Journal of Applied Analysis and Computation
Volume 9, Number 4, August 2019, 1425–1442 Website:http://jaac.ijournal.cn
DOI:10.11948/2156-907X.20180270

ASYMPTOTIC BEHAVIOR OF A STOCHASTIC VIRUS DYNAMICS MODEL WITH INTRACELLULAR DELAY AND HUMORAL IMMUNITY*

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Abstract In this paper, we formulate a stochastic virus dynamics model with intracellular delay and humoral immunity. By constructing some suitable Lyapunov functions, we show that the solution of stochastic model is going around each of the steady states of the corresponding deterministic model under some conditions. Then, numerical simulations are given to support the theoretical results. Finally, we propose several more effective way to control the spread of the virus by analyzing the sensitivity of the threshold of spread.

Keywords Stochastic virus dynamics model, intracellular delay, humoral immunity, Lyapunov functional.

MSC(2010) 60H10, 92B05, 92D30.

1. Introduction

The modeling of the dynamics of viral infection across host cells is a classical problem in the field of population dynamics and dispersal [1, 15, 34, 35]. Since mathematical modeling and analysis of virus dynamics can be used to clarify and test different hypothesis, providing new insights into pathogenesis, improving diagnosis and treatment strategies which raise hopes of viral infected patients, and estimate key parameter values that control the infection process. Mathematical models of the viruses that infect the human body play a significant role in understanding the in-host virus dynamics and in suggesting antiviral treatment [4, 5, 8].

Recently, many researchers have devoted their interest to study virus dynamics model with intracellular delay or humoral immunity [4–7, 9, 10, 25, 26, 31, 40]. The intracellular time delay between infection of a healthy cell and production of new virus particles is called the latent period [7, 25, 26]. The latent period describes the finite time interval from the time when the infectious virus binds to the receptor of a target cell to the time when the first virion is produced from the same target cell [9, 31]. Immunity is a biological term that describes a state of having sufficient

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[*]This work was partially supported by the National Natural Science Foundation of China(No. 11601405).

biological defenses to avoid infection, disease or other unwanted biological invasion [10]. Humoral immunity is the aspect of immunity which is mainly based on the B cells which produce antibodies to attack the virus particles [4].

Since the virus is very sensitive to the environment in natural bio-chemical system [13], the parameters involved in the virus dynamics model, especially death rates, always exhibit random fluctuation to a greater or lesser extent. White noise (Brownian motion) is the name given to the irregular movement of pollen grains, suspended in water, observed by the Scottish botanist Robert Brown in 1828. The motion was later explained by the random collisions with the molecules of water. This random fluctuation can be described very well [22, 23].

Following the idea of the literature [22, 23], we assume that death rates are random variable which equal to the an average value plus an error term. According to the central limit theorem, the error terms may be approximated by a normal distribution. More concretely, death rates $\mu_x dt$, $\mu_y dt$, $\mu_v dt$ and $\mu_z dt$ are replaced $\mu_x dt+\sigma_1 dB_1(t)$, $\mu_y dt+\sigma_2 dB_2(t)$, $\mu_v dt+\sigma_3 dB_3(t)$ and $\mu_z dt +\sigma_4 dB_4(t)$ respectively in a small subsequent time interval dt, where $dB_i(t) = B_i(t+dt)-B_i(t)$ $(i = 1, 2, 3, 4)$ is the increment of a Brownian motion that follows a normal distribution $N(0, dt)$ with mean 0 and variances dt. The expectation and variance of the term $\mu_x dt + \sigma_1 dB_1(t)$ are $\mu_x dt$ and $\sigma_1 dt$, respectively, and he other three terms have simliar properties. This reasonable way of introducing stochastic environment noise into biologically population dynamic models has been pursued in [3, 11, 12, 14, 16–21, 23, 24, 28–30, 32, 33, 36–39].

In this work, we are concerned with the following stochastic model with intracellular delay and humoral immunity:

$$\begin{cases} dx(t) = \left[\Lambda - \mu_x x(t) - \dfrac{\beta x(t)v(t)}{1+\alpha v(t)}\right] dt + \sigma_1 x(t) dB_1(t), \\ dy(t) = \left[\dfrac{\beta e^{-m\tau} x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} - \mu_y y(t)\right] dt + \sigma_2 y(t) dB_2(t), \\ dv(t) = [ky(t) - \mu_v v(t) - pz(t)v(t)]dt + \sigma_3 v(t) dB_3(t), \\ dz(t) = [qz(t)v(t) - \mu_z z(t)]dt + \sigma_4 z(t) dB_4(t), \end{cases} \tag{1.1}$$

with initial conditions

$$\begin{aligned} & x(\theta) = \varphi_1(\theta),\ y(\theta) = \varphi_2(\theta),\ v(\theta) = \varphi_3(\theta),\ z(\theta) = \varphi_4(\theta), \\ & (\varphi_1(\theta), \varphi_2(\theta), \varphi_3(\theta), \varphi_4(\theta)) \in C,\ \varphi_i(\theta) \geq 0,\ \varphi_i(0) > 0,\ \theta \in [-\tau, 0],\ i = 1, 2, 3, 4 \end{aligned}$$

where $x(t)$ denotes the concentration of the un-infected target cells, $y(t)$ denotes the concentration of infected cells, $v(t)$ denotes the concentration of free virus particles, $z(t)$ denotes the density of the pathogens-specific lymphocytes. Free virus infects un-infected cells to produce infected cells at the saturation infection rate $\frac{\beta x(t)v(t)}{1+\alpha v(t)}$, $\alpha > 0$ is a constant. $B_i(t)$ are the white noises, i.e., $B_i(t)$ are independent standard Brownian motions defined on a complete probability space $(\Omega, \mathcal{F}, \mathbb{P})$ with a filtration $\{\mathcal{F}_t\}_{t\geq 0}$ satisfying the usual conditions (i.e., it is increasing and right continuous while $\mathcal{F}_0$ contains all $\mathbb{P}$-null sets), $\sigma_i^2 > 0$ denote the intensities of the white noise, $i = 1, 2, 3, 4$; C is the Banach space $C\left([-\tau, 0]; \mathbb{R}^4_+\right)$ of continuous functions from the interval $[-\tau, 0]$ to $\mathbb{R}^4_+$ and $\mathbb{R}^4_+ = \{x = (x_1, x_2, x_3, x_4) \in \mathbb{R}^4 : x_i > 0, i = 1, 2, 3, 4\}$. Other parameters are described in Table 1 and assumed to be positive constants.

When $\sigma_i = 0$, $i = 1, 2, 3, 4$, model (1.1) reduces to the deterministic model, which is a generation of the classic three-dimensional virus dynamics model proposed

Table 1. Parameter symbols used in the model (1.1) and their biological meanings

Parameter	Biological meaning
Λ	The produced rate of un-infected cells
μ_x	The death rate of un-infected cells
τ	The time between viral entry into a target cell and the production of new virus particles
m	The death rate for infected but not yet virus-producing cells
μ_y	The death rate of infected cells
k	The produced rate of the free virus particles from the infected cells
μ_v	The death rate of the free virus particles
p	The removed rate of pathogens by the immune system
q	The proliferate rate of the pathogens-specific lymphocytes in contact with the pathogens
μ_z	The death rate of the pathogens-specific lymphocytes

in [27], and was studied by Xiang et al. [31] very recently. They proved the following results.

Theorem 1.1. *The deterministic model of stochastic model (1.1) has one basic reproduction number* $R_0 = \frac{k\Lambda\beta e^{-m\tau}}{\mu_x\mu_y\mu_v}$, *one immune response reproductive ratio* $R_1 = \frac{qk\Lambda\beta e^{-m\tau}}{\mu_y\mu_v(q\mu_x+\alpha\mu_x\mu_z+\beta\mu_z)}$ *and three steady states: the un-infected steady state is* $E_0 = (x_0,0,0,0) = \left(\frac{\Lambda}{\mu_x},0,0,0\right)$, *the un-immune infected steady state* $E_1 = (x_1,y_1,v_1,0) = \left(\frac{\mu_y\mu_v(1+\alpha v_1)}{k\beta e^{-m\tau}}, \frac{\mu_v v_1}{k}, \frac{\mu_x}{\beta+\alpha\mu_x}(R_0-1),0\right)$ *and the positive equilibrium point* $E_2 = (x_2,y_2,v_2,z_2) = \left(\frac{q\Lambda+\mu_z\Lambda\alpha}{q\mu_x+\alpha\mu_x\mu_z+\beta\mu_z}, \frac{\mu_z\Lambda\beta e^{-m\tau}}{\mu_y\mu_v(q\mu_x+\alpha\mu_x\mu_z+\beta\mu_z)}, \frac{\mu_z}{q}, \frac{\mu_v}{p}(R_1-1)\right)$. *And the following statements hold:*

- *(i) The un-infected steady state* E_0 *is globally asymptotically stable, if* $R_0 < 1$,
- *(ii) The un-immune infected steady state* E_1 *is globally asymptotically stable, if* $R_0 > 1$, $R_1 < 1$,
- *(iii) The immune infected steady state* E_2 *is globally asymptotically stable, if* $R_1 > 1$.

The rest of this paper is organized as follows. In Section 2, we show the dynamical behavior of the model (1.1). In Section 3, some numerical simulations are given to support our theoretical results. Finally, we provide a brief discussion and the summary of the main results.

2. The dynamical behavior of the model (1.1)

First of all, the following theorem shows there exists a unique global positive solution of the model (1.1) for any positive initial value

Theorem 2.1. *For any given initial value* $X(0) = (x(0),y(0),v(0),z(0)) \in \mathbb{R}_+^4$, *there is a unique positive solution* $X(t) = (x(t),y(t),v(t),z(t))$ *of model (1.1) on* $t \geq 0$ *and the solution will remain in* R_+^4 *with probability 1, namely* $(x(t),y(t),v(t),z(t)) \in \mathbb{R}_+^4$ *for all* $t \geq 0$ *almost surely.*

Proof. The proof of this theorem is rather standard and hence is omitted □

2.1. Asymptotic behavior around the un-infected steady state $E_0 = (x_0, 0, 0, 0)$

Let un-infected steady state E_0 de given in *Lemma* 1.1. In this section, we will study the asymptotic behavior of model (1.1) around E_0.

Theorem 2.2. *Let $X(t) = (x(t), y(t), v(t), z(t))$ be the solution of model (1.1) with initial value $X(0) \in \mathbb{R}^4_+$. If the following conditions are satisfied*

$$R_0 < 1, \quad \mu_x > \sigma_1^2, \quad \mu_y > \frac{1}{2}\sigma_2^2, \quad q\mu_v > \frac{1}{2}\sigma_3^2 \quad \textit{and} \quad p\mu_z > \frac{1}{2}\sigma_4^2 \tag{2.1}$$

where R_0 is given in Lemma 1.1, then

$$\begin{aligned}
&\lim_{t\to\infty} sup \frac{1}{t}\mathbb{E}\int_0^t (x(s)-x_0)^2\, ds \leq D_{x_0}, \lim_{t\to\infty} sup \frac{1}{t}\mathbb{E}\int_0^t y^2(s)\, ds \leq D_{y_0},\\
&\lim_{t\to\infty} sup \frac{1}{t}\mathbb{E}\int_0^t v^2(s)\, ds \leq D_{v_0}, \lim_{t\to\infty} sup \frac{1}{t}\mathbb{E}\int_0^t z^2(s)\, ds \leq D_{z_0}
\end{aligned}$$

where

$$\begin{aligned}
D_{x_0} &= \frac{\sigma_1^2 x_0^2}{\mu_x - \sigma_1^2}, \quad D_{y_0} = \left(\frac{4e^{-2m\tau}\left(\mu_x + \mu_y\right)^2}{\left(\mu_y - \frac{1}{2}\sigma_2^2\right)^2} + \frac{2e^{-m\tau}\sigma_1^2}{\mu_y - \frac{1}{2}\sigma_2^2}\right) D_{x_0} + \frac{2e^{-m\tau}\sigma_1^2 x_0^2}{\mu_y - \frac{1}{2}\sigma_2^2},\\
D_{v_0} &= \left(\frac{4kq}{q\left(q\mu_v - \frac{1}{2}\sigma_3^2\right)\left(q\mu_v - \frac{1}{2}\sigma_3^2\right)} + \frac{4kq}{q\left(q\mu_v - \frac{1}{2}\sigma_3^2\right)\left(p\mu_z - \frac{1}{2}\sigma_4^2\right)}\right) D_{y_0}, \\
D_{z_0} &= \left(\frac{4kq}{p\left(p\mu_z - \frac{1}{2}\sigma_4^2\right)\left(q\mu_v - \frac{1}{2}\sigma_3^2\right)} + \frac{4kq}{p\left(p\mu_z - \frac{1}{2}\sigma_4^2\right)\left(p\mu_z - \frac{1}{2}\sigma_4^2\right)}\right) D_{y_0}.
\end{aligned} \tag{2.2}$$

Proof. Since the un-infected steady state $E_0 = (x_0, 0, 0, 0)$ is an equilibrium, we have

$$\Lambda = \mu_x x_0. \tag{2.3}$$

Define

$$V_1(t) = \frac{k}{2}\left(x(t) - x_0\right)^2.$$

Using (2.1), (2.3) and $It\hat{o}'s$ formula, we get

$$\begin{aligned}
\mathscr{L}V_1(t) =& k\left(x(t)-x_0\right)\left(\Lambda - \mu_x x(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)}\right) + \frac{k}{2}\sigma_1^2 x^2(t)\\
=& -k\mu_x\left(x(t)-x_0\right)^2 - \frac{k\beta\left(x(t)-x_0\right)^2 v(t)}{1+\alpha v(t)}\\
&- \frac{k\beta x_0\left(x(t)-x_0\right)v(t)}{1+\alpha v(t)} + \frac{k}{2}\sigma_1^2\left(x(t)-x_0+x_0\right)^2\\
\leq& -k\left(\mu_x - \sigma_1^2\right)\left(x(t)-x_0\right)^2 - \frac{k\beta x_0\left(x(t)-x_0\right)v(t)}{1+\alpha v(t)} + k\sigma_1^2 x_0^2.
\end{aligned}$$

Then, setting

$$V_2(t) = V_1(t) + ke^{m\tau}x_0 y(t+\tau) + \mu_y e^{m\tau}x_0 v(t) + k\mu_y e^{m\tau}x_0 \int_t^{t+\tau} y(s)\,ds.$$

One can obtain that

$$\begin{aligned}
\mathscr{L}V_2(t) \leq & -k\left(\mu_x - \sigma_1^2\right)(x(t)-x_0)^2 - \frac{k\beta x_0\,(x(t)-x_0)\,v(t)}{1+\alpha v(t)} + k\sigma_1^2 x_0^2 \\
& + \left(\frac{\beta e^{-m\tau}x(t)v(t)}{1+\alpha v(t)} - \mu_y y(t+\tau)\right) ke^{m\tau}x_0 + \mu_y e^{m\tau}x_0 \\
& \times (ky(t) - \mu_v v(t) - pz(t)v(t)) + k\mu_y e^{m\tau}x_0\,(y(t+\tau)-y(t)) \\
= & -k\left(\mu_x - \sigma_1^2\right)(x(t)-x_0)^2 - \frac{k\beta x_0\,(x(t)-x_0)\,v(t)}{1+\alpha v(t)} + k\sigma_1^2 x_0^2 \\
& + \frac{k\beta x_0\,(x(t)-x_0)\,v(t)}{1+\alpha v(t)} + \frac{k\beta x_0^2 v(t)}{1+\alpha v(t)} \\
& - \mu_y e^{m\tau}\mu_v x_0 v(t) - p\mu_y e^{m\tau}x_0 z(t)v(t) \\
\leq & -k\left(\mu_x - \sigma_1^2\right)(x(t)-x_0)^2 + k\sigma_1^2 x_0^2 + \left(\frac{R_0}{1+\alpha v(t)} - 1\right)\mu_y e^{m\tau}\mu_v x_0 v(t) \\
\leq & -k\left(\mu_x - \sigma_1^2\right)(x(t)-x_0)^2 + k\sigma_1^2 x_0^2. \qquad (2.4)
\end{aligned}$$

Integrating (2.4) from 0 to t and then taking the expectation on both sides, one can see that

$$\mathbb{E}V_2(t) - \mathbb{E}V_2(0) \leq -k\left(\mu_x - \sigma_1^2\right)\mathbb{E}\int_0^t (x(s)-x_0)^2\,ds + k\sigma_1^2 x_0^2 t.$$

That is to say

$$\lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t (x(s)-x_0)^2\,ds \leq D_{x_0}$$

where D_{x_0} is defined in (2.2). We define the following Lyapunov function

$$V_3(t) = \frac{1}{2}\left(e^{-m\tau}x(t) - e^{-m\tau}x_0 + y(t+\tau)\right)^2 + \left(\frac{\mu_y}{2} - \frac{1}{4}\sigma_2^2\right)\int_t^{t+\tau} y^2(s)\,ds.$$

Then

$$\begin{aligned}
\mathscr{L}V_3(t) = & \left(e^{-m\tau}x(t) - e^{-m\tau}x_0 + y(t+\tau)\right)\left(e^{-m\tau}\Lambda - \mu_x e^{-m\tau}x(t) - \mu_y y(t+\tau)\right) \\
& + \frac{e^{-m\tau}}{2}\sigma_1^2 x^2(t) + \frac{1}{2}\sigma_2^2 y^2(t+\tau) + \left(\frac{\mu_y}{2} - \frac{1}{4}\sigma_2^2\right)\left(y^2(t+\tau) - y^2(t)\right) \\
\leq & -\mu_x e^{-2m\tau}(x(t)-x_0)^2 - \left(\mu_y - \frac{1}{2}\sigma_2^2\right)y^2(t+\tau) \\
& - e^{-m\tau}(\mu_x+\mu_y)(x(t)-x_0)\,y(t+\tau) + e^{-m\tau}\sigma_1^2 x_0^2 + e^{-m\tau}\sigma_1^2(x(t)-x_0)^2 \\
& + \left(\frac{\mu_y}{2} - \frac{1}{4}\sigma_2^2\right)\left(y^2(t+\tau) - y^2(t)\right) \\
\leq & -\left(\mu_y - \frac{1}{2}\sigma_2^2\right)y^2(t+\tau) + \left(\frac{\mu_y}{2} - \frac{1}{4}\sigma_2^2\right)y^2(t+\tau)
\end{aligned}$$

$$
\begin{aligned}
&+\frac{2e^{-2m\tau}\left(\mu_x+\mu_y\right)^2}{\mu_y-\frac{1}{2}\sigma_2^2}\left(x(t)-x_0\right)^2+e^{-m\tau}\sigma_1^2x_0^2\\
&+e^{-m\tau}\sigma_1^2\left(x(t)-x_0\right)^2+\left(\frac{\mu_y}{2}-\frac{1}{4}\sigma_2^2\right)\left(y^2(t+\tau)-y^2(t)\right)\\
=&-\left(\frac{\mu_y}{2}-\frac{1}{4}\sigma_2^2\right)y^2(t)+\left(\frac{2e^{-2m\tau}\left(\mu_x+\mu_y\right)^2}{\mu_y-\frac{1}{2}\sigma_2^2}+e^{-m\tau}\sigma_1^2\right)\left(x(t)-x_0\right)^2\\
&+e^{-m\tau}\sigma_1^2x_0^2. \qquad (2.5)
\end{aligned}
$$

Integrating (2.5) from 0 to t and then taking the expectation on both sides yield that

$$
\begin{aligned}
\mathbb{E}V_3(t)-\mathbb{E}V_3(0)\leq&-\left(\frac{\mu_y}{2}-\frac{1}{4}\sigma_2^2\right)\mathbb{E}\int_0^t y^2(s)\,ds+e^{-m\tau}\sigma_1^2x_0^2t\\
&+\left(\frac{2e^{-2m\tau}\left(\mu_x+\mu_y\right)^2}{\mu_y-\frac{1}{2}\sigma_2^2}+e^{-m\tau}\sigma_1^2\right)\mathbb{E}\int_0^t\left(x(s)-x_0\right)^2\,ds.
\end{aligned}
$$

Then we can get

$$
\lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t y^2(s)\,ds\leq D_{y_0}.
$$

Define

$$
V_4(t)=\frac{1}{2}\left(qv(t)+pz(t)\right)^2+2p\left(\mu_v+\mu_z\right)z(t).
$$

We obtain

$$
\begin{aligned}
\mathscr{L}V_4(t)\leq&-\frac{q}{2}\left(q\mu_v-\frac{1}{2}\sigma_3^2\right)v^2(t)-\frac{p}{2}\left(p\mu_z-\frac{1}{2}\sigma_4^2\right)z^2(t)\\
&+\left(\frac{2kq}{q\mu_v-\frac{1}{2}\sigma_3^2}+\frac{2kq}{p\mu_z-\frac{1}{2}\sigma_4^2}\right)y^2(t). \qquad (2.6)
\end{aligned}
$$

Integrating (2.6) from 0 to t and then taking the expectation on both sides result in

$$
\begin{aligned}
\mathbb{E}V_4(t)-\mathbb{E}V_4(0)\leq&-\frac{q}{2}\left(q\mu_v-\frac{1}{2}\sigma_3^2\right)\mathbb{E}\int_0^t v^2(s)\,ds-\frac{p}{2}\left(p\mu_z-\frac{1}{2}\sigma_4^2\right)\mathbb{E}\int_0^t z^2(s)\,ds\\
&+\left(\frac{2kq}{q\mu_v-\frac{1}{2}\sigma_3^2}+\frac{2kq}{p\mu_z-\frac{1}{2}\sigma_4^2}\right)\mathbb{E}\int_0^t y^2(s)\,ds.
\end{aligned}
$$

Then one can see that

$$
\lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t v^2(s)\,ds\leq D_{v_0},\quad \lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t z^2(s)\,ds\leq D_{z_0}
$$

where D_{v_0} and D_{z_0} are defined in (2.2). This completes the proof of Theorem 2.2. □

2.2. Asymptotic behavior around the un-immune infected steady state $E_1=(x_1,y_1,v_1,0)$

Let un-immune infected steady state E_1 be given in *Lemma* 1.1. In this section, we will study the asymptotic behavior of model (1.1) around E_1.

Theorem 2.3. *Let $X(t) = (x(t), y(t), v(t), z(t))$ be the solution of model (1.1) with initial value $X(0) \in \mathbb{R}^4_+$. If the following conditions are satisfied*

$$R_0 > 1, \quad R_1 < 1, \quad \mu_x > \sigma_1^2, \quad \mu_y > \sigma_2^2, \quad q\mu_v > \sigma_3^2 \quad \text{and} \quad p\mu_z > \frac{1}{2}\sigma_4^2 \tag{2.7}$$

where R_0 and R_1 are given in Lemma 1.1, then

$$\lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t (x(s)-x_1)^2\,ds \le D_{x_1},\ \lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t (y(s)-y_1)^2\,ds \le D_{y_1},$$
$$\lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t (v(s)-v_1)^2\,ds \le D_{v_1},\ \lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t z^2(s)\,ds \le D_{z_1}$$

where

$$\begin{aligned}
D_{x_1} =& \frac{\beta x_1^2 v_1}{\mu_x x_1 (1+\alpha v_1)(\mu_x - \sigma_1^2)}\left(\frac{\sigma_1^2 x_1}{2} + \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2}\right) \\
&+ \frac{x_1}{\mu_x - \sigma_1^2}\left(\frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2}\right) + \frac{\sigma_1^2 x_1^2}{\mu_x - \sigma_1^2}, \\
D_{y_1} =& \left(\frac{4e^{-m\tau}(\mu_x + \mu_y)}{(\mu_y - \sigma_2^2)^2} + \frac{2e^{-m\tau}\sigma_1^2}{\mu_y - \sigma_2^2}\right) D_{x_1} + \frac{e^{-m\tau}\sigma_1^2 x_1^2 + \sigma_2^2 y_1^2}{\mu_y - \sigma_2^2}, \\
D_{v_1} =& \left(\frac{4kq}{q(q\mu_v - \sigma_3^2)^2} + \frac{4kq}{q(q\mu_v - \sigma_3^2)(p\mu_z - \frac{1}{2}\sigma_4^2)}\right) D_{y_1} + \frac{2\sigma_3^2 v_1^2}{q\mu_v - \sigma_3^2}, \\
D_{z_1} =& \left(\frac{4kq}{p(q\mu_v - \sigma_3^2)(p\mu_z - \frac{1}{2}\sigma_4^2)} + \frac{4kq}{p(p\mu_z - \frac{1}{2}\sigma_4^2)^2}\right) D_{y_1} + \frac{2q\sigma_3^2 v_1^2}{p\left(p\mu_z - \frac{\sigma_4^2}{2}\right)}.
\end{aligned} \tag{2.8}$$

Proof. Since the un-immune infected steady state E_1 is an equilibrium, we have

$$\begin{cases}
\Lambda = \mu_x x_1 + \dfrac{\beta x_1 v_1}{1+\alpha v_1}, \\
\dfrac{\beta e^{-m\tau} x_1 v_1}{1+\alpha v_1} = \mu_y y_1, \\
k y_1 = \mu_v v_1.
\end{cases} \tag{2.9}$$

First, defining some C^2 functions as follows

$$\begin{aligned}
V_5(t) &= x(t) - x_1 - x_1 Ln\frac{x(t)}{x_1}, \\
V_6(t) &= y(t) - y_1 - y_1 Ln\frac{y(t)}{y_1}, \\
V_7(t) &= \frac{\mu_y}{k}\left(v(t) - v_1 - v_1 Ln\frac{v(t)}{v_1}\right) + \frac{p\mu_y}{kq} z(t).
\end{aligned}$$

Using (2.7), (2.9) and $It\hat{o}'s$ formula, we arrive at

$$\mathscr{L}V_5(t) = \left(1 - \frac{x_1}{x(t)}\right)\left(\Lambda - \mu_x x(t) - \frac{\beta x(t) v(t)}{1+\alpha v(t)}\right) + \frac{\sigma_1^2 x_1}{2}$$

$$
\begin{aligned}
&= \Lambda - \mu_x x(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)} - \frac{x_1\Lambda}{x(t)} + \mu_x x_1 + \frac{\beta x_1 v(t)}{1+\alpha v(t)} + \frac{\sigma_1^2 x_1}{2}\\
&= \mu_x x_1\left(2 - \frac{x_1}{x(t)} - \frac{x(t)}{x_1}\right) + \frac{\sigma_1^2 x_1}{2} + \frac{\beta x_1 v_1}{1+\alpha v_1}\\
&\quad \times\left(1 - \frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1} - \frac{x_1}{x(t)} + \frac{(1+\alpha v_1)v(t)}{(1+\alpha v(t))v_1}\right),
\end{aligned}
$$

$$
\begin{aligned}
\mathscr{L}V_6(t) &= \left(1 - \frac{y_1}{y(t)}\right)\left(\frac{\beta e^{-m\tau}x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} - \mu_y y(t)\right) + \frac{\sigma_2^2 y_1}{2}\\
&= \frac{\beta e^{-m\tau}x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} - \mu_y y(t)\\
&\quad - \frac{\beta e^{-m\tau}x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)}\frac{y_1}{y(t)} + \mu_y y_1 + \frac{\sigma_2^2 y_1}{2}\\
&= \left(\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1} - \frac{y(t)}{y_1} - \frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1}\frac{y_1}{y(t)} + 1\right)\\
&\quad \times \frac{\beta e^{-m\tau}x_1 v_1}{1+\alpha v_1} + \frac{\sigma_2^2 y_1}{2},
\end{aligned}
$$

$$
\begin{aligned}
\mathscr{L}V_7(t) &= \frac{\mu_y}{k}\left(1 - \frac{v_1}{v(t)}\right)(ky(t) - \mu_v v(t) - pz(t)v(t))\\
&\quad + \frac{p\mu_y}{kq}(qz(t)v(t) - \mu_z z(t)) + \frac{\sigma_3^2 v_1}{2}\\
&= \mu_y y(t) - \mu_v\frac{\mu_y}{k}v(t) - p\frac{\mu_y}{k}z(t)v(t) - \mu_y y(t)\frac{v_1}{v(t)} + \mu_v\frac{\mu_y}{k}v_1 + p\frac{\mu_y}{k}z(t)v_1\\
&\quad + \frac{p\mu_y}{kq}(qz(t)v(t) - \mu_z z(t)) + \frac{\sigma_3^2 v_1}{2}\\
&= \frac{\beta e^{-m\tau}x_1 v_1}{1+\alpha v_1}\left(\frac{y(t)}{y_1} - \frac{v(t)}{v_1} - \frac{v_1 y(t)}{y_1 v(t)} + 1\right) + p\frac{\mu_y}{k}z(t)(v_1 - \frac{\mu_z}{q}) + \frac{\sigma_3^2 v_1}{2}.
\end{aligned}
$$

Since $R_1 < 1$, one can get

$$v_1 < \frac{\mu_z}{q}.$$

It follows that

$$\mathscr{L}V_7(t) \le \frac{\beta e^{-m\tau}x_1 v_1}{1+\alpha v_1}\left(\frac{y(t)}{y_1} - \frac{v(t)}{v_1} - \frac{v_1 y(t)}{y_1 v(t)} + 1\right) + \frac{\sigma_3^2 v_1}{2}.$$

We define the following Lyapunov functions

$$
\begin{aligned}
V_8(t) &= V_5(t) + e^{m\tau}V_6(t) + e^{m\tau}V_7(t)\\
&\quad + \frac{\beta x_1 v_1}{1+\alpha v_1}\int_{t-\tau}^{t}\left[\frac{(1+\alpha v_1)x(s)v(s)}{(1+\alpha v(s))x_1 v_1} - 1 - Ln\frac{(1+\alpha v_1)x(s)v(s)}{(1+\alpha v(s))x_1 v_1}\right]ds,\\
V_9(t) &= e^{m\tau}V_6 + e^{m\tau}V_7\\
&\quad + \frac{\beta x_1 v_1}{1+\alpha v_1}\int_{t-\tau}^{t}\left[\frac{(1+\alpha v_1)x(s)v(s)}{(1+\alpha v(s))x_1 v_1} - 1 - Ln\frac{(1+\alpha v_1)x(s)v(s)}{(1+\alpha v(s))x_1 v_1}\right]ds.
\end{aligned}
$$

Then it is easy to obtain

$$\mathscr{L}V_8(t) \le \mu_x x_1\left(2 - \frac{x_1}{x(t)} - \frac{x(t)}{x_1}\right) + \left(1 - \frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1} - \frac{x_1}{x(t)} + \frac{(1+\alpha v_1)v(t)}{(1+\alpha v(t))v_1}\right)$$

$$
\begin{aligned}
&\times \frac{\beta x_1 v_1}{1+\alpha v_1} + \frac{\sigma_1^2 x_1}{2} + \frac{\beta x_1 v_1}{1+\alpha v_1} \\
&\times \left(\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1} - \frac{y(t)}{y_1} - \frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1}\frac{y_1}{y(t)} + 1 \right) \\
&+ \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\beta x_1 v_1}{1+\alpha v_1}\left(\frac{y(t)}{y_1} - \frac{v(t)}{v_1} - \frac{v_1 y(t)}{y_1 v(t)} + 1 \right) + \frac{\sigma_3^2 v_1 e^{m\tau}}{2} \\
&+ \left(\frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1} - Ln\frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1} \right)\frac{\beta x_1 v_1}{1+\alpha v_1} \\
&- \frac{\beta x_1 v_1}{1+\alpha v_1}\left(\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1} - Ln\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1} \right) \\
=&\mu_x x_1\left(2 - \frac{x_1}{x(t)} - \frac{x(t)}{x_1}\right) - \frac{\beta x_1 v_1}{1+\alpha v_1} \\
&\times \left(\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1}\frac{y_1}{y(t)} + \frac{x_1}{x(t)} + \frac{v_1 y(t)}{y_1 v(t)} - 3 \right) \\
&+ \frac{\beta x_1 v_1}{1+\alpha v_1}\left(\frac{(1+\alpha v_1)v(t)}{(1+\alpha v(t))v_1} - \frac{v(t)}{v_1} \right) + \frac{\beta x_1 v_1}{1+\alpha v_1} \\
&\times \left(Ln\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1} - Ln\frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1} \right) \\
&+ \frac{\sigma_1^2 x_1}{2} + \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2} \\
\leq&\mu_x x_1\left(2 - \frac{x_1}{x(t)} - \frac{x(t)}{x_1}\right) - \frac{\beta x_1 v_1}{1+\alpha v_1} \\
&\times \left(Ln\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1} + Ln\frac{y_1}{y(t)} + Ln\frac{x_1}{x(t)} + Ln\frac{v_1 y(t)}{y_1 v(t)} \right) \\
&+ \frac{\beta x_1 v_1}{1+\alpha v_1}\left(\frac{(1+\alpha v_1)v(t)}{(1+\alpha v(t))v_1} - \frac{v(t)}{v_1} \right) + \frac{\beta x_1 v_1}{1+\alpha v_1} \\
&\times \left(Ln\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1} - Ln\frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1} \right) \\
&+ \frac{\sigma_1^2 x_1}{2} + \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2} \\
=&\mu_x x_1\left(2 - \frac{x_1}{x(t)} - \frac{x(t)}{x_1}\right) + \frac{\beta x_1 v_1}{1+\alpha v_1} \\
&\times \left(Ln\frac{1+\alpha v(t)}{1+\alpha v_1} - \frac{v(t)}{v_1} + \frac{(1+\alpha v_1)v(t)}{(1+\alpha v(t))v_1} \right) + \frac{\sigma_1^2 x_1}{2} + \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2} \\
\leq&\mu_x x_1\left(2 - \frac{x_1}{x(t)} - \frac{x(t)}{x_1}\right) + \frac{\beta x_1 v_1}{1+\alpha v_1} \\
&\times \left(\frac{1+\alpha v(t)}{1+\alpha v_1} - 1 - \frac{v(t)}{v_1} + \frac{(1+\alpha v_1)v(t)}{(1+\alpha v(t))v_1} \right) + \frac{\sigma_1^2 x_1}{2} + \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2} \\
=&\mu_x x_1\left(2 - \frac{x_1}{x(t)} - \frac{x(t)}{x_1}\right) - \frac{\beta x_1 v_1}{1+\alpha v_1}\frac{\alpha(v(t)-v_1)^2}{(1+\alpha v_1)(1+\alpha v(t))v_1} \\
&+ \frac{\sigma_1^2 x_1}{2} + \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2}
\end{aligned}
$$

$$
\begin{aligned}
&\le \mu_x x_1 \left(2 - \frac{x_1}{x(t)} - \frac{x(t)}{x_1}\right) + \frac{\sigma_1^2 x_1}{2} + \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2},\\
\mathscr{L}V_9(t) \le &\left(\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1} - \frac{y(t)}{y_1} - \frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1}\frac{y_1}{y(t)} + 1\right)\\
&\times \frac{\beta x_1 v_1}{1+\alpha v_1} + \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\beta x_1 v_1}{1+\alpha v_1}\left(\frac{y(t)}{y_1} - \frac{v(t)}{v_1} - \frac{v_1 y(t)}{y_1 v(t)} + 1\right) + \frac{\sigma_3^2 v_1 e^{m\tau}}{2}\\
&+ \left(\frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1} - Ln\frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1}\right)\frac{\beta x_1 v_1}{1+\alpha v_1}\\
&- \frac{\beta x_1 v_1}{1+\alpha v_1}\left(\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1} - Ln\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1}\right)\\
&= \frac{\beta x_1 v_1}{1+\alpha v_1}\left(-\frac{x(t)}{x_1} + 1 + \frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1} - \frac{(1+\alpha v_1)v(t)}{(1+\alpha v(t))v_1}\right)\\
&+ \frac{\beta x_1 v_1}{1+\alpha v_1}\left(-\frac{v(t)}{v_1} + \frac{(1+\alpha v_1)v(t)}{(1+\alpha v(t))v_1}\right)\\
&- \frac{\beta x_1 v_1}{1+\alpha v_1}\left(-3 + \frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1}\frac{y_1}{y(t)} + \frac{x_1}{x(t)} + \frac{v_1 y(t)}{y_1 v(t)}\right)\\
&+ \frac{\beta x_1 v_1}{1+\alpha v_1}\left(\frac{x(t)}{x_1} + \frac{x_1}{x(t)} - 2\right)\\
&+ \frac{\beta x_1 v_1}{1+\alpha v_1}\left(Ln\frac{(1+\alpha v_1)x(t-\tau)v(t-\tau)}{(1+\alpha v(t-\tau))x_1 v_1} - Ln\frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1}\right)\\
&+ \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2}\\
&\le \frac{\beta x_1 v_1}{1+\alpha v_1}\left(-\frac{x(t)}{x_1} + 1 + \frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1} - \frac{(1+\alpha v_1)v(t)}{(1+\alpha v(t))v_1}\right)\\
&+ \frac{\beta x_1 v_1}{1+\alpha v_1}\left(\frac{x(t)}{x_1} + \frac{x_1}{x(t)} - 2\right) + \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2}.
\end{aligned}
$$

Let

$$V_{10}(t) = \frac{1}{2}(x(t) - x_1)^2.$$

We have

$$
\begin{aligned}
\mathscr{L}V_{10}(t) =&(x(t) - x_1)\left(\Lambda - \mu_x x(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)}\right) + \frac{\sigma_1^2 x^2(t)}{2}\\
=& - \mu_x (x(t) - x_1)^2 + \frac{\beta x_1 v_1}{1+\alpha v_1}(x(t) - x_1) - \frac{\beta (x(t) - x_1)^2 v(t)}{1+\alpha v(t)}\\
&- \frac{\beta x_1 (x(t) - x_1)v(t)}{1+\alpha v(t)} + \frac{\sigma_1^2 (x(t) - x_1 + x_1)^2}{2}\\
\le& - (\mu_x - \sigma_1^2)(x(t) - x_1)^2\\
&+ x_1 \frac{\beta x_1 v_1}{1+\alpha v_1}\left(\frac{x(t)}{x_1} - 1 - \frac{(1+\alpha v_1)x(t)v(t)}{(1+\alpha v(t))x_1 v_1} + \frac{(1+\alpha v_1)v(t)}{(1+\alpha v(t))v_1}\right) + \sigma_1^2 x_1^2.
\end{aligned}
$$

Choosing

$$V_{11}(t) = \frac{\beta x_1^2 v_1}{\mu_x x_1 (1+\alpha v_1)} V_8 + x_1 V_9 + V_{10}.$$

We can see

$$\mathscr{L}V_{11}(t) \leq -\left(\mu_x - \sigma_1^2\right)(x(t) - x_1)^2 + \frac{\beta x_1^2 v_1}{\mu_x x_1 (1 + \alpha v_1)} \left(\frac{\sigma_1^2 x_1}{2} + \frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2}\right) + x_1 \left(\frac{\sigma_2^2 y_1 e^{m\tau}}{2} + \frac{\sigma_3^2 v_1 e^{m\tau}}{2}\right) + \sigma_1^2 x_1^2. \tag{2.10}$$

Integrating (2.10) from 0 to t and then taking the expectation on both sides lead to

$$\mathbb{E}V_{11}(t) - \mathbb{E}V_{11}(0) \leq -\left(\mu_x - \sigma_1^2\right) \mathbb{E} \int_0^t (x(s) - x_1)^2 \, ds + D_{x_1} \left(\mu_x - \sigma_1^2\right) t$$

where D_{x_1} is defined in (2.8). Then we can get

$$\lim_{t \to \infty} sup \frac{1}{t} \mathbb{E} \int_0^t (x(s) - x_1)^2 \, ds \leq D_{x_1}.$$

Define

$$V_{12}(t) = \frac{1}{2}\left(e^{-m\tau} x(t) - e^{-m\tau} x_1 + y(t+\tau) - y_1\right)^2 + \frac{\left(\mu_y - \sigma_2^2\right)}{2} \int_t^{t+\tau} (y(s) - y_1)^2 \, ds,$$

We can get

$$\begin{aligned}
\mathscr{L}V_{12}(t) &= \left(e^{-m\tau} x(t) - e^{-m\tau} x_1 + y(t+\tau) - y_1\right) \left(e^{-m\tau}\Lambda - \mu_x e^{-m\tau} x(t) - \mu_y y(t+\tau)\right) \\
&\quad + \frac{e^{-m\tau}}{2} \sigma_1^2 x^2(t) + \frac{1}{2} \sigma_2^2 y^2(t+\tau) \\
&\quad + \frac{\left(\mu_y - \sigma_2^2\right)}{2} \left[(y(t+\tau) - y_1)^2 - (y(t) - y_1)^2\right] \\
&= \left(e^{-m\tau} x(t) - e^{-m\tau} x_1 + y(t+\tau) - y_1\right) \\
&\quad \times \left(-\mu_x e^{-m\tau}(x(t) - x_1) - \mu_y (y(t+\tau) - y_1)\right) + \frac{e^{-m\tau}}{2} \sigma_1^2 x^2(t) \\
&\quad + \frac{1}{2} \sigma_2^2 y^2(t+\tau) + \frac{\left(\mu_y - \sigma_2^2\right)}{2} \left[(y(t+\tau) - y_1)^2 - (y(t) - y_1)^2\right] \\
&= -\mu_x e^{-2m\tau}(x(t) - x_1)^2 - \mu_y (y(t+\tau) - y_1)^2 \\
&\quad - e^{-m\tau}(\mu_x + \mu_y)(x(t) - x_1)(y(t+\tau) - y_1) + \frac{e^{-m\tau}}{2} \sigma_1^2 (x(t) - x_1 + x_1)^2 \\
&\quad + \frac{1}{2} \sigma_2^2 (y(t+\tau) - y_1 + y_1)^2 + \frac{\left(\mu_y - \sigma_2^2\right)}{2} \left[(y(t+\tau) - y_1)^2 - (y(t) - y_1)^2\right] \\
&\leq -\left(\mu_y - \sigma_2^2\right)(y(t+\tau) - y_1)^2 + \frac{\left(\mu_y - \sigma_2^2\right)}{2} (y(t+\tau) - y_1)^2 \\
&\quad + \frac{2e^{-m\tau}(\mu_x + \mu_y)}{\left(\mu_y - \sigma_2^2\right)} (x(t) - x_1)^2 + e^{-m\tau} \sigma_1^2 x_1^2 + e^{-m\tau} \sigma_1^2 (x(t) - x_1)^2 \\
&\quad + \sigma_2^2 y_1^2 + \frac{\left(\mu_y - \sigma_2^2\right)}{2} [(y(t+\tau) - y_1)^2 - (y(t) - y_1)^2] \\
&= -\frac{\left(\mu_y - \sigma_2^2\right)}{2} (y(t) - y_1)^2 \\
&\quad + \left(\frac{2e^{-m\tau}(\mu_x + \mu_y)}{\left(\mu_y - \sigma_2^2\right)} + e^{-m\tau} \sigma_1^2\right)(x(t) - x_1)^2 + e^{-m\tau} \sigma_1^2 x_1^2 + \sigma_2^2 y_1^2.
\end{aligned} \tag{2.11}$$

Integrating (2.11) from 0 to t and then taking the expectation on both sides, we have

$$\begin{aligned}\mathbb{E}V_{12}(t)-\mathbb{E}V_{12}(0)\leq&-\frac{\left(\mu_y-\sigma_2^2\right)}{2}\mathbb{E}\int_0^t(y(s)-y_1)^2\,ds+(e^{-m\tau}\sigma_1^2x_1^2+\sigma_2^2y_1^2)t\\&+\left(\frac{2e^{-m\tau}\left(\mu_x+\mu_y\right)}{\left(\mu_y-\sigma_2^2\right)}+e^{-m\tau}\sigma_1^2\right)\mathbb{E}\int_0^t(x(s)-x_1)^2\,ds.\end{aligned}$$

In other words,

$$\lim_{t\to\infty}sup\frac{1}{t}\mathbb{E}\int_0^t(y(s)-y_1)^2\,ds\leq D_{y_1}$$

where D_{y_1} is defined in (2.8). At last, we define the following C^2 functions.

$$V_{13}(t)=\frac{1}{2}\left(qv(t)-qv_1+pz(t)\right)^2+2p(\mu_v+\mu_z)z(t).$$

We obtain

$$\begin{aligned}\mathscr{L}V_{13}(t)=&(qv(t)-qv_1+pz(t))[q(ky(t)-\mu_vv(t)-pz(t)v(t))+p(qz(t)v(t)-\mu_zz(t))]\\&+\frac{q}{2}\sigma_3^2v^2(t)+\frac{p}{2}\sigma_4^2z^2(t)+2p(\mu_v+\mu_z)(qz(t)v(t)-\mu_zz(t))\\=&(qv(t)-qv_1+pz(t))[kq(y(t)-y_1)-q\mu_v(v(t)-v_1)-p\mu_zz(t)]\\&+\frac{q}{2}\sigma_3^2v^2(t)+\frac{p}{2}\sigma_4^2z^2(t)+p(\mu_v+\mu_z)(qz(t)v(t)-\mu_zz(t))\\\leq&-q\left(q\mu_v-\sigma_3^2\right)(v(t)-v_1)^2-p\left(p\mu_z-\frac{\sigma_4^2}{2}\right)z^2(t)\\&+p(\mu_v+\mu_z)z(t)(qv_1-\mu_z)+kq^2(v(t)-v_1)(y(t)-y_1)\\&+kpq(y(t)-y_1)z(t)+q\sigma_3^2v_1^2\\\leq&-q\left(q\mu_v-\sigma_3^2\right)(v(t)-v_1)^2-p\left(p\mu_z-\frac{\sigma_4^2}{2}\right)z^2(t)\\&+kq^2(v(t)-v_1)(y(t)-y_1)+kpq(y(t)-y_1)z(t)+q\sigma_3^2v_1^2\\\leq&-q\left(q\mu_v-\sigma_3^2\right)(v(t)-v_1)^2-p\left(p\mu_z-\frac{\sigma_4^2}{2}\right)z^2(t)\\&+\frac{q}{2}\left(q\mu_v-\sigma_3^2\right)(v(t)-v_1)^2+\frac{2kq}{q\mu_v-\sigma_3^2}(y(t)-y_1)^2\\&+\frac{p}{2}\left(p\mu_z-\sigma_4^2\right)z^2(t)+\frac{2kq}{p\mu_z-\frac{1}{2}\sigma_4^2}(y(t)-y_1)^2+q\sigma_3^2v_1^2\\=&-\frac{q}{2}(q\mu_v-\sigma_3^2)(v(t)-v_1)^2+\frac{2kq}{q\mu_v-\sigma_3^2}(y(t)-y_1)^2\\&-\frac{p}{2}\left(p\mu_z-\frac{\sigma_4^2}{2}\right)z^2(t)+\frac{2kq}{p\mu_z-\frac{1}{2}\sigma_4^2}(y(t)-y_1)^2+q\sigma_3^2v_1^2.\end{aligned}\tag{2.12}$$

Integrating (2.12) from 0 to t and then taking the expectation on both sides give

$$\mathbb{E}V_{13}(t)-\mathbb{E}V_{13}(0)\leq-\frac{q}{2}\left(q\mu_v-\sigma_3^2\right)\mathbb{E}\int_0^t(v(s)-v_1)^2\,ds$$

$$+\left(\frac{2kq}{q\mu_v-\sigma_3^2}+\frac{2kq}{p\mu_z-\frac{1}{2}\sigma_4^2}\right)\mathbb{E}\int_0^t (y(s)-y_1)^2\,ds$$
$$-\frac{p}{2}\left(p\mu_z-\frac{\sigma_4^2}{2}\right)\mathbb{E}\int_0^t z^2(s)\,ds+q\sigma_3^2v_1^2t.$$

Then we have

$$\lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t (v(s)-v_1)^2\,ds\le D_{v_1},\ \lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t z^2(s)\,ds\le D_{z_1}$$

where D_{v_1} and D_{z_1} is defined in (2.8). This completes the proof of Theorem 2.3. □

2.3. Asymptotic behavior around the positive equilibrium point $E_2=(x_2,y_2,v_2,z_2)$

Let immune infected steady state E_2 be given in *Lemma* 1.1. In this section, we will study the asymptotic behavior of model (1.1) around E_2.

Theorem 2.4. *Let $X(t)=(x(t),y(t),v(t),z(t))$ be the solution of model (1.1) with initial value $X(0)\in\mathbb{R}_+^4$. If the following conditions are satisfied*

$$R_1>1,\quad \mu_x>\sigma_1^2,\quad \mu_y>\sigma_2^2,\quad q\mu_v>\sigma_3^2\quad \text{and}\quad p\mu_z>\sigma_4^2$$

where R_1 is given in Lemma 1.1, then

$$\lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t (x(s)-x_2)^2\,ds\le D_{x_2},\ \lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t (y(s)-y_2)^2\,ds\le D_{y_2},$$
$$\lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t (v(s)-v_2)^2\,ds\le D_{v_2},\ \lim_{t\to\infty} sup\frac{1}{t}\mathbb{E}\int_0^t (z(s)-z_2)^2\,ds\le D_{z_2}$$

where

$$\begin{aligned}
D_{x_2}=&\frac{\beta x_2^2v_2}{\mu_x x_2(1+\alpha v_2)\left(\mu_x-\sigma_1^2\right)}\left(\frac{\sigma_1^2x_2}{2}+\frac{\sigma_2^2y_2e^{m\tau}}{2}+\frac{\mu_y\sigma_3^2v_2e^{m\tau}}{2k}+\frac{p\mu_y\sigma_4^2z_2e^{m\tau}}{2kq}\right)\\
&+\frac{x_2}{\mu_x-\sigma_1^2}\left(\frac{\sigma_2^2y_2e^{m\tau}}{2}+\frac{\mu_y\sigma_3^2v_2e^{m\tau}}{2k}+\frac{p\mu_y\sigma_4^2z_2e^{m\tau}}{2kq}\right)+\frac{\sigma_1^2x_2^2}{\mu_x-\sigma_1^2},\\
D_{y_2}=&\left(\frac{4e^{-m\tau}(\mu_x+\mu_y)}{\left(\mu_y-\sigma_2^2\right)^2}+\frac{2e^{-m\tau}\sigma_1^2}{\mu_y-\sigma_2^2}\right)D_{x_2}+\frac{e^{-m\tau}\sigma_1^2x_2^2+\sigma_2^2y_2^2}{\mu_y-\sigma_2^2},\\
D_{v_2}=&\left(\frac{4kq}{q\left(q\mu_v-\sigma_3^2\right)^2}+\frac{4kq}{q\left(q\mu_v-\sigma_3^2\right)\left(p\mu_z-\sigma_4^2\right)}\right)D_{y_2}\\
&+\frac{2q\sigma_3^2v_2^2+2p\sigma_4^2z_2^2+p(\mu_v+\mu_z)\sigma_4^2z_2}{q\left(q\mu_v-\sigma_3^2\right)},\\
D_{z_2}=&\left(\frac{4kq}{p\left(p\mu_z-\sigma_4^2\right)\left(q\mu_v-\sigma_3^2\right)}+\frac{4kq}{p\left(p\mu_z-\sigma_4^2\right)^2}\right)D_{y_2}\\
&+\frac{2q\sigma_3^2v_2^2+2p\sigma_4^2z_2^2+p(\mu_v+\mu_z)\sigma_4^2z_2}{p\left(p\mu_z-\sigma_4^2\right)}.
\end{aligned}$$

Proof. The proof is similar to *Theorem* 2.3 and hence is omitted. □

3. Numerical simulation

To illustrate the theoretical results obtained above, some numerical simulations are displayed in the following figures. We show the dynamics of the model (1.1) by fixing value of the parameters. Some of the values of parameters are taken in the reference [31] and the rest of the parametric values are assumed for numerical requirements.

Example 3.1. Let $(x(0), y(0), v(0), z(0)) = (3.000, 3.000, 1.000, 3.000)$, $\Lambda = 0.900$, $\beta = 0.300$, $\mu_x = 0.200$, $\alpha = 0.200$, $\mu_y = 0.300$, $k = 0.500$, $\mu_v = 0.100$, $p = 0.050$, $q = 0.200$, $\mu_z = 0.300$, $\tau = 15.000$, $m = 0.300$, $\sigma_1 = 0.100$, $\sigma_2 = 0.100$, $\sigma_3 = 0.100$, $\sigma_4 = 0.100$. By calculating, we obtain $R_0 \approx 0.250 < 1$, $\mu_x > \sigma_1^2$, $\mu_y > \frac{1}{2}\sigma_2^2$, $q\mu_v > \frac{1}{2}\sigma_3^2$ *and* $p\mu_z > \frac{1}{2}\sigma_4^2$. By virtue of *Theorem* 2.2 and Figure 1, we can observe that population $y(t)$, $v(t)$ and $z(t)$ of model (1.1) will go to extinction with probability one.

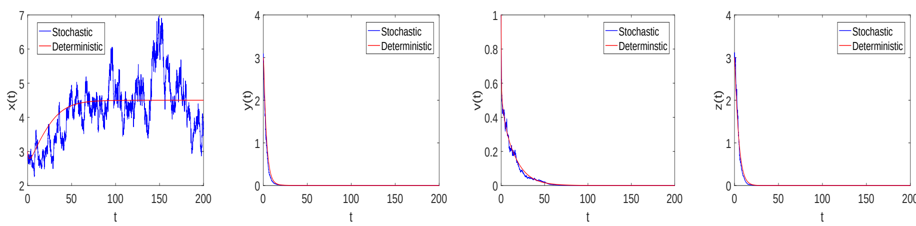

Figure 1. The solutions $x(t)$, $y(t)$, $v(t)$ and $z(t)$ for the stochastic model (1.1) with parameters in *Example* 3.1.

Example 3.2. Let $(x(0), y(0), v(0), z(0)) = (3.000, 3.000, 1.000, 3.000)$, $\Lambda = 0.900$, $\beta = 0.300$, $\mu_x = 0.200$, $\alpha = 0.200$, $\mu_y = 0.300$, $k = 0.500$, $\mu_v = 0.100$, $p = 0.050$, $q = 0.200$, $\mu_z = 0.300$, $\tau = 7.000$, $m = 0.300$, $\sigma_1 = 0.100$, $\sigma_2 = 0.100$, $\sigma_3 = 0.100$, $\sigma_4 = 0.100$. By calculating, we obtain $R_0 \approx 2.755 > 1$, $R_1 \approx 0.776 < 1$, $\mu_x > \sigma_1^2$, $\mu_y > \sigma_2^2$, $q\mu_v > \sigma_3^2$ *and* $p\mu_z > \frac{1}{2}\sigma_4^2$, the conditions of *Theorem* 2.3 are satisfied. Then from Figure 2, we can see that only population $z(t)$ of model (1.1) will go to extinction with probability one.

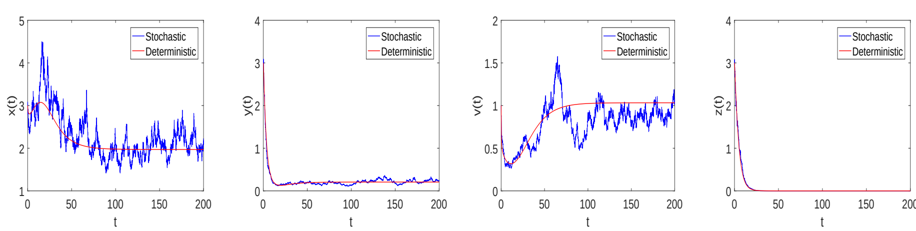

Figure 2. The solutions $x(t)$, $y(t)$, $v(t)$ and $z(t)$ for the stochastic model (1.1) with parameters in *Example* 3.2.

Example 3.3. Let $(x(0), y(0), v(0), z(0)) = (3.000, 3.000, 1.000, 3.000)$, $\Lambda = 0.900$, $\beta = 0.300$, $\mu_x = 0.200$, $\alpha = 0.200$, $\mu_y = 0.300$, $k = 0.500$, $\mu_v = 0.100$, $p = 0.050$, $q = 0.200$, $\mu_z = 0.300$, $\tau = 3.000$, $m = 0.300$, $\sigma_1 = 0.100$, $\sigma_2 = 0.100$, $\sigma_3 = 0.100$, $\sigma_4 = 0.100$. By calculating, we obtain $R_0 \approx 9.148 > 1$, $R_1 \approx 2.577 > 1$, $\mu_x > \sigma_1^2$,

$\mu_y > \sigma_2^2$, $q\mu_v > \sigma_3^2$ *and* $p\mu_z > \sigma_4^2$, the conditions of *Theorem* 2.4 are satisfied. Then from Figure 3, we can see that the populations of model (1.1) are permanent.

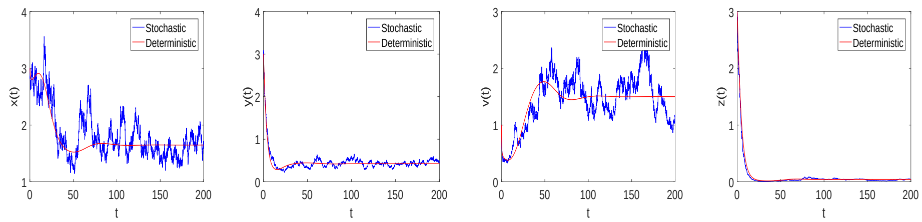

Figure 3. The solutions $x(t)$, $y(t)$, $v(t)$ and $z(t)$ for the stochastic model (1.1) with parameters in *Example* 3.3.

4. Discussion and summary

In this work, we discussed the long-term behavior of a stochastic viral model with intracellular delay and humoral immunity. We show that the solution of stochastic model (1.1) is going around the steady states of deterministic model under some conditions by constructing some suitable Lyapunov functions. And our theoretical results has been verified by numerical simulation.

To assist policymakers in targeting prevention and treatment resources for maximum effectiveness, we study the relationship between the basic reproduction number R_0 (the immune response reproductive ratio R_1) and the parameters of the basic reproduction number R_0 (the immune response reproductive ratio R_1) by sensitivity index. The normalized forward sensitivity index of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter [2], which can be defined as follows.

Definition 4.1 ([2]). The normalized forward sensitivity index of a variable y, that depends differentiably on a parameter x, is defined as:

$$A_y^x = \frac{\partial x}{\partial y} \times \frac{y}{x} = y\frac{\partial}{\partial y} Lnx.$$

The sensitivity indices for R_0 and R_1 are respectively shown in Table 2 and Table 3.

Table 2. Sensitivity indices for R_0

Parameter	Index	Parameter	Index
k	$+1.000$	τ	$-m\tau$
Λ	$+1.000$	μ_x	-1.000
β	$+1.000$	μ_y	-1.000
m	$-m\tau$	μ_v	-1.000

The Table 2 and Table 3 indicates that the following several ways would be more effective to control the spread of the virus.

(i) We should increase the time between viral entry into a target cell and the production of new virus particles (τ), the death rate for infected but not yet

Table 3. Sensitivity indices for R_1

Parameter	Index	Parameter	Index
q	$\frac{\alpha\mu_x\mu_z+\beta\mu_z}{q\mu_x+\alpha\mu_x\mu_z+\beta\mu_z}$	μ_x	$\frac{-q\mu_x-\alpha\mu_x\mu_z}{q\mu_x+\alpha\mu_x\mu_z+\beta\mu_z}$
k	$+1.000$	μ_y	-1.000
Λ	$+1.000$	μ_v	-1.000
β	$\frac{q\mu_x+\alpha\mu_x\mu_z}{q\mu_x+\alpha\mu_x\mu_z+\beta\mu_z}$	μ_z	$\frac{-\alpha\mu_x\mu_z-\beta\mu_z}{q\mu_x+\alpha\mu_x\mu_z+\beta\mu_z}$
m	$-m\tau$	α	$\frac{-\alpha\mu_x\mu_z}{q\mu_x+\alpha\mu_x\mu_z+\beta\mu_z}$
τ	$-m\tau$		

virus-producing cells (m), the death rate of the free virus particles (μ_v) and infected cells (μ_y).

(ii) We should reduce the produced rate of free virus from infected cells (k).

Acknowledgements. We would like to thank the anonymous referees and the editor for very helpful suggestions and comments which led to improvements of our original paper.

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