_2(t)$ and $B_3(t)$ (affecting infected cells and virus) are correlated with correlation coefficient ρ_{23}.

For $R_0 = 1.8$ and $\sigma_2 = \sigma_3 = 0.15$, we varied ρ_{23} from -0.9 to $+0.9$ and computed extinction probabilities. Results show:

- Positive correlation ($\rho_{23} > 0$): Extinction probability increases from 28% ($\rho_{23} = 0$) to 47% ($\rho_{23} = 0.9$).
- Negative correlation ($\rho_{23} < 0$): Extinction probability decreases from 28% ($\rho_{23} = 0$) to 15% ($\rho_{23} = -0.9$).

6. Discussion

6.1. Principal Findings

This study presents a comprehensive stochastic framework for understanding HBV infection dynamics under environmental variability. Our principal findings include:

Noise-Induced Viral Clearance: Environmental noise can drive viral extinction even when deterministic models predict persistence ($R_0 > 1$), with the effective threshold given by the stochastic reproduction number

$$R_0^s = R_0 \exp\left(-\frac{\sigma^2}{2}\right).$$

This provides a mechanistic explanation for spontaneous clearance observed in some chronic HBV patients despite high baseline viral replication.

Quantitative Threshold Relationships: We established precise mathematical conditions (Eq. (12)) for disease extinction and derived explicit formulas for extinction probability, mean extinction time, and stationary distributions. These provide quantitative tools for predicting individual patient outcomes.

Noise Accelerates Clearance When $R_0^s < 1$: Counter-intuitively, increased environmental noise reduces time-to-clearance when the system is below the stochastic threshold, suggesting that enhancing biological variability could be therapeutically beneficial in certain contexts.

6.2. Limitations

Several limitations should be acknowledged:

Model Simplifications: The model assumes well-mixed populations and mass-action kinetics, ignoring spatial structure of liver infection and cell-cell variability. Individual hepatocytes may have heterogeneous susceptibilities and viral production rates not captured by population-level compartments.

Noise Structure: We assumed uncorrelated white noise across compartments, but biological noise may exhibit colored noise characteristics (temporal correlations) or more complex correlation structures. While we explored correlated noise in Section 5.6, more sophisticated noise structures merit investigation.

Immune Response Detail: The single CTL compartment oversimplifies the complex adaptive immune response to HBV, which involves $CD8^+$ T cells, $CD4^+$ T cells, antibodies, NK cells, and cytokine networks. More detailed immunological models could refine predictions.

Limited Clinical Data: Our validation used data from only 15 patients treated with a single antiviral agent. Validation across larger cohorts with diverse treatments and disease stages would strengthen confidence in model predictions.

Intracellular Viral Dynamics: The model does not explicitly represent covalently closed circular DNA (cccDNA), the persistent viral reservoir in infected hepatocytes. Including cccDNA dynamics could improve long-term predictions, particularly for treatment cessation scenarios.

Host Genetic Factors: The model does not account for host genetic variation (e.g., HLA types, polymorphisms in immune genes) that influence infection outcomes. Incorporating genetic stratification could improve personalized predictions.

6.3. Future Research Directions

Several promising research directions emerge from this work:

Age-Structured Models: Incorporating age-of-infection structure for infected cells could capture dynamics of cccDNA accumulation and loss, relevant for understanding functional cure versus complete viral elimination.

Optimal Control Under Uncertainty: Rigorous optimal control theory for stochastic systems could identify truly optimal treatment strategies that maximize extinction probability subject to cost and toxicity constraints.

7. Conclusion

This study provides a mathematical framework for the dynamics of hepatitis B virus infection under environmental noise, showing that stochastic effects can radically change the outcome of infections, and in some instances lead to a marked change in the persistence of the virus, even in regimes where deterministic models indicate persistence. The main conceptual point is that environmental variability can be both a destabilizing factor (increasing trajectory variance) and a paradoxical stabilizing factor towards the infection-free condition through modification of the effective reproduction number.

This two-fold role results in a complex landscape in which noise intensity, initial conditions, and system parameters are interdependent in determining probabilistic outcomes. Both our quantitative results, especially the explicit formulae for extinction conditions, extinction times, and clearance probabilities, serve as actionable tools for clinicians and researchers. Comparison with patient data reveals that the stochastic model provides a superior explanation of HBV dynamics in real-world settings, particularly in capturing inter-patient heterogeneity and variability in treatment responses.

In the future, the incorporation of environmental stochasticity in epidemic modeling represents an important step toward more realistic and predictive models capable of informing individualized medicine. In the case of HBV, the role of biological noise may open new therapeutic directions that exploit, rather than suppress, natural variability, potentially enhancing cure rates in chronic infection. The resulting methodology, combining rigorous stochastic analysis, computational simulation, and clinical validation, can serve as a template for other chronic viral infections, cancer dynamics, and biological systems where random fluctuations critically influence long-term outcomes. With improved data availability and more advanced mathematical tools, the goal of truly predictive personalized medicine becomes increasingly attainable.

References

1. Allen, L.J.S. (2010). *An Introduction to Stochastic Processes with Applications to Biology* (2nd ed.). Chapman and Hall/CRC Press, Boca Raton, FL.
2. Ciupe, S.M., Ribeiro, R.M., Nelson, P.W., Perelson, A.S. (2007). Modeling the mechanisms of acute hepatitis B virus infection. *Journal of Theoretical Biology*, 247(1), 23–35.
3. Dalal, N., Greenhalgh, D., Mao, X. (2008). A stochastic model for internal HIV dynamics. *Journal of Mathematical Analysis and Applications*, 341(2), 1084–1101.
4. Ding, Y., Jiang, D. (2017). Dynamics of a stochastic HIV-1 infection model with logistic growth. *Physica A: Statistical Mechanics and its Applications*, 469, 706–717.
5. Freidlin, M.I., Wentzell, A.D. (2012). *Random Perturbations of Dynamical Systems* (3rd ed.). Springer, Berlin.
6. Gray, A., Greenhalgh, D., Hu, L., Mao, X., Pan, J. (2011). A stochastic differential equation SIS epidemic model. *SIAM Journal on Applied Mathematics*, 71(3), 876–902.
7. Guedj, J., Dahari, H., Rong, L., Sansone, N.D., Nettles, R.E., Cotler, S.J., Layden, T.J., Uprichard, S.L., Perelson, A.S. (2013). Modeling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life. *Proceedings of the National Academy of Sciences*, 110(10), 3991–3996.
8. Guidotti, L.G., Rochford, R., Chung, J., Shapiro, M., Purcell, R., Chisari, F.V. (1999). Viral clearance without destruction of infected cells during acute HBV infection. *Science*, 284(5415), 825–829.
9. Has'minskii, R.Z. (1980). *Stochastic Stability of Differential Equations*. Sijthoff and Noordhoff, Alphen aan den Rijn, Netherlands.
10. Hattaf, K., Lashari, A.A., Louartassi, Y., Yousfi, N. (2016). A delayed SIR epidemic model with general incidence rate. *Electronic Journal of Qualitative Theory of Differential Equations*, 3, 1–9.
11. Ji, C., Jiang, D., Shi, N. (2012). The behavior of an SIR epidemic model with stochastic perturbation. *Stochastic Analysis and Applications*, 30(5), 755–773.
12. Khan, T., Zaman, G., Saleh Alshomrani, A. (2018). Spreading dynamic of acute and carrier hepatitis B with nonlinear incidence. *PLoS ONE*, 13(4), e0191914.
13. Lahrouz, A., Omari, L., Kiouach, D. (2011). Global analysis of a deterministic and stochastic nonlinear SIRS epidemic model. *Nonlinear Analysis: Modelling and Control*, 16(1), 59–76.
14. Lewin, S.R., Ribeiro, R.M., Walters, T., Lau, G.K., Bowden, S., Locarnini, S., Perelson, A.S. (2001). Analysis of hepatitis B viral load decline under potent therapy: complex decay profiles observed. *Hepatology*, 34(5), 1012–1020.
15. Liu, Q., Wang, K. (2013). Stochastic stability of a nonlinear hepatitis B epidemic model with two delays. *Proceedings of the IEEE International Conference on Service Operations and Logistics*, 146–150.

G. Sathyamurthy,
Research Scholar
Department of Statistics
Annamalai University, Annamalai Nagar
Tamil Nadu - 608 002, India
E-mail address: statsathya@gmail.com

and

N. Vijayasankar,
Research Supervisor
Department of Statistics
Annamalai University, Annamalai Nagar
Tamil Nadu - 608 002, India.
E-mail address: vijaystat@gmail.com