Dynamical Behavior of Nonautonomous and Stochastic HBV Infection Model

by

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A dissertation submitted to the Graduate Faculty of
Auburn University
in partial fulfillment of the
requirements for the Degree of
Doctor of Philosophy

Auburn, Alabama
December 12, 2020

Keywords: Endamic equilibrium, HBV infection, stochastic HBV, ergodicity, stationary distribution

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Abstract

Mathematical modeling of population and transmission dynamics of an infectious disease considered a critical theoretical epidemiology method provides a strong understanding of the virus dynamics. This dissertation studies the Hepatitis B Virus Infection dynamical behavior with different approaches using mathematical modeling and dynamic systems theory.

Firstly, we propose an autonomous differential equations system, where all the parameters are constants. We show the basic solution properties, such as the existence and uniqueness of solutions, and as with any population model, we show that the solution is always positive. Next, we show the system has exactly two equilibrium points. We then discuss the stability analysis at each equilibrium point, then we obtain sufficient conditions that make the system exponentially stable by constructing an appropriate Liponouv function.

Secondly, we consider the case where the target cells' production rate is time-dependent, making the system nonautonomous. We use tools from the nonautonomous dynamical systems to show the solution exists, unique, and stay positive for all time. Then we prove that the system has a pullback absorbing and a positively invariant set, which implies the system has a unique global pullback attractor that guarantees the existence of entire solution. However, the results provide sufficient conditions for the existence of nonautonomous attractors and Singleton attractors.

Thirdly, We consider the HBV infection model with stochastic perturbation, and we investigate the longtime dynamics behavior of the stochastics model. First, we show the existence, uniqueness, and positiveness of solutions. For the stability analysis, we prove that if the reproductive number corresponding to the deterministic system $\mathcal{R}_0 < 1$ and the parameters satisfy some conditions, then the system is almost surely exponentially stable. Furthermore, we provide sufficient conditions that guarantee that a unique stationary ergodic distribution exists for $\mathcal{R}_0 > 1$, which implies the stochastic model's stability around the endemic equilibrium of the corresponding deterministic model by constructing suitable stochastic Lyapunov functions.

Finally, we provide numerical results to illustrate and support the theoretical results of this study. All the simulation codes are written using MATLAB.

Acknowledgments

First, I would like to thank my supervisor, Dr. Maggie Han, for her support and excellent intellectual guidance, continued support, encouragement, and patience throughout the years. She provided plenty of valuable advice and offered a motivational push for my work.

Next, I would like to thank my Ph.D. committee members, Dr. Georg Hetzer, Dr. Dmitry Glotov, and Dr. Hans Werner Van Wyk, for their valuable feedback and support. I would also like to thank Dr. Mark Dougherty for reading and evaluating my dissertation.

Finally, I would like to thank all my family members (parents, sisters, and brother) for their consistent encouragement and support. Special thanks to my wife Tayba and my daughter Elaph.

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Chapter 1

Introduction.

Hepatitis B is a liver infection disease is transmitted by blood or other body fluids from an infected to an uninfected person. It is considered one of the major diseases in the world. It is difficult to know when you became infected during the initial infection. Symptoms include vomiting, yellowing, fatigue, dark urine, and abdominal pain. These symptoms often last for a few weeks and rarely cause initial infection death. Symptoms of disease onset may take from 30 to 180 days. People who develop the disease at birth have a 90% chance of getting the disease while less than 10% of the patients appear after the age of five. Most chronic sufferers have no symptoms, but over time complications may appear more serious, including liver cirrhosis and liver cancer. Such complications can lead to 15 to 25% of those with the disease [5].

In the USA there are more than 1.2 million cases of Hepatitis B virus, and about 350 million in the world are carrying the virus, it is considered a common disease. To read more see [5, 6].

There are five viruses causing hepatitis, which are virus A, B, C, D, and E. Hepatitis A and E transmitted through contaminated food, water, or stool of an infected person. Hepatitis B and C are transmitted via an infected person's blood; these viruses might cause cute and chronic hepatitis. Viruses B and D might also be transmitted through body contact with an infected person. The most popular hepatitis in the united states is the Hepatitis B virus, which is the one we are going to study its dynamics behavior here in this thesis.

Mathematical Modeling of Virus Dynamics. Mathematical modeling plays a large role in understanding many phenomena in the world, for example in epidemiology it provides an understanding of the underlying mechanisms that influence the spread of disease and, in the process, it suggests control strategies. For within-host virus dynamics, mathematical models based on an understanding of biological interactions can also provide nonintuitive insights into the dynamics of the host response to viruses and can suggest new avenues for experimentation. Ordinary Differential Equations, Partial differential equations, and Integral Equations are usually used to model virus dynamics or any other world phenomena. Most virus dynamical models are developed from the Basic Virus Infection Model (BVIM) [1].

Basic Virus Infection Model (BVIM) is a general mathematical model for a basic dynamic of virus-host cell interaction was developed [10–12]. Figure 1 shows the basic idea of the virus replication. The BVIM is considered to be the simplest model to understand the interaction between virus that carries the disease and the host cells, introduced by Nowak [10] as follows:

$$\begin{cases} \frac{dx}{dt} &= \lambda - \mu_1 x - \beta x z \\ \frac{dy}{dt} &= \beta x z - \mu_2 y \\ \frac{dz}{dt} &= p y - \mu_3 z \end{cases} \tag{1.1}$$

where x, y and z are numbers of uninfected cells, infected cells and free virus, respectively. The parameters a, b, c are the death rates of the uninfected cells, infected cells and free virus, respectively. β is the constant rate between uninfected x cells and the free virus z. λ represents a constant production of the uninfected cells. We get infected cells "y" when the virus "z" attacks the healthy cells "x" at the rate of $\beta x z$ which will die at the rate of $\mu_2 y$. The free virus produced from the infected cells

The system 1.1 has two equilibrium points

- disease-free equilibrium $(\lambda/\mu_1, 0, 0)$, and
- endemic equilibrium

$$(x^*, y^* z^*) = (\frac{\mu_2\mu_3}{\beta p}, \frac{\lambda}{\mu_2} - \frac{\mu_1\mu_3}{\beta p}, \frac{\lambda p}{\mu_2\mu_3} - \frac{\mu_1}{\beta}.) \tag{1.2}$$

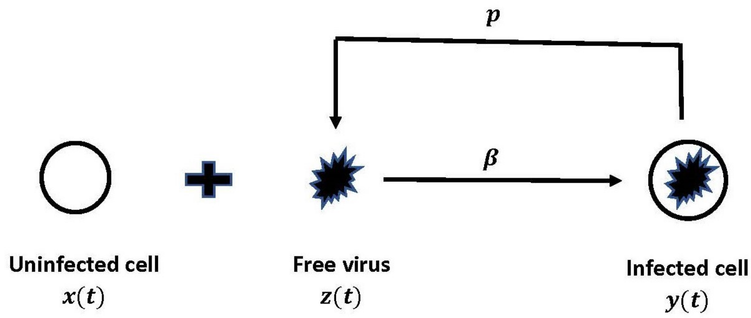


Figure 1.1: Virus Replication

To study the stability analysis of system 1.1, we need to introduce and construct the basic reproduction number.

Basic Reproduction Number. The basic reproduction number (sometimes called basic reproduction rate or basic reproductive ratio, denoted as which is used for measuring the transmission potential of a disease. It is thought of as the number of secondary infections produced by a typical case of the infection in a population that is totally susceptible. However, it ca be measured by counting the number of secondary cases following the introduction of an infection into a totally susceptible population. There are several factors that affect the basic reproduction number such as: (1) the rate of contacts in the host population; (2) the probability of infection being transmitted during contact; (3) the duration of infectiousness. Generally, for an epidemic to occur in a susceptible population, R0 must be greater than 1, so that the number of cases is increasing. If R0 < 1, the number of cases decreases.

The system 1.1 has a basic reproductive ratio $R_0 = \frac{\beta\lambda k}{abc}$.

- If $R_0 < 1$ then the infection cells will decrease.
- If $R_0 > 1$ then the infection cells will increase.

The immune response plays important role since it reduces the virus load. Adding the immune response affect to the system 1.1 we get the following extended model

$$\begin{aligned} \dot{x} &= \lambda - \mu_1 x - \beta x z \\ \dot{y} &= \beta x z - \mu_2 y - p y w \\ \dot{z} &= k y - \mu_3 z \\ \dot{w} &= d y w - \mu_4 w \end{aligned} \tag{1.3}$$

where w is the magnitude of the Cytotoxic T Lymphocytes (CTL) which has a rate of proliferation dyw, and rate of decay lw.

There are some other simple models that have been introduced see [10–12].

The model 1.3 has been modified by Perelson and Nelson [11] by adding the logistic term to the first equation in the system 1.1, the models becomes

$$\begin{aligned} \dot{x} &= \lambda - \mu_1 x - p x (1 - \frac{x + y}{X_{max}}) \\ \dot{y} &= -\mu_2 y + k x z \\ \dot{z} &= -\mu_3 z + N \beta y \end{aligned} \tag{1.4}$$

where, μ_1, μ_2, and μ_3 are the death rate of the healthy cells x, infected cells y and the free virus z respectively. p is growth rate, X_{max} is the carrying capacity. These are not the only models that have been introduced to understand the behavior of the HBV virus, there many other models some of which have partial differential equations instead of ordinary differential equations.

In the second chapter, we discuss the autonomous HBV model, where all the parameters are constants. We use concepts and theorems from the theory of autonomous dynamical systems, which is now a well-established area, but still, we consider it to understand the behavior of many dynamic systems.

In the third chapter, we study a nonautonomous HBV model; by that means, one or some of the parameters must be time-dependent; we consider the case when the production number

λ is time-dependent $\lambda(t)$. We introduce some preliminary concepts from the theory of nonautonomous dynamical systems that we need to study the stability analysis.

In the fourth chapter, we extend the deterministic model in chapter 2 to be a stochastic model by including standard white noise, making the model more realistic; we introduce some concepts from Stochastic Differential Equations and Probability Theory. We prove some basic solutions properties to the stochastic systems (existence, uniqueness, and positiveness). We also discuss the stability in probability for the disease-free equilibrium. We show the existence of the unique ergodic stationary distribution, which leads to the stability of the endemic equilibrium.

Finally, at the end of each chapter, we present numerical simulations to support our theoretical results, where all the parameter sets satisfy sufficient conditions of each model stability. All the simulation codes are written in MATLAB.

Chapter 2

Autonomous HBV Infection Model

This chapter discusses the autonomous case of the HBV infection model, where all the parameters are constants. We start by showing the basic properties of solutions, such as existence, uniqueness, and positiveness of solutions. We then discuss the stability analysis using tools from dynamic systems theory; at the end of this chapter, we show numerical simulations to support the theoretical results.

2.1 Model Formulation

We denote $x(t)$ the uninfected "Target" cells, $y(t)$ the infected cells, and $z(t)$ the free virus at any time t. $x(t)$ has a constant production rate λ and death rate μ_1, and when the virus $z(t)$ attacks $x(t)$ that produces infected cells $y(t)$ at rate $(1-\eta)\beta$, death rate μ_2, assuming that there are some infected cells recovered at rate q. y(t) produces a new free virus $z(t)$ at rate $(1-\epsilon)p$, and death rate μ_3. Putting all of these information together we get the following model

$$
\begin{cases}
\frac{dx}{dt} &= \lambda - \mu_1 x - (1-\eta)\beta xz + qy \\
\frac{dy}{dt} &= (1-\eta)\beta xz - \mu_2 y - qy \\
\frac{dz}{dt} &= (1-\epsilon)py - \mu_3 z
\end{cases}
\tag{2.1}
$$

Table 2.1 summarized all the parameters in 2.1.

Notice that η and ϵ are small positive fractions between 0 and 1, then $(1-\eta) > 0$ and $(1-\epsilon) > 0$, also all other parameters $\beta, q, p, \mu_1, \mu_2$ and μ_3 are positive.

Parameter	Description
λ	*Production rate of uninfected cells x.*
μ_1	*Death rate of x-cells.*
μ_2	*Death rate of y-cells.*
μ_3	*Free virus cleared rate.*
η	*Fraction that reduced infected rate after treatment with anti-viral drug.*
ϵ	*Fraction that reduced free virus rate after treatment with anti-viral drug.*
p	*Free virus production rate y-cells*
β	*Infection rate of x-cells by free virus z.*
q	*Spotaneous cure rate of y-cells by non-cytolytic process.*

Table 2.1: Parameters descriptions

Notations Through out this thesis we will consider the following.

- $\mathbb{R}^3 = \{(x, y, z)|\ x, y, z \in \mathbb{R}\}$, and $\mathbb{R}^3_+ = \{(x, y, z) \in \mathbb{R}^3|\ x \geq 0,\ y \geq 0,\ z \geq 0\}$.
- If $\mathbf{u} = (x, y, z)^T \in \mathbb{R}^3$ then the system (2.1) can be written as

$$\frac{d\mathbf{u}(t)}{dt} = f(\mathbf{u}(t)) \tag{2.2}$$

where

$$f(\mathbf{u}(t)) = f(x(t), y(t), z(t)) = \begin{pmatrix} \lambda - \mu_1 x - (1-\eta)\beta xz + qy \\ (1-\eta)\beta xz - \mu_2 y - qy \\ (1-\epsilon)py - \mu_3 z \end{pmatrix} \tag{2.3}$$

and $u_0 = u(t_0) = (x(t_0), y(t_0), z(t_0)) = (x_0, y_0, z_0)$.

2.2 Properties of Solutions

In this section we prove some basic properties of solutions (existence and uniqueness), since the we are studying a population model, we need ensure that the solution is always positive.

2.2.1 Existence, Uniqueness, Positiveness

In this subsections we show the existence and uniqueness of system 2.1 solutions.

Theorem 2.2.1 (Local Existence). *For any given $t_0 \in \mathbb{R}$ and $(x_0, y_0, z_0) \in \mathbb{R}^3_+$ there exists $T_{max} = T_{max}(t_0, x_0, y_0, z_0)$ such that the system from (2.1) has a solution $(x(t; t_0, x_0, y_0, z_0), y(t; t_0, x_0, y_0, z_0),$ on $[t_0, t_0 + T_{max})$. Furthermore, If $T_{max} < \infty$ then the solution will blow up, i.e.,*

$$\limsup_{t \to T_{max}} \left(|x(t_0 + t; t_0, x_0, y_0, z_0)| + |y(t_0 + t; t_0, x_0, y_0, z_0)| + |z(t_0 + t; t_0, x_0, y_0, z_0)| \right) = +\infty \tag{2.4}$$

Proof. It is clear that this function $f(u(t))$ in equation 2.3 is continuous and its derivatives with respect to x, y and z are also continuous. Therefore, we have the system (2.1) has a unique local solution.

It is well known that solutions of the ordinary differential equations may blow up in finite time. □

Since the system 2.1 is a population system, then it is very important to make sure that the solution is always positive.

Lemma 2.2.2. *suppose $(x(t_0), y(t_0), z(t_0)) \in \mathbb{R}^3_+$ is the initial vlaue of the system 2.1, then the solution $(x(t), y(t), z(t))$ is positive for all $t \in [t_0, t_0 + T_{max})$.*

Proof. By contradiction suppose not, then there exists $\tau \in [t_0, t_0 + T_{max})$ such that $x(t) > 0, y(t) > 0$ and $z(t) > 0$ on $[t_0, \tau)$ this implies one of the following cases

(i) $x(\tau) = 0$ and $y(\tau) > 0$ (ii) $x(\tau) > 0$ and $y(\tau) = 0$ (iii) $x(\tau) = 0$ and $y(\tau) = 0$

Now we will show that none of the above cases is possible.

Claim Case (i) is not possible.

Proof. From the basic definition of the derivative we have.

$$\frac{dx}{dt}(\tau) = \lim_{t \to \tau} \frac{x(t) - x(\tau)}{t - \tau} = \lim_{t \to \tau} \frac{x(t)}{t - \tau} \leq 0 \qquad \to \quad (1)$$

from the first equation in 2.1 we have

$$\begin{aligned}\frac{dx}{dt}(\tau) &= \lambda(\tau) - \mu_1 x(\tau) - (1-\eta)\beta x(\tau)v(\tau) + qy(\tau) \\ &= \lambda(\tau) + qy(\tau) \geq py(\tau) > 0 \qquad \rightarrow \quad (2)\end{aligned}$$

That a contradiction, therefore, case(1) is not possible. □

Claim Case (ii) is not possible.

Proof. We know that

$$\frac{dy}{dt}(\tau) = \lim_{t\to\tau} \frac{y(t)-y(\tau)}{t-\tau} = \lim_{t\to\tau} \frac{y(t)}{t-\tau} \leq 0 \qquad \rightarrow \quad (3)$$

from the second equation in 2.1 we have

$$\frac{dy}{dt}(\tau) = (1-\eta)\beta v(\tau)x(\tau) > 0 \qquad \rightarrow \quad (4)$$

from (3) and (4) we have a contradiction, thus, case(2) is not possible. □

Similarly, case(iii) is also not possible.

Notice that, $z(t)$ has explicit solution that depends on $y(t)$, thus, if $y(t)$ is positive that implies $z(t)$ is also positive for all $t \geq t_0$.

Therefore, the statement in the lemma is correct. □

Now we show the global existence of solution, which is enough to show that the solution of the system 2.1 is bounded

Theorem 2.2.3 (Global Existence "Boundedness")**.** *For given $t_0 \in \mathbb{R}$ and $(x_0, y_0, z_0) \in \mathbb{R}^3_+$, the solution $(x(t), y(t), z(t))$ exists for all $t \geq t_0$ and moreover,*

$$0 \leq x(t) + y(t) \leq M \qquad \textit{and} \quad 0 \leq z(t) \leq e^{\mu_3(t-t_0)} z_0 + (1-\epsilon)\, M \left(\frac{1-e^{-\mu_3(t-t_0)}}{\mu_3}\right)$$

where $M = Max\left\{x_0 + y_0 \ , \ \frac{\lambda}{min(\mu_1,\mu_2)}\right\}$

Proof.

It is enough to show that $|x(t)| + |y(t)| < \infty$ on $(t_0 \, , \, t_0 + T_{max})$.

By adding the first two equations in 2.1 we get

$$\frac{dx}{dt} + \frac{dy}{dt} = \lambda - \mu_1 x - \mu_2 y \tag{2.5}$$

$$\leq \lambda - min\{\mu_1, \mu_2\}[x(t) + y(t)]. \tag{2.6}$$

Let $v(t) = x(t) + y(t)$ the equation 2.5 becomes

$$v(t) \leq \lambda - min\{\mu_1, \mu_2\}\, v(t).$$

By the ODE comparison principle we have

$$v(t) \leq Max\left\{v_0 \ , \ \frac{\lambda}{\min(\mu_1, \mu_2)}\right\}$$

then 2.4 implies that $T_{max} = +\infty$.

It is clear that for t large we have

$$v(t) \leq \frac{\lambda}{\min\{\mu_1, \mu_2\}}$$

Which means both $x(t)$ and $y(t)$ are bounded. It is clear that $z(t)$ is also bounded directly by solving the third equation in system 2.1. $\square$

2.3 Equilibrium Solutions.

The equilibria of the system 2.1 is all the points in $\mathbb{R}^3$ such that $\dot{x} = \dot{y} = \dot{z} = 0$, this is implies the following equations

$$\begin{aligned} \lambda - \mu_1 x - (1-\eta)\beta x z + q y &= 0 \\ (1-\eta)\beta x z - \mu_2 y - q y &= 0 \\ (1-\epsilon) p y - \mu_3 z &= 0 \end{aligned}$$

By solving the above system of equations we found that the system 2.1 has only two two equilibrium points which are

1. Disease-free equilibrium $(\bar{x}_0\,,\,\bar{y}_0\,,\,\bar{z}_0) = \left(\frac{\lambda}{\mu_1}\,,\,0\,,\,0\right)$ and
2. Endemic equilibrium

$$(\bar{x}\,,\,\bar{y}\,,\,\bar{z}) = \left(\frac{\mu_1\mu_3(\mu_2+p)}{q\beta\mu_2(1-\eta)(1-\epsilon)}\,,\,\frac{\lambda}{\mu_2} - \frac{\mu_1\mu_3(\mu_2+p)}{q\beta\mu_2(1-\eta)(1-\epsilon)}\,,\,\frac{q\lambda(1-\epsilon)}{\mu_2\mu_3} - \frac{\mu_1(\mu_2+p)}{\beta\mu_2(1-\eta}\right)$$

2.4 Stability Analysis.

In the previous section we have seen that the system 2.1 has exactly two (disease-free and epidemic) equilibrium points. In this subsection we will discuss the stability analysis of the system 2.1 at each equilibrium point.

Lemma 2.4.1. *The system 2.1 is exponentially stable at its equilibrium points* $(\bar{x}, \bar{y}, \bar{z})$ *if the following conditions hold*

$$\begin{cases} 2\mu_1 + (1-\eta)\beta\bar{z} & > \quad (1-\eta)\beta\frac{\lambda}{min(\mu_1,\mu_2)} + q \\ 2\mu_2 + q & > \quad (1-\eta)\beta\left(\bar{z} + \frac{\lambda}{min(\mu_1,\mu_2)}\right) + (1-\epsilon)p \\ 2\mu_3 & > \quad (1-\epsilon)p + \frac{(1-\eta)\lambda\beta}{min(\mu_1,\mu_2)} \end{cases} \tag{2.7}$$

Proof. In fact, it is enough to show that

$$|x-\bar{x}| \to 0, \quad |y-\bar{y}| \to 0, \quad and \quad |z-\bar{z}| \to 0, \quad as \quad t \to \infty \tag{2.8}$$

Since $x-\bar{x}$, $y-\bar{y}$, and $z-\bar{z}$ satisfies the system 2.1. From system 2.1 we have

$$\begin{cases} \frac{d}{dt}(x-\bar{x}) = -(\mu_1+(1-\eta)\beta\bar{z})(x-\bar{x}) + q(y-\bar{y}) - (1-\eta)\beta x(z-\bar{z}) \\ \frac{d}{dt}(y-\bar{y}) = (1-\eta)\beta\bar{z}(x-\bar{x}) - (q+\mu_2)(y-\bar{y}) + (1-\eta)\beta x(z-\bar{z}) \\ \frac{d}{dt}(z-\bar{z}) = (1-\epsilon)p(y-\bar{y}) - \mu_3(z-\bar{z}) \end{cases} \tag{2.9}$$

Now, let $X = x-\bar{x}$, $Y = y-\bar{y}$ and $Z = z-\bar{z}$ then system 2.9 becomes

$$\frac{dX}{dt} = -(\mu_1+(1-\eta)\beta\bar{z})X + qY - (1-\eta)\beta xZ \tag{2.10}$$

$$\frac{dY}{dt} = (1-\eta)\beta\bar{z}X - (q+\mu_2)Y + (1-\eta)\beta xZ \tag{2.11}$$

$$\frac{dZ}{dt} = (1-\epsilon)pY - \mu_3 Z \tag{2.12}$$

Now, since $X = X_+ - X_-$, where X_+ and X_- are the positive and negative part of the function X, and also we have

$$XX_+ = (X_+ - X_-)X_+ = X_+^2$$

$$-XX_- = -(X_+ - X_-)X_- = X_-^2$$

$$(X_+ \pm X_-)^2 = X_+^2 + X_-^2 = |X|^2$$

This implies that

$$\dot{X}X_+ = \frac{1}{2}\frac{d}{dt}X_+^2 \qquad \text{and} \qquad -\dot{X}X_- = \frac{1}{2}\frac{d}{dt}X_-^2$$

Now multiplying equation 2.10 by X_+ gives

$$\dot{X}X_+ = -[\mu_1+(1-\eta)\beta\bar{z}]XX_+ + qYX_+ - (1-\eta)\beta xZX_+$$

$$\frac{1}{2}\frac{d}{dt}X_+^2 = -[\mu_1 + (1-\eta)\beta\bar{z}]X_+^2 + qYX_+ - (1-\eta)\beta xZX_+ \tag{2.13}$$

If we multiply equation 2.10 by X_- we get

$$\frac{1}{2}\frac{d}{dt}X_-^2 = -[\mu_1 + (1-\eta)\beta\bar{z}]X_-^2 + qYX_- + (1-\eta)\beta xZX_- \tag{2.14}$$

adding equation 2.13 and equation 2.14 we get

$$\frac{1}{2}\frac{d}{dt}(X_+^2 + X_-^2) = -[\mu_1 + (1-\eta)\beta\bar{z}](X_+^2 + X_-^2) + qY(X_+ - X_-) + (1-\eta)\beta xZ(X_+ - X_-)$$

$$\begin{aligned}
\frac{1}{2}\frac{d}{dt}|X|^2 &= -[\mu_1 + (1-\eta)\beta\bar{z}]|X|^2 + q(Y_+ - Y_-)(X_+ - X_-) + (1-\eta)\beta x(Z_+ - Z_-)(X_+ - X_-) \\
&= -[\mu_1 + (1-\eta)\beta\bar{z}]|X|^2 + q(Y_+X_+ + Y_-X_- - Y_-X_+ - Y_+X_-) \\
&\quad +(1-\eta)\beta x(X_+Z_- + X_-Z_+ - X_+Z_+ - X_-Z_-) \\
&\leq -[\mu_1 + (1-\eta)\beta\bar{z}]|X|^2 + \frac{1}{2}qY_+^2 + \frac{1}{2}qX_+^2 + \frac{1}{2}qY_-^2 + \frac{1}{2}X_-^2 - q(Y_-X_+ + Y_+X_-) \\
&\quad +\frac{1}{2}(1-\eta)\beta x(X_+^2 + Z_-^2 + X_-^2 + Z_+^2) - (1-\eta)\beta x(X_+Z_+ + X_-Z_-) \\
&\leq -[\mu_1 + (1-\eta)\beta\bar{z}]|X|^2 + \frac{1}{2}q|Y|^2 + \frac{1}{2}(1-\eta)\beta x|X|^2 + \frac{1}{2}q|X|^2 + \frac{1}{2}(1-\eta)\beta x|Z|^2 \\
&\quad -q(Y_-X_+ + Y_+X_-) - (1-\eta)\beta x(X_+Z_+ - X_-Z_-)
\end{aligned}$$

Thus,

$$\begin{aligned}
\frac{1}{2}\frac{d}{dt}|X|^2 \leq &- [\mu_1 + (1-\eta)\beta\bar{z} - \frac{1}{2}q - \frac{1}{2}(1-\eta)\beta x]|X|^2 + \frac{1}{2}q|Y|^2 + \frac{1}{2}(1-\eta)\beta x|Z|^2 \\
&- q(Y_-X_+ + Y_+X_-) - (1-\eta)\beta x(X_+Z_+ - X_-Z_-)
\end{aligned} \tag{2.15}$$

Similarly, by using the same computational technique we got

$$\frac{1}{2}\frac{d}{dt}|Y|^2 \leq \frac{1}{2}(1-\eta)\beta\bar{z}|X|^2 - [(q+\mu_2) - \frac{1}{2}(1-\eta)\beta\bar{z} - \frac{1}{2}(1-\eta)\beta x]|Y|^2 + \frac{1}{2}(1-\eta)\beta x|Z|^2 - (1-\eta)\beta\bar{z}(X_+Y_- + X_-Y_+) - (1-\eta)\beta x(Z_+Y_- + Z_-Y_+) \tag{2.16}$$

and

$$\frac{1}{2}\frac{d}{dt}|Z|^2 \leq -[\mu_3 - \frac{1}{2}(1-\epsilon)]|Z|^2 + \frac{1}{2}(1-\epsilon)p|Y|^2 - (1-\epsilon)p(Y_+Z_- + Y_-Z_+) \tag{2.17}$$

Now, by adding 2.15 , 2.16 and 2.17 we get

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\left(|X|^2+|Y|^2+|Z|^2\right) \leq &- \left[\mu_1 + \frac{1}{2}(1-\eta)\beta\bar{z} - \frac{1}{2}q - \frac{1}{2}(1-\eta)\beta x\right]|X|^2 \\ &- \left[\mu_2 + \frac{1}{2}q - \frac{1}{2}(1-\eta)\beta\bar{z} - \frac{1}{2}(1-\eta)\beta x - (1-\epsilon)p\right]|Y|^2 \\ &- \left[\mu_3 - \frac{1}{2}(1-\epsilon)p - (1-\eta)\beta x\right]|Z|^2 - [q(Y_+X_- + Y_-X_+) \\ &+ (1-\eta)\beta x(X_+Z_+ + X_-Z_-) + (1-\eta)(X_+Y_- + X_-Y_+) \\ &(1-\eta)\beta x(Z_+Y_-Z_-Y_+) + (1-\epsilon)p(Y_+Z_- + Y_-Z_+)]\end{aligned} \tag{2.18}$$

Therefore,

$$\frac{d}{dt}\left(|X|^2+|Y|^2+|Z|^2\right) \leq -\nu_1|X|^2 - \nu_2|Y|^2 - \nu_3|Z|^2 - W \tag{2.19}$$

where

$$\begin{aligned}\nu_1 &= 2\mu_1 + (1-\eta)\beta\bar{z} - (1-\eta)\beta x - q \\ \nu_2 &= \mu_2 + q - (1-\eta)\beta\bar{z} - (1-\eta)\beta x - (1-\epsilon)p \\ \nu_3 &= 2\mu_3 - (1-\epsilon)p - (1-\eta)\beta x \\ W &= q(Y_+X_- + Y_-X_+) + (1-\eta)\beta x(X_+Z_+ + X_-Z_-) + (1-\eta)(X_+Y_- + X_-Y_+) \\ &\quad +(1-\eta)\beta x(Z_+Y_-Z_-Y_+) + (1-\epsilon)p(Y_+Z_- + Y_-Z_+)\end{aligned}$$

Condition 2.21 guaranteed that ν_1, ν_2, an ν_3 are always positive. Since $W \geq 0$ then the inequity 4.2.2 still holds after removing W.

Now Let $k = \min n \{\nu_1, \nu_2, \nu_3\}$ and let $V(t) = |X(t)|^2 + |Y(t)|^2 + |Z(t)|^2$ then the inequality 4.2.2 becomes

$$\frac{dV(t)}{dt} \leq -kV(t)$$

$$0 \leq V(t) \leq V_0 e^{-kt} \longrightarrow 0 \quad \text{as} \quad t \to \infty \tag{2.20}$$

□

2.4.1 Stability at disease-free equilibrium

Substituting $(\bar{x}, \bar{y}, \bar{z}) = (\lambda/\mu_1, 0, 0)$ in condition 2.7 we get the following conditions

$$\begin{cases} 2\mu_1 & > & (1-\eta)\beta\frac{\lambda}{\mu^*} + q \\ 2\mu_2 + q & > & (1-\eta)\beta\frac{\lambda}{\mu^*} + (1-\epsilon)p \\ 2\mu_3 & > & (1-\epsilon)p + \frac{(1-\eta)\lambda\beta}{\mu^*} \end{cases} \tag{2.21}$$

where $\mu^* = min(\mu_1, \mu_2)$

Theorem 2.4.2. *The autonomous dynamic systems 2.1 is exponentially stable if the conditions 2.21 satisfied.*

Proof. Consider the Lyapunov function

$$V(x, y, z) = \frac{1}{2}[(x - \lambda/\mu_1)^2 + y^2 + z^2]$$

which is clearly positive, and by following the some computations in the proof of Lemma 2.4.1 we get $V' \leq 0$. That completed the proof. □

2.4.2 Stability at the endemic equilibrium

Substituting the endemic equilibrium $((\bar{x}\,,\,\bar{y}\,,\,\bar{z}))$ where

$$\begin{cases} \bar{x} & = & \frac{\mu_1\mu_3(\mu_2+p)}{q\beta\mu_2(1-\eta)(1-\epsilon)}, \\ \bar{y} & = & \frac{\lambda}{\mu_2} - \frac{\mu_1\mu_3(\mu_2+p)}{q\beta\mu_2(1-\eta)(1-\epsilon)}, \\ \bar{z} & = & \frac{q\lambda(1-\epsilon)}{\mu_2\mu_3} - \frac{\mu_1(\mu_2+p)}{\beta\mu_2(1-\eta)} \end{cases} \tag{2.22}$$

in condition 2.7 we get the following conditions

$$\begin{cases} \mu_1\mu_2\mu_3 + (1-\epsilon)(1-\eta)\lambda\beta q & > & \frac{(1-\eta)\lambda\beta\mu_2\mu_3}{min(\mu_1,\mu_2)} + q\mu_2\mu_3 + p\mu_1\mu_3 \\ 2\mu_2^2 + \mu_1\mu_2 + p\mu_1 + q & > & \frac{(1-\eta)(1-\epsilon)\beta\lambda q}{\mu_3} + \frac{(1-\eta)\lambda\beta}{\min\mu_1,\mu_2} \\ 2\mu_3 & > & (1-\epsilon)p + \frac{(1-\eta)\lambda\beta}{min(\mu_1,\mu_2)} \end{cases} \tag{2.23}$$

Theorem 2.4.3. *The solution of system 2.1 is exponentially stable at the endemic equilibrium 2.22 if conditions 2.23.*

.

Proof. The proof follows by Lemm 2.4.1. □

2.5 Numerical Results

Some numerical results are presented in this section to support the stability analysis result of the autonomous system 2.1. All the simulation code have been written in MATLAB.

2.5.1 Autonomous Case at disease-free equilibrium

At the disease-free equilibrium point $(\lambda/\mu_1, 0, 0)$, parameters have to satisfy condition 2.21, where parameters in Table 2.2 satisfied that and result represented as follows.

Table 2.2: List of parameters that satisfied conditions 2.21

parameters	λ	μ_1	μ_2	μ_3	β	η	ϵ	p	q
values	9.8135	2	3	7	0.2	0.2	0.5	0.01	5

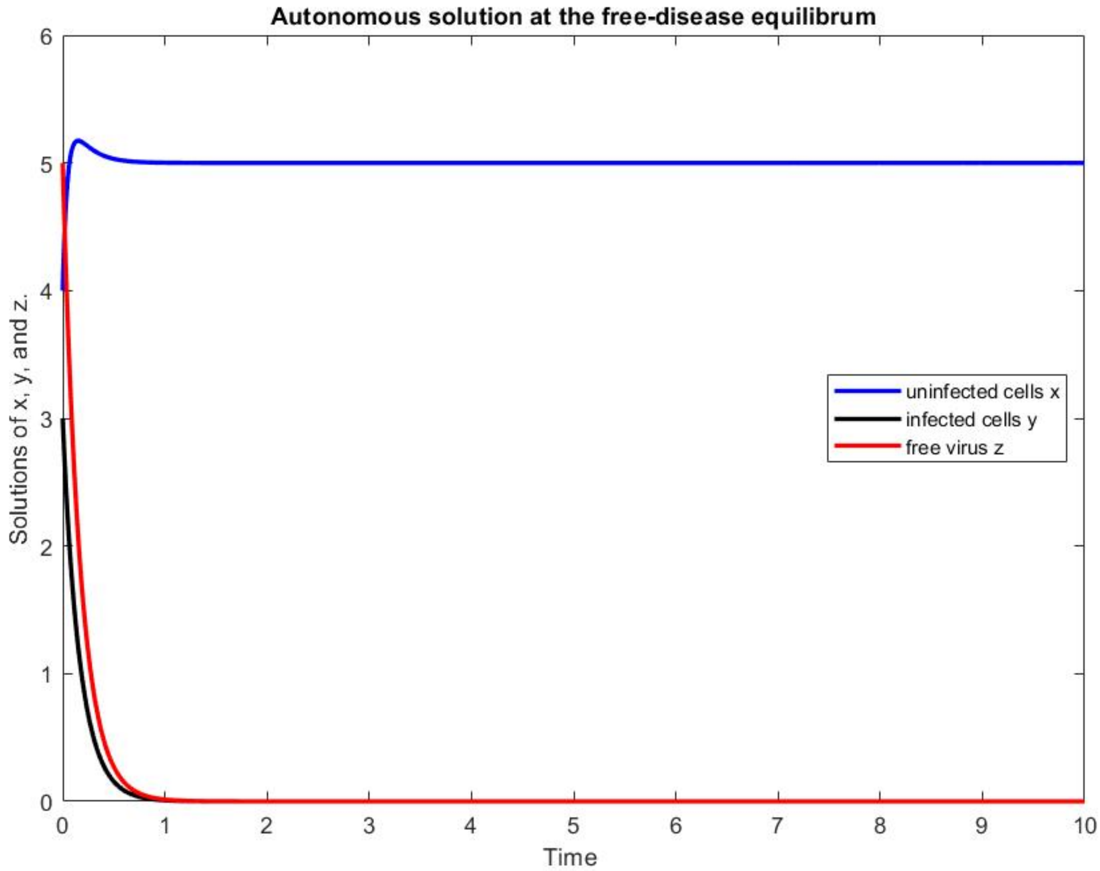


Figure 2.1: Autonomous case solution at disease-free equilibrium

2.5.2 Autonomous Case at epidemic equilibrium

Table 2.3: List of parameters that satisfied conditions 2.23

parameters	λ	μ_1	μ_2	μ_3	β	η	ϵ	p	q
values	100	5	7	2	0.7	0.2	0.2	2	6

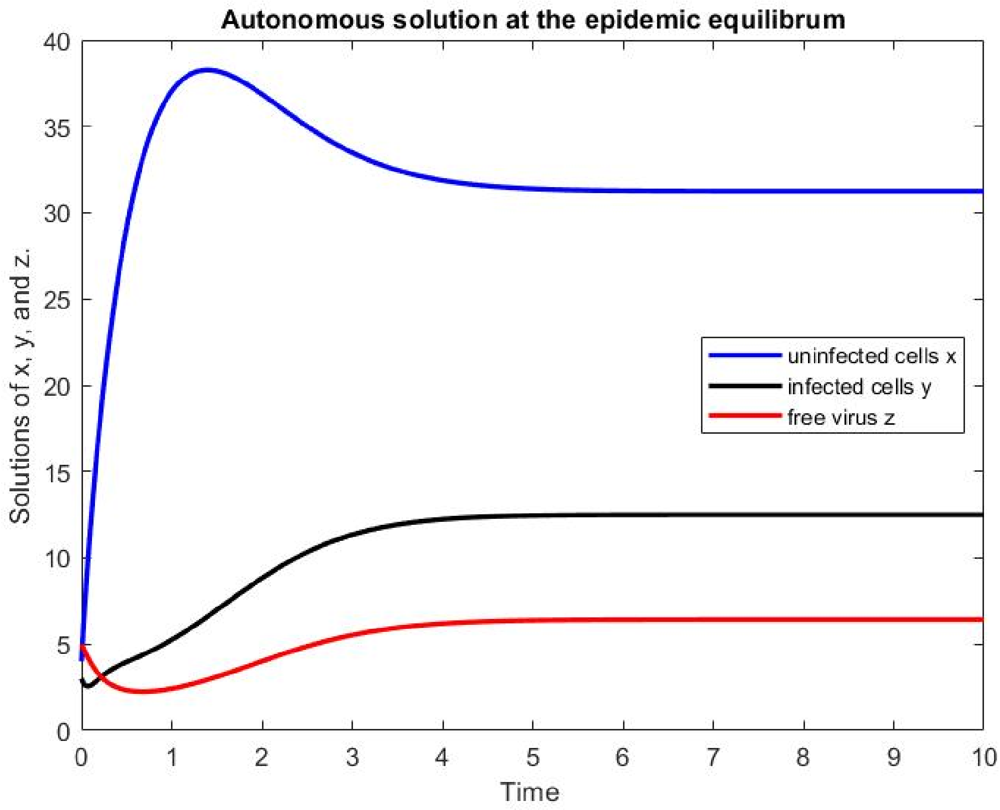


Figure 2.2: Autonomous case solution at epidemic equilibrium

If any of the stability conditions did not hold then we get completely different results see Figure 2.4.

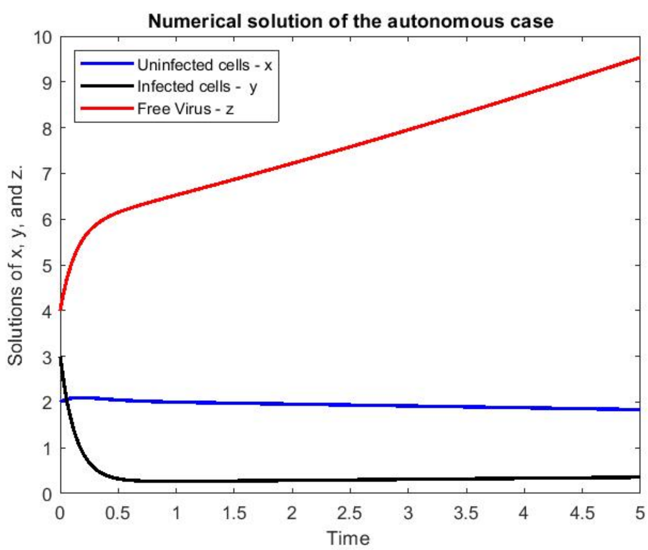


Figure 2.3: Autonomous case solution a when the inequities in 2.21 or **??** did not hold

Chapter 3

Nonautonomous HBV Model

This chapter considers the nonautonomous HBV infection model; we discuss the case where the production number λ is time-dependent. We provide first some preliminary of Nonautonomous Dynamical Systems. Then we discuss the stability analysis. The proof follows by Lemm 2.4.1.

3.1 Preliminary

Before discussing the stability analysis of the nonautonomous HBV infection model, let us first introduce some basic concepts from the theory of nonautonomous dynamic systems that we need to understand the HBV model analysis. We start with some definitions and theorems from [22–24].

The autonomous dynamical system formulation as a group or semi-group of mappings depends on the fact that such systems depend only on the elapsed time $t - t_0$ since starting and not directly on the current time t or starting time t_0 themselves. For a nonautonomous system both the current time t and starting time t_0 are important rather than just their difference.

There are several ways to formulate a nonautonomous dynamic systems (Process, Skew product follow), in this study we focus on the process formulation [22].

Consider the initial value problem of a non-autonomous ODE.

$$\frac{du(t)}{dt} = f(t, u(t)), \qquad u(t_0) = u_0. \tag{3.1}$$

The solution $\phi(t, t_0, u_0)$ of equation 3.1 depends on the actual time t and the initial time t_0.

Define

$$\mathbb{R}^2_{\geq} := \{(t, t_0) \in \mathbb{R}^2 \ : \ t \geq t_0\}$$

Definition 3.1.1 (Process formulation, [22].)**.** A process is a continuous mappings $\phi(t, t_0, \dot{)} : \mathbb{R}^n \to \mathbb{R}^n$ which satisfies the initial and evolution properties as follows

i. $\phi(t_0, t_0, u_0) = u_0$ for all $u_0 \in \mathbb{R}^n$.

ii. $\phi(t_2, t_0, u) = \phi(t_2, t_1, \phi(t_1, t_0, u))$. for all $t_0 \leq t_1 \leq t_2$ and $u_0 \in \mathbb{R}^n$.

Definition 3.1.2 (Invariant, Positive Invariant, and Negative Invariant families for process)**.** Let ϕ be a process on $\mathbb{R}^n$. A family $\mathcal{A} = \{A(t) : t \in \mathbb{R}\}$ of nonempty subsets of $\mathbb{R}^n$ is said to be:

1. Invariant with respect to ϕ, or ϕ-invariant if

$$\phi(t, t_0, A(t_0)) = A(t) \qquad \text{for all} \quad t >\geq t_0.$$

2. Positive Invariant, or or ϕ-Positive invariant if

$$\phi(t, t_0, A(t_0)) \subset A(t) \qquad \text{for all} \quad t >\geq t_0.$$

3. Negative Invariant, or or ϕ- negative

$$\phi(t, t_0, A(t_0)) \supset A(t) \qquad \text{for all} \quad t >\geq t_0.$$

Definition 3.1.3 (Nonautonomous Attractivity)**.** Let ϕ be a process. A nonempty, compact subset $\mathcal{A}$ of $\mathbb{R}^n$ is said to be

i. Forward attracting if

$$\lim_{t \to \infty} dist(\phi(t, t_0, u_0), A(t)) = 0 \qquad \text{for all } u_0 \in \mathbb{R}^n \text{ and } t_0 \in \mathbb{R}\,,$$

ii. Pullback attracting if

$$\lim_{t \to -\infty} dist(\phi(t, t_0, u_0), A(t)) = 0 \qquad \text{for all } u_0 \in \mathbb{R}^n \text{ and } t_0 \in \mathbb{R}\,.$$

Definition 3.1.4. A family $\mathcal{B} = \{B(t) \,:\, t \in \mathbb{R}\}$ of nonempty compact subsets of $\mathbb{R}^n$ is called pullback obserbing family for the process ϕ if for each $t_1 \in \mathbb{R}$ and every family $\mathcal{D} = \{D(t) \,:\, t \in \mathbb{R}\}$ of nonempty subset of $\mathbb{R}^n$ there exists some $T = T(t_1, \mathcal{D} \in \mathbb{R}_+$ such that

$$\phi(t_1, t_0, D(t_0)) \subseteq B(t_1) \qquad \text{for all } \; t + 0 \in \mathbb{R} \; with \; t_0 \leq t_1 - .T$$

Theorem 3.1.5. *If the process ϕ on $\mathbb{R}^n$ has a ϕ-invariant pullback absorbing family $\mathcal{B} = \{b(t) : t \in \mathbb{R}\}$ of non-empty compact subset of $\mathbb{R}^n$, then ϕ has a unique global pullback attractor $\mathcal{A} = \{A(t) :\, t \in \mathbb{R}\}$.*

Notice that, a pullback attractor consists of entire solutions.

Definition 3.1.6. A nonautonomous dynamical system ϕ satisfies the uniform strictly contracting property if for each $R > 0$, there exist positive constants K and α such that

$$|\phi(t, t_0, x_0) - \phi(t, t_0, y_0)|^2 \leq K e^{-\alpha(t - t_0)} |x_0 - y_0|^2 \qquad (3.2)$$

for all $(t, t_0) \in \mathbb{R}^2_{\geq}$ and $x_0,\; y_0 \in \bar{\mathbb{B}}(0; R)$, where $\bar{\mathbb{B}}$ is a closed ball centered at the origin with radius $R > 0$.

Remark. The uniform strictly contracting property, together with the existence of a pullback absorbing, implies the existence of a global attractor that consists of a single entire solution.

3.2 Model Formulation

When the productive number λ in 2.1 is time-dependent $\lambda(t)$, that changes the system from autonomous to a nonautonomous model represented as follows

$$\begin{cases} \frac{dx}{dt} &= \lambda(t) - \mu_1 x - (1-\eta)\beta x z + q y \\ \frac{dy}{dt} &= (1-\eta)\beta x z - \mu_2 y - q y \\ \frac{dz}{dt} &= (1-\epsilon) p y - \mu_3 z \end{cases} \tag{3.3}$$

which can be written as

$$\frac{du(t)}{dt} = f(t, u(t)), \quad where \quad u(t) = (x(t), y(t), z(t))^T \in \mathbb{R}^3, \quad and \quad t \in \mathbb{R}.$$

with initial condition $u_0 = (x_0, y_0, z_0)^T$

3.3 Solution Properties

The existence of local solution follows from the fact that $f(t, u(t))$ is continuous and its derivative is also continuous. The following Lemma prove the positiveness

Lemma 3.3.1. *Let* $\lambda : \mathbb{R} \to [\lambda_m\,,\, \lambda_M]$*, then for any* $(x_0, y_0, z_0) \in \mathbb{R}^3_+ := \{(x, y, z) \in \mathbb{R}^3 : x \geq 0, y \geq 0, z \geq 0\}$ *all the solutions of the system (3.3 - 3.3) corresponding to the initial point are:*

i. Non-negative for all

ii. Uniformly bounded.

Proof. i. The proof is similar to the positiveness of the autonomous case that introduced earlier.

ii. Set $\|X(t)\|_1 = x(t) + y(t) + z(t)$, if we combine the three equations in (3.3 - 3.3) we get:

$$\dot{x}(t) + \dot{y}(t) + \dot{z}(t) = \lambda(t) - \mu_1 x - (\mu_2 - (1-\epsilon)p)y - \mu_3 z \tag{3.4}$$

assume $\mu_2 > (1-\epsilon)p$ and let $\alpha = min\mu_1, \mu_2 - (1-\epsilon)p, \mu_3$, then we get

$$\frac{d}{dt}\|X(t)\|_1 \leq \lambda_M - \alpha\|X(t)\|_1 \tag{3.5}$$

this implies that

$$\|X(t)\|_1 \leq max\{x_0 + y_0 + z_0, \frac{\lambda_M}{\alpha}\} \tag{3.6}$$

Thus, the set $B_\epsilon = \{(x,y,z) \in \mathbb{R}^3_+ : \epsilon \leq x(t) + y(t) + z(t) \leq \frac{\lambda_M}{\alpha} + \epsilon\}$ is positively invariant and absorbing in $\mathbb{R}^3_+$.

□

3.4 Stability Analysis

This section discusses the stability analysis of the systems 3.3; first, we show the uniform strictly contracting property, then we prove that the system has a positively absorbing set. Then we provide sufficient conditions that make the system 3.3 stable.

Theorem 3.4.1. *The nonautonomous system (3.3 - 3.3) satisfies a uniform strictly contracting property, if* $\mu_2 > (1-\epsilon)p$.

Proof. Let

$$\begin{cases} (x_1, y_1, z_1) & = & (x(t,t_0,x_0^1), y(t,t_0,y_0^1), z(t,t_0,z_0^1)) \\ \text{and } (x_2, y_2, z_2) & = & (x(t,t_0,x_0^2), y(t,t_0,y_0^2), z(t,t_0,z_0^2)) \end{cases} \tag{3.7}$$

and are two solutions of the system (3.3 - 3.3) by similar computational in autonomous case we get

$$\begin{cases} \frac{d}{dt}(x_1 - x_2) = -(\mu_1 + (1-\eta)\beta z_1))(x_1 - x_2) + q(y_1 - y_2) - (1-\eta)\beta x_2(z_1 - z_2) \\ \frac{d}{dt}(y_1 - y_2) = (1-\eta)\beta z_1(x_1 - x_2) - (q + \mu_2)(y_1 - y_2) + (1-\eta)\beta x(z_1 - z_2) \\ \frac{d}{dt}(z_1 - z_2) = (1-\epsilon)p(y_1 - y_2) - \mu_3(z_1 - z_2) \end{cases} \tag{3.8}$$

Now, let $X = x_1 - x_2$, $Y = y_1 - y_2$ and $Z = z_1 - z_2$ then system 3.8 becomes

$$\frac{dX}{dt} = -(\mu_1 + (1-\eta)\beta z_1)X + qY - (1-\eta)\beta x_2 Z \tag{3.9}$$

$$\frac{dY}{dt} = (1-\eta)\beta z_1 X - (q+\mu_2)Y + (1-\eta)\beta x_2 Z \tag{3.10}$$

$$\frac{dZ}{dt} = (1-\epsilon)pY - \mu_3 Z \tag{3.11}$$

This implies that

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}|X|^2 \leq & -[\mu_1 + (1-\eta)\beta z_1 - \frac{1}{2}q - \frac{1}{2}(1-\eta)\beta x_2]|X|^2 + \frac{1}{2}q|Y|^2 + \frac{1}{2}(1-\eta)\beta x_2|Z|^2 \\ & - q(Y_- X_+ + Y_+ X_-) - (1-\eta)\beta x(X_+ Z_+ - X_- Z_-)\end{aligned} \tag{3.12}$$

Similarly, by using the same computational technique we got

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}|Y|^2 \leq & \frac{1}{2}(1-\eta)\beta z_1|X|^2 - [(q+\mu_2) - \frac{1}{2}(1-\eta)\beta\bar{z} - \frac{1}{2}(1-\eta)\beta x_2]|Y|^2 + \frac{1}{2}(1-\eta)\beta x_2|Z|^2 \\ & - (1-\eta)\beta z - 1(X_+ Y_- + X_- Y_+) - (1-\eta)\beta x(Z_+ Y_- + Z_- Y_+)\end{aligned} \tag{3.13}$$

and

$$\frac{1}{2}\frac{d}{dt}|Z|^2 \leq -[\mu_3 - \frac{1}{2}(1-\epsilon)]|Z|^2 + \frac{1}{2}(1-\epsilon)p|Y|^2 - (1-\epsilon)p(Y_+ Z_- + Y_- Z_+) \tag{3.14}$$

Now, by adding 2.15 , 2.16 and 2.17 we get

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\left(|X|^2+|Y|^2+|Z|^2\right) \leq &-\left[\mu_1+\frac{1}{2}(1-\eta)\beta z_1-\frac{1}{2}q-\frac{1}{2}(1-\eta)\beta x_2\right]|X|^2\\ &-\left[\mu_2+\frac{1}{2}q-\frac{1}{2}(1-\eta)\beta z_1-\frac{1}{2}(1-\eta)\beta x_2-(1-\epsilon)p\right]|Y|^2\\ &-\left[\mu_3-\frac{1}{2}(1-\epsilon)p-(1-\eta)\beta x\right]|Z|^2-[q(Y_+X_-+Y_-X_+)\\ &+(1-\eta)\beta x(X_+Z_++X_-Z_-)+(1-\eta)(X_+Y_-+X_-Y_+)\\ &(1-\eta)\beta x_2(Z_+Y_-Z_-Y_+)+(1-\epsilon)p(Y_+Z_-+Y_-Z_+)]\end{aligned} \tag{3.15}$$

Since x_2 and z_1 are bounded, assume that $\gamma_2 = max\{x_2\}$ and $\gamma_1 = max\{z_1\}$.

Therefore,

$$\frac{d}{dt}\left(|X|^2+|Y|^2+|Z|^2\right) \leq -\nu_1|X|^2-\nu_2|Y|^2-\nu_3|Z|^2-W \tag{3.16}$$

where

□

$$\begin{aligned}\nu_1 &= 2\mu_1+(1-\eta)\beta\gamma_1-(1-\eta)\beta\gamma_2-q\\ \nu_2 &= \mu_2+q-(1-\eta)\beta\gamma_1-(1-\eta)\beta\gamma_2-(1-\epsilon)p\\ \nu_3 &= 2\mu_3-(1-\epsilon)p-(1-\eta)\beta\gamma_2\\ W &= q(Y_+X_-+Y_-X_+)+(1-\eta)\beta x(X_+Z_++X_-Z_-)+(1-\eta)(X_+Y_-+X_-Y_+)\\ &\quad +(1-\eta)\beta x(Z_+Y_-Z_-Y_+)+(1-\epsilon)p(Y_+Z_-+Y_-Z_+)\end{aligned}$$

Let $\alpha = min\{\nu_1, \nu_2\nu_3\}$, then equation 3.16 becomes

$$\frac{d}{dt}\left(|X|^2+|Y|^2+|Z|^2\right) \leq -\alpha(|X|^2+|Y|^2+|Z|^2)-W \tag{3.17}$$

Which have a solution

$$|X|^2 + |Y|^2 + |Z|^2 \leq Ke^{-\alpha(t-t_0)}(|X_0|^2 + |Y_0|^2 + |Z_0|^2) \tag{3.18}$$

Notice that, for ν_1, ν_2, ν_3 to positive following conditions must hold.

$$2\mu_1 + (1-\eta)\beta b_1 \quad > \quad (1-\eta)\beta \frac{\lambda_M}{min(\mu_1, \mu_2)} + q \tag{3.19}$$

$$2\mu_2 + q \quad > \quad (1-\eta)\beta \left(b_1 + \frac{\lambda_M}{min(\mu_1, \mu_2)} \right) + (1-\epsilon)p \tag{3.20}$$

$$2\mu_3 \quad > \quad (1-\epsilon)p + \frac{(1-\eta)\beta\lambda_M}{min(\mu_1, \mu_2)} \tag{3.21}$$

Theorem 3.4.2. *Suppose* $\lambda : \mathbb{R} \to [\lambda_m\, ,\, \lambda_M]$, *where* $0 < \lambda_m < \lambda - M < \infty$, *is continuous, then the system (3.3 - 3.3) has a pullback attractor* $\mathcal{A} = \{A(t) :\ t \in \mathbb{R}\}$ *inside* $\mathbb{R}^3_+$. *Moreover, if* $\mu_2 > (1-\epsilon)p$, *and the conditions (3.19 - 3.21) hold then the solution of the system is exponentially stable.*

3.5 Numerical Results

3.5.1 Nonautonomous Case

Figure 3.1 shows the solutions of the system 3.3 using an appropriate set of parameters that satisfied the necessary conditions. We approximate the healthy cells' productive function by $\lambda(t) = cos(2t + \pi/3) + 10$, which is a positive and bounded function. On the interval $[0,\ 5]$ for the other parameters in the table 3.1.

Table 3.1: Set of parameters that satisfy the required conditions

μ_1	μ_2	μ_3	β	η	ϵ	p	q	λ_M
2	3	7	0.2	0.2	0.5	0.01	5	12

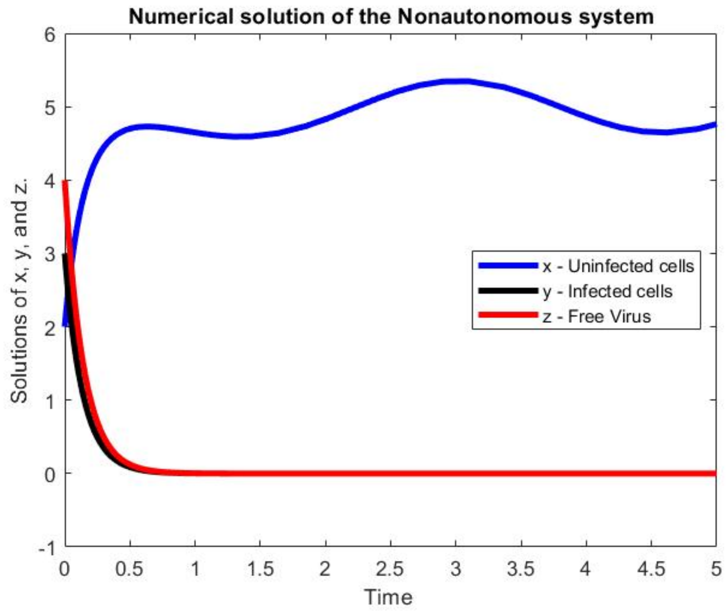


Figure 3.1:

3.5.2 Comparison between Autonomous and Nonautonomous solutions

The set of parameters in table 3.2 was chosen very carefully such that the required conditions hold. But when we run the simulation for autonomous and nonautonomous using the same set of parameters we got completely different results, see Figures 3.2 and 3.3.

Table 3.2: This set of parameters satisfy both Auto/nonatunamous conditions

μ_1	μ_2	μ_3	β	η	ϵ	p	q	λ_M
6	7	0.1	0.3	0.5	0.1	5	10	20

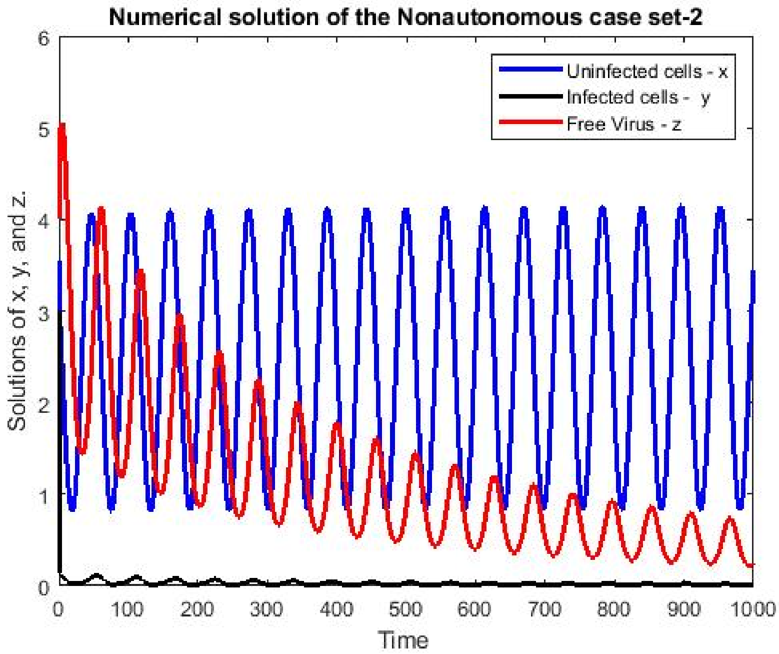


Figure 3.2: The result is showing the stability of the nonautonomous model

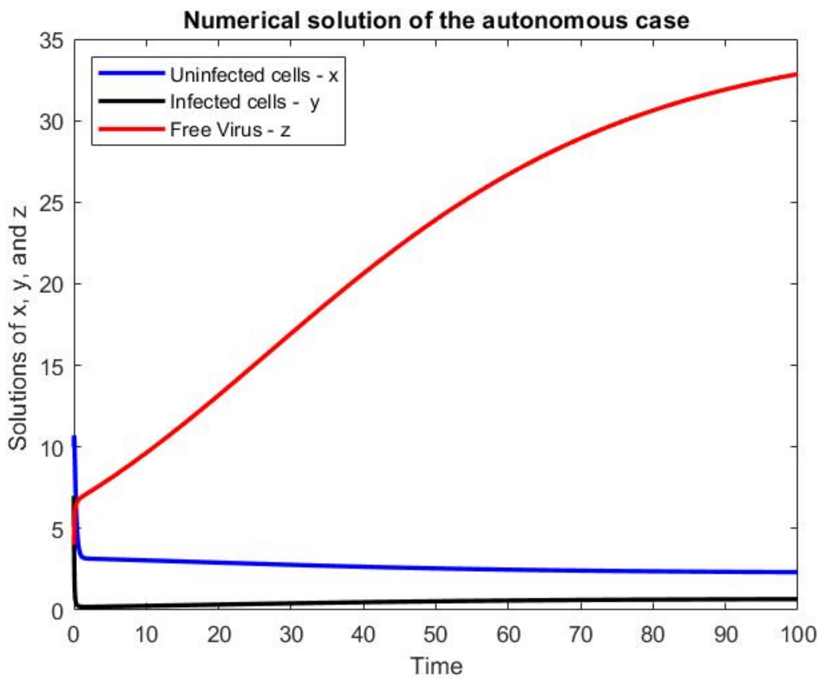


Figure 3.3: The free virus solution $z(t)$ blowup

These results show that the nonautonomous systems are more accurate than the nonautonomous systems.

Chapter 4

Stochastic HBV Model

All the previous studies and experimental data showed the importance of stochastic noise in evolution models, including the Hepatitis B virus infection dynamics. The stochastic model gives more realistic results than the deterministic model.

4.1 Model Formulation

In chapter 2, we introduced the deterministic model 2.1 and we have discussed its stability analysis. In this chapter we consider the importance of stochastic noise, and we include white noise in the parameters of system 2.1 by replacing $\mu_1 \to \mu_1 - \sigma_1 dW_1(t)$, $\mu_2 \to \mu_2 - \sigma_2 dW_2(t)$, and $\mu_3 \to \mu_3 - \sigma_3 dW_3(t)$, where $W_1,\ W_2,$ and W_3 are independent standard Brownian motions. They satisfy $W_1(0) = W_2(0) = W_3(0) = 0$. Hence, the stochastic system corresponding to system 2.1 has the following form.

$$dx(t) = (\lambda - \mu_1 x - (1-\eta)\beta x z + q y)dt + \sigma_1 x dW_1(t) \tag{4.1}$$

$$dy(t) = ((1-\eta)\beta x z - \mu_2 y - q y)dt + \sigma_2 y dW_2(t) \tag{4.2}$$

$$dz(t) = ((1-\epsilon)p y - \mu_3 z)dt + \sigma_3 z dW_3(t) \tag{4.3}$$

All other parameters are defined in the Table 2.1.

The system (4.1 - 4.3) can be written as

$$du_t = f(u(t), t)dt + B(u, t)dW\,, \qquad t \geq 0 \tag{4.4}$$

with the initial $u_0 \in \mathbb{R}^3$, where, $u(t) = (x(t), y(t), z(t))$,

$$f(u,t) = \begin{pmatrix} \lambda - \mu_1 x - (1-\eta)\beta xz + qy \\ (1-\eta)\beta xz - \mu_2 y - qy \\ (1-\epsilon)py - \mu_3 z \end{pmatrix}, \quad B(u,t) = \begin{pmatrix} \sigma_1 x & 0 & 0 \\ 0 & \sigma_2 y & 0 \\ 0 & 0 & \sigma_3 z \end{pmatrix}, \quad \text{and } dW = \begin{pmatrix} dW_1 \\ dW_2 \\ dW_3 \end{pmatrix}$$

4.2 Preliminary.

Before we discuss the solution properties and stability analysis of the stochastic system (4.1-4.3), we would like to introduce some of the definitions and theorems that we need in this study, all of these concepts are from [2].

In general, equation 4.4 can be written as d-dimensional stochastic equation in the complete probability $(\Omega, \mathcal{F}, \mathbb{P})$ with a filtration $\{\mathcal{F}_t\}_{t\geq 0}$ as

$$du_t = f(u,t)dt + B(u,t)dW\,, \qquad t \geq 0 \tag{4.5}$$

where $f(u,t) : \mathbb{R}^d \times [t_0, T] \to \mathbb{R}^d$ and $B(u,t) : \mathbb{R}^d \times [t_0, T] \to \mathbb{R}^{d\times n}$ are Borel measurable, the white noise $W(t) = (w_1(t), w_2(t), \cdots, w_n(t)) \in \mathbb{R}^n$, $t \geq 0$. Let $0 \leq t_0 \leq T < \infty$, and the initial value u_0 to be $\mathfrak{F}_{t_0}$-measurable $\mathbb{R}^d$ random variable such that $E|u_0|^2 < \infty$, equation 4.5 known as stochastic differential equation of Itô type.

Definition 4.2.1 ([2], page 48). The stochastic process $\{u(t)\}_{0\leq t_0\leq T}$ in $\mathbb{R}^d$ is said to be a solution of equation 4.5 if the following properties hold

i. $\{u(t)\}$ is a continuous and $\mathcal{F}_t$-adapted;

ii. $\{f(u(t), t)\} \in \mathcal{L}^1([t_0, T]; \mathbb{R}^d)$ and $\{B(u(t), t)\} \in \mathcal{L}^2([t_0, T]; \mathbb{R}^{d\times n})$;

iii. equation 4.5 holds for every $t \in [t_0, T]$ with probability 1.

A solution $\{u(t)\}$ is said to be unique if for any other solution $\{\bar{u}(t)\}$ we have the following condition

$$P\{u(t) = \bar{u}(t) \text{ for all } t_0 \leq t \leq T\} = 1$$

Lemma 4.2.2. *for any $v > 0$, the following inequality hols*

$$v \leq 2(v + 1 - \ln(v)) - (4 - 2\ln 2)$$

Proof. The proof is straight forward, since the function $f(v) = v + 2 - 2\ln(v)$ has a minimum at $v = 2$. $\square$

In general, d-dimensional stochastic equation can be written as

$$du(t) = f(u(t), t)dt + B(u(t), t)dW(t) \tag{4.6}$$

where $u(t) = (x_1(t), x_2(t), \cdots, x_d(t))$ with the initial $u(t_0) = u_0 \in \mathbb{R}^d$, and W(t) is the m-dimensional white noise defined on a complete probability space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, \mathbb{P})$.

It$\hat{o}$ Formula Define a differential operator L to be

$$L = \frac{\partial}{\partial t} + \sum_i = 1^d f_i(u, t)\frac{\partial}{\partial x_i} + \frac{1}{2}\sum_{i,j=1}^{d}[W^T(u, t)W(u, t)]_{ij}\frac{\partial^2}{\partial u_i \partial u_j}$$

Now, let $V(u, t)$ be a nonnegative twice differentiable function define on $\mathbb{R}^d \times [t_0, \infty)$, when the operator act on V, we get:

$$LV = V_t + V_u f_i(u, t) + \frac{1}{2}trace[W^T(u, t)V_{uu}W(u, t)]$$

where $v_t = \frac{\partial V}{\partial t}$, $V_u = (\frac{\partial V}{\partial x_1}, \frac{\partial V}{\partial x_2}, \cdots \frac{\partial V}{\partial x_d})$, and $V_{uu} = \left(\frac{\partial^2 V}{\partial u_i \partial u_j}\right)_{d\times d}$.

Then It$\hat{o}$ formula defined as

$$dV = LV(u(t), t)dt + V_u(u(t), t)B(u(t), t)dW(t) \tag{4.7}$$

Now we will discuss the solution properties of the system (4.1 - 4.3) .

4.3 Existence, Uniqueness, and Positiveness of Solution.

When we study the dynamics of a population model the most important properties are to show that the solution is global and positive for all time $t \geq 0$. The coefficients of the above stochastic system are locally Lipschiz and satisfy the linear growth condition (see [**?**])

Theorem 4.3.1. *For any initial value $u_0 \in \mathbb{R}^3_+$, there exists a unique solution for the system (4.1 - 4.3) for all $t \geq 0$. Furthermore, the solution will remain positive for all time $t \geq 0$ with probability 1, i.e., $u(t) \in \mathbb{R}^3_+$ for all $t \geq 0$ almost surely.*

Proof. It is clear that we have a unique local solution since all the coefficients of the equations (4.1 - 4.3) are continuous and locally Lipschiz, in other word for any initial $u_0 \in \mathbb{R}^3_+$, there is a unique local solution $u(t) \in \mathbb{R}^3_+$ for all $t \in [0, \tau)$. To show the solution is global we need to show that $\tau = \infty$ almost surely.

Let $n_0 \geq 0$ be large enough such that $u_0 \in [1/n_0, n_0]$, and let $n > n_0$ and define

$$\tau_n = \inf\{t \in [0, \tau) : u(t) \notin (1/n, n)\}$$

Now we want to show that τ_n is an empty set, and we assume also that $\inf \Phi = \infty$. Clearly τ_n is an increasing sequence as n increased. Let $\tau_\infty = \lim_{n\to\infty} \tau_n$, we have $\tau_\infty < \tau$ a.s. by definition.

To complete this proof we need to show that $\tau_\infty = \infty$ a.s. with implies that $\tau = \infty$. By contradiction if the statement is not true then there is a pair of constant $T > 0$ and $\epsilon \in (0, 1)$ such that $P\{\tau_\infty > T\} > \epsilon$ which means there is an integer $n_1 > n_0$ such that

$$P\{\tau_n < T\} \geq \epsilon \quad \text{for all} \quad n \geq n_1. \tag{4.8}$$

Now let us define a function $G(u)$ as

$$V(u(t)) = V(x(t), y(t), z(t)) = x + 1 - \ln x + y + 1 - \ln y + z + 1 - \ln z$$

which is a non-negative function because of the inequality $v+1-\ln v \geq 0$ see [3]. By applying Itô formula on $G(u)$ we get

$$\begin{aligned}
dV &= [(1-\frac{1}{x})(\lambda-\mu_1 x-(1-\eta)\beta xz+qy)\\
&\quad +(1-\frac{1}{y})((1-\eta)\beta xz-\mu_2 y-qy)\\
&\quad +(1-\frac{1}{z})((1-\epsilon)py-\mu_3 z)+\frac{1}{2}(\sigma_1^2+\sigma_2^2+\sigma_3^2)]dt\\
&\quad +\sigma_1(x-1)dW_1+\sigma_2(y-1)dW_2+\sigma_3(z-1)dW_3\\
&= [\lambda-\mu_1 x-(1-\eta)\beta xz+qy-\frac{\lambda}{x}+\mu_1+(1-\eta)\beta z+q\frac{y}{x}\\
&\quad +(1-\eta)\beta xz-\mu_2 y-qy-(1-\eta)\beta\frac{xz}{y}+\mu_2+q\\
&\quad +(1-\epsilon)py-\mu_3 z-(1-\epsilon)p\frac{y}{z}+\mu_3]dt+\frac{1}{2}(\sigma_1^2+\sigma_2^2+\sigma_3^2)]dt\\
&\quad +\sigma_1(x-1)dW_1+\sigma_2(y-1)dW_2+\sigma_3(z-1)dW_3\\
&= [\lambda+\mu_1+\mu_2+\mu_3+q+\frac{1}{2}(\sigma_1^2+\sigma_2^2+\sigma_3^2)+(1-\epsilon)py+(1-\eta)\beta z\\
&\quad -(\mu_1 x+\mu_2 y+\mu_3 z+\frac{\lambda}{x}+\frac{qy}{x}+(1-\eta)\frac{\beta xz}{y})]dt\\
&\quad +\sigma_1(x-1)dW_1+\sigma_2(y-1)dW_2+\sigma_3(z-1)dW_3
\end{aligned}$$

this implies that

$$\begin{aligned}
dV &\leq [\lambda+\mu_1+\mu_2+\mu_3+q+\frac{1}{2}(\sigma_1^2+\sigma_2^2+\sigma_3^2)+(1-\epsilon)py+(1-\eta)\beta z]dt\\
&\quad +\sigma_1(x-1)dW_1+\sigma_2(y-1)dW_2+\sigma_3(z-1)dW_3
\end{aligned}$$

Let $a=\lambda+\mu_1+\mu_2+\mu_3+q+\frac{1}{2}(\sigma_1^2+\sigma_2^2+\sigma_3^2)$, and $b=\max\{(1-\epsilon)p,(1-\eta)\beta\}$ and since we have $v \leq v+1-\ln v$ then we get

$$dV(t) \leq [a+bV(t)]dt+\sigma_1(x-1)dW_1+\sigma_2(y-1)dW_2+\sigma_3(z-1)dW_3$$

let $c = \max\{a, b\}$ and integrate the above inequalty, if $t_1 \leq T$ we get

$$\begin{aligned}\int_0^{\tau_n \wedge t_1} dV(u(t)) &\leq \int_0^{\tau_n \wedge t_1} c(1 + V(u(t)))dt \\ &+ \int_0^{\tau_n \wedge t_1} \sigma_1(x-1)dW_1 + \int_0^{\tau_n \wedge t_1} \sigma_2(y-1)dW_2 + \int_0^{\tau_n \wedge t_1} \sigma_3(z-1)dW_3\end{aligned}$$

by definition this implies that

$$\begin{aligned}EV(u(\tau_n \wedge t_1)) &\leq V(u_0) + E\int_0^{\tau_n \wedge t_1} c(1 + V(u(t)))dt, \\ &\leq V(u_0) + ct_1 + cE\int_0^{\tau_n \wedge t_1} V(u(t))dt, \\ &\leq V(u_0) + cT + cE\int_0^{t_1} V(\tau_n \wedge t_1)dt, \\ &= V(u_0) + cT + c\int_0^{t_1} EV(\tau_n \wedge t_1)dt,\end{aligned}$$

From the Gronwall inequality we have

$$EV(\tau_n \wedge t_1) \leq c_1 = (V(u_0) + cT)e^{cT} \tag{4.9}$$

Set $\Omega_n = \{\tau_n \leq T\}$ for $n \leq n_1$ and by inequality 4.8, $P(\Omega_n) \geq \epsilon$. Notice that there is some of $x, y,$ or z such that $u(\tau_n, \omega) = n$ or $1/n$, for every $\omega \in \Omega$ that means $V(u(\tau_n, \omega))$ is greater than $n - 1 - \ln(n)$ and $\frac{1}{n} + 1 - \ln(1/k) = \frac{1}{n} + 1 + \ln(n)$, i.e.,

$$V(u(\tau_n, \omega)) \geq [n - 1 - \ln(n)] \wedge [(1/n) + 1 + \ln(n)] .$$

from the inequalities 4.8 and 4.9 we get

$$\begin{aligned}c_1 &\geq E[1_{\Omega_n}(\omega)V(u(tau_n, \omega))] \\ &\geq E\left([n - 1 - \ln(n)] \wedge [(1/n) + 1 + \ln(n)]\right),\end{aligned}$$

where 1_{Ω_n} is the indicator function of Ω_n, passing the limit for $n \to \infty$ gives $c_1 = \infty$ which a contradiction. Therefore $\tau_\infty = \infty$ a.s., which complete the proof. $\square$

4.4 Stability Analysis

In this section we discuss the stability analysis of the system (4.1 - 4.3), but first let us recall some definitions and theorems that we need in this process, you can find more details in [2] and [24].

Definition 4.4.1 ([2], page 110, 119)**.** (i) The trivial solution of equation 4.5 is said to be stable in probability if for every $\epsilon \in (0,1)$ and $r > 0$ there is $\delta = \delta(\epsilon, r, t_0) > 0$ such that

$$\mathbb{P}\{|u(t; t_0, u_0)| < r \text{ for all } t \geq t_0\} \geq 1 - \epsilon$$

whenever $|u_0| < \delta$. Otherwise, it is said to be stochastically unstable.

(ii) The trivial solution is said to be stochastically asymptotically stable if it is stochastically stable and for every $\epsilon \in (0,1)$ and $r > 0$ there is $\delta = \delta(\epsilon, r, t_0) > 0$ such that

$$\mathbb{P}\{\lim_{t\to\infty} u(t; t_0, u_0) = 0\} \geq 1 - \epsilon$$

whenever $|u_0| < \delta$.

(iii) The trivial solution is said to be stochastically asymptotically stable in the large if it is stochastically stable and, moreover, for all $u_0 \in \mathbb{R}^d$ and $r > 0$ there is $\delta = \delta(\epsilon, r, t_0) > 0$ such that

$$\mathbb{P}\{\lim_{t\to\infty} u(t; t_0, u_0) = 0\} = 1.$$

(iv) The trivial solution of equation 4.5 is said to be almost surely exponentially stable if

$$\lim_{t\to\infty} \sup \frac{1}{t} \ln |u(t; t_0, u_0)| < 0$$

for all $u_0 \in \mathbb{R}^d$.

Notice in our system the first equation 4.1 has no direct equilibrium point in $\mathbb{R}$, but for 4.2 and 4.3 they do have equilibrium point at $(y, z) = (0, 0)$. In the following theorem we will show that the trivial solution $(0, 0)$. For now let us focus on y, z and we will come back to x and show it is stable in distribution. The coming theorem shows that 4.2 and 4.3 are exponentially stable, under certain conditions on the parameters.

Theorem 4.4.2. *In the system* $(4.1 - 4.3)$, $y(t)$ *and* $z(t)$ *are almost surely exponentially stable if the following conditions hold:*

(a) $(1-\epsilon)p - q - \mu_2 + \frac{1}{2}\sigma_2^2 < 0$;

(b) $[(1-\eta)\beta\gamma - \mu_3][(1-\epsilon)p - q - \mu_2] \leq [1-\epsilon)p - q - \mu_2 + \frac{1}{2}\sigma_2^2][(1-\eta)\beta\gamma - \mu_3 + \frac{1}{2}\sigma_3^2]$.

where $\gamma = \max\{x\}$.

Proof. By adding equations 4.2 and 4.3 we get

$$d(y+z) = [((1-\epsilon)p - \mu_2 - q)y + ((1-\eta)\beta x - \mu_3)z]\, dt + \sigma_2 y dW_2 + \sigma_3 z dW_3 \qquad (4.10)$$

Define $V(y, z) = \ln(y(t) + z(t))$ for $y, z \in \mathbb{R}_+$, then Itô formula gives

$$\begin{aligned}
dV &= \left[\frac{1}{y+z}[((1-\epsilon)p - q - \mu_2)y] + \frac{1}{y+z}[((1-\eta)\beta x - \mu_3)z] + \frac{1}{2}\frac{\sigma_2^2 y^2}{(y+z)^2} + \frac{1}{2}\frac{\sigma_3^2 z^2}{(y+z)^2}\right] dt \\
&\quad + \frac{y}{y+z}\sigma_2 dW_2 + \frac{z}{y+z}\sigma_3 dW_3 \\
&= \frac{1}{(y+z)^2}\left[(y+z)[((1-\epsilon)p - q - \mu_2)y + ((1-\eta)\beta x - \mu_3)z] + \frac{1}{2}\sigma_2^2 y^2 + \frac{1}{2}\sigma_3^2 z^2\right] \\
&\quad + \frac{y}{y+z}\sigma_2 dW_2 + \frac{z}{y+z}\sigma_3 dW_3 \\
&\leq \frac{1}{(y+z)^2}\left[(y+z)[((1-\epsilon)p - q - \mu_2)y + ((1-\eta)\beta\gamma - \mu_3)z] + \frac{1}{2}\sigma_2^2 y^2 + \frac{1}{2}\sigma_3^2 z^2\right] \\
&\quad + \frac{y}{y+z}\sigma_2 dW_2 + \frac{z}{y+z}\sigma_3 dW_3, \\
&= \frac{1}{(y+z)^2}\left\{\begin{pmatrix} y & z \end{pmatrix}\begin{pmatrix} (1-\epsilon)p - q - \mu_2 + \frac{1}{2}\sigma_2^2 & (1-\eta)\beta\gamma - \mu_3 \\ (1-\epsilon)p - q - \mu_2 & (1-\eta)\beta\gamma - \mu_3 + \frac{1}{2}\sigma_3^2 \end{pmatrix}\begin{pmatrix} y \\ z \end{pmatrix}\right\} \\
&\quad + \frac{y}{y+z}\sigma_2 dW_2 + \frac{z}{y+z}\sigma_3 dW_3
\end{aligned}$$

If the theorem conditions hold, then the matrix

$$\begin{pmatrix} (1-\epsilon)p - q - \mu_2 + \frac{1}{2}\sigma_2^2 & (1-\eta)\beta\gamma - \mu_3 \\ (1-\epsilon)p - q - \mu_2 & (1-\eta)\beta\gamma - \mu_3 + \frac{1}{2}\sigma_3^2 \end{pmatrix}$$

is negative-definite, that means it has negative eigenvalue, let λ_{max} be the largest eigenvalue then the above inequality can be written as

$$dV(y,z) \quad \leq \quad \left[-|\lambda_{max}| \frac{1}{(y+z)^2}(y^2+z^2) \right] dt + \frac{\sigma_2 y}{y+z} dW_2 + \frac{\sigma_3 z}{y+z} dW_3$$

Using the fact that $y^2 + z^2 \geq 2yz$ we get $(y^2+z^2)/(y+z)^2 \geq 1/2$. Hence

$$dV = d\ln(y(t)+z(t)) \leq -\frac{1}{2}|\lambda_{max}|dt + \frac{\sigma_2 y}{y+z} dW_2 + \frac{\sigma_3 z}{y+z} dW_3$$

By integrating the above inequality, and using the fact from [2] that

$$\limsup_{t\to\infty} \frac{1}{t}|W_i(t)| = 0 \quad \text{for } i = 2,3,$$

we get

$$\limsup_{t\to\infty} \frac{1}{t} \ln(y(t)+z(t)) \leq -\frac{1}{2}|\lambda_{max}| < 0 \quad \text{almost surely}$$

This completes the proof. □

Remark 4.4.3. We got stability of the components y and z without the help of the productive number R_0 whether $R_0 < 1$ or $R_0 > 1$. Notice also the conditions in Theorem 4.4.2 can not hold in the deterministic case when $\sigma_2 = \sigma_3 = 0$.

Now, we want to show the stability of the first component $x(t)$, we will show that $x(t)$ is stable in distribution, which means it is stable around the mean value λ/μ_1. Before doing that let us first introduce some of the Lemmas that we need.

Lemma 4.4.4. *Let $W_1(t)$ be one-dimensional standard Brownian motion, then*

$$E\{e^{\sigma_1(W_1(t)-W_1(s))}\} = e^{\frac{\sigma_1^2}{2}(t-s)}, \quad \textit{for} \;\; s \leq t.$$

Proof. Let $W = W_1(t) - W_1(s)$, from the definition of the Brownian motion, we have $W \sim N(0, t-s)$, thus

$$\begin{aligned} E\{e^{\sigma_1 W}\} = E\{e^{\sigma_1 (W_1(t) - W_1(s))}\} &= \int_{-\infty}^{\infty} e^{\sigma_1 w} \cdot \frac{1}{\sqrt{2\pi(t-s)}} \cdot e^{-\frac{w^2}{2(t-s)}}\, dw \\ &= \frac{1}{\sqrt{2\pi(t-s)}} \int_{-\infty}^{\infty} e^{-\frac{(w+\sigma_1(t-s))^2}{2(t-s)}} \cdot e^{\frac{\sigma_1^2}{2}(t-s)}\, dw \\ &= e^{\frac{\sigma_1^2}{2}(t-s)}. \end{aligned}$$

□

Lemma 4.4.5. *Let $x_1(t)$ be a solution of*

$$dx_1(t) = (\lambda - \mu_1 x_1(t))dt + \sigma_1 x_1(t) dW_1(t) \tag{4.11}$$

then $\lim_{t\to\infty} E[x_1(t)] = \lambda/\mu_1$, *for any initial* $x_1(0) \in \mathbb{R}_+$.

Proof. For any initial value $x_1(0) \in \mathbb{R}_+$, there is a unique solution $x_1(t)$ of equation 4.11 which as the following explicit form

$$x_1(t) = x_1(0) e^{-(\mu_1 + \frac{1}{2}\sigma_1^2)t} + \lambda \int_0^t e^{-(\mu_1 + \frac{1}{2}\sigma_1^2)(t-s)} \cdot e^{\sigma_1(W_1(t) - W_1(s))}\, ds$$

By taking the expectation of the above equation with the fact that $W_1(0) = 0$ we get

$$E[x_1(t)] = E\left[x_1(0) e^{-(\mu_1 + \frac{1}{2}\sigma_1^2)t} + \lambda \int_0^t e^{-(\mu_1 + \frac{1}{2}\sigma_1^2)(t-s)} \cdot e^{\sigma_1(W_1(t) - W_1(s))}\, ds\right]$$

By applying Lemma 4.4.5 we get

$$E[x_1(t)] = x_1(0) e^{-\mu_1 t} + \frac{\lambda}{\mu_1}(1 - e^{-\mu_1 t})$$

Thus,

$$\lim_{t\to\infty} E[x_1(t)] = \frac{\lambda}{\mu_1}$$

□

Lemma 4.4.6. *If $x_1(t)$ is a solution of equation 4.11, then for any initial value $x_1(0) \in \mathbb{R}_+$ we have the following*

i. *$x_1(t)$ admits a unique stationary distribution π.*

ii. *$x_1(t)$ satisfied the following*

$$\lim_{t\to\infty} \frac{1}{t}\int_0^t x_1(s)ds = \int_0^\infty x_1 \pi dx_1 = \int_0^\infty f(x_1)dx_1 = \frac{\lambda}{\mu_1}$$

Proof. i. Define a twice continuously differentiable function $V(x_1) = x_1 - 1 - \ln x_1$, then from Itô formula we get

$$LV(x_1) = (1 - \frac{1}{x_1})(\lambda - \mu_1 x_1) + \frac{1}{2}\sigma_1^2 = -\mu - 1 - \frac{\lambda}{x_1} + \lambda + \mu_1 + \frac{1}{2}\sigma_1^2.$$

By choosing sufficiently small ϵ and let $\mathbb{D} = (\epsilon, 1/\epsilon)$, then

$$LV(x_1) \leq -1, \quad \text{for any} \quad x_1 \in \mathbb{D}^c.$$

This completes the proof.

iii. From the ergodicity of x_1 we get

$$\mathbb{P}\left\{\lim_{t\to-\infty} \frac{1}{t}\int_0^t x_1(s)ds = \int_0^\infty x_1\pi(dx_1)\right\} = 1$$

Hence

$$\lim_{t\to-\infty} \frac{1}{t}\int_0^t x_1(s)ds = \int_0^\infty x_1\pi(dx_1) = \int_0^\infty f(x_1)x_1 dx_1 = \frac{\lambda}{\mu_1}, \quad \text{Almost surely.}$$

where we used the fact $\lim_{t\to\infty} E[x_1(t)] = \lambda/\mu_1$.

□

Theorem 4.4.7. *Let $(x(t), y(t), z(t))$ be a solution of the system $(4.1 - 4.3)$ and $x_1(t)$ is a solution of equation 4.11, the under the condition of Theorem 4.4.2 we have*

$$\lim_{t\to\infty}[x(t) - x_1(t)] = 0 \quad \textit{in probability}. \tag{4.12}$$

Proof. From the comparison theorem of stochastic differential equations, we have $x(t) \leq x_1$ i.e.,

$$x(t) - x - 1(t) \leq 0 \tag{4.13}$$

to complete this proof we need to show that $\liminf_{t\to\infty}[x(t)-x_1(t)] \geq 0$ a.s. Let us introduce the following stochastic differential equation, which will help us in this proof

$$dx_r(t) = [\lambda - (\mu_1 + r)x_r(t)]dt + \sigma_1 x_r(t)dW_1 \tag{4.14}$$

with the initial $x_r(0) = x(0)$. Remember our main equation 4.1.

$$dx(t) = [\lambda - \mu_1 x - (1-\eta)\beta xz + qy]dt + \sigma_1 x dW_1(t)$$

Recall equation 4.11

$$dx_1(t) = (\lambda - \mu_1 x_1(t))dt + \sigma_1 x_1(t)dW_1(t)$$

from the fact that

$$\liminf_{t\to\infty}[x(t)-x_1(t)] = \liminf_{t\to\infty}(x(t)-x_r(t))+(x_r(t)-x_1(t)] \geq \liminf_{t\to\infty}[x(t)-x_r(t)]+\liminf_{t\to\infty}[x_r(t)-x_1(t)].$$

we will prove the following claims.

Claim 1: $\liminf_{t\to\infty}[x(t) - x_r(t)] \geq 0$ a.s.

Proof. By subtracting the above equation we get

$$\begin{aligned} d(x(t) - x_r(t)) &= [-\mu_1(x - x_r) + rx_r - (1-\eta)\beta xz + qy]dt + \sigma - 1(x - x_r)dW_1 \\ &= [-(\mu_1 + r)(x - x_r) + (r - (1-\eta)\beta z)x + qy]\, dt + \sigma_1(x - x_r)dW_1. \end{aligned}$$

which as a solution

$$x(t) - x_r(t) = \phi(t) \int_0^t \phi^{-1}(s)((r - (1-\eta)\beta z)x + qy)dx(s)$$

where

$$\phi(t) = e^{-(\mu_1 + r + \frac{1}{2}\sigma_1^2)t + \sigma_1 W_1(t)}.$$

From Theorem 4.4.2 we have that $y(t) \to 0$ and $z(t) \to 0$ a.s. as $t \to \infty$.

Thus, for all $\omega \in \Omega$, if $t > T$, then

$$x(t) - x_r(t) = \phi(t) \left(\int_0^T \phi^{-1}(s)((r - (1-\eta)\beta z)x + qy)dx(s) + \int_T^t \phi^{-1}(s)((r - (1-\eta)\beta z)x + qy)dx(s) \right)$$

Hence $x(t) - x_r(t) \geq \phi(t)\kappa(T)$, where

$$\kappa(T) = \int_0^T \phi^{-1}(s)((\epsilon - (1-\eta)\beta z)x(s) + qy(s))dx(s)$$

Since $|\kappa(T)| < \infty$ and $\phi(t) \to 0$ a.s.

Therefore,

$$\liminf_{t\to\infty} [x(t) - x_r(t)] \geq 0 \qquad a.s. \tag{4.15}$$

□

Claim 2: $\liminf_{t\to\infty}[x_r(t) - x_1(t)] \geq 0$ a.s.

Proof. From equations 4.1 and 4.11 we have

$$d(x_r(t) - x_1(t)) = [-\mu_1(x_r(t) - x_1(t)) - rx_r]dt + \sigma_1(x_r(t) - x_1(t))dW(t).$$

which has a solution in the form

$$x_r(t) - x_1(t) = -r \int_0^t x_r e^{-(\mu_1+\sigma_1^2/2)(t-s)-\sigma_1(W_1(t)-W_1(s))} ds$$

x_r is the solution for equation 4.14, which has the following explicit form

$$x_r = \lambda \int_0^t e^{-(\mu_1+r+\sigma_1^2/2)(t-s)+\sigma_1(W_1(t)-W_1(s))} ds$$

Therefore,

$$|x_r(t) - x_1(t)| = r \int_0^t x_r e^{-(\mu_1+\sigma_1^2/2)(t-s)-\sigma_1(W_1(t)-W_1(s))} ds.$$

By taking the expectation and applying the result in Lemma 4.4.4 we get

$$\begin{aligned} E|x_r(t) - x_1(t)| &= rE\left[\int_0^t x_r e^{-(\mu_1+\sigma_1^2/2)(t-s)-\sigma_1(W_1(t)-W_1(s))} ds\right] \\ &= r\int_0^t E\left[x_r e^{-(\mu_1+\sigma_1^2/2)(t-s)-\sigma_1(W_1(t)-W_1(s))} ds\right] \\ &= r\int_0^t E\left[x_r e^{-(\mu_1+\sigma_1^2/2)(t-s)}\right] \cdot E\left[e^{-\sigma_1(W_1(t)-W_1(s))} ds\right] \\ &= r\int_0^t e^{-\mu_1(t-s)} E[x_r] ds, \qquad \text{Using Lemma 4.4.4.} \end{aligned}$$

But

$$E[x_r] = \lambda \int_0^t e^{-(\mu_1+r)(t-s)} ds \le \frac{\lambda}{\mu_1 + r}.$$

Thus,

$$E|x_r(t) - x_1(t)| \le \frac{\lambda r e^{-\mu_1 t}}{\mu_1 + r}(e^{\mu_1 t} - 1)$$

That means

$$\lim_r \to 0 \lim_t \to E|x_r(t) - x_1(t)| = 0$$

That implies

$$\lim_{r\to 0} \lim_{t\to\infty} |x_r(t) - x_1(t)| = 0 \qquad \text{In probability.} \tag{4.16}$$

□

Therefore, 4.13, 4.15, and 4.16 complete the proof. □

Theorem 4.4.8. *Let* $(x(t), y(t), z(t))$ *be the solution of the system* $(4.1 - 4.3)$ *with the initial* $(x(0), y(0), z(0)) \in \mathbb{R}^3_+$*, and assume that the conditions of Theorem 4.4.2 hold, then*

$$\lim_{t\to\infty} \frac{1}{t}\int_0^t x(s)ds = \frac{\lambda}{\mu_1}, \quad a.s. \text{ and } \quad x(t) \to \pi \quad as \quad t \to \infty,$$

where, $x(t) \to \pi$ *means the convergence in distribution.*

Proof. The proof follows directly from Lemma 4.4.6 and Theorem 4.4.7. □

4.5 Existence of Ergodic Stationary Distribution.

Let $U(t)$ be a Markov process in $\mathbb{R}^d$ represented by the following stochastic differential equations.

$$dU(t) = f(U(t))dt + \sum_{k=1}^{n} B_k(U(t))dW_k(t) \tag{4.17}$$

The diffusion matrix is define as

$$A(u) = (a_{ij}(u)), \quad \text{where} \quad a_{ij}(u) = \sum_{k=1}^{n} B_k^i(u)B_k^j(u) \tag{4.18}$$

Lemma 4.5.1. *(See [36,37]) The model 4.6 is positive recurrent if there exists a boundary open subset $D \subset \mathbb{R}^d$ with a regular boundary and*

(A1) There is a positive number M such that

$$\sum_{i,j=1}^{d} a_{ij}(u)\xi_i\xi_j \geq |\xi|^2, \quad u \in D \text{ and } \xi \in \mathbb{R}^d. \tag{4.19}$$

(A2) There exists a nonnegative C^2-function $V : D^c \to \mathbb{R}$ such that $LV(u) < -\theta$ for some $\theta > 0$, and any $u \in D^c$. Moreover, the positive recurrent process $u(t)$ has a unique stationary distribution $\pi(\cdot)$, and

$$\mathbb{P}\{\lim_{T\to\infty} \frac{1}{T}\int_0^T f(U(t))dt = \int_{\mathbb{R}^d} f(u)\mu(du)\} = 1 \tag{4.20}$$

for all $u \in \mathbb{R}^d$, where $f(\cdot)$ is an integrable function with respect to the measure $\pi(\cdot)$.

Theorem 4.5.2. *Assume that $R_0 > 1$. Under conditions $\sigma_1^2 \geq \mu_1 - \mu^*$, $\sigma_2^2 \geq \mu_2 - \mu^* + \frac{1}{2}(1-\epsilon)p$, and $\mu_3 \geq \mu_3 - \frac{1}{2}(1-\epsilon)p$. The system (4.1 -4.3) has a unique ergodic stationary distribution $\pi(\cdot)$.*

Proof. We have seen that the system 4.1 - 4.3 has a unique positive solution $x(t), y(t), z(t)$ for any initial value $(x_0, y_0, z_0) \in \mathbb{R}_+^3$.

The diffusion matrix of the system is given by

$$A = \begin{pmatrix} \sigma_1^2 x^2 & 0 & 0 \\ 0 & \sigma_2^2 y^2 & 0 \\ 0 & 0 & \sigma_3^2 z^2 \end{pmatrix}$$

Then

$$\sum_{i,j=1}^{3} a_{ij}(u)\xi_i\xi_j = \sigma_1^2 x^2 \xi_1^2 + \sigma_2^2 y^2 \xi_2^2 + \sigma_3^2 z^2 \xi_3^2 \geq M|\xi|^2, \tag{4.21}$$

where, $M = \min\{\sigma_1^2 x^2, \sigma_2^2 y^2, \sigma_3^2 z^2\}$, thus condition $(A1)$ satisfied.

Now, we want to show that condition $(A2)$ is also satisfied by constructing a nonnnegative Lyapunov function V such that $LV < 0$.

Consider the positive functions

$$V_1(x,y) = \frac{1}{2}(x - \bar{x} + y - \bar{y})^2, \quad \text{and} \quad V_2(z) = \frac{1}{2}(z - \bar{z})^2$$

Now let

$$V(x,y,z) = V_1(x,y) + V_2(z) = \frac{1}{2}(x - \bar{x} + y - \bar{y})^2 + \frac{1}{2}(z - \bar{z})^2$$

By applying It$\hat{o}$ formula we get

$$LV_1(x,y) = (x - \bar{x} + y - \bar{y})(\lambda - \mu_1 x - \mu_2 y) + \frac{1}{2}\sigma_1^2 x^2 + \frac{1}{2}\sigma_2^2 y^2$$

since we have $\lambda - \mu_1\bar{x} - \mu_2\bar{y} = 0, \quad \Rightarrow \quad \lambda = \mu_1\bar{x} + \mu_2\bar{y}$, then we get

$$\begin{aligned} LV_1(x,y) &= (x - \bar{x} + y - \bar{y})[-\mu_1(x - \bar{x}) - \mu_2(y - \bar{y})] + \frac{1}{2}\sigma_1^2 x^2 + \frac{1}{2}\sigma_2^2 y^2, \\ &= -\mu_1(x - \bar{x})^2 - \mu_2(y - \bar{y})^2 - \mu_1(x - \bar{x})(y - \bar{y}) - \mu_2(x - \bar{x})(y - \bar{y}) + \frac{1}{2}\sigma_1^2 x^2 + \frac{1}{2}\sigma_2^2 y^2 \end{aligned}$$

By using the fact that, $x^2 \leq 2(x-a)^2 + 2a^2$, we get

$$\frac{1}{2}\sigma_1^2 x^2 \leq \sigma_1^2 (x - \bar{x})^2 + \sigma_1^2 \bar{x}^2 \quad \text{and} \quad \frac{1}{2}\sigma_2^2 y^2 \leq \sigma_2^2 (y - \bar{y})^2 + \sigma_2^2 \bar{y}^2$$

thus

$$
\begin{aligned}
LV_1(x,y) &\leq -\mu_1(x-\bar{x})^2 - \mu_2(y-\bar{y})^2 - 2\mu^*(x-\bar{x})(y-\bar{y}) + \sigma_1^2(x-\bar{x})^2 + \sigma_1^2\bar{x}^2 \\
&\quad +\sigma_2^2(y-\bar{y})^2 + \sigma_2^2\bar{y}^2
\end{aligned}
$$

where $\mu^* = \min\{\mu_1, \mu_2\}$, and since $-2\mu^*(x-\bar{x})(y-\bar{y}) \leq \mu * (x-\bar{x})^2 + \mu^*(y-\bar{y})^2$, then

$$
LV_1(x,y) \leq -(\mu_1 - \mu^* - \sigma_1^2)(x-\bar{x})^2 - (\mu_2 - \mu^* - \sigma_2^2)(y-\bar{y})^2 + \sigma_1^2\bar{x} + \sigma_2^2\bar{y} \tag{4.22}
$$

Similarly,

$$
LV_2(z) \leq -(\mu_3 - \frac{1}{2}(1-\epsilon)p - \sigma_3^2)(z-\bar{z})^2 + \frac{1}{2}(1-\epsilon)p(y-\bar{y})^2 + \sigma_3^2\bar{z}^2
$$

Thus,

$$
\begin{aligned}
LV(x,y,z) &= LV_1(x,y) + LV_2(z) \\
&\leq -(\mu_1 - \mu^* - \sigma_1^2)(x-\bar{x})^2 - (\mu_2 - \mu^* - \sigma_2^2)(y-\bar{y})^2 + \sigma_1^2\bar{x} + \sigma_2^2\bar{y} \\
&\quad -(\mu_3 - \frac{1}{2}(1-\epsilon)p - \sigma_3^2)(z-\bar{z})^2 + \frac{1}{2}(1-\epsilon)p(y-\bar{y})^2 + \sigma_3^2\bar{z}^2 \\
&= -(\mu_1 - \mu^* - \sigma_1^2)(x-\bar{x})^2 - (\mu_2 - \mu^* + \frac{1}{2}(1-\epsilon)p - \sigma_2^2)(y-\bar{y})^2 - (\mu_3 - \frac{1}{2}(1-\epsilon)p - \sigma_3^2 \\
&\quad +\sigma_1^2\bar{x} + \sigma_2^2\bar{y} + \sigma_3^2\bar{z}^2 \\
&= -k_1(x-\bar{x})^2 - k_2(y-\bar{y})^2 - k_3(z-\bar{z})^2 + \omega
\end{aligned}
$$

where $k_1 = \mu_1 - \mu^* - \sigma_1^2$, $k_2 = \mu_2 - \mu^* + \frac{1}{2}(1-\epsilon)p - \sigma_2^2$, $k_3 = \mu_3 - \frac{1}{2}(1-\epsilon)p - \sigma_3^2$, and $\omega = \sigma_1^2\bar{x} + \sigma_2^2\bar{y} + \sigma_3^2\bar{z}^2$

Since k_1, k_2, k_3 are positive, and by the same computation in [38], we obtained

$$
\limsup_{t\to\infty} \frac{1}{t}\int_0^t [k_1(x(s)-\bar{x})^2 + k_2(y(s)-\bar{y})^2 + k_3(z(s)-\bar{z})^2]ds \leq \omega.
$$

then the ellipsoid

$$k_1(x-\bar{x})^2 + k_2(y-\bar{y})^2 + k_3(z-\bar{z})^2 + \omega = 0$$

lies entirely in $\mathbb{R}^3_+$, so we can take any neighborhood D of this ellipsoid, such that

$$LV(u) < -\theta, \quad \text{for all} \quad u \in D^c.$$

Therefore, condition (A2) also holds, and that completes the proof. □

4.6 Numerical Results for the stochastic model

In this section we discuss some of the numerical results of the system $(4.1-4.3)$ to support our previous analytic result. The method we use is Euler-Maruyama method. The approximate solution of the system we (4.1 - 4.3) can be written as follows

$$x_{k+1} = x_k + (\lambda - \mu_1 x_k - (1-\eta)\beta x_k z_k + q y_k)\Delta t + \sigma_1 x_k \Delta W_{1k} \quad (4.23)$$

$$y_{k+1} = y_k + ((1-\eta)\beta x_k z_k - \mu_2 y_k - q y_k)\Delta t + \sigma_2 y_k \Delta W_{2k} \quad (4.24)$$

$$z_{k+1} = z_k + ((1-\epsilon)p y_k - \mu_3 z_k)\Delta t + \sigma_3 z_k \Delta W_{3k} \quad (4.25)$$

where $\Delta W_{ik} = W_{i(k+1)} - W_{ik}$, for $i = 1, 2, 3$ which is normally distributed for more information about this method see [29, 32]. We used Matlab to simulate above system.

After we have chosen the parameters carefully such that the sufficient and necessary conditions in Theorem 4.4.2 hold, which are given below

parameters	λ	μ_1	μ_2	μ_3	β	η	ϵ	p	q	σ_1	σ_2	σ_3
values	100	20	5	7	0.6	0.6	0.2	2	5	–	–	–

Table 4.1:

we are going to represent the following numerical results dependent upon the values of σ_1, σ_2, and σ_3.

When $\sigma_1 = \sigma_2 = \sigma_3 = 0$ the stochastic model becomes deterministic, the solution given as follows

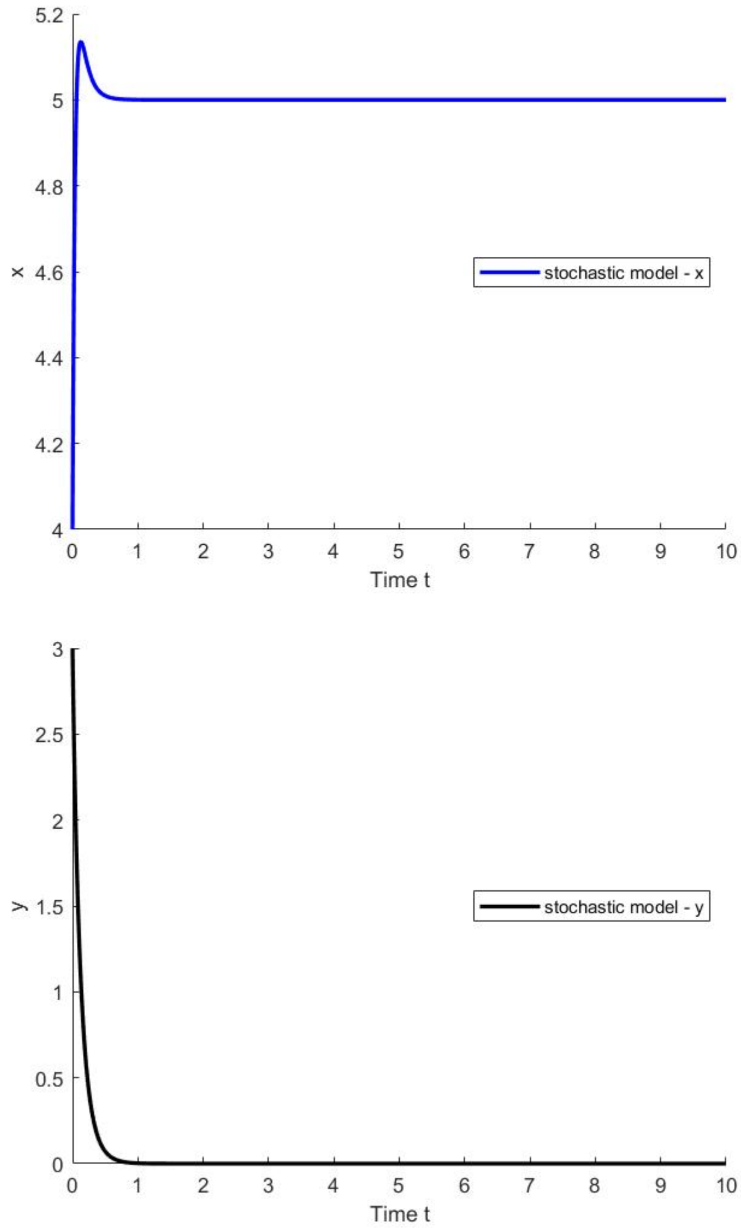


Figure 4.1: Stochastic model without noise

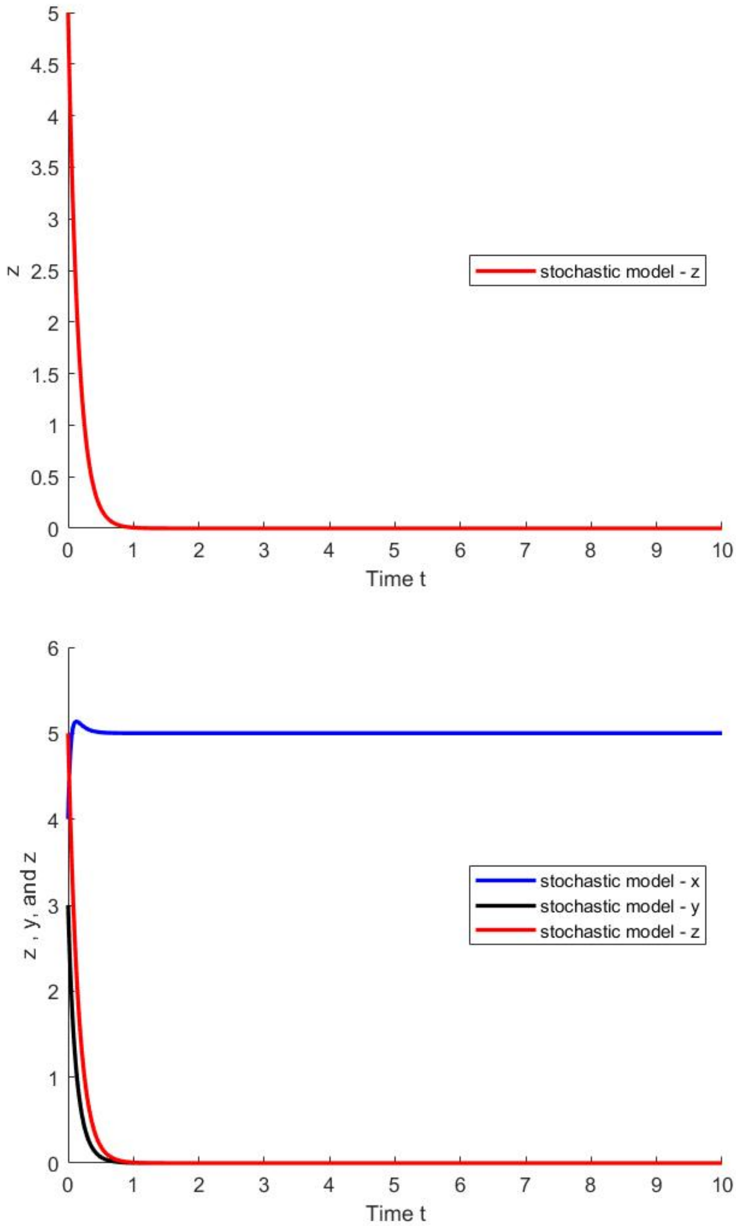
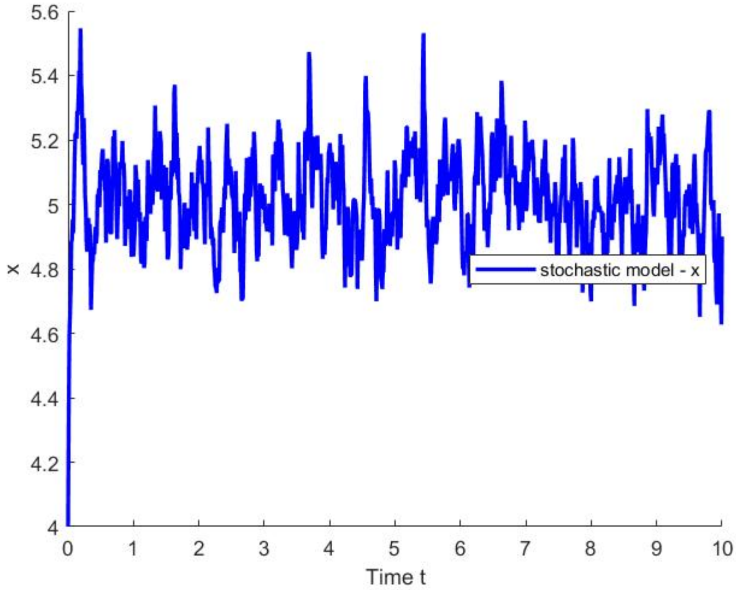


Figure 4.2: Stochastic model without noise

Figure 4.3 represents the stochastic solution of $x(t), y(t)$, and $z(t)$ with the noise $\sigma_1 = 1.2$, $\sigma_2 = 0.9$, and $\sigma_3 = 1.4$.



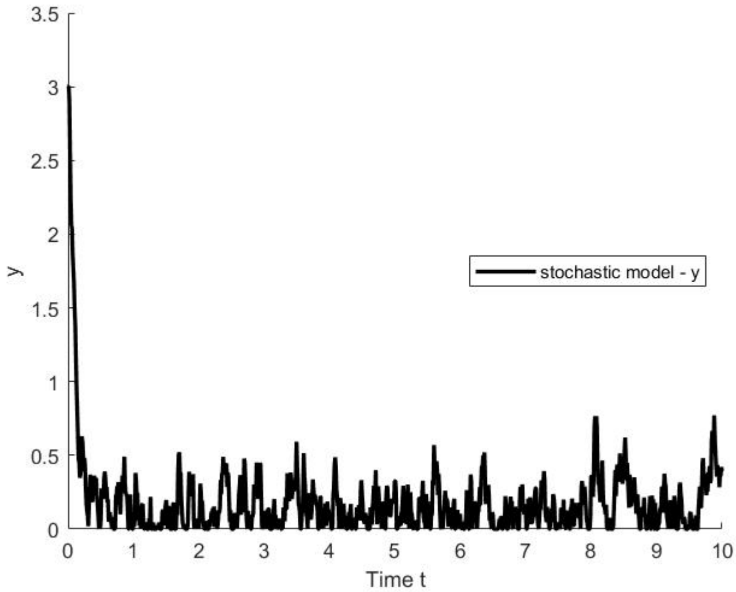


Figure 4.3: Stochastic model with large noise

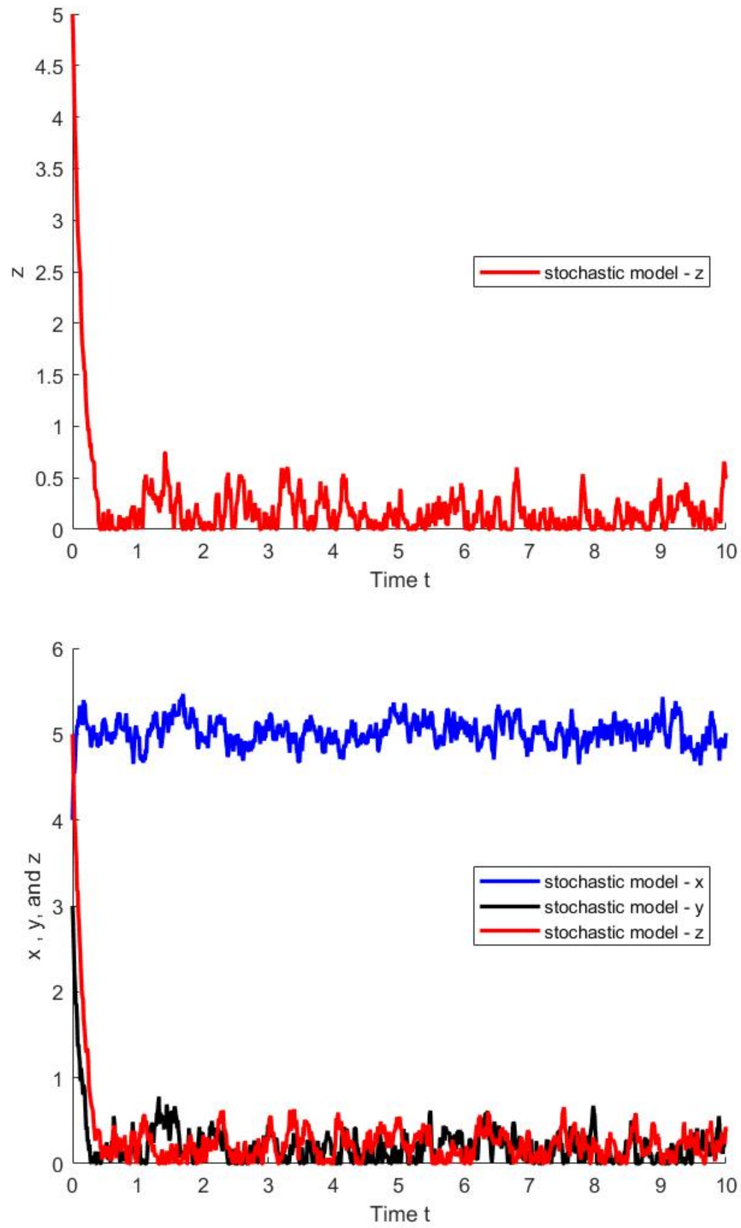


Figure 4.4: Stochastic model with large noise

Figure 4.5 shows the difference between stochastic model and deterministic model. The deterministic solution is represented by the dashed lines.

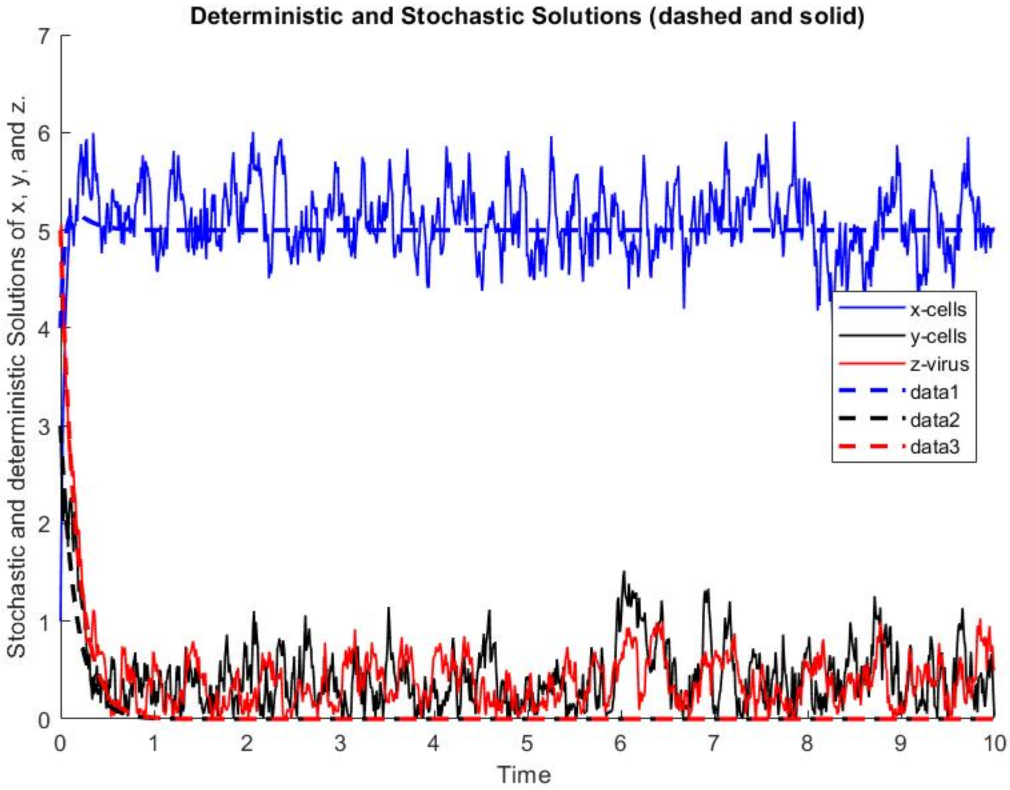


Figure 4.5: Combining Stochastic and Deterministic Solutions

Chapter 5

Conclusion

We have analyzed the stability of the HBV infection model using different approaches, we considered the autonomous, nonautonomous, and stochastic HBV infection models, with conclusions as follows.

Autonomous HBV Infection Model. We have studied the model 2.1 where all parameters are time-dependent. We have shown the basic properties of solutions (existence, uniqueness, and positiveness), then we found the system 2.1 has two (disease-free and endemic) equilibrium points. Then we discussed the stability analysis at each of them, and we have got two necessary conditions that ensure the stability of the system 2.1.

Nonautonomous HBV Infection Model. The nonautonomous theory has been used to discuss the HBV infection model when the production rate of the uninfected cells is time-dependent $\lambda(t)$, we have also shown here the basic properties of solutions, then we prove the system (4.1-4.3) satisfied a uniform strictly contracting property when $\mu_2 > (1 - \epsilon)p$, we prove also the system has pullback attractor which exponentially stable under certain conditions.

Stochastic HBV Infection Model. We used tools from the stochastic dynamic systems to study the stability analysis of the stochastic HBV infection model (4.23-4.25), before doing that, we have shown the basic properties of solutions, then we studied the stability in two different ways. First, we prove that system 4.24 and 4.25 are exponential stable at $(0, 0)$, which is still the equilibrium point for 4.24 and 4.25, then we shown that 4.23 is stable in probability under some conditions. Secondly, we prove the systems (4.23-4.25) have a unique ergodic stationary distribution $\pi(\cdot)$.

Numerical Results. At the end of each chapter we have represented the numerical results of the HBV infection models. All the simulations codes are written in MATLAB, the parameters sets were chosen carefully such that the required conditions satisfied.

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