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Citation: Chin. Phys. B . 2020, 29(9): 090201 . **doi:** 10.1088/1674-1056/ab8c3f
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Dynamical analysis for hybrid virus infection system in switching environment*

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(Received 5 March 2020; revised manuscript received 16 April 2020; accepted manuscript online 23 April 2020)

We investigate the dynamical behavior of hybrid virus infection systems with nonlytic immune response in switching environment, which is modeled as a stochastic process of telegraph noise and represented as a multi-state Markov chains. Firstly, The existence of unique positive solution and boundedness of the new hybrid system is proved. Furthermore, the sufficient conditions for extinction and persistence of virus are established. Finally, stochastic simulations are performed to test and demonstrate the conclusions. As a consequence, our work suggests that stochastic switching environment plays a crucial role in the process of virus prevention and treatment.

Keywords: dynamical behavior, hybrid virus infection system, switching environment, extinction

PACS: 02.50.–r, 05.40.–a **DOI:** 10.1088/1674-1056/ab8c3f

1. Introduction

Infectious diseases have always been harmful to our body and minded throughout the development of human beings, especially viral infectious diseases.[1–9] It is therefore critical to find which factors will affect viral diseases. Academically, the research of the impact of environmental noise on systems has achieved satisfactory results. Many scholars have studied how HIV can cause AIDS by infecting human body, to establish virus infection systems.[10–13] Importantly, Bartholdy *et al.*[14] constructed the virus model with nonlytic immune responses to describe the basic dynamics of the interaction among susceptible host cells, a virus population, and immune responses. Moreover, Wodarz *et al.*[9] investigated the dynamics of the models based on the basic reproduction number. The effects of stochastic noise and delay effect on the virus infection model were studied theoretically by Li *et al.*,[15,16] they have shown that enough white noise can cause virus population to die out without constraint. Wang *et al.*[17] investigated global stability of viral infection model with lytic and nonlytic immune responses. The author mainly analyzed the stability of disease-free steady state and disease steady state by using LaSalle's invariance principle and central manifold theorem. At the same time, they also derived a different type of conditions for the global stability of the disease steady state by using a geometrical approach. After that, they considered the dynamical behavior of a virus infection model with delayed nonlytic immune response.[18] The local stabilities of two boundary equilibria were established in the research. It was found that time delay can change the stability of the equilibrium and can lead to the existence of Hopf bifurcations.

In the real biological systems, some important parameters of the epidemic model are usually influenced by random switching of external environmental regimes.[19] For example, in the actual medical treatment of HIV patients, drug treatment is generally instantaneous, the numbers of T cells and infected T cells change greatly in a very short period of time, which corresponds to the switching of the virus survival environment in two different states.[20] Therefore, based on the biological system in random environment, the infectious disease model with certain parameters is not realistic. It is of great significance to study the random switching of environmental state for studying the number change of susceptible host cells, a virus population, and immune responses, so as to analyze the dynamic behavior of the infectious disease model.

The purpose of this article is to explore the effect of the stochastic switching environment on the virus infection model with nonlytic immune responses. The stochastic switching environment (or telegraph noise) is expressed as multi-state Markov chains. They consist of sudden instantaneous transitions between two or more sets of parameter values in the underlying model corresponding to two or more different environments or regimes.[21,22] The switching is memoryless and the waiting time for the next switch has an exponential distribution. We can hence model the switching between environments by a finite state continuous time Markov chain with state space $\mathbb{S} = 1, 2, \ldots, M$, where M is the number of different environments.

Many researchers have studied the effects of telegraph noise on the population model. For example, the SIS model has been discussed in literature.[23–29] For example, Gray *et*

*Project supported by the National Natural Science Foundation of China (Grant No. 11571009) and the Applied Basic Research Programs of Shanxi Province of China (Grant No. 201901D111086).

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al. studied the behavior of this system.[21] Note that the model assumes that the system switches between the two regimes and the Markov switching is independent of the state of the system. The explicit solution and the conditions for extinction and persistence of the stochastic SIS epidemic model were established in the research. Zhang *et al.* investigated the influence of telegraph noise on the stochastic SIS epidemic model with vaccination.[30] They established sufficient conditions for the existence of a unique ergodic stationary distribution by constructing stochastic Lyapunov functions with regime switching.

Markov environment has also been extensively studied in other biological fields. For example, Anderson[31] studied the optimal development strategy of animal population under Markov environment. Padilla and Adolph[32] raised a mathematical model to predict the expected adaptation of phenotypic plastic organisms in a variable environment. Further, they discussed the importance of time delays in this model. Moreover, Peccoud and Ycart[33] proposed a Markov model for gene induction process. Caswell and Cohen[34] took over the impact of the spectrum of the environmental change when the partial focusing coexists.

In this paper, we establish a virus infection model with nonlytic immune responses under stochastic switching environment. Furthermore, we establish the impact of switching environment on the virus infection model, particularly the stochastic character such as extinction and persistence. One of the advantages of this study is that we use a new approach to analyze and derive the properties of the stochastic virus infection model, rather than using the Fokker–Planck equation. Another advantage is that the threshold for extinction and persistence of virus are obtained by strict mathematical proofs. Most importantly, this study is the first attempt to consider the extinction and persistence of the virus infection model with nonlytic immune responses under stochastic switching environment, which fills the gap in the existing literature.

The main contents of other parts are summarized. Section 2 introduces the stochastic virus model under stochastic switching environment. Then, we briefly introduce some fundamental concepts of finite state Markov chains. In Section 3, sufficient conditions for extinction and persistence are established. Section 4 shows the stochastic simulations to verify the theorems in Section 3 and illustrates our results. The last section summarizes the conclusions and future directions of the research.

2. Model and preliminary

In the process of virus infection, the host immune system reacts with innate and antigen-specific immune responses. At the macro level, these two types of reactions can be roughly divided into lytic and nonlytic components. Lytic components can kill infected cells directly, whereas nonlytic effect can only inhibit virus replication through soluble mediators. As a part of the innate response, natural killer cells can lyse infected cells, and cytokines secreted by various cell types can inhibit viral replication in a nonlytic fashion. In the practical antigen-specific response, cytotoxic T lymphocytes kill infected cells, whereas antibodies neutralize free virus particles and thus inhibit the infection of susceptible cells. In order to investigate the role of direct lytic and nonlytic inhibition of viral replication by immune cells in viral infections, Wodarz *et al.*[9] and Bartholdy *et al.*[14] constructed a mathematical model describing the basic dynamics of the interaction between susceptible host cells, a virus population, and immune responses, which is described by the following differential equation:

$$\begin{cases} \dot{x}(t) = \lambda - \delta x(t) - \dfrac{\beta x(t) y(t)}{1+qz(t)}, \\ \dot{y}(t) = \dfrac{\beta x(t) y(t)}{1+qz(t)} - ay(t) - py(t)z(t), \\ \dot{z}(t) = cy(t) - bz(t). \end{cases} \tag{1}$$

The model details the changes in host-cell number and strength of the immune response as the infection develops over time. Here $x(t)$ denotes the number of susceptible host cells, $y(t)$ denotes the number of virus population, and $z(t)$ denotes the number of the immune responses. The relationship is shown in Fig. 1.

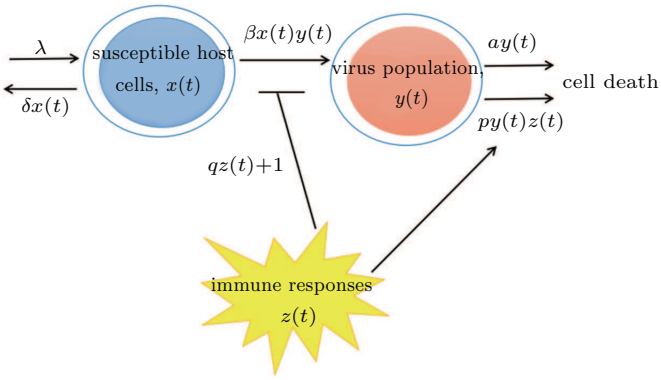


Fig. 1. Schematic diagram of our virus infection model.

The overdot above a variable represents the derivative with respect to time t. Susceptible host cells are generated at a constant rate λ from a source and die at a rate $\delta x(t)$ and become infected by virus at a rate $\beta x(t)y(t)$ without the immune responses. Viral replication is inhibited by the immune response at a rate $1+qz(t)$. This corresponds to nonlytic antiviral activity. Infected cells die at a rate $ay(t)$, and are killed by the immune system at a rate $py(t)z(t)$ for modeling lyric effector mechanisms. Here we assume that the rate of enhancement of immune response is directly proportional to the number of infected cells, namely $cy(t)$,[9] and that its rate of attenuation is directly proportional to the current intensity, namely, $bz(t)$ (see. Table 1).

Table 1. Some parameters of the system (2). All parameters are supposed to be nonnegative.

Parameters	Interpretation
λ	growth rate of susceptible host cells
β	transmission coefficient between x and y
δ	death rate of x
a	death rate of y
b	death rate of z
c	scale factor of immune response

Note that system (1) has not included the dynamics of free virus explicitly because it is assumed that the turn over of free virus is much faster than that of infected cells.[9,14] This allows them to make a quasi steady-state assumption, whereby the amount of free virus is simply proportional to the number of infected cells. Hence, the number of infected cells can be considered as a measure of virus load.

Next we review some basic theories about Markov chains. Throughout this paper, unless stated otherwise, we let $(\Omega,\mathcal{F},\mathcal{F}_{t\geq 0},\mathbb{P})$ be a complete probability space with filtration $\mathcal{F}_{t\geq 0}$ satisfying the usual conditions (i.e. it is increasing and right continuous while $\mathcal{F}_0$ contains all $\mathbb{P}$-null sets). Furthermore, let $r(t)$ $(t\geq 0)$ be a continuous-time Markov chain on the probability space taking values in finite state space $\mathbb{S}=\{1,2,\ldots,M\}$, with generator $\Gamma=(\nu_{ij})_{M\times M}$ defined as

$$\begin{aligned}&\mathbb{P}\{r(t+\Delta t)=j\mid r(t)=i\}\\&=\begin{cases}\nu_{ij}\Delta t+o(\Delta t), & \text{if } i\neq j,\\ 1+\nu_{ii}\Delta t+o(\Delta t), & \text{if } i=j,\end{cases}\end{aligned}\tag{2}$$

where $\Delta t>0$, $\nu_{ij}\geq 0$ is the transition rate from state i to j for $i\neq j$ and $\nu_{ii}=-\Sigma_{1\leq j\leq M,j\neq i}\nu_{ij}$ for $i=1,2,\ldots,M$.[35] Moreover, we define $\Pi=(\pi_1,\pi_2,\ldots,\pi_M)$ as the stationary distribution of Markov chains which is unique. If $M=2$,

$$\pi_1=\frac{\nu_{21}}{\nu_{12}+\nu_{21}}\quad\text{and}\quad\pi_2=\frac{\nu_{12}}{\nu_{12}+\nu_{21}}.$$

For any function ν on the set of states $\mathbb{S}$, we define some notions:

$$\hat{\nu}=\max_{k\in\mathbb{S}}\nu(k),\quad\check{\nu}=\min_{k\in\mathbb{S}}\nu(k).$$

After recalling these fundamental concept of Markov chains, Now, in order to express clearly and simplify, we introduce two-state Markovian switching into (1), which becomes the following stochastic virus infection model:

$$\begin{cases}\dot{x}(t)=\lambda_{r(t)}-\delta_{r(t)}x(t)-\dfrac{\beta_{r(t)}x(t)y(t)}{1+q_{r(t)}z(t)},\\ \dot{y}(t)=\dfrac{\beta_{r(t)}x(t)y(t)}{1+q_{r(t)}z(t)}-a_{r(t)}y(t)-p_{r(t)}y(t)z(t),\\ \dot{z}(t)=c_{r(t)}y(t)-b_{r(t)}z(t),\end{cases}\tag{3}$$

where $r(t)$ is a right-continuous Markov chain with state space $\mathbb{S}=1,2$. We will concentrate on analyzing this model.

For the sake of researching the survival and extinction, we need to define appropriately persistence and extinction. Here our definitions are inspired by the works of Yang and Mao[35] and Liu and Wang.[36] The useful definitions are as follows:

(1) The virus $y(t)$ will go to extinction if $\lim\limits_{t\to+\infty}y(t)=0$.

(2) The virus $y(t)$ will be strongly persistent in the mean if $\liminf\limits_{t\to+\infty}\frac{1}{t}\int_0^t y(s)\,\mathrm{d}s>0$.

3. Theoretical analysis and results

The objective of this section is to study extinction and persistent of system (3). First, we prove that solutions of system (3) are positive and ultimately bounded.

Theorem 1 All solutions of system (3) are positive for $t>0$ and there exists $M>0$, such that all the solutions satisfy $x(t),y(t),z(t)<M$ for all large t.

Proof The positive solution of system (3) has been studied in Ref. [17]. Here we mainly demonstrate the ultimate boundedness.

Since all solutions to Eqs. (3) are positive, from the first equation of Eqs. (3) we have

$$\begin{aligned}\dot{x}(t)&=\lambda_{r(t)}-\delta_{r(t)}x(t)-\frac{\beta_{r(t)}x(t)y(t)}{1+q_{r(t)}z(t)}\\&<\hat{\lambda}-\check{\delta}x(t).\end{aligned}\tag{4}$$

Therefore, we obtain

$$x(t)<\frac{\hat{\lambda}}{\check{\delta}}+1,\quad\text{for all large } t,\ \text{say } t>t_0.$$

Adding the first two equations yields

$$\begin{aligned}\dot{x}(t)+\dot{y}(t)&=\lambda_{r(t)}-\delta_{r(t)}x(t)-a_{r(t)}y(t)-p_{r(t)}y(t)z(t)\\&<\hat{\lambda}-\check{\delta}x(t).\end{aligned}$$

Let $C>0$ such that $\check{\delta}C>\hat{\lambda}+1$. Then, so long as

$$x(t)+y(t)\geq C+\frac{\hat{\lambda}}{\check{\delta}}+1,t>t_0,$$

we have $\dot{x}(t)+\dot{y}(t)<-1$. Clearly, there must exist $t_1>t_0$ such that

$$x(t)+y(t)<C+\frac{\hat{\lambda}}{\check{\delta}}+1,\quad\text{for all}\ \ t>t_1.$$

The asymptotic bound for $y(t)$, namely, $y(t)<C+\dfrac{\hat{\lambda}}{\check{\delta}}+1$, together with the differential inequality

$$\dot{z}(t)<\hat{c}\left(C+\frac{\hat{\lambda}}{\check{\delta}}+1\right)-\check{b}z,\quad\text{for large } t$$

leads immediately to the asymptotic bound $z(t)\leq\frac{\hat{c}}{\check{b}}(C+\frac{\hat{\lambda}}{\check{\delta}}+1)$, for large t.

Next we concentrate on talking about the conditions for extinction and persistence of our virus model (3). The reproductive ratio of the virus model (1) is shown by $R_0 = \frac{\lambda\beta}{a\delta}$ in Refs. [9,14,15,17]. This ratio describes the average number of new infected cells produced by an infected cell at the beginning of the infectious process. It is easy to find out that if $R_0 < 1$, the disease-free steady state $E_0 = (\frac{\lambda}{\delta}, 0, 0)$ is the only stable state, corresponding to the extinction of the free virus. When $R_0 > 1$, in addition to the disease-free state which is unstable, there is only one disease steady state $E_1 = (\bar{x}, \bar{y}, \bar{z})$, and there is another equilibrium point

$$E_1 = \{\bar{x}, \bar{y}, \bar{z}\} = \left\{ \frac{c\lambda(1+q\bar{z})}{c\delta + (b\beta + c\delta q)\bar{z}}, \frac{b\bar{z}}{c}, -\frac{pc\delta + ab\beta + ac\delta q}{2(bp\beta + c\delta pq)} + \frac{\sqrt{(pc\delta + ab\beta + ac\delta q)^2 - 4p(b\beta + c\delta q)(ac\delta - c\lambda\beta)}}{2(bp\beta + c\delta pq)} \right\}, \quad (5)$$

where E_1 is called the disease state, in which the virus can build infection and survive. Moreover, under certain conditions, the disease state E_1 is globally asymptotically stable. The global stability of steady state E_1 is proved in detail by Wang *et al.*[17]

Now let us recall that $r(t)$ is a Markov chain with state space $\mathbb{S} = 1, 2$. If $r(t) = 1$, then we will be in state 1, and if $r(t) = 2$ then in state 2. For convenience, we give the following alternative condition on the value of R_0 in different states:

$R_0 < 1$ if and only if $\alpha_{r(t)} < 0$;

$R_0 \geq 1$ if and only if $\alpha_{r(t)} \geq 0$; where

$$\alpha_{r(t)} = \beta_{r(t)}\lambda_{r(t)} - \delta_{r(t)}a_{r(t)}.$$

Theorem 2 Extinction. If

$$R_0^* = \frac{(\pi_1\beta_1 + \pi_2\beta_2)(\pi_1\lambda_1 + \pi_2\lambda_2)}{(\pi_1 a_1 + \pi_2 a_2)(\pi_1\delta_1 + \pi_2\delta_2)} < 1,$$

then, for any given initial $(x(0), y(0), z(0))(x(0), y(0), z(0)) \in (0, M)^3$, the solution of the stochastic virus infection model (3) has the properties as follows:

$$\liminf_{t\to\infty} x(t) \leq \frac{\pi_1\lambda_1 + \pi_2\lambda_2}{\pi_1\delta_1 + \pi_2\delta_2} \text{ a.s.} \quad (6)$$

$$\limsup_{t\to\infty} x(t) \geq \frac{\pi_1\lambda_1 + \pi_2\lambda_2}{\pi_1\delta_1 + \pi_2\delta_2} \text{ a.s.} \quad (7)$$

and

$$\lim_{t\to\infty} y(t) = 0 \text{ a.s.} \quad (8)$$

$$\lim_{t\to\infty} z(t) = 0 \text{ a.s.} \quad (9)$$

In other words, the number of susceptible host cells will reach the neighborhood of the level $\frac{\pi_1\lambda_1 + \pi_2\lambda_2}{\pi_1\delta_1 + \pi_2\delta_2}$ a.s., and the disease will die out almost surely (a.s.).

Proof Let us prove assertion (6) first. If this were not true, then we can find an $\varepsilon > 0$ sufficiently small for $\mathbb{P}(\Omega_1) > 0$, where

$$\Omega_1 = \left\{ \omega \in \Omega : \liminf_{t\to\infty} x(t) > \frac{\pi_1\lambda_1 + \pi_2\lambda_2}{\pi_1\delta_1 + \pi_2\delta_2} + \varepsilon \right\}. \quad (10)$$

On the one hand, by the ergodic theory of the Markov chains, we have $\mathbb{P}(\Omega_2) = 1$, where, for any $\omega \in \Omega_2$,

$$\lim_{t\to\infty} \frac{1}{t}\int_0^t \left(\lambda_{r(s)} - \delta_{r(s)}\left[\frac{\pi_1\lambda_1 + \pi_2\lambda_2}{\pi_1\delta_1 + \pi_2\delta_2} + \varepsilon\right]\right) \mathrm{d}s$$

$$= \pi_1\left(\lambda_1 - \delta_1\left[\frac{\pi_1\lambda_1 + \pi_2\lambda_2}{\pi_1\delta_1 + \pi_2\delta_2} + \varepsilon\right]\right) + \pi_2\left(\lambda_2 - \delta_2\left[\frac{\pi_1\lambda_1 + \pi_2\lambda_2}{\pi_1\delta_1 + \pi_2\delta_2} + \varepsilon\right]\right)$$

$$= -(\pi_1\delta_1 + \pi_2\delta_2)\varepsilon. \quad (11)$$

Now consider any $\omega \in \Omega_1 \cap \Omega_2$. Then there is a positive number $T = T(\omega)$ such that $x(t) \geq \frac{\pi_1\lambda_1 + \pi_2\lambda_2}{\pi_1\delta_1 + \pi_2\delta_2} + \varepsilon, \forall t \geq T$. On the other hand,

$$dx(t) = \left[\lambda_{r(t)} - \delta_{r(t)}x(t) + \frac{\beta_{r(t)}x(t)y(t)}{q_{r(t)}z(t) + 1}\right]\mathrm{d}t \leq (\lambda_{r(t)} - \delta_{r(t)}x(t))\,\mathrm{d}t. \quad (12)$$

It follows from Eq. (12) that

$$x(t) \leq x(0) + \int_0^T (\lambda_{r(s)} - \delta_{r(s)}x(s))\,\mathrm{d}s + \int_T^t \left(\lambda_{r(s)} - \delta_{r(s)}\left[\frac{\pi_1\lambda_1 + \pi_2\lambda_2}{\pi_1\delta_1 + \pi_2\delta_2} + \varepsilon\right]\right)\mathrm{d}s$$

for all $t \geq T$. Dividing both sides by t and then letting $t \to \infty$, we obtain

$$\limsup_{t\to\infty} \frac{x(t)}{t} \leq -(\pi_1\delta_1 + \pi_2\delta_2)\varepsilon,$$

where Eq. (11) has been used. This implies

$$\lim_{t\to\infty} x(t) = 0.$$

However, this contradicts Eq. (10). This required assertion (6) must therefore hold.

Let us prove assertion (8) before we prove assertion (7). By integrating the first equation of model (3) and then dividing both sides by t, we obtain

$$\frac{x(t) - x(0)}{t} = \frac{1}{t}\int_0^t (\lambda_{r(s)} - \delta_{r(s)}x(s) - \frac{\beta_{r(s)}x(s)y(s)}{q_{r(s)}z(s) + 1})\,\mathrm{d}s \leq \frac{1}{t}\int_0^t (\lambda_{r(s)} - \delta_{r(s)}x(s))\,\mathrm{d}s.$$

We compute

$$\frac{1}{t}\int_0^t \delta_{r(s)}x(s)\,\mathrm{d}s \leq \frac{1}{t}\int_0^t \lambda_{r(s)}\,\mathrm{d}s - \frac{x(t) - x(0)}{t}. \quad (13)$$

Finding the limit of both sides of Eq. (13) and using the properties of conditional expectation, we have

$$(\pi_1\delta_1 + \pi_2\delta_2)\lim_{t\to\infty} \frac{1}{t}\int_0^t x(s)\,\mathrm{d}s \leq \pi_1\lambda_1 + \pi_2\lambda_2.$$

That is to say,

$$\lim_{t\to\infty}\frac{1}{t}\int_0^t x(s)\,\mathrm{d}s \le \frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2}+\varepsilon.$$

From model (3), it is easy to find

$$\mathrm{d}\ln y(t) = \left[\frac{\beta_{r(t)}x(t)}{q_{r(t)}z(t)+1} - a_{r(t)} - p_{r(t)}z(t)\right]\mathrm{d}t.$$

Integrating this equation and dividing on both sides by t yield

$$\begin{aligned}&\frac{\ln y(t)-\ln y(0)}{t}\\ &= \frac{1}{t}\int_0^t\left(-a_{r(s)}+\frac{\beta_{r(s)}x(s)}{q_{r(s)}z(s)+1}-p_{r(s)}z(s)\right)\mathrm{d}s\\ &\le \frac{1}{t}\int_0^t(\beta_{r(s)}x(s)-a_{r(s)})\,\mathrm{d}s. \end{aligned}\tag{14}$$

Taking the limit of both sides of Eq. (14), we hence obtain

$$\begin{aligned}&\limsup_{t\to\infty}\frac{1}{t}\ln(y(t))\\ &\le [\pi_1\beta_1+\pi_2\beta_2]\frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2}-(\pi_1a_1+\pi_2a_2).\end{aligned}$$

Thus, if

$$(\pi_1\beta_1+\pi_2\beta_2)(\pi_1\lambda_1+\pi_2\lambda_2)<(\pi_1a_1+\pi_2a_2)(\pi_1\delta_1+\pi_2\delta_2),$$

we have

$$\lim_{t\to\infty}y(t)=0.$$

Therefore, assertion (19) must hold.

Next let us prove assertion (7). The proof of assertion (7) is very like to Eq. (6). If this were not true, then we can find a value of $\varepsilon>0$ sufficiently small for $\mathbb{P}(\Omega_3)>0$, where

$$\Omega_3=\{\omega\in\Omega:\limsup_{t\to\infty}x(t)<\frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2}-\varepsilon\}.\tag{15}$$

By the ergodic theory of the Markov chain, we also have $\mathbb{P}(\Omega_4)=1$, where for any $\omega\in\Omega_4$,

$$\begin{aligned}&\lim_{t\to\infty}\frac{1}{t}\int_0^t\left(\lambda_{r(s)}-\delta_{r(s)}\left[\frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2}-\varepsilon\right]\right)\mathrm{d}s\\ &=\pi_1\left(\lambda_1-\delta_1\left[\frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2}-\varepsilon\right]\right)\\ &\quad+\pi_2\left(\lambda_2-\delta_2\left[\frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2}-\varepsilon\right]\right)\\ &=(\pi_1\delta_1+\pi_2\delta_2)\varepsilon.\end{aligned}$$

Now consider any $\omega\in\Omega_3\cap\Omega_4$. Then there is a positive number $T=T(\omega)$ such that $x(t)\ge\frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2}-\varepsilon,\forall t\ge T$. On the other hand, from the model (3) we have

$$\begin{aligned}x(t)-x(0) &= \int_0^t(\lambda_{r(s)}-\delta_{r(s)}x(s))\,\mathrm{d}s-\int_0^t\frac{\beta_{r(s)}x(s)y(s)}{q_{r(s)}z(s)+1}\mathrm{d}s\\ &\ge \int_0^T(\lambda_{r(s)}-\delta_{r(s)}x(s))\,\mathrm{d}s\\ &\quad+\int_T^t\left(\lambda_{r(s)}-\delta_{r(s)}\left[\frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2}\right]\right)\mathrm{d}s\\ &\quad-\int_0^t\frac{\beta_{r(s)}x(s)y(s)}{q_{r(s)}z(s)+1}\mathrm{d}s\end{aligned}$$

$\forall t\ge T$. Dividing both sides by t and then letting $t\to\infty$, we obtain

$$\limsup_{t\to\infty}\frac{x(t)}{t}\ge(\pi_1\delta_1+\pi_2\delta_2)\varepsilon,$$

where Eq. (8) has been used. This implies that

$$\lim_{t\to\infty}x(t)=\infty.$$

However, this contradicts Eq. (15). This required assertion (7) must therefore hold. The proof of assertion (9) is straightforward, so it is omitted.

Note that if both $\alpha_1<0$ and $\alpha_2<0$, then clearly the corresponding R_0 values for both subsystems (state 1 and state 2) will be less than one, thus both subsystems will die out, hence virus will become extinct, and of course this is unsurprising. However, if only one of α_1 and α_2 is negative, say state 1, then we will have $\alpha_1<0$ while $\alpha_2>0$ in state 2. In other words, one subsystem will go extinct whilst the other will persist. It turns out that if the rate of the Markov chain switching from state 2 to state 1 is relatively faster than that from state 1 to 2, then the effect from state 1 will predominate, thus making the overall system die out. This reveals the important role of the Markov chain in the extinction. In Section 4, we show some simulations to illustrate this case.

Apart from extinction, the persistence of the virus is also important in the analysis of models of a particular disease. As a result, the following theorem shows that the virus will be persistent in this case.

Theorem 3 Mean strong persistence. If

$$R_0^*=\frac{(\pi_1\beta_1+\pi_2\beta_2)(\pi_1\lambda_1+\pi_2\lambda_2)}{(\pi_1a_1+\pi_2a_2)(\pi_1\delta_1+\pi_2\delta_2)}>1,$$

then virus population $y(t)$ tends to strong persistence in the mean a.s.

Proof From the second equation of model (3), we have

$$\begin{aligned}\frac{y(t)-y(0)}{t} &= \frac{1}{t}\int_0^t\left[\frac{\beta_{r(s)}x(s)}{q_{r(s)}z(s)+1}\right.\\ &\quad\left.-a_{r(s)}y(s)-p_{r(s)}y(s)z(s)\right]\mathrm{d}s.\end{aligned}\tag{16}$$

Following from the model (3) and (16), we can reach

$$\begin{aligned}&\frac{x(t)-x(0)}{t}+\frac{y(t)-y(0)}{t}\\ &=\frac{1}{t}\int_0^t(\lambda_{r(s)}-\delta_{r(s)}x(s)-a_{r(s)}y(s)-p_{r(s)}y(s)z(s))\,\mathrm{d}s.\end{aligned}\tag{17}$$

Then we have

$$\begin{aligned}&\frac{1}{t}\int_0^t\lambda_{r(s)}\,\mathrm{d}s\\ &=\frac{1}{t}\int_0^t(\delta_{r(s)}x(s))\,\mathrm{d}s-\frac{x(t)-x(0)}{t}-\frac{y(t)-y(0)}{t}\end{aligned}$$

$$-\frac{1}{t}\int_0^t (a_{r(s)}y(s))\,\mathrm{d}s - \frac{1}{t}\int_0^t (p_{r(s)}y(s)z(s))\,\mathrm{d}s.$$

By conditional expectation and letting $t\to\infty$, we obtain

$$\begin{aligned}
&\lim_{t\to\infty}\frac{1}{t}\int_0^t x(s)\,\mathrm{d}s\\
&= \frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2} - \frac{\pi_1 a_1+\pi_2 a_2}{\pi_1\delta_1+\pi_2\delta_2}\lim_{t\to\infty}\frac{1}{t}\int_0^t y(s)\,\mathrm{d}s\\
&\quad - \frac{1}{\pi_1\delta_1+\pi_2\delta_2}\lim_{t\to\infty}\frac{1}{t}\int_0^t (p_{r(s)}y(s)z(s))\,\mathrm{d}s\\
&\le \frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2} - \frac{\pi_1 a_1+\pi_2 a_2}{\pi_1\delta_1+\pi_2\delta_2}\lim_{t\to\infty}\frac{1}{t}\int_0^t y(s)\,\mathrm{d}s. \quad (18)
\end{aligned}$$

From Eq. (14), we can compute

$$\frac{1}{t}\int_0^t (\beta_{r(s)}x(s))\,\mathrm{d}s \ge \frac{lny(t)-lny(0)}{t} + \frac{1}{t}\int_0^t a_{r(s)}\,\mathrm{d}s.$$

Then we have

$$\begin{aligned}
&\frac{1}{t}\int_0^t x(s)\,\mathrm{d}s\\
&\ge \frac{1}{\pi_1\beta_1+\pi_2\beta_2}\frac{\ln y(t)-\ln y(0)}{t} + \frac{\pi_1 a_1+\pi_2 a_2}{\pi_1\beta_1+\pi_2\beta_2}. \quad (19)
\end{aligned}$$

Taking the limit of both sides of Eq. (19) and combining with Eq. (18), we have

$$\begin{aligned}
&\frac{\pi_1 a_1+\pi_2 a_2}{\pi_1\beta_1+\pi_2\beta_2}\\
&\le \frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2} - \frac{\pi_1 a_1+\pi_2 a_2}{\pi_1\delta_1+\pi_2\delta_2}\lim_{t\to\infty}\frac{1}{t}\int_0^t y(s)\,\mathrm{d}s. \quad (20)
\end{aligned}$$

Then we can arrive at

$$\liminf_{t\to\infty}\frac{1}{t}\int_0^t y(s)\,\mathrm{d}s \le \left(\frac{(\pi_1\beta_1+\pi_2\beta_2)(\pi_1\lambda_1+\pi_2\lambda_2)-(\pi_1\delta_1+\pi_2\delta_2)(\pi_1 a_1+\pi_2 a_2)}{(\pi_1\beta_1+\pi_2\beta_2)(\pi_1\delta_1+\pi_2\delta_2)}\right)\left(\frac{\pi_1\beta_1+\pi_2\beta_2}{\pi_1 a_1+\pi_2 a_2}\right).$$

Consequently, we can derive that if

$$(\pi_1\beta_1+\pi_2\beta_2)(\pi_1\lambda_1+\pi_2\lambda_2) > (\pi_1 a_1+\pi_2 a_2)(\pi_1\delta_1+\pi_2\delta_2),$$

then

$$\liminf_{t\to\infty}\frac{1}{t}\int_0^t y(s)\,\mathrm{d}s > 0 \ \text{ a.s.}$$

Therefore assertion must hold.

4. Stochastic simulation and discussions

In this section, we use the Euler and Gillespie algorithm to verify and illustrate the theoretical results in Section 3. The parameters used in this section are approximated and taken from Refs. [9,14,17,20]. For model (3), we consider the following discretization equations:

$$\begin{aligned}
x_{k+1} &= x_k + (\lambda_{r(t)} - \delta_{r(t)}x(t) - \frac{\beta_{r(t)}x(t)y(t)}{1+q_{r(t)}z(t)})\Delta t,\\
y_{k+1} &= y_k + (\frac{\beta_{r(t)}x(t)y(t)}{1+q_{r(t)}z(t)} - a_{r(t)}y(t) - p_{r(t)}y(t)z(t))\Delta t,\\
z_{k+1} &= z_k + (c_{r(t)}y(t) - b_{r(t)}z(t))\Delta t.
\end{aligned}$$

The evolution of virus over time is depicted in Figs. 2 and 3. For all the numerical simulations, we choose the same initial value $(x(0),y(0),z(0)) = (1.5,9,5)$ and parameters $p_1 = 0.0220$, $p_2 = 0.0320$, $q_1 = 0.0300$, $q_2 = 0.0400$, $b_1 = 0.1230$, $b_2 = 0.2010$.

In terms of Fig. 2, we fix parameters $v_{12} = 0.6$ and $v_{21} = 0.9$, it is clear that $\pi_1 = 0.6$ and $\pi_2 = 0.4$. In Fig. 2(a), we deduce that $\alpha_1 = -0.4270 < 0$, $\alpha_2 = -0.6064 < 0$, $R_0^* < 1$ and the theoretical value $\frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2} = 1.9760$, and averaging after integration of $x(t)$, it follows that the simulated value is 1.9450. Furthermore, in Fig. 2(b), we compute that $\alpha_1 = -0.4270 < 0$, $\alpha_2 = 0.0019 > 0$, $R_0^* < 1$, and theoretical value $\frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2} = 3.6143$. By averaging after integration of $x(t)$, it follows that the simulated value is 3.5905. On the one hand, we find that the simulated value is very close to the theoretical value, which can verify the correctness of the theoretical value in Theorem 2. On the other hand, from Figs. 2(a) and 2(b) we can see that the solution of model (3) obeys $\lim_{t\to\infty} y(t) = 0$, the number of susceptible cells $x(t)$ reaches the neighborhood of the theoretical value $\frac{\pi_1\lambda_1+\pi_2\lambda_2}{\pi_1\delta_1+\pi_2\delta_2}$ a.s., and $\lim_{t\to\infty} z(t) = 0$. Thus, the curves of Fig. 2 supports the conclusions in Theorem 2.

Moreover, comparing Fig. 2(a) and Fig. 2(b), we can find an important and fascinating phenomenon. In Fig. 2(b), the parameter values for state $r(t) = 1$ satisfy $\alpha_1 < 0$ and the parameter values for state $r(t) = 2$ satisfy and $\alpha_2 > 0$. Based on the results[17] of the deterministic model (1), the virus population $y(t)$ in state $r(t) = 1$ will be extinct, and $y(t)$ in state $r(t) = 2$ will be persistent. However, if switching rate of Markov chain from state 2 to state 1 is comparatively faster than that from 1 to 2, it will satisfy $R_0^* < 1$, then the virus population $y(t)$ in the stochastic model (3) will be extinct. This behavior indicates that in the presence of telegraph noise, the virus will experience extinction. In other words, the presence of telegraph noise is conducive to the extinction of the virus. In this case, patients could be completely cured by effective therapy.

Figure 3 illustrates the results of Theorem 3. Here we choose the parameters $v_{12} = 0.6$ and $v_{21} = 0.9$, therefore the unique stationary distribution $\pi_1 = 0.6$, $\pi_2 = 0.4$ and $R_0^* > 1$. According to Theorem 3, in consideration of Theorem 3, we realize that $y(t)$ will be strong persistence in the mean. The simulation results of Fig. 3 verify the theoretical results. Moreover, we find a equilibrium point $E^* = (x^*,y^*,z^*)$, where

$$E^* = \{x^*, y^*, z^*\} = \left\{ \frac{\pi_1 c_1 \lambda_1 (1+q_1\bar{z}_1) + \pi_2 c_2 \lambda_2 (1+q_2\bar{z}_2)}{\pi_1 c_1 \delta_1 + (b_1\beta_1 + c_1\delta_1 q_1)\bar{z}_1 + \pi_2 c_2 \delta_2 + (b_2\beta_2 + c_2\delta_2 q_2)\bar{z}_2}, \frac{\pi_1 b_1 \bar{z}_1 + \pi_2 b_2 \bar{z}_2}{\pi_1 c_1 + \pi_2 c_2}, \right.$$
$$\frac{\pi_1(-(p_1c_1\delta_1 + a_1b_1\beta_1 + a_1c_1\delta_1 q_1))}{2\pi_1(b_1p_1\beta_1 + c_1\delta_1 p_1 q_1) + 2\pi_2(b_2p_2\beta_2 + c_2\delta_2 p_2 q_2)}$$
$$+ \frac{\pi_1(\sqrt{(p_1c_1\delta_1 + a_1b_1\beta_1 + a_1c_1\delta_1 q_)^2 - 4p_1(b_1\beta_1 + c_1\delta_1 q_1)(a_1c_1\delta_1 - c_1\lambda_1\beta_1)})}{2\pi_1(b_1p_1\beta_1 + c_1\delta_1 p_1 q_1) + 2\pi_2(b_2p_2\beta_2 + c_2\delta_2 p_2 q_2)}$$
$$+ \frac{\pi_2(-(p_2c_2\delta_2 + a_2b_2\beta_2 + a_2c_2\delta_2 q_2))}{2\pi_1(b_1p_1\beta_1 + c_1\delta_1 p_1 q_1) + 2\pi_2(b_2p_2\beta_2 + c_2\delta_2 p_2 q_2)}$$
$$\left. + \frac{\pi_2(\sqrt{(p_2c_2\delta_2 + a_2b_2\beta_2 + a_2c_2\delta_2 q_)^2 - 4p_2(b_2\beta_2 + c_2\delta_2 q_2)(a_2c_2\delta_2 - c_2\lambda_2\beta_2)})}{2\pi_1(b_1p_1\beta_1 + c_1\delta_1 p_1 q_1) + 2\pi_2(b_2p_2\beta_2 + c_2\delta_2 p_2 q_2)} \right\}.$$

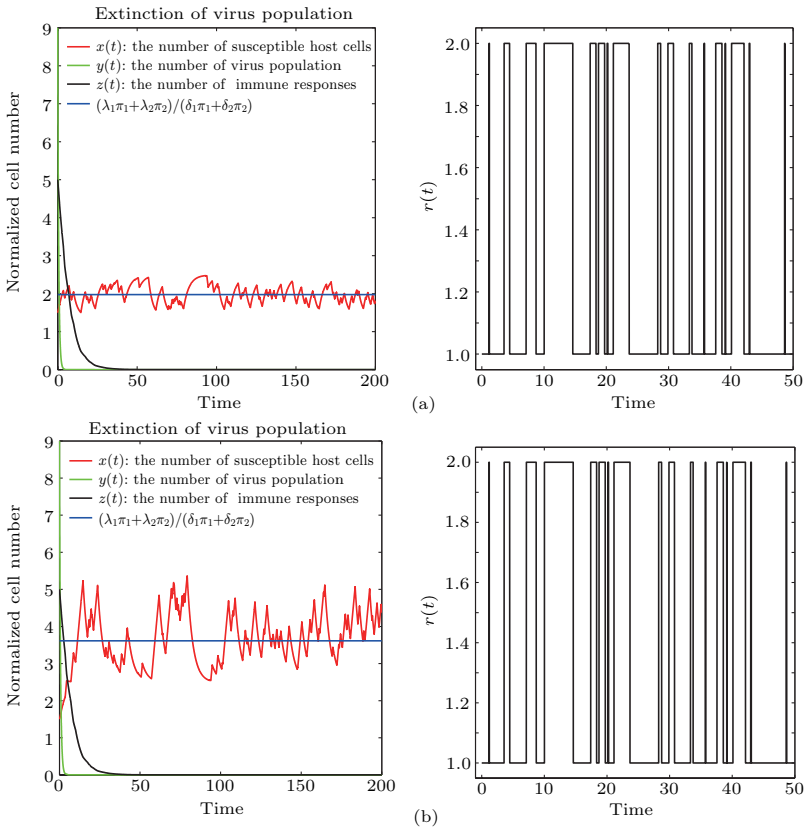


Fig. 2. Sample path $x(t)$, $y(t)$, $z(t)$ and its corresponding Markov chain $r(t)$ for the stochastic virus infection model (3), using the parameters $c_1 = 0.0100$ and $c_2 = 0.0150$: (a) $\lambda_1 = 0.7130$, $\lambda_2 = 0.5181$, $\beta_1 = 0.0123$, $\beta_2 = 0.0115$, $\delta_1 = 0.2861$, $\delta_2 = 0.3743$, $a_1 = 1.523$, and $a_2 = 1.636$, (b) $\lambda_1 = 0.7130$, $\lambda_2 = 0.5181$, $\beta_1 = 0.0123$, $\beta_2 = 0.0115$, $\delta_1 = 0.2861$, $\delta_2 = 0.0101$, $a_1 = 1.523$, $a_2 = 0.401$, with the initial value $(x(0), y(0), z(0)) = (1.5, 9, 5)$, and the exponential distribution for the switching times of $r(t)$, with $r(0) = 1$.

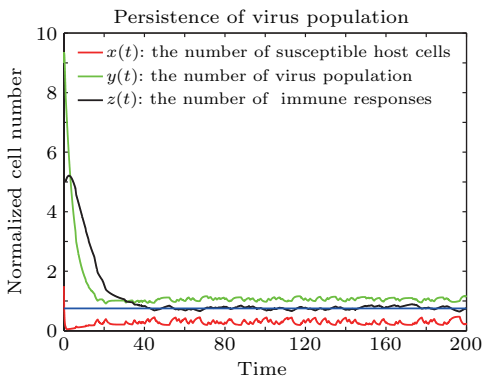


Fig. 3. Sample path $x(t)$, $y(t)$, $z(t)$ for the stochastic virus infection model (3) for parameters $\lambda_1 = 0.2134$, $\lambda_2 = 0.3340$, $\beta_1 = 0.6223$, $\beta_2 = 0.5159$, $\delta_1 = 0.4123$, $\delta_2 = 0.2061$, $a_1 = 0.101$, $a_2 = 0.201$, $c_1 = 0.1100$, and $c_2 = 0.1150$, with the initial value $(x(0), y(0), z(0)) = (1.5, 9, 5)$.

5. Conclusion

In summary, we have investigated the dynamical analysis of the virus infection model in stochastic switching environment. Firstly, the existence of unique positive solution and boundedness of a new hybrid system is proved. Then, the threshold condition for extinction and persistence of virus population is derived by the rigorous theoretical proofs. The biological significance of this threshold is similar to that of basic reproduction number. It is found that if R_0^* is less than 1, then the virus population will tend to zero and the total number of susceptible host cells will converge towards the preinfection number of host cells. That is to say, the disease will die out theoretically in terms of the clinical outcome.[9] If R_0^*

is greater than 1, then virus population will tend to strong persistence in the mean a.s. In addition, the equilibrium point E^* for persistence has been given. Lastly, the correctness of the theoretical results is confirmed by numerical simulation.

In general, stochastic switching environment could play a crucial role in the process of virus evolution and treatment. Our study shows that even if a virus is persistence in a stochastic environment without switching, the virus could be extinct in a stochastic switching environment. This reveals that the presence of stochastic switching environment is beneficial to extinction of disease. The present results could be further expanded to multi-state switching environment. More complex stochastic environment could also be approximated by telegraph noise. It should be noticed that the methods of dynamical analysis in our work can be used and expanded to investigate other population dynamical models.

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